Risks of NSAIDs

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Drugs

Drug Safety and Availability

Drug Alerts and Statements

Medication Guides

Drug Safety Communications

Drug Shortages

Postmarket Drug Safety Information for Patients and Providers

Information by Drug Class

Medication Errors

Drug Safety Podcasts

Safe Use Initiative

Drug Recalls

Drug Supply Chain Integrity

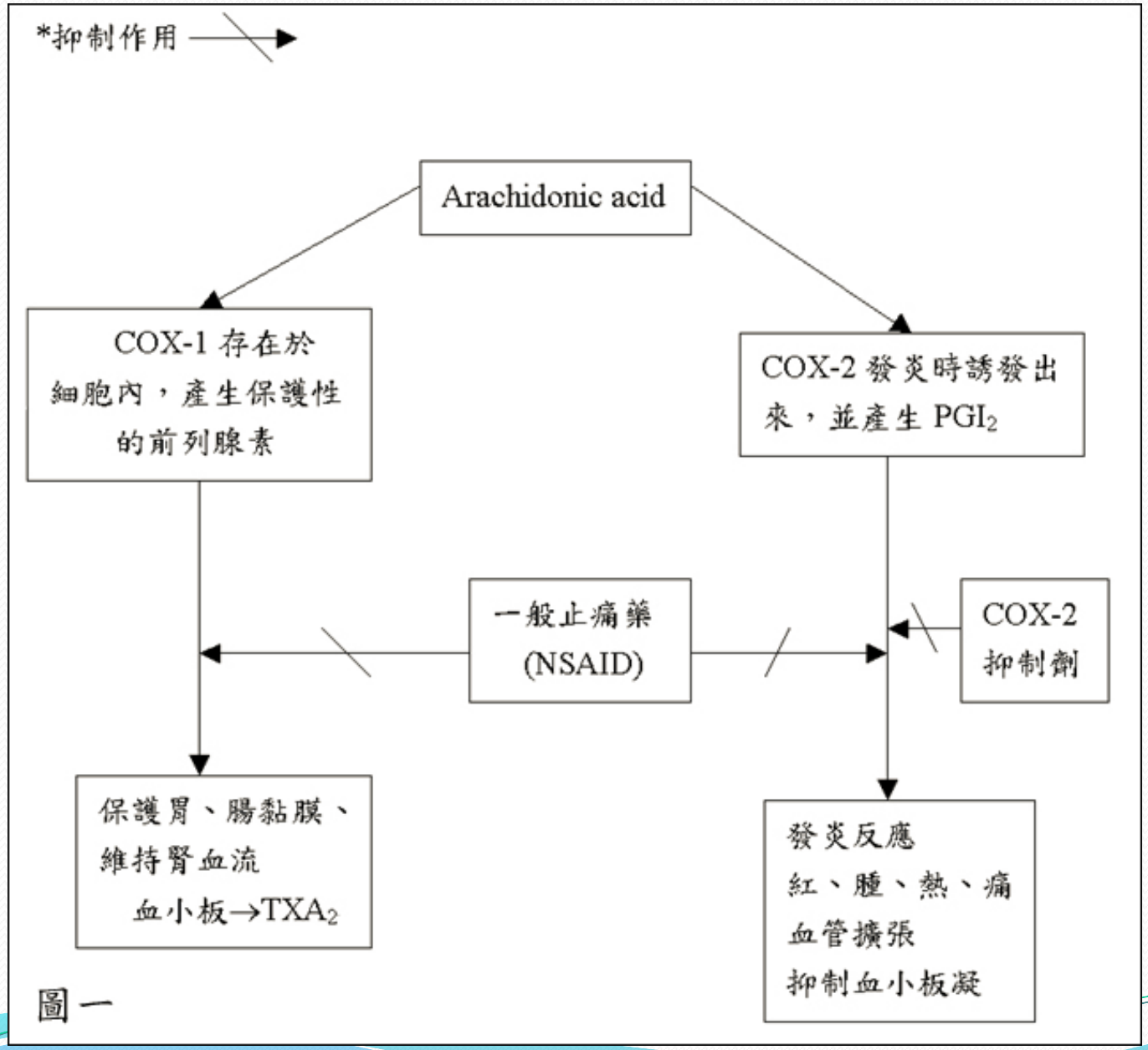
FDA Drug Safety Communication: FDA strengthens warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) can cause heart attacks or strokes

[7-9-2015]

Safety Announcement

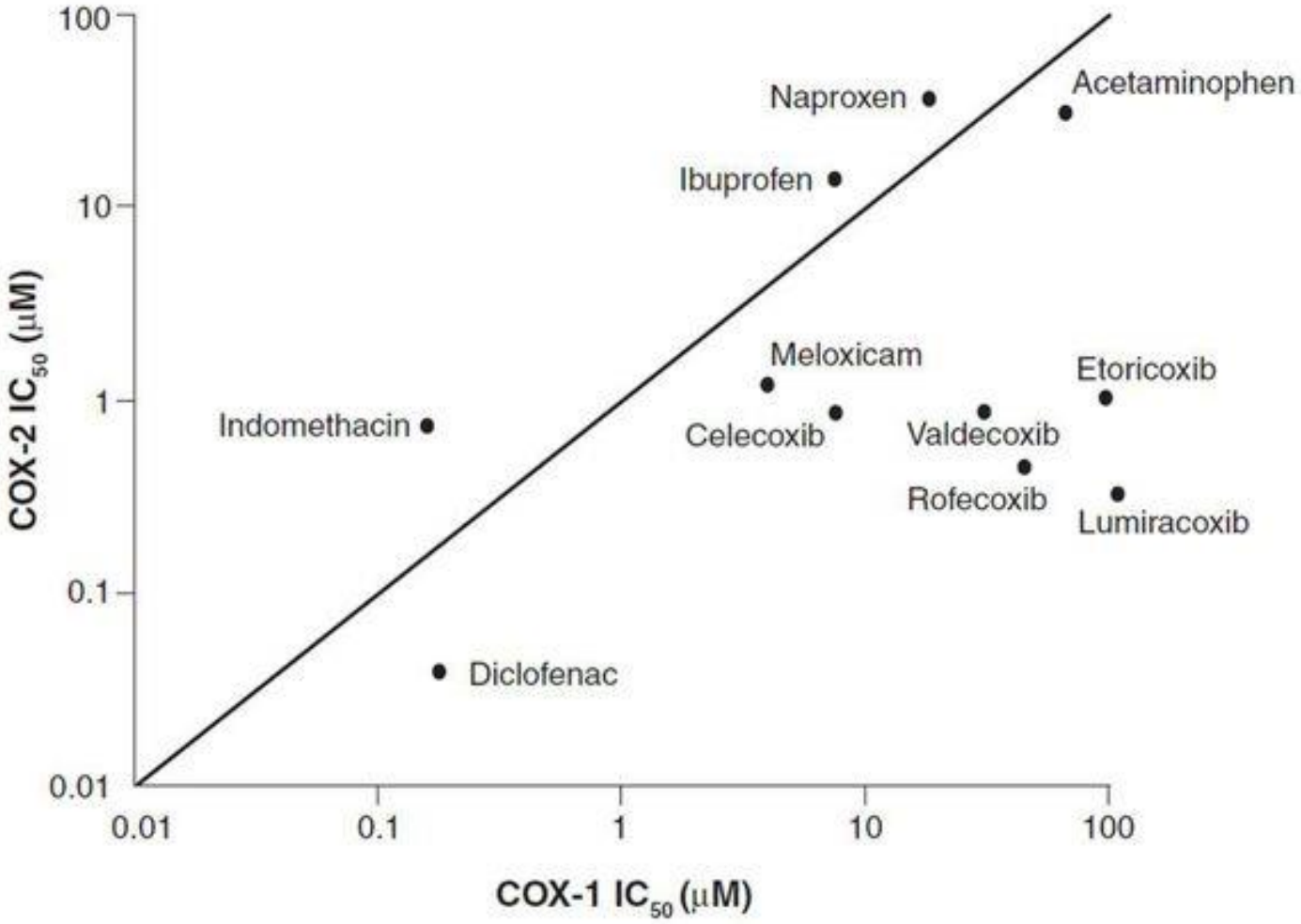
The U.S. Food and Drug Administration (FDA) is strengthening an existing label warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) increase the chance of a heart attack or stroke. Based on our comprehensive review of new safety information, we are requiring updates to the drug labels of all prescription NSAIDs. As is the case with current prescription NSAID labels, the Drug Facts labels of over-the-counter (OTC) non-aspirin NSAIDs already contain information on heart attack and stroke risk. We will also request updates to the OTC non-aspirin NSAID Drug Facts labels.

Patients taking NSAIDs should seek medical attention immediately if they experience symptoms such as chest pain, shortness of breath or trouble breathing, weakness in one part or side of their body, or slurred speech.


*抑制作用
Arachidonic acid
COX-1 存在於細胞內，產生保護性的前列腺素
COX-2 發炎時誘發出來，並產生 PGI_2
一般止痛藥 (NSAID)
COX-2 抑制劑
保護胃、腸黏膜、維持腎血流
血小板→TXA_2
發炎反應
紅、腫、熱、痛
血管擴張
抑制血小板凝

圖一

Figure 1. Concentrations of selected nonsteroidal antiinflammatory drugs required to inhibit 50% of the cyclooxygenase-1 (COX-1) and COX-2 enzymatic reactions in assays of whole human blood (50% inhibition concentrations [IC_{50}]). Reproduced with permission from *Arthritis & Rheumatism*, 2005; 52:1968-78.



April 2005 FDA Action

Based on assessments of cardiovascular (CV) risk in RCTs evaluating the efficacy of COX-2 selective and non-selective NSAIDs in OA/RA/chemoprevention indications, and the discussion of such studies at the Feb 2005 AC meeting, FDA made the following conclusions

- The three approved COX-2 selective NSAIDs (i.e., celecoxib, rofecoxib, and valdecoxib) are associated with an increased risk of serious adverse CV events compared to placebo. The available data do not permit a rank ordering of these drugs with regard to CV risk.
- Data from large long-term controlled clinical trials that have included a comparison of COX-2 selective and non-selective NSAIDs do not clearly demonstrate that the COX-2 selective agents confer a greater risk of serious adverse CV events than non-selective NSAIDs.
- Long-term placebo-controlled clinical trial data are not available to adequately assess the potential for the non-selective NSAIDs to increase the risk of serious adverse CV events.

April 2005 FDA Action (2)

- Pending the availability of additional long-term controlled clinical trial data, the available data are best interpreted as being consistent with a class effect of an increased risk of serious adverse CV events for COX-2 selective and non-selective NSAIDs.
- Short-term use of NSAIDs to relieve acute pain, particularly at low doses, does not appear to confer an increased risk of serious adverse CV events (with the exception of valdecoxib in hospitalized patients immediately post-operative from coronary artery bypass (CABG) surgery).
- Valdecoxib is associated with an increased rate of serious and potentially life-threatening skin reactions compared to other COX-2 selective agents and is the only NSAID with a boxed warning for this adverse event in its approved package insert. In the absence of any demonstrated advantage over nonselective NSAIDs, the overall benefit versus risk profile for valdecoxib is unfavorable for marketing.

April 2005 FDA Action (3)

Based on these conclusions, the following actions were taken:

- Withdrawal of valdecoxib
- Revision of the labeling of all NSAIDs to include the following
  - A boxed warning highlighting the potential for increased risk of CV events with these drugs and the well-described, serious, and potentially life-threatening gastrointestinal (GI) bleeding associated with their use.
  - Addition of a contraindication for use in patients immediately post-operative from CABG surgery.
  - Dispensing of a Medication Guide with every prescription NSAID at the time it is dispensed to better inform patients about the CV and GI risks.
- Revision of non-prescription (OTC) NSAID labeling to include more specific information about the potential GI and CV risks, and information to assist consumers in the safe use of those drugs.
- Agency request for sponsors of non-selective NSAIDs to conduct and submit a comprehensive review and analysis of available controlled clinical trial databases to further evaluate the potential for increased CV risk.

European Medicines Agency Recommendations: 2005-6

- COX-2 selective NSAIDs
  - Contraindications stating that COX-2 inhibitors must not be used in patients with established ischaemic heart disease and/or cerebrovascular disease (stroke), and also in patients with peripheral arterial disease
  - Reinforced warnings to healthcare professionals to exercise caution when prescribing COX-2 inhibitors to patients with risk factors for heart disease, such as hypertension, hyperlipidaemia (high cholesterol levels), diabetes and smoking
  - Given the association between cardiovascular risk and exposure to COX-2 inhibitors, doctors are advised to use the lowest effective dose for the shortest possible duration of treatment
- Non-selective NSAIDs
  - Non-selective NSAIDs are important treatments for arthritis and other painful conditions.
  - It cannot be excluded that non-selective NSAIDs may be associated with a small increase in the absolute risk for thrombotic events especially when used at high doses for long-term treatment.
  - The overall benefit-risk balance for non-selective NSAIDs remains favourable when used in accordance with the product information, namely on the basis of the overall safety profile of the respective non-selective NSAID, and taking into account the patient's individual risk factors (e.g. gastrointestinal, cardiovascular and renal).

Prescription NSAID Labeling

Boxed Warning

Cardiovascular Risk

- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. (See **WARNINGS** and **CLINICAL TRIALS**).

- TRADENAME is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see **WARNINGS**).

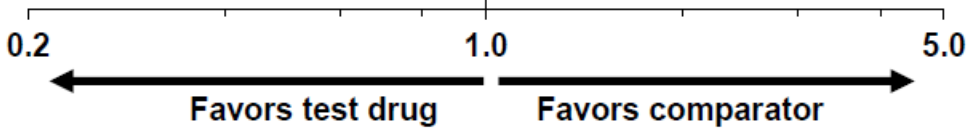
Gastrointestinal Risk

- NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events. (See **WARNINGS**).

MACE Events

CNT: Meta-Analysis of Randomized Controlled Trials

Parameters	Rate Ratio (95% CI)
Individual NSAID comparisons	
Celecoxib[a] vs. Placebo	1.36 (1.00 - 1.84)
Diclofenac vs. Placebo	1.41 (1.12 - 1.78)
Ibuprofen vs. Placebo	1.44 (0.89 - 2.33)
Naproxen vs. Placebo	0.93 (0.69 - 1.27)
Celecoxib comparison	
Celecoxib[a] vs. Diclofenac[b]	0.94 (0.54 - 1.63)
Celecoxib[a] vs. Ibuprofen[b]	1.01 (0.48 - 2.13)
Celecoxib[a] vs. Naproxen[b]	0.93 (0.46 - 1.88)

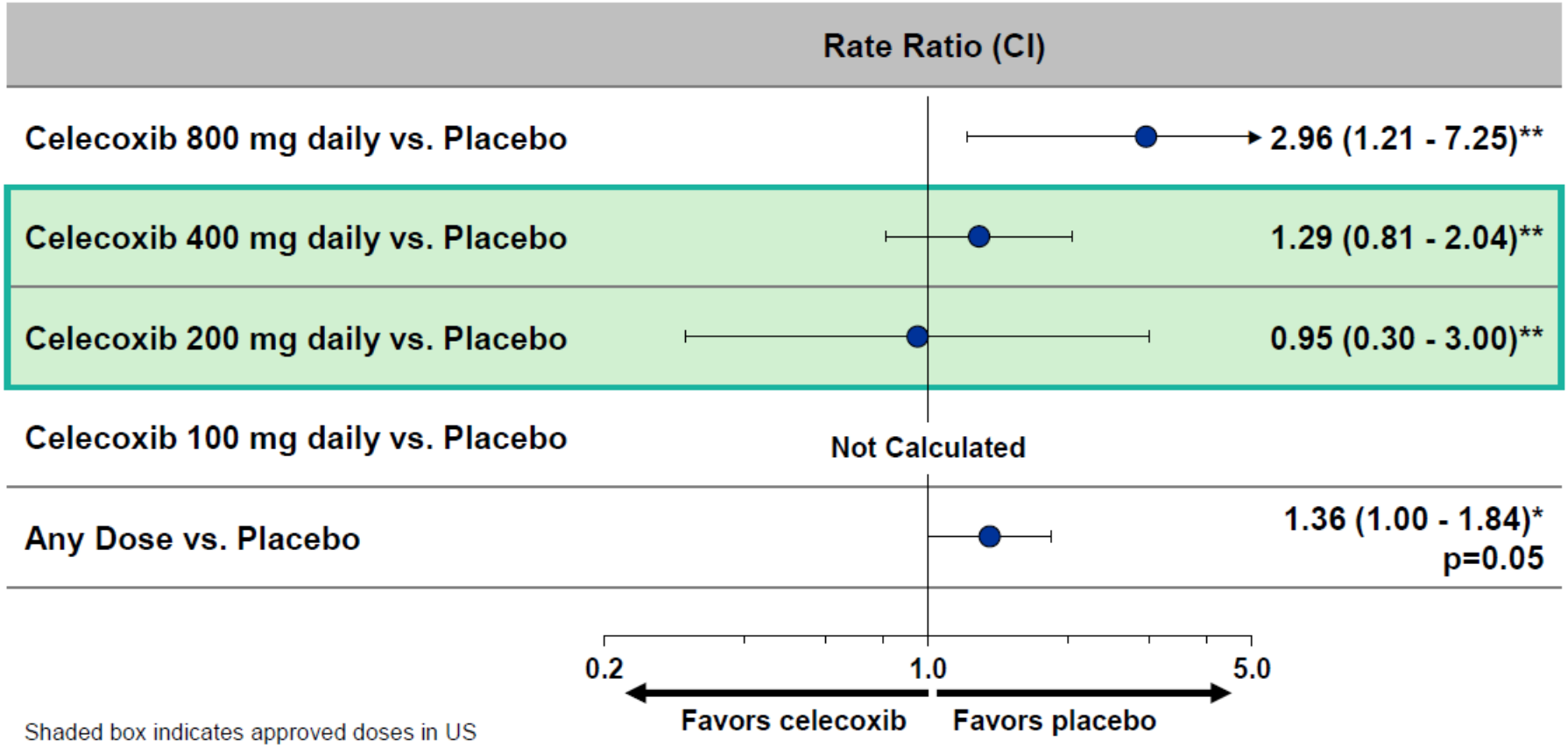


Bhala N et al. Lancet 2013;382:769-779 and Supplement

Note: MACE includes major vascular events; [a]Any dose; [b]Any dose included, but almost all doses were maximum prescription: diclofenac 150 mg daily ("rarely 100 mg"); ibuprofen 2400 mg daily; and naproxen 1000 mg daily ("rarely 440 mg")

MACE Events: Celecoxib Dose Results

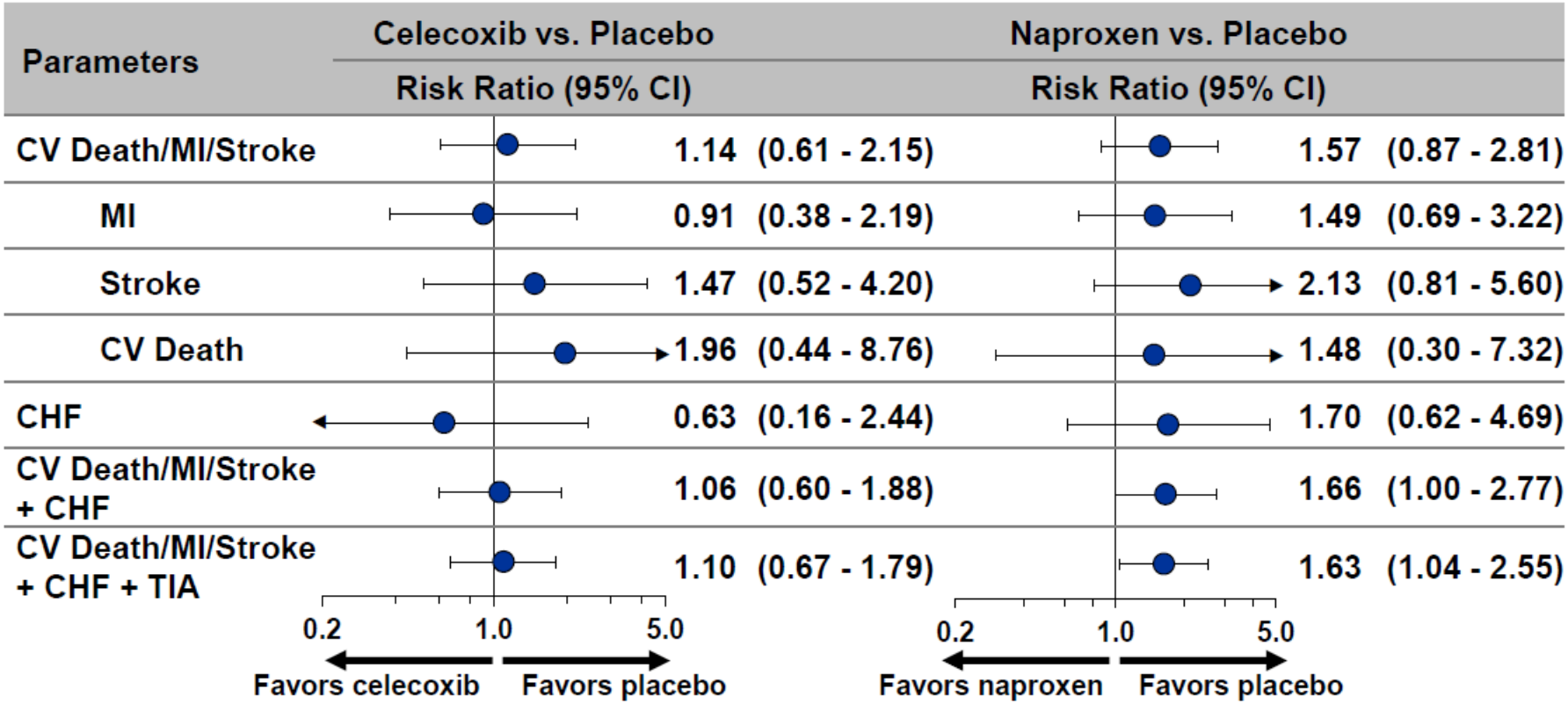
CNT: Meta-Analysis of Randomized Controlled Trials



Shaded box indicates approved doses in US
*95% CI; **99% CI
Bhala N et al. Lancet 2013;382:769-779 and Supplement

Cardiovascular Events

ADAPT: Randomized Controlled Trial



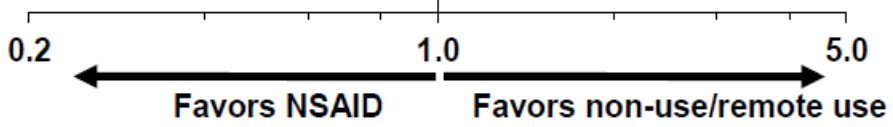
TIA, transient ischemic attack

Martin BK et al. PLoS Clin Trials 2006;1:e33

Cardiovascular Events

McGettigan and Henry Meta-Analysis of Observational Studies

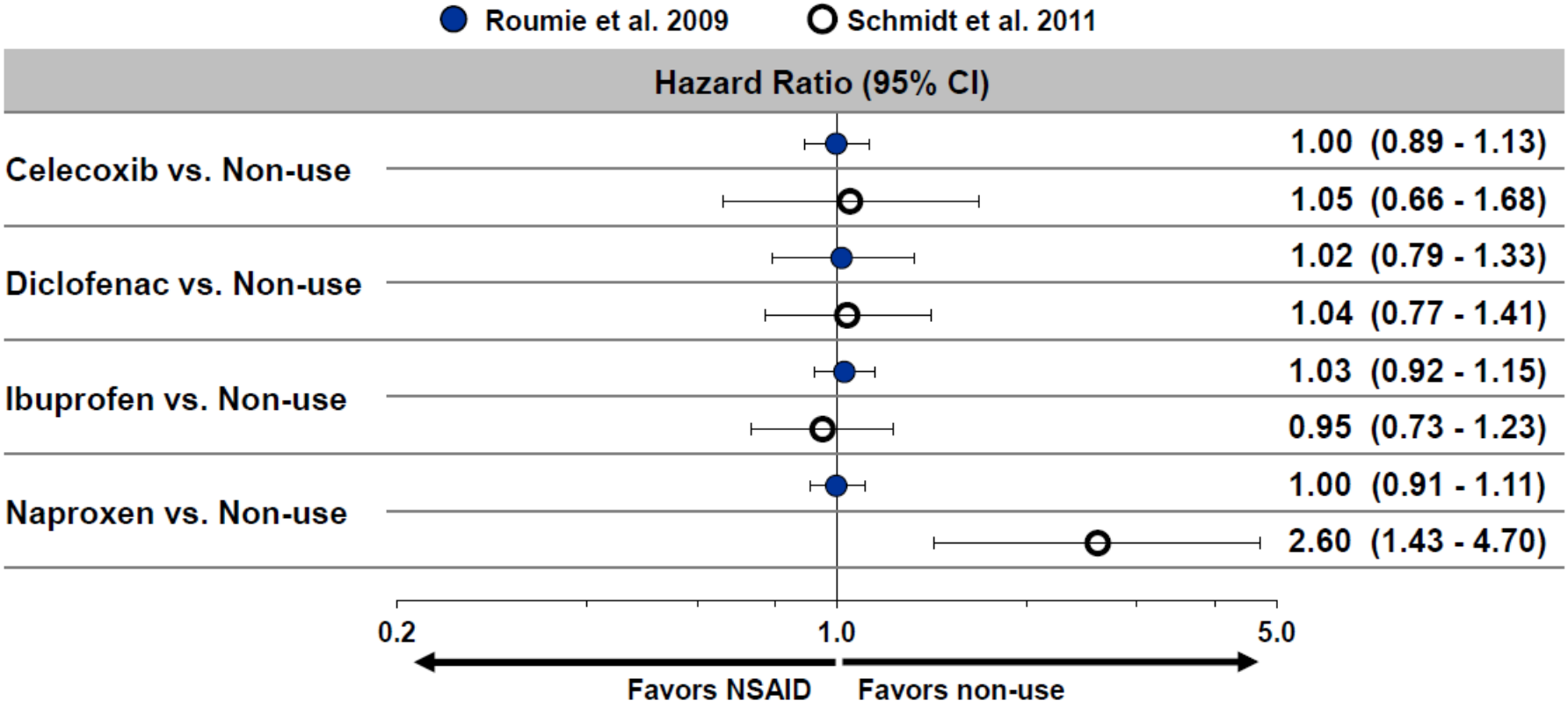
Drug vs. Non-use/Remote use	Total Number of Studies	Pooled Risk Ratio (95% CI)
Naproxen	41	1.09 (1.02 - 1.16)
Ibuprofen	38	1.18 (1.11 - 1.25)
Celecoxib	35	1.17 (1.08 - 1.27)
Rofecoxib	34	1.45 (1.33 - 1.59)
Diclofenac	29	1.40 (1.27 - 1.55)
Indomethacin	14	1.30 (1.19 - 1.41)
Piroxicam	8	1.08 (0.91 - 1.30)
Meloxicam	7	1.20 (1.07 - 1.33)
Etodolac	5	1.55 (1.28 - 1.87)
Etoricoxib	4	2.05 (1.45 - 2.88)
Valdecoxib	5	1.05 (0.81 - 1.36)



McGettigan P, Henry D PLoS Med 2011;8:e1001098

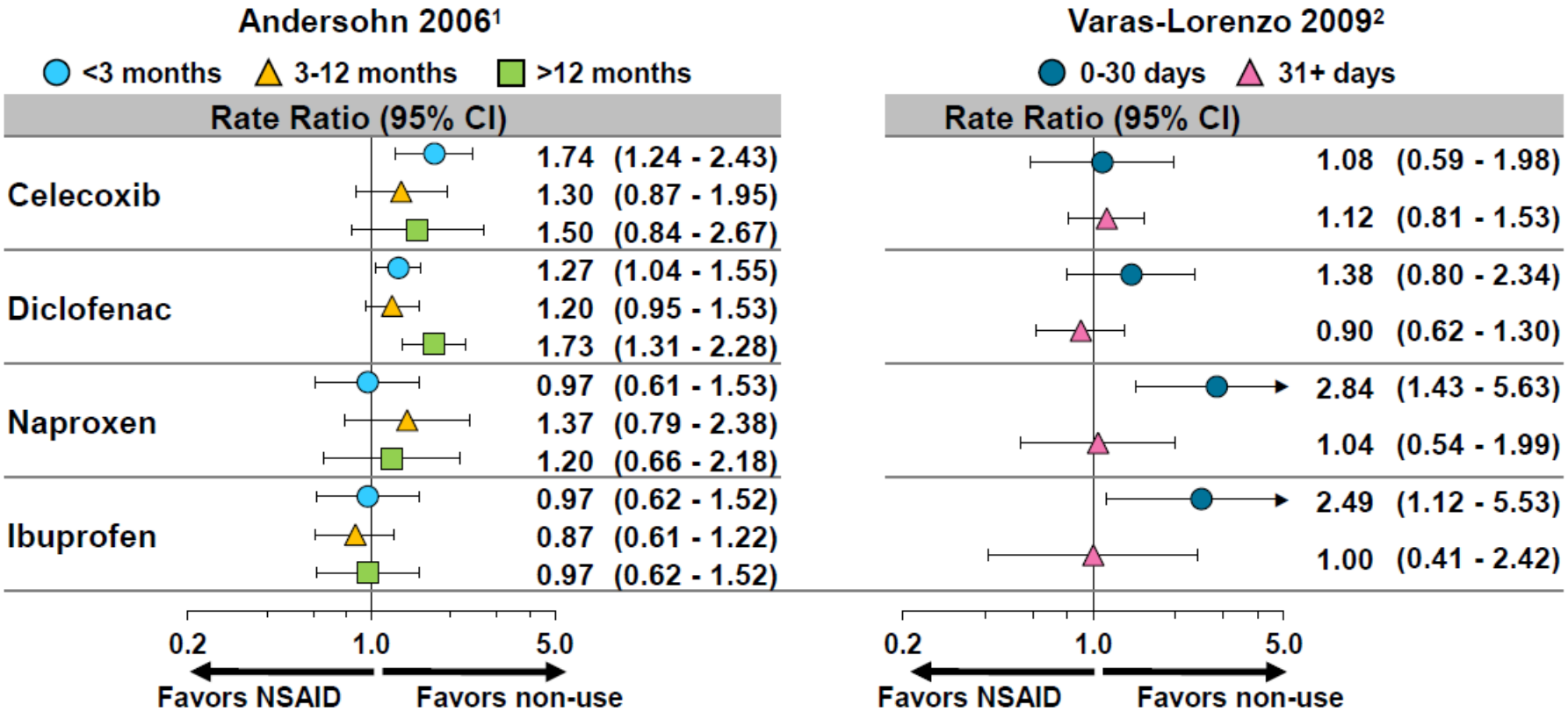
MACE Events

Individual Observational Studies



Roumie CL et al. Pharmacoepidemiol Drug Saf 2009;18:1053-1063; Schmidt M et al. Pharmacotherapy 2011;31:458-468

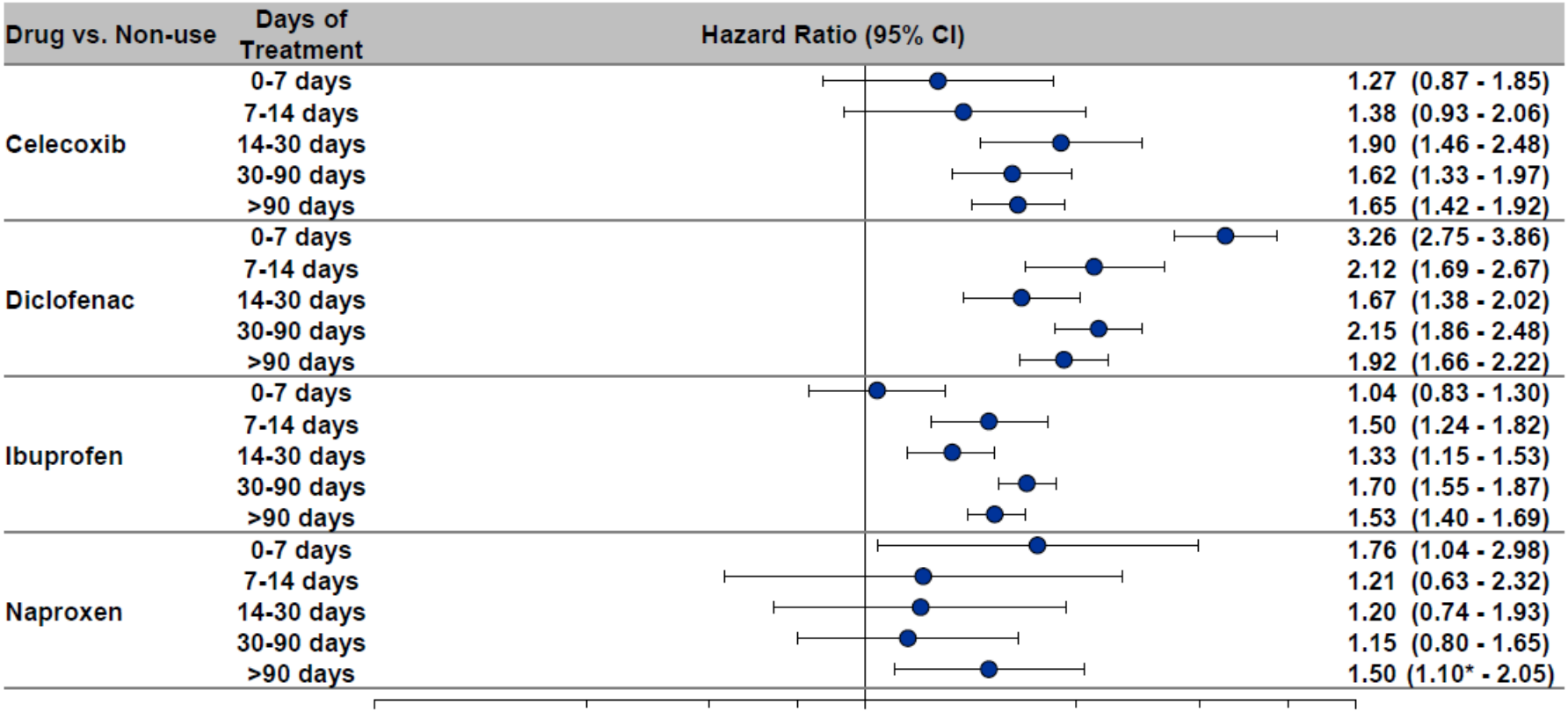
Latency Period for Increased Risk of MI
Observational Studies



[1]Andersohn F et al. Circulation 2006;37:1725-1730; [2]Varas-Lorenzo C et al. Pharmacoepidemiol Drug Saf 2009;18:1016-1025

Death/Recurrent MI Associated with NSAID Treatment

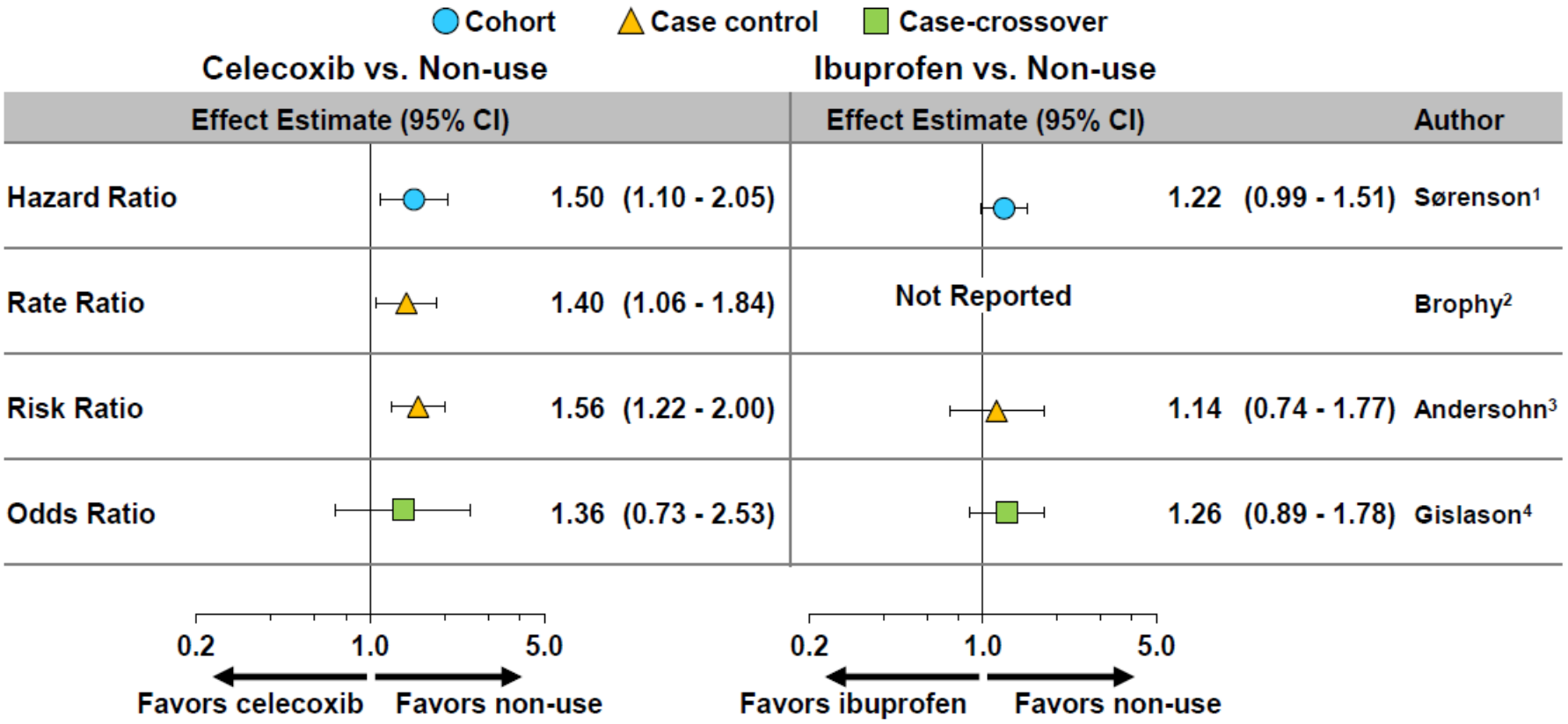
Danish National Patient Registry, Schjerning Olsen et al. 2011



*calculated by Pfizer

Schjerning Olsen AM et al. Circulation 2011;123:2226-2235

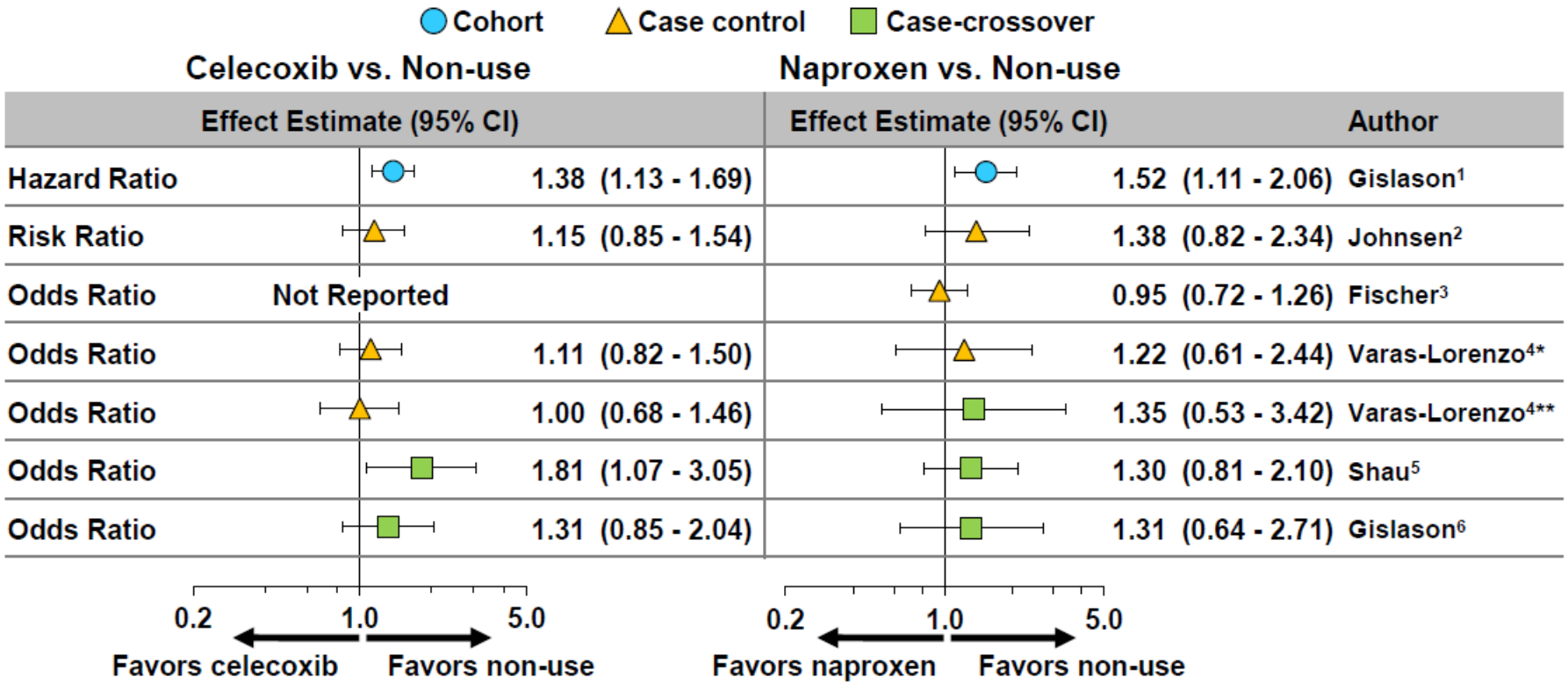
Risk of MI in a Post-MI Population
Individual Observational Studies



[1]Sørensen R et al. J Cardiovas Nurs 2008;23:14-19; [2]Brophy JM et al. Heart 2007;93:189-194; [3]Andersohn F et al. Circulation 2006;113:1950-1957; [4]Gislason G et al. Circulation 2006;113:2906-2913

Risk of MI in a High Baseline CV Risk (Non-MI) Population

Individual Observational Studies



*patients with hypertension; **patients with coronary heart disease

[1]Gislason G et al. Arch Intern Med 2009;169:141-149; [2]Johnsen S et al. Arch Intern Med 2005;165:978-984; [3]Fischer LM et al. Pharmacotherapy 2005;25:503-510; [4]Varas-Lorenzo C et al. Pharmacoepidemiol Drug Saf 2009;18:1016-1025; [5]Shau WY et al. BMC Cardiovascular Disorders 2012;12:1471-2261; [6]Gislason G et al. Arch Intern Med 2009;169:141-149

NSAIDs and Thrombotic CV Event Risk

Specific questions explored in literature review

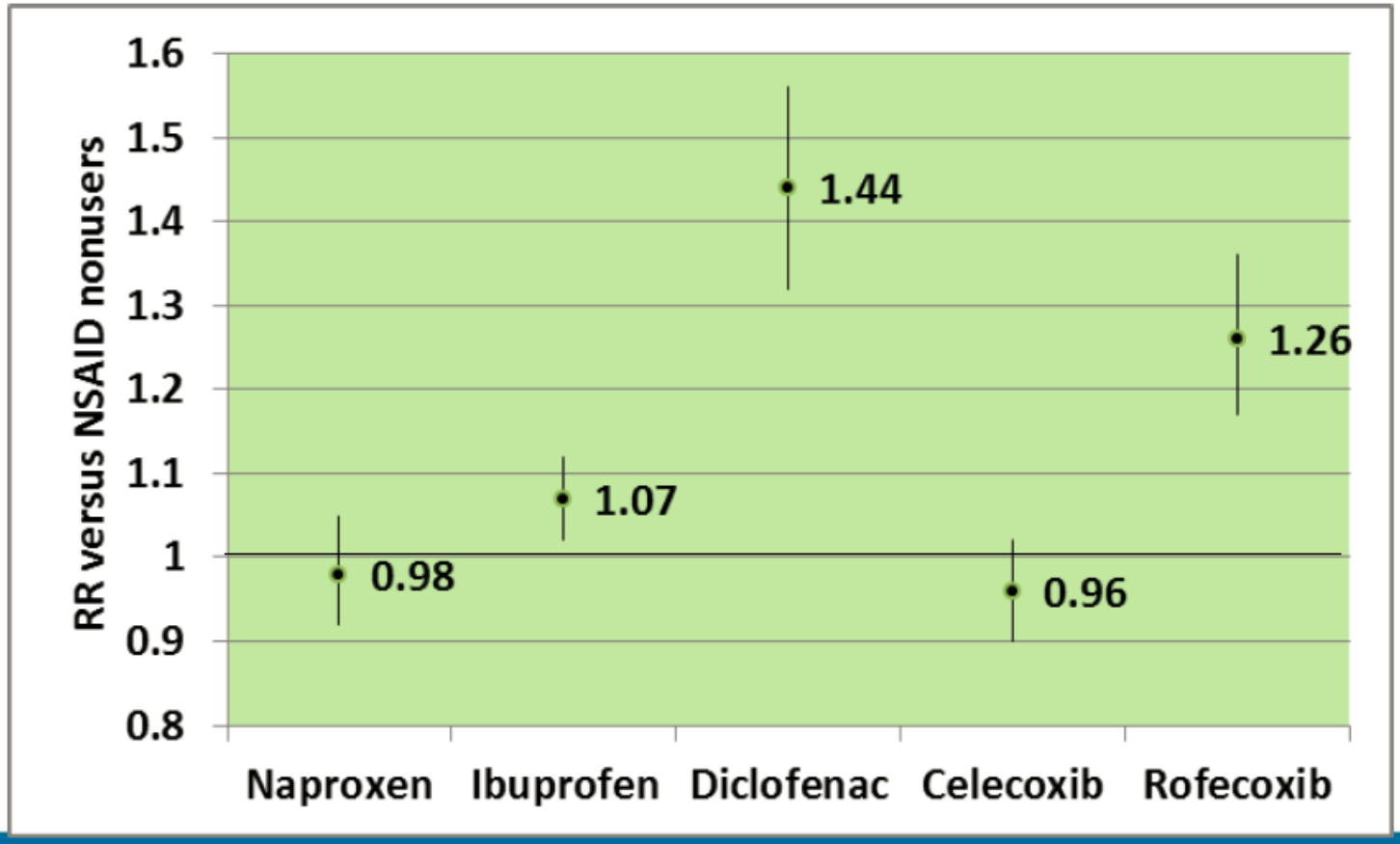
1. Does thrombotic CV risk vary by compound?
2. Is risk present from the start of NSAID treatment?
3. Are there patient subgroups who are more vulnerable to risk?
4. Do higher dosages convey more risk?
5. Is risk observed at nonprescription NSAID dosages?
6. Is NSAID use associated with stroke?
7. What is the effect of concomitant aspirin on thrombotic CV risk?

1. Does thrombotic CV risk vary by compound?

- Findings from epidemiology studies vary
- More data are available on frequently used NSAIDs
- In general, some frequent patterns across studies:
  - Lower thrombotic CV risk estimates: naproxen
  - Higher thrombotic CV risk estimates: diclofenac, rofecoxib
- Risk estimates reflect not only the compound but the doses at which it was used in the study
- Differences in CV risk estimates by compound could reflect use by different types of patients
  - Hence, need to examine datasets where treatment randomized

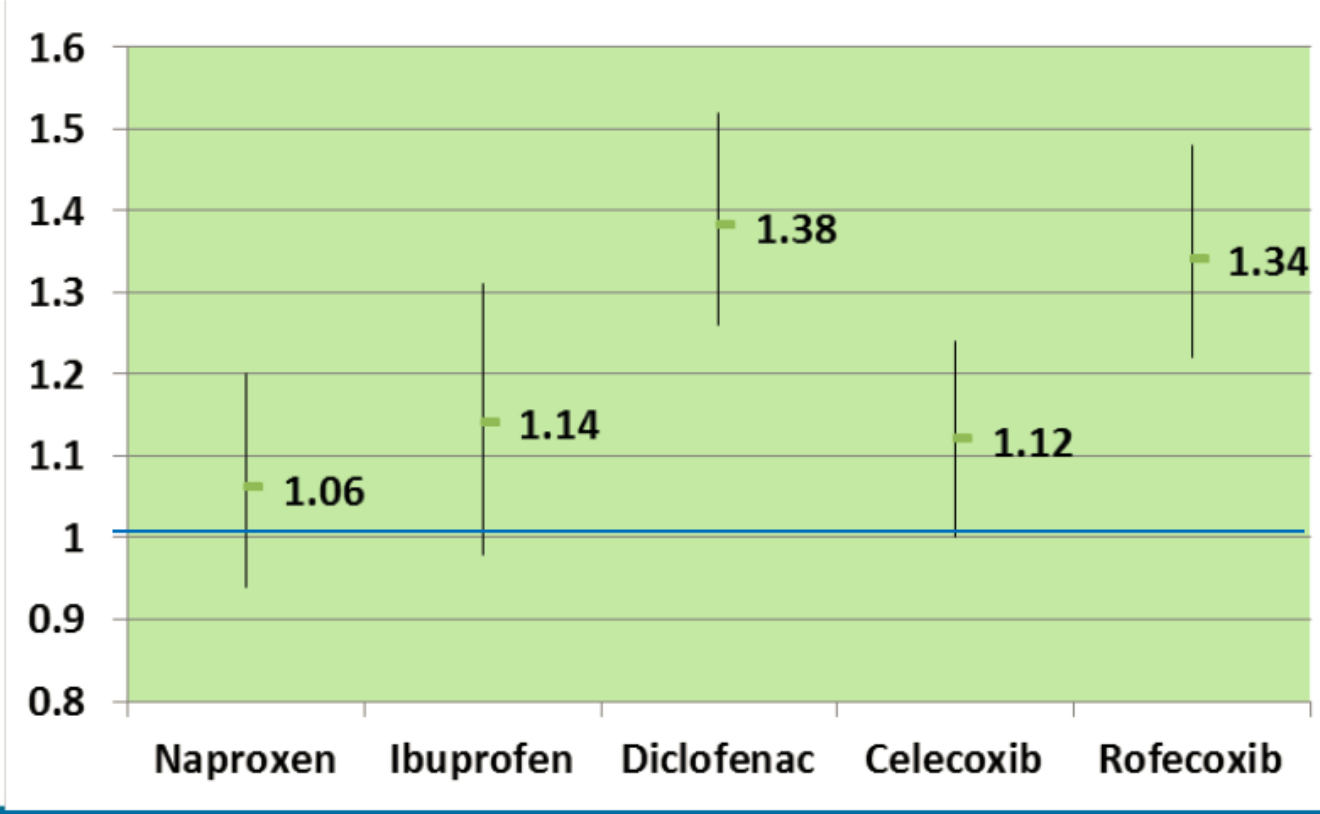
Summary Relative Risk Estimates For Myocardial Infarction (MI) from 16 Observational Studies of NSAIDs

(Hernandez-Diaz et al., Basic Clin. Pharmacol. Toxicol., 2006)



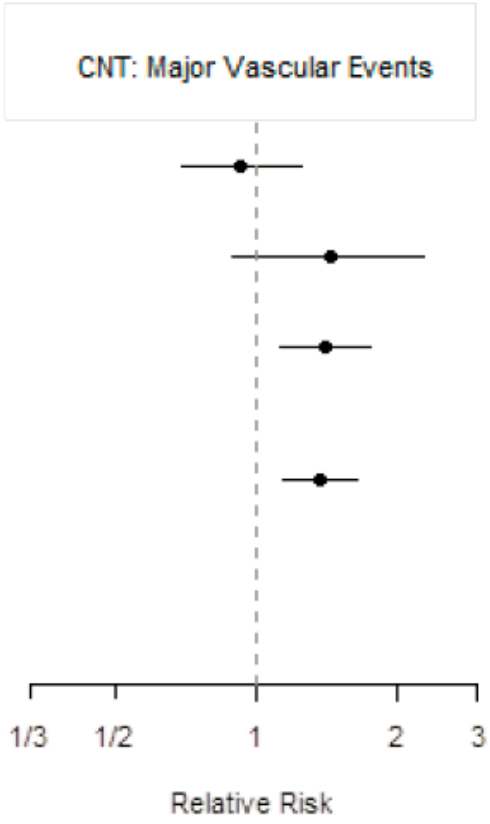
Summary Relative Risk Estimates for MI with Frequently Used NSAIDs: SOS Meta-analysis of 25 Observational Studies

(Varas-Lorenzo et al. Pharmacoepidemiol. Drug Saf. 2013)
(reference: nonusers or remote NSAID users)

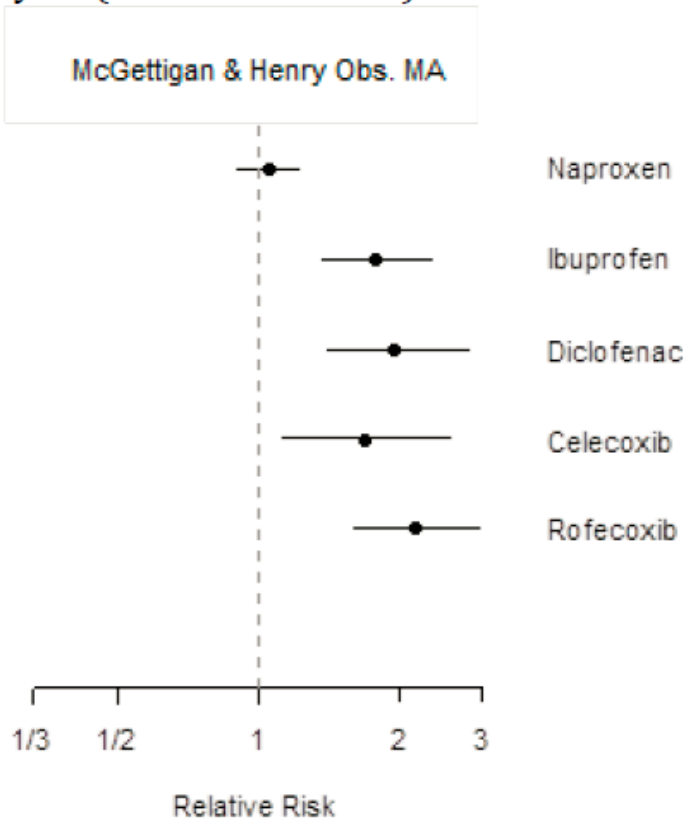


Risk Estimates by Compound for Higher Dose Levels

RR versus placebo, CNT clinical trial meta-analysis (CNT Collaboration, Lancet 2013)



RR for CV events versus nonuse or remote use: observational study meta-analysis (PLoS Med. 2011)



(Graph courtesy of Dr. Mat Soukup, FDA Office of Biostatistics)

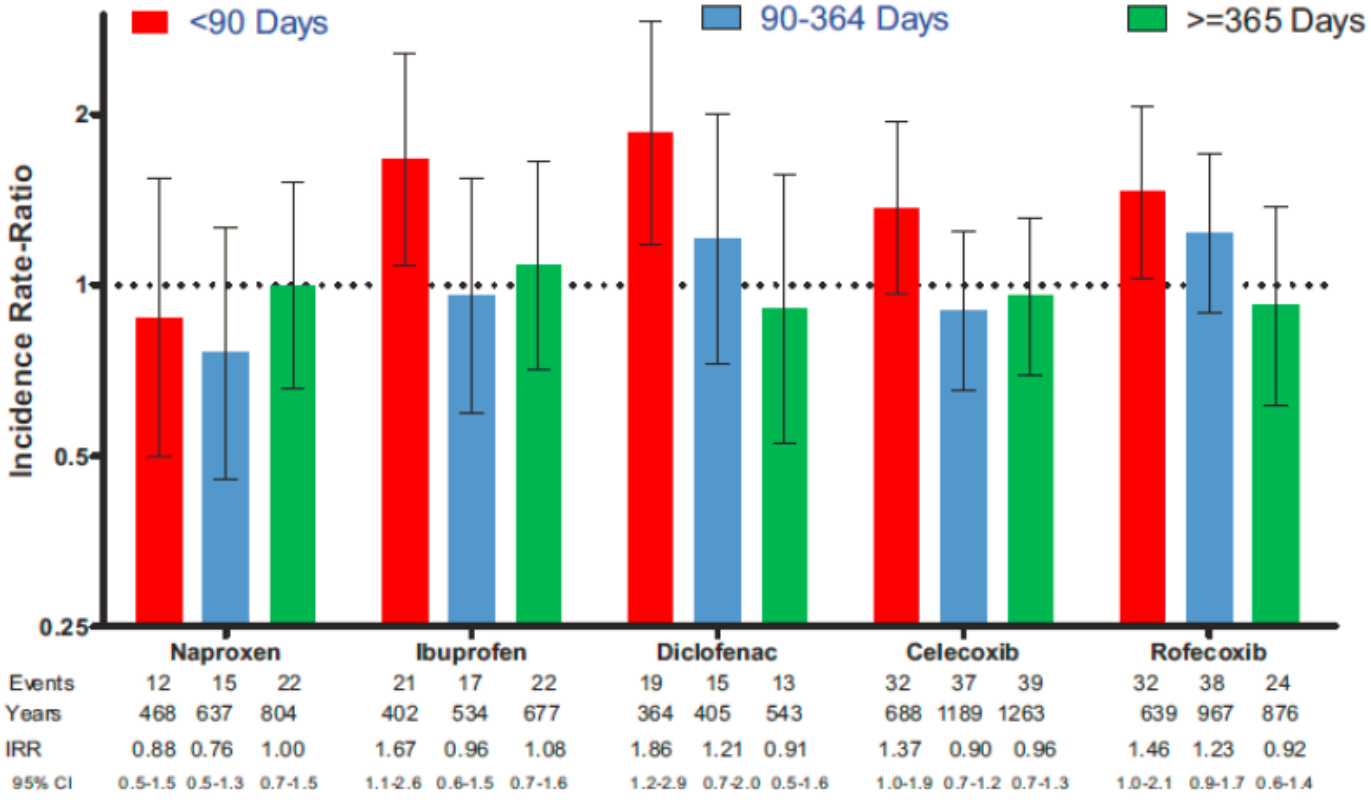
1. Does thrombotic CV risk vary by compound?

- Evaluation is confounded by dose, however:
- Lesser risks generally seen with naproxen

2. Is risk present from the start of NSAID treatment?

- Various time courses for CV risk reported
- Different mechanisms may operate at different times (Grosser et al. 2006)
  - Platelet aggregation, reduced vasodilation→ immediate risk
  - Atherogenesis, vascular remodeling→ long term risk
- McGettigan and Henry (PLoS Med 2011) reported that in their systematic review of NSAID observational studies, 9 out of 12 studies analyzing new users of NSAIDs showed elevated cardiovascular risk in first month
- For comparison, two clinical trials of coxibs given for 10-14 days after coronary artery bypass grafting (CABG) found an increased risk of MI and stroke (see NSAID class labeling)

Multinational Cohort of 48,566 Patients Recently Hospitalized for Myocardial Infarction, Revascularization, or Unstable Angina, Outcome= MI or Coronary Death (Ray et al., 2009)



	Naproxen			Ibuprofen			Diclofenac			Celecoxib			Rofecoxib		
Events	12	15	22	21	17	22	19	15	13	32	37	39	32	38	24
Years	468	637	804	402	534	677	364	405	543	688	1189	1263	639	967	876
IRR	0.88	0.76	1.00	1.67	0.96	1.08	1.86	1.21	0.91	1.37	0.90	0.96	1.46	1.23	0.92
95% CI	0.5-1.5	0.5-1.3	0.7-1.5	1.1-2.6	0.6-1.5	0.7-1.6	1.2-2.9	0.7-2.0	0.5-1.6	1.0-1.9	0.7-1.2	0.7-1.3	1.0-2.1	0.9-1.7	0.6-1.4

Figure. Occurrence of coronary heart disease by total duration of NSAID current use. Reference category is nonuse of any NSAID.

Case-control Study of MI in Finland

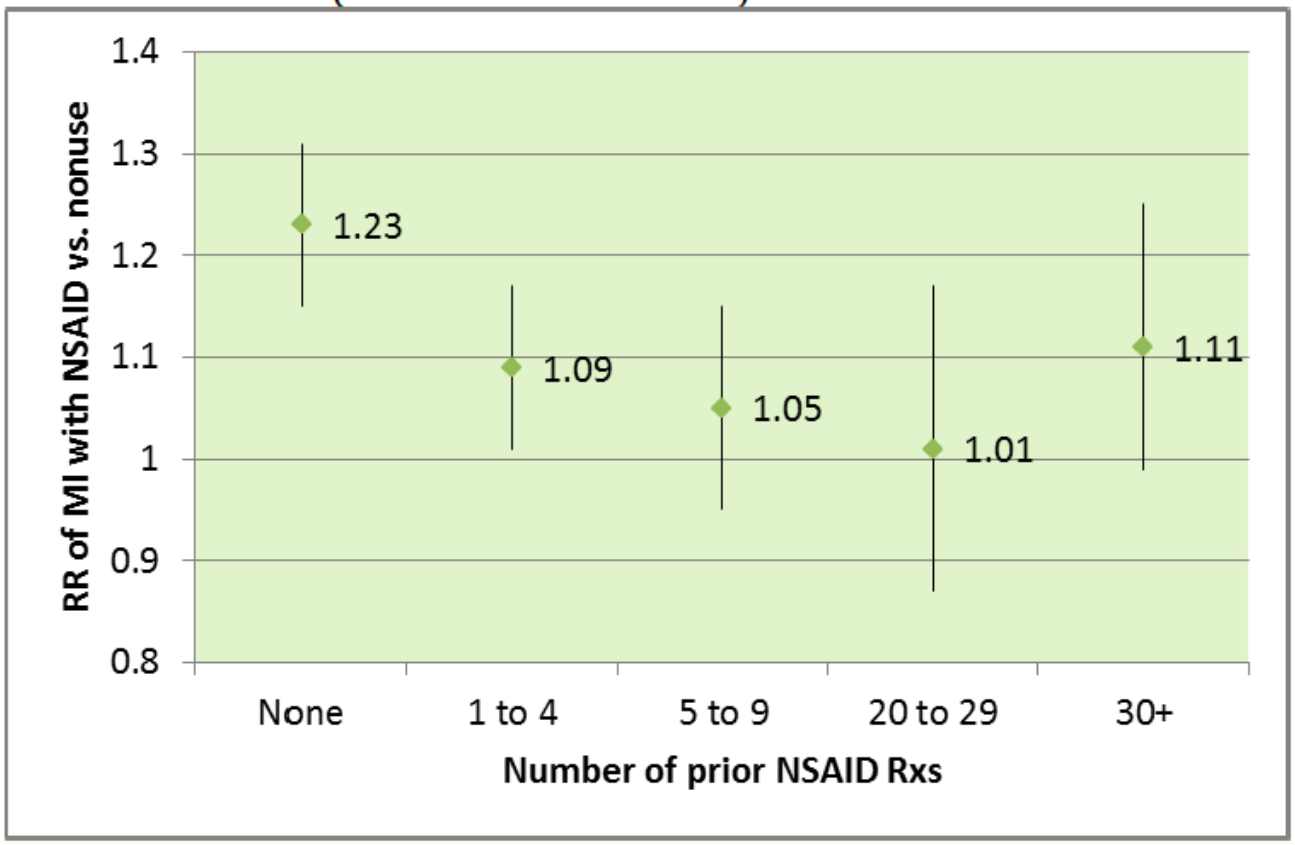
(Helin-Samivaara et al. Eur Heart J 2006)

Table 4 Risk of first time MI among current users of NSAIDs stratified by the duration of continuous therapy (days) in categories

	Cases	Controls	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]
Non-users	20 645	92 524	1.00 (Reference)	1.00 (Reference)
Any NSAIDs				
1–14	542	1 509	1.55 (1.39–1.73)	1.39 (1.23–1.58)
15–30	436	1 344	1.37 (1.22–1.54)	1.22 (1.06–1.40)
31–90	670	1 807	1.43 (1.29–1.58)	1.25 (1.11–1.41)
91–180	631	1 551	1.74 (1.57–1.93)	1.54 (1.36–1.74)

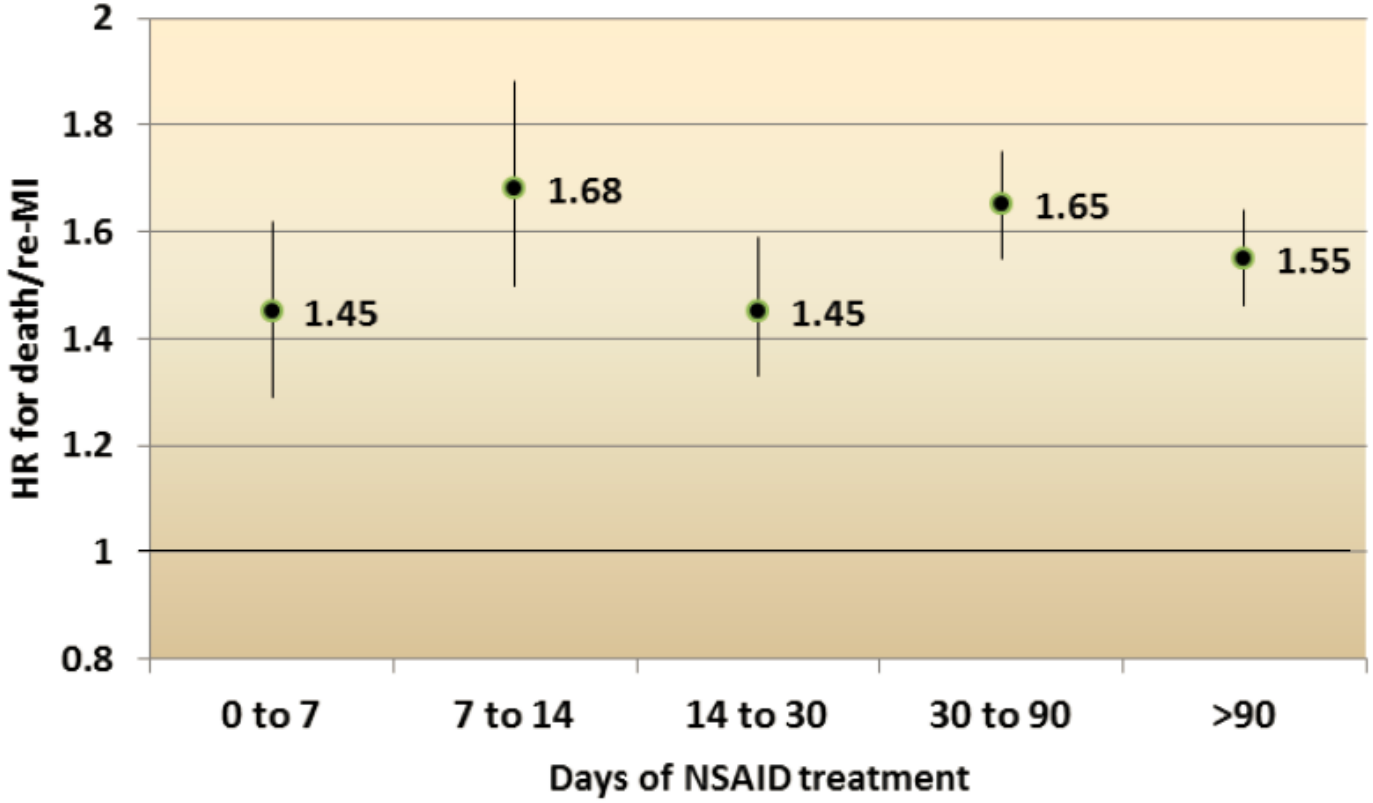
Risk of MI with Traditional NSAIDs by Number of Prior NSAID Rxs, General Practice Research Database

(van Staa et al. 2008)



Risk of Death/Re-MI Associated with NSAID Treatment Population: Danish Post-MI Patients

(Source: Schjerning Olsen et al. Circulation 2011)



2. Is risk present from the start of NSAID treatment?

- Risk is observable from start of NSAID treatment

3. Are there patient subgroups who are more vulnerable to risk?

- Post MI
- Heart failure
- Hypertension
- Other CV risk factors

Example of Similar Relative Risks in Different CV Risk Groups, VA & Medicare Claims Analysis, Outcome = MI

(Abraham et al., Aliment.Pharmacol.Ther. 2007)

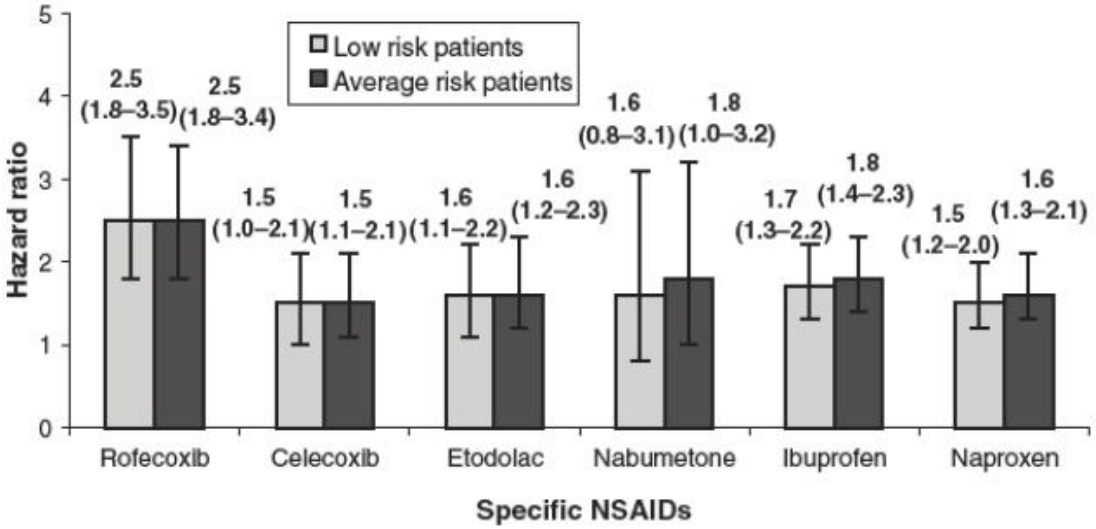
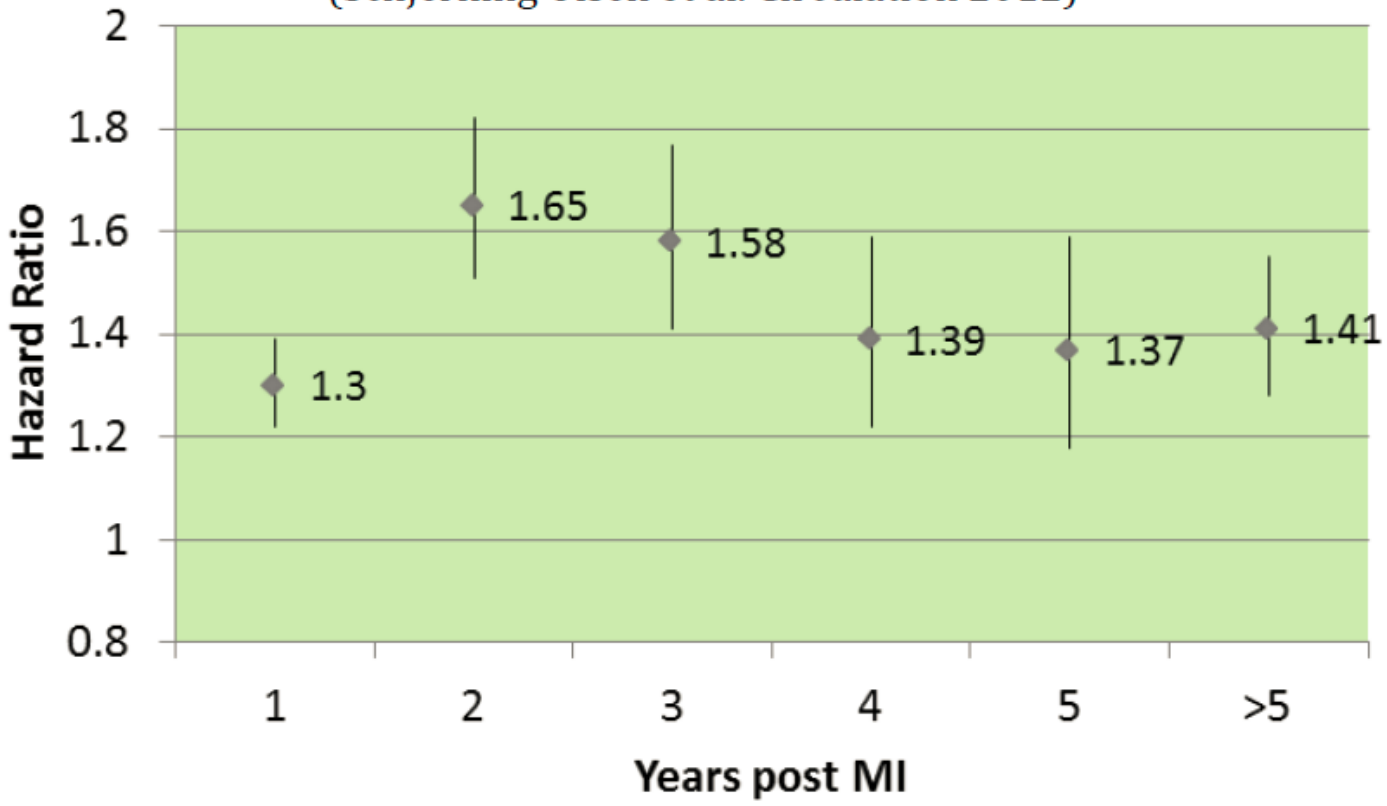


Figure 3. Multivariate analysis examining specific-NSAIDS and risk of MI among average and low-risk patients.
* Where reference category is periods of no NSAID exposure. NSAID, non-steroidal anti-inflammatory drug; and MI, myocardial infarction. Analysis of low-risk patients excludes patients with a history of MI or revascularization procedures, and those with concomitant anticoagulant or anti-platelet agent use.

Coronary Death or MI Hazard Ratios During NSAID Treatment, in Post-MI Patients, by Year After MI, Danish National Health Data

(Schjerning Olsen et al. Circulation 2012)



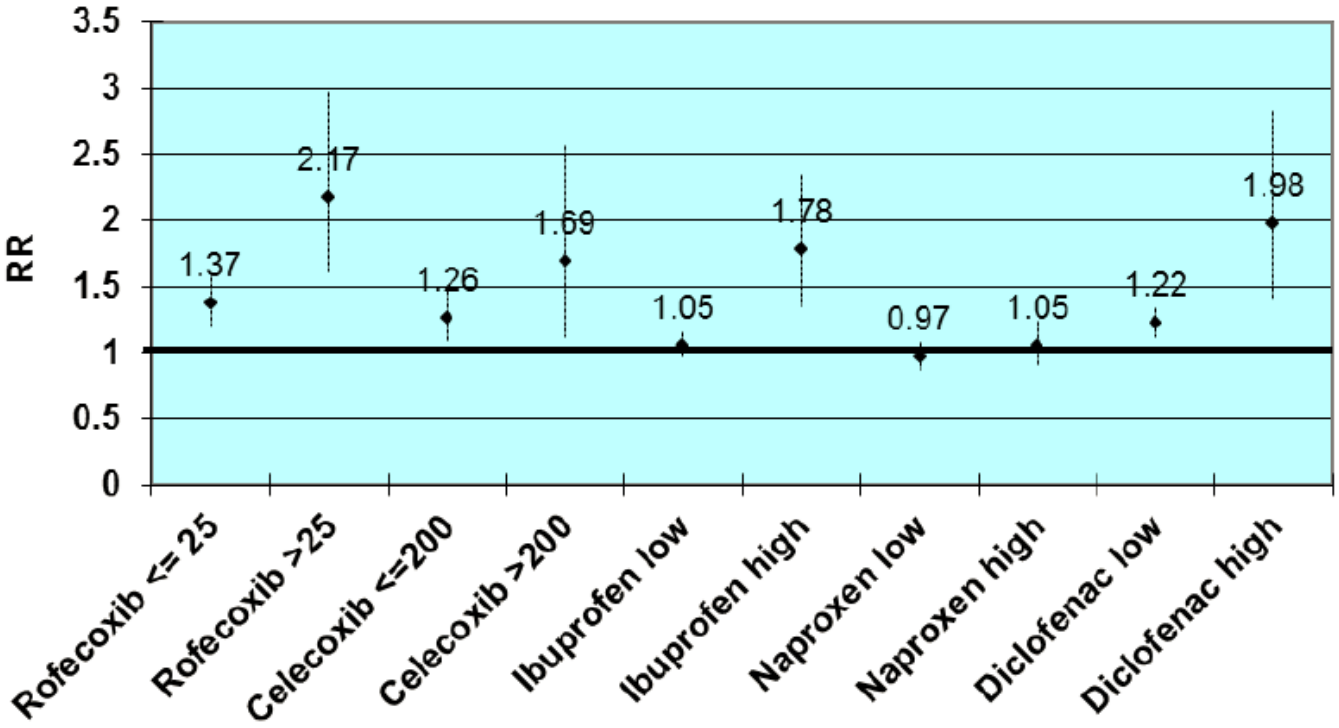
3. Are there patient subgroups who are more vulnerable to risk?

- Vulnerable patients experience more CV events, but CV events are also increased in healthy individuals

4. Do higher dosages convey more risk?

- From 8/2006 to 8/2011, 15 published observational studies analyzed CV risk by NSAID dose
- 12/15 showed evidence of dose-relatedness for CV risk
- Randomized clinical trial meta-analyses have shown CV risk dose dependency for celecoxib
- Hypothesized that naproxen's anti-platelet activity could produce inverse dose response (greater CV risk at lower dose) (CNT, Lancet 2013)
  - No study showing that pattern was identified

Summary relative risk estimates by dose, serious cardiovascular events, observational study meta-analysis
(McGettigan and Henry, PLoS Medicine 2011)



4. Do higher dosages convey more risk?

- Higher dosages are observed to convey greater risk

5. Is risk observed at nonprescription NSAID dosages?

Nonprescription NSAID doses

Ibuprofen ≤ 1200 mg/d

Ketoprofen ≤ 75 mg/d

Naproxen ≤ 660 mg/d

5. Is risk observed at nonprescription NSAID dosages?

- CV risk appears lower at nonprescription doses, but is still observable

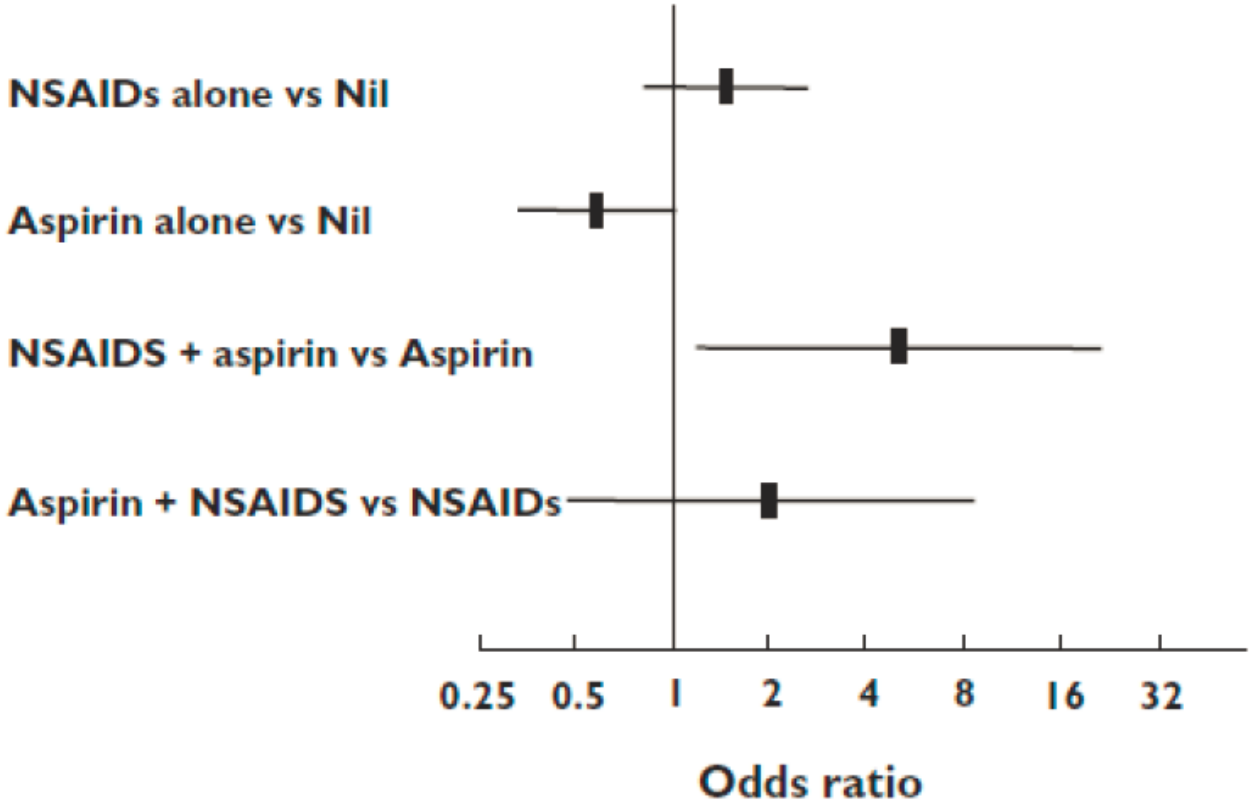
6. Is NSAID use associated with stroke?

- Stroke is associated with NSAID use in observational studies

7. What is the effect of concomitant aspirin on thrombotic CV risk?

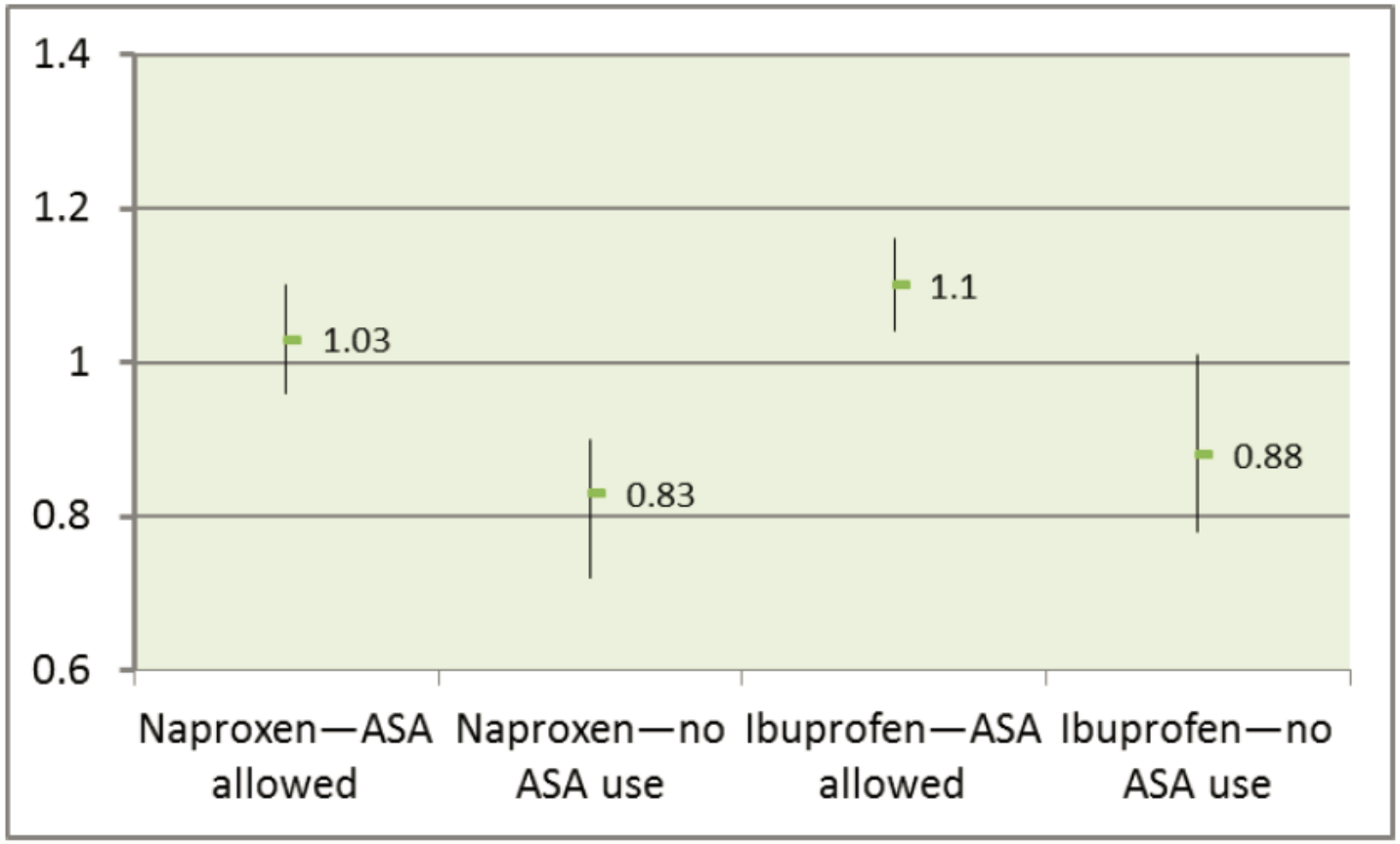
ORs for Nonfatal MI by ASA Use in a Case-control Study

(Source: Figure 2, Hawkey et al., Br J Clin Pharmacol 2006)



Summary MI Relative Risk Estimates from 16 Observational Studies of Nsaids, by ASA Use

(Hernandez-diaz Et Al., Basic Clin.Pharmacol.Toxicol. 2006.)



7. What is the effect of concomitant aspirin on thrombotic CV risk?

- Naproxen and ibuprofen interfere with ASA cardioprotection
- Mixed findings regarding
  - cardioprotective effect of naproxen without ASA
  - ASA amelioration of NSAID-related CV risk

Conclusions
Review of Published Epidemiology Data on NSAID Thrombotic CV Risk (slide 1 of 2)

- Risk by compound
  - Confounded by dose
  - Lesser CV risks generally seen with naproxen
    - Perhaps not for stroke
- Risk can be observed without latency period
- Patient vulnerabilities
  - Absolute risks much higher for vulnerable patients
  - Relative risks may be similar for healthy versus high-risk patients
  - Risk can be seen in apparently healthy population
- Risk appears dose-related

Conclusions (slide 2 of 2)

- Nonprescription doses:
  - Ketoprofen—no data
  - Naproxen & ibuprofen: CV risk appears less at nonprescription doses, but still observable in some studies
- Stroke: associated with NSAID use in observational studies
- Aspirin:
  - Naproxen and ibuprofen can interfere with ASA cardioprotection
  - Mixed findings regarding a cardioprotective effect of naproxen without ASA
  - Mixed findings regarding ASA amelioration of NSAID-related CV risk

Summary - 1

- Non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, either of which can be fatal. There are a large number of studies that support this finding, with varying estimates of how much the risk is increased. Estimates of increased risk range from 10 percent to 50 percent or more, depending on the drugs and the doses studied. This risk may occur as early as the first weeks of treatment and may increase with duration of use.
- Remain alert for the development of cardiovascular adverse events throughout the patient's entire treatment course, even in the absence of previous cardiovascular symptoms.

Summary - 2

- Inform patients to seek medical attention immediately if they experience symptoms of heart attack or stroke such as chest pain, shortness of breath or trouble breathing, sudden weakness or numbness in one part or side of the body, or sudden slurred speech.
- Encourage patients to read the Medication Guide for prescription NSAIDs and the Drug Facts label for over-the-counter (OTC) NSAIDs.
- Based on available data, it is unclear whether the risk for cardiovascular thrombotic events is similar for all non-aspirin NSAIDs.
- The increase in cardiovascular thrombotic risk has been observed most consistently at higher doses.

Summary - 3

- The relative increase in serious cardiovascular thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known cardiovascular disease or risk factors for cardiovascular disease. However, patients with known cardiovascular disease or risk factors had a higher absolute incidence of serious cardiovascular thrombotic events due to their increased baseline rate.
- To minimize the risk for an adverse cardiovascular event in patients treated with an NSAID, prescribe the lowest effective dose for the shortest duration possible.
- Some NSAIDs, including those in OTC products such as ibuprofen and naproxen, can interfere with the antiplatelet action of low dose aspirin used for cardioprotection by blocking aspirin's irreversible COX-1 inhibition.