Angiotensin Receptor Blockers Do Not Increase Risk of Myocardial Infarction

Ross T. Tsuyuki, BSc(Pharm), PharmD, MSc, FCSHP; Michael A. McDonald, MD, FRCP(C)

The efficacy and safety of angiotensin-converting enzyme (ACE) inhibitors has been well established; these agents have shown an overwhelming and unequivocal benefit in placebo-controlled trials across a spectrum of patients at risk for cardiovascular events.1–9 What has been less clear, however, is whether inhibition of the renin-angiotensin-aldosterone system with angiotensin receptor blockers (ARBs) yields benefits of comparable scale. ARBs selectively inhibit the angiotensin II type 1 receptor, and it is axiomatic that this might offer theoretical advantages over ACE inhibitors by preventing the effects of angiotensin II generated by non-ACE-dependent pathways.10–12 In large-scale clinical trials, ARBs have been shown to effectively lower blood pressure,13–15 prevent progression to renal failure in patients with diabetes mellitus and proteinuria,16–18 and reduce the incidence of major cardiac events in patients with heart failure.19,20 These medications are also better tolerated than ACE inhibitors and are recommended in the American College of Cardiology/American Heart Association guidelines for patients with chronic heart failure or left ventricular dysfunction after myocardial infarction (MI) who are unable to tolerate ACE inhibitors and by the 2006 Canadian Cardiovascular Society consensus conference recommendations on heart failure.21–23

Response by Strauss and Hall p 860

Debate has surfaced recently on the relative safety of ARBs with respect to MI. In a controversial editorial in the British Medical Journal,24 Verma and Strauss drew attention to results from certain individual trials and concluded that ARBs increase MI, and they suggested that patients may need to be informed of these risks. Although supported by some,25 many members of the scientific community criticized the editorial for its nonsystematic approach to the existing data.26,27 As a “negative” editorial, it received significant attention in the medical community, and concerns about ARB safety were widely reported by the media both locally and internationally.

Our group was concerned about these conclusions drawn from selected studies and recently published a systematic review using all published data on the risk of MI and ARBs, and this review showed no increase in risk.28 Since then, independent systematic reviews and further data have been published that support our assertion that ARBs do not increase the risk of MI.29–31 This review will outline the available evidence for ARB safety with respect to MI events in a broad group of high-risk patients. We will also provide our perspective on questions surrounding the role of ARBs for important patient subpopulations.

Need for a Systematic Review of All ARB Data on MI Risk

Simply put, the best way to answer a clinical question is to systematically and thoroughly evaluate all available data in an unbiased fashion. This is the premise behind the science of systematic reviews or meta-analysis. When we read the editorial by Verma and Strauss that concluded that ARBs...
cause MI,24 we were both intrigued and puzzled; intrigued because, like ACE inhibitors, ARBs were expected to reduce MI, yet puzzled because they had only reported data from trials that supported their conclusion. As such, we decided to conduct our own formal systematic review. Our question was: “Do ARBs increase the risk of MI?” We conducted a thorough search of the published literature using Medline, Embase, and the Cochrane register of controlled trials and by hand-searching the reference lists of retrieved articles. We included all trials that compared the use of ARBs with ACE inhibitors or placebo that reported MI events. Two reviewers decided which trials to include and abstracted the data, with any disagreements resolved by the vote of a third reviewer. We used standard Cochrane techniques to combine the data, using a random effects model to account for potential variations between studies.

A total of 24 studies met our inclusion criteria, and 19 had data on MI, representing a total of 31,569 patients.13,16–19,32–46 Use of ARBs was not associated with an increased risk of MI compared with placebo (odds ratio [OR] 0.94, 95% confidence interval [CI] 0.75 to 1.16) nor when compared with ACE inhibitors (OR 1.01, 95% CI 0.87 to 1.16).28 With ORs very close to unity and narrow CIs, we concluded that the use of ARBs is not associated with an increased risk of MI. Our conclusions are consistent with those of similar meta-analyses conducted by Verdecchia et al.,29 who reported ORs of 1.02 to 1.03 (95% CIs of 0.96 to 1.11 and 0.96 to 1.09, respectively) for MI with ARBs compared with any control, and Volpe et al.,30 who reported a relative risk of 1.036 (95% CI 0.966 to 1.110) for ARBs compared with any control.

**Effect of ARBs on MI in Important Subpopulations**

**ARBs in Patients With Hypertension**

Much of the concern over ARB use and the association with increased rates of MI stems from the results of recent hypertension trials. In particular, the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial,14 which involved 15,245 patients, found no significant difference in a composite cardiac mortality and morbidity outcome between the ARB valsartan and amlodipine. However, patients randomized to treatment with amlodipine had 19% fewer MIs, a finding that may or may not be attributable to the consistent, modest blood pressure–lowering advantage of amlodipine at all time points throughout the study. Further insights in hypertensive patients have come from a Blood Pressure Lowering Treatment Trialists’ Collaboration (BPLTTC) presentation at the 2005 European Society of Hypertension meeting that focused on blood pressure–independent effects of ACE inhibitors and ARBs in reducing major cardiac events.48 In this analysis, meta-regression plots of blood pressure reduction from individual trials versus relative risk of cardiac events were constructed to tease out whether there was a protective effect of the medications beyond blood pressure reduction. For stroke and heart failure events, no difference was seen for ACE inhibitors and ARBs, which suggests that clinical benefits of these agents in hypertensive patients are attributable to the blood pressure–lowering effects alone. For coronary heart disease, a statistically significant 9% (95% CI 14% to 3%) reduction in risk of events beyond blood pressure lowering was seen with ACE inhibitors, whereas no such effect was seen with ARBs. This simply suggests that the efficacy of ARBs is dependent only on blood pressure lowering.

Although the BPLTTC analysis is elegant, some caveats are worth noting. First, there is still no suggestion that ARBs are associated with an increased incidence of MI, only that there is no evidence to support a blood pressure–independent effect on coronary heart disease outcomes. Second, an acknowledged limitation of the study is the relative paucity of ARB trials. Sixteen ACE inhibitor trials of 104,993 subjects were available for analysis compared with 5 trials of ARBs with 32,603 subjects. The ARB trials included Irbesartan Diabetic Nephropathy Trial (IDNT),17 Losartan Intervention For Endpoint reduction in hypertension (LIFE),15 Reduction of Endpoints in Non–insulin-dependent diabetes mellitus with Angiotensin II Antagonist Losartan (RENAAL),16 Study on COgnition and Prognosis in the Elderly (SCOPE),13 and VALUE,14 each of which was a major component of the neutral systematic reviews discussed above.28–30

**ARBs in Patients With Diabetes Mellitus**

The value of ARB medications in patients with type 2 diabetes mellitus and nephropathy has been well established in several landmark studies. IDNT17 was a randomized evaluation of 1715 patients with type 2 diabetes mellitus that compared irbesartan with amlodipine and placebo. In this study, irbesartan was associated with a lower incidence of heart failure than either amlodipine or placebo, but it was not associated with a significant difference in the rate of MI. Similarly, in the RENAAL study of 1513 patients with diabetes mellitus and nephropathy, losartan conferred significant benefits over placebo with respect to progression of renal disease, without any suggestion of increased MI events in the treatment group.16 These trials have also been included in the systematic reviews presented.

A prior systematic review by Strippoli and colleagues49 assessing ACE inhibitors and ARBs in diabetic nephropathy concluded that the data for ACE inhibitors are far more robust than for ARBs and that their comparative effect on overall survival cannot yet be ascertained. While demonstrating a reduction in mortality in the ACE inhibitor trials only, this review has been criticized for combining heterogeneous patient populations. Most of the ACE inhibitor data come from studies in type 1 diabetes mellitus, and the ARB data come from studies in type 2 diabetes mellitus, 2 patient groups with strikingly different baseline risk profiles.50
Data that specifically examined MI rates in diabetic patients are also wanting. No difference in event rates was seen, however, in the 250-patient Diabetic Exposed to Telmisartan and Enalapril (DETAIL) study between ACE inhibitor- and ARB-treated groups. Currently, it would appear that ARBs are proven efficacious therapies for patients with type 2 diabetes mellitus and proteinuria and that despite their relative safety with regard to MI risk, further research is required to delineate the potential benefits of ARBs on atherosclerotic heart disease events.

### ARBs in Patients With Heart Failure and After MI

A meta-analysis of heart failure trials demonstrated a reduction in all-cause mortality and heart failure hospitalizations with ARB therapy compared with placebo, with no significant outcome difference between ARBs and ACE inhibitors. Our own analysis that specifically examined MI events included a large number of heart failure trials and similarly showed no increased risk of MIs with ARB use versus placebo or versus ACE inhibitors. That many of the ARB versus placebo heart failure trials evaluated in this systematic review included patients cotreated with ACE inhibitors raises the possibility that the absence of MI risk in the ARB arms (and by extension, the benefits of ARBs observed in some of the trials) may have been confounded by the background ACE inhibitor therapy. In the VALIANT (VALsartan In Acute myocardial iNfarcTion) trial of very high-risk patients with left ventricular dysfunction/heart failure after MI, combination therapy with captopril and valsartan did not demonstrate any benefit compared with captopril alone (hazard ratio 0.98, 97.5% CI 0.89 to 1.09) for mortality, and no difference was seen between the captopril and valsartan monotherapy groups (hazard ratio 1.00, 97.5% CI 0.90 to 1.11). A recently published evaluation of atherosclerotic events in VALIANT3 demonstrated no significant difference in the rate of adjudicated MI between captopril, valsartan, and combination therapy subgroups, which suggests that concomitant ACE inhibitor therapy does not appreciably affect risk of death in ARB-treated patients. In support of this observation, an analysis from the overall CHARM (Candesartan in Heart failure Assessment in Reduction of Mortality) program actually showed a reduction in the outcome of cardiovascular death or nonfatal MI in the candesartan group over placebo (hazard ratio 0.87, 95% CI 0.79 to 0.96) that was similar across the predetermined subgroups, which included patients taking background ACE inhibitors. The authors concluded that inhibition of the renin-angiotensin-aldosterone system with candesartan offers additional protection against cardiac events that is similar in magnitude to the protection offered by ACE inhibition alone in SOLVD (Studies Of Left Ventricular Dysfunction) and other heart failure trials.

### Do ARBs Increase the Risk of MI?

If an agent causes harm, it is likely that it would produce its deleterious effects across a wide spectrum of patients. In the case of ARBs and MI risk, one would expect to observe an overall effect of ARBs on risk of MI.

<table>
<thead>
<tr>
<th>Study</th>
<th>ARB Group n/N</th>
<th>Control Group n/N</th>
<th>OR (random) 95% CI</th>
<th>Weight %</th>
<th>OR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCOPE (2003)</td>
<td>70/2147</td>
<td>63/2460</td>
<td>5.60</td>
<td>1.11</td>
<td>0.78, 1.56</td>
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<td>Hamada et al. (2004)</td>
<td>110/745</td>
<td>110/745</td>
<td>0.09</td>
<td>1.03</td>
<td>0.90, 25.96</td>
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<td>RENAAL (2001)</td>
<td>50/751</td>
<td>50/751</td>
<td>4.83</td>
<td>0.93</td>
<td>0.87, 1.03</td>
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<tr>
<td>CHARM-Added (2003)</td>
<td>49/1276</td>
<td>69/1272</td>
<td>4.71</td>
<td>0.62</td>
<td>0.42, 0.92</td>
</tr>
<tr>
<td>CHARM-Alternative (2003)</td>
<td>75/1013</td>
<td>84/1013</td>
<td>4.37</td>
<td>1.61</td>
<td>1.11, 2.34</td>
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<tr>
<td>CHARM-Preserved (2003)</td>
<td>57/1513</td>
<td>73/1513</td>
<td>5.39</td>
<td>0.77</td>
<td>0.64, 1.01</td>
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<td>SPICE (2000)</td>
<td>3/170</td>
<td>3/171</td>
<td>0.24</td>
<td>0.69</td>
<td>0.49, 1.35</td>
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<td>Val-HeFT (2001)</td>
<td>0.70</td>
<td>0.70</td>
<td>6.57</td>
<td>1.14</td>
<td>0.86, 1.45</td>
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<td>DETAIL (2004)</td>
<td>10/120</td>
<td>10/120</td>
<td>0.92</td>
<td>1.39</td>
<td>0.93, 3.64</td>
</tr>
<tr>
<td>ELITE (1997)</td>
<td>4/355</td>
<td>4/370</td>
<td>0.59</td>
<td>1.62</td>
<td>0.61, 1.74</td>
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<tr>
<td>ELITE II (2000)</td>
<td>21/1578</td>
<td>28/1574</td>
<td>1.81</td>
<td>1.11</td>
<td>0.66, 1.85</td>
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<tr>
<td>HEVEIN (2002)</td>
<td>7/170</td>
<td>7/171</td>
<td>0.10</td>
<td>0.20</td>
<td>0.01, 4.18</td>
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<tr>
<td>REPLACE (2001)</td>
<td>2/303</td>
<td>2/303</td>
<td>0.29</td>
<td>0.08</td>
<td>0.01, 2.02</td>
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<td>Di Pasquale et al. (1999)</td>
<td>2/33</td>
<td>2/33</td>
<td>0.10</td>
<td>0.29</td>
<td>0.01, 5.82</td>
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<td>OPTIMAAL (2002)</td>
<td>389/3244</td>
<td>379/2733</td>
<td>14.04</td>
<td>1.01</td>
<td>0.67, 1.08</td>
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<td>Spinar et al. (2000)</td>
<td>5/500</td>
<td>5/500</td>
<td>0.49</td>
<td>1.38</td>
<td>0.33, 4.90</td>
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<td>Bakris et al. (2002)</td>
<td>1/138</td>
<td>0.287</td>
<td>0.09</td>
<td>7.34</td>
<td>0.34, 383.491</td>
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<tr>
<td>IDNT (2003)</td>
<td>44/759</td>
<td>73/1136</td>
<td>4.67</td>
<td>1.20</td>
<td>0.61, 1.77</td>
</tr>
<tr>
<td>ALPINE (2003)</td>
<td>1/196</td>
<td>1/196</td>
<td>0.11</td>
<td>1.00</td>
<td>0.66, 1.61</td>
</tr>
<tr>
<td>Kondo et al. (2003)</td>
<td>3/203</td>
<td>3/203</td>
<td>0.34</td>
<td>1.00</td>
<td>0.20, 5.01</td>
</tr>
<tr>
<td>LIFE (2002)</td>
<td>198/4605</td>
<td>188/4598</td>
<td>1.01</td>
<td>1.05</td>
<td>0.66, 1.99</td>
</tr>
<tr>
<td>MOSSES (2005)</td>
<td>17/710</td>
<td>20/765</td>
<td>1.50</td>
<td>0.83</td>
<td>0.43, 1.59</td>
</tr>
<tr>
<td>VALIANT (2003)</td>
<td>587/4905</td>
<td>559/4928</td>
<td>16.12</td>
<td>1.06</td>
<td>0.85, 1.32</td>
</tr>
<tr>
<td>VALUE (2004)</td>
<td>369/7649</td>
<td>313/7556</td>
<td>13.96</td>
<td>1.18</td>
<td>0.91, 1.43</td>
</tr>
</tbody>
</table>

Total (95% CI): 34216
Total events: 2045 (ARB Group), 1994 (Control Group)
Test for heterogeneity: Chi² = 31.08, df = 23 (P = 0.12), I² = 20.0%
Test for overall effect: Z = 0.55 (P = 0.59)

Overall effect of ARBs on risk of MI.
increase in MI across the entire spectrum of cardiovascular risk and with a variety of background therapies. We have updated our 2005 systematic review by comparing ARBs with any control, and we have now included VALIANT. MOSES (MOrbidity and mortality after Stroke–Eprosartan vs nitrendipine for Secondary prevention) (MI data from S. Luders, MD, e-mail communication, March 13, 2006), ALPINE (Antihypertensive treatment and Lipid Profile In a North of Sweden Efficacy evaluation), LIFE, VALUE, a study by Kondo et al, and combined comparative arms from a study by Bakris et al and IDNT. The results were combined with a random effects model and are shown in the Figure.

In our inclusive, systematic review of 25 trials, 13–19,32–46,53–57 68 711 patients at risk for MI, and >4000 events, we now have even stronger evidence that ARBs do not increase the risk of MI, with a pooled OR of 1.03 (95% CI 0.93 to 1.13). Although few of these studies were designed to test equivalence, with a point estimate very close to unity and narrow CIs, it is clear that there is no increased risk of MI associated with ARB use. Thus, it appears reasonable to conclude that ARBs are a safe and efficacious alternative to ACE inhibitors for patients at high risk for ischemia and MI. We are not advocating the superiority of ARBs over ACE inhibitors, only stating that they do not increase the risk of MI. ACE inhibitors remain the agents of choice for reducing MI.

Optimal neurohormonal blockade in this era of ever-evolving cardiovascular therapy is a moving target. Results from the prospective ONTARGET and TRandESCEND trials (ONGoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial/Telmisartan Randomized Assessment study in ACE-in intolerant subjects with cardiovascular Disease) are eagerly awaited to better define the role of ARBs in protecting patients at risk for MI and other atherosclerotic heart disease–related events. In the interim, however, we find no evidence that these agents increase the risk of MI based on a systematic review of all published trials of ARBs. This highlights the importance of assessing all available evidence by systematic methods before drawing any conclusions.

Acknowledgments
The authors would like to recognize the contributions of their colleagues from their original systematic review: Drs Scot H. Simpson, Gabor Gyenes, and Justin A. Ezekowitz.

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References


Response to Tsuyuki and McDonald

Martin H. Strauss, MD, FRCP; Alistair S. Hall, MB ChB, PhD, FRCP(UK)

An axiom is defined as a saying that is widely accepted on its own merits; a proposition (in logic) that is not susceptible of proof or disproof; its truth is assumed to be self-evident. Tsuyuki and McDonald state that angiotensin receptor blockers (ARBs) “selectively inhibit the angiotensin II type 1 receptor and it is axiomatic that this might offer theoretical advantages over” angiotensin-converting enzyme inhibitors (ACEIs). We point out that (1) ACEIs, via inhibition of ACE, attenuate AT2-mediated effects, whereas (2) ARBs block AT1 receptors, with resultant augmentation of angiotensin II that results in an unopposed stimulation of AT2 receptors. AT2 receptors, although capable of causing vasodilation, may promote plaque rupture via a matrix metalloproteinase-1–dependent mechanism (Figure 1F in our article). Each strategy has opposite and paradoxical effects on the AT2 receptor. Therefore, investigating and not presupposing the clinical role of the AT2 receptor is key. Using the Tsuyuki and McDonald meta-analysis data, despite the inclusion of studies with partial ACEI use but the exclusion of the 1 trial with complete background ACEI use (CHARM-Added) and of those that had a very short duration, an odds ratio for myocardial infarction (MI) of 1.07 (1.00 to 1.14; \( P = 0.05 \)) is still apparent. In this fashion, the Tsuyuki-McDonald meta-analysis actually supports the presence of an ARB-MI paradox. It is our contention that as guidelines for vascular disease, diabetes mellitus, hypertension, and heart failure evolve, recognition of the distinction between ACEIs and ARBs should influence the recommendations for treatment of patients at high risk of MI. Two further messages are relevant. As newer pharmacological agents are introduced into clinical practice, novel mechanisms of action, even if eloquent and persuasive, should not be interpreted as surrogates for efficacy with regard to MI and death. Second, equivalence should not be accepted as the conclusion of a trial that proves “noninferiority” nor as the “default” conclusion of a “superiority” trial that fails to prove its primary hypothesis.
Response to Tsuyuki and McDonald
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