Aortic Pressure Augmentation Predicts Adverse Cardiovascular Events in Patients With Established Coronary Artery Disease

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Abstract—Pulse pressure (PP), a marker of arterial stiffness, predicts cardiovascular risk. We aimed to determine whether augmentation pressure (AP) derived from the aortic pressure waveform predicts major adverse cardiovascular events (MACE) and death independently of PP in patients with established coronary artery disease (CAD). We prospectively followed-up 297 males undergoing coronary angiography for 1186 ± 424 days. Ascending aortic pressure tracings obtained during catheterization were used to calculate AP (difference between the second and the first systolic peak). Augmentation index (AIx) was defined as AP as a percentage of PP. We evaluated whether AP and AIx can predict the risk of MACE (unstable angina, acute myocardial infarction, coronary revascularization, stroke, or death) and death using Cox regression. All models evaluating AP included PP to assess whether AP adds to the information already provided by PP. Both AP and AIx significantly predicted MACE. The hazard ratio (HR) per 10 mm Hg increase in AP was 1.20 (95% confidence interval [CI], 1.08 to 1.34; $P<0.001$); the HR for each 10% increase in AIx was 1.28 (95% CI, 1.11 to 1.48; $P=0.004$). After adjusting for other univariate predictors of MACE, age, and other potential confounders, AP remained a significant predictor of MACE (HR per 10 mm Hg increase=1.19; 95% CI, 1.06 to 1.34; $P=0.002$), as did AIx (adjusted HR, 1.28; 95% CI, 1.09 to 1.50; $P=0.003$). AP was a significant predictor of death (HR per 10 mm Hg increase=1.18; 95% CI, 1.02 to 1.39; $P=0.03$). Higher AIx was associated with a trend toward increased mortality (HR=1.22; 95% CI, 0.98 to 1.52; $P=0.056$). Aortic AP predicts adverse outcomes in patients with CAD independently of PP and other risk markers. (*Hypertension*. 2005;45:980-985.)

Key Words: arterial stiffness ■ cardiovascular events ■ coronary angiography ■ coronary artery disease ■ prospective study

Increased arterial stiffness has been shown to correlate with coronary risk factors.[1–4] In addition, measures of arterial stiffness correlate with the presence of angiographic coronary artery disease (CAD).[5–7] An increased pulse pressure (PP), which has been associated with increased arterial stiffness, is an adverse cardiovascular risk predictor.[8–10] The pressure waveform of the proximal aorta is affected by arterial stiffness and likely to be more informative than the pulse pressure alone.

The central aortic pressure wave is composed of a forward-traveling wave generated by left ventricular ejection and a later-arriving reflected wave from the periphery.[1–4] As aortic and arterial stiffness increase, transmission velocity of both forward and reflected waves increase, which causes the reflected wave to arrive earlier in the central aorta and augment pressure in late systole. Therefore, augmentation of the central aortic pressure wave is a manifestation of wave reflection. This can be expressed in absolute terms as the augmented pressure (AP), or as a percentage of PP as the augmentation index (AIx). AIx has been shown to be predictive for the presence of CAD[5–7] and has been shown to predict adverse outcomes in patients with end-stage renal disease.[11] However, whether central pressure augmentation can predict adverse outcomes independently of PP and angiographic severity of CAD in patients with established coronary disease is unknown.

In this study, we aimed to determine whether AP and AIx can predict the incidence of major adverse cardiovascular events (MACEs) or all-cause mortality in patients with angiographic CAD.

Methods

Study Population

We studied a cohort of 420 male veterans undergoing clinically indicated coronary angiography at the Miami Veterans Administration Medical Center between October 1998 and February 2000. The study was approved by the Hospital's Institutional Review Board and written informed consent was obtained from all patients. For this study, only subjects with coronary artery stenosis on angiography of
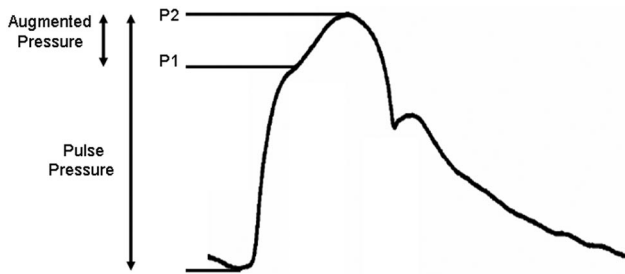
Figure 1. Representation of a central aortic pressure waveform and calculation of the augmentation pressure and pulse pressure. The augmentation index is the augmentation pressure expression as a proportion of the pulse pressure.

>10% were included and those with more than mild valvular heart disease were excluded.

A full demographic and clinical characterization was performed at study entry. Data recorded included age, ethnicity, height, weight, peripheral blood pressure, ejection fraction (EF) (measured by ventriculography at the time of coronary angiography or echocardiography within 1 month of the date of cardiac catheterization), current smoking, previous myocardial infarction, history of peripheral vascular disease, congestive heart failure, diabetes mellitus, stroke, or revascularization procedures (coronary artery bypass surgery or percutaneous coronary intervention), and family history of CAD. The indication for cardiac catheterization and the medications that patients were receiving at that time were also recorded. Brachial blood pressure values were based on a single cuff pressure taken in the recumbent position the morning before cardiac catheterization.

Angiographic Studies
Coronary angiography was performed and images of the coronary tree were obtained in routine standardized projections. The number of coronary vascular territories with at least one 50% or greater diameter stenosis before percutaneous or surgical coronary revascularization was used as an index of CAD severity (0-vessel, 1-vessel, 2-vessel, or 3-vessel disease). Left main lesions were categorized as 2-vessel disease.

Laboratory Analysis
Peripheral blood samples were collected just before the cardiac catheterization. Blood was allowed to clot for 30 minutes at room temperature and serum collected after centrifugation. Serum samples were stored in aliquots at −80°C until analyzed. Total cholesterol and triglycerides (Roche Diagnostics) and high-sensitivity C-reactive protein (Dade-Behring) levels were determined. High-density lipoprotein lipids were measured after precipitation of apolipoprotein B−containing lipoproteins.[12] Very-low-density lipoprotein and low-density lipoprotein cholesterol were estimated by calculation.

Pulse Waveform Analysis
Central aortic pressure was recorded invasively via a low-compliance fluid-filled catheter positioned in the ascending aorta. The system was inspected for the presence of bubbles or clots before pressure recordings. Only waveforms that were technically adequate on visual inspection were included in the analysis; waveform analysis was performed manually. The analyzer of the pressure waveforms was blinded to the outcome and all clinical and laboratory variables. Similarly, the assessment of outcomes during follow-up was blinded to variables derived from waveform analysis. The merging point of the incident and the reflected wave (inflection point) was identified on the aortic pressure waveform. The first and second systolic peaks (P_1 and P_2) of the aortic pressure waveform were analyzed (Figure 1). AP was calculated as the difference between the second and first systolic peaks ($P_2 - P_1$). AIx was defined as AP expressed as a percentage of PP. When the inflection point could not be identified (because of superimposition of the incident

and reflected wave, which occurred in 27.9% of cases), an augmentation pressure of zero was assigned. To assess the reproducibility of manual calculation of the AIx, 12 consecutive beats were analyzed in 15 patients. The average coefficient of variation in these analyses was 8.8%.

Because arterial elasticity is not constant but instead depends on its distending pressure, the mean arterial pressure (MAP) was incorporated into all models including AP or AIx, so that anticipated effects of distending pressure can be differentiated from real differences in the elasticity of the arterial wall.[13] Similarly, AIx reflects the interaction between ventricular ejection and the properties of the arteries,[6,14] and it can be affected by changes in left ventricular systolic function. Heart rate can also influence pulse wave velocity and central pressure augmentation.[14–16] Therefore, the EF and heart rate (RR interval preceding the cardiac cycle in which the AP was calculated) were included in all models evaluating AP or AIx. In addition, PP was included in all models evaluating AP. By means of adding AP to models already containing PP, one can estimate hazard ratios (HRs) for different levels of AP after adjustment for PP and, importantly, test whether the addition of AP to a model already

TABLE 1.   Baseline Characteristics of Study Subjects

Characteristic (n=297)	Value
Age, y (±SD)	63.8±10.3
Body height, m (IQR)	1.75 (1.70–1.80)
Heart rate, bpm (IQR)	70 (63–76)
Augmentation index, % (IQR)	5.06 (0–10)
Current smoking, %	90 (30.3)
Diabetes mellitus, %	105 (35.4)
History of hypertension, %	270 (90.1)
Total cholesterol, mg/dL (IQR)	173 (145–207)
LDL cholesterol, mg/dL (IQR)	94.6 (73.2–117.2)
HDL cholesterol, mg/dL (IQR)	35 (29.5–43)
Triglycerides, mg/dL (IQR)	190 (142–242)
Creatinine, mg/dL (IQR)	1.1 (0.9–1.4)
CRP, mg/dL (IQR)	0.46 (0.19–1.09)
Aortic SBP, mm Hg (IQR)	136 (120–150)
Aortic diastolic blood pressure, mm Hg (IQR)	70 (65–80)
Aortic pulse pressure, mm Hg (IQR)	65 (50–80)
Congestive heart failure (%)	44 (14.81)
Ejection fraction, % (IQR)	50 (35–60)
Medications (%)	
Nitrates	143 (48.2)
β-blockers	181 (60.9)
Angiotensin-converting enzyme inhibitors	138 (46.4)
Aspirin	193 (65)
Calcium channel blockers	79 (26.6)
Statins	131 (44.1)
Diuretics	68 (22.9)
Digoxin	43 (14.5)
Vessels with >50% stenosis (%)	
0	37 (12.5)
1	68 (22.9)
2	61 (20.5)
3	131 (44.1)

CRP, C-reactive protein; IQR, interquartile range; LDL, low-density lipoprotein.

TABLE 2. Univariate Predictors of Major Adverse Cardiovascular Events (n=297)

Predictor	Hazard Ratio (95% CI)	P
Diastolic blood pressure (per 10-mm Hg increase)	0.83 (0.71–0.96)	0.01
Diabetes mellitus	1.56 (1.10–2.21)	0.01
Current smoking	1.63 (1.13–2.34)	0.009
Congestive heart failure	1.94 (1.29–2.91)	0.002
Left ventricular ejection Fraction (per 10% increase)	0.86 (0.77–0.95)	0.005
Digoxin use	1.68 (1.10–2.57)	0.02
C-reactive protein (per mg/dL increase)	1.08 (0.99–1.18)	0.07
Aspirin use	0.68 (0.47–0.96)	0.03
Vessels affected with significant (>50%) luminal stenoses	1.17 (0.99–1.38)	0.07

containing PP significantly improves the predictive ability of the model (ie, whether AP adds significant prognostic information to that already provided by PP). Finally, given that age and height affect wave reflections, these variables were included among the potential confounders in multivariate analyses.

Definitions of Events and Follow-Up

Events were documented by patient interview and review of electronic hospital records. The primary combined endpoint was the first occurrence of any of the following MACEs: death from any cause, myocardial infarction, unstable angina, revascularization with either percutaneous coronary intervention or coronary artery bypass graft surgery (if these procedures were not a direct result of the angiographic findings during the index cardiac catheterization), and stroke. The secondary endpoint was death from any cause. The diagnosis of myocardial infarction was performed by the presence of suggestive symptoms, with either electrocardiographic evidence (new Q waves in 2 or more leads) or cardiac marker evidence of infarction, according to the standard Thrombolysis In Myocardial Infarction (TIMI) and American College of Cardiology definition. Unstable angina was defined as ischemic discomfort at rest for at least 10 minutes prompting rehospitalization, combined with one of the following: ST-segment or T-wave changes, cardiac marker elevations that were above the upper limit of normal but did not meet the criteria for myocardial infarction, or a second episode of ischemic chest discomfort lasting >10 minutes and that was distinct from the episode that had prompted hospitalization.

Statistical Analysis

Normally distributed continuous variables are expressed as mean±standard deviation. Non-normally distributed continuous variables are expressed as median (interquartile range). Proportions are expressed as counts and percentages. Univariate and multivariate survival analyses were performed with Cox regression. Analyses were performed separately for MACE and all-cause mortality. Multivariate analysis was performed incorporating all univariate predictors of the outcome and other potential confounders. All probability values are 2-tailed. Values of $P<0.05$ were considered statistically significant. All analyses were performed with the statistical package NCSS for Windows (Kaysville, Utah).

Results

Among the 420 patients who signed the informed consent, 360 had CAD. Nine patients were excluded from this study secondary to significant valvular disease. Out of the 351 remaining patients, acceptable pressure waveforms on visual inspection were available in 312 subjects. Fourteen patients
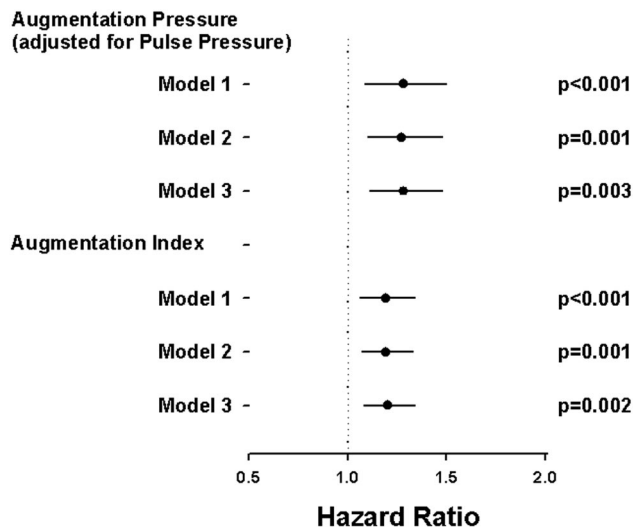
Figure 2. Augmentation pressure and augmentation index as predictors of major adverse cardiovascular outcomes. Hazard ratios and 95% confidence intervals for each 10-mm Hg increase in augmentation pressure (adjusted for pulse pressure) or 10% increase in augmentation index (AIx). Both augmentation pressure and AIx were adjusted for mean aortic pressure, heart rate, and ejection fraction in all models. Model 2 also included univariate predictors of major adverse cardiovascular events shown in Table 2. Model 3 included variables in model 2, age, height, and other potential confounders (angiotensin-converting enzyme inhibitor, β-blocker, statin use, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol).

were lost to follow-up and 1 patient died 1 day after cardiac catheterization and was excluded from the analysis. The final analysis was performed with data from 297 patients. The baseline characteristics of our patient population are shown in Table 1.

Predictors of MACE

The mean follow-up among patients who did not have a MACE was 1186±424 days. During the follow-up period, 43.1% of patients had a MACE. Univariate predictors of MACE are shown in Table 2.

Augmentation Pressure and MACE

Absolute augmentation pressure significantly predicted MACE (Figure 2). There was a 20% increase in the risk of MACE for every 10 mm Hg increase in augmentation pressure (95% confidence interval [CI], 8% to 34%; $P<0.001$). This indicates that AP added significant prognostic information to that already provided by PP. After adjusting for univariate predictors of MACE (Table 2), AP significantly predicted MACE (adjusted HR per 10 mm Hg increase=1.19; 95% CI, 1.07 to 1.33; $P=0.001$). After also adjusting for age, height, and other potential confounders (angiotensin-converting enzyme inhibitor, β-blocker, statin use, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol), AP remained a significant predictor of MACE (adjusted HR per 10 mm Hg increase=1.19; 95% CI, 1.06 to 1.34; $P=0.002$).

AIx as a Predictor of MACE

AIx significantly predicted the risk of MACE (Figure 2). There was a 28% increase in the risk of MACE for every 10%

TABLE 3.   Univariate Predictors of All-Cause Mortality (n=297)

Predictor	Hazard Ratio (95% CI)	P
Diastolic blood pressure (per 10-mm Hg increase)	0.74 (0.60–0.93)	0.01
Peripheral vascular disease	1.96 (1.1–3.51)	0.02
Diabetes mellitus	1.98 (1.18–3.31)	0.009
Congestive heart failure	3.03 (1.74–5.28)	0.0001
Left ventricular ejection fraction (per 10% increase)	0.70 (0.59–0.82)	<0.0001
Aspirin use	0.55 (0.32–0.93)	0.02
Hematocrit (per point increase)	0.92 (0.88–0.96)	0.0006
Statin use	0.54 (0.31–0.93)	0.03
Digoxin use	2.62 (1.47–4.68)	0.001
Serum creatinine (per mg/dL increase)	1.15 (1.01–1.31)	0.03

increase in AIx (95% CI, 11% to 48%; $P<0.001$). After adjusting for univariate predictors of MACE (Table 2), AIx remained a significant predictor of MACE (adjusted HR per 10% increase=1.27; 95% CI, 1.10 to 1.48; $P=0.001$). After also adjusting for age, height, other potential confounders (angiotensin-converting enzyme inhibitor, β-blocker, statin use, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol), the correlation between AIx and MACE persisted (adjusted HR=1.28; 95% CI, 1.09 to 1.50; $P=0.003$).

Aortic Pressures and MACE

Interestingly, centrally measured diastolic blood pressure was a predictor of MACE; for every 10 mm Hg increase in aortic diastolic blood pressure, the HR was 0.83 (95% CI, 0.71 to 0.96; $P=0.01$), indicating that *lower* aortic diastolic blood pressure values were associated with a *higher* risk of MACE in our population. As expected, aortic diastolic blood pressure closely correlated with mean aortic blood pressure ($r=0.71$; $P<0.0001$); therefore, we did not include aortic diastolic blood pressure in the models described (which included the MAP) to avoid problems with colinearity. To test whether AP or AIx predict MACE independently of aortic diastolic blood pressure, both aortic systolic blood pressure and aortic diastolic blood pressure were entered in the model and mean aortic blood pressure was withdrawn (aortic systolic and diastolic pressures did not closely correlate in our population). In these models, the adjusted HR for each 10% increase in AIx was 1.33 (95%CI: 1.14 to 1.55; $P=0.0002$); the adjusted HR for each 10-mm Hg increase in AP was 1.23 (95%CI=1.10 to 1.37; $P=0.0002$).

After adjusting for EF and MAP, there was a trend for an increased risk of MACE with increasing aortic PP (HR per 10 mm Hg increase in PP: 1.084; 95% CI, 0.997 to 1.178; $P=0.057$). Brachial PP did not predict MACE in our population.

Predictors of All-Cause Mortality

During the follow-up period, 19.5% of patients died. Univariate predictors of death are shown in Table 3.

AP and Death

AP was a significant predictor of death. For every 10-mm Hg increase in AP, there was an 18% increase in the risk of death (95% CI, 2% to 39%; $P=0.03$). When adjusted for univariate predictors of death (Table 3), an increased AP was associated with a trend toward increased mortality (HR for 10 mm Hg increase: 1.16; 95% CI, 0.99 to 1.35; $P=0.06$).

AIx and Death

Higher AIx (adjusted for EF, HR, and mean arterial blood pressure) was associated with a trend toward increased mortality (HR=1.22; 95% CI, 0.98 to 1.52; $P=0.056$). When adjusted for univariate predictors of death, the adjusted HR per 10% increase in AIx was 1.01; the correlation did not reach statistical significance ($P=0.1$).

Aortic Pressures and Death

Aortic diastolic blood pressure inversely correlated with the risk of death (HR per 10-mm Hg increase=0.74; 95% CI, 0.60 to 0.93; $P=0.01$). When adjusted for EF and MAP, PP predicted mortality (adjusted HR per 10-mm Hg increase in PP=1.17; 95% CI, 1.03 to 1.32; $P=0.01$). Brachial PP did not predict mortality.

Discussion

We investigated whether AP, a marker of aortic stiffness and wave reflection from the periphery, predicts adverse cardiovascular outcomes in patients with established CAD. We found a significant independent correlation between AP (adjusted for PP) and the risk of MACE. This indicates that AP added significant prognostic information to that already provided by PP and other risk markers and potential confounders. Similar results were obtained when AIx a single composite term was analyzed. AP predicted all-cause mortality; when additional adjustments were performed, including age and other predictors of death, a trend for increased death with increased AP persisted. A trend toward prediction of death was found when AIx was adjusted for heart rate, EF, and MAP, but not when further adjustment was performed for other predictors of mortality. These results raise the possibility that AIx, although practical as a single composite value, might not contain all the prognostic information contained in both values (AP and PP) expressed separately. Our study has not proven this concept, which needs to be tested in other populations and confirmed by means of prospective validation.

Although peripheral PP is the most commonly measured marker of arterial stiffness, the information contained within the waveform of the proximal aorta is of particular interest because the blood pressure profile at this site determines left ventricular load and coronary blood flow.[13] AP results form the pressure wave generated by the left ventricle, conducted by large arteries, and reflected at peripheral impedance small arteries and arterioles (and conducted back by large arteries to the proximal aorta). Therefore, central pressure augmentation is affected by large-artery stiffness as well as the tone of impedance vessels, which, in turn, is influenced by the tone of arterial smooth muscle. It has been shown that nitric oxide contributes to the functional regulation of stiffness.[17–19] By

affecting the timing and magnitude of wave reflection, increased arterial stiffness has the potential to directly impair coronary blood flow in patients with CAD.[20–22] Interestingly, high carotid AIx has been shown to be an independent predictor of cardiac ischemic threshold during exercise in patients with CAD.[22] Therefore, AP is determined by the cumulative and integrated influence of various structural, hemodynamic, and metabolic stimuli and can ultimately impair coronary blood flow. Arterial stiffness might be not only a risk marker but also a therapeutic target for patients at risk for CAD, as well as for patients with established CAD. Importantly, noninvasive recordings of radial arterial pressure waveforms using radial tonometry and a generalized transfer function now allow for determinations of central pressure augmentation.[23,24]

Our study is in agreement with previous studies that have shown that measures of arterial stiffness predict adverse cardiovascular outcomes in different populations,[11,25–33] such as patients with end-stage renal disease,[11,25,26] hypertension,[27–29] diabetes mellitus,[30] and patients older than 70 years,[31] all of which are populations at high risk for CAD. Adding to this line of evidence, we have shown that increased AP predicted adverse cardiovascular outcomes in patients with established CAD independently of age, the angiographic severity of CAD, and other risk markers. It should be noted, however, that changes in AP may be partially independent of changes in arterial stiffness. The factors that determine central pressure augmentation are diverse, complex, and incompletely understood. Central pressure augmentation likely represents a composite marker of disease-related adverse changes in hemodynamics that vary throughout different sections of the arterial tree and deserve further mechanistic characterization.

Our study has limitations. We did not test the frequency–amplitude performance of the catheterization laboratory amplifiers, which might affect the accuracy of measurements of augmentation pressure. In addition, left ventricular dysfunction is a poor prognostic indicator that tends to *decrease* pressure augmentation. Although we performed adjustments for EF in all models, these adjustments might not account for changes on the pattern of ventricular ejection. We should note that these limitations would be expected to *obscure* the predictive ability of AP rather than to underlie the correlation between pressure augmentation and outcomes. Finally, statistical modeling for medication use might not incorporate the effect of individual agents prescribed in different doses.

Careful analysis of the frequency–amplitude performance of the entire measurement system is recommended for those who wish to undertake similar work. This can be achieved with the use of electrical pressure generators capable of generating pressure waves in a liquid system at different frequencies, as performed by Smulyen et al,[34] or using the "pop-test" method as previously described.[35]

The inverse association of centrally measured diastolic blood pressure with the risk of MACE in our population deserves further mention. We found that lower aortic diastolic blood pressure were associated with a higher risk of MACE and death. These findings are consistent with those from the Systolic Hypertension in the Elderly Program (SHEP) trial, in which subjects with isolated systolic hypertension were treated with chlorthalidone and atenolol (versus placebo) in a stepwise manner;[36] in this trial, a decrease of 5 mm Hg in diastolic blood pressure was associated with an increase in the risk of major adverse cardiovascular events (HR=1.11; 95% CI, 1.05–1.16). Our findings are also consistent with a recent preliminary from the large International Verapamil SR/trandolapril (INVEST) Study.[37] Whether the correlation of diastolic blood pressure with adverse outcomes in patients with CAD is related to increased arterial stiffness, comorbid conditions, or a combination of both remains unclear. The association of diastolic blood pressure and the risk of MACE in our population and the way it relates to arterial stiffness and comorbid conditions is the focus of a separate analysis.

Perspectives

Several studies indicate that markers of arterial stiffness are reliable predictors of cardiovascular events in the wide spectrum of atherosclerosis progression. Measures of arterial stiffness can identify nonhypertensive subjects at risk for hypertension, identify hypertensive, diabetic, and elderly subjects who are at increased risk for vascular events and death, predict mortality in patients with established renal disease, and predict adverse cardiovascular outcomes in patients with established angiographic coronary artery disease. The technology to noninvasively evaluate arterial stiffness and wave reflections is available and suitable for clinical use. Further studies are needed to further quantify the extent to which measures of arterial stiffness can improve risk stratification and, most importantly, to determine whether its reduction is capable of independently predicting clinical benefit of therapeutic interventions in different populations.

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