Prognostic Value of Coronary Flow Reserve in Patients with Dialysis-Dependent ESRD

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ABSTRACT

Capillary rarefaction of the coronary microcirculation is a consistent phenotype in patients with dialysis-dependent ESRD (dd-ESRD) and may help explain their excess mortality. Global coronary flow reserve (CFR) assessed by positron emission tomography (PET) is a noninvasive, quantitative marker of myocardial perfusion and ischemia that integrates the hemodynamic effects of epicardial stenosis, diffuse atherosclerosis, and microvascular dysfunction. We tested whether global CFR provides risk stratification in patients with dd-ESRD. Consecutive patients with dd-ESRD clinically referred for myocardial perfusion PET imaging were retrospectively included, excluding patients with prior renal transplantation. Per-patient CFR was calculated as the ratio of stress to rest absolute myocardial blood flow. Multivariable Cox proportional hazards models, including age, overt cardiovascular disease, and myocardial scar/ischemia burden, were used to assess the independent association of global CFR with all–cause and cardiovascular mortality. The incremental value of global CFR was assessed with relative integrated discrimination index and net reclassification improvement. In 168 patients included, median global CFR was 1.4 (interquartile range, 1.2–1.8). During follow-up (median of 3 years), 36 patients died, including 21 cardiovascular deaths. Log–transformed global CFR independently associated with all-cause mortality (hazard ratio, 0.01 per 0.5-unit increase; 95% confidence interval, <0.01 to 0.14; $P<0.001$) and cardiovascular mortality (hazard ratio, 0.01 per 0.5-unit increase; 95% confidence interval, <0.01 to 0.15; $P=0.002$). For all-cause mortality, addition of global CFR resulted in risk reclassification in 27% of patients. Thus, global CFR may provide independent and incremental risk stratification for all–cause and cardiovascular mortality in patients with dd-ESRD.

Cardiovascular disease is the leading cause of mortality in patients with dialysis-dependent ESRD (dd-ESRD), accounting for at least 40% of deaths.[1] Even after adjustment for traditional cardiovascular risk factors, the risk of cardiovascular death is 10- to 20-fold higher in these patients compared with in the general population.[2] Capillary rarefaction of the coronary and renal microcirculations has been a consistent pathologic phenotype in clinical and experimental models of renal impairment.[3–6] This observation has led to the hypothesis that myocardial ischemia, tissue hypoxia, and the resulting myocardial injury may explain the excess cardiovascular morbidity and mortality in patients with dd-ESRD.

Table 1. Baseline characteristics

Characteristics	All Patients (n=168)	Global CFR ≤1.4 (n=81)	Global CFR >1.4 (n=87)	P Value
Demographics				
Age, yr	62 [53–69]	64 [55–71]	60 [50–66]	0.01
Women	66 (39)	25 (31)	41 (47)	0.03
Race				0.17
White	59 (35)	35 (43)	24 (28)	
Black	71 (42)	30 (37)	41 (47)	
Nonwhite Hispanic	24 (14)	9 (11)	15 (17)	
Other	14 (8)	7 (9)	7 (8)	
Renal history				
Medical etiology of CKD[a]	118 (70)	59 (73)	59 (68)	0.48
Duration of dialysis, yr				0.61
<1	60 (36)	32 (40)	28 (32)	
1–3	45 (27)	20 (25)	25 (29)	
>3	63 (38)	29 (36)	34 (39)	
Cardiovascular history				
Any overt CVD	72 (43)	41 (51)	31 (36)	0.05
Myocardial infarction	54 (32)	30 (37)	24 (28)	0.19
PCI	28 (17)	18 (22)	10 (12)	0.06
Coronary artery bypass	17 (10)	13 (16)	4 (5)	0.01
Stroke	16 (10)	7 (9)	9 (10)	0.71
Revascularized PAD	7 (4)	5 (6)	2 (2)	0.21
Cardiovascular risk factors				
Diabetes	102 (61)	52 (64)	50 (58)	0.37
Hypertension	156 (93)	79 (98)	77 (89)	0.02
Dyslipidemia	103 (61)	53 (65.4)	50 (57.5)	0.29
BMI, kg/m^2	27 [23–33]	27 [24–31]	27 [23–34]	0.36
Family history of CAD	29 (17)	14 (17)	15 (17)	0.99
Tobacco use	14 (8)	6 (7)	8 (9)	0.68
Medications				
Aspirin	93 (55)	47 (58)	46 (53)	0.50
β-Adrenergic blockers	121 (72)	65 (80)	56 (64)	0.02
Statin	107 (64)	57 (70)	50 (58)	0.08
ACE inhibitors/ARB	80 (48)	34 (42)	46 (53)	0.16
Serum laboratories				
Phosphorus, mg/dl (n=92)	4.8 [3.8–6.1]	4.8 [3.7–6.1]	4.7 [4.0–6.1]	0.89
Calcium, mg/dl (n=112)	9.2 [8.3–9.7]	8.7 [8.1–9.7]	9.3 [8.6–9.8]	0.18
iPTH, pg/ml (n=79)	257 [112–368]	255 [86–420]	260 [143–346]	0.88
Resting hemodynamics				
Heart rate, bpm	72 [65–82]	70 [63–83]	72 [65–80]	0.85
SBP, mmHg	150 [128–176]	148 [126–172]	153 [129–178]	0.07
Imaging parameters				
Rest LVEF, %	52 [44–60]	50 [40–57]	54 [46–62]	0.004
BSA–indexed left ventricular mass, g/m^2 (n=163)	79 [67–92]	80 [70–98]	77 [66–89]	0.03
Ischemia + scar, % myocardium	0 [0–9]	6 [0–16]	0 [0–3]	<0.001
Ischemia, % myocardium	0 [0–4]	1 [0–9]	0 [0–1]	<0.001
Peak hyperemic MBF, ml/g per minute	1.6 [1.2–2.2]	1.30 [1.0–1.6]	2.0 [1.5–2.8]	<0.001
LAD territory	1.7 [1.2–2.3]	1.4 [1.0–1.7]	2.0 [1.5–3.0]	<0.001
LCx territory	1.6 [1.2–2.2]	1.2 [1.1–1.6]	2.0 [1.5–2.6]	<0.001
RCA territory	1.6 [1.1–2.1]	1.3 [1.0–1.6]	2.0 [1.5–2.7]	<0.001
Rest MBF, ml/g per minute	1.1 [0.9–1.4]	1.1 [0.9–1.4]	1.0 [0.8–1.4]	0.67
LAD territory	1.1 [0.9–1.5]	1.2 [1.0–1.5]	1.1 [0.9–1.5]	0.40
LCx territory	1.1 [0.8–1.4]	1.1 [0.9–1.3]	1.1 [0.8–1.4]	0.91
RCA territory	1.1 [0.8–1.4]	1.1 [0.8–1.4]	1.0 [0.8–1.4]	0.91

Table 1. Continued

Characteristics	All Patients (*n*=168)	Global CFR ≤1.4 (*n*=81)	Global CFR >1.4 (*n*=87)	*P* Value
LAD CFR	1.4 [1.2–1.8]	1.2 [1.0–1.3]	1.8 [1.5–2.1]	<0.001
LCx CFR	1.4 [1.2–1.8]	1.2 [1.0–1.3]	1.8 [1.5–2.0]	<0.001
RCA CFR	1.5 [1.2–1.8]	1.2 [1.0–1.4]	1.8 [1.5–2.2]	<0.001

Continuous variables are presented as medians with IQRs or means±SDs. Binary variables are presented as absolute numbers and percentages. CVD, cardiovascular disease; PCI, percutaneous coronary intervention; PAD, peripheral arterial disease; BMI, body mass index; CAD, coronary artery disease; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; iPTH, intact parathyroid hormone; SBP, systolic BP; LVEF, left ventricular ejection fraction; BSA, body surface area; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; RCA, right coronary artery.
[a]Medical etiology of CKD refers to CKD resulting primarily from hypertension, diabetes, and/or heart failure.
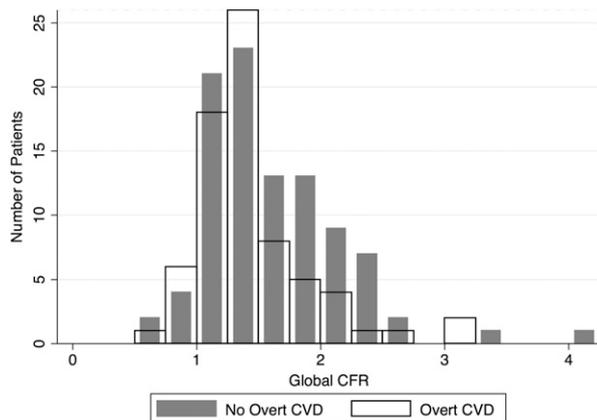

Figure 1. CFR<2.0 is highly prevalent in patients with dd-ESRD even in the absence of overt cardiovascular disease (CVD). Overt CVD was defined as one or more of prior myocardial infarction, stroke, percutaneous coronary intervention, coronary artery bypass, or peripheral arterial revascularization.

Coronary flow reserve (CFR) as assessed by positron emission tomography (PET) is a quantitative, reproducible, and sensitive marker of myocardial perfusion and ischemia that integrates the hemodynamic effects of epicardial stenosis, diffuse atherosclerosis, and microvascular dysfunction.[7,8] Addition of CFR has been shown to improve the value of traditional risk assessment for cardiac death in a variety of patient populations, including high-risk cohorts, such as patients with diabetes and patients with mild to moderate CKD.[9–12] This study was designed to test the hypothesis that global CFR provides independent and incremental risk stratification in patients with dd-ESRD.

RESULTS

Baseline Characteristics

We identified 203 consecutive patients with dd-ESRD who underwent stress myocardial perfusion PET with measurement of CFR during the study period. Two patients who had previously undergone heart transplantation and 33 patients who had previously undergone renal transplantation were excluded. The remaining 168 patients comprised the study cohort (Table 1). The median age was 62 years old (interquartile range [IQR], 53–69), 39% of the patients were women, 61% of the cohort had diabetes, 93% had hypertension, and 43% had overt cardiovascular disease. The median left ventricular ejection fraction as assessed by PET was 52% (IQR, 44%–60%).

Coronary Hemodynamics

The median global myocardial blood flow (MBF) at rest was 1.1 (IQR, 0.9–1.4) ml/min per gram, which increased to 1.6 (IQR, 1.2–2.2) ml/min per gram during peak hyperemia. The corresponding median global CFR was 1.4 (IQR, 1.2–1.8). Figure 1 shows the high relative frequency of global CFR <2.0 in this population, even in the absence of overt cardiovascular disease. As shown in Table 1, rest MBF was similar in patients with global CFR above and below the cohort median value. Consequently, abnormalities in global CFR were driven primarily by diffusely impaired peak hyperemic MBF involving all three coronary artery territories. Supplemental Table 1 shows PET imaging parameters stratified by all-cause mortality during follow-up (primary endpoint).

All–Cause and Cardiovascular Mortality

During follow-up (median of 3 years), 36 all-cause deaths occurred (annual unadjusted mortality rate of 10%). The primary cause of death was cardiovascular in 21 patients, noncardiovascular in 11 patients, and unknown in four patients. All-cause mortality was significantly higher among patients with global CFR ≤1.4 than in those with global CFR >1.4 (log–rank chi squared =15.5; *P*<0.001) (Figure 2A). Cardiovascular mortality was also significantly higher among patients with CFR≤1.4 than in those with CFR>1.4 (log–rank chi squared =12.3; *P*<0.001) (Figure 2B). Log–transformed global CFR was independently associated with all-cause mortality (hazard ratio, 0.01 per 0.5-unit increase; 95% confidence interval [95% CI], <0.01 to 0.14; *P*<0.001) in a multivariable Cox proportional hazards model adjusting for age, overt cardiovascular disease, and myocardial scar/ischemia burden (Table 2, model 2). Additionally, log–transformed global CFR was independently associated with cardiovascular mortality (hazard ratio, 0.01 per 0.5-unit increase; 95% CI, <0.01 to 0.15; *P*=0.002) in a multivariable Cox proportional hazards model adjusting for the same covariates as above (Table 3, model 2).
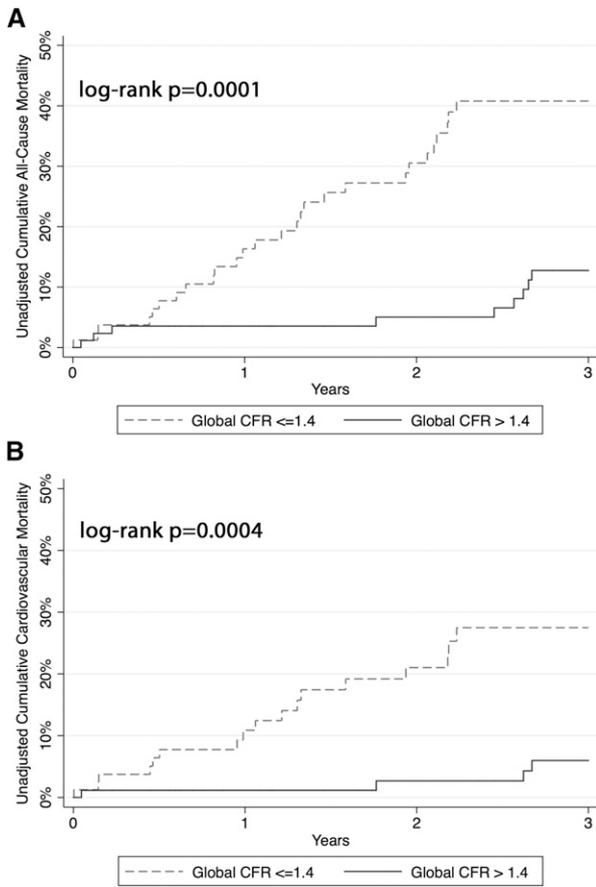
Figure 2. Clinical outcomes stratified by global CFR above and below the median value in patients with dd-ESRD. (A) Unadjusted cumulative all-cause mortality. (B) Unadjusted cumulative cardiovascular mortality.

Risk Reclassification by Global CFR

Addition of global CFR to the base Cox proportional hazards model for all-cause mortality provided incremental prognostic information (increase in global chi squared from 42.2 to 54.3; $P=0.001$) (Table 2, model 2). Addition of global CFR to the base Cox proportional hazards model for cardiovascular mortality also provided incremental prognostic information (increase in global chi squared from 31.5 to 40.5; $P=0.003$) (Table 3, model 2). After adjusting for age, overt cardiovascular disease, and myocardial scar/ischemia burden, log–transformed global CFR improved risk discrimination for all-cause mortality (relative integrated discrimination index [IDI], 0.19; 95% CI, <0.01 to 0.43). Log–transformed global CFR also improved risk reclassification (categorical net reclassification improvement [NRI], 0.22; 95% CI, 0.08 to 0.34; continuous NRI, 0.77; 95% CI, 0.38 to 1.15). Favorable risk reclassification was seen in the high pre–CFR risk stratum (>3% per year mortality; categorical NRI, 0.25; 95% CI, 0.12 to 0.36), which accounted for 74% of patients. High-risk patients who were downward reclassified to low ($n=1$) or intermediate ($n=25$) risk on the basis of log–transformed global CFR experienced

annualized mortality rates of 0% and 2%, respectively, compared with 17% annualized mortality among those who remained in the high-risk category. Overall, 27% of patients were reclassified.

Risk discrimination improvement for cardiovascular mortality was comparable in magnitude with that seen with all-cause mortality but was not statistically significant (relative IDI, 0.17; 95% CI, −0.04 to 0.50). Log-transformed CFR did substantially improve risk reclassification for cardiovascular mortality (categorical NRI, 0.48; 95% CI, 0.29 to 0.73; continuous NRI, 0.78; 95% CI, 0.27 to 1.26).

DISCUSSION

To our knowledge, this is the first study to link global CFR, a precise quantitative measure of coronary function and myocardial ischemia, to clinical outcomes in a large cohort of patients with dd-ESRD. We found that approximately 80% of patients in our cohort had global CFR values <2.0, with values >2.0 considered to be low risk in other patient cohorts.[11] Importantly, we have also shown that global CFR provides risk stratification for all–cause and cardiovascular mortality independent of traditional risk factors, including age, known cardiovascular disease, and myocardial scar/ischemia burden. This novel finding highlights the significant clinical effect of diffuse atherosclerosis and microvascular dysfunction in this relatively understudied patient population. Finally, our results suggest a potentially important role of global CFR for risk reclassification in patients with dd-ESRD, generally assumed until now to be at uniformly high risk for mortality.

Exactly how impaired global CFR associates with increased clinical risk cannot be determined from this study. Two potential mechanisms could, however, explain our findings. First, impaired global CFR may result from significant myocardial capillary rarefaction, a well known phenomenon in patients with dd-ESRD.[4] In experimental uremic rat models, myocardial capillary rarefaction has been associated with increased myocardial ischemia and myocardial infarct size.[6] Myocardial ischemia resulting from supply-demand mismatch may lead to low–level myocardial injury and regional wall motion abnormalities and may explain the association between elevated high–sensitivity cardiac troponin T and incident heart failure in patients with dd-ESRD without coronary artery disease.[13,14] Second, impaired global CFR may also reflect microvascular dysfunction resulting from arteriolar remodeling,[15] endothelial dysfunction, and/or increased extravascular resistance (*i.e.*, left ventricular hypertrophy or interstitial fibrosis), all of which have been documented in patients with uremia[16] and may be contributors to subclinical myocardial ischemia and injury.

Our results support the hypothesis that diffuse atherosclerosis and microvascular dysfunction, as measured by global CFR, are important markers of clinical risk in patients with dd-ESRD and that quantitation of global CFR may be a clinically useful tool to improve risk stratification in these patients.[16]

Table 2. Addition of CFR to a multivariable Cox regression model for all-cause mortality (primary end point)

Fit Statistic	Model 1		Model 2 (Model 1 + ln CFR)	
	Estimate/HR (95% CI)	P Value	Estimate/HR (95% CI)	P Value
Global chi squared	42.2	Reference	54.3	0.001
Age, yr	1.04 (1.01 to 1.08)	0.02	1.04 (1.01 to 1.08)	0.04
Overt CVD	2.39 (1.04 to 5.47)	0.04	2.50 (1.10 to 5.66)	0.03
Ischemia + scar, % myocardium	1.05 (1.03 to 1.08)	<0.001	1.04 (1.02 to 1.06)	0.001
ln CFR (per 0.5-unit increase)			0.01 (<0.01 to 0.14)	<0.001

Model 2 adds ln CFR to model 1. Overt cardiovascular disease (CVD) was defined as one or more of the following: prior myocardial infarction, stroke, percutaneous coronary intervention, coronary artery bypass, or peripheral arterial revascularization. HR, hazard ratio.

Table 3. Addition of CFR to a multivariable Cox regression model for cardiovascular mortality (secondary end point)

Fit Statistic	Model 1		Model 2 (Model 1 + ln CFR)	
	Estimate/HR (95% CI)	P Value	Estimate/HR (95% CI)	P Value
Global chi squared	31.5	Reference	40.5	0.003
Age, yr	1.01 (0.97 to 1.06)	0.53	1.01 (0.96 to 1.05)	0.77
Overt CVD	4.47 (1.26 to 15.94)	0.02	4.75 (1.35 to 16.76)	0.02
Ischemia + scar, % myocardium	1.06 (1.03 to 1.09)	<0.001	1.04 (1.01 to 1.07)	0.002
ln CFR (per 0.5-unit increase)			0.01 (<0.01 to 0.15)	0.002

Model 2 adds ln CFR to model 1. Overt cardiovascular disease (CVD) was defined as one or more of the following: prior myocardial infarction, stroke, percutaneous coronary intervention, coronary artery bypass, or peripheral arterial revascularization. HR, hazard ratio.

Diffuse atherosclerosis and microvascular dysfunction may partially explain why the association between elevated LDL cholesterol and myocardial infarction is attenuated in patients with advanced CKD[17] and may also help us understand previously observed discrepancies between traditional cardiovascular risk assessment and outcomes after renal transplantation.[18] Additional studies are needed to determine whether longitudinal improvement in global CFR is associated with risk reduction. If that can be shown, it may be appropriate to use global CFR as a surrogate for mortality in future clinical trials involving patients with dd-ESRD.

As with any diagnostic test, the potential benefits of measuring global CFR should be weighed against the associated risks. The radiation dose associated with PET myocardial perfusion imaging is approximately 4.6 millisievert (mSv) or less depending on the protocol and radiopharmaceutical dose. This is generally considered low-level radiation, which is slightly higher than the 3-mSv dose from background radiation in the United States. However, any CFR–based risk stratification strategy should always be weighed against alternative strategies that do not require radiation exposure.

Our study is subject to limitations inherent to a single–center, retrospective study design, including higher-risk patients clinically referred for evaluation of symptoms or as part of prerenal transplant evaluation. Consequently, our results should be extrapolated to other populations with caution, particularly the subset of patients with dd-ESRD not referred for cardiovascular risk stratification. Nevertheless, with limited exclusion criteria, we believe that our study cohort is fairly representative of patients with dd-ESRD clinically referred for cardiovascular risk stratification at most large medical centers.

A second limitation is that we were unable to rigorously characterize the duration of CKD and dialysis before CFR evaluation. Future studies that do so could more precisely illuminate the effects of CKD and dialysis on CFR. A third consideration is that all patients in our cohort were tested during the interdialytic interval. Whether volume shifts during this period affect global CFR and/or its association with mortality cannot be determined from our data. However, consistent evidence from experimental animals and humans suggests that endothelium–dependent or –independent coronary vasodilatory function is not affected by volume overload.[19–21] Finally, our sample size limited the number of confounding variables that we could adjust for in our multivariable Cox survival analyses and may have limited our power to detect weak associations of baseline characteristics with global CFR.

In summary, our study is the first to show that global CFR provides independent and incremental risk stratification in patients with dd-ESRD. A relatively preserved global CFR helps identify patients with dd-ESRD at significantly lower clinical risk, and as such, it may be an appropriate surrogate end point in future clinical trials involving this high-risk population.

CONCISE METHODS

Study Sample
Consecutive patients with dd-ESRD clinically referred for stress myocardial perfusion PET imaging at the Brigham and Women's Hospital between January 1, 2006 and November 30, 2012 were retrospectively included in the study cohort. Patients were referred for evaluation of known or suspected coronary artery disease and/or

prerenal transplant evaluation. Patients who had undergone heart and/or renal transplantation were excluded. For individuals with multiple PET studies, only the first scan was included. Demographic factors and relevant medical history, including coronary artery disease risk factors and medication use, were ascertained at the time of the PET study by review of medical records and patient interview.[9–11] A history of overt cardiovascular disease was defined as one or more of the following: prior myocardial infarction, stroke, percutaneous coronary intervention, coronary artery bypass, or peripheral arterial revascularization. Medical etiology of CKD was defined as CKD resulting primarily from hypertension, diabetes, and/or heart failure. Serum laboratory values obtained for clinical purposes in the 90-day period before PET were averaged if multiple values were available. The study was approved by the Partners Healthcare Institutional Review Board and conducted in accordance with institutional guidelines.

PET Imaging

Patients were studied using a whole–body PET–computed tomography scanner (Discovery RX or STE Lightspeed 64; GE Healthcare, Milwaukee, WI). Myocardial perfusion was assessed at rest and during peak hyperemia using ^{82}Rb or ^{13}N-ammonia as the flow tracer, which has been described previously.[11] Hyperemic stress was achieved using intravenous dipyridamole, adenosine, or regadenoson as per standard protocol. Prior data have shown equivalence in the hyperemia achieved with these agents and more importantly, no agent-specific effect on the association between global CFR and patient outcomes.[11,22] To ensure stability of intravascular volume and serum electrolytes, it is standard practice in our nuclear cardiology laboratory not to administer intravenous vasodilator stress agents on the day of dialysis. CFR measurements are obtained through post-processing of PET images and therefore, do not involve additional radiation exposure, imaging time, or cost to the patient. Computed tomography was used only for attenuation correction. The average radiation exposure for the entire PET study was ≤4.6 mSv.

For semiquantitative assessment of myocardial scarring and ischemia, 17–segment visual interpretation of gated myocardial perfusion images was performed by experienced operators using a standard five–point scoring system.[23] Global rest, stress, and difference (stress − rest) scores reflecting the total left ventricular burden of ischemia and/or scar were converted to percentage of myocardium by dividing by the maximum score of 68. For each of these variables, higher scores reflect larger areas of myocardial scar and/or ischemia. Rest and stress left ventricular ejection fractions were calculated from gated myocardial perfusion images using commercially available software (4DM; Invia, Ann Arbor, MI).

Absolute global MBF (in milliliters per minute per gram) was quantified at rest and peak hyperemia using automated factor analysis and a validated two–compartment kinetic model as previously described.[24] Per–patient global CFR was calculated as the ratio of stress to rest absolute MBF for the entire left ventricle. MBF and CFR values were not clinically available to referring physicians.

Outcomes

The prespecified primary end point was all-cause mortality. Vital status was ascertained by integrating data from the Social Security Death Index, the National Death Index, and the Partners Healthcare Research Patient Data Registry. Secondary analysis was performed for cardiovascular mortality. Cause of death was determined by blinded adjudication by two independent cardiologists as described previously.[25]

Statistical Analyses

Statistical significance was assessed with Wilcoxon tests, Fisher exact tests, and chi-squared tests for continuous, dichotomous, and categorical variables, respectively. Two–sided P values <0.05 were considered significant. Cox proportional hazards models were used to assess the association of global CFR with all–cause and cardiovascular mortality after controlling for age, overt cardiovascular disease, and myocardial scar/ischemia burden. Because global CFR followed a log-normal distribution, it was transformed with the natural log before inclusion in the Cox models. Patients who underwent renal transplantation after PET were censored on the date of transplantation. Incremental value of global CFR was assessed with the global chi squared statistic for improved model fit, relative IDI for risk discrimination, and NRI for risk reclassification; 95% CIs for NRI were determined by bootstrapping. We used risk categories of <1%, 1%–3%, and >3% per year risk of mortality for the categorical NRI. All statistical analyses were performed with Stata, version 13 (StataCorp LP, College Station, TX), SAS, version 9.4 (SAS Institute, Cary, NC), or R 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

DISCLOSURES

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REFERENCES

1. Collins AJ, Foley RN, Chavers B, Gilbertson D, Herzog C, Ishani A, Johansen K, Kasiske BL, Kutner N, Liu J, St Peter W, Guo H, Hu Y, Kats A, Li S, Li S, Maloney J, Roberts T, Skeans M, Snyder J, Solid C, Thompson B, Weinhandl E, Xiong H, Yusuf A, Zaun D, Arko C, Chen SC, Daniels F, Ebben J, Frazier E, Johnson R, Sheets D, Wang X, Forrest B, Berrini D, Constantini E, Everson S, Eggers P, Agodoa L: US Renal Data System 2013 Annual Data Report. *Am J Kidney Dis* 63 [Suppl]: A7, 2014

2. Foley RN, Parfrey PS, Sarnak MJ: Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 32[Suppl 3]: S112–S119, 1998

3. Charytan DM, Padera R, Helfand AM, Zeisberg M, Xu X, Liu X, Himmelfarb J, Cinelli A, Kalluri R, Zeisberg EM: Increased concentration of circulating angiogenesis and nitric oxide inhibitors induces endothelial to mesenchymal transition and myocardial fibrosis in patients with chronic kidney disease. *Int J Cardiol* 176: 99–109, 2014

4. Amann K, Breitbach M, Ritz E, Mall G: Myocyte/capillary mismatch in the heart of uremic patients. *J Am Soc Nephrol* 9: 1018–1022, 1998

5. Amann K, Wiest G, Zimmer G, Gretz N, Ritz E, Mall G: Reduced capillary density in the myocardium of uremic rats–a stereological study. *Kidney Int* 42: 1079–1085, 1992

6. Dikow R, Kihm LP, Zeier M, Kapitza J, Törnig J, Amann K, Tiefenbacher C, Ritz E: Increased infarct size in uremic rats: Reduced ischemia tolerance? *J Am Soc Nephrol* 15: 1530–1536, 2004

7. Gould KL: Does coronary flow trump coronary anatomy? *JACC Cardiovasc Imaging* 2: 1009–1023, 2009

8. Gould KL, Johnson NP, Bateman TM, Beanlands RS, Bengel FM, Bober R, Camici PG, Cerqueira MD, Chow BJ, Di Carli MF, Dorbala S, Gewirtz H, Gropler RJ, Kaufmann PA, Knaapen P, Knuuti J, Merhige ME, Rentrop KP, Ruddy TD, Schelbert HR, Schindler TH, Schwaiger M, Sdringola S, Vitarello J, Williams KA Sr., Gordon D, Dilsizian V, Narula J: Anatomic versus physiologic assessment of coronary artery disease. Role of coronary flow reserve, fractional flow reserve, and positron emission tomography imaging in revascularization decision-making. *J Am Coll Cardiol* 62: 1639–1653, 2013

9. Murthy VL, Naya M, Foster CR, Gaber M, Hainer J, Klein J, Dorbala S, Blankstein R, Di Carli MF: Association between coronary vascular dysfunction and cardiac mortality in patients with and without diabetes mellitus. *Circulation* 126: 1858–1868, 2012

10. Murthy VL, Naya M, Taqueti VR, Foster CR, Gaber M, Hainer J, Dorbala S, Blankstein R, Rimoldi O, Camici PG, Di Carli MF: Effects of sex on coronary microvascular dysfunction and cardiac outcomes. *Circulation* 129: 2518–2527, 2014

11. Murthy VL, Naya M, Foster CR, Hainer J, Gaber M, Di Carli G, Blankstein R, Dorbala S, Sitek A, Pencina MJ, Di Carli MF: Improved cardiac risk assessment with noninvasive measures of coronary flow reserve. *Circulation* 124: 2215–2224, 2011

12. Murthy VL, Naya M, Foster CR, Hainer J, Gaber M, Dorbala S, Charytan DM, Blankstein R, Di Carli MF: Coronary vascular dysfunction and prognosis in patients with chronic kidney disease. *JACC Cardiovasc Imaging* 5: 1025–1034, 2012

13. Bansal N, Hyre Anderson A, Yang W, Christenson RH, deFilippi CR, Deo R, Dries DL, Go AS, He J, Kusek JW, Lash JP, Raj D, Rosas S, Wolf M, Zhang X, Shlipak MG, Feldman HI: High-sensitivity troponin T and N-terminal pro-B-type natriuretic peptide (NT-proBNP) and risk of incident heart failure in patients with CKD: The Chronic Renal Insufficiency Cohort (CRIC) Study. *J Am Soc Nephrol* 26: 946–956, 2015

14. McIntyre CW, Burton JO, Selby NM, Leccisotti L, Korsheed S, Baker CS, Camici PG: Hemodialysis-induced cardiac dysfunction is associated with an acute reduction in global and segmental myocardial blood flow. *Clin J Am Soc Nephrol* 3: 19–26, 2008

15. Törnig J, Gross ML, Simonaviciene A, Mall G, Ritz E, Amann K: Hypertrophy of intramyocardial arteriolar smooth muscle cells in experimental renal failure. *J Am Soc Nephrol* 10: 77–83, 1999

16. Amann K, Ritz E: Microvascular disease–the Cinderella of uraemic heart disease. *Nephrol Dial Transplant* 15: 1493–1503, 2000

17. Tonelli M, Muntner P, Lloyd A, Manns B, Klarenbach S, Pannu N, James M, Hemmelgarn B; Alberta Kidney Disease Network: Association between LDL-C and risk of myocardial infarction in CKD. *J Am Soc Nephrol* 24: 979–986, 2013

18. Jeloka TK, Ross H, Smith R, Huang M, Fenton S, Cattran D, Schiff J, Cardella C, Cole E: Renal transplant outcome in high-cardiovascular risk recipients. *Clin Transplant* 21: 609–614, 2007

19. Carabello BA, Nakano K, Ishihara K, Kanazawa S, Biederman RW, Spann JF Jr.: Coronary blood flow in dogs with contractile dysfunction due to experimental volume overload. *Circulation* 83: 1063–1075, 1991

20. Akasaka T, Yoshida K, Hozumi T, Takagi T, Kaji S, Kawamoto T, Ueda Y, Okada Y, Morioka S, Yoshikawa J: Restricted coronary flow reserve in patients with mitral regurgitation improves after mitral reconstructive surgery. *J Am Coll Cardiol* 32: 1923–1930, 1998

21. Symons JD, Gunawardena S, Kappagoda CT, Dhond MR: Volume overload left ventricular hypertrophy: Effects on coronary microvascular reactivity in rabbits. *Exp Physiol* 86: 725–732, 2001

22. Chan SY, Brunken RC, Czernin J, Porenta G, Kuhle W, Krivokapich J, Phelps ME, Schelbert HR: Comparison of maximal myocardial blood flow during adenosine infusion with that of intravenous dipyridamole in normal men. *J Am Coll Cardiol* 20: 979–985, 1992

23. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, Pennell DJ, Rumberger JA, Ryan T, Verani MS; American Heart Association Writing Group on Myocardial Segmentation and Registration for Cardiac Imaging: Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation* 105: 539–542, 2002

24. El Fakhri G, Kardan A, Sitek A, Dorbala S, Abi-Hatem N, Lahoud Y, Fischman A, Coughlan M, Yasuda T, Di Carli MF: Reproducibility and accuracy of quantitative myocardial blood flow assessment with (82)Rb PET: Comparison with (13)N-ammonia PET. *J Nucl Med* 50: 1062–1071, 2009

25. Taqueti VR, Hachamovitch R, Murthy VL, Naya M, Foster CR, Hainer J, Dorbala S, Blankstein R, Di Carli MF: Global coronary flow reserve is associated with adverse cardiovascular events independently of luminal angiographic severity and modifies the effect of early revascularization. *Circulation* 131: 19–27, 2015