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Which COX-inhibitor to which patient; an analysis of contemporary evidence including pharmacology and medicinal chemistry

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Which COX-inhibitor to which patient; an analysis of contemporary evidence including pharmacology and medicinal chemistry

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Abstract. NSAIDs are among the most used drugs in the world. It is estimated that 30 million people take NSAIDs daily world-wide, without including drugs sold over the counter. They are effective in alleviating pain and inflammation. Even though they are very common there does not appear to be any clear-cut guidelines to when which NSAID should be used. It has therefore been the purpose of this thesis to analyze if there is a need to differentiate between different NSAIDs according to contemporary evidence. Since the withdrawal of rofecoxib in 2004 there has been a general idea that coxibs as a group are cardiotoxic, recent evidence suggests that this holds true for all NSAIDs however. As such this work included 5 drugs, three common over the counter non-selective NSAIDs; naproxen, ibuprofen and diclofenac as well as the two coxibs currently on the Swedish market; celecoxib and etoricoxib. Pubmed and google scholar were searched for relevant studies on the subject. The results showed that there is a need to differentiate between NSAIDs, however the clinical setting is complex and a one-size fits all solution is difficult to come by. Naproxen and moderate doses of celecoxib (100 mg b.i.d.) show the best cardiovascular profiles whilst etoricoxib, celecoxib and diclofenac show the best gastrointestinal profiles. Coxibs show similar upper GI-profiles as tNSAIDs if combined with PPI however PPI are not without adverse events and the lower GI is not affected by PPI. Longer half-life is in general the better option in situations with lasting pain since it has been shown that lower dosing intervals increase adherence. In terms of pain management there does not appear to be any differences in efficacy amongst different NSAIDs

Summary

Icke-steroida anti-inflammatoriska droger, eller NSAID som de brukar förkortas, är bland de mest använda medicinerna i världen. Det uppskattas att över 30 miljoner människor tar NSAID på recept dagligen. Flertalet NSAID säljs receptfritt och är inte inkluderade i dessa estimeringar. Läkemedlen tas mot smärta, feber och inflammation. Deras verkningsmekanism kan enkelt förklaras som att de stoppar bildandet av ämnen i kroppen som kallas för prostanoider. Prostanoider har många funktioner i kroppen. Dessa funktioner inkluderar både upprätthållning av kroppens funktioner på ett balanserat sätt, så kallad homeostas, och förmedling av smärta, feber och inflammation. För att prostanoider ska kunna bildas krävs en enzymatisk omvandling. Denna sker av ett enzym som kallas cyclooxygenas, eller COX. Det är till detta enzym som NSAID binder för att stoppa bildandet av prostanoider. Det finns dock två olika varianter av COX, COX-1 och COX-2. De två olika varianterna ansvarar för bildandet av olika typer av prostanoider. COX-1 ansvarar i stor utsträckning för att upprätthålla homeostatiska mekanismer medan COX-2 nästan enbart används vid inflammation och sjukdom. De NSAID som kom ut först på marknaden stoppar COX-1 och COX-2 i ungefär lika stor utsträckning. Detta har lett till allvarliga biverkningar i magen och resten av tarmen, då COX-1 är involverat i produktionen av en skyddande barriär. Därför utvecklades det på 1990-talet NSAID som mycket hellre binder till den sjukdomsrelaterade varianten av COX, COX-2. Detta blev dock inte den framgångssaga som forskarna hade hoppats på och ett av prototypläkemedlen, rofecoxib drogs tillbaka från marknaden 2004 eftersom den visade sig öka risken för allvarliga biverkningar på hjärtat. Detta dömde ut hela gruppen av de nya läkemedlen, vilka som grupp kallas coxiber eller selektiva NSAID som farliga för hjärtat. På senare år har vetenskapliga studier kommit som visar på att de biverkningar som ses hos coxiber med avseende på hjärtat snarare gäller för hela gruppen NSAID mediciner än specifikt för coxiber. Trots att alla NSAID, selektiva eller icke-selektiva har olika kemiska egenskaper, så som hur länge de utövar sin effekt eller hur gärna de binder till de olika varianterna av COX, så finns det inga tydliga riktlinjer för när vilka NSAID ska användas. Därför undersöktes det i detta arbete; vilken COX-hämmare till vilken patient - En analys av kontemporär evidens inklusive läkemedelskemi och farmakologi. Eftersom tiden inte var obegränsad undersöktes fem läkemedel, naproxen, ibuprofen, diklofenak, etoricoxib samt celecoxib. Databaserna pubmed och google scholar söktes efter vetenskapliga studier som hanterade ämnet. Resultatet av analysen visade att det finns en anledning att särskilja på dessa läkemedel. Däremot är den kliniska verkligheten komplicerad och det finns förmodligen inte något allmängiltigt svar på vilken COX-hämmare som ska ges till vilken patient.

PREFACE

This thesis has been written as part of the Bachelor of Science Program in Pharmacy, 180 credits at Linnaeus University. It entails 15 credits and 10 weeks of work.

I would like to give my sincerest gratitude to my supervisor, associate professor Ran Friedman without whose help this thesis would not have been possible. I would also like to thank my family for their patience and support, especially my children Joosha and Yusra who are a constant source of strength and motivation. Lastly, special appreciation and thanks goes to my dearest friend Dr. Mehdi Cherkaoui for his patience with me, my ideas and questions throughout my studies and my father for always pushing and motivating me.

ABBREVIATIONS

ABP – ambulatory blood pressure

AERD – aspirin-exacerbated respiratory disease

AR – absolute risk

AUC – area under the curve

b.i.d. – bis in die

BP – blood pressure

CI – confidence interval

COX – cyclooxygenase

DBP – diastolic blood pressure

IC_{50} – inhibitory concentration 50

LS – least square

MACE – major adverse cardiovascular events

mmHg – millimeter mercury

NSAID - non- steroidal anti-inflammatory drug

PGG_2 – prostaglandin G_2

PGH_2 – prostaglandin H_2

PPI - proton pump inhibitor

q.d. – quaque die

RCT – randomized controlled trial

RR – relative risk

SBP – systolic blood pressure

SAR – structure activity relationship

t.i.d. – ter in die

tNSAID – traditional NSAID

WMD – weighted mean difference

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INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used drugs worldwide (1). As a group the NSAIDs are very effective anti-inflammatory, antipyretic and analgesic agents (NSAIDs have been known to reduce the need for opioids by as much as 1/3). Although there are many (around 70) different NSAIDs in use on the worldwide market they all have the same basic mechanism of action; cyclooxygenase (COX) inhibition and thus inhibition of prostaglandin synthesis. There are two known COX isoforms that are thought to be related to COX-inhibitors; while COX-1 is found throughout the body in numerous tissues involved in homeostatic mechanisms, COX-2 is a mediator of pain and inflammation. As with all other medications adverse events need to be taken into consideration when administering NSAIDs. Among its other activities COX-1 is involved in the production of prostaglandins that both inhibit gastric-acid secretion and produce protective features of the gastric mucosa (2). Traditional NSAIDs (tNSAIDs), which are non-selective of the two COX isoforms can therefore cause serious gastro-intestinal side effects, including perforations of the gastro-intestinal canal. NSAIDs are thought to cause more than 100 000 hospitalizations and 10 000 deaths annually in the US alone. Studies show that these rates might be decreasing due to awareness of the dangers but the high gastro-intestinal risk caused concern during the 1990s (3). This lead to the development of COX-2 selective NSAIDs – coxibs, patients could not take unselective NSAIDs for long periods of time, and hence they could not be used for chronic pain or inflammation. Coxibs were thought to revolutionize the market because of their selectivity to the COX isoform mediating illness with less side effects (4). The story was not the success everyone had hoped for and although some coxibs are still on the market one of the prototype drugs, rofecoxib, was withdrawn in 2004 because of a substantial increased risk in serious cardiovascular events. This lead to a view that COX-2 selective NSAIDs, although having a better safety profile when it comes to gastro-intestinal toxicity, had a higher risk of cardiovascular events (2). This view has been challenged in recent years and new studies show that NSAIDs increase risk of cardiovascular events regardless of COX-2 selectivity (5). Although all the NSAIDs, traditional and coxib, vary in their selectivity and pharmacokinetics there does not appear to be any clear-cut analysis of which NSAID should be used when and if there is a need to differentiate between them. The scope of this work is therefore to analyze the issue and see if there is a need to do so - which cox-inhibitor to which patient according to contemporary evidence. This will be done by looking at pharmacological, chemical and clinical contemporary evidence. Moreover, there are some studies that suggest that proton pump inhibitors (PPIs) in combination with tNSAIDs are at least as effective as coxibs in preventing NSAID induced gastropathy (6). These studies do not however seem to take into consideration potential adverse events of PPIs and as such this will also be covered in this work. Because of time-management issues and the overall size of this study 5 different drugs will be covered; naproxen, ibuprofen, diclofenac, celecoxib and etoricoxib. These drugs were chosen specifically because celecoxib and etoricoxib are the only coxibs approved for use of on the Swedish market and naproxen, ibuprofen and diclofenac are very commonly used and sold over the counter in numerous countries all over the world. Patient groups covered will be those with chronic and acute pain and/or fever regardless of cause with

consideration to cardiovascular safety profile, gastro-intestinal profile and old age (75 years of age or older).

Cyclooxygenase-1, 2 and the mechanism of action of COX-inhibitors

Cyclooxygenases are membrane-bound enzymes that interact with arachidonic acid in the presence of oxygen and heme to produce prostaglandin H_2 (PGH_2) (4). This is done in two steps; first two oxygen molecules are incorporated into the arachidonic acid at C11 and C15. This makes an endoperoxide intermediate, PGG_2, which is highly unstable. The intermediate is further catalyzed in a peroxidase reaction to PGH_2. PGH_2 is then transformed to other prostanoids by isomerases, reductases or synthases (2). An illustration of the biosynthesis of prostaglandin H_2 and its products can be seen below in figure 1.

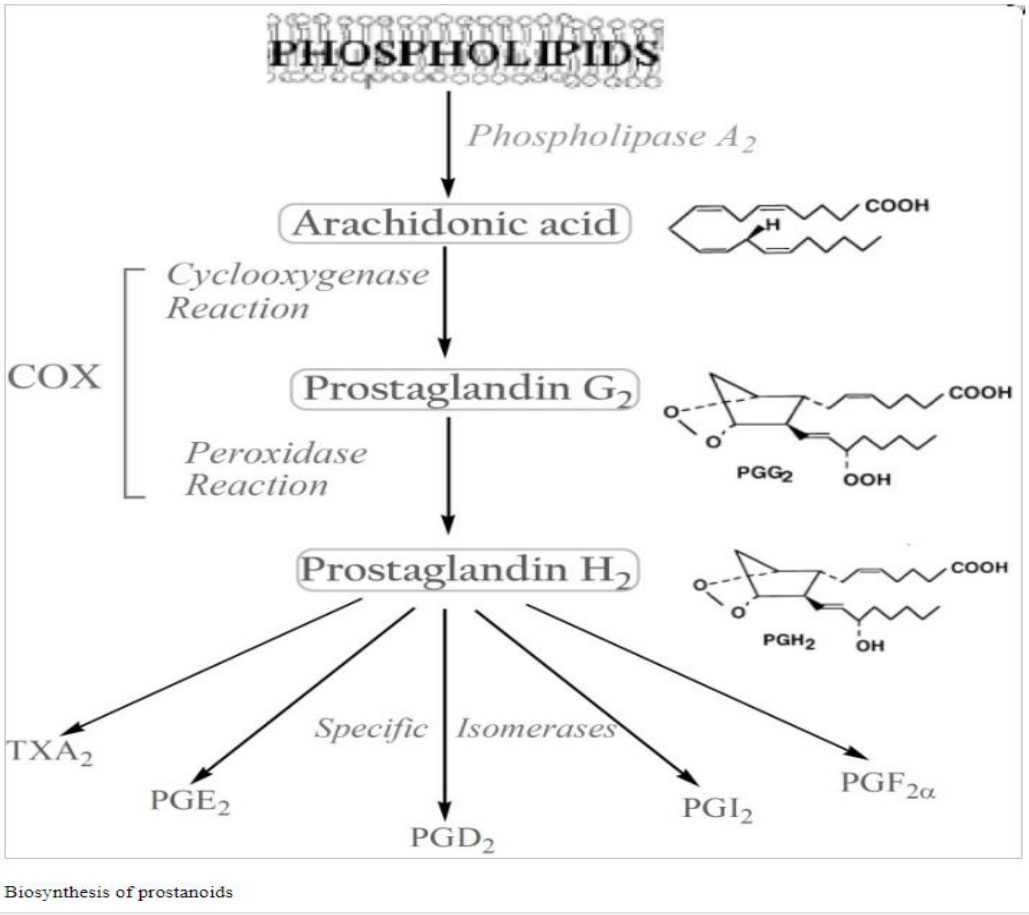

Figure 1. An illustration of the biosynthesis of prostanoids which also depicts the role of COX. The figure is reproduced from reference (7) with cc license.

Sequentially COX-1 and 2 are about 600 amino acids long with about 60 % sequence identity and both are heme containing (4,7) . They differ in that COX-1 has the amino

acid isoleucine at position 434 and 523 while COX-2 has the amino acid valine in these positions. This makes for a structural modification that creates an additional side pocket (4,7). COX-2 also lacks a 17-amino acid long sequence in the N-terminus that is present in COX-1 but has an 18-amino acid long sequence at the C-terminus instead (4). Additionally, there is an arginine at position 513 instead of histidine in COX-2 that enables interactions with polar moieties (7). An illustration of differences in COX-1 and 2 in the additional binding pocket is seen in figure 2.

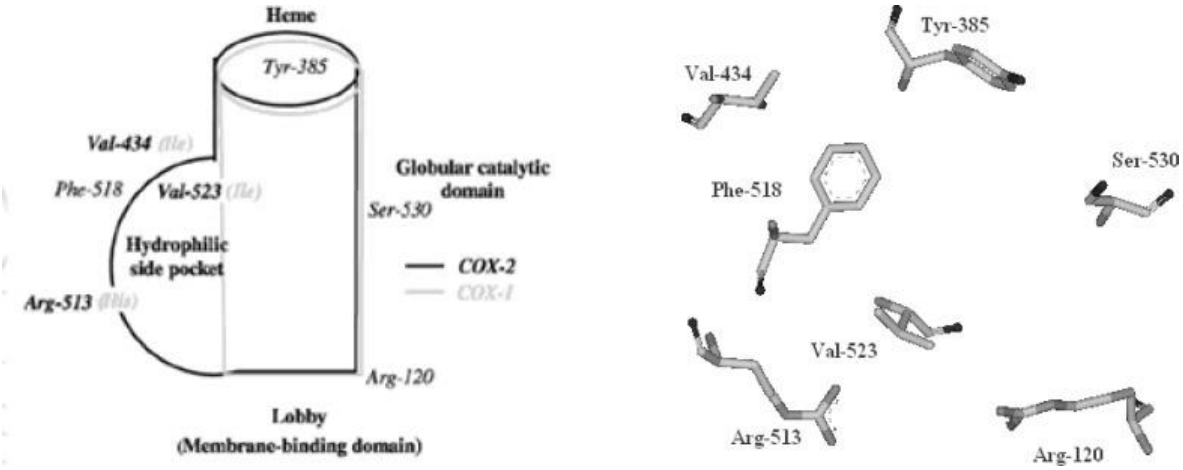

Figure 2. The structural differences of COX1-1 and 2 at the allosteric site. The different amino acids at position 434, 513 and 523 are illustrated. The additional side pocket created by the substitution of Ile for Val in COX-2 can be seen in the figure. The figure is reproduced from reference (7) with cc license.

NSAIDs inhibit prostaglandin synthesis by competitively binding to the COX enzymes (2). NSAIDs have three main therapeutic functions; anti-inflammation, analgesia and antipyretics. These can all be explained by prostaglandin synthesis inhibition; the anti-inflammatory effect is achieved by the decrease in PGE_2 and prostacyclin, which reduces vasodilation and thus indirectly oedema. The analgesic effect stems from a decreased sensitization to inflammatory mediators (ex. bradykinin, 5-hydroxytyptamine) in nociceptive nerve endings due to lack of prostaglandins. The antipyretic effect is inhibited by decreased interleukin-1 stimulated prostaglandin release in the central nervous system. The prostaglandins released by interleukin-1 stimulation can alter the hypothalamic temperature set point, which then causes an increase in body temperature (2). There is evidence of additional mechanism by which NSAIDs exert their therapeutic effects, such as interactions with endocannabinoids. Although there are hypotheses for these mechanism they are not fully elucidated and will therefore not be covered in this work (8).

Pharmacology and medicinal chemistry

General SAR of tNSAIDs

All tNSAIDs have an acidic center essential for their activity. As such most NSAIDs are derivatives of arylalkanoic acids (figure 3) and indeed this is true for the tNSAIDs covered in this work. One aromatic system provides a therapeutic anti-inflammatory effect. The ideal structure for binding is however two conjugated aromatic rings that can take a noncoplanar orientation. There is usually one carbon atom adjacent to the acidic center and the aromatic/heteroaromatic ring. A longer distance between the structures decreases potency (3).

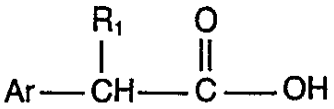

Figure 3. The basic structure of arylalkanoic acids. Ar – depicts the aromatic ring structure.

The acidic center is essential to activity because anchoring to a cationic argienine residue (Arg^{120}) of COX in its active site is necessary for the inhibitory effect (7). The pH of inflamed tissue is about 6,8 and as such the drugs must have a pKa low enough to generate its conjugate base. Lipophilic groups increase distribution in tissues as passage over membranes is facilitated and as such potency is increased (4).

General SAR of coxibs

Coxibs are divided into two major structural classes; tricyclics and non-tricyclics. Both celecoxib and etoricoxib belong to the tricyclics, which are ortho-diarylheterocycles. The central heterocyclic ring can consist 4, 5 or 6 members (7). All the coxibs of this group also have a rigid sidechain, such as a sulfone group or a sulfonamide group. Coxibs are limited in their binding capacity to COX-1 since the larger isoleucine (compared to valine in COX-2) at position 523 blocks access of the rigid sidechain of coxibs to the allosteric site (4).

Celecoxib

Celecoxib has a pyrazole as its core with a sulfonamide group at paraposition in the aryl ring binding to the first nitrogen of the core pyrazole. The other aryl ring has a methyl-group at para position. The structure of celecoxib can be seen below in figure 4.

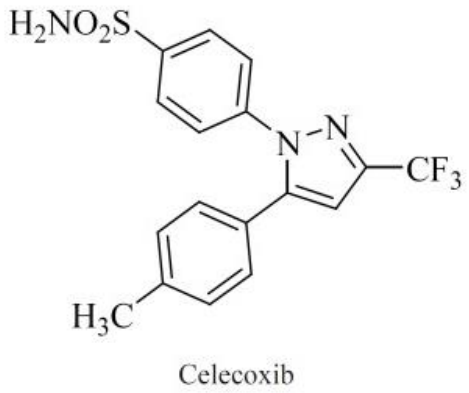

Figure 4. The structure of celecoxib

The IC_{50} of celecoxib 16 μM for COX-1 and 0.54 μM for COX-2, COX-1/COX-2 ratio of 29.6 (9). Celecoxib reaches peak plasma concentrations after 2-3 hours. Its metabolism is mainly hepatic and catalyzed by CYP2C9 and CYP3A4. Less than 3 % is excreted unchanged in urine. The metabolites have no significant COX activity and it has a half-life of about 11 hours. Celecoxib inhibits CYP2D6 (10).

Etoricoxib

Etoricoxib is a 1,2-diarylpyridine derivative with a 6-membered core. Unlike celecoxib it has a methanesulfinate group where celecoxib has sulfonamide, making it a sulfone rather than a sulfonamide. Etoricoxib also has a pyridine with a methyl group rather than the benzene ring with a methyl group at the same position found in celecoxib (7). The structure of etoricoxib and celecoxib for structural comparison can be seen in figure 5 below.

The IC_{50} COX-1/COX-2 ratio is 344. It is as such much more selective and potent than its chemical cousin celecoxib (9). It has an elimination half-life of about 20 hours. The metabolism is hepatic by CYP3A4, with excretion of the metabolites in urine and

faeces and with less than 1 % eliminated unchanged. The area under the plasma-time curve (AUC) increases proportionately to dose taken orally from 5 to 120 mg, indicating first order elimination kinetics. Etoricoxib is well absorbed and reaches maximum plasma concentrations after approximately 1 hour (11).

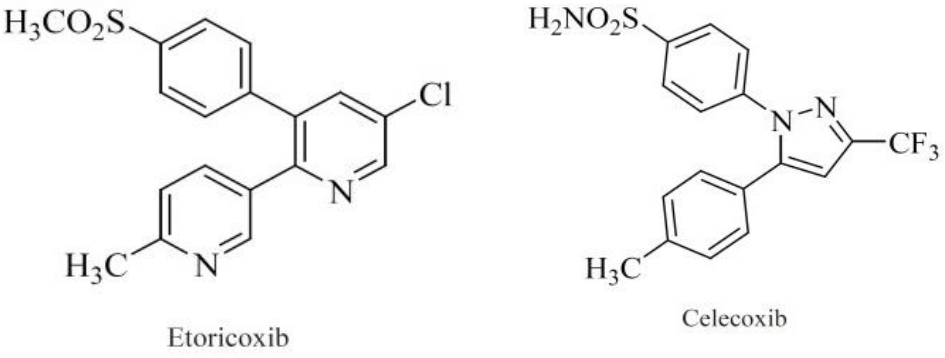

Figure 5. The structures of etoricoxib and celecoxib for easy comparison of the two.

Naproxen

Naproxen is a bicyclic acid with a small lipophilic CH_3O bound to one end of the molecule, increasing its potency, and a methyl group (also lipophilic) and carboxylic group to the other. There is one carbon atom adjacent to the aromatic ring and carboxyl group, which is also ideal for activity and potency. The structure of naproxen can be seen in figure 6 below (4).

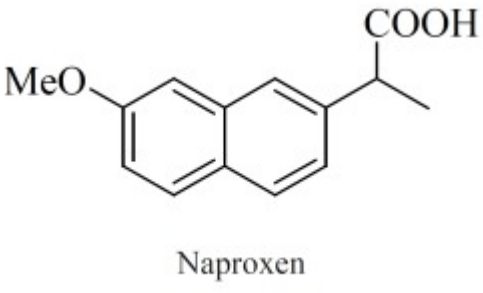

Figure 6. The structure of naproxen

Naproxen has a pKa of 4,2 and is highly bound to plasma proteins (99,6 %). It has an elimination half-life of about 13 hours. The absorption rate is decent with peak plasma concentrations reached after 2-4 hours. More than half of an administered dose is eliminated as unchanged drug. The rest is biotransformed hepatically via CYP3A4 and

CYP1A2 (4) Its IC_{50} is 32.01 µM for COX-1 and 28.19 µM for COX-2, giving a COX-1/COX-2 ratio of 1.14 (12).

Diclofenac

Diclofenac is a heteroarylacetic acid derivative. It does have the acidic center with one carbon atom's distance to an aromatic ring and has the second aromatic ring in a non-coplanar orientation that is ideal for binding (4). Even though diclofenac is a tNSAID it has a greater affinity for COX-1 than COX-2, with a COX-1/COX-2 almost equal to that of celecoxib; 29.2 (9). The structure of diclofenac can be seen in figure 7 below.

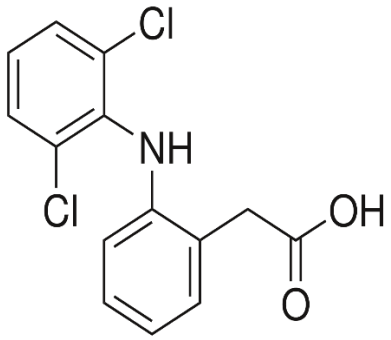

Figure 7. The structure of diclofenac

Diclofenac has a pKa of 4,0. It has close to 100 % intestinal absorption however the bioavailability is only about 60 % because of extensive first pass metabolism. Elimination half-life is 1-2 hours and peak plasma concentrations are reached after 1,5-2,5 hours. Onset of action is about 30 min (4).

Ibuprofen

Ibuprofen has only one aromatic ring, decreasing its potency. It does however have one carbon atom adjacent to the acidic center and the aromatic ring and it has lipophilic sidechains increasing its distribution in tissue (4). The structure of ibuprofen can be seen in figure 8.

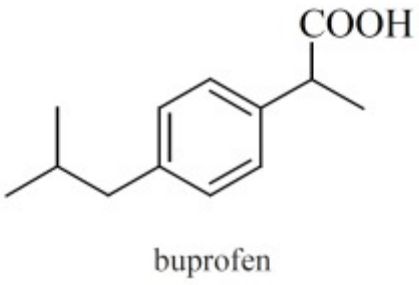

Figure 8. The structure of ibuprofen.

Ibuprofen has an IC_{50} of 5.9 µM for COX-1 and 9.9 µM for COX-2. This gives a COX-1/COX-2 ratio of 0.6 (12). Its elimination half-life is about 2 hours. Maximum plasma concentrations are reached in 2 hours after oral administration. Its pKa is 4,4 and its extensively (>99%) plasma bound. The drug is metabolized mainly by CYP2C9 but also to a lesser extent by CYP2C19. All its metabolites are inactive (4). Key characteristics of the studied drugs can be seen in table 1 below.

Table 1. Key characteristics of study drugs.

	IC_{50} ratio	pKa	Elmination Half-life	COX selectivity
Diclofenac	29.2	4.0	1-2 h.	COX-2
Naproxen	1.14	4.2	about 13 h	Unselective
Ibuprofen	0.60	4.4	about 2 h	Slight favour of COX-1
Celecoxib	29.6		about 11 h	COX-2
Etoricoxib	344		about 20 h	Highly COX-2 selective

Adverse events of COX inhibitors

Cardiovascular adverse events

NSAIDs, regardless of selectivity have been shown to cause serious cardiovascular side effects in long term usage. These side effects are uncommon however serious in nature. They include myocardial infarction, blood pressure elevation, stroke, transient ischemic attack, angina pectoris among others (5).

Gastrointestinal adverse events

COX-1 mediated PGE_2 protection of the gastric mucosa is greatly reduce by tNSAIDs and to some extent by coxibs. This makes the upper GI canal vulnerable to the acid-secretion, whilst the lower GI canal mucosa becomes susceptible to damage induced by bile and the gut flora (2, 4).

Aspirin exacerbated respiratory disease (AERD)

Although uncommon in the general population this condition has a prevalence of up to 20 % in adult asthmatics (13). It is characterized by exacerbated bronchospasms with asthma and rhinitis when taking tNSAIDs. Although some reports of reaction intolerance to coxibs have been made no reports have been made to patient with AERD tolerating COX-1 inhibitors (14).

Kidney and COX inhibition

Both COX isoforms are constitutively expressed in the kidneys and although COX-1 is more common COX-2 is also involved in homeostasis mechanism. The effects of prostaglandins vary in different parts of the kidney but the overall result is sodium and water retention for both selective and non-selective COX inhibitors. The effects are not deemed clinically relevant in healthy adults however at risk patients such as the elderly or people with high blood pressure might need to take these effects into consideration (15).

Proton pump inhibitors; mechanism of action and side effects

PPIs are often administered in combination with NSAIDs for their gastro-protective features. The fact that gastro-intestinal side effects are so tightly correlated to NSAID use (or at least thought to be) and the frequency of co-administration of PPIs warrants a brief explanation of the physiology of acid secretion. The mechanism of action for PPIs and their potential side effects will also be briefly explained.

Physiology

The human stomach includes a multitude of different cells. Endogenous hydrogen chloride production is maintained through the gastrin-ECL-parietal cell axis. Briefly explained this is the process; gastrin is secreted from G-cells. This stimulates the ECL-cells to secrete histamine. Histamine then binds to the histamine-2 receptors on the parietal cells. This leads to cyclic adenosine monophosphate (cAMP) activation intracellularly which through a reaction cascade activates the H^+/K^+-ATPase, also known as the proton pump (2).

PPIs

PPIs are inverse agonists that irreversibly inhibit the proton pumps. The drugs are acid activated prodrugs consisting of a substituted pyridine and a benzimidazole. The different pKa of the two moieties (about 4,0 for pyridine and 1,0 for benzimidazole) allows for two important pharmacological aspects; accumulation in canaliculi of the parietal cells (because it's a base) and activation only in acidic environments. PPIs

have short half-lives, about 1 hour. One single does have an inhibitory effect on acid-secretion for 2-3 days however due to irreversible binding of H^+/K^+-ATPase and accumulation in the canaliculi. There is an increase in antisecretory effect for about 5 days, at which point a plateau is reached (2,(16).

Adverse effects

There is evidence to support several severe adverse events for PPI use in older adults, defined as > 60 years of age. These include osteoporotic fractures, vitamin B12 deficiency, *Clostridium difficile* infection and acute interstitial nephritis. Although the study material for this evidence is large with several meta-analysis supporting it is not possible to definitively establish causality because no randomized controlled trials have been conducted (17).

Methods

This is a literary analysis. First standard literature was used to gather background information. This included books in pharmacology, physiology and medicinal chemistry. After this the databases deemed relevant were searched. This included pubmed, google scholar and UpToDate. Review articles, randomized controlled trials and meta-analysis were included if deemed relevant. An attempt was made to always find articles as new as possible, preferentially no more than 4 years old. The specific search phrases used were NSAIDs and adverse events, which gave 6527 results. NSAIDs vs coxibs (569 results), NSAID + PPI vs coxibs in terms of gastropathy (497 results), NSAIDs and the elderly (64 600 results), cardiovascular safety of celecoxib (24 000 results), cardiovascular profile of celecoxib vs traditional NSAIDs (9080 results), naproxen vs celecoxib (37 results), etoricoxib and diclofenac; which is safer (2950 results), and adverse events of proton pump inhibitors (60 000 results). To limit the vast number of studies yielded from the searches the following inclusion criteria were applied; any studies published before 2005 were excluded from the results. They had to include at least two of selected drugs or be a direct comparison between tNSAIDs and coxibs in terms of efficacy (pain management) or safety profile. The included studies also had to look at NSAID use for pain management (other than the ones that analyzed PPI use) with either BP, GI or CV profiles included in the primary analysis. When the studies were randomized controlled trials, they had to include at least 80 patients and be double blinded. The studies also had to be available in full text via Linnaeus university and be written in Swedish or English. When relevant studies were found studies citing the originally found study were looked at to see if any relevant and/or newer material could be found. The Swedish medical agency (läkemedelsverket) was also contacted for information on their current recommendations and guidelines of NSAID use. The studies finally included in the analysis were 1, and 18-34. The various included aspects of analysis, the design of this study and the amount of time given made it impossible to determine if any studies relevant to this topic were missed and thus not included.

Results

Cardiovascular profile of tNSAIDs and coxibs

Both tNSAIDs and coxibs increase blood pressure

Both tNSAIDs and coxibs increase blood pressure. This effect holds true for shorter treatment periods (week/s) and longer periods (months/years) (1, 18, 19).

In a double-blinded randomized multicenter non-inferiority substudy of the PRECISION trial the change in mean 24-h systolic blood pressure (SBP) was compared for celecoxib, ibuprofen and naproxen to test for celecoxib's non-inferiority after four months of treatment (1). Inclusion criteria were age $\geq$ 18, arthritis pain requiring daily NSAID treatment and established or increased risk of cardiovascular disease. Patients were randomized to receive either 100 mg celecoxib bis in die (b.i.d.), 600 mg ibuprofen ter in die (t.i.d.) or 375 mg naproxen b.i.d. If sufficient pain reduction was not achieved by these doses they could be increased to 200 celecoxib b.i.d., 800 mg ibuprofen t.i.d. and 500 mg naproxen t.i.d.

A monitor was used to measure ambulatory blood pressure (ABP) every 20 min during the day, defined as between the hours of 06:00 and 21:59, and every 30 min during the night (22:00-05:59). If the measurements were not done at these time intervals patients were recalled to the lab to repeat the study within 3 days. 117 patients were needed for 80 % power. Assuming 35% dropout rate 180 randomized patients were need per arm to achieve this. The number of patients included were enough to reach meaningful conclusions based on the power calculation. The study design allowed for enrolment to stop once the number of evaluable patients was reached if the dropout rate was lower than 35%.

444 patients were randomized; 146 to celecoxib, 147 to naproxen and 151 to ibuprofen. Mean daily doses were 208 ± 34 mg, 852 ± 98 mg and 2031 ± 237 mg respectively. Interestingly the dose of naproxen was increased by more than one standard deviation on average as compared to the original intended dose of 375 mg b.i.d. The three arms had similar baseline characteristics in terms of age, weight, use of other medications, BMI, men/women ratio, overall cholesterol levels, and blood pressure. The only statistically significant difference was HDL levels between celecoxib and naproxen (49.1 ± 15.79 mg/dL and 52.9 ± 17.31 respectively).

The primary endpoint was change in 24-h ambulatory SBP. Secondary endpoints included 24-h average diastolic blood pressure (DBP), pulse pressure (SBP-DBP), mean awake BP and mean sleep BP. The study showed no statistically significant difference in increase of mean 24-h ambulatory SBP between celecoxib and naproxen. Ibuprofen was however associated with a significant increase in mean ambulatory 24-h SBP and new onset hypertension as compared to celecoxib. This trial showed no relevant differences in analgesic activity among the three drugs The results of the primary endpoint measured in least square mean can be seen in **table 2** below (1).

The strengths of the study are its similar baseline characteristics and randomized design. Even though a power calculation has been made the low number of participants can decrease the value of the results. The fact that the study was sponsored by Pfizer increases the risk of bias. The low dose of celecoxib used might influence the results, however the doses of the other drugs were also below maximum doses on average. Interestingly the world health organization defines hypertension as 140/90 or above while this study it was defined as 131/81 or above.

Table 2. Primary endpoint results in substudy of PRECISON trial. Changes in LS mean ambulatory SBP (expressed in mmHg) and new onset hypertension (expressed in %) are shown in the table.

	Change in LS mean 24-h ambulatory SBP (mmHg) after 4 months	New onset hypertension (%), defined as SBP 131 or above or DBP 81 or above
Celecoxib (N = 146)	-0.3 mmHg [95% confidence interval (CI), -2.25, 1.74]	10.3 %
Naproxen (N = 147	1.6 mmHg (95% CI, -0.40, 3.57)	19.0 %
Ibuprofen (N = 151)	3.7 mmHg (95% CI, 1.72, 5.58)	23.2 %

To examine the effect of coxibs om blood pressure a meta-analysis of 19 randomized controlled trials (RCTs) involving coxibs, where BP data was available, was analyzed (19). The authors statistically combined the weighted mean difference (WMD) in blood pressure of coxibs as compared to tNSAIDs and placebo. Relative risk (RR) of developing hypertension and clinically relevant BP elevations were also looked at by pooling results. The studies included a combined 45.451 patients. The coxibs that were included were celecoxib, etoricoxib and rofecoxib.

The results showed that the WMD between celecoxib and tNSAIDs is +0.14 mmHg for SBP and +0.15 mmHg for DBP. The difference between celecoxib and placebo was however +2.60 mmHg for SBP and +0.99 for DBP. The study also showed a difference between coxibs and tNSAIDs overall, +2.83 mmHg and +1.34 mmHg SBP and DBP respectively. The tNSAIDs were looked at as a group and no distinction was made between different tNSAIDs.

The RR of developing hypertension was 1.61 (95% confidence interval [CI], 0.91-2.84; P = .10) and 1.25 (95% CI, 0.87-1.78; P = .23) for coxibs vs placebo and coxibs vs tNSAIDs respectively. The contribution of individual coxibs to relative risk of developing hypertension was different, 0.81 for celecoxib, 1.23 for etoricoxib and 2.63

for rofecoxib as compared to placebo and 0.82, 1.38 and 1.78 as compared to tNSAIDs. The most commonly used tNSAID was naproxen (19). The inclusion of rofecoxib limits the value of this analysis since its detrimental effects are well known and it has been removed from the market because of them.

A third study looked at ambulatory BP after 14 days of treatment with either 90 mg etoricoxib (N=21) quaque die (q.d.), 200 mg celecoxib (N=21) b.i.d., 500 mg naproxen (N=21) b.i.d. or placebo (N=20) (18). The study was double-blinded, randomized, placebo controlled and multi-centered. Patients between the age of 60 and 85 were eligible for inclusion. They had to have a good general health, defined by medical history, routine tests and physical examination. Baseline characteristics were those found on day 1 prior to intake of the first dose. They were similar among the four groups. There was an even ratio of men/women among the four groups and within the groups (approximately 50%). Ambulatory 24-h BP was measured with a ABP monitor. Measurements were taken every 15 min when the patients were awake and every 20 min when they were asleep. BP was a secondary endpoint of the study.

All the drugs studied increased BP significantly as compared to placebo. The increase was greatest for etoricoxib (7.7 mmHg SBP, 3.2 mmHg DBP) and lowest for celecoxib (2.4 mmHg SBP, 1.1 mmHg DPB). The increase for naproxen was 3.6 mmHg SBP and 1.4 mmHg DBP (18). The doses and methods of this study were very good in that they used high doses for all included drugs, not using doses far below maximum for one drug and close to or at maximum for another. The double blinded randomized design also strengthens the value of the study. The short treatment period and low number of participants does however greatly limit the generalizability of the results.

Although the results from these studies are interesting it is hard to draw any real-life conclusions from them. On the one hand it is highly unlikely that an increase of 1-4 mmHg is clinically relevant. On the other hand NSAIDs are the most commonly used drugs world-wide with millions of users daily. The huge amount of people increases the probability of adverse events although the percentages of these adverse events are low. Most users of NSAIDs take them temporarily though, which also limits the value of these findings. The foremost conclusion that can be drawn from this is that overall in terms of effects on blood pressure celecoxib is non-inferior to tNSAIDs. Etoricoxib is associated with a higher increase in BP but the clinical relevance of this increase is hard to determine.

Cardiovascular safety

The working group for cardiovascular pharmacotherapy of the European society of cardiology made a review of cardiovascular safety of non-aspirin NSAIDs (including coxibs) (20). They looked at major adverse cardiovascular events (MACE) from RCTs, meta-analyses and observational studies.

In one meta-analysis of 145 373 patients conducted by Kearney *et al*. RR for vascular events of coxibs, ibuprofen (800 mg t.i.d.), high dose diclofenac (75 mg twice daily), and high dose naproxen (500 mg twice daily) was looked at. Treatment periods varied among the RCTs included, 112 studies were shorter term (mean 11 week) and 9 were long term with over one year of treatment. The analysis looked at coxibs as a group

and found no different heterogeneity between different coxibs. The results showed the following; RR coxibs 1.42, 95% CI (1.13-1.78); RR high dose ibuprofen 1.51, 95% CI (0.96-2.37); RR high dose diclofenac 1.63, 95% CI (1.12-2.37); RR high dose naproxen 0.92, 95%CI (0.67-1.26). Thus, according to this meta-analysis coxibs as a group are comparable in cardiovascular risk with high dose ibuprofen and diclofenac but not with naproxen, which is a safer choice in terms of MACE. Looking at coxibs as a group gives little relevant insight about the individual drugs contribution to the results (20).

Another meta-analysis (N=116 429) looked at by the group showed inconclusive results since different NSAIDs had varied safety profiles depending on outcome. All NSAIDs (non-selective and coxib) however increased cardiovascular risk and naproxen seemed least harmful (20).

The group also looked at a study showing a dose-dependent increased risk for celecoxib. In a double-blinded RCT 2035 patients were given 200 mg celecoxib b.i.d., 400 mg celecoxib b.i.d., or placebo. Risk of MACE was 2.3%, 3.4% and 1%, respectively. This further strengthens the argument that moderate doses of celecoxib might be safe whilst high dose regimens should be avoided in patients with an increased cardiovascular risk.

Celecoxib is non-inferior to naproxen and ibuprofen in terms of cardiovascular safety (21). This was shown in a randomized, multicenter, double-blind, noninferiority trial (the PRECISION trial) of 24 081 participating patients. The patients, who suffered from osteoarthritis or rheumatoid arthritis, were all at increased cardiovascular risk. They were above 18 years of age and required daily intake of NSAIDs to manage pain due to arthritis. If the pain could be managed adequately with paracetamol they were excluded. The patients were randomized to one of three groups; 100 mg celecoxib (N=8072) twice a day, 600 mg of ibuprofen three times a day or 375 mg of naproxen twice a day. The study had a mean treatment duration of 20.3±16.0 months and a mean follow-up period of 34.1±13.4. For celecoxib to be determined as non-inferior the original study-design required a hazard-ratio that did not exceed 1.12 with a one sided 97.5% CI of less than 1.33 for noninferiority. Assessment of the on-treatment population included events that occurred while the drug was taken and 30 days after possible discontinuation. 762 events were required to achieve 90% power. It was estimated that a 20.000 sample size would be needed based on the assumptions that the annual event rate would be 2% and treatment discontinuation would be 40%. These requirements could not be met, event rate was lower and dropout was higher. The study was therefore changed to provide 80% power. With an upper 97.5% CI for noninferiority in the on treatment population changed to 1.40. The study now required 580 events in the intention to treat (ITT) population and 420 in the on treatment population. 31,857 patients were screened. Of these 24,222 underwent randomization. Of these 141 were excluded and 24,081 patients were included in the analysis. Baseline characteristics were similar across the three groups with no statistically significant differences. About 64 % of the participants were women however the large sample sizes make the result relevant for men as well. The average age was approximately 63 years old. The primary composite outcome was time to even adverse cardiovascular events as defined by the Antiplatelet Trialists Collaboration (APTC). These included deaths from cardiovascular causes (including hemorrhagic), nonfatal stroke and nonfatal myocardial infarction. Secondary outcomes of cardiovascular nature included

coronary revascularization, hospitalization for unstable angina and transient ischemic attack (TIA).

Of the patients receiving celecoxib 2.3% in the group had a primary outcome event occur during the treatment period. The corresponding numbers were 2.5%, 2.7% for naproxen and ibuprofen, respectively. The adjusted hazard ratios for celecoxib vs. naproxen was 0.93 and 0.85 for celecoxib vs. ibuprofen. The results in the secondary outcome (major adverse cardiovascular events) were 4.2% for celecoxib, 4.3% for naproxen and 4.8% for ibuprofen. (21). All baseline characteristics and results of the study can be seen in tables 3 and 4 below. The moderate dose of celecoxib used in this study only provides evidence for moderate doses of the drug; the results of this study are not applicable to high dose regimens. The study was sponsored by Pfizer which might increase risk of bias.

Table 3. Population baseline characteristics of the PRECISION trial

Table 1. Baseline Characteristics of Patients in the Intention-to-Treat Population.*

Characteristic	Celecoxib Group (N=8072)	Naproxen Group (N=7969)	Ibuprofen Group (N=8040)
Age — yr	63.0±9.5	63.3±9.4	63.2±9.4
Female sex — no. (%)	5175 (64.1)	5096 (63.9)	5174 (64.4)
Race — no. (%)†			
White	6058 (75.0)	5926 (74.4)	5991 (74.5)
Black	1090 (13.5)	1134 (14.2)	1108 (13.8)
Asian	164 (2.0)	172 (2.2)	173 (2.2)
Unspecified or other	760 (9.4)	737 (9.2)	768 (9.6)
Body-mass index‡	32.7±7.3	32.6±7.3	32.5±7.4
Primary arthritis diagnosis — no. (%)			
Osteoarthritis	7259 (89.9)	7178 (90.1)	7208 (89.7)
Rheumatoid arthritis	813 (10.1)	791 (9.9)	832 (10.3)
Current aspirin use — no. (%)	3701 (45.8)	3652 (45.8)	3712 (46.2)
Cardiovascular risk category — no. (%)			
Primary prevention	6209 (76.9)	6186 (77.6)	6206 (77.2)
Secondary prevention	1863 (23.1)	1783 (22.4)	1834 (22.8)
History of diabetes — no. (%)	2843 (35.2)	2768 (34.7)	2885 (35.9)
History of hypertension — no. (%)	6296 (78.0)	6145 (77.1)	6303 (78.4)
History of dyslipidemia — no. (%)	5080 (62.9)	4966 (62.3)	5002 (62.2)
Current smoker — no. (%)	1689 (20.9)	1631 (20.5)	1680 (20.9)
Current statin use — no. (%)	4367 (54.1)	4304 (54.0)	4307 (53.6)
Current DMARD use — no. (%)	572 (7.1)	602 (7.6)	584 (7.3)
Systolic blood pressure — mm Hg§	125.3±10.5	125.0±10.6	125.4±10.4
Diastolic blood pressure — mm Hg	75.5±8.0	75.4±8.0	75.5±7.9
Creatinine level — mg/dl	0.9±0.23	0.9±0.22	0.9±0.22
HAQ disability index¶	1.1±0.61	1.1±0.61	1.1±0.61
VAS score — mm‖	54.0±23.5	54.1±24.0	54.1±23.6

* Plus–minus values are means ±SD. Percentages may not total to 100 because of rounding. DMARD denotes disease-modifying antirheumatic drug.
† Race was self-reported.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ P=0.044 for the comparison among the three treatment groups.
¶ The Health Assessment Questionnaire (HAQ) disability index is based on 20 questions in eight categories regarding daily functioning; overall scores range from 0 to 3, with 0 indicating no disability and 3 indicating complete disability.
‖ Visual Analogue Scale of Pain (VAS) scores range from 0 to 100 mm, with higher scores indicating worse pain; differences greater than 13.7 mm are considered to be clinically significant.

Table 4. Results of PRECISION trial. Number of MACE gastrointestinal events for the study drugs can be seen in the table.

Table 2. Adjudicated Outcomes in the Intention-to-Treat Population.

Outcome	Celecoxib Group (N=8072)	Naproxen Group (N=7969)	Ibuprofen Group (N=8040)	Celecoxib vs. Naproxen*		Celecoxib vs. Ibuprofen*	
				Adjusted Hazard Ratio (95% CI)	P Value	Adjusted Hazard Ratio (95% CI)	P Value
	number of patients (percent)						
Primary APTC end point†	188 (2.3)	201 (2.5)	218 (2.7)	0.93 (0.76–1.13)	0.45	0.85 (0.70–1.04)	0.12
Major adverse cardiovascular events‡	337 (4.2)	346 (4.3)	384 (4.8)	0.97 (0.83–1.12)	0.64	0.87 (0.75–1.01)	0.06
Composite of serious gastrointestinal events	86 (1.1)	119 (1.5)	130 (1.6)	0.71 (0.54–0.93)	0.01	0.65 (0.50–0.85)	0.002
Clinically significant gastrointestinal events§	55 (0.7)	56 (0.7)	72 (0.9)	0.97 (0.67–1.40)	0.86	0.76 (0.53–1.08)	0.12
Iron-deficiency anemia of gastrointestinal origin§	33 (0.4)	69 (0.9)	64 (0.8)	0.47 (0.31–0.71)	<0.001	0.51 (0.33–0.77)	0.002
Renal events	57 (0.7)	71 (0.9)	92 (1.1)	0.79 (0.56–1.12)	0.19	0.61 (0.44–0.85)	0.004
Hospitalization for congestive heart failure	45 (0.6)	48 (0.6)	46 (0.6)	0.92 (0.62–1.39)	0.70	0.98 (0.65–1.47)	0.91
Hospitalization for hypertension	24 (0.3)	34 (0.4)	40 (0.5)	0.69 (0.41–1.17)	0.17	0.60 (0.36–0.99)	0.04
Death from any cause	132 (1.6)	163 (2.0)	142 (1.8)	0.80 (0.63–1.00)	0.052	0.92 (0.73–1.17)	0.49
Components of composite end points							
Death from cardiovascular causes	68 (0.8)	86 (1.1)	80 (1.0)	0.78 (0.57–1.07)	0.13	0.84 (0.61–1.16)	0.30
Nonfatal myocardial infarction	76 (0.9)	66 (0.8)	92 (1.1)	1.14 (0.82–1.59)	0.43	0.82 (0.61–1.11)	0.21
Nonfatal stroke	51 (0.6)	57 (0.7)	53 (0.7)	0.88 (0.61–1.30)	0.52	0.95 (0.65–1.40)	0.81
Hospitalization for unstable angina	55 (0.7)	64 (0.8)	65 (0.8)	0.86 (0.60–1.23)	0.40	0.84 (0.59–1.21)	0.35
Revascularization	174 (2.2)	161 (2.0)	198 (2.5)	1.07 (0.87–1.33)	0.52	0.87 (0.71–1.07)	0.18
Hospitalization for TIA	18 (0.2)	18 (0.2)	27 (0.3)	0.99 (0.51–1.90)	0.97	0.66 (0.37–1.20)	0.18

* Hazard ratios and P values were estimated with the use of a Cox proportional-hazards model with adjustment for stratification factors.
† The primary composite outcome in the time-to-event analysis was the first occurrence of an adverse event that met Antiplatelet Trialists Collaboration (APTC) criteria (death from cardiovascular causes, including hemorrhagic death; nonfatal myocardial infarction; or nonfatal stroke). The P value for the noninferiority of celecoxib as compared with either naproxen or ibuprofen with regard to this outcome was <0.001.
‡ The composite outcome of major adverse cardiovascular events included the components of the primary APTC outcome plus coronary revascularization or hospitalization for unstable angina or transient ischemic attack (TIA).
§ Definitions are provided in the Supplementary Appendix.

In an observational study of 1.4 million participants, the risk of acute myocardial infarction and sudden cardiac death was looked at for patients taking tNSAIDs or

coxibs (22). The data was gathered from Kaiser Permanente in California, a health care provider for roughly 6 million people. All patients between the ages of 18 and 84 taking NSAIDs on a prescription for any duration of time between the 1st of January 1999 and December 31 2001 were included. Exclusion criteria were cancer of any kind, HIV/aids, renal failure, liver failure, severe respiratory disease, organ transplant and less than 12 month health plan coverage before starting an NSAID treatment. The outcome was serious coronary heart disease, defined as acute myocardial infarction or sudden cardiac death. Patients with death of unknown cause were also included. For every primary event 4 controls were randomly selected. These controls were also part of the study, i.e., the controls could become primary events. Controls were matched with primary events based on age, sex and healthcare region. All tNSAIDs were included but only the coxibs rofecoxib and celecoxib. A total of 1 394 764 patients were included in the analysis. Of these 40 405 took celecoxib, 991 261 took ibuprofen and 435 492 took naproxen (some patients took more than one NSAID during the study period). 8143 primary events and 31 496 controls were gathered from this. Patients were defined as current users if the primary event overlapped with use of NSAID. Use of NSAID was defined by the prescription, if there were tablets left on the prescription patients were deemed current users. Recent users had 1-60 days since the prescription ran out and remote users had more than 60 days since the prescription ran out. Odds ratios for risk of acute myocardial infarction with use of NSAID compared to remote use can be seen in table 5 below. Studies of this kind always have limited value. No direct causality can be shown since it is not an RCT. Also, although number of primary events (cases) are given there is nothing to compare them to; the study does not mention how many patients were taking each of the NSAIDs currently, only how many were taking them whilst having a primary event occur, no percentages but only comparison to the control. It is interesting that celecoxib shows a decreased risk even if it is of little value due to the many limitations of the study. Adherence to treatment was based amount prescribed, assuming perfect adherence. Additionally, risk factors such as smoking were unknown.

Table 5. Results of observational study – odds ratios for risk of acute MI

Control	1
Celecoxib (cases; 126)	0.84, 95% CI (0.67–1.04)
Ibuprofen (cases; 670)	1.06, 95% CI (0.96–1.17)
Naproxen (cases; 367)	1.14, 95% CI (1.00–1.30)

In a pooled analysis (the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) program) of three randomized double-blinded controlled trials the number of thrombotic cardiovascular events were compared for diclofenac and etoricoxib (23). The study was conducted between June 2002 and May 2006. This was done at 1380 sites in 46 countries. The studies included were the MEDAL study, the Etoricoxib vs Diclofenac Sodium Gastrointestinal Tolerability and Effectiveness (EDGE) study and the EDGE II study. The studies were deemed suitable for pooling based on similar

entry criteria. These included diagnosed arthritis or osteoarthritis in need of chronic NSAID use (based on clinician's judgement), 50 years of age or older. The dosages were similar across the three studies. In the MEDAL study patients received 90 or 60 mg etoricoxib q.d. or 75 mg diclofenac b.i.d. The EDGE and EDGE II both had 90 mg etoricoxib q.d. however in EDGE patients were given diclofenac 50 mg t.i.d. whilst in EDGE II patients were given 75 mg b.i.d. Patients in all three studies who were at high risk of upper GI adverse events were given PPI or misoprostol. High risk was defined as age > 65 or medical history of upper GI complications. Patients returned every 4 months for checkups and compliance to treatment regimen was based on pill count. There were scheduled phone contacts between visits. The primary composite endpoint was first occurrence of thrombotic cardiovascular events. This included myocardial infarction, intracardiac thrombus, resuscitated cardiac arrest, thrombotic stroke, unstable angina pectoris, cerebrovascular thrombosis, peripheral venous thrombosis, pulmonary embolism, peripheral arterial thrombosis, TIA, and sudden or unexplained death, whether these events were fatal or not. The primary analysis had a power of 91%. A definition of non-inferiority was set at a HR of less than 1.30 for etoricoxib vs diclofenac, with an upper limit 95% CI. The number of events needed for 91% power (635) was calculated, assuming a true underlying HR of 1.0. Secondary endpoints included prespecified safety endpoints for gastrointestinal, hypertension, renal dysfunction or hepatic adverse events and discontinuations as a result of these adverse events. It was the per protocol population that was used for the primary analysis. The per protocol population included all patients from first intake of NSAID to 14 days after the last dose was taken. Patients only had to take 75% of their study medication and were allowed to use other NSAIDs up to 10% of the time.

33 302 patients were included in the primary analysis. Of these 23504 were from the MEDAL study, 7111 from the EDGE study and 4086 from EDGE II. Baseline characteristics were similar with no statistically significant differences however no distinction was made between doses and treatment intervals when assessing baseline characteristics. 6769 patients received etoricoxib 60 mg, 10 643 patients received 90 mg etoricoxib, 3518 patients received 50 mg diclofenac (t.i.d.) and 13 771 patients received 75 mg diclofenac (b.i.d.). The mean treatment time was 18.2 months for etoricoxib and 17.7 months for diclofenac. 21 395 patients used their assigned NSAID between 12 and 23 months and 12 854 for 24 months or longer. 1399 were excluded from the per protocol population (from 34 701 to 33 302).

There were a total of 320 (1.90 %) thrombotic cardiovascular events in the etoricoxib group (n=16 819) and a total of 323 (1.96 %) events in the diclofenac group (n=16 483). The hazard ratio for etoricoxib compared to diclofenac was 0.95 (95 % CI 0.81-1.11). Total number of fatal thrombotic events were 43 patients in both groups, with a HR of 0.96 (95% CI 0.63-1.46). Again, in these totals no distinction was made between dosages or dosage intervals.

Based on the results in this study etoricoxib is non-inferior to diclofenac. The high dose of 90 mg etoricoxib used in a large amount of the study population strengthens the result. It is interesting that diclofenac was administered b.i.d. at 75 mg in most cases. Its high potency (IC_{50} 0.38 μM for COX-1 and 0.013 μM for COX-2) should mean that 50 mg gives more than satisfactory results. It is true that the low half-life of 1-2 hours requires an increase in dosage beyond what is necessary for a therapeutic effect in vitro to make the effect last for a reasonable amount of time. 50 mg should however account for that even with the high first pass metabolism of diclofenac and

t.i.d. administration would provide more even plasma levels throughout the day. The incidence of congestive heart failure was higher in EDGE II (75mg b.i.d.) than EDGE (50 mg t.i.d.). The difference was very small though (0.1 vs 0.2 %) and no calculations have been made for its significance (23).

Based on the evidence listed above patients with increased risk of cardiovascular adverse events of any cause should use moderate doses of celecoxib or naproxen (possibly high dose naproxen). These drugs should only be used when unavoidable as they are not without negative impact on cardiovascular adverse events but rather the lesser of evils. There is conflicting information regarding whether celecoxib or naproxen would be better. This holds true when looking at cardiovascular adverse events assuming no other systems are affected.

Gastrointestinal toxicity

In the MEDAL program (N=34 701, average study period 18 months) that compared diclofenac and etoricoxib in terms of cardiovascular safety, rates of upper gastrointestinal adverse events were looked at (23). These included perforations, bleeding, obstruction and ulcers. Etoricoxib had 0.67 events per 100 patient-years (95% CI 0.57–0.77) and diclofenac had 0.97 events per 100 patient years (0.85–1.10), which gives a HR of 0.69 (0.57–0.83). The rates of complicated upper GI events were not significantly different, 0.30 vs 0.32 events per 100 patient years for etoricoxib and diclofenac respectively. 50% of the patients included in the study were given PPI or misoprostol, greatly reducing rate of upper GI adverse events. The rates of lower GI events were 0.32 for etoricoxib and 0.38 for diclofenac per 100 patient years. The HR was 0.84 (0.63-1.13) (23).

In the PRECISION trial (N=24 081), where cardiovascular safety was compared for celecoxib naproxen and ibuprofen, gastrointestinal adverse events from long term treatment (20.3 ± 16 months) were also looked at. Celecoxib had significantly less serious gastrointestinal events; HR celecoxib vs. naproxen 0.71 (95% CI 0.54-0.93), HR celecoxib vs. ibuprofen 0.65 (95% CI 0.5-0.85). Iron deficiency of GI origin was also significantly less for celecoxib vs naproxen and ibuprofen, HR 0.47 (0.31-0.71); 0.51 (0.33-0.77), 95% CI respectively (19). All the results of the study can be seen in table 4. above.

Another study compared the upper gastrointestinal safety of celecoxib as compared to diclofenac and naproxen. The study was double blinded, multicenter, multinational and randomized patients to either 100 mg celecoxib b.i.d., 200 mg celecoxib b.i.d., diclofenac 50 mg b.i.d. or 500 mg naproxen b.i.d.

Inclusion criteria were 18 years of age, osteoarthritis of the hip, knee, or hand that required daily analgesia treatment and had lasted for more than six months. The major

exclusion criteria were any active GI disease that precluded NSAID therapy, more than two past ulcers, and ulcer in the last 30 days before randomization. The analysis was done on the ITT population. 13 274 patients were randomized. Of these 13 194 received at least one dose and were included in the ITT. The patients were divided accordingly; 4393 were given 100 mg celecoxib b.i.d., 4407 200 mg celecoxib b.i.d., 905 500 mg naproxen b.i.d., 3489 diclofenac b.i.d. The results were analyzed in groups, celecoxib group or NSAID group, no distinctions were made between different doses or individual drug or dose contributions. Baseline characteristics had no statistically significant differences. Mean age was 62 years and 76% of the participants were women. The study lasted for 12 weeks. The study concluded that celecoxib is as effective in terms of analgesia and anti-inflammation but with significantly fewer upper gastrointestinal events; 0.1/100 patient years for celecoxib and 0.8/100 patient years for NSAIDs, odds ratio 7.02 (95% CI 1.46-33.8 P=0.008) (24).

There is overwhelming evidence from observational, RCT and meta-analysis studies suggesting a better GI profile of coxibs over tNSAIDs in long term treatment (21, 23, 24, 25, 26).

Coxib vs tNSAIDs + PPI

tNSAIDs induce damage on the entire GI-tract (27). PPI + tNSAID treatment show similar efficacy in preventing upper GI complications as celecoxib and etoricoxib. The addition of a PPI to tNSAID therapy does not prevent lower GI adverse events however. PPIs might even worsen intestinal damage as it according to experimental evidence possibly can induce dysbiosis (27).

One meta-analysis compared rates of dyspepsia between coxibs and tNSAIDs + PPI, as compared to a baseline use of tNSAIDs alone. 30 RCT were included in the analysis; 26 that compared coxibs and tNSAIDs and 4 that compared tNSAIDs to tNSAIDs + PPI. Specifically, the reduction in relative and absolute risk (RR and AR) were looked at. Coxibs vs tNSAIDs showed a RR reduction of 12%, with an AR of 3.7%. tNSAIDs vs tNSAIDs + PPI showed a RR reduction of 66% and an AR of 9%. According to these findings the addition of PPI to non-selective cox-inhibitors is more effective in reducing the risk of dyspeptic complications than coxibs, as compared to non-selective use alone. Limited value can be drawn from this analysis since contributions of individual drugs were not taken into consideration, neither were potential adverse events of PPI (28).

It is clear from contemporary evidence that in terms of gastrointestinal toxicity celecoxib and etoricoxib are better choices than tNSAIDs.

All NSAIDs show similar efficacy in pain management

There is conflicting evidence with regards to efficacy amongst NSAIDs. Two studies suggest that etoricoxib in superior to both celecoxib and tNSAIDs in pain management (29, 30). One of these studies had only 102 patients and the other was sponsored by a

company with monetary interest in etoricoxib, greatly reducing the generalizability and increasing bias.

A Cochrane review found no significant difference between different NSAIDs in management of chronic lower back pain. 3 of the studies included in the trial compared efficacy of different NSAIDs. This included a comparison between diclofenac and ibuprofen 100 mg and 1600 mg/day for 14 days, respectively and diclofenac and etoricoxib 150 mg, 60mg/day for four weeks, respectively (31). In the review of the cardiovascular safety of non-aspirin NSAIDs it was concluded that pain relief is similar for different selective and non-selective NSAIDs (20). Similar results were seen in two other reviews (32, 33).

Recommendations from the Swedish medical agency

The Swedish medical agency does not differentiate between different NSAIDs in their current recommendations other than the fact that ibuprofen or naproxen are recommended for use in children (both for musculoskeletal pain, recurring headaches, arthritis pain etc.). Their evidence for use of NSAIDs in musculoskeletal pain is based on clinical experience. Which NSAID that should be used seems to be entirely up to the prescriber with no recommendations for one over the other. Some cautions are however given, NSAID use in the elderly should be avoided if possible because of their inherent increased risk of cardiovascular and gastrointestinal complications. They also recommend the use of PPI when there is a risk for gastrointestinal side effects. They claim that increased COX-2 selectivity increases cardiovascular risk. Increased cardiovascular risk based on COX-2 selectivity is inconclusive with the results analyzed in this work, where etoricoxib is non-inferior to diclofenac in high doses and where moderate doses of celecoxib is non-inferior to naproxen and better than ibuprofen (34).

Discussion

The results of this study show that there is not a one size fits all solution when it comes to NSAID use. The clinical setting is too complex and there are a multitude of factors that need to be taken into consideration when choosing which NSAID should be used for which patient. Etoricoxib is the best choice for patients at risk of GI complications, it also has one of the worst cardiovascular profiles however. In terms of cardiovascular safety celecoxib or naproxen proved the best choices. However, the dose-dependent increased risk of celecoxib reduces its value in patients with severe pain (20). Thus, patients with an increased risk of cardiovascular adverse events in pain so severe high dose regimens are required naproxen is the best choice. In patients who are at increased risk of both cardiovascular and GI adverse events celecoxib is the best choice. The elderly fit in to this category.

The results of this study do also show that there is a need to differentiate between NSAIDs. They are equally effective in pain reduction; diclofenac is not superior to all other tNSAIDs in terms of pain management (20). They do however show different

side effect profiles and pharmacology. The fear that exists amongst prescribers for coxibs is according to contemporary evidence somewhat unfounded; tNSAIDs show similar cardiovascular profiles and in many cases coxibs are even a better choice than tNSAIDs. There is a clear dose-event relationship. The rate of adverse events, both CV and GI, are uncommon.

The increased affinity for COX-2 does clinically improve gastro-intestinal side effects (10,23-26). The addition of a PPI to tNSAID treatment does also reduce upper GI complications very well, as well or better than coxibs (27, 28). There are however two problematic aspects of this. COX-1 inhibition induces damage along the entire GI-tract, and researchers often fail to take into consideration potential side effects of PPIs. PPI have no benefit to the lower GI and as such coxibs are the better choice in terms of lower GI adverse events. Although the side-effects from PPI are not common they are serious in nature and because of the huge amount of people taking NSAIDs they might become clinically relevant; 30 million people consume prescription NSAIDs daily. On top of that 60% of all over the counter analgesic medication sold in the USA are NSAIDs (35). It is important to note that COX-2 selectivity is not absolute, coxibs also inhibit COX-1 and show an increased GI risk relative to placebo. This risk is a lot lower for coxibs, but it is there; 1.8-fold for coxibs, 1.9-fold for diclofenac, 4.0-fold for ibuprofen, and 4.2-fold for naproxen (20). Although the risk of GI complications is a lot lower for coxibs relative tNSAIDs (except diclofenac) the addition of a PPI even to coxib regimens should be taken into consideration in long term treatments of high risk patients.

Interestingly, even though diclofenac shows almost the same selectivity for COX-2 as celecoxib (IC_{50} ratios of 29 and 30 respectively) their difference in half-life makes celecoxib superior. Because diclofenac has such a short half-life (1-2 hours) it is administered in doses far exceeding those necessary to inhibit COX-2 and as a result COX-1 is also inhibited. As the plasma concentrations of the drug decrease less of COX-1 is inhibited while COX-2 remains inhibited due to the higher affinity. This creates windows of COX-2 selectivity during the dosing interval, something that is not seen with celecoxib. Even though diclofenac is inferior to celecoxib in terms of GI events because of its pharmacokinetics it is still the best choice of over the counter tNSAID covered in this work (9, 18). The best choice in terms of GI events alone is etoricoxib, it has a COX-1/COX-2 IC_{50} more than 10 times higher than celecoxib in vitro (344 vs 30) (9).

There is a notion that the most common side effects of NSAIDs are gastrointestinal. The large RCT studies included in this work had far more cardiovascular adverse events than GI events regardless of selectivity (23,24).

Etoricoxib increases blood pressure more than celecoxib and tNSAIDs when looked as a group (18,19). It also shows an increased risk of cardiovascular events compared to ibuprofen naproxen and celecoxib (20). A possible explanation for this increased cardiovascular risk compared to other coxibs is its sulfone group. It has been shown that sulfone COX-2 inhibitors increase oxidative modification susceptibility through a non-enzymatic process. This is believed to be because sulfone coxibs interact differently with phospholipids than sulfonamides (celecoxib). This effect is not seen with tNSAIDs either (36). It is not known why diclofenac shows an increased cardiovascular risk comparable to that of etoricoxib. Some researchers have suggested that this is due to its COX-2 selectivity however the fact that celecoxib is superior to diclofenac in this aspect proves that this hypothesis is only part of the explanation.

Another interesting aspect that might be relevant to take into consideration is adherence. There is evidence that suggests that increased dosing interval decreases adherence. This holds especially true among the elderly (37). It is therefore possible that choosing the medication with the longest half-life is the best option. This is also yet another evidence in support of that PPIs should only be used when imperative.

In conclusion; it is highly unlikely that the adverse events of NSAIDs would be clinically relevant in single dose or very short term (days) usage such as for a tension head-ache in otherwise healthy individuals. In these situations, there is little need to differentiate between NSAIDs other than in terms of lasting effect and how often to take the medication. Because of the much longer half-life of naproxen compared to diclofenac or ibuprofen it can be a more convenient choice in situations where the pain is lasting, such as minor musculoskeletal injuries. It is however relevant for patients who already are at an increased risk of adverse events associated with NSAIDs. The elderly fit in to this category; they are at an increased risk of a multitude of illness' and often victims of polypharmacy. The COX-2 selective inhibitor celecoxib might prove to be a better alternative in moderate doses to these types of patients. It shows a better GI-profile than non-selective inhibitors, a similar or better cardiovascular profile than etoricoxib and tNSAIDs, and has a half-life long enough that its only taken twice a day.

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