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Review

The fear for adverse bleeding and cardiovascular events in hemophilia patients using (non-)selective non-steroidal anti-inflammatory drugs: A systematic review reporting on safety

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ABSTRACT

(Non-)selective non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used for musculoskeletal related pain. These cheap and easily accessible drugs may be of great value for hemophilia patients in developing countries and countries with a high rate of opioid poisoning, but also in developed countries due to potential joint protective effects. However, fear for adverse bleeding and cardiovascular events during the use of these drugs restrains prescription within this population. To give a complete overview of all publications reporting on safety, a systematic search till March 2021 was performed. All studies were reviewed and critically appraised and this resulted in 19 studies eligible for inclusion. Most studies with (non-)selective NSAIDs showed no evident risk for relevant adverse bleeding or cardiovascular events. However, some studies had a high risk of bias and studies reporting on cardiovascular events were limited. Future studies with longitudinal follow-up in well-defined large patient populations, including older patients, focusing on both adverse bleeding and cardiovascular events are required to confirm the alleged safe use.

1. Introduction

Hemophilia, an inherited coagulation disorder caused by deficiency of coagulation factor VIII (A) or IX (B), is characterized by recurrent bleeding. In patient with severe hemophilia, 73–90% of all bleeding occur in the joints and muscles [1]. Despite clotting factor substitution, patients nowadays still experience (subclinical) joint bleeds. Blood in the joint leads to direct apoptosis of chondrocytes and triggers an inflammatory response with proliferation of synoviocytes and neoangiogenesis. The formation of new fragile blood vessels makes the joint more vulnerable to repeated bleeds [2]. This leads to a vicious circle resulting in chronic inflammation and subsequently degeneration of cartilage and bone, so-called hemophilic arthropathy (HA). Except for preventing additional joint bleeds, interference with this vicious circle is impossible. Disease-modifying drugs are lacking and treatment is focused on reducing pain, preserving joint function and maintaining participation in society. If conservative treatment options like pain management and physiotherapy fails, major surgical interventions such as arthrodesis and prosthesis are often necessary. These major orthopedic interventions, together with chronic pain and limited function caused by the arthropathy, have a huge impact on participation in society and quality of life [3].

A commonly used option in pain management of rheumatic diseases is the use of non-steroidal anti-inflammatory drugs (NSAIDs). In patients with osteoarthritis (OA) and rheumatoid arthritis (RA), NSAIDs are the main form of treatment. NSAIDs are more effective than simple analgesics and cause clinically important improvements in pain, according to different studies, and should be considered in symptomatic patients according to the EULAR guidelines [4–6]. Besides the well-established analgesic effects, NSAIDs are cheap and easily accessible drugs and might be of value in improving joint health in developing countries where expensive clotting factor substitution therapy is not always

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available. Moreover, the proportion of patients receiving opioids is increasing in the Netherlands, accompanied by a decrease in NSAID prescription. Mortality caused by opioid poisoning increased in this period from 3.9% of 1343 hospitalized patients in 2013 to 4.6% of 2055 hospitalized patients in 2017 [7]. In the United States, nearly 50,000 people died from opioid involved overdoses. Obviously, a safe alternative is important for those with chronic (arthropathy) pain [8].

Besides pain reduction, these drugs may also have a disease modifying potential. The selective cyclooxygenase (COX)-2 inhibitor celecoxib showed in vitro a significant beneficial effect on both early- and late-stage OA, whereas healthy cartilage remained unaffected [9]. Besides this potential chondroprotective property, NSAIDs may also protect cartilage by their anti-inflammatory effect. This lies in the inhibition of the prostaglandin production by COX. The isoform COX-1 is widely expressed in most tissues including gastrointestinal mucosa and regulates tissue homeostasis, the production of acid and mucus, renal blood flow and platelet aggregation [10]. Acetylsalicylic acid (ASA) was the first NSAID on the market in 1899 and Indomethacin and Ibuprofen were the first non ASA-NSAIDs made in 1964 and 1969 respectively [11–13]. In patients with a bleeding disorder, the use of these drugs is limited by the fact that inhibition of this production leads to gastrointestinal and anti-platelet side effects [14]. Later on, selective COX-2 inhibitors were developed. COX-2 is not expressed in most normal tissues and its expression increases rapidly by stimuli such as pro-inflammatory cytokines and growth factors. A randomized double-blind study with over 8000 patients with RA showed that patients treated with the selective COX-2 inhibitor rofecoxib experienced statistically significantly fewer clinically important upper gastrointestinal events compared to naproxen [15,16]. Selective COX-inhibition also leads to fewer treatment withdrawals due to gastrointestinal side effects compared to non-selective COX-inhibition. Regarding the effects on proteoglycan synthesis and release in vitro, non-selective NSAIDs showed negative effects, whereas specific COX-2 inhibitors have cartilage protective properties in early and late stage OA and leave healthy cartilage unaffected [9,17,18]. A systematic review evaluating the disease modifying effects of NSAIDs on cartilage, synovium and bone in OA suggested that celecoxib can potentially slow down OA progression in humans due to chondroprotective, synovial hyperplasia-preventative and bone destruction-inhibitory effects of celecoxib in vitro and in vivo. Considering that the pathophysiology of HA resembles that of OA, one might hypothesize that NSAIDs may have additional joint protective effects [19].

However, there are concerns about these selective COX-2 inhibitors as they depress the atheroprotective agent prostacyclin, but not the COX-1 derived pro-aggregatory and vasoconstrictive thromboxane A2, which may predispose patients to stroke and heart attack [10]. A meta-analyses (2013) using data from over 300.000 individuals showed that major vascular events like non-fatal myocardial infarction or stroke and vascular death were increased by about a third by a coxib or diclofenac, mainly due to an increase in major coronary events. Compared with placebo, of 1000 patients on a coxib or diclofenac during a year, three more had major vascular events (one fatal). Ibuprofen also significantly increased major coronary events, but not major vascular events. Naproxen did not significantly increase major vascular events. Vascular death was increased significantly by coxibs and diclofenac, non-significantly by ibuprofen, but not by naproxen. These effects were independent of baseline characteristics, including vascular risk. Heart failure risk was roughly doubled by all NSAIDs [20]. Regarding blood pressure, all NSAIDs in therapeutical doses can increase blood pressure. A meta-analysis including 50 studies showed that NSAIDs elevate mean blood pressure by approximately 5.0 mmHg [21]. Over a few years, a 5 to 6 mmHg increase in diastolic blood pressure might be associated with a 67% increase in total stroke occurrence and a 15% increase in coronary disease [22].

A Cochrane review assessing the toxicity of rofecoxib for RA patients showed that patients taking rofecoxib had a greater risk of having any cardiovascular events than patients taking naproxen [23]. Although patients with hemophilia have a reduced cardiovascular disease incidence, hemophilia does not protect against atherosclerosis and individual risk assessment and proper follow-up remain necessary. An overview of the safety profile on both adverse bleeding events and cardiovascular events of selective and non-selective NSAIDs in patients with hemophilia is currently missing. In this systematic review we aimed to give a complete overview of all publications reporting on NSAIDs and safety in patients with hemophilia.

2. Methods

2.1. Systematic search

Cochrane, Embase and Pubmed databases were systematically searched till March 2021 with search terms ‘hemophilia’ OR ‘bleeding disorder’ AND ‘non-steroidal anti-inflammatory agents’ OR ‘cyclooxygenase’ OR ‘analgesic’. The search was performed under supervision of a librarian. Supplementary file 1 shows the detailed search strategy. Conference abstracts from 2017 to the search date were included. Two independent authors (EB, MM) screened all publications on title and abstract and selected the studies eligible for full text screening. Any disagreements were resolved through discussion with a haematologist (LV). Studies were included when they reported about adverse bleeding or cardiovascular events in PWH while using NSAIDs, including COX-inhibitors and aspirin (>600 mg). Non-English articles, articles only including animal or in vitro experiments, articles only reporting about efficacy of NSAIDs in patients with hemophilia (PWH) and not mentioning adverse events and articles without full-text availability were excluded. Case reports with less than three patients and expert opinions were also excluded. After title and abstract screening, full-text screening was performed and data were extracted (EB, MM). Reference lists of the included articles were reviewed. We allocated all studies to two categories (clinical / laboratory), based on their reported outcome. Articles reporting both outcomes were allocated to both categories.

2.2. Critical appraisal

All included articles were critically appraised using the Joanna Briggs Institute (JBI) critical appraisal checklists [24,25]. This tool uses different checklists for different study designs. The appropriate checklist was chosen and bias was assessed by answering the questions (EB, MM). In order to give a summary of the amount of bias and quality of the study, the questions were allocated to the appropriate bias category (information bias, selection bias, confounding) and statistical analysis quality [26]. Risk of bias was graded as low, intermediate or high risk of bias. For a detailed explanation of the risk of bias assessment, see supplementary file 2/3. Sub-studies with different designs within an article were appraised separately.

3. Results

3.1. Search results and selection

Our search resulted initially in 1476 articles, after removing duplicates. After title/abstract screening and full-text screening, 19 articles were eligible for inclusion (see Fig. 1). Seven studies reported on clinical outcomes and were therefore allocated to the first category in Table 1. Two studies in this category included patients with bleeding and examined NSAID use [27,28]. These studies are displayed in *Italics* in Table 1. The rest of the studies included patients using NSAIDs and examined adverse (bleeding) events.

Eight articles reported on laboratory outcomes and were therefore allocated to the second category. An additional four articles covered both categories and were allocated to both.

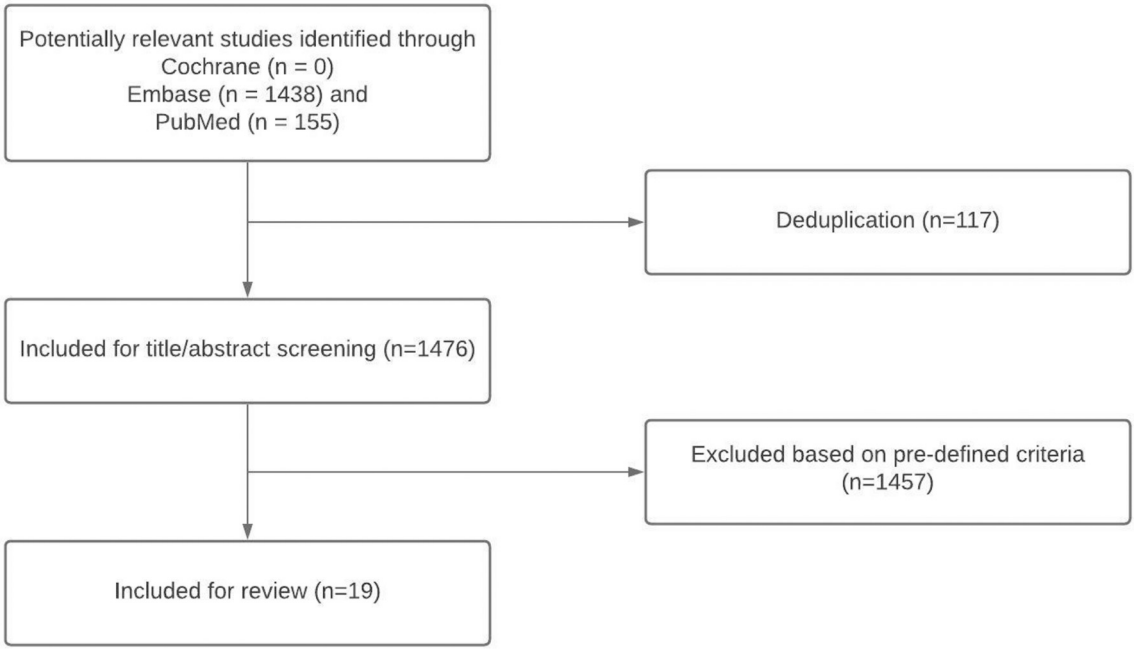

Fig. 1. flow diagram.

3.2. Studies focusing on clinical outcomes

Salicylate use was reported in three studies. One old study (1973) investigating gastrointestinal bleeds showed that 8 out of 107 bleeding episodes were linked to salicylates; 4/8 of the patients had a history of dyspepsia [29]. Another study (1982) described 7 patients using choline magnesium trisalicylate for 6 weeks and reported no statistically significant differences for gastrointestinal bleeds and joint bleeds as compared to placebo [30]. In a big multi-center cohort study with 42 upper gastrointestinal bleeding cases in patient with hemophilia and hepatitis C infection (25/42 with severe hemophilia, 6/42 with clinical signs of hepatic decompensation, 17/42 with human immunodeficiency virus co-infection, 5/42 chronic Hepatitis B surface antigen carriers), 40/42 subjects denied aspirin use. One patient had used aspirin two weeks earlier and data on one other patient was missing. Unfortunately, the total amount of patients using aspirin was not mentioned in this article and information on treatment regimens was lacking [27]. In conclusion, these studies suggests no increased bleeding risk during salicylate use.

A total of six studies reported on traditional NSAIDs. Four prospective double blind cross-over studies demonstrated no statistically significant differences in hemorrhages during traditional NSAID use or placebo [28,30–32]. These studies were performed in the '80 and investigated patients with different severities of hemophilia. Two studies reported no statistically significant differences in factor use during the trial and the two other studies only reported no difference in factor use *associated with bleeding episodes*. Information on pre-trial on-demand treatment regimens was lacking. In a big multi-center cohort study of PWH and hepatitis C virus, a statistically significantly increased likelihood of bleeding when using traditional NSAIDs during short periods (< one month prior to the bleeding) was described. However, only 35/1969 (1.8%) of the patients used traditional NSAIDs for this short period and the likelihood for bleeding was based on only three bleeding events. This increased likelihood was not seen with prolonged use of traditional NSAIDs. This was concluded on only two events in 217 patients using traditional NSAIDS for at least one month. A multivariate model adjusting for age, hepatic decompensation and platelets showed no association between bleeding risk and recent use of traditional NSAIDs. A multivariate analysis in a subset of 35 pairs (upper gastrointestinal bleeding case matched with controls for detection of *Helicobacter pylori*) without hepatic decompensation showed a 2.2-fold increased bleeding risk for patients with recent traditional NSAIDs use [27]. However, this association did not reach statistical significance. Again, information on factor replacement therapy was missing. A post hoc analysis using data from a cross-sectional study with 268 patients with moderate/severe hemophilia >40 years reported about 70 patients using traditional NSAIDs/COX-inhibitors, of whom 54 were treated on-demand or on prophylactic basis for less than five years. They showed that regular use of NSAIDs/COX-inhibitors (> three months per year) had a statistically significant association with a higher number of hematuria episodes.

Six studies reported on clinical adverse events in hemophilia patients on selective COX-2 inhibitors (celecoxib, rofecoxib, etoricoxib). The post hoc analysis mentioned above reported a statistically significant association of episodes of hematuria and NSAID or COX-2 use, but the authors do not distinguish between NSAIDs and COX-2 inhibitors. As such, no conclusion can be made whether the use of COX-2 inhibitors lead to an increased bleeding risk. In the big multi-center cohort study of PWH and hepatitis C virus, only 17 patients used coxibs for less than one month and experienced no bleeding events. In 267 patients using it for more than one month the likelihood of bleeding was not increased (based on six events). The multivariate analysis in 35 pairs without hepatic decompensation showed a non-statistically significant *decreased* upper gastrointestinal bleeding risk with recent coxib use (0.7-fold) [27]. Two studies documented a total of >995 days of rofecoxib and > 269 days of celecoxib respectively [33,34]. In the rofecoxib group, two small bleeds (mouth bleed, hematuria) were reported. Joint bleed episodes decreased after rofecoxib in two patients with target joints, which may point towards a protective joint effect of rofecoxib. During celecoxib, no bleeding events were seen. Also, no cardiovascular events were reported for both rofecoxib and celecoxib. These studies were performed retrospectively and included patients with variable dosing of factor replacement and inhibitors. Moreover, cardiovascular events were not expected as these studies included relatively young patients (3–54 years old). Also, severity of hemophilia was not reported and these factors may potentially limit the value of these results. Another study with 30 patients with severe hemophilia using celecoxib on a 15 days on/off schedule for two months, reported no relevant adverse events [35].

Table 1
All studies summarized and allocated to different categories based on outcome.

Rf	Population	NSAID + outcome measurement	Conclusion
Clinical outcomes			
2	PWH + HCV 13–89 yr On aspirin: unknown On tNSAIDs: 252 On COXIBs: 284 *Nested case-control with UGI bleeding cases (n = 42, of whom 25 had severe hemophilia) and matched controls for H. pylori detection (n = 42). 35 pairs without hepatic decompensation. Treatment regimens unclear.* Mean follow-up: 17.4 months	Self-reported questionnaire: traditional NSAIDs (naproxen, ibuprofen, diclofenac) coxibs (celecoxib, rofecoxib) and aspirin. *UGI bleeding: haematemesis, occult blood in stools with endoscopically ulcer, melena accompanied by a drop of Hb of at least 2 g/dL or requiring transfusion.*	Cohort univariate model:**SS:** Likelihood for bleeding significantly increased for usage of tNSAIDS for <1 month prior to the bleeding event (n = 3 events; RH: 3.66; 95% CI: 1.1–11.9). **NSS:** Risk was not increased by usage of tNSAIDS for >1 month (n = 2 events; RH: 0.42, 95% CI: 0.10–1.74). No bleeding events with coxibs usage <1 month. Bleeding risk was not increased by coxibs usage for at least 1 month (n = 6 events; RH: 1.05; 95% CI: 0.43–2.41). Cohort multivariate model: **NSS:** Adjusting for age, HD and platelets, bleeding risk was not associated with recent use of tNSAIDs (RH: 0.8 (0.3–2.2)) or coxibs (RH: 1.0 (0.4–2.3)). Nested case-control multivariate: **NSS:** 35 pairs without hepatic decompensation; UGI bleeding risk increased with recent tNSAIDs use (2.2-fold, 95% CI: 0.2–23.9) and reduced with recent coxib use (0.7-fold, 95% CI: 0.1–3.10). *11 of the 42 with UGI bleeds reported using drugs (n = 5 on tNSAIDs; n = 6 on coxibs). 40/42 denied asprin use. One patient had used aspirin two weeks earlier and data on one other patient was missing.*
4	*PWH A/B (n = 32) (22–66 yr)* *History of dyspepsia, n = 17; no dyspepsia, n = 15. Melaena/ haematemesis within the last 10 yr*	*Identification of a GI bleed was visualized by a barium meal or confirmed by patients who had surgery. Differentiation between dyspeptic and eupeptic group based on symptoms.*	*A total of 107 bleedings were found. Only 8/107 episodes were linked to salicylates (4 patients with history of dyspepsia and 4 patients without history of dyspepsia).*
5	PWH A/B moderate/ severe (n = 15)	Cross-over: Ibuprofen 3–4 daily 400 mg (4 months), placebo (4 months). Minor bleeds: epistaxis, oozing from gums, prolonged bleeding from venipunctures, and extensive subcutaneous bruises. Major bleeds: requiring factor administration.	**NSS:** Minor hemorrhages while on ibuprofen (n = 41), while on placebo (n = 18). Major hemorrhages: also no significant differences during study and till 4 months after the study.
6			

Table 1 (*continued*)

Rf	Population	NSAID + outcome measurement	Conclusion
	PWH A/B moderate/ severe (n = 15, 17–40 yr)	Cross-over: Ibuprofen 4 × 400 mg (2 months) and placebo (2 months). Evaluation at week 0, 4, 8, 12, 16. Diary of bleeding episodes and factor replacements associated with bleeds.	**NNS:** There was no difference in the amount of bleeding episodes or the amount of factor replacement associated with bleeds between the drug and placebo group. No statistics given.
11	PWH moderate/severe (n = 268, only n = 70/ 285 use NSAID/COX-2, 40–98 yr). 54/70 treated on demand/ ≤5 yr prophylaxis; 16/ 70 > 15 yr frequent prophylaxis	History of NSAID and/ or COX-2 inhibitor use: >3 months per year. Post hoc analyses from a cross sectional study for hematuria. No distinguishment was made between NSAIDS and COX-2 inhibitors.	**SS:** Association of additional episodes of hematuria and NSAID/ COX-2. OR = 2.37 (95% CI: 1.46–3.85); P < 0.001, while adjusted for frequency of prophylaxis and severity of hemophilia.
13	PWH A/B (n = 28) treated for acute hemarthrosis (n = 8), chronic synovitis (n = 7), target joints (n = 4) and pain (n = 9) (3-37 yr)	Rofecoxib; dosing regimens were chosen empirically (12,5-25 mg during 5 days – indefinitely) Information based on follow-up clinic visits, physical therapy examinations and nursing notes.	Total > 995 days of rofecoxib documented. Bleeding events: two (mouth bleed, hematuria), all resolved. No other AEs events (including cardiovascular events). Joint bleeding episodes decreased after rofecoxib in n = 2 with target joints.
14	PWH A/B (n = 12) treated with celecoxib for chronic synovitis (n = 8), target joint (n = 1) or pain (n = 3) (9–54 yr)	Celecoxib 200-400 mg daily Information based on follow-up clinical visits, physical therapy examinations and nursing notes.	Total > 269 days of celecoxib documented. No AEs (including hypertension or other cardiovascular events).
15	PWH A, severe, with pain due to advanced HA (n = 30) and control group (n = 30). (21–50 yr)	2 months (15 days on 15 days off) of Celebrex 200 mg	Two (6.6%) reported a mild headache, which was associated with the use of celecoxib. No further AEs were noted.
16	PWH mild/moderate/ severe + HA (n = 11) (23–44 yr)	Cross-over: Ibuprofen 3× daily 400 mg (2 months) and placebo (2 months)	Completed trial: n = 9; one patient on ibuprofen developed dyspepsia after 3 weeks. Side effects (headache, dysuria, dyspepsia, abdominal distention and itch): n = 5; only one patient was taking active drug at that time. **NNS:** no difference in bleeding episodes and factor use in ibuprofen and placebo.
18	PWH moderate/ severe, A/B + HA (n = 8) (28-67 yr). No history of peptic-ulcer or GI bleed.	Cross-over: Choline magnesium trisalicylate 2× daily 1000 mg (6 weeks) and placebo, followed by: Ibuprofen 4 daily 400 mg and placebo Questionnaires for side effects (bleeding, infusion)	Completed CMT trial: 7 (1 lack of efficacy); IBU: 6 (1 lack of efficacy, 1 BT > 15 min) **NNS:** no significant GI bleeds, no significant increase in joints bleedings or factor use.
19	PWH A/B (>12 yr, weight above 40 kg) Part 1: n = 102 Part 2: n = 93 (75 patients who completed part 1 entered part 2; 18 patients who discontinued part 1	Part 1 (6 weeks): etoricoxib 90 mg daily vs placebo, n = 51 in both groups Part 2 (6 months): etoricoxib 90 mg daily (n = 74) vs rofecoxib 25 mg daily (n = 19)	Part 1: completed trial n = 76 (lack of efficacy in both groups, n = 1 in each group due to adverse event) **SS:** clinical AE in patients on etoricoxib vs placebo: 51% vs 29% (p = 0.043), only two

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Table 1 (*continued*)

Rf	Population	NSAID + outcome measurement	Conclusion
	due to lack of efficacy entered part 2) Patients with serious adverse events during part 1 were ineligible for continuation.	AE were documented by patients and investigators.	(both etoricoxib group) related to bleeding (traumatic arthropathy and hemarthrosis, duodenal ulcer bleed). Discontinuation due to AE: 1 in placebo group (asthma) and 1 in drug group (duodenal ulcer bleed). **NSS:** No difference in incidence joint bleeds and factor use. Part 2: discontinuation due to AE (hemorrhagic duodenal ulcer, erosive gastritis, edema, subdural hematoma, dark stool, abdominal pain, heart-burn, and nausea): 9 out of 74 paients in etoricoxib group, 0 out of 19 patients in rofecoxib group. **NSS:** incidence SAE similar in both drugs. Type of SAE; Eterocoxib: hemorrhoids, hemorrhagic duodenal/ gastric ulcer, erosive gastritis, amputation, subdural hematoma. Rofecoxib: hemorrhage and hypotension. **NSS:** No difference in incidence of joint bleedings and factor replacement. Part 1 + 2: There were no serious thrombotic cardiovascular events in any groups. Renovascular AEs were uncommon. Hypertension occurred in one patients on etoricoxib (part 1), in one patient on rofecoxib (part 2) and in one patient on etoricoxib (part 2). Lower extremity edema occurred in one patient on etoricoxib (part 1) and in one patient on rofecoxib (part 2). Congestive heart failure did not occur.
Laboratory outcomes			
1	PWH A severe ($n = 3$) Healthy volunteers ($n = 10$)	Salicylate choline 870 mg oral; BT (incision arm)	Mean BT before drug use: mean 4.6 min; after drug use mean 5.3 min. No statistics given.
3	PWH A/B: $n = 74$ (4–68 yr) 8/74 on drug	Indocin & Motrin: doses not specified BT, PF	No statistical quantification given. We refer to Fig. 1 of the article. No conclusion can be made if PWH have a longer bleeding time while on drugs, compared to PWH not on drugs.
5			

Table 1 (*continued*)

Rf	Population	NSAID + outcome measurement	Conclusion
	PWH A/B ($n = 15$) Group 1: drug, placebo Group 2: placebo, drug	Ibuprofen 3–4 daily 400 mg (4 months), placebo (4 months). Laboratory tests: hematocrit values, platelet aggregation, bleeding times	**SS:** Ht drop while on ibuprofen (15–25%) highly significant in group 1 ($n = 4$). **NSS:** in group 2 ($n = 1$). No association between decrease in Ht and minor/major bleeding or BT. **NSS:** Platelet aggregation: no decrease in drug and placebo group. **NSS:** Prolonged BT during both drug and placebo period, $n = 3$; prolonged BT only during drug, $n = 3$; prolonged BT only during placebo, $n = 1$.
6	PWH A/B moderate/ severe ($n = 15$, 17–40 yr)	Cross-over: Ibuprofen 4×400 mg (2 months) and placebo (2 months). Tests on week 0, 4, 8, 12, 16: Hb, Ht, RBC, WBC, platelets, reticulocytes, prothrombin time. Test on day 1, week 8, week 16: BT	**NNS:** No difference was found in any test between the drug or placebo group. Hb, Ht and RBC tended to slightly decrease in the drug group compared to the placebo group, although non-significant.
7	PWH A/B, mild/severe ($n = 35$)	Aspirin 1 g BT (Ivy)	**Severe A ($n = 11$):** mean control BT 6 min (3–15 min), 2 h after aspirin 10–40 min or longer. After asprin: 5 patients needed plasma / clotting factor to stop the incision bleeding and 2 patients developed a hematoma after mild trauma. **Severe B ($n = 8$):** mean control BT 5.5 min (3–8 min); after aspirin 7–40 min or longer. After aspirin: 2 patients needed transfusion or plasma after incision. **Mild A ($n = 14$):** mean control BT 5 min (3–9 min), after aspirin 11.5 min (7–21.5). No statistic given. **Mild B ($n = 2$):** 1 patient: 5.5 min (10.5 after aspirin); 1 patient 11.5 control (15 after aspirin).
8	PWH A/B: $n = 9$ (16–36 yr) Five participants used in study 7.	Aspirin 1 g BT and platelet aggregation (ADP, epinephrine, collagen)	Mean BT initial: 6.0 min, after aspirin 24.5 min; three patients had a BT > 40 min. BT remained prolonged after 24-48 h post intake of aspirin. Aggregation with ADP similar before and after aspirin; with collagen negligible after aspirin; with epinephrine diminished after aspirin.
9	PWH A/B: $n = 12$ (18–40 yrs)	Ibuprofen 600 mg orally or lactose placebo (single dose) Hb, platelet, RBC, adhesiveness, PCV, BT and platelet	BT (mean ± SE) in drug group ($n = 6$) pretreatment 2.8 ± 0.4 min; 2 h after the drug 3.8 ± 0.6 min; 24 h after the drug 2.6 ± 0.2 min. BT in placebo

(*continued on next page*)

Table 1 (*continued*)

Rf	Population	NSAID + outcome measurement	Conclusion
		aggregation (ADP, epinephrine, collagen)	group ($n = 6$) pretreatment 3.6 ± 1.0 min; 2 h after the drug 3.3 ± 1.0 min; 24 h after the drug 2.8 ± 0.5 min. Hb, platelet and RBC, adhesiveness, PCV remained stable throughout the study for all groups. Aggregation: ADP, epinephrine, collagen inhibited at 2 h post drug. Returned to normal after 24 h.
10	PWH A/B ($n = 10$)	Single dose aspirin 1 g: Duke BT, ADP, adrenaline induced aggregation before drug and 2 h and 3 days after.	No statistics performed for hemophilia patients. BT seems to increase 2 h after aspirin. We refer to fig. 2 of the article. 3 days after aspirin, BT return to baseline.
12	PWH on ibuprofen alone: $n = 5$ (29 ± 4 yrs)	Ibuprofen 4 × 400 mg daily Arachidonic Acid platelet aggregation, platelet adhesive index, BT at baseline and 1, 2, 3 and 4 h after ibuprofen.	Arachidonic Acid platelet aggregation before – after 1 h – 2 h – 3 h – 4 h (mean % ± SE): 50 ± 14; 47 ± 14; 29 ± 9; 53 ± 11; 60 ± 2. Platelet adhesive index before – after 1 h – after 2 h – after 3 h – after 4 h (mean % ± SE): 33 ± 7; 39 ± 8; 42 ± 9; 45 ± 5; 40 ± 6. BT before – after 1 h (mean min ± SE): 7.6 ± 1.1–9.4 ± 1.3.
16	PWH + HA ($n = 7$) (23-44 yr)	Benoxaprofen 2× daily 300 mg (1 week); Salsalate 2× daily 1000 mg. BT, PCV, PT, KCCT, platelet count, platelet aggregation and β-TG, 5-HT	**NNS:** No difference in any test during salsalate or benoxaprofen compared to baseline (BT undefined). PWH on benoxaprofen: inhibition to collagen. 1 PWH reported mild dyspepsia during salsalate.
17	PWH + HA ($n = 9$)	Salsalate 3 g daily for 2 weeks BT, platelet aggregation: ADP and collagen	**NNS:** No effect on BT (pre-salsalate: 7.4 min ± SD = 4.2 vs post-salsalate: 7.7 min ± SD = 1.6) ADP or collagen induced aggregation.
18	PWH severe/ moderate, A/B + HA ($n = 8$) (28-67 yr). No history of peptic-ulcer or GI bleed.	Cross-over: Choline magnesium trisalicylate 2× daily 1000 mg (6 weeks) and placebo, followed by: Ibuprofen 4 daily 400 mg and placebo BT, platelet aggregation: ADP, collagen, epinephrine, ristocetin.	**NNS:** no difference was found in BT and PA during drugs and placebo. Although 4 BTs deviated from the normal (1 placebo, 3 ibuprofen) and 1 patient had a striking decrease of platelet aggregation in the CMT trial.

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Abbreviations: ADP = adenine di-phosphate, (S)AE = (serious) adverse events, BT = bleeding time, β -TG = β -thromboglobulin, CI = confidence interval, CMT = choline magnesium trisalicylate, COXIBs = cyclooxygenase inhibitors, COX-2 = cyclo-oxygenase 2, (U)GI = (upper) gastrointestinal, HA = hemophilic arthropathy, Hb = hemoglobin, HCV = hepatitis C virus, HD = hepatic decompensation, *H. pylori* = *Helicobacter pylori*, hr = hour, KCCT = kaolin cephalin clotting time, min = minutes, (m)g = (milli)gram, (t)NSAIDs = (traditional) non-steroidal anti-inflammatory drugs, OR = odds ratio, PWH = patients with hemophilia, Rf = reference, RH = relative hazard, RBC/WBC = red/white blood cell count, SD = standard deviation, SE = standard error, (N)SS = (non)-statistically significant, platelet aggregation = PA, PCM = paracetamol, PCV = packed cell volume, PT = prothrombin time, yr = year, ZDV = zidovudine, 5-HT = 5-hydroxytryptamine.

Clotting factor treatment regimens were not reported for these patients. The last study found a statistically significantly increased risk for adverse events in patients (12–71 years old) with mild, moderate or severe hemophilia on etoricoxib (51%) compared to placebo (29%) [36]. Important to note is that only two patients (3.9%), both in the etoricoxib group, had adverse events related to bleeding (traumatic arthropathy with hemarthrosis and duodenal ulcer bleeding). There were no differences in joints bleeds and factor use associated with joint bleeds. Again, pre-existent clotting factor treatment regimens were not included in the baseline characteristics. In part two of this study, etoricoxib and rofecoxib were compared during six months of treatment. No statistically significant differences in serious adverse events were seen in the etoricoxib group (6.8%; hemorrhoids, hemorrhagic duodenal/gastric ulcer, erosive gastritis, amputation, subdural hematoma) compared to the rofecoxib group (5.3%; hemorrhage, hypotension). Joint bleeds and factor replacement were also comparable and there were no serious thrombotic cardiovascular events in any groups. Renovascular adverse events like hypertension, lower extremity edema and congestive heart failure were very uncommon (Table 2 in article Tsoukas).

3.3. Studies focusing on laboratory outcomes

Seven studies reported on laboratory outcomes in relation to adverse events in patients using salicylates. The bleeding time, historically performed by making an incision and timing how long it takes to stop bleeding, was often used to assess platelet function. In one study, 7/19 patients with severe hemophilia required plasma concentrates to control the bleeding at the incision site for the bleeding test [37]. In patients with mild hemophilia, there were no abnormal bleeding times and these did not significantly differ from healthy controls. Two old studies (1971/1972) also reported prolonged bleeding time after aspirin, but without reporting statistics [38,39]. Two other studies (1985/1991) reported no statistically significant differences in bleeding time and platelet aggregation before and after salicylate ingestion [28,40]. The last study compared choline magnesium trisalicylate with placebo and reported no differences. However, one patient on choline magnesium trisalicylate had a striking decrease of platelet aggregation. It is important to note that some of these studies are old and of poor quality and do not always describe the performed tests in detail.

Seven studies reported on laboratory outcomes in PWH using NSAIDs. In two cross-over studies PWH were examined during four months of ibuprofen and four months of placebo treatment [31,32]. There were no statistically significant differences in bleeding time or platelet aggregation. Slightly decreases in hemoglobine, hematocrit and red blood cell count were observed but it was unclear whether this was related to subclinical gastrointestinal bleeds or plasma volume expansion. There was no association between decrease in hematocrit and minor/major bleeding or bleeding time. Another cross-over study with patients who used ibuprofen during six weeks and placebo during 6 weeks showed also no difference in bleeding time and platelet aggregation [30]. Another study reported a prolonged bleeding time two hours after the ingestion of ibuprofen in normal subjects as well as in those with mild and severe forms of hemophilia [41]. However, there was no change in clinical requirements of transfusions. In patients using ibuprofen platelet aggregation showed no clear trend one, two, three

and four hours after ingestion [42]. Bleeding times were slightly prolonged but no statistics were performed. Patients on benoxaprofen also showed no differences in bleeding time and platelet aggregation after one week usage and laboratory outcomes were comparable to baseline [28]. In one old study (1981) with only three hemophilia patients a mean bleeding time of 4.6 min before salicylate use and 5.3 min after salicylate use was reported, but they did not specify drug doses, nor did they perform statistics or report interpretable results [43].

No studies were identified with laboratory outcomes in PWH using COX-2 inhibitors.

3.4. Critical appraisal

Table 2 shows the results of the critical appraisal assessment.

4. Discussion

This systematic review provides an overview of the safety profile of selective and non-selective NSAIDs, including COX-inhibitors, in patients with hemophilia. These drugs are already prescribed in patients with hemophilia to treat arthropathic pain. However, due to fear for anti-platelet side effects and gastrointestinal bleeding, there is a lot of restraint in prescribing these drugs by a majority of clinicians. This fear is mainly based on the historically known side effects seen during the use of non-selective, old-fashioned drugs. With the introduction of selective inhibitors, the use of NSAIDs in patients with bleeding disorders becomes an attractive option, especially if reduction of pain is accompanied by cartilage protection, as seen in other rheumatic diseases [9,17–19].

The studies in our review reported no thrombotic cardiovascular events during the use of selective COX-2 inhibitors. Regarding adverse clinical bleeding events or increased factor replacement use, different results were found for the different COX-inhibitors. Celecoxib showed no evident increased bleeding risk, while use of rofecoxib resulted in two small bleeding events. Recent use of both celecoxib and rofecoxib actually showed a trend towards *reduced* upper gastrointestinal bleeding risk and rofecoxib resulted in less joint bleeds episodes, but these results were all not statistically significant [27,33–36]. An increased risk for adverse events was reported for patients on etoricoxib compared to placebo [36]. However, only two patients (3.9%) had bleeding related adverse events. It is important to note that evidence is limited as some studies reported no statistics, had a short follow-up or used small patient populations.

Regarding traditional NSAIDs, we can conclude that the majority of the studies reported no statistically significant differences in hemorrhages during traditional NSAID use or placebo. One study showed a trend towards an increased bleeding risk for patients with recent traditional NSAID use, however this did not reach statistical significance and importantly, was based on a small number of patients and events. After correcting for age, hepatic decompensation and platelet count, bleeding risk was no longer associated with recent use of traditional NSAIDs. In a study with hemophilia patients on regular traditional NSAIDs or COX-inhibitors (> three months per year), a statistically significant association with a higher number of macroscopic hematuria episodes was demonstrated. Unfortunately, this study did not report about the number of patients using COX-inhibitors hampering solid conclusions.

Most studies reporting on laboratory outcomes showed either no statistically significant differences in PWH using traditional NSAIDS or placebo regarding bleeding time, platelet aggregation or transfusion requirement. Two studies showed slightly prolonged bleeding time after ingestion of ibuprofen, but no statistics were performed.

The studies included in this review had several limitations. As we intended to give a complete overview, we also included old studies with low quality and a high risk of bias. Therefore, we assessed all studies with the JBI critical appraisal tool as described in our *Methods* section. Besides, study designs and populations were very heterogeneous, hampering good comparisons. It is difficult to generalize results from one study to the whole population. Eyster et al. only included patients who had been infected with hepatitis C virus and although their attempt to correct for hepatic decompensation and subsequent possible bleeding tendency, the results cannot be extrapolated to those who have never been infected with hepatitis C virus [27]. Moreover, it is hard to state whether adverse events are actually caused by using NSAIDs. There are several other factors that can influence bleeding tendency in patients with hemophilia. It is important to take severity of hemophilia and access and adherence to prophylactic treatment regime into account. Detailed information on this was lacking in some studies. The existence of comorbidities also needs attention. Eyster et al. showed that hepatic decompensation and the presence of *H. pylori* antibodies result in an increased risk for upper gastrointestinal bleeding [27]. Optimizing circumstances, e.g. eradicate Helicobacter. pylori and prescribing gastroprotective drugs, may decrease risk for adverse bleeding events, especially in countries where prophylactic treatment and close monitoring is not routinely available [44]. Besides, follow-up time in most studies was probably too short to draw conclusions on adverse cardiovascular events. In the general population, it was shown that NSAIDs

Table 2
Critical appraisal.

Study	INFORMATION BIAS	SELECTION BIAS	CONFOUNDING	STATISTICAL QUALITY
Binder	+	−	NA	−
Eyster 2007 (cohort)	+/−	−	+	+
Eyster 2007 (case control)	+	+	+	+
Eyster 1981	−	+/−	−	−
Forbes	−	+	+/−	+
Hasiba	+	−	NA	−
Inwood	+	+/−	NA	+/−
Kaneshiro	−	−	−	−
Kasper	+	+/−	NA	−
McIntyre	+	+/−	NA	−
Praga	−	−	−	−
Qvigstad	+/−	+	+	+
Ragni	+/−	+/−	−	−
Rattray 2005	−	−	−	−
Rattray 2006	−	−	−	−
Rodriguez-Merchan	−	+/−	NA	−
Steven	+	−	NA	+/−
Sweeney	+/−	−	−	−
Thomas	+	+/−	NA	−
Tsoukas	+	+	NA	+/−

Low risk of bias(+) Intermediate risk of bias (+/−) High risk of bias(−).

increase mean blood pressure [21]. This is also an important risk factor for cardiovascular disease and intracranial bleeds, especially in patients with hemophilia where a higher prevalence of hypertension is already existing [45]. Unfortunately, limited data exists on renovascular adverse events in patients with hemophilia on NSAIDs.

It is unclear whether changes in laboratory measurements (e.g. bleeding time) actually reflect clinical adverse events and whether all clinical events are detected. Small joint bleeds that are not detected by the patients, the so-called subclinical bleeding, have effect on joint health as well and NSAIDs may diminish these subclinical bleeds. These outcome measures may have different clinical implications and therefore we allocated all articles to two different categories, based on their outcome. Another limitation is the registration of medication use and adverse events, as most studies use self-reported documentation. Heterogeneous study designs, retrospective studies, cross-sectional studies or studies with a short follow-up are not always appropriate to evaluate potential adverse events.

5. Summary and future considerations

The fear for increased bleeding risk during use of NSAIDs, including COX-inhibitors, is not supported by the current literature. However, some of the studies are of low quality with a high risk of bias, included specific (e.g. hepatitis C positive) patients or didn't distinguish between COX-inhibitors and traditional NSAIDs. Also, some populations were relatively small and self-reported medication and adverse events registration was used. Causality is difficult to examine as there are several other factors that can influence bleeding tendency such as appropriate factor replacement therapy and severity of hemophilia. This information was not always available and follow-up is mostly relatively short.

In conclusions, these effective analgesic, cheap and easily accessible drugs may be of great value in developing countries and countries with a high rate of opioid poisoning, but also in developed countries due to potential joint protective effects.

5.1. What is needed to move the field forward

Future (randomized controlled) trials with longitudinal follow-up in large patient populations, including older patients, should be performed to confirm the alleged safe use of these drugs. These studies should include joint healt examinations, for example by ultrasounds of the main joints, to investigate the joint protective effects of anti-inflammatory treatment in vivo.

Practice points

- (Non-)selective NSAIDs are cheap, easily accessible and commonly prescribed analgesics for musculoskeletal pain.
- They may be of great value for patients with hemophilic arthropathy due to their potential joint-protective effects.
- Fear for increased bleeding risk and thrombotic cardiovascular events during the use of (non)-selective NSAIDs restrains prescription within the hemophilia population.
- Most (non-)selective NSAIDs had no evident risk for relevant adverse bleeding or cardiovascular events.
- Old studies with a high risk of bias, including specific and small patients populations, using self-reported registrations and not providing information on other factors that can influence bleeding tendency, hampered solid conclusions.

Research agenda

- To confirm the alleged safe use of these drugs, future (randomized controlled) trials with longitudinal follow-up in well-defined large patients populations should be performed.
- Joint health examinations should be included to investigate joint protective effects of anti-inflammatory treatment in vivo.

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Declaration of Competing Interest

None.

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Appendix A. Supplementary data

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