Selecting an ACE inhibitor:

A Question of Class Effect?

All members of a drug class are not therapeutically equivalent. In recent years, the concept of class effect has been under considerable debate, largely fueled by evidence of differing efficacy and toxicity of agents within common drug classes, including the widely prescribed class of ACE inhibitors.

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Angiotensin-converting enzyme (ACE) inhibitors are commonly used drugs in the management of a variety of cardiovascular (CV) and renal disorders. In the past decade, the indications for use of ACE inhibitors have expanded considerably to include:

- hypertension,
- left ventricular (LV) dysfunction,
- heart failure,
- stable coronary heart disease,
- diabetic nephropathy and
- other vascular conditions.

Beyond their shared process of inhibiting the production of angiotensin II, ACE inhibitors differ significantly in chemical structure, pharmacology and pharmacokinetics. Differences in potency of ACE inhibition, conversion from prodrug to active metabolite, drug lipophilicity, route of elimination and duration of action have been documented. Whether or not these differences translate into differing health benefits, in the absence of large head-to-head comparative trials, requires a careful and informed analysis of the literature.

About the author...

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Principles of class effect

A universally-accepted definition of "class effect" does not yet exist, and others believe that a proper definition is not even possible. Most agree, however, that the concept of class effect is an important one to consider for all parties involved, including patients, physicians and payers.

In general, drugs are grouped into classes based upon similar chemical structure, mechanism of action or pharmacologic effect. A more clinically relevant and complete definition of class effect must include consideration of a specific drug's:

- therapeutic efficacy,
- side-effect and safety profile and
- cost-effectiveness.

Ideally, supportive evidence for each of these properties for any individual agent should also be available.

ACE inhibitors and levels of evidence

Post-MI and/or heart failure

In patients with LV dysfunction following MI and in those with symptomatic systolic heart failure, five different ACE inhibitors have demonstrated important clinical benefits vs. placebo. These include captopril, 50 mg, three times daily; enalapril, 10 mg, twice daily (bid); lisinopril, 40 mg, once daily (od); ramipril, 5 mg, bid; and trandolapril, 4 mg, od, all of which were associated with statistically significant reductions in total mortality and subsequent heart failure when individually compared against placebo. Additionally, fosinopril and quinapril have been shown to improve exercise tolerance and New York Heart Association functional class in heart failure, but have not been associated with survival benefit. Head-to-head comparisons of ACE inhibitors in these populations have not been performed.

Over 90% of cases treated with ramipril fall into either a cost-saving or cost-neutral situation.

Coronary heart disease (or equivalent) with preserved LV function

Four different ACE inhibitors have been evaluated for endpoint reduction in patients with established coronary disease and preserved LV function. In the Heart Outcomes Prevention Evaluation (HOPE) study, ramipril, 10 mg, od, was studied in a broad population of patients aged 55 years or older, all of whom either had established vascular disease in any major arterial bed, or were diabetic with additional risk factors. In this study, ramipril was associated with a significant reduction in the primary composite endpoint of CV death, MI and stroke and additionally reduced total mortality.

In the EUropean trial on Reduction Of cardiac events with Perindorpil in stable coronary Artery disease (EUROPA), perindopril, 8 mg, od, was tested in patients aged 18 years and older with established coronary disease, and was associated with a significant reduction in the composite of CV death, MI and resuscitated cardiac arrest. The Prevention of Events with Angiotensin-Converting Enzyme inhibition (PEACE) trial compared trandolapril, 4 mg, od, to placebo in subjects aged 50 or older with confirmed coronary disease, and found a non-significant reduction in the primary endpoint of CV death, MI, stroke and revascularization.

Finally, the Ishemic Management with Accupril post-bypass Graft via Inhibition of angiotensin-coNverting Enzyme (IMAGINE) study assessed the potential benefits of quinapril, 40 mg, od, started within seven days of bypass surgery in subjects with normal LV function, and failed to show any significant benefit on ischemic outcomes.

The event rates in both the PEACE and IMAGINE trials were lower than those observed in HOPE and EUROPA, likely reflecting the more contemporary evidence-based management that patients received in the later trials. Both PEACE and IMAGINE were also likely underpowered to show a true benefit.

Hypertension

Numerous studies have confirmed that ACE inhibitors are beneficial at lowering BP compared to placebo. Additionally, several large trials have compared ACE inhibitors to other antihypertensive drug classes, showing similar degrees of BP lowering and similar effects on prevention of MI and stroke. Although one study did demonstrate a significant advantage for enalapril vs. a diuretic,

no published studies have shown survival differences based upon the type of antihypertensive drug used. As well, there have been no head-to-head comparisons of ACE inhibitor effects on clinical events in hypertension.

More recently, evidence has been accumulating to suggest that ACE inhibitors form a necessary cornerstone in the management of hypertension, which usually requires two or three different agents to be effectively controlled. The Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA), comparing two different strategies of antihypertensive therapy, randomized patients to either a combination of amlodipine and perindopril or a combination of atenolol and thiazide diuretic. The amlodipine/perindopril strategy resulted in a slightly lower BP, and was associated with a significant reduction in all-cause mortality.

Diabetic nephropathy

Captopril has been shown to reduce the risk of death or progression to end-stage renal disease in patients with Type 1 diabetes. In Type 2 diabetes, a variety of ACE inhibitors are known to reduce proteinuria and stabilize renal function. However, none have been shown prospectively to reduce the risk of death, specifically in patients with diabetic nephropathy and head-to-head ACE inhibitor studies have not been performed.

However, diabetics with nephropathy in the HOPE study (Micro-HOPE) experienced similar and significant reductions in major CV endpoints with ramipril as did the overall population, as well as reductions in renal endpoints.

Cost-effectiveness of ACE inhibitors

Numerous analyses have been published suggesting that ACE inhibitors, in general, are cost-effective when compared to placebo, particularly in patients with established coronary heart disease and in those with heart failure and/or LV dysfunction. In several such analyses, ramipril and lisinopril were associated with an incremental cost between $2,000 and $5,800 (USD) per life-year gained, an extremely low additional cost compared to other widely accepted treatments in modern medicine. A detailed analysis from the HOPE study, applied to Medicare in the US and to the Canadian health-care system, revealed that > 90% of cases treated with ramipril fall into either a cost-saving or cost-neutral situation, or into a cost-effectiveness situation with an incremental cost-effectiveness ratio < $10,000 per cardiac death, MI or stroke saved.

Since ACE inhibitors have not been shown to be superior to other drugs in the management of hypertension, their cost-effectiveness in this condition remains controversial. In patients with diabetic nephropathy, ACE inhibitors are likely cost-effective given that they can prevent progression to end-stage renal disease. However, the incremental cost per life-year gained ranges from $30,000 to $80,000. This cost-effectiveness is likely underestimated, since the majority of patients with diabetes die of CV disease, and ACE inhibitors are known to exert protective effects upon the CV system.

Comparative safety profiles of ACE inhibitors

The safety profile associated with ACE inhibitors is relatively consistent.[1] In clinical trials of various ACE inhibitors compared to placebo, adverse effects have been generally mild and have seldom resulted in the discontinuation of treatment. Adverse effects, such as cough, hyperkalemia, renal dysfunction and angioedema, occur in relatively the same percentage of patients, regardless of the specific ACE inhibitor used across different trials.

However, as head-to-head comparisons of the safety profile of drugs within a class are rare occurrences, small differences between different ACE inhibitors in safety and tolerability cannot be excluded. Given the excellent safety profile and vast clinical trial evidence associated with various ACE inhibitors, it seems unlikely that significant differences in safety exist between drugs.

In perhaps the largest group of patients, those with established vascular disease, diabetes, or at high risk for developing CV disease, only ramipril and perindopril have been definitively shown to prevent CV events.

Convenience and patient compliance

It is generally accepted that once-daily dosing results in improved patient compliance compared to medications requiring more frequent dosing. With the exception of captopril, all currently available ACE inhibitors can be dosed once daily, though there still may be differences in duration of action. Since safety profiles appear to be similar between ACE inhibitors, convenience and compliance are relatively minor issues when selecting a specific ACE inhibitor (captopril excluded).

Optimal dosing

Optimal dosing of ACE inhibitors is a significant factor in determining if the drug will be associated with the anticipated clinical benefit. In the Assessment of Treatment with Lisinopril and Survival (ATLAS) trial, high-dose lisinopril (40 mg, od) was associated with greater clinical benefit on heart failure than was low-dose lisinopril (10 mg, od).

The importance of adequate ACE inhibitor dosing in heart failure was recently emphasized by Luzier,[2] who showed that the strongest predictor of readmission for heart failure was the lack of ACE inhibitor prescription at hospital discharge. Importantly, the second most powerful predictor was an inadequate prescribed dose of ACE inhibitors. In the Study to Evaluate Carotid Ultrasound changes in patients treated with Ramipril and vitamin E (SECURE), a substudy of HOPE, patients receiving 2.5 mg of ramipril demonstrated greater progression of carotid intimal medial thickness (IMT) than did patients receiving 10 mg of ramipril, despite similar reductions in BP compared to placebo. Carotid IMT is a strong predictor of CV outcome.

Determining drug differences

The average family physician likely encounters several patients per day in whom an ACE inhibitor may be considered for various conditions, ranging from hypertension to vascular diseases and heart failure. The informed clinician must weigh the overall evidence surrounding each drug's therapeutic efficacy, side-effect and safety profile, and cost-effectiveness when determining which specific agent to use for an individual patient.

In patients with confirmed coronary heart disease and preserved LV function, both perindopril,

8 mg, od, and ramipril, 10 mg, od, have clearly been shown to reduce ischemic events, including CV death, MI and stroke. Additionally, ramipril was found to similarly benefit patients with other vascular diseases, such as those with peripheral arterial and cerebrovascular disease, as well as diabetics with additional risk factors. The HOPE-TOO extension study, in which both groups received open label ACE-inhibition, largely with ramipril, confirms the early benefits of ramipril therapy in high risk patients; HOPE-TOO demonstrated a sustained 17% significant reduction in the primary endpoint over seven years of followup, as well as a significant 34% reduction in the incidence of new diabetes.

In contrast, the PEACE study failed to demonstrate a significant benefit of trandolapril on clinical outcomes in patients with coronary heart disease. Whether this was the result of study design, patient population, or drug potency or dose, cannot be determined from the PEACE study alone. A trend to fewer events was noted with trandolapril that, although not statistically significant, was certainly consistent with the ACE inhibitor studies in similar populations. Therefore, although one might conclude that the benefits in these trials support the notion of class effect, it remains entirely possible that one ACE inhibitor may exert a greater effect on clinical outcomes than another.

Wienbergen *et al.* examined the impact of treatment with ramipril vs. other ACE inhibitors in a retrospective analysis of 14,608 consecutive patients with ST-elevation acute MI. Of these patients, 4.7% received ramipril, 39% received other ACE inhibitors and 56.3% received no ACE inhibitors. Treatment with ramipril was associated with a significantly lower mortality rate and a lower rate of non-fatal major adverse coronary and cerebrovascular events compared to therapy with other ACE inhibitors. Heart failure rates were not significantly different between ramipril and the other ACE inhibitor at discharge.

Pilote *et al.* conducted a retrospective study that used hospital discharge and prescription databases containing information on over 18,000 patients 65 years or older who were admitted to hospital post-MI. In this database, ramipril use was associated with the lowest mortality rate, one that was significantly lower than treatment with enalapril, fosinopril, captopril, quinapril or lisinopril. The mortality rate associated with perindopril use was not statistically different from ramipril. Recognizing that such studies are limited by incomplete patient data and differences in background therapy and co-morbidities, both studies support the use of drugs that have already been validated in large clinical trials, specifically ramipril and perindopril.

Concluding thoughts

Although the concept of class effect is an attractive one, it is one that remains poorly defined. Comparative trials of drugs within classes are desperately needed to confirm or refute the concept of class effect, particularly after the lessons learned with statins and the risk of rhabdomyolysis.

Applying these principles to the ACE inhibitor class reveals:

- In uncomplicated hypertension, there are insufficient data to support the use of one ACE inhibitor over another.
- In LV dysfunction with/without heart failure, one may choose from many different ACE inhibitors, but attention must be paid to optimal dosing in such patients.
- In perhaps the largest group of patients, those with established vascular disease, diabetes, or at

high risk for developing CV disease, only ramipril and perindopril have been definitively shown to prevent CV events.

Despite increasing drug costs, an approach that restricts access to proven ACE inhibitors in favour of less expensive, less proven ACE inhibitors cannot be justified. PCard

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Resources

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