Smärtbehandling med coxiber, del 1

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Frågor ställs via sms, scanna kod:

Region Sörmland

Skillnader mellan coxiber, någon som föredras?

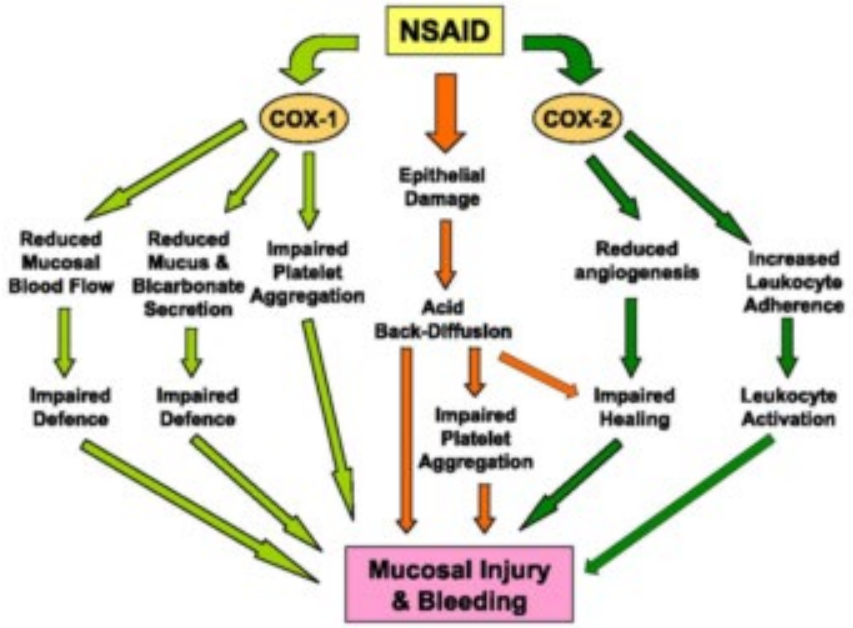


Fig. 2 *Mechanisms contributing to gastric mucosal injury and bleeding with nonsteroidal anti-inflammatory (NSAID) therapy, as depicted by Wallace in 2008 [27]. Cyclooxygenase-1 (COX-1) inhibition reduces the mucosal defense mechanisms whereas COX-2 inhibition impairs healing and increases inflammatory activity. Epithelial damage due to direct cytotoxic effects is also involved. Reproduced with permission of the American Physiological Society.*

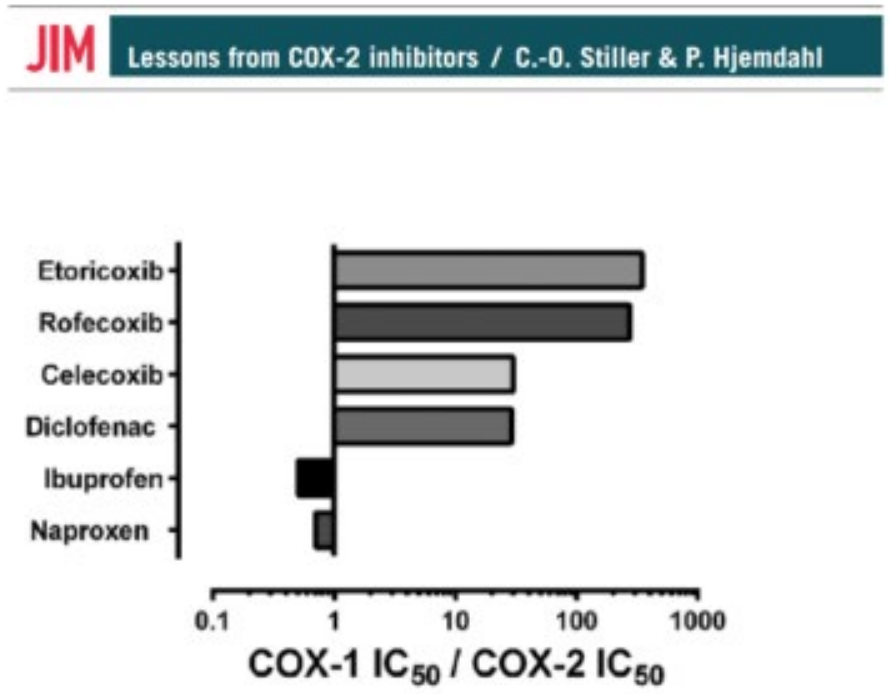


Fig. 3 *Biochemical selectivity of cyclooxygenase (COX) inhibitors defined as concentrations required for 50% inhibition of COX-1 and COX-2 mediated responses, respectively, in whole blood assays in vitro. The COX-2 response was PGE_2 production by circulating monocytes stimulated by bacterial endotoxin, and the COX-1 response was thromboxane formation by platelets in clotting whole blood. Data are extracted from the work of Sciulli et al. [41].*

Verkningsmekanismer för COX- hämmare (NSAID)

- **<u>Hämning av perifer syntesen av prostaglandiner, COX-2</u>**
  - Prostaglandiner ökar känsligheten av nociceptorer för H+, K+, cytokiner, serotonin, kinin.
  - Prostaglandiner ökar perifera receptoriska fält
- **<u>Hämning av prostaglandin syntes i dorsalhornet, COX-1 och COX-2</u>**
  - COX-1 i **gliaceller** producerar PGE2 som ökar smärtsignaleringen från primärafferenter.
  - COX-2 i dorsalhorns**neuron** producerar PGE2 som ökar smärtsignaleringen från primärafferenter.

Cyklooxigenashämmare (COX-hämmare)

Blockerar syntes av prostaglandiner COX-1 / COX-2:

- Effekt mot smärta, inflammation

- Risken är dosberoende för:
  - **Ulkus** (COX-1 > COX-2), *COX-2 hämmare kan minska sårläkning*
  - **Blödning** (Hämmar tromboxan), COX-1
  - **Risk för blodpropp** (hämmar prostacyklin), COX-2
  - **Njursvikt** (motverkar skyddande effekt av PGE_2 på glomerulär filtration), COX-1=COX-2
  - **Hypertoni** (vätskeretention) COX-1=COX-2
  - **Försluter duktus arteriosus** (kontraindikation under graviditet) COX-1=COX-2

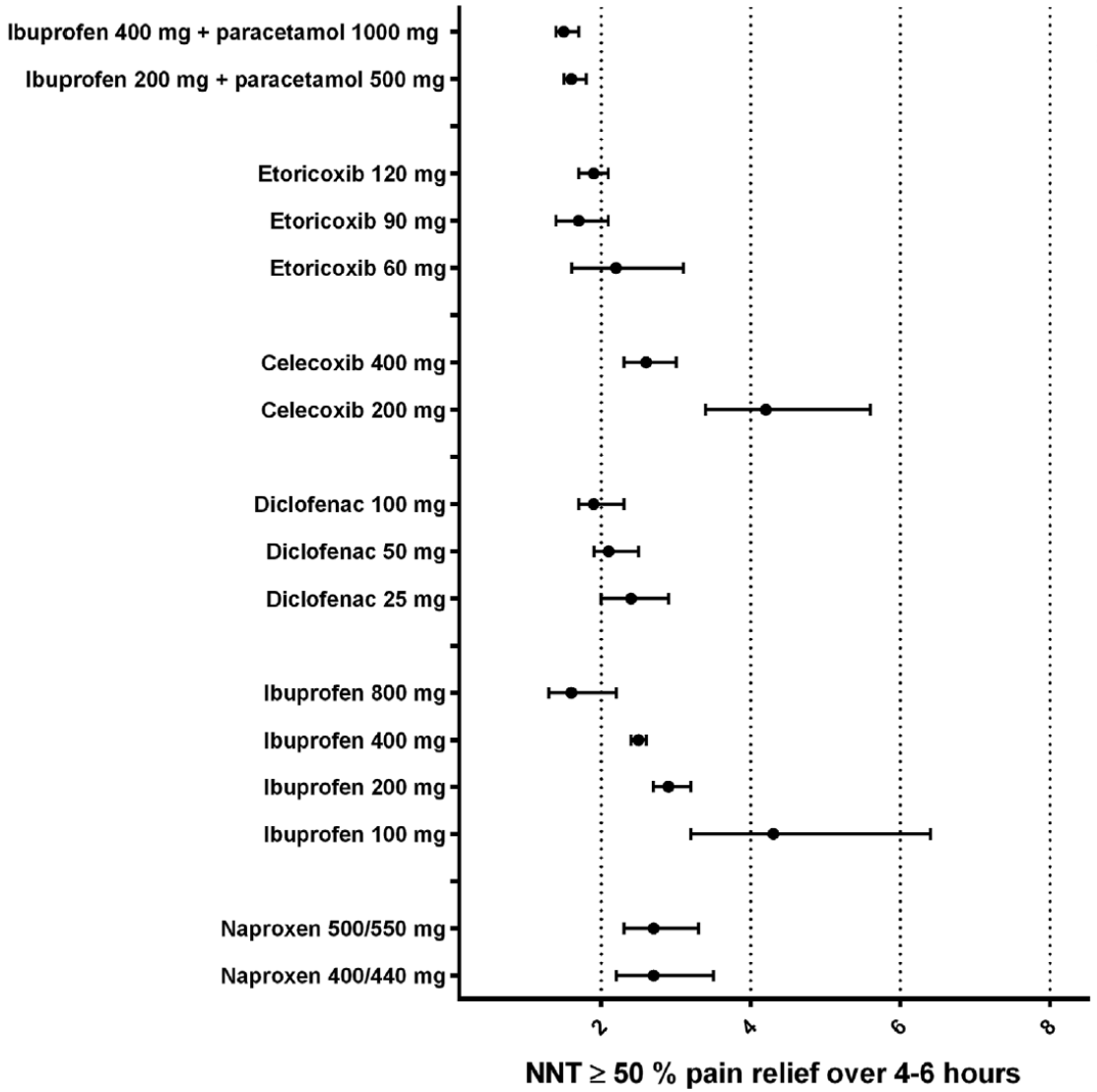


Fig. 8 *Numbers needed to treat with 95% confidence intervals to obtain a reduction in pain intensity of at least 50% over 4–6 h after surgery (dental surgery to a large extent) after a single dose. Data extracted from a Cochrane review by Moore et al. [82]. The analgesic effect is dose dependent for ibuprofen, celecoxib, and diclofenac and probably also for etoricoxib. Data for naproxen are insufficient to determine a dose–response for acute pain. The combination of ibuprofen 400 mg with paracetamol 1000 mg resulted in pain reduction comparable to the maximal doses of cyclooxygenase inhibitors. Redrawn from reference 82.*

Akut/kortvarig smärta

Vävnadsskadesmärta (nociceptiv smärta)

Som basbehandling ges paracetamol i kombination med COX-hämmare i adekvat dosering. Vid behov av ytterligare analgetika kan opioid-behandling övervägas. Den kan i flertalet fall avslutas inom 3–5 dygn och bör inte pågå längre än 2 veckor vid ett och samma smärttillstånd. Efter 2 veckors behandling med opioider ökar risken för beroendeutveckling. Kvarstående smärta under längre tid, efter exempelvis operation, motiverar sällan opioidbehandling.

Paracetamol

paracetamol	⇨	Paracetamol …, Alvedon, Pamol, Panodil, Paracut

Paracetamol kan kombineras med såväl COX-hämmare som opioider.

COX-hämmare (NSAID)

Lägsta effektiva dos och kortast möjliga behandlingstid bör eftersträvas.

I första hand

naproxen	⇨	Naproxen …, Pronaxen

I andra hand

ibuprofen	⇨	Ibuprofen …, Brufen, Ibumax, Ibumetin, Ipren
ibuprofen		Brufen Retard

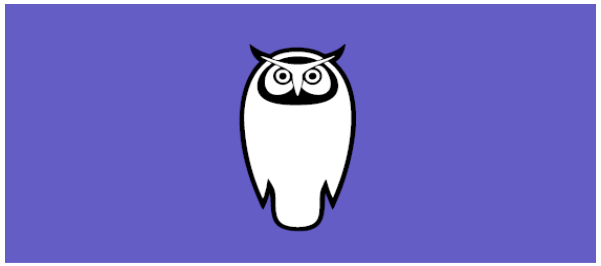
Högsta rekommenderade dos är 1200 mg per dygn till vuxna.

Ibuprofen kan motverka den antitrombotiska effekten av acetylsalicylsyra (ASA); janusinfo.se. Vid lågdos-ASA-behandling, kombinera med annan COX-hämmare.

Vid ökad risk för gastrointestinala biverkningar

celecoxib	⇨	Celecoxib …, Celebra

Behandling med COX-hämmare (NSAID) hos äldre, sid 178.
För ulkusprofylax vid behandling med COX-hämmare, sid 106.



KLOKA LISTAN

Kraftig ökning av coxiber framför traditionella NSAID – *är det bra eller bör vården tänka annorlunda?*

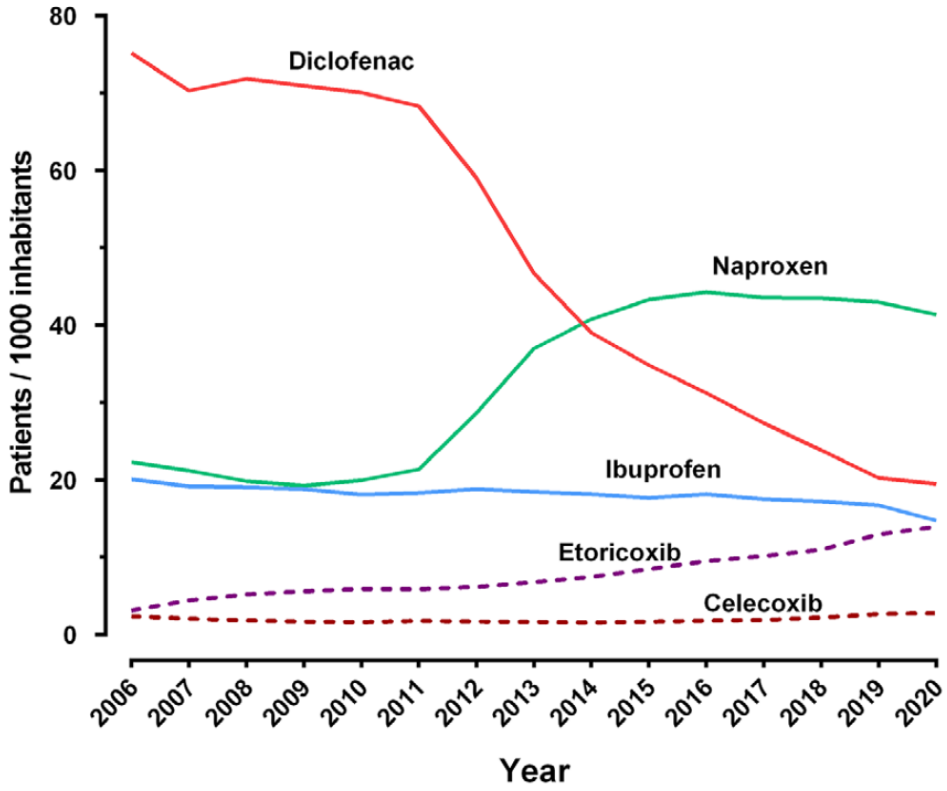
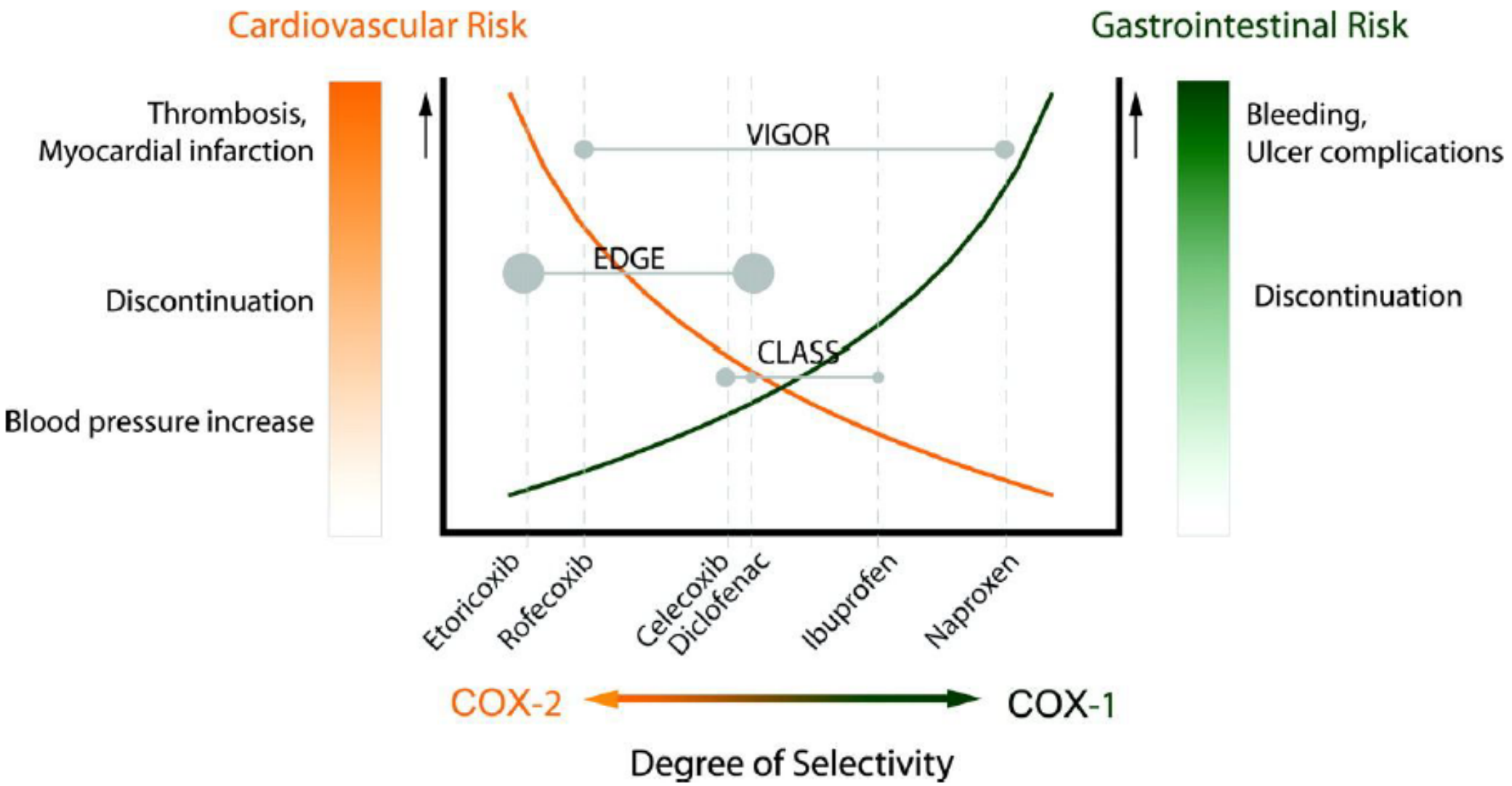


Fig. 1 *Pharmacy claims per 1000 inhabitants of the most commonly prescribed cyclooxygenase inhibitors in Sweden in the years 2006–2020 according to data from the Swedish National Board of Health and Welfare [2].*


Cardiovascular Risk
Gastrointestinal Risk
Thrombosis,
Myocardial infarction
Discontinuation
Blood pressure increase
VIGOR
EDGE
CLASS
Bleeding,
Ulcer complications
Discontinuation
Etoricoxib
Rofecoxib
Celecoxib
Diclofenac
Ibuprofen
Naproxen
COX-2
COX-1
Degree of Selectivity

Altman 2007

Långtidsbehandling med coxiber (vs kortare tid)?

Table 2. *Adverse event rate per 10,000 person-years at doses suitable for treatment of osteoarthritis pain*

	Symptomatic ulcer	Gastrointestinal bleed
No treatment	14	7
Paracetamol (3000 mg)	14	7
Naproxen (750 mg)	112 (66–169)	30 (15–49)
Ibuprofen (1200 mg)	80 (27–161)	30 (6–73)
Diclofenac (100 mg)	56 (41–74)	28 (19–39)
Naproxen (750 mg) + PPI	41 (112 × 0.37)	14 (30 × 0.46)
Celecoxib (200 mg)	38 (11–80)	20 (4–50)
Ibuprofen (1200 mg) + PPI	30 (80 × 0.37)	14 (30 × 0.46)
Etoricoxib (30 mg)	30 (21–40)	23 (14–33)
Diclofenac (100 mg) + PPI	21 (56 × 0.37)	13 (28 × 0.46)
Celecoxib (200 mg) + PPI	10 (38 × 0.25)	5 (20 × 0.25)
Etoricoxib (30 mg) + PPI	8 (30 × 0.25)	6 (23 × 0.25)

Note: The relative risk (mean [95% CI]) for symptomatic ulcers with the addition of a proton pump inhibitor (PPI) to NSAIDs (diclofenac, naproxen, ibuprofen) is 0.37 (0.30–0.46) and 0.25 (0.03–0.78) for COX-2 inhibitors. The relative risk for gastrointestinal bleed with addition of PPI to NSAIDs (diclofenac, naproxen, ibuprofen) is 0.46 (0.07–2.92) and 0.25 (0.03–0.78) for COX-2 inhibitors. The adverse event rate for each NSAID or COX-2 inhibitors combined with proton pump inhibitors (PPI) was based on the data provided for each drug adjusted for the relative risk with PPI.

Smärtbehandling med coxiber, del 2

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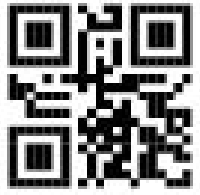


Region Sörmland

	Effektstorlek	Risk för biverkningar
Artrossmärta (skala 0–100)		
Perorala NSAID	⊕⊕ Låg tillförlitlighet för en ***mycket liten*** effekt på smärta, 7 skalsteg bättre än placebo	⊕⊕ Låg tillförlitlighet för en ***liten*** riskökning för behandlings-avbrott pga. biverkningar jämfört med placebo Riskkvot 1,16 (95 % KI, 1,02 till 1,32)

66 % placeboeffekt

Lite bättre effekt än paracetamol

Relativt liten risk för biverkningar

Arthritis Care & Research
Vol. 72, No. 5, May 2020, pp 641–651
DOI 10.1002/acr.23884

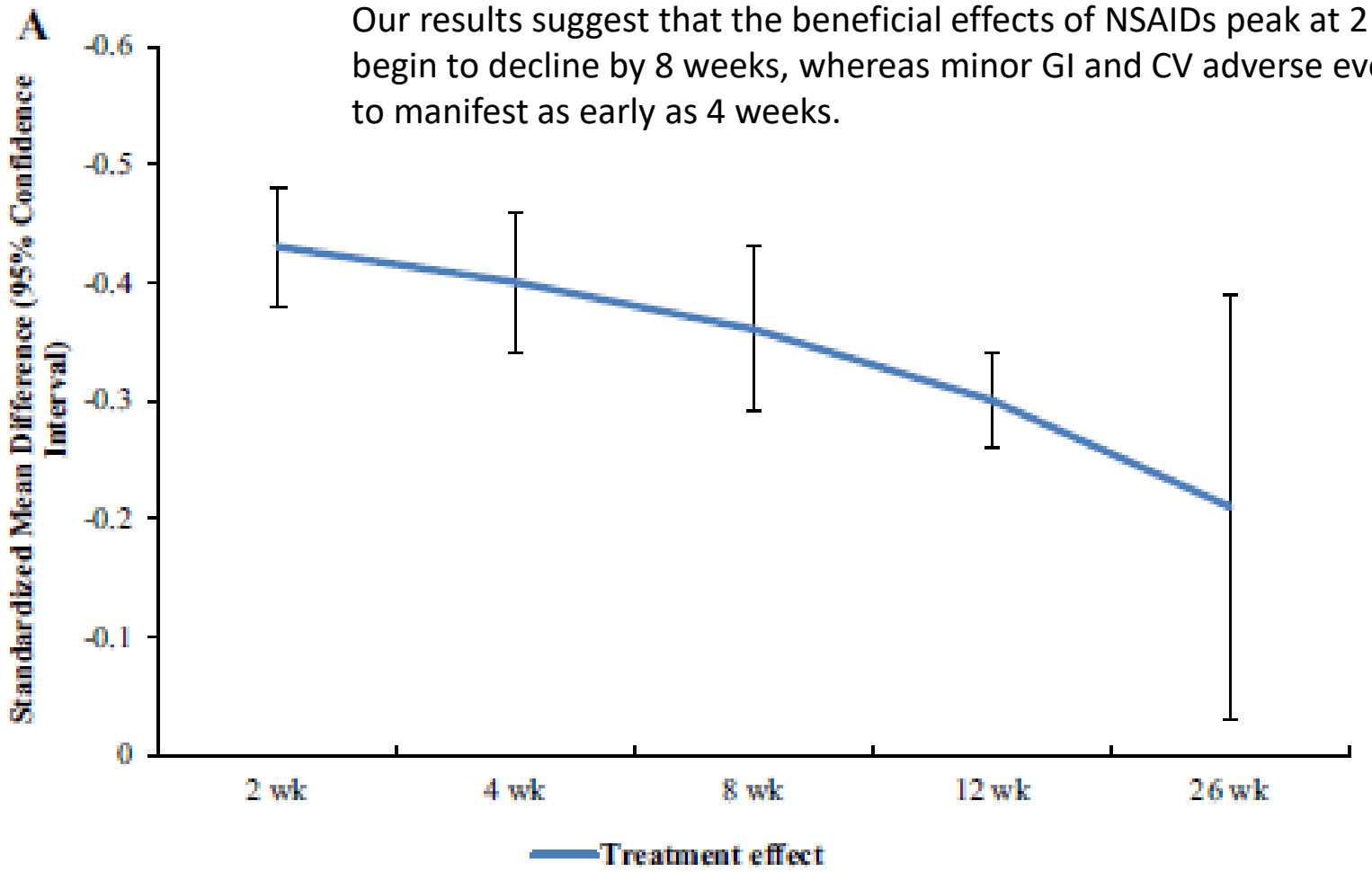
American College of Rheumatology
Empowering Rheumatology Professionals

Duration of Symptom Relief and Early Trajectory of Adverse Events for Oral Nonsteroidal Antiinflammatory Drugs in Knee Osteoarthritis: A Systematic Review and Meta-Analysis

Mikala C. Osani, Elizaveta E. Vaysbrot, Mengyu Zhou, Timothy E. McAlindon, and Raveendhara R. Bannuru

small, SMD = 0.2
medium, SMD = 0.5
large, SMD = 0.8

Our results suggest that the beneficial effects of NSAIDs peak at 2 weeks and begin to decline by 8 weeks, whereas minor GI and CV adverse events begin to manifest as early as 4 weeks.

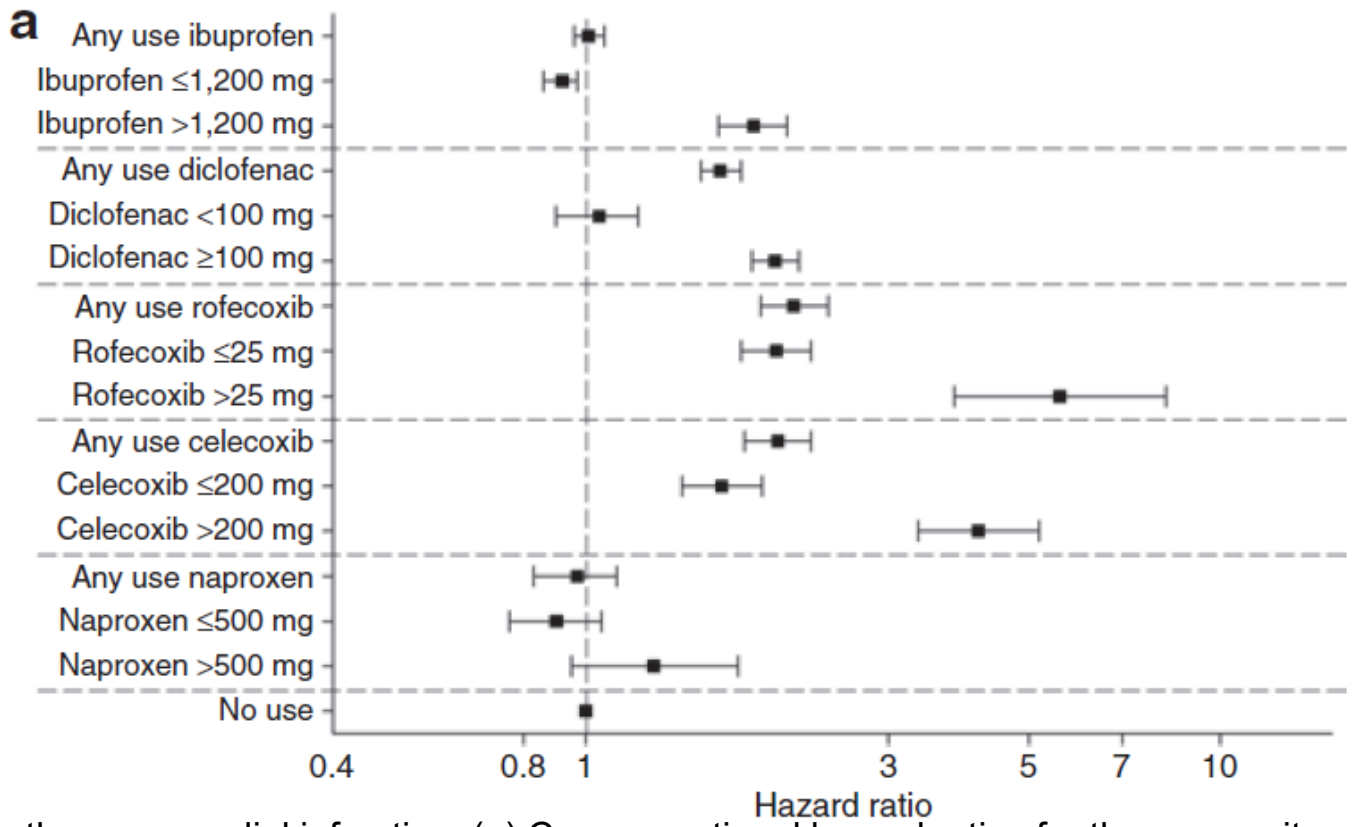


	Effektstorlek	Risk för biverkningar
	Artrossmärta (skala 0–100)	
Paracetamol	⊕⊕⊕ Måttlig tillförlitlighet för en ***mycket liten*** effekt på smärta, 3 skalsteg bättre än placebo	⊕⊕⊕ Måttlig tillförlitlighet för en biverkningsfrekvens som är ***jämförbar*** med placebo Riskkvot 1,01 (95 % KI, 0,92 till 1,11)
Perorala NSAID	⊕⊕ Låg tillförlitlighet för en ***mycket liten*** effekt på smärta, 7 skalsteg bättre än placebo	⊕⊕ Låg tillförlitlighet för en ***liten*** riskökning för behandlings-avbrott pga. biverkningar jämfört med placebo Riskkvot 1,16 (95 % KI, 1,02 till 1,32)
Opioider (exkl tramadol)	⊕⊕⊕ Måttlig tillförlitlighet för en ***mycket liten*** effekt på smärta, 6 skalsteg bättre än placebo	⊕⊕⊕ Måttlig tillförlitlighet för en ***stor*** riskökning för behandlings-avbrott pga. biverkningar jämfört med placebo Riskkvot 3,76 (95 % KI, 2,93 till 4,82)
Tramadol	⊕⊕ Låg tillförlitlighet för en ***mycket liten*** effekt på smärta, 4 skalsteg bättre än placebo	⊕⊕ Låg tillförlitlighet för en ***stor*** riskökning för behandlings-avbrott pga. Biverkningar jämfört med placebo Riskkvot 2,64 (95 % KI, 2,17 till 3,20)

Risk of Myocardial Infarction and Death Associated With the Use of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) Among Healthy Individuals: A Nationwide Cohort Study

EL Fosbøl[1], GH Gislason[2], S Jacobsen[3], F Folke[1], ML Hansen[1], TK Schramm[1], R Sørensen[1], JN Rasmussen[4], SS Andersen[1], SZ Abildstrom[1], J Trærup[5], HE Poulsen[5], S Rasmussen[4], L Køber[2] and C Torp-Pedersen[1]

Diklofenak och Cox-2 hämmare medför en ökad risk för **död eller hjärtinfarkt hos hjärtfriska**



Risk of death or myocardial infarction. (**a**) Cox proportional hazard ratios for the composite end point of death and myocardial infarction associated with exposure to nonsteroidal anti-inflammatory drugs (NSAIDs) in a study population of 1,028,437 individuals characterized by no prior concomitant pharmacotherapy and no comorbidity. Error bars illustrate the 95% confidence interval

Efter genomgången hjärtinfarkt

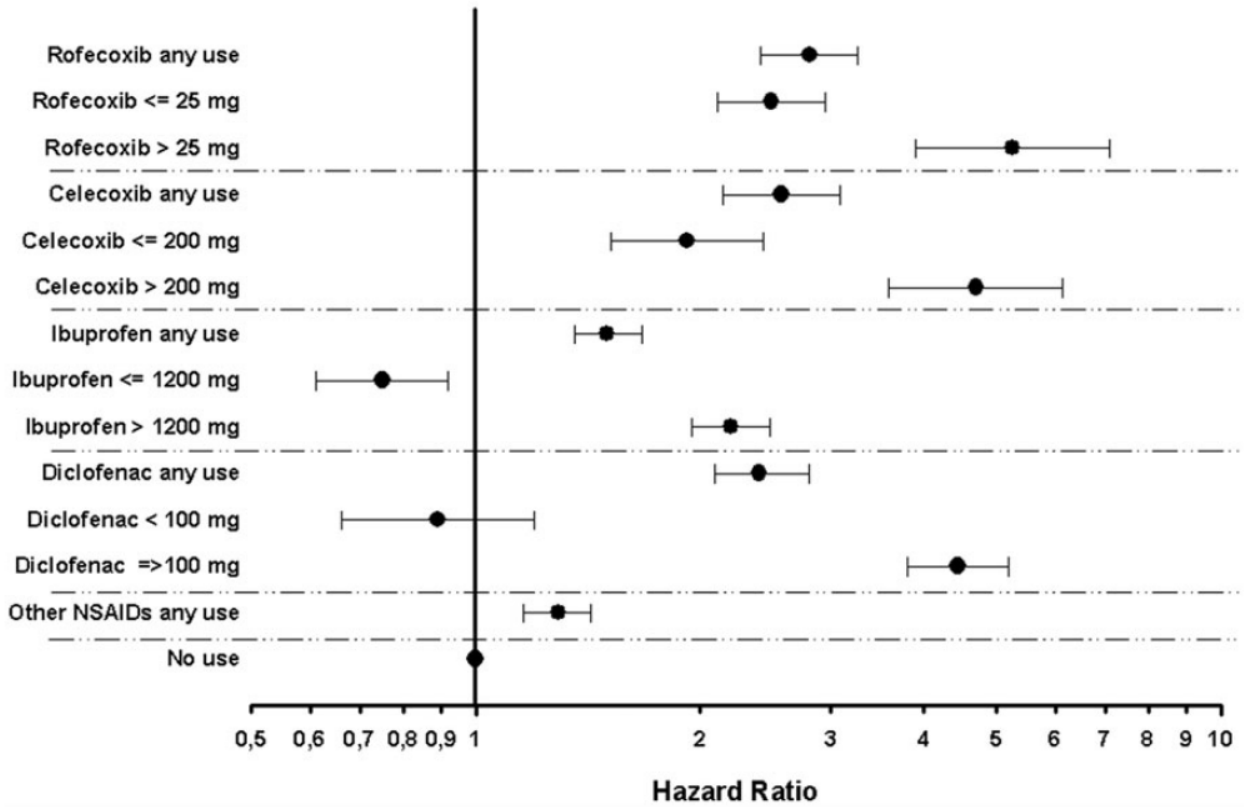
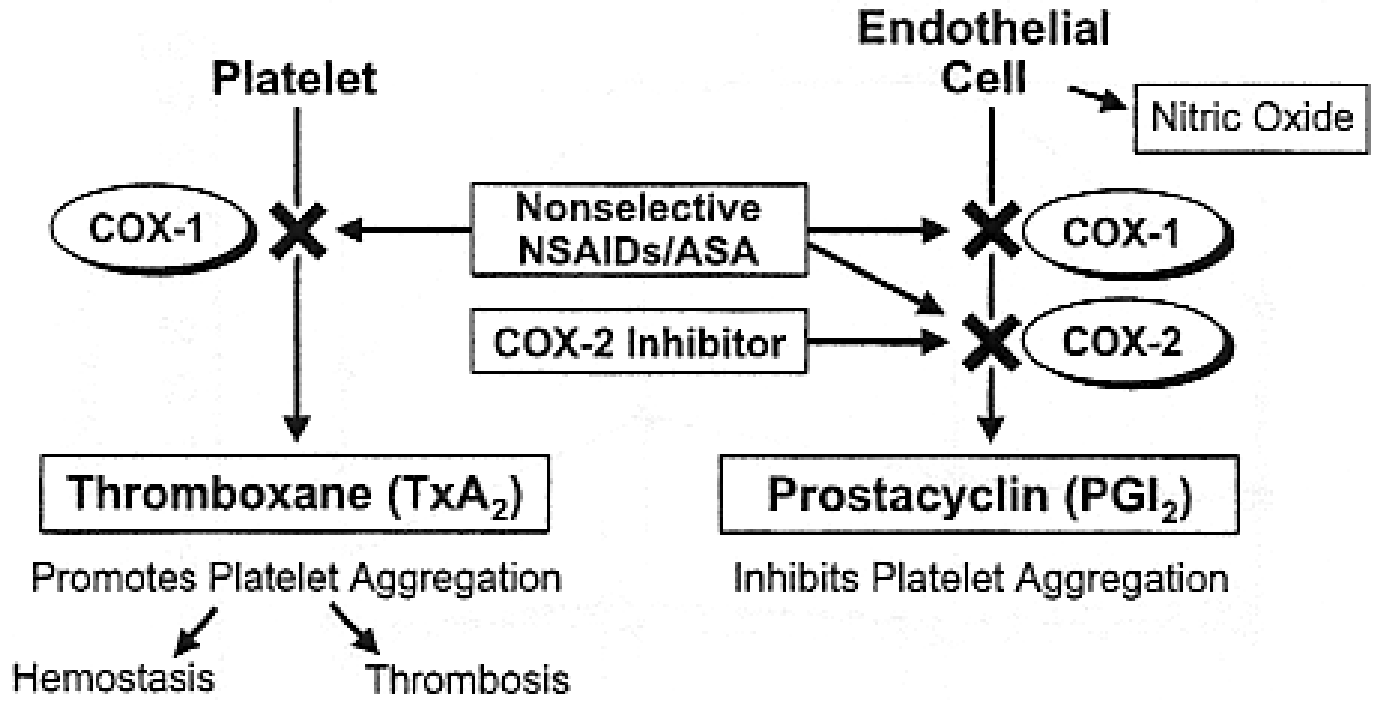


Fig. 6 *Dose-dependent increases in mortality with cyclooxygenase (COX) inhibitor treatment after acute myocardial infarction. High-dose COX-2 inhibitor and diclofenac treatment carry the greatest risks of dying. From the work of Gislason et al. [75], with the permission of the American Heart Association.*

COX-1 och COX-2 effekter på trombocyter och koagulation



Effects of nonselective NSAIDs, COX-2 inhibitors, and aspirin on thromboxane and prostacyclin synthesis.

Weir et al 2003

Hur ska man tänka kring användandet av geler ?

Smärtstillande gel – ett alternativ för äldre - Janusinfo.se

Cochrane Library

Cochrane Database of Systematic Reviews

Topical analgesics for acute and chronic pain in adults - an overview of Cochrane Reviews (Review)

Derry S, Wiffen PJ, Kalso EA, Bell RF, Aldington D, Phillips T, Gaskell H, Moore RA

Summary of findings for the main comparison. Topical NSAIDs compared with topical placebo for acute musculoskeletal pain in adults

Topical NSAIDs compared with topical placebo for acute musculoskeletal pain in adults

Patient or population: adults with strains, sprains, or muscle pull

Settings: community

Intervention: topical NSAID (topical diclofenac, ibuprofen, and ketoprofen gels only shown here for efficacy)

Comparison: topical placebo

Outcomes	Probable out-come with intervention	Probable out-come with comparator	RR, NNT, NNTp, or NNH (95% CI)	No of studies, participants	Quality of the evidence (GRADE)	Comments
Topical diclofenac gel (as Emulgel) **Clinical success (eg 50% reduction in pain)**	780 in 1000	200 in 1000	RR 3.4 (2.7 to 55) NNT 1.8 (1.5 to 2.1)	2 studies 314 participants	High	Consistent results in 2 moderately sized recent studies of high quality
Topical ibuprofen gel **Clinical success (eg 50% reduction in pain)**	420 in 1000	160 in 1000	RR 2.7 (1.7 to 4.2) NNT 3.9 (2.7 to 6.7)	2 studies 241 participants	Moderate	Modest effect size and numbers of participants
Topical ketoprofen gel **Clinical success (eg 50% reduction in pain)**	720 in 1000	330 in 1000	RR 2.2 (1.7 to 2.8) NNT 2.5 (2.0 to 3.4)	5 studies 348 participants	Moderate	Modest effect size and numbers of participants, but studies small, with none recent

Summary of findings for the main comparison.

Topical NSAIDs compared with topical placebo for chronic musculoskeletal pain in adults

Patient or population: adults with chronic musculoskeletal pain (osteoarthritis)

Settings: community

Intervention: topical NSAID (topical diclofenac and ketoprofen only for efficacy outcomes); treatment duration 6 to 12 weeks

Comparison: topical placebo

Probable outcome with intervention	Probable outcome with intervention	Probable outcome with comparator	RR, NNT, NNTp, or NNH (95% CI)	No of studies, participants	Quality of the evidence (GRADE)	Comments
Topical diclofenac gel or solution **Clinical success (for example 50% reduction in pain)**	600 in 1000	500 in 1000	RR 1.2 (1.1 to 1.3) NNT 9.8 (7.1 to 16)	6 studies 2342 participants	Moderate	Adequate numbers of studies, participants, and events, and consistency of effect, but the size of the effect was modest and could be overturned by null effect studies
Topical ketoprofen gel **Clinical success (for example 50% reduction in pain)**	630 in 1000	480 in 1000	RR 1.1 (1.01 to 1.2) NNT 6.9 (5.4 to 9.3)	4 studies 2573 participants	Moderate	Adequate numbers of studies, participants, and events, but there was inconsistency of effect between studies (I^2 = 83%). The size of the effect was modest and could be overturned by null effect studies

Lokala biverkningar med med topikala NSAID

Topical NSAIDs compared with topical placebo for acute musculoskeletal pain in adults						
All topical NSAIDs **Local adverse events**	46 in 1000	50 in 1000	RR 1.0 (0.80 to 1.2) NNH not calculated	42 studies 6125 participants	High	Large number of studies and participants with consistent results

Topical NSAIDs compared with topical placebo for chronic musculoskeletal pain in adults						
Topical diclofenac gel or solution **Local adverse events**	140 in 1000	78 in 1000	RR 1.8 (1.5 to 2.2) NNH 16 (12 to 23)	15 studies 3658 participants	Moderate	Adequate numbers of studies, participants, and events, but there was inconsistency of effect (I^2 = 76%), possibly due to differences in data collection. The size of the effect was modest and could be overturned by additional studies
Topical ketoprofen gel **Local adverse events**	150 in 1000	130 in 1000	RR 1.0 (0.85 to 1.3)	4 studies 2621 participants	Moderate	Adequate numbers of studies, participants, and events, and consistency of effect (no effect), but the size of the effect was modest and could be overturned by additional studies

Miljöaspekt – finns riktlinjer för t ex gel?

P. Sathishkumar et al. / Science of the Total Environment 698 (2020) 134057

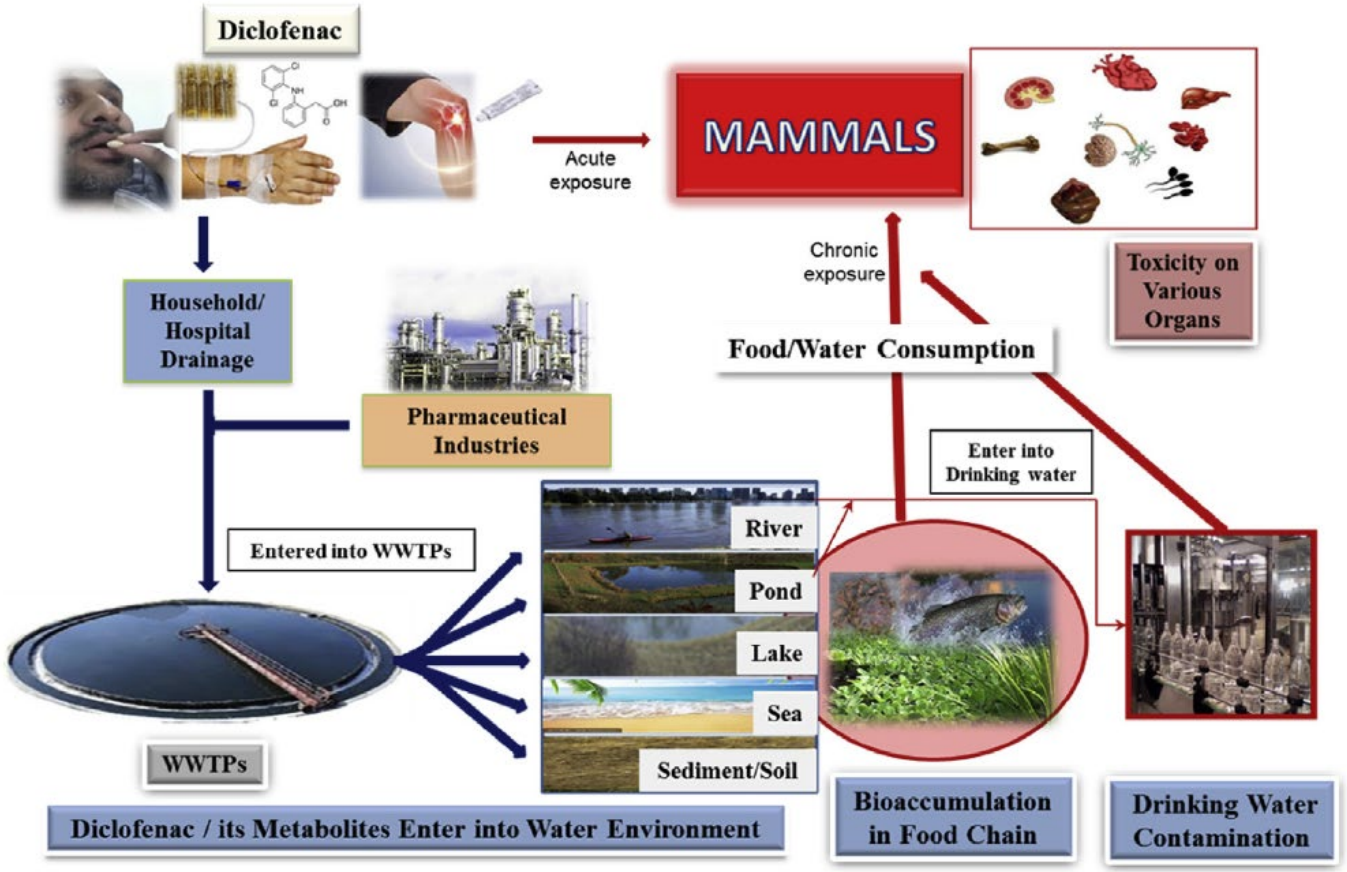


Fig. 2. Environmental distribution, bioaccumulation, biomagnifications and ecological risk of diclofenac towards mammals.

Miljöaspekt – finns riktlinjer för t ex gel?

GRAPHICAL ABSTRACT