Who dares to use NSAIDs?

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NSAID contraindications (SPC)

1. Gastrointestinal / bleeding

- history of GI bleeding/p
- active, or history of recu pisodes)
- active bleeding, blood-f

2. Cardiovascular

- heart failure (NYHA Clas
- ischaemic heart disease
- or cerebrovascular disease (COXIBs)

- severe renal failure
- significant dehydration
- severe hepatic failure
- last trimester of pregnancy
- hypersensitivity

ELSEVIER
Surgical Clinics of North America
Volume 102, Issue 1, February 2022, Pages 105-115

Multimodal Analgesia in the Era of the Opioid Epidemic

Thomas Arthur Nicholas IV, Raime Robinson

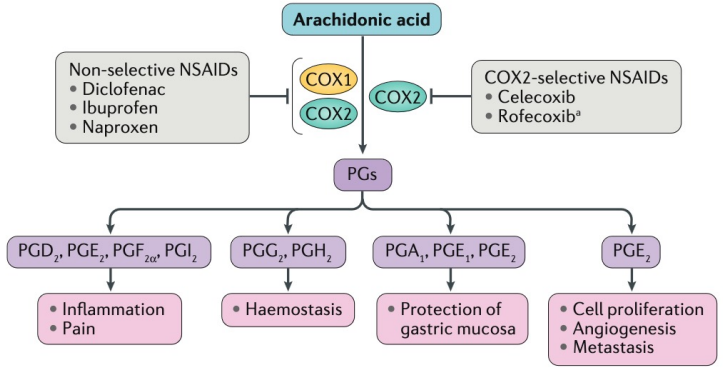
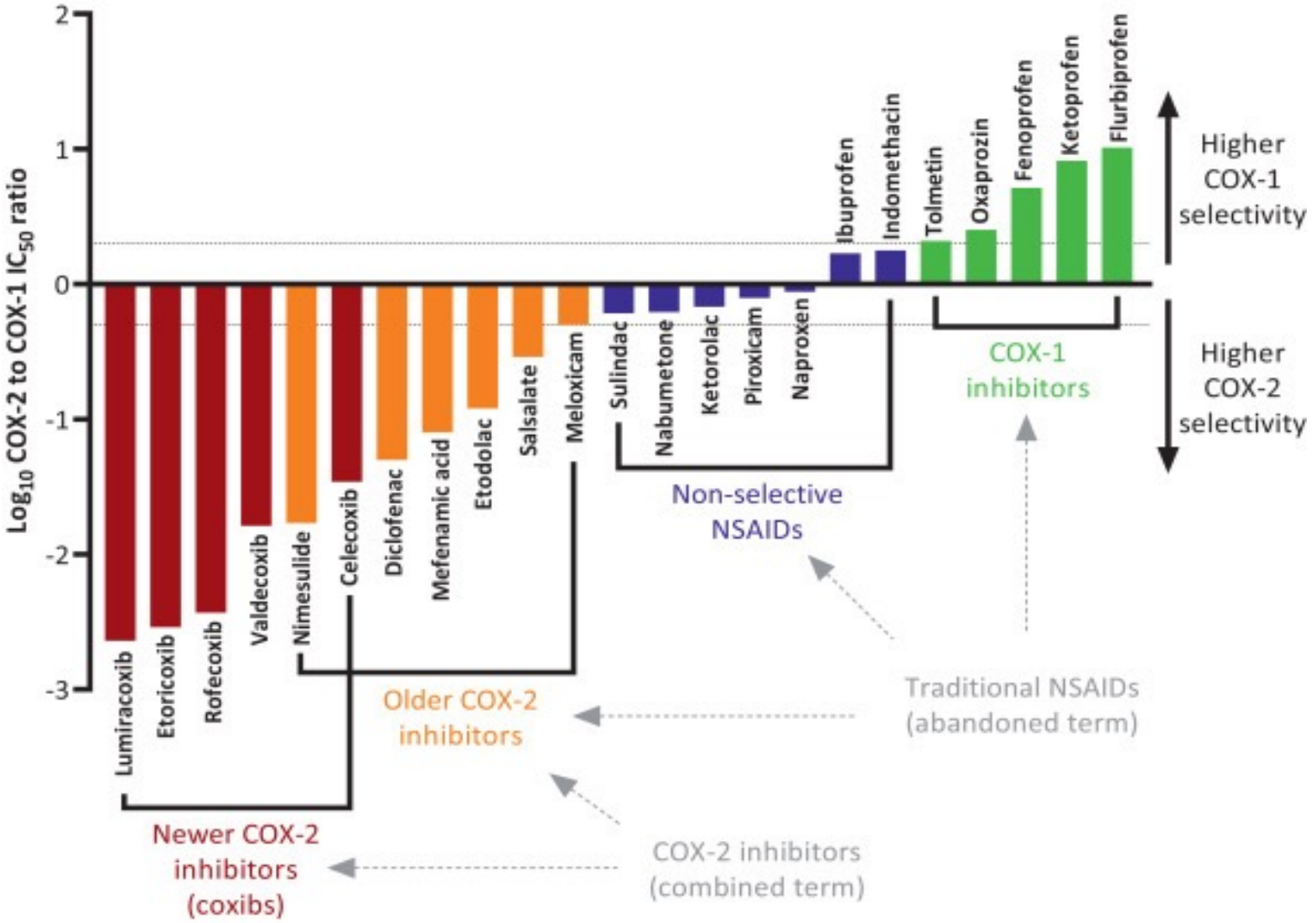


Fig. 1 | **Mechanism of action of NSAIDs.** Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the cyclooxygenase isoenzymes COX1 and COX2 with varying degrees of specificity for the COX2 isoform. As a result, the conversion of arachidonic acid to prostaglandins (PGs) is inhibited. The main effects of PGs throughout the body are listed.

How NSAIDs differ from each other?

- Pharmacokinetics
  - full absorption
  - small volume of distribution
  - equal analgesic effect if used in equipotent doses
- Pharmacodynamics
  - nonselective vs COX2-selective NSAIDs

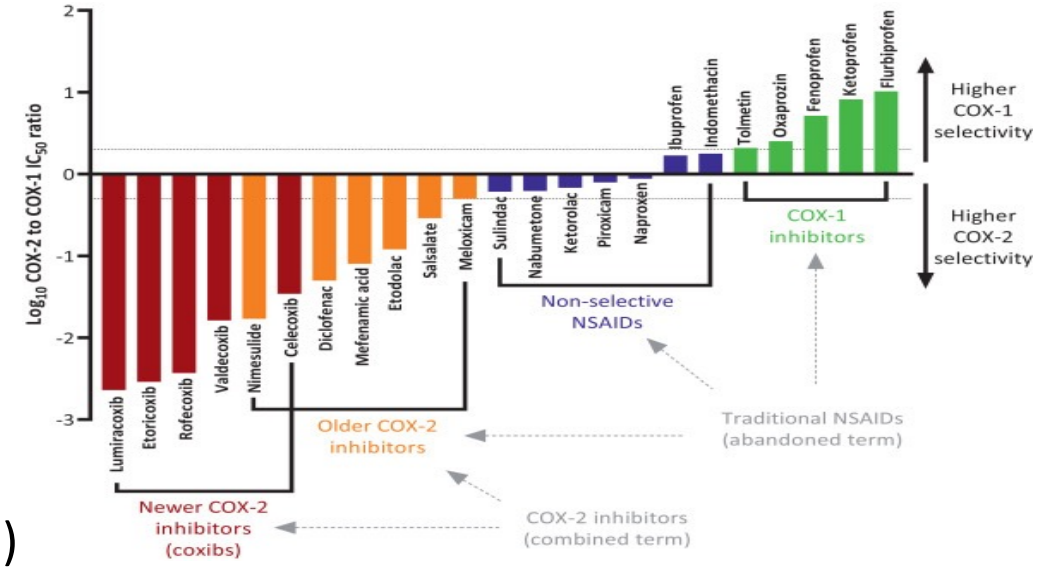


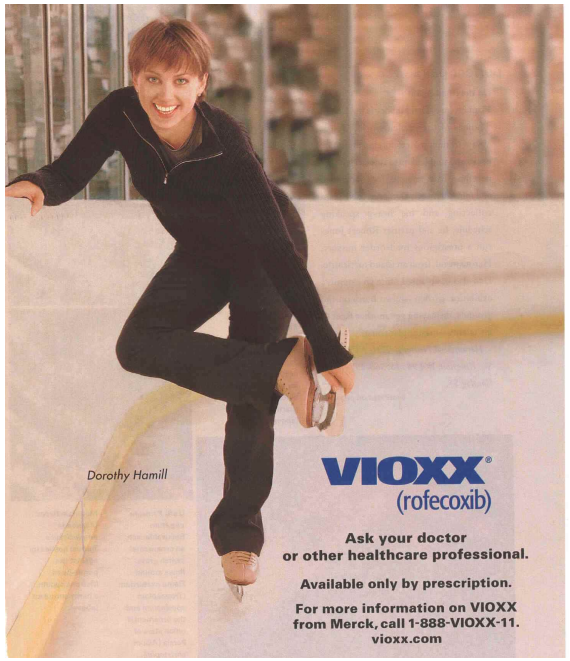
Bonnesen, K., & Schmidt, M. (2021). Re-categorization of non-aspirin NSAIDs according to clinical relevance: Abandoning the´ traditional NSAID´ terminology. *Canadian J Cardiol*

NSAIDs and gastrointestinal adverse effects

Ways reduce GI ADRs?

- PPI
- COX-selectivity?
- Meta-analysis
  - 280 studies NSAID vs placebo (> 124 thousand patients)
  - 474 studies NSAID vs other NSAID (>229 thousand patients)
- All NSAIDs increase risk of bleeding
  - coxibs 1,81 (1,2-2,8, p=0,0070) median doses used not described
  - diclofenac 1,89 (1,2-3,1, p=0,0106)
  - ibuprofen 3,97 (2,2-7,1, p<0,0001)
  - naproxen 4,22 (2,7-6,6, p<0,0001)





Emberson et al. Vascular and upper gastrointestinal effects of NSAIDs: meta-analyses of individual participant data from randomised trials. Lancet 2013;382

Doses of NSAIDs

- GI adverse effects and dose
- The Oxford League Table of Analgesic Efficacy

Medicine	mg	NNT*
Ibuprofen	600/800	1,7
Diclofenac	100	1,8
Paracetamol + codeine	1000 + 60	2,2
Ibuprofen	400	2,5
Naproxen Ibuprofen	500/550 200	2,7

*NNT (Numbers Needed to Treat) - calculated for the proportion of patients with at least 50% pain relief over 4-6 hours compared with placebo in randomised, double-blind, single-dose studies in patients with moderate to severe pain

http://www.bandolier.org.uk/booth/painpag/Acutrev/Analgesics/lftab.html

NSAID + SSRI – increased GI bleeding risk?

C4 **Ibuprofeen**
süsteemne

Tsitalopraam
süsteemne

Combined use of SSRIs and NSAIDs was shown to increase the risk for upper GI bleeding 12.2-fold (95 % CI 7.1-19.5) when compared to subjects not receiving any of these drugs

Digestive Diseases and Sciences (2023) 68:1975–1982
https://doi.org/10.1007/s10620-022-07788-y

ORIGINAL ARTICLE

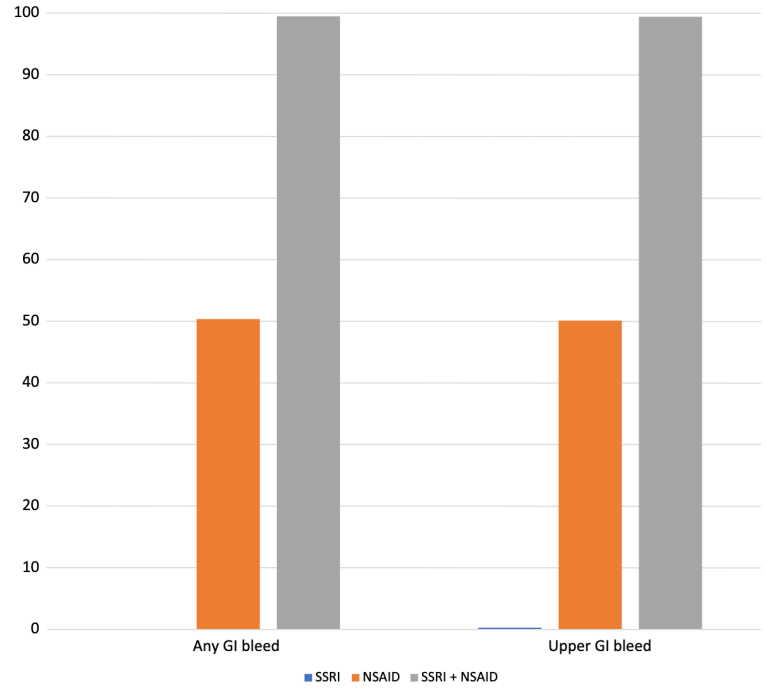
Risk of Gastrointestinal Bleeding with Concurrent Use of NSAID and SSRI: A Systematic Review and Network Meta-Analysis

Hossein Haghbin[1] · Nuruddinkhodja Zakirkhodjaev[2] · Faiza Fatima Husain[3] · Wade Lee-Smith[4] · Muhammac

Received: 14 April 2022 / Accepted: 5 December 2022 / Published online: 16 December 2022

Network meta-analysis comparing NSAIDs, SSRIs, and combined SSRI/NSAIDs to assess the risk of GI bleeding

Fig. 3 Netranking with P-scores demonstrating the likelihood of bleeding with respective intervention. The higher the P-score, the greater the probability of bleeding



NSAIDs and cardiovascular adverse effects

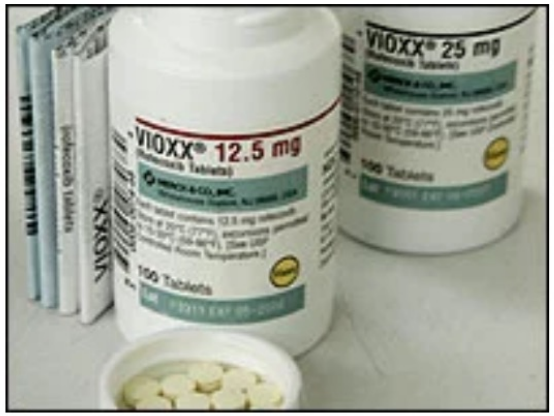
Timeline: The Rise and Fall of Vioxx

November 10, 2007 · 2:40 PM ET

By Snigdha Prakash, Vikki Valentine

Shortly before the FDA approved Vioxx in 1999, drug maker Merck launched a study it hoped would prove that Vioxx was superior to older painkillers, because it caused fewer gastrointestinal problems. Instead, the study would eventually show Vioxx could be deadly, causing heart attacks and strokes.

Five years after Vioxx's launch, Merck withdrew the drug from the market. By that time, Merck had sold billions of dollars of the drug worldwide. A timeline of Vioxx's rise and fall:



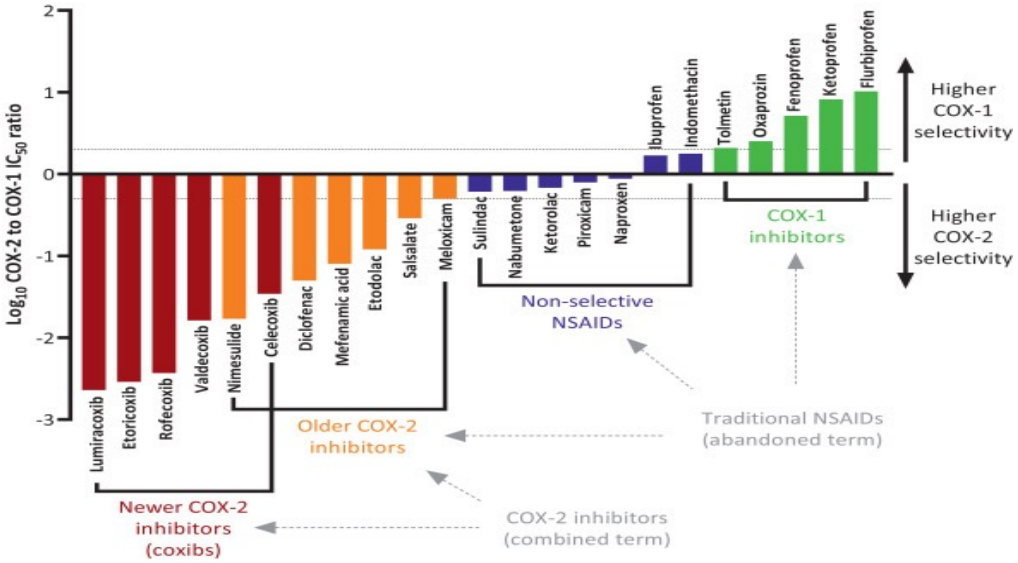
Merck voluntarily withdrew Vioxx from the market in 2004. Research published in the medical journal *Lancet* estimates that 88,000 Americans had heart attacks from taking Vioxx, and 38,000 of them died.

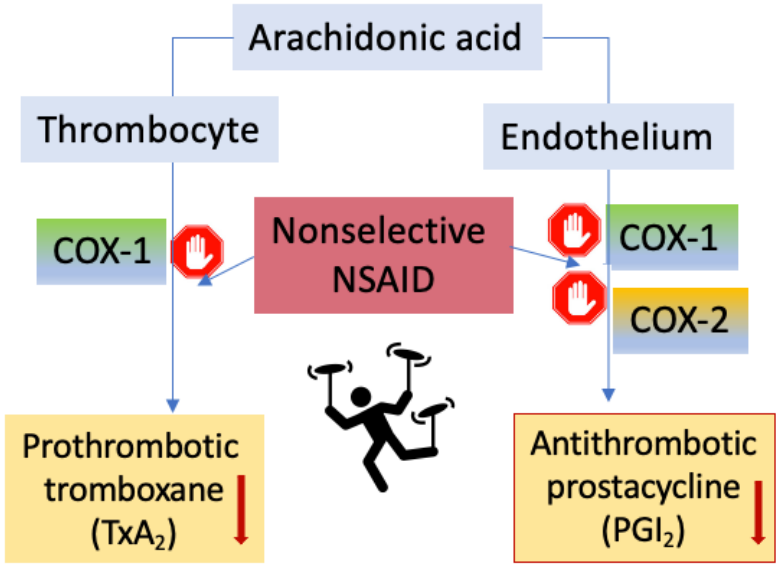
Brendan McDermid/EPA/Corbis

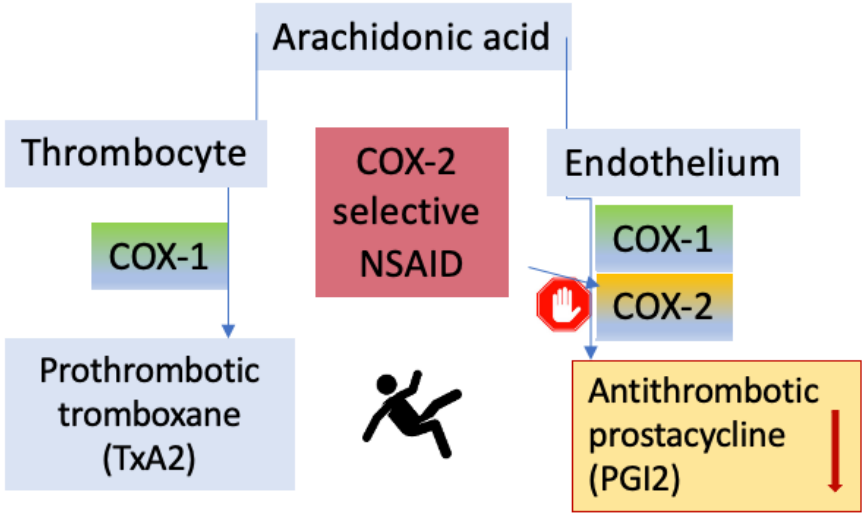
NSAID and risk of heart attack

The risk of heart attack and stroke with NSAIDs, either of which can lead to death, was first described in 2005

2018 **FDA Drug Safety Communication: FDA strengthens warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) can cause heart attacks or strokes**







PRECISION trial

ORIGINAL ARTICLE

Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis

Steven E. Nissen, M.D., Neville D. Yeomans, M.D., Daniel H. Solomon, M.D., M.P.H., Thomas F. Lüscher, M.D., Peter Libby, M.D., M. Elaine Husni, M.D., David Y. Graham, M.D., Jeffrey S. Borer, M.D., Lisa M. Wisniewski, R.N., Katherine E. Wolski, M.P.H., Qiuqing Wang, M.S., Venu Menon, M.D., et al., for the PRECISION Trial Investigators*

- RCT, double-blind study
- Aim: to assess the noninferiority of celecoxib with regard to the primary composite outcome of cardiovascular death (including hemorrhagic death), nonfatal myocardial infarction, or nonfatal stroke
- Patients at increased cardiovascular risk and rheumatoid arthritis or osteoarthritis (>24 000) assigned:
  - celecoxib 100 mg x 2 (max dose 400mg daily)
  - ibuprofen 600 mg x 3
  - naproxen 375 mg x 2 with matching placebo
- Mean treatment duration 20 months, follow-up period 34 months
- Primary outcome event occurred in 2.3% patients in celecoxib, 2.5% in naproxen and 2.7% in ibuprofen group (HR for celecoxib vs. naproxen, 0.93; 95% CI, 0.76 to 1.13; HR for celecoxib vs. ibuprofen, 0.85; 95% CI, 0.70 to 1.04; P<0.001 for noninferiority in both comparisons)
- trial showed the noninferiority of moderate doses of celecoxib, as compared with naproxen or ibuprofen, with regard to the primary APTC cardiovascular outcome
- 68.8% of the patients stopped taking the study drug

Nissen SE, et al. N Engl J Med. 2016; 375:2519–29. 10.1056/NEJMoa1611593

European Heart Journal (2017) 38, 1843–1850
doi:10.1093/eurheartj/ehw387

SCOT trial

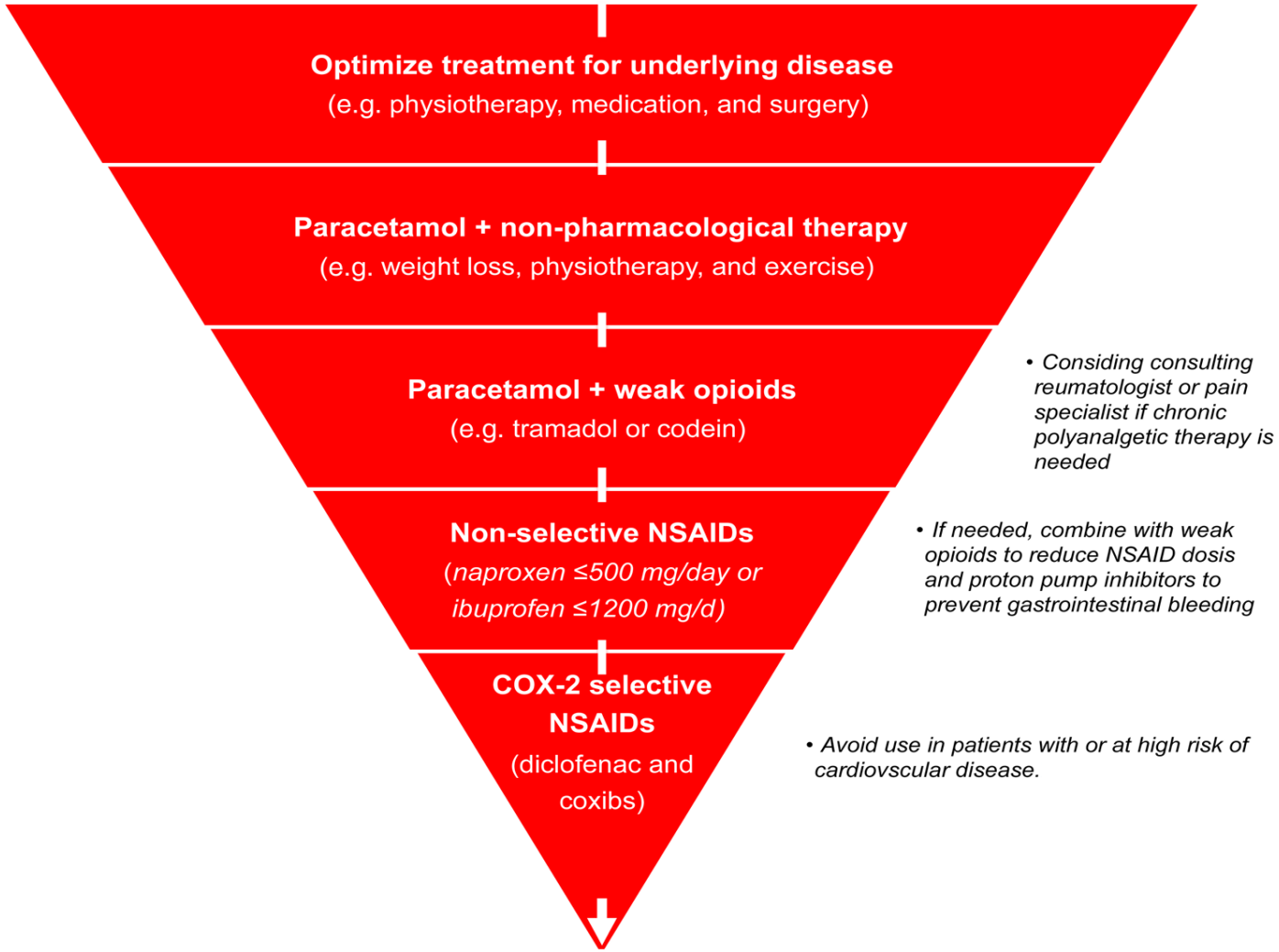
Randomized trial of switching from prescribed non-selective non-steroidal anti-inflammatory drugs to prescribed celecoxib: the Standard care vs. Celecoxib Outcome Trial (SCOT)

Thomas M. MacDonald[1]*, Chris J. Hawkey[2], Ian Ford[3], John J.V. McMurray[4],

- Patients aged > 60 years with osteoarthritis or rheumatoid arthritis, no established CV disease
- taking chronic prescribed nsNSAIDs
- Randomized to switch to celecoxib or to continue previous nsNSAID
- Primary endpoint: hospitalization for non-fatal myocardial infarction or other acute coronary syndrome, non-fatal stroke or CV death
- 7297 participants randomized, median 3-year follow-up
- Primary CV event rate similar for celecoxib, 0.95 per 100 patient years, and nsNSAIDs, 0.86 per 100 patient-years (HR ¼ 1.12, 95% confidence interval, 0.81–1.55; P ¼ 0.50)
- In subjects 60 years and over, free from CV disease and taking prescribed chronic nsNSAIDs, CV events were infrequent and similar on celecoxib and nsNSAIDs.
- There was no advantage of a strategy of switching prescribed nsNSAIDs to prescribed celecoxib.
- high withdrawal rate
- mean doses per day: 170mg for celecoxib, 80mg for diclofenac, 675 mg for ibuprofen, 581 mg for naproxen

MacDonald et al. "RCT trial of switching from prescribed non-selective non-steroidal anti-inflammatory drugs to prescribed celecoxib: the Standard care vs. Celecoxib Outcome Trial (SCOT)." *Eur heart j* 38.23 (2017): 1843-1850.

Stepwise approach to pharmacological treatment of musculoskeletal pain in patients with or at high risk of ...



Eur Heart J, Volume 37, Issue 13, 1 April 2016, Pages 1015–1023, https://doi.org/10.1093/eurheartj/ehv505

VS

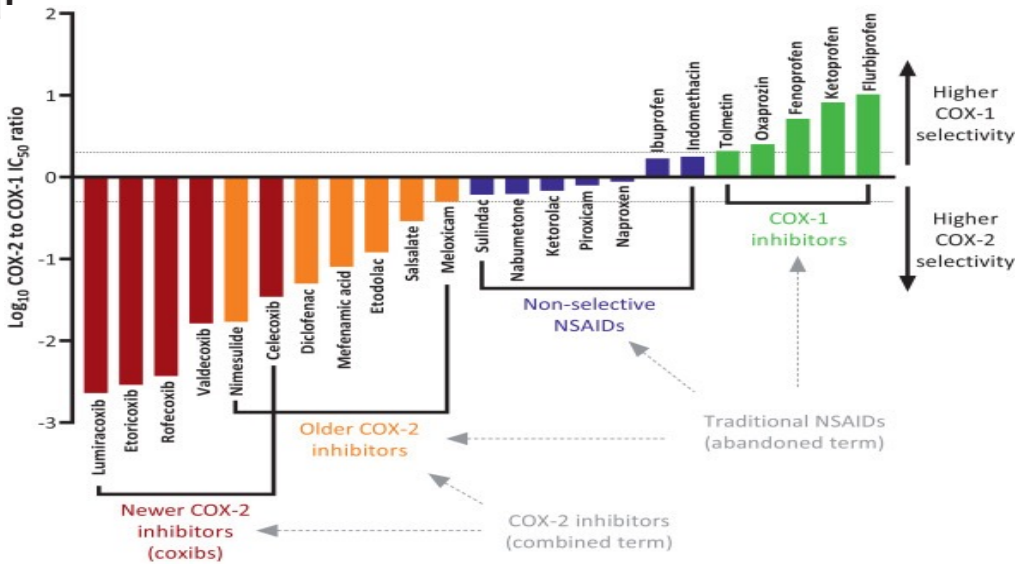
Box 1 | **Clinical guide to NSAID use in patients with cardiovascular risks**

- Patients and clinicians should share decision-making through an understanding of the personal benefit–risk balance for the patient involved and by adopting an holistic perspective on overall function and wellness in addition to the acute need for pain control
- Agree on whether the underlying cause of the pain can be addressed definitively and, if so, the time frame and actions needed to achieve this outcome
- Address the pain situation
  - Define the desired or needed therapeutic benefits
  - Consider the non-pharmacological and pharmacological options available to help to achieve these benefits
  - Set out the benefits and risks in each case
  - When considering nonsteroidal anti-inflammatory drugs (NSAIDs), identify the patient's cardiovascular, gastrointestinal, renal and other physiological risks that are potentially vulnerable to NSAID-associated adverse effects
  - Review existing medications and the potential effect of adding NSAID therapy
- Prioritize non-pharmacological approaches and instigate them first, if at all possible
  - Set a date to review their effectiveness
  - Keep a patient pain/effect diary
- Depending on the site and intensity of the pain, a topical NSAID might be helpful[81]
- If use of a systemic NSAID is chosen
  - Use should be viewed as a temporary adjunct to non-pharmacological measures
  - Adhere to regulator-approved product information advice (in general: lowest dose, shortest time)
  - Set a review date within a few days, a therapeutic benefit target and a stop rule
  - Keep a patient pain/effect diary
- Of the four widely investigated NSAIDs (celecoxib, diclofenac, ibuprofen and naproxen)
  - Select ibuprofen or naproxen as first alternatives (with gastroprotection) — both have an effective analgesic dose range within the lower end of cardiovascular thrombotic risk estimates, and gastrointestinal risks can be offset to some extent with gastroprotection[34]
  - Celecoxib doses up to 200 mg per day have similar cardiovascular risk estimates but seem to have poorer analgesic effects; at doses >200 mg per day, the cardiovascular thrombotic risk escalates
  - Avoid diclofenac
  - All four NSAIDs increase the risk of heart failure
- Adjunctive paracetamol might help to minimize NSAID needs
- Within 1 week, review the benefits of NSAID use and the patient's diary record and check for adverse effects, aiming to down-titrate or cease the NSAID use while adjusting or up-titrating non-pharmacological measures
- Make a plan for ongoing support, prioritizing non-pharmacological measures to optimize the patient's wellness, function and fitness, and to minimize the need for pharmacological measures
- For patients for whom this approach is unsuccessful, consider referral to a multidisciplinary pain team for assistance

Schjerning, et al. "Cardiovascular effects and safety of (non-aspirin) NSAIDs." *Nature Reviews Cardiology* 17.9 (2020): 574-584.

Non-steroidal anti-inflammatory drug (NSAID) therapy in patients with hypertension, cardiovascular renal or gastrointestinal comorbidities: joint APAGE/APLAR/APSDE/APSH/APSN/PoA recommendations

Cheuk-Chun Szeto,[1,2] Kentaro Sugano,[3,4] Ji-Guang Wang,[5,6] Kazuma Fujimoto,[7,8] Samuel Whittle,[9,10] Gopesh K Modi,[2,11] Chen-Huen Chen,[12,13] Jeong-Bae Park,[13,14] Lai-Shan Tam,[1,10] Kriengsak Vareesangthip,[2,15] Kelvin K F Tsoi ,[16] Francis K L Chan [16]



Guideline statements 2.1

We recommend chronic NSAID therapy be avoided if possible in patients at a high cardiovascular risk. [2B]

2.2 For patients at a high cardiovascular risk in whom chronic NSAID therapy cannot be avoided, naproxen and celecoxib can be considered. [2B]

Szeto, Cheuk-Chun, et al. "Non-steroidal anti-inflammatory drug (NSAID) therapy in patients with hypertension, cardiovascular, renal or gastrointestinal comorbidities: joint APAGE/APLAR/APSDE/APSH/APSN/PoA recommendations." *Gut* 69.4 (2020): 617-629

NSAID and heart failure

- Mechanism:
  - sodium and water retention
  - reduced formation of the vasodilator

prostacyclin in the vessel wall ->

increased blood pressure

- Are all NSAIDs equally guilty?
- Arfe *et al.*:
- traditional NSAIDs and COX 2 inhibitors

are associated with an increased risk of

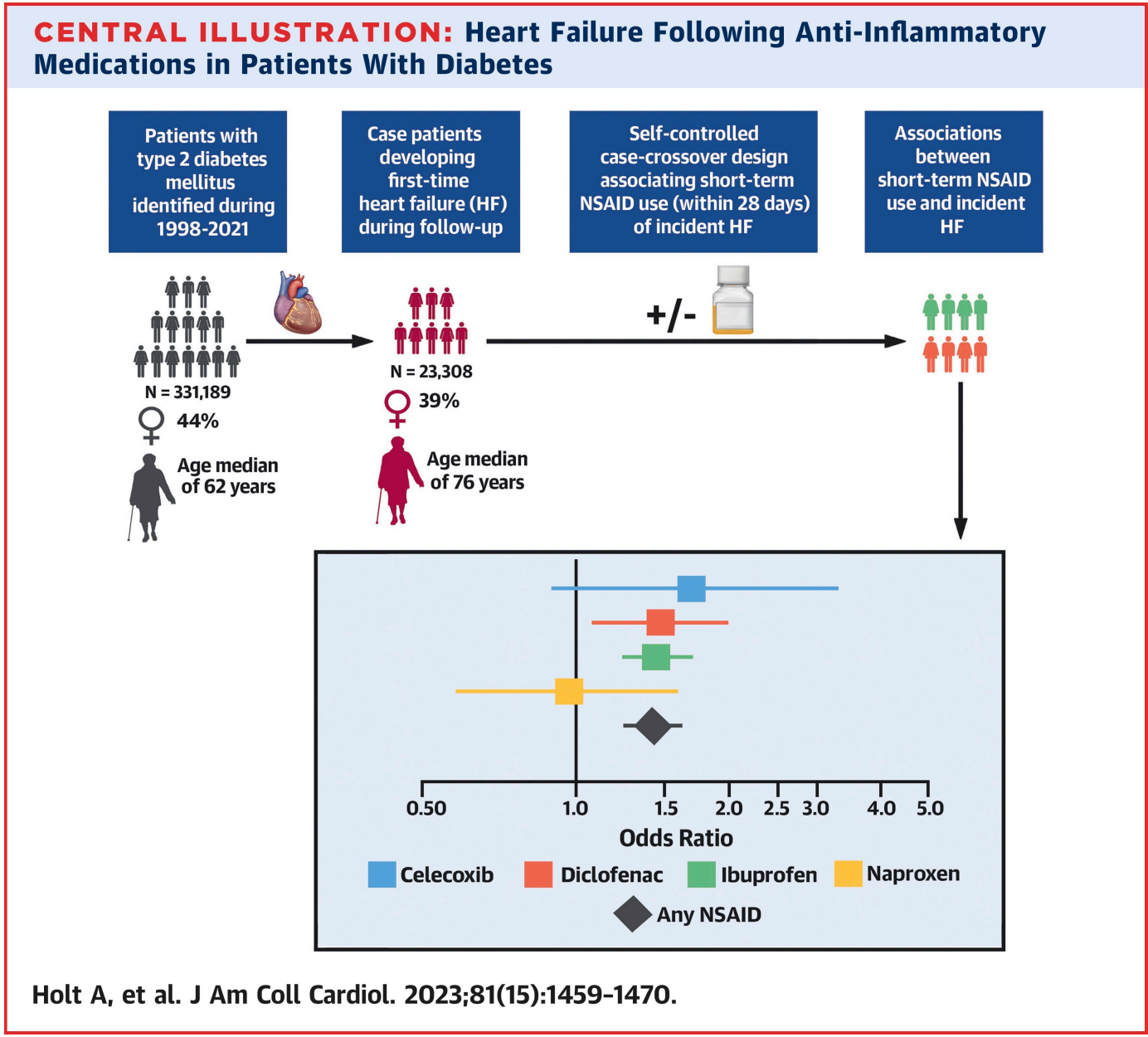
hospital admission for heart failure

current users of any NSAID had a 20% higher risk of

heart failure than past users

- risk seems to vary between drugs and

according to the dose



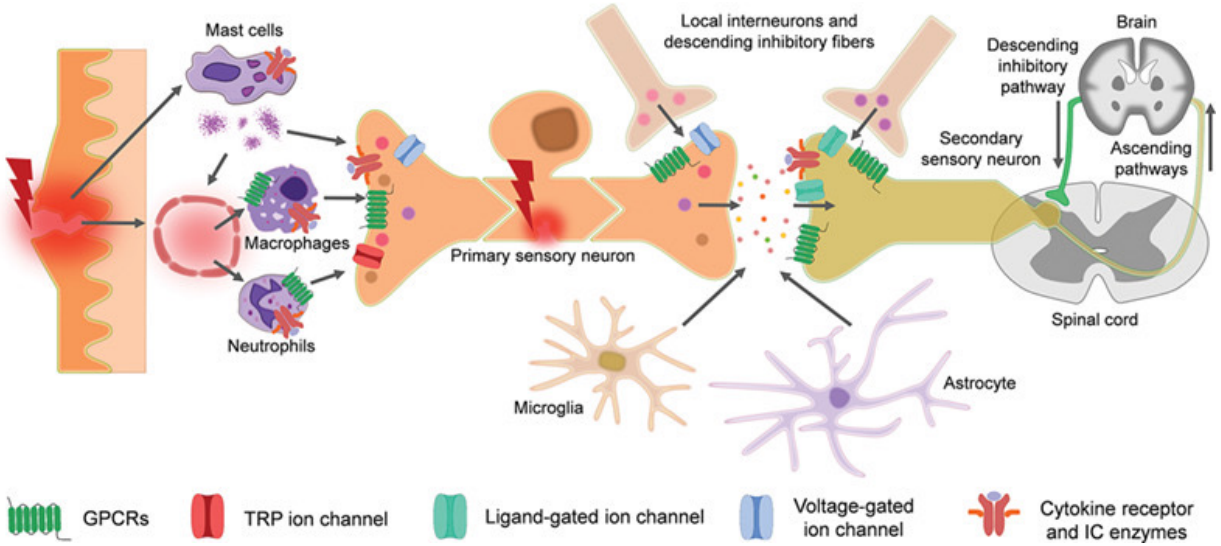
Holt A, et al. J Am Coll Cardiol. 2023;81(15):1459-1470.

Arfe et al. NSAIDs and risk of heart failure in four European countries: nested case-control study. BMJ. 2016;354:i4857

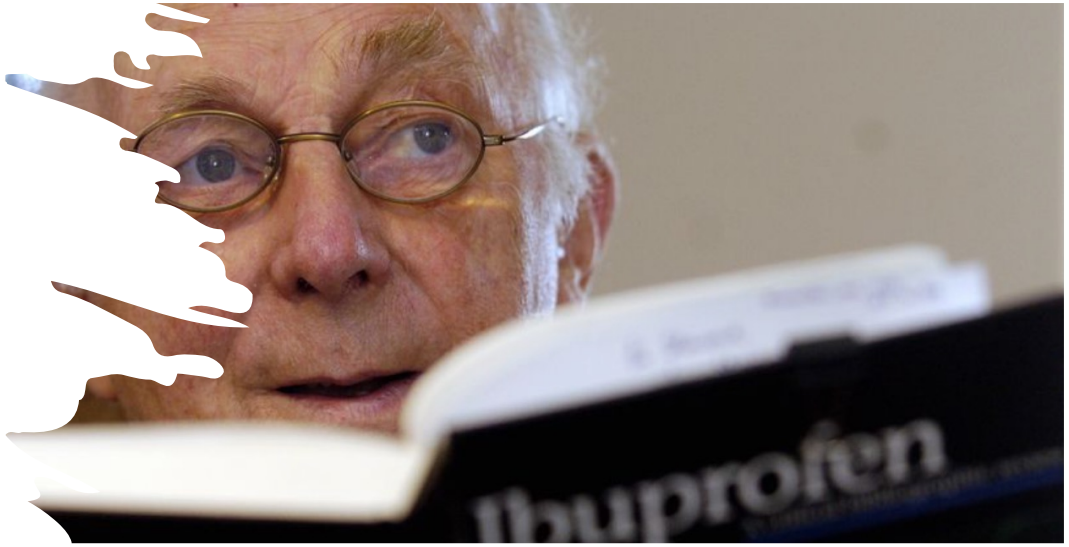
Conclusions

- GI ADR: dose, COX-2 selectivity, drug-drug interactions
- Heart failure: naproxen?
- NSAID users have increased risk for MI, no safe time-window for patients with cardiovascular disease
- Cardiovascular risk of individual NSAIDs not clear
- No good guidelines for NSAID use in patients with cardiovascular use
- NSAIDs are commonly used in patients with CV diseases
- Ibuprofen / naproxen / celecoxib?
- Patient-based selection despite relative contraindications

Moore "Coronary Risks Associated with Diclofenac and Other NSAIDs: An Update." *Drug Safety* (2020): 1-18. Schjerning et al "Cardiovascular effects and safety of (non-aspirin) NSAIDs." *Nature Rev Cardiology* (2020): 1-11.
Gislason “Increased mortality and cardiovascular morbidity associated with use of NSAIDs in chronic heart failure”. Arch. Intern. Med. 169, 141–149 (2009).
Gislason “Risk of death or reinfarction associated with the use of selective COX-2 inhibitors and NSAIDs after acute myocardial infarction”. Circulation 113, 2906–2913 (2006)
Moore "Coronary Risks Associated with Diclofenac and Other NSAIDs: An Update." *Drug Safety* (2020): 1-18.



Main target categories for the development of novel anti-inflammatory and analgesic drugs.



Ibuprofen 50

He claims he was also the first to establish its value for a hangover – confirmed by many scientist then!

Thank you for listening!

Bálint "Challenges to develop novel anti-inflammatory and analgesic drugs." *Wiley Interdisciplinary Reviews: Nanomed Nanobiotechnol* 9.3 (2017)