



Canadian Cardiovascular Society

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Canadian Cardiovascular Society Antiplatelet Guidelines

ASA – NSAID Drug/Drug Interaction

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Objectives

Interpret the Canadian Cardiovascular Society Guideline recommendations regarding the use of antiplatelet therapy in patients taking Non-Steroidal Anti-Inflammatory Drugs.

Recognize how traditional NSAID and Coxibs affect platelet function.

Identify the drug interaction between NSAID and ASA.

Evaluate the evidence regarding the clinical effect of the concomitant use of NSAID and ASA.



George

George, a 64 year old male is in your office complaining of L knee pain of 8 months duration.

History, physical exam and X-rays of the knee indicate a diagnosis of osteoarthritis.

He notes some improvement with the use of OTC ibuprofen.

He has a past history of:

Coronary artery disease,
with NSTEMI 3 years
prior

Hypertension

Hyperlipidemia

GERD

Current medications include:

ASA 81 mg OD

Atenolol 50 mg OD

Ramipril 10 mg OD

Hydrochlorothiazide 12.5 mg OD

Atorvastatin 40 mg OD

Omeprazole 20 mg OD





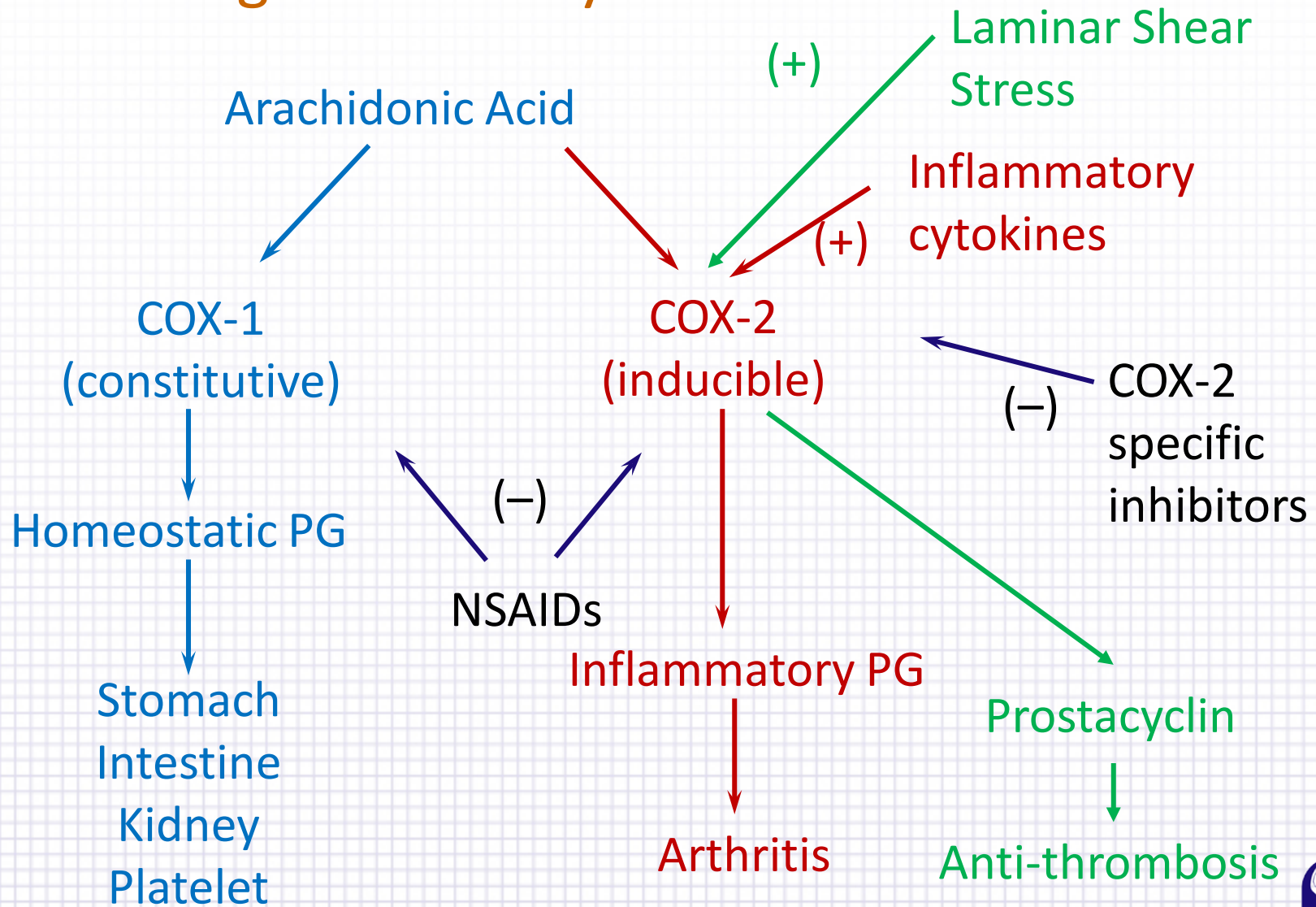
Polling question

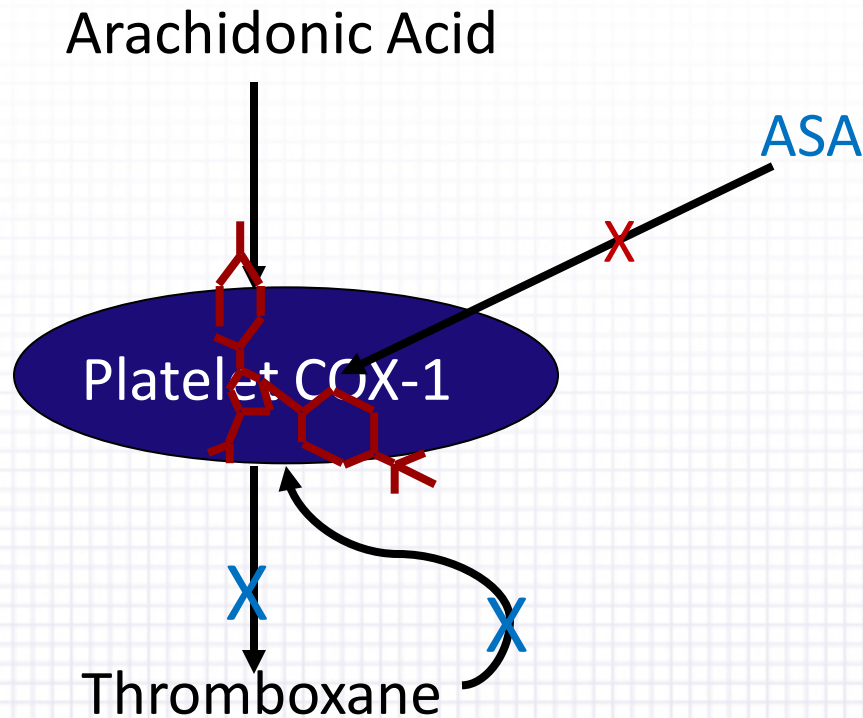
Other than physical measures and intra-articular steroid, how would you manage George's knee OA pain?

- A. Analgesics followed by traditional NSAID if required
- B. Analgesics followed by Coxib if required
- C. Analgesics only. I would avoid the use of traditional NSAID and Coxibs.



Prostaglandin biosynthesis



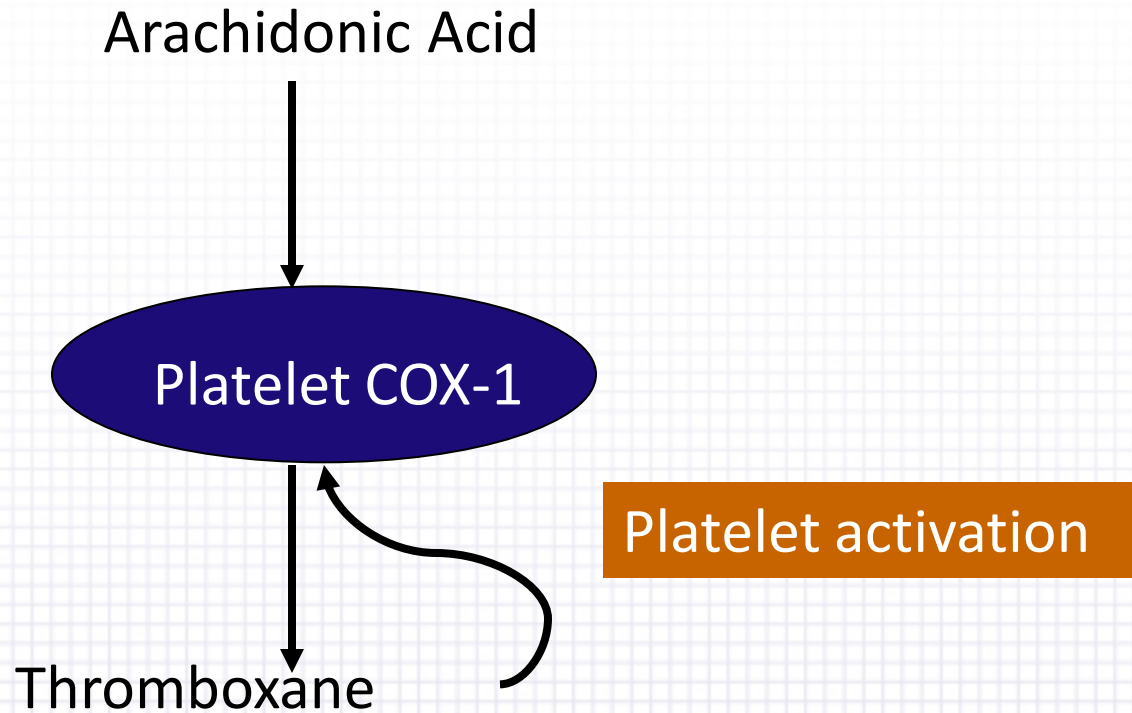


Although it has a short serum half life, ASA forms **permanent** covalent bond to platelet COX-1 halting thromboxane synthesis.

Traditional NSAID

Forms weak **temporary** bond to platelet COX-1 blocking ASA binding



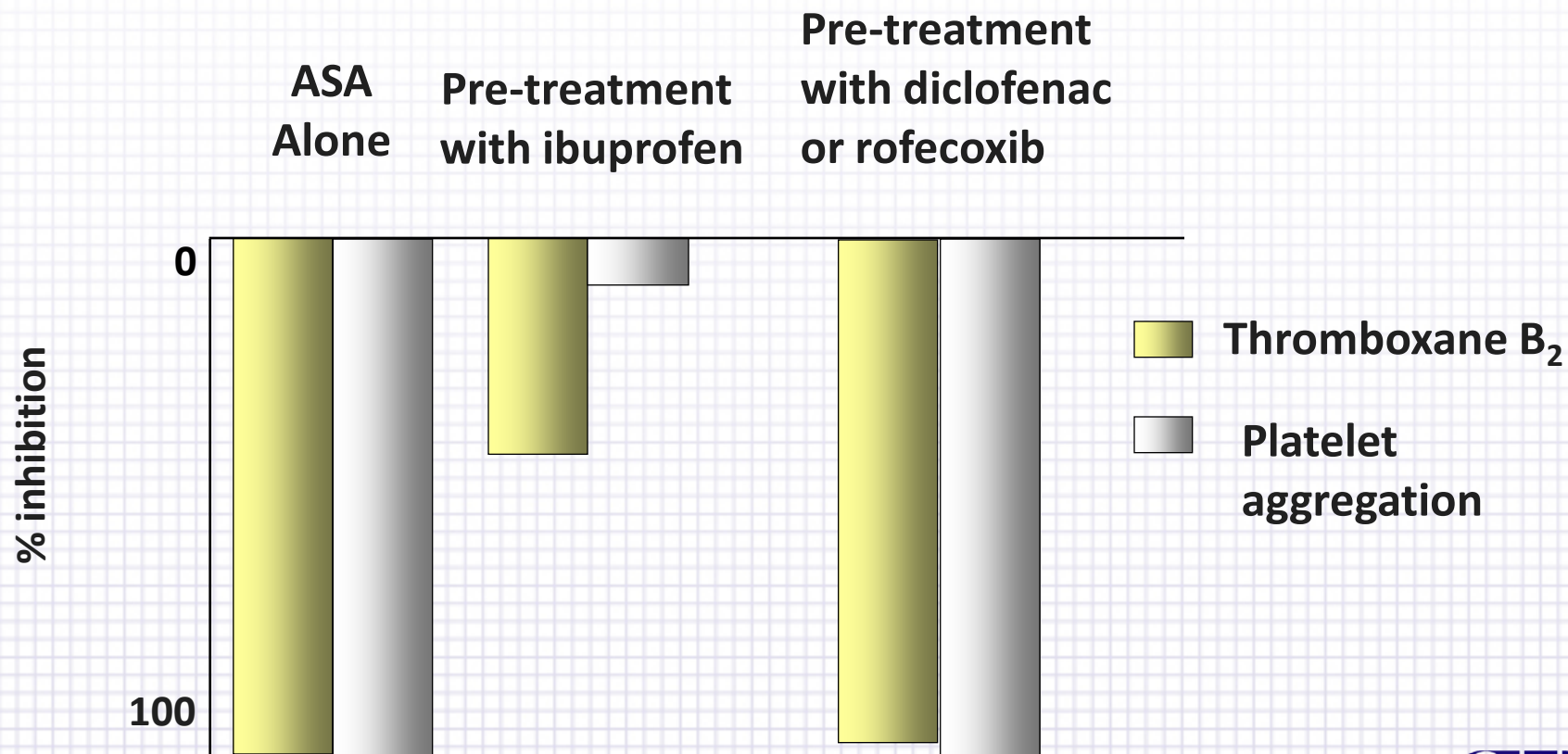


When serum levels of **traditional NSAID** fall, platelet becomes active again.



ASA NSAID platelet interaction

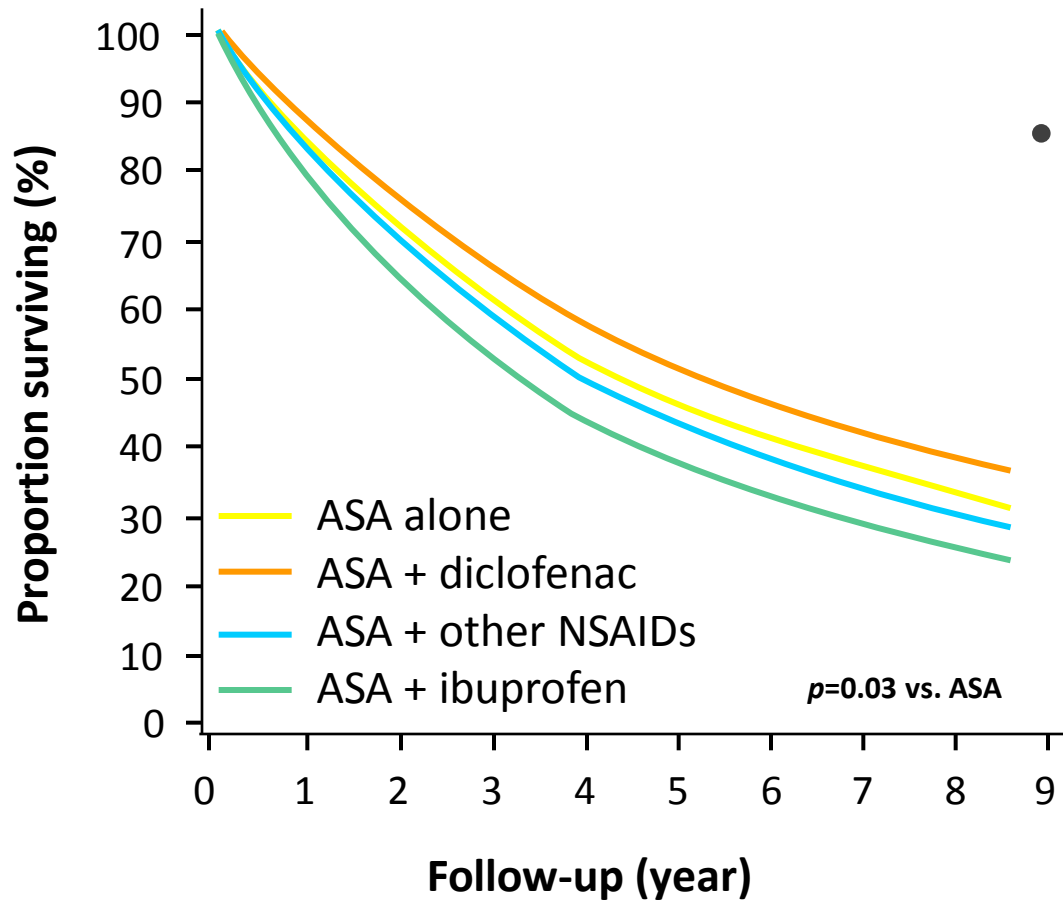
Inhibition of Platelet COX-1 by ASA Measured 24 Hours Post ASA





ASA NSAID Interaction

- Observational study
- n=7,107 post CV event discharge
- Ibuprofen users had a significantly increased risk of CV and all-cause mortality compared to ASA alone





Aspirin, NSAIDs and risk of myocardial infarction

USPHS, n=22,071

Follow up 60 months

Placebo vs ASA 325mg q2d (44% MI reduction)

NSAID use:

None

1-59 days per year

> 60 days per year





MI and NSAID use in ASA users from USPHS

GROUP \ NSAID USE	ASA	PLACEBO
None	1	1
< 59 days	1.18 NS	1.17 NS
≥ 60 days	2.81 P<0.05	0.21 NS





TARGET

Composite cardiovascular outcomes in the ibuprofen sub-study of high-risk patients

Composite cardiovascular outcomes*	Lumiracoxib (%)	Ibuprofen (%)	p
No aspirin	0.92	0.80	NS
Low-dose aspirin	0.25	2.14	0.03
Overall	0.56	1.61	0.05

*Composite end point includes nonfatal and silent MI, stroke, and cardiovascular death .

Total TARGET population n=18,325

High C/V Risk population n=3042

Ibuprofen substudy n=1343

Naproxen substudy n=1699





TARGET

Composite cardiovascular outcomes in the naproxen sub-study of high-risk patients

Composite cardiovascular outcomes*	Lumiracoxib (%)	Naproxen (%)	p
No aspirin	1.57	0	0.02
Low-dose aspirin	1.48	1.58	NS
Overall	1.51	0.95	NS

*Composite end point includes nonfatal and silent MI, stroke, and cardiovascular death .

Total TARGET population	n=18,325
High C/V Risk population	n=3042
Ibuprofen substudy	n=1343
Naproxen substudy	n=1699





Naproxen effect

Like other traditional NSAIDs, naproxen competes with ASA to bind COX-1.

Although it has a stronger antiplatelet effect than other NSAID it remains a reversible inhibitor.

Clinical benefit of naproxen in prevention of CV events is not established.

May be the best choice if a traditional NSAID is absolutely needed.



Do Coxibs interfere with ASA cardioprotection?

A new cyclooxygenase-2 inhibitor, rofecoxib (VIOXX), did not alter the antiplatelet effects of low-dose aspirin in healthy volunteers.

[J Clin Pharmacol. 2000] PMID: 11185674

Celecoxib, ibuprofen, and the antiplatelet effect of aspirin in patients with osteoarthritis and ischemic heart disease.

[Clin Pharmacol Ther. 2006] PMID: 16952493

The COX-2 selective inhibitor, valdecoxib, does not impair platelet function in the elderly: results of a randomized, controlled trial.

[J Clin Pharmacol. 2003] PMID: 12751271

Lumiracoxib does not affect the ex vivo antiplatelet aggregation activity of low-dose aspirin in healthy subjects.

[J Clin Pharmacol. 2005] PMID: 16172182

Celecoxib does not affect the antiplatelet activity of aspirin in healthy volunteers. [J Clin Pharmacol. 2002]



Risk estimate for hospitalization for MI for NSAID Users compared with non-users

Case control study of 10,280 MI events

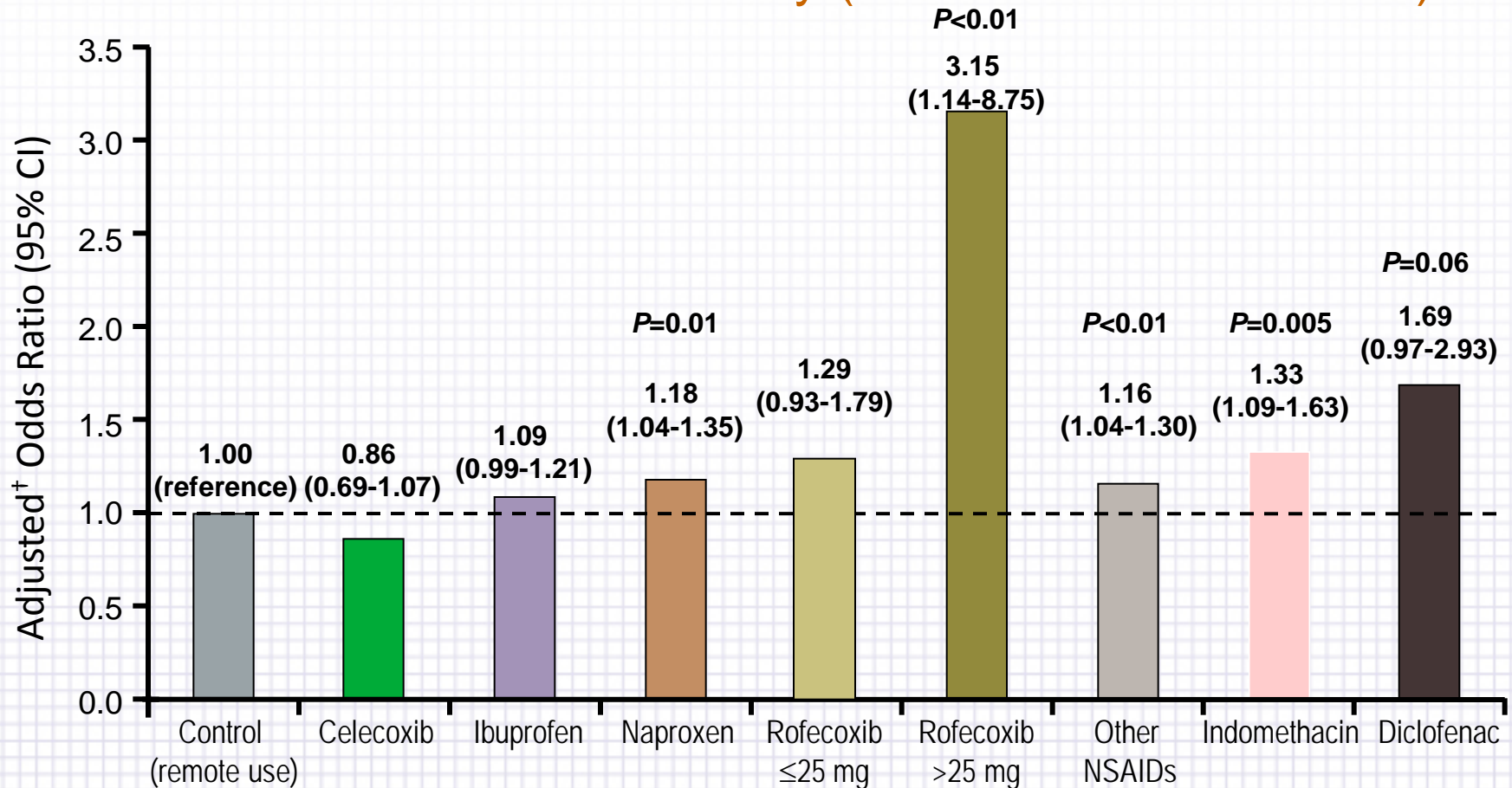
Drug	Adjusted Relative Risk	95% CI
Rofecoxib	1.80	1.47-2.21
Celecoxib	1.25	0.97-1.62
COX-2 “selective” agents*	1.45	1.09-1.93
Naproxen	1.50	0.99-2.29
Other NSAIDs	1.68	1.52-1.85
High-dose ASA	1.34	1.18-1.52

***Etodolac, meloxicam, nabumatone**



Risk of AMI and SCD with current use of COX-2 selective and NS-NSAIDs

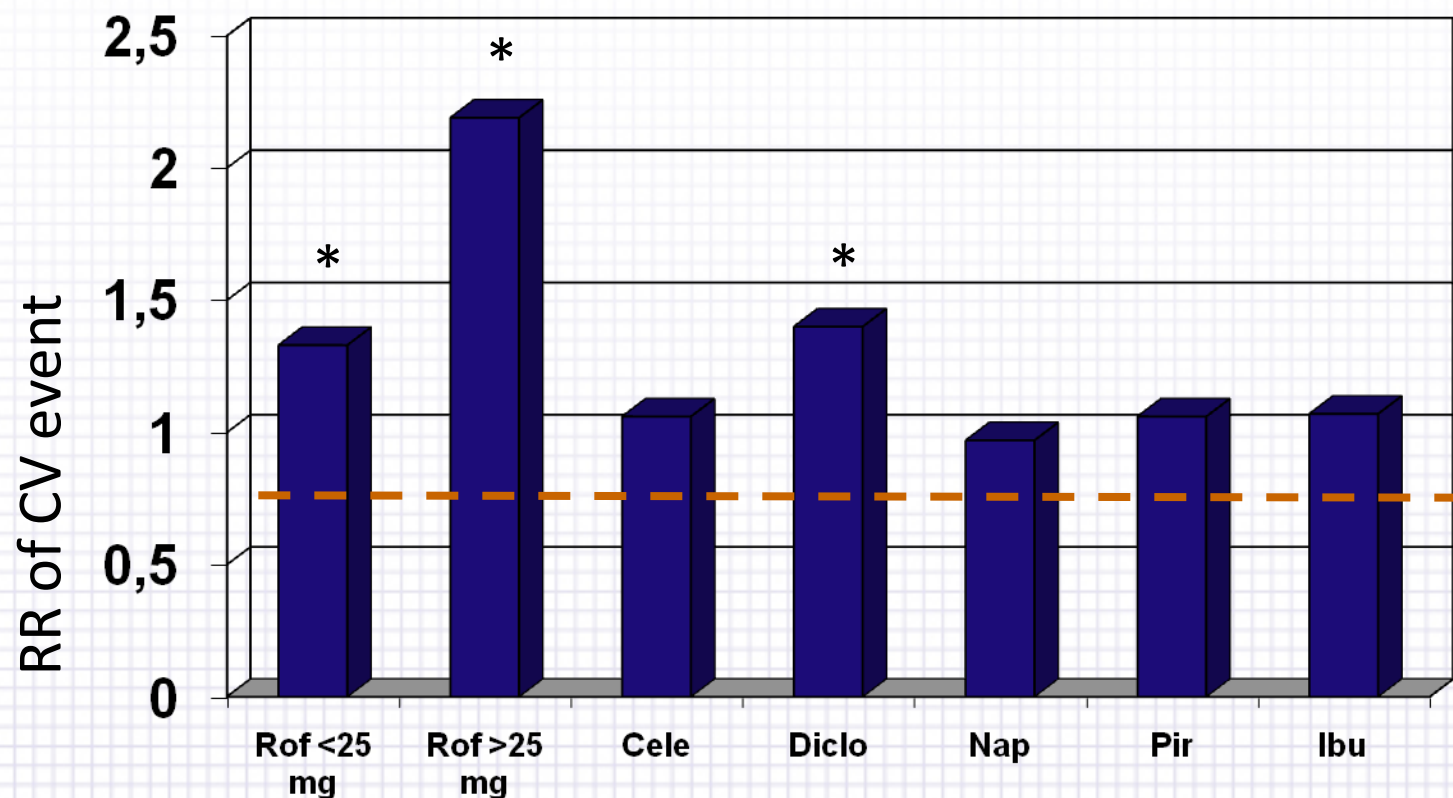
Case-control observational study (1.4 m from Kaiser data)



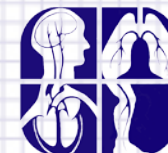
†Adjusted for age, gender, health plan region, medical history, smoking, and medication use.



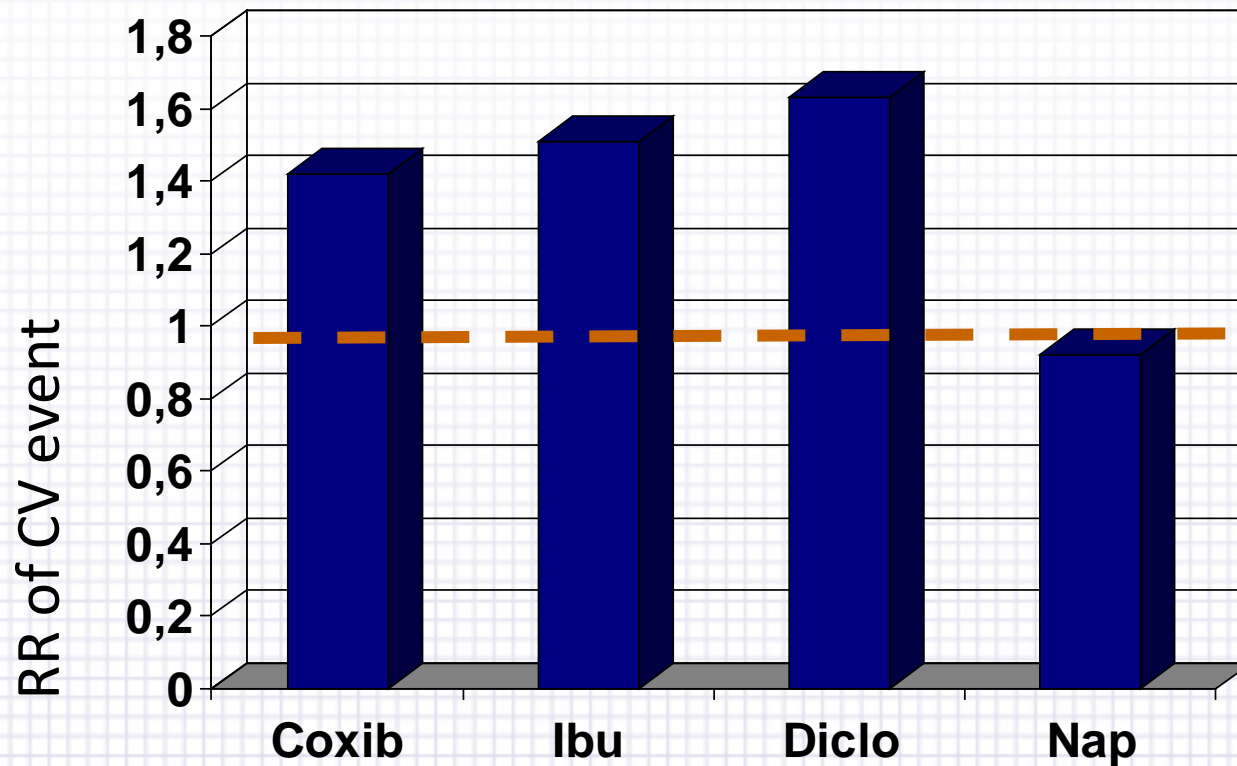
Systematic review of observational studies



* $p < 0.05$



Meta analysis of randomized controlled trials of CV events in NSAID users



George

The patient is advised to avoid the use of OTC ibuprofen due to the well established adverse drug interaction with ASA.

He is advised to use acetaminophen in doses up to 2 – 4 grams/day.

If acetaminophen fails other interventions should be attempted including:

- Physiotherapy

- Intra-articular steroid

- Surgery

- Higher potency analgesics

If these fail or are inappropriate, a coxib may be tried with monitoring of BP, renal function and hemoglobin.





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Interaction between Acetylsalicylic Acid and Nonsteroidal Anti-inflammatory Drugs

RECOMMENDATIONS

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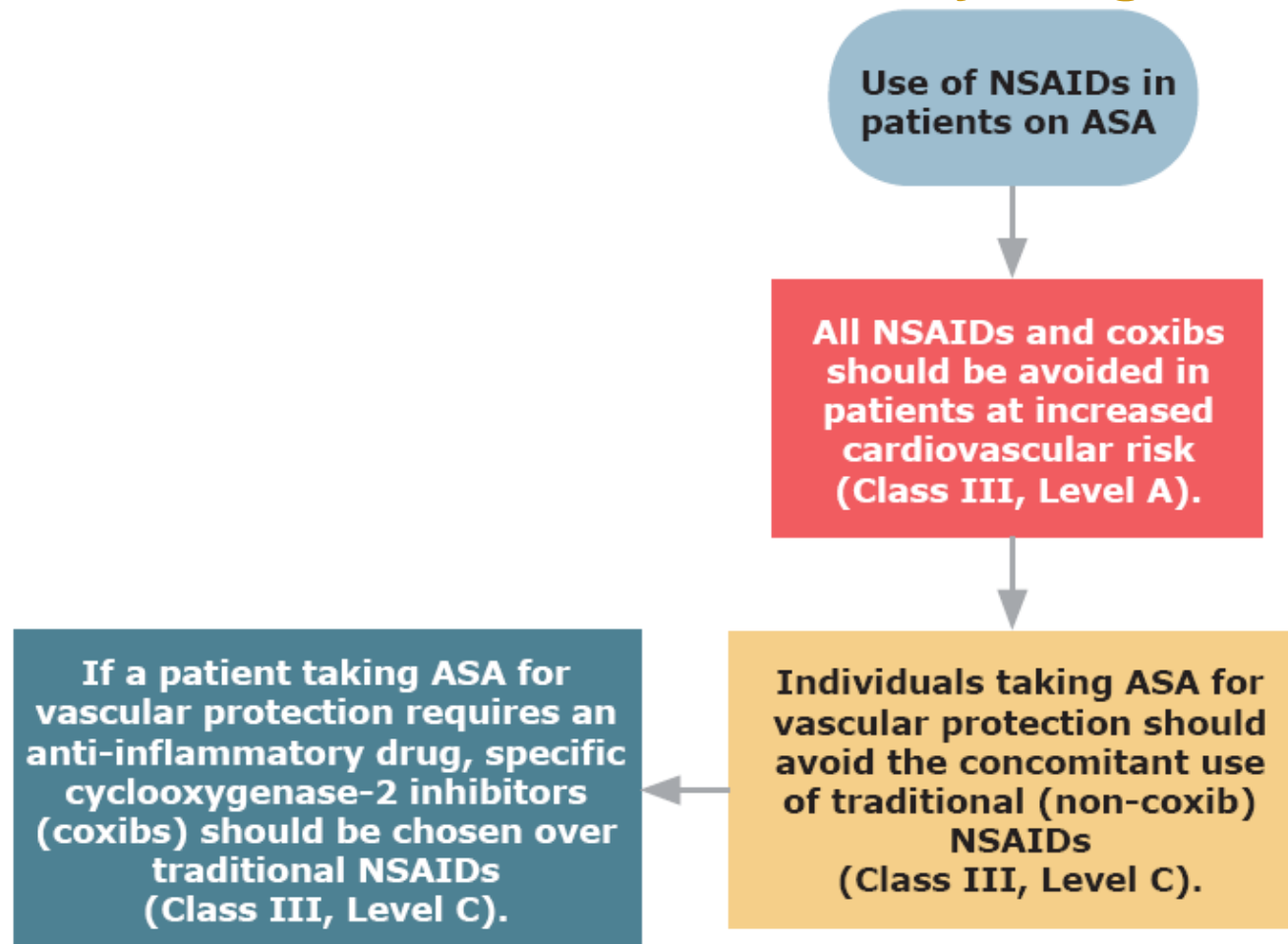


Interaction between acetylsalicylic acid and nonsteroidal anti-inflammatory drugs

1. Individuals taking low-dose ASA (75-162 mg daily) for vascular protection should avoid the concomitant use of traditional (non-coxib) NSAIDs (Class III, Level C).
2. If a patient taking low-dose ASA (75-162 mg daily) for vascular protection requires an anti-inflammatory drug, specific cyclooxygenase-2 inhibitors (coxibs) should be chosen over traditional NSAIDS (Class IIb, Level C).
3. Both coxib and traditional NSAIDs increase cardiovascular risk and if possible, should be avoided in patients at risk of ischemic vascular events (Class III, Level A).



Interaction between acetylsalicylic acid and nonsteroidal anti-inflammatory drugs



What if...

**GEORGE HAS A CONTRAINDICATION FOR
COXIBS, BUT NEEDS AN NSAID?**



“What if”

If a traditional NSAID is required, some evidence suggests that naproxen may be the best choice due to its more potent antiplatelet effect.

It should be used in combination with gastroprotection either a PPI or misoprostol.

Blood pressure, hemoglobin and renal function should be monitored.



