PHARMACOTHERAPY

LETTERS TO THE EDITOR

ARB Superiority Over ACE Inhibitors in Coronary Heart Disease: An Alternative Viewpoint

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Recently, *Pharmacotherapy* published a study showing a 31% reduction in major adverse cardiovascular events (MACE) and a 44% reduction in cardiovascular mortality, comparing angiotensin receptor blockers (ARBs) with angiotensin-converting enzyme inhibitors (ACEIs) in coronary heart disease.[1] In modern medicine, it is difficult to find any drug that reduces MACE by a third and mortality by nearly half compared with active therapy, especially when they share essentially the same pharmacologic mechanism. Moreover, these findings contradict randomized clinical trials with adjudicated outcomes that show little difference in MACE comparing ACEIs with ARBs,[2, 3] and only moderate risk reduction comparing ARBs with placebo.[4, 5]

These unexpected findings likely stem from major design flaws involving inappropriate use of "future" information to define "baseline" exposure. For example, the researchers excluded, as unexposed, anyone treated for less than 3 months and anyone without high adherence. Given that antihypertensive adherence rates rarely exceed 50%, such patients likely made up half or more of the originally eligible cohort. Their inappropriate exclusion causes significant underestimation of time at risk and overestimation of outcome incidence in both groups. Moreover, these criteria probably differentially excluded more ACEI than ARB users because ACEIs are associated with more adverse effects and lower persistence.[6, 7] Accordingly, person-time among the ACEI group would be more greatly underestimated, and incidence rates more greatly overestimated, than in the ARB group, consistent with a (false) finding of ARB benefit.

The researchers also introduced immortal time bias by requiring patients to survive 3 months after starting combination therapy to be included in either group. This 3-month period is "immortal" because, by definition, no patient could have died, else they would have been excluded for achieving less than 3 months of therapy.[8] A similar 1-month immortal period is introduced for all nonfatal outcomes by ignoring events within 30 days. In both cases, incidence rates presented are biased because cumulative person-time is lengthened arbitrarily, whereas zero outcomes could have occurred during that period, by design. Every single included patient contributed this immortal time; thus the additional event-free person-time is not trivial. Further, the immortal time for fatal outcomes is 3 times that for nonfatal outcomes (3 vs 1 mo, respectively), possibly explaining the surprising finding that mortality is reduced more than MACE.

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Readers should be wary of any cohort study that uses information captured during follow-up to ascertain baseline exposure. Such approaches often violate fundamental epidemiological principles and lead to substantially biased results.

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Author's Reply

We read with attention the alternative viewpoint of Dr. Smith with regard to our study recently published in *Pharmacotherapy*.[1] Our study compared the effects of angiotensin II receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs) on the risk of major adverse cardiovascular and cerebrovascular events (MACCE) when used in combination with statins in patients with established coronary heart disease (CHD). In both the overall and propensity score–matched populations, use of statin ARBs resulted in a significantly lower rate of MACCE compared with the use of statin ACEIs.[1] These results may be somewhat surprising because ARBs are often recommended as an alternative to ACEIs in patients with CHD.

To minimize false positives of MACCE, patients treated for less than 3 months or with low medication adherence were excluded. In addition, we applied the same exclusion criteria for both statin-ACEI and statin-ARB cohorts and excluded events that occurred within 1 month or 3 months of the treatment. Again, this was to minimize incorrect events because they are unlikely related to the effects of medications. We understand that immortal periods may have been introduced to both cohorts; however, given the retrospective nature of the study design, limited information was available to identify the patient cohorts. We used clinic visits and prescription records to determine the exposure to medications or events.

The use of ARBs has rapidly expanded in Korea because the cost of ARB prescriptions increased from 28.0% in 2005 to 46.6% in 2009 for the entire group of antihypertensive medications.[2] This shows that ARBs are not just used as a replacement for ACEIs. They are now one of the most widely used antihypertensive medications in Korea.

Dr. Smith argues that the underestimation of person-time and overestimation of incident rates for the statin-ACEI cohort are due to the different side-effect profile and medication adherence. Our study used the propensity score model and matched the cohorts at a 1:1 ratio based on patient characteristics to reduce such bias. Moreover, the calculated person-years were not strikingly different (3111.1 vs 3337.6 person-years in statin-ACEI and statin-ARB cohorts, respectively).[1]

Given the high volume of ARB consumed and the comparable person-years between the cohorts, we would argue that the person-time and the incidence rates did not favor one side over another. In addition, the nationwide database we used in our study was large enough to match the cohorts even with strict inclusion and exclusion criteria, although the variance of patient characteristics could have produced a difference.

In conclusion, we acknowledge that our study has limitations and the findings need to be interpreted carefully. The bias in question may not have been adjusted completely in our study. Our findings do not suggest that ARBs are superior to ACEIs when used in combination with statins. Instead, our data from Korea revealed differences between the two cohorts, and thus it warrants further comparative studies on the subject in other countries to confirm the results obtained.

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