Cardiovascular risk of non-steroidal anti-inflammatory drugs

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Summary
Non-steroidal anti-inflammatory drugs (NSAIDs) belong to the most widely used drugs. Results of recent large meta-analyses have shown that the cardiovascular risk of NSAIDs is more serious than originally believed and is not associated exclusively with coxibs; it is also increased when using so called traditional NSAIDs. Data obtained to date show the safest drugs of this class in terms of cardiovascular risk are naproxen and ibuprofen at low doses. The position of naproxen as the safest NSAID has been challenged by some more recent findings. The authors examine some results of meta-analyses and conclusions of regulatory agencies.

Key words: cardiovascular risk – coxibs – diclofenac – ibuprofen – naproxen – non-steroidal anti-inflammatory drugs

Kardiovaskulární riziko nesteroidních antirevmatik

Souhrn
Nesteroidní protizánětlivé léky (non-steroidal anti-inflammatory drugs – NSAIDs) patří k nejčastěji používaným léčivům. Výsledky rozsáhlých metaanalýz klinických studií publikovaných v posledních letech ukázaly, že kardiovaskulární riziko nesteroidních antirevmatik je závažnější, než se doposud myslelo a není vázáno výlučně na koxiby. Zvyšují ho ale i tzv. tradiční nesteroidní antirevmatika. Z dosavadních poznatků vyplývá, že z pohledu kardiovaskulárního rizika k nejbezpečnějším přípravkům patří naproxen a ibuprofen v malých dávkách. Pozice naproxenu jako nejbezpečnějšího nesteroidního antirevmatika je některými novějšími nálezy poněkud zpochybňována. Autoři přispívají do diskuse o některých výsledcích metaanalýz klinických studií i závěrech regulátorů.

Klíčová slova: diklofenak – ibuprofen – kardiovaskulární riziko – koxiby –naproxen – nesteroidní antirevmatika

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs), a relatively old class of drugs, rank among the most widely prescribed drugs worldwide. The first non-salicylate NSAID was phenylbutazone, synthesized by Geigy in 1946 and put on the market under the trademark Butazolidin in 1949 [1]. Initial experience with Butazolidin was published in 1952 [2]; in the 1960s, the drug was followed by ibuprofen, mefenamic acid and indomethacin and, later, by a host of other agents, with the development of novel NSAIDs culminating in so called coxibs. While having different chemical structures, the mode of action of all NSAIDs is identical, i.e., inhibition of cyclooxygenase, a molecule playing a crucial role in the metabolism of arachidonic acid.

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It did not take long after their introduction into clinical practice that NSAIDs were shown to have serious side effects, particularly gastrointestinal, cardiovascular, and renal ones, cause fluid retention, and raise blood pressure; and the spectrum of undesirable effects keeps on expanding [3,4].

Treatment with non-selective NSAIDs (nsNSAIDs) is associated with a higher risk of side effects as they inhibit not only COX-2 but, also, COX-1. The advent of coxibs offered the same analgesic effect while reducing the risk of gastrointestinal complications.

The issue of cardiovascular effects of NSAIDs first received attention after the introduction of rofecoxib into clinical practice and its subsequent withdrawal from the market by the manufacturer. In the ensuing years, it became apparent that other nsNSAIDs are also associated with increased cardiovascular risk. Reports of major regulatory agencies regarding cardiovascular risk in individual years are shown in tab. 1. The European Medical Agency (EMA) warned against the increased cardiovascular risk associated with diclofenac, particularly when given at high doses, as early as 2013 [5]. A detailed

evaluation of this issue culminated with the FDA requiring stronger label warnings about the cardiovascular risk of NSAIDs [6]. The agency stated that myocardial infarction or stroke may occur already within the first months of treatment. The risk of experiencing cardiovascular events increases with longer duration of therapy and use of higher doses. The increase in relative risk in individual clinical trials is in the range of 10–50 % and over, and depends on the type of the NSAID, doses used, and duration of therapy.

These conclusions were formulated by the FDA after analyzing a host of clinical trials, most importantly three trials, a British, Swiss, and a Danish one (tab. 2). In 2013, a British group published a meta-analysis of 280 randomized trials comparing NSAIDs with placebo and 474 randomized trials with head-to-head comparison of various NSAIDs [7]. The bulk of data related to COX-2 inhibitors, diclofenac, ibuprofen, and naproxen. The incidence of major cardiovascular events (MACEs) increased by about a third in patients receiving coxibs or diclofenac. Compared with placebo, COX-2 inhibitors were associated with a significantly increased risk of MACEs [relative risk (RR) = 1.4; 95% confidence interval (95% CI): 1.1–1.7; p = 0.0009), similar to that of diclofenac (RR = 1.4; 95% CI: 1.1–1.8; p = 0.0036)]. The risk related primarily to myocardial infarction and vascular death representing another 3 MACEs (fatal in 1) in 1 000 patients treated with COX-2 inhibitors or diclofenac for a period of 1 year. Vascular death was increased significantly by coxibs and diclofenac, non-significantly by ibuprofen, but not by naproxen (1.08; 0.48–2.47, p = 0.80).

The year 2011 saw the publication of a study by Swiss authors who had conducted a meta-analysis of 31 clinical trials comparing diclofenac, ibuprofen, naproxen, and 4 coxibs (celecoxib, etoricoxib, rofecoxib and lumiracoxib) with placebo in 116 429 patients totaling 115 000 patient-years [8]. Except for naproxen, all NSAIDs – particularly diclofenac and etoricoxib – were associated with increased risk of cardiovascular death. The study did not document an increased risk for coxibs as compared with other NSAIDs.

A study conducted in Denmark and published in 2011 analyzed data of a total of 83 677 patients from national registries over the 1997–2006 period. The study designed to follow up, in myocardial infarction survivors, the risk of death and infarction recurrence in relation to NSAID therapy demonstrated that even short-term therapy with traditional NSAIDs, and diclofenac in particular, raised the risk of death and infarction recurrence [9].

Another study analyzed data obtained between 2002 and 2011. The study assessed the impact of NSAIDs (COX-2 inhibitors, diclofenac, naproxen, ibuprofen, and other NSAIDs) on the risk of bleeding and other MACEs within 30 days of discharge from hospitalization for the first-ever myocardial infarction. The study included 61 971 patients with a mean age of 67 years receiving anticoagulation and/or antiplatelet therapy. Patients treated with NSAIDs were found to be at significantly increased risk of thrombotic cardiovascular events, being 11.2 (10.5–11.9) compared with 8.3 (8.2–8.4) per 100 patient-years in those not treated with NSAIDs. In the adjusted analysis, an increase risk for the combined cardiovascular end point was associated with NSAIDs (HR 1.40; 1.30–1.49) compared with no NSAID treatment [10].

The increase in cardiovascular risk associated with NSAID therapy was confirmed by other studies. A large meta-analysis including a total of 30 case-control and 21 cohort studies involving a total of 2.7 million exposed patients documented increased cardiovascular risk for diclofenac and high-dose ibuprofen, while the risk was lowest with naproxen and low-dose ibuprofen [11].

Another meta-analysis by Spanish authors analyzed data from 25 clinical trials and 100 000 myocardial infarction patients. The risk of myocardial infarction was statistically significantly higher in patients receiving high-dose NSAIDs, except for naproxen [12].

Regarding other cardiovascular side effects of NSAIDs, mention should be made of an increased incidence of heart failure associated with NSAID therapy. While an increase in the risk of heart failure in NSAID-treated pa-

Tab. 1. Milestones in terms of cardiovascular safety of non-steroidal anti-inflammatory drugs

year	event
2004	rofecoxib withdrawn from the market by the manufacturer
2005	valdecoxib withdrawn from the market
2005	EMA report: treatment with coxibs raises the risk of cardiovascular events
2006	EMA report: increased incidence of thrombotic events even in patients treated with non-selective NSAIDs
2012	EMA report: diclofenac is associated with higher risk than other non-selective NSAIDs
2013	EMA restrict use of diclofenac
2014	EMA report: evaluation of high-dose ibuprofen, and blood pressure increases associated with etoricoxib therapy
2015	FDA: strong warning regarding the cardiovascular risk associated with NSAID therapy

EMA – European Medicines Agency **FDA** – Food and Drug Administration **NSAID** – non-steroidal anti-inflammatory drug

tients was demonstrated earlier, it was relatively low [13]. However, in the CNT trial [7], the risk of heart failure was double with all NSAIDs; besides, there was an increase in the risk of hospitalization for heart failure, especially with high-dose diclofenac (150 mg/d), naproxen (100 mg/d), and ibuprofen (2 400 mg/d).

Similarly, a small yet statistically significant risk of developing atrial fibrillation while on NSAID therapy was documented [14].

In its strong warning issued in June 2015, the FDA stated that use of NSAIDs increases the incidence of cardiovascular events including stroke. This claim was challenged by a number of experts:

1. Most data obtained from clinical trials relate to COX-2 inhibitors and, to a smaller extent, diclofenac, ibuprofen, and naproxen. No background information to assess other NSAIDs is available as very few clinical trials regarding their cardiovascular safety have been conducted.
2. The association between NSAIDs and stroke has been documented less conclusively in the relevant literature than with other cardiovascular events. The above British CNT trial [7] did not show an increased risk of stroke in patients receiving NSAIDs. In the Swiss trial [8], increased risk was statistically significant only for diclofenac (RR 2.86; 95% CI 1.09–8.36), while being only at the limit of statistical significance with ibuprofen (RR 3.36; 95% CI 1.0–11.6).
3. Results of meta-analyses of clinical trials depend on the quality of individual trials whereas data reported from observational studies may not be robust enough and more conclusive evidence is warranted. A weakness of the CNT trial is that it was designed as a head-to-head comparison of the effects of various drugs.
4. The cardiovascular risk associated with NSAID use is relatively low, yet significant. Compared with placebo, the absolute risk rises by 0.3 % per year. In a group of patients treated with 5 different coxibs including rofecoxib, the annual incidence of all major cardiovascular events was 1.2 %, with the figure being 0.9 % for placebo[15]; hence the results of the SCOT (Standard Care

Tab. 2. Major trials of cardiovascular risk of non-steroidal anti-inflammatory drugs published since 2011.
Adapted from [34] and data from the respective trials

trial years conducted	design	treatment	results	limitations
SCOT [16] 2008–2013	PROBE, MC patients with OA or RA (n = 7 297)	celecoxib ≤ 200 mg bid vs tNSAID	MACE (per 100 PY): 1.14 vs 1.10 (HR 1.04; 95% CI 0.81–1.33)	withdrawal from treatment: 48.2 % vs 31.5 %
PRECISION [27] 2006–2016	MC, patients randomized to celecoxib, ibuprofen and naproxen	mean daily celecoxib/ ibuprofen/naproxen dose: 209/2 045/852 mg/d	primary endpoint: celecoxib 2.3 % vs 2.7 % and 2.5 % of ibuprofen and naproxen	statistical power for non-inferiority was relax to 80 %
Bally et al [33] 2010–2013	IPD meta-analysis	5 NSAIDs	all NSAIDs increase CV risk	data analysis from databases
Danish Registry [9] 1997–2006	retrospective review of national registry	all used NSAID	risk for death or recurrent MI all NSAIDs: HR 1.55; 95% CI 1.46–1.64	observational design; informational bias
McGettigan [11] 2000–2010	meta-analysis of 51 studies	all used NSAIDs	highest overall risk – rofecoxib (1.45) and diclofenac (1.40), lowest – naproxen (1.09) and ibuprofen (1.18)	retrospective analysis, heterogeneity of the studies
Trelle et al [8] 1999–2009	network meta-analysis of 31 large scale, randomized controlled trials	7 types of used NSAIDs	highest risk of MI – rofecoxib (RR 2.12; 1.26–2.12) naproxed seemed least harmful	the study analyzed only 7 NSAIDs the quality of the study is limited by the quality of the underlying data
CNT study [7] Electronic search strategy: Medline 1946–2009 EMBASE 1974–2009	meta-analysis of 639 randomized trials	coxibs and tNSAIDs	rofecoxib and celecoxib: a similar risk for major CV events diclofenac and high-dose of ibuprofen – CV risk comparable to coxibs	drug doses were much higher than used what was the role of aspirin and aspirin-like effect of NSAIDs unpublished trials were not available for analysis
Gunter et al [30] 2000–2013	meta-analysis of 26 studies, randomized, controlled trials and prospective cohort studies	coxibs and tNSAIDs	COX-2 selectivity may not play a role in the CV risk rofecoxib – the only drug to demonstrate CV harm	several comparisons suffer from lack of data and studies meloxicam was not included in the analysis

CV – cardiovascular **IPD** – individual patient data **MACE** – major adverse cardiovascular events **MC** – multicenter **MI** – myocardial infarction **NSAIDs** – non-steroidal anti-inflammatory drugs **PROBE** – prospective randomised, open-label, blinded endpoint evaluation **PY** – person-years

versus celecoxib Outcome Trial) study come as no surprise [16]. In patients without a history of cardiovascular disease, NSAIDs did not raise the risk of myocardial infarction and stroke. Out of 7 279 patients, 96 % were diagnosed to have osteoarthritis, with the remaining ones having rheumatoid arthritis. The authors noted that use of earlier nsNSAIDs – same as celecoxib – in that particular population was reasonably safe. The same conclusions were drawn by British authors assessing NSAID use in rheumatoid arthritis patients [17].

5. Regarding a patient´s individual preference, some patients may accept, in an effort to improve their quality of life, a small increase in absolute risk. Patients experiencing chronic pain related to osteoarthritis may have preferences other than guideline authors. Although, in elderly patients, NSAIDs can only be used for short-term therapy, this class of drugs was taken on a long-term basis by 8.2 % of elderly 70-year+ males. The mean duration of therapy was 4.9 years, with recommended proton pump inhibitors received by only 25 % of patients [18]. This was so because NSAIDs are much more effective than paracetamol [19], which, moreover, does not seem to be as safe as believed to date [20]. Still, in high-risk patients, we do avoid using NSAIDs at all or their use should be limited to periods as short as possible.
6. The mechanism of NSAID increasing cardiovascular risk is not well understood and it seems that COX-2 has a much broader role to play [21,22]. A recent report demonstrated that COX-2 inhibition results in an increase in the levels of asymmetrical dimethylarginine (ADMA), an inhibitor of endothelial NO synthase (eNOS), as well as suppressed prostacyclin formation and endothelial dysfunction. This finding obtained in experiment has been confirmed in 16 healthy volunteers [23]. Other authors have suggested a protective effect of COX-2 against atherosclerosis irrespective of local prostacyclin production, with a key role ascribed to the RGL1 gene. Inhibition of COX-2 is associated with increased numbers of T-lymphocytes in atherosclerotic plaques and increased numbers of Th-1 type cytokines in plasma [24]. In another study comparing naproxen and meclophenamate sodium, NSAIDs showed in experiment different levels of cardiotoxcity due to increasing production of radical oxygen species (ROS) with subsequent mitochondrial and proteasome dysfunction [25]. This would be in line with the results of several analyses not documenting a correlation between increased cardiovascular risk and COX-2 selectivity of individual NSAIDs [8]. On the other hand, it should be noted that some older NSAIDs (diclofenac, etodolac, nimesulide and meloxicam) exhibit COX-2 selectivity similar to that of celecoxib [26].

Publication of results of PRECISION study (Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen) were eagerly awaited [27]. Primary endpoints (incidence of cardiovascular death, myocardial infarction, and stroke) occurred in 2.3 %, 2.7 %, and 2.5 % in the celecoxib, ibuprofen, and naproxen groups, respectively (tab. 2). The authors concluded that the cardiovascular risk of medium-dose celecoxib is not higher compared with both NSAIDs. On the contrary, the study showed that naproxen is not as safe as believed based on previous data. The study did not provide evidence documenting naproxen superiority over the other two drugs in terms of safety. In fact, some authors had pointed out earlier that robust statistical data suggesting a small cardiovascular risk of naproxen are essentially lacking [28].

Conduct of the study was subject to criticism for a number of reasons; it was performed in a population at low cardiovascular risk, involving as it was predominantly osteoarthritis patients. Of the total of 24 081 patients whose data were eventually analyzed, 21 645 had osteoarthritis, with only 2 436 patients diagnosed to have rheumatoid arthritis. The study principal investigator estimated that heart disease and diabetes were present in 20–25 % and 35 % of patients, respectively. On the other hand, while 46 % of the patients were treated with aspirin, it was not known whether or not they were actually taking aspirin at the time of cardiovascular event or gastrointestinal bleeding. Further criticisms focused on celecoxib dosing, limitations on dose escalation (unlike the other two compared drugs) as well as the large number (16 500) of dropouts and the fact that over 6 500 participants (25 %) were lost to follow-up. As patient data were not compared with those obtained in the placebo group, some authors have suggested its results were simply uninterpretable [29].

Worse still, results from the most recent trials make the issue of cardiovascular risk more complicated rather than simpler. Gunter et al, performing a meta-analysis of 26 studies [30], concluded that the cardiovascular risk of NSAIDs need not depend on their COX-selectivity. Rofecoxib was the only NSAID shown to be associated with a significant cardiovascular risk. When excluding rofecoxib from analyses, the results of other coxibs did not differ from those obtained from the groups of nsNSAIDs or placebo. On the other hand, the authors of a recent study documented a 3.4-fold increase in the risk of myocardial infarction in patients with acute respiratory infection using NSAIDs and an OR = 3.41 (2.80–4.16); in patients not treated with NSAIDs, infection increased the risk of myocardial infarction by a factor of 2.7 (2.29–3.06) [31]. The highest risk was shown in patients receiving parenteral NSAIDs, with an OR = 7.22 (4.07–12.81).

Even more extreme results were reported by Zingler et al [32] analyzing the effect of NSAID use in patients with and without cardiovascular disease. Moreover, the authors sought to demonstrate an association between NSAID use and cardiovascular events in patients with inflammation, particularly those with rheumatoid arthritis, osteoarthritis, or any other inflammatory condition. The conclusion was that NSAIDs actually reduce the risk

of first-ever myocardial infarction experienced by patients with inflammation and elevated CRP levels. The authors suggested that chronic use of NSAIDs by these patients is not associated with increased cardiovascular risk but, on the contrary, with a decrease in overall mortality. Likewise, the authors believed the higher risk of cardiovascular events in that population was due to their inflammatory condition, not NSAID use.

Recently Bally et al published a study [33] in which they performed an individual patient data analysis of studies from healthcare databases. Investigators found that all traditional NSAIDs, including naproxen, appear to be associated with an increased risk of acute myocardial infarction.

Conclusions

The controversy related to cardiovascular risk of NSAID use thus goes on, and data obtained to date should be taken into account until additional ones become available. As it is, both coxibs and non-selective NSAIDs pose an increased risk to patients with cardiovascular disease. The cardiovascular risk of individual anti-inflammatory drugs is also affected by other factors such as COX-2 selectivity, dose, half-life, increase in blood pressure, and interaction with aspirin [34,35]. Most results suggest that cardiovascular risk is smaller with low-dose naproxen and ibuprofen. Given our current knowledge about the cardiovascular risk of NSAIDs, our preference in clinical practice should be naproxen or low-dose ibuprofen (up to 1 200 mg/d) [36,37]. Coxibs should be preferred in patients at low cardiovascular and high gastrointestinal risk. Should higher doses of ibuprofen be necessary, the clear option is naproxen. This, however, does not imply that naproxen is generally the safest NSAID; on the contrary, it belongs to the NSAIDs producing most often gastrointestinal complications. In conclusion, when selecting a NSAID, the patient´s health status should to be assessed thoroughly including their comorbidities and current therapy to tailor their NSAID therapy accordingly.

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