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
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?)

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

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**REFERENCES**