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Circulation 2006;114;838-854
DOI: 10.1161/CIRCULATIONAHA.105.594986
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0009-7322. Online ISSN: 1524-4539

CONTROVERSIES IN CARDIOVASCULAR MEDICINE

Do angiotensin receptor blockers increase the risk of myocardial infarction?

Angiotensin Receptor Blockers May Increase Risk of Myocardial Infarction
Unraveling the ARB-MI Paradox

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

"To know that we know what we know, and to know that we do not know what we do not know, that is true knowledge."

—Copernicus (1473–1543)

Angiotensin-converting enzyme inhibitors (ACEIs) play an important role in the management of patients at increased cardiovascular (CV) risk. ACEIs reduce both myocardial infarction (MI) and mortality in patients with symptomatic congestive heart failure or asymptomatic left ventricular dysfunction,[1] as evidenced by a class I recommendation in the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines.[2] Early administration of an ACEI after an MI reduces 30-day mortality by ≈7%.[3] In patients with established vascular disease but normal left ventricular function, ACEIs reduce mortality,[4] MI,[4,5] stroke,[4,6] and new-onset congestive heart failure.[4,6] ACEIs are recommended as standard therapy in patients with established vascular disease in the ACC[7] and European Society of Cardiology[8] guidelines, and this recommendation is independent of left ventricular function or concomitant hypertension.

The unique cardioprotective benefits of ACEIs are also observed in patients with diabetes mellitus, who may or may not have coexistent atherosclerosis,[9] and are considered a first priority in macrovascular risk reduction by the Canadian Diabetes Association and others.[10] Additionally, ACEIs exert powerful nephroprotection and offer marked CV risk reduction in diabetic patients with concomitant nephropathy.[11,12]

Angiotensin II (Ang II) type 1 (AT_1) receptor blockers (ARBs), first introduced in 1995, also inhibit the renin angiotensin system (RAS) in a mechanistically distinct fashion from ACEIs. Compared with ACEIs, which reduce the synthesis of Ang II, ARBs competitively and selectively bind to the AT_1 receptor, preventing its activation by Ang II. In particular, this is able to reduce vascular resistance and also aldosterone release and hence help to reduce cardiac afterload and prevent salt and water retention. Given this profile, the assumption early on, even before major clinical trials were conducted, was that ARBs would have similar if not greater systemic effects than might result from the use of ACEIs, because AT_1 blockade would offer a more complete inhibition of the RAS. This assumption, coupled with the better tolerability of ARBs, as well as concerns for the long-term development of tolerance to ACEIs ("escape phenomenon"), has led to the widespread popularity of ARBs for the treatment of patients with hypertension and congestive cardiac failure.

Accumulating data thus far confirm that ARBs indeed have many of the same clinical benefits as ACEIs, including effective blood pressure lowering,[13–15] improvement of congestive heart failure symptoms,[16–18] inhibition of diabetic renal disease,[19,20] reduction in stroke rates,[14,15,21] and likely the prevention of new onset of diabetes mellitus[22] and atrial fibrillation.[23] However, despite these obvious similarities, it has become clear that these 2 classes of

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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(*Circulation.* 2006;114:838-854.)

Circulation is available at http://www.circulationaha.org

DOI: 10.1161/CIRCULATIONAHA.105.594986

medication have significant differences with regard to their ancillary pharmacological properties and thereby also their profile at a molecular/cellular level. Furthermore, these differences have important clinical sequelae. Available data indicate that whereas ACEIs produce marked and consistent reduction of MI and CV death across diverse patient populations, the same cannot be said of ARBs.

Defining the ARB-MI Paradox

"How wonderful that we have met with a paradox. Now we have some hope of making progress."

—Niels Bohr (1885–1962)

The major ARB trials in high-risk patients have thus far demonstrated almost a complete lack of reduction in MI and mortality despite significant reductions in blood pressure. Paradoxically, rates of MI in some trials have actually increased with ARBs,[13,16] which suggests that ARBs and ACEIs may exert distinctive effects on both the coronary circulation and atherosclerotic plaque stability.

This unexpected relationship of ARBs with MI may be aptly described as the "ARB-MI paradox" and was first raised as an issue in 2004.[24] This report focused on a 19% relative increase in MI with valsartan (compared with amlodipine) in the 15 245-patient Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial.[13] This editorial sparked tremendous discussion, debate, and controversy and resulted in a plethora of commentaries,[25–27] systematic reviews,[28,29] and meta-analyses,[30–33] the results of which have served to confuse rather than clarify the issue. To date, there is no consensus on whether ARBs have a tendency to increase MI, but there is also no substantive evidence to indicate that ARBs are able to reduce MI. This is a paradox in itself.

In this report, we strive to provide a comprehensive treatise on the available evidence (or the lack there of) evaluating the effect of ARBs on MI and CV death. The need for such an evaluation has been highlighted to us repeatedly, because the results of 9 of 11 key clinical trials of ARB treatment have reported an excess of MI that achieved statistical significance in 2 cases (VALUE and CHARM-Alternative [the Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity Alternative Trial]). We will highlight the strengths and limitations of the currently available meta-analyses and contrast them with a meta-analysis that endeavors to avoid those deficiencies. We also seek to clarify the statistical principles of noninferiority, imputed placebo, and meta-regression analysis, which are central to the ongoing clinical and scientific debate.

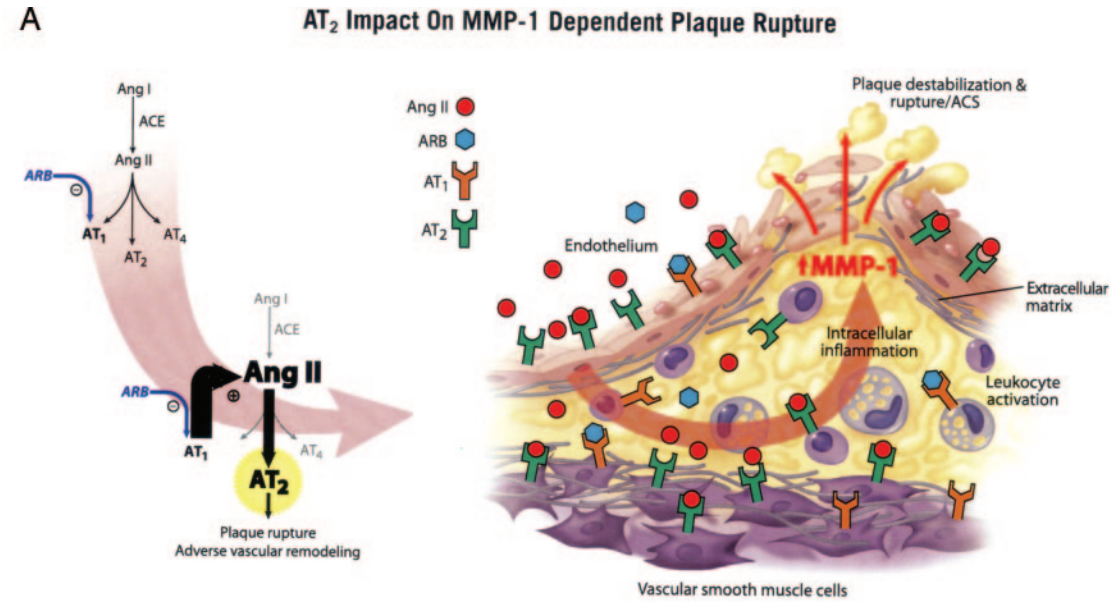
To confirm the existence of an ARB-MI paradox, it is essential that we first examine the impact that blood pressure changes per se have on MI and mortality, and then, that we evaluate whether ARBs and ACEIs offer blood pressure–dependent and/or blood pressure–independent effects on these outcomes. We propose that on the basis of an objective assessment of the available data, the ARB-MI paradox does indeed exist; that it is biologically, pharmacologically, and pathologically plausible; and most important, that it has strong clinical relevance.

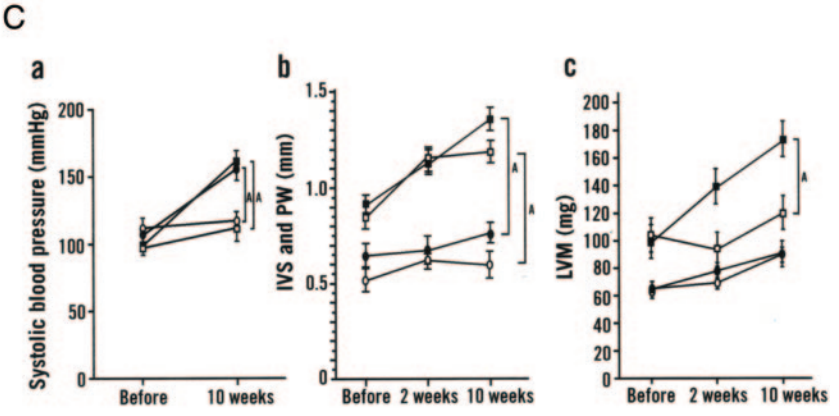
ARBs May Increase MI: Biological Plausibility

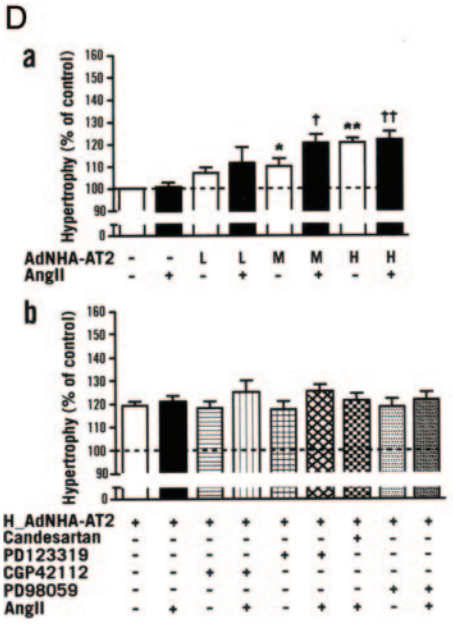
Ang II has a central role in CV disease both via its hemodynamic effects and through direct vascular effects. Ang II activates the AT_1 receptors, which mediate many of the well-known effects of Ang II, including aldosterone release with salt and water retention, vasoconstriction, increased cardiac contractility, cellular proliferation, and hypertrophy, as well as prooxidative and proinflammatory effects.[34] In the long term, activation of AT_1 leads to hypertension, cardiac and vascular hypertrophy, atherosclerosis, and MI. ARBs and ACEIs both attenuate the effects of Ang II, each by unique mechanisms. ACEIs decrease the synthesis of Ang II, whereas ARBs bind to the AT_1 receptors, thereby preventing their activation.

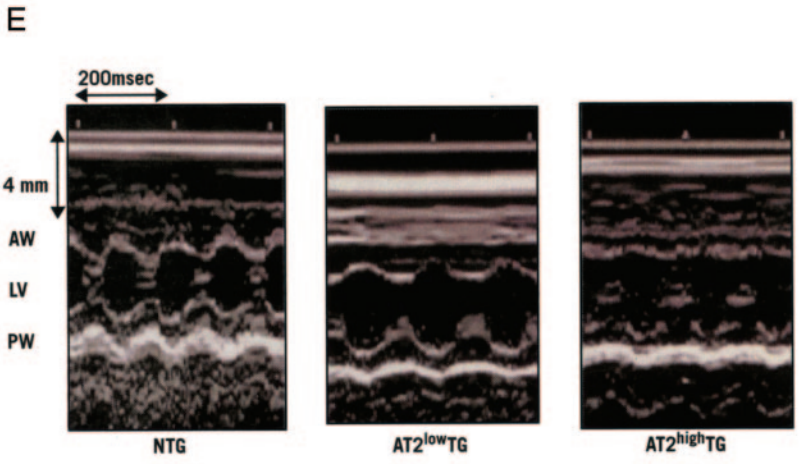
As a consequence of AT_1 blockade, ARBs increase Ang II levels several-fold above baseline by uncoupling a negative-feedback loop (Figure 1A).[34] Increased levels of circulating Ang II result in unopposed stimulation of the AT_2 receptors, which are, in addition, upregulated. The role of the AT_2 receptor in adults is not well defined, and some have suggested that its expression may be limited to embryogenesis and/or early development. It has been proposed that AT_2 receptors mediate vasodilatation and nitric oxide (NO) release,[35] effects that may counterbalance the AT_1-mediated effects, and that stimulation of the AT_2 receptor during AT_1 blockade with an ARB would result in dual benefits (antagonism of Ang II and increased NO).

Unfortunately, recent data suggest that AT_2 receptor stimulation may be less beneficial than previously proposed and may even be harmful under certain circumstances through mediation of growth promotion, fibrosis, and hypertrophy,[34,36] as well as proatherogenic and proinflammatory effects (Figure 1B).[35,37–40] In transgenic mice, the chronic overexpression of AT_2 has the potential to cause Ca^{2+}- and pH-dependent contractile dysfunction in ventricular myocytes, as well as loss of the inotropic response to Ang II.[41] AT_2-deficient mice are protected against cardiac hypertrophy (Figure 1C),[42] whereas overexpression of AT_2 in human cardiac myocytes is associated with increased cardiac hypertrophy (Figure 1D).[43] In addition, a critical role for an AT_2 receptor in mediating dilated cardiomyopathy and cardiac hypertrophy has been demonstrated (Figure 1E).[44,45] More recently, Benndorf and colleagues[46] have clearly demonstrated that AT_2 receptors inhibit vascular endothelial growth factor–induced angiogenesis in endothelial cells. AT_2 stimulation may in addition inhibit hypoxia-induced neovascularization, a critical adaptive response in the chronically ischemic myocardium.[34] In the kidney, AT_2 may stimulate inflammation by upregulating glomerular RANTES.[47] Recent evidence in human myocytes suggests that Ang II may promote plaque rupture by augmenting matrix metalloproteinase-1 in an AT_2-dependent fashion and by preventing growth of vascular smooth muscle cells with reduced collagen deposition and additional cellular apoptosis within advanced plaques (Figure 1F).[48]









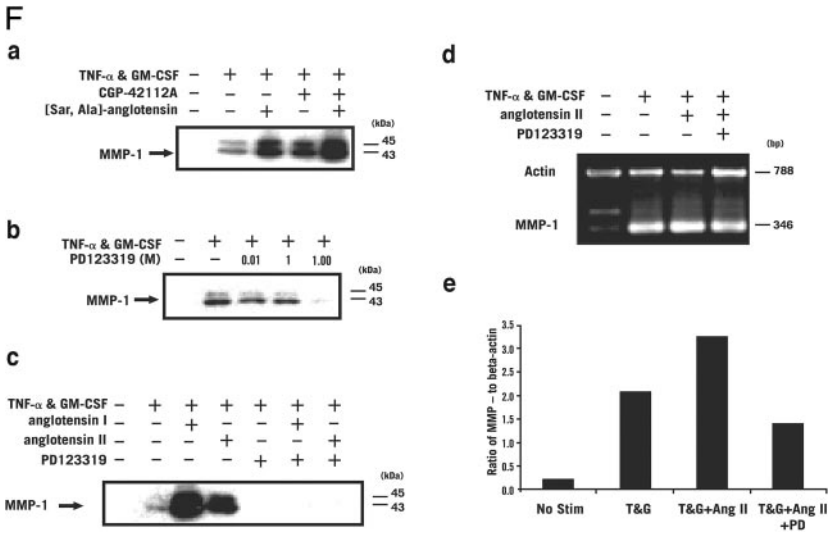


Figure 1. A, ARBs selectively block AT_1 receptors, which leads to a marked counterregulatory upregulation in Ang II.[34] The resultant augmented Ang II release stimulates AT_2 receptor and postreceptor signaling, which has been shown in humans to promote leukocyte dependent matrix metalloproteinase (MMP)-1 release.[48] This may explain, in part, the ARB-MI paradox. B, Cardiac hypertrophy is not induced in the AT_2-null mouse by pressure overload or chronic Ang II infusion. The heart of an AT_2-null mouse treated with 4.2 ng/kg per min Ang II for 3 weeks shows protection against hypertrophy compared with wild-type controls. AT_2 receptor stimulation during long-term ARB stimulation, in addition to inducing plaque rupture, may also promote adverse ventricular remodeling. From Senbonmatsu et al,[40] with permission. C, Evidence for AT_2 receptor–mediated cardiac myocyte enlargement during in vivo pressure overload. a, Systolic blood pressure in *Agtr2*$^-$/Y and wild-type mice. ● indicates aortic-banded *Agtr2*$^-$/Y mice; ■, aortic-banded wild-type mice; ○, sham-operated *Agtr2*$^-$/Y mice; and □, sham-operated wild-type mice. $^AP<0.05$. b, Interventricular septum (IVS) and left ventricular posterior wall (LVPW) in aortic-banded *Agtr2*$^-$/Y and wild-type mice. ●, IVS in aortic-banded *Agtr2*$^-$/Y mice; ■, IVS in aortic-banded wild-type mice; ○, LVPW in aortic-banded *Agtr2*$^-$/Y mice; □, LVPW in aortic-banded wild-type mice. $^AP<0.05$. c, Left ventricular mass (LVM) of *Agtr2*$^-$/Y and wild-type mice. ● indicates aortic-banded *Agtr2*$^-$/Y mice; ○, sham-operated *Agtr2*$^-$/Y mice; ■, aortic-banded wild-type mice; □, sham-operated wild-type mice. $^AP<0.05$. From Senbonmatsu et al,[42] with permission. D, AT_2 receptor causes constitutive growth of cardiomyocytes and does not antagonize AT_1 receptor–mediated hypertrophy. Increased AT_2 receptor expression results in Ang II–independent hypertrophy. (A) Unstimulated (white bars) or Ang II–stimulated (black bars) cardiomyocytes infected with increasing amounts of AdNHA-AT_2 receptors (low [L], medium [M], and high [H]). (B) AT_2 receptor–induced constitutive hypertrophy was unaffected by cotreatment with AT_1 and AT_2 receptor ligands or an inhibitor of ERK1/2 signaling. From D'Amore et al,[43] with permission. E, Ventricular-specific expression of AT_2 receptors causes dilated cardiomyopathy and heart failure in transgenic (TG) mice. Representative images of in vivo 2D targeted M-mode echocardiogram of LV chamber in nontransgenic (NTG), low-expressing transgenic lines (AT_2^{low}TG), and high-expressing transgenic lines (AT_2^{high}TG) of mice. Left ventricular (LV) anterior and posterior wall thicknesses were significantly decreased in AT_2^{high}TG mice and were accompanied by diastolic and systolic LV chamber enlargement. These indices were preserved in AT_2^{low}TG mice. Midwall fractional shortening was depressed in both TG lines, with more severe depression in AT_2^{high}TG mice. From Yan et al,[44] with permission. F, Ang II, through AT_2 receptors and cyclooxygenases, plays a central role in production of MMP-1 by monocytes stimulated with tumor necrosis factor (TNF)-α and GM-CSF (granulocyte macrophage-colony stimulating factor), which may lead to atherosclerotic plaque rupture. (A) Effect of AT_2 receptor agonist CGP-42112A in the absence or presence of [Sar^1, Ala^8]-Ang II on MMP-1 production by monocytes stimulated with TNF-α and GM-CSF. (B) Effect of the AT_2 receptor antagonist PD123319 on MMP-1 production by TNF-α– and GM-CSF–stimulated monocytes. (C) PD123319 inhibition of cytokine Ang I (100 μmol/L) and Ang II (100 μmol/L) stimulated MMP-1 production. (D, E) PD123319 (PD; 100 μmol/L) decreases the ratio of MMP-1 to β-actin transcription in monocytes stimulated with TNF-α (T) and GM-CSF (G) plus Ang II (100 μmol/L). From Kim et al,[48] with permission.

Also implicating stimulation of Ang II and AT_2 in the genesis of coronary atheroma is a study conducted in 509 United Kingdom families with premature coronary artery disease that found an association between a common, functional, X-linked Ang II type 2 receptor gene polymorphism (−1332 G/A) and premature coronary disease (Figures 2B and 2C).[49] An excess of the G allele was observed, which suggests that the increased premature coronary artery disease risk was mediated by increased AT_2 receptor expression (Figure 2A).[50] These data raise the biological plausibility that ARBs may promote plaque vulnerability and propensity to rupture.

The biology of the AT_4 receptor is less well defined but has been linked to the release of plasminogen activator inhibitor (PAI-1).[51] PAI-1 is a major inhibitor of fibrinolysis and a powerful independent predictor of death after transmural MI.[52] For the same reduction in blood pressure, ACEIs offer a greater PAI-1 reduction than ARBs in insulin-resistant hypertensive subjects (Figure 3A).[53] Whether Ang II–mediated AT_4 stimulation (during chronic ARB therapy) is responsible for the observed paradoxical increase in PAI-1 remains to be determined. Irrespective of the mechanism, from a biological standpoint, the observation that ARBs increase PAI-1 relative to ACEIs may point to an adverse effect of these agents on plaque vulnerability.

Another of the unique properties of ACEIs not shared by ARBs is their effect on increased bradykinin bioavailability. Bradykinin inhibits both platelet aggregation and circulating PAI-I levels and is one of the most potent stimulators of tissue plasminogen activator. Furthermore, bradykinin promotes vasodilatation via the release of prostacyclin, NO, and endothelium-derived hyperpolarizing factor. Long-term treatment with ACEIs augments both bradykinin-

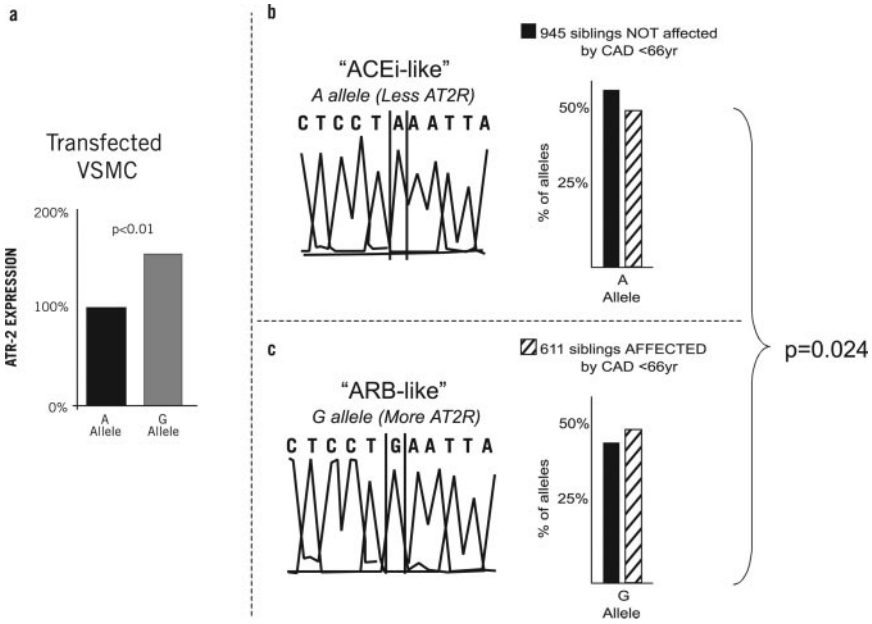


Figure 2. Summary of data regarding the X-linked AT_2 receptor gene polymorphism (−1332 G/A). A, Data suggest that the G allele is associated with increased AT_2 receptor expression in vitro (created from data from Warnecke et al[50]). B, Electropherogram of the AT_2 receptor gene polymorphism (−1332 G/A) A allele and its frequency in siblings (from 509 families) who were not (solid black bars) or were (striped bars) affected by coronary artery disease before the age of 66 years. C, Electropherogram of the AT_2 receptor gene polymorphism (−1332 G/A) G allele and its frequency in siblings (from 509 families) who were not (solid black bars) or were (striped bars) affected by coronary artery disease before the age of 66 years (created from data from Alfakih et al[49]). The probability value is derived from the X-TDT (X-linked transmission disequilibrium test) indicating a significant excess of the G allele in association with early coronary artery disease.

induced peripheral vasodilatation and the release of tissue plasminogen activator to levels that approximate those seen during systemic thrombolytic therapy.[54]

Bradykinin is also a key mediator of ischemic preconditioning, a unique cytoprotective phenomenon that allows myocardial cells to withstand injury from prolonged exposure to ischemia if first exposed to repeated brief bouts of ischemia.[55] Ischemic preconditioning can limit both infarct size and ischemia-mediated ventricular arrhythmias[55] and may contribute to the vascular protective effects of ACEIs. The relative lack of effect of ARBs on bradykinin may limit the aforementioned effects.

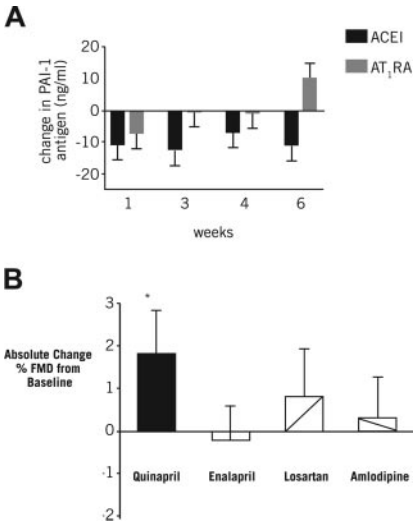


Figure 3. A, Change in PAI-1 over time in response to treatment with ramipril (ACEIs) or losartan (AT_1 receptor antagonist [AT_1RA]) in patients with essential hypertension and insulin resistance taking hydrochlorothiazide. The decrease in PAI-1 antigen over time was significantly greater during ACEIs than during AT_1RA ($P=0.043$), whereas the changes in mean arterial pressure and tissue plasminogen activator were similar in the 2 treatment groups. From Brown et al,[53] with permission. B, Absolute change in percent flow-mediated vasodilation (FMD) after therapy compared with pretreatment baseline values. Only ACEIs with quinapril resulted in a significant improvement in brachial FMD (*$P<0.02$). From Anderson et al,[57] with permission.

The effects of ARBs on endothelial dysfunction, the earliest marker of atherosclerosis, have been disappointing. ACEIs consistently improve coronary and systemic endothelial function.[56–58] In contrast, ARBs have only a modest effect (Figure 3B).[57] ACEIs also have the unique ability to alter gene expression by binding to ACE, which is a nonreceptor endothelial cell surface protein. ACE binding elicits outside-in signaling transduction molecules,[59] one of which has been shown to increase both the expression and activity of cyclooxygenase-2 (COX-2).[60] COX-2 increases prostacyclin (PGI_2) and prostaglandin E_2, although it does not increase thromboxane A_2, and it may be another mechanism that contributes to the vascular protection conferred by ACEIs. ARBs have limited data specific to COX-2 that include the existence of a major metabolite of losartan (EXP3179) that reportedly inhibits COX-2, an effect that might potentially be deleterious.[61,62]

Blood Pressure–Independent Effects of ACEIs on MI and Mortality

The profound benefits of ACEIs on MI and mortality in patients with heart failure seem disproportionate to the 6-mm Hg drop in mean systolic pressure from an initial mean blood pressure of 116/72 mm Hg.[1] In some hypertension trials that compared ACEIs to non-ACEI therapy, ACEIs produced a greater reduction in both fatal and nonfatal MI, even when similar blood pressure levels were achieved.[63,64] Although it appears that ACEIs may have a blood pressure–independent benefit, it is difficult to remove blood pressure as a variable unless blood pressure levels are less than 115/75 mm Hg, because even a systolic blood pressure of 120 to

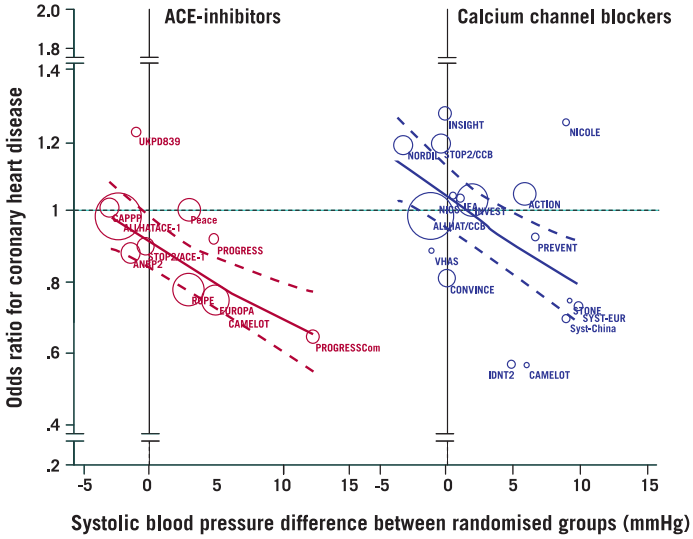


Figure 4. Relationship between ORs for coronary heart disease (CHD) and differences in achieved systolic blood pressure between randomized groups in trials with experimental treatment based on ACEIs or calcium channel blockers (CCBs). Circles represent individual trials and have a diameter proportional to the inverse of the variance of the ORs in individual trials. From Verdecchia et al,[70] with permission.

139 mm Hg and a diastolic pressure of 80 to 89 mm Hg have an associated increased CV risk.[65]

The challenge is how to best quantify the impact of even small changes in blood pressure on vascular events. This is well illustrated by a meta-analysis of the "trilogy" of ACEIs-versus-placebo trials in vascular disease[66]: Heart Outcomes Prevention Evaluation (HOPE),[4] EUropean trial of Reduction Of cardiac events with Perindopril in stable coronary Artery disease (EUROPA),[5] and Prevention of Events with ACE inhibition study (PEACE).[6] Initial mean blood pressures in these trials were so-called normal (133/79 to 139/78 mm Hg) and fell by only a mean of 3/1.5 to 5/3 mm Hg, yet CV mortality was reduced by 17.4% (643 deaths with ACEIs and 778 with placebo, $P<0.01$).[66] Despite these impressive results, there was no substantive evidence that the benefit of ACEIs was independent of blood pressure lowering.[67] Even a meta-analysis of 162 341 patients from the Blood Pressure Lowering Treatment Trialists Collaboration (BPLTTC)[68] that suggested that ACEIs had a greater impact on MI and death than calcium channel blockers was not able to exclude the possibility that the blood pressure differential in favor of ACEIs was not the sole reason for the difference in outcome. The discussion becomes even more complex as evidence accumulates that some antihypertensive agents, for example, some β-blockers, may not reduce MI or death in hypertensive patients despite significant blood pressure reductions.[69]

Two recent meta-analyses have provided strong evidence for a blood pressure–independent effect of ACEIs. Both meta-analyses included a meta-regression analysis, an extension to meta-analysis that seeks to test the relationship between outcome and possible explanatory variables. In this way, it is possible to investigate the factors that may account for between-study heterogeneity. Here, the influence of different decreases in blood pressure is investigated on the size of effect observed in the studies. The first of these analyses included 179 122 patients in trials that compared treatment with ACEIs or calcium channel blockers to comparators that included placebo and active treatments of diuretics and β-blockers.[70] A 10-mm Hg fall in systolic pressure translated into a 15% relative risk (RR) reduction of MI and CV death. Even so, ACEIs had a further 12% RR reduction above that achieved by blood pressure lowering (Figure 4). These results are almost identical to a second meta-regression analysis of 137 356 high-risk patients from the BPLTTC, in which patients randomized to ACEIs had an additional 9% RR reduction of MI and CV death above that predicted by blood pressure lowering alone (discussed in detail below; presented European Society of Hypertension 2005).[27]

In the next section, we highlight how these blood pressure–independent vascular protective effects (MI and CV death) of ACEIs noted above may not hold true for ARBs.

Relative Lack of Vascular Protection in ARB Hypertension Trials: Heightened Risk Despite Lower Blood Pressure

In the LIFE (Losartan Intervention For Endpoint reduction in hypertension) trial (n=9193),[14] losartan treatment was associated with a 5% statistically nonsignificant increase of MI (198/4605 versus 188/4588, unadjusted, or 7% adjusted) compared with atenolol despite a 1.7-mm Hg lower mean pulse pressure and a major reduction in stroke. Candesartan was associated with a 10% statistically nonsignificant increase in fatal plus nonfatal MI (14% for nonfatal MI) in SCOPE (Study on COgnition and Prognosis in Elderly)[15] (n=4937) despite a mean 3.2/1.6-mm Hg lower blood pressure than in the control group. In the VALUE trial (n=15 245),[13] treatment with valsartan 160 mg was associated with a statistically significant increase (19%; $P=0.02$) in total MI (fatal and nonfatal MI) compared with amlodipine 10 mg. Importantly, this trial recruited "high-risk" patients with hypertension, 80% of whom had symptomatic vascular disease. A post hoc analysis of serial median matching[71] and a division of the follow-up period into consecutive intervals suggested that the MI rate was a reflection of the blood pressure differential of 1.8/1.5 mm Hg in favor of amlodipine, although these analyses have been criticized.[72] In VALUE, the predicted odds ratio (OR) for MI was 0.98 for a

systolic blood pressure gradient of 2.2 mm Hg compared with the observed 1.19 ($P=0.03$), which led one expert to conclude, "with regards to myocardial infarction, the results of valsartan-based treatment were worse, or conversely, those of amlodipine-based treatment were better, than predicted from the gradient in the achieved systolic blood pressure."[72]

It has been suggested that the comparator therapies in some of the above trials may have reduced the incidence of MI rather than the ARB increasing its incidence.[73] Atenolol, as discussed, does not appear to reduce MI despite causing reductions in blood pressure.[69] Amlodipine does improve symptoms of angina and reduces hospitalizations and revascularizations in patients with coronary artery disease, but it does not appear to reduce MI or death compared with placebo despite lowering blood pressure by 4.8/2.5 mm Hg,[74] although that trial was not powered for these end points. A similar lack of vascular protection has been noted with other dihydropyridines.[75] Thus, at the present time, the balance of published information clearly points toward an increase in rates of MI with valsartan in the VALUE trial that cannot be explained by a differential blood pressure between valsartan and amlodipine nor by a unique vascular protective effect of the latter.

ARB Congestive Heart Failure Trials: Poor Performance With Respect to MI

Two early heart failure trials suggested a potential mortality benefit for ARBs. In the pilot trial ELITE (Evaluation of Losartan In The Elderly) I,[76] (n=722) losartan 50 mg once daily was associated with a lower all-cause mortality rate than captopril 50 mg 3 times per day (4.8% versus 8.7%), although with very few deaths, the trial was not powered for mortality but rather for renal safety and tolerability. In a post hoc analysis of a small subgroup in Val-HEFT (Valsartan-Heart Failure Trial)[17] (n=226/5010) who received neither an ACEI nor a β-blocker, valsartan 160 mg versus placebo had a lower mortality rate, although once again, the trial was not powered to test for this. The MI rate was not reported. In the pilot trial RESOLVD (Randomized Evaluation of Strategies fOr Left Ventricular Dysfunction; n=768),[77] the benefit of candesartan 16 mg for the primary end points of quality of life, tolerability, ventricular function, and exercise tolerability was no different than for enalapril 20 mg. However, the trial was stopped 6 weeks prematurely by the data safety monitoring committee because candesartan was associated with both an increase in mortality (6.1% versus 3.7%) and hospitalizations for heart failure (10.7% versus 3.7%, $P=0.048$), although the study was not formally powered for these unexpected end points. The occurrence of MI and stroke was not reported.

In ELITE II (n=3152),[78] losartan 50 mg was compared with captopril 50 mg 3 times daily, and total mortality was increased nonsignificantly by 13% in the losartan-treated group (280 versus 250 deaths) or, alternatively, was reduced by 13% in the captopril-treated group. Furthermore, losartan was associated with a 30% statistically nonsignificant increase in the secondary end point of sudden cardiac death or resuscitated arrest, an end point for which benefit had been expected on the basis of the findings of ELITE I. Of note, the results of ELITE II cannot provide any insight into the issue of whether losartan is more effective than placebo, which is a true measure of drug efficacy. Furthermore, although emphasis was placed on the lower treatment-withdrawal rates for losartan than for captopril (9.7% versus 14.7%, $P<0.001$), it should be remembered that the excess cardiac event rates occurred with losartan despite better treatment compliance. Some have speculated that twice the dose of losartan might have produced a more comparable effect to captopril, but it could also be argued that twice the dose could potentially have accentuated the trend toward harm seen with losartan compared with captopril. Furthermore, all 4 of the trials (OPTIMAAL [OPtimal Trial In Myocardial infarction with the Angiotensin II Antagonist Losartan], VALIANT [VALsartan In Acute myocardial iNfarcTion], ELITE I, and ELITE II) that have sought to compare ARBs with ACEIs have chosen to study captopril, a first-generation, short-acting sulfhydryl ACEI. Furthermore, they did so over a shorter duration of follow-up than was required in the index SAVE (Survival And Ventricular Enlargement) trial (captopril versus placebo) for captopril to achieve statistical significance (Figure 5).

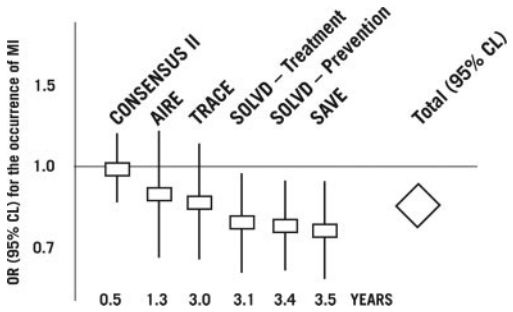


Figure 5. Schematic representation of randomized, controlled trials giving long-term treatment with either ACEIs or placebo in the context of impaired left ventricular function and MI. Data are shown as the OR (95% CI; *y*-axis) for the occurrence of MI ordered by duration of follow-up (*x*-axis). The OR for the overall effect in the studies as a whole is also shown.

The CHARM program[79] (n=7599) consists of 3 parallel trials that compared 32 mg of candesartan with placebo in patients with symptomatic heart failure. Candesartan reduced all-cause mortality (hazard ratio 0.91, 95% confidence interval [CI] 0.83 to 1.0, $P=0.055$), but the benefits apparently all occurred in the first year of treatment. To quote the investigators, "this treatment difference in cardiovascular death was most striking in the first year without additional divergence in subsequent years."[79] This suggests an immediate but limited hemodynamic benefit of candesartan. This is further emphasized by the fact that the combined end point of death or readmission for heart failure was dependent primarily on the prevention of signs and symptoms of fluid retention. In sharp contrast, ACEIs have additional long-term benefits with regard to MI and mortality (Figure 5), and these continue to accrue through many years of follow-up.[80] Although a reanalysis of CHARM suggests candesartan reduces the composite outcome of CV death or nonfatal MI,[81] all patients in CHARM-Added, and a proportion of those in CHARM-Preserved, had concomitant treatment with

ACEIs. This has the potential to mask any possible deleterious effects of AT_2 receptor activation. The CHARM investigators have also concluded that the mortality rate in the patients who were compliant with candesartan therapy was no different than in those patients compliant for placebo, which led to the conclusion that in CHARM, a compliant patient had no mortality benefit with candesartan compared with placebo (MI not reported).[82]

The CHARM Overall program[79] cannot provide insight into the ARB-MI paradox because it was conducted largely on the background of ACEI therapy. Furthermore, it mixed 3 unique and heterogeneous populations into 1 population. Rather, each trial must be analyzed independently. In CHARM-Alternative[16] (the only study not to require/permit background ACEI treatment), candesartan was associated with a 52% statistically significant increase in total MI ($P=0.025$) compared with placebo despite a blood pressure reduction of 4.4/3.9 mm Hg in favor of candesartan. Could this be a random play of chance denoted by the probability value ($P=0.025$)? On the side of a treatment benefit, the play of chance would have been considered to have been effectively ruled out ($P<0.05$). CHARM-Added[83] included ACEIs as background therapy, as did Val-HEFT, and as such, the effects of ARBs cannot be determined independent of those of ACEIs at the present time. CHARM-Preserved[84] included patients with diastolic dysfunction and is discussed separately.

In summary, in patients with chronic heart failure, the results of ARBs with regard to MI and CV death have been modest at best and may be comparable to the effects of placebo under certain circumstances.[82]

Trials of Post-MI Patients With Heart Failure: How Well Did ARBs Fare?

OPTIMAAL[85] and VALIANT[18] compared losartan 50 mg and valsartan 160 mg twice daily, respectively, to captopril 50 mg 3 times daily in patients with signs or symptoms of congestive heart failure within 10 days of an MI. In VALIANT, there was a mean follow-up of just 2 years, and there was no difference for the primary end point of mortality. In OPTIMAAL, losartan versus captopril was associated with a significant increase in CV mortality (OR 1.17, CI 1.01 to 1.34) after a 2.7-year mean follow-up. Because both studies derived their primary justification for selecting a 3-times daily ACEI regimen from the SAVE study, it is relevant to note that the mean follow-up in SAVE was 3.5 years and that the MI and mortality benefit of captopril compared with placebo did not reach statistical significance before that time. In this context, it is not surprising that it may have been impossible for captopril to achieve superiority over an ARB in VALIANT simply because the duration of the trial was too short.

In VALIANT, the potential benefit of captopril may also have been masked because 39% of the patients received an average of 5 days of nonstudy ACEIs after the MI but before randomization, whereas in OPTIMAAL, all patients were ACEI naïve. ACEIs are known to reduce mortality in the early post-MI period (7% RR reduction at 30 days), with 85% of the benefit in the first week,[3] and therefore, early use of nonstudy ACEIs in VALIANT may have influenced the results. The mortality rates in VALIANT for ACEI-naïve patients compared with those who received prerandomization ACEIs has not been published[18,86,87] but may differ significantly, as did the unadjusted 30-day mortality in VALIANT patients who had received nonrandomized β-blockers versus those who did not, whereby the mortality rate was reduced by 54% (6.6% versus 3.0%, $P<0.001$).[88]

Although mortality and MI rates were statistically no different in VALIANT, the trial was designed to prove "superiority" and not "equivalence." A secondary statistical analysis did prove that valsartan 160 mg BID was "noninferior" to captopril, but again, it did not prove them equivalent. Importantly, the validity of a noninferiority analysis is dependent on the fact that the comparator (captopril) is being used in an optimal and similar fashion that directly relates to the index placebo-controlled trials (ie, SAVE), and as we have seen, this was not the case owing to the shorter duration of follow-up. In this regard, it is interesting to note that the benefits of ACEIs seen with regard to prevention of MI seem to be time-dependent, which suggests that the duration of follow-up in VALIANT and OPTIMAL may have been insufficient to permit the benefits from captopril to become fully apparent (Figure 5).

It has been suggested by some that ARBs and ACEIs may now be considered to be equivalent and interchangeable in the post-MI setting. The literal translation of the word "noninferiority" (had this been adequately proven) suggests that valsartan would indeed be clinically equivalent, interchangeable, or an alternative to captopril, although this does not reflect the definition of the statistical term.[89,90] Noninferiority as a statistical term simply defines that valsartan relative to captopril is "not substantially worse than the gold standard" but not necessarily equivalent.[91] This is best reflected in the final printed labeling of valsartan (US Food and Drug Administration document NDA 21-283/S-011, available at www.fda.gov), which states that noninferiority makes it "unlikely that valsartan has less than about half of the estimated effect of captopril" and confirms valsartan 160 mg twice daily as a second-line therapy for ACEI-intolerant patients.

The VALIANT study also reported an imputed placebo analysis, a concept that may be unfamiliar to many clinicians. This statistical analysis hypothesizes that if VALIANT had included a placebo arm, valsartan would have achieved 99.6% of the benefits that were seen with ACEI therapy compared with placebo in the historic post-MI trials of SAVE, AIRE (Acute Infarction Ramipril Efficacy study), and TRACE (TRAndolapril Cardiac Evaluation). Unfortunately, an imputed placebo analysis of VALIANT would only be valid if the concomitant medical therapy, invasive interventions, and duration of follow-up in VALIANT were comparable to those in SAVE/AIRE/TRACE, which, of course, is not the case. Perhaps more importantly, the fact that 39% of VALIANT patients received nonstudy ACEIs after MI and before randomization makes an imputed placebo analysis tenuous at best.[92]

Hence, in patients with post-MI heart failure, valsartan may be considered as a second-line alternative therapy to an ACEI, with the recognition that the evidence for noninferiority offered in this case appears tenuous.

ARBs in Diastolic Dysfunction: Surprising Lack of Mortality Benefit

The CHARM-Preserved[84] trial compared candesartan to placebo in patients with heart failure and an ejection fraction of 40% to 60%. Although most physicians would elect to describe this population as having mild systolic dysfunction, because there was no measure of diastolic function per se, this trial still provides unique insights. CHARM-Preserved was a high-risk population with comorbidities that closely resembled those of patients in HOPE,[4] including diabetes mellitus, coronary artery disease, revascularization, prior stroke, or peripheral vascular disease, and a mortality rate of 11% compared with 8% in HOPE. Despite the fact that the mean follow-up duration in CHARM-Preserved was just 3 years compared with 5 years for HOPE, and despite there being a robust mean blood pressure reduction in favor of candesartan versus placebo of 7/3 mm Hg, there was not a single life saved with candesartan (candesartan 244 deaths versus placebo 237 deaths). However, there was a reported nonsignificant reduction in MI (candesartan 57 versus placebo 73; $P=0.15$). This was in the context of 20% concomitant use of ACEIs, which, together with the blood pressure reduction, may have masked any AT_2 receptor–mediated effects. Even so, these observations contrast sharply with the fall in mean blood pressure of only 3/1.5 mm Hg in HOPE,[4] in which ramipril reduced mortality by 16% ($P<0.005$) and MI by 20% ($P<0.001$).

An aspect that is often discussed relates to the uniqueness of the CHARM-Preserved trial, ie, no similar trial has been done with ACEIs in this population. Although this may appear to be the case, clinicians should be reminded that left ventricular dysfunction is a spectrum that does not conform to a mere ejection fraction below or above 40%. Because ACEIs have proven benefits in patients with low ejection fractions (<40%) and preserved ejection fractions (ie, HOPE, EUROPA), it may be inappropriate to discount their first-line use in the intermediate ejection fraction category, ie, patients with so-called diastolic dysfunction.

ARBs and Diabetic Renal Disease: More Evidence of the ARB-MI Paradox

Diabetes mellitus is associated with an increased incidence of vascular complications, which are attenuated primarily by ACEIs compared with ARBs,[26] although both classes of drugs may prevent the new onset of diabetes mellitus.[22] In a meta-analysis of hypertension trials in patients with diabetes mellitus,[93] ACEIs reduced both total mortality (43%, $P=0.01$) and MIs (63%, $P<0.001$) compared with other drugs. In Micro-HOPE,[9] ramipril reduced both MI and CV death (22% and 37% respectively, $P\leq0.01$) with a mean blood pressure reduction of only 3/2mmHg compared with placebo. In the diabetes subgroup of LIFE,[94] losartan produced no reduction in MI despite having a similar mortality reduction as was seen in Micro-HOPE.

Nephropathy is a common microvascular complication of diabetes mellitus, and both ACEIs and ARBs offer similar renal protection according to a meta-analysis from the Cochrane group.[11] Renal disease is also a harbinger and surrogate marker for vascular disease in patients with diabetes mellitus that can be quite malignant in nature. In a study by Lewis et al,[12] patients with type 1 diabetes mellitus had a combined rate of mortality and MI of 9.9% despite an average age of only 35 years. ACE inhibition with captopril 25 mg 3 times daily reduced the combined end point of death, dialysis, and transplantation by 48% despite only small differences in blood pressure. The number of patients needed to treat with captopril to prevent 1 death was only 33, and the benefits continued to accrue throughout the 3-year trial period.

In the more recent Irbesartan Diabetic Nephropathy Trial (IDNT)[19] in patients with type 2 diabetes mellitus, CV risk was even greater than in the trial by Lewis et al,[12] with 30% of the patients having at least 1 cardiac event over 2.6 years (821 CV events in 1715 patients). The total rates of CV death plus nonfatal MI for the 3 arms of IDNT were placebo 15.3% (CV death 8.1%, nonfatal MI 7.2%), irbesartan 15.7% (CV death 9.0%, nonfatal MI 6.7%), and amlodipine 10.9% [CV death rate 6.5%, nonfatal MI 4.4%; US Food and Drug Administration advisory briefing NDA 20-757(S-021), available at www.fda.gov]. Irbesartan, surprisingly, had a complete lack of effect on the combined end point of MI and CV death compared with placebo (15.7% versus 15.3%), despite a further mean blood pressure reduction of 4/3 mm Hg. In RENAAL (Reduction of Endpoints in Non–insulin-dependent diabetes mellitus with Angiotensin II Antagonist Losartan),[20] which was also a study of diabetic nephropathy in patients with type 2 diabetes mellitus, losartan both reduced MI by 26% and delayed the need for dialysis by 40 days. However, once dialysis was required, losartan was associated with a 29% (P=NS) increase in mortality [US Food and Drug Administration Advisory Briefings NDA 20-386 (S-028), available at www.fda.gov].

CV events are responsible for the overriding morbidity in patients with diabetic nephropathy, and it appears that the effects of ACEIs and ARBs on these events are profoundly different. In a Cochrane meta-analysis,[11] ACEIs reduced mortality by 21% (RR 0.79, CI 0.63 to 0.99), whereas ARBs produced a 0% reduction in mortality (RR 0.99, CI 0.85 to 1.17). Although some have suggested that the choice of an ARB versus an ACEI in diabetic nephropathy should be determined by the etiology of the diabetes (specifically, an ARB in type 2 diabetes mellitus, based on IDNT and RENAAL, and an ACEI in type 1 diabetes mellitus, based on the study by Lewis et al[12]), this has clearly been refuted.[11] In fact, the RENAAL trial was terminated prematurely when data became available that not only did ACEIs attenuate the deterioration of renal function in those with underlying renal disease, but that an elevated creatinine level was a marker for increased vascular events, which, in turn, were profoundly reduced by ACEIs.[95] Although some have argued that an ACEI should have been chosen as the comparator in both IDNT and RENAAL,[96] the overwhelming evidence for a cardioprotective effect of ACEIs over ARBs makes them the logical first choice for patients with diabetes mellitus, regardless of underlying renal function. ARBs in diabetic nephropathy appear to lack the unique vascular protective properties of ACEIs, despite similar hemodynamic and renal benefits.

ACEIs and ARBs significantly reduce end-stage renal disease in nondiabetic patients as well (RR 0.87, 95% CI 0.75 to 0.99)[97] compared with other antihypertensive agents despite similar reductions in blood pressure. Furthermore, ACEIs have a profound impact on renal function even with serum creatinine levels of 3.1 to 5 mg/dL.[98] Renal disease per se is also an independent marker for CV events.[99] After an MI, even mild renal disease is a major risk factor for CV complications.[100] In an analysis of the SAVE database, the total mortality was 2-fold greater in patients with an estimated glomerular filtration rate <45, with the absolute benefit of ACEIs on mortality not only preserved but increased by more than 2-fold.[101] In HOPE, chronic renal disease was also a marker for increased vascular events, and once again, the absolute benefit of ACEIs was enhanced.[95] ACEIs also reduced mortality in high-risk blacks with renal disease, and this effect appeared to be blood pressure–independent.[64]

Can Systematic Reviews and Meta-Analyses Resolve the ARB-MI Paradox?

Some systematic reviews of the major ARB trials have concluded that ARBs do not prevent MI or prolong survival, even when compared with placebo,[29] whereas others conclude that their effects are "either neutral, or may actually increase the rates of MI despite similar levels of blood pressure reduction."[28] A meta-analysis[33] of hypertension trials (n=29 375; LIFE,[14] VALUE,[13] and SCOPE[15]) found that MI was significantly increased with ARBs (RR 1.12, 95% CI 1.01 to 1.26, P=0.041) compared with non-ACEI therapy, whereas other meta-analyses have found a more neutral effect.[30–32] The discordant results of the meta-analyses may reflect the high degree of dependence on the trials that have been included or excluded in the analysis.

For example, in a meta-analysis by Tsuyuki and colleagues (n=31 569, 19 trials),[31] there was no overall increase in MI with ARBs, but trials with non-ACEI therapy as the comparators were excluded despite those trials showing an increased incidence of MI with ARBs.[33] Almost half of the trials were less than 3 months in duration and therefore had event rates so low that the potential to demonstrate an adverse impact of an ARB may have been "diluted." Just as importantly, this meta-analysis did not include the more important end point of CV mortality, which may differ from MI. Exclusion of mortality is particularly relevant in OPTIMAAL,[85] in which losartan and captopril had similar MI rates, but CV mortality was increased significantly with losartan (RR 1.17, CI 1.01 to 1.34, P=0.032) compared with captopril. This meta-analysis also included CHARM-Added and Val-HEFT, in which patients received background ACEIs. This prevents adequate exploration of the dual consequences of ARB administration in the absence of ACEIs, namely, simultaneous AT_1 receptor blockade and AT_2 receptor activation. Even so, Tsuyuki and colleagues concluded that their analysis could not exclude that ARBs increase MI compared with placebo or ACEIs by as much as 16%.

In a large meta-analysis by Volpe et al (n=56 254, 11 trials),[32] there was a potential 18% increase in MI with ARBs compared with placebo (RR 0.99, 95% CI 0.84 to 1.18) and a possible 13% increase compared with other active therapy (RR 1.04, 95% CI 0.96 to 1.13). MI overall tended to increase with ARBs (RR 1.04, CI 0.97 to 1.11), but unfortunately, there was no assessment of CV mortality. In the meta-analysis by Volpe et al,[32] the MI data for VALIANT favored valsartan, but McMurray et al[86] reported that the number of patients with MI was in fact greater with valsartan than with captopril (587 versus 559, respectively). CHARM-Added and Val-HEFT were appropriately excluded from the meta-analyses given the fact that these studies permitted background ACEI therapy.

In a meta-analysis from Verdecchia et al (n=64 381, 11 trials, >1-year duration, minimum 500 patients),[30] CV mortality and MI overall were not increased; however, the rate of MI in the subgroup of ARB as compared to non-ACEI therapy was increased (OR 1.16 P=0.017, fixed-effect model), which is a consistent finding with other meta-analyses.[33] Although no difference was shown in MI incidence for ARBs compared with ACEIs, this is not consistent with their finding that MI was increased with ARB compared with non-ACEI therapy.[27] These results appear to be mutually exclusive and not biologically plausible. This apparent paradox may reflect the inclusion of trials with short durations of follow-up and background ACEI use (VALIANT, CHARM-Added, and Val-HEFT), which would make any true effects of AT_2 receptor activation on coronary plaque stability more difficult to evaluate.

Although these meta-analyses appear to suggest that ARBs do not increase MI, they also confirm that ARBs do not reduce MI, regardless of whether the comparator is a placebo or non-ACEI therapy.[30–32] This is despite the presence of significant blood pressure reductions that favor the ARB. The blood pressure effect alone ought to produce an observable benefit, unless opposed by an alternative tendency to increase MI, namely, a biphasic response that creates net neutrality. The conclusion of "vascular neutrality" for ARBs may therefore be an illusion and may simply reflect the inherent inadequacies of each of these meta-analyses.

To circumvent the challenges in the meta-analysis above, we performed a meta-analysis to evaluate the hypothesis that attenuation of both AT_1 and AT_2 receptor–mediated effects (with ACEIs) is preferable to isolated AT_1 receptor antagonism but with additional AT_2 receptor stimulation, as is the case with ARB therapy. Consequently, we systematically considered the data with regard to the effect of ARBs (in the absence of ACEIs) on the risk of major vascular events and included randomized, controlled trials with at least 100 patients in each group, with treatment for at least 6 months, and that had been published in the English language from1980 to March 2005. Only studies with a Jadad score (quality of research and report) of at least 3 were included. Major clinical end points were evaluated, including (1) global death, (2) CV death, (3) stroke (fatal and non fatal), and (4) MI (fatal and nonfatal). Because the primary objective of the analysis was to assess the clinical profile for use of ARBs in the absence of concomitant ACEI therapy, trials in which concomitant nonstudy ACEIs were prescribed were excluded (ie, CHARM-Preserved, CHARM-Added, and Val-HEFT). For the reasons explained above, use of nonstudy ACEIs early in VALIANT should disqualify this trial from meta-analysis, because there was background use of ACEIs, but this conclusion is hypoth-

	Number at Risk	Number of Events	Control Event Rate	Odds Ratio (95% CL)	P Value Overall Effect
ARB versus ACEi					
Global Death	19,419	3,474	17.42%	1.06 (0.99-1.14)	0.10 *
CV Death	19,419	2,910	14.59%	1.06 (0.98-1.15)	0.14
Non CV Death	19,419	564	2.8%	1.05 (0.89-1.25)	0.55
Stroke	18,697	704	3.9%	0.91 (0.79-1.06)	0.25
MI	19,419	1,990	10.05%	1.04 (0.95-1.15)	0.37

(* p<0.10; ** p<0.05; *** p<0.01; **** p<0.001)

Figure 6. Summary of meta-analyses for treatment with an ARB compared with an ACEI. Trials included ELITE I, ELITE II, DETAIL, OPTIMAAL, and VALIANT. Data shown are (1) clinical end points assessed; (2) number of patients in trials; (3) number of events observed in trials; (4) event rate in the control (ACEI) groups; (5) OR (95% confidence limits) for the overall effect seen in the trials; and (6) statistical significance of observed overall effect.

esis driven, and therefore VALIANT was included as per other meta-analyses.

Where 2 or more active comparators were studied (ie, ALLHAT [Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial] and STOP-2 [Swedish Trial in Old Patients No. 2]), both arms were included. Where 1 comparator arm was placebo and another was an active comparator, data were included as appropriate for comparisons against placebo (placebo-arm only included) or else all comparators (both control arms included). Trials were excluded if there was an absence of study end points (ie, TOMHS), no control group (ie, ATLAS), or combination therapy (ie, INVEST). The data included were those that the investigators reported and avoided the inclusion of multiple events for a single patient. The data were combined to obtain a summary estimate of the treatment effects as an OR with the 95% CI of the estimate also systematically calculated (Review Manager 4.2.8 software, Cochrane Collaboration; intent-to-treat analyses). Tests of homogeneity of the studies were performed with the Cochran Q statistic. When this failed to reach a statistical significance level of $P<0.05$, a fixed-effect model (Yusuf-Peto) was constructed; otherwise, a random-effects model (DerSimonian-Laird) was derived.

Our analysis compared (1) ARBs versus ACEIs, (2) ARBs versus placebo, (3) ARBs versus placebo or active comparator other than ACEIs, and (4) ARBs versus placebo or all active comparators including ACEIs. Unfortunately, previous meta-analyses failed to compare the effects of ARBs on MI with the documented effects of ACEIs on MI using similar methodologies. Therefore, we performed a similar meta-analysis for ACEIs to have a "benchmark" against which to measure the results of the ARB analysis.

Five trials compared ARBs versus ACEIs (n=19 419, follow-up 0.92 to 2.7 years: ELITE; ELITE II; OPTIMAAL; DETAIL [Diabetics Exposed to Telmisartan And EnalaprIL]; and VALIANT). Four of the trials included captopril 50 mg 3 times daily in symptomatic heart failure compared with losartan 50 mg daily in 3 trials and valsartan 160 mg twice daily in another. The overall event rates were global death, 17.4%; CV death, 14.6%; noncardiovascular death, 2.8%; stroke, 3.9%; and MI, 10.1% (Figure 6). All end points other than stroke were more likely to

	Number at Risk	Number of Events	Control Event Rate	Odds Ratio (95% CL)	P Value Overall Effect
ARB versus placebo					
Global Death	9,626	1,579	16.9%	0.94 (0.66-1.24)	0.24
CV Death	9,626	1,035	11.0%	0.95 (0.83-1.08)	0.43
Non CV Death	9,626	529	5.6%	0.98 (0.82-1.17)	0.81
Stroke	9,626	421	4.7%	0.84 (0.69-1.02)	0.09 *
MI	9,626	454	4.90%	1.05 (0.76-1.47)	0.76
ARB versus placebo / non ACEi comparator					
Global Death	34,631	4,127	12.2%	0.96 (0.90-1.03)	0.26
CV Death	34,631	2,118	6.3%	0.95 (0.87-1.04)	0.27
Non CV Death	34,631	1,998	5.8%	0.99 (0.91-1.09)	0.87
Stroke	34,631	1,581	4.7%	0.94 (0.75-1.19)	0.61
MI	34,631	1,547	4.4%	1.13 (1.02-1.25)	0.02 **
ARB versus placebo / non ACEi comparator / ACEi					
Global Death	55,050	7,601	14.0%	1.01 (0.96-1.06)	0.80
CV Death	54,050	5,028	9.2%	1.01 (0.95-1.07)	0.71
Non CV Death	54,050	2,562	4.7%	1.00 (0.93-1.09)	0.89
Stroke	53,318	2,285	4.4%	0.92 (0.79-1.08)	0.32
MI	54,050	3,537	6.3%	1.08 (1.01-1.16)	0.03 **

(* p<0.10; ** p<0.05; *** p<0.01; **** p<0.001)

Figure 7. Summary of meta-analyses for treatment with an ARB vs placebo; placebo or non-ACEI comparator; and placebo or any comparator, including ACEIs. Trials included IDNT, CHARM-Alternative, SCOPE, RENAAL, LIFE, VALUE, ELITE, ELITE-2, DETAIL, OPTIMAAL, and VALIANT. Data shown are (1) clinical end point assessed; (2) number of patients in trials; (3) number of events observed in trials; (4) event rate in the control groups; (5) OR (95% confidence limits) for the overall effect seen in the trials; and (6) statistical significance of observed overall effect.

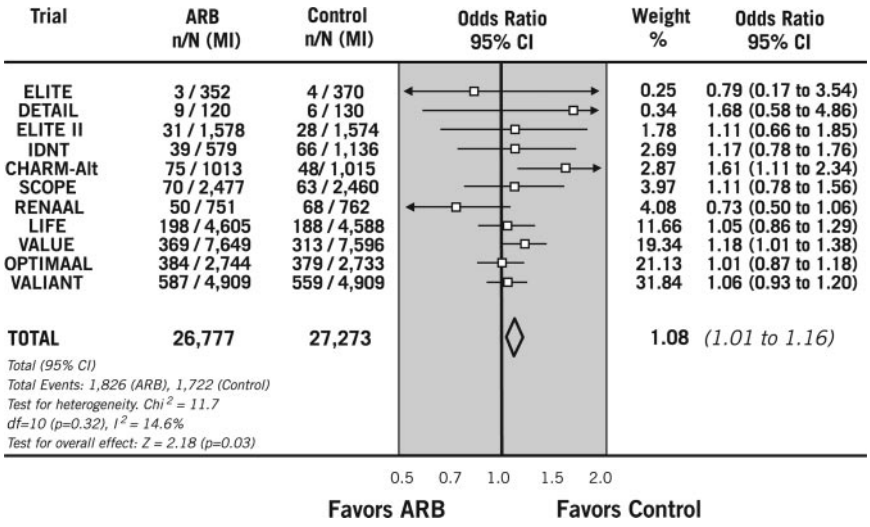


Figure 8. Forest plot of MI meta-analyses for treatment with an ARB vs placebo, non-ACEI comparators, or ACEI. Trials included IDNT, CHARM-Alternative, SCOPE, RENAAL, LIFE, VALUE, ELITE, ELITE-2, DETAIL, OPTIMAAL, and VALIANT. Data shown are (1) trial name; (2) number of events/patients randomized to ARB; (3) number of events/patients randomized to control; (4) graphical representation of OR (95% CI) for each trial; (5) relative weight/contribution of each trial to meta-analysis; and (6) OR (95% CI) for each trial. Testing for the heterogeneity of these trials allowed the null hypothesis to be rejected (P=0.32) and the overall treatment effect to assessed by the fixed-model method described by Yusuf and Peto (OR 1.08, 95% CI 1.01 to 1.16, P=0.03).

occur with ARBs than with ACEIs, with global death showing a trend in favor of ACEIs (OR 1.06, 95% CI 0.99 to 1.14, P=0.10). A sensitivity analysis that included the RESOLVD-Pilot study further emphasized this trend.

Four trials compared ARBs and placebo (n=9626, follow-up 2.6 to 3.7 years: CHARM-Alternative, SCOPE, RENAAL, and IDNT). The overall event rates were global death, 16.9%; CV death, 11.0%; noncardiovascular death, 5.6%; stroke, 4.7%; and MI, 4.9% (Figure 7). Four end points (global death, CV death, noncardiovascular death, and stroke) were found to be less likely in patients treated with ARBs than in controls, with global death only marginally reduced (OR 0.94, 95% CI 0.66 to 1.24, P=0.24). Stroke showed a strong trend toward reduction (OR 0.84, 95% CI 0.69 to 1.02, P=0.09), whereas in contrast, the risk of MI did not.

Two trials compared ARBs and non-ACEI comparators (n=24 438, follow-up 4.2 to 4.7 years: LIFE and VALUE). The overall event rates for ARBs compared with either placebo or a non-ACEI comparator were global death, 12.2%; CV death, 6.3%; noncardiovascular death, 5.8%; stroke, 4.7%; and MI, 4.4% (Figure 7). Three end points (global death, CV death, and stroke) were less likely with ARBs than with control, with global death marginally reduced by ARBs (OR 0.96, 95% CI 0.90 to 1.03, P=0.26). In contrast, CV death showed no sign of benefit with ARBs, whereas MI was increased significantly by 13% (95% CI 2% to 25%; P=0.02).

In total, there were 11 trials that compared ARBs with either placebo or any active comparator (n=55 050; Figures 7 and 8). The overall event rates were global death, 14.0%; CV death, 9.2%; noncardiovascular death,4.7%; stroke, 4.4%; and MI, 6.3%. Only stroke was less likely in patients treated with ARBs than in those given a placebo. Global death was not reduced by ARBs (OR 1.01, 95% CI 0.96 to 1.06, P=0.8), whereas MI was significantly increased by 8% (95% CI 1% to 16%, P=0.03). Of note was the fact that 9 of the 11 trials demonstrated an excess of MI that achieved statistical significance in 2 trials (1 compared with placebo and 1 against an active comparator). The Cochran Q statistic for this analysis also indicated that the effects seen in these trials were homogeneous. Sensitivity analyses with the exclusion of VALIANT (excess risk 9%; 95% CI 0% to 19%; P=0.04) or the inclusion of CHARM-Preserved and Val-HEFT (excess risk 7%; 95% CI 0% to 14%; P=0.05) had no impact on this key observation.

Figure 9 summarizes the parallel analyses that were conducted for treatment with an ACEI. A total of 23 trials compared ACEIs with placebo (n=68 631), whereas an additional 14 trials were included in analysis of ACEIs compared with either placebo or active non-ARB comparator (131 524 patients). Finally, we analyzed ACEIs compared with placebo and all active comparators including ARBs (150 943 patients). The overall event rates for any comparator were global death, 13.0%; CV death, 8.4%; noncardiovascular death, 4.7%; stroke, 4.2%; and MI, 5.8%. Importantly, these event rates are almost identical to those seen in the ARB analysis. Four end points (global death, CV death, stroke, and MI) were found to be reduced with ACEIs compared with placebo. Global death, CV death, and MI were significantly reduced in comparisons with (1) placebo or non-ARB comparator or (2) any randomized control. In all cases, and in contrast with the ARB analyses, these differences were strongly statistically significant. In contrast, stroke was reduced significantly when ACEIs were compared with placebo but showed no net benefit in the combined analyses. This is in keeping with shared benefits that result from treatment with ACEIs or other active drugs (including ARBs) that reflect the endocrine/hemodynamic actions of these agents, ie, blood pressure–related actions. Conversely, comparator drugs (including ARBs) were significantly inferior to ACEIs with regard to the prevention of MI. This may reflect an additional specific plaque-stabilizing effect of ACEIs that is not related to blood pressure reduction.

The results of our meta-analysis suggest that compared with placebo, ACEIs reduce MI and CV death, whereas there is no evidence than an ARB is better than a placebo. ACEIs tend to be superior in direct comparison with ARBs and with all active comparators, whereas ARBs tend to do worse than other active comparators. Despite some 200 000 patient encounters, our

	Number at Risk	Number of Events	Control Event Rate	Odds Ratio (95% CL)	P Value Overall Effect
ACEi versus placebo					
Global Death	68,631	7,840	12.2%	0.88 (0.84-0.92)	<0.00001 ****
CV Death	65,497	5,661	9.3%	0.84 (0.76-0.92)	0.0001 ****
Non CV Death	64,487	2,138	3.3%	0.98 (0.90-1.07)	0.70
Stroke	56,373	1,948	3.8%	0.83 (0.71-0.98)	0.03 **
MI	66,986	4,655	7.6%	0.82 (0.77-0.87)	<0.00001 ****
ACEi versus placebo / non ARB comparator					
Global Death	131,524	15,169	12.2%	0.90 (0.85-0.95)	0.0002 ****
CV Death	124,244	8,937	7.4%	0.87 (0.80-0.94)	0.0008 ****
Non CV Death	123,234	5,620	5.0%	0.99 (0.93-1.05)	0.69
Stroke	117,106	4,781	4.3%	0.93 (0.81-1.07)	0.29
MI	128,523	6,440	5.1%	0.84 (0.79-0.88)	<0.00001 ****
ACEi versus placebo / non ARB comparator / ARB					
Global Death	150,943	18,643	13.0%	0.91 (0.86-0.95)	<0.00001 ****
CV Death	143,663	11,847	8.4%	0.88 (0.82-0.95)	0.0005 ****
Non CV Death	142,653	6,184	4.7%	0.98 (0.93-1.04)	0.56
Stroke	135,803	5,485	4.2%	0.94 (0.83-1.06)	0.31
MI	144,790	8,377	5.8%	0.86 (0.82-0.90)	<0.00001 ****

(* p<0.10; ** p<0.05; *** p<0.01; **** p<0.001)

Figure 9. Summary of meta-analyses for treatment with an ACEI vs placebo; placebo or non-ARB comparator; placebo, non-ARB comparator, or ARB comparator. Trials included CAMELOT, DIABHYCAR, Collaborative Study, BENEDICT (BErgamo NEphrologic Diabetes Complications Trial), PROGRESS, CONSENSUS (COoperative North Scandinavian ENalapril SUrvival Study), SAVE, AIRE, TRACE, SOLVD (Studies Of Left Ventricular Dysfunction) Prevention, SOLVD Treatment, FOSINOPRIL, MARCATOR (Multicenter American Research trial with Cilazapril after Angioplasty to prevent Transluminal coronary Obstruction and Restenosis), MERCATOR (Multicenter European Research trial with Cilazapril after Angioplasty to prevent Transluminal coronary Obstruction and Restenosis), SCAT, PART-2, QUIET (QUinapril Ischemic Event Trial), HOPE, EUROPA, PEACE, CONSENSUS II, PREVEND IT (PREvention of renal and Vascular ENd-stage Disease Intervention Trial), ALLHAT, ANBP-2, HYVET (HYpertension in the Very Elderly Trial) Pilot, ABCD, FACET (Fosinopril versus Amlodipine Cardiovascular Events randomized Trial), CAPP, STOP-2, UKPDS 39, J-MIND (Japan Multicenter Investigation of Antihypertensive Treatment for Nephropathy), CARMEN (Carvedilol ACE-Inhibitor Remodelling Mild CHF Evaluation), FLOSEQUINAN, VeHFT-2, ELITE, ELITE-2, DETAIL, OPTIMAAL, and VALIANT. Data shown are (1) clinical end point assessed; (2) number of patients in trials; (3) number of events observed in trials; (4) event rate in the control groups; (5) OR (95% confidence limits) for the overall effect seen in the trials; and (6) statistical significance of observed overall effect.

meta-analysis, as well as others, may not have completely addressed the ARB-MI paradox, because a blood pressure differential existed in many trials in favor of ARBs, and these differences were not accounted for. In other words, it has not been possible to fully explore the hypothesis that ARBs may act to reduce MI via blood pressure reduction (presumed shared AT_1 receptor attenuation effect) while at the same time making MI more likely via a blood pressure–independent (presumed AT_2 receptor stimulation effect) mechanism. To address this issue further, meta-regression analyses have been attempted by 2 groups and applied to the ACEI/ARB data, providing important additional insights.

Meta-Regression Analysis May Help to Resolve the ARB-MI Paradox

The first of these analyses was by Verdecchia and colleagues,[70] who included 179 122 patients in trials with ACEIs or calcium channel blockers with comparators that included diuretics, β-blockers, or placebo (Figure 4). A 10-mm Hg fall in systolic pressure translated into a 15% RR reduction in MI and CV death. What was noteworthy was that patients treated with ACEIs had a further 12% RR reduction above that achieved by blood pressure lowering alone, which strongly supports the premise that ACEIs offer blood pressure–independent benefits on vascular outcomes.

The BPLTTC carefully addressed the ARB-MI paradox by completing a meta-regression analysis of 21 large-scale, randomized trials of ACEIs and ARBs that included 137 356 patients. This analysis included 16 trials with ACE inhibitors {AASK (African American Study of Kidney disease and hypertension), ABCD (H) [Appropriate Blood pressure Control in Diabetes trial (hypertensive subgroup)], ABCD (N) [Appropriate Blood pressure Control in Diabetes (non-hypertensive subgroup)], ALLHAT, ANBP2 (Second Australian National Blood Pressure Study), CAPPP (CAPtopril Prevention Project), DIABHYCAR (non–insulin-dependent DIABetes, HYpertension, microalbuminuria or proteinuria, CARdiovascular events, and Ramipril study), EUROPA, HOPE, JMIC-B (Japan Multicenter Investigation for Cardiovascular diseases/Bayer), PART-2 (Prevention of Atherosclerosis with Ramipril Therapy), PEACE, PROGRESS (Perindopril Protection Against Recurrent Stroke Study), SCAT (Simvastatin and enalapril Coronary Atherosclerosis Trial), STOP-2, and UKPDS-HDS (United Kingdom Prospective Diabetes Study–Hypertension in Diabetes Study)} and 5 trials with ARBs (IDNT-placebo and calcium channel blocker, LIFE, RENAAL, SCOPE, and VALUE) The reduction in systolic blood pressure was plotted against the RR of the prespecified end points of stroke, heart failure, and coronary heart disease. The BPLTTC concluded that although there were no differences in risk reduction between ACEIs and ARBs with respect to the outcomes of stroke and heart failure, there was a highly statistically significant benefit of ACEIs relative to ARBs on MI and CV death (15% RR reduction; $P=0.001$; Figure 10).[27] Furthermore the benefits of ACEIs were significantly greater than that of blood pressure lowering alone (9% [3% to

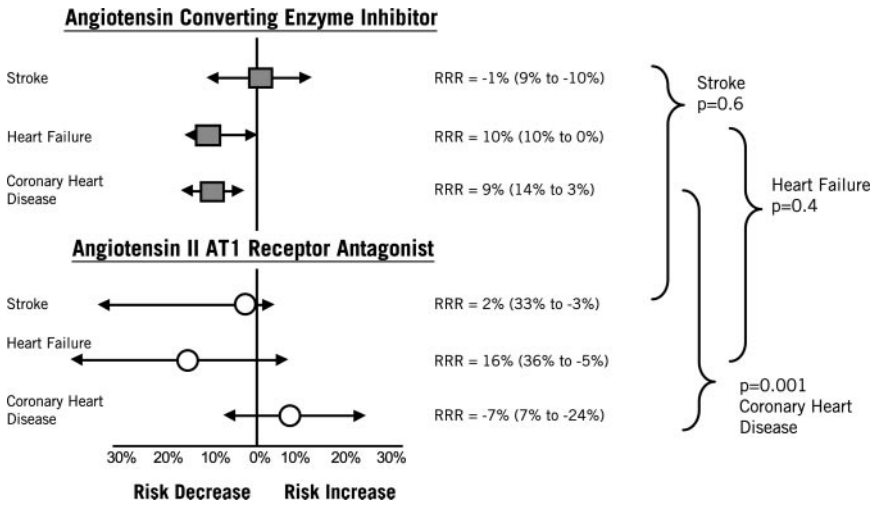


Figure 10. Summary of finding of BPLTTC regression meta-analysis for ACEIs or comparator [AASK, ABCD(H), ABCD(N), ALLHAT, ANBP2, CAPPP, DIAB-HYCAR, EUROPA, HOPE, JMIC-B, PART-2, PEACE, PROGRESS, SCAT, STOP-2, and UKPDS-HDS) or for ARB or comparator (IDNT, LIFE, RENAAL, SCOPE, and VALUE). Data shown are the blood pressure–independent effects expressed as an RR reduction (95% CI) for the clinical end points of stroke, heart failure, and coronary heart disease (MI and CV death). The reported statistical significance of differences between ACEIs and ARBs are also indicated. Adapted from Turnbull F. Blood pressure–independent effects for agents inhibiting the renin-angiotensin system. In: Program and abstracts from the Fifteenth European Meeting on Hypertension; June 17–21, 2005; Milan, Italy. Plenary Session. Available at: http://www.medscape.com/viewarticle/507293.

14%]) and were similar to the meta-regression analysis of Verdecchia et al.[70] Surprisingly, patients treated with ARBs did not exhibit the predicted effects on MI and CHD mortality with regard to blood pressure lowering alone; in fact, a statistically nonsignificant increased risk was observed independent of any change in blood pressure (−7% [7% to −24%], $P>0.05$).

The BPLTTC confirmed the superiority of ACEIs over ARBs in the prevention of MI and death, and Verdecchia and colleagues have provided convincing meta-regression analysis that ACEIs confer benefits on MI and CHD beyond what can be accounted for by simple reductions in blood pressure. In our opinion, this body of evidence is sufficiently compelling to support the first-line use of ACEIs over ARBs for coronary vascular protection in high-risk patients, irrespective of the effects of each agent on blood pressure.

Conclusions and Implications for the Future

The evidence is persuasive that the reduction in incidence of both MI and CV death seen with ACEIs is above that achieved by blood pressure lowering alone[27,70] and is significantly greater than that achieved by ARBs in high-risk patients.[27] All meta-analyses support the existence of an ARB-MI paradox, either by a demonstration of increased risk of coronary heart disease events or by a demonstration of a lack of blood pressure–related vascular benefits.[30–33] After adjustment for blood pressure differentials, not only are MI and CV death unaltered with ARBs, but they actually show a tendency to increase, such that compared with the clear benefits seen with ACEIs, the effects seen with ARBs are significantly inferior (Figure 10). It is truly paradoxical that 9 of the 11 key ARB trials showed an excess in rates of MI, an observation that is difficult to discount in clinical practice (Figure 8). Discussion will continue as ongoing trials such as ONTARGET/TRANSCEND (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial/Telmisartan Randomized AssessmeNt Study in ACE-iNtolerant subjects with cardiovascular Disease)[102] provide further comparative information.

As evidenced by our discussion, not only is there biological plausibility, but the available clinical evidence and meta-analyses, including our own, suggest that ARBs are indeed inferior to ACEIs with respect to MI and CV death. When clinicians are faced with the choice of using either an ACEI or an ARB in high-risk patients, they should be cognizant of the unique differences between each class of medications, particularly with respect to MI and CV death. There is no cogent evidence to support the equivalence of these 2 regimens with respect to coronary outcomes. Evidence would therefore dictate that reaching for an ACEI instead of an ARB prevents more MIs and vascular deaths, and as such, ACEIs should be the first choice across the spectrum of cardiometabolic risk reduction.

Acknowledgments

The authors would like to thank Dr Subodh Verma for constructive criticism of this article and for assistance with editing and formulation of the figures.

Disclosures

Dr Strauss has received honoraria from Sanofi-Aventis, Pfizer, Abbott, and Tanabe; has served as an expert witness for Sanofi-Aventis; and has served as a consultant/advisory board member for Sanofi-Aventis and Pfizer. Dr Hall has received research grants from Astra-Zeneca, Servier UK, and Sanofi-Aventis UK; has received honoraria from Astra-Zeneca and Servier UK; and has been paid consultant fees by Servier UK.

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Response to Strauss and Hall

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We read with great interest the article by Drs Strauss and Hall. Interestingly, their conclusion is that angiotensin receptor blockers (ARBs) are inferior to angiotensin-converting enzyme inhibitors (ACEIs) with respect to myocardial infarction (MI) and cardiovascular death. In our article, we make no claim to the contrary and support the rationale for choosing ACE inhibitors as first-line agents for prevention of MI. Our basic thesis was simple: ARBs do not increase risk of MI. Drs Strauss and Hall provide a very nice review of the biological plausibility for potential harm by ARBs. However, although biological plausibility and basic science insights into mechanisms of disease are extremely important, they do not form the basis for evidence-based therapeutic decisions. We wholeheartedly agree that a properly conducted systematic review provides the highest level of evidence for therapeutic decisions, and we applaud the authors for attempting their own. We are also pleased to note that their conclusions, despite some differences in the trials included, are very similar to those of our very inclusive systematic review. For example, the 95% confidence interval (CI) for all end points was 0.79 to 1.25, which indicates a statistically nonsignificant difference between ARBs and ACEIs. Similarly, no significant difference in MI rates is seen in the key ARB-versus-placebo comparison (odds ratio 1.05, 95% CI 0.76 to 1.47) or in the ARB-versus-ACEI evaluation (odds ratio 1.04, 95% CI 0.95 to 1.15%). In conclusion, although Drs Strauss and Hall have coined the phrase “the ARB paradox,” we are left wondering where the paradox is.

Correction

In the Controversies in Cardiovascular Medicine article "Angiotensin Receptor Blockers May Increase Risk of Myocardial Infarction: Unraveling the ARB-MI Paradox" by Strauss and Hall that appeared in the August 22, 2006, issue of the journal (*Circulation*. 2006;114:838–854), the first two sentences of the second paragraph under "ARB Congestive Heart Failure Trials: Poor Performance With Respect to MI" (page 844) contained two instances of the word "candesartan." In both instances, "candesartan" should be replaced by "losartan," to read as follows:

"In ELITE II (n=3152),[78] losartan 50 mg was compared with captopril 50 mg 3 times daily, and total mortality was increased nonsignificantly by 13% in the losartan-treated group (280 versus 250 deaths) or, alternatively, was reduced by 13% in the captopril-treated group. Furthermore, losartan was associated with a 30% statistically nonsignificant increase in the secondary end point of sudden cardiac death or resuscitated arrest, an end point for which benefit had been expected on the basis of the findings of ELITE I."

The authors regret these errors. These sentences have been corrected in the current online version of the article.

DOI: 10.1161/CIRCULATIONAHA.106.179390

(*Circulation.* 2006;114:e576.)

***Circulation* is available at http://www.circulationaha.org**