CME CREDIT

ONE MINUTE CONSULT

BRIEF QUESTIONS AND ANSWERS ON CURRENT CLINICAL CONTROVERSIES

Q: What are 'tissue ACE inhibitors,' and should they be used instead of other ACE inhibitors?

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A: CERTAIN ANGIOTENSIN-CONVERTING enzyme (ACE) inhibitors, particularly quinapril and ramipril, have greater tissue activity than other ACE inhibitors and have therefore been labeled "tissue ACE inhibitors."

In numerous studies, quinapril improved endothelial function to a greater extent than other ACE inhibitors with less tissue activity.[1] The reason for this is unknown.

And in one important trial, the Heart Outcomes Prevention Evaluation (HOPE)[2] study, ramipril lowered the risk of atherosclerotic events in patients without heart failure, but with known atherosclerosis or diabetes and one cardiovascular risk factor.

Thus, the question becomes: Are tissue ACE inhibitors better for patients than other ACE inhibitors?

SURROGATE END POINTS VS CLINICAL OUTCOMES

Most studies of tissue ACE inhibitors to date have been small and measured only surrogate end points such as endothelial function, ejection fraction, exercise tolerance, hemodynamic changes, and left ventricular remodeling—not clinical outcomes such as mortality or hospitalization rates. One intuitively expects that an improvement in surrogate end points would mean a better clinical outcome, but numerous examples show this does not always hold true, and the US Food and Drug Administration does not recognize improvement in surrogate end points as a reason to approve new drugs for heart failure.

Only long-term clinical outcomes carry weight. This does not mean that drugs such as quinapril or ramipril are not safe and effective, but rather that tissue ACE inhibitor activity has not been proven to affect clinical outcomes such as mortality or hospitalization rates.

Pharmaceutical companies often use studies of surrogate end points to emphasize the favorable qualities of their drug. Physicians must realize that the link between improvement in surrogate end points and clinical outcome is not established.

The HOPE trial, a study that found that a tissue ACE inhibitor had a positive effect on clinical outcomes, compared ramipril with placebo. Thus, it is not clear whether the benefit resulted from a class effect common to all ACE inhibitors, or from ramipril's ability to penetrate tissue.

Improvement in surrogate end points does not ensure improved clinical outcome

INVESTIGATING A CLASS EFFECT

With so many ACE inhibitors available, the challenge for investigators will be to determine which effects are a class effect of ACE inhibitors and which are idiosyncratic to a particular drug or subset of drugs, such as tissue ACE inhibitors.

Prevention of ischemic events in patients with left ventricular systolic dysfunction

Prevention of ischemic events in patients with left ventricular systolic dysfunction may well be a class effect of ACE inhibitors: it was observed with captopril in the Survival and Ventricular Enlargement (SAVE) trial[3] and with enalapril in both the treatment and prevention phases of the Studies of Left Ventricular Dysfunction (SOLVD) trial.[4] Neither captopril nor enalapril are considered tissue ACE inhibitors.

However, trandolapril failed to prevent ischemic events after acute myocardial infarc-

tion in the Trandolapril Cardiac Evaluation (TRACE) study,[5] in which the drug was started several days after myocardial infarction.

Prevention of ischemic events in patients without left ventricular systolic dysfunction

The tissue ACE inhibitor ramipril is the only ACE inhibitor so far shown to prevent ischemic events in patients without left ventricular dysfunction. The HOPE trial found that administration of ramipril 10 mg daily reduced the incidence of myocardial infarction, stroke, or death from cardiovascular causes, when compared with placebo. This benefit appeared independent of ramipril's ability to lower blood pressure.

However, it is unknown if this effect is unique to ramipril or might be found with other ACE inhibitors.

Two trials are underway that may help us answer this question. The Prevention of Events with ACE Inhibition (PEACE) trial is assessing whether the ACE inhibitor trandolapril can prevent myocardial infarction and other ischemic events in patients with a normal ejection fraction. The European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA) is exploring whether perindopril can prevent myocardial infarction or other ischemic events in patients with stable coronary disease without heart failure.

Some properties of ACE inhibitors appear to be a class effect

If the results of PEACE and EUROPA are positive, one might surmise that the effects of ramipril on ischemic events are likely a class effect, as the agents being used are not considered tissue ACE inhibitors. But until the results of these two studies are available, we simply do not have enough data to make a judgment.

RECOMMENDATIONS FOR ACE INHIBITOR USE PENDING FURTHER STUDIES

Assuming that all ACE inhibitors are equal is somewhat naive at this time. We simply do not yet know if the results of ramipril as described in the HOPE study can be achieved with other ACE inhibitors. On the other hand, certain properties of ACE inhibitors appear to be effective across the board, such as the prevention of ischemic events in patients with heart failure. Because many of the lesser known ACE inhibitors have not been studied in large clinical trials, we do not have sufficient data to know if they are equivalent to the more widely used ACE inhibitors such enalapril, lisinopril, captopril, and ramipril. A good rule of thumb is to prescribe the ACE inhibitor that was used in a particular trial to achieve the positive clinical outcome seen in that trial for your own patient.

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CME ANSWERS

Answers to the credit test on page 263 of this issue

1 **C** 2 **D** 3 **E** 4 **A** 5 **E** 6 **C** 7 **B** 8 **A** 9 **E** 10 **A** 11 **C**