

Question 4: Low Dose ASA and CV Events

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

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Highlights

- **“CLASS” TRIAL SUGGESTED ASPIRIN REVERSED COX-2 GI AND CV EFFECTS:** Dr. Wood said that the CLASS trial “wasn’t a randomized comparison, although it does give some evidence that the G.I. benefit was antagonized by aspirin and the cardiovascular benefit was reversed as well...” Dr. Bathon said that the available data suggest that aspirin “seems to undo the GI benefit”.
- **ASPIRIN DATA LIMITED:** Dr. Nissen said “the amount of data we have ... is limited. It would be useful ... to study this in a more formal way with larger sample sizes whether, in fact, aspirin is an effective antagonist to the toxicity of this class of drugs”. Dr. Gross said “there is just not enough good evidence to comment on this one way or the other..” Dr. Wood said he agreed with Dr. Gross that there is insufficient evidence to answer the question.
- **ASPIRIN HAS LIMITED EFFECTS IN PREVENTING CARDIAC DISEASE:** Dr. Farrar said “Aspirin is not a panacea for cardiac vascular disease.” And in the COX-2 setting “it is clear to me that it doesn't work”.
- **COX-2 INHIBITORS NOT SUITABLE FOR HIGH CV RISK PATIENTS:** Dr. Cush said that if you “need aspirin for cardiovascular prophylaxis ... then you certainly shouldn't be on a COX-2 inhibitor.”
- **GI HOSPITALIZATIONS MAY BE LESS FREQUENT IN PATIENTS ON ASPIRIN+COX-2s THAN ASPIRIN+NSAIDS:** Dr. Nissen asked if any study compared GI toxicity with conventional NSAID+aspirin with a COX-2 inhibitor+aspirin. Dr. Cryer said there was only epidemiology data and this suggested hospitalizations are reduced with the COX-2 inhibitor+aspirin; however, with regard to “the traditional characterization of G.I. events” the two regimens appear equivalent.
- **LUMIRACOXIB CV RISK WAS REDUCED IN ASPIRIN SUBSET:** Dr. Villalba said that with lumiracoxib, the aspirin subset had no difference in MIs, whereas in the non-aspirin subset lumiracoxib had more MIs than naproxen (“like, 10 to 2 myocardial infarctions”).

- **TARGET TRIAL:** Dr. Cryer said that in the TARGET trial in the 18,000 patients, there were no

statistically significant differences with respect to low-dose aspirin and G.I. events”.

Discussion Text: Question No. 4

DR. WOOD: So let's move on the Question No. 4; if the available data support a conclusion that one or more COX-2 selective agents increase the risk of cardiovascular events, and we have clearly made that decision already, then please comment on the role, if any, of concomitant use of low-dose aspirin in reducing cardiovascular events in patients treated with COX-2-selective NSAIDs. I am not sure how we can do that, apart from the sort of biological basis. There are not any randomized trials in which we have got data from that, are there? Ones that are on the market here?

DR. HENNEKENS: If we accepted a global risk assessment and aggressive management of cardiovascular risk based on federal and AHA guidelines, that embedded in both of those sets of guidelines are guidelines for the aggressive management with statins and aspirin rather than a recommendation that is for a specific drug in specific response to this class of drug.

DR. WOOD: No; but I think the question here, Charlie, is that if we accept that this drug, in itself, carries a risk of cardiovascular disease--let me rephrase the question. I think the question that is being asked here is do we think that the cardiovascular risk produced by these drugs, or any one of these drugs, can be reversed by the

administration of aspirin. That is what we are trying to get at.

DR. HENNEKENS: I wanted to rephrase the answer and say that I think aggressive assessment and management of all cardiovascular risks of these patients is what is indicated. I think it would be a mistake to limit it based on a pharmacologic argument to this one particular agent. And, in addition, there are exiting federal and NIH guidelines--AHA guidelines; I'm sorry--for the management of these patients for both statins and aspirin which would kick in. That, to me, makes much more rational sense.

DR. WOOD: No, no. I understand that. But let me just correct it. This could apply to a patient independently of their--a patient who was not eligible for aspirin under AHA or federal guidelines. So the question that is being put here is whether a patient who is taking these drugs who would not otherwise be eligible for aspirin under federal AHA guidelines should take aspirin to counteract the adverse effects of this drug. Am I right; John?

DR. JENKINS: Yes. That is exactly correct. That would be a logical place you might go if you think these drugs have a cardiovascular risk. Based on the mechanisms proposed, you might think you can take a low-dose aspirin and reverse it. But we want to know your thoughts about whether that has any

value in reversing the cardiovascular risk and what the impact is on the G.I. benefit because this will come down to a question we will have to address in the labeling for these products whether there should be any comment about use of low-dose aspirin.

DR. WOOD: So I guess the study that speaks to that most, I suppose, would be the CLASS study. It wasn't a randomized comparison, although it does give some evidence that the G.I. benefit was antagonized by aspirin and the cardiovascular benefit was reversed as well, I suppose. Steve?

DR. NISSEN: I understand the spirit of what you are asking here and let me see if I can frame this. You are asking whether we have evidence that the mechanism-specific effect of these drugs can be reversed by concomitant administration of aspirin. I have looked at all the data. I looked at that APC data. I looked at everything else. Just there is no compelling evidence of it. It goes both ways and this is actually one of the biggest disappointments for the whole class because, when this whole hypothesis was first raised, there were people who said, don't worry about these drugs. Just give everybody a baby aspirin every day and you can reverse the cardiovascular toxicity of the COX-2 inhibitors. It turns out that that hypothesis, and I have said a number of times, the road to hell is paved with biological plausibility, and this is another example of that the, in fact, it was plausible but it appears to be wrong. Having said that, the amount of data we have upon which to make that judgment is limited. It would be useful, at some point in the future, if this class of drugs is to survive in the long run, to study this

in a more formal way with larger sample sizes that will let people like Ralph and Tom and others calculate with more precision whether, in fact, aspirin is an effective antagonist to the toxicity of this class of drugs.

DR. WOOD: Dr. Bathon.

DR. BATHON: I agree with Steve that, with the available data that we have so far, the addition of aspirin not only does not appear to reduce the cardiotoxicity but it also seems to undo the G.I. benefit. But, more importantly, if somebody is on an aspirin with a COX-2, you no longer have COX-2 selectivity anyway, so it doesn't make rational sense to put the two together. If somebody needs aspirin, then there is no particular advantage to them being on a COX-2 drug unless one argues that aspirin plus a nonselective NSAID has higher G.I. toxicity, perhaps, than aspirin plus a COX-2 selective agent and I don't know that we have those data.

DR. WOOD: Dr. Domanski.

DR. DOMANSKI: I think it is important to paraphrase Dr. FitzGerald--he may still be here--but I have learned from him. It is clear that there is--at least it seems clear that there is a derangement caused by these drugs and no particular reason to believe that aspirin mitigates the derangement.

DR. WOOD: It is always dangerous to paraphrase Garret. I will tell you that. Dr. Platt?

DR. PLATT: It seems to me the arguments for aspirin, if we accept them, could clearly move these drugs into second-line status. Those who didn't

think so before, I think, lose the rationale there is for treating these drugs as just regular NSAIDs.

DR. WOOD: Dr. Gross?

DR. GROSS: I think there is just not enough good evidence to comment on this one way or the other and the question raised was not a primary endpoint on any of the studies we used.

DR. WOOD: Dr. Farrar.

DR. FARRAR: I think we need to be careful. Aspirin is not a panacea for cardiac vascular disease. I think the cardiologists would know better than I but, in my discussions with a couple of people last night and in the past with some of my colleagues at the University of Pennsylvania, it is clear that, in people with cardiac risk, serious cardiac risk, aspirin is probably useful in the general population. It is not at all clear and the benefit is actually reasonably small. So I am not sure why there is a sense of loss that it doesn't work. But it is clear to me that it doesn't work. The only evidence that seemed to suggest it at all was the APPROVe study and it was the outlier.

DR. WOOD: Any other comments? Dr. Cush?

DR. CUSH: To, again, paraphrase and reinforce what Joan said in that, if you probably need aspirin for cardiovascular prophylaxis and its modest effects on that, then you certainly shouldn't be on a COX-2 inhibitor.

DR. NISSEN: There was one question I had for our G.I. colleagues that never got answered and maybe you can help with

this. Is there a comparison of a conventional NSAID plus aspirin for cardiac protection versus a COX-2 inhibitor plus aspirin. Is there a quantitative difference in the risk of G.I. toxicity?

DR. CRYER: It depends on how you make the comparison. If you derive your comparison--and I am speaking about data that, to my knowledge, has not yet hit the peer-review published world. If you make the determination, epidemiologically, based upon hospitalizations for upper G.I. bleeding, the data would suggest that a COX-2 specific inhibitor plus aspirin appears to be a regimen that is associated with a lower rate of hospitalizations than nonselective NSAID plus aspirin. If you make the determination based upon the traditional characterization of G.I. events, the two arms appear equivalent.

DR. WOOD: At a personal level, I agree with Dr. Gross. I don't think there is any evidence base that we can answer that on, however attractive the underlying hypothesis might be. I don't think we need to go around and vote on that. Does anyone else have anything they want to say on that that has not been said? Yes, Ralph?

DR. D'AGOSTINO: Maybe the FDA could remind us. There was--I can't find it quickly, but there was concern in one of the non-inferiority trials that, if the study had too many individuals that were taking aspirin, not randomized to aspirin but taking aspirin, it was going to pull the two groups together. Could somebody from the FDA just remind us where that concern--

DR. VILLALBA: In the lumiracoxib studies, the subgroup on aspirin showed that--in the non-aspirin group, there is a clear signal for lumiracoxib versus naproxen. There were, like, 10 to 2 myocardial infarctions, while in the subgroup using aspirin, there was no difference.

DR. CRYER: I had forgotten about the TARGET--this is Cryer, again, to answer Dr. Nissen's question. I had forgotten about the TARGET trial and I will just remind the group of yesterday's presentation. In the 18,000 patients, there were no differences with respect to low-dose aspirin and G.I. events, no statistically significant differences.

DR. WOOD: Any other comments on that? Yes?

DR. FLEMING: Fleming. The data are pretty limited. If you look at all 18,000 patients, it was 24, 23 in those that are aspirin users but it was 35, 27 in those that were not. So it is rather fragile while, in other studies like APPROVe, there was no evidence of interaction.

DR. WOOD: I am going to jump to Question 6 because Question 6 we have to take a vote on. So I want to make sure we get that under our belt and then we will come back to Question 5. Question 6 is, do you recommend that the labeling for these products include information regarding the absence of long-term controlled clinical-trial data to assess the potential cardiovascular effects of these drugs. If so, please describe how you recommend that information be conveyed, warning, precaution. I have a sense, John, that we have already covered that, to some extent, haven't we?

DR. JENKINS: Again, noting that this question is about the agent other than the three we just discussed. This is about the other twenty.

DR. WOOD: I'm sorry. Then we will keep going on 5, then. I beg your pardon. So we have dealt with 4. Let's go on to 5.