Commentary

Dose response of ACE inhibitors: implications of the SECURE trial

Eva Lonn

McMaster University, Hamilton, Ontario, Canada

Correspondence: Eva Lonn, lonnem@mcmaster.ca

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Abstract

The choice of the appropriate dosage of ACE inhibitor in clinical practice is an important one. The available evidence suggests that in chronic heart failure as well as in chronic coronary artery disease, high doses of angiotensin-converting enzyme (ACE) inhibitor are more effective than low ones. The current recommended clinical approach is to target ACE inhibitor dosing regimens to be similar to those used in the clinical trials, which demonstrated mortality and morbidity benefits. When titrated appropriately, ACE inhibitors are generally well tolerated and target doses can be achieved and maintained in the majority of patients with atherosclerotic vascular disease, with or without heart failure.

Keywords ACE inhibitors, atherosclerosis, coronary artery disease

Angiotensin-converting enzyme (ACE) inhibitors have been used extensively in the management of hypertension and heart failure. Recent trials, primarily the Heart Outcomes Prevention Evaluation (HOPE) study, also demonstrate a clear role for these agents in reducing the risk for adverse cardiovascular outcomes in patients without heart failure and with preserved left ventricular (LV) ejection fraction [1]. Experimental research and recent clinical studies also show favorable effects of ACE inhibitor therapy on the arterial vascular wall. The Study to Evaluate Carotid Ultrasound changes in patients treated with Ramipril and vitamin E (SECURE), a substudy of the HOPE trial, thus demonstrated reduced progression of carotid atherosclerosis in patients treated with ramipril [2]. Other investigations have revealed improved endothelial function in patients receiving ACE inhibitors [3,4].

What are 'optimal' doses of ACE inhibitors to be used in different clinical settings? This question is encountered frequently by clinicians and remains controversial. A number of surveys suggest that clinicians often prefer the use of low doses of ACE inhibitors, and the perception that low doses are as effective as high ones is quite prevalent. In addition, clinicians frequently titrate ACE inhibitor dose according to blood pressure and rely on 'adequate' blood pressure control as a marker of the effectiveness of this therapy, not only in patients treated for hypertension, but also in those treated for heart failure and for reduction of cardiovascular risk.

In this commentary, several lines of evidence have been extracted from clinical trials in chronic heart failure, coronary artery disease (CAD) and atherosclerosis to show that the size of the ACE inhibitor dose matters, higher doses are more effective than lower doses and the duration of therapy is important.

Clinical trials comparing high and low doses of ACE inhibitors in chronic heart failure

Several clinical trials in heart failure have specifically addressed the question of optimal ACE inhibitor dose (Table 1) [5–8]. With the exception of the Assessment of

ACE = angiotensin-converting enzyme; ATLAS = Assessment of Treatment with Lisinopril and Survival trial; CAD = coronary artery disease; HOPE = Heart Outcomes Prevention Evaluation study; LV = left ventricular; NETWORK trial = Network of general practitioners and hospital physicians involved in the study of low versus high doses of enalapril in patients with heart failure trial; NYHA = New York Heart Association; SECURE = Study to Evaluate Carotid Ultrasound changes in patients treated with Ramipril and Vitamin E; QUIET = Quinapril Ischemic Event Trial.

Table 1

Trials exploring ACE inhibitor dosing regimens in heart failure

Trial	ACE-I regimens (daily doses)	Major findings
NETWORK (n=1532)	Enalapril 2.5 mg bid vs 5 mg bid vs 10 mg bid Follow-up: 5.5 months	No difference in hospitalizations for heart failure; trend towards fewer deaths with increasing dose
ATLAS (n=3164)	Lisinopril 2.5–5 mg od vs 32.5–35 mg od Follow-up:46 months	Trends towards reduced total and CV mortality and significant reduction in mortality and all-cause hospitalizations for high-dose lisinopril
CHIPS (n=298)	Captopril 25 mg bid vs 50 mg bid Follow-up: 2 years	Trend towards reduced hospitalizations for heart failure and towards reduced fatal and nonfatal cardiac events for high-dose captopril
HEDS (n=248)	Enalapril 20 mg vs 60 mg Follow-up: 12 months	No significant differences in survival, clinical and hemodynamic variables

ACE-I = angiotensin-converting enzyme inhibitor; ATLAS = Assessment of Treatment with Lisinopril and Survival; CHIPS = Captopril in Heat Insufficient Patients Study; HEDS = High Enalapril Dose Study; NETWORK = Network of General Practitioners and Hospital Physicians Involved in the Study of Low versus High Doses of Enalapril in Patients with Heart Failure trial.

Treatment with Lisinopril and Survival (ATLAS) trial, these studies have been underpowered, both with regard to the number of patients studied and the duration of treatment and follow-up. Furthermore, some of these studies, such as the Network of General Practitioners and Hospital Physicians Involved in the Study of Low versus High Doses of Enalapril in Patients with Heart Failure (NETWORK) trial (which found no conclusive benefit for higher versus lower dose enalapril) enrolled mainly patients with mild, New York Heart Association (NYHA) class I heart failure. The ATLAS trial, a much larger study with adequate long-term follow-up lasting 46 months, enrolled a significant proportion (84%) of patients with more advanced, class III or IV NYHA heart failure symptoms. This study identified a significant 12% lower risk for death or all-cause hospitalization and a 24% reduction in hospitalizations for heart failure in patients treated with high-dose compared to those treated with low-dose lisinopril. The extended analysis of the ATLAS study, including patients at high risk for cardiovascular death (such as diabetics and those with LV ejection fraction of less than 25%), showed similar benefit in the combined endpoint of mortality and all-cause hospital admissions. These findings support the use of higher doses of ACE inhibitors in patients with chronic heart failure [9]. 'Very high' ACE inhibitor doses (i.e. higher than those usually employed in clinical practice) are unlikely to provide additional benefit [8].

A number of prospective observational studies have reported that heart failure patients discharged from hospital and maintained on 'high' ACE inhibitor doses had improved clinical outcomes compared to those receiving low dose therapy. The benefits included lower rates of death and re-hospitalization, thus incurring lower costs [10,11]. The ability to achieve adequate doses of ACE inhibitors for the treatment of chronic heart failure in general practice is also well documented. Studies such as the prospective evaluation by Messner Pellenc found that a daily dose of 20 mg of enalapril could be reached in a high proportion of heart-failure patients with good tolerability and improved outcomes [12].

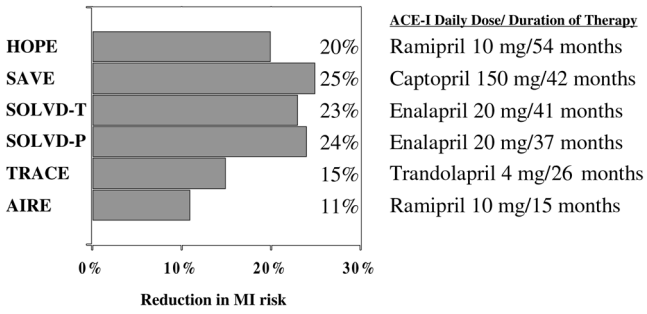
Clinical practice guidelines, published by both the Agency for Health Care Policy and Research and the American College of Cardiology/American Heart Association, reflect the findings of these studies. These recommend that when managing chronic heart failure, every effort should be made to increase the dose of ACE inhibitors to the target doses shown in clinical trials to decrease mortality and morbidity, for example at least 150 mg daily of captopril or at least 20 mg daily of enalapril or lisinopril [13,14].

ACE inhibitor dose in chronic coronary artery disease

A number of large randomized controlled clinical trials have demonstrated the beneficial effects of ACE inhibitors in coronary artery disease in patients with prior, recent or remote myocardial infarction [15–19]. Such trials have enrolled patients either with heart failure or with documented LV systolic dysfunction and, more recently in the HOPE trial, patients with preserved LV ejection fraction without heart failure symptoms. In addition to improved mortality rates and a reduction in heart-failure-related outcomes, the major randomized clinical trials of ACE inhibitors in CAD have also demonstrated a reduction in acute ischemic events. These large clinical trials have not compared different ACE inhibitor dosing regimens, but invariably used 'high' target ACE inhibitor doses. Among these studies, those with longer duration of treatment and follow-up showed more pronounced benefits (Fig. 1).

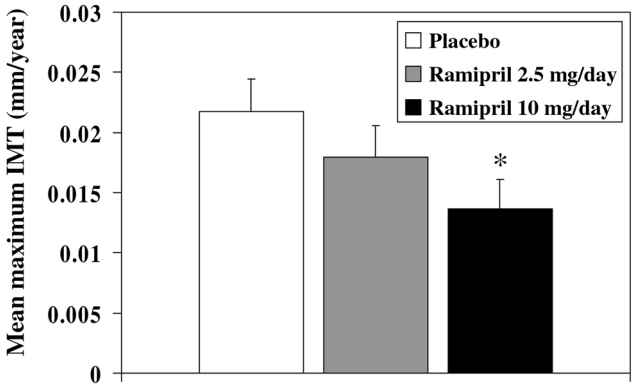
Notably, the Quinapril Ischemic Event Trial (QUIET) [20], used an intermediate dose of quinapril (20 mg daily) and failed to demonstrate a clear benefit for ACE inhibitor

Figure 1



The effect of ACE inhibitor therapy on myocardial infarction in chronic coronary artery disease. ACE inhibitor dose and duration of therapy in the major large clinical trials of ACE inhibitors in coronary artery disease are shown. Reduction in myocardial infarction risk was obtained with prolonged administration of high doses of ACE inhibitors. AIRE = Acute Infarction Ramipril Efficay study; HOPE = Heart Outcomes Prevention Evaluation study; SAVE = Survival and Ventricular Enlargement Trial; SOLVD-P = Studies of Left Ventricular Enlargement – Prevention arm; SOLVD-T = Studies of Left Ventricular Enlargement – Treatment arm; TRACE = Trandolapril Cardiac Evaluation study.

Figure 2



The effect of ramipril on carotid atherosclerosis in the SECURE trial. There was a dose-dependent benefit with reduction in atherosclerosis progression attained with ramipril whcih was more effective at the higher dose of 10 mg/day than in the lower dose of 2.5 mg/day. $P = 0.033$ overall ramipril effect. *$P = 0.028$ for ramipril 10 mg/day versus placebo. Mean maximum IMT = average of maximum intimal-medial thickness across 12 predefined carotid arterial segments.

therapy in patients with preserved LV systolic function. By contra-distinction, the Trial on Reversing Endothelial Dysfunction (TREND) substudy of QUIET, which used a higher ACE inhibitor daily dose of 40 mg of quinapril, did show significant improvement in coronary endothelial function in actively treated patients. The failure to demonstrate a statistically significant advantage for quinapril in the QUIET trial may be related to multiple factors, such as the low event rates, the inadequate sample size, the duration of the study and the suboptimal compliance. It remains possible, however, that the chosen ACE inhibitor dose may have also contributed to the overall disappointing results of this study.

In the absence of clinical trials that compare high-dose versus low-dose ACE inhibitor regimens in chronic CAD, the most prudent approach is to aim for the relatively high target doses used in the large randomized clinical trials.

Studies of ACE inhibitors in atherosclerosis

A large body of experimental evidence suggests that prolonged ACE inhibitor therapy may have beneficial effects on atherogenesis, both by inhibiting the formation of tissue and circulating angiotensin II and by bradykinin potentiation. These ACE inhibitor actions result in decreased proliferation and migration of smooth muscle cells, decreased accumulation and activation of inflammatory cells, decreased oxidative stress, and increased endothelial nitric oxide formation, leading to improved endothelial function [21]. Increased ACE activity has been demonstrated in human coronary artery lesions [22], and long-term ACE inhibitor therapy has been shown to reduce the area of atherosclerotic lesions in normotensive animal models of atherosclerosis. Interestingly, in all the experimental animal model studies of atherosclerosis that demonstrated beneficial effects of ACE inhibitors, high drug doses were used (e.g. captopril 3–25 mg/kg/day, cilazapril 10 mg/kg/day, quinapril 10 mg/kg/day) [23–26].

A number of clinical studies have evaluated the effect of ACE inhibitor therapy on the progression of atherosclerosis. The results of these studies are not fully concordant. The best demonstration of a clear effect of ACE inhibitor therapy on retarding the anatomic progression of atherosclerosis is provided by the SECURE substudy of HOPE. This study enrolled 732 high-risk patients aged 55 years or more with vascular disease or diabetes and at least one other risk factor, but without a history of heart failure or a low LV ejection fraction. Patients were randomized to treatment with 2.5 mg ramipril/day, 10 mg ramipril/day, or a placebo, and the progression of atherosclerosis was monitored by B-mode carotid ultrasound. There was an overall benefit associated with the use of ramipril. Although the study was not powered to compare the two doses of ramipril, there was a trend suggesting a dose-dependent effect with the highest benefit for the group on 10 mg ramipril/day (Fig. 2). A dose of 10 mg ramipril/day was also used in the large parent HOPE trial, where it was shown to have clear benefits on a range of clinical endpoints. Furthermore, it is notable that blood pressure lowering with the two doses of ramipril used in the SECURE trial did not parallel the effects on atherosclerosis. This finding confirms that blood pressure is not an adequate surrogate marker for determining the most effective ACE inhibitor dose, when treating either patients without hyper-

Table 2

Effect of ramipril on echocardiographic measurements of left ventricular mass and function in a substudy of HOPE

Echocardiographic variable	Placebo	Ramipril 2.5 mg/day	Ramipril 10 mg/day
Δ LVMI (g/m^2)	3.98 ± 25.23	4.15 ± 22.77	−2.02 ± 27.12*
Δ LVEF (%)	−2.02 ± 1.54	−1.54 ± 8.94	−0.17 ± 8.62†
Δ LVEDV (ml)	4.16 ± 30.89	−0.43 ± 33.3	−5.90 ± 35.17††
Δ LVESV (ml)	5.31 ± 20.49	2.90 ±17.68	−1.90 ± 18.71††
New wall motion abnormalities	31	30	23

*$P < 0.05$. † $P = 0.06$. †† $P < 0.01$. Δ refers to study-end minus baseline measurement. HOPE = Heart Outcomes Prevention Evaluation study; LVMI = left ventricular mass index; LVEF = left ventricular ejection fraction; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume.

tension or hypertensives with baseline, well-controlled blood pressure. The SECURE trial supports the notion that the effect on the vascular wall is dependent on dose, and that higher ACE inhibitor dose regimens are associated with higher benefit. Recent additional data from the echocardiographic substudy of the HOPE trial also show similar dose-dependent beneficial effects of ramipril on LV mass and function (Table 2) [27].

Conclusions

The choice of ACE inhibitor dose to be used in clinical practice remains a very important and difficult one. Although the evidence that is currently available does not clearly identify the optimal ACE inhibitor dose level to be used in different clinical settings, it suggests the following:

1. Higher doses of ACE inhibitors are better than lower doses in chronic heart failure and in coronary artery disease.
2. Duration of therapy is important. In patients with atherosclerotic vascular disease (with or without LV systolic function and with or without clinical manifestations of heart failure) prolonged therapy is associated with improved outcomes.
3. The safest and most logical clinical approach needs to be based on principles of evidence-based medicine. The currently available evidence supports the use of those specific ACE inhibitors shown to reduce mortality and morbidity in clinical trials. The target doses used in these clinical trials were 10 mg ramipril/day, 20–40 mg enalapril/day, 150 mg captopril/day, 10–35 mg lisinopril/day or 4 mg trandolapril/day. The use of other ACE inhibitors that have not been tested in large-scale clinical trials with mortality and/or morbidity endpoints, and the use of lower target ACE inhibitor doses cannot be endorsed [28].
4. There are no adequate surrogate markers to aid clinicians in the choice of the most effective ACE inhibitor dose. The use of blood pressure and even the use of clinical symptoms appear to be inadequate in determining optimal ACE inhibitor dose level.
5. High ACE inhibitor doses, when titrated appropriately, are generally well tolerated and can be achieved and maintained in the majority of patients with atherosclerotic vascular disease and/or chronic heart failure. In those who cannot tolerate target doses, the highest tolerated dose should be used.

CAD remains the main killer of men and women in our society. An aggressive approach to therapy with comprehensive risk factor modification and use of multiple drugs as well as non-pharmaceutical approaches can improve significantly both quality of life and survival in most patients. Maximizing doses of drugs that are shown to be effective is an important component of this aggressive treatment strategy and should be applied rigorously.

Competing interests

Dr Lonn received research grants and speakers honoraria from Aventis and King Pharmaceuticals.

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