

Issues in Projecting Increased Risk of Cardiovascular Events to the Exposed Population: Robert O'Neill PhD

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

February 16-18, 2005, Hilton Gaithersburg, 620 Perry Parkway, Gaithersburg, Maryland.

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Highlights

- **PROBLEM NOT WELL STUDIED:** There is very little published on projecting risk to an exposed population so that he will just try to identify a logical framework to address the issue.
- **PROBLEM DIFFICULT AND ASSUMPTION-DEPENDENT:** It is “a very difficult problem” to get an estimate, and any estimate is not precise but sensitive to “all the assumptions you have to make”.
- **INFORMATION NEEDED:** We need to know how many people are on drug, for how long, at the level of the national population. And we have to integrate information from both clinical trials and epidemiology studies. Terms such as “event definitions” are important.

TIME MATTERS:

- **BOTH TOTAL RISK AND RISK PER UNIT TIME MAY BE A FUNCTION OF TIME ON DRUG:** His most important point is that “time matters”. With a hazard ratio that is constant over time, the total risk increases with increasing time. In addition, if the hazard per unit time increases with time, there is “escalation” of risk as duration of therapy increases. He pointed out that, when risk escalates with increasing time, as appeared to be the case in the VIGOR (RR 2.28) and APPROVe (RR 1.92) trials, the calculated relative risk is an average risk over the entire time period, but the relative risk during the latter part of the time period is higher than this average.
- **OBSERVATIONAL DATA CANNOT IDENTIFY EARLY RISK BECAUSE OF “TIME FROM NEW USE” PROBLEMS AND LACK OF A PARALLEL GROUP TO EXCLUDE EFFECT OF PRIOR NSAID:** With regard to identifying increased risk early when

there is a “power issue”, he does not believe that Dr. Graham’s observational data with increased risk in a population that only had short-term therapy “adds anything to our knowledge about early risk, for the points I made yesterday” <Note: His comments the previous day questioned whether “time from new use” was correctly identified, and that, without a parallel group, an early effect might just reflect the effect of discontinuing the previous NSAID>.

- **VERY LIMITED DATA ON NUMBERS OF PEOPLE IN U.S. POPULATION EXPOSED AND ON DURATION OF THERAPY:** Unfortunately, “we have no data in the United States” that provides information on “how many people are exposed for how long a period of time”. However, they were able to do a “projection based upon the IMS National Prescription data” that examined this question, and this showed “Surprisingly enough, a very

small percentage of the millions of people that are prescribed the drug are on the drug for more than a year”.

- **IMS PRESCRIPTION DATA USED TO GENERATE VERY CRUDE AND UNRELIABLE ESTIMATE:** They used the IMS information and a “number of assumptions many of which are not verifiable” to come up with a “crude estimate” which we “probably don’t believe” but which is definitely “very variable”.
- **ESTIMATE OF “PATIENT-YEARS” NO GOOD FOR NON-PROPORTIONAL HAZARDS:** He thinks that we need to move “away from summarizing non-proportional hazards in person-years. It is not a good idea. It begs the question as to whether the risk is constant or whether the risk is dependent on time”. This is a major problem with the epidemiology literature.

OTHER POINTS:

- **NO EASY WAY OF COMBINING DATA FROM DIFFERENTLY DESIGNED CLINICAL TRIALS:** A major problem with clinical trials is trying to integrate the information from several clinical trials that may differ in the patient population or the dosage used.
- **HIS CONCLUSION:** “So the point here is that this is a very difficult exercise to project. This was just a

framework to say, here is how you might think about it”.

- **HIS “ESTIMATE” BASED ON NUMBER AT RISK AND RISK IF EXPOSED:** After Dr. O’Neill’s talk, Dr. Wood asked him to clarify what he meant by “estimate”. Dr. O’Neill said he meant: “An estimate of the absolute numbers of individuals that might have been at risk, and had these events if they were exposed”.

Presentation Text

DR. O'NEILL: What I was asked to do is essentially provide a framework. This is a very difficult problem of projecting risk to the population. Very little has been published about how to do this appropriate so I was intending to go through sort of the logic and the framework of how you might think about this.

It requires the integration of exposure data at the national population level and it needs information relative to how long people are on drugs and it uses information from the clinical trials as well as from the epidemiology studies to the extent that they are relevant to the question that is being asked.

This is a very difficult problem. It was not intended to give any estimate, any single number. It was intended to show how hard it is to get there and, at the end of the day, how variable and sensitive the estimate might be to all the assumptions you have to make.

So I used the Vioxx VIGOR and APPROVe studies as an example of the process that one might go through. I made the point that event definitions and many things matter. But I guess if there is anything that I would like people to take home is that time matters. The hazard rate matters. And the hazard ratio matters as a function of time when you do any of these projections.

I would just recall two slides. One would be the VIGOR study which is Slide 12 so that everybody could remind themselves and Slide 16. The VIGOR study shows a separation of curves. Behind that is what is called a hazard

rate. I believe the data supports that the escalation of the risk increases with duration of exposure. Merck and we have talked about this in the past and sort of have different views of this, but we seem to feel that that risk does escalate.

That does not mean that there is no risk in that picture early on. I think David Graham has made this point that it may be a power issue but, nonetheless, it is what it is and I am not convinced that the epidemiological studies at this stage add anything to our knowledge about early risk for the points I made yesterday because I think time zero matters in terms of looking at the risk, in terms of how long you are on.

The next slide is Slide 16 which is the APPROVe study. Similar pattern, only delayed a year. So instead of the curve separating at approximately six months, four months, they separate a little later on. The idea here is that the relative risks that are summary relative risks for both of these trials, for VIGOR, for thrombotic event, it is approximately 2.28 and, for APPROVe, it is approximately 1.92 for confirmed thrombotic events is an average relative risk averaged over all the time points so that the relative risk at different times is a function of time.

That is an important concept when, then, you go and you look at the national projection of how many people are exposed for how long a period of time. I won't go through that because they are in the slides. But we have no data in the United States to do this. So we did a projection based upon the IMS National

Prescription data, another separate database that allowed us to look at how long exposure, success of exposures, might be to get an idea of how long individuals may stay on the drug.

Surprisingly enough, a very small percentage of the millions of people that are prescribed the drug are on the drug for more than a year. That is in one of the slides on the Caremark. So what this meant is you multiply all these estimates which, essentially, are time. We calculated a time-specific difference in absolute incidence rates for the different trials, made a projection and essentially used in that projection a number of assumptions many of which are not verifiable, and then came up with some crude estimate of what might even be an upper bound on a confidence interval for any estimate.

We probably don't believe it because there is no real methodology to support that estimate but nonetheless to say that an estimate is very variable.

So the bottom line, and the conclusions here, given the time frame, is that purpose of the projection effort was essentially just to provide--this is the last slide; it is Slide 47--it is essentially to provide a framework for considering how you would think about developing an estimate and to provide a range of estimates and, also, essentially, to point out that there are many limitations to any estimate that you would provide.

We are not supporting any, or putting forward any, one estimate but I do believe that we need to understand this problem by moving away from summarizing non-proportional hazards in person-years. It is not a good idea. It

begs the question as to whether the risk is constant or whether the risk is dependent on time.

If there is one problem with the epidemiological literature, it constantly reports person-year risk as opposed to every one of the clinical trials we have seen presents a Kaplan-Meier curve that looks at the time-dependent risk. Unless you understand that, you can't come to grips with comparing one drug to another.

You can't come to grips with comparing a drug to itself. If you look at the VIGOR study relative to the APPROVe study, they are in different populations. One is in a population of R.A. The other is in a polyp prevention trial. One is at 50 milligrams. The other is at 25 milligrams.

There are many things that need to be sorted out. So the point here is that this is a very difficult exercise to project. This was just a framework to say, here is how you might think about it. Most of the estimates are fraught with a lot of danger and have to have many caveats placed on them were you to bank on any one estimate alone.

That is pretty much my bottom line.

DR. WOOD: Bob, just to make sure everybody in the audience understands what you are talking about with estimates, what you are talking about are absolute numbers of people—

DR. O'NEILL: An estimate of the absolute numbers of individuals that might have been at risk, and had these events if they were exposed--if they

were exposed. This is a model projection.

DR. WOOD: Right. I just wanted to clarify that. So it is not the relative risk. It is not the same as what Milt was talking about.

DR. O'NEILL: Right. Exactly. This is a long discussion to get into the concept of attributable risk in its own right. Given the time, I wouldn't be able to do that.

DR. WOOD: So you are talking about the number of people, these sort of numbers that are out there.

DR. O'NEILL: Right; to go through that exercise. It is hard enough to interpret a single study or a collection of studies. To go to an estimate of what the increased number of events might be at the exposed level is what this effort was about, all the different, five different separate interlinked but disparate databases that you would need to get there to make this kind of an estimate.