

The PreSAP Trial (Prevention of Colorectal Sporadic Adenomatous Polyps): Bernard Levin MD

JOINT MEETING OF THE ARTHRITIS ADVISORY COMMITTEE AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

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Highlights

- **PreSAP TRIAL STATUS:** Drug administration in the PreSAP trial was stopped at the same time drug administration was stopped in the APC trial. It is assumed that in other respects the trial is continuing with collection of efficacy and safety data.
- **PreSAP TRIAL DESIGN:** The PreSAP was a 3-year double blind trial of celecoxib 400 mg QD and placebo in 1561 patients with a history of sporadic adenomas. It was conducted at 106 sites in 32 countries.
- **CARDIOVASCULAR SAFETY ANALYSIS:** The same data safety monitoring board (DSMB) as for the APC trial initiated cardiovascular adjudication of cardiovascular serious adverse events but "...some of this information is still in a preliminary status."
- **HIERARCHY OF ENDPOINTS:** The analysis is using a hierarchy of endpoints similar to the APC trial. In the APC trial hierarchy, subsequent endpoints subsumed the data from the endpoints earlier in the hierarchy.

The hierarchy was: cardiovascular death, non-fatal MI, stroke, heart failure, angina and CV procedure.

COMPARISON WITH RESULTS IN THE APC TRIAL:

- **BASELINE:** Baseline characteristics were "somewhat similar to the APC trial in terms of age and gender. What is different is that the smoking status is higher, 25 percent, and baseline aspirin use is lower." Treatment groups at baseline were "somewhat similar in age, gender and baseline cardiovascular risk".
- **CARDIOVASCULAR EVENT RATES:** Compared with the APC trial, the placebo cardiovascular event rate was 6.4 ("about double that in the APC trial") and the hazard ratio was non-significant at 1.1.
- **EFFECT OF BASELINE RISK FACTORS:** As in the APC trial, there was "no statistical evidence of a differential hazard ratio by baseline risk groups. Of course, there are few events and it has limited power."

- **REASONS FOR DIFFERENCES IN RESULTS:** “What, of course, is most tantalizing to everyone involved is: Why is there a difference in this trial compared to the APC trial? At this point, all we have to go on is the frequency of the schedule of administration of celecoxib.”
- **EVENTS INFREQUENT:** “The number of events is low” and “and when this is magnified, similar to what Dr. Hawk showed, the curves are essentially similar.”
- **OVERALL MORTALITY:** Not discussed.
- **PLANNED META-ANALYSES:** As Dr. Hawk mentioned, there are plans to analyze the ASP and PreSAP trials together, and to analyze these 2 trials together with 4 other NIH-funded celecoxib trials, all of at least 2 years duration of therapy.
- **EFFICACY:** No efficacy results are yet available from the PreSAP trial.

Presentation Text

Thank you very much, Dr. Hawk. Mr. Chairman, committee members, it is my honor to present a summary of the data in the PreSAP trial. My co-principal investigator, Dr. Nadir Arba, in Tel Aviv University, and I have been aligned with this trial since its birth with Searle, Pharmacia and Pfizer.

In this trial, depicted here are 1561 patients with sporadic adenomas who were randomized in a 3:2 manner and stratified by aspirin use and clinical center into celecoxib 400 mg daily for 36 months and placebo for 36 months. Colonoscopy was performed after 12 and 36 months of exposure evaluating recurrence, and collection of all pathological endoscopic information.

As you have already heard from Dr. Hawk, some of this information is still in a preliminary status. This study involved 106 clinical research sites in 32 countries. Patients were enrolled from

March, 2001 and completed approximately one year later.

The cohort characteristics at baseline are shown in this slide, somewhat similar to the APC trial in terms of age and gender. What is different is that the smoking status is higher, 25 percent, and baseline aspirin use is lower. Some of this data may still be in a preliminary format so I am not going to discuss it significantly further.

Depicted here, and somewhat similar terms to that which Dr. Hawk showed, is the incidence and hazard ratio of the hierarchical cardiovascular composite endpoints. Again, the blue column that is highlighted reflects the death from cardiovascular causes--myocardial infarction, stroke or heart failure.

- I would draw to your attention the placebo rate of 6.4, approximately double that in the APC trial, and a hazard ratio of 1.1.
- Similar to the APC trial, the cardiovascular events examined by

baseline subgroups were somewhat similar in age, gender and baseline cardiovascular risk.

- There was no statistical evidence of a differential hazard ratio by baseline risk groups. Of course, there are few events and it has limited power.

Depicted here on this Kaplan-Meier estimate, one can see that the number of events is low, and when this is magnified, similar to what Dr. Hawk showed, the curves are essentially similar.

There are a number of issues which arise from these two trials:

- Perhaps the most important one which concerns us as the investigators, apart from the safety, is the efficacy and we don't have that information yet. We have some idea with the signal from the Vioxx trial about which you heard earlier. It is tantalizing. That will help us to make risk/benefit assessments for future.
- We have to take into consideration in any of those discussions the relative gastrointestinal and cardiovascular safety referent to other non-steroidal anti-inflammatory drugs. Overall toxicity and safety, of course, are prime concerns when it comes to asymptomatic individuals and the public, and we don't have any information in these trials yet on gastrointestinal ulceration.
- The cross trials meta-analysis that Dr. Hawk alluded to will also provide a great deal of information. What, of course, is most tantalizing to everyone involved is why is there a difference in this trial compared to the APC trial? At this point, all we have to go on is the frequency of the schedule of administration of

celecoxib. We don't have any other information from the patients enrolled in this trial on other possible factors.

- In this trial there was no increased risk of cardiovascular adverse effects, but one overall would want to consider whether one could mitigate any increased risk by better clinical management if that were necessary.
- Some of the differences, but that doesn't really apply to this trial, might be in metabolic polymorphisms but there is no evidence for that and we don't have that information.

So, for future research there are many questions that are of great importance. COX-2 remains a relevant oncology target and, as Dr. Hawk already presented, we want to consider the possibilities that there are other pharmacological targets besides COX-2 in the prevention and therapy of cancer. We already have some information on that, the effect of these agents, and they don't all do the same, on 15-lipoxygenase-1 and also on the modulation of PPOD delta.

But primarily what we are interested in now is establishing efficacy or determining efficacy in these two trials and that information should be forthcoming in the next few months.

Thank you for your attention.

Presentation Slides



Celecoxib in Adenoma Prevention - The PreSAP Trial

FDA Advisory Committee on

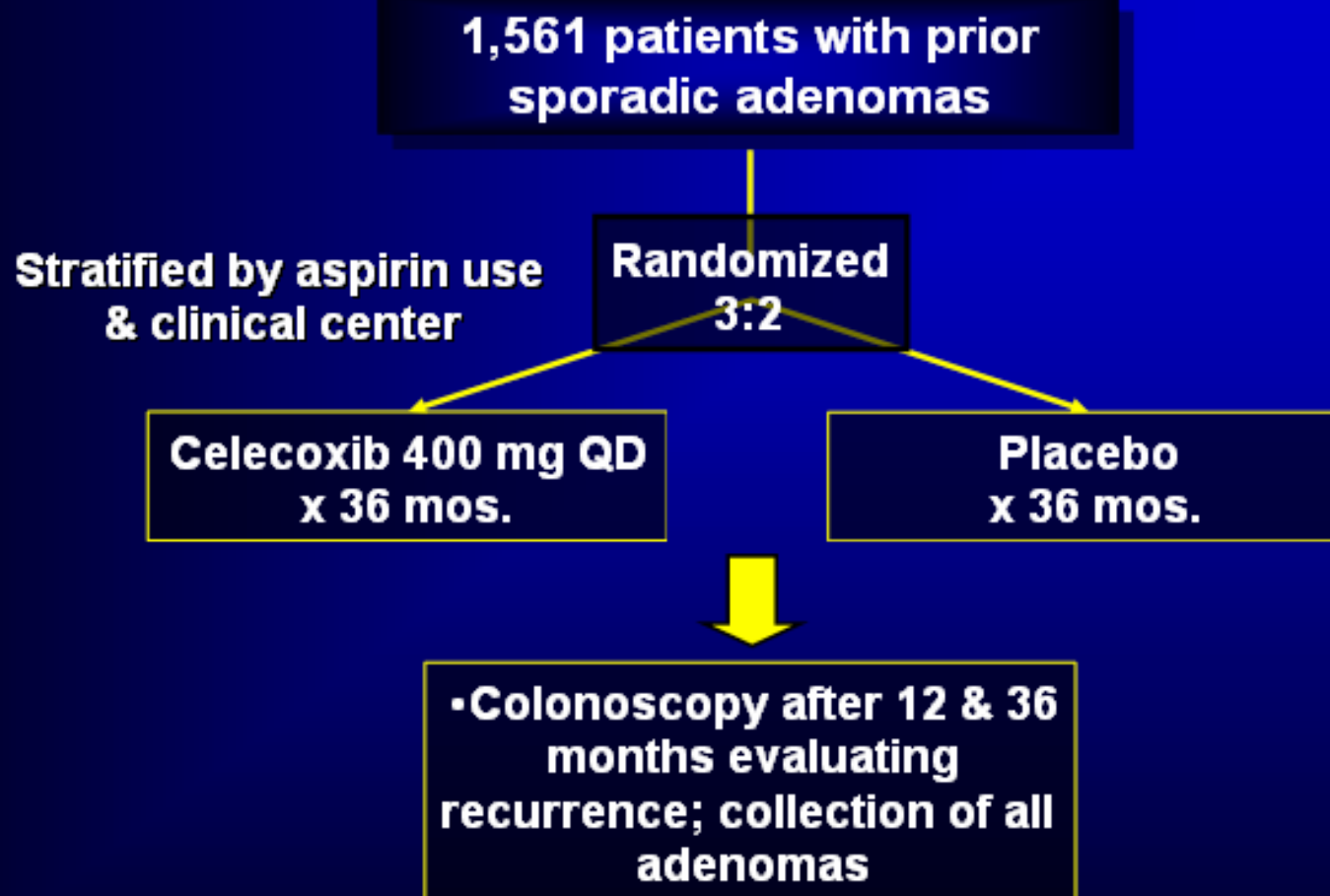
COX-2 Inhibitors &

Gaithersburg, Maryland
NSAIDs

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Pfizer's PreSAP Trial



106 clinical research sites in 32 countries

PreSAP Trial - Cohort Characteristics at Baseline

Baseline characteristic	Placebo N = 628	Celecoxib 400mg QD N = 933
Age in years (mean ± SD)	60.4 ± 10.0	61.1 ± 10.0
	%	%
Male	64.6	67.4
Any cardiovascular history	45.9	49.6
MI*	3.5	2.6
Cerebrovascular disease*	0.6	1.0
CHF*	0.2	0.8
Angina*	7.5	9.0
Hypertension*	33.1	36.8
Diabetes*	21.8	17.6
Current smoker	24.4	23.0
Baseline aspirin use	15.6	16.2
Baseline lipid-lowering drug use	5.9	5.9

*Results are preliminary – results not available for all patients at time of analysis

Incidence & Hazard Ratio for Hierarchical CV Composite Endpoints in the PreSAP Trial

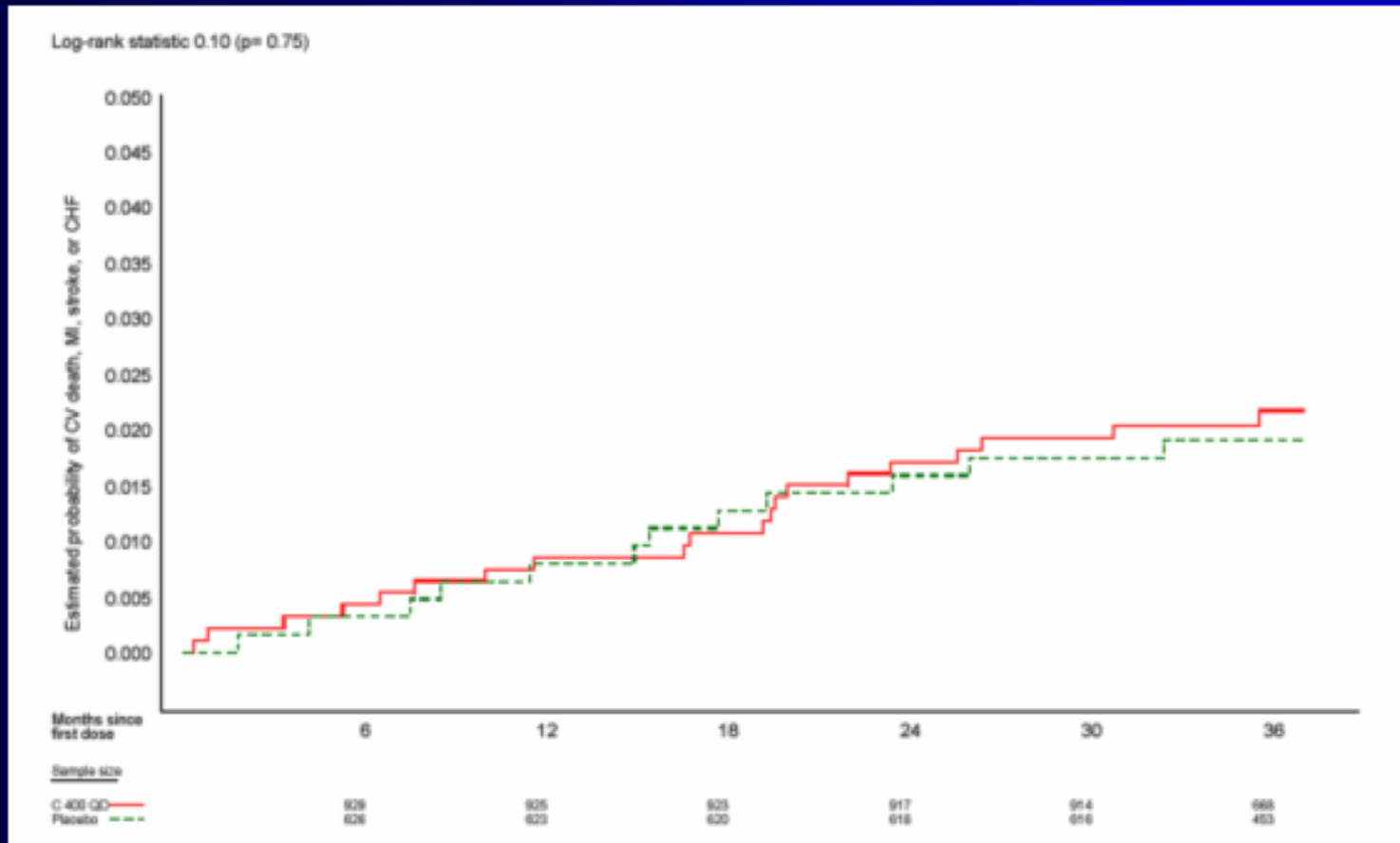
Endpoint	Number of patients (%)		Rate/1000 patient-years		Hazard Ratio with 95% Confidence Interval*
	Placebo	400 mg QD	Placebo	400 mg QD	
Death from CV causes	4 (0.6)	2 (0.2)	2.1	0.7	0.3 (0.1, 1.8)
Death from CV causes or MI	7 (1.1)	11 (1.2)	3.7	3.9	1.1 (0.4, 2.7)
Death from CV causes, MI, or stroke	12 (1.9)	19 (2.0)	6.4	6.8	1.1 (0.5, 2.2)
Death from CV causes, MI, stroke, or heart failure	12 (1.9)	20 (2.1)	6.4	7.2	1.1 (0.6, 2.3)
Death from CV causes, MI, stroke, heart failure, or angina	15 (2.4)	28 (3.0)	8.0	10.1	1.3 (0.7, 2.3)
Death from CV causes, MI, stroke, heart failure, angina, or need for a cv procedure	17 (2.7)	34 (3.6)	9.1	12.3	1.3 (0.8, 2.4)

*Relative to placebo

PreSAP - CV Events by Baseline Subgroups

- **Examined cardiovascular risk in various risk subgroups**
 - Age, gender, baseline cv risk, etc.
- **No statistical evidence of a differential hazard ratio by baseline risk groups**
- **Few events**
- **Limited power**

Kaplan-Meier Estimates of the Risk of Serious CV Events in the PreSAP Trial by Treatment Arm*



Issues Arising from the CV Safety Data with Celecoxib in the APC and PreSAP Trials

- **Context**

- Efficacy
- Risk:benefit assessments
- Relative GI and CV safety compared to other NSAIDs

- **Toxicity**

- Overall safety
 - GI ulceration
- Accuracy & precision
 - Cross-trials meta-analysis

- Mechanisms

- Dose
- Frequency
- Duration
- Pharmacokinetics
- Mitigation or risk management
- Risk segregation
 - Baseline risks
 - Metabolic polymorphisms

- **Future Research**