**REVIEW ARTICLE**

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# Nonsteroidal anti-inflammatory drugs in clinical practice — are there any new reports?

## ABSTRACT

Nonsteroidal anti-inflammatory drugs (NSAIDs) show high efficacy in anti-inflammatory and analgesic therapy and are the most widely used drugs worldwide. In addition to their efficacy, the widespread use of NSAIDs has been fostered by their wide availability, especially as some are available without a prescription. Unfortunately, this group of drugs is also fraught with adverse effects, including serious ones.

Due to the widespread use of NSAIDs, updated data on this group of drugs is critical for practitioners to make the right therapeutic decisions. Each patient requires individualised therapy because, in the case of NSAIDs, the choice of a specific drug, in relation to the type and nature of pain and potential adverse effects, is very important.

Over the years, attempts have been made to develop an algorithm for the selection of NSAIDs according to the risk of developing complications associated with drugs of this group in individual cases, taking into account the so-called ‚golden mean' of NSAIDs and the knowledge of interactions between some NSAIDs and cardioprotective acetylsalicylic acid.

This study is another attempt to summarise this issue. With the current state of knowledge, resulting primarily from the publication of the large PRECISION study, which is limited to only three molecules, there remains the fundamental question of expanding the knowledge to include such commonly used drugs as diclofenac, ketoprofen, meloxicam and etoricoxib. In addition to the results of the PRECISION study, this version includes a study by an expert group on other NSAIDs on the Polish market and presents an algorithm for selecting NSAIDs according to individual gastroenterological and cardiovascular risk.

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## MECHANISM OF ACTION OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

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The anti-inflammatory and analgesic effects of nonsteroidal anti-inflammatory drugs (NSAIDs) are related to the blocking of cyclooxygenases. This mechanism also underpins most adverse effects of NSAIDs [1].

The production of prostaglandins (PGs) depends on the release of arachidonic acid from cell membrane phospholipids via phospholipase A2 following cell stimulation, for example, by cell damage. Arachidonic acid then undergoes a series of enzymatic reactions (the arachidonic acid cascade), where two main pathways can be identified: cyclooxygenase (COX) and lipoxygenase (LOX). The LOX pathway produces leukotrienes (e.g. ketoprofen is one of the few NSAIDs to inhibit this pathway), while the COX pathway

leads to the production of prostanoids: PG, prostacyclin and thromboxanes (TX) [1, 2].

Two forms of COX are known: COX-1 and COX-2. The two isoforms are approximately 60% homologous, have similar active sites and molecular weights, but they are encoded by different genes, found in different cells, and show different activities. COX-1, a constitutive enzyme, protects the gastric mucosa via the PGs produced and affects blood vessels. COX-2 is produced by damaged tissues, endothelial cells, macrophages and fibroblasts. It is the inducible form of the enzyme and plays an important role in inflammatory processes [1, 2].

NSAIDs act as competitive COX inhibitors, blocking COX by acetylating the enzyme. During this reaction, the acetyl group of NSAIDs binds covalently to the hydroxyl group of serine (Ser-530 in human platelets), located at the N-terminal end of the COX molecule. This blockade is irreversible. Serine acetylation causes nonspecific inhibition of the enzyme-substrate reaction by blocking access of arachidonic acid to the COX catalytic centre. Thus, NSAIDs inhibit the endoperoxide synthesis complex reaction only at its first COX-mediated stage and do not affect the reaction in which peroxidase is involved [3].

## DIVISION OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

NSAIDs are a group of drugs with a variety of chemical structures and possible uses but with at least three important features in common: identical pharmacological properties, a similar basic mechanism of action and similar adverse effects. Due to the wide variety of drugs in this group, they are often divided into smaller, more consistent subgroups. NSAIDs can be divided according to their chemical structure.

However, the most clinically relevant division of NSAIDs appears to be based on their ability to inhibit the activity of particular COX isoenzymes.

NSAIDs are divided as follows:
— selective COX-1 inhibitors — for example, acetylsalicylic acid at a cardiac dose of 75–150 mg;
— nonselective COX-1 inhibitors (so-called classic NSAIDs) — which have a greater affinity for COX-1 than for COX-2. This group includes ibuprofen (with the high-

est affinity for COX-2 in this group), diclofenac, ketoprofen and naproxen (with intermediate affinity for COX-2), and acetylsalicylic acid in the classic dose, piroxicam and indomethacin (with the lowest affinity for COX-2 in this group);
— preferential COX-2 inhibitors — having a higher affinity for COX-2 than for COX-1. This group includes, for example, nimesulide, meloxicam and aceclofenac;
— selective COX-2 inhibitors (so-called coxibs) — having 200 times or more higher affinity for COX-2 than COX-1. Those currently available include celecoxib and etoricoxib [4, 5].

## USE OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Despite tremendous advances in pharmacotherapy and the introduction of many new drugs, NSAIDs are still widely used and hold an important place in rheumatology and in the broader pain management strategy. According to international therapeutic standards, NSAIDs are the primary group of drugs in seronegative spondyloarthropathies (so-called first-line drugs) [6]. NSAIDs are also used in rheumatoid arthritis, juvenile idiopathic arthritis, other autoimmune diseases with associated arthritis, regional pain and overload syndromes of the so-called soft tissue rheumatism, and especially frequently in osteoarthritis (OA) and spondyloarthritis [7]. When choosing NSAIDs in OA, it is worth looking at their chondroprotective effect, i.e. their protective effect on articular cartilage. Some NSAIDs, e.g. coxibs, in addition to their anti-inflammatory effects, stimulate articular cartilage by increasing the synthesis of glycosaminoglycans (GAGs) and hyaluronate and encouraging the formation of cartilage's extracellular substance (matrix) [8]. Unfortunately, some reports indicate that naproxen and ibuprofen inhibit articular cartilage glycosaminoglycan synthesis [9].

NSAIDs are used in the management of virtually all types of pain, including cancer pain. They are the first step of the so-called analgesic ladder. Amongst others, they are indicated as analgesics for post-traumatic and muscular pain, pain after surgery or tooth extraction, neuralgia, root syndromes, discopathy, renal and hepatic colic, migraine and menstrual pain. For more severe pain, they can be used in combination with opioids [10].

Unfortunately, all NSAIDs can cause characteristic adverse effects, which include dyspeptic symptoms and damage to the gastric and duodenal mucosa (erosions, ulcers, gastrointestinal bleeding, perforation), impaired renal function and renal papillary necrosis, liver damage, increased cardiovascular risk and increased symptoms of circulatory failure, haemolytic anaemia, granulocytopenia or impaired platelet function, ototoxic effects, hypersensitivity reactions (skin lesions, aspirin-induced asthma). Introducing selective COX-2 inhibitors (so-called coxibs) into medical practice seemed to be a major breakthrough. These compounds have over two hundred times higher affinity for COX-2 than COX-1. In large clinical trials, selective COX-2 inhibitors have indeed been shown to cause fewer gastrointestinal side effects, but selective COX-2 inhibition is not an indicator of a reduction in overall complications during treatment [11].

## CARDIOVASCULAR COMPLICATIONS ASSOCIATED WITH NSAID USE

NSAID use in cardiac patients is addressed in several different papers, which are mentioned below.

The European Society of Cardiology (ESC) guidelines for the treatment of non-ST-elevation myocardial infarction (NSTEMI) indicate that NSAIDs, such as ibuprofen and naproxen, can inhibit the irreversible blockade of this enzyme by acetylsalicylic acid through combining with COX-1 [12]. Selective COX-2 blocking is also associated with a risk of prothrombotic effects. For this reason, the use of these drugs in combination therapy with acetylsalicylic acid should be avoided (Recommendation Class III, Level of Evidence C) [13]. Aceclofenac, celecoxib, di-

clofenac and ketoprofen should be preferred as these drugs do not exhibit this effect and can be combined with acetylsalicylic acid [14].

In contrast, the ESC guidelines for ST-elevation myocardial infarction (STEMI) do not recommend NSAIDs for analgesic use in anginal pain. These guidelines emphasise that NSAIDs other than acetylsalicylic acid, including selective COX-2 inhibitors, increase the risk of death, re-ischaemia, cardiac rupture and other complications, and for this reason, their use should be discontinued in STEMI.

NSAIDs should also be used with particular caution in heart failure, as they double the risk of acute heart failure, may worsen renal function and may even increase the risk of gout exacerbation [15, 16].

A meta-analysis (Safety Of non-Steroidal anti-inflammatory drugs (SOS project) 2014) on the use of NSAIDs in four European countries showed a 24% increase in hospitalisation for heart failure, including a significant increase in heart failure in patients treated with indomethacin (55%), nabumetone and rofecoxib (48%), piroxicam (28%), ibuprofen (24%), diclofenac (21%), nimesulide (19%), naproxen (18%), ketoprofen (4%) and a reduction of 3% (statistically insignificant) in those treated with aceclofenac and 4% (statistically insignificant) in those treated with celecoxib. However, considering all components of the SOS project, i.e. hospitalisations for heart failure, ischaemic stroke and myocardial infarction, and adding them up, the risk increase is distributed slightly differently: ketoprofen — 3%, celecoxib — 4%, meloxicam — 7%, aceclofenac — 8%, nimesulide — 13%, naproxen — 14%, diclofenac — 27% (Fig. 1) [17–19].

In 2016, the position paper on the safety of NSAIDs by the working group for Cardio-
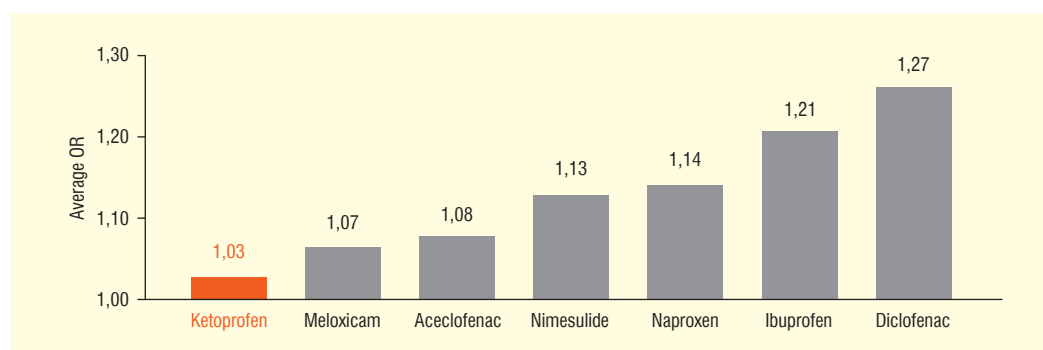


**Figure 1.** Risk of cardiovascular complications. Relative risk value for cardiovascular complications according to nonsteroidal anti-inflammatory drug (NSAID). Own idea based on the SOS study. OR — odds ratio

vascular Pharmacotherapy of the European Society of Cardiology was published. Based on the findings of the Kearney and Trelle meta-analyses, the paper concluded that naproxen has the least adverse cardiovascular effects. The position of diclofenac as a cardiovascular-safe drug has been questioned, as the cardiovascular risk increases by more than 40% compared to placebo. This resulted in the European Medicines Agency (EMA) issuing an alert regarding the safety of diclofenac, especially in patients at vascular risk [20].

In the PRECISION study, involving more than 24,000 patients (predominantly osteoarthritis patients) with a mean follow-up time of 34 months, celecoxib was confirmed to be safer in terms of the risk of gastroenterological complications than naproxen and ibuprofen, and it was also found to show better cardiovascular safety than ibuprofen. At the same time, celecoxib use has been shown to have a significantly lower risk of renal damage than ibuprofen use. A growing body of data suggests that celecoxib differs significantly from other coxibs, especially rofecoxib, which is considered in most meta-analyses and whose results may be skewed. This is supported by the results of a meta-analysis by Gunter et al. in which celecoxib and naproxen significantly reduced the risk of myocardial infarction compared with other NSAIDs. However, the comparisons involved only three molecules, including celecoxib, which is not marketed in Poland due to its poor efficacy [21].

In conclusion, NSAIDs (both nonselective NSAIDs and COX-2 inhibitors) should not be used 3–6 months after an acute coronary syndrome, regardless of treatment modality, due to the increased cardiovascular risk found for high doses of nonselective NSAIDs and COX-2 inhibitors regardless of dose [22].

The use of NSAIDs for cardiac arrhythmias also requires particular caution. Atrial fibrillation (AF) is the most commonly diagnosed arrhythmia and affects almost 2% of the global population. The incidence increases with age, and almost 30% of people over 80 have persistent AF. Anticoagulants, including a new group of drugs (novel oral anticoagulants, NOACs), are used to prevent stroke in these patients. These include the factor X inhibitors — rivaroxaban and apixaban — and the direct thrombin inhibitor — dabigatran. When using these drugs, naproxen is not recommended as it interacts with them [23].

## HYPERTENSION AND NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

The results of numerous studies indicate that NSAIDs may increase blood pressure (BP), especially systolic blood pressure. In people with normal BP, the hypertensive properties of NSAIDs are less severe than in patients with arterial hypertension (AH).

Among NSAIDs, the most pronounced increase in BP is observed for the use of ibuprofen, indomethacin and naproxen. In the PRECISION-ABPM study, in which BP was well controlled with hypotensive drugs in most patients, celecoxib did not affect BP compared to naproxen and ibuprofen. The greatest, statistically significant BP increase was observed in patients treated with ibuprofen. Increases in BP in 24-hour ambulatory blood pressure monitoring (ABPM) to values meeting criteria for AH were twice as rare in patients treated with celecoxib than in those on ibuprofen and naproxen [24]. Another study of NSAIDs found aceclofenac, ketoprofen and nimesulide to have no effect on either systolic or diastolic blood pressure [25–27]. In contrast to full-dose NSAIDs, low-dose acetylsalicylic acid (75 mg) has no significant hypertensive effect. The Hypertension Optimal Treatment (HOT) Study, which involved more than 18,000 patients with AH, found only an insignificant increase in BP of 0.6/0.3 mm Hg in patients treated with acetylsalicylic acid [28, 29].

On 28 June 2013, the Coordination Group for Mutual Recognition and Decentralised Procedures — Human (CMDh) approved by a majority vote new safety recommendations for medicinal products containing diclofenac, available as capsules, tablets, suppositories or injections, with systemic action. They aim to minimise the risk of cardiovascular complications from the use of these drugs. In patients with significant cardiovascular risk factors (e.g. AH, hyperlipidaemia, diabetes, smoking), diclofenac should only be used after careful consideration [30].

Three mechanisms lead to AH due to NSAID use. The production of prostaglandin E2 (PGE2) and prostacyclin (PGI2), which exhibit vasodilatory effects, is reduced under the influence of NSAIDs, leading to an increase in vascular tone and making the vascular walls more sensitive to endothelin. NSAIDs also reduce the production of PGE2 by cells in the interstitium, mainly in the renal medulla. This increases sodium

and water reabsorption in the renal tubules, causing fluid retention in the body. In addition, once COX activity is reduced, arachidonic acid is metabolised to a greater extent by cytochrome P450, and its metabolites formed via this pathway (including epoxyeicosatetraenoic acid and hydroxyeicosatetraenoic acid) exhibit hypertensive properties [31, 32]. If AH develops during NSAID use in patients with a diagnosed cardiovascular condition, the dose of NSAIDs should be discontinued or reduced, and if this management does not improve, hypotensive drugs should be used. Calcium antagonists are preferred (no significant increase in systolic blood pressure has been observed with concomitant administration of NSAIDs as opposed to other groups of hypotensive drugs) [33–36].

At the same time, studies have also shown that NSAIDs can reduce hyperalgesia. Secondary hyperalgesia leads to chronic pain. Pain is accompanied by other symptoms such as anxiety, insomnia and depression. Inflammatory pain has a highly detrimental impact on the cardiovascular system. Its presence causes an increase in BP, tachycardia, increased oxygen consumption and many other effects. Thus, the paradoxically positive effect of NSAIDs on the cardiovascular system should not be overlooked [37].

## GASTROENTEROLOGICAL COMPLICATIONS DURING THE USE OF NSAIDS

The vast majority of adverse effects associated with NSAID use are gastrointestinal. COX-1 inhibition results in a reduced PGE2 effect, decreased submucosal flow and mucus and bicarbonate production, with increased *Helicobacter pylori* cytotoxicity and decreased gastric juice volume, which leads to a decrease in pH, inhibition of angiogenesis and cell proliferation, which compromises healing processes. There is also direct damage to the gastrointestinal mucosa through the activation of free radicals and myeloperoxidase. The entire gastrointestinal tract is affected, although the upper part is much more frequently affected than the lower. The most commonly observed gastrointestinal symptoms are dyspepsia (epigastric pain, postprandial fullness or early satiety), loss of appetite, belching, various abdominal pains, nausea and vomiting, increased symptoms of gastro-oesophageal reflux disease and bowel movement disorders: diarrhoea, constipation and flatulence.

Less common symptoms include weight loss and signs of gastrointestinal bleeding (vomiting blood/matter resembling coffee grounds and/or blood in stools or tarry stools) [38].

The most common factors that increase the risk of gastroenterological adverse effects of NSAIDs are old age (> 70), renal and hepatic disease, a history of peptic ulcer disease, smoking, alcohol abuse, dialysis, *Helicobacter pylori* infection, COX isoenzyme blocking with predominance of COX-1, high NSAID dose, use of > 1 NSAID, use of H2 blockers (they do not protect against complications due to NSAIDs) and the concomitant use of other drugs that damage the gastrointestinal mucosa (corticosteroids, bisphosphonates, anticoagulants, mucolytics). A critical consideration is the combination of NSAIDs with low doses of acetylsalicylic acid (especially in cardiac patients), which is associated with a significantly higher risk of gastroenterological complications [39].

The most serious complication with the use of NSAIDs is gastrointestinal bleeding, especially upper gastrointestinal bleeding. It always poses a risk to health and life. The high cost of hospitalisation and intensive care, including endoscopic therapy, is not insignificant. It has been shown that there is approximately 2–3 times less risk of gastrointestinal bleeding when using coxibs and diclofenac than when using indomethacin or naproxen. For this reason, the choice of product and appropriate additional prevention is important [40, 41].

Several clinical trials and meta-analyses have shown that including a proton pump inhibitor (PPI) can be of definite benefit and can prevent or significantly reduce most complications, but only those involving the upper gastrointestinal tract. As a preventative dose, for example, 20 mg of pantoprazole or an equivalent dose of another PPI once daily is recommended. Because of the adverse effects, it is recommended to use PPIs selectively in patients with an increased risk of gastrointestinal complications. However, there is no need to concomitantly use PPIs in young patients with no history of gastric and duodenal ulcer disease or gastrointestinal bleeding if past NSAID tolerance has been good, the current duration of therapy is short and the NSAIDs used are among the "safer" drugs. Patients with concomitant increased cardiovascular and gastrointestinal risks should take PPIs regardless of whether they are using a nonselec-
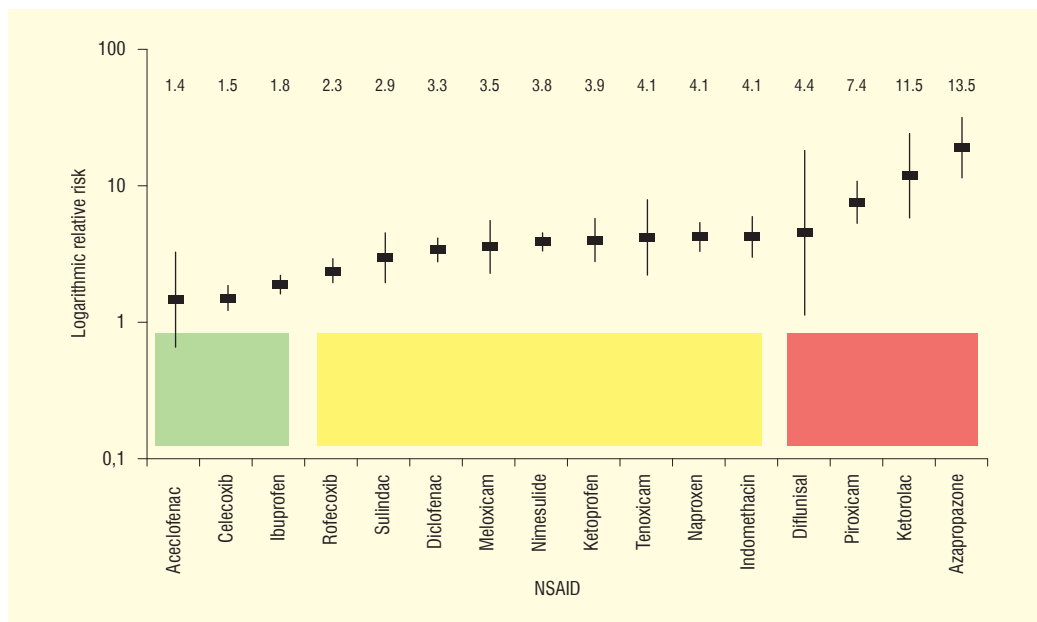
**Figure 2.** Safety of non-steroidal anti-inflammatory drugs (NSAIDs) — SOS project

tive NSAID or COX-2 inhibitors. An alternative for patients at very high risk is opioids [42].

In the CONCERN study in patients taking concomitant acetylsalicylic acid, there were more than twice as many gastrointestinal bleeding events in those patients who used celecoxib compared with patients treated with naproxen. During an 18-month follow-up, a comparable number of major cardiovascular events were reported in both groups [43].

Entirely new light was shed on the gastroenterological safety of NSAID use by the European Commission-funded SOS research project, which included a literature review of the risk of gastroenterological (meta-analysis of 28 studies) and cardiovascular complications (meta-analysis of 25 studies) after the use of NSAIDs. It showed the lowest risk (RR, *relative risk*) of gastrointestinal complications for aceclofenac (RR = 1.4), celecoxib (RR = 1.5) and ibuprofen (RR = 1.8); medium for diclofenac (RR = 3.3), meloxicam (RR = 3.9), nimesulide (RR = 3.8) and ketoprofen (RR = 3.9); and the highest risk for piroxicam (RR = 7.4) (Fig. 2).

It is worth noting, however, that the dose of ketoprofen used in these studies was 300 mg, while the dose currently allowed by the summary of product characteristics (SmPC) is 200 mg per day, which directly translated into a reduction in the risk of gastric complications, and did not at all affect the efficacy of the therapy used [44]. In a 2016 study by Rafaniello, a 2.5-fold decrease in the number of gastroen-

terological complications was demonstrated after a reduction in the dose of ketoprofen, following the use of 200 mg of ketoprofen (Fig. 3) [45].

In addition, it is important to note that the shorter the drug's half-life (T1), the shorter the inhibition of cytoprotective prostanoid synthesis in the gastrointestinal tract, kidneys and cardiovascular system. Molecules with a short half-life include dexketoprofen, ketoprofen, ibuprofen and diclofenac. Moreover, special formulations of NSAIDs, such as the use of right-handed enantiomers of NSAIDs or NSAID salts, are recommended to improve safety [46].

It should also not be forgotten that most NSAIDs are metabolised in the liver. Table 1 summarises relevant information on the hepatic metabolism of NSAIDs and their effect on the activity of individual cytochrome P450 isoenzymes.

Knowledge of the effects of individual NSAIDs on hepatic metabolism enables effective prevention of adverse drug interactions. A prudent choice of NSAIDs must be made in patients taking statins (atorvastatin), antibiotics (such as clarithromycin or azithromycin), i.e. drugs that are highly metabolised in the liver by cytochrome CYP3A4 (e.g. paracetamol). In addition, it is important to note that omeprazole and metronidazole, by inhibiting CYP2C9, may exacerbate the effects and increase the risk of adverse effects when using NSAIDs metabolised by this cytochrome, such
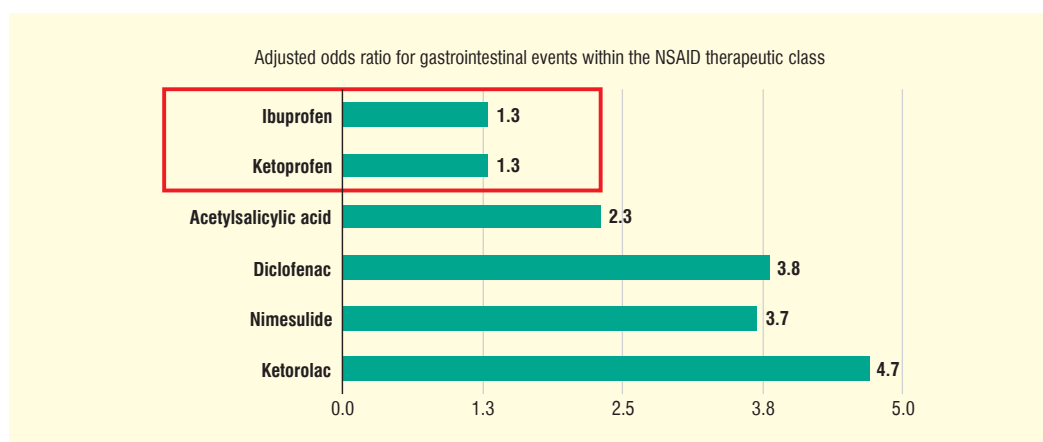
**Figure 3.** Analysis of the Italian database of adverse reactions to nonsteroidal anti-inflammatory drugs (NSAIDs)

**Table 1.** Hepatic metabolism of nonsteroidal anti-inflammatory drugs (NSAIDs)

| Nonopioid analgesic | Hepatic metabolism CYP | Cytochrome P450 isoenzyme subject to CYP inhibition |
|---|---|---|
| Celecoxib | 2C9, 3A4 | 2D6, 2C8 |
| Diclofenac | 2C9, 3A4 | 2C9, 2E1, 3A4 |
| Etoricoxib | 3A4 | |
| Ibuprofen | 2C9, 2C19 | 2C9 |
| Indomethacin | 2C9, 2C19 | 2C9, 2C19 |
| Ketoprofen, dexketoprofen | conjugation | |
| Mefenamic acid | 2C9 | 2C9 |
| Meloxicam | 2C9, 3A4 | |
| Metamizole | Hydrolysis to 4-N-methylantipyrine | 3A4 |
| Naproxen | 1A2, 2C9 | |
| Nimesulide | 2C9, glucuronic acid conjugation | |
| Paracetamol | 1A2, 2C9, 2D6, 2E1, 3A4 | 3A4 |

as celecoxib, diclofenac, ibuprofen, meloxicam or mefenamic acid [47–49].

## NEPHROLOGICAL COMPLICATIONS OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Analgesic nephropathy is a slowly progressive, drug-induced renal tubulo-interstitial disease (especially induced by combination drugs containing paracetamol and/or NSAIDs combined with codeine or caffeine, as well as phenacetin-containing preparations) characterised by a progressive clinical course and ultimately by bilateral renal atrophy, often with the development of renal papillary necrosis. This nephropathy is caused by the "traditional" analgesics: paracetamol (acetaminophen) and NSAIDs, especially salicylates, and the renal damage associat-ed with them is an important and significant health problem, especially among the elderly. Typical analgesic-induced nephropathy is a chronic kidney disease characterised by renal papillary necrosis and chronic interstitial nephritis [50–53]. The effects of NSAIDs may be associated with a wide range of tubular, interstitial, glomerular and vascular damage. The renal effects of NSAIDs are well understood and occur quite rarely in the acute form, and are primarily associated with an increased risk of chronic renal failure. More attention should be paid to elderly long-term and regular NSAID users. Patients starting therapy should be monitored regularly, taking into account drug interactions [54].

Special attention should be drawn to two groups of patients susceptible to this form of renal failure: patients with latent renal disease and the elderly. Patients with latent (undiag-

nosed) renal disease are particularly susceptible, with more than 30% of them likely to develop deterioration of renal function after exposure to NSAIDs. Renal disease can lead to increased PG production and this mechanism largely determines maintaining renal blood flow and glomerular function. In the elderly, susceptibility to the renal effects of NSAIDs is caused by several reasons, which include:

— a frequently reduced albumin concentration, which leads to a reduction in the protein-bound fraction of NSAIDs and thus a higher free drug concentration;
— reduced total body water content, leading to increased NSAID concentrations;
— reduced metabolism of NSAIDs in the liver, which may result in increased blood concentrations of the drug.

All of the above factors can combine to increase NSAID toxicity in this group of patients [55, 56]. NSAIDs with a long half-life, such as meloxicam or naproxen, are not recommended in this group. Drugs such as ibuprofen, indomethacin and naproxen are not removed in haemodialysis [57].

Drug forms and selection

According to current recommendations for pain management, NSAIDs can be taken orally, intravenously or applied topically. The use of this group of drugs in suppositories and intramuscular injections is absolutely not recommended due to the adverse effects of NSAID administration by these routes on their pharmacokinetic profile and, therefore, the speed of analgesic effect and analgesic effect itself, which depends on the concentration of the drug at the site of nociception. The more severe the inflammation in a patient suffering from pain, the more potent the COX-2 inhibitory NSAID should be selected for therapy [58, 59].

## TOPICAL MEDICATIONS

Topical NSAIDs can be applied to intact skin in forms such as creams, gels, ointments, patches and sprays. The individual forms differ in their skin penetration and level of absorption. Drugs based on gel and microemulsion formulations appear to have better absorption properties than creams. In addition to the formula of application, the chemical characteristics of the administered drug are also important. In the case of topically applied NSAIDs, the molecular weight of the drug, lipophilicity and extent of absorption of the active ingredients appear to be the most important.

Once applied to the skin, the drugs are absorbed, reaching therapeutic concentrations in the surrounding tissues. The serum concentration of topically applied NSAIDs is significantly lower than that of orally applied NSAIDs, therefore the risk of adverse effects is significantly reduced. In a study on diclofenac, its serum concentration after topical application was shown to be approx. 0.4–2.2% of the concentration of that drug when administered orally. Other advantages of using topical forms of NSAIDs include the protection of the active ingredients from the action of gastric enzymes and the avoidance of the first-pass effect in the liver. The main adverse effects of topical NSAIDs are various types of skin irritation, generally of mild intensity. According to the data, for diclofenac, such reactions are more frequent compared to placebo, while for ketoprofen they are comparable to placebo. For osteoarthritis of the knee, topically applied ketoprofen was shown to be effective in reducing pain at a level comparable to that of orally administered celecoxib. The results of a Cochrane systematic review indicate that topical application of diclofenac or ketoprofen significantly reduces pain in patients with chronic musculoskeletal diseases [60–67].

## ORAL MEDICATIONS

Various oral forms of NSAIDs are available on the Polish market: capsules, tablets, gel capsules, water-soluble formulations in sachets—these are used according to the patient's preference and swallowing function. The individual forms of NSAIDs also differ in their onset of action and time to pain relief in the patient. Water-soluble formulations in sachets will have the fastest effect: they reach maximum concentration in the blood after 15–20 minutes. NSAIDs in salt form (sodium, lysine) are faster to relieve pain. Traditional capsules or tablets, depending on the molecule, relieve pain after an hour (ketoprofen or diclofenac), up to 5 hours (meloxicam). The usual treatment of pain involves administering the drug 1 to 3 times a day, which depends on the half-life of the NSAID. Unfortunately, the convenience of administering the drug once daily, although very important, also carries the risk of adverse effects, e.g. the half-life of meloxicam is about 20 hours, so it can be administered once daily, but during this time it negatively affects COX-1 and COX-2. Extended-release forms (with the prefix SR, DUO, PRT, Retard) are

also available and are used once daily. Such forms are convenient and preferred for patients who forget to take their medication or who receive polytherapy for other conditions. Unfortunately, such forms may be responsible for more frequent enteropathies, without always yielding satisfactory therapeutic results. In order to provide adequate analgesic and anti-inflammatory therapy, the patient must have continuity of drug action twenty-four hours a day so that they do not need a rescue medication used on an ad hoc basis. Insufficient action of NSAIDs may be associated with too low a dose of the drug or too long intervals between doses, resulting in too short a maximum concentration period. In this situation, the patient initiates additional treatment on their own. In many cases, they take another NSAID. A new form of the well-known molecule, ketoprofen forte SR, which can be used twice daily, will soon be available on the Polish market. Each dose will provide 12-hour analgesia and will be a compromise between a single administration of the drug once daily and multiple administrations, e.g. 3 times daily, to fully provide comfort to the patient with pain [68–72].

## CONCLUSIONS

NSAIDs are among the most commonly used drugs worldwide. The widespread use of NSAIDs is due to their high analgesic and anti-inflammatory efficacy, but also to their easy availability, including without a prescription. Unfortunately, this is accompanied by a relatively high risk of various adverse effects, resulting from the mechanism of action of NSAIDs themselves and the presence of comorbidities, but also associated with the concomitant use of other drugs or dietary supplements.

Therefore, the appropriate choice of drug for the individual patient seems to be so important. It is possible to choose from a number of medications from this group, differing slightly in their mechanism of action—which gives the possibility to select a drug depending on the risk of complications (Fig. 4).

In addition, the risk of side effects can be reduced through:
— keeping NSAID therapy as short as possible and using the minimum effective dose;
— educating the patient about possible side effects, the risks of using NSAIDs without medical supervision (e.g. ibuprofen) and an absolute necessity to contact the doctor in case of symptoms suggestive of dangerous NSAID complications;
— paying attention to the drugs the patient is taking for their hepatic metabolism—checking for interactions at the level of cytochrome P-450 isoenzymes and, if possible, discontinuing drugs that increase the risk of NSAID adverse effects;
— using safer forms of the drug (SR form, enteral), which prolongs the absorption and action of the drug, reduces gastrointestinal symptoms, although it may increase the incidence of enteropathy;
— topical use of NSAIDs with proven efficacy in patients at high cardiovascular and gastroenterological risk; with the general rule of avoiding NSAIDs;
— blood pressure monitoring during and up to 3 months after NSAID treatment, especially in patients with coexisting diabetes,
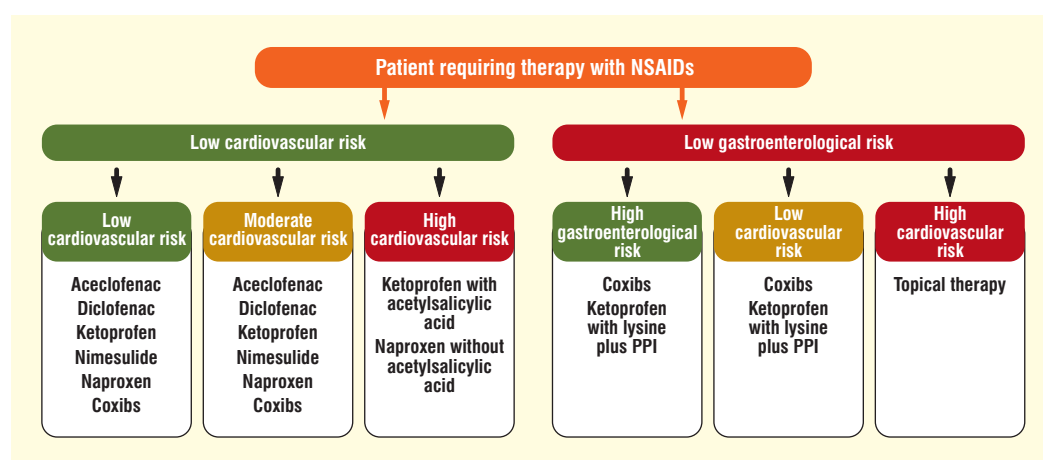


**Figure 4.** Author's proposal of an algorithm for the selection of nonsteroidal anti-inflammatory drugs (NSAIDs) according to cardiovascular and gastroenterological risk. PPIs — proton pump inhibitors

hypertension, renal impairment and those treated with angiotensin-converting enzyme inhibitors or sartans;
— in patients at high gastroenterological risk, periodic monitoring of blood counts during NSAID treatment;
— avoidance of NSAIDs until six months after an acute coronary syndrome event;
— in patients with hypertension, preference for NSAIDs that do not increase blood pressure, such as ketoprofen, aceclofenac, nimesulide;
— in patients on cardiovascular doses of acetylsalicylic acid (secondary prevention) and taking NSAIDs, continuing treatment with acetylsalicylic acid, but with a two-hour interval; ibuprofen should be avoided absolutely and consideration should be given to the potential adverse interaction (reduction in antiplatelet efficacy of acetylsalicylic acid) when using naproxen; ketoprofen or celecoxib should be preferred;
— in patients at high cardiovascular risk and low gastroenterological risk, in whom acetylsalicylic acid is not necessary (primary prevention), naproxen should be preferred;
— in patients on modern anticoagulant therapy with non-vitamin K antagonist oral anticoagulants (NOACs) — due to interactions — naproxen is rather not recommended; and
— in patients at high gastroenterological risk and low cardiovascular risk, preferring selective COX-2 inhibitors, possibly preferential COX-2 inhibitors (aceclofenac or ketoprofen with lysine) and in this situation, always NSAIDs should be given with an additional PPI.

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The authors report no conflict of interest with respect to the article.

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