

## Current Indications for ACE Inhibitors and HOPE for the Future

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### AUDIENCE

This activity is designed for pharmacists, physicians, nurses and other healthcare professionals involved in caring for patients with cardiovascular diseases.

### GOALS

To review the current therapeutic uses of angiotensin-converting enzyme (ACE) inhibitors and to discuss their use in the prevention of coronary artery disease since publication of the Heart Outcomes Prevention Evaluation (HOPE) trial.

### OBJECTIVES

1. Summarize the results of the HOPE trial and the potential impact on the treatment of coronary artery disease.
2. Review the therapeutic uses of ACE inhibitors in the treatment of hypertension, heart failure, acute myocardial infarction, and diabetic and nondiabetic nephropathy.
3. Identify the different mechanisms of action with the therapeutic benefits of ACE inhibitors.
4. Review the evidence supporting the use of ACE inhibitors in cardiovascular and noncardiovascular diseases.
5. Identify the trials conducted that support or contradict the findings of the HOPE trial.

Angiotensin-converting enzyme (ACE) inhibitors are effective in several disease states such as congestive heart failure, myocardial infarction, and diabetes. This article reviews the evidence supporting the clinical use, efficacy, and cost effectiveness of ACE inhibitors in these various disease states. With the findings of the Heart Outcomes Prevention Evaluation trial, these agents may now have a positive impact on the primary prevention of coronary artery disease. New and ongoing trials will provide more information about the role of ACE inhibitors in coronary artery disease.

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Angiotensin-converting enzyme (ACE) inhibitors were first introduced in the 1980s, with captopril being the first agent available for use in the United States (Table 1). Today there is convincing data from clinical trials documenting that ACE inhibitors lower blood pressure,<sup>1</sup> preserve kidney function in individuals with diabetes mellitus,<sup>2,3</sup> reduce mortality and morbidity in patients with heart failure,<sup>4-7</sup> and decrease mortality and the incidence of heart failure in patients with myocardial infarction (MI).<sup>8-13</sup> There is new evidence to support ACE inhibitor use in preventing cardiac ischemia in high-risk but stable patients with heart disease.<sup>14,15</sup> High risk is defined as having a history of stable coronary artery disease (CAD), peripheral vascular disease, or stroke and as having diabetes mellitus and at least 1 coronary risk factor. Publication of the results of several trials and others in progress will further define the role of ACE inhibitors in this area.



### CONTINUING EDUCATION CREDIT

This course has been approved for a total of two (2) contact hours of continuing education credit (0.2 CEUs) by the University of Tennessee College of Pharmacy. The University of Tennessee College of Pharmacy is approved by the American Council on Pharmaceutical Education as a provider of continuing pharmaceutical education. ACPE Program Number: 064-999-02-206-H-01. This course expires on May 31, 2004.

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### ... MECHANISM OF ACTION ...

Although the mechanism of action of ACE inhibitors is not fully understood, these agents block angiotensin-converting enzyme, leading to decreased production of angiotensin II, a potent vasoconstrictor. The ACE inhibitors also block the breakdown of endogenous bradykinin by ACE, resulting in increased accumulation of bradykinin, a direct vasodilator (Table 2). The reduction in circulating angiotensin II and the elevated bradykinin lev-

els are responsible for many of the observed benefits of ACE inhibitors.<sup>16</sup> It is important to note that complete shutdown of angiotensin II production is not possible because other enzymes, such as chymase, can convert angiotensin I to angiotensin II (**Figure**).

... **CARDIOVASCULAR DISEASE** ...

Evidence from human trials<sup>14,15</sup> demonstrates that ACE inhibitors possess antiatherosclerotic and anti-ischemic properties. The mechanisms underlying the antiatherosclerotic and anti-ischemic effects of ACE inhibitors are unclear. The proposed mechanisms include (1) inhibition of atherosclerosis by limiting smooth muscle migration and proliferation in the vasculature of the myocardium<sup>16</sup>; (2) prevention of thrombus formation by inhibiting platelet activation and coagulant factors through suppression of thromboxane A<sub>2</sub> and enhancement of nitric oxide effect via bradykinin accumulation<sup>16</sup>; and (3) enhanced fibrinolysis through the inhibition of endothelin, a procoagulant that can worsen atherosclerosis.<sup>16</sup>

... **HOPE TRIAL** ...

Published in 1999, the Heart Outcomes Prevention Evaluation (HOPE) trial is the first large-scale trial (to our knowledge) to provide strong evidence that ACE inhibitors decrease morbidity and mortality in patients without previous MI or systolic heart failure. The study enrolled patients 55 years or older with a history of stable CAD, peripheral vascular disease, or stroke and patients with diabetes mellitus and at least 1 coronary risk factor. Patients were randomized to receive either ramipril, 10 mg daily, or placebo. The study was terminated early because 14.0% of the 9297 patients in the ramipril group compared with 17.8% in the placebo group experienced an MI, stroke, or cardiovascular mortality ( $P < .001$ ). The reduction in CAD events seemed to be independent of the blood pressure-lowering effect, suggesting an antiatherosclerotic mechanism.<sup>14</sup> A newly completed trial, the Study to Evaluate Carotid Ultrasound Changes in Patients Treated with Ramipril and Vitamin E (SECURE), confirmed that ramipril slows the process of atherosclerosis.<sup>17</sup>

The HOPE trial showed not only the secondary prevention of CAD but also a marked reduction in the number of newly diagnosed diabetic cases in the ramipril group. This reduction is thought to

**Table 1.** Angiotensin-Converting Enzyme Inhibitors Currently Available in the United States

|                          |
|--------------------------|
| Benazepril hydrochloride |
| Captopril*               |
| Enalapril maleate*       |
| Fosinopril sodium        |
| Lisinopril               |
| Moexipril                |
| Quinapril hydrochloride  |
| Ramipril                 |
| Trandolapril             |

\*Available in generic formulation.

**Table 2.** Mechanisms of Action of Angiotensin-Converting Enzyme (ACE) Inhibitors

| Disease State                    | Mechanism of Action  |
|----------------------------------|--|
| Heart failure                    | Inhibition of neurohormones (angiotensin II, aldosterone, endothelin, norepinephrine) responsible for deleterious cardiac remodeling <sup>16</sup>   |
| Hypertension                     | Inhibition of ACE, thereby decreasing angiotensin II and the degradation of bradykinin <sup>16</sup>   |
| Myocardial infarction            | Mechanism of action similar to that for heart failure to prevent ischemia, permanent heart failure, and sudden cardiac death <sup>12</sup>   |
| Diabetic/nondiabetic nephropathy | Exact mechanism unknown but known renal protective effects through reduction in proteinuria and progression of renal dysfunction <sup>2,29,30</sup>  |
| Cardiovascular disease           | Proposed mechanisms of action include inhibition of atherosclerosis by limitation of smooth muscle proliferation of the myocardium, inhibition of platelet activation, inhibition of endothelin, and enhancement of nitric oxide <sup>16</sup> |

be mediated by an increase in insulin sensitivity.<sup>14</sup> Angiotensin II has been considered an important component in the endocrine functions of the pancreas. The presence of angiotensin II seems to help regulate blood perfusion to the pancreas through vasoconstriction properties.<sup>18</sup> Many patients with diabetes mellitus are also at an increased risk of CAD owing to the presence of hypertension and hyperlipidemia. Therefore, the antihypertensive and anti-ischemic actions of ramipril would possibly benefit this patient population and prevent the progression of macrovascular complications. The HOPE trial provides exciting and compelling evidence suggesting that patients with established CAD could benefit from the use of ramipril.

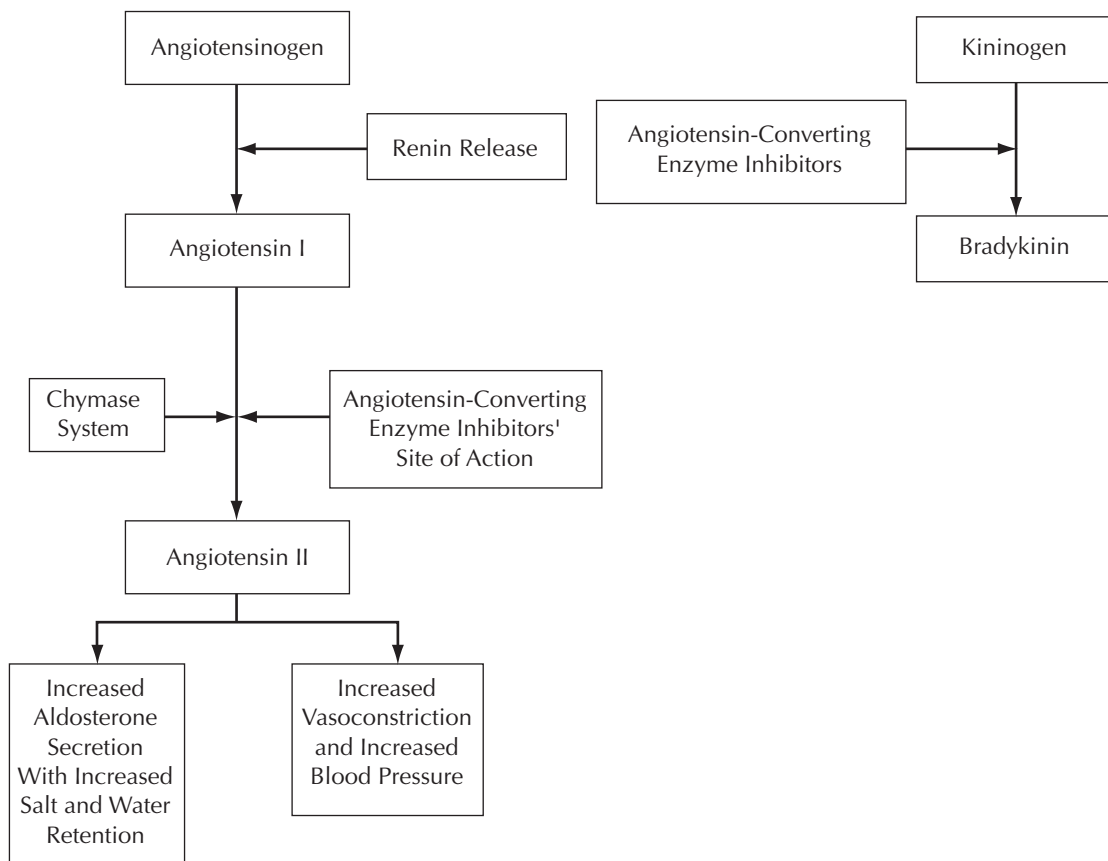
Although there is limited information on “class benefits,” the 2001 American Heart Association/American College of Cardiology (AHA/ACC) guidelines recommend consideration of ACE inhibitors

for chronic therapy in all patients with coronary or other vascular disease unless contraindicated.<sup>19</sup> The guideline does not specify a certain agent, although this recommendation is based primarily on the results of the HOPE trial using ramipril.<sup>19</sup> Data from ongoing trials such as the Prevention of Events with ACE Inhibition (PEACE) trial<sup>20</sup> and the European Trial on Reduction of Cardiac Events with Perindopril in Stable CAD (EUROPA)<sup>21</sup> should provide additional answers on class effects and dose-dependent benefits. We review several completed and ongoing trials that may help define the role of ACE inhibitors in the treatment of CAD.

... REVIEW OF COMPLETED TRIALS ...

Before the HOPE trial, other trials (Table 3) that investigated the benefit of ACE inhibitors in the treatment of CAD had encouraging results, including

**Figure.** Renin-Angiotensin-Aldosterone System



the Captopril Prevention Project (CAPP),<sup>22</sup> the Quinapril Ischemic Event Trial (QUIET),<sup>23</sup> the Trial on Reversing Endothelial Dysfunction (TREND),<sup>15</sup> and the Simvastatin/Enalapril Coronary Atherosclerosis Trial (SCAT).<sup>24</sup> The CAPP compared captopril with conventional therapy of a diuretic, a  $\beta$ -adrenergic blocking agent, or both in the management of primary hypertension. The study enrolled 10,985 individuals aged 25 to 66 years who were followed for 6.1 years. The primary endpoints were similar to those of the HOPE trial and included MI, cardiovascular mortality, and stroke. The CAPP found that captopril was as effective as conventional therapy in preventing cardiovascular morbidity and mortality.<sup>22</sup>

The QUIET<sup>23</sup> and the TREND<sup>15</sup> trials, using different quinapril hydrochloride regimens, produced mixed results. QUIET showed no significant difference at 3-year follow-up with quinapril (20 mg/d) compared with placebo in the primary outcome of time to first cardiac event or angiographic progression.<sup>23</sup> Questions were raised about whether the quinapril dose was too low to show benefit. This controversy was tested with TREND using a dose of 40 mg daily.<sup>15</sup>

TREND, which comprised 129 patients randomized to receive quinapril (40 mg daily) (n = 64) or placebo (n = 65), sought to determine whether use of quinapril would improve endothelial dysfunction in individuals with a known history of CAD. The primary outcome was improvement in endothelial function in patients with CAD as the only contributor to endothelial dysfunction. After 6 months of follow-up, patients in the treatment group had an improvement in the primary outcome compared with the placebo group. The ACE inhibitors were postulated to improve endothelial vasomotor dysfunction by increasing the concentration of bradykinin, which enhances the release of nitric oxide.<sup>15</sup>

The results of SCAT, with average follow-up of 48 months, were recently released. SCAT is a multicenter, double-blind, placebo-controlled trial studying the effects of simvastatin and/or enalapril on total cholesterol reduction as evidenced by angiography. The study hoped to prove that ACE inhibitors possess an antiatherosclerotic effect, thus reducing the progression of atherosclerotic plaques, which could potentially advance to plaque rupture. The study

**Table 3.** Summary of Coronary Artery Disease Trials

| Trial*               | Agent   | Outcomes   | Results  |
|----------------------|---|--|--|
| CAPP <sup>22</sup>   | Captopril (50 mg/d) vs diuretic or $\beta$ -adrenergic blocking agent | Cardiovascular mortality   | 6.1-y follow-up with captopril as effective in prevention of cardiovascular morbidity and mortality                                |
| QUIET <sup>23</sup>  | Quinapril hydrochloride (20 mg/d) vs placebo                          | Time to first cardiac event or angiographic progression  | No significant difference at 3-y follow-up   |
| TREND <sup>15</sup>  | Quinapril (40 mg/d) vs placebo  | Improvement in endothelial dysfunction in patients with known coronary artery disease                                | After 6-mo follow-up, the treatment group had an improvement in the primary outcome  |
| SCAT <sup>24</sup>   | Simvastatin and/or enalapril maleate (10 mg twice daily) vs placebo   | Total cholesterol reduction as evidenced by angiography  | No angiographic difference between the enalapril and placebo groups, although lower clinical events (myocardial infarction, death) |
| PEACE <sup>20</sup>  | Trandolapril  | Cardiovascular death, nonfatal MI, or revascularization  | Study results will be available in 2003  |
| EUROPA <sup>21</sup> | Perindopril   | Overall mortality, nonfatal myocardial infarction, unstable angina, and cardiac arrest with successful resuscitation | Study currently in progress  |

\*See the "Review of Completed Trials" section of the text for expansion of the trial names.

enrolled 460 patients with documented atherosclerosis and a left ventricular ejection fraction greater than 35%. The dose of enalapril used in the study was 10 mg twice daily. The study endpoints were quantitative coronary angiography and clinical events defined as MI, death, hospitalizations related to angina, revascularization, stroke, and cancer. The enalapril and placebo groups showed no differences in the quantitative coronary angiography endpoint, but the enalapril group had fewer combined clinical events of death, MI, and stroke ( $P = .043$ ).<sup>24</sup> The trials cannot be directly compared owing to differences in enrollment size, length of follow-up, patient population, and endpoints.

Although the HOPE trial and CAPP were similar in population size (>9000 participants), length of follow-up (>4 years), and primary endpoints, the results cannot be compared because of differences in the populations. In relatively young patients with diastolic hypertension, CAPP suggests that ACE inhibitors are as effective as diuretics,  $\beta$ -adrenergic blocking agents, or both in preventing cardiovascular morbidity and mortality.<sup>14,22</sup>

SCAT demonstrated that fewer patients taking enalapril experienced the combined endpoint of death, MI, and stroke ( $P = .043$ ), although the endpoint of quantitative coronary angiography was similar to that in the placebo group.<sup>24</sup> QUIET showed no apparent effect of quinapril on the progression of coronary atherosclerosis using angiography. The investigators questioned whether a 20-mg dose of quinapril was adequate to show antiatherosclerotic effects.<sup>23</sup> A small trial, TREND, using a 40-mg dose of quinapril, showed improvement in vasomotor dysfunction in patients with CAD.<sup>15</sup>

In patients with CAD, it is possible that ACE inhibitors positively affect endothelial function, plaque formation, and stabilization, which cannot be easily measured by changes in coronary angiography. However, in a large clinical trial such as HOPE, the benefit is readily demonstrable.<sup>24</sup> We eagerly await the results of 2 large trials, PEACE<sup>20</sup> and EUROPA,<sup>21</sup> to confirm the impressive results of the HOPE<sup>14</sup> trial.

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... REVIEW OF TRIALS IN PROGRESS ...

Two trials, PEACE<sup>20</sup> and EUROPA,<sup>21</sup> are currently under way and should provide some answers as to the potential antiatherosclerotic class effect with ACE inhibitors. The PEACE trial is currently evaluating the use of trandolapril in patients with CAD

and an ejection fraction of 40% or greater. The study will address the primary outcomes of cardiovascular death, nonfatal MI, or revascularization occurrence with use of this ACE inhibitor. A total of 8100 patients will be enrolled and followed for at least 4 years. The study results are expected to be available by 2003.<sup>20</sup>

The EUROPA trial is also currently under way to assess the efficacy of perindopril in the reduction of cardiovascular events in patients with stable CAD, similar to the objective of the HOPE trial. Patients eligible for study enrollment are those with documented CAD and no evidence of heart failure requiring treatment. The primary endpoints in this study are overall mortality, nonfatal MI, unstable angina, and cardiac arrest with successful resuscitation. The anticipated duration of the study is 3 to 5 years, with approximately 10,000 patients enrolled from 24 different countries.<sup>21</sup> The results of this study will provide additional information to the findings of the HOPE trial and the antiatherosclerotic effects of ACE inhibitors.

The results of additional clinical trials studying the antiatherosclerotic effects of ACE inhibitors may help increase the use of ACE inhibitors in the appropriate patient populations. Today, with the results of the HOPE trial, ramipril is being used in patients for the secondary prevention of CAD. Patients presenting with evidence of CAD and the ability to tolerate an ACE inhibitor should be considered for ramipril therapy.<sup>14</sup> In addition to ACE inhibitors, research is currently under way to assess the potential use of angiotensin receptor blockers (candesartan<sup>25</sup> and valsartan<sup>26</sup>) for anti-ischemic effects. The unveiling of study results for ACE inhibitors and angiotensin receptor blockers could further define the role of these agents for the secondary prevention of CAD.

Without considering the impact of ongoing trials, the use of ACE inhibitors is expected to increase. With the 2001 AHA/ACC guidelines promoting chronic ACE inhibitor therapy for all patients with MI and strong consideration for those with coronary and vascular disease, use of ACE inhibitors will likely rival that of aspirin.<sup>19</sup> Although, we are not aware of any formal analysis of cost effectiveness for the secondary prevention of CAD, we expect such studies in the near future.

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... HYPERTENSION ...

In the treatment of hypertension, ACE inhibitors exert their blood pressure-lowering effects through



the inhibition of ACE (Figure). This inhibition results in reduced angiotensin II production and decreased degradation of bradykinin, resulting in vasodilation.<sup>16</sup> Two trials compared ACE inhibitor use with the standard therapy of  $\beta$ -adrenergic blocking agents and diuretics. The CAPPP<sup>22</sup> and the Swedish Trial in Old Patients With Hypertension-2 study,<sup>1</sup> using lisinopril or enalapril, both studied the effects of ACE inhibitors in patients with hypertension. Both trials had cardiovascular mortality as the primary endpoint. Although no significant difference was seen with ACE inhibitors compared with the conventional antihypertensives of  $\beta$ -adrenergic blocking agents and diuretics, it was concluded that these agents were equally efficacious in effects on cardiovascular mortality.<sup>1,22</sup> Because ACE inhibitors did not show a distinct advantage for the treatment of hypertension,  $\beta$ -adrenergic blocking agents and diuretics are still considered first-line agents.<sup>27</sup> According to the Sixth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and based on clinical evidence, only  $\beta$ -adrenergic blocking agents and thiazide diuretics are considered drugs of choice for the treatment of hypertension without comorbidities.<sup>27</sup> ACE inhibitors are used as first-line agents in patients with diabetic<sup>2,27-30</sup> or nondiabetic<sup>31</sup> nephropathy and in patients with heart failure secondary to left ventricular dysfunction also presenting with hypertension.<sup>27</sup> There are several ongoing trials with ACE inhibitors that include patients with hypertension; however, no new large, randomized trials are ongoing because ACE inhibitors have a known benefit in patients with hypertension.

... HEART FAILURE ...

There is overwhelming evidence supporting the use of ACE inhibitors in treating heart failure due to impaired function of the left ventricle. Many clinical trials, using different ACE inhibitors, have shown that these agents decrease morbidity, mortality, and hospitalization rates and improve functional status.<sup>4-7</sup> The benefit of ACE inhibitors in heart failure was originally thought to result from vasodilation. Researchers have now found that progression of heart failure results from deleterious cardiac remodeling in response to cardiac injury.<sup>16</sup>

The pathophysiology of heart failure involves activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system, resulting in a surge of neurohormones such as angiotensin II, aldosterone, endothelin, and norepinephrine in

response to injury of the myocardium. Immediately after myocardial injury, these neurohormones help maintain cardiac output; however, the presence of elevated levels eventually leads to myocardial toxic effects and deleterious remodeling of the heart. The focus of managing heart failure today is inhibition of this neurohormonal process, thereby preventing ischemia, arrhythmias, cardiovascular remodeling, and hypertrophy.<sup>16</sup>

Several trials demonstrate the effectiveness of ACE inhibitors in heart failure, including the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS),<sup>4</sup> Studies of Left Ventricular Dysfunction (SOLVD),<sup>5</sup> the Vasodilator-Heart Failure Trial II (V-HeFT II),<sup>7</sup> and the Survival and Ventricular Enlargement (SAVE) study<sup>6</sup> (Table 4). Inclusion criteria for most of these heart failure trials included an ejection fraction of less than 40%, with results showing an improvement in ejection fraction and in heart failure classification status. Although several trials evaluated dosing regimens, it is still not clear what doses of ACE inhibitors should be used to gain optimal benefit. The Assessment of Treatment With Lisinopril and Survival (ATLAS) trial<sup>32</sup> found that high-dose lisinopril decreased disease progression and significantly decreased the number of hospitalizations compared with low-dose lisinopril. However, results from 2 other trials<sup>33,34</sup> indicated that high doses did not significantly improve survival compared with conventional dosing regimens. Current dosing recommendations for ACE inhibitors in heart failure call for titration to the maximum dose used in clinical trials (Table 5). Note that maximum doses may be difficult to achieve owing to the addition of  $\beta$ -adrenergic blocking agents as standard therapy for heart failure that was not established when most heart failure trials were conducted.

More recent heart failure clinical trials, such as the Valsartan Heart Failure Trial (Val-HeFT),<sup>35</sup> the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) trial,<sup>25</sup> and the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD),<sup>36</sup> investigated initiation of an angiotensin receptor blocker in addition to an ACE inhibitor for the management of heart failure. To date, angiotensin receptor blockers have not replaced ACE inhibitors because they have not yet convincingly shown a decrease in mortality.<sup>37,38</sup> In the Evaluation of Losartan in the Elderly Study (ELITE),<sup>36</sup> losartan was found to significantly reduce all-cause mortality compared with captopril; however, all-cause mortal-

**Table 4.** Clinical Trials Using ACE Inhibitors in the Management of Heart Failure

| Trial*                 | Agent   | Design  | Outcomes  | Results  |
|------------------------|---|---|---|--|
| CONSENSUS <sup>4</sup> | Enalapril, 2.5 mg/d (up to 20 mg twice daily)                 | Randomized, placebo-controlled trial              | Reduction in mortality in severe heart failure                                    | 40% reduction in mortality at 6 mo ( $P = .002$ ), 31% decreased mortality at 1 y ( $P = .001$ ), improvement in NYHA class  |
| SOLVD <sup>5</sup>     | Enalapril (5 or 10 mg twice daily)                            | Randomized, placebo-controlled trial              | Long-term survival in patients with left ventricular dysfunction                  | 16% risk reduction in long-term survival ( $P = .0036$ )   |
| SAVE <sup>6</sup>      | Captopril (50 mg 3 times daily)                               | Randomized, placebo-controlled trial              | Decrease in morbidity and mortality   | 19% mortality risk reduction, 25% reduced risk of recurrent MI ( $P = .0015$ ), 32% reduced risk of death after recurrent MI ( $P = .029$ )                          |
| V-HeFT II <sup>7</sup> | Enalapril (20 mg/d) or hydralazine plus isosorbide dinitrate  | Randomized trial                                  | Efficacy of enalapril   | Enalapril group had a significant reduction in mortality ( $P = .016$ )  |
| ATLAS <sup>32</sup>    | Lisinopril, high dose vs low dose (2.3-5.0 vs 32.5-35.0 mg/d) | Randomized, double-blinded trial                  | All-cause mortality, risk of death or hospitalization                             | High-dose group had nonsignificant risk reduction in deaths, significant reduction in deaths or all-cause hospitalizations, decreased heart failure hospitalizations |
| NETWORK <sup>33</sup>  | Enalapril (2.5, 5.0, or 10.0 mg daily)                        | Randomized, variable-dose, multicenter trial      | All-cause mortality, readmit to hospital for heart failure                        | No dosage correlation with enalapril and clinical outcome  |
| Val-HeFT <sup>35</sup> | Valsartan (160 mg twice daily) with placebo and ACE inhibitor | Randomized, placebo-controlled, multicenter trial | Morbidity and mortality   | Study currently in progress, significant effect on all-cause mortality and morbidity compared with placebo   |
| RESOLVD <sup>36</sup>  | Candesartan and enalapril vs candesartan or enalapril alone   | Randomized, placebo-controlled, multicenter trial | Change in NYHA class, quality of life, walk distance, neurohormones               | No difference in NYHA class, quality of life, or walk distance, increased ejection fraction seen with combination than with either agent alone                       |
| CHARM <sup>25</sup>    | Candesartan ( $\leq 32$ mg) vs placebo                        | Randomized, placebo-controlled, multicenter trial | All-cause mortality, cardiovascular mortality, and heart failure hospitalizations | Study currently in progress  |

ACE = angiotensin-converting enzyme; MI = myocardial infarction; NYHA = New York Heart Association.

\*See the "Heart Failure" section of the text for expansion of the trial names.

ity was not a primary endpoint. The Losartan Heart Failure Survival Study (ELITE II)<sup>38</sup> disputed the results of ELITE,<sup>37</sup> indicating that losartan compared with captopril did not show greater reduction in all-cause mortality when considered as a primary endpoint. Currently, the primary role of angiotensin receptor blockers in the treatment of heart failure is

in patients who develop severe cough due to ACE inhibitors. Unlike ACE inhibitors, angiotensin receptor blockers do not increase circulating bradykinin levels, which directly results in cough reduction. Angiotensin receptor blockers also do not provide bradykinin-induced vasodilation benefits for patients with heart failure. An angiotensin receptor

blocker can also be added to ACE inhibitors to improve heart failure symptoms.<sup>35,36</sup> If a patient truly has a contraindication to an ACE inhibitor due to severe renal failure or angioedema, hydralazine and isosorbide dinitrate treatment should be initiated based on the evidence provided in the Val-HeFT trial.<sup>35</sup>

As of this writing, valsartan has received an “approval” letter from the Food and Drug Administration for treatment of heart failure in patients not taking ACE inhibitors. The Val-HeFT showed significant overall reductions in morbidity and hospitalizations with valsartan vs placebo.<sup>35</sup>

... ACUTE MI ...

In the early 1990s, ACE inhibitors were proven to be effective in patients after MI, specifically anterior MI. Different ACE inhibitors demonstrated similar benefits. Patients with acute MI are often at risk for arrhythmic events and hemodynamic changes that can result in ischemia, heart failure, and sudden cardiac death.<sup>12</sup> Several trials have been conducted using ACE inhibitors in patients after MI. The trials are difficult to compare, however, because they vary according to study design and patient population.

**Table 5.** Angiotensin-Converting Enzyme Inhibitors: Food and Drug Administration–Approved Doses in Chronic Heart Failure

| Drug                     | Starting Dose | Target Dose |
|--------------------------|---------------|-------------|
| Captopril                | 6.25 mg tid   | 50 mg tid   |
| Enalapril maleate        | 2.5 mg bid    | 20 mg bid   |
| Lisinopril               | 5 mg qd       | 20 mg qd    |
| Ramipril                 | 1.25 mg bid   | 5 mg bid    |
| Quinapril hydrochloride  | 5 mg qd       | 40 mg qd    |
| Benazepril hydrochloride | 5 mg qd       | 40 mg qd    |

bid = twice daily; tid = 3 times daily; qd = every day.

Some trials studied the effects of ACE inhibitors for short-term treatment of MI when therapy was initiated early.<sup>9,10</sup> Other trials studied patients with signs and symptoms of heart failure.<sup>12</sup> Still another trial studied initiation of ACE inhibitors late after MI and for long-term management<sup>6</sup> (Table 6).

**Table 6.** ACE Inhibitors in the Management of Acute MI

|   | Trial*                             |                                    |                                 |                                       |  |                                   |
|---|------------------------------------|------------------------------------|---------------------------------|---------------------------------------|--|-----------------------------------|
|   | GISSI-3 <sup>9</sup><br>(N=19,394) | ISIS-4 <sup>10</sup><br>(N=58,050) | TRACE <sup>13</sup><br>(N=1749) | SMILE <sup>8</sup><br>(N=1556)        | SAVE <sup>6</sup><br>(N=2231)          | AIRE <sup>12</sup><br>(N=2006)    |
| Patient population                      | Acute MI                           | Acute MI                           | Acute MI, LV dysfunction        | Acute MI (anterior), no history of HF | Acute MI, EF <40%                      | Acute MI, clinical evidence of HF |
| Agent                                   | Lisinopril (5-10 mg daily)         | Captopril (50 mg twice daily)      | Trandolapril (1-4 mg daily)     | Zofenopril (7.5-30.0 mg twice daily)  | Captopril (12.5-50.0 mg 3 times daily) | Ramipril (5 mg twice daily)       |
| Initiation time                         | <24 h                              | <24 h                              | 2-6 d after MI                  | <24 h                                 | 3-16 d after MI                        | 3-10 d after MI                   |
| Follow-up                               | 6 mo                               | 5 wk                               | 24-50 mo                        | 12 mo                                 | 3.5 y (average)                        | 15 mo (average)                   |
| Absolute risk reduction in mortality, % | 0.8<br>P = .02                     | 0.5<br>P = .02                     | 7.6<br>P = .01                  | 4.0<br>P = .01                        | 5.0<br>P = .02                         | 6.0<br>P = .002                   |

ACE = angiotensin-converting enzyme; EF = ejection fraction; HF = heart failure; LV = left ventricular; MI = myocardial infarction. \*See the “Acute MI” and “Pharmacoeconomic Analysis” sections of the text for expansion of the trial names.



The Trandolapril Cardiac Evaluation (TRACE) trial<sup>13</sup> studied ACE inhibitors for long-term management after MI, but in this study the medication was started early. In contrast, ACE inhibitors were initiated later after MI in the SAVE study.<sup>6</sup> Because of the inconsistency in study design, practitioners are left to speculate about the appropriate time to initiate an ACE inhibitor, in which patients to initiate therapy, and for what duration. Current recommendations by the AHA/ACC are to treat all patients indefinitely after MI; start early in stable high-risk patients (anterior MI, previous MI, and Killip class II).<sup>19</sup>

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... DIABETIC AND NONDIABETIC  
NEPHROPATHY ...

Not only have ACE inhibitors been proven to be beneficial in diabetic nephropathy,<sup>2</sup> but there is also new "hope" for the prevention of CAD<sup>14</sup> and the reduction of diabetic complications<sup>40</sup> in these patients. Patients with uncontrolled diabetes and hypertension are at risk for developing microvascular complications, including diabetic nephropathy. Proteinuria at any level will increase the risk and further the progression of nephropathy. Patients presenting with diabetes and hypertension should have a target blood pressure of less than 130/85 mm Hg and less than 120/75 mm Hg if proteinuric, which is defined as an excess of 1 g of protein excreted in urine per 24 hours.<sup>27</sup> To delay the progression of diabetic nephropathy, treatment should be aimed at controlling the diabetes as well as the hypertension. Several antihypertensive agents have been used in patients with diabetes mellitus to reach the blood pressure goal; however, ACE inhibitors have proved to be more beneficial in reducing the progression of diabetic nephropathy than other antihypertensive agents because of their renal protective effects. Several ACE inhibitors have shown these beneficial effects in clinical trials<sup>2,28-30</sup>; therefore, the renal protective effect is considered a class effect. The ACE inhibitors demonstrate a renal protective effect through a reduction in proteinuria, with resultant reduction of progression of renal dysfunction.<sup>2,30,31</sup>

The impact that ACE inhibitors have made on diabetic nephropathy has increased interest in researching the use of these agents in nondiabetic nephropathy. The Ramipril Efficacy in Nephropathy (REIN) trial observed the effects of ramipril vs placebo plus another antihypertensive agent on the primary outcomes of glomerular filtra-

tion changes and time to end-stage renal disease. Although there was no statistically significant difference in the primary endpoint, the ramipril group showed a significant reduction in the composite of progression to end-stage renal disease or proteinuria.<sup>39</sup> Maschio et al<sup>30</sup> observed the effects of benazepril hydrochloride treatment in 583 patients with renal insufficiency. Only 21 patients presented with diabetic nephropathy, whereas the other cases of renal insufficiency were due to other causes. The primary outcome of the study was a doubling of the baseline serum creatinine concentration or the need for dialysis. After 3 years of follow-up, the results revealed a significant reduction in the primary endpoint in the treatment group (n = 31) compared with those receiving placebo (n = 57) ( $P < .001$ ).<sup>30</sup> The results of the REIN trial and the trial conducted by Maschio and colleagues have shown ACE inhibitors to be effective in not only diabetic nephropathy but nondiabetic nephropathy as well.<sup>39,40</sup>

Ensuring that blood pressure is at goal will minimize the risk of progression to renal failure. It is controversial whether the renal protective effects of ACE inhibitors are due to the blood pressure-lowering effects or to another unknown mechanism of action. Other antihypertensive agents have not shown the beneficial effects of minimizing renal disease progression as have the ACE inhibitors. Because the blood pressure-lowering effects seen with non-ACE inhibitor antihypertensives do not correspond with renal protective effects, researchers<sup>2,3,40</sup> have speculated that another mechanism of action responsible for renal protection may exist.

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... ADVERSE EFFECTS AND  
CONTRAINDICATIONS ...

Despite the positive outcomes associated with the use of ACE inhibitors, contraindications exist that could potentially lead to negative outcomes. Contraindications to the use of ACE inhibitors include hypersensitivity, bilateral renal artery stenosis, angioedema, and pregnancy. The most common adverse effects include cough, hyperkalemia, and renal insufficiency. Despite the fact that ACE inhibitors are often used in nephropathy to prevent the progression of renal insufficiency, these agents can cause an initial rise in the serum creatinine level.<sup>3</sup> The ACE inhibitors are perhaps underused because of concern about renal insufficiency. Occasionally when ACE inhibitors are initiated, a

small increase in serum creatinine concentration can be observed, especially in patients presenting with a serum creatinine level greater than 124  $\mu\text{mol/L}$  ( $>1.4$  mg/dL).<sup>41</sup> However, this initial increase is usually only temporary and will often resolve or stabilize within a couple of months. The ACE inhibitors should not be used in patients with serum creatinine levels greater than 265  $\mu\text{mol/L}$  ( $>3.0$  mg/dL). Close monitoring of renal function and electrolytes is essential. Although concern exists, these agents have been shown to be beneficial in patients with a significant degree of renal insufficiency.<sup>3</sup>

#### ... PHARMACOECONOMIC ANALYSIS ...

Although clinical evidence is the determining factor in the consideration of an agent for a particular disease state, pharmacoeconomic evidence helps guide medical practice to facilitate healthcare cost reductions. Several trials are available that have evaluated the cost effectiveness of ACE inhibitors, with most focusing on heart failure and MI.<sup>42-46</sup> A few studies have focused on the use of ACE inhibitors in hypertension and diabetic and nondiabetic nephropathy.<sup>42,47-49</sup>

In conducting a literature search, several pertinent articles regarding the pharmacoeconomics of ACE inhibitors were obtained. Concerning the use of these agents in hypertension, patients enrolled in the SOLVD who presented with hypertension and left ventricular dysfunction were evaluated via a retrospective analysis on the cost effectiveness of enalapril. Patients in the trial were divided into 2 groups: the treatment group (patients with heart failure requiring medical treatment) and the prevention group (patients with left ventricular dysfunction not requiring medications). Results revealed that use of enalapril significantly reduced the risk of first hospitalization due to heart failure and other reasons for hospitalization compared with patients receiving placebo. Life expectancy was also prolonged an average of 2.14 years, with more benefit seen in the prevention group than in the treatment group. The clinical benefits were also associated with cost savings when calculated per year of life saved. The overall cost savings per lifetime for each patient treated with an ACE inhibitor was not statistically significant. However, the authors concluded that based on the clinical benefits and cost reductions, ACE inhibitors seem to be an appropriate choice for patients with hypertension and left ventricular dysfunction.<sup>42</sup> The treatment of hypertension and cost effectiveness with

ACE inhibitors is comparable to those with other antihypertensive agents; however, agents such as thiazide diuretics and  $\beta$ -adrenergic blocking agents would seem to be much more cost effective.<sup>47</sup>

Heart failure is a disease state requiring a variety of drugs for medical management and therefore is associated with high healthcare costs. The ACE inhibitors are included among these medications. Studies such as the ATLAS trial<sup>32</sup> have shown that patients receiving higher doses of lisinopril have better clinical outcomes than patients taking lower doses. This raises the question of whether ACE inhibitors are in fact cost effective at doses required for medical management of heart failure. As mentioned in the previous paragraph, patients in the SOLVD who had heart failure had significant reductions in death and hospitalization rates, therefore decreasing healthcare costs in the short term.<sup>42</sup> In the SAVE study,<sup>6</sup> ACE inhibitors significantly reduced death, hospitalization, progression of heart failure, and recurrent MI. In conducting an economic analysis with the results of the SAVE study, Tsevat et al<sup>50</sup> found ACE inhibitors to be cost effective over a wide range of ages, with the cost savings increasing directly with patient age. Another prospective study evaluating the use of clinical pharmacists and the titration of ACE inhibitors to higher doses significantly lowered healthcare costs of heart failure management through reduction in hospitalizations.<sup>51</sup> Although there are economic analyses using ACE inhibitors for the management of heart failure, it is difficult to interpret the data without direct comparison of the cost benefits associated with the different agents available.

Patients who experience an MI will also have left ventricular dysfunction or heart failure. A variety of medications are used in patients with MI, and ACE inhibitors are now being used as well because of the reduction in morbidity and mortality associated with MI.<sup>6,8-10,13</sup> Several economic analyses have been conducted evaluating the use of ACE inhibitors in these patients, with 3 primary studies observing the economic benefits of 3 different patient groups: low-risk patients in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto (GISSI-3) trial, intermediate-risk asymptomatic patients in the Acute Infarction Ramipril Efficacy (AIRE) trial, and high-risk patients in the SAVE study. The GISSI-3 trial found that treatment with lisinopril is cost effective, with more economic benefits ( $\$83$  per life saved) seen in patients older than 70 years with an anterior MI than in patients younger than 70 years with a nonanterior MI ( $\$3196$  per life saved).<sup>44</sup> The

results of the economic analysis of the SAVE study conclude that captopril administered to patients in a high- to intermediate-risk group is cost effective in terms of additional life-years gained. It has also been concluded that the use of ACE inhibitors in this particular patient population is comparable to other agents prescribed after MI.<sup>46</sup> Finally, the cost-effective analysis of the AIRE trial also found ramipril to be cost effective in patients with high-risk MI, with the benefits seen up to 3.8 years.<sup>45</sup> With the findings of all 3 economic studies, the economic benefits are seen for the early treatment of MI in all 3 risk groups, with long-term cost-effective benefits seen in certain high- or intermediate-risk patients.<sup>44-46</sup>

Finally, ACE inhibitors have also been found to be cost effective for the treatment of diabetic nephropathy<sup>48</sup>; however, only 1 economic analysis, to our knowledge, has been done to assess the use of ACE inhibitors in all patients with type 2 diabetes mellitus, including those with nondiabetic nephropathy.<sup>49</sup> This economic analysis concluded that administering an ACE inhibitor to all patients with type 2 diabetes mellitus was not cost effective.<sup>49</sup> In patients with diabetic nephropathy, ACE inhibitors have been found to be cost effective through delaying the progression of nephropathy to end-stage renal disease, which is associated with significant healthcare costs.<sup>48</sup>

Angiotensin-converting enzyme inhibitors are cost effective in a variety of disease states.<sup>44-46,50,51</sup> As more practitioners begin to use ACE inhibitors for the secondary prevention of CAD, more pharmacoeconomic analyses may become available. With many generic preparations of the ACE inhibitors currently becoming available, perhaps the cost effectiveness of using these agents will become much more apparent.

... SUMMARY ...

With the results of the HOPE trial, compelling evidence suggests that patients with established CAD could benefit from the use of ramipril and possibly other ACE inhibitors. The benefits seen in the HOPE trial seem to be related to an antiatherosclerotic mechanism of action in patients with a high risk for cardiovascular disease; however, evidence is still limited, and practitioners await future clinical trials. It is important to note that the 2001 update of the AHA/ACC guidelines recommend greater use of ACE inhibitors after MI and for patients with high-risk CAD. In addition to CAD, clinical trials have proven ACE inhibitors to be safe and effective in the treat-

ment of hypertension, post-MI, heart failure, and diabetic and nondiabetic nephropathy. Compelling positive clinical and economic evidence has prompted the increased use of ACE inhibitors. The greatest potential for growth is in the secondary prevention of CAD. The results of the EUROPA and PEACE trials, expected to be released within the next few years, should provide clinicians with more answers as to the role of ACE inhibitors in the management of CAD.

**Acknowledgment**

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**CONTINUING PHARMACY EDUCATION**



This course has been approved for a total of two (2) contact hours of continuing education credit (0.2 CEUs) by the University of Tennessee College of Pharmacy. The University of Tennessee College of Pharmacy is approved by the American Council on Pharmaceutical Education as a provider of continuing pharmaceutical education. ACPE Program Number: 064-999-02-206-H-01. This course expires May 31, 2004.

**Instructions**

After reading the article "Current Indications for ACE Inhibitors and HOPE for the Future," select the best answer to each of the following questions.

**1. Which of the following is not a contraindication to angiotensin-converting enzyme (ACE) inhibitor use?**

- a) bilateral renal artery stenosis
- b) pregnancy
- c) asymptomatic hypotension
- d) angioedema

**2. Which of the following is not a preferred indication for ACE inhibitor use?**

- a) nondiabetic nephropathy
- b) hypertension
- c) myocardial infarction (MI)
- d) all of the above are preferred indications

**3. What is the primary mechanism of ACE inhibitors in the management of heart failure?**

- a) neurohormonal inhibition
- b) hemodynamic preload and afterload reduction
- c) increase in cardiac output
- d) inhibition of the sodium/potassium adenosine triphosphatase pump

**4. Which of the following trials demonstrates the effectiveness of ACE inhibitors in the treatment of heart failure?**

- a) CONSENSUS
- b) SMILE
- c) ISIS-4
- d) GISSI-3

**5. What events were not significantly reduced in the HOPE trial?**

- a) number of newly diagnosed patients with diabetes mellitus
- b) MI
- c) stroke
- d) onset of renal insufficiency

**6. What is the target dose of captopril?**

- a) 25.0 mg twice daily
- b) 50.0 mg twice daily
- c) 12.5 mg 3 times daily
- d) 50.0 mg 3 times daily

*(CPE questions continued on following page)*

**Current Indications for ACE Inhibitors and HOPE for the Future**

ACPE Program Number: 064-999-02-206-H-01

(PLEASE PRINT CLEARLY)

Name \_\_\_\_\_

Home Address \_\_\_\_\_

City \_\_\_\_\_

State/ZIP \_\_\_\_\_

Daytime Phone # \_\_\_\_\_

States in Which CE Credit is Desired \_\_\_\_\_

Please circle your answers:

- |            |             |             |             |
|------------|-------------|-------------|-------------|
| 1. a b c d | 6. a b c d  | 11. a b c d | 16. a b c d |
| 2. a b c d | 7. a b c d  | 12. a b c d | 17. a b c d |
| 3. a b c d | 8. a b c d  | 13. a b c d | 18. a b c d |
| 4. a b c d | 9. a b c d  | 14. a b c d | 19. a b c d |
| 5. a b c d | 10. a b c d | 15. a b c d | 20. a b c d |

Please complete the Program Evaluation on following page, and send with \$15 fee, payable to University of Tennessee, to:

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University of Tennessee College of Pharmacy  
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Knoxville, TN 37902

...CPE QUIZ...

7. In the HOPE trial, which of the following was not part of the inclusion criteria?

- a) patients with an isolated systolic hypertension
- b) patients older than 55 years
- c) history of coronary artery disease
- d) patients with diabetes mellitus and 1 coronary risk factor

8. According to the ATLAS trial, ACE inhibitors:

- a) at high doses, a trend in the reduction of mortality was shown
- b) at low doses, decreased the risk of hospitalization
- c) evaluated high-dose vs low-dose enalapril administration
- d) evaluated the primary outcome of MI

9. Which of the following patients would benefit from the initiation of ramipril administration?

- a) history of coronary artery disease
- b) renal insufficiency
- c) patients with a history of hypertension
- d) all of the above

10. Which one of the following trials did not study the use of angiotensin receptor blockers in the management of heart failure?

- a) RESOLVD
- b) NETWORK
- c) CHARM
- d) Val-HeFT

11. What is the goal blood pressure for a patient with renal insufficiency, diabetes, and proteinuria?

- a) <140/90 mm Hg
- b) <130/85 mm Hg
- c) <120/75 mm Hg
- d) <120/80 mm Hg

12. Which trials studied the effects of ACE inhibitors in nondiabetic nephropathy?

- a) REIN
- b) RESOLVD
- c) CHARM
- d) ATLAS

13. Which of the following statements regarding the use of ACE inhibitors after MI is true?

- a) ACE inhibitors should be initiated in all patients after MI.
- b) ACE inhibitors are preferred within 24 hours after MI with an ejection fraction less than 40%.
- c) ACE inhibitors should be initiated within 48 hours indefinitely.
- d) ACE inhibitors should be initiated intravenously within the first few hours of MI.

14. What dose of ramipril was used in the HOPE trial?

- a) 2.5 mg daily
- b) 15.0 mg daily
- c) 10.0 mg daily
- d) 2.5 mg twice daily

(CPE questions continued on following page)

CPE PROGRAM EVALUATION (064-999-02-206-H-01)

The University of Tennessee College of Pharmacy would like to have your opinion. Please fill out the questionnaire below, tear off along the dotted line, and mail along with your CPE test form. We thank you for your evaluation, which is most helpful.

Please circle your answers:

|  |                |              |                 |                   |
|--|----------------|--------------|-----------------|-------------------|
| My pharmacy practice setting is:                               | Independent    | Chain        | Hospital        | Consultant        |
| The objectives of the lesson were achieved:                    | Yes            | No           |                 |                   |
| The quality of presentation of the material was:               | Excellent      | Good         | Fair            | Poor              |
| The information presented will be useful to me in my practice. | Strongly agree | Mildly agree | Mildly disagree | Strongly disagree |

How long did it take you to read the material and respond to the Continuing Education questions: (Please specify the number of hours.)

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...CPE QUIZ...

**15. Which 2 trials compared the effects of angiotensin receptor blockers with ACE inhibitors in the treatment of heart failure?**

- a) REIN, NETWORK
- b) ELITE , ELITE II
- c) CONSENSUS, SAVE
- d) CHARM, HOPE

**16. Which of the following statements is false?**

- a) ACE inhibitors have been shown to decrease morbidity and mortality in heart failure.
- b) ACE inhibitors are considered first-line treatment for hypertension without comorbidities.
- c) After MI, patients with an ejection fraction less than 40% can benefit from use of an ACE inhibitor.
- d) Candesartan is currently being studied for its possible antiatherosclerotic effects.

**17. Which of the following statements regarding ACE inhibitors is false?**

- a) When initiated, an initial increase in serum creatinine concentration may occur.
- b) Patients with a serum creatinine level greater than 265  $\mu\text{mol/L}$  ( $>3.0$  mg/dL) are at risk for increased renal failure.
- c) The initial rise in serum creatinine concentration will often stabilize in 2 to 3 months.
- d) ACE inhibitors are contraindicated in patients with creatinine clearance less than 0.67 mL/s ( $<40$  mL/min).

**18. Angiotensin II is responsible for all of the following except:**

- a) endothelial injury
- b) decreased systemic vascular resistance
- c) neurohormonal release
- d) vasoconstriction

**19. Inhibition of the neurohormonal process in heart failure will:**

- a) cause vasoconstriction
- b) cause ischemia
- c) prevent cardiovascular remodeling
- d) enhance cardiac output

**20. Which is true regarding the SAVE trial?**

- a) There is no significant change in risk of recurrent MI.
- b) There is an increase in the risk of stroke.
- c) A nonsignificant change in the onset of heart failure after MI was found.
- d) There is reduction in risk of death after recurrent MI.

Please fill out the University of Tennessee College of Pharmacy program evaluation that accompanies this quiz (page 492).