

The following abstracts, from peer-reviewed journals containing literature on vascular compliance and hypertension, were selected for their relevance to this conference and to a managed care perspective.

Low-Dose Perindopril/Indapamide Fixed Combination

An open multicenter trial has found that a fixed low-dose combination of perindopril and indapamide is safe and effective as first-line treatment in patients with mild to moderate essential hypertension and mild to severe chronic renal failure not requiring dialysis. The trial consisted of a 2-week single-blind placebo washout period followed by 12 weeks of active treatment with a fixed-dose combination of 2-mg perindopril/0.625-mg indapamide once a day or every other day at week 0. Dosage was adjusted to 4-mg perindopril/1.25-mg indapamide at weeks 2, 4, or 8 if necessary. After 12 weeks of treatment, 14 patients were receiving 2-mg perindopril/0.625-mg indapamide daily, 3 were receiving this dose every other day, and 6 were receiving 4-mg perindopril/1.25-mg indapamide. Supine blood pressure readings decreased from 170.4±19.2/101.5±6.7 mm Hg before treatment to 146.5±19.7/86.5±10.6 mm Hg after 12 weeks of treatment. Pharmacokinetic analysis, using a population pharmacokinetic approach, was performed at week 8 and showed that the area under the curve for indapamide and perindoprilat (the active metabolite of perindopril) increased with the severity of renal failure. No interaction was noted between perindopril and indapamide. Mean serum levels of creatinine, sodium, and potassium remained stable during the study, and no significant modifications in weight or heart rate occurred. Of the 26 patients enrolled in the study, 23 completed the protocol and 3 were withdrawn: 1 for urticaria, 1 for nausea, and 1 for deterioration of renal function after vomiting and dehydration. The impairment of renal function in this patient, however, was considered unrelated to treatment.

Meyrier A, Dratwa M, Sennesael J, Lachaud-Pettiti V. Fixed low-dose perindopril-indapamide combination in hypertensive patients with chronic renal failure. *Am J Hypertens* 1998;11:1087-1092.

Therapeutic Coverage of Amlodipine vs Perindopril

The development of long-acting antihypertensive agents to permit single daily doses in an attempt to enhance compliance with therapy has focused attention on the duration of the therapeutic effect over the entire 24-hour dosing interval. Of particular interest is the antihypertensive activity over the trough period at the end of the dosing interval. Because once-a-day antihypertensive agents are generally taken in the morning, the trough effects usually coincide with the early-morning blood pressure surge when the risk of cardiovascular events is highest. In this double-blind, randomized, parallel-group, multicenter study, 47 patients with mild to moderate hypertension (diastolic blood pressure between 90 and 109 mm Hg) were allocated to treatment with amlodipine (5 to 10 mg once a day) and 49 to treatment with perindopril (4 to 8 mg once a day) for 60 days. Trough-to-peak ratios were calculated by global and individualized approaches from 24-hour ambulatory blood pressure recordings made after a 2-week placebo washout period and again after the active treatment period. Residual blood-pressure lowering after a single-blind, single-dose omission was also evaluated with further 24-hour ambulatory blood pressure monitoring. Both drugs produced comparable decreases in systolic and diastolic blood pressure between days 0 and 60. However, both systolic and diastolic blood pressures were lower 48 hours after the last dose in patients receiving amlodipine than in those receiving perindopril. In addition, the study results showed no statistically significant difference in trough-to-peak ratios between amlodipine and perindopril. Both drugs were generally well tolerated, with leg edema the most frequently reported adverse effect in those receiving amlodipine (19.1%) and cough the most common adverse effect in those receiving perindopril (14.3%).

Zannad F, Bernaud CM, Fay R, for the General Physicians Investigators Group. Double-blind, randomized, multicentre comparison of the effects of amlodipine and perindopril on 24h therapeutic coverage and beyond in patients with mild to moderate hypertension. *J Hypertens* 1999;17:137-146.

Noninvasive Early Detection of Vascular Disease

According to the authors of this article, a noninvasive technique to measure alterations in arterial pulse wave contours should be helpful in screening subjects for early evidence of vascular disease and in monitoring the response to therapy. They report the development and validation of such a technique for calculating capacitive and oscillatory systemic arterial compliance with the use of pulse wave analysis and a modified Windkessel model. In comparing the results obtained with the noninvasive pulse wave technique (radial artery) with those obtained from simultaneous intra-arterial waveform recordings (brachial artery) in 78 subjects, the authors noted a close correlation between both sets of measurements. Use of the technique in 32 subjects with hypertension and 31 age-matched controls and in 29 postmenopausal women with symptomatic coronary artery disease and 23 age-matched postmenopausal women with no evidence of vascular disease confirmed a decrease in oscillatory compliance in the disease states and an increase in both capacitive and oscillatory compliance in response to vasodilatory drugs.

Cohn JN, Finkelstein S, McVeigh G, et al. Noninvasive pulse wave analysis for the early detection of vascular disease. *Hypertension* 1995;26:503-508.

Effects of Remodeling and Hypertrophy on Arterial Compliance

In a study of 83 never-treated patients with essential hypertension (> 140 mm Hg systolic and/or 90 mm Hg diastolic) and 50 normotensive controls, investigators found that arterial compliance in hypertensives is dependent on arterial hypertrophy or remodeling pattern. Arterial compliance in the hypertensive patients was characterized either by radial artery hypertrophy (seen in 58 patients) or remodeling (seen in 25 patients), with hypertrophy defined as an increased vascular mass irrespective of the arterial wall thickness-to-radius ratio, and remodeling defined as an increased wall thickness-to-radius ratio and a normal vascular mass. Internal diameter and wall thickness of the radial artery were measured by a high-resolution echo-tracking system, and the lumen cross-section pressure curve was determined from 2 simultaneous and continuous recordings of arterial diameter and blood pressure. The cross-sectional compliance pressure curve was then calculated, and isobaric compliance was calculated at 100 mm Hg. Compared with normotensive controls, isobaric compliance of the radial artery was increased in hypertensive patients with hypertrophy but not different in hypertensive patients with remodeling. These results, say the investigators, suggest that in the presence of hypertension only arterial hypertrophy is an adaptive process leading to normal operating compliance through an increased isobaric compliance.

Mourad JJ, Girerd X, Boutouyrie P, Safar M, Laurent S. Opposite effects of remodeling and hypertrophy on arterial compliance in hypertension. *Hypertension* 1998;31(part 2):529-533.

Resistive Index, Vascular Compliance, and Vascular Resistance

To evaluate the relationship between the resistive index and both vascular compliance and vascular resistance, the authors of this report constructed an *in vitro* model that used a pulsatile pump, a blood-mimicking fluid, and variable compliance and resistance. The authors found that the resistive index was independent of vascular resistance in the absence of vascular compliance, but dependent on vascular resistance in the presence of vascular compliance, with increases in the resistive index paralleling increasing resistance. Specifically, the higher the compliance, the more the resistive index was affected by vascular resistance. The authors conclude that the resistive index is misnamed and should instead be called the impedance index because both resistance and compliance interact to alter the Doppler arterial waveform. They also acknowledge that a greater understanding of the relationship between the resistive index and both vascular compliance and vascular resistance may enable investigators involved in future studies that include both resistance and compliance to improve the detection of various pathologic conditions.

Bude RO, Rubin JM. Relationship between the resistive index and vascular compliance and resistance. *Radiology* 1999;211:411-417.

Differing Effects of Antihypertensive Agents on Large Artery Properties

In this review article describing the disparate effects of various classes of antihypertensive agents on the large arteries, the authors draw a clear distinction between two large artery properties: distensibility and compliance. Distensibility is a determinant of the pulsatile stress on the artery wall and is thought to play an important role in aging and atherosclerosis. Compliance reflects the buffering capacity of the arteries and is a major determinant of the afterload on the heart. As large arteries become stiffer in patients with hypertension, both distensibility and compliance decreases. Although a reduction in blood pressure can, by itself, improve arterial distensibility and compliance, not all antihypertensive agents produce an improvement in these properties even though they are lowering blood pressure effectively. Specifically, nonselective β -blockers, clonidine, direct vasodilators, urapidil, and some diuretics lower blood pressure but have no effect on arterial compliance. In contrast, angiotensin-converting enzyme (ACE) inhibitors, selective β -1 blockers, β -blockers with vasodilatory action, calcium antagonists, some diuretics (particularly thiazides), ketanserin, and nitrates lower blood pressure and improve large artery compliance. The authors cite a recent study in which the ACE inhibitor perindopril produced greater improvement in large artery distensibility and compliance than the combination diuretic amiloride/hydrochlorothiazide. It thus seems likely, the authors note, that the action of perindopril consists of an indirect effect (reduction in blood pressure) as well as a direct effect on large artery properties. The same study also found that perindopril reduced the afterload on the heart to a greater extent than amiloride/hydrochlorothiazide by a more pronounced decrease in systemic vascular resistance and by an increase in large artery compliance.

Van Bortel LMAB, Kool MJF, Spek JJ. Disparate effects of antihypertensive drugs on large artery distensibility and compliance in hypertension. *Am J Cardiol* 1995;76:46E-49E.

Hypertension as a Syndrome of Cardiovascular Risk Factors

Hypertension is more than elevated systolic and diastolic pressure, but a complex inherited syndrome of cardiovascular risk factors that contribute to heart disease in patients with high blood pressure, say the authors of this report. The risk factors included in the hypertension syndrome are lipid abnormalities, insulin resistance, changes in renal function, endocrine changes, obesity, prothrombotic tendencies and abnormalities of coagulation factors, left ventricular hypertrophy and diastolic dysfunction, and adverse changes in vascular structure and arterial compliance. Furthermore, an increasing body of evidence indicates that elevated blood pressure may be a late manifestation of this disease process. This is the case in many patients whose high blood pressure was preceded by some or all of the associated cardiovascular risk factors. Accordingly, the realization that hypertension is a syndrome may have some important implications for effective management. Specifically, the authors point out the need to diagnose these patients early in the disease process and treat them appropriately.

Neutel JM, Smith DHG. Hypertension: Where have we gone wrong and how can we fix it? *Am J Hypertens* 1998;11:150S-157S.

Risk Factor or Disease Marker?

As the authors of this review article note, it is a matter of debate whether reduced vascular compliance is a risk factor for cardiovascular disease (by preceding its development) or a disease marker (ie, occurring as a consequence of established cardiovascular disease). In presenting data for both cases, they point to hypertension, where abnormalities in vascular compliance might be both a risk factor and a disease marker. For example, alterations in arterial wall tone and structure increase blood pressure, which results in reduced arterial compliance, a marker for hypertension. On the other hand, decreased compliance due to sclerotic changes in vessels arising from diseases that may or may not raise blood pressure becomes a risk factor for the development of hypertension. The authors review the structural and functional determinants of vascular compliance, methods to estimate compliance, the effect of selected cardiovascular drugs on compliance, cardiovascular risk factors and vascular compliance, and diseases associated with abnormalities in vascular compliance. Arterial compliance decreases with age and is reduced in hypertension, atherosclerosis, and diabetes. Whether abnormal compliance results from a disease process or a primary vascular wall abnormality, it may help explain inconsistencies in the natural history of the disease processes. Moreover, if reduced compliance occurs before clinical manifestations of disease are apparent, it could be helpful in identifying patients at risk, thereby permitting earlier and more cost-effective preventive treatment. As the authors point out, abnormalities in vascular compliance may represent a way of improving risk stratification, which will, in turn, improve the cost-benefit effect of preventive therapy.

Glasser SP, Arnett DK, McVeigh GE, et al. Vascular compliance and cardiovascular disease. A risk factor or a marker? *Am J Hypertens* 1997;10:1175-1189.

Pulse Pressure and Recurrent Events

Pulse pressure, which is related to conduit vessel stiffness, is strongly linked to subsequent cardiac events after myocardial infarction (MI) in patients with impaired left ventricular function, say the authors of this report. Their conclusion is based on an evaluation of this relationship between baseline pulse pressure measured by sphygmomanometry 3 to 16 days after MI and adverse subsequent events in 2231 patients enrolled in the Survival and Ventricular Enlargement (SAVE) trial. SAVE was a randomized, double-blind, placebo-controlled trial designed to determine whether long-term treatment with captopril would improve survival in patients with significant left ventricular dysfunction but no overt heart failure after MI. In this evaluation, increased pulse pressure was associated with increased age, female sex, left ventricular ejection fraction, history of prior MI, diabetes, and hypertension, and the use of calcium channel blockers and digoxin. Over a period of 42 months, 503 deaths, 422 cardiovascular deaths, and 303 MIs occurred; pulse pressure was significantly related to each of these endpoints as a univariate predictor. After controlling for age, left ventricular ejection fraction, mean arterial pressure, gender, treatment arm (captopril or placebo), smoking history, history of prior MI, diabetes, or hypertension, and treatment with β -blockers, calcium channel blockers, digoxin, aspirin, or thrombolytic agents, a multivariate analysis revealed that pulse pressure was a significant predictor of total mortality and recurrent MI. The relative risk for total mortality was 1.08 per 10-mm Hg increment in pulse pressure. The relative risk for recurrent MI was 1.12.

Mitchell GF, Moyé LA, Braunwald E, et al, for the SAVE Investigators. Sphygmomanometrically determined pulse pressure is a powerful independent predictor of recurrent events after myocardial infarction in patients with impaired left ventricular function. *Circulation* 1997;96:4254-4260.

Risk Stratification of Treated Hypertensives

Although long-term control of blood pressure can be achieved in a general population, cardiovascular disease events still account for most of the morbidity and mortality among these treated hypertensives, say the authors of this report. In this prospective cohort study of participants in a worksite-based antihypertensive treatment program (1973 through 1994), the authors sought to define the distribution and determinants of cardiovascular disease events among the participants and to stratify them into risk groups on the basis of pretreatment clinical profiles. They studied 8690 systematically treated patients who had at least 6 months of followup (average, 5.7 years) and, at study entry, a systolic blood pressure of ≥ 160 mm Hg or a diastolic blood pressure of ≥ 95 mm Hg. After 1992, the blood pressure level required for study entry was $\geq 140/90$ mm Hg. Blood pressure control was achieved by the first year of therapy and maintained through 18 years. In nearly 50,000 person-years of followup, there were 468 cardiovascular disease events, which accounted for 68% of all deaths in the cohort. A risk stratification scheme was then constructed. The authors selected 5 pretreatment factors—history of heart attack, stroke, diabetes, age ≥ 55 years, and pulse pressure ≥ 60 mm Hg—to stratify patients into 4 groups. The 2999 patients with no risk factors were at low risk, the 3042 with 1 risk factor were at moderate risk, the 2237 with 2 risk factors were at high risk, and the 412 with 3 or more risk factors were at very high risk. These results demonstrate that it is possible to stratify patients according to the likelihood of subsequent events, despite adequate blood pressure control, on the basis of readily identifiable pretreatment factors. They also suggest that such a risk stratification scheme could help physicians target more aggressive therapy to patients at higher risk for subsequent cardiovascular events.

Alderman MH, Cohen H, Madhavan S. Distribution and determinants of cardiovascular events during 20 years of successful antihypertensive treatment. *J Hypertens* 1998;16:761-769.

Economic Value of Antihypertensive Medications

This paper assessed the economic value of antihypertensive medications by comparing the likelihood of coronary heart disease and stroke events and subsequent event treatment costs. The study used duration of blood pressure reduction to profile event risk reduction of 3 antihypertensive medications. Clinical data were used to determine the duration of blood pressure reduction achieved with use of 2 angiotensin-converting enzyme inhibitors and one angiotensin II receptor antagonist. Trough-to-peak ratios were used to calculate the reduction in risk of coronary heart disease and stroke events associated with each medication. The researchers found that different medications can be assessed across a number of different estimates of event treatment costs and population sizes. The method used for assessing the economic value of antihypertensive medications can be applied to other drug classes and can be further refined by integrating patient population and other risk-related data.

Roth MS, Davenport RC, Simpson W. Assessing the economic value of antihypertensive medications. *Am J Manag Care* 1998;4:1267-1275.