Published in final edited form as:

Pharmacotherapy. 2019 February ; 39(2): 204–206. doi:10.1002/phar.2216.

ARB superiority over ACE inhibitors in Coronary Heart Disease: An Alternative Viewpoint

SM Smith^{1,2}, J Lee³, and S Lee³

¹Department of Pharmacotherapy & Translational Research, College of Pharmacy, University of Florida, Gainesville, Florida.

²Center for Integrative Cardiovascular and Metabolic Disease, University of Florida, Gainesville, Florida.

³College of Pharmacy, Ajou University, Suwon, South Korea.

Keywords

angiotensin receptor blocker; ACE inhibitors; Epidemiology; coronary heart disease; Study design

Recently, *Pharmacotherapy* published a study showing a 31% reduction in major adverse cardiovascular events (MACE) and 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 one-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 ACE-Is to ARBs,^{2,3} and only moderate risk reduction comparing ARBs to 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 <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 ACE-I than ARB users, since ACE-Is are associated with more adverse effects and lower persistence.^{6,7} Accordingly, person-time among the ACE-I 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 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 <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 thrice that for nonfatal outcomes (3 vs. 1 month, respectively), possibly explaining the surprising finding that mortality is reduced more than MACE.

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

Acknowledgments

Disclosures

Dr. Smith receives research funding from the National Heart, Lung, and Blood Institute (K01 HL138172).

References

1. Lee J, Lee S. Comparative Effectiveness of Combination Therapy with Statins and Angiotensin-Converting Enzyme Inhibitors versus Angiotensin II Receptor Blockers in Patients with Coronary Heart Disease: A Nationwide Population-Based Cohort Study in Korea. *Pharmacotherapy* 2018;38(11):1095–1105. [PubMed: 30225928]
2. Li EC, Heran BS, Wright JM. Angiotensin converting enzyme (ACE) inhibitors versus angiotensin receptor blockers for primary hypertension. *Cochrane Database Syst Rev* 2014(8):Cd009096.
3. Yusuf S, Teo KK, Pogue J, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008;358(15):1547–1559. [PubMed: 18378520]
4. Yusuf S, Teo K, Anderson C, et al. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. *Lancet* 2008;372(9644):1174–1183. [PubMed: 18757085]
5. Dahlof B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002;359(9311):995–1003. [PubMed: 11937178]
6. Cheng J, Zhang W, Zhang X, et al. Effect of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on all-cause mortality, cardiovascular deaths, and cardiovascular events in patients with diabetes mellitus: a meta-analysis. *JAMA Intern Med* 2014;174(5):773–785. [PubMed: 24687000]
7. Sanders GD, Coeytaux R, Dolor RJ, et al. Angiotensin-Converting Enzyme Inhibitors (ACEIs), Angiotensin II Receptor Antagonists (ARBs), and Direct Renin Inhibitors for Treating Essential Hypertension: An Update. Comparative Effectiveness Review No. 34. (Prepared by the Duke Evidence-based Practice Center under Contract No. 290–02-0025.) In. Rockville, MD: Agency for Healthcare Research and Quality; 6 2011.
8. Suissa S Immortal time bias in pharmaco-epidemiology. *Am J Epidemiol* 2008;167(4):492–499. [PubMed: 18056625]