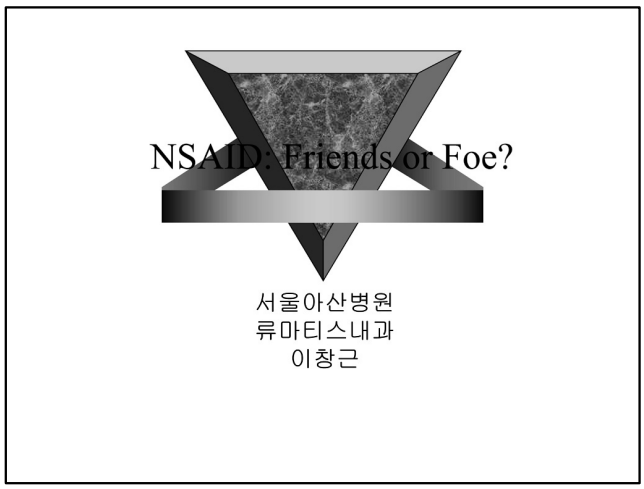
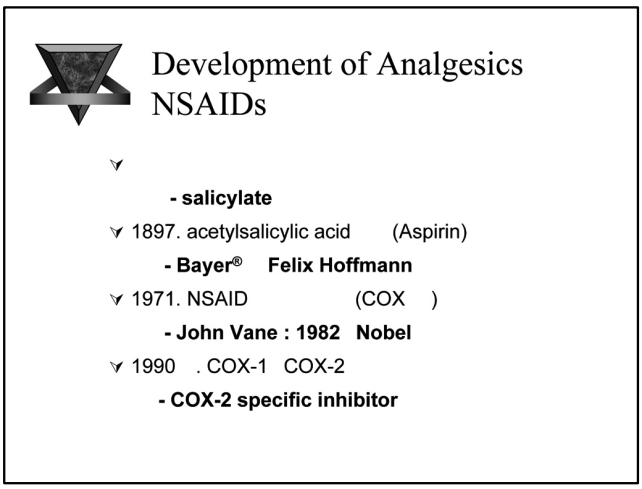
[연수강좌]

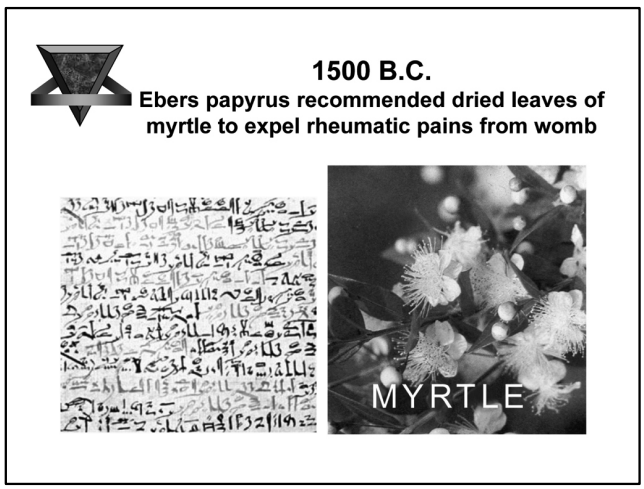
NSAID 어떻게 처방할 것인가?

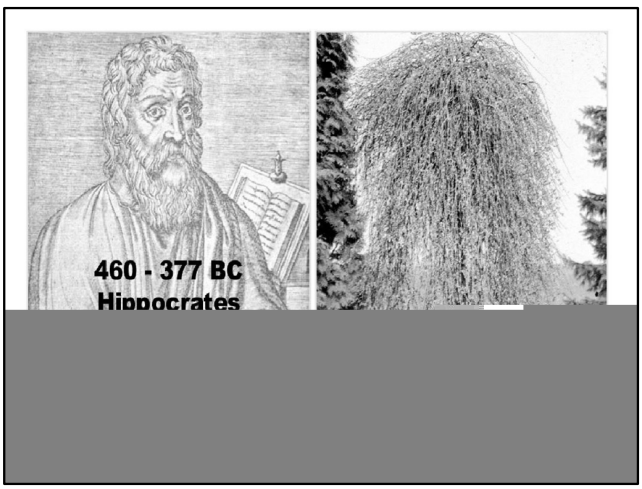
이 창 근

서울아산병원 류마티스 내과

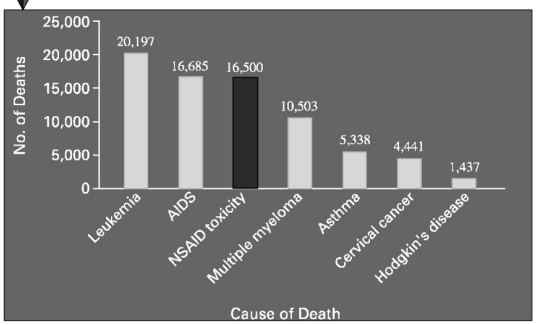






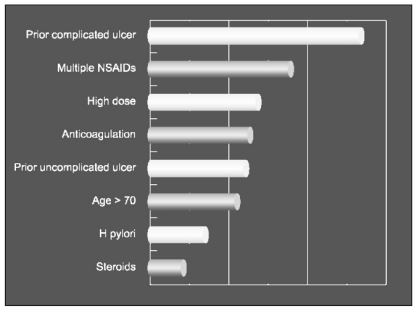


US Mortality Data



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)

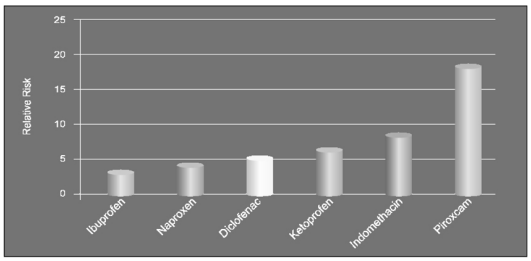
Weil J et al, BMJ 1995;310:827

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

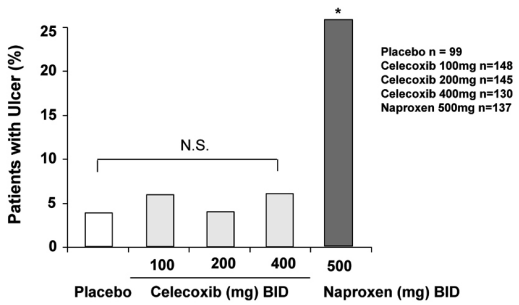
Risk group	Drug	Relative Risk
Low	Ibuprofen	2.0 (1.4-2.8)
	Diclofenac	4.2 (4.2-6.8)
Medium	Naproxen	9.1 (5.5-15.1)
	Indomethacin	11.3 (6.3-20.3)
	Piroxicam	13.7 (7.1-26.3)
High	Ketoprofen	23.7 (7.6-74.2)
	Azapropazone	31.5 (10.3-96.9)

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

NSAID Ulcers and Ulcer Complications

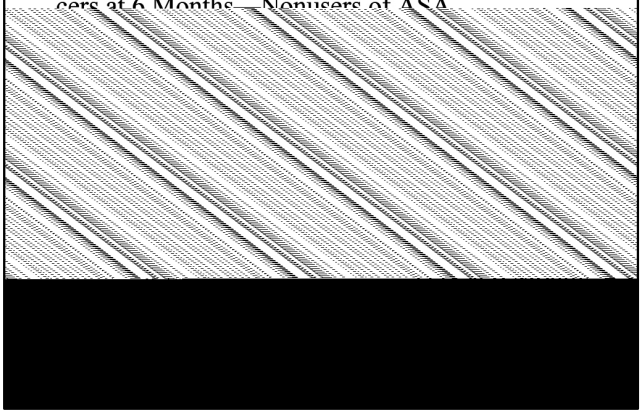
- Endoscopic Ulcer point prevalence: 10-30%
- Ulcer Complications: 1-2% per year
- Most (>80%) Hospitalizations for GI Bleed occur without previous symptoms

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



Simon LS, JAMA 1999;24:1921-1927

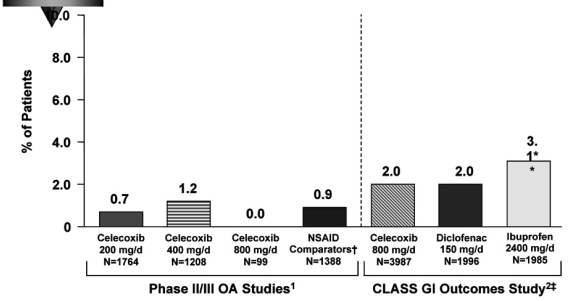
CLASS: Ulcer Complications and Symptomatic Ulcers at 6 Months—Nonusers of ASA



Hypertension

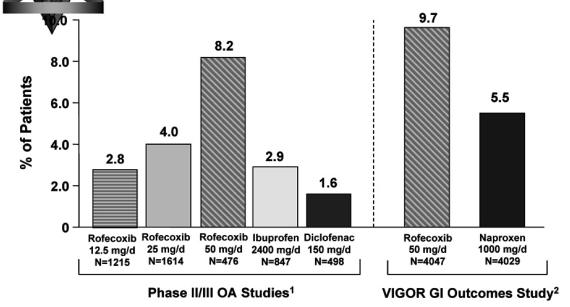
- The effect on systolic BP (3-7 mm Hg) is more pronounced than on diastolic BP (1-3 mmHg)
- 716% of patients exposed to coxib in RCT

Incidence of hypertension in celecoxib trials*



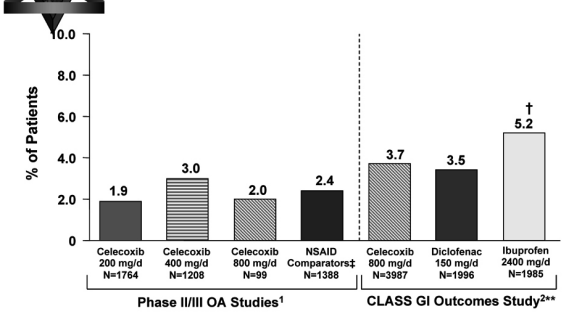
**P≤0.05 vs celecoxib.
*Investigator reported; †naproxen, diclofenac; ‡data from entire study period.
1. Summary basis for approval, FDA.
2. FDA Arthritis Advisory Committee Meeting. February 7, 2001. Gaithersburg, Maryland.

Incidence of hypertension in rofecoxib trials*



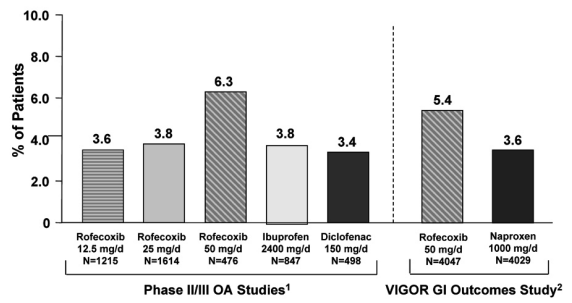
*Investigator reported
1. Summary basis for approval, FDA.
2. FDA Arthritis Advisory Committee Meeting. February 8, 2001. Gaithersburg, Maryland.

Incidence of peripheral edema in celecoxib trials*



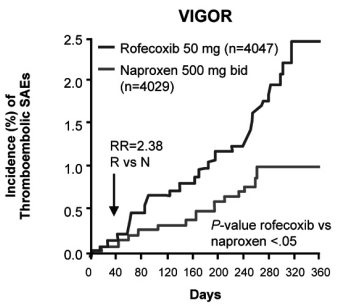
*Peripheral edema includes both upper and lower extremity edema (investigator reported).
†P<0.05 vs celecoxib; ‡naproxen, diclofenac; **data from entire study period.
1. Summary basis for approval, FDA.
2. FDA Arthritis Advisory Committee Meeting. February 7, 2001. Gaithersburg, Maryland.

Incidence of lower-extremity edema in rofecoxib trials*



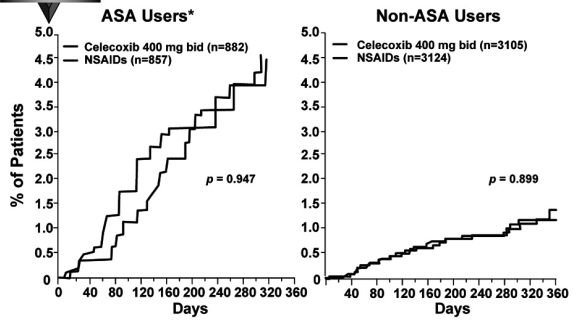
*Investigator reported.
1. Summary basis for approval, FDA.
2. FDA Arthritis Advisory Committee Meeting. February 8, 2001. Gaithersburg, Maryland.

Serious Thromboembolic Cardiovascular Adverse Events in Non-ASA Users



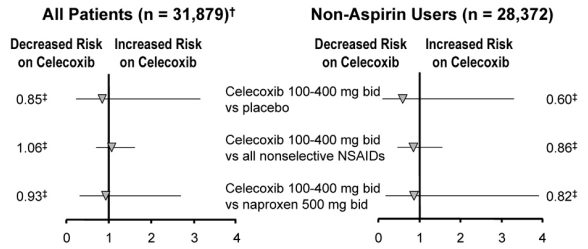
SAEs=serious adverse effects.
Mukherjee D et al. *JAMA*. 2001: 286: 954-959.

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

[redacted]

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