Non-steroidal anti-inflammatory drugs and risk of venous thromboembolism: a systematic review and meta-analysis

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Abstract

Objective. The aim of this study was to integrate and examine the association between NSAID use and venous thromboembolism (VTE).

Methods. We conducted a systematic review and meta-analysis of studies that reported odds ratios, relative risks, hazard ratios or standardized incidence ratios for VTE among NSAID users compared with non-users. Pooled risk ratios and 95% CIs were calculated using a random effects generic inverse variance model.

Results. Six studies with 21 401 VTE events were identified and included in the data analysis. The pooled risk ratio of VTE in NSAID users was 1.80 (95% CI 1.28, 2.52).

Conclusion. Our study demonstrated a statistically significant increased risk of VTE among NSAID users. This finding has important public health implications given the prevalence of NSAID use in the general population.

Key words: systematic review, epidemiology, meta-analysis, NSAIDs, respiratory.

Introduction

Venous thromboembolism (VTE), which includes deep venous thrombosis (DVT) and pulmonary embolism (PE), is a common illness with a reported annual incidence of 1–2 new cases per 1000 population [1, 2]. Recognition of its risk factors and appropriate preventive interventions for this condition are crucial, as morbidity and mortality from PE are high, with a reported 30-day case fatality rate as high as 8–10% [1–3]. Several medical conditions, including immobilization, surgery, pregnancy and cancer, are recognized as risk factors for VTE.

NSAIDs, one of the most commonly used medications around the world [4], are well known for their potential adverse effects. For example, in the recent past, rofecoxib was withdrawn from the market after a randomized placebo-controlled trial found an increased incidence of myocardial infarction and sudden cardiac death among rofecoxib users [5]. A subsequent meta-analysis confirmed this finding and also found an increased incidence among other non-specific cyclooxygenase (COX) inhibitor users [6]. Since arterial and venous thrombosis share several pathophysiological mechanisms [7, 8], NSAIDs might increase the risk of VTE. However, the epidemiological data on VTE risk among NSAID users is limited and conflicting. Thus, to further investigate this association, we conducted a systematic review and meta-analysis of observational studies that compared the risk of VTE in NSAID users vs non-users. We did not include randomized controlled trials in this meta-analysis because VTE is a less common adverse effect that generally requires a larger sample size and a longer duration of follow-up.
Materials and methods

Search strategy

Two investigators (P.U. and N.S.) independently searched published studies indexed in Medline, Embase and the Cochrane database from inception to December 2013. The search terms were compiled from the names of individual drugs, the therapeutic class and the mode of action in conjunction with the terms pulmonary embolism, deep venous thrombosis and venous thromboembolism. The detailed search strategy is provided as supplementary material, available at Rheumatology Online. A manual search of the references of selected retrieved studies was also performed. Abstract and unpublished studies were not included.

Study selection

The inclusion criteria were as follows: (i) case-control or cohort studies published as original studies to evaluate the association between use of NSAIDs and risk of VTE; (ii) odds ratios (ORs), relative risks (RRs), hazard ratios (HRs) or standardized incidence ratios with 95% CIs were provided and (iii) random participants without VTE were used as the reference group for case-control studies and participants who did not use NSAIDs were used as the reference group for cohort studies. Study eligibility was independently determined by each investigator noted above. Any disagreements were resolved by consensus. The quality of the included studies was independently evaluated by each investigator using the Newcastle-Ottawa quality assessment scale [9]. Our search strategy yielded 597 potentially relevant articles. Five hundred and twenty-seven articles were excluded because they were not case-control or cohort studies. Seventy articles underwent full-length article review. Thirty-eight of these were excluded because they did not report the exposure of interest (use of NSAIDs), 35 were excluded because they did not report the outcome of interest (VTE) and 1 was excluded because it used the same database as was used by another study. Six studies (one cohort study and five case-control studies) with 21,401 VTE events met our eligibility criteria and were included in the analysis [10–15]. Fig. 1 outlines our search methodology and selection process. The detailed characteristics and quality assessment of these six studies are described in Tables 1 and 2.

Data extraction

A standardized data collection form was used to extract the following information: last name of the first author, title of the article, year of publication, country where the study was conducted, study size, study population, definition of NSAID exposure, verification of NSAID use, verification of VTE, confounder assessed and adjusted effect estimates with 95% CIs. The two investigators independently performed this data extraction.

Statistical analysis

Review Manager 5.2 software (Cochrane Collaboration, Oxford, UK) was used for the data analysis. We reported the pooled effect estimate of VTE using the combination of data from case-control and cohort analyses to increase the precision of our estimates. We used the ORs of case-control studies as an estimate of the RRs to pool these data with the RR of the cohort study, as the outcome of interest was relatively uncommon [16]. If the cohort study provided a HR, the HR was used as an estimate of the RR. Adjusted point estimates and standard errors were extracted from individual studies and were combined by the generic inverse variance method of DerSimonian and Laird [17]. Given the high likelihood of between-study variance with the different study designs, definitions of NSAID use and populations, we used a random effects model rather than a fixed effects model. All of the studies reported the VTE risk of all NSAIDs (non-selective and selective COX-2 inhibitors) use while three studies also provided data on the VTE risk of selective COX-2 inhibitors [13–15]. Pooled RRs were calculated for all NSAIDs and for selective COX-2 inhibitors. Statistical heterogeneity was assessed using Cochran’s Q test. This statistic was complemented with the I² statistic, which quantifies the proportion of total variation across studies that is due to heterogeneity rather than chance. A value of I² of 0–25% represents insignificant heterogeneity, 25–50% low heterogeneity, 50–75% moderate heterogeneity and 75–100% high heterogeneity [18]. This study was exempted from ethical approval by the institutional review board of the Bassett Medical Center, Cooperstown, NY, USA.

Results

Our meta-analysis demonstrated a statistically significantly increased VTE risk among subjects who used NSAIDs with a pooled risk ratio of 1.80 (95% CI 1.28, 2.52). The statistical heterogeneity was high, with an I² of 95%. Three studies reported a risk ratio for participants who used selective COX-2 inhibitors. The VTE risk among selective COX-2 inhibitor users was also significantly elevated, with a pooled risk ratio of 1.99 (95% CI 1.44–2.75). Figs. 2 and 3 present the forest plots of our findings.

Sensitivity analysis

With the concern over high heterogeneity, we performed jackknife sensitivity analysis by excluding one study at a time. The results of this sensitivity analysis suggested that our results were robust, as the pooled risk ratios remained significantly elevated, ranging from 1.62 to 2.21, while the corresponding 95% CI bounds remained >1.

Publication bias

Funnel plots to evaluate publication bias are shown in Fig. 4. The graph is asymmetric, suggesting that publication bias in favour of positive studies may be present.
Discussion

This is the first systematic review and meta-analysis of published observational studies assessing the risk of VTE among NSAID users. Our study demonstrates a significant association between NSAID use and VTE, with an overall 1.80-fold increased risk compared with subjects who did not use NSAIDs. VTE risk appears to be even higher among selective COX-2 inhibitor users, with a 1.99-fold increased risk, although the CI overlaps. The VTE risk found in this study is slightly higher than the coronary artery thrombosis risk seen in another meta-analysis (ranging from 0.96 to 1.36) [6]. With the widespread use of these medicines, this increased risk may have important public health implications.

Heterogeneity between studies was present in this meta-analysis. We suspect that differences in study design, definitions of NSAID exposure and population were the main source of heterogeneity. Three studies were done in hospitalized subjects [12, 13, 15] and three studies included both ambulatory and hospitalized subjects [10, 11, 14]. One study included only patients with PE [13], whereas the rest of the studies included patients with DVT and/or PE. The definition and method of verification for NSAID exposure also varied from study to study, with some studies using a pharmacology-linked

VTE: venous thromboembolism.
# Table 1: Main characteristics of case-control studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Cases</th>
<th>Case verification</th>
<th>Controls</th>
<th>Period of inclusion</th>
<th>Age range, years</th>
<th>Female, %</th>
<th>Cases, n</th>
<th>Controls, n</th>
<th>Definition of NSAID exposure</th>
<th>Verification of NSAIDs use</th>
<th>Confounder assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td>2007</td>
<td>Hospitalized or non-hospitalized patients who were diagnosed with DVT and/or PE identified from the General Practice Research Database, covering 3 million people</td>
<td>Patients needed to receive anticoagulant</td>
<td>Sex- and age-matched subjects randomly selected from same database</td>
<td>1994-2000</td>
<td>20-79</td>
<td>NA</td>
<td>6550</td>
<td>10000</td>
<td>Most recent prescription lasted until the index date or ended in the 30 days before the index date</td>
<td>Pharmacy record from the same database</td>
<td>Sex, age, BMI, smoking, fracture, surgery, cancer, visits to the family physician last year</td>
</tr>
<tr>
<td>France</td>
<td>2008</td>
<td>Patients who were admitted at the Brest University Hospital with a diagnosis of DVT and/or PE</td>
<td>NA</td>
<td>Sex- and age-matched hospitalized patients randomly selected from the same hospital</td>
<td>2000-2004</td>
<td>18-96</td>
<td>58.5</td>
<td>402</td>
<td>402</td>
<td>Current use of NSAIDs at the time of admission</td>
<td>Structured interview and validation from information provided by the National Health Service of France</td>
<td>None</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>2011</td>
<td>Hospitalized patients who were diagnosed with PE identified from the PHARMO record linkage system, covering 2 million people</td>
<td>Confirmed by CT or V/Q scan</td>
<td>Sex- and age- and region-matched subjects randomly selected from the same database</td>
<td>1990-2006</td>
<td>18-96</td>
<td>57.0</td>
<td>4433</td>
<td>16802</td>
<td>Most recent prescription lasted until the index date or ended in the 90 days before the index date</td>
<td>Pharmacy record from the same database</td>
<td>Hospitalization, pregnancy, fracture, surgery, cancer, diabetes, CAD, stroke, PVD, diabetes mellitus, RA, COPD, CHF, OA, obesity, medication, liver disease, renal failure, osteoporosis</td>
</tr>
<tr>
<td>Denmark</td>
<td>2013</td>
<td>Hospitalized or non-hospitalized patients who were diagnosed with DVT and/or PE identified from the Danish National Patient Registry</td>
<td>NA</td>
<td>Sex- and age-matched hospitalized patients randomly selected from the same database</td>
<td>1999-2006</td>
<td>53.7</td>
<td>83686</td>
<td>8218</td>
<td>1402</td>
<td>Most recent prescription lasted until the index date or ended in the 60 days before the index date</td>
<td>Structured phone interview</td>
<td>Hospitalization, pregnancy, fracture, surgery, cancer, diabetes, CAD, stroke, PVD, diabetes mellitus, RA, COPD, CHF, OA, obesity, medication, liver disease, renal failure, osteoporosis</td>
</tr>
<tr>
<td>Sweden</td>
<td>2013</td>
<td>Female patients who were admitted at one of the participating hospitals with a diagnosis of DVT and/or PE</td>
<td>Radiological evidence of VTE + patient needed to receive anticoagulants</td>
<td>Sex- and age-matched hospitalized patients randomly selected from the Swedish population register</td>
<td>2003-2009</td>
<td>18-64</td>
<td>100</td>
<td>1433</td>
<td>1402</td>
<td>Use of NSAIDs during the 90 days before the index date</td>
<td>Pharmacy record from the same database</td>
<td>Age</td>
</tr>
</tbody>
</table>

**NSAIDs and risk of VTE**

CAD: coronary artery disease; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; DVT: deep venous thrombosis; NA: not available; PE: pulmonary embolism; PHARMO: PHARMO Institute, Utrecht, The Netherlands; PVD: peripheral vascular disease; V/Q scan: ventilation-perfusion scan; VTE: venous thromboembolism.
database [10, 11, 13, 14], while other studies used a structured or phone interview [12, 15]. Controlling for confounders might also contribute to this heterogeneity, as it was done differently between studies, from virtually no correction to control for a large number of confounders. It should be noted that, from our sensitivity analysis, exclusion of the study by Bergendal et al. [15], the only study that exclusively included only female participants, noticeably decreased the statistical heterogeneity, with a reduction in $I^2$ from 95% to 78%.

Why NSAIDs may increase the risk of VTE is unclear. The pathophysiology of increased arterial thrombosis risk (and thus coronary artery events) is explained by a thromboxane–prostacyclin imbalance. Inhibition of the
COX-2 enzyme has been shown to inhibit the synthesis of prostacyclins, potent platelet activation inhibitors, while stimulating the release of thromboxane, a potent platelet aggregation facilitator, from the activated platelets. The activation and aggregation of platelets might, in turn, induce a coagulation cascade and clotting [4, 19, 20]. This mechanism might explain the increased risk of venous thrombosis we observed in this study. In fact, the VTE risk of selective COX-2 inhibitors appears to be higher than overall NSAIDs, although without statistical significance, as the CI overlaps.

Also, aspirin, a specific and irreversible COX-1 inhibitor, has proved effective for VTE prevention [21, 22]. This might provide further evidence that the increased VTE risk comes primarily from COX-2 inhibition.

Even though the six studies included in this meta-analysis were of high quality, there are some limitations and thus our results should be interpreted with caution. First, we cannot exclude the possibility of publication bias in favour of positive studies, as the funnel plot is asymmetric. Second, the statistical heterogeneity in this study is high and thus the data from individual studies might be too heterogeneous to combine. Third, most of the included studies were conducted using a medical registry-based database, raising the possibility of coding inaccuracy. Fourth, this is a meta-analysis of observational studies and thus can only demonstrate an association, not establish cause and effect, so we cannot be certain that NSAIDs themselves or other potential confounders increase the risk of VTE. For example, patients may have been prescribed NSAIDs for underlying illnesses causing pain and immobility or for chronic inflammatory disorders, which are linked to a higher VTE risk compared with the general population [23–25]. We could not perform a meta-regression to adjust for these potential confounders as the primary studies do not provide sufficient data to do so. Furthermore, all NSAIDs were evaluated as one group in this study, but not all individual NSAIDs may increase VTE risk.

In conclusion, the results of our meta-analysis demonstrate a statistically significantly increased VTE risk among NSAID users. Physician should be aware of this association and NSAIDs should be prescribed with caution, especially in patients at high baseline risk of VTE.

**Rheumatology key messages**

- This is the first meta-analysis to investigate the association between NSAIDs and venous thromboembolism.
- This study demonstrated a statistically significant increased risk of venous thromboembolism among NSAID users.

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**Supplementary data**

Supplementary data are available at Rheumatology Online.

**References**


