

ACE Inhibitors for Reducing Global CV Risk: Evidence Against a Class Effect

by Domenic A. Sica, MD



Introduction

Cardiovascular disease (CVD) is the leading cause of death in the United States.¹ Despite advances in our understanding of CVD and its multiple risk factors, and the availability of safe and effective pharmacotherapies, according to the American Heart Association, nearly 900,000 individuals in the United States die from CVD each year.² These dismal figures indicate that there is still much more to be done in the prevention and treatment of CVD in the clinical setting.

Many patients have multiple risk factors that contribute to their overall CVD risk. The Framingham Heart Study, among many other studies, established that individual CVD risk factors behave in an additive or even super-additive fashion when combined.³ The management of an individual's global cardiovascular risk is therefore of the utmost importance, and represents the cornerstone of effective clinical practice for patients with or at risk for CVD.

An enormous amount of data concerning CVD risk assessment and risk reduction exists in the medical literature. However, not all of these data may seem applicable in a primary care setting. In this clinical bulletin, we will present data that are useful for the primary care practitioner concerning multiple risk factors for CVD. We will discuss the rationale for treating hypertension aggressively to reduce CVD risk. We will review treatment guidelines concerning prehypertension, systolic blood pressure, and nocturnal "dipping," and how each of these can affect an individual's risk for cardiovascular events. Our hope is that this paper will aid the reader in understanding how the treatment of hypertension can provide significant and multifactorial benefits to patients, and that ultimately, the reader will view evidence-based hypertension management as a stepping stone for global cardiovascular risk management.

Overview

Heart disease and stroke, the major forms of CVD in developed nations, are both primarily due to atherosclerosis and are the first and third leading causes of death, respectively, in the United States.¹ Inactivity, obesity, high blood pressure (BP), dyslipidemia, diabetes, and smoking are all modifiable risk factors for CVD and have traditionally been targeted for the primary and secondary prevention of end-organ diseases and atherosclerosis-related morbidity and mortality. The biggest gains have been made in smoking cessation, where the rate of smoking has declined from 50% to 23% in the time span from 1960 to 2000.⁴ In contrast, obesity and diabetes mellitus are increasing and have now become prominent risk factors for CVD (Figure 1).⁵

Obesity

Abdominal obesity (primarily assessed by determining waist circumference) often occurs together with a collection of cardiovascular and metabolic risk factors, namely, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol levels, high BP, and elevated fasting glucose levels. Collectively, these factors make up what is known as the metabolic syndrome. Patients with even nominal abnormalities in any 3 of these 5 areas are at greater risk for the development of both diabetes and CVD.^{4,6}

About 47 million adults in the United States (25% of the population) have 3 or more components of the metabolic syndrome, with abdominal obesity being the most common. These numbers are expected to continue to rise as the epidemic of obesity increases not only among adults but also among children and adolescents. The Centers for Disease Control and Prevention reports that approximately 17% of American children and adolescents aged 6 to 19 years old are overweight.⁷ In addition, the metabolic syndrome is becoming highly prevalent even in this age group.⁸

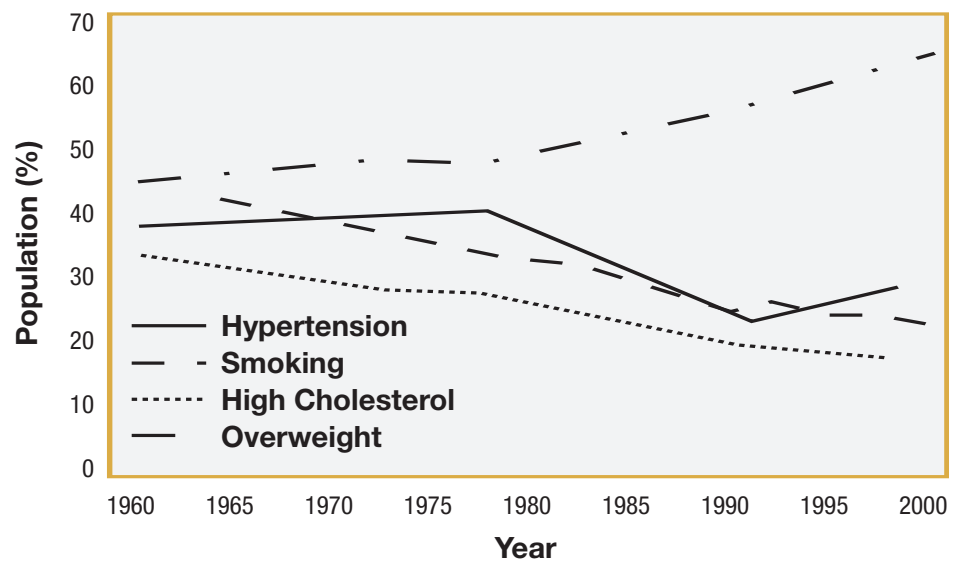


Figure 1. Prevalence of cardiovascular risk factors in US adults (1961–2000). Hypertension is defined as blood pressure $\geq 140/90$ mm Hg or current use of antihypertensive medication; high total cholesterol is defined as ≥ 240 mg/dL (≥ 6.21 mmol/L); and overweight is defined as body mass index ≥ 25 kg/m². National Institutes of Health. National Heart, Lung, and Blood Institute. *Fact Book Fiscal Year 2002*.⁵



Hypertension

Hypertension is one of the modifiable risk factors that is associated with increased CVD risk, and it is the most common primary diagnosis made in the United States. Despite our awareness of the significant morbidity and mortality associated with hypertension, control rates are still far below the Healthy People 2010 goal of 50%. In fact, 30% of individuals with hypertension in the United States are not even aware that they have it.⁹ The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) highlights the importance of achieving BP control to reduce CVD events. An increase in BP accelerates the risk for myocardial infarction, stroke, heart failure, and kidney disease. Effective BP reduction can lead to mean reductions of 20% to 25% in myocardial infarction, 35% to 40% in stroke, and >50% in heart failure.⁹ The following sections offer brief overviews of some of the most important aspects of hypertension management:

Prehypertension — For individuals 40 to 70 years of age, there is a log-linear relationship between CVD risk and BP in that CVD risk doubles with each 20/10-mm Hg BP increase above a threshold value of 115/75 mm Hg.^{9,10} This was an important consideration in JNC 7's genesis of the term "prehypertension," defined as systolic BP from 120 to 139 mm Hg or diastolic BP from 80 to 89 mm Hg.⁹ Patients with prehypertension are at considerable risk for the progression to hypertension and already appear to be at increased CVD risk. The treatment of prehypertension, however, is still a matter of some debate.¹¹

Systolic blood pressure — For much of the 20th century, the risks associated with hypertension were most commonly attributed to the level of diastolic BP. Since the mid 1990s, however, a paradigm shift has occurred, and systolic BP is now recognized as a much more significant marker of CVD risk and a more appropriate primary target of therapy than diastolic BP.^{9,10,12}

Nocturnal blood pressure — The risk of end-organ damage from high BP, such as left ventricular hypertrophy and renal disease, appears to be heightened by a "non-dipping" BP pattern (<10% decline in nocturnal vs daytime BP).^{10,13} Interestingly, non-dippers tend to have a greater than average reduction in nocturnal BP with both nonpharmacologic and pharmacologic treatment; that is, the normal nocturnal BP dip tends to be restored. The ability of an antihypertensive medication to convert a non-dipping nocturnal BP pattern to one characterized by dipping is increasingly being viewed as a clinically useful feature of a number of different antihypertensive medications.¹³

Whether certain classes of antihypertensive drugs confer benefits beyond those associated solely with their degree of BP lowering remains a heavily debated matter.

Role of BP treatment in disease state prevention — Whether certain classes of antihypertensive drugs confer benefits beyond those associated solely with their degree of BP lowering remains a heavily debated matter.¹⁴ Evidence favoring such benefits, however, has come from placebo-controlled trials of an angiotensin-converting enzyme (ACE) inhibitor, in which subjects recruited on the basis of high CVD risk (rather than high BP) experienced benefits that appeared to be greater than what would be expected from the differences in BP lowering alone.¹⁵

Current Guidelines for Treating Elevated Blood Pressure

The most appropriate clinical approach to reducing CVD risk should be based on an all-inclusive assessment of global (absolute) risk in individual patients.

Most clinical guidelines (with certain exceptions, such as those from the American Diabetes Association) focus primarily on the management of individual CVD risk factors, such as high BP, hypercholesterolemia, and diabetes. Currently, JNC 7 states that the goal BP level for healthy individuals should be less than 140/90 mm Hg; however, those with diabetes or renal disease should follow a stricter goal of less than 130/80 mm Hg.⁹ The most appropriate clinical approach to reducing CVD risk should be based on an all-inclusive assessment of global (absolute) risk in individual patients.^{16,17} It is logical that global risk be used as the main determinant of who to treat, how to treat, and how aggressively to treat. Thus, in some situations, patients at low risk for CVD with mildly elevated BP levels would not be recommended for antihypertensive drug therapy, whereas others at high global CVD risk but with lower BP would become candidates for BP-lowering treatment. Such a global-risk approach, however, goes beyond the current JNC 7 BP guidelines, and, although intuitively beneficial, would benefit from additional formal testing in clinical trials.

Hypertension Treatment Options

Many drug options are available for the pharmacologic management of hypertension. The approach currently recommended by JNC 7 suggests that a thiazide-type diuretic be the first medication used in most patients with stage 1 hypertension, but that an ACE inhibitor, an angiotensin-receptor blocker (ARB), β -blocker, or calcium-channel blocker (CCB) are also suitable for first-line use.⁹ The choice of the best antihypertensive agent for a particular patient may be affected by both demographic characteristics and, in particular, the presence of concomitant diseases. For example, an older, overweight black man will in most instances have a more robust fall in BP with a diuretic or CCB as monotherapy than he would on treatment with a β -blocker, ACE inhibitor, or an ARB.¹⁸

The presence of concomitant medical conditions also impacts the manner in which hypertension is treated, especially the choice of initial therapy. For example, a patient with hypertension who also has angina may benefit doubly from either a β -blocker or a CCB, because these drugs will treat both the angina and the hypertension. A logical choice in an elderly male with benign prostatic hyperplasia (BPH) and difficult-to-treat hypertension would be an α_1 -adrenoceptor antagonist (α_1 -blocker), because α_1 -blockers lessen BPH symptomatology and are valuable in multi-drug antihypertensive regimens.¹⁹

An ACE inhibitor or an ARB would be a suitable choice in a patient with hypertension and heart failure, high coronary risk, or proteinuria, because these agents reduce the morbidity and mortality that attend these conditions.⁹ As such, the end-organ protection features of ACE inhibitor therapy may be beneficial since these drugs are at best comparable with other drug classes (response rates from 40% to 70% in stage 1 or stage 2 hypertension), including diuretics, β -blockers, and CCBs, for BP control.²⁰

HOPE Study

The Heart Outcomes Prevention Evaluation (HOPE) study was a landmark trial employing the ACE inhibitor ramipril in a population at high risk for CVD. Study subjects were older than 55 years of age and had either established diabetes or evidence of a prior vascular event or existing vascular disease. Diabetes was an inclusion criterion in this study because, even in the absence of clinically evident CVD, it may elevate the risk of future cardiovascular events to approach that of patients with established CVD who do not have diabetes. HOPE study subjects had the following major CVD risk factors at baseline: 55% were ≥ 65 years of age, 88% had CVD, 47% had hypertension, and 38% had diabetes.¹⁵

The benefits (of ramipril) were present in all subgroups, independent of the presence or absence of diabetes, hypertension, evidence of CVD or microalbuminuria, or the use of other BP-lowering, lipid-lowering, or antihypertensive medications.

This study demonstrated that a 10-mg/d dose of ramipril reduced the combined primary outcome of myocardial infarction, stroke, or cardiovascular death by 22% vs placebo. The benefits were present in all subgroups, independent of the presence or absence of diabetes, hypertension, evidence of CVD or microalbuminuria, or the use of other BP-lowering, lipid-lowering, or antihypertensive medications. Ramipril proved particularly beneficial in patients with chronic kidney disease, reducing the onset of microalbuminuria or the progression of proteinuria. Furthermore, ramipril significantly reduced the development of new cases of diabetes, and it provided microvascular and macrovascular benefits in subjects with established diabetes.^{15,21}

Long-term Benefits in the HOPE Study

The benefits of ramipril observed during the active period of the HOPE study were studied during an additional 2.6 years of post-trial follow-up for cardiovascular death, stroke, and hospitalization for heart failure. Of the initial 267 study centers and 9297 patients, 174 centers and 4528 patients agreed to perform further follow-up. Surprisingly, despite equalization in the rates of use of ACE inhibitors in the 2 groups (72%, ramipril group vs 68%, placebo group), by the end of this follow-up trial, additional reductions in myocardial infarction, revascularization, and the development of diabetes were observed during the follow-up phase (Figure 2). These benefits were consistent regardless of patient risk or ancillary treatments.²²

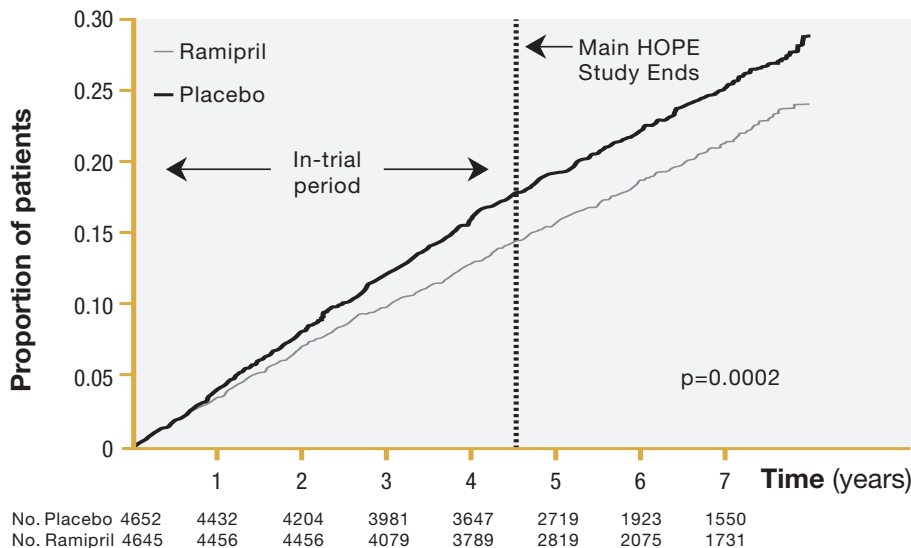


Figure 2. Kaplan-Meier estimates of the composite outcome of myocardial infarction, stroke, or cardiovascular death in the ramipril group and the placebo group in the HOPE study extension. Printed with permission from *Circulation*. 2005;112:1339-1246.²²

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ACE Inhibitors and Class Effect

The question of whether all ACE inhibitors have comparable clinical benefits (a “class effect”) has been openly debated for some time. ACE inhibitors are structurally heterogeneous and can be further distinguished by differences in rate and extent of absorption, plasma protein and/or tissue binding, half-life, and mode of metabolism and excretion. These differing pharmacologic features have been advanced as evidence against a class effect for ACE inhibitors beyond what is a common ability of ACE inhibitors to reduce BP. Thus, the concept of “class effect” may best be suited for application to the BP effects of ACE inhibitors, where scant differences exist amongst the numerous ACE inhibitors. Due to strong evidence for benefits beyond BP lowering in outcomes trials, a prudent assumption regarding ACE inhibitors is that the observed benefits derive only from the compound being tested, for the outcome being studied, and at the per-protocol dose and frequency of dosing, rather than from any ACE inhibitor at any dose, and for any outcome.^{23,24}

Evidenced-based Findings in Primary Care

The HOPE study showed substantial benefits in mortality and morbidity from the use of ramipril, which were attained over and above conventional treatment in a large group of subjects at high risk of future cardiovascular events. These results were of sufficient significance to prompt the American Heart Association to include it in its Top 10 list of annual research advances. Although the HOPE study results might seem to be broadly applicable to the use of any ACE inhibitor in clinical practice, relatively little evidence is available that other ACE inhibitors would indeed offer the same benefit; thus, the issue of evidence-based medicine arises.

To put evidence-based medicine into practice requires that the best available patient-centered research evidence be combined with individual clinical expertise, thus combining the art and science of medicine.

Evidence-based medicine is the sensible use of contemporary best evidence in making decisions about the care of individual patients. To put evidence-based medicine into practice requires that the best available patient-centered research evidence be combined with individual clinical expertise, thus combining the art and science of medicine. External clinical evidence derived from patient-centered research should be continuously subjected to careful scientific scrutiny, and conclusions and practices should be reconfigured as needed, as either confirmatory or refuting information becomes available.

Implementation of Evidence-based Findings in Clinical Practice

The HOPE Translated Into PracticeS (TIPS) study assessed the practicality and tolerability of ramipril titration to a target dose of 10 mg/d (as used in the HOPE study) in a clinical practice setting. HOPE study criteria were used to recruit 3881 patients with high CVD risk in primary and specialist care settings in 9 countries by 439 investigators. Dose titration of ramipril from 2.5 mg to 10 mg/d took place over 9 to 12 weeks. A 10-mg/d target dosage was attained in 73% of patients, with only 9.8% of patients discontinuing treatment (including 5.9% due to any drug-attributed side effects and 4% specifically related to cough). This study showed that a large majority of patients in a wide range of clinical practice settings with high CVD risk can be treated successfully with ramipril, and most can be titrated to 10 mg/d with good tolerability.²⁵

Conclusion

As the numbers of Americans with or at risk for CVD continues to rise, it becomes even more imperative that clinicians utilize strategies for effective CVD risk management. An evidence-based approach focuses on global risk assessment and a multifactorial approach to CVD risk reduction.

The HOPE study was a landmark trial, documenting the benefit of the ACE inhibitor ramipril in decreasing CVD events in high-risk patients beyond that expected from the degree of BP-lowering alone. HOPE results can be translated into clinical practice using an evidence-based approach to the management of hypertension and the reduction of multiple CVD risk factors. Although other ACE inhibitors lower BP and may have indications for use in heart failure and after myocardial infarction, they lack the full range of clinical trial evidence available for ramipril in HOPE and related trials. Furthermore, dosage and administration vary across this therapeutic class.

Despite the plethora of publications from landmark trials and clinical practice guidelines, CVD and its complications still represent a significant health problem that needs to be better addressed in the primary care setting. By making careful choices about therapy and treatment, practitioners can maximize the benefits to their patients by utilizing therapies for which there is evidence for beneficial effects beyond the numerical values of a single target.

Next Steps

In order to apply this knowledge in your practice, we urge you to strive to:

- Educate patients about the metabolic syndrome and the dangers of obesity and hypertension
- Counsel patients and their families about the benefits of lifestyle modifications to achieve BP control and to reduce global cardiovascular risk
- Target BP reduction in patients with or at risk for CVD using treatments that are proven to be safe and effective
- Reduce global cardiovascular risk by prescribing evidence-based pharmacologic therapies with established risk-reduction benefits beyond just the target risk factor
- Observe treatment guidelines concerning the treatment of prehypertension to halt progression to hypertension and otherwise reduce CVD risk

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