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Original article

Incidence of venous thromboembolism following initiation of non-steroidal anti-inflammatory drugs in U.S. women

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Abstract

Objective. To evaluate the risk of venous thromboembolism (VTE, i.e. deep vein thrombosis or pulmonary embolism, or both) following new use of NSAIDs in a long-term cohort of U.S. women.

Methods. We investigated initiation of coxibs and traditional NSAIDs (excluding aspirin) and incident VTE in 39 876 women enrolled in the Women's Health Study from 1993–95 and followed with yearly questionnaires until 2012. We defined initiation as the first reported use of NSAIDs for $\geq$4 days per month. Incident VTE was confirmed by an end point committee. We estimated hazard ratios (HRs) and risk differences (RDs, expressed as percentages) comparing NSAID initiation with non-initiation and acetaminophen initiation (active comparator) via standardization using a propensity score that incorporated age, BMI, calendar time, and relevant medical, behavioural, and socioeconomic variables updated over time.

Results. The HR (95% CI) for risk of VTE in the as treated analyses comparing initiation with non-initiation, was 1.5 (1.2, 1.8) for any NSAID, 1.3 (1.1, 1.7) for traditional NSAIDs, and 2.0 (1.3, 3.1) for coxibs, with 2-year RDs 0.11, 0.08 and 0.32, respectively. When comparing the risk of VTE after initiation of any NSAID with that after acetaminophen initiation, the HRs were 0.9 (0.6, 1.5), 0.9 (0.5, 1.5) and 1.4 (0.6, 3.4), with 2-year RDs 0.03, –0.01, and 0.13, respectively.

Conclusion. New use of NSAIDs was associated with increased VTE risk compared with non-use, but the association was null or diminished when compared with acetaminophen initiation. Elevated VTE risks associated with NSAID use in observational studies may in part reflect different baseline risks among individuals who need analgesics and may overstate the risk patients incur compared with pharmacologic alternatives.

Key words: NSAIDs, non-steroidal anti-inflammatory drugs, venous thromboembolism, deep vein thrombosis, pulmonary embolism, pharmacoepidemiology

CLINICAL SCIENCE

Rheumatology key messages

- Initiation of NSAID use, compared with non-use, was associated with increased venous thromboembolism risk in women.
- Non-users of NSAIDs who initiated acetaminophen had venous thromboembolism risks similar to those who initiated NSAIDs.
- Elevated venous thromboembolism risk in users of NSAIDs may reflect underlying differences in patients with *vs* without pain.

Introduction

NSAIDs are among the most commonly used drugs worldwide. An estimated 15% of U.S. women used NSAIDs at least three times per week in 2010 [1]. Venous thromboembolism [VTE, i.e. deep vein thrombosis (DVT) or pulmonary embolism (PE), or both] is a substantial public health problem affecting an estimated 350 000–600 000 Americans and possibly contributing to 100 000 deaths annually [2]. Approximately 1 in 1000

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adults aged 40–60 years and 8 in 1000 aged >80 years are affected [3].

NSAID use compared with non-use is associated with 1.5- to 3-fold VTE risks in multiple non-experimental studies [4–10]. However, a biologic explanation for an association is unclear. NSAIDs inhibit prostaglandins through inhibition of cyclooxygenase (COX) enzyme binding sites, thereby reducing inflammation. The association of COX-2 selective inhibitors (coxibs) with serious arterial cardiovascular outcomes is well established, and a mechanism has been posited whereby COX-2 inhibition reduces the synthesis of prostacyclin that normally functions as an inhibitor of platelet activation [11, 12].

Opinions differ regarding whether arterial and venous thrombotic diseases are aetiologically connected or distinct [13–16]. Shared strong risk factors include obesity and older age; other strong cardiovascular risk factors (i.e. hypertension, diabetes and smoking) are modestly associated with VTE [16]. The composition of arterial and venous thrombi and triggers for their formation differ [17]. It is possible that biologic actions of COX inhibition could increase the propensity for both venous and arterial thrombosis [18]; however, the associations seen in non-experimental studies could also be explained by confounding by indication.

Randomized trials of sufficient size to evaluate VTE risk have not been conducted, presumably owing to the low event rate [19]. At the same time, the limited scope of treatment options for individuals with chronic pain [20] coupled with national calls for improved prevention of VTE [2] underscore the importance of defining the risk of VTE associated with NSAIDs. We therefore undertook this study to evaluate the risk of VTE following new use of NSAIDs in a long-term cohort of U.S. women.

Methods

Data source

The Women's Health Study (WHS) is a double-blind randomized controlled trial of low-dose aspirin, vitamin E, and beta-carotene for the primary prevention of cardiovascular disease and cancer in U.S. women [21–23]. From 1993 to 1995, 39 876 female health professionals aged ≥45 years were allocated to a regimen of aspirin (100 mg every other day) or placebo and Vitamin E (600 IU every other day) or placebo in a 2 × 2 factorial design. The trial also initially included a beta-carotene component, which was discontinued after 2 years' median treatment duration [24].

Additional eligibility criteria for enrolment included: post-menopausal or having no intention of becoming pregnant; no prior history of coronary heart disease, cerebrovascular disease, or cancer (except non-melanoma skin cancer); not taking aspirin, aspirin-containing medications, NSAIDs, Vitamins A or E, or beta-carotene more than once per week; willingness to forgo the use of non-study aspirin, aspirin-containing medications, and NSAIDs; not taking anticoagulants or CSs; and successful completion of a 3-month placebo run-in [25].

Participants were followed annually through till the scheduled end of the trial (31 March 2004) and for post-trial observation afterward. Data were collected via written questionnaires that participants returned by mail. Complete descriptions are available elsewhere [25, 26]. The current study includes questionnaires of all WHS participants through till 7 years post-trial.

NSAID use

Questions regarding current use of non-aspirin NSAIDs were included in 19 of 20 questionnaires administered: before randomization (baseline); every 12 months through till 120 months following randomization; at trial conclusion in 2004; and 1, 2, 3, 4, 5 and 7 years after trial conclusion for participants (~90%) in the observational follow-up phase. We classified self-reported use of traditional NSAIDs (i.e. non-aspirin non-COX selective NSAIDs), coxibs (COX-2 inhibitors), and any NSAID (not including aspirin). Details are provided in Supplementary Table S1, available at *Rheumatology* online. We defined regular use as 4 or more days of self-reported use in the past month, which corresponded most closely with the WHS entry criteria.

VTE outcomes

Each year women were asked whether they had been newly diagnosed with DVT or PE since their last questionnaire. As VTE was a secondary trial end point, reported events underwent medical records verification by an Endpoint Committee of physician reviewers with consent of the participant. Events discovered during medical record reviews for other study end points were also captured. DVT was confirmed based on a positive venous ultrasonogram or venography report. PE was confirmed based on a positive angiogram or CT scan of the chest, or a ventilation–perfusion scan with two or more mismatched defects. Deaths due to PE were confirmed according to autopsy reports, symptoms, circumstances of death, and medical history, as judged by Endpoint Committee adjudicators. VTE events were also classified as provoked (cancer diagnosed before or within 3 months after the VTE, or trauma or surgery within 3 months before the VTE) or unprovoked (otherwise) [27]. Date of diagnosis for the first confirmed VTE was utilized for the current analysis. We did not evaluate subsequent VTE; however, women with self-reported history of DVT or PE at study entry (2.9% of WHS participants) were included in the analysis.

Covariates

Covariates were ascertained before randomization and were updated whenever possible. Race, education, and history of VTE before study enrolment were collected once at baseline. Age was calculated at every questionnaire. BMI, smoking (current, previous but not current, or never), physical exercise, alcohol use, multivitamin use,

menopausal status (pre-menopausal, post-menopausal, or uncertain), and hormone replacement therapy use (current, previous but not current, never) were reassessed only on some questionnaires. The last recorded values were carried forward to later questionnaires, where they were not asked for or missing unless described otherwise. Missing values were not imputed with later values with the exception of baseline height.

BMI was calculated from self-reported height and weight and carried forward by linear interpolation. Self-reported weight was highly correlated with measured weight ($r = 0.97$) among similar women in the Nurses' Health Study [28]. Menopausal status was imputed to post-menopausal for all women at ages $\geq$60 years in the absence of self-report data indicating otherwise [29]. Physical exercise was classified as 0, >0 to <3.75, 3.75 to <7.5, 7.5 to <15, 15 to <22.5, and $\geq$22.5 or greater met-h per week [30]. One met-h represents the metabolic equivalent of one additional hour of resting metabolic rate. 7.5 met-h represents the minimum physical activity for adults recommended by Federal guidelines [31].

Cancer and incident cardiovascular disease underwent medical record verification [21, 23, 32]. Self-reported incident diabetes was verified via a physician-conducted telephone interview or validated self-administered questionnaire [33]. Self-reported peptic ulcer disease and gastrointestinal bleeding were verified with a follow-up questionnaire until 2005.

Hypertension was defined as a self-reported diagnosis, self-reported use of antihypertensive medication, or self-reported systolic blood pressure of $\geq$140 mmHg or diastolic blood pressure of $\geq$90 mmHg. Atrial fibrillation, OA, RA [34, 35], osteoporosis, major orthopaedic event (fracture or joint replacement), migraine headaches, chronic lung disease, and coagulation disorder diagnoses were self-reported. Dates of first lifetime incidence, whether before enrolment or during follow-up, were identified for all diagnoses and events of interest. Self-reported concurrent regular use ($\geq$4 days in the past month) of acetaminophen, non-study aspirin, and aspirin-containing medications was asked each year, and of statins on 13 questionnaires.

Study design

We constructed a new user design that treated the questionnaire as the unit of analysis [36, 37]. Using each woman's sequential questionnaires, we defined initiation as the first report of regular NSAID use ($\geq$4 days in the past month) following study entry, or following a washout period of two or more consecutive reports of non-regular use of any non-aspirin NSAID spanning at least 18 months. That is, a report of no regular NSAID use on a woman's first questionnaire following either study entry or a washout was classified as a non-initiation, and a report of regular use was classified as an initiation (Supplementary Fig. S2, available at *Rheumatology* online).

Each woman's follow-up time was thereby conceptualized as a sequence of discrete observations, with individual women potentially contributing both non-initiations and initiations to the analysis over the duration of her study participation. The up-to-date covariate values on the first day of the inter-questionnaire period preceding the questionnaire date (the eligibility period) were used as the predictors of initiation or non-initiation for each questionnaire.

We designed as treated (AT) and initial treatment (IT) analyses with at-risk periods beginning on the questionnaire date (index date). The at-risk follow-up period for VTE was constructed separately for each questionnaire, and the same inter-questionnaire period(s) of an individual woman's calendar time could be contained in the at-risk follow-up period of more than one eligible questionnaire (Supplementary Fig. S3, available at *Rheumatology* online) [36, 38]. For AT design, the at-risk follow-up time for each questionnaire was censored on the earliest of: (i) the first reported treatment change (stopping, or switching to or adding a different non-aspirin NSAID or the active comparator); (ii) death, withdrawal, or end of study follow-up; or (iii) 3. 5 years after the questionnaire index date. For IT design, treatment changes, starting, stopping, switching and/or adding of therapy was ignored. Women who stopped, switched, or added treatment could again become eligible to initiate or not initiate on a later questionnaire after completing a washout.

Missing NSAID use values occurring during a washout or at-risk follow-up period were carried forward from the last non-missing observation for the purpose of establishing the duration of continued use or non-use; however, we required non-missing responses for all variables used to define the beginning and end of washout, eligibility, and at-risk periods.

We excluded as ineligible all questionnaires with confirmed VTE before the questionnaire index date, as the woman was no longer at risk of first incident VTE; this entailed the exclusion of 421 otherwise eligible questionnaires (53 initiations, 368 non-initiations) for which VTE occurred during the initiation eligibility period. We did not consider beginning the at-risk period earlier than the questionnaire index date because it would introduce immortal time bias [39].

Coxibs were commercially available in the U.S. for ~1.3 years before WHS questionnaires began capturing coxib use with a separate question. For all questionnaires without the coxib question (72 months post-randomization and earlier), we considered the value of coxib use as non-use if returned on or before 31/12/1998 (date celecoxib released in the USA), and missing if returned after 31/12/1998; those classified as missing were excluded as ineligible to initiate or not initiate, because their exposure data were incomplete. A total of 324 124 eligible questionnaires of 38 493 women were included (Supplementary Fig. S1, available at *Rheumatology* online).

We compared initiation of any NSAID, traditional NSAIDs (exclusive of coxibs), and coxibs (exclusive of traditional NSAIDs) with non-initiation of any NSAID. We also compared initiation of traditional NSAIDs and

coxibs with non-initiation by frequency of use at the time of initiation (4–20 days and 21+ days in the past month). We compared initiation of coxibs with initiation of traditional NSAIDs, and initiation of each NSAID type with initiation of acetaminophen, an active comparator with similar indications and without known haemostatic effects. Acetaminophen use was asked about in the same manner as that of NSAIDs on each questionnaire, and we used the same criteria to classify regular use (≥4 days in the past month). For the acetaminophen comparator analyses, we required non-use of any non-aspirin NSAID and acetaminophen during the washout period. We did not restrict according to concurrent aspirin use for any analyses.

The study conforms with the ethical standards of the 1964 Declaration of Helsinki and its later amendments, and U.S. Federal Policy for the Protection of Human Subjects. Free and informed written consent of participants was obtained. The Partners Healthcare and University of North Carolina Institutional Review Boards approved the current study.

Analytic methods

We used a propensity score (PS) to control for confounding. The PS incorporated all covariates previously described, with values updated over time (Supplementary Table S2, available at *Rheumatology* online). Variables for the PS were selected on the basis of substantive knowledge and causal diagram analysis with the goal of including important confounders and preserving causal pathways [40]. Randomized low-dose aspirin was not associated with VTE risk in the WHS population [27], but moderate-dose aspirin is employed as a VTE preventive in some post-surgical and other high-risk settings [41, 42]; therefore, we included non-study aspirin in the PS. We omitted concurrent acetaminophen use from the PS for the acetaminophen active comparator analyses.

The PS was estimated using separate logistic regression models for 2 calendar-year periods [43]. We used the PS to construct weights to standardize the comparator group to the treatment group, known as standardized morbidity ratio weighting [44]. We multiplied standardized morbidity ratio weights by the marginal odds of treatment received, which redistributed their values around a mean of 1 [45]. This stabilization improved the precision of the final estimates and provided a scale by which to interpret the magnitude of the weights.

We used standardized morbidity ratio weighted Cox proportional hazard models to estimate the relative and absolute effects of NSAID initiation on time to and cumulative incidence of VTE [46]. A robust variance was used to account for weighting and multiple questionnaires from the same woman in either or both treatment groups [47]. Risks for 2 years of treatment, risk differences (RDs), and number needed to treat for harm (NNTH) or benefit (NNTB) to one additional woman were calculated from the adjusted survival curves [48]. CIs for the RD and NNTH/NNTB were obtained by 1000 bootstraps using the weighted copy method for the PS models [49]. We plotted weighted Kaplan–Meier curves to illustrate the standardized cumulative incidence of VTE [50]. The proportional hazard assumption was assessed using graphical methods and Schoenfeld residual tests.

Sensitivity analyses

We repeated our main analyses using 2-years, 3-years, and no restriction on maximum at-risk follow-up time, with restriction to women (97%) without previous history of VTE before study entry, and with restriction to questionnaires with eligibility period lengths of <27 months (99%). A 27 months eligibility period limit would allow no more than one missing yearly questionnaire during the period, permitting a 3 months grace period for late returns.

Results

While all 39 876 WHS participants were non-regular users of NSAIDs at study entry by design, 10% reported using NSAIDs regularly 12 months after study enrolment, and 31% in 2011. Of the 39 876 participants, 29 527 women (74%) reported regular use of an NSAID at some time during their study follow-up; 71% used traditional NSAIDs and 24% used coxibs at some time. VTE was confirmed during follow-up in 951 WHS participants, of which 382 (40%) were classified as unprovoked. The first confirmed event was PE for 408 participants (with accompanying DVT in 61%), and DVT without PE for 543 participants.

Compared with non-initiation, we saw a modestly elevated apparent risk of VTE after NSAID initiation, and greater risk with coxibs than with traditional NSAIDs. The 2-year risks (%) of VTE among women who initiated any NSAID, traditional NSAIDs, and coxibs, respectively, were 0.36, 0.32 and 0.64 in the AT analysis; among non-initiators, these risks standardized to the initiators on all covariates were 0.25 (RD = 0.11), 0.24 (RD = 0.08) and 0.32 (RD = 0.32), respectively (Table 1, Supplementary Fig. S4, available at *Rheumatology* online). The AT hazard ratios (HRs) (95% CI) were 1.5 (1.2, 1.8) for any NSAID, 1.3 (1.1, 1.7) for traditional NSAIDs, and 2.0 (1.3, 3.1) for coxibs. HRs were closer to the null value for the IT analyses (Table 2). In AT analyses stratified into low (1–20 days/month) and high (21+ days/month) frequency of use at initiation, HRs were similar to each other and to the overall HR for both traditional NSAID and coxib initiation, suggesting that increased risk for coxibs was not simply a function of their typically more frequent use patterns (Table 3).

In contrast to comparisons with non-initiation, associations were null or diminished when compared with acetaminophen initiation. The 2-year risks (%) of VTE among women not using acetaminophen who initiated any NSAID, traditional NSAIDs, and coxibs, respectively, were 0.39, 0.36 and 0.61; among acetaminophen initiators, these risks standardized to the NSAID initiators on all covariates were 0.36 (RD = 0.03, NNTH = 3419), 0.36

Table 1 Risk (%) and risk difference for VTE within 2 years of NSAID initiation or non-initiation

	2-year risk (%)[a]			2-yr RD (%) (95% CI)[a]	
	Initiation	Non-initiation	Non-initiation$_{WT}$	Crude	Adjusted
As treated					
Any NSAID	0.36	0.23	0.25	0.12 (0.05, 0.21)	0.11 (0.03, 0.19)
Traditional NSAIDs	0.32	0.23	0.24	0.09 (0.01, 0.17)	0.08 (0.00, 0.17)
Coxibs	0.64	0.27	0.32	0.37 (0.07, 0.71)	0.32 (0.01, 0.65)
Initial treatment					
Any NSAID	0.36	0.26	0.28	0.09 (0.03, 0.16)	0.08 (0.02, 0.14)
Traditional NSAIDs	0.33	0.26	0.27	0.07 (0.01, 0.14)	0.06 (0.00, 0.13)
Coxibs	0.59	0.29	0.35	0.30 (0.06, 0.53)	0.24 (0.00, 0.47)

[a]2-year risks (expressed as percentages) and RDs were estimated from crude and stabilized SMR weighted survival curves. RDs were adjusted by standardizing the non-initiations to the initiations by all variables in the PS. VTE: venous thromboembolism; WT: weighted; RD: risk difference; SMR: standardized morbidity ratio; PS: propensity score.

Table 2 Incidence rates and hazard ratios for VTE comparing NSAID initiation with non-initiation

	NSAID initiation			Non-initiation			HR (95% CI)[a]	
	Events[b]	PY	IR	Events	PY	IR	Crude	Adjusted
As treated								
Any NSAID	140	76 649	1.8	1284	1 081 357	1.2	1.5 (1.3, 1.9)	1.5 (1.2, 1.8)
Traditional NSAIDs	98	60 732	1.6	1269	1 070 375	1.2	1.4 (1.1, 1.7)	1.3 (1.1, 1.7)
Coxibs	24	7484	3.2	744	556 977	1.3	2.4 (1.6, 3.6)	2.0 (1.3, 3.1)
Initial treatment								
Any NSAID	312	173 611	1.8	1903	1 314 498	1.4	1.2 (1.1, 1.4)	1.2 (1.0, 1.3)
Traditional NSAIDs	252	147 029	1.7	1876	1 303 529	1.4	1.2 (1.0, 1.4)	1.1 (1.0, 1.3)
Coxibs	51	18 945	2.7	1070	678 905	1.6	1.7 (1.3, 2.3)	1.4 (1.1, 1.9)

[a]HRs were estimated using Cox proportional hazard models and adjusted by standardizing the non-initiations to the initiations on all covariates in the propensity score. At-risk follow-up time was restricted to maximum 5 years for all analyses. [b]VTE events (deep vein thrombosis, pulmonary embolus, or both). VTE: venous thromboembolism; HR: hazard ratio; PY: person-years; IR: crude incidence rate per 1000 PY.

Table 3 As treated hazard ratios for VTE stratified by frequency of use at time of initiation

	NSAID Initiation			Non-initiation			HR (95% CI)[a]	
	Events[b]	PY	IR	Events	PY	IR	Crude	Adjusted
Traditional NSAIDs								
4–20 days/month	73	46 726	1.6	1269	1 070 375	1.2	1.3 (1.0, 1.7)	1.3 (1.0, 1.7)
21+ days/month	25	14 005	1.8	1269	1 070 375	1.2	1.5 (1.0, 2.3)	1.3 (0.9, 2.0)
Coxibs								
4–20 days/month	7	2360	3.0	396	293 331	1.4	2.2 (1.0, 4.6)	1.9 (0.9, 4.1)
21+ days/month	16	4698	3.4	744	556 977	1.3	2.5 (1.5, 4.2)	2.0 (1.2, 3.5)

[a]HRs were estimated using Cox proportional hazard models and adjusted by standardizing the non-initiations to the initiations on all covariates in the PS. As treated follow-up time was defined as continued use at 4+ days/month for both initial frequency categories. At-risk follow-up time was restricted to maximum 5 years for all analyses, except coxibs initiating at 4–20 days/month was restricted to 2 years because the proportional hazard assumption was not met after 2 years. [b]VTE events (deep vein thrombosis, pulmonary embolus, or both). VTE: venous thromboembolism; HR: hazard ratio; PY: person-years; IR: crude incidence rate per 1000 PY.

Table 4 Risk differences for VTE within 2 years of initiation using as treated active comparator design

	2-yr risk (%)[a]			RD (%) (95% CI)[a]		NNTH/NNTB[b]
	NSAID	Comparator	Comparator$_{WT}$	Crude	Adjusted	Adjusted
Coxibs *vs* traditional NSAIDs	0.64	0.36	0.39	0.28 (−0.02, 0.65)	0.25 (−0.09, 0.63)	NNTH 395
Any NSAID *vs* acetaminophen	0.39	0.31	0.36	0.09 (−0.09, 0.27)	0.03 (−0.46, 0.15)	NNTH 3419
Traditional NSAIDs *vs* acetaminophen	0.36	0.31	0.36	0.05 (−0.15, 0.25)	−0.01 (−0.55, 0.11)	NNTB 16 468
Coxibs *vs* acetaminophen	0.61	0.40	0.48	0.20 (−0.25, 0.79)	0.13 (−0.40, 0.76)	NNTH 777

[a]2-year risks (expressed as percentages), RDs and NNTH/NNTB were estimated from crude and stabilized SMR weighted survival curves. RDs and NNTs were adjusted by standardizing the non-initiations to the initiations by all variables in the PS. [b]The null value of RD = 0 corresponds to the null value of NNT=infinity. A negative value for RD corresponds to NNTB. The 95% confidence limits for NNTH/NNTB are equal to the inverse of the 95% confidence limits of the adjusted RD. VTE: venous thromboembolism; RD: risk difference; NNTH/NNTB: number needed to treat for one additional woman to be harmed (NNTH) or to benefit (NNTB); WT: weighted; SMR: standardized morbidity ratio; PS: propensity score.

Table 5 Incidence rates and hazard ratios for VTE using as the as treated active comparator design

	NSAID initiation			Active comparator			HR (95% CI)[a]	
	Events[b]	PY	IR	Events	PY	IR	Crude	Adjusted
Coxibs *vs* traditional NSAIDs	24	7484	3.2	58	33 499	1.7	1.8 (1.1, 3.0)	1.8 (1.1, 2.9)
Any NSAID *vs* acetaminophen	47	25 363	1.9	36	22 036	1.6	1.1 (0.7, 1.8)	0.9 (0.6, 1.5)
Traditional NSAIDs *vs* acetaminophen	34	20 154	1.7	36	22 036	1.6	1.0 (0.6, 1.7)	0.9 (0.5, 1.5)
Coxibs *vs* acetaminophen	8	2341	3.4	22	10 683	2.1	1.7 (0.7, 3.7)	1.4 (0.6, 3.4)

[a]HRs were estimated using Cox proportional hazard models and adjusted by standardizing the non-initiations to the initiations on all covariates in the PS. At-risk follow-up time was restricted to a maximum of 5 years for all analyses, except coxibs *vs* acetaminophen, which was restricted to 2 years because the proportional hazard assumption was not met after 2 years. All active comparator analyses were restricted to a comparable calendar time period after availability of coxibs. Non-use of the comparator medication was required for each analysis. Regular use was defined as response of 4+ days/month use in the past month for all medications. [b]VTE events (deep vein thrombosis, pulmonary embolus, or both). VTE: venous thromboembolism; HR: hazard ratio; PY: person-years; IR: incidence rate per 1000 PY; PS: propensity score.

(RD = –0.01, NNTB = 16 468), and 0.48 (RD = 0.13, NNTH = 777), respectively (Table 4, Supplementary Fig. S5, available at *Rheumatology* online). The AT HRs (95% CI) for VTE were 0.9 (0.6, 1.5) for any NSAID, 0.9 (0.5, 1.5) for traditional NSAIDs, and 1.4 (0.6, 3.4) for coxibs (Table 5).

Sample sizes were small, particularly for coxibs (8 VTE events during AT follow-up, all within the first 2 years). We restricted the at-risk follow-up time for coxib *vs* acetaminophen initiation to 2 years for estimation of the HR, because the proportional hazard assumption was not met after 2 years (Supplementary Fig. 5SD, available at *Rheumatology* online).

Sensitivity analyses suggested that our findings were robust to our decisions to include women with prior history of VTE and ignore longer eligibility period lengths for a small (<1%) proportion of questionnaires, and to variations in maximum follow-up time restriction for AT analyses with the exception of coxibs *vs* acetaminophen analysis (Supplemental Tables S3–S6, available at *Rheumatology* online). For IT analyses, HRs decreased towards the null with increasing duration of maximum follow-up time.

Discussion

Our analyses comparing NSAID initiation with non-initiation showed associations similar in magnitude to those of some previous studies [4, 7], with stronger associations for coxibs that did not appear to be explained by differences in frequency of use. Coxib initiation was associated with 80% greater VTE risk than traditional NSAIDs in head-to-head comparison (Table 5). Compared with acetaminophen initiation, traditional NSAIDs did not show increased risk, and coxibs showed only modest relative and absolute risk increases.

Six previous pharmacoepidemiologic studies of NSAIDs use and VTE have reported relative risks compared with non-use of the order of ~1.5–3.0, with

stronger associations for coxibs (Supplementary Table S7, available at *Rheumatology* online) [4–9]. Lee *et al*. [7] reported attenuated risk increases [odds ratio (OR) 1.4] in a case–control study restricted to individuals with knee OA. Goy *et al*. [19] conducted a pooled analysis of data from 14 trials of randomized rofecoxib *vs* placebo that reported VTE as secondary outcomes. A difference in VTE incidence was not detected, but power was very low due to the small numbers of events (8 in 9217 person-years compared with 9 in 9092 person-years, respectively). Biere-Rafi *et al*. [5] reported elevated risk of PE for current use of acetaminophen and tramadol compared with non-use [adjusted OR 1.7 (95% CI) (1.4, 2.1) and 4.0 (2.8, 5.8), respectively] in a case–control study of NSAIDs and PE in a Dutch population-based registry, but did not directly compare NSAIDs with acetaminophen or tramadol use. The authors suggested that, since these drugs have no known haemostatic effects, underlying conditions associated with PE risk may be broadly associated with the reasons for taking pain killers. In our study, the HR comparing acetaminophen initiation with non-initiation, both groups exclusive of NSAID use, was 1.3 (95% CI: 0.9, 1.9) (data not shown). Pragmatically, the large sample size requirement for a randomized trial of VTE outcomes will necessitate that further work rely heavily on observational designs [19].

Our study design offers several advantages in terms of confounding and other biases. The rich WHS covariates include lifestyle variables not captured by claims data, and VTE ascertainment that captures all clinically significant events, including those without a hospitalization (e.g. sudden death). Previous studies of NSAIDs and VTE risk have leveraged a variety of population-based data sources, and most utilized case–control designs with exposure definitions based on prevalent use. We implemented a new user design [51] in a long-term follow-up cohort of women initially not using NSAIDs where users were identified at the start of treatment, outcomes were ascertained during follow-up, and pretreatment covariates were utilized for appropriate confounding control, as would be done in a randomized trial. Our active comparator analyses furthermore compared new NSAID users with only the subset of NSAID non-users who initiated acetaminophen. This design increases the similarity of the groups on both measured and unmeasured characteristics, because only individuals with indication for use of an analgesic are included [52–54]. NSAIDs and acetaminophen are not perfectly exchangeable in terms of reasons for use in the observational setting, but they are similar. Moreover, they represent viable clinical alternatives, in contrast with non-treatment of pain [54].

Our study has limitations. While dates of confirmed VTE were known, drug use information was only available cross-sectionally at yearly intervals. Thus, it was not known when initiation began, or whether a non-initiator may have started and stopped between questionnaires. Likewise, when treatment change was detected during AT follow-up, the precise date of change was unknown. When initiation or treatment change and VTE occurred during the same interval, the true exposure status at the time of the VTE was unclear. However, in this scenario it seems more plausible that regular NSAID use would stop as a consequence of experiencing a VTE than that initiation would occur. Our analyses assume that the use or non-use reported on a questionnaire continued until the day of the next questionnaire. Our interpretation of the comparison of NSAIDs with acetaminophen assumes that acetaminophen should not cause VTE; however, the possibility of a biologic association of both NSAIDs and acetaminophen with VTE cannot be ruled out [55, 56]. Data were not available in the WHS to perform subgroup analysis on individual NSAIDs.

In conclusion, using a rich data source and a robust study design, we found that the risk of VTE associated with new use of NSAID among women was not high. Importantly, little risk from NSAIDs was seen when compared with initiation of acetaminophen, an active comparator with similar treatment indication but not implicated in causing thrombosis. Apparent increased risks seen in observational studies comparing users with non-users may in part reflect different baseline risks in individuals who need pain medications, and may overstate the risks that patients with an indication for analgesics incur in choosing NSAIDs compared with another clinical alternative. Since non-treatment is generally not a viable option for pain, we suggest that clinicians consider the possibility that NSAID use may impart little or no additional VTE risk to patients with pain compared with other treatment options.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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