
Article:
Laskier, V., Guy, H., Fisher, M. et al. (4 more authors) (2019) Effectiveness and safety of betrixaban extended prophylaxis for venous thromboembolism compared with standard-duration prophylaxis intervention in acute medically ill patients : a systematic literature review and network meta-analysis. Journal of Medical Economics, 22 (10). pp. 1063-1072. ISSN 1369-6998

https://doi.org/10.1080/13696998.2019.1645679

Effectiveness and safety of betrixaban extended prophylaxis for venous thromboembolism compared with standard-duration prophylaxis intervention in acute medically ill patients: a systematic literature review and network meta-analysis

Vicki Laskier[a*], Holly Guy[a], Mark Fisher[a], W. Richey Neuman[b], Iwona Bucior[b], Alexander T. Cohen[c], Shijie Ren[d]

[a]FIECON Ltd, Hertfordshire, St Albans, UK; [b]Portola Pharmaceuticals, Inc., South San Francisco, CA, USA; [c]Guy's and St. Thomas' Hospitals, London, UK; [d]The University of Sheffield, Sheffield, UK

*Vicki, Laskier, FIECON Ltd

Hodgkin Huxley House

30 Farringdon Lane

London, EC1R 3AW

Tel: +44 1727 225 601, Email: vicki.laskier@fiecon.com

LinkedIn: https://uk.linkedin.com/in/victoria-laskier

Effectiveness and safety of betrixaban extended prophylaxis for venous thromboembolism compared with standard-duration prophylaxis intervention in acute medically ill patients: a systematic literature review and network meta-analysis

Aims: To determine the clinical effectiveness and safety of venous thromboembolism (VTE) prophylaxis using United States- (US) and Europe-approved anticoagulants relative to extended-duration VTE prophylaxis with betrixaban. Low molecular weight heparins (LMWHs), unfractionated heparin (UFH), fondaparinux sodium and placebo were each compared to betrixaban, as standard-duration VTE prophylaxis for hospitalized, nonsurgical patients with acute medical illness at risk of VTE.

Materials and methods: A systematic literature review was conducted up to June 2019 to identify randomized controlled trials (RCTs) of VTE prophylaxis in hospitalized, nonsurgical patients with acute medical illness at risk of VTE. Studies that reported the occurrence of VTE events (including death) and, where possible, major bleeding, from treatment initiation to 20-50 days thereafter were retrieved and extracted. A Bayesian fixed effect network meta-analysis was used to estimate efficacy and safety of betrixaban compared with standard-duration VTE prophylaxis.

Results: Seven RCTs were analyzed, which compared betrixaban with LMWHs, UFH, fondaparinux sodium, or placebo. There were significantly higher odds (median odds [95% credible interval]) of VTE with LMWHs (1.38 [1.12-1.70]), UFH (1.60 [1.05-2.46]) and placebo (2.37 [1.55-3.66]) compared with betrixaban. There were significantly higher odds of VTE-related death with placebo (7.76 [2.14-34.40]) compared with betrixaban. No significant differences were observed for the odds of major bleeding with all comparators, VTE-related death with any active standard-duration VTE prophylaxis, or of VTE with fondaparinux sodium, compared with betrixaban.

Limitations and conclusions: In this indirect comparison, betrixaban was shown to be an effective regimen with relative benefits compared with LMWHs and UFH. This indicates that betrixaban could reduce the burden of VTE in at-risk hospitalized patients with acute medical illness who need extended prophylaxis, though without direct comparative evidence, stronger conclusions cannot be drawn.

Keywords: Venous thromboembolism; pre-exposure thromboprophylaxis; network meta-analysis; primary thromboprophylaxis; betrixaban

Short title: Extended versus standard-duration VTE prophylaxis

Introduction

Venous thromboembolism (VTE) is a common cause of morbidity and mortality, particularly in patients hospitalized with an acute medical illness. A model developed in the United States (US) estimated that 196,134 VTE-related events occurred in US acutely ill hospitalized patients in 2003.[1] Approximately one third of all symptomatic VTE results in death.[2] Though many patients survive VTE, some require intensive care and treatment which can last for several months. Furthermore, not all survivors of VTE are restored to their previous state of health; approximately 30% of surviving patients will experience a recurrent VTE episode within 10 years of their first episode.[3] Additionally, surviving patients can experience severe complications including chronic thromboembolic pulmonary hypertension (CTEPH) and post-thrombotic syndrome (PTS) which reduce quality of life and are costly to treat.[4], [5]

Though the highest risk of VTE in the acute medically ill population occurs during hospitalization, the risk persists following discharge. It is reported that 45%-75% of all VTEs in the acute medically ill population occur post-discharge.[6]–[9] Therefore, it is necessary that thromboprophylaxis continues beyond hospitalization in many patients, when standard-duration thromboprophylaxis typically ends, to minimize the risk of VTE. This is particularly important among those who have multiple risk factors for VTE, including previous hospitalization for an acute medical illness, increased age, reduced mobility, history of cancer or VTE, and obesity. Previous studies have investigated extended-duration VTE prophylaxis in patients hospitalized with an acute medical illness to address the risk of VTE after hospital discharge.[10]–[12] However, in these studies extended-duration prophylaxis lead to

increased major bleeding, causing the treatment's harms to exceed its benefits. The duration of hospitalization for patients with an acute medical illness has fallen in the US.[13]–[16] At the same time, the number of medical hospitalizations in patients aged 45-74 has increased,[17] and is likely to increase further as the population ages.[18] These changes increase the need for a VTE prophylaxis regimen which may protect high risk patients from VTE events following hospital discharge, without raising their risk of major bleeding.

Betrixaban is a factor Xa inhibitor which was the first and only direct oral anticoagulant (DOAC) to be approved by the US Food and Drug Administration for extended-duration VTE prophylaxis of hospitalized, acutely ill medical patients.[19] Whilst there have been studies of extended-duration VTE prophylaxis with other DOACs, none have been approved in any market. Hence, it is of great interest to understand how standard-duration VTE prophylaxis compares to betrixaban. In the Acute Medically Ill VTE Prevention with Extended Duration Betrixaban (APEX) study (NCT01583218), betrixaban demonstrated effective extended-duration VTE prophylaxis lasting up to 42 days without an increase in the risk of major bleeding, compared with standard-duration VTE prophylaxis lasting up to 14 days with enoxaparin, a low molecular weight heparin (LMWH).[20] However, no studies have compared betrixaban with alternative VTE prophylaxis (including LMWHs other than enoxaparin, unfractionated heparin (UFH), fondaparinux sodium), or placebo. LMWHs other than enoxaparin are of interest since they are also recommended for prophylactic use in the US, the UK and other markets.[21]–[23]

The purpose of this study was to determine the relative clinical effectiveness of extended-duration VTE prophylaxis with betrixaban from hospitalization through post-discharge compared with standard-duration VTE prophylaxis regimens which cease during hospitalization or at hospital discharge, using other available interventions, including LMWHs, UFH, fondaparinux sodium and placebo, for hospitalized, nonsurgical patients with

acute medical illness at risk of VTE evaluated 20-50 days following the initiation of prophylaxis.

Methods

A systematic literature review (SLR) was performed to identify randomized controlled trials (RCTs) of betrixaban and standard-duration VTE prophylaxis. This SLR was conducted to identify studies to be considered for inclusion in a network meta-analysis (NMA).

Identification of relevant studies

We sought studies which answered the following review question:

> What is the efficacy and safety of betrixaban, LMWHs, UFH, fondaparinux sodium and placebo in adults who are hospitalized for an acute medical condition and are at risk of VTE?

We identified and updated a clinical evidence review performed in December 2008, which related to interventions for thromboprophylaxis in hospitalized patients and was performed by the National Institute of Health and Care Excellence (NICE).[24] Three search iterations were undertaken to update the 2008 NICE SLR, with the first performed in December 2016, the second performed in December 2017 and the third performed in June 2019. The search strategy presented in supplementary online materials (Supplementary material 1) was used to search EMBASE, Medline, Medline® In-Process, HTA Database, NHS Economic Evaluation Database and the Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library). Complementary "grey" literature sources were also searched to identify data from recent or ongoing trials during the past three years that had not been archived in a database. Unpublished or non-journal "grey" literature sources included: clinicaltrials.gov, the manufacturer's repository of evidence, manufacturers of comparator

products' websites and conference proceedings. All references identified were deduplicated after search compilation. The first and second iteration of searches were reviewed by two independent health economists. Reviewers identified relevant search results by assessing: title and abstract in the first pass of search results, and the entire publication during the second pass. Any discrepancies between the reviewers in the first and second iterations were discussed and resolved with a third, independent reviewer, in alignment with the Centre for Reviews and Dissemination's guidance for undertaking reviews in healthcare.[25] The third iteration of searches was a pragmatic SLR update to ensure that the search is up to date at the time of preparing for this manuscript and all essential studies were included in the analyses. As such, it was reviewed by one health economist only at first and second pass.

The studies were assessed by applying eligibility criteria which were defined according to the PICOS (population, interventions, comparators, outcomes and study type) principle.[25] Included studies: were performed in acute, medically ill hospitalized adult patients at risk of VTE; compared a combination of betrixaban, fondaparinux sodium, LMWHs, UFH, no treatment or placebo; reported mortality, VTE incidence or adverse events; and were RCTs. The full eligibility criteria can be found in supplementary online materials (Table S1, Supplementary material 2).

Data extraction and quality assessment

All studies identified by the SLR were extracted by one reviewer and assessed independently by another reviewer. A pre-prepared extraction grid was designed to collect data from each study regarding: primary study reference; eligibility criteria; settings; trial drugs; concomitant medications; statistical methods; participant baseline characteristics; and all relevant recorded outcomes. During the feasibility assessment which followed extraction, studies were assessed according to Australian Pharmaceutical Benefits Advisory Committee (PBAC) guidance to

identify heterogeneity across studies. This entailed a comparison of: study designs, population characteristics, treatment types and durations, and outcomes, to ensure comparability with the APEX study.[26] Baseline demographics which informed the assessment of heterogeneity are shown for all studies considered, in Table S2 (Supplementary Material 3). The studies were then assessed for bias using the Cochrane guidance.[27], [28]

Statistical analysis

Analyses were performed using WinBUGS (version 1.4.3, Imperial College and Medical Research Council, UK) and RStudio (version 1.0.143, RStudio, Inc., Boston, Massachusetts).[29], [30] WinBUGS was run via RStudio using the package R2WinBUGS.[31] The outcomes considered were: VTE, VTE-related death, major bleeding, pulmonary embolism (PE), asymptomatic deep vein thrombosis (DVT) and symptomatic DVT reported 20-50 days following the initiation of thromboprophylaxis. For each outcome analyzed, median odds ratios with 95% credible intervals (CrI) for each comparator were generated relative to betrixaban, since it was of interest to know how other treatments compared to betrixaban. Uncertainty was quantified using 95% credible intervals, which are the Bayesian analogue of confidence intervals, in accordance with NICE Decision Support Unit guidance which used this approach to quantify uncertainty of model results. All outcomes were evaluated using a standard Bayesian fixed effect NMA on the logit scale.[32] The treatment effects of all LMWHs were assumed identical, aligning with NICE clinical guidelines for VTE which assume a class effect among LMWHs.[22] The standard non-informative priors were used for treatment effects and study-specific baseline effects.[32] Convergence of all parameters (including treatment effects, study-specific baseline effects and odds ratios) were assessed using trace plots and Brooks-Gelman-Rubin plots for each model.[33] If there were zero events, and hence convergence issues, a continuity correction was made.[32] To handle other issues with convergence, the variance of the prior

distributions were reduced. Model fit was assessed using median residual deviance and number of unconstrained data points.

Sensitivity analysis

In the base case, studies with a placebo arm which were performed prior to the year 2000, were excluded. The year 2000 was an arbitrary threshold between the two earliest identified placebo-controlled studies (Belch 1981 and PREVENT 2002), which were conducted over twenty years apart.[34], [35] The threshold was applied to avoid exclusion of more recent studies conducted since best supportive care had improved relative to older studies. These more recent studies were expected to show relatively small additional benefits of pharmacological prophylaxis compared to best supportive care, and therefore show newer treatments to be relatively less efficacious compared to placebo.

To examine this threshold's effect, studies performed prior to 2000 that included a placebo arm were included in a sensitivity analysis. Additionally, to understand differences in treatment effect across all definitions of DVT, a sensitivity analysis was performed combining all DVT outcomes reported 20-50 days after initiation of thromboprophylaxis in one measure. If a study reported multiple definitions of DVT, each type of recorded DVT was considered to be from a unique study and was added to the composite measure. Finally, to examine the effect of only using full dose betrixaban, a sensitivity analysis was performed excluding all betrixaban patients with severe renal impairment or those that received a concomitant P-glycoprotein inhibitor who received half-doses of the study medications in the APEX study.

Results

Systematic literature review

The SLR identified 1,681 references. Figure 1 shows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram demonstrating the flow of reference identification to NMA inclusion. The 16 unique studies identified from the SLR which were considered for NMA inclusion evaluated betrixaban, LMWHs (enoxaparin, nadroparin, dalteparin and certoparin), UFH, fondaparinux sodium, and placebo.

Data extraction and quality assessment

Among the 16 studies identified, the timing of outcomes was a major confounding factor identified in the heterogeneity assessment. In order to appropriately compare outcomes across studies of betrixaban for extended duration VTE prophylaxis, it was determined that outcomes not reported 20-50 days following the initiation of pharmacological thromboprophylaxis would not be suitable for inclusion in the NMA. Nine studies were excluded from inclusion in the NMA on this basis.[36]–[44] Whilst study design, population characteristics, treatment arms and outcomes were thoroughly compared, there were no aspects that were deemed to be major confounding factors in the heterogeneity assessment. There was mild concern about variation in duration of active treatment and follow-up time, however this was not deemed to be limiting as all treatment durations received were within their license. Hence, heterogeneity assessment did not prompt exclusion of any further studies.

Table 1 provides a summary of the studies included in the NMA. Supplementary online materials (Table S3) provides definitions of each of the outcomes included in or excluded from the analysis, by study. Additionally, Table S3 provides a summary of the

demographics of patients enrolled in each study included in the analysis. The definitions of: acute medically ill; average population age; and average population weight were identified as minor confounding factors in the heterogeneity assessment, though no study was excluded from the NMA on this basis.

The results of the bias assessment are summarized in Figure 2. All studies were randomized, and randomization method was evaluated as appropriate where reported;[20], [45]–[48] Belch 1981 and PREVENT did not report the method of randomization so appropriateness was unclear.[34], [35] Concealment of treatment was adequate in all studies,[20], [35], [45], [46], [48] except Belch 1981 and Forette 1995 which were open label.[34], [47] In most studies, the groups enrolled were similar at baseline;[20], [35], [45], [48] though information on baseline characteristics was inadequate in Belch 1981, CERTIFY and Forette 1995.[34], [46], [47] There were equal drop-out rates amongst the study arms included and it does not appear that any data has been omitted from the reported results.[20], [34], [35], [45]–[48] The intention-to-treat (ITT) populations were reported in LIFENOX.[48] In APEX, ARTEMIS, CERTIFY and PREVENT, the ITT populations were restricted by results of a venography.[20], [35], [45], [46] The appropriate use of the ITT populations was not clear in Belch 1981 and Forette 1995.[34], [47] The graph displaying the risk of bias amongst studies included in the NMA is presented in Figure 3.

Base case analyses results

The network diagrams for each analysis can be found in supplementary online materials (Figure S1-S8, Supplementary material 5).

Four studies and a total of 14,024 participants were included in the analysis of VTE.[20], [35], [45], [46] There were significantly higher odds (median odds [95% CrI]) of a VTE with LMWHs (OR, 1.38; 95% CrI, 1.12-1.70), with UFH (OR, 1.60; 95% CrI, 1.05-

2.46), or with placebo (OR, 2.37; 95% CrI 1.55-3.66), relative to betrixaban (Figure 4A). There was not a significant difference between betrixaban and fondaparinux sodium in the odds of VTE.

Five studies and a total of 23,346 participants were included in the VTE-related death analysis.[20], [35], [45], [46], [48] There were significantly higher odds of a VTE-related death with placebo relative to betrixaban (OR, 7.76; 95% CrI, 2.14-34.40) (Figure 4B). The odds of a VTE-related death with LMWHs, UFH, and fondaparinux sodium were not significantly different to betrixaban.

Four studies and a total of 14,283 participants were included in the major bleeding analysis.[20], [35], [46], [47] There were no significant differences in the odds of major bleeding with placebo, LMWHs, or UFH compared with betrixaban (Figure 4C). It was not possible to form a comparison against fondaparinux sodium as major bleeding was only reported as an outcome in ARTEMIS up to 2 days after treatment, which is a maximum of 16 days – outside of the Day 20-50 inclusion.

Four studies and a total of 14,855 participants were included in the symptomatic DVT analysis.[20], [35], [45], [46] There was no significant difference in the odds of symptomatic DVT with betrixaban compared with any of the included comparators. The median odds ratio of comparators relative to betrixaban was greater than 1.5 in all cases (Figure 4D), suggesting higher (albeit non-significant) odds of symptomatic DVT with placebo, LMWHs, UFH, and fondaparinux sodium compared with betrixaban.

Three studies and a total of 13,142 participants were included in the asymptomatic DVT analysis.[20], [35], [46] There were significantly higher odds of an asymptomatic DVT with LMWHs (OR, 1.34; 95% CrI, 1.07-1.69), UFH (OR, 1.63; 95% CrI, 1.04-2.57), and placebo (OR, 2.81; 95% CrI, 1.68-4.73) (Figure 4E). It was not possible to form a

comparison against fondaparinux sodium as asymptomatic DVT was only measured to Day 15 in ARTEMIS.

Five studies and a total of 14,898 participants were included in the PE analysis.[20], [35], [45]–[47] The odds of a PE were not significantly different with betrixaban compared with any of the included comparators (Figure 4F). The median odds ratio of LMWHs, UFH, and placebo relative to betrixaban was greater than 1.0 (Figure 4F), suggesting higher (albeit non-significant) odds of PE with placebo, LMWHs, and UFH compared with betrixaban. On the other hand, the median odds ratio of fondaparinux sodium relative to betrixaban was less than 1.0 (Figure 4F), suggesting lower (albeit non-significant) odds of PE with fondaparinux sodium compared with betrixaban.

For each outcome, the median residual deviance (7.4, 10.1, 6.6, 5.3 and 10.1 for VTE, major bleeding, symptomatic DVT, asymptomatic DVT, and PE, respectively) was close to the number of data points used (8, 8, 8, 6 and 10 respectively). This indicates that the models are a good fit to the data. For VTE-related death, the median residual deviance was 21.2, which is much higher than the number of data points used (10). This indicates that the VTE-related death model may not be a good fit to the data.

Sensitivity analysis results

Only one study, Belch 1981, was completed before 2000 with a placebo arm. The only outcome that this study contributed to was PE. Therefore, the PE analysis was rerun with Belch 1981 included as a sensitivity analysis including a total of 14,998 participants.[20], [34], [35], [45]–[47] The odds ratio of a PE with placebo relative to betrixaban was greater than in the base case, though it was lower for the other comparators. The significance of the results did not change and neither did the preference for any treatment over betrixaban.

The sensitivity analysis that considered all types of recorded DVT included eleven

different DVT results from five studies.[20], [35], [45]–[47] There were 37,249 participants included in the analysis. The odds of any type of DVT were significantly greater with LMWHs (OR, 1.36; 95% CrI, 1.10-1.70), UFH (OR, 1.63; 95% CrI, 1.20-2.21) and placebo, (OR, 2.74; 95% CrI, 1.90-4.00) compared with betrixaban. Though the median odds ratio of any DVT relative to betrixaban was above one for fondaparinux sodium, the difference in odds was not significant.

For the sensitivity analyses considering only patients on the full study dose from the APEX study, the total number of studies included in each analysis remained the same. There were, however, fewer patients for each analysis due to the exclusion of betrixaban patients with severe renal impairment and patients taking P-glycoprotein inhibitors from the APEX study. There were 12,387, 21,709, 12,738, 11,505, 13,218, and 13,261 participants included in the analysis of VTE, VTE-related death, major bleeding, asymptomatic DVT, symptomatic DVT, and PE, respectively. Mostly, the significance of differences between treatments remained the same as in the full-population analyses. The only changes were of the odds ratio of a symptomatic DVT with placebo (OR, 3.08; CrI, 1.05-9.28) and of a PE with LMWH (OR, 3.74; CrI, 1.36-13.32) relative to betrixaban. This sensitivity analysis showed significantly lower odds of a VTE for betrixaban compared with placebo and LMWH.

Discussion

The results of the NMA showed a significant reduction in VTE morbidity and mortality with betrixaban compared with LMWH, UFH, and placebo. Reducing VTE events would reduce recurrent VTE morbidity and complications such as CTEPH and PTS, which are very costly to manage and severely impact quality of life.[49], [50] This further indicates that extended VTE prophylaxis with betrixaban may lead to prolonged patient health benefits.

Additionally, the results showed a significant reduction in asymptomatic DVT with betrixaban compared with LMWHs, UFH, and placebo. Asymptomatic DVT is associated with chronic complications such as PTS,[51] and may progress to symptomatic DVT,[52] which requires anticoagulation treatment lasting months and leads to rehospitalization for many patients. Symptomatic DVT is also associated with a risk of recurrent VTE and complications such as PTS. It is evident that reducing asymptomatic DVT may reduce risk of future, more serious events which are associated with poorer quality of life and increased healthcare costs. Furthermore, following an asymptomatic DVT event, patients have an increased risk of death compared with patients who have not experienced a DVT event.[53]

There was a strong trend of fewer symptomatic DVT and PE events with betrixaban compared with the other treatments available, with the point estimate of all odds ratios favoring betrixaban with few exceptions. Many of the results from the analysis did not achieve statistical significance, which may be due to a lack of head-to-head evidence. The conclusions of the analysis could have been stronger had direct evidence comparing betrixaban to placebo, UFH or fondaparinux sodium been available.

This analysis demonstrated no significant difference between betrixaban and any of the comparators for the occurrence of major bleeding. This benefit in safety was also seen in the APEX study, as there was no significant difference in major bleeding between betrixaban and enoxaparin.[20] Adverse events which are associated with VTE prophylaxis such as major bleeding (which includes intracranial hemorrhage) can be costly to treat and are associated with reduced long term quality of life. However non-major bleeding is increased in extended prophylaxis and therefore appropriate management of the risk-benefit ratio and identification of at-risk patients for extended VTE-prophylaxis are essential in addressing the growing need for VTE prophylaxis extending beyond hospitalization.[54]–[56]

The results of the NMA for betrixaban versus fondaparinux sodium are uncertain. The analysis showed no significant difference between the two regimens. This may indicate that betrixaban is not superior to fondaparinux sodium as extended-duration prophylaxis. However, the treatment effect of fondaparinux sodium was based only on the ARTEMIS trial. This trial had fewer participants compared with other trials included in the NMA. All DVT events recorded in the first 15 days were asymptomatic DVT detected by venography and the only symptomatic events recorded in the primary outcome of the trial were adjudicated fatal PE. Furthermore there were no asymptomatic events recorded after the first 15 days that could be included in the analysis. Therefore, inclusion of ARTEMIS focused on reports of symptomatic events which were measured until day 32. At the end of follow-up the placebo arm reported twice as many fatal PE and four times more non-fatal PE events than the fondaparinux sodium arm, and both arms reported zero incidence of symptomatic DVT. These factors have contributed to uncertainty in the results for fondaparinux sodium in the NMA and may have led to an overestimation of the treatment effect associated with fondaparinux sodium as the incidence of asymptomatic events has not been considered due to incompatible timing. Of note however, a larger proportion of patients in the fondaparinux sodium arm experienced fatal PE (0.7% fatal PE for fondaparinux patients compared to, for example, 0.3% fatal VTE for betrixaban patients in APEX); as such, fewer patients in this arm remained alive for the duration of the trial to be at risk of non-fatal VTE events, possibly causing the burden of such events to be underrepresented relative to the placebo arm.[39]

The main limitation of this analysis is the small number of studies that were available for comparison. In particular, studies of DOACs for extended VTE prophylaxis were not considered as they are not approved in this indication in any market, and many studies identified by the SLR were not suitable for comparison with the results of the APEX study as outcomes were not reported within the interval of 20-50 days following prophylaxis

initiation.[36]–[44] Overall however, the timeframe of 20-50 days following the initiation of VTE prophylaxis enabled the selection of the most suitable and comparable studies based on the time at which patients were assessed in the APEX study (following completion of their extended-duration VTE prophylaxis regimen), enabling comparisons to be drawn with betrixaban.

Another limiting factor was the lack of head-to-head data available for betrixaban; had there been more studies completed for betrixaban against other treatments there would have been more data to form stronger conclusions.

Additionally, no adjustment was made for the duration of treatment in the different studies. This may have caused overestimation of the benefits of longer-duration treatment, since such regimens provided a longer timeframe for treatment benefit to be observed. However, the treatment durations compared were all within their licensed indication, and therefore the differences in treatment duration are inherently linked to the differences in treatment effect.

Finally, the exclusion of studies containing placebo treatment conducted prior to the year 2000 to account for changing clinical practice in best supportive care may have caused overlooked bias due to changing methods to confirm clinical endpoints in studies over time. However, as all treatment arms within a study would use the same diagnostic measures, systematic differences in the method of diagnosing patients should not have affected the estimates of incremental treatment effect observed. Moreover, a feasibility assessment was conducted to investigate such heterogeneity, among other factors, and no major differences in the endpoint measures between studies were identified for relevant endpoints for each study. A sensitivity analysis including the Belch 1981 study confirmed that results were robust to the year of publication among studies included.The use of a fixed effect NMA enabled estimation of treatment effects in the included studies. A random effects model would be

required to generalize the results beyond the included studies and remove any bias that may be attributed to anticipated confounding factors between the studies. However, due to the small number of studies and nature of VTE events, informative priors using external information would be needed for this kind of analysis. As such, fixed effect models have been used, limiting assessment of between-study heterogeneity, possibly producing artificially small credible intervals for results. The small number of studies also restricted the use of funnel plots for robust bias and quality assessment.

Conclusions

In this indirect comparison, extended-duration VTE prophylaxis from hospital admission through post-discharge with betrixaban was a comparatively safe and effective regimen. Results showed that betrixaban extended-duration VTE prophylaxis provides relative benefit with respect to the efficacy and safety outcomes considered, when compared to regimens for standard VTE prophylaxis. Given the need for an effective extended-duration VTE prophylaxis with a good safety profile, betrixaban shows potential to contribute to reducing the burden of VTE in hospitalized, nonsurgical patients with acute medical illness at risk of VTE, however in the absence of direct comparative evidence stronger conclusions cannot be drawn.

WORD COUNT: 3,759/10,800

Transparency

Declaration of Funding

This research was supported by Portola Pharmaceuticals, Inc.

Declaration of financial/other relationships

VL, HG and MF are employees of FIECON Ltd, a health-economics outcomes research agency, which performed the analyses presented in the manuscript, funded by Portola Pharmaceuticals, Inc. RN and IB were employees of Portola Pharmaceuticals, Inc, at the time of the research project.

SR is a Research Fellow at The University of Sheffield and performed the analyses presented in the manuscript in collaboration with FIECON Ltd, funded by FIECON Ltd.

ATC has received consulting fees, research support, and honoraria from AbbVie, ACI Clinical, Aspen, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Boston Scientific, CSL Behring, Daiichi-Sankyo, GlaxoSmithKline, GLG, Guidepoint Global, Johnson and Johnson, Leo Pharma, Medscape, McKinsey, Navigant, ONO, Pfizer, Portola, Sanofi, Takeda, Temasek Capital, and TRN.

Author contributions

VL, HG, MF, AC and SR were involved in the design and execution of the analysis. All authors were involved in the interpretation of the results, drafting and revising this manuscript, and provided final approval of the version to be published. All authors vouch for the accuracy of the content included in the full manuscript.

Acknowledgements

Augusta Connor is thanked for her editing to bring the publication to press.

Previous Presentations

The base case results were presented in a poster submitted to both the American College of Clinical Pharmacy (ACCP) and the Academy of Managed Care Pharmacy in 2018. The abstract for the poster was published in the abstract book of the conference of ACCP. There

has not yet been a full publication of the results.

Data Availability Statement

Raw data were generated at Portola Pharmaceuticals. Derived data supporting the findings of this study are available from the corresponding author (VL) on request.

References

[1] G. Piazza, J. Fanikos, M. Zayaruzny, and S. Z. Goldhaber, "Venous thromboembolic events in hospitalised medical patients," *Thromb. Haemost.*, vol. 102, no. 3, pp. 505–510, Sep. 2009.

[2] J. A. Heit, A. T. Cohen, and F. A. Andersen Jr., "Estimated annual number of incident and recurrent, non-fatal and fatal venous thromboembolism (VTE) events in the US.," *Blood*, no. 106, p. 910, 2005.

[3] J. A. Heit, F. A. Spencer, and R. H. White, "The epidemiology of venous thromboembolism," *J Thromb Thrombolysis*, vol. 41, pp. 3–14, 2016.

[4] V. Pengo *et al.*, "Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism," *N Engl J Med*, vol. 350, no. 22, pp. 2257–2264, May 2004.

[5] P. Prandoni *et al.*, "The clinical course of deep-vein thrombosis. Prospective long-term follow-up of 528 symptomatic patients," *Haematologica*, vol. 82, no. 4, pp. 423–428, Aug. 1997.

[6] A. C. Spyropoulos *et al.*, "Predictive and associative models to identify hospitalized medical patients at risk for VTE," *Chest*, vol. 140, no. 3, pp. 706–714, Sep. 2011.

[7] A. N. Amin, H. Varker, N. Princic, J. Lin, S. Thompson, and S. Johnston, "Duration of venous thromboembolism risk across a continuum in medically ill hospitalized patients," *J Hosp Med*, vol. 7, no. 3, pp. 231–238, Mar. 2012.

[8] T. Pendergraft, M. Atwood, X. Liu, H. Phatak, L. Z. Liu, and G. Oster, "Cost of venous thromboembolism in hospitalized medically ill patients," *Am J Health Syst Pharm*, vol. 70, no. 19, pp. 1681–1687, Oct. 2013.

[9] J. A. Heit, D. J. Crusan, A. A. Ashrani, T. M. Petterson, and K. R. Bailey, "Effect of a near-universal hospitalization-based prophylaxis regimen on annual number of venous thromboembolism events in the US," *Blood*, vol. 130, no. 2, pp. 109–114, 13 2017.

[10] A. T. Cohen *et al.*, "Rivaroxaban for thromboprophylaxis in acutely ill medical patients," *N Engl J Med*, vol. 368, no. 6, pp. 513–523, Feb. 2013.

[11] S. Z. Goldhaber *et al.*, "Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients," *N Engl J Med*, vol. 365, no. 23, pp. 2167–2177, Dec. 2011.

[12] R. D. Hull *et al.*, "Extended-duration venous thromboembolism prophylaxis in acutely ill medical patients with recently reduced mobility: a randomized trial," *Ann Intern Med*, vol. 153, no. 1, pp. 8–18, 2010.

[13] Weiss AJ, Elixhauser A, for Agency for Healthcare Research and Quality. Overview of hospital stays in the United States, 2012 (2014). https://www.hcup-us.ahrq.gov/reports/statbriefs/sb180-Hospitalizations-United-States-2012.pdf (accessed 2018 March 20).

[14] Organisation for Economic Co-operation and Development. Health at a glance 2017: OECD indicators. https://www.oecd-ilibrary.org/docserver/health_glance-2017-en.pdf?expires=1536312324&id=id&accname=guest&checksum=9A2183B01DA4247F63CA207618BB50BB (accessed 2018 March 20).

[15] US Department of Health and Human Services. CMS Statistics 2015. https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/CMS-Statistics-Reference-Booklet/Downloads/2015CMSStatistics.pdf (accessed 2018 May 24).

[16] US Department of Health and Human Services. CMS Statistics 2016. https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/CMS-Statistics-Reference-Booklet/Downloads/2016_CMS_Stats.pdf (accessed 2018 May 24).

[17] Agency for Healthcare Research and Quality, Rockville, MD. Statistical Brief #225: Healthcare Cost and Utilization Project (HCUP) (2017). www.hcup-us.ahrq.gov/reports/statbriefs/sb225-Inpatient-US-Stays-Trends.jsp. (accessed 2018 June 28).
[18] Jacobsen LA, Kent M, Lee M and Mather M, for the Population Reference Bureau. America's Aging Population, Population Bulletin 66, no. 1 (2011). https://assets.prb.org/pdf11/aging-in-america.pdf (accessed 2018 June 28).
[19] Food and Drug Administration. FDA approved betrixaban (BEVYXXA, Portola) for the prophylaxis of venous thromboembolism (VTE) in adult patients. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm564422.htm (accessed 2018 March 20).
[20] A. T. Cohen *et al.*, "Extended thromboprophylaxis with betrixaban in acutely ill medical patients," *N Engl J Med*, vol. 375, no. 6, pp. 534–544, Aug. 2016.
[21] ASH Clinical Practice Guidelines on Venous Thromboembolism, 04-Feb-2019. [Online]. Available: /VTE/. [Accessed: 26-Feb-2019].
[22] NICE, "Clinical Guideline. Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism (Update).," 2017. [Online]. Available: https://www.nice.org.uk/guidance/indevelopment/gid-cgwave0795/consultation/html-content-2.
[23] A. Johnston *et al.*, "A systematic review of clinical practice guidelines on the use of low molecular weight heparin and fondaparinux for the treatment and prevention of venous thromboembolism: Implications for research and policy decision-making," *PLoS One*, vol. 13, no. 11, Nov. 2018.
[24] NICE. "Venous thromboembolism: reducing the risk for patients in hospital: Clinical guideline. (2010, 2015). nice.org.uk/guidance/cg92 (accessed 2016 October 27)." .
[25] Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking reviews in health care (2009). https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf (accessed 2016 October 20).
[26] Pharmaceutical Benefits Advisory Committee. Guidelines for preparing a submission to the PBAC (2010). https://pbac.pbs.gov.au/content/information/files/pbac-guidelines-version-5.pdf (accessed 2017 June 26).
[27] Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.
[28] Higgins JPT, Green S (editors), for the Cochrane Collection. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0: Chapter 8: Assessing risk of bias in included studies (2011). www.handbook.cochrane.org (accessed 2018 June 5).
[29] D. J. Lunn, A. Thomas, N. Best, and D. Spiegelhalter, "WinBUGS - A Bayesian modelling framework: Concepts, structure, and extensibility," *Statistics and Computing*, vol. 10, no. 4, pp. 325–337, Oct. 2000.
[30] RStudio Team. RStudio: Integrated Development for R. RStudio, Inc., Boston, (2016). http://www.rstudio.com/ (accessed 2017 October 28).
[31] S. Sturtz, U. Ligges, and A. Gelman, "R2WinBUGS: A Package for Running WinBUGS from R," *Journal of Statistical Software*, vol. 12, no. 3, pp. 1–16, 2005.
[32] Dias S., Welton N.J., Sutton A.J., Aeds A.E. NICE DSU Technical Support Document 2: A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials (September 2016). http://scharr.dept.shef.ac.uk/nicedsu/wp-content/uploads/sites/7/2017/05/TSD2-General-meta-analysis-corrected-2Sep2016v2.pdf (accessed 2017 July 78).

[33] S. Brooks and A. Gelman, “General Methods for Monitoring Convergence of Iterative Simulations,” *Journal of Computational and Graphical Statistics*, vol. 7, no. 4, pp. 434–455, 1998.
[34] J. J. Belch, G. D. Lowe, A. G. Ward, C. D. Forbes, and C. R. Prentice, “Prevention of deep vein thrombosis in medical patients by low-dose heparin,” *Scott Med J*, vol. 26, no. 2, pp. 115–117, Apr. 1981.
[35] A. Leizorovicz *et al.*, “Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients,” *Circulation*, vol. 110, no. 7, pp. 874–879, Aug. 2004.
[36] J. F. Bergmann and E. Neuhart, “A multicenter randomized double-blind study of enoxaparin compared with unfractionated heparin in the prevention of venous thromboembolic disease in elderly in-patients bedridden for an acute medical illness: The enoxaparin in medicine study group,” *Thromb. Haemost.*, vol. 76, no. 4, pp. 529–534, Oct. 1996.
[37] I. Mahé, J. F. Bergmann, P. d’Azémar, J. J. Vaissie, and C. Caulin, “Lack of effect of a low-molecular-weight heparin (nadroparin) on mortality in bedridden medical in-patients: a prospective randomised double-blind study,” *Eur. J. Clin. Pharmacol.*, vol. 61, no. 5–6, pp. 347–351, Jul. 2005.
[38] J. Harenberg, P. Roebruck, and D. L. Heene, “Subcutaneous low-molecular-weight heparin versus standard heparin and the prevention of thromboembolism in medical inpatients: The heparin study in internal medicine group,” *Haemostasis*, vol. 26, no. 3, pp. 127–139, Jun. 1996.
[39] S. V. Ishi *et al.*, “Randomised controlled trial for efficacy of unfractionated heparin (UFH) versus low molecular weight heparin (LMWH) in thrombo-prophylaxis,” *J.Assoc.Physicians India*, vol. 61, no. 12, pp. 882–886, 2013.
[40] M. M. Samama *et al.*, “A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients: prophylaxis in medical patients with enoxaparin study group,” *N. Engl. J. Med.*, vol. 341, no. 11, pp. 793–800, Sep. 1999.
[41] F.-X. Kleber *et al.*, “Randomized comparison of enoxaparin with unfractionated heparin for the prevention of venous thromboembolism in medical patients with heart failure or severe respiratory disease,” *Am. Heart J.*, vol. 145, no. 4, pp. 614–621, Apr. 2003.
[42] E. Lechler, W. Schramm, and C. W. Flosbach, “The venous thrombotic risk in non-surgical patients: epidemiological data and efficacy/safety profile of a low-molecular-weight heparin (enoxaparin). The Prime Study Group,” *Haemostasis*, vol. 26 Suppl 2, pp. 49–56, 1996.
[43] F. A. Lederle *et al.*, “The prophylaxis of medical patients for thromboembolism pilot study,” *Am. J. Med.*, vol. 119, no. 1, pp. 54–59, Jan. 2006.
[44] S. M. Schellong *et al.*, “An open-label comparison of the efficacy and safety of certoparin versus unfractionated heparin for the prevention of thromboembolic complications in acutely ill medical patients: CERTAIN,” *Expert Opin.Pharmacother.*, vol. 11, no. 18, pp. 2953–2961, 2010.
[45] A. T. Cohen *et al.*, “Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial,” *BMJ*, vol. 332, no. 7537, pp. 325–329, Feb. 2006.
[46] H. Riess *et al.*, “A randomized, double-blind study of certoparin vs. unfractionated heparin to prevent venous thromboembolic events in acutely ill, non-surgical patients: CERTIFY Study,” *J. Thromb. Haemost.*, vol. 8, no. 6, pp. 1209–1215, Jun. 2010.

[47] B. Forette and Y. Wolmark, “Calcium nadroparin in the prevention of thromboembolic disease in elderly subjects: Study of tolerance (translated by EMBASE),” *Presse Med*, vol. 24, no. 12, pp. 567–571, Mar. 1995.
[48] A. K. Kakkar, C. Cimminiello, S. Z. Goldhaber, R. Parakh, C. Wang, and J. F. Bergmann, “Low-molecular-weight heparin and mortality in acutely ill medical patients,” *N.Engl.J.Med.*, vol. 365, no. 26, pp. 2463–2472, 2011.
[49] T. Lanitis *et al.*, “Cost-effectiveness of apixaban versus low molecular weight heparin/vitamin k antagonist for the treatment of venous thromboembolism and the prevention of recurrences,” *BMC Health Serv Res*, vol. 17, p. 74, Jan. 2017.
[50] R. Pesavento and P. Prandoni, “Prevention and treatment of the post-thrombotic syndrome and of the chronic thromboembolic pulmonary hypertension,” *Expert Rev Cardiovasc Ther*, vol. 13, no. 2, pp. 193–207, Feb. 2015.
[51] J. Kelly, A. Rudd, R. R. Lewis, and B. J. Hunt, “Screening for subclinical deep-vein thrombosis,” *QJM*, vol. 94, no. 10, pp. 511–519, Oct. 2001.
[52] M. Dennis, N. Mordi, C. Graham, P. Sandercock, and CLOTS trials collaboration, “The timing, extent, progression and regression of deep vein thrombosis in immobile stroke patients: observational data from the CLOTS multicenter randomized trials,” *J. Thromb. Haemost.*, vol. 9, no. 11, pp. 2193–2200, Nov. 2011.
[53] P. T. Vaitkus *et al.*, “Mortality rates and risk factors for asymptomatic deep vein thrombosis in medical patients,” *Thromb. Haemost.*, vol. 93, no. 1, pp. 76–79, Jan. 2005.
[54] M. C. Christensen, S. Mayer, and J.-M. Ferran, “Quality of life after intracerebral hemorrhage: results of the factor seven for acute hemorrhagic stroke (FAST) trial,” *Stroke*, vol. 40, no. 5, pp. 1677–1682, May 2009.
[55] B. O. Hütter, J. M. Gilsbach, and I. Kreitschmann, “Quality of life and cognitive deficits after subarachnoid haemorrhage,” *British Journal of Neurosurgery*, vol. 9, no. 4, pp. 465–476, Jan. 1995.
[56] A. Shah, A. Shewale, C. J. Hayes, and B. C. Martin, “Cost-effectiveness of oral anticoagulants for ischemic stroke prophylaxis among nonvalvular atrial fibrillation patients,” *Stroke*, vol. 47, no. 6, pp. 1555–1561, Jun. 2016.

Figures

Tables

Table 1. Summary of studies included in the network meta-analysis[a]

Study	Key eligibility criteria	Interventions	Baseline characteristics	Outcomes analyzed	Setting	Reference
APEX	Aged ≥40 years; cause of hospitalization either acute heart failure, acute respiratory failure, acute infection, acute rheumatic disorders or acute ischemic stroke; at least one additional VTE risk factor of either ≥75 years, or 60-74 years with D-dimer ≥2 ULN, or 40-59 with D-dimer ≥2 ULN and history of VTE or cancer; expected to be immobilized for ≥3 days.	Betrixaban 80 mg once daily (loading dose of 160 mg for first dose)for 35-42 days (n=3,759) Enoxaparin 40 mg once daily for 10±4 days (n=3,754)	Age 76 years; Male 45%; Weight 80 kg	VTE, VTE related death, major bleeding, PE, asymptomatic and symptomatic DVT	Patients were enrolled from 35 countries in North America, Europe, South America, South Africa, Asia and Australia	[20]
ARTEMIS	Aged ≥60 years; acutely ill with congestive heart failure, or acute respiratory illness with chronic	Fondaparinux sodium 2.5 mg once daily for	Age 75 years; Male 42%; Weight 70 kg	VTE, VTE related death,	35 centres in eight countries	[45]

	lung disease, or clinically diagnosed acute infection or inflammatory disorder; expected be immobilized for ≥4 days.	6-14 days (n=429) Placebo once daily for 6-14 days (n=420)		PE, symptomatic DVT		
Belch 1981	Aged ≥40 and ≤80 years; admitted to hospital with heart failure or chest infection.	UFH 5000 units/8 hours until mobile (n=50) No prophylaxis (n=50)	Age 66 years; Male 69%; Weight 22% obese	PE[b]	1 centre in Scotland	[34]
CERTIFY	Hospitalized medical patients; ≥70 years; acute medical illness; significant decrease in mobility expected for ≥4 days.	Certoparin 3000 units once daily (n=1,624) for 8-20 days UFH 5000 units/8 hours (n=1,615) for 8-20 days	Age 79 years; Male 41%; Weight 72 kg	VTE, VTE related death, major bleeding, PE, symptomatic and asymptomatic DVT	Recruited from 172 centres between January 2007 and June 2009	[46]

Forette 1995	Aged ≥70 years; admitted to hospital for an estimated minimum duration of 4 weeks for a recent and presumed transient decrease in their locomotor autonomy; absence of existing DVT.	Nadroparin 3075 units per day for 28 days (n=146) UFH 5000 units twice daily for 28 days (n=149)	Age 83 years; Male 75%; Weight 59 kg	Major bleeding, PE, all[c] DVT	Hospital setting (35 centres in France)	[47]
LIFENOX	Aged ≥40 years; hospitalized for acute decompensation of heart failure, active cancer (unless for planned chemotherapy), or severe systemic infection; additional risk factor of chronic pulmonary disease, or obesity, or history of VTE or aged ≥60 years; expected hospitalization of at least 6 days.	Enoxaparin 40 mg once daily for 6-14 days (n=4,174) Placebo once daily for 6-14 days (n=4,145)	Age 65 years; Male 63%; BMI 23	VTE related death	Hospital setting. 193 sites in China, India, Korea, Malaysia, Mexico, the Philippines, and Tunisia. Recruitment began	[48]

					in January 2008 and was completed in September 2010	
PREVENT	Aged ≥40 years; acute medical condition with projected hospitalization of 4 days and 3 days of prior immobilization; hospitalization for acute congestive heart failure; acute respiratory failure; infection without septic shock; acute rheumatologic disorders; inflammatory bowel disease.	Dalteparin 5000 units once daily for 14 days (n=1,856) Placebo once daily for 14 days (n=1,850)	Age 69 years; Male 48%; BMI 27	VTE, VTE related death, major bleeding, PE, symptomatic and asymptomatic DVT	Between July 2001 and April 2002, 3706 patients were enrolled at 219 study centres in 26 countries	[35]

[a]VTE = venous thromboembolism, ULN = upper limit of normal, DVT = deep vein thrombosis, PE = pulmonary embolism, UFH = unfractionated heparin, BMI = body mass index

[b]only included as a sensitivity analysis in this network meta-analysis

[c]the type of DVT reported in Forette 1995 was not specified so it could only be considered for the all DVT analysis