Treatment of acute pulmonary embolism with dabigatran versus warfarin

A pooled analysis of data from RE-COVER and RE-COVER II

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Summary

Dabigatran was non-inferior to warfarin for prevention of recurrent venous thromboembolism (VTE), and dabigatran had a lower rate of bleeding compared with warfarin in two large-scale randomised trials, RE-COVER and RE-COVER II. In this study, we investigate the efficacy and safety of dabigatran versus warfarin according to the index event that qualified the patient for enrollment, either symptomatic pulmonary embolism (PE) with or without deep-vein thrombosis (DVT), or DVT alone. We then analyse the anticoagulant effect of dabigatran vs warfarin on patients enrolled with PE. The pooled dataset for the efficacy analysis consisted of 2553 and 2554 patients who were randomised to dabigatran and warfarin, respectively. Recurrent VTE/VTE-related death during the study period and additional 30-day follow-up occurred in 2.7 % of all patients on dabigatran and in 2.4 % on warfarin (hazard ratio [HR] 1.09 [95 % confidence interval 0.77, 1.54]). In patients with PE as their index event, recurrent VTE/VTE-related death occurred in 2.9 % vs 3.1 % of patients (HR 0.93 [0.53, 1.64]). There were significantly fewer major bleeding events in patients treated with dabigatran than with warfarin (HR 0.60 [0.36, 0.99]). The pattern was similar both in patients with PE and in those with DVT alone as the index event. These analyses of the pooled dataset from the RE-COVER and RE-COVER II trials indicate that dabigatran is as effective as warfarin in preventing recurrent VTE, regardless of whether patients present with symptomatic PE (with or without DVT) or with symptomatic DVT alone. Dabigatran was also associated with a lower risk of bleeding than warfarin, regardless of the index event.

Keywords

Dabigatran, pulmonary embolism, venous thrombosis, warfarin

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Introduction

Pulmonary embolism (PE) is the third most common cause of cardiovascular mortality in the United States and accounts for 100,000 to 180,000 deaths each year (1). Anticoagulation remains the foundation of therapy for acute PE and deep-vein thrombosis (DVT), collectively called venous thromboembolism (VTE). In randomised controlled trials of novel anticoagulants compared with warfarin, the frequency of recurrent VTE is the most commonly utilized endpoint to assess efficacy of therapy. This standard approach does not account for the broad spectrum of VTE and gives equal weight to a potentially life-threatening PE and clinically less important DVT. Using this traditional scheme, for example, an acute popliteal DVT is assessed as a treatment failure equal in magnitude to an acute extensive bilateral PE.

Dabigatran etexilate was compared with warfarin in the treatment of acute VTE in two large scale randomised controlled trials, RE-COVER (2) and RE-COVER II (3). These trials, which had virtually identical protocols, compared six months of treatment with dabigatran 150 mg twice daily vs dose-adjusted warfarin therapy, following initial parenteral anticoagulation. In both trials, and in a pooled analysis (3), dabigatran was non-inferior to warfarin for prevention of recurrent VTE, and dabigatran had a lower rate of bleeding. The current study is a pre-specified subgroup analysis of pooled data from RE-COVER and RE-COVER II in which we investigate the efficacy and safety of dabigatran vs warfarin according to the index event that qualified the patient for enrollment, either symptomatic PE with or without DVT, or DVT alone. We then analyse the anticoagulant effect of dabigatran vs warfarin on patients enrolled with PE.

Methods

Study population and trial design

The study design, population, and outcomes of the RE-COVER and RE-COVER II trials have been published previously (2, 3). Patients ≥ 18 years of age who had acute, symp-

Table 1: Qualifying index VTE events in the RE-COVER and RE-COVER II pooled dataset.

Qualifying event[a]	Dabigatran (N = 2553)	Warfarin (N = 2554)	Total (N = 5107)
No symptomatic PE, n (%)	1758 (68.9)	1747 (68.4)	3505 (68.6)
Symptomatic DVT only	1755 (68.7)	1744 (68.3)	3499 (68.5)
Neither symptomatic PE nor symptomatic DVT	3 (0.1)	3 (0.1)	6 (0.1)
Symptomatic PE, n (%)	795 (31.1)	807 (31.6)	1602 (31.4)
Symptomatic PE and symptomatic DVT	226 (8.9)	240 (9.4)	466 (9.1)
Symptomatic PE only	569 (22.3)	567 (22.2)	1136 (22.2)

[a]Results of objective testing for initial symptomatic DVT/PE performed locally. If a patient had more than one event, the last event prior to randomisation was classified as the qualifying event. DVT, deep-vein thrombosis; PE, pulmonary embolism.

tomatic, objectively verified proximal DVT of the legs, or PE, and for whom six months of anticoagulant therapy was considered to be an appropriate treatment, were eligible for inclusion. Patients received parenteral anticoagulation and were randomised to warfarin or warfarin-placebo, taken in parallel with the parenteral anticoagulant. The latter was continued for ≥ 5 days, until the International Normalised Ratio (INR) was ≥ 2 at two consecutive measurements. After discontinuing parenteral therapy, patients continued warfarin (therapeutic INR range, 2.0–3.0) or received dabigatran 150 mg twice daily for six months (double-dummy, 'oral-only' treatment period). Randomisation was stratified according to the presence or absence of symptomatic PE at baseline. Testing for initial symptomatic DVT/PE was performed locally. If a patient had more than one event, the last event prior to randomisation was classified as the qualifying event (e.g. for a patient who first had a DVT then subsequently a PE, PE would be designated as the index event).

Table 2: Demographics, baseline characteristics and risk factors for VTE recurrence of patients with symptomatic DVT alone and with symptomatic PE as the index event.

	Index event: symptomatic DVT alone		Index event: symptomatic PE	
	Dabigatran N = 1758	Warfarin N = 1747	Dabigatran N = 795	Warfarin N = 807
Age, mean, years (± SD)	54.5 (± 15.8)	54.3 (± 16.2)	55.6 (± 16.3)	55.6 (± 16.2)
Male, n (%)	1100 (62.6)	1090 (62.4)	420 (52.8)	431 (53.4)
Race				
White Black Asian	1536 (87.4) 30 (1.7) 192 (10.9)	1504 (86.1) 32 (1.8) 211 (12.1)	670 (84.3) 24 (3.0) 100 (12.6)	689 (85.4) 19 (2.4) 99 (12.3)
Non-Hispanic	1694 (96.4)	1665 (95.3)	781 (98.2)	796 (98.6)
Weight, mean, kg (± SD)	83.7 (± 18.9)	83.1 (± 18.8)	85.8 (± 20.5)	84.7 (± 19.4)
BMI, mean, kg/m^2 (± SD)	28.4 (± 5.4)	28.2 (± 5.4)	29.1 (± 6.2)	28.8 (± 6.1)
Creatinine clearance, mean, ml/min (± SD)	106.8 (± 41.9)	105.6 (± 38.8)	107.5 (± 43.0)	106.2 (± 44.0)
Risk factors for recurrent VTE, n (%)				
Previous VTE	392 (22.3)	351 (20.1)	183 (23.0)	173 (21.4)
Active cancer at baseline or during study	121 (6.9)	119 (6.8)	52 (6.5)	43 (5.3)
Thrombophilia[a]	125 (7.1)	124 (7.1)	84 (10.6)	75 (9.3)
Recent prolonged immobilisation	231 (13.1)	254 (14.5)	135 (17.0)	127 (15.7)
Current smoker	409 (23.3)	409 (23.4)	140 (17.6)	144 (17.8)
Concomitant therapy				
CV medication	907 (51.6)	891 (51.0)	433 (54.5)	447 (55.4)
At least one antithrombotic, anticoagulant or NSAID	532 (30.3)	484 (27.7)	239 (30.1)	213 (26.4)

[a]More than half of patients were not tested for thrombophilia: no index PE, dabigatran 1221 (69.5 %), warfarin 1198 (68.6 %); with index PE, dabigatran 455 (57.2 %), warfarin 487 (60.3 %). BMI, body mass index; CV, cardiovascular; DVT, deep-vein thrombosis; PE, pulmonary embolism; SD, standard deviation; VTE, venous thromboembolism.

Table 3: Efficacy and safety outcomes by treatment group and index event.

Outcome	Symptomatic PE as index event	Dabigatran Events/n (%)	Warfarin Events/n (%)	P-value (interaction)
VTE or VTE-related death[a]	No	45/1758 (2.6)	37/1747 (2.1)	0.4848
	Yes	23/795 (2.9)	25/807 (3.1)	
Components of the primary endpoint				
VTE-related death[a]	No	0/1758 (0)	0/1747 (0)	0.9999
	Yes	2/795 (0.3)	3/807 (0.4)	
Non-fatal PE[a]	No	9/1758 (0.5)	8/1747 (0.5)	0.9789
	Yes	14/795 (1.8)	13/807 (1.6)	
DVT[a]	No	36/1758 (2.0)	29/1747 (1.7)	0.4299
	Yes	7/795 (0.9)	9/807 (1.1)	
PE (fatal or non-fatal)[a]	No	11/1758 (0.6)	10/1747 (0.6)	0.9040
	Yes	16/795 (2.0)	16/807 (2.0)	
MBE[b]	No	20/1697 (1.2)	32/1694 (1.9)	0.7598
	Yes	4/759 (0.5)	8/768 (1.0)	
MBE/CRBE[b]	No	73/1697 (4.3)	134/1694 (7.9)	0.4243
	Yes	36/759 (4.7)	55/768 (7.2)	
Any bleeding[b]	No	230/1697 (13.6)	328/1694 (19.4)	0.9629
	Yes	124/759 (16.3)	175/768 (22.8)	

[a]Until the end of the post-treatment period. [b]During the double-dummy period. CRBE, clinically relevant non-major bleeding event; DVT, deep-vein thrombosis; MBE, major bleeding event; PE, pulmonary embolism; VTE, venous thromboembolism.

Study outcomes

Outcomes were centrally adjudicated. The primary efficacy outcome was recurrent, symptomatic, objectively confirmed VTE or VTE-related death, from the time of randomisation (i.e. start of parenteral therapy plus either warfarin or warfarin-placebo) to the end of the pre-specified post-treatment follow-up (6 months + 30 days). Safety outcomes included assessment of major bleeding events (MBEs), the composite of MBEs or clinically relevant non-major bleeding events (CRBEs), and any bleeds. In this analysis, bleeding events were assessed from the start of the six-month double-dummy period (treatment with oral dabigatran or warfarin alone) until the end of the six-month treatment period. Thus, the safety analysis excludes events associated with parenteral therapy either in combination with warfarin or with warfarin-placebo prior to commencing dabigatran treatment, and compares dabigatran with warfarin at their full pharmacological effect.

Statistical analyses

The population for efficacy analysis consisted of patients who were randomised and received at least one dose of study medication. The safety analysis set consisted of patients who received dabigatran or warfarin during the six-month double-dummy, oral-only treatment period. Patients were categorised into two subgroups according to their qualifying event for study entry (index event), i.e. as symptomatic PE (occurring with or without symptomatic DVT), or no symptomatic PE (for those with symptomatic DVT only or with neither symptomatic PE nor symptomatic DVT being objectively confirmed). The hazard ratios (HRs) and 95% confidence intervals (CIs) for within-subgroup treatment comparisons were based on the Cox regression analysis model, stratified by study. P-values for treatment/subgroup interaction were from the Cox model, stratified by study, with treatment and subgroup as main factors. Statistical analyses were performed with SAS® version 9.2 (Cary, NC, USA). The study was approved by the ethics committee or institutional review board in all jurisdictions, and patients provided written consent.

Results

Patients

The pooled dataset for the efficacy analysis consisted of 2553 and 2554 patients who were randomised to dabigatran and warfarin, respectively, and received at least one dose of study medication (3). The safety analysis for bleeding events included 2456 and 2462 patients who received dabigatran and warfarin, respectively, during the six-month double-dummy oral-only treatment period. 31.4% of patients (31.1% of the dabigatran group and 31.6% of the war-

farin group) in the pooled dataset had symptomatic PE as their index event (▶Table 1). Of patients with PE as the index event, 71% had symptomatic PE alone; the remainder had symptomatic PE with DVT.

Patient characteristics were mostly similar across patients with PE and those with DVT alone as the index event, and across treatment groups (▶Table 2). However, among those with PE as the index event, there was a higher proportion of women, a higher prevalence of risk factors for VTE recurrence (thrombophilia, recent prolonged immobilisation), and a lower proportion of current smokers.

Total mean duration of treatment with study medication was similar between subgroups with PE and with DVT alone as the index

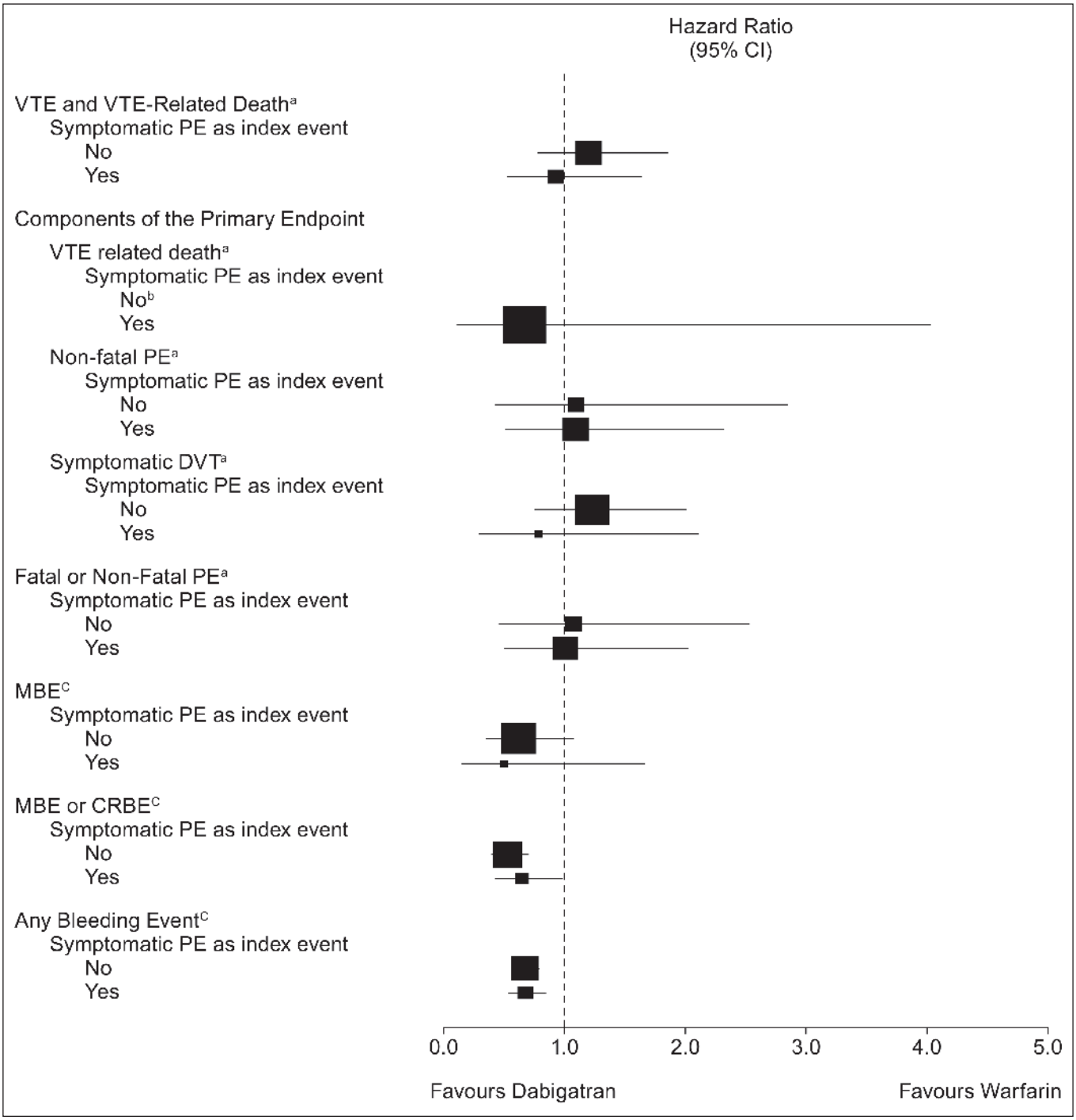

Figure 1: Forest plot of efficacy and safety outcomes by treatment group and index event. [a]Until the end of the post-treatment period. [b]During the double-dummy period. CRBE, clinically relevant non-major bleeding event; DVT, deep-vein thrombosis; HR, hazard ratio; MBE, major bleeding event; PE, pulmonary embolism; VTE, venous thromboembolism.

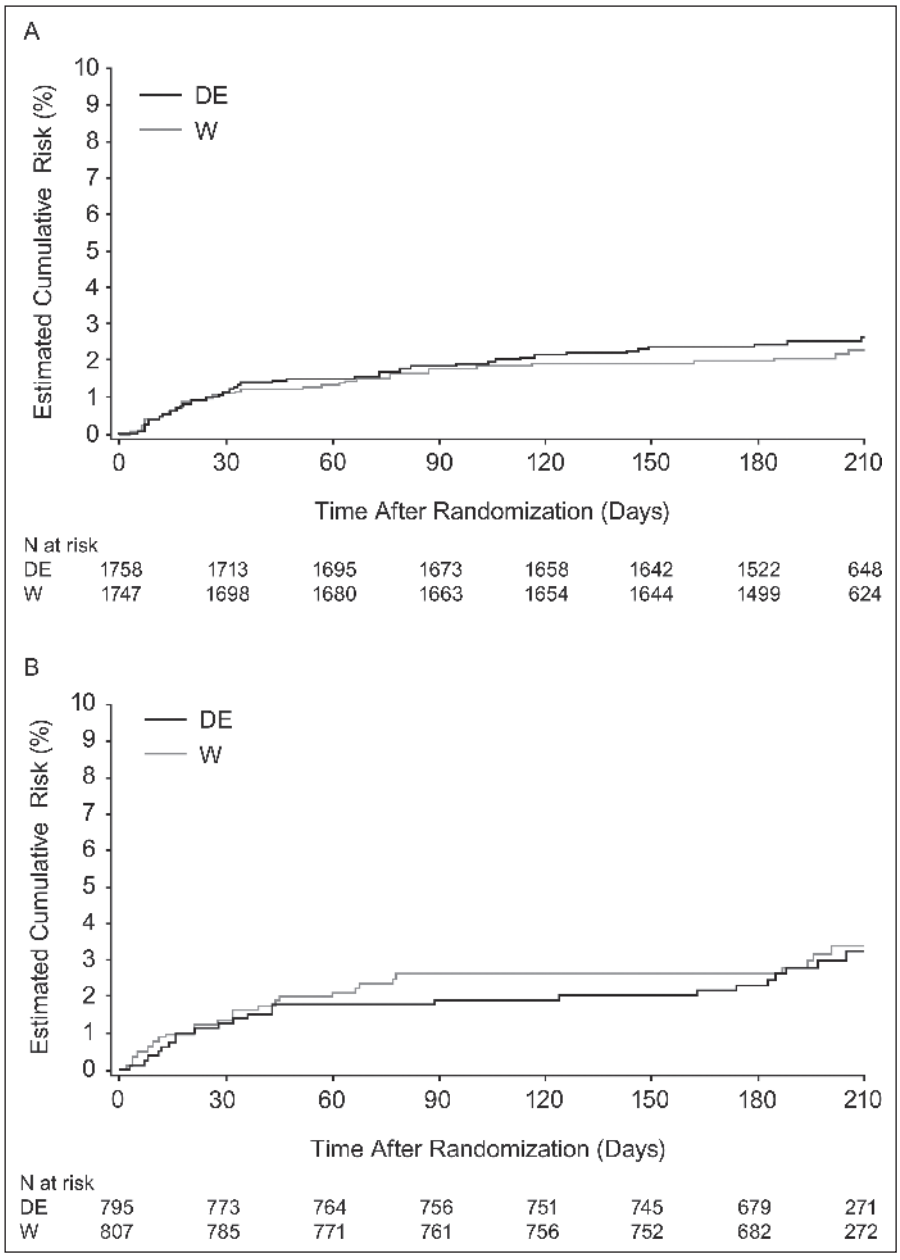

Figure 2: Kaplan–Meier cumulative event rates for VTE and VTE-related death until the end of post-treatment period with dabigatran and warfarin, in patients with (A) symptomatic DVT alone and with (B) symptomatic PE at baseline. DVT, deep-vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

event, in both treatment groups (162–164 days). The mean time from index event symptoms to randomisation was 6.1 days among patients with index PE and 7.6 days in those with index DVT.

Efficacy outcomes

In the overall pooled population, recurrent VTE/VTE-related death during the study period and additional 30-day follow-up occurred in 2.7% of all patients on dabigatran and in 2.4% on warfarin (HR 1.09 [95% CI 0.77, 1.54]). In patients with baseline DVT alone, with dabigatran vs warfarin, recurrent VTE/VTE-related death occurred in 2.6% vs 2.1% of patients (HR 1.20 [0.78, 1.86]). In patients with PE as their index event, recurrent VTE/VTE-related death occurred in 2.9% vs 3.1% of patients (HR 0.93 [0.53, 1.64]) (►Table 3, ►Figure 1). Cox regression analyses showed no statistically significant interaction (P = 0.48), indicating similar treatment effects regardless of index event (►Table 3). There were also no significant differences in rates of PE (fatal or non-fatal), for dabigatran vs warfarin-treated patients, regardless of the index event (►Table 3, ►Figure 1). Cox regression analyses again showed no statistically significant interactions (►Table 3). Recurrent PE (fatal or non-fatal) was more frequent in patients with PE vs those with DVT alone as an index event (occurring in 2.0% vs 0.6% of patients), irrespective of treatment (►Table 3). ►Figure 2 shows cumulative event rates for VTE and VTE-related death with dabigatran and warfarin, in patients with PE and with DVT alone as their index event. ►Figure 3 shows cumulative event rates for PE in the same format. Additional analyses do not indicate any

sex-related efficacy or safety differences in patients treated with dabigatran compared with warfarin.

Safety outcomes

In the overall population, there were significantly fewer MBEs in patients treated with dabigatran than with warfarin (HR 0.60 [0.36, 0.99]). The pattern was similar, although without statistically significant differences, both in patients with PE and in those with DVT alone as the index event. MBEs with dabigatran vs warfarin in patients with baseline DVT alone occurred in 1.2% vs 1.9% of patients (HR 0.62 [0.35, 1.08]). In patients with baseline PE, MBEs occurred in 0.5% vs 1.0% of dabigatran vs warfarin patients, respectively (HR 0.50 [0.15, 1.67]) (►Table 3). MBE/CRBEs and any bleeds were significantly less frequent with dabigatran than with warfarin in patients with PE as well as those with DVT alone as the index event (►Table 3). Cox regression analyses showed no statistically significant treatment-by-index-event interaction for any of these bleeding endpoints, indicating a similar pattern of treatment effects for dabigatran vs warfarin, regardless of the index event (►Table 3).

Discussion

These analyses of the pooled dataset from the RE-COVER and RE-COVER II trials indicate that dabigatran is as effective as war-

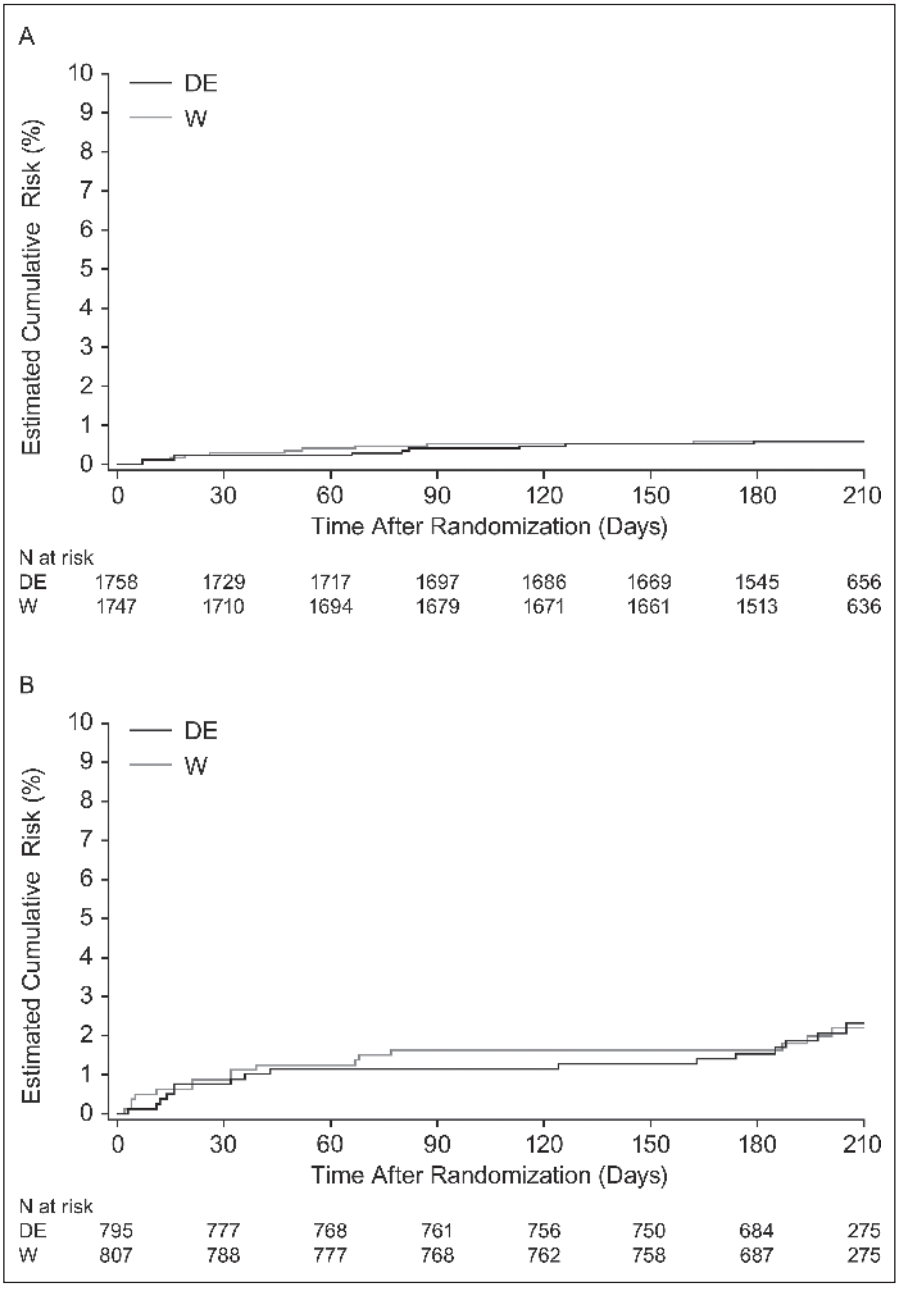

Figure 3: Kaplan–Meier cumulative event rates for centrally adjudicated PE until the end of post-treatment period with dabigatran and warfarin, in patients with (A) symptomatic DVT alone and with (B) symptomatic PE at baseline. DVT, deep-vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

farin in preventing recurrent VTE, regardless of whether patients present with symptomatic PE (with or without DVT) or with symptomatic DVT alone. The overall risk of VTE recurrence and/or VTE-related death was higher in patients who presented with PE compared with those with DVT alone, regardless of treatment. Furthermore, patients with PE at baseline were three times more likely to suffer recurrent PE than those with baseline DVT alone (2.0% vs 0.6% of patients). Likewise, patients with DVT at baseline were twice as likely to suffer recurrent DVT as those who had PE at baseline (1.9% vs 1% for the combined treatment groups). These findings are consistent with data from a patient-level meta-analysis of seven prospective studies in patients with a first acute VTE (4).

Dabigatran was also associated with a lower risk of bleeding than warfarin, regardless of the index event. MBEs showed a similar pattern of results with dabigatran vs warfarin in patients both with PE and with baseline DVT alone, although this did not reach statistical significance. However, in the total pooled dataset (not stratified by index event), the lower risk of MBEs with dabigatran vs warfarin was statistically significant: 1.0% vs 1.6% (HR 0.60 [0.36, 0.99]) (3). The risk reduction with dabigatran vs warfarin was significant for MBEs/CRBEs: 4.3% vs 7.9% in patients with baseline DVT alone (HR 0.53 [0.40, 0.70]) and 4.7% vs 7.2% in patients with baseline PE (HR 0.65 [0.43, 0.99]). The incidence of any bleeding was also significantly lower in the dabigatran than in the warfarin groups, irrespective of the index event.

In our dataset, patients with PE represented one-third of the overall study population, which reflects the epidemiology of VTE (5). By pooling data from RE-COVER and RE-COVER II, we included 1600 patients with PE in our pre-specified analysis, thus increasing the statistical power to evaluate efficacy and safety.

Rivaroxaban is the only novel oral anticoagulant that was compared with warfarin in a large-scale trial of patient presenting exclusively with symptomatic acute PE (6). There were no significant differences between rivaroxaban and warfarin either for recurrent VTE or for MBEs/CRBEs, although the risk of MBEs was lower with rivaroxaban (1.1%) compared with warfarin (2.2%). Edoxaban in HOKUSAI-VTE (7) and apixaban in AMPLIFY (8) were non-inferior compared with warfarin for the efficacy endpoint of preventing recurrent VTE. In these latter trials, bleeding event rates were lower with the novel agents compared with warfarin.

There are limitations to these analyses. Information on the extent of PE was not collected from investigators at baseline. Patents with very extensive PE might have been excluded by investigators. Strengths of these analyses include the double-blind, double-dummy design. Furthermore, the two protocols were virtually identical, and RECOVER II replicated the results of RECOVER. Both trials had pre-specified stratification and analysis according to presence or absence of symptomatic PE at baseline.

Conclusions

Our findings support the use of dabigatran as a fixed-dose oral anticoagulant regimen for patients presenting with symptomatic acute PE. Dabigatran had a lower risk of bleeding compared with warfarin, regardless of whether patients initially presented with symptomatic PE or DVT.

What is known about this topic?

- Dabigatran is noninferior to warfarin for prevention of recurrent venous thromboembolism (VTE).
- Dabigatran has a lower rate of bleeding than warfarin when used to prevent recurrent VTE.

What does this paper add?

- Dabigatran is as effective as warfarin regardless of whether patients present with symptomatic pulmonary embolism (PE) (with or without deep-vein thrombosis [DVT]) or with symptomatic DVT alone.
- The overall risk of VTE recurrence was higher in patients who presented with PE compared with those with DVT alone, regardless of whether they received dabigatran or warfarin.
- Patients with PE at baseline were three times more likely to suffer recurrent PE than those with baseline DVT alone.

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Conflicts of interest

Samuel Z. Goldhaber receives honoraria for consulting activities from Bayer, Boehringer-Ingelheim, BMS, Daiichi, Janssen, Novartis, and Portola. Dr. Goldhaber receives research support from BiO2 Medical, Boehringer-Ingelheim, BMS, BTG EKOS, Daiichi, National Heart Lung and Blood Institute of the National Institutes of Health, Janssen, and the Thrombosis Research Institute. Henry Eriksson, MD receives honoraria for lecturing and consulting activities ffrom Boehringer-Ingelheim, Bayer, Phizer, and LeoPharma. Ajay Kakkar, MD receives honoraria for consulting activities from Boehringer Ingelheim, Bayer, Jansen, Daiichi Sankyo, and Sanofi. Dr. Kakkar receives research support from Bayer. Sebastian Schellong, MD receives honoraria for lecturing and for consulting activities from Boehringer Ingelheim, Bayer, Bayer Health Care, BMS, Daiichi Sankyo, and Pfizer. Martin Feuring is employed by Boehringer Ingelheim. Joerg Kreuzer is employed by Boehringer Ingelheim. Mandy Fraessdorf is employed by Boehringer Ingelheim. Sam Schulman, MD receives honoraria for consulting activities from Boehringer Ingelheim, Bayer, Daiichi, Bristol- Myers-Squibb, and research grants from Boehringer Ingelheim, Baxalta, and Octapharma.

References

1. Office of the Surgeon General (US) and National Heart LaBIU. The Surgeon General's Call to Action to Prevent Deep Vein Thrombosis and Pulmonary Embolism. Available at: http://www.ncbi.nlm.nih.gov/books/NBK44178/. Accessed November 13, 2015.
2. Schulman S, Kearon C, Kakkar AK, et al. Dabigatran vs warfarin in the treatment of acute venous thromboembolism. N Engl J Med 2009; 361: 2342–2352.
3. Schulman S, Kakkar AK, Goldhaber SZ, et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. Circulation 2014; 129: 764–772.
4. Baglin T, Douketis J, Tosetto A, et al. Does the clinical presentation and extent of venous thrombosis predict likelihood and type of recurrence? A patient-level meta-analysis. J Thromb Haemost 2010; 8: 2436–2442.
5. White RH. The epidemiology of venous thromboembolism. Circulation 2003; 107: I4-I8.
6. Buller HR, Prins MH, Lensin AW, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med 2012; 366: 1287–1297.
7. Buller HR, Decousus H, Grosso MA, et al. Edoxaban vs warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med 2013; 369: 1406–1415.
8. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med 2013; 369: 799–808.

