

# Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers: Is There a Difference in Response and Any Advantage to Using Them Together in the Treatment of Hypertension?

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*In April 2008, a panel was convened to discuss the effects of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers in the treatment of hypertension and the possible added benefit of using these agents together. The panel was moderated by Marvin Moser, MD, Clinical Professor of Medicine at Yale University School of Medicine, and included Clive Rosendorff, MD, PhD, Professor of Medicine at Mount Sinai School of Medicine and William B. White, MD, Division Chief, Hypertension and Clinical Pharmacology and Professor, Calhoun Cardiology Center at the University of Connecticut Health Center, Farmington. (J Clin Hypertens. 2008;10:485–492) ©2008 Le Jacq*

**DR MOSER:** Our plan is to briefly discuss how angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) work in the treatment of hypertension and whether there is a difference in outcomes with these agents; we will also review newer data that relate to using a combination of these 2 classes of medications. In addition, I would like to discuss possible renal protection with ACEIs and ARBs and their effect on cardiac events. Obviously, data from the Heart Outcomes Prevention Evaluation (HOPE) as well as the results from a recent trial, Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET), are of importance. Have or should the results of these trials change treatment practices?

We are all aware that blocking the renin-angiotensin system (RAS) with an ACEI, decreasing the generation of angiotensin II and its effects on vascular smooth muscle, is effective in reducing both blood pressure (BP) and heart failure. In combination with other medications, usually a diuretic, a decrease in the progression of renal disease is also noted. It has also been established that the

use of RAS blockade will result in less new-onset diabetes than when other drugs such as diuretics or  $\beta$ -blockers are used. Whether this is of clinical significance is still debatable.

ARBs, which block the RAS more peripherally than do ACEIs, will also lower BP and appear to have a definite effect on reducing morbidity and mortality not only in hypertensive persons without significant target organ damage but also in hypertensive individuals with cardiovascular disease.

The one major study in very high-risk patients, HOPE, suggested that the addition of an ACEI, in this case ramipril, to a program that included many other antihypertensive drugs including diuretics reduced cardiovascular events across a wide range of diseases: not only stroke but coronary heart disease events, heart failure, etc, when compared with a regimen that did not include an ACEI.

Now some experts suggest that an ARB might be more effective over time because it effectively blocks the actions of angiotensin II peripherally. Would you summarize the pros and cons of that argument? Are ACEIs more or less effective? Do they have any actions other than blocking the generation of angiotensin II, which might be useful or

detrimental? Is an ARB or an ACEI better; is there any difference in outcome?

DR ROSENDORFF: The actions of angiotensin II on the various subtypes of angiotensin II receptors is quite complex. We also have to recognize that angiotensin II generation is dependent upon enzyme activity, both renin and the angiotensin-converting enzyme.

DR MOSER: Well, what does an angiotensin converting enzyme do? It blocks the conversion of an inactive peptide to active angiotensin II, but it has other effects that may play a major role in its BP-lowering ability; is that correct?

DR ROSENDORFF: ACEIs block the formation of angiotensin II, but not completely. There are other enzymes that may allow for the progressive increase in angiotensin II, even in the presence of an ACEI. ACEIs are also kininase inhibitors and thus block the breakdown of bradykinin and other kinins. This is both a plus and a minus. The enhancement of bradykinin will increase the BP-lowering effect since bradykinin is a vasodilator. But it is also thought that the kinins are responsible for some of the troublesome side effects of ACEIs, such as cough and angioedema. The advantages of ACEIs are that they reduce angiotensin II, which causes not only vasoconstriction but also bad effects on tissues and on the vascular system. Angiotensin II will enhance oxidative stress and vascular smooth muscle proliferation, will impair endothelial function, and is proinflammatory and prothrombotic. So ACEIs are vasodilator but also vasoprotective. Now we also know that they are both cardioprotective and renoprotective. The downside is that the kinins may produce the cough and angioedema. There is also a potential downside in reactive hyperreninemia, but that's another story.

DR MOSER: Alright, so basically an ACEI produces most of its effect by blocking the generation of angiotensin II and increasing the availability of bradykinins, which will increase prostaglandins and nitric oxide and produce vasodilation. Is that the way bradykinin works?

DR ROSENDORFF: It works through the B<sub>2</sub> receptor to affect the prostaglandin pathway. I think the pathway responsible for the cough and angioedema hasn't been precisely identified but seems to depend upon the enhancement of kinin action.

DR MOSER: But bradykinin increase may increase nitric oxide production, too, which is a vasodilating effect.

DR ROSENDORFF: Yes, both prostacyclin and nitric oxide are increased by bradykinin.

DR MOSER: What percentage of the BP lowering

from ACEIs do you think results from the increase in bradykinin? Is this just a guesstimate that you have to make?

DR ROSENDORFF: I really don't know the answer to that. There have been some studies in animals in which the bradykinin effects have been blocked, and I think the effect may be quite substantial.

DR WHITE: A few years ago, Dr Nancy Brown and her colleagues from Vanderbilt studied this in humans using a bradykinin antagonist and determined that approximately 40% of the hemodynamic effects of the ACEIs were in fact due to their effect on bradykinin.

DR MOSER: Right. It is true that after a while there is an escape from angiotensin-converting enzyme inhibition. In addition, angiotensin II may be generated through other mechanisms, such as the chymase pathway. Yet BP lowering may continue. There may be a physiologic advantage to an ACEI, with vasodilation through other channels. As Clive pointed out, however, this may also contribute to adverse effects and limit its usefulness. Now, what about ARBs, Bill? Will you describe what they do and what their possible advantages might be?

DR WHITE: There are several ARBs that have relatively homogeneous BP effects but are fairly heterogeneous from a pharmacologic perspective. All of these agents have the ability to inhibit the effects of angiotensin II at the angiotensin II receptor type 1 (AT<sub>1</sub>) site. This results in reduced vascular resistance, smooth muscle contraction, and BP and also alleviates some of the nonhemodynamic effects, including reductions in inflammation, cytokine generation, and prothrombotic factors. ARBs also seem to have this benefit on the cardiac myocyte and in the renal bed. The use of ARBs results in the same hemodynamic benefits that have been observed with ACEIs insofar as that they provide afterload reduction in patients with heart failure, and they also reduce filtration fraction and intraglomerular hypertension in patients with renal disease.

DR MOSER: Is there any advantage to using an ARB compared with an ACEI other than better tolerability? Or is the bradykinin effect actually providing an advantage of an ACEI over an ARB?

DR WHITE: That is a very important question. From the clinical perspective, the BP-lowering effect of ARBs and ACEIs are equivalent as long as you appropriately compare the right doses in patients with hypertension. In some circumstances, ACEIs may actually be more effective than ARBs, for example, in the treatment of congestive heart failure. I do not think there has been a study that

has demonstrated that ARBs are in fact better than ACEIs. In patients with renal disease due to diabetes, especially type 2 diabetes, we simply have more information on ARBs than we do on ACEIs. That occurred because of the timing and the amount of sponsorship and design of trials that came out in the last decade.

On the other hand, as has been remarked upon, there is a difference in the tolerability profiles of these 2 classes of drugs. ARBs seem to be better tolerated across large populations, especially in people who might be susceptible to the effects of bradykinin. Angioedema and bronchospastic coughing may be particularly important in African American populations and hypertensive patients who smoke cigarettes.

DR MOSER: What's the percentage of angioedema with ACEIs in most of the clinical trials? Is it 1%, a half percent, what are we talking about?

DR WHITE: Actually, it is fairly low, about half a percent if you include all varieties of angioedema—not just life-threatening cases but facial or head edema as well. In the African American population, it's about 3 or 4 times more prevalent.

DR MOSER: Swollen tongues are often ignored.

DR WHITE: But they could be life-threatening. There have been some reports of lingual edema that has led to death in patients taking ACEIs.

DR MOSER: The cough is another matter, though; it occurs in about 10% to 15% of patients, and some reports claim an incidence as high as 20% with ACEIs.

DR WHITE: Right.

DR MOSER: Clive, are there any differences among the ACEIs and ARBs that you know of in terms of BP-lowering ability? Are there studies that have differentiated them?

DR ROSENDORFF: The answer to that is probably no. All the studies that I'm aware of that have compared drugs within each class, or even 2 drugs from the 2 different classes, have not shown significant differences in BP response. Many of them, however, have been designed in such a way as to minimize the probability that that would be the outcome. Most of them have been designed so that BP is not the primary outcome.

DR MOSER: But there are some studies that suggest differences, aren't there? For example, I believe that candesartan has been shown to be somewhat more effective than losartan in decreasing BP. Then there was a meta-analysis that reported some differences among the ARBs: telmisartan was shown to be more effective and longer-acting

than some of the other agents in this class. Do you believe these data are of clinical significance?

DR ROSENDORFF: Well, a millimeter or two difference may or may not be important, depending on whether you believe that small changes in BP drive differences in cardiovascular end points. I think it's unlikely, in fact, that a few millimeters are anything but a statistical aberration or maybe a function of the numbers of patients in the studies or the way in which the drugs were administered. All of these are variables that need to be controlled but are very hard to control in clinical trials.

DR MOSER: So you're of the opinion that, basically, most ACEIs and most ARBs are similar in their BP-lowering effects.

DR ROSENDORFF: Yes.

DR MOSER: Do you think that some may have specific effects in other areas that may not be related to BP?

DR ROSENDORFF: Well, there are a few interesting variations in terms of their pharmacology. Of course, the pharmacokinetics are very different in some of them. They have different plasma half-lives and different AT<sub>1</sub> receptor binding affinities. They may also have additional actions. As an example, the ARB telmisartan has been shown to be a selective activator of peroxisome proliferator-activated receptor- $\gamma$ .

DR MOSER: And what does that mean?

DR ROSENDORFF: Peroxisome proliferator-activated receptor- $\gamma$  agonists, like thiazolidinediones or glitazones, are drugs that increase insulin sensitivity. But in contrast to the glitazones, telmisartan doesn't result in weight gain, so that's a very interesting pharmacologic action. We don't know whether that will translate into any human benefit, but it certainly warrants looking at.

DR MOSER: Is this action unique to telmisartan, Bill?

DR WHITE: That actually appears to be the case. The molecular property may be unique to telmisartan, but it's also my understanding that this has not yet translated into any major differences in glycemic clamp studies in humans. But I would like to put in my two words about differences in BP effect. I think that you mentioned one study with candesartan and losartan. There were actually 2 studies that demonstrated that candesartan had a better BP-lowering effect than losartan at the appropriate maximal doses. Results led to a label change for that drug in a special US Food and Drug Administration advisory meeting. Similarly, we've performed studies with 24-hour BP monitoring with telmisartan, valsartan, and losartan, and in some of

these studies, one can demonstrate that for several hours of the dosing period there are differences in BP-lowering effect. So in some instances, one ARB may actually be more effective in the same patient compared with another.

DR MOSER: Do you think the differences are clinically relevant?

DR WHITE: I think that for individual patients they are. For an entire population, 1 or 2 mm Hg may be of significance. But for an individual patient for whom the morning BP rises to 160 or 170 mm Hg systolic at the end of a dosing period, the duration of action of the drug may be important, and the difference in effectiveness can be considerable.

DR ROSENDORFF: Yes, but would a 2-, 3-, or 4-mm Hg difference in systolic BP effect be important in individual patients if you are trying to get the systolic BP down from 165 mm Hg to <140 mm Hg? It doesn't really matter whether one drug will lower pressure by 3 or 4 mm Hg more than another, does it?

DR WHITE: No, I wasn't referring to small changes in individuals. Rather, I was talking about having a much more substantial reduction in an individual patient. In a large trial in which a 4-mm Hg difference in BP in a population is observed, the differences are not distributed normally. Perhaps 75% or so of the patients have virtually the same reduction in pressure with each drug, but 25% may have very substantial mean differences of several mm Hg.

DR MOSER: We can probably agree that there is some difference in BP-lowering ability among ARBs as well as among ACEIs . . .

DR WHITE: That's right.

DR MOSER: . . . and it may relate to the fact that some of these are short-acting, like captopril, for example.

DR WHITE: Right.

DR MOSER: Now let's discuss some of the studies in very high-risk patients, because the objective of treatment is to prevent cardiovascular events. One study in patients at high risk for cardiovascular disease was HOPE. In this study, ramipril, which is an effective ACEI, was added to other drugs. All participants were receiving at least 1 or 2 other agents. Only about half of the patients were hypertensive. The addition of an ACEI to the other drugs, compared with the addition of placebo to the other drugs, resulted in a dramatic difference in outcome in terms of combined end points, which included heart failure, coronary heart disease events, stroke, etc. Do you believe these results

were specific to ramipril? Would the results have been the same if you had studied lisinopril or one of the other ACEIs?

DR ROSENDORFF: There was actually a triad of trials that were somewhat similar: HOPE, the European Trial on Reduction of Cardiac Events With Perindopril in Stable Coronary Artery Disease (EUROPA), and the Prevention of Events With Angiotensin-Converting Enzyme Inhibition (PEACE) trial. The HOPE patients were the sickest and the PEACE patients the least sick. The 3 drugs in these studies were ramipril in HOPE, perindopril in EUROPA, andtrandolapril in PEACE. Results in 2 of those studies were positive, HOPE and EUROPA in the sicker cohorts. In the PEACE cohort, in which the patients had experienced more lipid lowering, had started off with lower BP levels, and had had more prior percutaneous coronary interventions and therefore perhaps more patent coronary arteries, the results were essentially negative; the addition of an ACEI did not appear to impact outcome. So we had 2 out of 3 positive findings and 1 negative result. These results were encouraging enough for people to look at ARBs with the same trial design, that is in high-risk patients not all of whom were hypertensive and vs placebo, or further to compare ARBs and ACEIs to see whether combining the 2 classes of drugs might give even better results.

DR MOSER: Do you think that the PEACE results were negative because people were less sick? We all know that when you study the sickest group of people, you see benefit more quickly. The older the patient and the more risk factors, the better the results of any 2- to 3-year treatment program.

DR ROSENDORFF: Exactly.

DR MOSER: The question then is, were results due to treatment with a specific ACEI or to the type of patient studied? What's your guess?

DR ROSENDORFF: Originally, in HOPE it was reported that the BP differences between the ramipril plus other drugs group and the placebo plus other drugs group was very small; it was about 3/2 mm Hg. Everybody said, "That difference is probably insignificant, so the reason for the positive results is that there are specific effects of ACEIs that are independent of BP lowering." But then there was the HOPE substudy, which involved 24-hour ambulatory BP monitoring; it showed that there was in fact a substantial difference in the BP values between the 2 groups.

DR MOSER: Especially in the nighttime readings.

DR ROSENDORFF: So the question was still open, was it something specific to ramipril, was it

something that is a function of ACEIs but is independent of BP lowering, or was it just the BP lowering?

DR MOSER: What do you think, Bill?

DR WHITE: I used to think that it was probably not so tightly linked to the specific ACEI. However, now there are meta-analyses that suggest that cardiovascular event reductions are better with ramipril and perindopril than with other ACEIs. One has to give some credibility where we have the evidence. In HOPE, I recall reviewing the substudy on ambulatory BP, and I was struck by the fact that they gave 10 mg of the drug at dinner-time. The nocturnal BP was reduced by about 17 mm Hg systolic in that substudy. This was a large BP reduction, but it was only measured in a very small number of people participating in the trial. In EUROPA, there was about a 10-mm Hg reduction in systolic BP with perindopril compared with a regimen that did not include an ACEI. At baseline, the population in EUROPA was in fact a bit more hypertensive than the population in HOPE. The BP differences for these ACEIs vs placebo probably accounted for at least some of the cardiovascular risk reduction benefit. The etiology of benefit in the trials is going to be one of those things that will be argued forever. Do these drugs work by BP reduction or BP reduction plus some direct effects on target organs? I don't think we're going to be able to answer it, quite frankly.

DR MOSER: Now, there are people who say, "So we have ACEIs that block the generation of angiotensin II, but there are other pathways by which angiotensin II is produced. The use of ACEIs results in a bradykinin increase, but ARBs block angiotensin II effects more completely at the vascular level. Are they equal in their effectiveness? Why not combine the two? Would it make more sense to block the RAS more completely?" Clive, is there evidence that ACEIs and ARBs are equal or that combining them may be even more beneficial in reducing cardiovascular events?

DR ROSENDORFF: Since we're talking theoretically, I think we have to understand that there are 2 major angiotensin receptors, the AT<sub>1</sub> receptor and the angiotensin II receptor type 2 (AT<sub>2</sub>). The AT<sub>1</sub> receptor is the one that mediates vasoconstriction and all of the bad effects on the vasculature. It's thought that the AT<sub>2</sub> receptor is kind of the mirror image of that, the good guy, if you like, which mediates or activates processes that inhibit cell growth and proliferation and extracellular matrix deposition—all of the good things in terms of vascular health. Almost every mechanism activated by the AT<sub>2</sub> receptor is the opposite of the

AT<sub>1</sub> receptor. If you give an ARB, the theory is that you're blocking the AT<sub>1</sub> receptor, or "bad" receptor, the one that mediates all the vascular toxic effects, but you're allowing circulating or tissue angiotensin to activate the receptor that mediates the beneficial effects of the AT<sub>2</sub> receptor. So that is a very attractive theoretic advantage of ARBs over ACEIs. I could never quite understand the rationale of combining the 2 classes of drugs, frankly.

DR MOSER: Well, the idea was to produce a more total blockade of the RAS.

DR ROSENDORFF: Well, yes. But you don't want to block the AT<sub>2</sub> receptor; you want to leave that active and you want to have enough angiotensin II circulating to activate the AT<sub>2</sub> receptor. So theoretically, that is the advantage of the ARB over the ACEI.

DR MOSER: Bill, do you think there's a theoretic advantage to using the two together?

DR WHITE: Well, I certainly used to think that would be the case, and I guess I still in part believe that if a high proportion of the angiotensin II that is generated in a cardiac myocyte is through an alternative pathway such as cardiac chymase and the ACEIs might not have a full blocking effect on angiotensin II removal in that particular target organ. That would be a rationale for having developed another class of drug especially for effects on heart muscle. We do have some evidence that in some of these earlier studies, such as the Valsartan Heart Failure Trial (Val-HeFT) and then later the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) study, there was a benefit of adding an ARB to the ACEI.

DR MOSER: In patients with heart failure?

DR WHITE: Yes. But I do agree with Clive, because I've actually never been very impressed that adding an ACEI to an ARB was that effective for reduction of BP. There are so many other options, for example, adding an ACEI (or an ARB) to a diuretic or a calcium antagonist, would be a more effective BP lowering regimen.

DR MOSER: Therefore, you don't think the idea of addressing the angiotensin escape by blocking it with an ARB is a great advantage?

DR WHITE: The basic scientists clearly felt this was going to be the case, but as research has been completed in humans in recent years, data have been underwhelming in hypertension. In patients with heart failure, however, and perhaps also with heavy proteinuria due to renal disease, specifically diabetic renal disease, there probably is a substantial added benefit to combining the 2 classes.

DR MOSER: What about the few studies in

which there was greater BP reduction and more proteinuria reduction, for example, the study with lisinopril and candesartan?

DR WHITE: I believe you are referring to the Candesartan and Lisinopril Microalbuminuria (CALM) study. Relatively low doses of the drugs were used, and when they were added together a better effect on BP was observed along with a larger reduction in proteinuria.

DR MOSER: And the other question is, why not just increase the ACEI or ARB to full doses?

DR WHITE: Well, of course, that's the most appropriate way to go. The tolerability really doesn't change dramatically according to dose.

DR MOSER: Alright. Clive, ONTARGET was just published. I think there were really 2 objectives here. One was to demonstrate whether an ARB, in this case telmisartan, was as effective as ramipril as an antihypertensive agent. Ramipril was chosen because of the data in high-risk patients. The second question was whether the combination of an ARB and an ACEI would be any better than an ACEI alone in end point reduction in patients with cardiovascular disease. Do you want to describe this trial in these very high-risk patients?

DR ROSENDORFF: It's a very large trial, with more than 25,000 patients enrolled. They were all high-risk; they had vascular disease and diabetes, but none of them had heart failure, which distinguishes this trial from another heart failure trial with a very similar design called Valsartan in Acute Myocardial Infarction (VALIANT). Only about 65% to 70% of the patients in ONTARGET were hypertensive.

DR WHITE: The average baseline BP values were not very high; they were about 140–142/80 mm Hg.

DR ROSENDORFF: There were 2 questions asked: first, is the ARB telmisartan noninferior to ramipril? The statistical analysis of the data is a little different in a noninferiority than in a superiority trial. The other interesting question was whether the combination of telmisartan and ramipril was superior to ramipril alone. The primary composite outcome variables were cardiovascular death, myocardial infarction, stroke, and hospitalization for congestive heart failure. There was a secondary outcome measure, cardiovascular death, myocardial infarction, and stroke, a composite that is identical to the HOPE primary outcome measure. There was a run-in period in which patients received ramipril for 3 days, then ramipril plus telmisartan for 7 days, then ramipril at a higher dose with telmisartan for another 11 to 18 days.

DR MOSER: For tolerability?

DR ROSENDORFF: A very unusual trial design, but obviously designed to weed out patients who were intolerant of the ACEI.

DR MOSER: All of these people, by the way, were receiving multiple other drugs: two-thirds were receiving statins and more than three-fourths were receiving aspirin, antiplatelet agents, diuretics, or calcium channel blockers. So they were all on many other drugs to reduce cardiovascular risk before the ACEI or the ARB was added, is that right?

DR ROSENDORFF: That is correct. Again, this was not specifically a hypertension trial.

DR MOSER: What about the first aspect of the study, telmisartan compared with ramipril? Was it superior?

DR ROSENDORFF: The BP decrease was similar, about 6 vs 7 mm Hg systolic and about 4 vs 5 mm Hg diastolic. There was no difference in BP effect, and there was absolutely no difference in the primary outcome variables. The Kaplan-Meier curves for the primary outcome were virtually superimposable; there was no difference between the 2 drugs.

DR MOSER: Is this an important observation, that an ARB is equal to an ACEI?

DR ROSENDORFF: Well, in patients with heart failure, VALIANT results showed no difference between valsartan and captopril, and the Evaluation of Losartan in the Elderly (ELITE) II showed no difference between losartan and captopril.

DR MOSER: But this was the highest-risk population studied to date, wasn't it?

DR WHITE: I think it's important, because this reflects the general vascular patient population that internal medicine doctors see in the United States. The other studies are important, but they were heart failure populations. ONTARGET included the kinds of patients who walk into the office with a history of hypertension, a remote history of coronary disease, peripheral vascular disease, or diabetes with microvascular disease of the eye or kidney. So we didn't really have a study like this before that reported that an ARB was as effective as an ACEI in reducing cardiovascular events. And as you know, this trial was set up to assess whether telmisartan was noninferior to ramipril. It was not set up to see whether telmisartan was superior to ACEIs.

DR MOSER: ONTARGET answered the question that many experts had had about an ACEI being more effective than an ARB. That opinion was probably based on the number of studies that were done and the lack of up-to-date data on ARBs. So in a very high-risk population, many of whom were not hypertensive, and were also

receiving other agents, the addition of an ACEI or an ARB (in this case, ramipril) compared with telmisartan didn't appear to make any difference in BP lowering or outcome; is that fair?

DR WHITE: Yes.

DR MOSER: What about the second part of ONTARGET? This is important because of all the debate, especially among nephrologists, about whether a combination of an ACEI and an ARB should be used because of the effect on proteinuria.

DR ROSENDORFF: Well, the combination did produce a greater BP decrease, about 2 or 3 mm Hg. If we believe the epidemiologic data, that decrease should translate into about a 4% or 5% risk reduction with the combination compared with the ACEI alone. But this just did not happen. Again, there was no difference between the 2 subsets.

DR MOSER: Absolutely no difference between an ACEI alone or a combination of an ACEI and an ARB?

DR ROSENDORFF: There was no difference. There were some differences in side effects, but no differences in the primary outcome variables.

DR MOSER: Okay, let's talk about side effects.

DR WHITE: Before we do, I just want to point out some new data presented at the American Society of Hypertension meeting in May 2008. We just completed a trial that evaluated the combination of telmisartan and ramipril in more than 1350 patients, using both clinical and ambulatory BP. Baseline BP values were about 155/102 mm Hg; this was more of a stage 2 population because we were looking at combination therapy. This was strictly a hypertension clinical trial; hence, it was different from the ONTARGET concept. We observed a larger BP reduction with telmisartan compared with ramipril, and there was also a greater reduction in 24-hour BP with the combination of telmisartan and ramipril compared with ramipril alone. For example, the reduction in systolic BP with telmisartan plus ramipril was 7 to 8 mm Hg greater than with ramipril alone. I think that we have to keep in mind that the BP reduction seen in ONTARGET was small because 80% of the patients were treated with other antihypertensive drugs and many were not hypertensive at baseline. In addition, add-on antihypertensive drugs used in ONTARGET were manipulated during the course of the trial to achieve normotensive BP levels.

DR ROSENDORFF: Most of the current definitions of target BP for this particular cohort of patients with diabetes or vascular disease in the ONTARGET group would be <130/80 mm Hg,

which implies that anything >130/80 mm Hg should be defined as hypertension in this type of patient. So perhaps the ONTARGET participants with systolic BP levels between 130 and 139 mm Hg should be reclassified as hypertensive.

DR WHITE: I was just pointing out that if the population had been more hypertensive at baseline, the degree of BP reduction achieved with the drugs may have been greater and the cardiovascular event results might have differed. The fact that there was only a 0.9/0.6-mm Hg difference in clinic BP values between telmisartan and ramipril was in part due to the concomitant treatment with many other medications and the level of BP with which patients came into the study.

DR MOSER: I would agree with that. The higher the pressure, the greater the decrease. So the conclusions from your short-term trial with no outcome data are that the combination appears to be more effective in hypertensive patients than in the ONTARGET patients and that telmisartan may be more effective than ramipril.

DR WHITE: Well, I would qualify that by saying that telmisartan is moderately better in hypertensive patients with BP levels in the range that you usually see when a patient begins treatment. Yes, telmisartan was more effective in lowering BP.

DR MOSER: That's something to think about. What about tolerability? We all agree that ARBs probably are as well tolerated as any other antihypertensive drugs. Are they better tolerated than ACEIs?

DR WHITE: It is important that everyone understands that the ONTARGET population had to be an ACEI-tolerant population. After all, they had a 2-in-3 chance of receiving an ACEI in the study for a long period of time. So most of the patients with any history of dizziness, light-headedness, hyperkalemia, coughing, rash, or angioedema were weeded out before the study began.

DR MOSER: Do you have any idea how many were excluded?

DR ROSENDORFF: It was about 11% of all the patients, or about 3000 to 4000 patients, who were involved in the initial screening.

DR WHITE: So while this wasn't a 100% real-world population who goes to the primary care doctor, there was still less cough and less angioedema with the ARB than with the ACEI or with the combination of the two. While these are not huge numbers, there was a trend that demonstrated a benefit in favor of the ARB. On the other hand, in the combination group there was a small but real increase in adverse effects that included light-headedness, hypotension, and some increases in

azotemia and hyperkalemia. Renal insufficiency was just a coded term that somebody checked off on a case report form. The actual hard end points such as dialysis and doubling of serum creatinine value were actually very minimally different with the combination regimen compared with the treatment groups receiving either agent alone.

DR MOSER: Let me summarize. What we've talked about here is the fact that RAS inhibition, whether it prevents the generation of angiotensin II or occurs peripherally by blocking the effects of angiotensin II at vascular smooth muscle, has resulted in not only lowering of BP but in the reduction in cardiovascular events, strokes, etc. Usually the drugs in the clinical trials have been used in combination with other drugs, most commonly diuretics, because, as we all know, in many cases BP is not going to be reduced to goal levels with just the RAS inhibitor, especially in elderly and African American patients.

The debate continued as to whether an ARB is as or more effective than an ACEI either in lowering BP or preventing cardiovascular events. There were theoretic reasons that some people thought the ACEI would be more effective because of its effect on increasing bradykinin, which is a vasodilator. Others believed, however, that a more effective blockade of angiotensin II at the periphery would prove to be a better approach.

Recent studies have reported confusing results in patients with heart failure and other cardiovascular events, but the most recent study, ONTARGET, tested head-to-head the use of one of the ARBs, telmisartan, with an ACEI, ramipril, which was the drug used in the HOPE study. Results indicated that BP response was similar and that cardiovascular end points were the same. There appeared to be no superiority of ramipril over telmisartan, with the caveat that this was not a BP trial and results may be different when the agents are given to patient with hypertension. It was a trial in patients at very high cardiovascular risk with previous histories of coronary or vascular disease, diabetes, etc.

The argument about whether the use of the 2 different classes of drugs together provides an added advantage to just using full doses of one or the other was

addressed in this study. There appeared to be no advantage in terms of outcome. BP lowering was somewhat better, but outcome in terms of heart failure, coronary disease, and stroke did not differ. The adverse effect profile of the ACEI was somewhat worse than with the ARB, especially as it related to cough and a slight increase in angioedema. Adverse effects were more frequent with the combination, especially hypotensive adverse effects, than with either drug alone.

So we are left with the conclusion that it appears that this particular ARB is equivalent to an ACEI in high-risk patients in terms of outcome. We know from some data from short-term studies that proteinuria, a marker of cardiovascular disease, is decreased by combination therapy, but in this study this was not noted.

DR WHITE: I think that's a fair summary. The only caveat would be that the population in ONTARGET was in fact excluded from having ACEI intolerance, which in a sense opens up a very rational therapy (ie, an ARB for the treatment of high-risk patients with a history of ACEI intolerance). Now we know we'll be protecting them at the same level against cardiovascular events, without all of the so-called bradykinin-induced adverse effects.

DR ROSENDORFF: As an aside, I would like very much to have seen the BP values lowered to meet the guidelines for diabetes or vascular disease, <130/80 mm Hg. The mean BP at the start was 141/82 mm Hg, and the BP decrease during the trial was 6/5 to 7/6 mm Hg, so systolic BP was not lowered to target values in the majority of patients. I agree with Bill that ARBs are now well established as being just as effective in preventing cardiovascular events as ACEIs. Further, I believe that ONTARGET settles the argument about whether combination of the 2 classes of drugs has effects that are superior to those of either class alone. The answer is no. There is no advantage in combining ACEIs and ARBs, and the side effects are compounded.

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