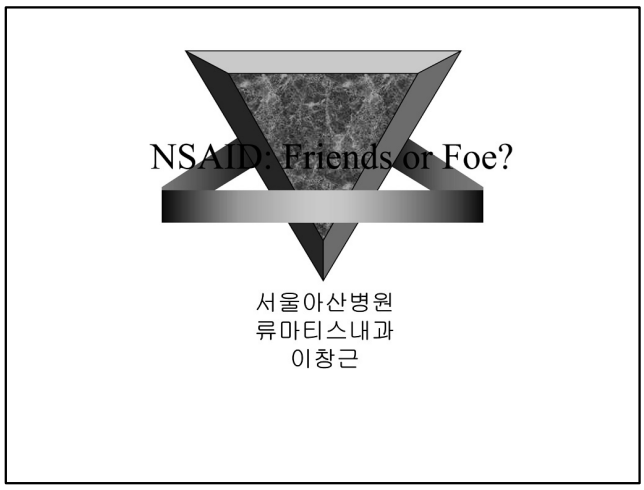
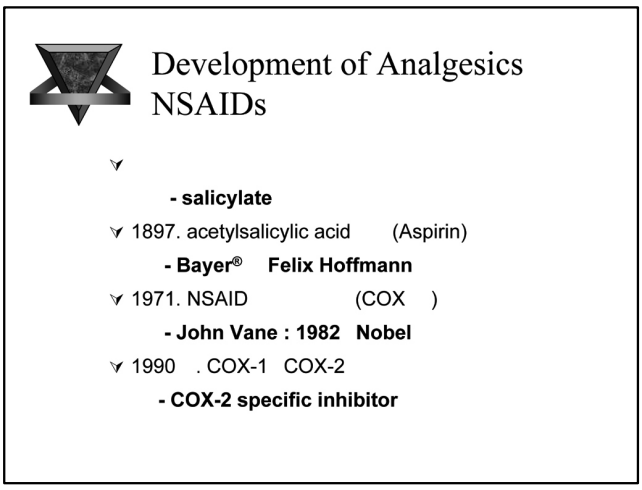
[연수강좌]

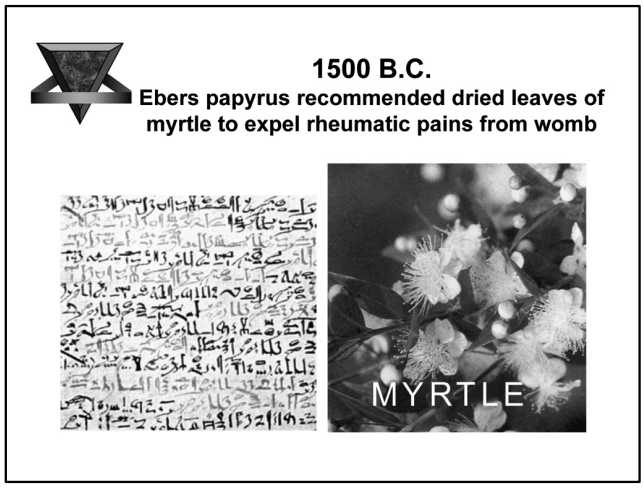
NSAID 어떻게 처방할 것인가?

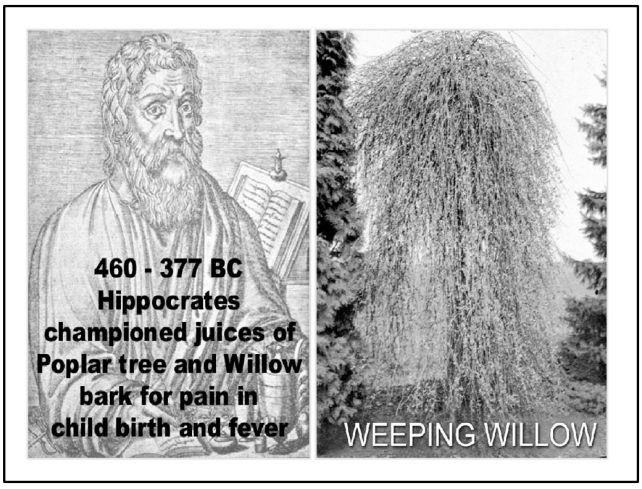
이 창 근

서울아산병원 류마티스 내과

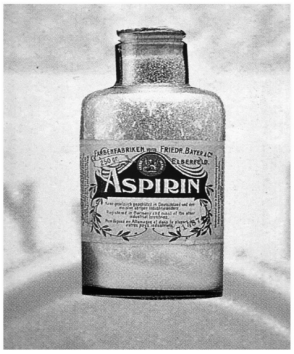




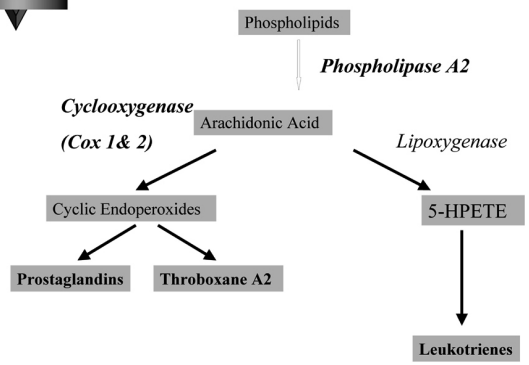




Aspirin was registered and marketed in March 1899



Cyclooxygenase/prostaglandin pathway



The Nonsteroidal Antinflammatory Drugs

NSAID	Trade name	Usual dose
Carboxylic acids		
Aspirin(acetylsalicylic acid)	Multiple	2.4-6 g/24h in 4-5 divided doses
Buffered aspirin	Multiple	Same
Enteric-coated salicylates	Multiple	Same
Salsalate	Disalcid	1.5-3.0 g/24h BID
Diflunisal	Dolobid	0.5-1.5 g/24h BID
Choline magnesium Trisalicylate	Trilisate	1.5-3 g124h BID-TID
Proprionice acids (ends in Profen, proxen)		
Ibuprofen	Motrin, Rufen, OTC	OTO :200-400 mg QID Rx: 400-800 mg; max 3200 mg/24h
Naproxen; Enteric	Naprosyn, Anaprox OTC:Alleve	250,375,500 mg BID; 225 mg BID
Fenoprofen	Nalfon	300-600 mg QID
Ketoprofen	Orudis; Oruvail	75 mg TID; q day 100 mg BID-TID
Flurbiprofen	Ansaid	
Oxaprozin	Daypro	600 mg; 2 tabs per day

The Nonsteroidal Antinflammatory Drugs

NSAID	Trade name	Usual dose
Acetic Acid Derivatives		
Indomethacin	Indocin, Indocin SR	25,50mg TID-QID SR: 75mg BID rarely >150 mg/24h
Tolmetin	Tolectin	400, 600, 800 mg; 800 to 2400 mg/24h
Sulindac	Clinoril	150, 200mg BID; some increase to TID
Diclofenac (plus misoprostol)	Voltaren; Cataflam; (Arthrotec)	50, 75mg BID (50 mg BID)
Etodolac	Lodine	200,300 mg BID-QID
Ketoralac	Toradol, only IV NSAID	
Fenamates		
Meclofenamate	Meclomen	50-100 mg TID-QID
Mefenamic acid	Ponstel	250 mg QID
Enolic acids		
Piroxicam	Feldene	10,20 mg q day
Pheny lbutazone	Butazolidin	100mg TID up to 600 mg/24h
Napthylkanones		
Nabumetone	Relafen	500mg BID up to 1500 mg/24h

Actions of aspirin-like drugs

Anti-inflammatory

Anti-pyretic

Analgesic

Side effects: **ulcerogenic**

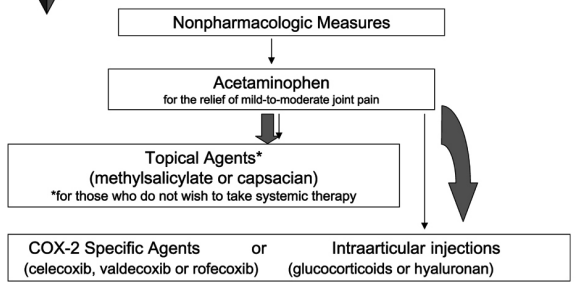
nephrotoxic

prolongs birth process

Adverse Events With Conventional NSAIDs

Frequency	Adverse Event
1. >10%	· Dyspepsia
2. 1-10%	· Gastric Bleeding/Ulcer
3. <1%	· Renal Insuffic · CNS-Confusion · Pulmonary · Hepatic · Hematologic · Rash

ACR Osteoarthritis Guidelines



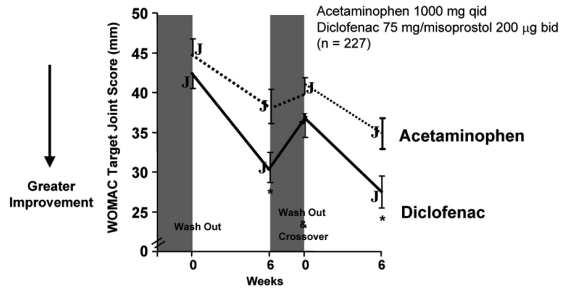
ACR Subcommittee on OA Guidelines. *Arthritis Rheum* 2000; 43: 1905-1915

Acetamiophen vs NSAID

- NSAID/coxib are generally more effective and preferred by patients
- Acetamniophen: 4 g daily (response 20-30%)
- The lowest effective oral dose should be used

Efficacy in OA

NSAIDs are an important treatment option



J: joint evaluation Scores

Pincus *et al*. Arthritis Rheum. 2001;44:1587-98.

GI Safety Issues

GI Adverse Effects Associated with Conventional NSAIDs

Upper GI Intolerance
- Dyspepsia : 5-50% → 5-15% DC NSAID
- Nausea
- Abdominal pain

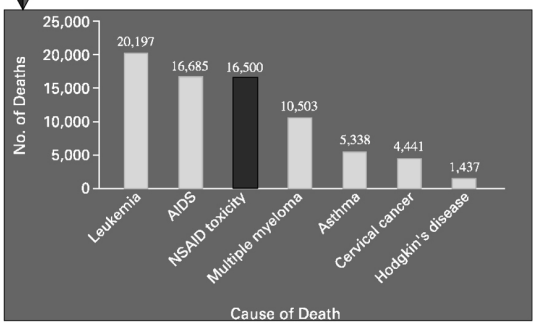
Asymptomatic Ulcers

Symptomatic Ulcers

Ulcer Complications: 1.3%
- Perforation
- Gastric outlet obstruction
- Bleeding

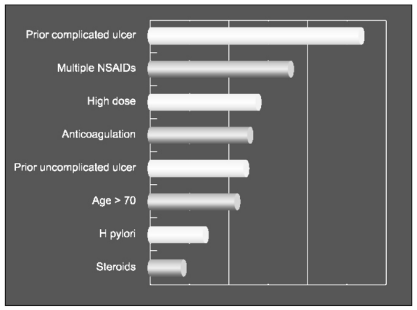
} **Mortality = 5-10%**

US Mortality Data



Singh *et al*. J Rheumatol 1999

NSAID Ulcer Complications: Risk Factors



Gabriel. Ann Intern Med 1991, Garcia Rodriguez. Lancet 1994, Silverstein. Ann Intern Med 1995

Risk factors for NSAID-induced gastroduodenal ulceration

Established	Possible
Advanced age	Concomitant infection with *H. pylori*
History of ulcer	Cigarette smoking
Concomitant use of steroid	Alcohol consumption
High-dose NSAIDs	
Multiple NSAIDs	
Concomitant use of anticoagulant	
Serious or multisystem disease	

Sleisenger & Fordtran's. 7th ed. 2002:408-430

Peptic Ulcer and Use of Oral Corticosteroids

Current oral corticosteroid use	Case Patients n (%)	Controls	RR (95%CI)
NSAID users			
< pd 10mg/d	6 (0.9)	6 (0.4)	2.4 (0.8-7.7)
≥ pd 10mg/d	13 (1.9)	4 (0.2)	7.4 (2.4-22.9)
None	660 (97.2)	1563 (99.4)	
Nonusers of NSAIDs			
< pd 10mg/d	5 (0.7)	25 (0.5)	1.2 (0.5-3.3)
≥ pd 10mg/d	5 (0.7)	27 (0.5)	0.9 (0.3-2.4)
None	726 (98.6)	5438 (99.0)	

Piper JM et al, Ann Intern Med 1991;114:735

Low Dose Aspirin is Safe ?

Daily aspirin use for >= one month	OR (95% CI)
Any dose	3.2 (2.3-4.4)
75 mg	2.3 (1.2-4.4)
105 mg	3.2 (1.7-6.5)
300 mg	3.9 (2.5-6.3)

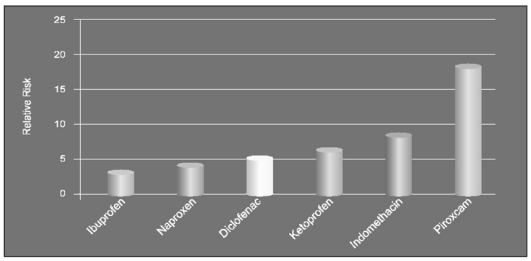
Weil J et al, BMJ 1995;310:827

GI Bleeding by Anticoagulant & NSAID Use

	Person-Years	No. of Events	Adjusted Incidence	RR (95% CI)
NSAID nonuser				
Oral anticoagulant nonuser	132556	277	2.1	1.0
Noncurrent oral anticoagulant user	607	2	2.4	1.2 (0.3-4.6)
Current oral anticoagulant user	1386	16	8.9	4.3 (2.6-7.2)
Current NSAID user				
Oral anticoagulant nonuser	26630	220	8.3	**4.0 (3.4-4.8)**
Noncurrent oral anticoagulant user	176	2	9.5	4.5 (1.2-18.4)
Current oral anticoagulant user	261	8	26.3	**12.7 (6.3-25.7)**

Shorr RI et al, Arch Intern Med 1993;153:1663

Risk of Bleeding Ulcer Associated with Individual NSAIDs



McCarthy DM, Am J Med 1998;107(6A):37S

Type of NSAID and Ulcers

Risk group	Drug	Relative Risk
Low	Ibuprofen	2.0 (1.4-2.8)
	Diclofenac	4.2 (4.2-6.8)
Medium	Naproxen	9.1 (5.5-15.1)
	Indomethacin	11.3 (6.3-20.3)
	Piroxicam	13.7 (7.1-26.3)
High	Ketoprofen	23.7 (7.6-74.2)
	Azapropazone	31.5 (10.3-96.9)

Sleisenger & Fordtran's. 7th ed. 2002:408-430

NSAID Ulcers and Ulcer Complications

- Endoscopic Ulcer point prevalence: 10-30%
- Ulcer Complications: 1-2% per year
- Most (>80%) Hospitalizations for GI Bleed occur without previous symptoms
- Inhibition of Prostaglandin Synthesis is principal Mechanism for GI damage
- Use of Antacids or H_2RA do not prevent NSAID induced Gastric Ulcers

Singh G. Am J Gastroenterol 1998;105:31S, Geis GS. J Rheumatol 1991;18:11-14

Healing of NSAID-induced Ulcer

- NSAID-induced Ulcer is slow to heal.
- Rate of Relapse/Rebleeding is high.
- Differential Diagnosis with Gastric Cancer is sometimes difficult.

Treatment of NSAID related GI Symptoms

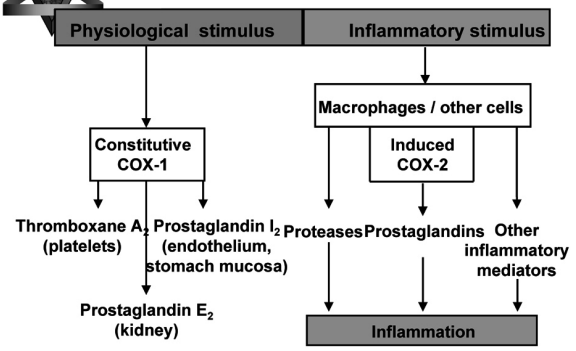
- Dyspesia :
  Empirical Tx with
  - H_2RA : 400 mg of cimetidine, 150 mg of ranitined or nizatidine, or 20 mg of famotidine, all twice daily
  - PPI : 20 mg of omeprazole, 30 mg of lansoprazole, 20 mg of rabeprazole, or 40 mg of pantoprazole
  - individualize therapy

Treatment of NSAID related GI Symptoms

- *H. pylori* infection :
  Treatment to eradicate infection only in pt with history of peptic ulcer
- Peptic ulcer :
  NSAID discontinued – H2RA or PPI
  NSAID continued –PPI
- Prophylactic therapy:
  concomitant treatement with misoprostol (≥200 ug tid), PPI, Cox-2 specific inhibitor

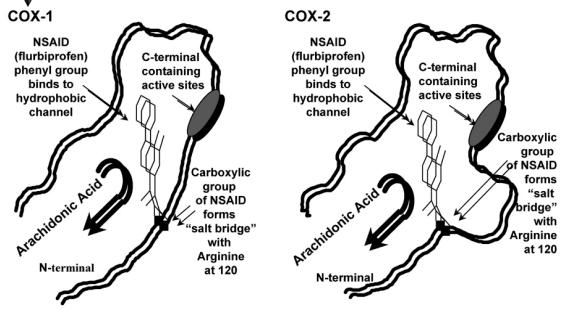
Why COX-2 Selective Inhibitor?

Actions of COX-1 and COX-2



Classical NSAID: Non-specific binding to COX-1 and COX-2

Terminal Carboxylic Acid Plays an Important Role

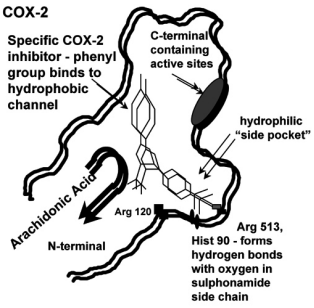


Kurumbail et al, Nature 1996; 384: 644-648

2006-05-16

Specific COX-2 Inhibitor Binding to COX-2

Exploitation of the Side-Pocket



Kurumbail et al, Nature 1996; 384: 644-648

2006-05-16

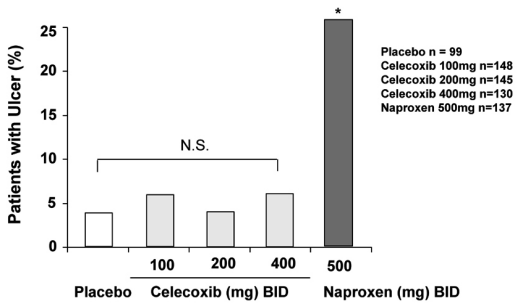
Classification of NSAID

Cox-1 preferential		Equipotent	Cox-2 preferential	Cox-2 specific
aspirin	diclofenac	nabumeton	meloxicam	celecoxib
ibuprofen	idomethacin	etodolac	nimesulide	rofecoxib
ketoprofen	piroxicam	tenoxicam		
naproxen	sulindac	fenclofenac		

Clinical Effects of Cox-2 specific inhibitors

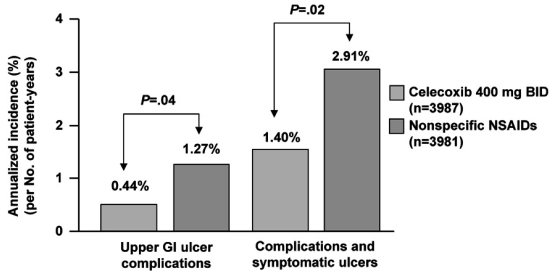
Similar to non-specific Cox inhibitors	**Different** from non-specific Cox-inhibitors
Anti-inflammatory	No anti-platelet effects
Analgesic	Reduced endoscopic GI erosion and ulceration
Anti-pyretic	renal effect e.g) possibly less alteration of GFR and RBF
renal effect e.g) sodium excretion, blood pressure	

Incidence of Gastroduodenal Ulcers Not Significantly Different From Placebo Even at 2X Maximum Therapeutic Dose



Simon LS, JAMA 1999;24:1921-1927

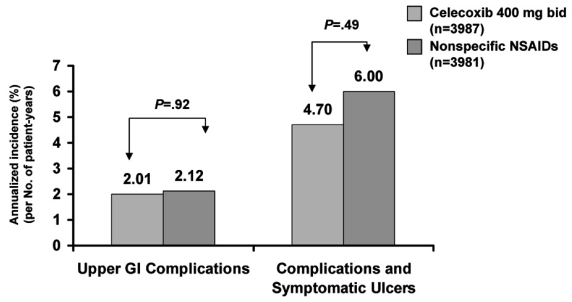
CLASS: Ulcer Complications and Symptomatic Ulcers at 6 Months—Nonusers of ASA



Serious GI toxicity such as bleeding, ulceration, and perforation can occur with or without warning symptoms in patients treated with NSAIDs. These GI events occur in approximately 1% of patients treated for 3-6 months and in 2% to 4% of patients treated for 1 year.

Silverstein FE et al. *JAMA*. 2000;284:1247-1255.

CLASS: Ulcer Complications and Symptomatic Ulcers at 6 Months – ASA Users



Silverstein FE et al. *JAMA*. 2000;284:1247-1255.

GI Safety Issues

- In patients with risk for perforation, ulcer, and bleeding, a coxib is still the NSAID of choice, depending on the patient's CV risks
- NSAID + PPI : alternative

CV Safety Issues

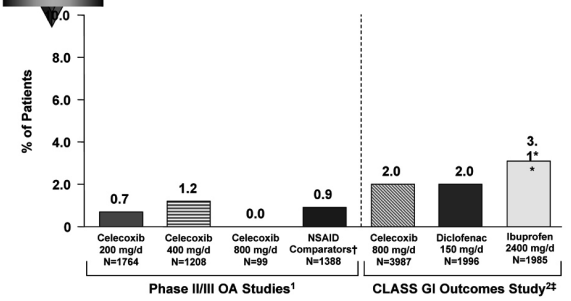
Hypertension

- In patients receiving antihypertensive drugs, remeasure BP within a few weeks after initiating NSAID or coxib
- If the introduction of the drug is associated with a rise in BP, the dose of the NSAID/coxib and/or the antihypertensive drug must be modified.
- NSAID/coxib antagonize the effect of ACE inhibitors, ARB and beta-adrenergic blockers
- Calcium channel blocker appear to be least influenced by NSAID/coxib

Hypertension

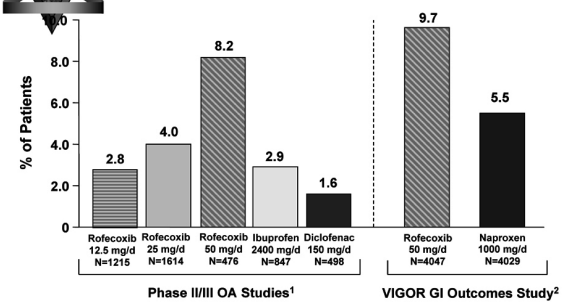
- The effect on systolic BP (3-7 mm Hg) is more pronounced than on diastolic BP (1-3 mmHg)
- 716% of patients exposed to coxib in RCT

Incidence of hypertension in celecoxib trials*



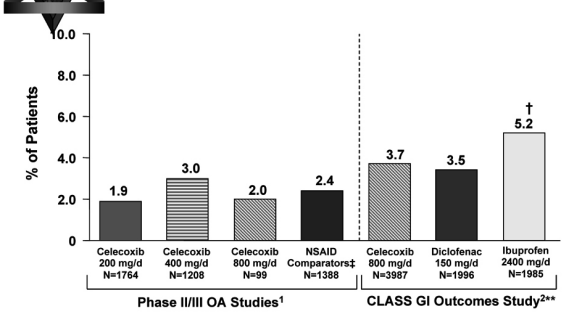
**P≤0.05 vs celecoxib.
*Investigator reported; †naproxen, diclofenac; ‡data from entire study period.
1. Summary basis for approval, FDA.
2. FDA Arthritis Advisory Committee Meeting. February 7, 2001. Gaithersburg, Maryland.

Incidence of hypertension in rofecoxib trials*



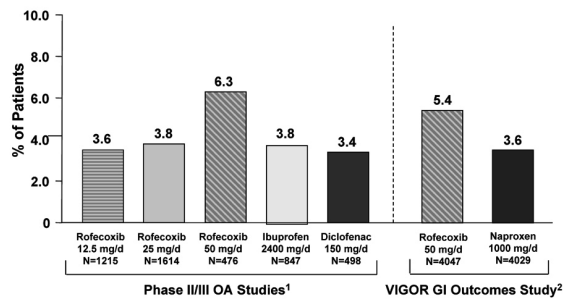
*Investigator reported
1. Summary basis for approval, FDA.
2. FDA Arthritis Advisory Committee Meeting. February 8, 2001. Gaithersburg, Maryland.

Incidence of peripheral edema in celecoxib trials*



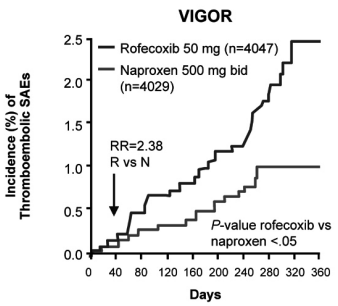
*Peripheral edema includes both upper and lower extremity edema (investigator reported).
†P<0.05 vs celecoxib; ‡naproxen, diclofenac; **data from entire study period.
1. Summary basis for approval, FDA.
2. FDA Arthritis Advisory Committee Meeting. February 7, 2001. Gaithersburg, Maryland.

Incidence of lower-extremity edema in rofecoxib trials*



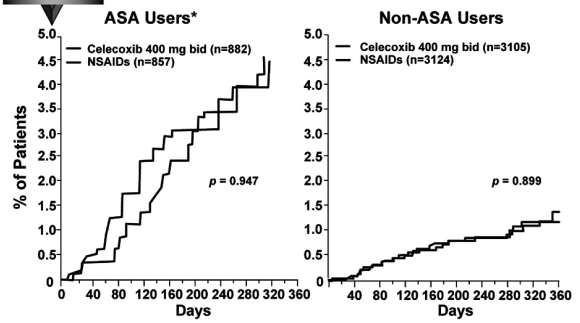
*Investigator reported.
1. Summary basis for approval, FDA.
2. FDA Arthritis Advisory Committee Meeting. February 8, 2001. Gaithersburg, Maryland.

Serious Thromboembolic Cardiovascular Adverse Events in Non-ASA Users



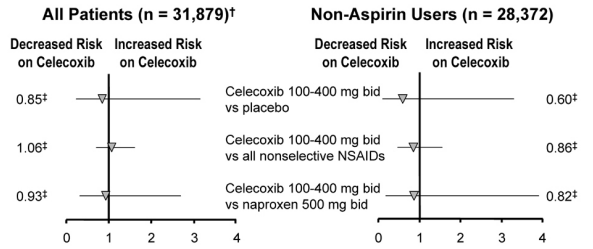
SAEs=serious adverse effects.
Mukherjee D et al. *JAMA*. 2001: 286: 954-959.

Thromboembolic Cardiovascular Adverse Events: CLASS



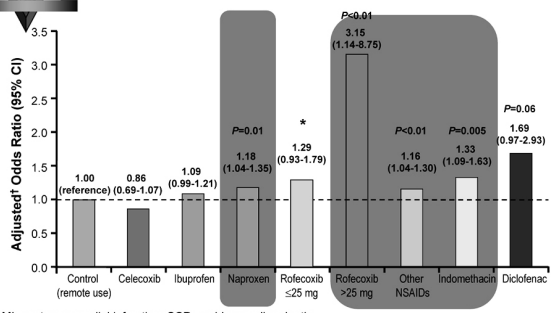
White et al. *Am J Cardiol.* 2002;89:425-430
*Data on file. Pfizer Inc., New York, NY.

Risk of Cardiovascular Events* for Celecoxib Relative to NSAIDs, Naproxen, and Placebo in Patients With Arthritis



*CV events = combined incidence of CV, hemorrhagic, and unknown death; nonfatal MI; nonfatal stroke;
†Aspirin users presumed to have increased CV risk; ‡*P* = NS.
Triangles represent relative risk; bars indicate 95% CI.
White WB et al. *Am J Cardiol.* 2003;92:411-418; Data on file, Pfizer Inc., New York, NY.

Risk of AMI and SCD With Current Use of COX-2 Selective and NS-NSAIDs



AMI=acute myocardial infarction; SCD=sudden cardiac death.
**P*=0.04 compared with celecoxib.
†Adjusted for age, gender, health plan region, medical history, smoking, and medication use.
Adapted from Graham et al. *Lancet.* 2005;365:475-81.

September 30, 2004: APPROVe Trial Halted Rofecoxib Withdrawn From Market

- Rofecoxib was voluntarily withdrawn from the US market due to findings that there were two times the risk of heart attack and an increased risk of stroke compared to patients taking placebo
- The increased risk was evident in those who had been on rofecoxib for longer than 18 months
- The trial was stopped early because of the increased risk of heart attack and stroke at the recommendation of the Data Safety Monitoring Board
- The study was a three year clinical trial in patients at risk for developing recurrent polyps in the colon and rectum to show that rofecoxib 25 mg/d helped prevent recurrence

APPROVe=Adenomatous Polyp Prevention on VIOXX.
Merck press release. September 30, 2004; Bresalier et al. *N Engl J Med.* 2005;352.

Celecoxib Studies in Patients with Adenomatous Polyps: Cardiovascular Events

- On December 17, 2004 new information was released about the cardiovascular safety of celecoxib based on an analysis of two long-term cancer-prevention trials
- As reported by the Data and Safety Monitoring Board (DSMB), the Adenoma Prevention with Celecoxib (APC) trial conducted by the National Cancer Institute showed an increased cardiovascular risk over placebo
- A statistically significant dose dependent cardiovascular risk was seen in patients taking 400 and 800 mg a day of celecoxib continuously for 2.8-3.1 years

Individual patient risk for cardiovascular events and other risks commonly associated with arthritis treatment should be taken into account for each prescribing situation.
CELEBREX should be administered at the lowest effective dose.

1. Solomon et al. *N Engl J Med.* 2005;352.

Adenoma Prevention with Celecoxib (APC) Trial

Agent	n/N	% of patients	Relative risk compared with placebo	95% confidence intervals
Placebo	6/679	0.9%	---	---
Celecoxib 400 mg	15/685	2.2%	2.3	0.9-5.5
Celecoxib 800 mg	20/671	3.0%	3.4	1.4-7.8

N=2035; Average duration of treatment = 33 months

Solomon et al. *N Engl J Med.* 2005;352.

Prevention of Spontaneous Adenomatous Polyposis (PreSAP) Trial

Fatal and nonfatal cardiovascular events

Agent	n/N	% of patients	Relative risk compared with placebo	95% confidence interval
Placebo	12/628	1.9%	---	---
Celecoxib 400 mg	20/933	2.1%	1.1	0.6-2.3

N=1561; Average duration of treatment = 33 months

FDA Advisory Committee Briefing Document: Celecoxib & Valdecoxib cardiovascular Safety. January 12, 2005.

The ADAPT Trial: Celecoxib and Naproxen Efficacy in Alzheimer's Prevention

- On December 20, 2004 the National Institute of Health suspended a clinical trial involving administering celecoxib or naproxen vs placebo to patients >70 years old at risk for developing Alzheimer's disease
- In this trial approximately 2,500 volunteer participants were randomly assigned to receive either naproxen, celecoxib or placebo. The trial was suspended after three years
- Data from the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT) indicated an apparent increase in cardiovascular and cerebrovascular events among those taking 220 mg bid of naproxen (OTC dose), over those taking placebo.
- Preliminary data from this study did not indicate an increased risk for heart attack or stroke for celecoxib
- Naproxen: Increased risk than placebo

Developments Leading to FDA Advisory Committee

- September 30, 2004: Rofecoxib was voluntarily withdrawn from the worldwide market due to increased cardiovascular risk for rofecoxib versus placebo in the APPROVe trial, an adenomatous polyp prevention study[1,2]
- December 17, 2004: In the Celecoxib Adenomatous Polyp Cancer (APC) trial, a statistically significant increase in cardiovascular events was seen in patients taking 400 and 800 mg a day of celecoxib for an average of 33 months over patients taking placebo[3]
- December 20, 2004: Data from the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT) indicated an apparent increase in cardiovascular and cerebrovascular events among those taking 220 mg bid of naproxen (OTC dose), over those taking placebo. No such increase was found for celecoxib[4]

1. Merck press release. September 30, 2004; 2. Freudenheim. *The New York Times.* October 1, 2004; C1-C4; 3. NCI Press Release. December 17, 2004; 4. NIH News Press Release. December 20, 2004.

Drug Label Change

- FDA will request that manufacturers of all prescription products containing non-selective NSAIDs revise their product labeling to include:
- A boxed warning: potential serious adverse CV events and the serious, and potentially life threatening GI adverse events associated with the use of this class of drug
- A contraindication in patients with who have recently undergone coronary artery bypass surgery
- A medication guide for patients regarding the potential for CV and GI adverse events associated with the use of this class of drugs.

Suggested Strategy for Prescription

	No elevated GI Risk	Elevated GI Risk
Not on ASA	NSAID alone	Coxib NSAID+PPI
On ASA	Coxib + PPI NSAID+ PPI*	Coxib + PPI NSAID + PPI*

*** Preferred on pharmacoeconomic grounds**

Renal Consideration

- Coxib, like nonselective NSAID, should be used with caution, in any patients with significant renal disease (proteinuria or GFR < 60 ml/min)
- Volume depletion is a risk factor for NSAID-induced acute renal failure. Consider recommending that patients hold their NSAID if they cannot eat or drink that day