Effect of raloxifene therapy on venous thromboembolism in postmenopausal women: A meta-analysis

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Summary
Raloxifene, a selective estrogen receptor modulator, is indicated for the prevention of osteoporosis in postmenopausal women. However, its effect on the risk of deep venous thrombosis (DVT) and pulmonary embolism (PE) is unclear. Therefore, we conducted a meta-analysis to evaluate the effect of raloxifene on these outcomes. To identify randomized controlled trials of raloxifene, a systematic search of PubMed, EMBASE, and Cochrane Collaboration databases was performed from the date of inception of these databases to October 2007. Search was limited to trials that were published in peer-reviewed English-language medical journals. Articles were included in the meta-analysis if they had reported on DVT, PE, or thromboembolic events. Nine trials, including 24,523 postmenopausal women, (median age 59.4 years, range 55 to 67 years; median follow-up 24 months, range 3 to 67 months) met inclusion criteria. Therapy with raloxifene was associated with a 62% increase in odds of either DVT or PE (odds ratio = 1.62; 95% confidence interval = 1.25 to 2.09; p-value < 0.001). Similarly, raloxifene therapy was associated with 54% increase in odds of DVT (odds ratio = 1.54; 95% confidence interval = 1.13 to 2.11; p-value = 0.006) and 91% increase in odds of PE alone (odds ratio = 1.91; 95% confidence interval = 1.05 to 3.47; p-value = 0.03). Raloxifene increases the risk of DVT and PE in postmenopausal women.

Keywords
Raloxifene, deep venous thrombosis, pulmonary embolism, venous thromboembolism

Introduction
Raloxifene, a selective estrogen receptor modulator, is approved in United States for the prevention of osteoporosis in postmenopausal women. Raloxifene functions as estrogen receptor agonist or antagonist in a tissue-specific fashion (1). Acting as an estrogen receptor agonist on bone, raloxifene prevents osteoporosis while acting as estrogen receptor antagonist on breast tissue it decreases the risk of breast cancer (2, 3).

On coagulation pathways, raloxifene has varied effects with changes in the concentration of both pro-coagulant and anti-coagulant coagulation factors (4–6). Two large randomized clinical trials have found that the raloxifene has a pro-coagulant effect with an overall increase in risk of venous thromboembolism (7, 8). However, these trials did not find a significantly increased risk of pulmonary embolism (PE), the major complication of deep venous thrombosis (DVT). We, therefore, performed a meta-analysis of all randomized clinical trials of raloxifene to evaluate its effect on the risk of DVT and PE.

Methods
We performed a systematic search of PubMed, EMBASE, and the Cochrane Collaboration databases from inception of these databases to October 2007 using the search term raloxifene and limiting our search to randomized controlled trials published in English language peer-reviewed medical journals. To locate additional articles that may have been missed, references of the retrieved articles were hand-searched.

Two investigators (JA, MF) independently screened the retrieved articles for inclusion in the meta-analysis, and differences between the investigators were adjudicated by the third investigator. All clinical trials that randomized post-menopausal women to raloxifene or a control arm and presented data on PE, DVT and/or overall incidence of thromboembolism were included. Unless a study specifically mentioned PE, all events of thromboembolism were considered DVT.

At least two investigators independently extracted data from relevant articles on specific data extraction forms. Differences
between the investigators were resolved with mutual consensus. Data were abstracted on population characteristics, study design, and study outcomes. If a study had more than two arms, data from arms comparing raloxifene with placebo or no treatment were used while data from other arms were excluded from the analysis. If a study had more than one arm that received different doses of raloxifene, outcome from each arm was recorded separately as well as combined to pool data for analysis.

Random-effects model was used for pooling of the study results using the Cochrane Collaboration’s Review Manager Version 4.2 software (The Cochrane Collaboration 2003). As the commonly prescribed dose of raloxifene is 60 mg daily, we separately pooled results from the studies or arms of the studies in which this dose was used. Statistical significance was defined as a p-value of less than 0.05. Heterogeneity between the studies was evaluated with Cochran’s Q and I² index statistic. Publication bias was assessed visually by examination of the funnel plot and statistically by Egger’s regression method (9) and trim-and-fill method (10). Quality of the included studies was assessed descriptively as well as quantitatively with a validated scale by Jadad et al. (11). This scale scores studies on a scale of 0–5 with higher scores given to studies with better quality and uses three aspects of study design that are related to bias reduction namely randomization, blinding, and description of patient drop-outs.

Results

Our search strategy found nine clinical trials that were relevant for this meta-analysis (Fig. 1) (7, 8, 12–18). One trial (12) was continuation of another trial (7), but as the data were reported separately for both trials, we included them as separate trials. None of the trials were designed to evaluate the effect of raloxifene on DVT or PE. Median age of the population was 59.4 years (range 55 to 67 years) and median duration of follow-up was 24 months (range 3 to 67 months). All studies, except two (14, 16), enrolled women regardless of their hysterectomy status (Table 1). Most of the studies excluded participants with previous history of thromboembolism or malignancy. The dose of raloxifene used in clinical trials was 60 mg once daily except in one trial which had two different doses of raloxifene (60 mg and 120 mg daily) in two different arms (7). All trials were randomized, double blind, and placebo-controlled and the majority of these trials were multinational. Six trials used intention-to-treat analysis for reporting of results. Compliance to drug therapy was reported by all trials except one (15). Quality of reporting of trials according to the scale by Jadad et al. was adequate with all studies scoring 4 or above. All studies were funded by pharmaceutical companies (Table 2).

Of the 279 combined events of DVT or PE that occurred in 24,523 postmenopausal women, 189 occurred in the women randomized to raloxifene arm (Fig. 2). Pooling of data from all trials found a 62% increase in odds of either DVT or PE with raloxifene therapy (odds ratio [OR] = 1.62; 95% confidence interval [CI] = 1.25 to 2.09; p-value < 0.001). Raloxifene therapy was associated with a 54% increase in odds of DVT (OR = 1.54; 95% CI = 1.13 to 2.11; p-value = 0.006) and 91% increase in odds of PE alone (OR = 1.91; 95% CI = 1.05 to 3.47; p-value = 0.03). Similar results were obtained when data from the raloxifene 120 mg daily arm of MORE trial was excluded from the analysis. Therapy with raloxifene 60 mg daily was associated with increased risk of either DVT or PE (OR = 1.58; 95% CI = 1.22 to 2.06; p-value < 0.001), DVT alone (OR = 1.50; 95% CI = 1.09 to 2.05; p-value = 0.01), or PE alone (OR = 1.86; 95% CI = 1.04 to 3.33; p-value = 0.04).

Tests for heterogeneity did not find significant heterogeneity between the studies. Evaluation for publication bias found an asymmetrical funnel plot, however, imputing missing studies and re-calculating pooled odds ratio with the help of trim and fill method did not change the results of meta-analysis. Moreover, Egger’s regression method also failed to find the presence of sig-
significant publication bias.

Discussion

In this meta-analysis of randomized, double-blind, placebo-controlled, clinical trials, we have found that therapy with raloxifene is associated with an increased risk of DVT and PE. This pro-thrombotic effect of raloxifene is present at its currently used therapeutic doses. It is noteworthy that this increased risk was noted despite exclusion of women with history of thromboembolic disease from clinical trials.

Osteoporosis in postmenopausal women is associated with significant morbidity and mortality (19). Until recently hormone replacement therapy was one of the most commonly used treatments for its prevention. However, randomized clinical trials have found an increased risk of cardiovascular and thromboembolic events with hormone replacement therapy (20, 21). These findings have limited the use of hormone replacement therapy for the prevention of osteoporosis. In this setting raloxifene, which has tissue-specific estrogen receptor agonist or antagonist properties, appears to be a promising agent. In fact, a large randomized controlled trial did not find an increased risk of cardiovascular events with raloxifene therapy in postmenopausal women (8). In contrast, by pooling the results from several clinical trials in this meta-analysis, we have found that raloxifene is associated with a clinically significant increase in thromboembolic events which is comparable to hormone replacement therapy (22).

Although the overall effect of raloxifene is pro-thrombotic, the underlying mechanism of this pro-thrombotic effect is poorly understood. Raloxifene decreases the plasma concentration of fibrinogen thus potentially exerting an anticoagulant effect (4, 14, 23–26). It has no effect on the plasma concentrations of factor VIIa and factor IX (4–6, 14). On the other hand, raloxifene increases the concentration of factor VIII and tissue-type plasminogen activator and decreases the concentrations of antithrombin, protein C, protein S, and free tissue-factor pathway inhibitor (TFPI) thus exerting a pro-coagulant effect (4–6, 24, 25, 27). In another study, treatment with raloxifene was associated with decreased sensitivity to activated protein C although this decrease was less than with hormone replacement therapy (28).

Clinical studies have found conflicting effects of raloxifene on plasma concentration of PAI-1 and D-dimers with no effect in some studies while a decrease was seen in other studies (4, 6, 14, 21).

Table 1: Characteristics and quality of studies included in meta-analysis.

<table>
<thead>
<tr>
<th>Study ID/Year (Ref. no.)</th>
<th>Total (N)</th>
<th>Study population</th>
<th>Mean age (years)</th>
<th>Ethnicity (%)</th>
<th>Duration of treatment (months)</th>
<th>ITT analysis performed</th>
<th>Modified Jadad Scale Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>MORE 2002 (7)</td>
<td>7,705</td>
<td>2 or more years after menopause; with osteoporosis</td>
<td>66.5</td>
<td>White (95.7%)</td>
<td>48</td>
<td>yes</td>
<td>5</td>
</tr>
<tr>
<td>RUTH 2006 (8)</td>
<td>10,101</td>
<td>Older than 54 years; 1 or more years after menopause; at high risk of CVD</td>
<td>67.5</td>
<td>White (84%)</td>
<td>67</td>
<td>yes</td>
<td>4</td>
</tr>
<tr>
<td>Palacios 2004 (17)</td>
<td>487</td>
<td>Age between 45/75 years; 2 or more years menopause</td>
<td>58.2</td>
<td>NR</td>
<td>8</td>
<td>yes</td>
<td>5</td>
</tr>
<tr>
<td>Johnston 2000 (13)</td>
<td>1,145</td>
<td>Age between 45–75 years; 2–8 years after menopause</td>
<td>54.6</td>
<td>NR</td>
<td>36</td>
<td>yes</td>
<td>5</td>
</tr>
<tr>
<td>De Valk-De Roo 1999 (14)</td>
<td>56</td>
<td>Women with hysterectomy</td>
<td>54.8</td>
<td>NR</td>
<td>24</td>
<td>no</td>
<td>4</td>
</tr>
<tr>
<td>CORE 2004 (12)</td>
<td>4,011</td>
<td>2 or more years after menopause; with osteoporosis</td>
<td>65.8</td>
<td>White (96.2%)</td>
<td>48</td>
<td>yes</td>
<td>5</td>
</tr>
<tr>
<td>Reginster 2003 (18)</td>
<td>596</td>
<td>Age less than 73 years; 2 or more years after menopause; with osteoporosis</td>
<td>61.8</td>
<td>White (99.8%)</td>
<td>18</td>
<td>yes</td>
<td>4</td>
</tr>
<tr>
<td>McClung 2006 (15)</td>
<td>410</td>
<td>Age between 47 to 74; more than 1 year after menopause; with osteoporosis</td>
<td>58.0</td>
<td>NR</td>
<td>24</td>
<td>no</td>
<td>4</td>
</tr>
<tr>
<td>Kessel 2003 (16)</td>
<td>187</td>
<td>Age between 42 to 80 years; 2 or more years after menopause</td>
<td>59.4</td>
<td>White (90%)</td>
<td>3</td>
<td>no</td>
<td>5</td>
</tr>
</tbody>
</table>

CVD = cardiovascular disease; ITT = intention to treat; NR = not reported.
One study, that evaluated the effect of raloxifene on von Willebrand factor found an increase in its concentration. Whether raloxifene alters the concentration of these coagulation pathway proteins through altering transcription of their genes or altering the translation of their messenger RNA remains unclear. At least one study, treatment with raloxifene increased TFPI concentration in human endothelial cell cultures and this increase was independent of any effect on the transcription of TFPI gene (30).

This meta-analysis has several potential limitations. Although there was no significant heterogeneity between the studies, tests for heterogeneity are known for their low power (31). Therefore, we used a random-effects model for this meta-analysis which incorporates heterogeneity between studies while pooling the results for meta-analysis. We did find publication bias, but when the study results were adjusted for publication bias using a trim-and-fill method, results of the meta-analysis did not change. Another potential limitation is that we excluded clinical trials that were not published in peer-review medical journals. However, as such trials had not gone through the rigorous process of peer-review, it is difficult to ascertain their quality. We may have missed some relevant clinical trials by limiting our search to articles published in English language and to three electronic databases, although supplementing our electronic search with manual search should have mitigated this limitation to some extent. Finally, as all studies included in this meta-analysis were designed to assess endpoints other than thromboembolic events, misclassification and ascertainment errors are possible resulting in under-reporting of thromboembolic events. Only a more complete reporting of rare but serious adverse events in clinical trials can mitigate this problem.

In conclusion, raloxifene therapy in post-menopausal women is associated with increased risk of both DVT as well as PE. Therefore, raloxifene should be judiciously used for prevention

![Figure 2: Forrest plot of the meta-analysis.](image-url)
References


