

Committee Questions to Dr. Hawk and Dr. Levin on APC and PreSAP

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

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Highlights.....	1
Discussion Text.....	2

Highlights

- **BASELINE DIFFERENCES BETWEEN ASP AND PRESAP TRIALS:** Dr. Farrar said that the ASP and PreSAP trials differed in baseline diabetes (2x in PreSAP), smoking (“substantially higher” in PreSAP), lipid-lowering drugs (“remarkably lower”) and these differences may be relevant to the different findings in the two trials. Dr. Levin agreed that the PreSAP population was “potentially a higher risk group” but that the “data is still a little bit preliminary”. Dr. O’Neill suggested that another difference between the trials might be the proportions of US to non-US patients; Dr. Hawk said he did not have those data.
- **COX-2 SUPPRESSION AS FUNCTION OF DOSING INTERVAL:** Dr. Gross suggested that the different dosing regimen (QD vs. BID) could have resulted in loss of sustained COX-2 inhibition over 24 hours and might explain the difference in cardiovascular hazard. Dr. Seibert (Pfizer) commented that AUCs are similar and steady state C-mins are “about 20% different” and “still exceed that which is necessary to inhibit COX-2” so that “we don’t see a clear differentiator there in the dosing regimen”.
- **EFFECT OF ASPIRIN:** Dr. Wood said that the APC/Pre-APC data suggest that cardiovascular risk was increased by aspirin. Dr. Hawk commented on a study by John Baron (NEJM) suggesting dose-dependent increase in events with aspirin but that “there are a lot” of trials showing that aspirin lowers cardiovascular risk.
- **ASP TRIAL STOPPING RULES:** Dr. Hennekens expressed concern that the “statistical stopping guideline” used may have resulted in the APC trial being stopped prematurely without adequate statistical justification. Dr. Hawk said that the data safety monitoring board had recommended halting drug administration but “that is my level of insight into the issue.”
- **CONSISTENCY OF ASP AND PRESAP CV DATA:** Dr. Furberg said that the 95% confidence interval for PreSAP cardiovascular results is consistent with “a 40 percent benefit and a 2.34-fold increase in risk” and are thus compatible with ASP. Dr.

D'Agostino, Dr. Nissen and Dr. Wood agreed with Dr. Furberg's comment.

- **CELECOXIB VS. ASPIRIN FOR COLORECTAL POLYPS:** In response to Dr. Cryer, Dr. Hawk said that celecoxib is more effective than aspirin in animal models but it is premature to speculate how effective celecoxib will be in the ASP/PreSAP trials, or whether there is a dose that is effective without an increased cardiovascular hazard.
- **POOLING DATA FROM ASP AND PRESAP TRIALS:** Dr. Nissen suggested that pooling the data from these two similarly designed trials each at 400 mg/day might "give us more stable estimates of the hazard ratio". Dr. Hawk said that a combined analysis "has been done based upon preliminary data that were analyzed back in

December". Dr. Fleming said that he had done a "back of the envelope calculation" that gave a "relative risk of about 1.82" for the meta-analysis which was of "borderline statistical significance" (apparently for the pooled data from the low and high dose levels).

- **CANCER TRIAL SHOWING INCREASED NSAID CV RISK VS. ACETAMINOPHEN:** Dr. Andrew Dannenberg (Cornell and a Pfizer consultant) described a not-yet-published study of acetaminophen versus non-selective NSAIDs in preventing oral cavity cancer that showed a reduced risk of oral cavity cancer with NSAIDs but this was accompanied by an increased cardiovascular risk with NSAIDs (hazard ratio 2.06).

Discussion Text

DR. WOOD: Thanks very much. Any questions? Dr. Farrar?

DR. FARRAR: If you could show the PreSAP cohort characteristics slide, which I guess is your second or third slide, I would ask my colleagues to look on page 6 of the presentation of the study and if you just compare the baseline characteristics, I was struck by the fact that you said that what was different in the trial was the rate in the placebo group. There are, in fact, several major differences in the two groups. The age is the same. Male distribution is approximately the same. Cardiac history is the same. But if you look at diabetes, there is more than twice the rate in the PreSAP than there is in the APC. The

smoking rate is substantially higher. The baseline aspirin use is half. The lipid-lowering drugs are remarkably lower. I don't know what that means, but Dr. FitzGerald suggested this morning that this whole system is very complex and I would simply posit that, in fact, there is probably an interaction there that may be very informative. We need a lot more information about your trials. Obviously you are working hard to do that and I think there is a lot of information to be gathered there.

DR. LEVIN: If I might answer that?

DR. WOOD: Go ahead.

DR. LEVIN: Yes, Dr. Farrar, I agree entirely. I didn't want to highlight these differences which suggest that this is potentially a higher risk group to begin with, distributed in countries where the prevalence of use of lipid-lowering drugs would be anticipated to be lower. But some of this data is still a little bit preliminary so I didn't want to hark on it but I think your point is very well made. Thank you.

DR. WOOD: Dr. Shafer?

DR. SHAFER: Yes, you showed a slide which, from my perspective, was somewhat unwelcome because I was trying to understand these things. That was the slide about the risk of the other NSAIDs which was based on unpublished data. I actually went looking for such data and had some trouble pulling it up. Are there published studies, or are there data that you are aware of, because this is relevant to the discussions that we are going to be having on Friday, suggesting cardiovascular risk from the other standard NSAIDs?

DR. WOOD: And while you are doing that, can you comment on the increased risk in that study of aspirin?

DR. SHAFER: I tried to avoid mentioning aspirin in my question.

DR. WOOD: I will do it for you, Steve!

DR. HAWK: The only other data that I am personally aware of is the study done in the Kaiser-Permanente database that we saw alluded to in an earlier presentation. I am not aware of other data. I put this up with all the caveats, and I believe I mentioned that this is

preliminary and so it violates some of the rules that we heard this morning. But it is particularly relevant to the Cancer Institute because, again, we have applicants suggesting that they should move now to traditional NSAIDs and that is a very important question to answer but we don't think the answer is there, that is, the absence of evidence doesn't necessarily prove that they are safer and I think that is an important context issue, at least for us.

DR. WOOD: But in commenting on that, the second line, it shows aspirin increases the risk of cardiovascular.

DR. HAWK: I wish that John Baron were here because John Baron did one of the three aspirin trials in adenoma prevention that I alluded to. I didn't have time to show the data but if you go into that study--it is published in The New England Journal of Medicine--he studied placebo versus aspirin at 81 mg versus 325 mg, and if you look at the adverse event table you see that the aspirin groups actually had more events in a dose-dependent manner than did placebo. I don't know what that means but it is very similar to the sorts of information we have from the APC trial. But, again, you know, there are a lot of long-term placebo-controlled trials showing that aspirin prevents cardiovascular risk in other settings. So I don't want to use that to impugn aspirin. I am merely stating what is published.

DR. WOOD: Dr. Hennekens?

DR. HENNEKENS: Dr. Hawk, I would make a comment that leads me to a question. The totality of evidence for aspirin from 135 trials for the treatment of secondary prevention shows a highly

statistically significant and clinically important 15 percent reduction in cardiovascular mortality. In contrast, in 5 trials of primary prevention with 55,180 or so patients, with much lower endpoints, there is not a statistically significant benefit of aspirin but the confidence intervals are still compatible with that. We need more data on this. So, with that as a background, as a chair or member of various data safety monitoring boards, I try to follow the principle of early stopping based on proof beyond a reasonable doubt that is likely to influence clinical practice, with some asymmetry in that you have greater concern about safety than efficacy but, nonetheless, included in this algorithm is the statistical stopping guideline whether you follow the teachings of O'Brien and Fleming or Land and de Mets or Peto and Haybittle. Intrinsic in this is that during the course of a trial, if you reach a statistically extreme p value then there is a high likelihood that by the scheduled end of the trial that p value will at least be at 0.05. But if you fail to achieve that extreme p value, then it is highly likely that by the end of the trial you may find no significant difference. So, one of the questions is what were the considerations in stopping this trial, and is the play of chance a likely explanation for the findings?

DR. HAWK: I would say that the trial was still blinded to efficacy and broader issues of safety. The data safety monitoring board still exists so I am not privy to all of their closed session discussions and deliberations. What I can tell you is that this trial was about three months away from the last patient going off of it. We were told that there was a cardiovascular risk and it was the considered opinion of the data safety

monitoring board that it would be the better part of valor to halt drug administration in this trial and continue to follow patients for relevant outcomes. That is what we did and that is my level of insight into the issue.

DR. WOOD: Dr. Furberg?

DR. FURBERG: Yes, I would like to make a plea that we are not making too much out of the findings from the PreSAP trial. For the combined outcome the hazard ratio is 1.1. The 95 percent confidence interval is very wide. So, the PreSAP findings are consistent with a 40 percent benefit and a 2.34-fold increase in risk. So, the trial doesn't add much to our knowledge.

DR. O'NEILL: You may not have this information right now but I notice the APC trial had 72 sites in the U.S. and the PreSAP trial looked like it had 132 sites. What is the relative U.S. versus non-U.S. distribution in those two trials?

DR. HAWK: In the APC trial there were 70-some sites in the U.S.

DR. O'NEILL: No, I mean denominator-wise, subjects. I am trying to see whether the placebo rate differs inside or outside U.S. in the two trials.

DR. HAWK: That is a very good question and I don't have those data.

DR. O'NEILL: Yes, I think that would be useful to have.

DR. WOOD: Byron?

DR. CRYER: I understand that in your APC trial results you haven't yet analyzed the potential polyp reduction

effects of celecoxib, but you pointed out a couple of very real observations, that aspirin is an effective agent for the reduction of polyps, associated with a 20-30 percent reduction of recurrent adenomas, and we heard earlier in the APPROVe trial that rofecoxib was associated with a 24 percent reduction of recurrent adenomatous formation. So, assuming, let's say, that celecoxib achieves a result that is in the same realm, let's say 20-30 percent and given that aspirin, as Dr. Hennekens pointed out, is such an effective agent for prevention of cardiovascular events, I was wondering if you could postulate as to potential reasons for us to use celecoxib for this indication over aspirin, assuming a similar endpoint.

DR. HAWK: Sure, I would be glad to. I think the answer will come with the data. What I am going to say is conjecture. In animal models aspirin is one of the least effective of the traditional NSAIDs. Celecoxib was one of the most effective in traditional animal models. So, we had reason to believe, both on the basis of an improved efficacy profile in animal models as well as potential for an improved safety assessment that existed at the time of the initiation of the trial, that in both ways we could improve the therapeutic index. I think we don't know if these cardiovascular events are occurring in patients that have efficacy or in the group that don't have efficacy. We don't know the level of efficacy here. So, it is very difficult to answer your question in a scientifically rigorous way. I can tell you the premise but I can't tell you the data because I don't yet know whether this drug is efficacious at all. I will say that in FAP settings there was a small Japanese trial done with rofecoxib which showed I believe

something on the order of a 10 percent reduction in adenoma burden. We saw about a 30 percent reduction in our randomized, placebo-controlled trial. That is a suggestion that in a different patient cohort celecoxib may be more efficacious but it is really speculation and what we really need are the data from these two trials in order to be able to answer your question accurately.

DR. CRYER: Just to reiterate, you pointed out data from animals and the human data with aspirin is quite good with respect to prevention of recurrent adenomatous polyps.

DR. HAWK: We were hoping for better.

DR. LEVIN: I think, Dr. Cryer, I might answer your question as well. It is valuable to look at the two studies. In particular, one study showed that there was, as you quote, approximately a 30 percent reduction. But what was particularly interesting was the effect on advanced adenomas, a 49 percent reduction. So, I think we don't have these data but the question will be, in my opinion, very relevant to what will be the impact of this or any other kind of they on the more significant lesions that have an enhanced propensity to develop into cancer. That might be an important differentiation between aspirin and rofecoxib or any other agent.

DR. WOOD: Dr. D'Agostino?

DR. D'AGOSTINO: Curt already raised the issue I was going to. I don't think the two studies contradict each other.

DR. WOOD: Peter?

DR. GROSS: I wonder if one of the factors to be considered is that when celecoxib is given once a day the suppression of prostacyclin and whatever else is going on does not last for 24 hours, whereas when celecoxib is given twice a day you get more sustained suppression.

DR. WOOD: All right. Dr. Nissen?

DR. NISSEN: I was going to echo what Curt had to say and also Ralph, but then I had a question. Clearly, the confidence intervals for these two trials, for virtually every endpoint, overlap. But because they are so similar in design, long before you have all the trials in this list you could combine APC and PreSAP and look at an analysis of the two combined which would give us more stable estimates of the hazard ratio. I think it might be useful. I am going to guess somebody has done that and, if you have, I sure would like to know about it. Maybe Tom has already done it on the back of an envelope. I can see him shaking his head. But I am trying to get a more stable estimate, particularly for the non-super-therapeutic dose, the 400 mg dose which was common to both trials--try to get more stable estimates for what the hazard ratios really are.

DR. HAWK: First of all, I want to highlight that the "super-therapeutic" dose is based upon our frame of reference that is different than the indication where we are applying it here, in cancer prevention. Here the only effective dose we have is 400 mg twice a day. So, I take your point but please take mine as well. In terms of the combined analysis, that has been done based upon preliminary data that were analyzed back in December. Since that period of time

we have confirmed all the events so that we can do the intent-to-treat analysis that was discussed here as well. So, I don't think it has been done yet on the mature data. Janet Wittes is in the audience. Janet, can you speak to that?

DR. WITTES: It is not done on very mature data but I am sure that if you calculate, you can do it by hand.

DR. SEIBERT: Dr. Hawk, perhaps I can clarify. Karen Seibert, from Pfizer, pharmacologist. We have evaluated 400 mg once daily versus 200 mg twice daily looking at the exposures. The total exposure as an AUC is about equivalent. As you might expect, the C-max for the 400 is about 30 percent higher. The C-min at 12 versus 24 hours for the 200 and 400 is about 20 percent different. The total exposure is the same. And we believe that the C-mins which are achieved at steady state still exceed that which is necessary to inhibit COX-2. We are happy to provide those data to this committee but we don't see a clear differentiator there in the dosing regimen.

DR. WOOD: Other questions? Richard?

DR. PLATT: I would like to circle back to Dr. Shafer's question. Were you asking if there are data about the other non-selective NSAIDs? Because in Tab S of our book there are a couple of articles that speak to that. They are observational studies but they seem to be saying that there doesn't appear to be excess risk.

DR. SHAFER: That is what I was wondering about, finding one that shows excess risk.

DR. PLATT: There does seem to be some literature that looked and didn't find it.

DR. WOOD: Dr. Fleming?

DR. FLEMING: Well, I have been, just out of curiosity, doing a back of the envelope calculation to see what it would look like on the primary endpoint, if we take the primary endpoint to be CV death, MI and stroke, and the standard error is the square root of 4 over the number of events, so just using that without doing a formal stratification, I would come out with a relative risk of about 1.82. So, one study says 10 percent increase; the other study says a relative risk over 3, and it is just barely over the statistical significance. So, it is borderline statistical significance in the meta-analysis with an estimate of about 80-85 percent relative increase.

DR. WOOD: So, they would be compatible, in other words. Any other questions? Yes?

DR. DANNENBERG: My name is Andrew Dannenberg, Weil Medical College, Cornell University. I am here today as a consultant for Pfizer, but I am one of the would-be authors of the data demonstrating an increased risk of cardiovascular death in those taking non-selective NSAIDs versus acetaminophen. That NIH-funded research is based on the following hypothesis: It is known that COX can activate tobacco carcinogens and convert them to mutagens. We, therefore, were interested in the possibility that NSAIDs could protect against tobacco smoke-induced oral cavity cancer. To be enrolled in that trial, which was led by a group in Norway and M.D. Andersen, a

retrospective study, one had to smoke 15 pack years or more. We observed a significant decrease in the risk of oral cavity cancer in those taking NSAIDs but not acetaminophen. However, when we looked at life span there was no apparent increase in life span despite the reduction in risk of oral cavity cancer. That led us to interrogate the data set to look at all causes of death. We noted a hazard ratio of 2.06 in those taking NSAIDs from the standpoint of death due to cardiovascular disease. By contrast, acetaminophen did not impact on the risk of cardiovascular death. So, that is a more complete description of the rationale for the study and how we arrived at interrogating the data set.

DR. WOOD: Thanks very much. Let's move on to the next presentation...