Treatment Efficacy and Risk of Bleeding Among Cancer Patients Treated for Venous Thromboembolism with Dabigatran Compared to Warfarin

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Abstract

Introduction: The special needs of cancer patients offer unique challenges in treating them for venous thromboembolism (VTE). Dabigatran is a novel oral anticoagulant (NOAC) that may be comparable to warfarin in clinical benefit and risks of bleeding. A meta-analysis and systematic review was performed to compare efficacy of prevention of VTE recurrence and risks of bleeding with dabigatran compared to warfarin.

Methods: Randomized-controlled trials (RCTs) from various sources comparing dabigatran with warfarin for the prevention of recurrence of VTE were then retrieved and analyzed. The efficacy outcomes looked into was recurrence of VTE and mortality related to VTE while the primary safety outcome looked into was major bleeding.

Results: This meta-analysis, which included the studies, RECOVER I, RECOVER II, REMEDY showed that VTE and VTE-related deaths occurred in six out of 174 (3.4%) of cancer patients treated with dabigatran while four out of 166 (3.6%) cancer patients treated with warfarin with a relative risk of 1.44 with a 95% CI of 0.41, 5.03 showing no significant difference between dabigatran and warfarin.

The REMEDY trial included a total of 60 cancer patients from a total of 1,430 patients in the dabigatran group versus 59 cancer patients from a total of 1,426 patients in the warfarin group. Under the outcome of major bleeding event, among all patients who received dabigatran, 13 patients had major bleeding events, while among those who received warfarin, 25 patients had major bleeding events with a hazard ratio of 0.52 and 95% CI of 0.27-1.02. With the RECOVER I, and RECOVER II, among cancer patients analysed, four patients of the 105 who received dabigatran had major bleeding; while three of the 100 patients who received warfarin had major bleeding with a HR of 1.23 (95% CI of 0.28-5.5).

Conclusion: The authors conclude that dabigatran is comparable to warfarin in the prevention of recurrence of VTE among cancer patients in terms of both benefits and risks.

Keywords: venous thromboembolism, novel oral anticoagulant, cancer

Introduction

Cancer patients are at increased risk for venous thromboembolism (VTE) due to multiple inter-related factors: hypercoagulability, debilitation, altered endothelium.[1] Cancer patients with VTE are also at increased risk of recurrent VTE despite treatment. Cancer patients pose a special therapeutic dilemma regarding risk-benefit interplay of the benefits of anticoagulation for deep venous thromboses (DVT) prophylaxis against the risks of bleeding. The current guidelines recommend treating VTE initially with low molecular weight heparin (LMWH) followed with overlap with warfarin.[2] LMWH, warfarin, and vena cava filters are among those recommended for the treatment of VTE recurrence[3] warfarin's clinical benefit has already been established through years of clinical practice and clinical studies. However, warfarin has a narrow therapeutic window, numerous food and drug interactions, and treatment requires regular laboratory monitoring and dose adjustment. LMWH requires multiple and regular subcutaneous injections.

The comparable efficacy and safety of novel oral anticoagulants (NOACs): dabigatran, rivaroxaban, apixaban, edoxaban versus LMWH and warfarin has already been established through several meta-analyses[4,5,6] and reviews.[7,8] The National Comprehensive Cancer Network (NCCN) has maintained the use of both LMWH and warfarin for VTE prophylaxis.[9] However, the same guidelines highlighted the potential benefits in the use of NOACs in the treatment and prophylaxis for VTE.[9] Rivaroxaban and apixaban,[10,11,12,13] in non-inferiority trials, has demonstrated comparable effects with warfarin in terms of VTE treatment and prophylaxis.

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Dabigatran is a novel oral anticoagulant recommended for VTE treatment and prophylaxis.[2] It is administered at a fixed dose with no need for laboratory monitoring making it less cumbersome especially for the cancer patient. However, guidelines have yet to establish or recommend its role in VTE prophylaxis[3] due in part to inadequate studies. NOACs offer the potential of comparable efficacy and risks of bleeding without the complications posed by the administration of warfarin or LMWH.

The authors performed a meta-analysis and systematic review to analyze the clinical benefits and risks associated with dabigatran compared to warfarin among cancer patients in the prevention of VTE.

Methods

The objectives of this meta-analysis is to evaluate the effectivity of dabigatran in the treatment of DVT and VTE among cancer patients in terms of preventing recurrence of VTE and preventing related deaths and to evaluate the risks of bleeding with dabigatran compared to warfarin.

A meta-analysis of relevant RCTs comparing the effects of dabigatran and warfarin in the treatment of patients with DVT or VTE was undertaken. The Pubmed and Cochrane database was searched using the following key terms: "Randomized controlled trial"; "Adult cancer patients with VTE"; "dabigatran versus warfarin" ; "Recurrence of VTE and/or related death; and risks of bleeding."

The researchers followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) for reporting of the studies retrieved and analyzed for this meta-analysis and systematic review of RCTs. For a study to be included, it should fulfill the following inclusion criteria: types of studies: RCTs; types of participants: adult cancer patients with VTE; types of interventions: dabigatran versus warfarin; types of outcome measures: recurrence of VTE and/or related death; and risks of bleeding.

Pubmed was searched for relevant articles using the key terms; population (cancer patients with VTE or deep venous thromboses (DVT)), Intervention (dabigatran and warfarin), outcome (treatment of VTE, DVT), and method (RCT). The search terms were inputted in the "advanced search page" of Pubmed, and there were three articles that were retrieved. None of which were articles that are relevant to the objectives.

However, the three articles were inconsistent with citations found in the review of literature and prior readings of the co-authors. Most articles included adult patients as their primary study population and only had cancer as a subgroup. This observation suggests to this meta-analysis's significance in terms of its potential to aid in the care of this under-studied group. Cancer as a search term was then removed from the search strategy to broaden the search.

The search terms were then: ((((deep vein thrombosis) OR venous thromboembolism)) AND randomized controlled trial) AND warfarin) AND dabigatran.

Search details were as follows: ((((“venous thrombosis”(MeSH Terms) OR (“venous”(All Fields) AND “thrombosis”(All Fields)) OR “venous thrombosis”(All Fields) OR (“deep”(All Fields) AND “vein”(All Fields) AND “thrombosis”(All Fields)) OR “deep vein thrombosis”(All Fields)) OR (“venous thromboembolism”(MeSH Terms) OR (“venous”(All Fields) AND “thromboembolism”(All Fields)) OR “venous thromboembolism”(All Fields))) AND (“dabigatran”(Supplementary Concept) OR “dabigatran”(All Fields))) AND (“warfarin”(MeSH Terms) OR “warfarin”(All Fields))) AND (“randomized controlled trial”(Publication Type) OR “randomized controlled trials as topic”(MeSH Terms) OR “randomized controlled trial”(All Fields) OR “randomised controlled trial”(All Fields))

The above search strategy yielded 36 articles. All the 36 articles' abstracts were then retrieved and reviewed by two of the co-authors independently. Upon independent review of the 36 articles, seven articles were acceptable for both co-authors. No articles were contested for inclusion. Figure 1 shows the PRISMA for the search method.

Reasons for exclusion of the 26 articles: 10 articles were merely reviews; five articles had different outcomes of interest; five articles had different intervention of interest; while six articles had a different population group.

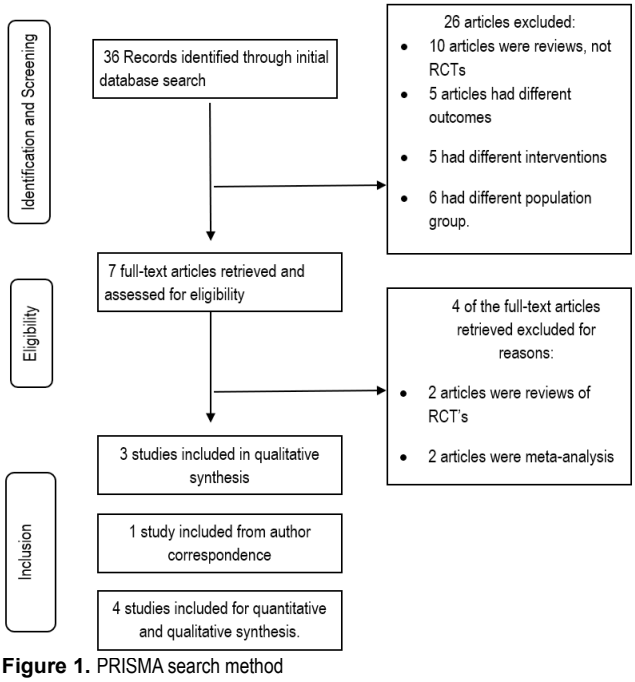

Figure 1. PRISMA search method

Table I Characteristics of the selected trials

Trials	Trial design	Intervention	Control	Total population/Cancer	Follow-up
RECOVER I	Randomized, double-blind, noninferiority trial	Dabigatran 150mg twice daily	Warfarin (INR 2.0-3.0)	2539/121	6 months + 30 days after treatment completion
RECOVER II	Randomized, double-blind, noninferiority trial	Dabigatran 150mg twice daily	Warfarin (INR 2.0-3.0)	2568/100	6 months + 30 days after treatment completion
REMEDY	Randomized, double-blind, noninferiority trial	Dabigatran 150mg twice daily	Warfarin (INR 2.0-3.0)	2737/119	18 months, extended to 36 months
RECOVER I + RECOVER II (cancer subset analysis)	N/A	Dabigatran 150mg twice daily	Warfarin (INR 2.0-3.0)	5107/221	N/A

Table II. Risks of bias of the selected trials

Trials	Selection bias	Performance bias	Attrition Bias	Detection bias
RECOVER I	Low	Low	Low	Low
RECOVER II	Low	Low	Low	Low
REMEDY	Low	Low	Low	Low

None of the seven articles that were included had cancer patients as their primary study population. One of the seven articles was merely a review/commentary of the REMEDY/RESONATE trial, a trial which in itself is included among the above seven articles. One article is a systematic review of the literature of phase three clinical trials.[8] Three articles were meta-analyses of randomized controlled trials. These two articles were included because the authors hoped to include an extensive search for randomized controlled trials, possibly some of which may have not been published but are included among the RCT's studied in these meta-analyses.[6,15]

Three of the seven articles[16,17,18] were RCTs comparing dabigatran and warfarin for the treatment of VTE. None of the three articles included cancer patients as their primary study population. However, on review of these articles, the authors mentioned including cancer patients in their study but no separate analysis of cancer patients was mentioned.

Correspondence between the author was pursued. To which the author promptly provided us with supplementary appendices of the three articles, which included a separate analysis for the subgroup of cancer patients. (Appendix) The supplementary appendices only included the analysis for their primary outcome (VTE recurrence and related death), however, and did not include rates of events for bleeding risk.

Although there were only three articles included, the databases were exhausted in the search for related studies with the intention of including as many significant studies as possible. The author provided us also with a copy of a fourth article[9] which included a more comprehensive analysis of the subgroup of cancer patients for the RECOVER and RECOVER II trials including risks of bleeding.

Study validity was then assessed using a pre-defined validity questionnaire. This was accomplished by two investigators independently. The efficacy outcome was recurrence of VTE and VTE-related death. The safety outcome was major and clinically relevant bleeding. Data analyses of the retrieved and chosen articles was done using RevMan software. Heterogeneity was measured with the I^2 test.

Results

A total of four studies[16,17,18,19] were included for final analysis. These are RECOVER I[16], RECOVER II[19], cancer subset analysis for both RECOVER I and RECOVER II[17], and REMEDY trial.[18] All the studies were RCTs comparing dabigatran versus warfarin evaluating treatment of VTE, prevention of recurrence, and risks of bleeding. None of three main studies (RECOVER I, RECOVER II, REMEDY), however, used cancer patients as the main study population, however, a subset analysis of cancer patients were done in all three studies. All three studies were non-inferiority trials. The fourth study was an analysis of the cancer patient subset of both RECOVER I and RECOVER II studies.[19] A summary of the characteristics of the included trials are summarized in Table I. Risks of bias were assessed by two investigators independent of one another. After independent assessment, conflicting views were then re-evaluated by all authors of this study. Risks of bias were described (excluding the cancer patients subset analysis study) is described in Table II.

The inclusion, exclusion criteria, outcome measures including primary benefit effect and risks are described in Table III. All three studies measured multiple benefit and safety outcomes. However, this meta-analysis analyzed only the primary outcome: VTE or related death as the primary benefit end-point; and major bleeding as the primary safety end-point.

The primary benefit end-point was VTE or VTE related deaths. This occurred in six of 174 (3.4%) cancer patients who received dabigatran, and four out of 166 (3.6%) cancer patients who received warfarin with a relative risk of 1.44 with a 95% CI of 0.41, 5.03 showing no significant difference between dabigatran and warfarin. The Table IV shows the number of

Table III. Inclusion criteria, exclusion criteria, benefit and safety outcomes of studies used for review

Trials	Inclusion criteria	Exclusion criteria	Benefit outcome	Risk outcome
"RECOVER I"	18 years of age or older who had acute, symptomatic, objectively verified proximal deep-vein thrombosis of the legs or pulmonary embolism and for whom six months of anticoagulant therapy was considered to be an appropriate treatment. Written informed consent	• Symptoms longer than 14 days • Pulmonary embolism with hemodynamic instability or requiring thrombolytic therapy • Another indication for warfarin therapy • recent unstable cardiovascular disease • High risk of bleeding • Liver disease • creatinine clearance of less than 30 Ml per minute • life expectancy of less than six months • Pregnancy or risk of becoming pregnant • Requirement for long-term antiplatelet therapy	Primary end point of venous thromboembolism or related death Secondary end point: symptomatic deep vein thrombosis; symptomatic nonfatal pulmonary embolism; death related to pulmonary embolism	Major bleeding event: fatal event; bleeding into critical organs; fall in hemoglobin level or need for blood transfusion. Any bleeding event
"RECOVER II" Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis	same as above	same as above	same as above	same as above
"REMEDY" Extended use of dabigatran, warfarin, or placebo in venous thromboembolism	Objectively confirmed symptomatic uni- or bilateral deep vein thrombosis (DVT) of the leginvolving proximal veins or pulmonary embolism (PE), treated with approved anticoagulanttherapy, or with study drug (in the placebo-control study previous study drug was introduced asan amendment), taken for (active-control study) three to six months or (placebo-control study) six to18 months at the time of screening Male or female, being 18 years of age or older Written informed consent	• Symptomatic DVT or PE at screening • Patients with primary PE with suspected origin other than leg, limbs • Actual or anticipated use of vena cava filter • Interruption of anticoagulant therapy for two or more weeks during the three to six months for the prior venous thromboembolism • Patients whoe in the investigator's opinion should not be treated with warfarin • Allergy to warfarin or dabigatran • Patients with excessive risk of bleeding • Known anemia • Need of anticoagulant treatment for other disorders • Recent unstable cardiovascular disease • Pregnancy or risk of becoming pregnant	Primary efficacy outcome, recurrent symptomatic and objectively verified VTE or death associated with VTE	Major bleeding: bleeding was defined as major if it was clinically overt and associated with a fall of the hemoglobin level of 20g/L or required transfusion of at least 2 units of red cells or, involved a critical organ or was fatal. Clinically relevant non-major bleeding:

Table IV. Benefit outcomes among cancer patients

Trials	Dabigatran treatment (%)	Warfarin treatment (%)
RECOVER I	2/64 (3.1%)	3/57 (5.3%)
RECOVER II	2/50 (4%)	2/50 (4%)
REMEDY	2/60 (3.3%)	1/59 (1.7%)
Total	6/174 (3.4%)	6/166 (3.6%)

Table V. Major bleeding and major or clinically relevant bleeding in the REMEDY trial

Intervention (Total population/ cancer population)	Major bleeding (%)	Major or clinically relevant bleeding (%)
Dabigatran (1430/60)	13 (0.9%)	80 (5.5%)
Warfarin (1426/59)	25 (1.7%)	145 (10.2%)
Hazard ratio (95% CI)	0.52 (0.27-1.02)	0.71 (0.41 – 0.73)

Table VI. Major bleeding events in both the RECOVER I and RECOVER II trials

	Major bleeding events (event/total and %)	Major bleeding events among cancer patients (events/total and %)
Dabigatran	18/2297 (0.8%)	4/105 (3.8%)
Warfarin	33/2310 (1.4%)	3/100 (3%)
Hazard ratio (95% CI)		1.23 (0.28-5.5)

benefit outcomes among cancer patients for each trial. Figure 2 shows the forest plot for the benefit outcomes.

A meta-analysis could not be achieved with the safety outcome of risks of bleeding due to inadequate data for the cancer patient subgroup. The researchers could not retrieve the safety outcome data on the REMEDY trial despite having contacted the authors. There was no separate analysis for cancer patients in the REMEDY trial that looked into risks of bleeding hence only the bleeding events for the whole population were reviewed.

In this systematic review, the REMEDY trial included a total of 1,430 patients, 60 of which had cancer, in the dabigatran group versus 1,426 patients, 59 of which had cancer, in the warfarin group. Under the outcome of major bleeding event, among those who received dabigatran, 13 patients had major bleeding events, while among those who received warfarin, 25 patients had major bleeding events with a hazard ratio of 0.52 and 95% CI of 0.27-1.02. Major or clinically relevant bleeding events occurred in 80 patients among those who received dabigatran and 145 patients among those who received warfarin with a HR of 0.71 with a 95% CI of 0.41 to 0.73. (Table V)

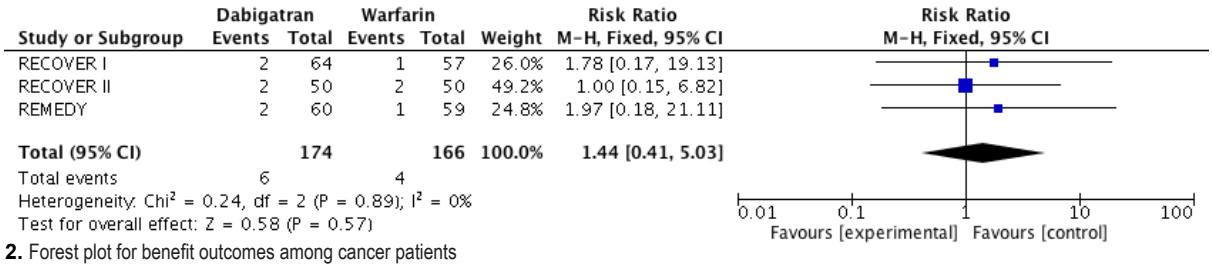

Figure 2. Forest plot for benefit outcomes among cancer patients

In a separate study, treatment with dabigatran or warfarin in patients with venous thromboembolism and cancer, conducted by the same authors of the RECOVER I and RECOVER II articles, the same authors of both trials did a sub-analysis of effects of dabigatran versus warfarin among the subgroup of cancer patients. For the total population of both the RECOVER I and RECOVER II studies, 18 of 2,297 patients who received dabigatran had major bleeding events; while 33 of 2,310 patients who received warfarin had major bleeding events. Among cancer patients analysed, four patients of the 105 who received dabigatran had major bleeding; while three of the 100 patients who received warfarin had major bleeding with a HR of 1.23 (95% CI of 0.28-5.5). (Table VI)

Discussion

In this meta-analysis, including three trials, the authors conclude that dabigatran is comparable to warfarin in the treatment of VTE with a relative risk of 1.44 with a 95% CI of 0.41, 5.03 in terms of efficacy in prevention of VTE and VTE related deaths.

The authors were not able to do a meta-analysis for the outcome risks of bleeding and instead the authors did a systematic review. In the systematic review to analyse risks of bleeding, the authors conclude that dabigatran is non-inferior to warfarin. The REMEDY trial shows superiority of dabigatran compared to warfarin for the entire population in terms of Major or Clinically relevant bleeding with a HR of 0.71 and 95% CI of 0.41–0.73. Both the RECOVER I and RECOVER II studies have shown that the dabigatran and W\ warfarin are equal in terms of risks of bleeding among cancer patients. The REMEDY trial did not do a separate analysis for the cancer population but still showed that dabigatran was comparable to warfarin in terms of risks of bleeding for the entire study population.

Conclusion

The authors conclude that dabigatran is comparable to warfarin in the treatment of VTE among cancer patients in terms of both benefits and risks. However, dabigatran may offer the benefit of fewer drug-to-drug interactions and lack of the need for regular therapeutic monitoring. Treatment of cancer patients involve multiple drugs predisposing them to drug-to-drug interactions. Cancer patients may also develop multiple nutritional problems owed to poor oral intake and chronic disease causing another cause for fluctuations in PT INR levels with warfarin use. Cancer patients are also prone to debilitation making frequent laboratory monitoring cumbersome.

The authors recommend further research on this field due to inadequate studies supporting use of NOACs for patients with malignancies. It is also the authors' recommendation to perform similar meta-analyses with other NOACs with the intention of corroborating whether or not findings are similar if not better with the other NOACs.

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