COMMENTS AND RESPONSES

Response to Yang and Chan. Metformin and the Risk of Cancer: Time-Related Biases in Observational Studies. Diabetes Care 2012;35:2665–2673

Yang and Chan (1) express uncertainty regarding immortal time bias, an established and rigorously founded principle in epidemiology and statistical sciences, and use data from the Hong Kong Diabetes Registry to quantify the effect of statin use on cardiovascular outcomes. Using the time-fixed approach, known to introduce immortal time bias, they find that statin use is associated with a 34% reduction in cardiovascular events, while the proper time-dependent approach led to a 47% increase in cardiovascular events. Unfortunately, observational research is not this simple. Two elements of the reasoning are untenable.

First, the time-fixed approach in these types of studies is simply erroneous. By this approach, a patient who was diagnosed with diabetes in 2005, starts treatment with statins in 2010, and is followed until 2012 will be considered as exposed to statins for the entire 7-year period from diagnosis to end of follow-up. This is downright incorrect since the patient was not exposed for the first 5 years and only exposed for the 2 years after starting statin treatment. Thus, the time period prior to the first statin prescription is unexposed but misclassified as exposed and is immortal since no events could have occurred during this time period, leading to immortal time bias (2). This bias can be prevented with the use of the appropriate time-dependent analyses, which correctly classify exposure during follow-up (3). Incidentally, misclassifying nonexposure to statins as exposed will, in fact, deflate the hazard ratio, not "inflate" it as the authors claim.

Second, it is problematic to use an example to disprove the bias when the example is weak. Indeed, observational studies are not suited to study intended effects of drugs, such as that of statin use on cardiovascular outcomes. Such studies will systematically be affected by intractable bias from "confounding by indication" (4,5). Indeed, the patients at risk for cardiovascular events are those who receive statins (the indication), while the patients in the comparison group do not receive them precisely because they are not indicated and thus are at a lower baseline risk of cardiovascular events. It is not surprising then that such a study would find an elevated risk of cardiovascular events with the use of statins, which is not a real increase but simply a reflection of bias from confounding by indication resulting from comparing patients with different baseline cardiovascular risk factors. The most sophisticated statistical analyses are hardly sufficient to adjust away such confounding, which is generally intractable (6). Thus, the hazard ratio of 1.47 estimated by the authors using the proper time-dependent approach is not surprising in an observational study subject to confounding by indication.

In summary, Yang and Chan's claim that time-fixed analyses are valid with time-dependent drug exposures is plainly untenable. On the contrary, such incorrect analyses will simply introduce immortal time–biased results and should not substitute the well-established methods that properly classify exposure during follow-up. Observational studies, an important component in the armamentarium of the assessment of drug effects, must be conducted with singular scientific rigor to avoid biases, including immortal time bias.

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