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Study Shows Uncertainty in Role of Statins in Primary Prevention For Women

FINDINGS OF A STUDY THAT EVALUATED PRIMARY PREVENTION CLINICAL STATIN TRIALS

A basic tentative modern Cardiology says that elevated cholesterol increases the risk of heart attacks, significantly lowering cholesterol should therefore reduce heart attack risk, statins reduce cholesterol and in some context adverse cardiac outcomes, but meta-analyses of primary prevention clinical statin trials for women with elevated cholesterols have found no statistically significant cardioprotective effects for women, so is it still appropriate or perhaps even illegal to market statins to women given the nonsignificant effect seen in women. Welcome to the Business of Medicine. I am Dr. Larry Kaskel, your host. My guest today is Theodore Eisenberg, Henry Allen Mark Professor of Law and adjunct professor of statistical sciences at Cornell University and he is here to discuss the results of the findings of a study that evaluated primary prevention clinical statin trials, which was recently published in Empirical Legal Study journal.

DR. LARRY KASKEL:

Counselor Eisenberg, welcome to the show.

THEODORE EISENBERG:

Hi, how are you?

DR. LARRY KASKEL:

I am good. Before we get to the results of the study, tell me why you even became interested in this and conducted the study in the first place?

THEODORE EISENBERG:

Sure, my wife went to a doctor as we advance in age, apparently some times the female cholesterol goes up. She went to the doctor who noticed the cholesterol was up and the doctor suggested that perhaps you should go on Lipitor. What gave her pause was the doctor said, of course before you do that, we will have to test your liver before and after and so therefore she came home and said why they do want to put me on a drug where they have to worry about my liver, does this work? and I had done some medical research in connection with litigation and tried to find evidence that not only did Lipitor reduce cholesterol, but it also better reduced, what you are

interested in which is bad heart outcomes and to my surprise, I couldn't find any evidence for any statin that there was a significant reduction in heart outcomes for reasonably healthy women.

DR. LARRY KASKEL:

Can you repeat that last sentence?

THEODORE EISENBERG:

I couldn't find any evidence for any statin that there was a significant reduction in adverse heart outcomes for reasonably healthy women.

DR. LARRY KASKEL:

And you said any study that includes studies done by the pharmaceutical giants.

THEODORE EISENBERG:

It includes the studies, I think, that they primary rely on to get FDA approval such as the ASCOT study for Lipitor where in fact the result for women was insignificant, but it was an increase in heart attack risk, not a decrease.

DR. LARRY KASKEL:

All right so, can you explain to our audience what is a meta-analyses study and are they better than regular studies or are they only better if they prove your thesis?

THEODORE EISENBERG:

A traditional meta-analyses, the analyst will not have access to the individual studies underlying data and the traditional meta-analyses works only from the published versions of the data and what the meta-analyses can allow you to do is to combine studies and perhaps support findings that trend in individual studies, but aren't significant in any individual study, but then when you combine the analyses into a single study that accounts for the uncertainty within each study, you get a single result that can point you in a reasonable direction. So, for example, suppose you had 10 small or moderate-sized studies, none of which showed a significant effect, but all of which went in the same direction, when you combine those to a meta-analyses, you might well find that there is a statistically significant effect and you might make policy based on that rather than dismiss each of the studies individually.

DR. LARRY KASKEL:

And counselor, can you tell me what the results in your findings were in your study?

THEODORE EISENBERG:

Well, I think there were 2 major findings. One, I think, was known before. When we combined the 5 major high-quality clinical trials of statins and these are different statins, but when we combined them, we found 2 things and this was looking at the primary prevention studies, one was that there were consistently statistically significant benefits in heart outcomes for men and what we found was there are equally consistently no significant benefits in heart outcomes for women. When you combine the 2 studies, you get an added result.

1. Significant protection for men.

2. No significant protection for women.

3. You get a statistically significant difference between men and women, which I do not think has been observed before in this context.

I mean there is lot of context where we know men and women are at different risk and I think we kind of knew, though not everyone acknowledged it, that there was no real evidence of protection for women in this context, but what there wasn't before was evidence of a significant difference between men and women. I think it is important because the National Cholesterol Education Program acknowledges that the benefits of statins for women are primarily based on extrapolation for men and so now that we had evidence that there is a statistically significant difference between the men and women, that position, I believe, is no longer so clearly scientifically supportable. You can't extract from 1 group to another when there is serious evidence that the groups are heterogeneous.

DR. LARRY KASKEL:

Let's not extrapolate, but let's take the results of your findings. How can a drug company support a claim that statins reduce the risk of heart attacks for women with this knowledge and this data out there? How can they do that?

THEODORE EISENBERG:

I think, at this point, one has to be quite careful in exactly what is they claim. If you look at through the 1 example I am most familiar with of course is Lipitor and they are advertising probably most people who watch TV at all or read the Wall Street Journal or other major media have seen a Lipitor ad in there and the one that's most striking to me is one with a picture of Robert Jarvik and a picture of the heart and in big fonts saying Lipitor reduces risk of heart attack by 36% and that's literally true in the following sense. In the 1 clinical trial on which their claim is based, which is known as the ASCOT trial, the combined results for men and women did reduce heart attacks by 36%. However, the results for men and women were different. There was a 41% reduction for men and a 10% increase for women, but the ad does not say reduction for women, but I think what the ad leaves out is at least as important as what it puts in. If I were a physician prescribing Lipitor for women, I would kind of want to know that the best point estimate of what it does is increase the risk even that is not significant.

DR. LARRY KASKEL:

You'd wanted to decrease the risk you mean.

THEODORE EISENBERG:

If I am prescribing it and they haven't told me that it increases the risk 10%, I think I would be angry.

DR. LARRY KASKEL:

All right, so let's explore that a little bit. Besides being angry, what else could you do for what is potentially misrepresentation or false advertising and will you take the case counselor?

THEODORE EISENBERG:

I won't take the case because these are expensive and these are very difficult cases to win, but I think there are at least 2 ways to reinforce potential misconduct by advertisers and by drug companies. One is private losses, the ideal plaintiff would be someone who has seen the ad, say look this drug reduces our risk of heart attack that plaintiff would be an otherwise healthy women and she would go into court and say I would like my money back because the evidence that Lipitor reduces my risk of heart attack is no greater than the evidence that Coca Cola reduces my risk of heart attack because Lipitor increased it by 10%, not decreased it for people in my group and I think that they should give me my money back even if I haven't suffered an adverse event because I paid for something that really there was no basis and my doctor may have read their label which says results were inconclusive for women, but it didn't tell him that actually risk increased for women. It is technically true results were inconclusive because the increase wasn't significant, but I think both me and my doctor should have been told a bit more than they told us and I think we wouldn't allow stocks to be sold on this basis. We shouldn't allow drugs to be sold on this basis.

DR. LARRY KASKEL:

And I would like to read to you counselor a quote from a book and this quote was written in the year 1865 – the men who have excessive faith in their theories or ideas are not only ill prepared for making discoveries, they also make very poor observations. Of necessity, they observe with a preconceived idea and when they device an experiment, they can see in its results only a confirmation of their theory. In this way, they distort observation and often neglect very important facts because they do not further their aim. So, I thought of that when I recently looked at the Jupiter trial and I know you have looked at that and is wondering if you would like to comment on what we have learnt or not learnt from the Jupiter study, statistically speaking.

THEODORE EISENBERG:

It's important to understand what the patient's population was in Jupiter. They excluded anyone with high cholesterol and they only included people with high C-reactive protein, which is as I understand it a marker for inflammation and so in some sense Jupiter is not directly comparable with the prior primary intervention studies that interest me with respect to women because in those studies people had on average either mildly or more than mildly elevated cholesterol and other risk factors. Suppose you treat our meta-analyses as one finding, so we don't have to talk about each individual study. The studies being ASCOT, ALLHAT, AFCAPS, and PROSPER, but we combine those for women and what we found is each of those studies showed a substantial reduction in cholesterol of women and none of them showed a cardioprotective effect. So, now you are over to Jupiter where you have taken out people with even moderately elevated cholesterol by current standards and you give them a different drug, not Lipitor in this case and they get a clear reduction in adverse cardiac outcomes. So, I mean you put those 2 next to each other and it seems to be saying, if you select people based on the risk factors in the 4 previous clinical trials that included some women, you get no result. If you select people based on C-reactive protein, you get a result, which seems to suggest that may be you shouldn't be giving these drugs to people selected on the criteria in the 4 studies, which would include high cholesterol that is we know from those studies statins do not work even though they lower cholesterol in those populations. We know from Jupiter, there is a beneficial effect for a different population. It seems to me that adds up to saying that cholesterol and perhaps other things have been a giant red herring in getting the right population on drugs that might help them.

DR. LARRY KASKEL:

Well, it has been very good for business for the last 20 to 30 years of treating cholesterol. I don't know that it has necessarily prolonged lives at all, but it has been very good for shareholders.

THEODORE EISENBERG:

Yeah and I don't want to over-claim. We are not saying that lowering cholesterol is never a good thing or worse thing is the evidence as we see it is that lowering the cholesterol in all the former primary prevention women studies didn't do any good and it seems to do some good when you don't have cholesterol as the filter or cholesterol as one of the filters.

DR. LARRY KASKEL:

Counselor, what would you tell a young physician coming out of their training that still believes in evidence-based medicine, if they were going into primary care treating patients with high cholesterol.

THEODORE EISENBERG:

Oh! well, this is really hard because I would say you really have to skeptically trust no one. You need to develop the skills to be able to read the studies and to evaluate the studies by yourself without input from interested parties because often on the face of the study, you will see things that will lead you to treat one way versus the other and I think the bottom line is I feel this is way about warriors too, we need more statistically sophisticated doctors and we need to give them the time to do the reading they need to do rather than to rely on third party supplying them summary information.

DR. LARRY KASKEL:

Well, we do unfortunately rely on the third party coming in for lunch, showing us a very pretty glossy poster showing a 50% reduction in risk and that is a relative risk reduction which has kind of taken over in the last 20 years and if you read the small print, they might tell you the absolute risk reduction and I asked the drug reps in my office, what is the absolute risk reduction and they usually don't know. They have to look it up and it is usually a very small number meaning 1% to 2%.

THEODORE EISENBERG:

It is a really bit scary because for example the ASCOT study, which was the one the FDA based approval of Lipitor with respect to it reducing heart attacks, so may be a dutiful physician gets to the point of reading the abstract, doesn't have time to read the whole article and actually think about each, you know, grass and table in it. The abstract doesn't tell him there is no result for women. The only way you get this is by, you know, reading the whole article yourself, which is I imagine rather difficult with respect to the time of most physicians, especially people with general practices, how can they read, you know, the heart literature, the lung literature, they must be very daunting. So, they have got to rely on things like national recommendations, one hopes perhaps more than, you know, drug company representatives, but the national recommendation in this case seemed to be not evidence based.

DR. LARRY KASKEL:

Counselor, in the news there has been a lot about preemption lately and I was wondering if you could explain how legal concept applies to marketing materials related to pharmaceuticals that have been approved by the FDA.

THEODORE EISENBERG:

I think 2 different aspects of preemption were separating. One is preemption with respect towards claims that a drug harmed someone. So, there wasn't adequate disclosure of the risk. That's not the central focus of what we were writing about, ours is about whether there is preemption of the advertising claims of drug companies and there even the FDA in its most extreme version has said advertising is different and that they have a much less aggressive view of state law actions being preempted with respect to advertising and they do with respect to things warned about on the label. My primary concern with Lipitor is not that it's hurting people necessarily, it's that of being sold a billion dollars or more a month to people many of whom believe it would reduce the heart attacks and there is no evidence of that and I think there is a strong case with those people if fully informed would want their money back.

DR. LARRY KASKEL:

Well, on that note, I would like to thank our guest, attorney Theodore Eisenberg, Henry Allen Mark Professor of Law and adjunct professor of statistical sciences at Cornell University. Thank you very much for coming on the show.

THEODORE EISENBERG:

Thank you very much.

DR. LARRY KASKEL:

I am Dr. Larry Kaskel, you have been listening to the Business Of Medicine on ReachMD XM160, The Channel for Medical Professionals and thanks for listening.

Hello, I am Dr. Susan Love from the Dr. Susan Love Research Foundation and a clinical professor at the David Geffen School of Medicine and you are listening to ReachMD, the Channel for Medical Professional.