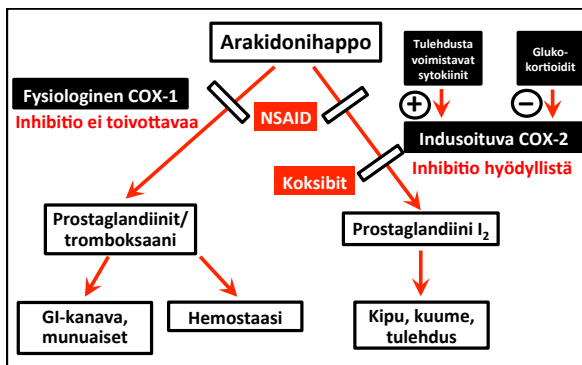


Tulehduskipulääkkeet tänään

Klaus Olkkola
Helsingin yliopisto ja HYKS

Tulehduskipulääkkeiden vaikutukset

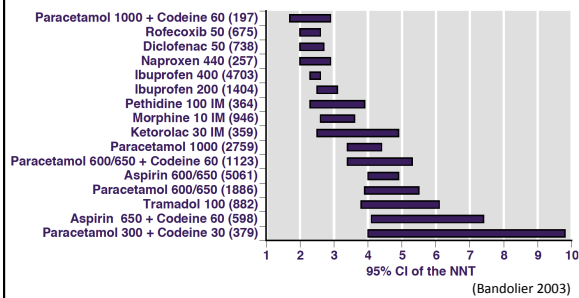
- Kipua lievittävä eli analgeettinen vaikutus
- Kuumetta alentava eli antipyreettinen vaikutus
- Tulehdusta lievittävä eli anti-inflammatorinen vaikutus
- Verihiutaleiden aggregaation esto



Tulehduskipuläkkeet

- **ASA**
- **Propionihappojohdokset**
 - Ibuprofeeni
 - Ketoprofeeni
 - Deksketoprofeeni
 - Naprokseeni
- **Etikkahappojohdokset**
 - Diklofenaakki
 - Etodolaakki
 - Indometasiini
 - Ketorolaakki
- **Meloksikaami**
- **Fenamaatit**
 - Tolfenaamihappo
 - Mefenaamihappo
- **Koksibit**
 - Etorikoksibi
 - Selekoksibi
 - Parekoksibi
- **(Parasetamoli)**

Kipulääkkeiden NNT-arvoja

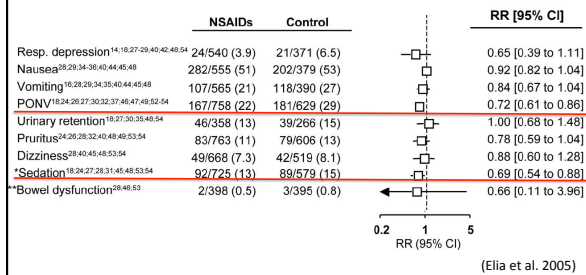


Parasetamolin ja tulehduskipulääkkeiden vaikutus morfiinin kulutukseen

Regimens	# patients with		WMD [95% CI]
	active	control	
Acetaminophen multiple dose ¹⁶⁻²⁵	379	334	-8.31 [-10.9 to -5.72]
NSAIDs			
single dose ²⁶⁻³²⁻³⁴⁻³⁶⁻⁴⁰⁻⁴²⁻⁴⁶⁻⁵⁰⁻⁵²⁻⁵³	533	496	-10.3 [-18.3 to -2.34]
multiple dose ¹⁶⁻¹⁸⁻²⁴⁻²⁷⁻²⁸⁻³⁰⁻³¹⁻³⁸⁻³⁹⁻⁴¹⁻⁴³⁻⁴⁴⁻⁴⁸⁻⁴⁹⁻⁵¹	495	398	-19.7 [-26.3 to -13.0]
continuous ¹⁴⁻²⁰⁻³⁰⁻³⁵⁻⁴⁵⁻⁴⁸⁻⁵⁴	276	253	-18.3 [-26.8 to -9.74]
COX-2 inhibitors			
*single dose ⁶⁰⁻⁶³⁻⁶⁴ (celecoxib 200 mg)	70	69	-7.22 [-10.6 to -3.82]
*single dose ³²⁻⁶⁰⁻⁶³⁻⁶⁵⁻⁶⁶ (rofecoxib 50 mg)	91	91	-27.8 [-44.3 to -11.4]
multiple low dose ⁵⁵⁻⁵⁷⁻⁶¹⁻⁶²	272	273	-9.99 [-13.4 to -6.58]
multiple high dose ³⁸⁻⁵⁵⁻⁵⁷⁻⁵⁸⁻⁶¹⁻⁶²	535	411	-13.3 [-17.8 to -8.81]

WMD mg morphine (Elia et al. 2005)

NSAID ja morfiinin haittavaikutukset



NSAID-lääkkeiden haittavaikutukset

Haittavaikutus	Ilmaantuvuus
Vatsavaivat	10–30 % käyttäjistä
Oireileva mahahaava ja GI-yliosan vuoto	3–5/1 000 käyttövuotta
Sydäninfarkti, aivoinfarkti	1–4/1 000 käyttövuotta
Keskushermosto-oireet	2–5 % käyttäjistä (indometasiini ⚠)
Ihoreaktiot	2–5 % käyttäjistä
Turvotukset, verenpaineen nousu	1–9 % käyttäjistä
Merkilliset suolivauriot	3–4/1 000 käyttövuotta
Munuaisten vajaatoiminta	alle 1 promille käyttäjistä
Keuhkoputkien supistuminen	alle 1 promille käyttäjistä
Keuhkoputkien supistuminen astmaattikoilla	10–20 %
Muut keuhkokuuutokset	alle 1 promille käyttäjistä
Verenkuvamuutokset	alle 1 promille käyttäjistä
Maksavaurio	alle 1 promille käyttäjistä

(Helin-Salmivaara 2013)

Tulehduskipulääkeulkuksen ja ulkuskomplikaation riskitekijät

- Ikä yli 65 vuotta
- Aikaisempi ulkus
- Glukokortikoidihoito
- Usean tulehduskipulääkkeen samanaikainen käyttö
- Suuri päivittäinen tulehduskipulääkeannos
- Veren hyytymistä estävät lääkkeet: varfariini, klopidogreeli (verenvuotoriski)
- SSRI-masennuslääkkeet (verenvuotoriski)
- Yleiskuntoa heikentävät sairaudet
- Helikobakteeri-infektio

Ruoansulatuskanavahaittojen ehkäisy

- Riskiryhmille parasetamoli ja/tai COX-2-painotteiset/selektiiviset tulehduskipulääkkeet
- Samanaikainen pieniannoksinen ASA vähentää COX-2-selektiivisten turvallisuutta GI-kanavan osalta epäselektiivisten tasolle
- Tramadoli tai muu opioidi
- Protonipumpun salpaaja tai prostaglandiiniainalogi (misoprostoli) NSAID:n rinnalle

The New England Journal of Medicine

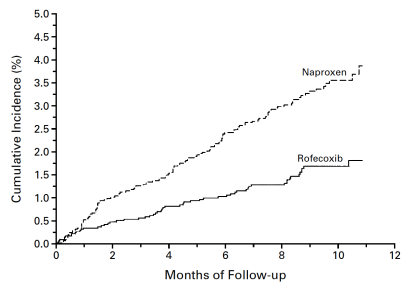
N Engl J Med 2000;343:1520-8

COMPARISON OF UPPER GASTROINTESTINAL TOXICITY OF ROFECOXIB AND NAPROXEN IN PATIENTS WITH RHEUMATOID ARTHRITIS

CLAIRE BOMBARDIER, M.D., LOREN LAINE, M.D., ALISE REICIN, M.D., DEBORAH SHAPIRO, DR.P.H., RUBEN BURGOS-VARGAS, M.D., BARRY DAVIS, M.D., PH.D., RICHARD DAY, M.D., MARCOS BOSI FERRAZ, M.D., PH.D., CHRISTOPHER J. HANKEY, M.D., MARC C. HOCHBERG, M.D., TORE K. KVIEK, M.D., AND THOMAS J. SCHNITZER, M.D., PH.D., FOR THE VIGOR STUDY GROUP

- We randomly assigned 8076 patients who were at least 50 years of age and who had rheumatoid arthritis to receive either 50 mg of rofecoxib daily or 500 mg of naproxen twice daily
- The primary end point was confirmed clinical upper gastrointestinal events (gastroduodenal perforation or obstruction, upper gastrointestinal bleeding, and symptomatic gastroduodenal ulcers)

Cumulative Incidence of the Primary End Point of a Confirmed Upper Gastrointestinal Event among All Randomized Patients



(Bombardier et al. 2000)

ORIGINAL ARTICLE

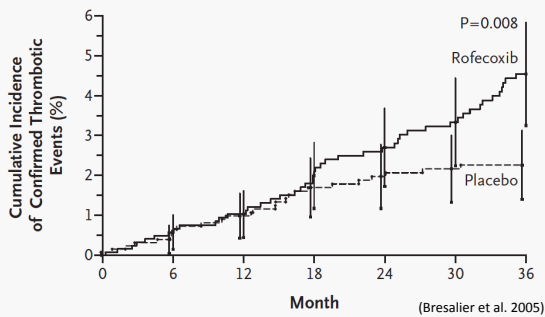
N Engl J Med 2005;352:1092-102

Cardiovascular Events Associated with Rofecoxib in a Colorectal Adenoma Chemoprevention Trial

Robert S. Bresalier, M.D., Robert S. Sandler, M.D., Hui Quan, Ph.D., James A. Bolognese, M.Stat., Bettina Oxenius, M.D., Kevin Horgan, M.D., Christopher Lines, Ph.D., Robert Riddell, M.D., Dion Morton, M.D., Angel Lanas, M.D., Marvin A. Konstam, M.D., and John A. Baron, M.D., for the Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial Investigators*

A total of 2586 patients with a history of colorectal adenomas underwent randomization: 1287 were assigned to receive 25 mg of rofecoxib daily, and 1299 to receive placebo

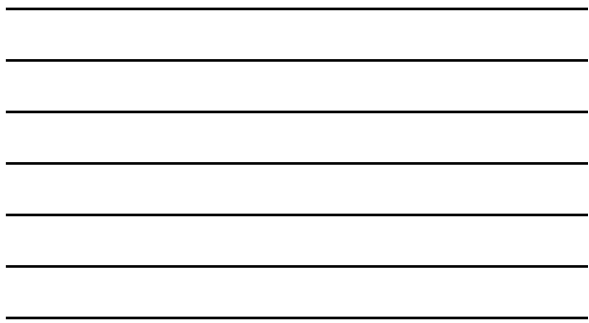
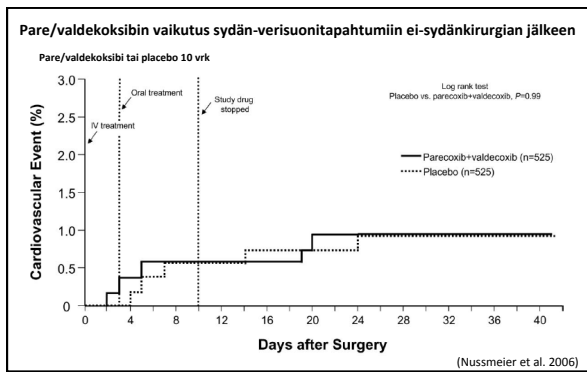
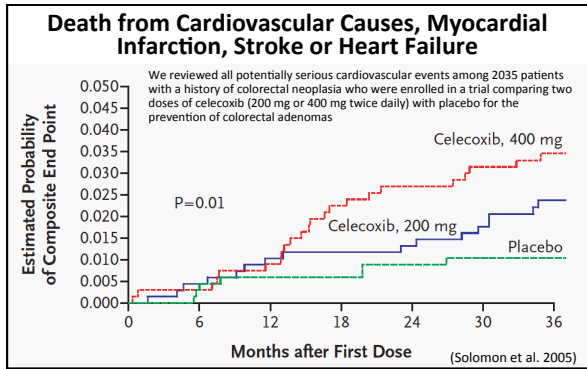
Cumulative Incidence of Confirmed Serious Thrombotic Events



Effect of COX-2-inhibitors and nonselective-COX inhibitors



- Sydänhaittojen riski liittyy sekä epäselektiivisten että COX-2-selektiivisten tulehduskipulääkkeiden käyttöön, erityisesti suurilla annoksilla ja sydänpotilailla
- Tromboembolia- ja sydäninfarktirisikin taustalla mahdollisesti muitakin mekanismeja (verenpaineen nousu ja suorat vaikutukset verisuonen seinämään ja sydämeen)



Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials

Summary

Background The vascular and gastrointestinal effects of non-steroidal anti-inflammatory drugs (NSAIDs), including selective COX-2 inhibitors (coxibs) and traditional non-steroidal anti-inflammatory drugs (NSAIDs), are not well characterised, particularly in patients at increased risk of vascular disease. We aimed to provide such information through meta-analyses of randomised trials.

Methods We undertook meta-analyses of 280 trials of NSAIDs versus placebo (24 513 participants, 68 312 person-years) and 474 trials of one NSAID versus another NSAID (22 296 participants, 102 656 person-years). The main outcomes were major vascular events (non-fatal myocardial infarction, non-fatal stroke, or vascular death), major coronary events (non-fatal myocardial infarction or coronary death), stroke, mortality, heart failure, and upper gastrointestinal complications (perforation, obstruction, or bleed).

Findings Major vascular events were increased by about a third by a coxib (rate ratio [RR] 1.37, 95% CI 1.14–1.64, $p<0.0009$) or diclofenac (1.41, 1.12–1.74; $p<0.0016$), chiefly due to an increase in major coronary events (coxibs 1.76, 1.12–2.37; $p<0.0012$; diclofenac 1.70, 1.19–2.41; $p<0.0012$). Ibuprofen also significantly increased major coronary events (2.22, 1.10–4.48; $p=0.0253$), but not major vascular events (1.44, 0.89–2.33). Compared with placebo, of 3000 patients allocated to a coxib or diclofenac for 3 years, three more had major vascular events, one of which was fatal. Naproxen did not significantly increase major vascular events (0.93, 0.69–1.27). Vascular death was increased significantly by coxibs (1.56, 99% CI 1.08–2.49; $p=0.0193$) and diclofenac (1.65, 0.95–2.85; $p=0.0387$), not significantly by ibuprofen (1.09, 0.56–4.41; $p=0.17$), but not by naproxen (1.08, 0.48–2.47; $p=0.30$). The proportional effects on major vascular events were independent of baseline characteristics, including vascular risk. Heart failure risk was roughly doubled by all NSAIDs: all NSAID regimens increased upper gastrointestinal complications (coxibs 1.81, 1.17–2.81; $p=0.0070$; diclofenac 1.89, 1.16–3.09; $p=0.0106$; ibuprofen 3.97, 2.22–7.10; $p<0.0001$; and naproxen 3.22, 2.72–3.86; $p<0.0001$).

Interpretation The vascular risks of high-dose diclofenac, and possibly ibuprofen, are comparable to coxibs, whereas high-dose naproxen is associated with less vascular risk than other NSAIDs. Although NSAIDs increase vascular and gastrointestinal risks, the size of these risks can be predicted, which could help guide clinical decision making.

Funding UK Medical Research Council and British Heart Foundation.

Introduction The vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs (NSAIDs), including selective COX-2 inhibitors (coxibs) and traditional non-steroidal anti-inflammatory drugs (NSAIDs), are not well characterised, particularly in patients at increased risk of vascular disease. We aimed to provide such information through meta-analyses of randomised trials.

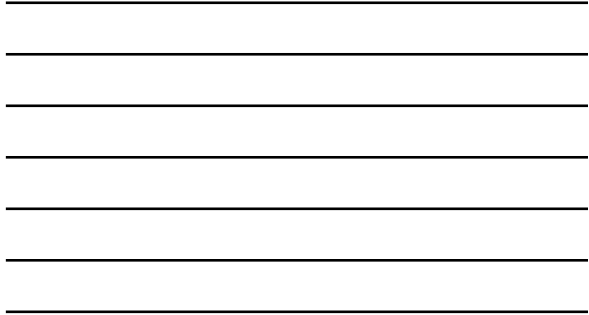
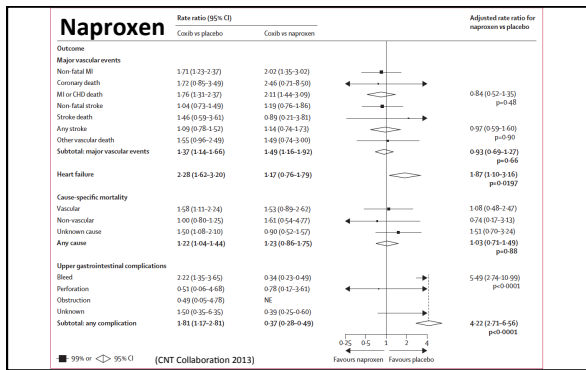
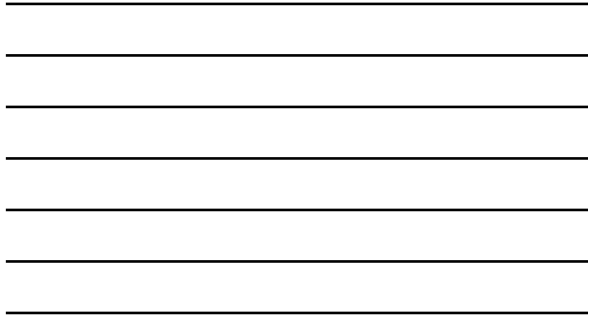
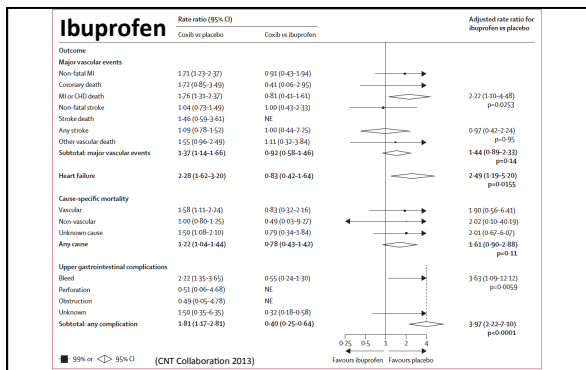
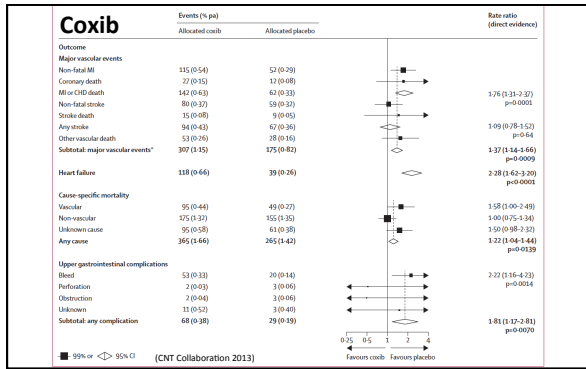
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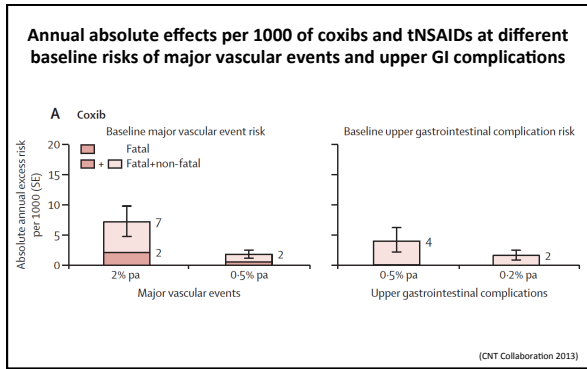
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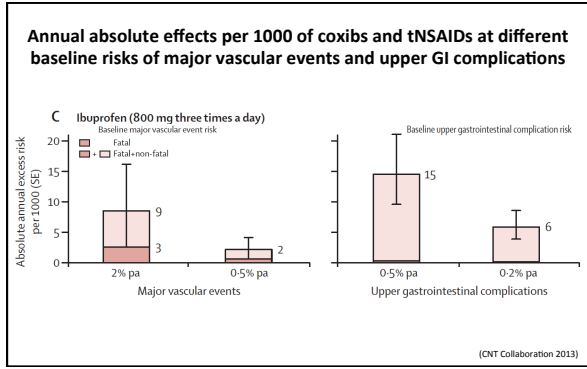
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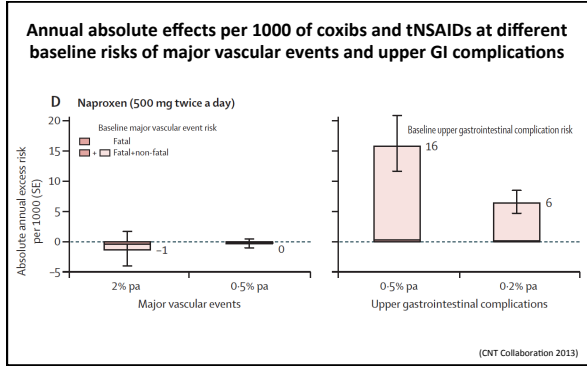
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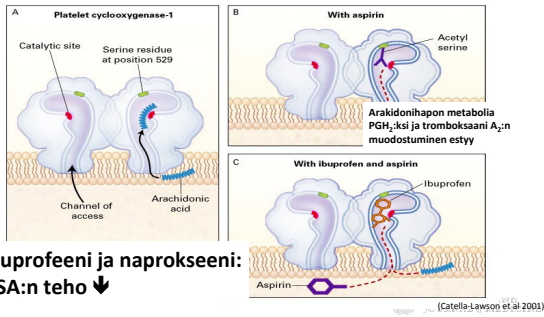








ASA:n ja ASA/ibuprofeenin vaikutus trombosyyttien COX-1-entsyymiin



Ibuprofeeni ja naprokseeni:
ASA:n teho ↓

Tulehduskipulääkkeen valinta ulkusvuoto- ja kardiovaskulaarisen riskin perusteella

	Pieni ulkusvuotoriski	Suurentunut ulkusvuotoriski	Suuri ulkusvuotoriski
Pieni kardiovas-kulaarinen riski	Ei-selektiivinen tulehduskipulääke	Ei-selektiivinen tulehduskipulääke + PPI tai misoprostoli tai COX-2-selektiivinen tulehduskipulääke	Analgeetti ensisijaisesti muista lääkeryhmistä
Suuri kardiovas-kulaarinen riski (potilaalla ASA-lääkitys tai sen indikaatio)	Naprokseeni (kun potilas ei käytä ASaA)	Analgeetti ensisijaisesti muista lääkeryhmistä; tulehduskipulääkkeistä naprokseeni (tai muu tulehduskipulääke) + PPI	Analgeetti muista lääkeryhmistä

(Helin-Salmivaara 2013)

Tulehduskipulääkkeet

- Tehokas lääkeryhmä, mutta määrättävä potilaille yksilöllisesti
- Tromboembolisten komplikaatioiden riski (sydän- tai aivoinfarkti) COX-2-selektiivisillä 2-kertainen, epäselektiivisillä 1.5-kertainen
- COX-2-selektiiviset kontraindisoituja: iskeeminen sydänsairaus, aivoverisuonten sairaus tai ääreisvaltimoiden sairaus
- COX-2-selektiivisiä varoen: sydänsairauksien riskitekijöitä (verenpaine ↑, kolesterolipitoisuus ↑, diabetes) tai tupakointi
- Edellä mainituille potilaille eivät perinteisetkään tulehduskipulääkkeet ole turvallisia
- Pienin tehokas annos ja mahdollisimman lyhytkestoinen hoito
