Pulse Pressure and Presence of Coronary Artery Calcification

Domenico Russo,* Luigi F. Morrone,† Stefania Brancaccio,* Paola Napolitano,* Ermanno Salvatore,‡ Rosanna Spadola,* Massimo Imbriaco,‡ Cinzia V. Russo,* and Vittorio E. Andreucci*
Departments of *Nephrology and ‡Radiology, University Federico II, Naples, and †Ospedale G. Rummo Benevento, Italy

Background: Coronary calcification (CAC) is found in early stages of CKD. Pulse pressure (PP) predicts CAC in dialysis patients. This study evaluates the accuracy of PP in predicting CAC in patients not yet on dialysis (CKD patients).

Methods: CKD patients (n = 388) underwent coronary calcium score (CAC score) and abdominal x-ray (n = 128) for estimating aorta calcification (AAC). Biochemistry and PP were measured every 3 and 6 months in patients with stage 4 to 5 and 2 to 3 CKD, respectively. The accuracy of PP and AAC was assessed by receiver operating characteristics analysis.

Results: PP correlated with CAC score in the whole cohort and in patients with stages 2 to 3 and stages 4 to 5 CKD. PP >60 mmHg predicted CAC score >0 (OR: 2.14; P < 0.001), ≥100 (OR: 2.92; P < 0.001), ≥400 (OR: 6.17; P < 0.001) after multivariable adjustment. Area under the curve (AUC) was 0.626 for CAC score >0, 0.676 for score >100, and 0.746 for score >400. PP >60 mmHg reduced the rate of event-free survival. AAC was found in 58% of patients and correlated with CAC score. AUC was 0.628 for CAC score >0, 0.652 for score >100, 0.831 for score >400.

Conclusion: PP may identify CKD patients with subclinical CAC who need further evaluation. Accuracy of PP and AAC is nearly similar in predicting CAC. High PP indicates vessel wall alterations leading to adverse outcome.


Coronary artery calcification (CAC) is present even in asymptomatic patients with stage 2 to 5 of chronic kidney disease (CKD) who are not yet on dialysis (1–3). The disease progresses rapidly and is associated with fatal and nonfatal cardiovascular events (4,5). It is likely that in CKD patients, who frequently die from coronary heart disease before dialysis initiation, CAC is an important risk factor for cardiovascular events as in patients on dialysis (ESRD patients) (6–9). However, unanswered questions are (1) how to distinguish CKD patients who may have CAC and need further cardiovascular tests and early therapeutic intervention and (2) what procedure should be used for the preliminary screening.

The numbers of patients with stages 2 to 5 of CKD are increasing worldwide (10,11), and CAC is found in less than half of this population (1–3). In addition, gold standard procedures such as electron beam or multislice computed tomography (EBCT or MSCT) are not suitable for screening large populations (12–14); EBCT is available in only few nephrology units and is expensive, MSCT is time consuming and exposes patients to large radiation doses. Therefore, in CKD patients, it is important to find simple and inexpensive tests for the preliminary screening. Standard radiographs, echocardiography, and pulse pressure may predict the presence of CAC in ESRD patients (15–18).

The aim of the present study was to evaluate the diagnostic accuracy of pulse pressure in predicting the presence of CAC in CKD patients. To our knowledge, no data are available on this issue.

Materials and Methods

This is a retrospective study carried out in consecutive outpatients who had been evaluated for presence of CAC from March 2002 to September 2006 at our institution after providing their written informed consent. Protocol for screening had been approved by our internal ethical board. The cohort was represented by 420 patients who had been selected on the basis of the following inclusion criteria: no symptoms of heart failure or coronary artery disease, no history of myocardial infarction and/or coronary bypass surgery or angioplasty, no stroke, no current arrhythmia, and no rapidly progressive renal disease. From the database of the initial cohort, we selected the files of 388 patients on the basis of the following further inclusion criteria: age > 18 yr, stage 2 to 5 CKD (not yet on dialysis), minimum 6 month follow-up in our clinic before the MSCT. Recruited patients were followed until the end of the study (June 2007) or occurrence of an event.

Physical examination was performed and routine blood chemistry; lipid profile; and serum concentrations of calcium (corrected for serum albumin), phosphorus, intact parathyroid hormone (i-PTH), homocysteine, and high-sensitivity C-reactive protein (hs-CRP) were assessed every 3 and 6 months in patients with stage 4 to 5 and 2 to 3 CKD, respectively. Biochemical determinations obtained 3 and 6 months apart were averaged. GFR was measured as 24-h creatinine clearance. Normal ranges for serum calcium, phosphorus, and i-PTH were established on the basis of the stage of CKD according to Kidney Disease Outcome Quality Initiative guidelines. i-PTH was assayed by a chemiluminescent immunometric method (Diagnostic Products Corporation, Los Angeles, CA; normal values in general population: 10 to 75 pg/ml; 10 to 75 ng/L).
In each patient, BP was measured by a manual sphygmanometer after 5 min in a seated position; the mean of three consecutive readings, taken 1 min apart, was recorded. Pulse pressure was calculated as the difference between peak systolic and trough diastolic arterial BP. In patients with stage 4 to 5 CKD, readings recorded 3 months apart before MSCT were averaged and used for statistical analysis; the reading closest to MSCT was used in other patients. According to guidelines of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, hypertension was defined as systolic BP (SBP) ≥140 mm Hg and/or diastolic BP (DBP) ≥90 mm Hg (19). Patients who used insulin or oral hypoglycemic drugs on a regular basis were considered diabetic.

The rates of occurrence of sudden death, cardiovascular events, and onset of dialysis were collected. The following cardiovascular events were recorded: myocardial infarction, cerebrovascular accident, coronary bypass graft, percutaneous coronary angioplasty, peripheral artery bypass, amputation, abdominal aortic aneurism repair, and carotid endarterectomy.

CAC score was assessed by MSCT (2). Calcific lesions in the abdominal aorta (AAC) were evaluated by lateral lumbar x-ray and graded by semiquantitative scoring system (20). Score of patients who had undergone the radiograph of the abdomen within 12 mo period (before or after) MSCT was recorded.

The correlation between the continuous variables (pulse pressure, CAC score, and abdominal aorta calcification score) was investigated using the Spearman rank coefficient (rho) because they were not normally distributed. The categorical variables were compared using the chi-square test.

Receiver operating characteristics (ROC) analyses were used to assess the diagnostic accuracy of pulse pressure for detecting CAC score >0, ≥100, and ≥400. The optimal cut-off for each value of CAC score was the corresponding value of pulse pressure that gave percent sensitivity and specificity closest to the point of a perfect marker (sensitivity and specificity of 100%). ROC analyses were also performed for AAC.

Logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for coronary calcification at the different score levels and at the value of pulse pressure ≥60 mm Hg. Adjustment was made for relevant covariates that had been found significant (P < 0.05) in univariate analysis.

Kaplan–Meier survival analysis was done using composite censoring variables: dialysis initiation, nonfatal cardiovascular disease, and death. Survival curves were generated by data collected from patients without coronary calcifications as well as from patients with CAC score >100 or >400, who did or did not have pulse pressure ≥60 mm Hg. The survival probability at various time points was computed using the log-rank test.

Data were expressed as mean ± SD unless otherwise indicated. A two-sided P value of < 0.05 was considered to indicate statistical significance. Statistical analysis was performed using NCSS 2004 statistical software (NCSS, Kaysville, UT).

Results
The mean duration of follow-up was 24.4 ± 12.7 mo (median: 24.5 mo) from the assessment of CAC score up to the end of the study or occurrence of an event.

Enrolled patients had glomerulonephritis (27%), diabetic nephropathy (16%), ischemic nephropathy (10%), interstitial nephropathy (3%), and unknown renal diseases (44%).

Duration of diabetes was 157 ± 113 mo. Hypertension was present in 322 patients (83%), with a mean duration of 95 ± 88 mo. BP was on target in 111 (40%) patients. Of treated but uncontrolled hypertensive patients, 92% had diastolic BP ranging from 80 to 95 mm Hg. Mean number of antihypertensive medications was 2.08 ± 0.9. A single antihypertensive medication (calcium channel blocker, converting enzyme inhibitors, angiotensin II receptor antagonist) was prescribed to 28% of patients. The association of converting enzyme inhibitors or angiotensin II receptor antagonists with calcium channel blocker was the most frequent (45%). Other demographic, clinical and laboratory characteristics are summarized in Table 1.

Deregament of mineral metabolism was not significantly different among patients with and without CAC (Table 2). On the basis of CKD stages, serum concentration of i-PTH and phosphorus above the upper normal limit was found in 39.5% and 19.3% of patients, respectively; concentrations below the lower normal limit were found in 7.9% and 5.4% of patients, respectively. Patients treated with oral calcitriol (n. 20; 5%) had GFR ranging from 10 to 32 ml/min and were equally distributed between patients with (6%) and without (4%) CAC. The use of phosphate binders was not different among patients with and without CAC, nor was the use of antihypertensive drug regimens.

CAC was found in 164 patients (42.3%); CAC score ranged from 3 to 3303 Agatston units. CAC score >100 and >400 was found in 64.6% and 26.2% of patients, respectively. Patients with CAC were more likely to be male and over 65 yr old, and to have GFR <60 ml/min, diabetes, hypertension, and hyperfibrinogenemia. On the contrary, no significant difference was observed for hs-CRP, LDL-C, and homocysteine.

In the entire cohort of patients, a significant positive correlation between pulse pressure and CAC score was observed (P = 0.28; P < 0.0001); the correlation remained significant but at lower level (P < 0.048) after adjusting for age, duration of hypertension, and diabetes. The correlation was confirmed in patients with stage 2 to 3 CKD (P = 0.30, P < 0.0002) as well as in those with stage 4 to 5 CKD (P = 0.26, P < 0.007). The cut-off value of pulse pressure ≥60 mm Hg was chosen because it was more frequently observed in patients with CAC than in those without CAC (50.7% versus 31.4%, P = 0.001) and was the best cut-off value to discriminate patients with CAC, as shown by ROC curve (as reported below). Unadjusted and adjusted ORs to estimate the risk of CAC in patients with pulse pressure ≥60 mm Hg, using patients without CAC as a reference group, are shown in Figure 1. Pulse pressure ≥60 mm Hg predicted CAC with score >0 (OR: 2.25; P < 0.001), CAC with score ≥100 (OR: 3.14; P < 0.001), and CAC with score ≥400 (OR: 6.56; P < 0.001) in univariate analysis. Pulse pressure ≥60 mm Hg was a significant predictor of CAC with score >0 (OR: 2.14; P < 0.001), ≥100 (OR: 2.92; P < 0.001), and ≥400 (OR: 6.17; P < 0.001) after adjusting for hypertension and duration of hypertension over 5 years. Finally, pulse pressure ≥60 mm Hg predicted CAC with score ≥400 (OR: 2.81; P < 0.05) after adjusting for gender, age >65 yr, diabetes mellitus, and GFR <60 ml/min. Thus, both in univariate and multivariate analysis, OR increased in parallel with CAC score values.

The areas under the curve (AUCs) for pulse pressure criteria to determine the presence or absence of CAC, CAC score ≥100

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and \( \geq 400 \) versus absence of CAC are shown in Figure 2. The values of AUC were 0.626 for presence of CAC, 0.676 for CAC score \( \geq 100 \), 0.746 for CAC score \( \geq 400 \). Each area was significantly different \(( P < 0.001)\) from AUC = 0.5; this value indicates a noninformative test. Thus, the value of AUC found in our patients with CAC score \( \geq 400 \) may be regarded as a moderately informative test \((21)\). The best cut-off value of pulse pressure was 60 mmHg for all of the AUCs, and the corresponding values of sensitivity and specificity were 51% and 69% for the presence or absence of CAC, 59% and 69% for CAC score \( \geq 400 \).

**Table 1. Demographic, clinical and laboratory findings of subjects \((N = 388)\)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender (%)</td>
<td>77.8</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>52.6 ± 12.7</td>
</tr>
<tr>
<td>Diabetes, type II (%)</td>
<td>15.8</td>
</tr>
<tr>
<td>GFR (mL/s)</td>
<td>1.05 ± 0.67 (64 ± 40 ml/min)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>134.3 ± 16.5</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>80.2 ± 7.8</td>
</tr>
<tr>
<td>Pulse pressure (mmHg)</td>
<td>53.9 ± 15.9</td>
</tr>
<tr>
<td>i-PTH (ng/L)</td>
<td>106.8 ± 126.8 (106.8 ± 126.8 pg/ml)</td>
</tr>
<tr>
<td>Serum calcium (mmol/L)</td>
<td>2.37 ± 0.14 (9.52 ± 0.57 mg/dl)</td>
</tr>
<tr>
<td>Serum calcium (mmol/L)</td>
<td>2.57 ± 0.14 (10.3 ± 0.57 mg/dl)</td>
</tr>
<tr>
<td>Serum phosphorus (mmol/L)</td>
<td>1.26 ± 0.29 (3.90 ± 0.91 mg/dl)</td>
</tr>
<tr>
<td>Ca ( \times ) P product (mg(^2)/dl(^2))</td>
<td>39.9 ± 8.59</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>3.04 ± 1.10 (117.6 ± 42.6 mg/dl)</td>
</tr>
<tr>
<td>Homocysteine (( \mu )mol/L)</td>
<td>182.7 ± 169.4 (24.7 ± 22.9 nmol/ml)</td>
</tr>
<tr>
<td>Fibrinogen (( \mu )mol/L)</td>
<td>10.8 ± 3.3 (367 ± 112.1 mg/dl)</td>
</tr>
<tr>
<td>HsCRP (mg/L)</td>
<td>0.49 ± 0.77</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation. Gender and diabetes mellitus are reported as proportion of population. GFR, glomerular filtration rate; hs-CRP, high-sensitivity C reactive protein; i-PTH, intact parathyroid hormone; LDL-C, low-density lipoprotein-cholesterol; Ca \( \times \) P, calcium-phosphorus product.

**Table 2. Clinical and laboratory characteristics of patients with and without coronary calcification (CAC)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Without CAC</th>
<th>With CAC</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients (%)</td>
<td>224 (57.7)</td>
<td>164 (42.3)</td>
<td>0.0022</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>72.3</td>
<td>85.4</td>
<td>0.0002</td>
</tr>
<tr>
<td>Age ( &gt; 65 ) yr old (%)</td>
<td>4.9</td>
<td>29.9</td>
<td>0.0000</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>6.8</td>
<td>22.8</td>
<td>0.0001</td>
</tr>
<tr>
<td>GFR( &lt; 60 ) ml/min (%)</td>
<td>44.5</td>
<td>61.6</td>
<td>0.0009</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>78.6</td>
<td>92.0</td>
<td>0.0004</td>
</tr>
<tr>
<td>Pulse pressure ( \geq )75th percentile (%)</td>
<td>31.4</td>
<td>50.7</td>
<td>0.003</td>
</tr>
<tr>
<td>Fibrinogen ( \geq )75th percentile (%)</td>
<td>19.0</td>
<td>32.7</td>
<td>0.01</td>
</tr>
<tr>
<td>hs-CRP ( \geq ) 75th percentile (%)</td>
<td>23.8</td>
<td>28.9</td>
<td>NS</td>
</tr>
<tr>
<td>i-PTH above upper normal limit (%)</td>
<td>39.6</td>
<td>39.3</td>
<td>NS</td>
</tr>
<tr>
<td>Calcium above upper normal limit (%)</td>
<td>38.1</td>
<td>43.2</td>
<td>NS</td>
</tr>
<tr>
<td>Phosphorus above upper normal limit (%)</td>
<td>22.3</td>
<td>16.3</td>
<td>NS</td>
</tr>
<tr>
<td>Ca ( \times ) P product above 55 mg(^2)/dl(^2) (%)</td>
<td>5.7</td>
<td>4.9</td>
<td>NS</td>
</tr>
<tr>
<td>LDL-C above upper normal limit (%)</td>
<td>67.6</td>
<td>58.2</td>
<td>NS</td>
</tr>
<tr>
<td>Homocysteine ( \geq )75th percentile (%)</td>
<td>24.8</td>
<td>25.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

Fibrinogen 75th percentile value = 418 mg/dl; hs-CRP 75th percentile value = 0.4 mg/L; homocysteine 75th percentile value = 28.4 mg/L. Upper normal limit for i-PTH: 60 pg/ml for GFR \( \geq \) 60 ml/min, 70 pg/ml for GFR range 59-30 ml/min, 110 pg/ml for GFR range 29-15 ml/min, and 300 pg/ml for GFR \(< 15 \) ml/min. Upper normal limit for serum phosphorus: 4.6 mg/dl for GFR \( \geq 15 \) ml/min and 5.5 mg/dl for GFR\(< 15 \) ml/min. Upper normal limit for serum calcium:10.5 mg/dl for GFR \( \geq 15 \) ml/min and 9.5 mg/dl for GFR \(< 15 \) ml/min. LDL-C upper normal limit:100 mg/dl. GFR, glomerular filtration rate (as creatinine clearance); hs-CRP, high-sensitivity C-reactive protein; i-PTH, intact parathyroid hormone; Ca \( \times \) P product, calcium-phosphorus product; LDL-C, low density lipoprotein-cholesterol.
and lower 95% confidence limits (95% CL).

Figure 1. Plot of unadjusted and adjusted odds ratios to estimate the risk of having coronary calcification in patients with pulse pressure ≥60 mmHg, assuming patients without CAC as reference group. Panel A illustrates the odds ratios and the 95% confidence limits (95% CL) for the predictor variable Pulse Pressure ≥60 mmHg, considering as dichotomic outcome variable coronary calcium score ≥0. Panels B and C indicate calcium score ≥100 and ≥400, respectively.

scoring ≥100, and 75% and 69% for CAC score ≥400, respectively.

Abdominal x-ray was performed in 128 patients, and AAC was found in 58% of them. The mean score was 4.81 ± 4.3. Compared with patients without AAC, those with AAC had significantly longer duration of diabetes (P < 0.01); no differences were found in lipid profile, serum concentrations of calcium, phosphorus, i-PTH, homocysteine, hs-CRP, or antihypertensive medication regimen. In these patients, a positive correlation between AAC and CAC score was observed (ρ = 0.32; P < 0.0002). In addition, the values of AUC for AAC
mmHg increase in diastolic BP (6). In the present study, a positive correlation was found between pulse pressure and CAC score in the entire cohort of patients, even after data were adjusted for age, diabetes, hypertension, and duration of diabetes and hypertension. In addition, the correlation remained significant in patients with both early (2 to 3) and advanced (4 to 5) stages of CKD, suggesting that pulse pressure and CAC may be related within a width range of GFRs. However, even a powerful statistical association may have no clinical relevance.

The OR estimating the risk for CAC in patients with pulse pressure ≥60 mmHg increased in parallel with CAC score (i.e., from score >0 up to score ≥400) in univariate and multivariate analysis. Of note, in multivariate analysis, the relationship between pulse pressure and CAC was more pronounced for score ≥400. Finally, after adjusting data for age over 65 yr, presence of diabetes mellitus, and GFR <60 ml/min, the relationship remained significant and the OR increased.

In ESRD patients, several studies have evaluated the relationship between pulse pressure and vascular calcifications, with contrasting results (17,22,30,31). In one study, significant positive association was observed between increasing values of pulse pressure and the number of calcified peripheral arteries assessed by a high-resolution B-mode echo-tracking system. In the other studies, pulse pressure did not correlate to the extent of CAC evaluated with EBCT and showed fair discriminatory value and low accuracy in predicting CAC; thus, it was excluded from the cardiovascular calcification index for predicting the presence of CAC. However, these interesting findings were observed in nonwhite ESRD-patients with mean dialysis vintage of 4.2 yr; almost half had diabetes, and many had heart failure and history of cerebro- and cardiovascular diseases. Importantly, timing of BP measurements and their relation to dialysis session was not reported; in ESRD patients, arterial BP greatly fluctuates depending on hydration status.

ROC curve and AUC indicated that pulse pressure ≥60 mmHg was the best cut-off point to predict CAC in our patients. Interestingly, in CKD patients, it has been observed that pulse pressure ≥60 mmHg is involved in diastolic dysfunction, left ventricular remodelling or hypertrophy, and cardiovascular disease progression, and is strongly correlated with pulse wave velocity (32–34). However, an association between pulse pressure and the presence of CAC has never been evaluated.

In this study, the achieved sensitivity (percentage of true positive patients) was 51%, 59%, and 75% for score >0, score ≥100, and score ≥400, respectively; whereas specificity (percentage of true negative patients) was 69% for each level of CAC score. The highest sensitivity and specificity (75% and 69%, respectively), as well as the largest AUC, were found in the presence of pulse pressure ≥60 mmHg and CAC score ≥400. Thus, pulse pressure ≥60 mmHg may predict the presence of CAC score ≥400 in 75% of patients (true positive patients) and may exclude it in 69% of patients (true negative patients). As a result, 31% of patients might be erroneously diagnosed as "calcified" (false positive patients), and 25% of patients might have missed the diagnosis (false negative patients). We are aware that false positive test may result in further unnecessary diagnostic procedures, but false negative tests may have even more detrimental effects, such as delay in diagnosis and care and consequent worse prognosis, especially in high-risk patients. Patients with CKD are at a high level of cardiovascular risk even when they are asymptomatic. In a review on accredited screening techniques for cardiovascular diseases (such as resting electrocardiogram and exercise treadmill testing), the median false negative rate in detecting asymptomatic subjects at high cardiovascular risk for coronary heart disease was 40% (34). In addition, the sensitivity and specificity of the artery intimal-media thickness, assessed by B-mode ultrasound, to correctly identify asymptomatic subjects with CAC score ≥400 were 60% and 75%, respectively (35,36).

AAC was found in 58% of 128 patients in whom this determination was available. The latter finding indicates that the abdominal calcification process starts in early stages of CKD, as has been found for coronary calcification (1–3). The mean AAC score was similar to that reported in ESRD patients (30); the prevalence rate was also similar (A. Bellasi, Medical Manager, Genzyme SpA, Modena, Italy, personal communication, September 2008). The absence of a difference between CKD and ESRD patients is probably due to selection bias.

Positive correlation was observed between AAC and CAC scores. Interestingly, the AUC for AAC score was lower than
that of pulse pressure in discriminating the presence/absence of CAC and CAC score $>100$, but higher in discriminating CAC score $>400$. This suggests that pulse pressure may be superior to AAC in predicting mild CAC, but not severe CAC. These findings are the first available for CKD patients. In ESRD patients, AAC score showed a good correlation with CAC assessed by EBCT (30).

Ascertaining the survival rate was not aim of this study; however, some interesting findings are worthy of few comments. Patients without CAC had better survival rate; survival of patients with score $>100$ was not different compared with that of patients with score $>400$, underlining that the risk for an outcome is evident even at low score. Pulse pressure $>60$ mmHg markedly impaired the survival in patients with score $>400$.

**Limitations of the Study**

Survival curves were done on the basis of composite outcomes, inclusive of initiation of dialysis that is not strictly dependent on arterial calcification. However, experimental studies have shown that arterial calcification may accelerate the progression of renal diseases (37,38). The low incidence of events observed during the study (despite the large cohort of CKD patients evaluated) did not allow additional survival evaluations. The presence of abdominal aorta calcification was not ascertained in all patients who had undergone MSCT. In some patients, a single value of pulse pressure was available for statistical analysis (as has been the case in many studies in ESRD patients). Despite these limitations, this is the first work to evaluate the usefulness of pulse pressure and AAC in predicting the presence of CAC in CKD patients.

**Conclusions**

The data of the present study suggest that pulse pressure may identify patients with subclinical CAC who likely need further evaluation for early therapeutic choice before coronary heart disease becomes symptomatic. High pulse pressure may indicate the presence of vessel wall alterations that lead to adverse outcome.

**Disclosures**

None.

**References**


Access to UpToDate on-line is available for additional clinical information at http://www.cjasn.org/