VIOXX™

Cardiovascular Safety: VIGOR Study

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VIGOR--Key Features

- Large comparative study
- No placebo arm
- Primary endpoint: PUBS
- 9 month median follow-up

Baseline Demographics

- ~ 80% female
- Over 70% under 65
- ~ 68% Caucasian
- ~ 50% had any cardiac risk factor

Baseline Demographics (cont.)

- Two groups evenly matched for: hypertension, diabetes, current smokers, hypercholesterolemia, past atherosclerotic disease (< 6 %)

Exclusions from VIGOR

- Angina or congestive heart failure with symptoms that occur at rest or minimal activity.
- Uncontrolled hypertension (diastolic blood pressure >95 mm Hg, or systolic blood pressure >165 mm Hg).
- Stroke or transient ischemic attack (TIA) within the previous 2 years.

Exclusions from VIGOR (cont.)

- Patients taking aspirin, even low-dose (325 mg or less, daily or every other day) or other antiplatelet agents (e.g., ticlopidine).
- Patients requiring the following concomitant medications: warfarin or heparin (or low molecular weight heparin).

Exclusions from VIGOR (cont.)

- Patients with a history of myocardial infarction or coronary arterial bypass grafting more than 1 year prior to study start may participate if they do not require any excluded concomitant medication.

Vascular Events Adjudication

- Blinded, external Vascular Event Committee.
- Composed of 3 separate subspecialty committees for cardiac, cerebrovascular, and peripheral vascular events, respectively.
- Prespecified criteria existed for defining vascular events (e.g. MI).

Adjudication SOP: Vascular Events of Primary Interest for Analysis

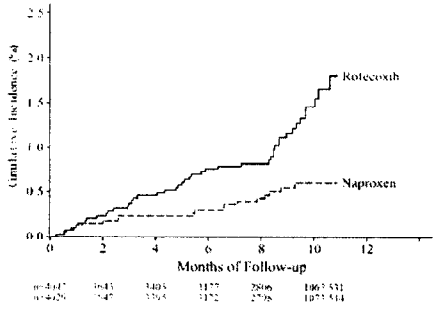
- Fatal and non-fatal acute MI
- Unstable angina pectoris
- Fatal and non-fatal ischemic stroke
- Fatal and non-fatal acute arterial thromboembolism (other than above)
- Sudden cardiac death/resuscitated cardiac arrest

Vascular Events of Secondary Interest for Analysis

- Fatal and non-fatal pulmonary embolism
- Fatal and non-fatal venous thrombosis
- Nonfatal cardiac (atrial or ventricular) thrombosis
- Transient ischemic attack

Confirmed thrombotic events= composite of vascular events of primary and secondary interest

Time to event plot. Confirmed serious CV thrombotic events in VIGOR



For the confirmed thrombotic serious adverse events, the p-value is 0.001.

Points to Consider

- No prospective, randomized, placebo-controlled trials to support cardiovascular benefit for naproxen.
- It is not known that rofecoxib is worse than placebo.

Conclusions

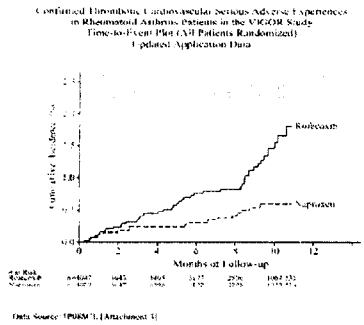
Regardless of mechanism (whether cardiovascular benefit with naproxen or cardiovascular risk with rofecoxib), the cardiovascular data favor naproxen.

Back
up
Slides

Serious CV events*

Event	Group	N	Patients with Events	Relative Risk Estimate	95% CI
All thrombotic events					
	Rofecoxib	4047	45		
	Naproxen	4029	19	0.42	(0.25, 0.72)

*Confirmed adjudicated events as of 10/11/00



For the confirmed thrombotic serious adverse events, the p-value is 0.001.

Serious Confirmed Adjudicated Events*

Event Category	Treatment Group	N	Patients With Events	Relative Risk	
				Estimate	95% CI
All thrombotic events	Rofecoxib	4047	45		
	Naproxen	4029	19	0.42	(0.25, 0.72)
All cardiac events	Rofecoxib	4047	28		
	Naproxen	4029	10	0.36	(0.17, 0.74)
All cerebrovascular events	Rofecoxib	4047	11		
	Naproxen	4029	8	0.73	(0.29, 1.80)
All peripheral vascular events	Rofecoxib	4047	6		
	Naproxen	4029	1	0.17	(0.00, 1.37)

* as of 10/11/00

Sample Size Calculations Based on the observed difference between rofecoxib and naproxen:

- using two sided alpha=0.05
- 80% power
- observed event rates (1.67% for rofecoxib and 0.7% for naproxen):

Sample Size Calculations

- Assuming exponential distribution, sample size per group=1866 (approximate 70 events in both group);
- Assuming one year accrual period and maximum follow-up 1 year, and still assume exponential distribution, sample size per group=4224;

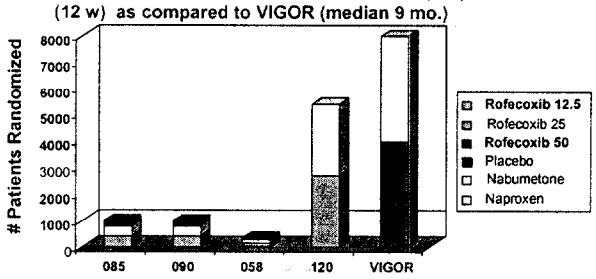
Given these sample size calculations, are outcomes from other studies consistent with VIGOR cardiovascular results?

Sample Size Calculations (cont.)

- Assuming a 35% drop out rate, one year accrual period, maximum follow-up 1 year and exponential distribution, sample size per group=4730;

Rofecoxib Overall Safety

Patients randomized to studies 085, 090, 058 (6 w) and 120 (12 w) as compared to VIGOR (median 9 mo.)



Composite Endpoint (10/11/00)

Event Category	Treatment Group	N	Number of Patients With Events	PYR	Rates	Relative Risk		
						Estimate	95% CI	
All Patients								
Cardiovascular deaths*, MI CVA	Rofecoxib	4047	35	2698	1.30			
	Naproxen	4029	18	2698	0.67	0.51	(0.29)	(0.91)

*Includes sudden death, unknown cause of death, fatal myocardial infarction, fatal stroke (hemorrhagic or ischemic), fatal subarachnoid hemorrhage, fatal primary intracranial hemorrhage, fatal gastrointestinal bleeding episode.

Composite Endpoint (cont.)

The risk ratio is 1.95 (rofecoxib vs. naproxen) with 95% CI (1.103, 3.438) and p-value=0.0216.

ardiovascular eaths[%]	Rofecoxib	4047	7	2700	0.26			
	Naproxen	4029	7	2699	0.26	1.00	(0.35,	2.85)
4I	Rofecoxib	4047	20	2699	0.74			
	Naproxen	4029	4	2699	0.15	0.20	(0.07,	0.58)
troke[f]	Rofecoxib	4047	11	2699	0.41			
	Naproxen	4029	9	2699	0.33	0.82	(0.34,	1.97)

CHF AE

AEs	Rofecoxib	4047	19	2696	0.70	2.11	(0.96, 4.67)	0.065
	Naproxen	4029	9	2698	0.33			

(CV events analysis, original table, 6/29/00)				
	Rofecoxib		Naproxen	
	(N=4047)		(N=4029)	
Demographic	n	(%)	n	(%)
Age				
Patient <65 Years Old	1059	(73.4)	2959	(73.4)
Patient ≥65 Years Old	997	(26.6)	1070	(26.6)
Past Cardiovascular History				
Past History of Atherosclerotic Cardiovascular Disease	218	(5.9)	216	(5.4)
Coronary Artery Disease	171	(4.2)	159	(3.8)
Myocardial Infarction	57	(1.4)	50	(1.2)
Cerebrovascular Disease	26	(0.6)	25	(0.6)
Cerebrovascular Accident	12	(0.3)	16	(0.4)
Peripheral Arterial Disease	56	(1.4)	49	(1.2)
Cardiovascular Risk Factors				
Any Cardiovascular Risk Factor	2047	(50.6)	1958	(49.3)
Hypertension	1217	(30.1)	1168	(29.0)
Diabetes Mellitus	240	(5.9)	254	(6.3)
Current Smoker	790	(19.5)	775	(19.3)
Hyperlipidemia/Lipemia	444	(8.5)	291	(7.1)
Indication for Aspirin Therapy				
Aspirin Therapy Indicated[1]	170	(4.2)	151	(4.2)

[1] Patients with past medical histories that met criteria for chronic vascular-protective aspirin therapy (past history of either cerebrovascular accident, transient ischemic attack, myocardial infarction, unstable or stable angina, coronary artery bypass graft surgery, or percutaneous coronary intervention)