OPERATOR: Good day, ladies and gentlemen, and welcome to AHRQ’s Effective Health Care Program, Applying Existing Evidence to Guide Prescription Medication Use. To submit a question or comment at any time during the Web conference, please click on the “Ask a Question” button on the bottom of your screen. Simply type your message into the box and click on the Submit button. If you get disconnected at any time from the Web conference, you may dial back in with 888-632-5065 or 201-604-0318, and when prompted, enter 89036596#. Again, that code is 89036596 followed by the pound sign.

At this time, it is my pleasure to turn the floor over to Amanda Brodt. Ma’am, the floor is yours.

AMANDA BRODT: Good afternoon, ladies and gentlemen. Thank you for standing by. On behalf of the Agency for Healthcare Research and Quality, also known as AHRQ, we welcome you to today’s Web conference, Applying Existing Evidence to Guide Prescription Medication Use, held by AHRQ’s Effective Health Care Program. My name is Amanda Brodt, and I’m a contractor for AHRQ’s Office of Communications and Knowledge Transfer, and I will be moderating today’s event.

This event is part of a series of Web conferences we are holding on the Effective Health Care Program research findings over the next few weeks, so we’re especially happy you were able to join us today and hope that you will for future events as well. We will highlight a number of these events at the end of our call.

Before we get started, I wanted to review some information about the Web conference technology we’re using today. If you have questions during the presentation, you may submit them electronically by entering them via the “Ask Question” button. The “Ask Question” button is located at the bottom of your screen. When you click on the button a box will appear, requesting that you enter your question. Once completed, press the “Submit” button. A selection of audience-submitted questions will be addressed during the moderated Q&A session at the end of the Web conference.

Also, if you are experiencing technical difficulties, please open the Web conference Frequently Asked Questions document under the Downloadable Files button on the bottom of your screen for troubleshooting ideas. You can also contact technical support by submitting your issue in the “Ask Question” box. Under the Downloadable Files button, you will also find the slides for this event, which may be helpful for reviewing the slide details and for accessing a document with speaker bio sketches.
Today’s Web conference includes closed captioning. The captioning appears in a box below the slides; go to the Windows Media Player or Real Player buttons on the main page. Finally, this presentation is being recorded, and it will be made available on the AHRQ Web site shortly. So, let’s get started with the presentation.

During this Web conference, Effective Health Care investigator Dr. Michael White and I will highlight the benefits of using patient-centered outcomes research in clinical decisionmaking. I will kick off the conference by giving you a brief overview of AHRQ’s Effective Health Care Program before I turn it over to Dr. White to share his research findings on the comparison of treatments for stable ischemic heart disease, including ACE inhibitors and ARBs.

As a reminder, you can submit questions electronically by entering them in the “Ask Question” box on the bottom of your screen. Once you enter your question into the box, press the Submit button. You can ask questions of either of us about comparative effectiveness research, the Effective Health Care Program, and the specific findings shared today. Though we will hold most questions until the end of the event, I encourage you to ask them throughout the event as you think of them. We will do our best to address as many questions as we can during the Q&amp;A session.

To begin, I will be discussing the AHRQ Effective Health Care Program and how you can utilize patient-centered outcomes research in your practice. Patient-centered outcomes research, also known as comparative effectiveness research, delivers unbiased, practical, evidence-based information to help you and your patients weigh different treatment options to make the most informed health care decisions. It compares drugs, devices, procedures, tests, and methods of health care delivery.

Patient-centered outcomes research shows which treatments have been shown to work best in different clinical situations and how they compare when it comes to benefits, harms, and side effects. It also tells us what is known and what is not. Most importantly, patient-centered outcomes research is descriptive, not prescriptive. It does not tell you how to practice medicine, it does not mandate a particular test or treatment for anyone, nor does it prohibit any test or treatment. It gives you the tools, not the rules, which you and your patients can use to make the best possible decisions.

Here at AHRQ, the investment in patient-centered outcomes research has been built around the framework displayed on your screen. The colored boxes and ovals show the different types of work involved with patient-centered outcomes research. Underneath is the research platform that supports this work, including research infrastructure, methods, development, and training of researchers. The research process starts with scanning the horizon to identify new and emerging clinical interventions that may impact health care in the U.S. That leads to a systematic review and a synthesis of current medical research to compare effectiveness. Evidence synthesis often tells us where the gaps lie between existing medical research and the needs of clinical practice.

We also promote and generate new scientific evidence and analytical tools to fill those critical gaps. All of the information gained needs to be communicated in a way that makes sense to the health care decisionmakers. This includes translating the research into plain language or making it accessible and useful to diverse audiences in order to improve health care. We also have made a
commitment to reach out to stakeholders and communities for input to make sure we get the research right. If it isn’t relevant and applicable, then we can’t expect it to have impact. The Effective Health Care Program has a cradle-to-grave research agenda that focuses on 14 priority conditions listed here. As you can see, one of the priority conditions is cardiovascular disease, and all of them include prescription medication.

Since the inception of the Effective Health Care Program, AHRQ has funded and completed dozens of patient-centered comparative effectiveness research projects. These projects include comprehensive reviews of diagnostic or treatment options for breast and prostate cancers, atrial fibrillation, diabetes, osteoarthritis, depression, and many other conditions. The Effective Health Care Program creates a variety of projects that are based on these research reviews and reports. These include executive summaries plus summary guides for clinicians, consumers, and policymakers. We have recently added to our portfolio a number of materials to support clinician education, including continuing education modules, interactive case studies, and faculty slide sets. We’ll soon be adding patient decision aids as well.

I would like to highlight our consumer guides that summarize the evidence in plain language and easy-to-read format. These guides are paired with our clinician guides to promote shared decisionmaking. Most of our consumer guides have also been translated into Spanish. The consumer guides can be found online or are available in print. We also have audio podcasts of the guides online as well. Currently, the Effective Health Care Program offers various decisionmaking resources about prescription medication for hypertension, high cholesterol, breast cancer, depression, and diabetes, among others. Today, Dr. Michael White will be discussing the research that he conducted leading to the effective health care findings presented in a clinician and consumer guide related to stable ischemic heart disease. The other highlights can also be found on the Effective Health Care Web site.

Finally, we want to encourage you to get involved in the Effective Health Care Program. Your participation is mutually beneficial. There are multiple points of involvement in our program: before, during, and after the research is completed. Before, you can nominate topics for research on our Web site. If there is a prescription medication, health-related topic that you feel should be addressed, we will give you instructions on how to nominate this topic at the end of the conference. During, you can give input on graphed (key) questions and reports. This kind of involvement helps you get the type of research that will really help answer those controversial questions, and it helps us by getting the research right. After the research is completed, you can disseminate the information to your colleagues and patients. You can implement findings in your clinical decisions. This helps both you and us by creating opportunities for better, more informed decisionmaking and making an impact on the quality of health care.

So let’s get started with today’s main presentation. We now have the pleasure of hearing from Dr. Michael White. Dr. White is an associate professor of pharmacy, director of cardiac pharmacology service, and director of the evidence-based practice center at the University of Connecticut/Hartford Hospital. The American College of Clinical Pharmacy has approved his fellowship training program and awarded him the American College of Clinical Pharmacy’s Young Investigator Award. Dr. White is also a University of Connecticut teaching fellow and a fellow of the American College of Clinical Pharmacists and the American College of Clinical
Pharmacologists. Dr. White’s research focuses on evidence-based practice, systematic review, and reducing drug-, herb-, and implantable device-induced diseases.

Dr. White, please begin.

C. MICHAEL WHITE: All right, welcome, everybody, and OK. Is my first slide there so everyone can see it?

BRODT: No. It’s not, Dr. White. I don’t see it, but we can advance your slides for you if that would be more helpful. If you just say next slide, we can move to the next slide for you.

WHITE: OK. On the next slide, we’re going to talk about the outline of what it is we’re going to be talking about today. And what I’m going to do is try to give you a background into the topic and what kind of things we’ve already talked about, go through some of the questions that we addressed inside our comparative effectiveness review, and then also give you some of the results for each of the key questions that we were discussing.

So, on slide number 14, what I wanted to talk about was the health impact of cardiovascular disease in the United States, where about 80 million American adults have one or more forms of cardiovascular disease and around 38 million people are estimated to be age 60 or older, so 16.8 million adults have ischemic heart disease, which is also known as coronary heart disease.

As we go on to the next slide, we’re going to talk about some standard therapies for stable ischemic heart disease, so here we’re not talking about acute coronary syndromes; we’re talking about chronic management. Standard therapy can reduce the occurrence of cardiovascular events, and they include antiplatelet therapy; statin therapy if your LDL cholesterol is elevated; beta blocker therapy, especially for your post-myocardial infarction patients; and then aggressive modification of risk factors, so if you’re a hypertensive patient, getting good control of your blood pressure, getting good control of other modifiable risk factors.

Now, ACE inhibitors and angiotensin receptor blockers have established benefits, and the American Heart Association and the American College of Cardiology both agree on these benefits in patients who have heart failure or people who have had myocardial infarction and also have left ventricular dysfunction. However, right now, they—there had been more limited information on their benefits in patients who had a myocardial infarction or other form of stable ischemic heart disease, but did not have left ventricular dysfunction, so their ejection fraction was greater than 40 percent. And that’s one of the areas that we wanted to hone in on because that was a practice gap.

On the next slide, we’re going to talk about the rationale for additional therapies in this patient population, so, despite standard medical therapy, these patients continue to experience considerable morbidity and mortality. Now, ACE inhibitors and angiotensin receptor blockers have established benefit in those other two populations, but the evidence for prophylactic use of ACEs and ARBs in patients without heart failure and post-myocardial infarction patients who had preserved left ventricular (LV) function was less clear.
But, as we go to this diagram, this just kind of shows you where ACE inhibitors and angiotensin receptor blockers work, and one of the things that I wanted you to realize is that, even though they both work on the rennin angiotensin aldosterone system, they don’t work in exactly the same place. Where ACE inhibitors are blocking angiotensin-converting enzyme, trying to prevent angiotensin I from turning into the biologically active angiotensin II, where angiotensin receptor blockers block the angiotensin II type I receptor, which are the receptors that cause that pharmacologic effect.

Now, a couple of quick caveats, and that is that even though angiotensin-converting enzyme can convert angiotensin I into angiotensin II, the heart and the vascular have non–ACE enzymes that can also generate angiotensin II. One may think that maybe an angiotensin receptor blocker might have some advantages over an ACE inhibitor because it blocks that final common pathway when the angiotensin II hits the receptors, regardless of where it was made; however, ACE inhibitors have something else that’s pretty unique, and that is that they are also a blocker of kininase and kininase II takes bradykinin, which is a vasodilator, and end up turning it into inactive products, so that when you use an ACE inhibitor, you actually get these two effects, and when you use an angiotensin receptor blocker, you get one effect, but that effect is magnified. So, they’re different, but they’re very similar, and they’re working in a similar system.

Here’s the development process for our project. The topic was nominated in a process, so you know it was identified that this was an important question and that this was going to improve patient care, you know, to have an evidence-based idea about what’s happening in this area. We put together a technical expert panel; from Boston we had JoAnne Foody, we—as a practicing cardiologist and researcher—we had Paul Thompson as a researcher from Hartford Hospital. We had a variety of practicing clinicians, we had, you know, the health-payers’ perspective, we had the patient perspective.

We brought these people together, and what we did is we developed key questions, questions that we thought would be important to all of our key stakeholders: to the clinician, to the health care decisionmaker, and to the patient. We didn’t want to leave out any of those important stakeholders. Now, what happened when we had those key questions is that we ended up posting them on the AHRQ Web site, so that anybody who had an interest in the area could log in, could see what the proposed key questions were, and then could make—could ask questions or could post comments or alterations of things for us to think about. We reviewed all of those. We made some changes where they were appropriate. We identified where some differences may be and ended up getting those key questions that were approved.

At that point, we put together the methodology for being able to answer questions with that technical expert panel. And then our evidence-based practice center went through and answered the questions. Now, after the answering of those questions, they sent it out to, I believe, 12 peer-reviewers and people who had different stakeholders—patient advocates, clinicians, health policy decisionmakers—and we got comments from them. But it also went back out for public comments so that anyone with an interest in this area could go on and could also post other comments. We had to go through and respond to all of those comments and, at that point, the final report was approved and is available on the Effective Health Care Web site.
Now, after it was approved, one of the groups within AHRQ called the Eisenberg Center ended up coming up with a slide set. And on the Effective Health Care Web site right now, there is one hour of continuing education based on that slide set with voice-over PowerPoint, and there are also slides that you can download. If there are certain slides from this presentation that you would like to add to some of your own presentations, they’re available for general consumption from the public.

OK, so on to the next slide, rating the strength of evidence. It isn’t valuable enough just to summarize what the evidence is and to say that this is significant or that’s not significant. It’s also important to grade the strength of the evidence because something may be significant, but it might be significant based on a study that had a lot of flaws. Or maybe something is not significant, but the problem is that it hasn’t really been analyzed very much, so you don’t know whether or not it’s not significant because it doesn’t really exist or whether that’s an effect that’s just due to being underpowered, so you’d be able to show that it has that effect.

One of the things we do is that we synthesize and summarize the data, but then we need to grade the strength of that evidence. And when we graded it, we used a standardized system called the GRADE system, and here we looked at four main domains. The domains consider at risk biases within the different studies, but consistency between those studies; the directness of those studies, were they actually measuring final health outcomes or were they measuring more surrogate endpoints or what they call intermediate health outcome; and then the precision of some of those studies. And, based on those different factors, we ended up rating the evidence as either being high evidence, moderate evidence, or low evidence.

It was kind of similar to what the American Heart Association and American College of Cardiology do when they grade different bodies for, you know, the evidence and the strength of the evidence that we were finding, where high evidence says there are consistent results from good-quality clinical trials and that further research is unlikely to change the conclusions. Now, moderate evidence means that the findings are supported. We have reasonable confidence in these findings, but further research could change the conclusion. And then low-quality evidence means that there are very few clinical trials or the trials are very small or, within these existing trials, there are important flaws that—so that we don’t have a lot of confidence in the results.

On to the next slide, where we’re addressing clinical questions. We wanted to look at the comparative effectiveness of different combination treatments; ACE inhibitor or ARB in addition to standard therapy versus standard therapy alone, so those ACE inhibitors and beta blockers and cholesterol-control medications, with or without an ACE inhibitor or ARB. Now, remember the population we’re talking about, patients with stable ischemic heart disease and preserved left ventricular function.

The second question we wanted to ask was, would adding an ACE inhibitor and ARB together plus standard therapy be better than just using an ACE inhibitor plus standard therapy? And one of the reasons why this question is important is that they know that, in patients who have congestive heart failure, when you use an ACE inhibitor and an angiotensin receptor blocker together that you get more benefits than when you use either of those two agents alone. But in the VALIANT Trial, in patients with left ventricular dysfunction, post-myocardial infarction, adding those two agents
together, an ACE inhibitor and an ARB, was no better than using an ACE inhibitor alone, but was associated with greater adverse effects, so what was the evidence here for combination therapy with two rennin angiotensin aldosterone system blockers versus only one of those, but again, in addition to standard medical therapy?

The last question was an ACE inhibitor or an ARB plus standard medical therapy versus standard medical therapy alone, but here we’re looking at a very select population--those people who are in proximity to a revascularization procedure. So, within a few days of a revascularization procedure or at the same time of a revascularization procedure, if you gave them an ACE or you gave them an ARB, what are these short- to moderate-term benefits that you would be likely to expect from therapy? And we looked at the benefits and the harms, and this is one of those things that they do in the Effective Health Care Program that’s very, very important.

Now, a lot of clinical trials are designed specifically to look at benefits, but not to look at harms. Some of those trials have run-in periods, where they put people in the clinical trial; they will put them on either an ACE inhibitor or an ARB and, over the course of a few weeks, they’ll get rid of people who are noncompliant, they’ll get rid of people who have adverse effects, and, at the end, it looks like the benefits are there, but that some of the harms are underpowered. And very rarely in clinical trials do they power them for harms, but by combining the results of this trial, through statistical pooling, with the results from several other trials, you can get a good handle on some of those harms, so not only looking at the benefits and harms, but also looking at some of those benefits in various subpopulations of people because not everybody is the average.

On to the next slide, where we’re talking about outcomes of interest; you can see that there’s a myriad of outcomes that we were looking at. For benefits, we were looking at important final health outcomes, like total mortality, cardiovascular death, non-fatal myocardial infarctions, stroke, the composite endpoint of cardiovascular death, nonfatal MI, or stroke;, and the need for a revascularization procedure and its impact on quality of life. When we looked at harms, we were looking at the important harms that you would expect from ACE inhibitor and ARB therapy: hyperkalemia, cough, angioedema, hypotension, rash, blood dyscrasias, syncope, and then withdrawal from the trial.

On to the next slide; here we’re talking about trials that evaluate the addition of an ACE inhibitor or ARB to standard medical therapy for stable ischemic heart disease and preserved left ventricular function. So, here we’re looking at the trials that ended up making it into this evaluation, and what you see is that there were only two angiotensin receptor blocker trials that were compared versus standard medical therapy and that the TRANSCEND Trial with telmisartan and then also this Kondo trial. And what you see when you look at that is that virtually all the patients in that analysis are really coming from the TRANSCEND Trial.

Now, for ACE inhibitors, you can see that there are a lot of very large clinical trials, so we have a lot of power to be able to evaluate some of those differences, if those differences were true, and the length of followup for these very large trials was also very long, which, you know, would increase your confidence in some of the results that we came up with.
On to the next slide, where we’re talking about drugs and target doses. Here you can see, for the ACE inhibitors, that in some of the larger trials they looked at ramipril. In some of the other trials, they looked at enalapril, they looked at perindopril, they looked at trandolapril, and then they also looked at zofenopril. So, they have one sulphydryl group containing ACE inhibitors, a couple of carboxyl groups containing ACE inhibitors, so that we had a good mix of some different types of ACE inhibitors. Some of the ACE inhibitors had good tissue specificity; some had less tissue specificity, so overall a good mix to be able to look at.

The TRANSCEND Trial, which virtually all the data in the ARB comparison came from, was with telmisartan, and then the Kondo trial was with candesartan. Then you can look at the target doses. And, you know, these are reasonable, modest doses of these therapies.

So, what were the benefits with a high level of evidence from adding an ACE inhibitor to standard medical therapy for stable ischemic heart disease with preserved left ventricular function? What we can say is that total mortality was reduced, and the number needed to treat was 91, so you would need to treat 91 patients in order to be able to prevent one extra patient from dying. That was about the same level that you would have to have for nonfatal myocardial infarction. You can see also that heart failure-related hospitalizations were significantly reduced, as was the need for revascularization.

Even these relative risk reductions, which ranged from 10 percent to 22 percent, depending on the outcome, were the same, pretty much, as the studies that were done in patients who had a myocardial infarction who had left ventricular dysfunction; what everyone already knew. The numbers needed to treat are higher here, and that’s because this population is not as at high risk of having subsequent events as people with a decreased left ventricular function.

The relative risks are the same, but you need to treat more people because the number of events that you can expect to see within the population is a little bit less. But what you can see when you’re looking at all this data is that, with a high level of evidence, adding an ACE inhibitor to standard medical therapy in these patients with preserved LV function is a beneficial thing to do. On the next slide, when you combine those things together, of course you also have a relative risk reduction, and you’d have to treat 56 people in order to have one fewer patient have a combined risk of death from a heart-related cause, suffering a nonfatal MI, or having a stroke.

So, those are the benefits, but what about the harms of adding these in therapy? And what we see is that there was an increased risk of syncope. There was an increased risk of ACE inhibitor-induced cough. There was really no big effect on angioedema, and the risk of hyperkalemia was elevated. However, in these studies, the level of evidence was low because a lot of these major clinical trials did have those run-in periods that I was telling you about before, where people who would be at higher risk for adverse effects would be eliminated at that point in the trial. Knowing what we know about this disease state, plus what we know from the use of ACE inhibitors and ARBs in other disease states, when you put it together and you’re trying to look at the balance of benefits to harms, it looks like the balance of benefits to harms is favorable.

Now, on to the next slide, where we’re looking at the ACE/ARB combination versus ACE inhibitor alone. And with this trial, what we found was that there was one very large trial called the
ONTARGET Trial, and in this trial there was no evidence of greater clinical benefit with the addition of an ACE inhibitor and ARB versus an ACE inhibitor alone, in addition to standard medical therapy. However, there was a third arm in this trial which looked at angiotensin receptor blocker therapy alone. And, in this trial, what they found was that angiotensin receptor blocker therapy provided similar benefits to ACE inhibitor therapy.

So, that is important information also. You start with an ACE inhibitor, because that’s where the greatest evidence of benefit resides, but if your patient can’t take an ACE inhibitor because of an ACE inhibitor-induced cough, an angiotensin receptor blocker seems to be a reasonable therapeutic alternative for your patient.

So, no additional benefits from the combination of an ACE and ARB, but look at the harms associated with the combination: increased number of discontinuations, increased hypotension, increased risk of syncope, increased risk of renal impairment, and increased risk of diabetes. When you look at the balance of benefits to harms, they’re not favorable in this case, with a moderate level of evidence.

On to the next slide; here we’re looking at the addition of an ACE inhibitor or an ARB to standard medical therapy versus standard medical therapy alone, in proximity to a revascularization procedure. There was a thought that, if you gave an ACE inhibitor really close to a revascularization procedure, it might decrease subsequent need for revascularization or improve other endpoints. There were a number of trials that were conducted in order to be able to evaluate that. As we look down, you see that only one of those really had looked at ARB therapy there, and that was the AACHEN study with candesartan, so that most of the data that we’re looking at are ACE inhibitor data.

What we found was, when we looked at all those clinical benefits that we were talking about previously—for the main question—we looked at them here—there were no clinical benefits from adding ACE inhibitors or ARBs in proximity to a revascularization procedure. However, there was, again, an increased risk of harms, so that the balance of benefits to harms was not favorable. So, what this seems to guide or direct us in therapy is that you shouldn’t be initiating an ACE or ARB therapy really close to a revascularization procedure, with the hope that you’re going to see short- to modest-term benefit.

It doesn’t mean that you couldn’t combine the two together with the thought that you were going to provide very long-term therapy and that the long-term benefits wouldn’t materialize. We’re talking about the use of these drugs specifically for short- to moderate-term therapy. You’re not going to get any additional benefits, but you are going to get some additional adverse effect.

On to the next slide, the final summary of results. We showed that adding an ACE inhibitor to standard therapy versus standard therapy alone is beneficial and that the benefits seemed to be greater than the harms: reduced total mortality, reductions in nonfatal MI, reductions in heart failure-related hospitalization, and the need for revascularization procedures. However, there was a possible increase in syncope, a possible increase in cough, and a possible increase in hyperkalemia.
Now let’s talk about those angiotensin receptor blocker trials. And before we talk about those, there’s one thing that I wanted to talk about specifically and let you know was that that one large trial, and there were two trials overall, but that one large trial looking at an angiotensin receptor blocker was a little bit different than what we would think of as standard ACE or ARB therapy.

In TRANSCEND, in order to get into the trial, the patients either had to have failed ACE inhibitor therapy or they had to be people that were not candidates for ARB therapy, so it was a very select group of patients. Now, even with this very select population, they were able to show a reduction in one or more of the following endpoints, and that was that combined endpoint of cardiovascular mortality, nonfatal myocardial infarction, and stroke.

This did increase some of the harms; the possible increase in hyperkalemia, so I think you need to take the data and add them to the data that we had from ONTARGET, showing that an ARB was a good substitute for an ACE inhibitor for some of the other endpoints to give you confidence. But, even with that level of confidence, what I would say and what I believe most clinicians would say after looking at the data, would be that ACE inhibitors are the agent that you should use first because the totality of the evidence in this population is clearly with ACE inhibitors, but that if you can’t take an ACE inhibitor, an ARB is still a therapeutic option that you could use with good relative confidence.

Now, adding an ACE inhibitor and an ARB together in the same patient versus using an ACE inhibitor alone was not associated with any additional clinical benefits, but it did increase the risk of harms. Since this is similar to another very large clinical trial, the VALIANT Trial in people with left ventricular dysfunction, it seems like that would preclude the standard recommendation to use those two therapies together. And then also adding an ACE inhibitor or an ARB in proximity to a revascularization procedure; no short- to moderate-term benefits, but increased risk of adverse effects or harms so that the balance of benefits to harms is not favorable.

Going on to the next slide; informed decisionmaking process using these project results. Number one, trying to review the critical evidence to help your patients understand the risk reductions after adding an ACE inhibitor to their regimen; what is the risk of cough and syncope and hyperkalemia after adding an ACE inhibitor, and what could that mean for your patient? Telling about the option of using an angiotensin receptor blocker if your patient is intolerant to an ACE inhibitor and then the harms of adding an ACE inhibitor or an ARB close to a revascularization procedure.

Try to explore each patient’s values by asking that specific patient: What worries you most about taking these types of medications? Do you have concerns about the cost of your medication? And then do you have any problems remembering to take your medication? Finally, encouraging your patients to get involved in their own medical care and realizing that the patient is a very important member of that health care team. Just like we did today, talk about the benefits and the risks of each choice. Talk about the impact that their comorbidities would have on the decision to add one of these therapies, and then discuss other things that they can do to help reduce the risk of heart attack and stroke.

On to the next slide, gaps in knowledge. There are some additional data that are needed to be able to address the benefits and harms in certain patient populations. One of those things that we looked
at was patients who were receiving antiplatelet therapy, and it seemed like ACE inhibitor therapy, which is where we have the most of our data, seem to work a little better in patients who were not receiving concomitant antiplatelet therapy.

Now, ACE inhibitors, through that bradykinin system, right? Remember that ACE inhibitors also block kininase II, and they preserve bradykinin; bradykinin helps to elicit the release of vasodilatory prostaglandin. Aspirin therapy and they said antiplatelet therapy, and a lot of those patients were probably receiving aspirin as their antiplatelet therapy, ends up blocking the production of precursors to prostaglandins, so you can see how one portion of that benefit would be attenuated. However, even with that, there were still significant benefits to patients who were receiving antiplatelet therapy.

Patients of different ethnicities, so, we don’t have good overall data on ethnic minorities. A lot of trials had some portion of ethnic minorities, but they didn’t break their studies up into those different ethnicities so that we could get a sense of whether or not certain ethnicities are benefiting more or less than other ethnicities, and in congestive heart failure, there have been subgroup analyses of other trials suggesting that there may be some differences in some of the medications that are taken in people with different ethnicity, so that would be important to do.

And, finally, patients who have genetic polymorphisms within the angiotensin-converting enzyme G or the angiotensin II type-1 receptor gene, and whether or not those people have an accentuated response or an attenuated response to ACE inhibitor or ARB therapy, we really couldn’t answer with this report.

On to the next slide, which looks to be the question slide, so if you want to submit a question, then you see this, and I’ll turn it over to the people at AHRQ who can give you some more information.

BRODT: Thank you, Dr. White. We appreciate your making the information and research we are sharing today salient to the clinician audience. Now, as Dr. White alluded to, we would love to hear any questions that anyone on the phone has had. If you have not already submitted a question, please type your question into the “Ask Question” box at the bottom of your screen.

And now I’ll just start with one, Dr. White, while we wait on a few that are coming in, but it sounds like ACE inhibitors should generally be tried before ARBs. When would ARBs be good substitutes?

WHITE: There are some things that the two drugs have in common, you know, like the ability to raise patients’ serum creatinine. And, in general, if you try an ACE or an ARB and the serum creatinines rise by less than 30 percent, then it’s OK to continue therapy. If it’s in that 30 to 50 percent range, you know, halving the dose and then retesting the patient in the next two to four weeks is reasonable. Greater than 50 percent reasonable, you take off the ACE or ARB and then look for reversible causes.

That would be true with ACEs and with angiotensin receptor blockers, so I don’t want to create the impression that if you can’t tolerate an ACE, that you can always go to an ARB, but if you have an ACE inhibitor-induced cough, which is thought to occur through that bradykinin-kallikrein system,
you would not get that effect with an angiotensin receptor blocker, so the chance of tolerance would be good. So, start with an ACE inhibitor; if you get an ACE inhibitor-induced cough, then taking that next step and using an angiotensin receptor blocker sounds like a reasonable, evidence-based thing to do.

BRODT: Great. Thanks, Dr. White. We had another question about—and I will state my ignorance on this and, Dr. White, you may know the reference to it, but is the information presented today different from conclusions reached in the October 2009 report referenced in the slide deck?

WHITE: No. There haven’t been any additional large clinical trials that have come out that would really have changed any of the conclusions that we had today. What I would say is that there is the potential, and it is from a single trial, and it’s recent data from recent (INAUDIBLE) meetings, suggesting that there may be a benefit for aldosterone receptor antagonist therapy to be added to the patient’s regimen if the patient’s serum creatinine is stable, if the patient’s blood pressure is still reasonable, so you might not want to add an ACE and an ARB together, but there may be some benefit to adding an ACE inhibitor and something like eplerenone.

You know, some people believe that the small additional reductions in relative risk aren’t worth some of the inconveniences and harms associated with therapy. AHRQ has not—and national organizations have not really been clamoring for a large evaluation into that, so that one trial isn’t siloed, not based on a very extensive review of the literature specifically about aldosterone receptor antagonists, but that’s the information that I have.

BRODT: Thanks, Dr. White. The next question’s actually a two-part question. Are there differences between ACE inhibitors that can help guide therapy, and are there differences between ARBs that can help guide therapy? You can do that in two parts, but . . .

WHITE: Yes. I believe there’s somewhere in the neighborhood of 13 ACE inhibitors and there are like six or seven angiotensin receptor blockers that are available. So, are there some differences? These are not things that we looked at in our comparative effectiveness review, but, in general, captopril and lisinopril are the only ACE inhibitors that are not prodrugs, so they go into the body in the active form.

And in pharmacokinetic studies with different ACE inhibitors, what you find is that the prodrug ACE inhibitors, the ones that need to be turned into the formulation, so when you give somebody enalapril, it has to be turned into enalaprilat, and that’s why when you give someone IV enalapril, IV Vasotec is enalaprilat rather than enalapril, because it bypasses the liver, and in that case you wouldn’t be able to activate therapy.

So, if your patient has significant liver dysfunction, you may have more predictable pharmacokinetics—when the maximum effect’s going to occur, the duration of the effect that you would be expecting if you were using captopril and lisinopril—and those agents are mostly renally eliminated also, so that pharmacokinetically that would look like the way to go.
There are some ACE inhibitors that are not true once-a-day drugs. They have a trough-to-peak ratio of less than 50 percent so that they do not have as smooth of a blood pressure reduction, and you get more robust blood pressure reduction an hour or two after therapy than at the end of the dosing interval and that may increase the risk for hypotension. So, if you look at a drug like Moexipril or Univasc, it is indicated for once-daily therapy, but is really not a true once-a-day drug.

Captopril is also not a true once-a-day drug, but no one really uses captopril in that manner, and it’s recommended for twice- or three-times-a-day therapy, and when it’s used and the dose is split in that way, the trough-to-peak ratio for 12 or 8 hours is above 50 percent.

For the angiotensin receptor blockers, there are some differences that can be important. If you look at losartan, losartan is the only angiotensin receptor blocker that requires a 50 percent dosage reduction in patients with significant liver disease. And then losartan is also a cytochrome P450 2C9 substrate, and so this has some very interesting drug interactions, where whether or not you use the drug with a 2C9 inducer or an inhibitor, so inducers like some of the anticonvulsants or rifampin and then some of the inhibitors like sulfamethoxazole, the pharmacological effect of losartan is reduced.

Now, telmisartan is an inhibitor of P-glycoprotein, and P-glycoprotein is the pump that helps to prevent some of digoxin’s absorption from the gut and also helps digoxin get pumped out into the renal kidney tubule, so it will raise digoxin concentrations, and other angiotensin receptor blockers don’t have that effect. So, I would say that those, overall, are some good differentiators between some of those agents.

The last thing is that captopril, very well tolerated, very good ACE inhibitor, but if you use higher-than-normal dosing of captopril, that you have an increased risk of some blood dyscrasia that doesn’t seem to be true with carboxyl-containing ACE inhibitors, which are almost all of them, or the phosphoenol-containing ACE inhibitor, monapril or Monopril or also known as fosinopril.

The last thing is that patients with renal dysfunction, they usually recommend for ACE inhibitors that you decrease the initial dose and then try to titrate to effect, but that you don’t have to do that with fosinopril because fosinopril, unlike the other agents, has compensatory dual routes of elimination, so that if your renal function is a little bit worse, then fecal elimination of the drug is enhanced.

BRODT: Great. Thanks, Dr. White. We have another question that actually references something that you mentioned in your presentation today about how the American College of Cardiology and the American Heart Association together issued clinical practice guidelines relative to the management of cardiovascular disease, including stable ischemic heart disease. What does AHRQ’s evidence synthesis add to what the AHA and ACC are currently doing in this area?

WHITE: What I’m hopeful of is that, when they go through to synthesize the evidence and try to update their guidelines for stable ischemic heart disease, you know, stable angina and also the chronic management of patients with myocardial infarction, that the evidence that we’ve put together and synthesized will help to give them the evidence base that they need in order to be able to make some of those decisions.
You know, we can’t force people to use the evidence that is created, but usually when that evidence is available, it ends up getting adopted in some form by those organizations because it pretty much undergoes some of the same processes by which they go through and synthesize some of that evidence.

BRODT: Great.

WHITE: And so just one thing that makes us different from groups that make clinical guidelines, though, is that, you know, what we do is tell people what the evidence is. We rate the strength of the evidence and then we talk about the applicability of the evidence; who does this evidence apply to? What we don’t do is make very specific clinical recommendations or guidelines in that, you know, we don’t have something based on expert opinion or expert opinion based on—based on—that evidence.

So, it’s kind of a step away from what you would do in clinical guidelines, but it kind of lays things out for the clinician. It lays things out for different organizations to be able to look at the information in a very concise manner, so that you’re not overly drawn away by a single study or by two different studies, or, you know, you think that one study may be conflicting with another trial. And, by putting it all together and looking at the evidence and saying, hey, you know, this one showed a significant effect, but that one did not show a significant effect.

Does that mean that this one showed that it didn’t work, or did they show that it may work, but you can’t say with 95 percent confidence that it worked and that, if you pool these two things together, the results are consistent. And there are tests that you can do in systematic review that can help you tease out some of those results.

And that’s exactly what we found in our study, and one of the things that seemed to be controversial is that two of the really large trials were showing a significant effect. One of the trials did not show a significant effect but was still in the direction of showing benefit, and when you pooled those things together you ran those tests for statistical heterogeneity, what the tests were telling was that any differences that you saw were likely differences just due to chance and not real differences between those trials and helped to give us a high strength of evidence for the recommendations that we had or for those different outcomes that we had.

BRODT: Dr. White, we have one last question I want to ask before we complete our hour that’s somewhat similar to the previous question, and I know you referenced that you’re not in the practice of making clinical guidelines and directing people in particular decisions, but we were asked, are there certain ACEs or ARBs that are better than others with respect to reducing cardiovascular events and/or stroke? In other words, are there data available that show that one drug may be better than another drug, or can they be considered me-too drugs?

WHITE: This is a very good question and, in general, what I would say is that you always need to be cautious about trying to extrapolate the benefits of one drug within a class immediately to other drugs in the class because there may be other differences that could be accounting for some of those effects. So let me just throw a couple of things out there.
For ACEs and ARBs, I have less concern about the interchangeability of the different agents, and a lot of that has to do, not with stable ischemic heart disease and our comparative effectiveness research, but with very large systematic reviews that were conducted in post-myocardial infarction patients with left ventricular dysfunction, for which there are very, very large clinical trials, over 100,000 patients being evaluated, and congestive heart failure trials, with over 100,000 patients, when you’re looking at different ACE inhibitors.

And what they found was that, you know, there was no difference between several of the different drugs, you know, several of the different ACE inhibitors that they had been evaluating with. So I think, realistically, what you’re looking at for ACEs and ARBs is a class effect. I think that some of those other factors that can help you decide between therapies are reasonable things.

Now, for our specific project, you always have the greatest confidence with the drugs that were actually studied, so you can see the drugs that were actually studied here. Some of them were ramipril, some of them were enalapril. One large trial was with trandolapril. And there’s nothing wrong with saying, you know, the best proof is proof, and I’m going to go with the agents and the doses that were studied.

With angiotensin receptor blockers, the data are ultimately more limited, so while it looks like they may be interchangeable, there really isn’t as much evidence to be able to say with 100 percent certainty that they are interchangeable. If you look at heart failure, and you look at two trials where they looked at the combination of two drugs together, it looked like maybe you were getting more robust effects from the CHARM Trial, where they added candesartan, than you did from the Val-HeFT Trial when you added valsartan, but then there’s a big caution because they weren’t a direct comparative trial.

One was a placebo-controlled trial; the other was a placebo-controlled trial. The populations, even though they were in heart failure, were a little bit different; some differences in terms of the countries that they were drawing some of their patients from, differences in some of the ethnicities, so it’s hard to be able to say that one would be clearly different than another. But, with ARBs, there may be more of an impetus to go through and try to use some of the drugs that have been specifically studied and shown to have mortality benefit. And if you’re going to use something like valsartan, remember that, in the clinical trial programs, valsartan was always dosed twice a day, so even though you can use it once a day for blood pressure reduction, there will be less confidence when you try to use the drug once a day if you had heart failure or if you were a post-myocardial infarction patient.

So I hope that was clear, but in general we shouldn’t extrapolate from one drug to another drug, but for ACE inhibitors, based on all of the data we have and all of the clinical trials across the main disease states, seem to be interchangeable.

BRODT: Great. Thank you for such a comprehensive answer, Dr. White, and all of our questions, in fact. Our time is almost up. If we didn’t get to your question today, please do e-mail us at ehc_clinicians@ahrq.hhs.gov. And to access all the resources mentioned today and print them out,
you can find them on the Effective Health Care Program Web site listed here, or you can order
them en masse for free through AHRQ’s publications clearinghouse.

Also on the Web site, you can become involved in a topic nomination and refinement process that I
described earlier as well as comment on draft reviews and reports. All of these features, in addition
to signing up for e-mail updates, can be easily navigated in the panel on the left-hand side of the
Effective Health Care Program Web site. So, you can also come to the site within the next week to
find out more about the other events that I mentioned earlier on the call.

On Friday, December 3, we’ll have another call on breast cancer. On Monday, December 6, we
have a call focusing on cardiac conditions. On Monday, December 13, we have a pharmacy call,
focused on the role of pharmacists in the patient-centered medical home that is being offered for
CPE (continuing pharmacy education) credit. And, on December 14, we have another Web
colference on diabetes.

I’d like to thank Dr. White for sharing his research findings with us today. It was very helpful. I
would also like to thank our many participants for joining us. We hope that the information
presented here informed you about how you can implement patient-centered outcomes research in
everyday practice. As we conclude this Web conference, let me remind you that this event will be
archived and available shortly on the Effective Health Care Program Web site.

Finally, as you leave the event, please do answer the one feedback question that we posed. Your
feedback is very important to us as we develop more resources and plan similar events. Have a
great day.

OPERATOR: Thank you. And again, once again, this does conclude today’s Web conference.
You may disconnect your lines at this time, and have a great day.

END