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Choosing and using non-steroidal anti-inflammatory drugs in haemophilia.

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Abstract

The management of pain and inflammation in haemophilic arthropathy is challenging due to the lack of anti-inflammatory analgesic agents perfectly suitable for this population. Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in the management of arthritis due to their analgesic and anti-inflammatory effects. Their use in persons with haemophilia (PWH), however, is limited due to increased risk of bleeding mainly from the upper gastrointestinal (UGI) tract. Cyclooxygenase-2 (COX-2) selective NSAIDs which have comparable analgesic effect to traditional NSAIDs (tNSAIDs) but with less UGI bleeding have been considered to be a suitable option for treatment of haemophilic arthropathy. COX-2 inhibitors, however, have an increased in the risk of cardiovascular (CV) disease. Although the atherosclerotic burden in PWH is similar to that in the general population, the risk of CV related deaths is lower. PWH have a higher risk of GI bleeding and lower risk of thrombotic disease compared to general population. Therefore, when PWH require anti-inflammatory/analgesic agents, it seems reasonable to use lowest possible dose of COX-2 inhibitors for the shortest period with a proton pump inhibitor cover (provided they do not have renal impairment or additional risk factors for CV disease) prior to starting COX-2 inhibitors. H. pylori infection should be tested for and eradicated prior to starting NSAID treatment in PWH. Furthermore, regular blood pressure and renal function test monitoring is required during COX-2 inhibitor treatment.
Introduction

Haemophilia A and B are characterised by bleeding, primarily into joints and muscles. Joint bleeding accounts for >90% of all serious bleeding episodes in person with haemophilia (PWH)[1]. Primary prophylaxis with factor concentrate has been shown to reduce the risk of haemophilic arthropathy [2]. However, despite regular prophylaxis, some PWH still develop arthropathy as do older patients who did not have primary prophylaxis. Haemophilic arthropathy is a chronic inflammatory and degenerative arthritic process that directly affects quality of life of the majority of adults with severe haemophilia [3]. Intra-articular haemorrhage causes synovial inflammation with hypertrophy and growth of friable new blood vessels that are vulnerable to further bleeding. Chronic synovitis predisposes the joint to recurrent bleeding and inflammation; within the joint, release of proteolytic enzymes activate osteoclasts and lead to destruction of cartilage matrix. Chronic inflammation causes fibrosis, cartilage degeneration and joint damage similar to osteoarthritis, with pain and reduced mobility. Chronic arthropathy is the main co-morbidity in the ageing PWH and joint damage increases with age in an almost linear fashion in both severe and moderate haemophilia [4]. Age-related osteoarthritic changes include degenerative joint changes, osteoporosis, muscle atrophy or sarcopenia and muscle weakness. Disturbance of gait and balance also contribute to the increasing pain and advanced haemophilic arthropathy in PWH [5]. Thus reducing pain and chronic inflammation are major components of haemophilic arthropathy management in addition to coagulation factor replacement for acute bleeding and prophylaxis.

Management of pain and inflammation in haemophilic arthropathy is challenging due to lack of anti-inflammatory analgesic agents perfectly suitable for this population[6]. Non-
steroidal anti-inflammatory drugs (NSAIDs) have been widely used in the management of arthritis due to their analgesic and anti-inflammatory effects. However, their use in PWH is limited due to increased risk of bleeding mainly from the upper gastrointestinal (UGI) tract [6] as a result of non-selective inhibition of cyclooxygenase (COX) 1 and 2, decrease platelet aggregation via suppression of COX-1 dependent thromboxane A2 and also inhibition of the production of gastroprotective prostaglandins primarily formed by COX-1 (Figure 1). The discovery of COX-2 selective NSAIDs which have comparable analgesic effect to tNSAIDs with no inhibition of the gastroprotective prostaglandins are alternatives for the treatment of haemophilic arthropathy [7].

Although, the World federation of haemophilia (WFH) guidelines for the management of haemophilia suggest the use of selective COX-2 inhibitors in the management of haemophilic arthropathy [8], there are no evidence based guidelines in pain management in PWH [9;10]. Compared to tNSAIDs, COX-2 inhibitors (coxibs) have significantly lower incidence of gastroduodenal ulcer complications and UGI bleeding [6;11;12]. Current evidence suggests that tNSAIDs and selective COX-2 inhibitors have a similar incidence of cardiovascular (CV) and renovacular adverse events [13;14]. In addition, there is emerging evidence that NSIADs are associated increase of stroke [15].

The epitome of age-related morbidity, CV disease, is a leading cause of mortality in elderly individuals, and presents a particular challenge when it occurs in PWH. Whilst the exact incidence of CV disease in haemophilia is unknown, incidence rates of conditions such as ischaemic heart disease (IHD) have steadily risen over the last 20-30 years, suggesting that cardiac problems are increasingly relevant in these individuals [6]. In addition, chronic renal disease can occur with increasing frequency in PWH in addition to the usual risk factors related to general population, because of haematuria, structural renal damage and frequent
use of antifibrinolytic drugs [16]. The aim of this review is to examine the available evidence on use of NSAIDs patients with haemophilia, risk of GI bleeding, CV risk and other risks associated with these drugs and to address the question of whether there are any NSAIDs that are more suitable for use in PWH. To achieve this a literature search was carried out on PubMed for publications in the last 30 years using the following words or phrases: h(a)emophilia, arthropathy, pain management of haemophilia, NSAIDs, COX-2 inhibitors, gastrointestinal bleeding, cardiovascular risk, stroke, renal disease, management of haemophilic arthropathy, Histamine receptor$_2$ blockers, proton pump inhibitors, misoprostol in preventing NSAID related bleeding and risk of thrombosis in haemophilia.

**What is the risk of GI bleeding in the general population and by how much is this increased when using NSAIDs?**

UGI bleeding is defined as bleeding from a gastrointestinal source proximal to the ligament of Treitz [17]. Bleeding from UGI is four times commoner than bleeding from lower GI tract [11;17]. Peptic ulcer disease remains the most common cause of UGI bleeding accounting for 21% to 40% of all bleeding episodes. The incidence of acute UGI bleeding in the UK ranges between 84-172 per 100,000 per year causing 50-70,000 hospital admissions per year [18]. *Helicobacter pylori* (*H. pylori*) infection and NSAID use are the most common causes of peptic ulcer disease [19;20]. The risks of GI and CV adverse effects are through to be due to the same mechanisms that NSAIDs exert their beneficial effects as anti-inflammatory and analgesic agents ie: by inhibition of COX-dependent prostaglandin synthesis [21]. COX-1 inhibition is associated with decreased platelet aggregation and GI toxicity increasing UGI bleeding [22;23]. Prostaglandin I$_2$ (PG I$_2$), has cardioprotective
properties, synthesised by COX-2 and promotes vasodilation and inhibition of platelet aggregation [22].

A meta-analysis of 16 randomised controlled trials (RCTs) involving almost 800,000 patients taking NSAIDs for at least 4 days, reported an odds ratio (OR) of 5.36 (95% CI, 1.79-16.1) vs placebo for severe UGI complications, including perforations, clinically relevant ulcers and bleeding [24]. The risk of GI complications with tNSAIDs is present from the first dose (with both short-term and long-term use), and strategies to prevent GI complications should be considered regardless of the duration of therapy [14]. Substitution of a coxib for a tNSAID has been shown to decrease the risk of GI toxicity including small but significant reduction of dyspepsia [25]. A Cochrane meta-analysis that compared the GI safety of coxibs with tNSAIDs concluded that coxibs were associated with significantly fewer gastroduodenal ulcers and fewer ulcer complications (including perforation, obstruction and bleeding), as well as fewer treatment withdrawals caused by GI symptoms when compared with tNSAIDs [26]. While protecting the stomach, proton pump inhibitors (PPI) do not prevent NSAID-induced damage in the rest of the gastrointestinal tract. A substantial number of patients who need NSAIDs are also taking low-dose aspirin for cardiovascular prophylaxis. From a GI perspective, the combination of aspirin plus a coxib provides a preferred option compared to aspirin plus a t-NSAID, for patients at high GI risk [14].

Pharmacokinetic characteristics of NSAIDs influence their safety and tolerability. NSAIDs with longer half-life and sustained-release forms such as diclofenac are associated with increased gastro-erosive effects as well as higher risk of bleeding and perforation [27;28]. A systematic review of observational studies on NSAIDs and upper GI bleeding/perforation published between 2000 and 2008 estimated the relative risk (RR) of upper GI
bleeding/perforation was 4.50 (95% confidence interval [95% CI] 3.82-5.31) for tNSAIDs and 1.88 (95% CI 0.96-3.71) for coxibs [28]. There is strong evidence to suggest that the GI and CV side effects and renal damage of NSAIDs are related to total daily dose [29-32]. Daily use of diclofenac sodium >75mg/day was associated with a 2-3-fold increase in GI complications compared with low or medium doses [29;32].

In addition to H. pylori infection which almost doubles the risk of GI bleeding [33], other risk factors that contribute to NSAIDs induced GI bleeding include, increasing age, co-existing medical illnesses such as ischaemic heart disease, congestive heart failure, renal failure, hepatic failure, thrombocytopenia or other haemostatic defects such as underlying bleeding disorders [34]. Patients who develop gastric or duodenal ulcers with or without bleeding should be tested for H. pylori infection and eradication therapy should be given [35]. A meta-analysis of randomized trials showed that H. pylori eradication therapy for prevention of recurrent ulcer bleeding is significantly more effective than short-term anti-secretory therapy alone (rebleeding 4.5 vs. 23.7%; odds ratio [OR] 0.18, 0.10–0.35) [36]. In those individuals who are at significant risk of developing UGI bleeding with NSAIDs, it is recommended that testing for H. pylori infection prior to commencing NSAIDs is performed. If positive, the infection should be eradicated prior to staring NSAIDs and a COX-2 inhibitor plus a PPI should be used [34;35].

In patients who develop NSAID induced UGI bleeding, NSAIDs should be stopped and a PPI should be commenced [35]. Those who require continued NSAIDs, COX-2 inhibitors with a PPI is recommended to reduce further risk of GI bleeding [34;35]. Combination of a COX-2 inhibitor and a PPI is associated with lower GI complications compared to a COX-2 inhibitor alone or combination of tNSAIDs plus a PPI [34]. PPIs do not offer protection beyond the
UGI and this has been shown in a large prospective RCT that found that clinically significant bleeding events occurring throughout the GI track were significantly greater in patients taking tNSAIDs in combination with omeprazole than in patients taking celecoxib [37;38].

The recommended strategies to decrease GI toxicity in NSAID users include co-therapy with misoprostol, histamine type-2 receptor antagonists (H2RAs) or PPIs and/or the use of COX-2 inhibitors [39;40]. The American College of Gastroenterology recommends that patients requiring NSAID therapy who are at high risk of bleeding should receive alternative therapy or, if anti-inflammatory treatment is absolutely necessary, a selective coxibs and/or co-therapy with misoprostol or high-dose PPI should be used [40]. Table 1 shows the tNSAIDs, COX-2 inhibitors, H2-receptors blockers and proton pump inhibitors available in UK.

What is the baseline risk of GI bleeding in haemophilia without NSAIDs?

UGI haemorrhage can occur in up to 25% of PWH and recurrent bleeding is common with a high mortality rate [41]. The absolute risk for developing UGI bleeding in a PWH is unknown. However, in a multicentre study with 2285 patients with haemophilia, there was a 1.3% annual incidence of clinically important UGI bleeding events [6]. This incidence is nearly 10 times greater than the 0.1% UGI bleeding rate reported in those without haemophilia (general population) [42]. The frequency and severity of bleeding may vary depending on the severity of haemophilia but there are no large studies exploring this issue. Mittal et al, in early 1980s, studied 243 PWH and reported that the type of haemophilia (A or B) and the presence or absence of an inhibitor or blood group had no relationship to the risk of GI bleeding [43]. However, this study reported that patients with severe haemophilia were at
higher risk of developing GI bleeding than mild haemophilia [43]. The possible explanations for this increased risk in severe haemophilia were lower threshold for bleeding in severe haemophilia with any underlying gastrointestinal pathology such as peptic ulcer disease, use of frequent analgesia such as NSAIDs for severe chronic arthropathy and development of chronic liver disease due to hepatitis transmitted by plasma or concentrates. Spontaneous haemorrhage in the bowel wall in severe haemophilia has been reported to occur in 4.85% of patients [43]. PWH continue to have arthropathic pain, especially those who have not had the benefits of primary prophylaxis. Despite the high prevalence of pain with significant impact on the quality of life of PWH, no high level evidence based guidelines on pain management of these patients are available. Use of NSAIDs, the standard analgesic and anti-inflammatory agents that are used in patients with arthritis without haemophilia, carry the additional risk of bleeding in PWH in addition to NSAIDs associated increased risk of cardiovascular, renal and other complications present also in the general population.

**What is the risk of NSAID related bleeding in Haemophilia?**

GI bleeding is often linked to the use of tNSAIDs such as ibuprofen, diclofenac sodium used to relieve pain associated with haemophilic arthropathy [6]. As well as UGI bleeding they may increase the risk of bleeding into haemophilic joints [44]. Studies assessing the safety and efficacy of NSAIDs in PWH are limited by small number of patients. A randomised, placebo controlled crossover study of 20 patients (age 17-40 years) with severe or moderate haemophilia A or B assessing the safety and efficacy of 1600mg ibuprofen daily for 16 weeks found no increase in the frequency of bleeding. Nobody had GI bleeding but one patient had dyspepsia and withdrew from the study. Due to the small number in this study,
it is difficult to draw a valid conclusion on safety of ibuprofen in PWH [45]. In a double blind controlled clinical trial using ibuprofen and placebo, pain was markedly reduced as assessed by pain score in eight out of nine patients using ibuprofen without significant bleeding or change in the use of factor concentrate [46]. Case reports of excessive bruising in one patient using ibuprofen [47] and three cases of GI bleeding after the use of over the counter NSAIDs have been published [48]. A multicentre, prospective, observational study of 2285 patients with haemophilia found that the risk of UGI bleeding was significantly increased after less than one month use of tNSAID (OR: 3.66; 95% confidence interval [CI]:1.1-11.9) but not with COX-2 inhibitors [6]. Furthermore it was reported that the relative risk of GI bleeding was significantly and independently increased with age >46 years (3.5; 95% CI: 1.1-10.6) and hepatic decompensation (4.4; 95% CI: 1.7-11.6). Presence of H. pylori positivity increased the likelihood of UGI bleeding but this did not reach statistical significance (odds ratio: 4.6; 95% CI: 0.3-83.9) [6]. Based on these finding the authors concluded that COX-2 inhibitors are safer alternative analgesic and anti-inflammatory agents for PWH with arthropathy [6]. Another small study of 12 patients using retrospective chart review found that celecoxib (COX-2 inhibitor) was safe and effective in treating chronic synovitis and joint pain in adults and children with haemophilia [49].

The first line of analgesia in PWH is often paracetamol/acetaminophen and this is also recommended by the latest WFH guidelines [8]. In addition to being a less effective analgesic agent, paracetamol may not be as safe in terms of gastrointestinal and cardiovascular aspects alongside its well-known hepatotoxicity [34]. A nested case control study found that paracetamol in any dose is associated with small but significantly increased risk of UGI complications (RR, 1.3; 95% CI 1.1-1.5). The RR was 3.6 (95% CI 2.6-5.1), if the
dose of paracetamol dose was more than 2g a day [50]. Regular use of paracetamol is associated with an increased risk of hypertension in both males [51] and females [52]. These side effects could be explained by the finding that paracetamol is a selective cyclooxygenase (COX)-2 inhibitor in humans [53]. This information suggests that paracetamol in PWH should be used with caution and risks and benefits of individual patients should be assessed at least when they are requiring frequent/high doses of paracetamol. The WFH 2012 guidelines on general care and management of haemophilia recommend COX-2 inhibitors pain due to chronic haemophilic arthropathy and advise avoiding other NSAIDs. Several expert reviews on management of haemophilic arthropathy also support the use of COX-2 inhibitors to relieve the pain in PWH [4,9;10;54;55]. However, due to the CV and renal risk of COX-2 inhibitors caution should be used in patients with hypertension and renal impairment. Due to the risk of GI bleeding PWH should receive COX-2 inhibitor and/or co-therapy with misoprostol or high-dose PPI [40]. Although, the prevalence of H.pylori infection is similar in PWH to patients without haemophilia [56], PWH are at higher risk of bleeding due to due to underlying coagulopathy [57]. Screening for and eradication of H.pylori prior to starting COX-2 inhibitors is recommended [40].

Cardiovascular, stroke and renal risks associated with NSAIDs in general population

In 2005, the European Committee for Medicinal Products for Human Use (CHMP) recognised an increased risk of thrombotic events, such as myocardial infarction and stroke with COX-2 inhibitors [58]. As a result, CHMP stated that COX-2 inhibitors must not be used in patients with established ischaemic heart disease and/or cerebrovascular disease [58]. The following year, they concluded that tNSAIDs also carry an increased risk of thrombosis, especially
when these drugs are used at high doses for a long period [59]. A large meta-analysis of cohort and nested case control studies found an increased risk of CV events for all tNSAIDs and COX-2 inhibitors [60]. Several other meta-analyses also found that tNSAIDs and COX-2 inhibitors have similar CV risk [61-63]. Naproxen appeared to be the least harmful in relation to CV risk, but this advantage has to be weighed against higher GI toxicity compared to COX-2 inhibitors [64]. There are no published randomised control trials specifically designed to compare CV, GI and renal safety of tNSAIDs and COX-2 inhibitors. The Prospective Randomized Evaluation of Celecoxib Integrated Safety vs Ibuprofen or Naproxen (PRECISION) [https://clinicaltrials.gov/NCT00346216] study is currently running and is designed to answer the question of overall benefit to risk balance of celecoxib when compared to two of the most commonly prescribed tNSAIDs in the treatment of arthritis pain. The thrombotic and renal risk of both tNSAIDs and COX-2 inhibitors are related to dose and duration of treatment. A pooled analysis of data from 7950 patients in 6 placebo controlled trials comparing celecoxib with placebo in conditions other than arthritis with a follow-up up to at least 3 years, found that the CV risk (primary end points combination of CV death, myocardial infarction, stroke, heart failure or thromboembolic events) increased with dose regimen (p=0.0005). Risk was lowest for celecoxib 400mg once daily dose (hazard ratio, 1.1; 95% CI, 0.6 to 2.0) and highest for 400mg twice daily dose (hazard ratio, 3.1; 95% CI, 1.5 to 6.1). The risk was further increased in those patients who had higher baseline risk of CV disease [65].

The benefits of low dose aspirin in secondary prevention of CV disease clearly outweigh the risk [66] and COX-2 inhibitors do not interfere with the anti-platelet effect of low dose aspirin [34]. However, tNSAIDs being COX-1 inhibitors impair thromboxane $A_2$ synthesis
hence platelet aggregation. It has been shown that with the exception of diclofenac and meloxicam, almost all other tNSAIDs can interfere with the anti-platelet effect of aspirin. COX-2 inhibitors are a better anti-inflammatory and analgesic option if anti-inflammatory drugs are essential for patients taking aspirin for CV protection [34]. It should be noted, however, that in 2005 the CHMP advice stated that “COX-2 inhibitors must not be used in patients with established ischaemic heart disease and/or cerebrovascular disease” [58].

Due to their increased cardiovascular risk, which is dependent on the dose, duration of therapy, and base-line cardiovascular risk, both t-NSAIDs and coxibs should be used with caution in patients with underlying prothrombotic states and/or concomitant cardiovascular risk factors. [34].

The nephrotoxicity of NSAIDs is well recognised. A case control study using data from a general practitioners database found that patients on NSAIDs had a 3-fold increased risk of developing acute renal failure compared to non-users. Patients on higher doses of NSAIDs had slightly higher risk (RR, 3.4; 95% CI, and 1.6-7.0) compared to low and medium doses (RR, 2.5; 95% CI, and 1.2-5.4) [67]. The nephrotoxicity of NSAIDs is mediated via nonspecific blocking of cyclooxygenase, subsequent inhibition of prostaglandin synthesis leading to vasoconstriction, and reversible renal impairment in volume-contracted states [68;69]. This may lead to acute tubular necrosis and acute renal failure. NSAIDs also produce interstitial nephritis and papillary necrosis, resulting in chronic renal failure [70]. Renal toxicity is not limited to tNSAIDs and clinical trials with celecoxib have shown renal effects similar to those observed with comparator tNSAIDs [71]. Patients at greatest risk for renal toxicity are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, ACE-inhibitors, angiotensin II receptor antagonists, and the elderly [71]. As the incidence of
renal adverse effects with t-NSAIDs and coxibs is similar, blood pressure should be monitored and managed appropriately in patients taking these drugs [34].

**What is the risk of cardiovascular, stroke and renal disease in patients with haemophilia?**

The risk factors for myocardial infarction and stroke such as diabetes mellitus, obesity, hypercholesterolemia and smoking in PWH appear to be similar to those of the general population [72]. However, a cross-sectional study of a cohort of 701 haemophilia patients aged 30 years or older found that the prevalence of hypertension is higher in PWH than in the general population [73]. The cause of this increased prevalence is unknown. Blood pressure measurements should be part of standard care in haemophilic patients aged 30 years or older. The low level of factor VIII or IX in haemophilia A and B which is associated with reduced thrombin generation should at least theoretically protect against a thrombotic risk [74]. Several surveys and cohort studies in PWH have shown that CV mortality was lower compared to general population [75]. Furthermore, the incidence of CV disease was higher in patients with mild haemophilia (3.4%) than moderate (0.7%) and severe (0.4%) disease (p<0.001) [76]. PWH have the same degree of atherosclerosis burden as the general population but there is reduced CV disease and CV morality in PWH [74]. It is postulated that the reduced thrombin generation in PWH may favourably affect the plaque phenotype/behaviour rather than plaque load.

In a surveillance study from 1993 to 1998, it was reported that PWH had a 50 fold increased risk of death from renal disease compared to the general population [77]. PWH have several...
risk factors contributing to renal damage including bleeding in the renal tract, increased prevalence of hypertension, NSAID use and HIV infection.

**Concluding remarks on NSAID use in Haemophilia**

tNSAIDs increase the risk of bleeding and other complications throughout the entire GI tract and the risk is increased further in patients with additional comorbidities such as coagulopathies. Even when tNSAIDs are used with PPI, the protection against GI bleeding is only in the UGI tract. COX-2 inhibitors carry a lower risk of GI bleeding compared to tNSAIDs and if used in patients at higher risk of GI bleeding they have a better outcome. Both tNSAIDs and COX-2 inhibitors carry increased risks of thrombotic and renal complications. The increased risk is GI, CV and renal complications vary across individual agents, dose, duration of treatment and conditions of use. PWH have higher risk of GI bleeding and renal disease while having a lower risk of thrombotic disease compared to the general population. Therefore, if a PWH requires anti-inflammatory/analgesic agents, it seems reasonable to use the lowest possible dose of COX-2 inhibitor for a short period of time with PPI cover, provided they do not have renal failure and additional risk factors for CV disease. Table 5 shows the estimated incidence of GI bleeding and MI or stroke in patients with haemophilia by NSAID type usage. Prior to starting COX-2 inhibitors, it is recommended to screen for, and if positive eradicate, *H. pylori* infection in PWH. Furthermore, regular blood pressure monitoring and renal function testing are required once COX-2 inhibitors are commenced. It must be appreciated that there is a balance between managing pain effectively to improve the quality of life in PWH and minimising the risk adverse events associated with these drugs.
**Figure 1. Effects on cyclooxygenase inhibition on vascular system and gastric mucosa**

- **COX-1**
  - Platelet
  - Thromboxane (TXA2)
    - Vasoconstrictor
    - Promotes platelet aggregation
    - Haemostasis
    - Thrombosis

- **COX-2**
  - Prostacyclin (PGI2)
    - Vasodilator
    - Inhibitor of platelet aggregation
    - Gastric mucosal protection

- **tNSAIDs / Aspirin**
  - Endothelial cell
  - Coxibs

*tNSAIDs: traditional non-steroidal anti-inflammatory drugs; COX: cyclo-oxygenase*

Adapted from Park et al; Vasc Health Risk Manag. 2014 [78].
Table 1. **tNSAIDs, COX-2 inhibitors, \( H_2 \)-receptors blockers and proton pump inhibitor available in UK**

<table>
<thead>
<tr>
<th>tNSAIDs</th>
<th>Non-COX selective</th>
<th>Indomethacin, Diclofenac, Piroxicam, Ibuprofen, Naproxen, Mefenamic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preferential COX-1</td>
<td>Aspirin</td>
</tr>
<tr>
<td></td>
<td>Preferential COX-2</td>
<td>Nabumetone, Meloxicam, Etodolac, Paracetamol</td>
</tr>
<tr>
<td>Selective COX-2 inhibitors</td>
<td>Etoricoxib, Celecoxib, Parecoxib</td>
<td></td>
</tr>
<tr>
<td>( H_2 )-receptor blocker</td>
<td>Cimetidine, Famotidine, Nizatidine, Ranitidine</td>
<td></td>
</tr>
<tr>
<td>Proton Pump Inhibitors (PPI)</td>
<td>Esomeprazole, Lansoprazole, Omeprazole, Pantoprazole, Rabeprazole Sodium</td>
<td></td>
</tr>
</tbody>
</table>

tNSAIDs: traditional non-steroidal anti-inflammatory drugs; COX: cyclooxygenase; \( H_2 \): Histamine\(_2\)
Table 2. Upper gastrointestinal bleeding risk with individual NSAIDs in general population

<table>
<thead>
<tr>
<th>Name of the non-steroidal anti-inflammatory drug</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib</td>
<td>1.0 (0.4-2.1)</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>2.6 (1.5-4.6)</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>3.1 (2.3-4.2)</td>
</tr>
<tr>
<td>Naproxen</td>
<td>7.3 (4.7-11.4)</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>8.6 (2.5-29.2)</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>9.0 (3.9-20.7)</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>9.8 (4.0-23.8)</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>12.6 (7.8-20.3)</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>14.1 (5.2-39.9)</td>
</tr>
</tbody>
</table>

Adapted from Lanas et al; Gut. 2006 [79]
Table 3. What is known about risks of using NSAIDs in general population and person with haemophilia

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a)</td>
<td>NSAIDs increase the risk of GI bleeding and tNSAIDs carry a higher risk of bleeding than COX-2 inhibitors. The risk is dose and treatment duration dependent</td>
</tr>
<tr>
<td>b)</td>
<td>Both tNSAIDs and COX-2 inhibitors have an increased risk of thrombotic and renal complications. These risks are dose and treatment duration dependent.</td>
</tr>
<tr>
<td>c)</td>
<td>The risk of GI bleeding and renal disease are higher while CV disease and related deaths are lower in PWH compared to the general population</td>
</tr>
</tbody>
</table>

tNSAIDs: traditional non-steroidal anti-inflammatory drugs; COX: cyclooxygenase; GI: gastrointestinal; CV: cardiovascular; PWH: person with haemophilia
Table 4. Summary of recommendations on use of NSAIDs in person with haemophilia

a) Balancing the pain benefit versus the increase risk of adverse events, COX-2 inhibitors at the lowest possible dose and for the minimum treatment duration are the most reasonable option to control arthritic pain in PWH.

b) Use of PPI in all PWH but especially severe/moderate haemophilia when using tNSAIDs or coxibs is recommended.

c) Screening and eradication of H. pylori infection is recommended in PWH prior to commencing NSAIDs.

d) Regular blood pressure and renal function test monitoring are required once COX-2 inhibitors are commenced.

PPI: proton pump inhibitors; NSAIDs: non-steroidal anti-inflammatory drugs;
COX: cyclooxygenase; PWH: person with haemophilia.
Table 5. The estimated incidence of GI bleeding and MI or stroke in patients with haemophilia by NSAID type usage.

<table>
<thead>
<tr>
<th>Group</th>
<th>Relative risk</th>
<th>Absolute risk – incidence per year per 1000 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Age 30</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General population [80]</td>
<td>-</td>
<td>0.87</td>
</tr>
<tr>
<td>Haemophilia with no NSAIDs [6, 42]</td>
<td>10.0</td>
<td>8.7</td>
</tr>
<tr>
<td>Haemophilia plus diclofenac [79]</td>
<td>3.1</td>
<td>27.0</td>
</tr>
<tr>
<td>Haemophilia plus ibuprofen [79]</td>
<td>4.1</td>
<td>35.7</td>
</tr>
<tr>
<td>Haemophilia plus naproxen [79]</td>
<td>7.3</td>
<td>63.5</td>
</tr>
<tr>
<td>Haemophilia plus indomethacin [79]</td>
<td>9.0</td>
<td>78.3</td>
</tr>
<tr>
<td>Haemophilia plus celecoxib [79]</td>
<td>1.0</td>
<td>8.7</td>
</tr>
<tr>
<td>Risk of MI or stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General population (Males only) [81]</td>
<td>-</td>
<td>0.3</td>
</tr>
<tr>
<td>Haemophilia with no NSAIDs [82]</td>
<td>0.59</td>
<td>0.18</td>
</tr>
<tr>
<td>Haemophilia + diclophenac [60]</td>
<td>1.4</td>
<td>0.25</td>
</tr>
<tr>
<td>Haemophilia + ibuprofen [60]</td>
<td>1.18</td>
<td>0.21</td>
</tr>
<tr>
<td>Haemophilia + naproxen [60]</td>
<td>1.09</td>
<td>0.20</td>
</tr>
<tr>
<td>Haemophilia + indomethacin [60]</td>
<td>1.3</td>
<td>0.23</td>
</tr>
<tr>
<td>Haemophilia + celecoxib [60]</td>
<td>1.17</td>
<td>0.21</td>
</tr>
</tbody>
</table>

Extreme caution should be exercised in using this table due to many limitations including the assumption that the risks are multiplicative, are not based on absolute measure in patients with haemophilia, the baseline GI risk is based on a single population and where meta-analysis data are used not all data included was uniform in the magnitude of the risk.

References


75. Kamphuisen PW, ten Cate H, Cardiovascular risk in patients with hemophilia, Blood. 2014;123:.1297-301.


81. Based on QRisk2 calculator (www.qrisk2.org)