Chronic kidney disease (CKD) is independently associated with an increased risk of cardiovascular disease.1,2 Patients with CKD are also at an increased risk of heart failure (HF), which is a major cause of morbidity and mortality in this population.3–6 Although several studies have been performed on predictors of overall cardiovascular risk in CKD (assessed using composite cardiovascular end points), the predictors of HF as a specific end point have not been adequately characterized in subjects with CKD. Of note, composite cardiovascular end points usually include several atherosclerotic and nonatherosclerotic events, for which risk factors may differ. HF in CKD has been proposed to be largely independent of atherosclerotic occlusive disease and more closely related to structural myocardial disease.3

**Background**—Chronic kidney disease is associated with an increased risk of heart failure (HF). We aimed to evaluate the role of large artery stiffness, brachial, and central blood pressure as predictors of incident hospitalized HF in the Chronic Renal Insufficiency Cohort (CRIC), a multiethnic, multicenter prospective observational study of patients with chronic kidney disease.

**Methods and Results**—We studied 2602 participants who were free of HF at baseline. Carotid-femoral pulse wave velocity (CF-PWV; the gold standard index of large artery stiffness), brachial, and central pressures (estimated via radial tonometry and a generalized transfer function) were assessed at baseline. Participants were prospectively followed up to assess the development of new-onset hospitalized HF. During 3.5 years of follow-up, 154 participants had a first hospital admission for HF. CF-PWV was a significant independent predictor of incident hospitalized HF. When compared with the lowest tertile, the hazard ratios among subjects in the middle and top CF-PWV tertiles were 2.33 (95% confidence interval, 1.37–3.97; \(P=0.002\)) and 5.24 (95% confidence interval, 3.22–8.53; \(P<0.0001\)), respectively. After adjustment for multiple confounders, the hazard ratios for the middle and top CF-PWV tertiles were 1.95 (95% confidence interval, 0.92–4.13; \(P=0.079\)) and 3.01 (95% confidence interval, 1.45–6.26; \(P=0.003\)), respectively. Brachial systolic and pulse pressure were also independently associated with incident hospitalized HF, whereas central pressures were less consistently associated with this end point. The association between CF-PWV and incident HF persisted after adjustment for systolic blood pressure.

**Conclusions**—Large artery stiffness is an independent predictor of incident HF in chronic kidney disease, an association with strong biological plausibility given the known effects of large artery stiffening of left ventricular pulsatile load.

(Circ Heart Fail. 2014;7:709-716.)

**Key Words:** heart failure ■ pulse wave analysis ■ renal insufficiency, chronic ■ vascular stiffness
HF risk in CKD. However, a recent study reported that moderate CKD increases the risk of HF even in the absence of hypertension (defined from brachial pressure measurements) or diabetes mellitus at baseline. Central pressure profiles have been investigated in the prediction of cardiovascular risk in patients with end-stage kidney disease, but the relationship between central pressures and incident HF has never been examined in earlier stages of CKD. Similarly, increased large artery stiffness has been proposed as a major contributor to HF risk in CKD because of its well-known effects on left ventricular pulsatile afterload, which promote left ventricular hypertrophy and myocardial dysfunction. Despite these important physiological considerations, the relationship among large artery stiffness, central pressures, and incident HF in CKD has not been investigated.

In this study, we aimed to evaluate the role of large artery stiffness, brachial, and central blood pressure as predictors of incident hospitalized HF in the Chronic Renal Insufficiency Cohort (CRIC), a multiethnic, multicenter prospective observational study of patients with CKD.

**Methods**

**Study Overview**

The CRIC Study is a prospective cohort study of 3939 participants enrolled from June 2003 to August 2008 through 7 clinical centers across the United States. Participants constitute a racially diverse group of men and women aged 21 to 74 years who were identified as having CKD, approximately half of whom were diabetic, and who were enrolled using age-stratified criteria for kidney function by estimated glomerular filtration rate. The level of estimated glomerular filtration rate used to define eligibility was based on the 4-variable Modification of Diet in Renal Disease estimating equation, using a correction of model discrimination, were computed for each Cox model. Analyses were performed using SAS 9.3 (SAS Institute, Cary, NC).

**Brachial and Central Pressure Measurements**

Study personnel in the CRIC Study were trained to take standard brachial blood pressure in the dominant arm using the American Heart Association standard protocol using a Tyco aneroid sphygmomanometer. Central arterial systolic and pulse pressures (PP) were incorporated into the CRIC protocol at the second year follow-up visit and measured supine after 5 minutes of rest using the SphygmoCorPVx System (AtCor Medical, West Ryde, Australia) via the right radial artery at all of the CRIC sites, as previously described. Briefly, the coordinator captured 10 s of a stable right radial artery waveform signal using a high-fidelity Millar applanation tonometer, from which the central arterial pressure profile was estimated using the generalized transfer function of the SphygmoCor device.

**Carotid-Femoral Pulse Wave Velocity Measurement**

Carotid-femoral pulse wave velocity (CF-PWV) measurements were incorporated in the CRIC protocol beginning with the 2-year follow-up visit at all study sites. CF-PWV measurements were performed in the supine position, after ≥5 minutes of rest using the right carotid and right femoral arteries as previously described. Briefly, the SphygmoCorPVx (AtCor Medical) device was used by trained, certified study personnel. CF distance was computed as the distance from the sternal notch to the umbilicus plus the distance from the umbilicus to the point of palpable femoral pulse minus the distance from the sternal notch to the point of the palpable carotid pulse. This distance was further adjusted, as we reported previously, by a correction factor for the exaggeration of the sternal notch to femoral measurement produced by large waist circumference. A Millar tonometer captured 10 s of acceptable carotid followed immediately by 10 s of femoral pulse waveforms (in series). The QRS complex timing was used as a fiducial point to compute the delay in pulse arrival between the carotid and the femoral sites.

**Propective Follow-Up and HF Event Adjudication**

After enrollment, participants were followed up until death or withdrawal of informed consent. The primary goals of the CRIC Study are to investigate standard and novel risk factors for CKD progression, as well as the incidence and progression of cardiovascular disease. This is accomplished by yearly in-person follow-up visits at which time a standard protocol assessing physical findings, interval medical history, ECG, and laboratory testing were performed. The interval medical history specifically queries hospitalized cardiovascular disease events at both the yearly in-person visits and by a 6-month interval telephone contact. Anytime an event is reported by the participant, records are sought and the deidentified medical records are sent to 2 CRIC investigator-physicians for adjudication (with discordances solved by consensus or an appeal to a third physician adjudicator when needed).

An HF event is adjudicated when there is hospitalization for clinical symptoms (dyspnea on exertion or rest, paroxysmal nocturnal dyspnea, and/or orthopnea) with ≥1 of the following objective findings: (1) radiographic evidence of pulmonary edema or pulmonary congestion; (2) physical examination findings consistent with congestive heart failure to include ≥2 of the following: inspiratory crackles (rales) involving ≥1/3 of the lower lung fields, S3 gallop on auscultation, elevated jugular venous pressure, or peripheral edema; (3) invasive hemodynamic or echocardiographic evidence of HF, including any of the following: pulmonary capillary wedge pressure ≥18 mm Hg, cardiac index <2.0 L/min per square meter of body surface area or left ventricular ejection fraction ≤35%. This analysis includes adjudicated, hospitalized incident HF events occurring through March 2011.

Because we aimed to assess the risk factors for incident HF in this study, this analysis excluded participants who were enrolled in the CRIC Study and who had a preexisting diagnosis of HF (n=214), those who had an incident HF event between enrollment and the first available measurement of CF-PWV (n=3).

**Statistical Analysis**

Baseline characteristics were described using mean with SD for continuous variables and number (%) for categorical data. Participant characteristics were analyzed in the entire sample and compared among tertiles of CF-PWV values. Survival across CF-PWV tertiles and various parameters of interest was examined with the Kaplan–Meier estimator. Cox proportional hazards models were used to analyze the relationship between various, independent variables of interest, including brachial and central systolic blood pressure (SBP), brachial and central PP, and CF-PWV. Hazard ratios (HRs) and 95% confidence intervals (CIs) were computed across tertiles of these variables, using the lowest tertile as the referent group, after testing the proportional hazards assumption. We constructed 3 types of models for each analysis: an unadjusted model (model 1); a model adjusted for age, race, sex, and enrollment site (model 2); and a model further adjusted for baseline values of various other potential confounders, including diabetes mellitus, proteinuria, the presence of chronic obstructive pulmonary disease, mean arterial pressure, heart rate, high-density lipoprotein–cholesterol, low-density lipoprotein–cholesterol, body mass index, triglycerides, history of myocardial infarction/revascularization, and current smoking. Harrell C values, an index of model discrimination, were computed for each Cox model. Analyses were executed in SAS 9.3 (SAS Institute, Cary, NC).
Results
Baseline characteristics of the study sample are shown in Table 1. The mean (SD) age of the study population was 59.9 years. Women constituted 43% of participants. Among the 2602 study participants included in this analysis, 46% were non-Hispanic white, 38% were non-Hispanic black, and 12% were Hispanic. Mean glomerular filtration rate was 45.3 mL/min per 1.73 m². The mean values of brachial systolic and diastolic pressures were 126.7 and 70.1 mmHg, respectively. Mean CF-PWV was 9.69 m/s. Diabetes mellitus was present in 31% of the sample, whereas a history of previous revascularization or myocardial infarction was present in 19% of the sample.

During a mean of 3.5 years of follow-up, 154 participants (5.9%) developed HF. Table 2 shows the association of various baseline characteristics and incident HF in unadjusted analyses. Factors associated with incident HF included age, blood pressure, the presence of chronic obstructive pulmonary disease, low-density lipoprotein-cholesterol, estimated glomerular filtration rate, urinary protein excretion, body mass index, diabetes mellitus, a history of myocardial infarction or coronary revascularization, aortic augmentation index corrected for a heart rate and CF-PWV (Table 2).

CF-PWV, Brachial Pressures, and Central Pressures as Predictors of Incident HF
Table 3 shows the HR (95% CI) associated with tertiles of (1) CF-PWV, (2) brachial systolic pressure, (3) central systolic pressure, (4) brachial PP, or (5) central PP. For each of these hemodynamic variables, Table 3 presents unadjusted analyses; analyses adjusted for demographic factors (age, race, sex, and enrollment site); and analyses further adjusted for diabetes mellitus, proteinuria, the presence of chronic obstructive pulmonary disease, low-density lipoprotein-cholesterol, estimated glomerular filtration rate, urinary protein excretion, body mass index, diabetes mellitus, a history of myocardial infarction or coronary revascularization, aortic augmentation index corrected for a heart rate and CF-PWV (Table 2).
When compared with subjects in the lowest tertile of brachial SBP, those in the highest tertile (but not those in the middle tertile) demonstrated a significantly increased risk of HF (HR, 4.89; 95% CI, 3.09–7.74; P<0.001). This association persisted in fully adjusted analyses (HR, 5.42; 95% CI, 2.92–9.93; P<0.001). Subjects in the highest tertile of central PP also demonstrated a greater risk of incident HF in unadjusted analyses, as well as in fully adjusted analyses (HR, 2.45; 95% CI, 1.14–5.27; P=0.05).

**Discussion**

In this study, we assessed the relationship between large artery stiffness (assessed as CF-PWV), brachial pressures, central pressures, and the risk of incident HF in a large cohort of subjects with CKD. We demonstrate, for the first time, that CF-PWV is associated with a pronounced increase in the risk of incident HF in this population, an association that persists after adjustment for blood pressure and other confounders. In addition, we demonstrate that brachial systolic and PP are both predictive of incident HF, whereas the association between central systolic and PP and incident HF was weaker and/or less consistent with increasing adjustment for covariates. Further characterization of risk factors for incident cardiovascular events in CKD is an important goal. In particular, prospective studies characterizing the factors related to incident HF in early CKD are lacking. HF is a major cause of morbidity and mortality in CKD. Our study is the first to investigate the associations between various factors present at baseline and incident HF in a large cohort of subjects with CKD. We demonstrate that HF is a common event in this cohort (Figure), and that large artery stiffening is an important independent risk factor for incident HF. CF-PWV is considered the gold standard index of large artery stiffness, whereas we included both SBP and CF-PWV to assess whether a measurement of the latter can be prognostic independently of the former; it should be recognized that SBP (and PP) are also importantly influenced by large artery stiffness. Thus, our study clearly demonstrates an independent association between large artery stiffening and incident HF in CKD, which has strong biological plausibility. Various
Table 3. Carotid-Femoral PWV, Central and Brachial Pressure Tertiles, and Risk of Incident Heart Failure (Events=154; Censored Participants With No Events=2448)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1 (Unadjusted)</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratios (95% CI)</td>
<td>P Value</td>
<td>Hazard Ratios (95% CI)</td>
</tr>
<tr>
<td>Carotid-femoral PWV, m/s</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤7.8</td>
<td>Harrell C=0.67 (0.47–1.00)</td>
<td>...</td>
<td>Harrell C=0.729 (0.58–0.91)</td>
</tr>
<tr>
<td>&gt;7.8 to ≤10.3</td>
<td>2.33 (1.67–3.25)</td>
<td>0.002</td>
<td>1.80 (1.05–3.10)</td>
</tr>
<tr>
<td>&gt;10.3</td>
<td>5.24 (3.22–8.53)</td>
<td>&lt;0.001</td>
<td>3.59 (2.14–6.03)</td>
</tr>
<tr>
<td>Brachial systolic blood pressure, mm Hg</td>
<td>Harrell C=0.642</td>
<td></td>
<td>Harrell C=0.721</td>
</tr>
<tr>
<td>≤116</td>
<td>Referent</td>
<td></td>
<td>Referent</td>
</tr>
<tr>
<td>&gt;116 to ≤133.3</td>
<td>1.36 (0.84–2.11)</td>
<td>0.21</td>
<td>1.22 (0.75–1.98)</td>
</tr>
<tr>
<td>&gt;133.3</td>
<td>3.21 (2.09–4.93)</td>
<td>&lt;0.001</td>
<td>2.39 (1.53–3.75)</td>
</tr>
<tr>
<td>Central systolic blood pressure, mm Hg</td>
<td>Harrell C=0.615</td>
<td></td>
<td>Harrell C=0.708</td>
</tr>
<tr>
<td>≤106</td>
<td>Referent</td>
<td></td>
<td>Referent</td>
</tr>
<tr>
<td>&gt;106 to ≤122.5</td>
<td>1.32 (0.83–2.09)</td>
<td>0.24</td>
<td>1.19 (0.74–1.89)</td>
</tr>
<tr>
<td>&gt;122.5</td>
<td>2.50 (1.64–3.80)</td>
<td>&lt;0.001</td>
<td>1.86 (1.20–2.89)</td>
</tr>
<tr>
<td>Brachial pulse pressure, mm Hg</td>
<td>Harrell C=0.680</td>
<td></td>
<td>Harrell C=0.74</td>
</tr>
<tr>
<td>≤46.7</td>
<td>Referent</td>
<td></td>
<td>Referent</td>
</tr>
<tr>
<td>&gt;46.7 to ≤62.7</td>
<td>1.64 (0.97–2.76)</td>
<td>0.063</td>
<td>1.25 (0.73–2.14)</td>
</tr>
<tr>
<td>&gt;62.7</td>
<td>4.89 (3.09–7.74)</td>
<td>&lt;0.001</td>
<td>3.35 (2.03–5.52)</td>
</tr>
<tr>
<td>Central pulse pressure, mm Hg</td>
<td>Harrell C=0.669</td>
<td></td>
<td>Harrell C=0.733</td>
</tr>
<tr>
<td>≤35.4</td>
<td>Referent</td>
<td></td>
<td>Referent</td>
</tr>
<tr>
<td>&gt;35.4 to ≤50.8</td>
<td>1.68 (1.01–2.78)</td>
<td>0.045</td>
<td>1.33 (0.79–2.24)</td>
</tr>
<tr>
<td>&gt;50.8</td>
<td>4.32 (2.75–6.80)</td>
<td>&lt;0.001</td>
<td>3.00 (1.84–4.91)</td>
</tr>
</tbody>
</table>

Model 1 is unadjusted; model 2 is adjusted for age, race, sex, and enrollment site; and Model 3 is additionally adjusted for diabetes mellitus, proteinuria, the presence of chronic obstructive pulmonary disease, mean arterial pressure, heart rate, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, body mass index, triglycerides, history of myocardial infarction/vascularization, current smoking, hemoglobin, human recombinant erythropoietin use, angiotensin-converting enzyme inhibitor use, β-blocker use, calcium channel blocker use, history of hypertension, fasting glucose, and serum albumin. CI indicates confidence interval; and PWV, pulse wave velocity.
ventricular afterload; and coronary artery disease, all of which may contribute to its associated with HF in CKD. Similarly, the association between kidney function and incident HF has been reported in previous studies that included individuals with and without established CKD (eg, older individuals) and has been shown to be independent of the presence of diabetes mellitus or hypertension at baseline. Renal dysfunction may lead to HF through several mechanisms, including plasma volume expansion, overactivity of the sympathetic nervous system, and the renin–angiotensin–aldosterone axis, hyperphosphatemia, and increased fibroblast growth factor-23 levels. The higher risk of HF among black participants is also consistent with previous data, demonstrating that blacks are more likely to develop CKD and HF and to progress from subclinical systolic and diastolic dysfunction and/or LV remodeling to frank HF than their white counterparts. Similarly, the Health, Aging and Body Compositions Study demonstrated an association between CKD and incident HF among older individuals, which was stronger for black, relative to white individuals, with a population-attributable risk for HF associated with moderate or high cystatin C levels of 47% for blacks versus 5% for whites, despite a similar prevalence of this abnormality at baseline. Finally, the observed association between body mass index and incident HF in our study is consistent with the well-known association between obesity and the risk of HF, previously reported in the general population.

Our study findings need to be interpreted in the context of its strengths and limitations. Our large, well-characterized, multi-ethnic sample, with an assessment of large artery stiffness using the gold standard measurement and the careful, systematic, adjudication of HF events, are important strengths of our study. In addition, our study population of mild to moderate diabetic and non-diabetic kidney disease represents one that has not been adequately represented in previous similar investigations. Our study also has limitations. We did not assess pulsatile left ventricular afterload or wave reflection magnitude, which will need to be assessed optimally using central pressure-flow analyses, to determine the pulsatile hemodynamic abnormalities better that are associated with incident HF in this population. Additional studies will also be required to assess the relationship between large artery stiffness, left ventricular remodeling at baseline and incident HF. Although we demonstrate an independent relationship between baseline large artery stiffness and future new-onset HF, our study cannot establish causality. Finally, our adjudication did not discriminate between HF with reduced ejection fraction and HF with preserved ejection fraction or did we have enough HF events to assess how the baseline predictors of HF relate to one type versus the other. This should be the focus of future studies in this cohort. We note that our study was not designed to address the potential enhancement in individual risk prediction provided by the use of CF-PWV in conjunction with, or addition to, existing clinical HF risk scores, or it intended to develop a CKD-specific risk score. This should be addressed in focus of future studies.

In conclusion, large artery stiffness independently predicts the onset of incident HF in subjects with CKD. These findings are important because they identify an important link between nonatherosclerotic vascular dysfunction and HF in this population. Our findings contribute to a better understanding of the

Figure. A. Incidental heart failure (HF) event rates among Chronic Renal Insufficiency Cohort Study participants without HF at study entry overall and by tertile of carotid-femoral pulse wave velocity (PWV). B. Kaplan–Meier curves for incident HF by tertile of carotid-femoral PWV. CHF indicates congestive heart failure.

Our study also found that older age, diabetes mellitus, a history of myocardial infarction, coronary revascularization, known arrhythmia, greater body mass index, lower estimated glomerular filtration rate, and urinary protein excretion were associated with incident HF. Older age is a well-known risk factor for HF, an observation that our study extends to the CKD population. Diabetes mellitus is associated with a variety of myocardial metabolic, structural, and functional abnormalities, with increased pulsatile left
determinants of HF risk in CKD and may be useful for the design of future intervention studies to reduce the risk of HF in this population.

Appendix

CRIC Study Investigators: Lawrence J. Appel, MD, MPH; Jiang He, MD, PhD; John W. Kusek, PhD; Mahboob Rahman, MD.

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Disclosures
Dr Chirinos has received research grants from the National Institutes of Health and the Department of Veterans Affairs for research related to arterial stiffness and has received consulting fees (modest) from Fukuda-Denshi and High Point Pharmaceuticals and received free equipment loans from Atcor Medical, IEM, Fukuda-Denshi and Health-Stats for research in arterial stiffness. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

Chronic kidney disease is associated with a markedly increased risk of heart failure (HF), but whether large artery stiffness or central hemodynamics can predict such risk is unknown. We studied 2602 participants who were free of HF at baseline. We assessed the carotid-femoral pulse wave velocity (the gold standard index of large artery stiffness), brachial, and central pressures as predictors of incident new-onset hospitalized HF during 3.5 years of follow-up. We found that carotid-femoral pulse wave velocity was a significant independent predictor of incident hospitalized HF. When compared with the lowest tertile, the hazard ratios among subjects in the middle and top carotid-femoral pulse wave velocity tertiles were 2.53 (95% confidence interval, 1.37–3.97; \( P=0.002 \)) and 5.24 (95% confidence interval, 3.22–8.53; \( P<0.0001 \)), respectively. After adjustment for multiple confounders, the hazard ratios for the middle and top carotid-femoral pulse wave velocity tertiles were 1.95 (95% confidence interval, 0.92–4.13; \( P=0.079 \)) and 3.01 (95% confidence interval, 1.45–6.26; \( P=0.003 \)), respectively. Brachial systolic and pulse pressure were also independently associated with incident hospitalized HF, whereas central pressures were less consistently associated with this end point. In conclusion, large artery stiffness is an independent predictor of incident HF in chronic kidney disease, an association with strong biological plausibility given the known effects of large artery stiffening of left ventricular pulsatile load. Implications of our study include (1) measurements of large artery stiffness may aid in the risk stratification for HF among patients with chronic kidney disease; (2) Interventions to reduce large artery stiffness should be tested in future studies to assess whether this approach can reduce the risk of incident HF in this population.
Arterial Stiffness, Central Pressures, and Incident Hospitalized Heart Failure in the Chronic Renal Insufficiency Cohort Study
for the CRIC Study Investigators

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