AFP Journal Club

The Story Behind the Study

The "ARB-MI Paradox": Real or a Fluke?

MARK A. GRABER, MD, FACEP, *University of Iowa Carver College of Medicine, Iowa City, Iowa*
ROBERT DACHS, MD, FAAFP, *Ellis Hospital Family Medicine Residency Program, Schenectady, New York*
ANDREA DARBY-STEWART, MD, *St. Joseph's Family Medicine Residency Program, Phoenix, Arizona*

Purpose

In *AFP* Journal Club, three presenters review an interesting journal article in a conversational manner. These articles involve "hot topics" that affect family physicians or "bust" commonly held medical myths. The presenters give their opinions about the clinical value of the individual study discussed. The opinions reflect the views of the presenters, not those of *AFP* or the AAFP.

Article

Bangalore S, Kumar S, Wetterslev J, Messerli FH. Angiotensin receptor blockers and risk of MI: meta-analyses and trial sequential analyses of 147,020 patients from randomised trials. *BMJ.* 2011;26;342:d2234.

For more information on evidence-based medicine (EBM) terms, see the EBM Toolkit at http://www.aafp.org/afp/ebmtoolkit.

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Do ARBs increase cardiovascular mortality?

Mark: Prior research suggests that angiotensin receptor blockers (ARBs) increase cardiovascular mortality or, at best, have no effect on cardiovascular mortality compared with placebo.[1,2] This has led to the so-called "ARB-MI paradox," which asks, "How can a drug that lowers blood pressure also increase cardiovascular mortality?" This meta-analysis was designed to determine whether the ARB-MI paradox is real or a statistical fluke.

What does this article say?

Mark: The meta-analysis included 37 randomized controlled trials with 39 total arms comparing an ARB to either placebo (17 arms) or an active drug (22 arms). Some studies had two arms, one with placebo and one with an active drug. To be included, studies had to have at least 100 patients and a follow-up period of at least one year (average follow-up was 3.3 years). Studies were identified by searching the PubMed, Embase, and CENTRAL databases, as well as U.S. Food and Drug Administration documents related to a drug's approval or labeling changes. Authors of published studies were contacted only if needed information was not included in the published study. The outcomes of interest were myocardial infarction (MI), cardiovascular death, angina pectoris, stroke, heart failure, and new-onset diabetes mellitus.

The meta-analysis included 147,020 participants and had a total follow-up of 485,166 patient-years. Studies were categorized by two reviewers as being at high risk of bias or low risk of bias using the Cochrane Collaboration criteria,[3] and the same two reviewers extracted the data (kappa of 0.96 indicated very high agreement). Heterogeneity among studies was also assessed. If studies are too heterogeneous (e.g., the outcome of one study is blood pressure only and the outcome of another is MI only), the results cannot be combined in a meta-analysis.

Although the study did not show an ARB-MI paradox, ARBs were no better than placebo at preventing cardiovascular outcomes: relative risk (RR) = 0.99 for MI (95% confidence interval [CI], 0.92 to 1.07); RR = 1.00 for overall death (95% CI, 0.97 to 1.02); RR = 0.99 for cardiovascular death (95% CI, 0.94 to 1.04); and RR = 0.95 for angina (95% CI, 0.85 to 1.06). However, ARBs modestly reduced the risk of diabetes, congestive heart failure, and stroke (RR = less than 10 percent).

Should we believe this study?

Bob: Yes. They did a lot of things right. To do a proper meta-analysis, you have to (1) include high-quality studies; (2) have more than one researcher extract the data to see if there is concurrence; (3) do an exhaustive literature search to make sure no important studies are missing; and (4) do a sensitivity analysis to see if the results hold true.

Andrea: A sensitivity analysis is designed to test whether changing something in the way you do the analysis will change your ▶

results. You might exclude studies that barely meet your "high-quality" criteria and see if the results are the same. You could also leave out studies that are outliers or see if one large trial is driving your results. For example, if one study has 10,000 participants and the other 30 studies have a total of 1,000 participants, it is clear that the results of your meta-analysis will be biased by the larger study.

Mark: For the sensitivity analysis in this meta-analysis, the authors looked at the overall results, and also at the results when only the highest-quality studies were included and when the possibly biased studies were examined separately. There was no difference in results, regardless of which subgroup of studies was examined.

Andrea: One thing the authors did not do well was their literature search. Generally, a literature search should include contacting drug companies and others to see if there are data available that haven't been published. This is something they didn't do. Unpublished studies from drug companies are likely to show their drug in a bad light. So, if anything, including unpublished studies would likely have strengthened the conclusion that ARBs do not prevent adverse cardiovascular outcomes.

Mark: Given that these results are from a well-done meta-analysis, why don't ARBs prevent cardiovascular outcomes compared with placebo? There are major differences between ARBs and angiotensin-converting enzyme (ACE) inhibitors. ACE inhibitors prevent the formation of angiotensin II. This prevents activation of angiotensin I and II receptors. ARBs only block angiotensin I receptors. This can lead to overstimulation of angiotensin II receptors, which can cause hypertrophic and antiangiogenic effects on the cardiovascular system. ACE inhibitors also increase bradykinins, etc, which reduces infarct size via vasodilation and other "preconditioning." This is something that ARBs do not do.

Bob: These results shouldn't be surprising. We know that blood pressure lowering is not always equally beneficial. One need only look at the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial). Despite lowering blood pressure, alpha blockers had less effect on cardiovascular outcomes than did other drugs. In fact, the doxazosin (Cardura) arm was stopped early because doxazosin was less cardioprotective.[4]

Andrea: Even though we measure it and swear by it as an end point, blood pressure is only a surrogate outcome. We care what happens to the patient, and despite lowering blood pressure, ARBs fail when it comes to outcomes we care about: MI, cardiovascular death, and angina.

What should the family physician do?

Mark: The take-home message is that ARBs are not cardioprotective. Consider something else when you reach for an antihypertensive medication (chlorthalidone, anyone?).

Main Points

- Despite lowering blood pressure, ARBs are not cardioprotective and have no effect on cardiovascular death, MI, or angina. At best, ARBs have a modest effect on the risk of diabetes, congestive heart failure, and stroke (less than a 10 percent relative risk reduction).
- Blood pressure, like many other measurements such as A1C, is a surrogate end point and does not necessarily reflect what is happening to the patient—the patient may not benefit even if his or her blood pressure is lowered.
- As always, look for patient-oriented outcomes that we care about, such as stroke, MI, and death. Blood pressure itself is not something we care about (unless that bonus is dependent on your patient meeting a blood pressure goal).

EBM Points

A good meta-analysis requires the following (among other things):

- A sensitivity analysis: exclude outliers, such as large, heavily weighted studies and studies of marginal quality, to check whether the results are the same
- An extensive literature search, including a search for unpublished material (such as from drug companies)
- An analysis of the quality of studies included in the meta-analysis (one set of criteria is published by The Cochrane Collaboration)
- More than one person extracting the data from each study (do the reviewers agree on something as basic as the data to be analyzed?)

If you conduct a journal club and would like to know the next article that will be discussed, please e-mail afpjournal@aafp.org with *"AFP* Journal Club notification" in the subject line.

Address correspondence to Mark A. Graber, MD, FACEP, at markagraber@gmail.com. Reprints are not available from the authors.

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