THE NORTHERN HOSPITAL

IBUPROFEN

"*Discobolus - The Discus Thrower*", *in marble, Roman, 2nd Century AD from Hadrian's Villa; copy of a Greek bronze original by Myron, c. 460 B.C.E, Vatican Museums, Rome.*

"*When you came into the hall,*" *he said, "didn't you notice a totally gorgeous statue up there, by Demetrios the portraitist?*"

"*Do you mean the discus-thrower?,*" *I said. "The one bent over into the throwing-position, with his head turned back to the hand that holds the discus, and the opposite knee slightly flexed, like one who will spring up again after the throw?* "

"*Not that one*", *he said, "that's one of Myron's works, the Diskobolos is what you speak of...* "

Lucian of Samosata, Philopseudes, c. 18 A.D.

In the aedileship of Marcus Scaurus there were 3000 statues on the stage in what was only a temporary theater. Mummius after conquering Achaia filled the city with statues though destined not to leave enough at his death to provide a dowry for his daughter - for why not mention this as well as the fact that excuses it. A great many were also imported by the Luculli. Yet it is stated by Mucianus who was three times consul that there are still three thousand statues in Rhodes, and no smaller number are believed to still exist at Athens, Olympia and Delphi. What mortal man could recapitulate them all, or what value can be found in such information? Still it may give pleasure just to allude to the most remarkable and to name the artists of celebrity, though it would be impossible to enumerate the total number of the works of each inasmuch as Lysippus is said to have executed 1500 works of art, all of them so skillful that each of them by itself might have made him famous….

Pliny the Elder, The Natural History, Bk. 34.34, 79 A.D

….The art rose to incredible heights in success and afterwards in boldness of design. To prove this success I will adduce one instance, and that not of a representation of either a god or a man; our own generation saw on the Capitol, before it last went up in flames burnt at the hands of the adherents of Vitellius, in the shrine of Juno, a bronze figure of a hound licking its wound, the miraculous excellence and absolute truth to life of which is shown not only by the fact of its dedication in that place but also by the method taken for insuring it; for as no sum of money seemed to equal its value, the government enacted that its custodians should be answerable for its safety with their lives…

Pliny the Elder, The Natural History, Bk. 34.37, 79 A.D

Following the Roman conquest of the Greek city states in the Second century B.C, the number of Greek works of Art that were looted and taken back to Rome was staggering. Pliny despaired of the task of describing all the masterpieces that filled Rome, stolen from the conquered Greek cities. Even after Mummius had conquered the Greek state of Achaea in 146 B.C, Athens, Olympia and Delphi, Pliny estimated, still had over three thousand works of art apiece. So much statuary had been taken that by the time of the mid-First century BC, three thousand statues were able to be crammed into a Roman theater as a backdrop for a temporary play. Pliny named many famous Greek Artists of extraordinary productivity and talent, amoung them Lysippus, a court sculptor to Alexander the Great, who produced over 1500 works, any one of which was so remarkable, that it alone would have ensured his fame. Pliny gave as an example of his work, an exquisite hound, so valued

it was deemed priceless, and installed in the Temple of Juno on the Capitol and whose custodians guarded it night and day, in fear of execution, should it be stolen.

Following the Roman occupation, the art of sculpture in bronze dramatically declined in Greece. Without any ongoing supply for plunder, Roman sculptors attempted to emulate the old Greek masters in marble. One such master was Myron of Eleutherae. His stunning bronze depictions of magnificent Olympic athletes were greatly admired in the mid-Fifth Century B.C. According to ancient commentators, he revolutionized the art of sculpture with his dynamic and contorted depictions of athletes, where previously they were depicted as simply standing or quite static.

Tragically however there are very few original Greek bronzes from this period that have survived. Virtually all we know of these works are due to Pliny the Elder, and the fortuitous preservation of much later Roman copies done in marble, a more durable and less expensive medium than bronze. As magnificent as many of these Roman copies are, in many cases they do not appear to have approached the skill of the original Greek masters. Myron's "Diskobolos" is a case in point. This work was well known in the Second Century AD, when many Roman copies of it existed. We know from the writings of Lucian and others that Myron's original Discus Thrower was a wonder of dynamic anatomical contortion. The head apparently was bent back at an alarming angle, the eyes glaring back at the discus, in intense concentration, at the very extreme of the Olympian's throwing arc. Later Roman copyists were unable to reproduce this muscular dexterity and so instead we find that they simply portrayed the athlete's head bent forward in a more neutral and static position, such as that seen in the Roman Discus Thrower that currently resides in the Vatican Museums.

In the mid-Fifth century B.C Olympic athletes would use various aromatic oils to soothe their aching muscles - and from the works of Myron we can see that aromatic oils would have been in quite some demand! But today we use modern medicines for sporting muscular aches and pains in the form of the drug class known as the NSAIDS, one of the currently most popular of this class being ibuprofen. One can't help thinking however that aromatic oils would be more suitable to a Myron athlete - muscular and glistening in the sunlight. Unlike the wondrous oils of Myron's time, ibuprofen has an analgesic "ceiling" above which no further analgesia can be obtained. Going beyond this ceiling only increases the likelihood of side effects such as peptic ulceration. This would have resulted in a dynamic - but somewhat less majestic - image of the Discobolus, completely doubled over in painful gastronomic contortions - not such an appropriate image for the memory of Myron or for His Holiness' Museums!

IBUPROFEN

Introduction

Ibuprofen (trade name in Australia, "**Nurofen**" amoung others) is a widely used non-steroidal anti-inflammatory drug, (**NSAID).**

Nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, are used for their mild to moderate **analgesic** and **anti-inflammatory** effects.

NSAIDs are one of the most frequently prescribed classes of drugs and adverse events related to their use are common.

Although the overall risk of a serious gastrointestinal adverse event such as overt bleeding or perforation is relatively low, there are subsets of patients at much higher risk.

The volume of NSAID use results in a substantial burden of morbidity and mortality, and incurs considerable health care costs.

If NSAIDs are needed, it is best to use the *lowest possible dose* of a *shorter-acting* NSAID for as *short a time* as possible

Ibuprofen is a relatively **shorter acting** NSAID, and hence has a lower propensity to cause GIT side effects than the longer acting non-selective agents.

It is commonly prescribe in the ED.

See also separate Document on NSAID overdose.

History

In 1971, a U.K. research team, headed by **Professor John Vane**, demonstrated that aspirin-like drugs could inhibit the synthesis of prostaglandins.

The biochemists **Sune K. Bergström, Bengt I. Samuelsson** and **John R. Vane** were jointly awarded the 1982 Nobel Prize in Physiology or Medicine for their research on prostaglandins.

Chemistry

Ibuprofen belongs to the **aryl-propionic acid** group of NSAIDs (which also includes, **naproxen** and **ketoprofen**).

Physiology

Cyclo-oxygenase **(or COX)** has 2 forms:

1. COX 1:

- Generation of PGs involved in GIT mucosal protection.
- Generation of thromboxane within platelets.

COX 1 is a **constitutive** enzyme, i.e one that is constantly produced whether or not a suitable substrate is present.

2. COX 2:

- Generation of PGs involved in the inflammatory process.
- Generation of PGs within the kidney.

COX 2 is an **inducible** isoform that is only produced in the presence of suitable substrates.

NSAIDs may **non-selectively** inhibit the COX enzyme or may **selectively** inhibit the COX-1 or COX-2 isoforms.

Classification

Accordingly NSAIDS can be classified as:

1. Non-selective COX inhibitors:

These older agents non-selectively inhibit COX 1 and COX 2.

By their COX 1 action they have side effects with respect to GIT ulceration and anti-platelet action.

By their COX 2 action they can have effects on renal function.

Examples include:

- Indomethacin
- **Ibuprofen**
- Aspirin
- Diclofenac
- Ketoprofen
- Ketorolac
- Mefenamic acid

- Naproxen
- Piroxicam
- Sulindac

2. Selective COX 2 inhibitors, (also termed coxibs):

These have fewer side effects as COX 1 is not inhibited to a large extent.

They may still have effects on renal function however.

Examples include:

- Celecoxib
- Meloxicam
- Etoricoxib
- Parecoxib

Note that some selective COX-2 inhibitors (such as meloxicam) are only selective at *low doses.*

Cyclo-oxygenase-2 (COX-2) selective NSAIDs reduce, but do not completely abolish, the risk of ulcer disease and complications.

Concomitant aspirin use negates the effect.

Most benefit occurs in those at least risk, with less risk reduction in those most at risk.

Moreover, COX-2 selective NSAIDs do not cause fewer *dyspeptic symptoms* than nonselective NSAIDs.

Their increased relative risk for adverse vascular events has limited the use of COX-2–selective NSAIDs in patients with cardiovascular risk factors.

The relative cardiovascular and cerebrovascular risk of nonselective NSAIDs is under evaluation. At the time of writing, naproxen appears to confer the least cardiovascular risk.

Preparations

There are *many* preparations available in Australia for ibuprofen. *Examples include:*

Ibuprofen as:

Tablets:

- 100 mg, 200 mg, 400 mg.

Capsules:

- 200 mg.

Liquid suspension:

- 20 mg/mL
- 40 mg/mL

Ampoules for IV injection:

- 5 mg/ ml (in 2 ml ampoules = 10 mg per ampoule)
- 100 mg/ ml (in 8 ml ampoules = 800 mg per ampoule)

Topical Gels:

- 5% preparations are available.

Fixed-dose (oral) combinations with paracetamol:

- Ibuprofen 150 mg + paracetamol 500 mg
- Ibuprofen 200 mg + paracetamol 500 mg

Mechanism of Action

NSAIDs exert their main effect by inhibition of the enzyme **cyclo-oxygenase (or COX)** with consequent reduction in the synthesis of **pro-inflammatory prostaglandins** derived from **arachidonic acid**, **(see Appendix 1 below).**

Inhibition of **COX-1** results in **impaired gastric cytoprotection** and **antiplatelet effects**

Inhibition of **COX−2** results in **anti-inflammatory** and **analgesic action**

Reduction in glomerular filtration rate and renal blood flow occurs with both COX−1 and COX−2 inhibition.

Most NSAIDs are non-selective, inhibiting both COX−1 and COX−2. Although selective COX−2 inhibitors have little or no effect on COX−1 at therapeutic doses, they can still be associated with GI adverse effects.

Aspirin irreversibly inhibits cyclo-oxygenase

Other NSAIDS reversibly inhibit cyclo-oxygenase

Ibuprofen is a **non-selective COX inhibitor**.

Pharmacodynamics

Therapeutic clinical effects of the NSAIDS as a class include:

1. Mild to moderate analgesic
2. Anti-inflammatory action.
3. Mild antipyretic

Note that non-selective NSAIDs can have some mild anti-platelet effects but are *unreliable as a therapeutic agent when compared to aspirin.*

The COX 2 inhibitors do not affect platelet activity.

Pharmacokinetics

Absorption:

- **Ibuprofen** can be given orally or topically.

  It is well absorbed orally

  Topical NSAID formulations are widely used in the treatment of local musculoskeletal disorders. This route is generally a safer alternative to oral NSAIDs, however they are usually absorbed only in small amounts and so may be somewhat less effective. [2]

Distribution:

- Ibuprofen has an apparent volume of distribution of 0.14 L/kg.
- Ibuprofen is highly bound (up to 99%) to plasma proteins.
- Ibuprofen can cross the human placenta.
- Ibuprofen is distributed into human breast milk, but only in small amounts.

Metabolism and excretion:

- Ibuprofen is extensively metabolised to inactive compounds in the liver, mainly by glucuronidation.
- Half-life is short at around 2 - 2.5 hours.

Indications

Mild to moderate pain

In particular:

1. Tension headache
2. Myalgias in general e.g. associated with infections
3. Soft tissue and musculoskeletal traumatic injury
4. Pleuritc pain
5. Inflammatory conditions:
    - Arthritis, arthralgia, tendonitis, fasciitis
6. Osteoarthritis
7. Gout
8. Dysmenorrhoea

Note that no single NSAID has been shown to be more effective than any other, but some patients do seem to respond better to one particular agent than to other agents.

Contraindications/ Precautions

Contraindications and precautions of the NSAIDS as a class include:

1. Renal impairment:

    All NSAIDs can cause renal impairment, especially in:

    - The elderly
    - Those who already have renal impairment
    - Those who are taking other nephrotoxic agents.

- Those who are dehydrated (as prostaglandins are important in maintaining renal blood flow when circulating blood volume is decreased).

2. Elderly, (generally > 65 years):

   - The elderly are at more risk of NSAID adverse effects, particularly renal impairment, heart failure, and GI ulceration..

3. Heart failure

   - Due to the sodium and water retaining properties.

4. Hypertension:

   - Due to the sodium and water retaining properties.

5. Gastritis / oesophagitis/ peptic ulcer disease:

   - The risk of GIT side effects is less with the COX-2 selective agents.

6. Known allergy to NSAIDS.

7. Asthma:

   - NSAIDs in general are a well recognized risk factor for asthma.

     If a person with asthma has taken NSAIDs previously without triggering asthma symptoms, the use of NSAIDs on a future occasion is not contraindicated.

Pregnancy

Ibuprofen is a category C class drug with respect to pregnancy.

Category C drugs are those drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Specialised texts should be consulted for further details.

The use of non-steroidal anti-inflammatory agents (NSAIDs) during the first trimester of pregnancy has not been associated with an increased risk of birth defects.

However, NSAID use has been associated with an increased risk of spontaneous abortion, but this has not been conclusively confirmed.

Maternal use of NSAID in late pregnancy has been associated with an increased risk of premature closure of the ductus arteriosus, persistent pulmonary hypertension of the newborn, nephrotoxicity and oligohydramnios.

Therefore, the use of all oral and topical NSAID preparations (except for low dose aspirin) is not recommended during pregnancy.

Monitor fetal circulation by fetal echocardiography in women treated with ibuprofen in late pregnancy.

Breastfeeding

Small amounts of ibuprofen are excreted into breast milk, but these amounts are unlikely to pose harm to the breastfed infant.

Ibuprofen is safe to use during breastfeeding.

Ibuprofen (and diclofenac) are currently the NSAIDS of choice in breast-feeding mothers.

Adverse Effects

Adverse effects of the NSAIDS as a class include:

1. Exacerbation of heart failure.

2. Exacerbation of hypertension

3. CVS events:

    - There is some evidence that cardiovascular harm (**stroke/ ACS**) is a general adverse effect of NSAIDs **other than aspirin. This risk is greatest with the selective COX 2 inhibitors, (see also Appendix 3 below).**

    - Low-dose aspirin may reduce the increased cardiovascular risk associated with NSAIDs, but it will increase gastrointestinal adverse effects.

4. GIT upset:

    - Nausea/ dyspepsia

    - Inflammation/ erosions/ ulceration:

      With the secondary complications of dyspepsia, GIT bleeding or perforation.

      Upper abdominal pain or discomfort has been reported in up to a half of NSAID users, but symptom analysis cannot reliably distinguish between NSAID-related dyspepsia and pain due to peptic ulceration.

About 15% to 30% of NSAID users have ulcers visible at endoscopy, but many of them are asymptomatic until complications such as anaemia, bleeding or perforation occur

Over-the-counter NSAIDs may also cause dyspeptic symptoms, but their risk of causing ulcer and bleeding appears to be lower than for **prescribed** NSAIDs, because of their lower dose, shorter half-life and generally shorter duration of use. [2]

The **Patient Risk factors** for NSAID-induced upper gastrointestinal bleeding or perforation are as follows, (in order of risk):

- ♥ **Older age**
- ♥ Past history of upper gastrointestinal bleeding
- ♥ Past history of peptic ulcer disease
- ♥ *Helicobacter pylori* infection
- ♥ Concomitant drugs, including (in order of risk) anticoagulants, antiplatelet drugs, SSRIs and corticosteroids
- ♥ Significant co-morbidity
- ♥ Smoking
- ♥ Excessive alcohol intake

Specific **NSAID risk factors** include:

- ♥ Higher doses
- ♥ Long duration of use:
    - ♥♥ The risk of ulcer is higher with longer-acting NSAIDs such as piroxicam and ketoprofen, than with shorter-acting agents such as **ibuprofen** and diclofenac.

5. Renal impairment:

Especially in:

- Elderly
- Those with pre-existing renal impairment
- Dehydration

NSAIDs, in general have been associated with acute interstitial nephritis with haematuria, proteinuria and, occasionally, nephrotic syndrome.

In the specific case of **ibuprofen** excessive **chronic** use may be associated with **renal tubular acidosis and** the potential for **life-threatening hypokalemia**. [5]

6. Allergic reactions.

- **Allergic type reactions are relatively common with the NSAIDs as a class.**

  NSAIDs, in general, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be fatal and may occur without warning. These serious adverse events are idiosyncratic and are independent of dose or duration of use.

7. Bleeding:

- **Aspirin** produces the strongest effect in this regard via its irreversible effect on COX.

  All other **non-selective** NSAIDs may *slightly* increase risk of bleeding via an antiplatelet effect mediated by reversible COX 1 inhibition.

  The COX 2 inhibitors do not affect platelet activity.

Rarely:

8 Hepatotoxicity

9 Blood dyscracias

And with ibuprofen:

10. There are many potential adverse drug reactions, including with:

- Aspirin:
  - ♥ Combination of ibuprofen with **aspirin** can result in *antagonism* of the irreversible platelet inhibition induced by aspirin and loss of its cardio-protective function.
- Warfarin:
  - ♥ Combination of ibuprofen with warfarin leads to an increased risk of gastrointestinal hemorrhage

- Steroids:
  - ♥ Combination of ibuprofen with steroids, may increase the risk of peptic ulcer disease.
- Diuretics and angiotensin-converting enzyme inhibitors:
  - ♥ Combination of ibuprofen with these agents may result in elevations of systolic blood pressure and worsening of renal function.
- Lithium:
  - ♥ Coadministration of ibuprofen with lithium may enhance lithium toxicity.
- Multiple drug interactions in general may also arise from:
  - ♥ The reduction in glomerular filtration induced by blockade of cyclooxygenase
  - ♥ Competitive displacement of the second drug from protein-binding sites, due to ibuprofen's high protein binding.

Dosing

Adults:

Standard oral **analgesic** dosing for adults is:

- Ibuprofen **200 - 400mg** orally **8 - 6 hourly** (i.e. TDS - QID) prn
- The maximum recommended daily dose is **2400 mg** (i.e. **12** 200 mg tablets or **6** 400 mg tablets).

Note that ibuprofen has a **ceiling analgesic** oral dose of **400 mg.**

Ibuprofen is frequently prescribed at doses greater than 400 mg orally, (up to 800 mg) on the assumption that a greater analgesic effect will be obtained. A study by Motov et al, however, has shown that maximal efficacy occurs at 400 mg, and that doses above this, add little extra benefit, at the cost increasing likelihood of adverse effects.

While the risk of adverse effects would be low with a **single** higher dosing, the risk increases with **repeated** dosing. The risk of adverse effects of NSAIDs, as a class, increases with dose and duration.

The **anti-inflammatory** ceiling dose of ibuprofen on the other hand, is much higher than its pure analgesic ceiling dose, with a dosing range of **2,400 to 3,200 mg/day**.

Fixed combination formulations:

If higher *efficacy* is desired then combination with paracetamol or oxycodone can be used.

As the main action of ibuprofen is local (i.e **at the site of inflammation**) and **paracetamol** and **codeine** work primarily **within the central nervous system**, they can be synergistic in combination. [1]

Children (3 months - 18 years):

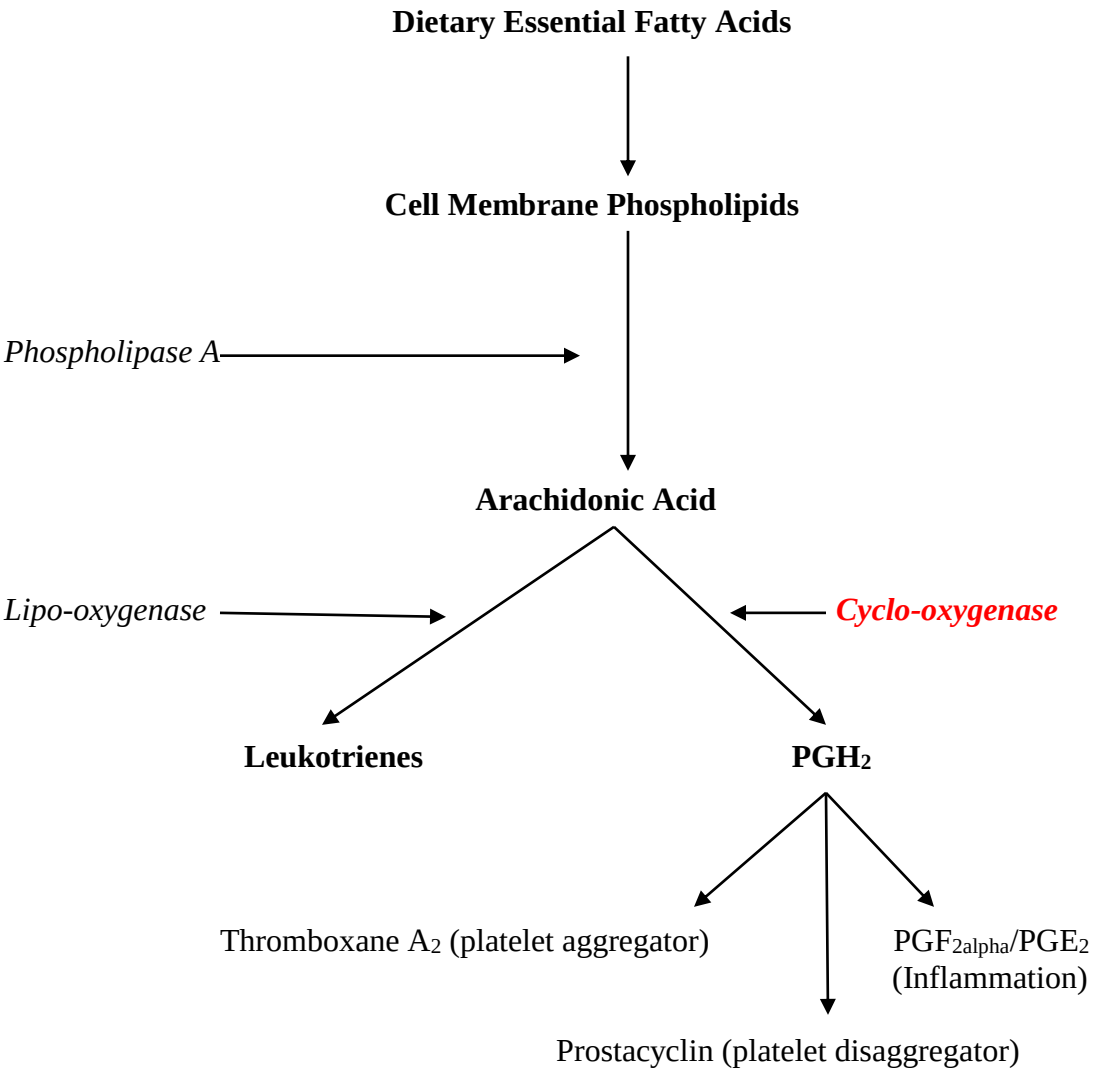
Standard oral dosing for children is:

- **5 - 10 mg/kg orally**, **(maximum 400 mg) 3 or 4 times daily** with food.
- The maximum recommended dose for children is **30 mg/kg/day** up to a maximum of **2.4 grams daily**

See also Appendix 2 below for further prescribing considerations.

Appendix 1

NSAID Action



Platelet aggregation will depend on the ratio:

Prostacyclin
Thromboxane A_2

Aspirin irreversibly inhibits cyclo-oxygenase.

Other NSAIDS reversibly inhibit cyclo-oxygenase

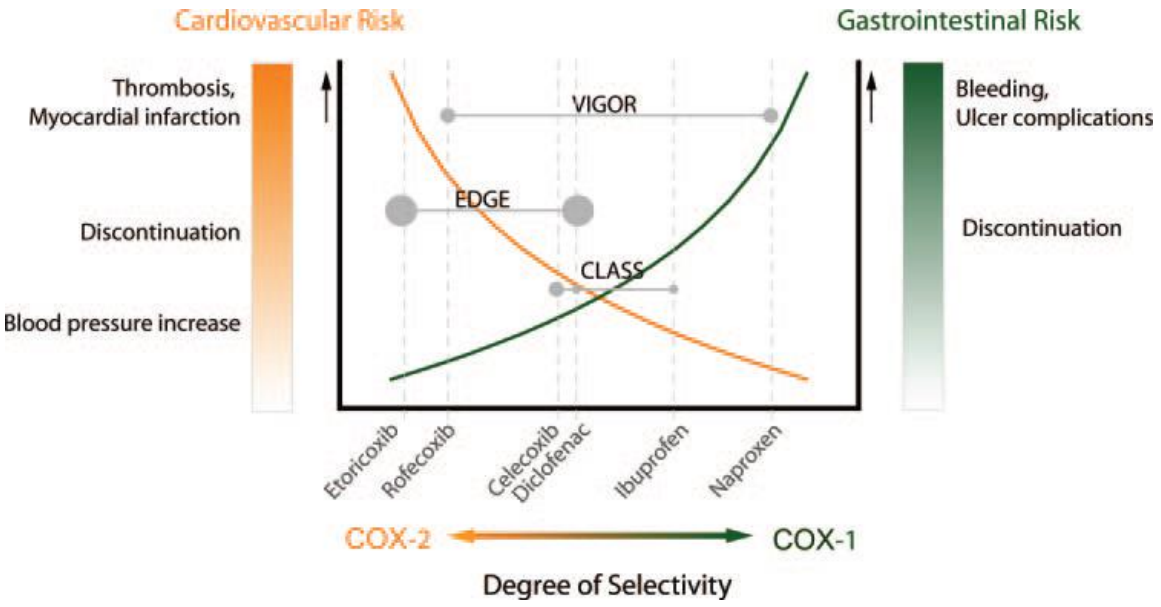
Appendix 2

Considerations in prescribing NSAIDs:

Important points to consider when prescribing Nonsteroidal anti-inflammatory drugs (NSAIDs) include: [2]

- Consider nonpharmacological treatment if appropriate.
- Consider the harm- benefit profile for NSAIDs in each patient and encourage patients to address modifiable cardiovascular risk factors.
- Use the minimal effective dose for the shortest time possible.
- Consider using alternatives such as fish oils or paracetamol to reduce the need for NSAIDs.
- Consider testing for *Helicobacter pylori* infection and treat if present.
- Choose an NSAID with a short half-life for use in the older patient and in patients with renal impairment.
- Use topical NSAIDs where appropriate.
- Use NSAIDs with low risk of gastrointestinal complications (eg ibuprofen, diclofenac).
- Use only one non-aspirin NSAID at a time.
- Monitor by assessing both adverse effects and the need for NSAID use.
- Co-prescription of a **proton pump inhibitor.**

Appendix 3



Increasing degrees of selectivity for COX-2 are associated with augmented cardiovascular risk, whereas increasing degrees of selectivity for COX-1 are associated with augmented GI risk, (From Elliott M. Antman et al. Use of Nonsteroidal Anti-inflammatory Drugs, An Update for Clinicians, A Scientific Statement From the American Heart Association. Circulation. 2007;115:1634-1642).(Vigor, Edge, Class refer to various clinical trials).

“The Last Day of Corinth”, oil on canvas, Tony Robert-Fleury, 1870, Musée d’Orsay.

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    - doi.org/10.1016/j.annemergmed.2019.05.037

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