DOI:
10.1016/j.thromres.2016.11.014

Document Version
Peer reviewed version

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PII: S0049-3848(16)30626-0
DOI: doi:10.1016/j.thromres.2016.11.014
Reference: TR 6517

To appear in: *Thrombosis Research*

Received date: 13 July 2016
Revised date: 6 October 2016
Accepted date: 13 November 2016

Please cite this article as: Beyer-Westendorf Jan, Lensing Anthonie W.A., Arya Roopen, Bounameaux Henri, Cohen Alexander T., Wells Philip S., Middeldorp Saskia, Verhamme Peter, Hughes Rodney, Kucher Nils, Pap Akos F., Trajanovic Mila, Prins Martin H., Prandoni Paolo, Weitz Jeffrey I., Choosing wisely: The impact of patient selection on efficacy and safety outcomes in the EINSTEIN-DVT/PE and AMPLIFY trials, *Thrombosis Research* (2016), doi:10.1016/j.thromres.2016.11.014

Choosing wisely: The impact of patient selection on efficacy and safety outcomes in the EINSTEIN-DVT/PE and AMPLIFY trials

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Brief title: EINSTEIN-DVT/PE adjusted to AMPLIFY patient selection criteria

Abstract word count:	**217**
Manuscript word count:	**2570**
Reference count:	**25**
Tables:	**3**
Figures:	**2**

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Summary

Background: The results of the EINSTEIN-DVT/PE and AMPLIFY trials, which compared rivaroxaban and apixaban with conventional anticoagulation therapy for acute venous thromboembolism (VTE), respectively, are often compared. However, the trials differed in duration of therapy (3-12 and 6 months, respectively) and in patient selection (few exclusion criteria and more stringent exclusion criteria, respectively).

Methods: To determine the effect of these methodological differences on outcomes, the patients enrolled in EINSTEIN-DVT/PE were divided into 2 cohorts; the 5253 patients that matched the exclusion criteria for AMPLIFY and were treated for at least 6 months (cohort 1) and the 2368 patients who would have been ineligible for AMPLIFY (cohort 2).

Results: Compared with patients in cohort 2, those in cohort 1 were older and more often male and there were more with unprovoked VTE, prior VTE, cancer and known thrombophilia. In cohort 1, rivaroxaban would have significantly reduced recurrent VTE (relative risk [RR], 0.64; 95% confidence interval [CI], 0.43-0.95) and major bleeding (RR, 0.50; 95% CI, 0.30-0.82) compared with conventional therapy, whereas the two treatments would have had similar effects on recurrent VTE (RR, 1.08; 95% CI, 0.65-1.79) and major bleeding (RR, 1.03; 95% CI, 0.48-2.18) in cohort 2.

Conclusions: This analysis illustrates the influence of patient selection and treatments duration on outcome results and highlights the limitations of cross-trial comparisons.

Funding: Drs Lensing, Pap, and Trajonovic are paid employees of Bayer Healthcare and devoted salaried time to this work; the other authors were unsupported.

Previous Presentation: This study was presented at the ISTH SSC 2016, 62nd Annual Meeting of the International Society on Thrombosis and Haemostasis; May, 2016, Montpellier, France.

Key words: anticoagulation, rivaroxaban, apixaban, venous thromboembolism.

Introduction

Recent randomised active-controlled trials that included over 27,000 patients have established the direct oral anticoagulants (DOACs) as efficacious and safe treatment options for patients with acute symptomatic venous thromboembolism (VTE).[1-6] With fixed dosing and no need for routine coagulation monitoring, the DOACs are convenient to administer and they are rapidly replacing vitamin K antagonists (VKA) for initial, long-term and extended VTE treatment.

Selection among the DOACs is challenging because they have not been compared in a head-to-head manner. Although the respective DOAC trials shared many similarities with regard to primary objective, comparator therapy, outcome definitions and central event adjudication, a number of differences existed in trial design and patient selection criteria. However, the impact of these trial differences on study outcomes is currently unknown. This gap in knowledge may have clinical consequences because indirect comparisons between DOACs have been conducted using meta-analytic or network meta-analytic techniques,[7-12] but the results of these analyses may be misleading because of differences in study design and patient selection criteria.[13-15] This creates challenges for physicians and other health care professionals as they seek to understand, interpret, and apply the results of the studies in their clinical practices.[16, 17]

To evaluate the impact of differences in trial design and inclusion and exclusion criteria on outcomes in DOAC VTE treatment trials we applied the main design features of the apixaban study (AMPLIFY) to patient cohorts from the studies with rivaroxaban (EINSTEIN DVT and EINSTEIN PE, which were performed as separate studies with a pre-specified pooled analysis) [1-3,18]. In both study programs initial heparin therapy was not required for patients receiving DOAC treatment and many patients had no heparin or received only a single heparin dose prior to randomization. More specifically, EINSTEIN DVT/PE and AMPLIFY shared the following features:

All three studies used the same blinded independent adjudication committee which employed identical diagnostic criteria for confirmation of the index and recurrent symptomatic VTE events and for the evaluation of suspected bleeding events. In all three studies, (a) recurrent VTE was evaluated for the intention-to-treat population, (b) bleeding events were evaluated for the on-treatment (+2 days) population, and (c)

haemoglobin, platelet count, alanine aminotransferase (ALT), and total bilirubin were measured at baseline.

In EINSTEIN-DVT/PE, patients randomised to the rivaroxaban arm were given the drug at a dose of 15 mg twice-daily for 21 days and the dose was then reduced to 20 mg once-daily thereafter. In AMPLIFY, patients randomised to receive apixaban were given the drug at a dose of 10 mg twice-daily for 7 days followed by 5 mg twice-daily thereafter. There was no downward adjustment of the doses of rivaroxaban or apixaban on the basis of clinical criteria such as older age, low body weight or moderate renal impairment. Heparin bridging was not given and the pre-randomization use of heparin was restricted to a limited number of doses. Comparator treatment in the trials consisted of enoxaparin (1 mg/kg body weight twice-daily) for a minimum of 5 days overlapping with a VKA (warfarin or acenocoumarol in EINSTEIN-DVT/PE and warfarin in AMPLIFY). Enoxaparin was stopped when the INR was 2 or higher and VKA was dose adjusted to maintain the INR between 2 and 3.

Patients were ineligible if they were allergic to the drugs used for comparator treatment, had limited life expectancy, had severe renal impairment, had bacterial endocarditis, used strong inhibitors of CYP3A4, or had received an investigational agent within the past 30 days prior to the first dose of study treatment. In addition, the studies excluded women who were pregnant or breast feeding and women of childbearing potential not taking adequate measures to prevent pregnancy.

On the other hand, EINSTEIN DVT/PE and AMPLIFY differed in a number design features.

The EINSTEIN-DVT/PE trials used a PROBE design (i.e., prospective, randomised, open, blinded endpoint evaluation), whereas the AMPLIFY trial was conducted in a double-blind, double-dummy manner and a point-of-care device was used to provide real or sham international normalised ratio (INR) values. The EINSTEIN-DVT/PE studies were conducted using a single protocol but applying separate randomization for patients with deep vein thrombosis (DVT) and for those with pulmonary embolism (PE) with or without accompanying DVT. In contrast, the AMPLIFY trial included patients with acute symptomatic VTE and stratified them according to presentation as DVT or PE.

Treatment duration- In EINSTEIN-DVT/PE, patients were eligible if they required anticoagulant therapy for a period of at least 3, 6 or 12 months. In AMPLIFY, patients were only eligible if they required anticoagulant therapy for at least 6 months.

VTE provoked by a transient risk factor- In EINSTEIN-DVT/PE, patients with provoked or unprovoked VTE could be included, whereas in AMPLIFY patients were ineligible if they had VTE provoked by a transient risk factor

High risk for bleeding- The exclusion criteria related to a potential for increased bleeding were more extensive for AMPLIFY than for EINSTEIN-DVT/PE. Although patients with overt bleeding and those considered at high risk of bleeding were excluded from all studies, the AMPLIFY trial also excluded those with haemoglobin < 9 g/dL, ALT >2 times upper limit of normal (ULN) rather than >3 times ULN as in EINSTEIN-DVT/PE, total bilirubin >1.5 times ULN, requirement for ASA >165 mg/day, requirement for dual antiplatelet therapy, platelet count <100 x 10^9/L, recent (<6 months) intracranial bleeding, intraocular bleeding, gastrointestinal bleeding, endoscopically verified ulcer disease, recent (<1 week) ischemic stroke or neurosurgery, or recent (< 2 months) head trauma, other major trauma, or major surgery. In addition, patients were excluded from AMPLIFY if they had an intracranial neoplasm, arteriovenous malformation or aneurysm.

Table 1 lists the relevant differences in treatment duration and exclusion criteria in the EINSTEIN-DVT/PE and AMPLIFY trials and indicates the adaptation of the EINSTEIN-DVT/PE cohort to reflect the AMPLIFY criteria.

Taken together, the EINSTEIN-DVT/PE and AMPLIFY trials especially differed in the duration of therapy and in patient selection. In the EINSTEIN-DVT/PE trials, there were few exclusion criteria and anticoagulation therapy could be given for 3, 6 or 12 months at the discretion of the treating physician.[2, 3, 18] In contrast, the exclusion criteria were more stringent for the AMPLIFY study, and all patients were treated for 6 months.[1]

To evaluate the impact of these trial design differences on treatment outcomes, we compared rates of recurrent VTE and major bleeding for EINSTEIN-DVT/PE patients

who received at least 6 months of anticoagulant therapy in those who met or did not meet the eligibility criteria employed in the AMPLIFY trial.

Methods

Detailed descriptions of the study design of the EINSTEIN-DVT/PE and AMPLIFY trials have been published.[1-3] and were registered at ClinicalTrials.gov, numbers NCT00440193, NCT00439777, and NCT00643201.

Differences in study design of the EINSTEIN-DVT/PE and AMPLIFY trials

The steps taken to adjust the data from EINSTEIN-DVT/PE to mimic the AMPLIFY design are listed in Table 1, which includes the number of patients involved. First, patients from EINSTEIN-DVT/PE with an intended treatment duration of 3 months were excluded because such patients were not enrolled in AMPLIFY. Second, the evaluation was truncated at 6 months in EINSTEIN-DVT/PE patients whose intended treatment duration was 12 months. Third, the exclusion criteria used in AMPLIFY were applied to identify a similar cohort of patients enrolled in the EINSTEIN-DVT/PE trials (EINSTEIN cohort 1), and a cohort who would not have been eligible for AMPLIFY (EINSTEIN cohort 2). Separate analyses were performed for both cohorts.

Statistical Analyses

For comparison of demographic and clinical characteristics of patients in EINSTEIN-DVT/PE cohort 1 and AMPLIFY, standardised difference scores were calculated.[19] For better comparison of outcome results, the EINSTEIN-DVT/PE results, which were originally expressed in hazard ratios, were presented as relative risk (RR). The 95% confidence intervals (CI) were calculated using the Mantel-Haenszel method and stratified according to the qualifying diagnosis (DVT or PE±DVT) and intended treatment duration (6 or 12 months). The times during which the INR was below, within or above the therapeutic range were calculated for each patient from the time of discontinuation of heparin until the end of treatment (including interruptions) and

were compared using multivariate ANOVA. Adverse events resulting in permanent discontinuation of study drug in the two EINSTEIN cohorts were compared using the chi-square test.

Outcome Measures

Efficacy and safety outcomes were defined identically in EINSTEIN-DVT/PE and AMPLIFY. The primary efficacy outcome was the adjudicated composite of recurrent symptomatic VTE (i.e. fatal or nonfatal PE and DVT). Major bleeding was defined as overt bleeding that was associated with a decrease in the hemoglobin level of 2 g/dL or more, required the transfusion of 2 or more units of blood, occurred in a critical site, or contributed to death.

Role of the funding source

Bayer HealthCare Pharmaceuticals and Janssen Research and Development, the funders of the EINSTEIN-DVT and EINSTEIN-PE studies, gathered, maintained, and extracted data. The authors had responsibility for interpreting the data and writing the article. JBW, AWAL, MPH, and JIW had access to the raw data. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

A total of 660 (8.0%) of the 8282 EINSTEIN-DVT/PE patients had an intended treatment of 3 months and were excluded from further analyses. Next, study duration was truncated at 6 months for 2681 patients who had a treatment duration > 6 months in EINSTEIN DVT/PE. As indicated in figure 1, application of the AMPLIFY eligibility criteria to the 7621 EINSTEIN-DVT/PE patients with an intended treatment duration of 6 or 12 months resulted in 1) a cohort of 5253 EINSTEIN-DVT/PE patients whose inclusion criteria matched those of patients enrolled in AMPLIFY (EINSTEIN-DVT/PE cohort 1) and 2) a cohort of 2368 EINSTEIN-DVT/PE patients who would not been eligible for enrollment in AMPLIFY (EINSTEIN-DVT/PE cohort 2),

Table 2 specifies the demographic and clinical characteristics of the patients included in the two EINSTEIN-DVT/PE cohorts and in AMPLIFY. Compared with patients in EINSTEIN-DVT/PE cohort 2, those in cohort 1 were older and more often male, and a greater proportion had unprovoked VTE, a history of prior VTE, or known thrombophilia. Compared with patients in AMPLIFY, patients in cohort 1 of EINSTEIN-DVT/PE were slightly older and more had PE, prior history of VTE, known thrombophilia, or active cancer. Overall, time spent with the INR below, within, and above the therapeutic range of 2.0 to 3.0 was similar for patients in cohort 1, cohort 2 and AMPLIFY (Table 2)**.** Adverse events leading to permanent discontinuation of study drug occurred with similar frequency in both EINSTEIN-DVT/PE cohorts and AMPLIFY.

Clinical Outcomes

Recurrent VTE occurred in 99 (1.9%) of 5253 patients in cohort 1 and 58 (2.5%) of 2368 patients in cohort 2 (RR, 0.76; 95% CI, 0.55-1.06), whereas major bleeding occurred in 67 (1.3%) of 5233 and 27 (1.1%) of 2358 patients in cohorts 1 and 2, respectively (RR, 1.19; 95% CI, 0.75-1.90; Table 3).

In EINSTEIN-DVT/PE cohort 1, the rate of recurrent VTE was significantly lower with rivaroxaban than with enoxaparin/VKA (1.5% and 2.3%, respectively; RR, 0.64; 95% CI, 0.43-0.95; p=0.027). In contrast, the rates of recurrent VTE with rivaroxaban and enoxaparin/VKA were similar in cohort 2 (2.6% and 2.3%, respectively; RR, 1.08; 95% CI, 0.65-1.79; p=0.77; Table 3 and Figure 2). Likewise, the rate of major bleeding was significantly lower with rivaroxaban than with enoxaparin/VKA in EINSTEIN-DVT/PE cohort 1 (0.8% and 1.7%, respectively; RR, 0.50; 95% CI, 0.30-0.82; p=0.0068) but not in cohort 2 (1.2% and 1.1%, respectively; RR, 1.03; 95% CI, 0.48-2.18; p=0.95; Figure 3).

The first recurrent VTE or major bleeding event in the intention-to-treat population occurred significantly less frequently with rivaroxaban than with enoxaparin/VKA in cohort 1 (2.4% and 4.0%, respectively; RR, 0.60; 95% CI, 0.44-0.81; p=0.0011) indicating a superior net clinical benefit with rivaroxaban. In contrast, the frequency of the first recurrent VTE or major bleeding event was similar with rivaroxaban and enoxaparin/VKA in cohort 2 (3.9% and 3.6%, respectively; RR, 1.06; 95% CI, 0.70-1.59; p=0.79).

Discussion

Our results indicate that had the AMPLIFY eligibility criteria been applied to patients enrolled in the EINSTEIN-DVT/PE trials, 31.1% of the patients would have been ineligible. Although ineligible for AMPLIFY, these patients were included in EINSTEIN DVT/PE and form cohort 2. Compared with patients in cohort 1 who met the AMPLIFY eligibility criteria, those in cohort 2 who did not meet these criteria had an almost 1.5- to 2-fold higher risk of recurrent VTE and major bleeding during rivaroxaban therapy. This difference shows that treatment duration and modest variations in eligibility criteria can impact on outcome results, thereby highlighting the limitations of cross study comparisons.

Casual inspection of the results of the EINSTEIN-DVT/PE and AMPLIFY trials suggests that apixaban and rivaroxaban are similarly efficacious because the rates of recurrent VTE are 2.3% vs. 2.1%, respectively, but that apixaban is associated with a lower absolute rate of major bleeding than rivaroxaban (0.6% vs. 1.0%, respectively) and a greater risk reduction in major bleeding compared with enoxaparin/VKA (RR, 0.31 vs. 0.54, respectively). However, the results of the current analysis suggest that had the AMPLIFY treatment duration and exclusion criteria been applied in EINSTEIN-DVT/PE, rivaroxaban would have significantly reduced the risk of recurrent VTE compared with enoxaparin/VKA (RR, 0.64; 95% CI, 0.43-0.95) and would have been associated with an even greater reduction in the risk of major bleeding (RR, 0.50; 95% CI, 0.30-0.82). Of note, compared with the AMPLIFY population, patients in EINSTEIN-DVT/PE cohort 1 still had a somewhat higher risk profile, since they more often had PE, prior VTE, known thrombophilia or active cancer, which has been shown to be a relevant risk factor for both VTE recurrence and bleeding during anticoagulation. [20, 21]. Therefore, our findings may even underestimate the impact of patient selection on outcomes in AMPLIFY.

It may be argued that the majority of patients in EINSTEIN DVT/PE cohort 2 had provoked VTE, for which current guidelines recommend a treatment duration of 3 months, whereas these patients were selected to receive at least 6 months of anticoagulant therapy by their attending physicians. However, the risk of VTE recurrence after provoked VTE has been shown to range between 7-10% in the first

two years after index event. [22, 23]. Furthermore, during anticoagulation we observed a numerically higher rate of recurrent VTE in patients with provoked VTE compared to those with unprovoked VTE, which likely reflects the co-morbidity profile of patients with provoked VTE chosen to continue anticoagulation beyond 3 months. In addition, in the benefit-risk evaluation of the EINSTEIN Extension study [24], patients with provoked VTE had a similar recurrent VTE risk as compared to patients with unprovoked VTE. The number needed to treat with rivaroxaban to prevent 1 recurrent VTE was 16 for patients with unprovoked VTE and 14 for patients with provoked VTE, respectively. Finally, while VTE provoked by surgical triggers indeed has a very low risk of recurrence, VTE events provoked by "soft triggers" have been shown to have a considerably high VTE recurrence risk [25] that may, together with other factors such as family history, clot burden of index event, d-dimer values or patients` preferences, guide the decision to prolong anticoagulation beyond 3 months.

According to the outcome event rates of EINSTEIN cohort 2, the EINSTEIN-DVT/PE studies included a large proportion of patients who appear to have both a higher risk of recurrent VTE and a higher risk of major bleeding than those that met the inclusion and exclusion criteria used in AMPLIFY. Although the use of more stringent exclusion criteria may help to optimize internal validity, increase study feasibility, reduce cost, and alleviate ethical concerns by excluding patients who might be harmed by study participation, limiting enrollment may distort demographic characteristics (see Table 2) and yield lower rates of study outcomes (see Table 3). Therefore, the use of more stringent exclusion criteria has the potential to limit the generalizability (the so-called external validity) of the results to real-world practice. Consequently, enrollment of the broadest possible patient population is important to avoid such bias,[17] and the product label needs to reflect the applied exclusion criteria used in the various phase 3 trials.

This post-hoc comparison of the EINSTEIN-DVT/PE and AMPLIFY studies was performed on prospectively collected data and was enabled by the similarities in study design, including documentation of the inception cohorts, use of the same comparator (enoxaparin/VKA), identical outcomes and central assessment of outcomes by the same blinded adjudication committee. Nonetheless, our study has limitations. First, because this is a post-hoc analysis, we cannot exclude the possibility that different results may be obtained if the EINSTEIN-DVT/PE studies had

been performed prospectively using the AMPLIFY trial design. Second, splitting the EINSTEIN-DVT/PE population into smaller subgroups reduces the statistical power of our analysis. However, because EINSTEIN-DVT/PE included over 8000 patients, even after excluding patients in cohort 2, cohort 1 still had a similar number of patients as was included in the AMPLIFY trial. Finally, because we did not have access to the raw data, only aggregate results from the AMPLIFY study could be used in this analysis. Despite these limitations, this post-hoc analysis suggests that had the AMPLIFY exclusion criteria and treatment duration been applied in the EINSTEIN-DVT/PE trials, rivaroxaban would have been superior to enoxaparin/VKA in both efficacy and safety.

This study suggests that modest differences in study design can have a major impact on study outcomes. In the absence of head-to-head trials comparing one agent with another, this fact needs to be considered when making treatment decisions on the basis of cross study comparisons. Furthermore, our findings suggest that indirect comparisons such as network-analyses may be misleading, if they do not fully adjust for trial differences.

Contributors

JBW, AWAL, MHP and JIW created the initial draft version of this manuscript. JBW, AWAL, MT, MHP and PP performed the classification of patients. ÁFP and AFP performed statistical analysis. All authors participated in writing and review of the article and accept full responsibility for its overall content.

Declaration of interests

JBW has received honoraria from Bayer Healthcare, Boehringer-Ingelheim, BMS/Pfizer, CSL Behring, Daiichi-Sankyo and LEO Pharma. His institution has received research funding from Bayer Healthcare, Boehringer-Ingelheim, BMS/Pfizer, CSL Behring, Daiichi-Sankyo and LEO Pharma.

RA has received research support from Bayer Healthcare and honoraria from Bayer Healthcare, Boehringer-Ingelheim and Pfizer.

AWAL, AFP and MT are employees of Bayer Healthcare.

HB has received research grant support from the Swiss National Foundation, Daiichi Sankyo, and Bayer Schering Pharma as well as honoraria for lectures or consultancy from Pfizer and Bayer Schering Pharma.

AC has served on advisory boards for Bayer, Bristol-Myers Squibb, Daiichi Sankyo, Johnson & Johnson, Pfizer, Portola, and Sanofi, and has received consulting fees, lecture fees, support for manuscript preparation, and payment for the development of educational presentations from Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, and Bristol-Myers Squibb.

PW has received research support from Bristol-Myers Squibb, Pfizer; has participated on scientific advisory boards for Bayer Schering Pharma, Pfizer, and Boehringer Ingelheim; and has received honoraria from Bayer Schering Pharma, Pfizer, and Biomerieux.

RH is a former employee of Bayer Healthcare and received lecturing/consulting fees for Pfizer, Sanofi Aventis, GSK and Leo Pharma.

NK has received speaker honoraria from Bayer Healthcare, BMS/Pfizer, and Daiichi-Sankyo. His institution has received research funding from Bayer Healthcare and BMS/Pfizer.

PV has received research support from Bayer, Boehringer-Ingelheim, Sanofi and Leo Pharma; has been a member of scientific advisory boards for Bayer, Boehringer, Daiichi Sankyo and Portola; and has received honoraria from Bayer, Boehringer, Pfizer and Daiichi Sankyo.

SM received Research Support from: Daiichi Sankyo, GSK, Aspen, BMS/Pfizer, Sanquin and Bayer and has participated on scientific advisory boards for Bayer, BMS/Pfizer, Boehringer Ingelheim and Daiichi Sankyo.

MHP has acted as a consultant to Bayer HealthCare, Sanofi-Aventis, Boehringer Ingelheim, GlaxoSmithKline, Daiichi Sankyo, LEO Pharma, ThromboGenics and Pfizer.

PP received consultancy fees from Bayer Healthcare Pharmaceuticals, Daiichi Sankyo, Boehringer Ingelheim, Pfizer and Sanofi.

JIW has served as a consultant and received honoraria from Bayer HealthCare, Janssen, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer; Daiichi Sankyo, Johnson and Johnson, Merck, Portola and Ionis Pharmaceuticals.

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Table 1. Comparison of treatment duration and exclusion criteria in AMPLIFY and EINSTEIN-DVT/PE and adjustment of EINSTEIN-DVT/PE data to reflect the AMPLIFY data**AMPLIFY**	**EINSTEIN-DVT/PE**	**EINSTEIN-DVT/PE adaptation to reflect AMPLIFY**	**No of patients affected**
Treatment Duration			
Planned treatment duration of at least 6 months	Planned treatment duration of 3, 6, or 12 months	Patients in the 3-month intended treatment duration group excluded	660
Total treatment duration of 6 months	Up to 12 months	Analysis censored at 6 months for patients with intended 12-months treatment duration	2681
Exclusion criteria			
General			
Patients with VTE provoked by a transient risk factor	Provoked VTE included	Patients with VTE provoked by a transient risk factor excluded	1817
Risk factors for bleeding at baseline			1518
Haemoglobin < 9 g/dL	No limitation for haemoglobin	Patients with Hb < 9 g/dL excluded	84
ALT > 2 times ULN	ALT ≥ 3 times ULN	Patients with ALT > 2 times ULN excluded	145
Total bilirubin >1.5 times ULN	No limitation for bilirubin	Patients with total bilirubin > 1.5 times ULN excluded	63
Requiring ASA >165 mg/day	ASA was discouraged	Patients using ASA > 165 mg (7-day post randomization window) excluded	18
Requiring dual antiplatelet therapy	No limitation for dual antiplatelet therapy	Patients using dual antiplatelet therapy (7-day post randomization window) excluded	16
Platelet count < 100 x 10^9/L	No limitation for platelet count	Patients with a platelet count < 100 x 10^9/L excluded	73
Heparin-induced thrombocytopenia (HIT)	Contraindication for use of heparin	Patients with (history of) HIT excluded	0
Recent bleeding (< 6 months): intracranial, intraocular, gastrointestinal, or endoscopically verified ulcer disease	Patients at high risk of bleeding excluded	Patients with intracranial, intraocular, gastrointestinal bleeding and those with endoscopically verified ulcer disease (< 6 months) excluded	21
Recent (< 1 week): ischemic stroke or neurosurgery	Patients at high risk of bleeding or recent surgery or trauma excluded	Patients with a stroke or neurosurgery (<1 week) excluded	5
At time of randomization: gross hematuria, evidence	Patients at high risk of	Patients excluded, if at time of	38

of poor healing of a major wound, major trauma or overt major bleeding, planned major surgery, intracranial neoplasm, arteriovenous malformation or aneurysm, documented hemorrhagic tendencies, or blood dyscrasias	bleeding excluded	randomization: gross hematuria, evidence of poor healing of a major wound, major trauma or overt major bleeding, planned major surgery, intracranial neoplasm, arteriovenous malformation or aneurysm, documented hemorrhagic tendencies, or blood dyscrasias	
Recent (< 2 months): head trauma, other major trauma, or major surgery	Patients at high risk of bleeding or those with recent surgery or trauma excluded	Patients with (< 2 months: head trauma, other major trauma, or major surgery excluded	1167
Other			
Creatinine clearance < 25 mL/min	< 30 mL/min	No correction	
Life expectancy < 6 months	<3 months	No correction	
Active and clinically significant liver disease	Identical	No correction	
2 doses of fondaparinux or a once-daily LMWH, or > 3 doses of a twice-daily LMWH, or continuous infusion of UFH for > 36 hrs; and/or > 2 doses of VKA	Identical	No correction	
Receiving concurrent investigational agents or has received an investigational agent within the past 30 days prior to the first dose of study treatment	Identical	No correction	
Thrombectomy, insertion of a cava filter, or use of a fibrinolytic agent to treat the current episode of DVT and/or PE	Identical	No corrections	
Subjects with cancer who will be treated for 6 months or more with LMWH therapy	Patients with cancer requiring long-term LMWH therapy were ineligible	No correction	
Bacterial endocarditis	Identical	No correction	
- Prisoners/subjects who are involuntarily incarcerated - Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness - Any condition, which in the opinion of the investigator, would put the subject at an unacceptable risk from participating in the study	Not specifically defined as exclusion criteria but these are general ineligibility criteria	No correction	

- 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.			
Women who were pregnant or breast feeding or women of childbearing potential not taking adequate measures to prevent pregnancy.	Identical	No correction	

Table 2. Demographic and clinical characteristics of EINSTEIN-DVT/PE patients who were and were not potentially eligible for the AMPLIFY study.

	Cohort 1: EINSTEIN-DVT/PE patients eligible for AMPLIFY; n=5253	Cohort 2: EINSTEIN-DVT/PE patients ineligible for AMPLIFY; n=2368	P-value cohort 1 vs cohort 2	AMPLIFY N=5395
Age — yr	59.4±16.0	53.0±17.6	P<0.0001	57.0±16.0
Male sex — no. (%)	3122 (59.4)	1060 (44.8)	P<0.0001	3167 (58.7)
Weight				
Mean — kg	83.5±18.4	81.8±19.5	P=0.0002	84.6±19.8
Weight				
Distribution; — no. (%)			P<0.0001	
≤60 kg	467 (8.9)	304 (12.9)		476(8.8)
>60 to < 100 kg	3977 (75.8)	1736 (73.4)		3868 (71.7)
> 100 kg	803 (15.3)	324 (13.7)		1040 (19.3)
Data missing	6 (0.1)	4 (0.2)		11 (0.2)
Qualifying diagnosis — no. (%)			P=0.034	
DVT	2098 (39.9)	888 (37.5)		3532 (65.5)
PE	2281 (43.4)	1112 (47.0)		1359 (25.2)
PE with DVT	821 (15.6)	349 (14.7)		477 (8.8)
Could not be evaluated	53 (1.0)	19 (0.8)		27 (0.5)
Time from onset of symptoms to randomization — days			P<0.0001	
Median	5.0	4.0		5.0
Interquartile range	(2.0-10.0)	(2.0-8.0)		(3.0-9.0)
Clinical presentation of VTE — no. (%)			P<0.0001	
Unprovoked	4797 (90.3)	262 (11.1)		4845 (89.8)
Provoked	456 (8.7)	2106 (88.9)		544 (10.1)
Not reported	-	-		6 (0.1)
Risk factors for recurrent VTE — no. (%)				
Previous VTE	1350 (25.7)	229 (9.7)	P<0.0001	872 (16.2)
Known thrombophilia	433 (8.2)	41 (1.7)	P<0.0001	133 (2.4)
Active cancer	291 (5.5)	111 (4.7)	P<0.034	143 (2.7)
Treatment with LMWH, heparin, or fondaparinux before randomization — no. (%)			P=0.10	
None	766 (14.6)	373 (15.8)		739 (13.7)
≤12 hr	460 (8.8)	214 (9.0)		712 (13.2)
>12 to 24 hr	2697 (51.3)	1135 (47.9)		2242 (41.6)
>24 to 48 hr	1263 (24.0)	613 (25.9)		1642 (30.4)
>48 hr	67 (1.3)	33 (1.4)		48 (0.9)
Data missing	-	-		12 (0.2)
Time spent in an INR interval of			P=0.0053	
< 2.0	21.0%	23.5%		23%
2.0 – 3.0	62.7%	60.9%		61%
> 3.0	16.3%	15.6		16%

Adverse events resulting in permanent discontinuation of study drug (DOAC vs enoxaparin/VKA	148 (5.7%) vs. 113 (4.3%)	48 (4.0%) vs. 53 (4.6%)	P=0.20*	6.1% vs 7.4%

Continuous variables are presented as means ± standard deviation. Percentages may not total 100 because of rounding. DVT denotes deep vein thrombosis, PE pulmonary embolism, VTE venous thromboembolism, INR international normalised ratio and LMWH low-molecular-weight heparin. *P-value calculated for all adverse events in cohort 1 versus all adverse events in cohort 2.

Table 3. Clinical outcomes in EINSTEIN-DVT/PE (original), EINSTEIN cohorts 1 and 2 and AMPLIFY

	Einstein-DVT/PE N=8281 (ITT)		Cohort 1: EINSTEIN-DVT/PE patients eligible for AMPLIFY; n=5253		Cohort 2: EINSTEIN-DVT/PE patients ineligible for AMPLIFY; n=2368		AMPLIFY n=5395	
	n (%)	RR (95% CI)	n (%)	RR (95% CI)	n (%)	RR (95% CI)	n (%)	RR (95% CI)
Recurrent VTE DOAC vs LMWH/VKA	86 (2.1%) vs 95 (2.3%)	0.90 (0.67-1.20)	38 (1.5%) vs 61 (2.3%)	0.64 (0.43-0.95; p=0.027)	31 (2.6%) vs 27 (2.3%)	1.08 (0.65-1.79; p=0.77)	59 (2.3%) vs 71 (2.7%)	0.84 (0.60-1.18)
Major bleeding DOAC vs LMWH/VKA	40 (1.0%) vs 72 (1.7%)	0.55 (0.38-0.81)	22 (0.8%) vs 45 (1.7%)	0.50 (0.30-0.82; p=0.0068)	14 (1.2%) vs 13 (1.1%)	1.03 (0.48-2.18; p=0.95)	15 (0.6%) vs 49 (1.8%)	0.31 (0.17-0.55)

RR denotes Relative Risk, DOAC non-vitamin K antagonist oral anticoagulants, LMWH low-molecular-weight heparin and VKA vitamin K antagonists

Table 4. Recurrent VTE and major bleeding according to risk factor profile in patients included in EINSTEIN but excluded in AMPLIFY (Cohort 2)

	Risk factor profile	Rivaroxaban	Enoxaparin/VKA	Hazard ratio (95% CI)	Pinteraction
Recurrent VTE					
	Provoked VTE transient risk factor	22/ 917 (2.4%)	21/900 (2.3%)	1.00 (0.55-1.82)	0.72
	Provoked VTE permanent risk factor	3/61 (4.9%)	3/50 (6.0%)	0.71 (0.14-3.54)	
	Unprovoked VTE	6/235 (2.6%)	3/205 (1.5%)	1.58 (0.39-6.36)	
Major bleeding					
	Provoked VTE transient risk factor	11/ 913 (1.2%)	9/897 (1.0%)	1.19 (0.49-2.88)	0.70
	Provoked VTE permanent risk factor	3/61 (4.9%)	2/50 (4.0%)	1.19 (0.19-7.39)	
	Unprovoked VTE	1/234 (0.4%)	2/203 (1.0%)	0.34 (0.03-3.70)	

Table 5. Major bleeding in patients included in EINSTEIN (Cohort 2) who met none, one or more than one bleeding exclusion criterion of the AMPLIFY study.

Bleeding exclusion criteria met	Cohort 2	Pinteraction	Hazard ratio (95% CI) versus none	Ptrend
none	6/838 (0.7%)	0.92		0.22
1	20/1403 (1.4%)		2.16 (0.87-5.39)	
>1	2/107 (1.9%)		2.71 (0.54-13.49)	
missing	0/8			

Figure 1: Flowchart of study cohort allocation and analyses