Editorial

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We Know Less than We Think, Part 2: Aspirin Therapy in Diabetes Not a Given After All

It's happened again. Another major clinical trial has come along to demonstrate that a principle about which we felt intrinsically confident—because it made so much sense—may not be so rock-solid after all. But, as is so often the case, there are multiple caveats and cautions to consider before we throw the baby out with the bathwater. As we'll see below, there is plenty of room for questioning how applicable the new clinical findings might really be to the actual patients we see day in and day out.

What I'm referring to here is the emerging controversy over aspirin therapy as cardiovascular prophylaxis in diabetic patients. For some time now, a major recommendation of the American Diabetes Association (ADA) has been to give aspirin to virtually all diabetic patients in an effort to reduce their cardiovascular risk.[1] No one would argue that diabetic patients have a remarkably high risk of cardiovascular complications. The only problem is that the aspirin recommendation is not based on any prospective data. No randomized, controlled clinical trial has ever demonstrated a benefit of aspirin therapy in this high risk patient population. Additionally, we know that aspirin is far from a universally benign agent; bleeding can be a frequent complication, with gastrointestinal or central nervous system bleeding sometimes rising to the life threatening level.

The new study that has shaken everything up, the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial, was presented this past November at the American Heart Association meeting in New Orleans, LA and published in the November 12 issue of the *Journal of the American Medical Assocation*.[2] This well designed, randomized, open-label, prospective trial enrolled a total of 2,539 Japanese patients, with type 2 diabetes and no history of atherosclerotic disease, from 163 medical centers. These patients were assigned randomly to receive low dose aspirin therapy (81 or 100 mg/day) or no aspirin therapy, with an average follow-up period of 4.4 years.[2]

There was, indeed, a positive trend pointing toward a reduction in all atherosclerotic events (a 20% relative risk reduction) for the overall study population, but it did not reach the level of statistical significance that is needed to consider this a meaningful finding. To confuse things a bit further, however, there was a statistically significant 32% reduction in all atherosclerotic events, both fatal and nonfatal, with aspirin therapy in the subset of diabetic patients who were older than 65 years.[2]

So what sense can we make of all this? The bottom line is that the primary hypothesis, that low dose aspirin therapy reduces cardiovascular events in diabetic individuals, simply was not validated in a statistically acceptable fashion. But the aspirin enthusiasts can take some heart (no pun intended) in the fact that there was a statistically significant benefit in the older patients.

It's also worth factoring in the decidedly modest costs that are associated with aspirin therapy in diabetic patients. The likelihood of serious bleeding is really very small when we're talking about the sort of low doses that were employed in the JPAD trial. Clearly, the dollar cost of aspirin therapy is vanishingly low for this 100-year-old generic preparation. So it may still be quite reasonable to continue to follow the ADA guidelines and prescribe low dose aspirin therapy somewhat liberally—unless there is a particular reason to believe that a given patient's bleeding risk is above average. And there is certainly merit to the argument that our obese patients with diabetes in the United States may be at considerably higher baseline cardiovascular risk than the comparatively thinner Japanese participants in the JPAD study.

Assuming the medical community manages to develop some compromise guidelines allowing for fairly liberal usage of aspirin in patients with diabetes, it's nonetheless very disconcerting to be reminded how many of our standard practices have been based on tradition and bias rather than on prospectively gathered, scientific data. It behooves all of us to be rather humble in our prescribing practices. We need to recognize that much of what we are doing represents our best guess about what is best for our patients, rather than a practice that has been validated beyond all reasonable doubt. It's probably not a bad thing for us to be brought up a little short periodically and reminded that we are practicing, for the most part, the art rather than the science of medicine. ●

Author disclosures

The author reports no actual or potential conflicts of interest with regard to this column.

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