

Committee Questions to Dr. Fitzgerald

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

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Highlights

IS LOW-DOSE ASPIRIN CARDIOPROTECTIVE IN COXIB SETTING?

- **URNS COXIB INTO NON-SELECTIVE NSAID?** Dr. Schafer (and several others over the course of the meeting) asked why addition of 100% COX-1 inhibition with low dose aspirin does not seem to prevent the cardiovascular toxicity of Vioxx – by turning it into a non-selective NSAID.
- **IMPACT OF LONG-LASTING ASPIRIN PLATELET EFFECT:** Dr. Fitzgerald, on this occasion and on other later occasions, did not give an answer that appeared satisfactory to all the Committee members. On this occasion, Dr. Fitzgerald said this was a function of time and that the long-lasting effects of aspirin meant that aspirin plus a COX-2 inhibitor would have longer-lasting COX-1 inhibition than a non-selective NSAID like ibuprofen plus a COX-2 inhibitor. Dr. Schafer said that this “cut in the opposite direction” because the long-lasting COX-1 selectivity of aspirin should give long-lasting protection against the adverse effects of COX-2 inhibition.
- **NOT “YING & YANG”:** Dr. Fitzgerald said that this was not a “Ying and Yang” situation and that “a priori one would expect that aspirin would damp rather than abolish the signal” and that the number of events on aspirin is “so vanishingly small that it is really conjecture”. In later discussion, he seemed to imply that prostacyclin has wide-ranging effects, not all of which are antagonized by thromboxane; thus the adverse effects of COX-2-inhibitor-induced inhibition of prostacyclin would not be fully counteracted by simultaneous COX-1 inhibition of thromboxane.
- **DOES COX-2 INHIBITION BY NON-SELECTIVE NSAIDS IMPLY THEY WILL BE CARDIOTOXIC?** Others later in the meeting suggested that this explanation would imply that non-selective NSAIDs should share the

cardiovascular toxicity demonstrated with the "COX-2 inhibitors".

- **IS IT PROSTACYCLIN OR COX-2 EXPRESSION WITH WIDE-RANGING EFFECTS?** Pfizer, in a subsequent presentation,

seemed to imply not that prostacyclin has wide-ranging effects, but that COX-2 expression has wide-ranging effects, not all of which are mediated by prostacyclin.

OTHER:

- **ARE NON-SELECTIVE NSAIDs SAFE FOR HEART?** Dr. Wood asked if non-selective NSAIDs are safe for the heart; Dr. Fitzgerald implied that he considered this to be the case.
- **UNCLEAR WHICH DRUGS ARE COX-2 SELECTIVE:** Dr. Abramson pointed out that, based on in vitro studies, COX-2 selectivity was a continuum and that there was a "cluster of 5 or 6 drugs" such as diclofenac, celecoxib, miloxicam and etodolac that are "comparably COX-2 selective" and a "complex story of what one might call functional COX-2 selectivity" because of "transient COX-1 inhibition" in the face of prolonged COX-2 inhibition. Dr. Fitzgerald responded by saying that individuals vary in the amount of COX-2 selectivity and that "the class is the mechanism by which the selective inhibition of COX-2 is attained". He did not state which drugs should be considered COX-2 selective.
- **DOSE-RESPONSE: INDIVIDUAL OR POPULATION FEATURE?** Dr. Nissen asked Dr. Fitzgerald to clarify that what he was saying was that there was sufficient dose overlap so that a low dose in one patient could be a high dose in another, but that he was not suggesting that the higher dose of a

drug was not associated on a population basis with more cardiovascular toxicity. Dr. Fitzgerald did not respond directly but agreed that there was "a dose-related effect for populations".

- **ARE BP DIFFERENCES BETWEEN COXIBS COX-2-DEPENDENT?** Dr. Nissen also asked if Dr. Fitzgerald was suggesting that the "striking" differences between celecoxib and rofecoxib seen in blood pressure effect were related to COX-2 selectivity. Dr. Fitzgerald said that with the available data selectivity and duration of action are confounded and you can't differentiate between the two. However, studies should be done to standardize the COX-2 selectivity seen and then see if blood pressure effects are purely a function of selectivity.
- **IDENTIFICATION OF PATIENTS AT HIGH-RISK FROM COX-2s:** Dr. Wood, Dr. D'Agostino and others asked how one could determine which patients should avoid COX-2 inhibitors. Dr. Bathon asked if the higher cardiovascular risk in patients with rheumatoid arthritis could be attributable to the high dosage of NSAIDs required to treat this

condition. Dr. Fitzgerald did not have definitive answers.

- **STANDARDS FOR NON-COXIB COX-2 SELECTIVE DRUGS:** Dr. Cryer asked if diclofenac-like drugs with similar COX-2 selectivity to celecoxib (he recalled that Dr. Fitzgerald had called diclofenac “celecoxib with hepatic side effects”) should meet the same safety testing standards. Dr. Fitzgerald said that this was one of the unanswered questions and that the same question

applies to other drugs such as meloxicam.

- **EXTRAPOLATION BETWEEN DISEASES:** Dr. Gibovsky suggested that it was difficult to extrapolate from one disease to another.
- **COMPARE COX-2 INHIBITION IN PATIENTS WITH AND WITHOUT CV EVENT:** Dr. Manzi suggested that it might be useful to compare the level of COX-2 inhibition in patients with and without cardiovascular events.

Discussion Text

DR. WOOD: Thank you. Just before you sit down, one thing you seemed to be saying is that we should exclude patients at high risk. The point estimate in the APPROVe trial for people with no symptomatic history of heart disease is 1.6 so that would be one way you would exclude people, I guess, but the point estimate remains 1.6. Does that bother you?

DR. FITZGERALD: No, as I alluded to, I think the nature of the information we have in the APPROVe trial so far remains to be played out. Clearly, there was an attempt to exclude people at high cardiovascular risk but we all know that people who are at risk slip through any exclusion criteria. So, one question is, is all that we are seeing people who, for one reason or another, are predisposed to thrombosis and they are the people that are having events? Or, are we seeing people who through atherogenesis transform their risk? Or, are we seeing some combination of the two? I don't think we know the answer to that.

DR. MANZI: I have a question for Dr. FitzGerald. This is really in reference to your suggestion that we exclude people with high thrombotic potential. I think there is clearly evidence that the natural aging process is associated with less effective fibrinolytic system, really increased thrombogenic potential with high levels of fibrinogen, PI-1 platelet aggregation, and considering that the elderly population is a huge target for non-steroidals, would you consider age as a risk?

DR. FITZGERALD: Well, I think, as you indicate, lots of things happen as we get older including the complexity of administering drugs and it ultimately culminates in death. But I think the issue of determining cardiovascular risk is actually a very challenging one because it includes continuous and discontinuous variables. It is easy to say if you have had a heart attack or a stroke you are statistically at greater risk of having another one. It is harder to say that at an

individual level, somebody who hasn't had a heart attack or a stroke has a cluster of variables that, in the eyes of their physician, determines their cardiovascular risk. With some of the discontinuous variables like some of the genetic mutations we can have an attributable risk that we can measure but, again, that can play geometrically into other small but absolute risks. So, unfortunately, I think it is where the art and science of medicine intersect.

DR. WOOD: Richard Cannon?

DR. CANNON: You asked my question.

DR. WOOD: Joan Bathon?

DR. BATHON: We know that patients with rheumatoid arthritis and other inflammatory conditions are at higher risk for developing acute MIs and strokes, and these are the very patients who are taking NSAIDs chronically. This is a big, confounding problem in interpreting some of the data and I am wondering if you have any thoughts. The reigning theory is that there is more atherosclerosis and RA due to vascular inflammation but I am wondering if you have any thoughts about whether the NSAIDs might be the sole contributor to increased events in these folks.

DR. FITZGERALD: Right. As I indicated, through a COX-2 inhibitory mechanism one would anticipate that the clinical substrate of underlying cardiovascular risk would be one of the modulators of either individual hazard or the ease of detecting hazard with this crude detector system we call clinical trials. As you know, the relative risk of heart attack or stroke and RA is

increased by about 50 percent on average compared to RA or no arthritis. As a population that would be one of the ingredients predisposing towards emergence of a hazard. Of course, within that population there is a very substantial inter-individual variability conditioned by many other factors that impinge on cardiovascular risk. So, at the time when we were naval gazing, looking at the contrast between CLASS and VIGOR, amongst the many things that were discussed was whether the preponderance of RA patients in VIGOR versus the preponderance of OA patients in CLASS may have been a factor. I think it is reasonable to say it may have been a factor but I don't think we can really take it beyond conjecture in light of any current evidence that I am aware of.

DR. WOOD: Garret, let's cut to the chase. Is what you are saying--that was such a long answer, I am not sure what it meant! (Laughter) Is what you are saying that you think that COX-2 inhibitors have an effect here that the most selective, so-called non-selective like diclofenac and naproxen may also have an effect, and the non-selective, non-steroidals do not have an effect, or at least have not been shown to have an effect? Is that your position? If it is not, correct that.

DR. FITZGERALD: No, I think that is pretty true.

DR. WOOD: So, that is what you wanted us to take away from all the mice and stuff, is it? (Laughter)

DR. FITZGERALD: You have such a way with words!

DR. WOOD: Because I am a Scot.
(Laughter)

DR. FITZGERALD: You are very economical with them.

DR. WOOD: Exactly.

DR. FITZGERALD: Unfortunately, reality is conditioned by a lot of different factors. I think one of the things, both in terms of benefit and hazard, we have paid insufficient attention to is variability in drug response between individuals, and I think actually one of the things that has got us to today is not paying enough attention to that. But I think one of the ways out of the challenge that faces us today if we are to conserve the value is to exploit that variability in imaginative ways. So, I think that that is a tractable issue.

DR. WOOD: Okay.

Dr. Abramson?

DR. ABRAMSON: Yes, Garret, even though you are under the weather I wanted to follow-up with Dr. Wood's question and put you on the spot a little bit. It is partly definitions because we use the word NSAIDs which we elect by inhibiting COX-2s. Based on your presentation, it is clearly a continuum and there are highly selective drugs. There is a cluster of five or six drugs, like diclofenac, that are in vitro at least comparably COX-2 selected. Then you have these very complex stories of what one might call functional COX-2 selectivity, which is based on the fact that the COX-1 inhibition may be more transient effectively than a more prolonged COX-2, which would give you imbalance. So, I guess the "put on

the spot" question is what do you define as the class? How do you propose we should think about this continuum and personalize medicine?

DR. FITZGERALD: I think you are right. I would remind all of us that COX-2 inhibitors are NSAIDs; they were never anything else. They are NSAIDs that are selective for COX-2 and, as you are rightly pointing out, this is a continuous variable and within each drug, as I tried to point out, there is the same continuous variable between individuals. So, my 800 mg of Celebrex may be your 200 mg of Celebrex for example. So, I think all I am trying to raise is that there is clearly a mechanism which reflects the selective inhibition of COX-2. That selective inhibition of COX-2, in terms of hazard, is modulated by COX-1 inhibition that occurs at the same time if it is sufficient to inhibit platelet activation for example. So, I can't simplify that because I believe there is that complexity, but within the class--and I am referring to the class as the mechanism by which selective inhibition of COX-2 is attained--I think there is clearly a mechanism that explains everything that we have seen. At the individual level this issue of a continuum comes into play because not only is there a continuum in terms of drug action and the degree of selectivity attained in an individual, but also many other factors impinging on cardiovascular risk that condition the emergence of that hazard at the individual level.

DR. WOOD: Steve?

DR. NISSEN: Yes, I have two quick questions. You know, I want to talk with you a little bit more about this issue of

dose dependency. I want to make sure we didn't misunderstand you. What you are saying I believe is that there is sufficient overlap in the biological effects that a low dose in one patient may be equivalent to a high dose in another. But you didn't mean to suggest that we don't see evidence, as I think we do see from the trials, that the higher the dose of the drug on a population basis, the more we see--

DR. FITZGERALD: No, no, clearly there is evidence of a dose-related effect in populations. I am talking more at the individual level, that the assurance to a population based on population type evidence that all you need to do is reduce the dose and you, as an individual, will be protected from hazard is a false one.

DR. NISSEN: Yes, but it is quite relevant obviously to our discussions on Friday because one of the strategies to limit risk with this class of drugs is to limit dose--

DR. FITZGERALD: Sure.

DR. NISSEN: --and it may not make the hazard go away but it may make it smaller, and we are going to have to explore that in some detail before we finish.

DR. FITZGERALD: Well, I think that distinction between reducing it as opposed to making it go away and the distinction between population hazard and individual hazard is an important one. It is the reason that I raised that particular point because I think that had not received sufficient attention.

DR. NISSEN: The second question I have is, you know, we have very few direct head-to-head trials amongst the so-called COX-2 inhibitors, but we do have for hypertension and there seemed to be really pretty striking differences in the hypertensive response between rofecoxib and celecoxib. Would your point of view be that those differences are strictly a matter of COX-2 selectivity of the two drugs, or do you think that it is possible that there is some dissociation in the hypertension response?

DR. FITZGERALD: I would make two points. I would say, first of all, that in that particular comparison, again on average, we would anticipate that selectivity and duration of action would be confounded and it would be impossible to really segregate the two. The second is that, in a sense you pressed my button, I believe we have not performed the studies in hypertension that let us address the key questions that are on the table, and that is standardizing for the degree of selectivity attained or the degree of COX-2 inhibition attained do drugs come apart? That question has been on the table since the mouse studies of Breyer and Kaufman, and perhaps the first signal of that is the epidemiological overview analysis from Australia. But, in fact, we have never performed a study to address the hypothesis and I think it is timely that we do.

DR. WOOD: I see. Dr. Cryer. Did you want to say something?

DR. CRYER: Dr. Cryer has a question.

DR. WOOD: Go ahead.

DR. CRYER: Garret, you clearly made the point that diclofenac appears to have

some COX-2 selectivity. In fact, I think you called it celecoxib with hepatic side effects. You also made the point that we should subject drugs already approved to the same requirements. So, the specific question I have for you is are you suggesting that we should evaluate diclofenac as well for its potential cardiac effects?

DR. FITZGERALD: Yes, I think there are quite a few unanswered questions on the table. I think clearly the diclofenac question is one of them. I think there are other drugs that fall into potentially the same situation, like meloxicam and nimesulide which, again, based on the IC-50 comparisons look awfully similar to diclofenac and Celebrex but we just don't have the information even at a more fundamental level than outcome studies. So, I think those questions are on the table. The reason I made the comparison between retention of approval and gaining approval is that, to me, if we do actually have to address some questions to determine the parameters within which drugs in this class can be administered safely and that would be a hurdle that any new drug would be required to overcome, in logic to me, it would be sensible to apply the same standard to the extended dosing of drugs that already are on the market as a condition of their retention of approval.

DR. WOOD: Dr. Shafer?

DR. SHAFER: Yes, this is the question we just talked about briefly at the break, but as you pointed out, low dose aspirin gives you 100 percent inhibition of COX-1. One might think then that low dose aspirin plus a COX-2 selective antagonist might give you the same risks as a non-selective NSAID. Yet, in all the

studies where they had aspirin present and they showed a CV risk, when they stratified by aspirin, among aspirin users the hazard didn't go away. Now, what did happen is that some statistically significant hazards became non-statistically significant hazards but the actual magnitude of the hazard, at least as far as I can tell in all the studies that I looked at, didn't change. I am having trouble understanding how that is consistent with the whole thing being the COX-2 imbalance.

DR. FITZGERALD: Right. So, one important missing dimension in your question is time. One of the key ingredients of aspirin's ability to afford cardioprotection is that while it inhibits COX-1 like ibuprofen does, it does it molecularly in a quite distinct fashion. This results in sustained maximal inhibition throughout the dosing interval. By contrast, in the typical non-steroidal you are in the red zone for platelet inhibition transiently in the dosing interval. Therefore, one would not expect the combination of, say, ibuprofen with a COX-2 inhibitor to be similar to aspirin with a COX-2 inhibitor in terms of cardiac protection.

DR. SHAFER: Doesn't that head in the opposite direction?

DR. FITZGERALD: In terms of which?

DR. SHAFER: The fact that the aspirin's effect is sustained because, you know, it is covalently bonded there--the fact that you are having a sustained aspirin effect means that you should absolutely--I mean, it would seem to me that that would really try to make the COX-2s look--

DR. FITZGERALD: Well, I will come back to what I said during my talk, and that is that I think a real mistake is to think of this as a yin and yang type of seesaw arrangement between thromboxane and prostacyclin. We know that prostacyclin acts as a general biological constraint on anything that will activate platelets, elevate blood pressure, accelerate atherogenesis, and so on. So, a priori we would expect that aspirin would damp rather than abolish the signal. Now, I would contend that, first of all, we have never formally addressed this and, in terms of the trials that have events, although we have attempted to look at the relationship to aspirin the numbers are so vanishingly small that it is really conjecture. But one would expect a signal to be damped. Indeed, from some of the epidemiology that is sort of what we are seeing, you know, a signal goes away at 25 mg of rofecoxib if they are on aspirin but not at 50, that sort of stuff. But I would be the first to agree that this is really a crude stab at the issue that you are trying to get at.

DR. WOOD: Yes, and these studies did not stratify by aspirin use. They were post hoc analyses in the majority of cases. Dr. D'Agostino?

DR. D'AGOSTINO: I would like to go back to the question that was asked right after the break about the age. If you tried to say, well, the perfect way of doing this is to make sure that people at high cardiovascular risk aren't going to take the drug, then males over 60, for example, are almost certain to be excluded. How realistic--

DR. FITZGERALD: Certainly I am not trying to be dictatorial--

DR. D'AGOSTINO: No, no, your suggestion is fine, it is just how do you implement it?

DR. FITZGERALD: Yes, so I think all one can really hope to do is set the bar at some low level and then signal it in a way that is explicit and leave it to the patient-doctor relationship to divine the individual behavior. I would love to say there is a different way of doing it but, yes, as we get older our cardiovascular risk goes up and multiple other things. But that is where the balance against value comes into play. As we get older with get arthritis; as we get older we get more GI bleeds on non-steroidals.

DR. WOOD: Okay, we got it. Let's not go too far there. One more question from Dr. Gibofsky.

DR. GIBOFSKY: Dr. FitzGerald, in response to Dr. Nissen, I believe, you raised the notion and asked us to think about population variation as a factor in addition to individual variation. One of the things that I am struggling with is exactly that, and one of the concerns I have is to what extent then can one extrapolate observations in populations of patients who may have Alzheimer's disease or who may have taken a drug for polyp prevention to the population of patients who are taking the drug for their arthritis?

DR. FITZGERALD: Well, I think in a way this whole cathartic experience is a cardinal point in the way that we look at drug development. You know, we have talked about individualized medicine for a long time and never really had to care,

and here is a situation where we actually do have to care and it is at the forefront of how we may or may not be able to find a way out of this. You are absolutely right, there may be factors associated with an incident disease which is under study which modulates the importance or non-importance of the signal; modulates the way that drugs are metabolized; may be associated with genetic variance that influence outcome as well.

DR. WOOD: Any other questions for the last two speakers? (No response)