Hypertension in older persons is characterized by increased systolic blood pressure, and isolated systolic hypertension (ISH) is the most common type of hypertension in this population. It is thought that ISH results from age-associated vascular stiffening and reduced compliance that can be revealed and quantified by analysis of arterial pressure waveforms. Evaluation of pulse wave velocity and other related measures has shown that arterial stiffness increases with advancing age and other cardiovascular (CV) risk factors including hypertension, the metabolic syndrome, diabetes, obesity, hypercholesterolemia, and elevated C-reactive protein. Many of these relationships have been demonstrated in patients without clinical CV disease and are independent of patient age. Arterial stiffness is significantly and independently associated with both target organ damage and increased risk for CV morbidity and mortality. The mechanisms underlying age- and disease-related arterial stiffening are not fully understood. However, assessment of changes in gene expression associated with increased arterial stiffness and gene polymorphisms that increase the risk for vascular stiffening suggests that components of the renin–angiotensin system, matrix metalloproteinases, intracellular signaling, and extracellular matrix components may all be involved in this process. Interventions aimed at these targets may reduce vascular stiffness, lower systolic blood pressure, decrease the prevalence of ISH, and improve outcomes for patients (particularly older patients) with hypertension or other CV conditions. Am J Hypertens 2004;17:39S–48S © 2004 American Journal of Hypertension, Ltd.

Key Words: Arterial stiffness, augmentation index, pulse wave velocity, aging, hypertension, obesity, diabetes, hypercholesterolemia.
disease (CVD) including systolo-diastolic hypertension. Measurement of arterial pressure waveforms in hypertension and related conditions increases the information about underlying disease and risk, because it provides the aortic systolic pressure and PP that the heart experiences, which is more informative than peripheral BP. This article reviews analysis of the pulse waveform and indices derived from it, such as augmentation index (AIx) and PWV; the effects of arterial stiffening on end-organs and survival; the relationships between arterial stiffening and well-known CV risk factors; and cellular mechanisms that may be involved in decreasing the elasticity of the wall of conduit arteries. It also briefly summarizes interventions that may affect, slow, or reverse arterial stiffening and reduce the associated CV risk.

Pulse Wave Analysis, AIx, and PWV

Although DBP and mean arterial pressure decrease progressively along the arterial tree, the pulsatile component, PP, increases from central arteries (aorta) to peripheral vessels as a result of the summation of the incident and the reflected waves along central and peripheral arteries (Fig. 1). As mentioned earlier, reflections of the pulse wave occur along the vascular tree at anatomic sites that have not been located and as a result of changes in the impedance as vessels branch out. One of the main sites of wave reflection may be the smaller resistance arteries. As these reflected waves race back, they sum with the advancing wave and distort it, resulting in paradoxically increasing systolic pressure as the waves progress from the origin of the aorta to peripheral vessels. Also as a result, the waveform is different in the aorta and in the periphery. Pulse pressure increases by 18% to 31% between the aortic arch and the brachial artery in younger individuals. However, as a consequence of aging, stiffer vessels result in acceleration of both the advancing and the reflected waves. The reflected waves occur earlier and go back along the aorta at greater speed, arriving not in diastole but in systole. Consequently, summation of the advancing and reflected waves occurs earlier in the cardiac cycle and amplifies the aortic systolic pressure. Amplification of PP thus changes dramatically with age (Fig. 1). In younger individuals, the summation of the forward and the backward wave at each point of the arterial tree results in progressive elevation of SBP in peripheral arteries. The more rapid pulse wave

FIG. 1. Propagation of the PP wave from central to peripheral arteries in patients 24, 54, and 68 years of age. In older patients, the more rapid propagation of PW reduces PP amplification, resulting in nearly identical central and peripheral BP. From ref. 8, reproduced with permission. PP = pulse pressure; PW = pulse wave.
propagation in older persons results in less amplification of PP from central to peripheral blood vessels, as the reflected waves have occurred earlier and traveled back faster and increased the peak aortic pressure, which is closer or similar to that in the periphery⁸ (Fig. 1).

The AIx is a hemodynamic measure related to arterial stiffness. It is defined as the increment in pressure from the first systolic shoulder to the peak pressure of the aortic pressure waveform expressed as a percentage of the peak pressure. The AIx is thought to be primarily determined by the intensity and timing of reflected waves. The central arterial PW is composed of a forward traveling wave generated by LV ejection and the later-arriving reflected wave from the periphery. As stiffness of arterial walls increases, transmission velocities of both forward and reflected waves increase. This causes the reflected wave to arrive earlier in the central aorta and augments pressure in systole, as mentioned earlier here. The increase in pressure related to the arrival of the reflected wave determines the AIx. The AIx reflects the load placed on the LV due to wave reflection, is a surrogate marker for arterial stiffness, and is thought to have a significant association with CV risk.⁹,¹⁰

Pulse wave velocity is the velocity of the PW along the arterial tree (measured with the time difference between the electrocardiographic R wave and the arrival of the wave to the carotid and a lower limb vessel, and the distance between the sites of measurement). Like AIx, PWV is considered to be an accurate measure of central vascular stiffness. There is a linear correlation between PWV and AIx in many studies, and both parameters increase with advancing age⁹ (Fig. 2). However, AIx is influenced by the level of BP, heart rate, gender, age, height (shorter individuals exhibit a greater AIx),¹¹,¹² and vasoactive drugs independent of changes in stiffness. In contrast, PWV is independent of these factors and relates to Young’s modulus of thin-walled elastic tubes. Thus, the two measures cannot be considered as interchangeable markers of vascular stiffness.⁹ The AIx is obtained by a transfer function that allows derivation of the aortic pulse waveform from a peripheral vessel (radial or carotid arteries). Questions have been raised as to the precision of the calculated AIx as a result of the variability of the transfer functions for each individual.¹³ Measurement of AIx is dependent on higher-frequency signals than BP, and the transfer function may be less precise and may have greater variability at these high frequencies. This also results in underestimation of central systolic pressure and overestimation of central diastolic pressure. In some studies, correlation of AIx and PWV is accordingly low, and the latter appears to be a more precise measure of the stiffness of central blood vessels. Some investigators have suggested that AIx could be replaced by simple calculation of central aortic pressure, which may be more precise than the derived aortic pulse waveform used to calculate AIx, or even direct determination of AIx from the peripheral pulse.¹⁴

Relationship Between Markers for Arterial Stiffness and Other Risk Factors for CVD

Results from a number of recent studies have demonstrated significant correlations between measures of arterial stiffness and other well-established risk factors for CVD.

Hypertension

Not surprisingly, there is a strong correlation between arterial stiffness and the incidence of hypertension. Liao et al measured carotid arterial elasticity by high-resolution
B-mode ultrasonography and expressed their results as adjusted arterial diameter change. Peterson’s elastic modulus, Young’s elastic modulus, and β stiffness index. They also assessed the incidence of hypertension (defined as SBP ≥160 mm Hg, DBP ≥95 mm Hg, or use of antihypertensive medication). Both sets of measures were taken from 6992 normotensive men and women 45 to 64 years of age at baseline who were enrolled in the population-based Atherosclerosis Risk in Communities (ARIC) Study and followed for 6 years. Adjusted cumulative incident rates of hypertension from the highest to the lowest quartiles of arterial elasticity, when measured by adjusted arterial diameter change, were 6.7%, 8.0%, 7.3%, and 9.6%, respectively. Study results indicated that each standard deviation decrease in arterial elasticity was associated with a 15% increase in the risk for hypertension, independent of other established risk factors and baseline SBP. These investigators suggested that the loss of arterial elasticity in large and medium arteries and the resulting adverse effects on target organs such as the kidneys may be responsible for the relationship between greater arterial stiffness and increased risk for hypertension that was observed in the ARIC cohort.15

Results from a more recent study also suggest that reduced aortic elasticity, as reflected by increased PP, may play a primary role in the development of hypertension. Mitchell et al16 used calibrated tonometry and pulsed Doppler to assess arterial stiffness and pulsatile hemodynamics in 128 patients with uncomplicated systolic hypertension and 30 age- and gender-matched normotensive patients in the control group. The PWV was assessed using tonometry and body surface measurements. Characteristic impedance (Zc) was calculated from the ratio of change in carotid pressure and aortic flow in early systole. Hypertensive patients had higher PP than patients in the control group; this was primarily attributable to higher Zc, which accounted for nearly one-half of the excess PP in men and more than two-thirds in women. Increased Zc in hypertensive patients was attributable to decreased effective aortic diameter. It should be emphasized that aortic diameter was not measured directly, which has generated some criticism of these results. These findings were considered to be consistent with the view that aortic function may play a primary active role in the pathophysiology of systolic hypertension. They also argue against the possibility that aortic degeneration, dilation, and wall stiffening develop secondary to hypertension. All of these results support the view that central aortic stiffness may be an attractive target for therapies aimed at reducing hypertension, particularly ISH.

**Obesity**

Obesity—a well-known risk factor for CVD—is related to arterial stiffness. Results from one recent correlational study that included 186 young adults (20 to 40 years old) and 177 older patients (41 to 70 years old) indicated that aortic stiffness, as reflected by PWV, was significantly correlated with higher body weight, body mass index (Fig. 3), waist and hip circumferences, and waist–hip ratio. These relationships were independent of patient age, SBP, ethnicity, and sex. One of the most important observations from this study was the early age at which a significant relationship between obesity and arterial stiffness became apparent. Obese individuals as young as 20 to 30 years of age had a PWV 47 cm/sec higher than that of age-matched nonobese patients. This corresponds to an increase in vascular stiffness associated with a 5-year increase in age and a plateau in middle age.17 Obesity was not associated with further increases in vascular stiffness in elderly patients.

**Metabolic Syndrome**

The clustering of CV risk factors referred to as metabolic syndrome is very common. Recent analysis of results from the Third National Health and Nutrition Education Survey (NHANES III) indicated that the age-adjusted prevalence of metabolic syndrome in the United States is 23.7%. The prevalence of the metabolic syndrome increases from 6.7% among persons 20 to 29 years of age to 43.5% among those 60 to 69 years old.18 Presence of the metabolic syndrome is an independent predictor of increased arterial stiffness. In the Baltimore Longitudinal Study on Aging analysis of 471 participants without clinical CVD and not receiving antihypertensive therapy, the metabolic syndrome was defined as three or more of the following: impaired glucose tolerance, hypertension, dyslipidemia, or obesity. The presence of the metabolic syndrome resulted in a disproportionate increase in carotid stiffness, as determined by B-mode ultrasonography, in multiple regression models that included age, gender, smoking, low-density lipoprotein cholesterol (LDL-C), and each individual component of the metabolic syndrome as continuous variables.19
Diabetes

Pulse wave velocity is significantly increased in patients with diabetes. Assessment of 397 individuals with diabetes and 174 individuals without this disease indicated that at any SBP, Doppler-derived aortic PWV was higher in patients with diabetes than in patients in the control group (Fig. 4). Moreover, PWV was an independent predictor of all-cause and CV mortality for the individuals enrolled in this trial. These results support the view that PWV is a powerful independent predictor of mortality across the entire spectrum of glucose tolerance. In a multivariate analysis, PWV displaced SBP from the list of other independent risk factors. This suggests that PWV may reflect a final common pathway on which BP and other risk factors operate to increase CV risk.

Schram et al also demonstrated that both peripheral and central arterial stiffness increase with deteriorating glucose tolerance status. They evaluated total systemic arterial compliance, aortic AIX, and carotid-femoral transit time (inversely related to PWV) in a population-based study of 261 individuals with normal glucose metabolism, 170 with impaired glucose metabolism, and 188 with type 2 diabetes. After correction for sex, age, heart rate, height, body mass index, and mean arterial pressure, type 2 diabetes was associated with decreased total systemic arterial compliance, increased aortic AIX, and decreased carotid-femoral transit time. Impaired glucose metabolism was also correlated, albeit less strongly, with decreased total systemic arterial compliance. These results are consistent with the view that deteriorating glucose tolerance is associated with a general increase in arterial stiffness that may explain, at least in part, the increased risk for CVD associated with both impaired glucose tolerance and diabetes.

Hypercholesterolemia

Assessments of the relationships between lipid profile abnormalities and arterial stiffness have produced somewhat variable results. Dart et al measured plasma cholesterol and indices of arterial stiffness, including AIX, systemic arterial compliance, and transverse expansion of the aortic arch (aortic distensibility) in 868 men and women 65 to 84 years of age who participated in the Australian National BP2 study. Multiple regression analysis indicated no significant associations between stiffness parameters and total cholesterol (TC) or high-density lipoprotein cholesterol (HDL-C). Toikka et al reported a significant positive correlation between the HDL-C/TC ratio and carotid artery compliance (as measured by ultrasonography) and negative correlations between oxidized LDL-C and compliance for both the carotid artery and the ascending aorta (as measured by magnetic resonance imaging) in a small cohort of healthy men 29 to 39 years of age. As in the study of Dart et al, aortic elasticity was not related to standard lipid variables. These results suggest that oxidative modification of LDL-C may play a role in the alteration of arterial wall elastic properties and that changes associated with this process are apparent in healthy young men.

In contrast to the results summarized in the preceding paragraph, Wilkinson et al reported that aortic PP, PWV, and AIX were all significantly higher in patients with hypercholesterolemia than in individuals with normal TC levels.

C-Reactive Protein

C-reactive protein (CRP) is a new marker that has been proposed to be a sensitive index for increased CVD risk, although it is not proven to be cardiac- or vascular-specific. In a recent correlational study that included 427 individuals free of clinically apparent CVD, diabetes, and hypercholesterolemia, there was a significant positive correlation between CRP and brachial and aortic PWV and PP. These correlations suggest that inflammation may be involved in arterial stiffening, and that this process may be ongoing in individuals without other clinically evident CVD.
Arterial Stiffness as a Predictor of Morbidity and Mortality

Target Organ Damage

Increased arterial stiffness is significantly associated with target organ damage. These relationships have been demonstrated for both the heart and the kidneys.

Pressure load is a stimulus for LV hypertrophy, and this is particularly true for aortic systolic pressure and PP. Results from 276 patients (79 normotensive and 197 otherwise healthy hypertensive individuals) who underwent echocardiography to assess LV structure, along with carotid ultrasound and applanation tonometry to determine the pressure-independent arterial stiffness index, \( \beta \), and pressure-dependent elastic modulus, indicated clear relationships between variables related to arterial stiffness and LV hypertrophy. Elastic modulus was significantly correlated with LV mass. The \( \beta \) index was inversely related to chamber diameter and directly related to LV relative wall thickness and to the ratio of wall thickness to chamber radius.26

Patients with end-stage renal disease have increased aortic stiffness. Aortic PWV is a strong independent predictor of overall and CV mortality in this population.27 It has also been suggested that arterial stiffness may be significantly related to renal function in normotensive and hypertensive populations.28 This view is supported by results from a study of 1290 patients with normal or elevated BP and plasma creatinine values \( \leq 130 \) \( \mu \)mol/L. These patients were divided into three tertiles according to the calculated creatinine clearance: for each group the BP, aortic PWV, and standard CV risk factors were determined. Elevated aortic PWV was significantly associated with reduced creatinine clearance in patients in the lowest tertile for this measure. This relationship was independent of mean BP, plasma glucose and cholesterol, obesity, and smoking habits and was stronger in younger (\( \leq 55 \) years of age) than in older patients. In a subset of untreated hypertensive patients enrolled in this trial, creatinine clearance was independently and positively correlated with common carotid artery compliance. All of these results support the conclusion that increased stiffness of central arteries is significantly and independently associated with evidence of kidney damage in patients with mild-to-moderate renal insufficiency.29

Cardiovascular Morbidity and Mortality

Aortic stiffness, as reflected by aortic PWV, has been shown to be an independent predictor of CV and all-cause mortality in patients with hypertension. Laurent et al.30 followed a cohort of 1980 patients with essential hypertension who underwent measurement of carotid–femoral PWV at study entry. The mean patient age at the time of enrollment was 50 years and the average follow-up was 112 months. During this period, there were 107 fatal events with 46 of CV origin. The PWV was significantly correlated with all-cause and CV mortality (Table 1). Odds ratios for all-cause and CV mortality for a 5 m/sec increment in PWV were 2.14 and 2.35, respectively. The increased CV risk with higher PWV was independent of previous CVD, age, and diabetes. The PP was not independently associated with all-cause mortality and was only marginally associated with CV mortality.

Aortic stiffness is also an independent predictor of primary coronary events in patients with hypertension. The predictive value of arterial stiffness for coronary heart disease (CHD) was assessed in 1045 patients who had essential hypertension but no other CVD. Aortic stiffness was determined from carotid–femoral PWV, and the risk of CHD was calculated using the Framingham equations. Mean age at entry was 51 years and the average follow-up was 5.7 years. Study results showed that coronary events (fatal and nonfatal MI, coronary revascularization, and angina pectoris) and all CV events were significantly related to increasing PWV (Table 2). The relative risks (RR) for CHD and CV events associated with an increase in PWV of 3.5 m/sec were 1.42 and 1.41, respectively. In the multivariate analysis, after adjustment for Framingham risk score, PWV remained significantly associated with the occurrence of coronary events.31

Mechanisms Leading to Stiffening of the Blood Vessel Wall

Gene Expression

The molecular mechanisms underlying the development of vascular stiffness are largely unknown. It is generally believed that the composition and structure of the extracellular matrix and cell-matrix interactions are critical.

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Table 1. Relative risk (odds ratios [OR]) for cardiovascular (CV) mortality according to pulse wave velocity (PWV) and other risk factors (modified from ref. 30)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>OR</th>
<th>Lower 95% CI</th>
<th>Higher 95% CI</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>PWV (5 m/sec)</td>
<td>2.35</td>
<td>1.76</td>
<td>3.14</td>
<td>(&lt;.0001)</td>
</tr>
<tr>
<td>Previous CVD (yes/no)</td>
<td>14.81</td>
<td>7.98</td>
<td>27.47</td>
<td>(&lt;.0001)</td>
</tr>
<tr>
<td>Age (10 y)</td>
<td>2.32</td>
<td>1.78</td>
<td>3.01</td>
<td>(&lt;.0001)</td>
</tr>
<tr>
<td>PP (10 mm Hg)</td>
<td>1.53</td>
<td>1.31</td>
<td>1.80</td>
<td>(&lt;.0001)</td>
</tr>
<tr>
<td>SBP (10 mm Hg)</td>
<td>1.26</td>
<td>1.12</td>
<td>1.42</td>
<td>(&lt;.0001)</td>
</tr>
<tr>
<td>Diabetes (yes/no)</td>
<td>4.23</td>
<td>1.96</td>
<td>9.15</td>
<td>(&lt;.001)</td>
</tr>
</tbody>
</table>

CI = confidence interval; CVD = cardiovascular disease.
determinants of arterial stiffness, but the signaling cascades involved in these processes are not fully understood. Durier et al33 attempted to relate arterial stiffness, as reflected by PWV analysis, to gene expression in tissue samples from the ascending aortas of patients undergoing bypass surgery. Patients were classified as having either a distensible or stiff aorta, and gene expression determined by mRNA analysis was compared in these two groups. A total of 35 genes had expression patterns that correlated with PWV (Fig. 5). These included protein phosphatase-1, catalytic subunit, β isoform (PPP1Cβ), also known as the catalytic subunit of myosin light-chain phosphatase, and Yotiao, an A kinase anchor protein. Several genes were also expressed in an all-or-none pattern, including protein kinase C–isoform (PKC₁). This kinase has been reported to be involved in long-term, sustained contractions and could be an important determinant in arterial stiffness. There were also relationships between extracellular matrix molecules and aortic stiffness. Expression of integrins α₂b, α₆, β₁, and β₂ differed between stiff and distensible aortas. The α₂b and α₆ integrin transcripts were present in all samples from stiff aortas and were absent in all samples from distensible aortas. Expression of proteoglycans and related proteins also differed between stiff and distensible aortas. Dermatopontin, neuroglycan-C, and osteomodulin gene transcripts were less abundant in stiff aortas compared with distensible aortas, whereas decorin and aggrecan transcripts were more abundant.

**Specific Genotypes**

**Renin–Angiotensin System** Results from clinical and experimental studies have suggested that actions of the renin–angiotensin system (RAS) may contribute to the development of arterial stiffness by altering the extracellular matrix in the vascular media. Elevated levels of angiotensin-converting enzyme (ACE) have been observed in individuals with increased thickness of the carotid wall. Benetos et al36 recently evaluated relationships between genetic polymorphisms for the ACE insertion/deletion (I/D) genes and angiotensin II type 1 receptors (AT₁) and aortic stiffness in patients with hypertension. Their study enrolled 134 patients with never-treated hypertension who underwent measurement of carotid–femoral PWV and assessment of ACE I/D and AT₁ genotypes. Arterial stiffness was significantly increased in patients with AT₁ CC homozygotes versus AT₁ AC heterozygotes and AT₁AA homozygotes. There was also a trend toward decreased PWV in patients with higher numbers of ACE D alleles.

A more recent and much larger study has confirmed the relationship between the ACE D gene and arterial stiffness. Results from 3001 patients ≥55 years old included in the Rotterdam study indicated that individuals with the ACE I/D and DD genotypes had significantly greater carotid stiffness than did patients with the II genotype. Medley et al determined whether a common promotor polymorphism (5A/6A) associated with differences in MMP-3 activity (the 5A allele has greater promoter activity than the 6A allele) was correlated with age-related arterial stiffening. They evaluated the MMP-3 5A/6A genotype in 203 patients with low CV risk and related it to ascending

### Table 2. Relative risk (RR) for primary coronary heart disease (CHD) and cardiovascular (CV) events according to pulse wave velocity (PWV), Framingham risk score, and classic CV risk factors (modified from ref. 31)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>RR</th>
<th>Lower 95% CI</th>
<th>Higher 95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PWV (3.5 m/s)</td>
<td>1.42</td>
<td>1.10</td>
<td>1.82</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>FRS (4 points)</td>
<td>1.51</td>
<td>1.10</td>
<td>2.05</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Age (10 y)</td>
<td>1.42</td>
<td>1.12</td>
<td>1.81</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Hypercholesterolemia (yes/no)</td>
<td>2.49</td>
<td>1.38</td>
<td>4.48</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>2.32</td>
<td>1.14</td>
<td>4.76</td>
<td>&lt;.02</td>
</tr>
<tr>
<td>All CV events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PWV (3.5 m/sec)</td>
<td>1.41</td>
<td>1.17</td>
<td>1.70</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>FRS (4 points)</td>
<td>1.57</td>
<td>1.25</td>
<td>1.98</td>
<td>&lt;.0001</td>
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<tr>
<td>Age (10 y)</td>
<td>1.47</td>
<td>1.23</td>
<td>1.76</td>
<td>&lt;.0001</td>
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<tr>
<td>SBP (10 mm Hg)</td>
<td>1.12</td>
<td>1.02</td>
<td>1.22</td>
<td>.015</td>
</tr>
<tr>
<td>PP (10 mm Hg)</td>
<td>1.16</td>
<td>1.02</td>
<td>1.32</td>
<td>.019</td>
</tr>
<tr>
<td>Hypercholesterolemia (yes/no)</td>
<td>1.73</td>
<td>1.09</td>
<td>2.76</td>
<td>.017</td>
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<tr>
<td>Diabetes (yes/no)</td>
<td>2.16</td>
<td>1.21</td>
<td>3.84</td>
<td>&lt;.01</td>
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<tr>
<td>Gender (male/female)</td>
<td>1.64</td>
<td>1.02</td>
<td>2.62</td>
<td>.036</td>
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</tbody>
</table>

CI = confidence interval; CVD = cardiovascular disease; FRS = Framingham risk score; PP = pulse pressure; SBP = systolic blood pressure.
aortic input impedance. Older (≥61 years of age) 5A/5A homozygotes had higher aortic impedance than heterozygotes, whereas there was no difference in the younger group. These results support the view that the MMP-3 genotype may be an important determinant of vascular remodeling and age-related arterial stiffening. Medley et al also evaluated the relationship between MMP-9 genotype (C-1562T promoter polymorphism) and arterial stiffness in 84 patients with CHD. Carotid applanation tonometry was used to assess central BP, and Doppler velocimetry was used to determine aortic stiffness. Individuals who were T-allele carriers (CT and TT) had stiffer large arteries and higher carotid PP and SBP than did those who were CC homozygotes. In aortic samples, MMP-9 gene expression was fivefold higher and active protein levels were more than twofold higher in T-allele carriers.

**Potential Interventions to Decrease Arterial Stiffness**

Some drugs have the potential to reduce arterial stiffness and could be used to decrease the severity of this CV risk factor. These include the following: agents that increase vascular levels of nitric oxide (NO) and enhance endothelial function (eg, isosorbide dinitrate, sinitrodil, nebivolol, cycletanine); drugs that interfere with deleterious extracellular matrix remodeling (eg, agents that interfere with the actions of the RAS); aminoguanidine derivatives that inhibit collagen cross-linking promoted by advanced glycation endproducts (AGE) (eg, AGE formation inhibitors); thiazolium derivatives that break AGE cross-links (eg, AGE cross-link breakers); and medications that decrease sodium-associated arterial stiffness (eg, thiazide diuretics, indapamide, spironolactone).8

**Conclusions**

The results summarized and discussed in this review indicate that increased stiffness of large arteries is closely associated with aging and is responsible for the very high prevalence of ISH in older individuals. One important conclusion that can be drawn is that arterial stiffness is also related to a large number of CV risk factors including hypertension, obesity, the metabolic syndrome and diabetes, hypercholesterolemia, and elevated CRP, among others. Many of these relationships have been demonstrated in patients without clinical CVD and are largely independent of patient age. Arterial stiffness is also significantly
associated with both target organ damage and increased risk for CV morbidity and mortality.

Although the etiologies of age- and disease-associated arterial stiffening are not completely understood, it is clear that multiple mechanisms contribute to this process. Assessment of changes in gene expression associated with increased arterial stiffness and genetic polymorphisms that increase the risk for this condition suggests that a wide range of molecules, including components of the RAS, intracellular signaling, extracellular matrix components, and MMP may be involved in the cascade of events that results in arterial stiffening. The large number of molecules likely to be involved in arterial stiffening suggests that there should be many potential targets for interventions aimed at stopping or even reversing this process. Agents that reduce vascular stiffness may contribute to lower SBP, decreased prevalence of ISH, and improved outcomes for patients with hypertension or other CV conditions.

References


