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Review Article

The Coxibs: Are we Ready to Admit Mistakes?

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Abstract

The article reviews and analyses ten most influential coxib studies. These studies modified the guidelines, changed the everyday praxis, and moved general medical opinion on coxibs. All these far-reaching changes were not supported by the data, however. The text shows clearly misconceptions, inaccuracies, as well as misinterpretations of the results even in the most cited studies. Closer insight into their methodology as well as critical view on the interpretation of their results bring often information that is not in accordance with the official – and widely accepted presentation.

Keywords: Coxib studies; Methodology; Results; Review; Analysis

Abbreviations

AP: Angina Pectoris; ASA: Acetylsalicylic Acid; BMI: Body Mass Index; CABG: Coronary Artery Bypass Grafting; CAD: Coronary Artery Disease; COX: Cyclooxygenase; CV: Cardiovascular; ECC: Extracorporeal Circulation; FDA: U.S. Food and Drug Administration; GIT: Gastrointestinal Tract; IC: Inhibitory Concentration; LVEF: Left Ventricular Ejection Fraction; MI: Myocardial Infarction; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; PE: Pulmonary Embolism; TIA: Transitory Ischemic Attack

Introduction

All medical specialists who are involved in treating pain remember clearly the massive popularity increase of COX-2 selectively inhibiting drugs, as well as its prompt disappearance. Based on several large studies, the results of which became the source of countless debates and analyses, the information concerning the safety of coxibs was supplemented and recommendations concerning their prescription have been re-evaluated. In September 2004, Merck withdrew Vioxx (rofecoxib) from the market, when an incentive for this was the FDA's decision to issue a public health recommendation that informed of its adverse effects. These new recommendations were broadly accepted and logically have brought about the return of traditional, non-selective anti-inflammatory drugs, which (in addition to those common with coxibs) carry a number of specific gastrointestinal risks. Is the return to the use of more risky drugs really the message of the conducted studies? Are the conclusions of many state health authorities really supported by the acquired data? Or are they simply repeating what is expected of them? Is bare data the source of our knowledge or it comes from somebody else's interpretation? What were the real results of the key studies? And what was their design? The answers are often surprising. Only a few medical doctors who take care of their patients within the everyday praxis could afford to invest their time and energy in studying the enormous amount of data that coxib studies had brought in the years of 2000 – 2005. That is the reason why this review of the coxib studies - most significant for opinion making - is presented. The studies are summarized in the Table 1 in a chronological order.

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Gastrointestinal Toxicity with Celecoxib vs. Nonsteroidal Anti-inflammatory Drugs for Osteoarthritis and Rheumatoid Arthritis (The Celecoxib Long-term Arthritis Safety Study (CLASS)) [1]

This long-term, multicentre, randomised, double-blind study was one of the first studies comparing selective COX-2 inhibitors to traditional Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), 7968 patients with the above-mentioned diagnoses were randomly assigned to one of the following treatment regimens: celecoxib 2 mg x 400 mg, ibuprofen 3 mg x 800 mg, or diclofenac 2 mg x 75 mg daily. Of the concomitant medication, all other NSAIDs and chronic administration of anti-ulcerous drugs were excluded. The administration of corticoids and acetylsalicylic acid for cardiovascular prevention continued. Following are main results:

Double incidence of "upper GIT" complications in the "traditional NSAIDs" group,

- Triple incidence of "upper GIT" complications in the same group, subgroup of patients not receiving ASA,
- In the group "traditional NSAIDs" higher number of other complications (bleeding outside of the GIT, elevation of urea / creatinine plasma levels, elevation of transaminases...)
- The incidence of both IM and combined products "cardiovascular events" and "cerebrovascular events" were the same in both groups and did not differ between subgroups either (use/non-use of ASA).

Author's comments

The same risk of cardiac, lower risk of gastrointestinal complications – in the favour of celecoxib, despite its being administered at supramaximal doses.

Table 1: Overview of analysed studies.

Name of the study				
Publication	**Name abbreviation**	**Patients**	**Comparison**	**Characteristics**
Gastrointestinal toxicity with celecoxib vs. nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis				
2000	CLASS	7968	Celecoxib x Ibuprofen x Diclofenac	M – R – B
Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis				
2000	VIGOR	8076	Rofecoxib x Naproxen	L – M – R – B
Efficacy and safety of the COX-2 inhibitors parecoxib and valdecoxib in patients undergoing coronary artery bypass surgery				
2003		462	Valde-/Parecoxib x Placebo	M – R – B
Comparison of lumiracoxib with naproxen and ibuprofen in the therapeutic arthritis research and gastrointestinal event trial				
2004	TARGET	18325	Lumiracoxib x Naproxen x Ibuprofen	M – R – B
Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial				
2005	APPROVe	2586	Rofecoxib x Placebo	L – M – R – B
Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery				
2005		1671	Valde-/Parecoxib x Placebo	M – R – B
Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention				
2005	APC	2035	Celecoxib x Placebo	L – M – R – B
Risk of myocardial infarction in patients taking COX-2 inhibitors or conventional NSAIDs: population based nested case-control analysis				
2005		95 567	Patients with their first MI x Control cases	E
Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis: a randomised comparison				
2006	MEDAL	33 302	Etoricoxib x diclofenac	L – M – R – B
Coxib and traditional NSAID Trialists´ Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials				
2013	CNT	353 809 (!)	Meta-Analysis of 754 studies	E

Legend: L: long-term; M: multicentre; R: randomised; E: retrospective; B: double-blind

Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis (Vioxx Gastrointestinal Outcomes Research (VIGOR)) [2]

The primary goal of this long-term, multicentre, randomised, double-blind study was to compare the incidence of "upper GIT" complications (ulceration, perforation, obstruction, bleeding) in patients with rheumatoid arthritis. Patients were older than 50 years (or patients older than 40 years with long-term administration of corticosteroids), patients taking acetylsalicylic acid were excluded. In the group "treated" (n=4047, rofecoxib 50 mg 1x daily), an event occurred in "Upper GIT" 2.1 x /100 patients per year, of which severe complications were 0.6 x /100 patients per year). In the control group (n=4029, naproxen 500 mg 2x daily), an event occurred in the "Upper GIT" of 4.5 x /100 patients per year, of which severe complications were 1.4 x /100 patients per year). The relative risk was 0.5 (P<0.001) and 0.4 (P=0.005), respectively. In the VIGOR study, the thrombogenic potential of COX-2 inhibitors was also evaluated. The incidence of serious cardiovascular thrombotic events (sudden death, fatal/non-fatal myocardial infarction, unstable angina, ischaemic stroke, TIA, and peripheral venous and arterial thromboses) was monitored. No statistically significant difference in incidence was observed with any of the peripheral complications or any of the CNS complications. Among the cardiac events, only one of the parameters showed a significant difference: incidence of non-fatal IM - in the rofecoxib group was 0.4%, in the naproxen group 0.1% (relative risk 4). Overall mortality and mortality from cardiovascular causes were similar in both groups.

Author's comments

Similarly to the CLASS study, the mortality was proved unraised in the coxib group, the therapeutic effect was similar with both drugs, and the incidence of "upper GIT" complications was less than half in the rofecoxib group. Non-fatal MI is the only endpoint the incidence of which achieved a significant difference between groups (18:4). Combined parameters containing the endpoint of non-fatal MI were also raised: "all cardiac events" (28:10) and "all cardiovascular thrombotic events" (45:19). From this point of view the conclusion of the study "Administration of rofecoxib increases the incidence of serious cardiovascular thrombotic events" seems to be rather inaccurate and generalizing. In order to explain the possible protective effect of naproxen, a more detailed insight into the mechanism of action of NSAIDs is needed. NSAIDs are traditionally divided into "non-selective" and "selective" to emphasize the superiority of COX-2 inhibition effect in coxibs. In fact, this view is incorrect because the inhibition ratio between both isoforms is specific for each preparation and these together represent a continuum, as shown in Figure 1. Comparing rofecoxib (IC_{80} 270) and naproxen (IC_{80} 0.7), it is obvious that their selectivity is exactly the opposite: naproxen is moderately selective to COX-1. Since the study excluded patients taking aspirin, it is evident that the rofecoxib group does not provide any antiplatelet

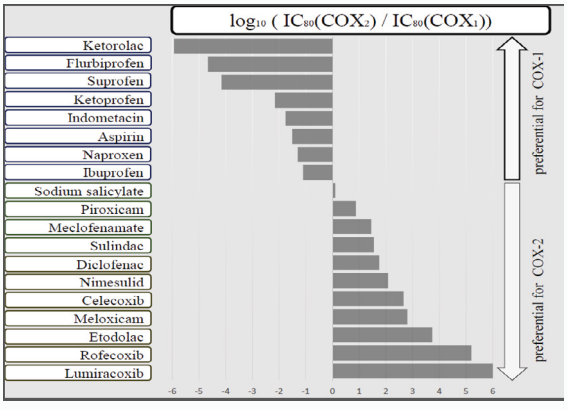

Figure 1: Inhibition ratio between both isoforms is specific for each preparation and these together represent a continuum.

prevention of possible thrombotic events. The Naproxen group provides this to some extent, and directly through a "control" drug. Although naproxen is not primarily intended and used for antiplatelet aggregation its selectivity (only slightly lower than that of aspirin) and its long half-life ensure a stable and clinically significant blockade of platelet COX-1. Note: preparations only moderately selective for the isoform COX-2 are called "preferential" rather than "selective", for example nimesulide: on the list of NSAIDs - sorted according to their selectivity - neighbors diclofenac (the most selective of "traditional" NSAIDs) and celecoxib (the least selective of the coxibs). This fact points out the shortcomings of the historical/didactic simple division of NSAIDs to "selective" and "non-selective". However, the design of most studies is based on this misconception.

Efficacy and Safety of the COX-2 Inhibitors Parecoxib and Valdecoxib in Patients Undergoing Coronary Artery Bypass Surgery [3]

The feared prothrombotic potential of selective COX-2 inhibitors has been investigated in the stress condition of coronary revascularization: Ott et al. [3] conducted a randomised, multicentre, double-blind, placebo-controlled study with valdecoxib (and its intravenous formulation parecoxib) as the study drug. Parecoxib 40 mg was administered early after extubation of the patient and then periodically every 12 hours, at least 3 days. Oral administration of 40 mg valdecoxib followed, every 12 hours with a total duration of 14 days. The baseline criteria included: age under 77 years, BMI under 40, body weight above 55 kg, LVEF more than 35%, and compensated blood pressure. Patients undergoing emergent surgery, patients with significant organ dysfunction, with a history of drug abuse, and those with an exceptionally unfavorable preoperative state were excluded. A total of 462 patients were randomised. As to pre-operative characteristics, the groups differed in the BMI parameter, with significantly more patients with BMI > 30 in the coxib group. Main results: it was demonstrated that coxibs exceeded placebo in pain control at all evaluated time intervals after surgery, as well as in various qualitative parameters of analgesia (pain in rest, strongest pain, mood, etc.). The total incidence of "non-serious adverse events" was similar in both groups. In the coxib group, there were significantly more supraventricular tachycardia, and events of hypotension, in the control group bronchospasm, fever, pleural effusion, and simple tachycardia were observed more often. Table 2 provides an overview of serious adverse events.

Table 2: Serious adverse events (based on study [3] data). The marked values are statistically significant (vs. control group, p<0.05).

Parameter	Control (151) n (%)	Coxib (311) n (%)	p
Sternal wound infections	0	10 (3·2)	0·035
Cerebrovascular event	1 (0·7)	9 (2·9)	0·177
Impaired renal function	0	6 (1·9)	0·184
Pleural effusion	1 (0·7)	7 (2·3)	0·283
Death	0	4 (1·3)	0·309
Gastrointestinal bleeding	0	3 (1·0)	0·554
Thrombophlebitis	0	3 (1·0)	0·554
Cardiac failure	2 (1·3)	3 (1·0)	0·664
Myocardial infarction	1 (0·7)	5 (1·6)	0·669
Pneumonia	3 (2·0)	4 (1·3)	0·688
Total	15 (9·9)	59 (19·0)	0·015

Author's comments

The often-cited conclusion "in the … coxib … group there were significantly more serious adverse reactions than in the control group" marked the beginning of abandoning of coxibs not only in CABG surgery, but in cardiac surgery generally. However, the only one of serious complications, the incidence of which differed significantly between groups, was the sternal wound infection. As the authors of the study admit, the size of the study was marginal to be able to demonstrate the expected double incidence of complications. Really, no other serious complication was found to be more frequent, and even all other complications in total did not reach the five percent level of significance - despite the fact that their incidence in the control group was unexpectedly low. The aim to find and demonstrate the prothrombogenic effect of a single factor in the situation of escalated activity of inflammatory and coagulation cascades – as can be detected at procedures requiring extracorporeal circulation - is pretty challenging. In addition, the study does not mention the amount of hemostyptics administered, antifibrinolytics etc. Due to strict input criteria, a relatively homogeneous sample was achieved but, as reported by the authors themselves, the results cannot be transferred to more than 30% of patients undergoing CABG surgery.

Comparison of Lumiracoxib with Naproxen and Ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET) [4]

A massive-sized study with one-year monitoring of patients over fifty years of age treated for osteoarthritis. Its aim was to assess the gastrointestinal and cardiovascular safety of lumiracoxib compared to naproxen and ibuprofen. The primary indicator was the number of gastrointestinal ulcer complications (bleeding, perforation, obstruction), the cardiovascular parameter was the combined product of myocardial infarction + stroke + sudden cardiac death. Brief results: in patients treated with lumiracoxib (dosing of 1 mg x 400 mg, n=9156), complications from GIT occurred three times less often than in the group with traditional NSAIDs. In the subgroup of patients who did not have acetylsalicylic acid in their chronic medication this difference was fourfold. In patients taking concomitant aspirin, the difference was not significant. The incidence of cardiovascular complications was the same in both groups.

Author's comments

The same risk of a cardiac event, lower gastrointestinal risk - in favour of coxibs.

Cardiovascular Events Associated with Rofecoxib in a Colorectal Adenoma Chemoprevention Trial (Adenomatous Polyp Prevention on Vioxx Trial (APPROVE)) [5]

This long-term, multicentre, randomised, double-blinded, placebo-controlled study was intended to determine the effect of three-years-long administration of rofecoxib on recurrence of neoplastic colon polyps in patients with a history of colorectal polyp. As a secondary endpoint, the incidence of severe thrombotic cardiovascular events was studied. In the treatment group (rofecoxib 25 mg 1x daily, n=1287), a thrombotic event occurred 1.5 times/100 patients per year, in the control group (placebo, n=1299) it occurred 0.78 times/100 patients per year. The relative risk was 1.92 (p=0.008) and was apparent after 18 months of drug administration. In particular,

more frequent were MI and ischemic stroke. Both overall mortality and cardiovascular mortality remained similar in both groups.

Author's comments

The study showed rofecoxib to bring an increased risk in case of regular administration for more than 18 months - this conclusion however should not be applied to different, short-term clinical settings as it stands for treating postoperative pain. In the "safer" control group placebo was administered. This does not pose any therapeutic alternative to NSAIDs, since its analgetic effect is unreliable, if any at all. Despite the higher occurrence of thrombotic events in the rofecoxib group, the data confirmed non-increased mortality.

Complications of the COX-2 Inhibitor Parecoxib and Valdecoxib after Cardiac Surgery [10]

In this randomised, double-blind, placebo-controlled trial 175 centres from 27 countries were involved. 1671 patients indicated for the CABG surgery were divided into three groups according to the application protocol: A: parecoxib 40 mg i.v. on the first postoperative day in the morning, continued with parecoxib 20 mg i.v. every 12 hours for three days, then valdecoxib 20 mg p.o. every 12 hours for the next seven days. B: placebo i.v. every 12 hours for three days, then valdecoxib 20 mg p.o. every 12 hours for the next seven days. C: placebo i.v. every 12 hours for three days, then placebo p.o. every 12 hours for the next seven days. The monitoring of all patients was kept for additional 30 days. All other commonly used medication remained unchanged, including ASA at 75-325 mg and routine thromboprophylaxis. The main endpoints were incidence of cardiovascular and GIT complications, renal function disorders and wound infections. Each of these parameters consisted of several other well-defined diagnoses. As a result, three significant differences between groups were found:

- Group A ("fully coxib") versus C (placebo) in cardiovascular complications (MI, cardiac arrest, cardioembolic stroke, ischemic stroke, TIA, deep phlebothrombosis, and PE),
- Group A ("fully coxib") versus C (placebo) in total complications, and
- Group B ("partly coxib") versus C (placebo) in total complications.

Author's comments

The methodologically mysterious, hybrid Group B is a source of interpretation problems. While the authors of the article consider it to be a "coxib" group and do not hesitate to associate it for statistical purposes with group A ("Pooled COX-2-inhibitor Group"), in fact it depends on when an undesirable event was recorded. If it occurs within the first three days, i.e. before the administration of the study drug, this event cannot be attributed to its influence. If three of the six cardiovascular events in group B occurred prior to the administration of valdecoxib, being on placebo medication, then these events should not be taken as complications of coxib administration. Either do they belong to placebo cases (analogically "Pooled Placebo Group") or should be eliminated from the study. What changes the overall results even more substantially, are the three deaths in group B which also occurred during the first three days. If we count these (undoubtedly not coxib-associated) events to placebo group, the p-value will be roughly above 0.05, which means that the difference between the groups is not statistically significant in either parameter. (From this point of view the time distribution of many other monitored events is missing).

Cardiovascular Risk Associated with Celecoxib in a Clinical Trial for Colorectal Adenoma Prevention (Adenoma Prevention with Celecoxib (APC) Study) [7]

Within a study investigating the effect of celecoxib on colorectal adenoma, evaluation of the incidence of cardio-vascular events was conducted. This was a three-year observation of 2035 patients who were randomised to one of three groups: in the first group patients received placebo, in the second group celecoxib 2 mg x 200 mg, and in the third one 2 mg x 400 mg per day. Both individual "endpoints" (events) and their various combinations were evaluated. The incidence of individual endpoints and composite indicators are listed in Table 3 and 4, respectively.

Table 3: The incidence of individual endpoints (based on study [7] data). The marked values are statistically significant (vs. placebo, p<0.05).

End Point	Placebo (n=679)	Celecoxib 2x200	Celecoxib 2x400 (n=671)	p
Death from any cause	6	6	9	
Death from CV cause	1	3	6	<0.01
Non-fatal MI	3	9	9	
Stroke	3	3	5	
Cardiac failure	2	1	4	<0.05
Thromboembolism	1	3	4	
Need for advanced life support	0	0	1	
Hospital admission for AP	5	4	2	
Arrhythmia	9	4	7	
CV interventions	7	9	6	
Other	9	11	14	

Table 4: The incidence of composite indicators (based on study [7] data). The marked values are statistically significant (vs. placebo, p<0.05).

Composite End Point	Placebo 2x400 (n=679)	Celecoxib 2x200 (n=685)	Celecoxib 2x400 (n=671)
1. death from CV cause	1	3	6
2. death from CV cause + non-fatal MI	4	12	15
3. death from CV cause + non-fatal MI + stroke	7	15	20
4. death from CV cause + non-fatal MI + stroke + heart failure	9	16	24
5. death from CV cause + non-fatal MI + stroke + heart failure + unstable AP	14	20	26
6. death from CV cause + non-fatal MI + stroke + heart failure + unstable AP + need for CV intervention	21	29	32

Author's comments

At the first glance, it is clear that the individual "events" are clinically not sharply defined, so that they can turn one into another easily and overlap with time. What is even more evident, is the prescribed dosage of celecoxib. According to recommendations, a single dose of 100 mg can be repeated to reach the maximum daily dose of 200 mg. Within the study, it was administered in the "weaker"

branch 400 mg and in the "stronger" one 800 mg of celecoxib per day, i.e. double or fourfold of the maximum daily doses for almost three years. It is not surprising that the Monitoring Security Committee decided (probably shortly before the end of the study) to suspend the administration of the study drug. What the authors do not mention is the fact that the increased incidence of adverse events was almost exclusively in the "strong" branch compared to the placebo group (in the "lower" dose group, only 1 of the 17 endpoints was more frequent). The level of increased risk for the fourth composite endpoint in the "weak" branch is presented as one of the main results (a hazard ratio 2.3 with 95% confidence interval 0.9-5.5). However, their incidence does not differ significantly. The values of the increased risk are presented by the authors for all individual and composite indicators - regardless of whether there is a difference between the groups in the occurrence of the indicator or not. The statistical significance of the incidence is not mentioned at all.

Risk of Myocardial Infarction in Patients Taking Cyclo-oxygenase-2 Inhibitor or Conventional NSAIDs: Population Based Nested Case-Control Analysis [8]

The source of information for this retrospective study is the United Kingdom general practitioner database QRESEARCH, comprising 7 million clinical records. Patients who had their first myocardial infarction (n=9218) in the period 2000-2004 were selected, each with up to ten controls (n=86349) of the same sex and age, corrected for co-morbidity, smoking, anopyrin administration, and other medications. The compared factor was the amount of non-steroidal anti-inflammatory drugs prescribed in the three-year period (with a subgroup of three months period) before the event. A total of 27 different NSAIDs were prescribed during the investigated period; for processing purposes they were divided into the following groups: celecoxib, rofecoxib, ibuprofen, diclofenac, naproxen, other selective, and other non-selective NSAIDs. The evaluation showed that the use of rofecoxib in the last three months significantly increases the risk of developing MI (relative risk 1.32), as does the use of ibuprofen (1.24) and diclofenac (1.55). When taking medication in a period earlier than three months prior to the event, higher risk was observed in diclofenac (1.13) and other NSAIDs (1.18) groups. Relative risks were similar in the subgroups of patients taking/not taking acetylsalicylic acid and with/without coronary artery disease. Repeated administration (more precisely: repeated prescription) of medication has been shown to be a significant risk factor for the development of MI – in patients to whom the medication has been prescribed more than three times, the relative risk was increased with diclofenac (relative risk 1.46), ibuprofen (1.14), naproxen (1.27), and other NSAIDs (1.28) compared to patients without prescription.

Author's comments

- The study did not confirm a specific adverse effect of developing MI either for rofecoxib or for celecoxib,
- The possible protective effect of naproxen was not confirmed,
- The relative risk was independent of the eventual concomitant use of aspirin
- Similar values have been observed in both "selective" and "non-selective" NSAIDs,
- Age over 65 years as well as the presence of CAD increased the risk only insignificantly.

Cardiovascular Outcomes with Etoricoxib and Diclofenac in Patients with Osteoarthritis and Rheumatoid Arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-Term Programme: A Randomised Comparison (MEDAL) [9]

The main purpose of this study was to compare the incidence of thrombotic cardiovascular events with prolonged use of etoricoxib and diclofenac. Prophylaxis with acetylsalicylic acid has been maintained and antiulcerative medication has been recommended in patients at high risk for upper GIT complications. Patients were over 50 years of age and were randomised into two groups. In the first one (n = 16483) they received diclofenac 2x daily 75 mg, in the second one (n = 16819) etoricoxib – 60 mg or 90 mg 1x daily. The average time of exposure to the drug was around 18 months. The primary comparative parameter was a composite indicator of cardiovascular thrombotization, which included: first myocardial infarction, unstable angina, intracardiac thrombus, cardiopulmonary resuscitation, ischemic stroke, cerebrovascular thrombosis, transitory ischemic attack, peripheral vein thrombosis, pulmonary embolism, peripheral arterial thrombosis, and sudden death. Main results: the risk ratio of thrombosis was 0.95 (with 95% confidence interval 0.81 – 1.11), discontinuation of the drug application due to its side effects was more common with etoricoxib for peripheral oedema and hypertension, diclofenac for GIT problems and elevation of liver enzymes.

Author's comments

- The study did not confirm the often mentioned "class effect" of coxibs,
- Etoricoxib was proved at least as safe as diclofenac.

Vascular and Upper Gastrointestinal Effect of Non-Steroidal Anti-inflammatory Drugs: Meta-Analyses of Individual Participant Data from Randomised Trials (Coxib and Traditional NSAIDs Trialists (CNT) Collaboration) [10]

This meta-analysis was published in Lancet in 2013. The time distance from other cited studies, its extent and the fact that it has been sponsored by UK Medical Research Council and the British Heart Foundation and not by commercial entities of the pharmaceutical market put it in the role of a certain “reference” study. A meta-analysis of 280 studies was conducted comparing the NSAID against placebo (124 513 participants), and 474 studies comparing two NSAIDs (229 296 participants). The main endpoint was "serious vascular events" (non-fatal MI, non-fatal stroke, sudden death), "serious coronary events" (non-fatal MI, fatal coronary lesions), stroke, mortality, cardiac failure and complications of "upper" GIT (perforation, obstruction, bleeding). The results are summarised in Table 5.

Author's comments

- The study does not discriminate among individual coxibs,
- A large number of studies contain a large number of dosing regimens that can hardly be compared,
- This holds also for mixing long-term studies (drug administration for several years) and short-term clinical settings (drug administration for several days),

Table 5: The most frequent complications of NSAIDs administration - hazard ratios for most prescribed drugs (based on study [10] data). The marked values are statistically significant (vs. control group, $p<0.05$).

Parameter	Coxibs	Diclofenac	Ibuprofen	Naproxen
Serious vascular events	1.37	1.41	1.44	0.93
Severe coronary events	1.76	1.7	2.22	0.84
Death from vascular causes	1.58	1.65	1.9	1.08
Cardiac failure	2.28	1.85	2.49	1.87
Mortality from any cause	1.22	1.2	1.61	1.03
Complications of GIT	1.81	1.89	3.97	4.22
Bleeding from the "upper" GIT	2.22	2.2	3.63	5.49

- Similar values of hazard ratio at cardiovascular risk for both the coxibs and traditional NSAIDs.

Conclusion

This Decalogue of selected studies is in no way presented as a complete list, since a number of other studies have been carried out, both before and after the period mentioned above. Only the most cited and discussed, the most influential studies have been analysed. Closer insight into their methodology and critical view on the interpretation of their results brings often information that is not in accordance with the official presentation. We should listen much more attentively to what the studies tell.

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