

# Extended-Duration Low-Intensity Apixaban to Prevent Recurrence in Patients with Provoked Venous Thromboembolism and Enduring Risk Factors: Rationale and Design of the HI-PRO Trial

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## Abstract

Patients with acute venous thromboembolism (VTE) in the setting of transient provoking factors are typically treated with short-term anticoagulation. However, the risk of recurrence may be increased in the presence of enduring risk factors. In such patients, the optimal duration of treatment remains uncertain. HI-PRO is a single-center, double-blind randomized trial. Patients with deep vein thrombosis (DVT) or pulmonary embolism (PE) following a major provoking factor, including major surgery or major trauma, who completed at least 3 months of standard-dose therapeutic anticoagulation and have at least one enduring risk factor (such as obesity or heart failure) will be considered for inclusion. Patients will be randomized to apixaban 2.5 mg twice daily or placebo for 12 months. The primary efficacy outcome will be symptomatic recurrent VTE—a composite of DVT and/or PE at 12 months after randomization. Secondary efficacy outcomes include a composite of death due to cardiovascular causes, nonfatal myocardial infarction, stroke or systemic embolism, major adverse limb events, or coronary or peripheral ischemia requiring revascularization at 12 months, and individual components of these outcomes. The primary safety outcome is major bleeding according to the International Society on Thrombosis and Haemostasis definition. The study plans to enroll 600 patients (300 per arm) to have 80% power for detecting a 75% relative risk reduction in the primary outcome. Active recruitment began in March 2021. HI-PRO will provide clinically meaningful data on whether patients with provoked VTE and enduring risk factors have fewer adverse clinical outcomes if prescribed low-intensity extended-duration anticoagulation.

## Keywords

- ▶ venous thromboembolism
- ▶ anticoagulation
- ▶ apixaban
- ▶ provoked

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## Introduction

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), results in thousands of cases of PE-related mortality,<sup>1–3</sup> debilitating post-PE syndrome,<sup>4,5</sup> and chronic thromboembolic pulmonary hypertension.<sup>6–14</sup> Similarly, DVT afflicts hundreds of thousands of patients. In addition to the risk of causing a PE, DVT may lead into postthrombotic syndrome—characterized by chronic leg edema, leg pain, and decreased quality of life.<sup>15</sup>

Historically, VTE has been dichotomized into *provoked* events (i.e., VTE in the setting of major transient reversible factors including major surgery, acute medical illness, or major trauma) and *unprovoked* events, with no readily identifiable triggers. Extended-duration anticoagulation without a defined stop date has become the favored treatment strategy for VTE for patients with a persistently increased risk for recurrence (active cancer, antiphospholipid antibody syndrome, unprovoked VTE).<sup>16–19</sup>

However, there remains clinical equipoise regarding the optimal duration of treatment for provoked VTE.<sup>19–22</sup> Some expert guidelines recommend short-term therapy for provoked VTE.<sup>18</sup> In contrast, others have reported that the risk of VTE recurrence in patients with an initial provoked event is as high as 25% at 10 years.<sup>23</sup> The European Society of Cardiology<sup>19</sup> and the European Society of Vascular Surgery<sup>24</sup> guidelines endorse short-term treatment for VTE only after trauma or surgery in otherwise low-risk patients. Even among patients with major transient reversible factors, some may have coexisting enduring provoking factors, such as obesity, heart failure, or inflammatory conditions that may increase the risk of recurrence.<sup>19,25</sup> Therefore, some guidelines consider extended treatment in patients with major provoking VTE risk factors plus coexisting enduring risk factors.<sup>19</sup>

The existing randomized trials of extended-duration anticoagulation with direct oral anticoagulants have been a major source for these recommendations.<sup>16,17,26,27</sup> The Reduced-dosed Rivaroxaban in the Long-term Prevention of Recurrent Symptomatic Venous Thromboembolism (EINSTEIN CHOICE) trial demonstrated the superiority of once-daily rivaroxaban compared with low-intensity aspirin for extended-duration treatment of VTE, after 6 to 12 months of full-dose anticoagulation. EINSTEIN CHOICE included both patients with provoked (60%) and unprovoked (40%) VTE.<sup>17,27</sup> In the AMPLIFY-EXT trial, 12 months of treatment with low-intensity apixaban compared with placebo reduced the risk of recurrent VTE and did not lead to significantly increase risk of bleeding. Yet, the vast majority (>90%) of AMPLIFY-EXT participants had unprovoked VTE. Therefore, the optimal duration of treatment for provoked VTE in the presence of enduring risk factors remains unknown.

Low-intensity apixaban may be an attractive option, with a favorable safety profile with respect to bleeding events compared with fully therapeutic anticoagulation, as well as a favorable efficacy profile compared with placebo or aspirin.<sup>28</sup> Extended-duration low-intensity treatment with apix-

aban, besides protecting against recurrent VTE, may also confer protection against thromboembolic events in the setting of atrial fibrillation. However, in addition to the potential for excess risk of bleeding, extended-duration anticoagulation may be inconvenient or costly. Therefore, we decided to test low-intensity apixaban against placebo in patients with provoked VTE and coexisting enduring risk factors. This manuscript summarizes the key features of the design and methodology of the investigator-initiated Extended-Duration Low-intensity Apixaban to Prevent Recurrence in High-Risk Patients with PROvoked Venous Thromboembolism (HI-PRO) trial.

## Methods

### Trial Design and Oversight

HI-PRO is an investigator-initiated single-center double-blind randomized controlled trial (RCT) with blinded endpoint adjudication. The study has been registered in clinicaltrials.gov: <https://www.clinicaltrials.gov/ct2/show/NCT04168203>. Patient recruitment, enrollment, and follow-up are planned from general cardiology and vascular medicine outpatient practices at the Brigham and Women's Hospital (BWH). The Institutional Review Board at BWH reviewed and approved the study protocol. All patients will provide written informed consent for participation. The Food and Drug Administration approved an investigational new drug application. A Data Safety and Monitoring Board, consisting of investigators not involved in the design or the conduct of the trial, will be in charge of the trial oversight.

### Patient Enrollment Criteria

Adult patients (aged 18 years or older) with acute objectively confirmed VTE due to a major provoking factor including major surgery, major trauma, acute medical illness, or periods of immobility and who have been treated with anticoagulation for at least 3 months, do not have an ongoing indication for or contraindication to anticoagulation, and have at least one enduring predisposing VTE risk factor will be considered for inclusion. Enduring predisposing factors include obesity (body mass index  $\geq 30$  kg/m<sup>2</sup>), history of heart failure, chronic lung disease (including obstructive or interstitial lung disease), atherosclerotic cardiovascular disease, chronic kidney disease with plasma creatinine  $<2.5$  mg/dL, or chronic inflammatory or autoimmune diseases. Major exclusion criteria are life expectancy  $<12$  months, pregnancy or breastfeeding, severe hepatobiliary disease (including Child–Pugh Class C), an indication or contraindication for anticoagulation, use of P2Y<sub>12</sub> platelet receptor antagonists, or recent or active bleeding. A full list of the study enrollment criteria is provided in ►Table 1.

### Study Intervention

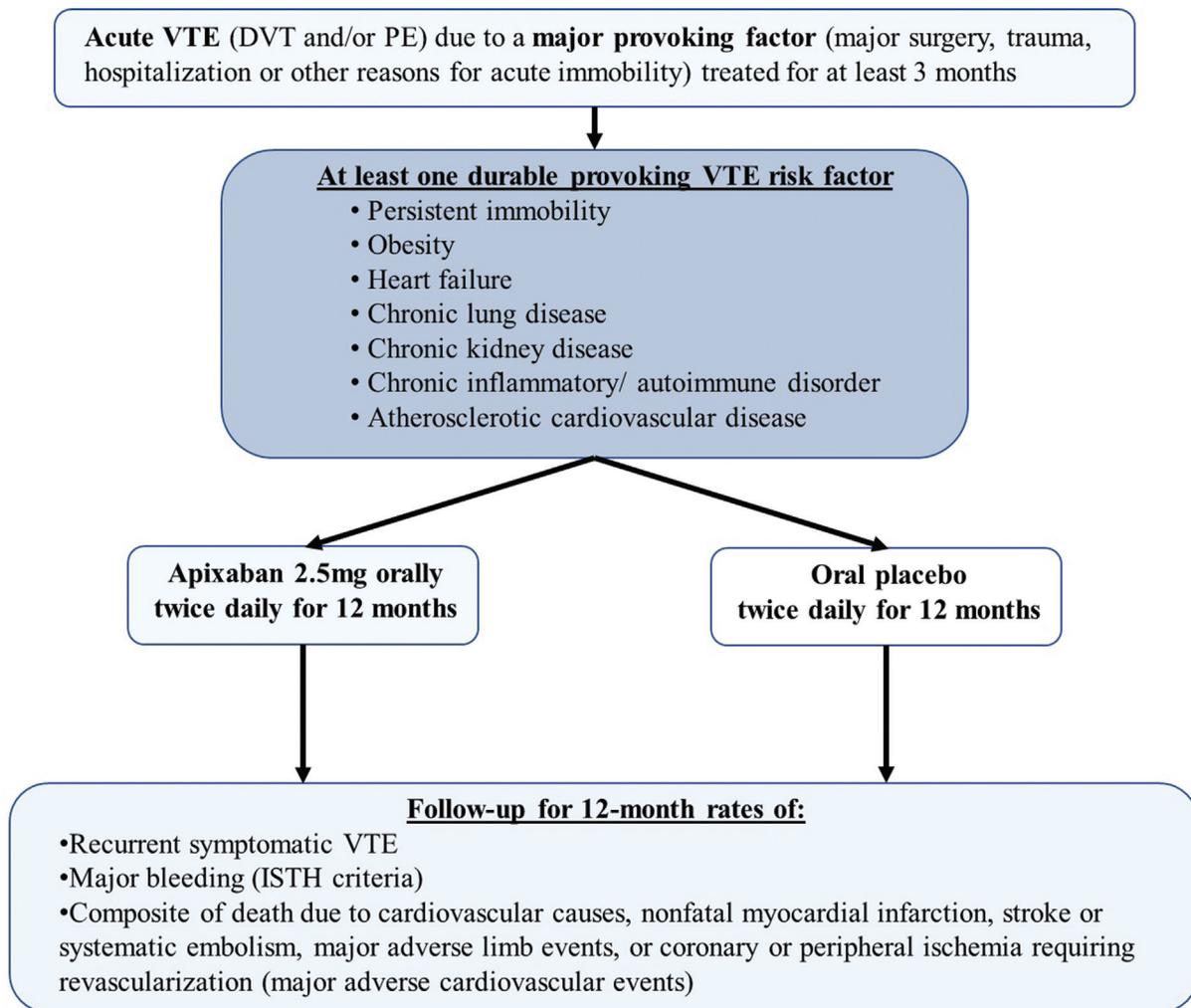
Eligible consenting patients will be randomized to apixaban 2.5 mg bid versus matching placebo (►Figs. 1 and 2). The intended duration of treatment is 12 months.

**Table 1** Study eligibility criteria

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> <li>• Age ≥ 18 years</li> </ul>	<ul style="list-style-type: none"> <li>• Life expectancy &lt; 12 months</li> </ul>
<ul style="list-style-type: none"> <li>• Objectively confirmed DVT and/or PE provoked by major surgery, major trauma, acute medical or surgical illness, or other reasons leading to acute immobility</li> </ul>	<ul style="list-style-type: none"> <li>• Active cancer within the past 5 years</li> </ul>
<ul style="list-style-type: none"> <li>• Treated for at least 3 months with standard therapeutic anticoagulant therapy</li> </ul>	<ul style="list-style-type: none"> <li>• Contraindication to antithrombotic or antiplatelet therapy</li> </ul>
<ul style="list-style-type: none"> <li>• Has not suffered symptomatic recurrence during prior anticoagulant therapy</li> </ul>	<ul style="list-style-type: none"> <li>• Requirement for ongoing anticoagulant therapy, dual antiplatelet therapy, P2Y12 inhibition, or aspirin at a dose of &gt;81 mg daily</li> </ul>
<ul style="list-style-type: none"> <li>• Outpatient follow-up at BWH</li> </ul>	<ul style="list-style-type: none"> <li>• Hemoglobin level &lt; 9 mg/dL or platelet count &lt; 100,000/mm<sup>3</sup></li> </ul>
<ul style="list-style-type: none"> <li>• At least one of the following enduring provoking VTE risk factors (some patients may have more than one):                             <ul style="list-style-type: none"> <li>- Persistent immobility (defined as paralysis, other inability to ambulate freely, bed-bound, wheelchair-bound)</li> <li>- Obesity (defined as BMI ≥ 30 kg/m<sup>2</sup>)</li> <li>- Heart failure (systolic, diastolic, or combined)</li> <li>- Chronic lung disease (COPD, asthma, interstitial lung disease)</li> <li>- Chronic kidney disease (eGFR &lt; 60 mL/min/1.73 m<sup>2</sup>)</li> <li>- Chronic inflammatory/autoimmune disorder (inflammatory arthritis, vasculitis, inflammatory bowel disease, chronic infection)</li> <li>- Atherosclerotic cardiovascular disease (coronary, cerebrovascular, or peripheral artery disease) (up to 35% in each study group may have atherosclerotic cardiovascular disease as a qualifying enduring risk factor)</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Plasma creatinine level &gt; 2.5 mg/dL or CrCl &lt; 25 mL/min (as determined by the Cockcroft–Gault equation)</li> </ul>
	<ul style="list-style-type: none"> <li>• ALT or AST level &gt;2 times the upper limit of the normal range, or a total bilirubin level &gt;1.5 times the upper limit of the normal range, or active or severe hepatobiliary disease</li> </ul>
	<ul style="list-style-type: none"> <li>• History of a platelet disorder such as Von Willebrand disease, or bleeding diathesis, or having had recent active bleeding</li> </ul>
	<ul style="list-style-type: none"> <li>• Pregnancy, breastfeeding, or omen of child-bearing potential who are unwilling or unable to use an acceptable method of birth control (such as oral contraceptives, other hormonal contraceptives [vaginal products, skin patches, or implanted or injectable products], or mechanical products such as an intra-uterine device or barrier methods [diaphragm, condoms, spermicides]) to avoid pregnancy for the entire study</li> </ul>
	<ul style="list-style-type: none"> <li>• &gt;6 month lapse without use of anticoagulation or antiplatelet agents</li> </ul>
	<ul style="list-style-type: none"> <li>• Prisoners or subjects who are involuntarily incarcerated</li> </ul>
	<ul style="list-style-type: none"> <li>• Patients who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness</li> </ul>
	<ul style="list-style-type: none"> <li>• Receiving concurrent non-FDA-approved or investigational agents or has received an investigational agent within the past 30 days prior to the first dose of study treatment (with the exception of approved medications being used for an approved indication, e.g., investigating a new dosing regimen for an approved indication)</li> </ul>
	<ul style="list-style-type: none"> <li>• Any condition, which, in the opinion of the investigator, would put the subject at an unacceptable risk from participating in the study</li> </ul>
	<ul style="list-style-type: none"> <li>• Any other medical, social, logistical, or psychological reason, which, in the opinion of the investigator, would preclude compliance with, or successful completion of, the study protocol</li> </ul>
	<ul style="list-style-type: none"> <li>• History of a severe hypersensitivity reaction to apixaban</li> </ul>
	<ul style="list-style-type: none"> <li>• Use of potent cytochrome P450 3A4 (CYP3A4) inhibitors</li> </ul>
<ul style="list-style-type: none"> <li>• Required prescription of a medication that is contraindicated to be co-administered with apixaban</li> </ul>	

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; BWH, Brigham and Women’s Hospital; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; DVT, deep vein thrombosis; eGFR, estimated glomerular filtration rate; FDA, Food and Drug Administration; PE, pulmonary embolism; VTE, venous thromboembolism.

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**Fig. 1** Study flow diagram. Please note that outcome ascertainment for the primary outcome will occur in the duration of active treatment, i.e., from the day of enrollment, until completion of 12 months of follow-up from the day of enrollment. DVT, deep vein thrombosis; ISTH, International Society on Thrombosis and Haemostasis; PE, pulmonary embolism; VTE, venous thromboembolism.

### Randomization

Consenting outpatients who meet the eligibility criteria will be with a 1:1 allocation ratio, using a computerized allocation program.

### Study Outcomes

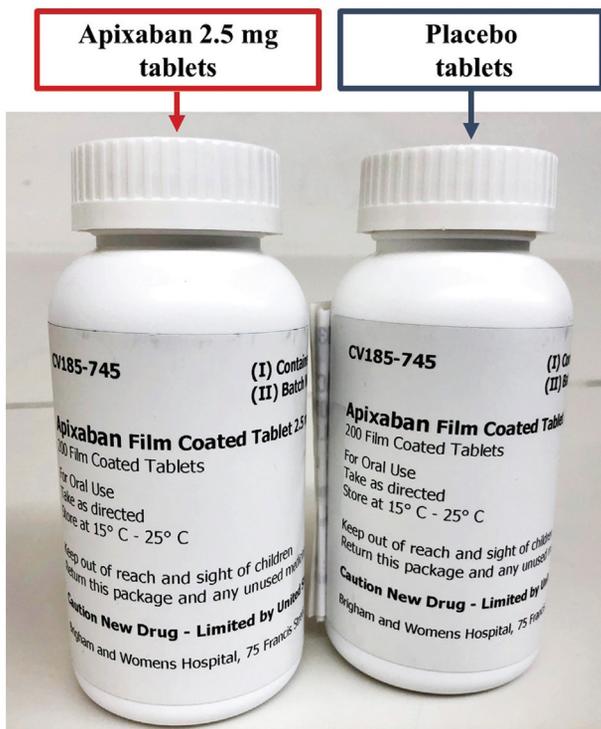
The primary efficacy outcome is symptomatic, recurrent VTE, defined as a composite of DVT and/or PE at 12 months from randomization. Secondary efficacy outcomes include a composite of death due to cardiovascular causes, nonfatal myocardial infarction, stroke or systemic embolism, major adverse limb events, or coronary or peripheral ischemia requiring revascularization at 12 months (► **Table 2**). The individual components of the primary and secondary outcomes will be assessed as exploratory outcomes.

The primary safety outcome is major bleeding according to the International Society on Thrombosis and Haemostasis definition: fatal bleeding or symptomatic bleeding in a critical area or organ including intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or

pericardial, or intramuscular with compartment syndrome, or bleeding causing a fall in hemoglobin level of 2 g/dL or more, or leading to transfusion of 2 or more units of whole blood or red cells.<sup>29,30</sup> Overt bleeding not meeting the criteria for major bleeding but associated with the need for medical or surgical intervention, or unscheduled contact with a health care worker, interruption, or discontinuation of the study drug will be considered as clinically relevant bleeding (► **Table 2**).<sup>31</sup> All efficacy and safety outcomes will be adjudicated by a clinical event committee whose members will be blinded to the randomized treatments.

### Additional Data Elements, Data Entry, and Monitoring

Additional data elements in the study include demographics, clinical comorbidities, and laboratory tests such as hemoglobin, platelet count, and plasma creatinine. Data will be entered into a secure web-based electronic case report form by trained research staff (REDCap).<sup>32</sup> The Data and Safety Monitoring Board will monitor the safety of the study and



**Fig. 2** Study medication: apixaban 2.5 mg tablets or placebo tablets.

consider the stopping criteria for safety and efficacy. Details about the stopping rules are summarized in ► **Table 3**.

**Statistical Analysis**

Categorical variables will be reported as percentages and 95% confidence interval estimates. Continuous data will be presented a mean with standard error, or if not normally distributed, median with interquartile range. With a two-sided alpha level of 0.05, the primary outcome event rate of 6% in the placebo arm<sup>17,33</sup> and a 75% relative risk reduction with apixaban, 279 patients would need to be enrolled in each arm to provide 80% power to detect a significant difference for the primary outcome between the two groups. Considering a 7% dropout rate due to loss to follow-up or postrandomization exclusion, the study plans to enroll 600 patients (300 per arm). BWH is a high-volume center for VTE, and such a sample is feasible to enroll from the inpatient and outpatient services of the hospital.

For efficacy, the primary analyses will be performed on the intention-to-treat cohort, consisting of all patients who were randomized. Analyses will be repeated in the modified intention-to-treat cohort consisting of all randomized patients who received at least one dose of the assigned treatment and did not undergo postrandomization exclusion, and in the per-protocol (on treatment) cohort consisting of those who continued the assigned treatment until

**Table 2** Study outcomes and definitions

Outcome	Definition
<i>Symptomatic recurrent VTE</i>	Symptomatic imaging-confirmed DVT and/or PE
<i>DVT</i>	Symptomatic DVT confirmed by ultrasonography, contrast venography, computed tomography, or magnetic resonance imaging
<i>PE</i>	Symptomatic PE confirmed by appropriate imaging studies including computed tomography, ventilation-perfusion imaging, or invasive angiography
<i>Major adverse cardiovascular events</i>	Composite of death due to cardiovascular cause, nonfatal myocardial infarction (MI), stroke or systemic embolism, major adverse limb events, or coronary or peripheral ischemia requiring revascularization
<i>Type I myocardial infarction</i>	Detection of a rise and/or fall of cTn with at least one value above the 99th percentile and with at least one of the following: <ul style="list-style-type: none"> <li>• Symptoms of acute myocardial ischemia</li> <li>• New ischemic electrocardiographic (ECG) changes</li> <li>• Development of pathological Q waves</li> <li>• Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology</li> <li>• Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy</li> </ul>
<i>Stroke</i>	Clinically identified new, sudden-onset focal neurologic deficit lasting ≥24 hours, not due to a readily identifiable nonvascular cause (i.e. brain tumor, trauma), as confirmed by neuroimaging (or autopsy) and a neurologist. All strokes during the study will be classified as primary hemorrhagic, nonhemorrhagic, infarction with hemorrhagic conversion, or unknown
<i>Acute limb ischemia</i>	Limb-threatening ischemia confirmed by limb hemodynamics or imaging that leads to an acute endovascular or surgical intervention within 30 days of onset of symptoms or absent pedal pulses
<i>Major adverse limb events</i>	Acute limb ischemia requiring thrombectomy, thrombolysis, or surgical revascularization; major amputation at or above the ankle; and/or need for acute revascularization
<i>Major bleeding (ISTH definition)</i>	Fatal bleeding, or symptomatic bleeding in a critical area or organ including intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with

(Continued)

**Table 2** (Continued)

Outcome	Definition
	compartment syndrome, or bleeding causing a fall in hemoglobin level of 2 g/dL or more; or leading to transfusion of two or more units of whole blood or red cells
<i>Clinically relevant nonmajor bleeding</i>	Overt bleeding that does not meet the criteria for major bleeding but associated with the need for medical or surgical intervention, or unscheduled contact with a health care worker, interruption, or discontinuation of the study drug

Abbreviations: cTn, cardiac troponin; DVT, deep vein thrombosis; ISTH, International Society on Thrombosis and Haemostasis; PE, pulmonary embolism.

**Table 3** Criteria for consideration of early termination of the study

	Definition
<i>Stopping for safety</i>	If there will be 3 cases of unprovoked intracranial hemorrhages or 3 cases of unprovoked major bleeding events in the apixaban arm, with confirmed adjudication and no protocol violation, such that the events are deemed to be related to the assigned treatment
<i>Stopping for futility</i>	If there will be fewer than 9 events in the placebo group at the time of completion of 12-month follow-up of the 300th patient in the interim statistical analysis, or if enrollment progress is slow such that there would not be a reasonable chance to complete enrollment of the target population
<i>Stopping for efficacy (superiority)</i>	If the interim analysis after completion of follow-up of the 300th patient indicates overwhelmingly superior efficacy with respect to the primary outcome

Abbreviations: DVT, deep vein thrombosis; ISTH, International Society on Thrombosis and Haemostasis; PE, pulmonary embolism.

completion of 12-month follow-up, death, or a thrombotic event. The primary efficacy analysis will be based on hazard models, adjusted for the competing risk<sup>34</sup> of mortality from non-VTE causes. For the assessment of safety, primary analyses will be performed in patients who were receiving treatment, defined as the time since initiation of the first dose of the study drug (or placebo) until 48 hours after administration of the last dose.

Prespecified subgroup analyses will be performed in patients presenting with PE versus DVT, the elderly (aged  $\geq 65$  years) versus younger patients, women versus men, patients with versus without chronic kidney disease, patients with and without atherosclerotic cardiovascular disease, those with or without low-dose aspirin use at baseline, and patients with ( $\geq 2$ ) versus those without multiple ( $< 2$ ) provoking risk factors. If the results of the subgroup analysis based on aspirin use show evidence of effect modification, in a prespecified analysis, we will replicate the primary analysis by adding baseline aspirin use and an aspirin–apixaban interaction term to the hazard model.<sup>35</sup>

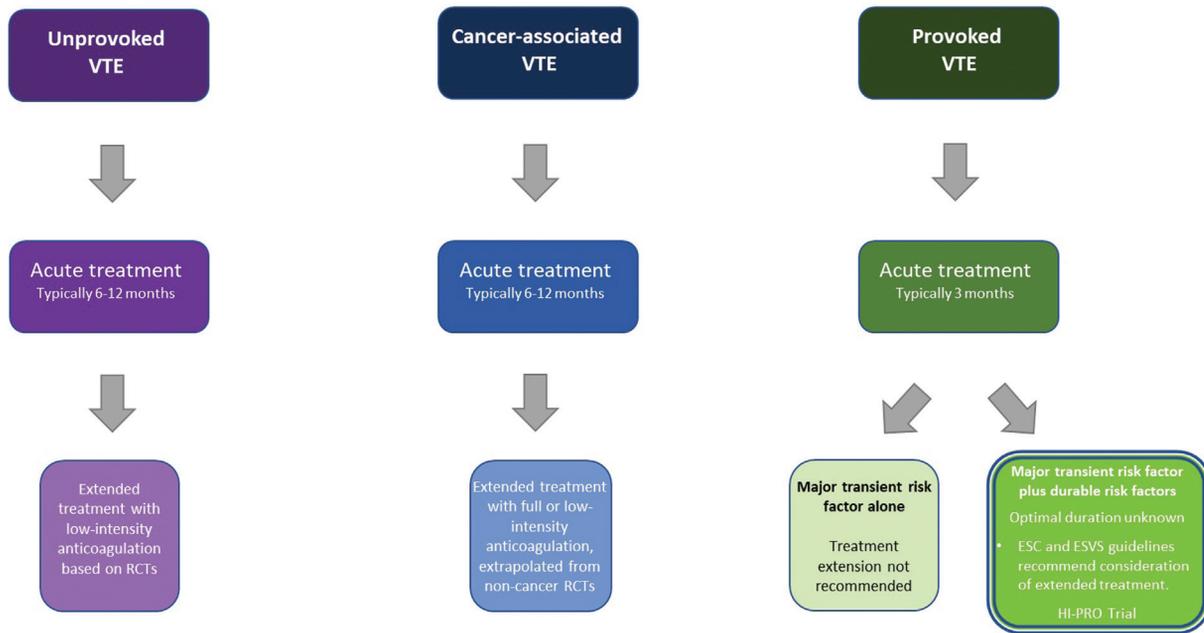
## Discussion

Extended-duration anticoagulation without an end date has become the standard treatment for unprovoked VTE<sup>25,36</sup> and in patients with active cancer who do not have a high risk of bleeding.<sup>37,38</sup> In contrast, the optimal duration of anticoagulation in patients with a transient strong provoking factor (such as surgery, trauma, or acute medical illness) and coexisting durable provoking factors (such as obesity or

heart failure) remains uncertain. There is concern for clinically meaningful risk of recurrent VTE in case of early cessation of treatment.

A simple dichotomy of *provoked or unprovoked VTE* may not be sufficient for clinical decision-making.<sup>25</sup> For example, a patient with provoked PE and multiple enduring risk factors may have a risk of recurrence similar to that of an unprovoked VTE patient. Further, the risk of recurrent events is nonproportional over time, with higher risk in the early period, whereas the risk of bleeding from anticoagulant therapy is spread over time.<sup>39–41</sup> In this context, the HI-PRO study in patients with provoked VTE and enduring risk factors will help determine whether extended-duration low-intensity anticoagulation, rather than short-term anticoagulation with an end date, can safely mitigate patient outcomes after early treatment of acute VTE (► Fig. 3).

Some points about the enrollment criteria deserve further attention. There is a bidirectional association between VTE and atherosclerotic cardiovascular disease,<sup>42,43</sup> likely related to the commonality of risk factors and pathobiology.<sup>44–46</sup> While there is a paucity of evidence about recurrent VTE in patients with versus those without atherosclerotic cardiovascular disease, based on the robust association with the first VTE event, the steering committee believed that this comorbidity was an important durable risk factor. Only up to 35% of enrolled patients will be enrolled based on this risk factor. We did not consider testing for genetic thrombophilia or posttreatment D-dimer among our enrollment criteria. In addition to medical uncertainties, particularly for patients with provoked VTE, from a practical perspective, such tests



**Fig. 3** Acute and extended treatment based on the initial type VTE. For patients with unprovoked VTE, results from multiple randomized trials indicate that extended duration anticoagulant treatment is associated with absolute and relative risk reduction for VTE, conferring benefit in patients who are not at high risk of bleeding. In patients with active cancer, although placebo controlled randomized trials of extended-duration treatment are lacking, expert guidelines recommend discussion of extended-duration anticoagulation with patients based on extrapolated data from noncancer unprovoked VTE. Among patients with provoked VTE, while current guidelines recommend short-term treatment, a subset of patients with durable risk factors may be at high risk for further recurrences. The HI-PRO trial seeks to answer whether extended-duration low-intensity anticoagulation with apixaban, compared with placebo, can safely reduce the rate of VTE recurrence. Individual patient data pooled analysis from the existing randomized trials of extended duration will similarly help improve the decision making for long-term management of patients with VTE. \*ELATE trial suggested that in patients receiving long-term treatment for VTE, full-intensity anticoagulation with vitamin-K antagonists is superior to low-intensity treatment. For direct oral anticoagulants (rivaroxaban and apixaban), only low-intensity anticoagulation has been studied in large-scale RCTs. HI-PRO, Extended-Duration Low-intensity Apixaban to Prevent Recurrence in High-Risk Patients with Provoked Venous Thromboembolism; RCT, randomized controlled trial; VTE, venous thromboembolism.

**Table 4** Trials of extended duration anticoagulation in patients with VTE

Trial name	Patients	Intervention	Main outcomes	Main results
AMPLIFY-EXT	2,482 patients with VTE who had previously completed 6–12 months of anticoagulation	Apixaban 2.5 mg bid, apixaban 5 mg bid, or placebo for 12 months	Composite of symptomatic VTE or all-cause death, major bleeding, clinically relevant bleeding	Apixaban 2.5 mg bid (HR: 0.33; 95% CI: 0.22–0.48) and apixaban 5 mg bid (HR: 0.36; 95% CI: 0.25–0.53) were superior to placebo. Clinically relevant nonmajor bleeding was not significantly different between low-intensity apixaban and placebo (HR: 1.29; 95% CI: 0.72–2.33) but higher with full-dose apixaban (HR: 1.82; 95% CI: 1.05–3.18)
RE-MEDY/RE-SONATE	Patients with VTE who completed at least 3 months of anticoagulation (2,856 patients in the active control study and 1,343 in the placebo-controlled study)	Dabigatran 150 mg bid vs. warfarin (active-control study; RE-MEDY), or vs. placebo (RE-SONATE)	Symptomatic recurrent VTE, major bleeding, composite of major or clinically relevant bleeding	Dabigatran 150 mg bid was superior to placebo (HR: 0.08; 95% CI: 0.02–0.25) and noninferior to warfarin (HR: 1.44; two-sided 95% CI: 0.78–2.64, noninferiority margin: 2.85, $p = 0.01$ ). Major or clinically relevant bleeding with dabigatran had a higher hazard compared with placebo (HR: 2.92; 95% CI: 1.52–5.60) but a lower hazard compared with warfarin (HR: 0.54; 95% CI: 0.41–0.71)
EINSTEIN-extension	1,197 patients with VTE who had completed 6–12 months of anticoagulation	Rivaroxaban 20 mg daily or placebo	Symptomatic recurrent VTE, major bleeding, major or clinically relevant bleeding	Rivaroxaban was superior to placebo (HR: 0.18; 95% CI: 0.09–0.39). Major bleeding occurred more frequently with rivaroxaban than placebo (HR: 5.19; 95% CI: 2.3–11.7)
EINSTEIN-CHOICE	3,365 patients with VTE who had completed 6–12 months of anticoagulation	Rivaroxaban 10 mg daily, rivaroxaban 20 mg daily, aspirin 100 mg daily	Symptomatic recurrent VTE, major bleeding, clinically relevant bleeding	Rivaroxaban 10 mg daily (HR: 0.26; 95% CI: 0.14–0.47) and rivaroxaban 20 mg daily (HR: 0.34; 95% CI: 0.20–0.59) were superior to aspirin. Risks of clinically relevant bleeding with rivaroxaban 10 mg daily and rivaroxaban 20 mg daily vs. placebo were as

(Continued)

**Table 4** (Continued)

Trial name	Patients	Intervention	Main outcomes	Main results
				follows: HR: 1.09; 95% CI: 0.59–2.00, and HR: 1.53; 95% CI: 0.87–2.69
PREVENT	508 patients with “idiopathic” VTE who had completed a median of 6.5 months of anticoagulation	Low-intensity warfarin (target INR: 1.5–2.0) or placebo	Symptomatic recurrent VTE, major bleeding, minor bleeding	Low-intensity warfarin was superior to placebo (HR: 0.36; 95% CI: 0.19–0.67). Minor bleeding occurred more frequently with low-intensity warfarin compared with placebo (HR: 0.36; 0.19–0.67)
PADIS-PE	371 patients with symptomatic “unprovoked” PE treated with anticoagulation for 6 months	Full-dose warfarin (target INR: 2.0–3.0) or placebo	Composite of symptomatic recurrent VTE and major bleeding, symptomatic VTE, major bleeding	Full-dose warfarin was superior to placebo for the primary outcome (HR: 0.22; 95% CI: 0.09–0.55) and for recurrent VTE (HR: 0.15; 95% CI: 0.05–0.43). There were 4 major bleeding events with warfarin and 1 with placebo. Nonmajor clinically relevant bleeding events were not reported
WODIT	267 patients with “idiopathic” DVT treated with 3 months of oral anticoagulation	Full-dose warfarin (target INR: 2.0–3.0) or no treatment	Symptomatic recurrent VTE, major bleeding	Full-dose warfarin was not superior to no-treatment (relative risk: 0.99; 95% CI: 0.57–1.73). There were 4 major bleeding events with warfarin and 2 with control. Nonmajor clinically relevant bleeding events were not reported
HI-PRO	Planning to enroll 600 patients with provoked VTE and at least one enduring risk factor <sup>a</sup>	Apixaban 2.5 mg bid or placebo for 12 months	Symptomatic recurrent VTE, major bleeding, clinically relevant bleeding	The trial is ongoing

Abbreviations: CI, confidence interval; HR, hazard ratio; INR, international normalized ratio; VTE, venous thromboembolism.

<sup>a</sup>See ► **Table 1** for details.

are rarely performed in patients with provoked VTE in our institution. This is in line with North American and European guidelines.<sup>19,47</sup>

Findings from the HI-PRO trial will be complementary to several other RCTs that have transformed the clinical practice of VTE over the past 2 decades (► **Table 4**). It is possible that the gradient of risk, or the net benefit profile, is distinct across specific patient subgroups. For example, patients with multiple enduring risk factors may have a more favorable net clinical benefit compared with those with a single risk factor. In this sense, a future individual patient-data pooled analysis inclusive of prior large trials of extended-duration anticoagulation including AMPLIFY-EXT,<sup>16</sup> RE-SONATE and REMEDY,<sup>48</sup> EINSTEIN-extension,<sup>49</sup> EINSTEIN CHOICE,<sup>17</sup> PREVENT,<sup>50</sup> WODIT,<sup>51</sup> PADIS-PE,<sup>52</sup> and HI-PRO will be very informative.

The limitations of HI-PRO should be also considered. Since patient enrollment is from a single academic institution, its generalizability may be limited. However, the internal validity of HI-PRO is robust, considering the double-blind design, with blinded endpoint adjudication. In addition, how the results will compare against other potential antithrombotic options will not be addressed in HI-PRO and merit future assessment by individual patient-data pooled analysis or network meta-analysis.

## Conclusion

Direct oral anticoagulants have transformed the care of patients with VTE. Recurrent VTE is a major adverse event in patients with acute provoked VTE and enduring risk factors. The HI-PRO trial will broaden our knowledge about

the optimal treatment duration for this important and commonly encountered issue.

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## Conflict of Interest

B.B. reports that he is a consulting expert, on behalf of the plaintiff, for litigation related to two specific brand models of IVC filters. J.F. has received consulting fees from Allergan, Boehringer-Ingelheim, Pfizer, and Portola/Alexion. S. Z.G. has received research support from Bayer, Bristol-Myers-Squibb, Boehringer-Ingelheim, Boston Scientific, Janssen, Daichi, and the National Heart, Blood, and Lung Institute; he has received consulting fees from Bayer, Agile, Boehringer-Ingelheim, and Pfizer. G.P. has received research grant support from Boston Scientific Corporation, Bayer, Bristol-Myers-Squibb/Pfizer, Portola/Alexion Pharmaceuticals, and Janssen Pharmaceuticals; and has received consulting fees from Amgen, Pfizer, Agile, and Prairie Education and Research Cooperative.

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