

Perindopril: Clinical Profile of a Unique ACE Inhibitor

Based on a presentation by Joel M. Neutel, MD

Presentation Summary

There are 3 major reasons to seek better antihypertensive agents: hypertension is often untreated, undertreated, or poorly controlled; therapy has not been successful in reducing the incidence of coronary artery disease; and hypertension is not simply a matter of high blood pressure per se, but is part of a complex inherited syndrome of cardiovascular risk factors that include decreased arterial compliance.

It is estimated that blood pressure is adequately controlled in only one quarter of the 43 million Americans with hypertension. Both lack of patient adherence to therapy and physicians' failure to treat hypertension early and aggressively contribute to poor blood pressure control.

Given this poor track record in controlling blood pressure and the multifactorial nature of hypertension, there is a growing need for new agents that are effective, simple to use, well tolerated, and formulated for once-a-day dosing. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers are useful in this regard because they block both the renin-angiotensin and bradycardic systems.

People at risk for developing hypertension—particularly those with a family history of the disease—should be identified early and managed appropriately because they tend to develop abnormalities that adversely affect endothelial structure and function long before they develop high blood pressure.

There are 3 major reasons to seek better ways to treat hypertension, according to Joel M. Neutel, MD, Chief of Clinical Pharmacology and Hypertension, VA Medical Center, Long Beach, California, and Director of Research, Orange County Heart Institute and Research Center, Orange, California. One is the fact that hypertension is

often untreated, undertreated, or poorly controlled. Two, antihypertensive therapy has not been successful in substantially reducing the incidence of coronary artery disease. Three, hypertension is not simply a disease of blood pressure levels, but is one component of an inherited syndrome of cardiovascular risk factors that include decreased arterial compliance.

Poor Blood Pressure Control

Although there are more than 100 antihypertensive agents available, many of which are very effective, hypertension is too often untreated or undertreated and blood pressure remains poorly controlled.

While awareness of hypertension increased between 1980 and 1991, there has been a disturbing downward trend ever since. According to data from the Third National Health and Nutrition Examination Survey, only 30 million of the 43 million Americans with hypertension are aware that they have the disease. Of those who are aware that they have hypertension, only 23 million are treated, and less than half of those treated achieve adequate blood pressure control.¹ "In other words, we are controlling only one quarter of our hypertensive population, and that is at the very modest goal of 140/90 mm Hg. We really should be aiming for 130/85 mm Hg or perhaps even 120/80 mm Hg," Dr. Neutel remarked.

One of the factors contributing to poor blood pressure control is lack of patient adherence to therapy—because of adverse side effects, inconvenient or complicated dosing schedules, and costs, among other reasons. Another factor is the inability of monotherapy to reduce blood pressure to recommended levels in a large percentage of patients; patients often require combinations of drugs to achieve these levels. A third factor is the failure of physicians to treat hypertension early and aggressively enough.

All of these are responsible for the disturbing trend of a growing number of hypertensive patients who are treated but whose blood pressure levels are not adequately controlled. One study, in fact, found that only 46% of men and 52% of women on active treatment had controlled blood pressure.²

"You have to remember that those patients remain at significant risk for developing coronary artery disease," said Dr. Neutel. A reanalysis of the

Multiple Risk Factor Intervention Trial [MRFIT] data demonstrated that the vast majority of hypertensive patients who go on to develop coronary artery disease have a diastolic blood pressure between 90 mm Hg and 104 mm Hg.³ "This is precisely where these inadequately treated patients fall," he explained.

Impact on Coronary Artery Disease

Simply putting patients on a drug does not protect them from disease, Dr. Neutel stressed. Rather, their blood pressures must be reduced to levels that are known to be protective, as shown by the MRFIT and Hypertension Optimal Treatment (HOT) studies. A meta-analysis of 17 different studies looking at the impact of antihypertensive therapy has shown that treatment reduced the incidence of stroke by an impressive 64%, but had little impact on coronary artery disease, reducing the incidence by only 16%.⁴

The Hypertension Syndrome

Another important reason to seek better ways to treat hypertension is the realization that hypertension is frequently only part of an inherited syndrome of cardiovascular risk factors (Figure 1).

Because the risk factors differ from patient to patient, no one drug will be appropriate for all individuals with hypertension. Moreover, since each of the components of the syndrome contributes to cardiovascular disease, it is no longer enough to treat just the high blood pressure, Dr. Neutel explained.

For example, endothelial changes in the vessels, which probably occur long before high blood pressure develops and may themselves contribute to the development of hypertension, set the stage for the development of atherosclerotic disease.

Selecting Antihypertensive Agents

The multifactorial nature of hypertension, the poor track record in con-

trolling blood pressure, and the high degree of patient in adherence to therapy must strongly influence the selection of antihypertensive agents. To have an impact on coronary artery disease, these agents should be effective, simple to use, well tolerated, and formulated for once-a-day dosing.

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers are important in this regard because they block both the renin-angiotensin and bradykinin systems, actions that would have a favorable impact on coronary artery disease, Dr. Neutel said.

Figure 1. The Hypertension Syndrome

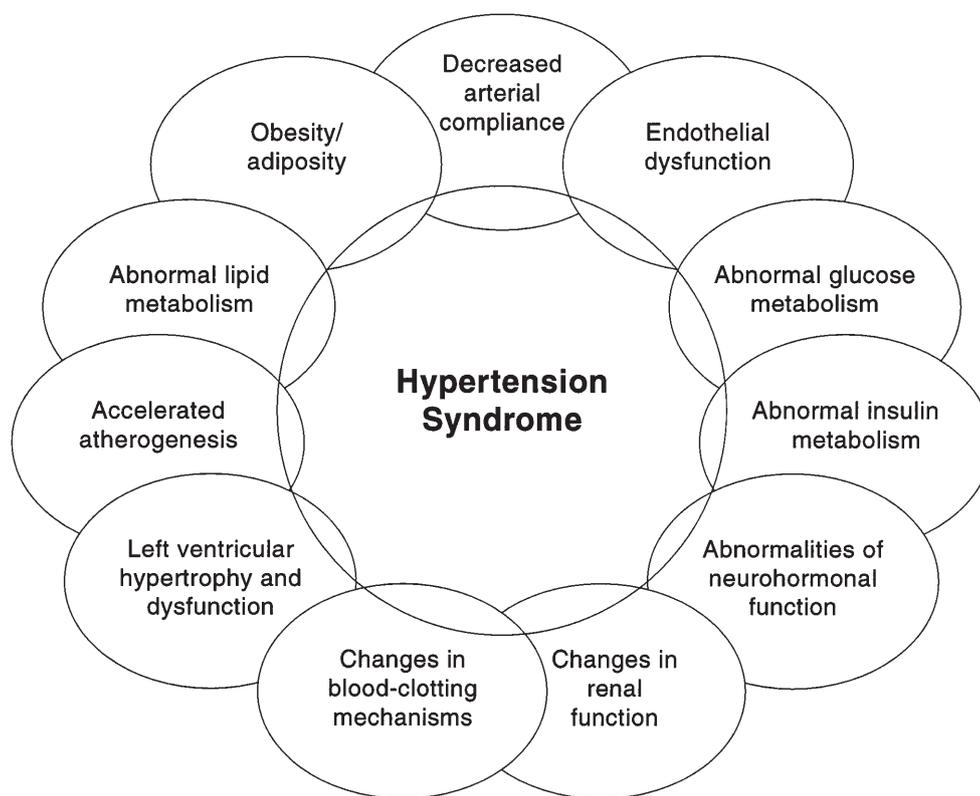


Figure 2. Calculating the Trough-to-Peak Ratio

$$\frac{\text{Trough level of drug at 24 hours minus trough level of placebo at 24 hours}}{\text{Peak level of drug at 6 hours minus peak level of placebo at 6 hours}} = \frac{-X}{-Y} = \text{_____ \%}$$

The same formula is used to calculate the trough-to-peak ratio for systolic blood pressure and for diastolic blood pressure.

Another criterion to consider when selecting an antihypertensive drug is duration of action, not only because it determines dosing frequency, but also because it determines whether a drug can provide full therapeutic efficacy for 24 hours.

Many antihypertensive drugs formulated for once-a-day dosing lose efficacy during the last 4 to 6 hours of the dosing interval. Since most patients take their medications in the morning, this loss of efficacy coincides with the early-morning blood pressure surge, when the risk of ischemic episodes and cardiovascular and cerebrovascular events is greatest. Providing adequate blood pressure control between 6:00 AM and noon would eliminate the early-morning surge in blood pressure and protect against the increased risk for ischemic events, he explained.

The Food and Drug Administration assesses 24-hour efficacy by calculating the trough-to-peak ratio for systolic and diastolic pressure, subtracting the effect of placebo. The general formula for calculating the ratio is shown in Figure 2.

Clinical Profile of Perindopril

Perindopril, an ACE inhibitor, is similar to other drugs in its class and to angiotensin receptor blockers in that these drugs are safe and efficacious. Its pharmacokinetics are outlined in Figure 3 and its side-effect profile in Table 1.

Perindopril is a very effective antihypertensive agent. It is extremely lipophilic, entering tissue very quickly, and it produces impressive reductions in blood pressure in a dose-dependent fashion. Thus far, doses of 2 mg, 4 mg, 8 mg, and 16 mg have been evaluated in clinical studies. Notably, reductions in both diastolic and systolic blood pressure are well maintained over time, particularly when compared with other agents.

In a randomized study of perindopril by Chrysant et al, sharp reduc-

tions in systolic and diastolic blood pressures occurred at 4 weeks, followed by substantial further reductions in blood pressure between 4 and 16 weeks, the end of the treatment period.⁵ "When you see that, you wonder whether it's the result of an effect on the vasculature that improves arterial compliance," Dr. Neutel said. He explained that this longer-term effect occurs with some of the ACE inhibitors and with an angiotensin receptor blocker. It is less common with calcium channel blockers, where the maximal reduction in blood pressure is achieved relatively soon and then levels off, providing little, if any, additional blood pressure reduction over time.

Using mean changes in supine systolic and diastolic blood pressure at peak (6 hours) and trough (24 hours) after dosing with 4 mg or 8 mg of perindopril versus placebo, Myers calculated the trough-to-peak ratios for perindopril according to the general formula shown in Figure 2. The ratio was 81% for systolic blood pressure and 96% for diastolic blood pressure,⁶ indicating that perindopril is very

Figure 3. Pharmacokinetics of Perindopril

■ Bioavailability	60%
■ Metabolism	Liver (small amount metabolized in plasma)
■ Half-life	1 hour
■ Half-life of active metabolite (perindoprilat)	9 - 10 hours
■ Excretion	Kidney
■ Steady state	1 week
■ Maximum % ACE inhibition	80% - 90%
■ Volume of distribution	400 L/hr

effective at trough. As such, it produces a nice, smooth reduction in blood pressure over a 24-hour period, as corroborated by 24-hour blood pressure monitoring.

Another way to look at perindopril's efficacy over 24 hours is to divide the day into various periods and look at mean office visits, 24-hour, daytime, and nighttime blood pressures. This was done by Kuwajima et al, who found that 10 weeks of therapy with 2 mg, 4 mg, and 8 mg of perindopril produced statistically significant reductions in blood pressure at all times during the 24-hour dosing interval.⁷ "This effect is undoubtedly due to the long half-life of the active metabolite of perindopril," Dr. Neutel explained. "This means that perindopril given once a day can provide 24 hours of efficacy, unlike many other ACE inhibitors."

The vascular abnormalities and hypertrophy that create the environment for atherosclerotic disease and vessel stiffness are stimulated by angiotensin II. Not surprisingly, blocking angiotensin II will provide some benefits in this regard.

One study demonstrated impressive improvements in brachial artery compliance and increases in brachial artery diameter after 4 weeks of placebo, 12 weeks of therapy with perindopril, and another 4 weeks of placebo.⁸ Values for both arterial compliance and brachial artery diameter returned to baseline within 4 weeks after stopping perindopril treatment. "The impressive effects of perindopril on arterial compliance are probably related to the drug's ability to get into the tissues and block the formation of angiotensin II," Dr. Neutel said.

Moreover, since most factors that influence the arteries influence the ventricle as well, he continued, it is not surprising that the investigators also found significant improvements in the left ventricular mass index in patients treated with perindopril.

Other randomized studies confirm perindopril's effect on vascular structure. In one, patients were randomized to 12 months of treatment with either perindopril or the β -blocker atenolol. Although the patients treated with atenolol had greater reductions in blood pressure, those treated with perindopril had significant improvements in the media-to-lumen ratio, as assessed by gluteal biopsies, when compared with the atenolol-treated patients.⁹ "This underscores that perindopril's effects are not blood-pressure dependent. Rather the changes occur in the structure of the vessel, probably as a result of angiotensin II blockade in the vessel wall," he said.

In another study, patients were randomized to 6 months of treatment with perindopril or a combination of amiloride plus hydrochlorothiazide.

Table 1. Frequency of Adverse Events (%)*

Adverse Event	Perindopril (n=789)	Placebo (n=223)
Cough	12.0	4.5
Back pain	5.8	3.1
Sinusitis	5.2	3.6
Viral infection	3.4	1.6
Upper extremity pain	2.8	1.4
Hypertonia	2.7	1.4
Dyspepsia	1.9	0.9
Fever	1.5	0.5
Proteinuria	1.5	0.5

*Events occurring in at least 1.0% of patients and at least 1.0% more common for perindopril than for placebo.

Arterial diameter (of the femoral artery) was similar following treatment in both groups, but there were significant improvements in arterial distensibility and left ventricular mass index in patients treated with perindopril despite similar changes in blood pressure.¹⁰ Other studies of perindopril have evaluated its effects in the elderly, on insulin tolerance and other metabolic parameters, and in hypertensive patients with hyperlipidemia or diabetes. In the study evaluating perindopril in 2927 patients over 70 years of age with predominantly systolic hypertension, there was a reduction in systolic blood pressure from 178 mm Hg at entry to 170 mm Hg at 1 month, 154 mm Hg at 3 months, and 150 mm Hg at 6 months. The diastolic blood pressure readings were 99 mm Hg at entry, 89 mm Hg at 1 month, 85 mm Hg at 3 months, and 83 mm Hg at 6 months.¹¹ "The slow and progressive reduction in systolic blood pressure suggests that there are some other changes occurring in these patients that may be related to the vessel wall," Dr. Neutel said.

An analysis of laboratory data from patients receiving perindopril and placebo found that the drug produced no significant changes in electrolyte or lipid levels in either group and no significant differences between the groups in insulin tolerance. Like other ACE inhibitors, perindopril had a significant protective effect on renal function.¹² Of particular note are the findings of a 6-week, placebo-controlled study by Overlack et al that demonstrated the clinical efficacy of perindopril in 3 subgroups of hypertensive patients: those with hyperlipidemia, those with diabetes who were between the ages of 40 and 65 years, and those with diabetes who were over the age of 65.¹³

Cardiovascular Risk

Even in hypertensive patients whose blood pressure has been low-

ered to normotensive levels, there is still a higher risk—about 30% higher—for cardiovascular disease and death than in people who were always normotensive (Table 2).¹⁴ This is because hypertension is only one of a number of cardiovascular risk factors that seem to be linked genetically.

Dr. Neutel described one of his own studies that evaluated a group of normotensive subjects who were the children of hypertensive adults (a mother or father who developed high blood pressure before the age of 55.)¹⁵

"It showed that the normotensive children of hypertensive parents were already different from age-matched, sex-matched, and blood-pressure-matched children of normotensive parents with regard to insulin resistance, creatinine clearance, albumin excretion, norepinephrine levels, epinephrine levels, plasma renin activity, cholesterol levels, and left ventricular mass index," he said.

Common to these abnormalities is that they all seem to have an impact on endothelial structure and function. Moreover, they occur long before these normotensive children of hypertensive parents develop high blood pressure themselves, he continued.

Table 2. Blood Pressure Control and Mortality Risk

Group	Relative Risk of Death
Normotensives	
Male	1.0
Female	1.0
Hypertensives, treated and not controlled	
Male	1.82
Female	1.97
Hypertensives, treated and controlled	
Male	1.36
Female	1.30

Source: Reference 14.

“The point is, we should be identifying these people much earlier,” he emphasized.

In another of his studies, Dr. Neutel and his coinvestigators demonstrated that proximal compliance in large vessels and reflective compliance in small vessels decreased dramatically as hypertension worsened, in other words, going from normotension to borderline hypertension to true hypertension. All of the changes in compliance in the small vessels and most of the changes in the large vessels had occurred before borderline hypertension had progressed to true hypertension.¹⁶

Dr. Neutel and his coinvestigators demonstrated that proximal compliance in large vessels and reflective compliance in small vessels decreased dramatically as hypertension worsened, in other words, going from normotension to borderline hypertension to true hypertension.

“As in the model of normotensive children of hypertensive parents, the findings suggest that changes in vascular structure occur long before the development of high blood pressure,” he said.

It is clear that hypertension remains a problem that requires new and better methods of early identification and treatment. Considering this, it would be wise for the medical community to embrace new therapies that improve things for the patient, he concluded.

... DISCUSSION HIGHLIGHTS ...

Member of the Audience: The 16-mg dose of perindopril seemed paradoxical.

Is there any explanation for that? Also, are there any studies comparing perindopril with angiotensin receptor blockers?

Dr. Neutel: The paradox that we see at the higher doses of drugs that block the renin-angiotensin system is consistent with all of these drugs. There seems to be a sigmoid-type curve and I am not quite sure why it occurs. There is an increase that flattens out and there may be another increase if you go to much higher doses. What you are seeing is exactly the same phenomenon you see at lower doses; that is, an increase between 4 mg and 8 mg, which then flattens out at the 16-mg dose. I am not sure if there are any data showing slightly greater efficacy at much higher doses.

There are some data to suggest that African-American patients, who generally do not respond well to angiotensin receptor blockers, will respond better to higher doses of these drugs. Perhaps it is another example of the sigmoid-type curve that is just a little different in various groups of patients.

There are no studies comparing perindopril with angiotensin receptor blockers. However, I think it is a very interesting comparison to study because both drugs have beneficial effects on arterial structure and function. What is even more interesting is combining the 2 drugs because there are data to suggest that they have different mechanisms of action and may act synergistically in reducing blood pressure.

Member of the Audience: How does liposolubility affect the activity?

Dr. Neutel: There is a good deal of controversy about the importance of the so-called tissue renin-angiotensin system and the circulating renin-angiotensin system. I think we underestimate the importance of the central

effects of ACE inhibitors and β -blockers as well.

There are differences in efficacy of lipophilic drugs, particularly in African-American patients, that may result from the ability of these drugs to cross the blood-brain barrier and exert central effects. We don't know very much about the central effects of these drugs, but they may be important and may explain some of the differences between the tissue and circulating systems.

Member of the Audience: Are the findings of your children's study based on ambulatory blood pressure data or casual blood pressure data? The reason I ask is that about 5 years ago we presented data at the American Society of Hypertension on uniparental hypertension, biparental hypertension, and no parental hypertension—the same as in your study. We found that you'd have the same phenomenon if you looked at the casual blood pressures. When we did ambulatory monitoring—and we did 96 hours of monitoring of these children and young adults—we found a graded dose response of parental input. We were unable to show that parental history had an independent effect on structure apart from what could be seen on ambulatory monitoring.

Dr. Neutel: We found a much greater correlation with ambulatory blood pressure than with casual blood pressure. And I should mention that the subjects in my study weren't children; they were young adults.

Member of the Audience: On one of your slides you showed that treated hypertensives became normotensive but still remained at higher risk. What was your definition of normotension in that group?

Dr. Neutel: If I remember correctly, it was 120/80 mm Hg.

Member of the Audience: The Framingham Group has recently been giving talks in which 120/70 mm Hg was cited as goal blood pressure in adults. If you look at drug development procedures, FDA drug approvals are based on statistically significant drops in blood pressure versus placebo. What the FDA has not been interested in is goal therapy.

Now, if you start to shift the goals lower and lower to 120/70 mm Hg in people who are 80 years old, what is the likelihood that you are going to be adequately treating more than single-digit figures, particularly since the clinician isn't treating in statistically significant fashion, but is left with goal therapy? It seems to me that we are going to be decreasing satisfactory treatment the lower we go because the drugs that are being developed aren't dealing with goal therapy. Yet, clinicians are giving them and now they have to go to an even lower goal pressure that is almost impossible to meet.

Dr. Neutel: You are preaching to the choir. I am a strong advocate of using combination therapy as first-line treatment in many of our hypertensive patients. I think it is impossible to reach the goal with monotherapy in at least 50% of patients, maybe even 60% or 70% of patients. Yet the FDA will not approve combinations as a first-line indication unless they have a side-effect profile that is better than that of each of their components.

That is a mistake and we all have to work towards changing it in the next few years. If we are truly going to control blood pressure, it is very hard to do it with monotherapy. I will also tell you that physicians don't titrate as frequently as we think they do.

Member of the Audience: One of your slides showed decreases in systolic and diastolic pressures. In doing the mathematics in my own mind, I came up with decreases in pulse pressure of

5 to 8 mm Hg. Is that a factor that is going to reduce cardiovascular mortality or should we be looking for greater decreases in pulse pressures in the future?

Dr. Neutel: That is a good question, and I am not sure that we have the answer. We do not know exactly how much is important and how much will have a benefit. I would imagine that the decreases will become greater. Data from The Framingham Study suggest that we should be aiming for greater decreases in pulse pressure.

Member of the Audience: Is there a tangible difference between ramipril, quinapril, and perindopril in terms of pharmacologic and pharmacodynamic effects?

Dr. Neutel: It is difficult to comment on the pharmacokinetics until there are head-to-head comparisons and we look at things like duration of action and ability to change arterial compliance. Also, there is not always a good correlation between pharmacokinetics and what you see clinically.

Member of the Audience: In one of your slides, you showed that, despite a decrease in the blood pressure, the cardiovascular risk was still higher in controlled hypertensive patients than in normotensive patients. This has little to do with blood pressure, but more to do with comorbidities since most hypertensive patients have a variety of risk factors such as advanced age, diabetes, and obesity. These risk factors are largely independent of blood pressure.

Given that the majority of hypertensives are obese, and that obesity produces left ventricular hypertrophy, it is unfortunate that none of the drugs we have can correct obesity. I don't think there will ever be an ideal drug that will eliminate all of these risk factors simultaneously.

Dr. Neutel: That is exactly the point.

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