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Renal Function and Risk Stratification of Diabetic and Nondiabetic Patients Undergoing Evaluation for Coronary Artery Disease

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OBJECTIVES The aim of this study was to evaluate the impact of renal function by estimated glomerular filtration rate (eGFR) on risk stratification of diabetic and nondiabetic patients undergoing myocardial perfusion imaging (MPI) by single-photon emission computed tomography for suspected ischemia.

BACKGROUND Coronary artery disease is the leading cause of death among diabetic persons; however, diabetic persons are a very heterogeneous group in terms of cardiovascular risk, necessitating further risk stratification.

METHODS Patients (n = 1,747, age 65 ± 10 years, 37% diabetic) undergoing MPI were followed for cardiac death (CD) for a mean of 2.15 ± 0.8 years. Chronic kidney disease (CKD) was defined by an eGFR <60 ml/min.

RESULTS In the presence of a normal scan, annual CD rate was 0.9% for those with no diabetes mellitus (DM) and no CKD, 0.5% in the DM alone group, 2.35% in CKD alone, and 2.9% in those with both DM and CKD ($p < 0.001$). Patients with DM+CKD had a 2.7-fold risk of CD compared with no DM no CKD ($p = 0.001$) after controlling for age, ejection fraction, history of coronary artery disease, and other risk factors. The risk of CD increased as a function of the presence and severity of perfusion defects, regardless of CKD or DM status. Presence of CKD conferred a several-fold higher risk of CD for the various strata of perfusion defects. Log-rank test for difference in probability of CD was nonsignificant for comparison between patients with no DM no CKD and those with DM alone ($p = 0.73$) but was significant for comparison between patients with no DM no CKD and patients with CKD alone ($p < 0.001$) or DM+CKD ($p < 0.001$).

CONCLUSIONS MPI and eGFR provide valuable risk stratification for diabetic and nondiabetic patients. Diabetic patients without CKD seem to have similar short-term cardiac outcomes compared with nondiabetic patients. Underlying CKD seems to identify a high-risk subgroup of diabetic patients. (J Am Coll Cardiol Img 2010;3:734–45) © 2010 by the American College of Cardiology Foundation

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The prevalence of diabetes mellitus (DM) continues to grow at an alarming rate. Recent figures estimate that 17.5 million people in the U.S. have diabetes, and with an aging population and an obesity epidemic, these figures are predicted to rise (1). The complications from diabetes are varied and involve multiple organ systems. However, 65% to 70% of diabetic mortality is principally caused

See page 746

by cardiovascular disease (2). Given this high burden of cardiovascular mortality, the National Cholesterol Education Program elevated type 2 diabetes to the highest risk category by making it a coronary heart disease risk-equivalent (3). However, diabetic persons are a heterogeneous group, and there are subgroups of diabetic persons at lower risk for cardiovascular complications and subgroups at high risk, in need of intensive risk factor modification, screening, treatment, and close clinical follow-up.

The impact of chronic kidney disease (CKD) on cardiovascular and all-cause mortality (ACM) has been well-established (4–9). In the most recent practice guidelines from the National Kidney Foundation and the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; it was recommended that individuals with CKD be considered in the highest risk group for cardiovascular disease (10,11).

With the strong links among CKD, diabetes, and cardiovascular mortality and the prevalence reaching epidemic proportions, the need for effective risk stratification of diabetic persons assumes unprecedented significance. Multiple studies have tried to address the issue of cardiac risk stratification of diabetic patients by noninvasive testing. In the recently published outcomes of the DIAD (Detection of Ischemia in Asymptomatic Diabetics) study, the event rate overall at 5 years was very low, and screening with myocardial perfusion imaging (MPI) by single-photon emission computed tomography did not seem to affect the risk profile. On the basis of these results, the authors concluded that routine screening in asymptomatic diabetic patients cannot be justified (12). To further investigate the issue of effective risk stratification, we examined the impact of renal function as measured by estimated glomerular filtration rate (eGFR) on risk stratifying diabetic and nondiabetic patients undergoing stress MPI for evaluation of suspected coronary artery disease (CAD).

METHODS

Population. This was an observational retrospective cohort of 1,747 consecutive patients with known or suspected CAD undergoing stress MPI between June 2002 and July 2005 at the William S. Middleton Memorial Veterans Hospital (VA), Madison, Wisconsin. The study was approved by the VA institutional review board.

Sources of data. With the VISTA (Veterans Affairs Information System Technology and Architecture) database, we reviewed inpatient and outpatient electronic records for patients. The VA, America's largest integrated health care system, has a uniform, fully electronic national record system called the CPRS (Computerized Patient Record System). It provides networked, robust, and timely retrieval of remote-site patient data. All clinic, emergency department visits, and hospital stay records including outpatient phone contacts are electronically stored in CPRS. Hospital stays outside the VA are either recorded in VA physician notes or scanned and stored electronically in the VA system. Manual extraction of patient information and records from the VISTA/CPRS interface program was performed by 3 investigators who were blinded to the renal and single-photon emission computed tomography (SPECT) data.

The initial patient visit (closest to the time of MPI) was used to determine demographic data, height, weight, cardiovascular symptoms, baseline electrocardiogram (ECG), and baseline cardiac risk factors. The presence of risk factors was determined by diagnosis documented by a physician, supportive laboratory data, or medications that would support these diagnoses. The presence of diabetes required physician documentation or the presence of diabetic medications including insulin and oral hypoglycemic agents. The presence of CAD required either a previous coronary event or a documented CAD diagnosis via cardiac stress testing or coronary angiography. Additional data including medications at the time of MPI and laboratory findings, specifically hemoglobin and creatinine levels, were obtained from CPRS. Laboratory data was obtained within a mean of 49 ± 20 days from the time of MPI evaluation.

Imaging and stress protocol. Rest-stress MPI imaging with technetium-99 Sestamibi or tetrofosmin

ABBREVIATIONS AND ACRONYMS

ACM = all-cause mortality
CAD = coronary artery disease
CD = cardiac death
CI = confidence interval
CKD = chronic kidney disease
DM = diabetes mellitus
ECG = electrocardiogram
EF = ejection fraction
eGFR = estimated glomerular filtration rate
HR = hazard ratio
LVEF = left ventricular ejection fraction
MI = myocardial infarction
MPI = myocardial perfusion imaging
NFMI = nonfatal myocardial infarction
SDS = summed difference score
SPECT = single-photon emission computed tomography
SRS = summed rest score
SSS = summed stress score

was performed. A symptom-limited treadmill exercise test was initiated in 32% of patients with standard protocols with a 12-lead ECG recording each minute of exercise. At near-maximal exercise (≥85% age predicted heart rate), a 20- to 30-mCi dose of technetium-99 or tetrofosmin was injected (actual patient dose varied with patient weight), and exercise continued for 1 min after injection. Image acquisition was initiated 15 min after isotope injection. Whenever possible, beta-blockers, calcium channel blockers, and caffeine products were discontinued 24 h before testing, and nitrate compounds were discontinued 6 h before testing.

If the patient was predetermined to be unable to undergo a treadmill protocol or unable to achieve 85% of maximal predicted heart rate, the test was performed pharmacologically with use of a 4-min adenosine infusion protocol (68% of the study group). Institutional protocol allowed for use of only adenosine for pharmacological MPI studies. Patients who were unable to exercise and had contraindications to adenosine (e.g., severe chronic obstructive pulmonary disease) generally underwent dobutamine stress echocardiography or cardiac catheterization. Technetium-99m was injected at the end of the third minute of infusion, and SPECT was initiated approximately 60 min after the end of the adenosine infusion (12). During both types of stress tests, blood pressure was measured and recorded at rest, at the end of each stress stage, and at peak stress. Maximal degree of ST-segment change at 80 ms after the J point of the ECG was measured and assessed as horizontal, up-sloping, or down-sloping.

SPECT acquisition protocol. The SPECT studies were performed with dual head cardio epic camera with a circular 180° acquisition for 64 projections at 20 to 25 s/projection (13). During imaging, a 10% window centered on the 140-keV peak was used for technetium-99m tracers. The low-pass Butterworth filter was used for all SPECT studies. Gated scan could not be performed in 5% of the patients because of arrhythmias, primarily atrial fibrillation.

Imaging interpretation and scintigraphic indexes. Semiquantitative visual interpretation was performed with short-axis and vertical long-axis, and myocardial tomograms were divided into 20 segments for each study, as previously described (14). A summed stress score (SSS) was obtained by adding the scores of the 20 segments of the stress sestamibi images with the QP/QS software (15,16). Each segment was scored with a 5-point scoring system (0: normal, 1: mildly reduced, 2: moderately reduced, 3: severely reduced, 4: absent uptake) (14,16). The sum of segment scores at stress (SSS), scores at rest (summed rest score [SRS]), and differences between stress and rest score (summed difference score [SDS]) were calculated (14–18). Patients were divided into groups on the basis of their SSS. Summed stress scores <4 were considered normal, 4 to 8 were considered mildly abnormal, and >8 were considered moderately to severely abnormal (15,16,18). Patients were also divided into groups on the basis of their SDS and SRS into normal (<2), mildly abnormal (2 to 6), and moderate to severely abnormal (>6) (17). High-risk scan was defined as moderate to severely abnormal MPI and/or left ventricular ejection fraction (LVEF) <40%. Presence of ischemia and scar was determined by the severity of SDS and SRS, respectively. Post-stress LVEF obtained in 95% of patients by gated SPECT was also assessed with QP/QS software. The studies were interpreted by 3 board certified nuclear cardiologists who were blinded to the demographic and laboratory data but not to sex.

Classification of renal dysfunction. Estimated glomerular filtration rate was calculated with the 4-variable modified diet in renal disease "MDRD" equation: GFR (ml/min/1.73 m^2) = 175 × $(S_{cr})^{-1.154}$ × $(Age)^{-0.203}$ × 0.742 (if female) × 1.210 (if African American) (19,20). The CKD was defined with the National Kidney foundation definition of an eGFR <60 ml/min/1.73 m^2 (21) and was present in 632 patients (36%). Serum creatinine used to calculate eGFR was obtained within 49 ± 20 days from the time of MPI. Thirty-two patients in acute renal failure (defined by an increase in serum creatinine of ≥0.5 mg/dl in <2 weeks or an increase of >20% over baseline if baseline serum creatinine was ≥2.5 mg/dl) were excluded.

Patient follow-up and end points. Patients were followed for a mean duration of 2.15 ± 0.8 years. The minimum duration of follow-up was 6 months (for those who had no events, shorter for those who died) with only 44 patients that had follow-up of <1 year. The primary end point was cardiac death (CD) defined as death from any cardiac cause including fatal myocardial infarction, sudden arrhythmic death, and decompensated heart failure; secondary end points were ACM and a composite of CD and nonfatal myocardial infarction (NFMI) (defined by the appropriate combination of elevated cardiac enzymes, electrocardiographic changes, and isch-

emic symptoms). Mortality data was gathered from the VA patient records and confirmed by the Social Security Death Index. Death status was determined as of month/year. Cause of death was adjudicated by 3 independent reviewers (blinded to the MPI and demographic data) through patient chart review including death certificate and physician's records. Conflicts were resolved by global consensus or by the senior investigator.

In clinical settings, patients with moderate or severe stress-induced ischemia are usually treated by coronary revascularization after the SPECT study. This sort of selection bias cannot be avoided in a cohort study. However, the estimation of event risks before revascularization on the basis of the prognostic database is meaningful for patient management. To address the issue of the impact of revascularization on outcomes, a separate analysis was carried out excluding patients with early revascularization defined as <60 days after the index perfusion study.

Statistical analysis. For analysis of baseline characteristics, all subjects were classified on the basis of the presence or absence of DM and then further stratified by the presence or absence of CKD (eGFR above or below 60 ml/min/1.73 m^2). Patients were hence classified into 4 groups on the basis of presence or absence of DM and CKD: 1) No DM No CKD; 2) DM only (no CKD); 3) CKD only (no DM); and 4) DM+CKD.

Student *t* tests or Wilcoxon rank sum tests (for skewed data) were used to compare subject characteristics across renal function levels within each diabetes status. Chi-square tests were used for comparing dichotomous or categorical variables.

Unadjusted annual event rates for those with and without scan defects on the basis of diabetes and CKD status were expressed as cases/100 person-years. Person-years were based on length of follow-up, calculated as the number of years from the examination to the CD event or censoring. Event rates on the basis of presence of ischemia and scar in each of the 4 groups were calculated in a similar manner. Furthermore, median SSS, SDS, and eGFR were calculated for patients with and without each of these outcomes and compared with Wilcoxon rank sum tests.

Logistic regression models were used to examine the effect of the presence or absence of DM and CKD on the prevalence of abnormal and high-risk scan after adjustment for age, history of myocardial infarction (MI), hypertension, hyperlipidemia, and LVEF.

Table 1. Baseline Characteristics

	Nondiabetic (n = 1,107)			Diabetic (n = 640)		
Characteristic	eGFR >60 ml/min (n = 759)	eGFR <60 ml/min (n = 348)	p Value	eGFR>60 ml/min (n = 356)	eGFR<60 ml/min (n = 284)	p Value
Age (yrs)	62 ± 10	70 ± 10	<0.0001	63 ± 8	69 ± 9	<0.0001
Men	98% (744)	95% (334)	0.07	99% (351)	96% (273)	0.08
Revascularization	32% (241)	35% (122)	0.3	32% (114)	32% (137)	0.84
Smoking history	31% (233)	23% (80)	0.01	28% (99)	24% (67)	0.27
Hypertension	69% (526)	75% (262)	0.04	81% (287)	84% (238)	0.12
Known CAD	40% (307)	45% (158)	0.13	41% (146)	43% (121)	0.74
History of MI	19% (142)	21% (72)	0.48	19% (68)	20% (56)	0.92
Hyperlipidemia	73% (544)	65% (226)	0.02	81% (289)	78% (221)	0.34
Angina	35% (267)	25% (87)	0.001	31% (109)	27% (76)	0.32
SOB	15% (112)	14% (48)	0.74	11% (41)	12% (33)	0.93
Mean eGFR	78 ± 14	46 ± 12	<0.0001	76 ± 12	42 ± 14	<0.001
BMI >30 kg/m^2	43% (328)	41% (143)	0.55	64% (229)	61% (175)	0.57
Pharm stress	60% (454)	76% (265)	<0.0001	65% (231)	84% (239)	<0.0001
Beta blockers	59% (425)	63% (208)	0.19	63% (209)	71% (196)	0.04
ACE inhibitors	50% (362)	54% (178)	0.24	72% (237)	69% (189)	0.5
CCB	16% (117)	32% (106)	<0.0001	20% (62)	29% (79)	0.005
Statin	64% (465)	69% (227)	0.15	70% (230)	71% (196)	0.68
LVEF	57 ± 12	51 ± 14	<0.001	54 ± 12	50 ± 14	<0.02
LVEF <40%	11% (83)	19% (66)	<0.0001	18% (64)	24% (68)	<0.05

ACE = angiotensin-converting enzyme; BMI = body mass index; CAD = coronary artery disease; CCB = calcium channel blocker; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; MI = myocardial infarction; Pharm = pharmacological; SOB = shortness of breath.

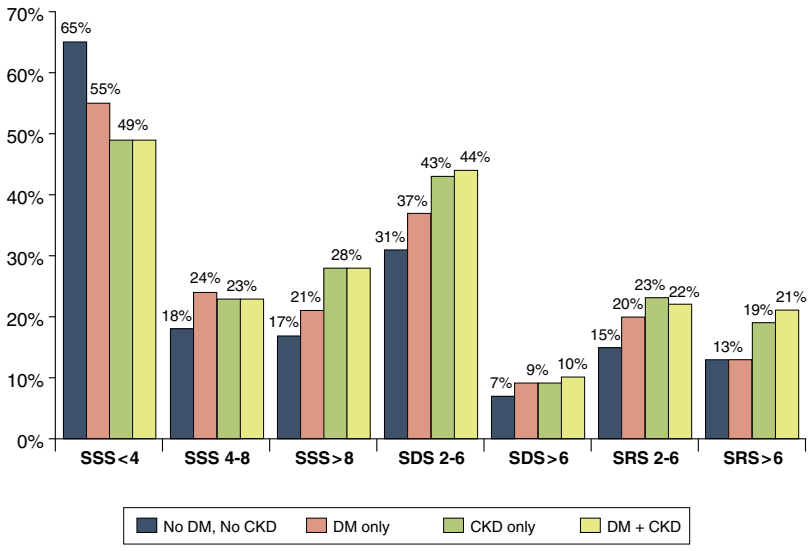

Figure 1. Stress Myocardial Perfusion Profiles on the Basis of DM/CKD Status

The presence and severity of perfusion abnormalities was more prevalent in the diabetes mellitus (DM) only ($p = 0.004$), chronic kidney disease (CKD) only ($p < 0.0001$), and DM+CKD groups ($p < 0.0001$) compared with No DM No CKD groups. Similarly, patients with DM only, CKD only, and DM+CKD had a lower percentage of normal scans and a higher prevalence of scar and ischemia compared with those without DM and CKD ($p = 0.03$ for DM only, $p < 0.0001$ for CKD only and DM+CKD, respectively). SDS = summed difference score; SRS = summed rest score; SSS = summed stress score.

The Cox proportional hazards models that examined presence or absence of DM and CKD in relation to CD were adjusted for potential confounders, including age, hypertension, hyperlipidemia, ejection fraction (EF) <40%, pharmacological stress test, history of MI, SSS >4, as well as cardiovascular characteristics/symptoms including angina, shortness of breath, and EF. Selection of variables for consideration for entry into the model was based on both clinical judgment (established prognostic variables) and whether findings from univariable analyses reached a significance level of $p < 0.15$. As such, sex and smoking were not included in the model. The first-order interaction between presence or absence of DM and CKD and SSS (SSS categories), SDS (presence of ischemia), or SRS (presence of scar) was tested by including each of them in the separate Cox proportional hazards model that also included the presence or absence of DM and CKD and the nuclear perfusion variable of choice. The proportionality assumption of the Cox model was assessed by including time-dependent interactions of each covariate with survival time in the model. There was no evidence of violation of this assumption for any covariate. Similar to the Hosmer-Lemeshow test for logistic regression, the goodness of fit test for the Cox proportional hazards model was performed (22). All statistical analyses were performed with SAS version 9.1.2 (SAS Institute, Cary, North Carolina). Statistical significance was defined as 2-tailed $p < 0.05$ for all tests.

The authors had full access to the data and take responsibility for the integrity of the data. All

Table 2. Adjusted OR (95% CI) for Abnormal MPI and High-Risk Scan

	Abnormal MPI		High-Risk Scan		SSS >8		EF <40%	
	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
No DM No CKD	Referent		Referent		Referent		Referent	
DM only	1.48 (1.41–1.93)	0.02	1.67 (1.10–2.56)	0.01	1.3 (0.92–1.7)	0.12	1.9 (1.3–2.7)	<0.0001
CKD only	2.00 (1.51–2.65)	0.001	2.04 (1.32–3.15)	0.001	1.7 (1.2–2.3)	0.001	2.04 (1.4–2.9)	<0.0001
DM+CKD	2.43 (1.79–3.29)	<0.0001	2.67 (1.73–4.12)	<0.0001	1.76 (1.2–2.4)	0.001	3.03 (2–4.4)	<0.0001

Abnormal myocardial perfusion imaging (MPI) (summed stress score [SSS] ≥4); high-risk scan (SSS >8 and/or ejection fraction [EF] <40%). Odds ratios (ORs) from logistic regression models controlling for age, history of myocardial infarction, hypertension, hyperlipidemia, and EF.
CI = confidence interval; CKD = chronic kidney disease; DM = diabetes mellitus.

authors have read and agree to the manuscript as written.

RESULTS

Baseline characteristics. Baseline characteristics of the 1,747 patients included in the analyses stratified by DM/CKD status are summarized in Table 1. Patients with CKD in both diabetic and nondiabetic groups were older, more likely to undergo pharmacological stress, and tended to take calcium channel blockers more frequently. They also had a lower mean EF and a higher prevalence of left ventricular systolic dysfunction (EF <40%) compared with those without CKD. Patients with CKD were more likely to be hypertensive and had lower prevalence of smoking, hyperlipidemia, and angina. Overall, diabetic patients were significantly more overweight and obese compared with nondiabetic persons. Diabetic patients with CKD were more likely to use beta blockers. By contrast, there was no difference in terms of history of CAD, MI, revascularization, or use of other drugs including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, statins, and nitrates.

Myocardial perfusion defects and left ventricular dysfunction on the basis of DM and CKD status. Figure 1 shows the distribution of perfusion abnormalities on the basis of DM and CKD status. The presence and severity of perfusion abnormalities was more prevalent in the DM only ($p = 0.004$), CKD only ($p < 0.0001$), and DM+CKD groups ($p < 0.0001$) compared with the no DM no CKD group. Similarly, patients with DM only, CKD only, and DM+CKD had a lower percentage of normal scans and a higher prevalence of scar and ischemia compared with those without DM and CKD ($p = 0.03$ for DM only, $p < 0.0001$ for CKD only and DM+CKD, respectively).

On the basis of logistic regression model controlling for age, history of MI, hypertension, hyperlipidemia, and EF, patients with DM only, CKD only, or DM+CKD had statistically significant higher odds of having an abnormal scan or a high-risk scan compared with those with no DM no CKD (Table 2).

Event rate on the basis of DM and CKD status. During a mean follow-up period of 2.15 ± 0.8 years, total events included 225 deaths from all causes, 119 CDs, and 185 composite (CD/NFMI) events. Patients with CKD only and DM+CKD had a 2- and 3-fold higher CD and all-mortality rate, respectively, compared with those in no DM No CKD and DM only groups (all log-rank $p < 0.0001$). There was no statistical difference in the event rate of CD, ACM, and CD/NFMI between patients with DM only and no DM no CKD groups. Even after excluding patients who underwent early revascularization (<60 days), a similar trend persisted for outcomes.

Patients who experienced any of the outcomes (CD, ACM, and CD/NFMI) during the course of

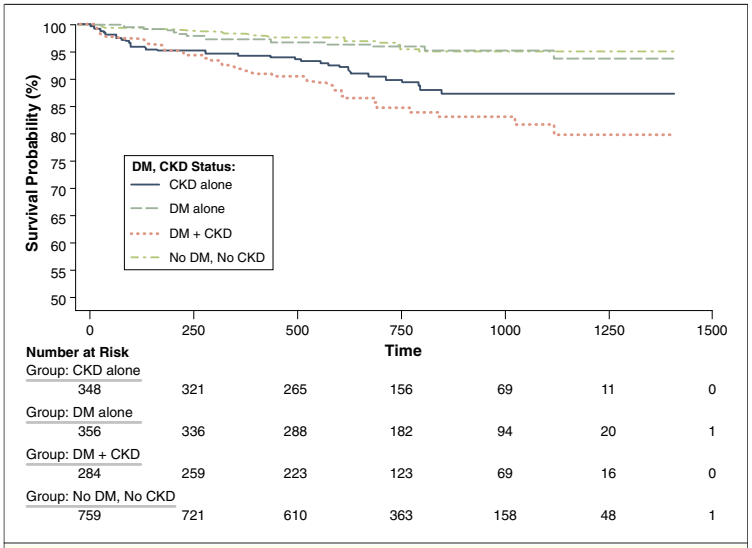

Figure 2. Kaplan Meier Survival Analysis for Freedom From Cardiac Death

Log-rank p value <0.0001 for comparisons between No DM No CKD and DM alone versus CKD alone and DM+CKD. The log-rank p test for No DM No CKD and DM only groups was not significant (log-rank p = 0.73). Abbreviations as in Figure 1.

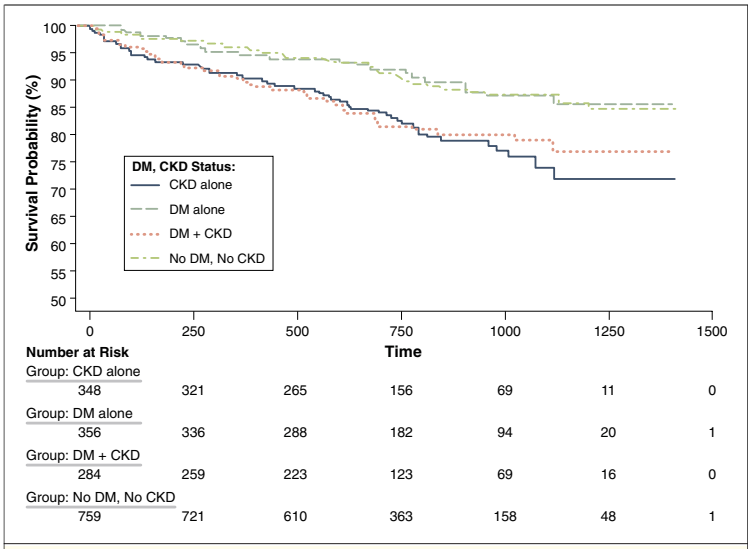

Figure 3. Kaplan Meier Survival Analysis for Freedom From All-Cause Mortality

Log-rank p value <0.0001 for comparisons between No DM No CKD and DM alone versus CKD alone and DM+CKD. The log-rank p test for No DM No CKD and DM only groups was not significant (log-rank p = 0.86). Abbreviations as in Figure 1.

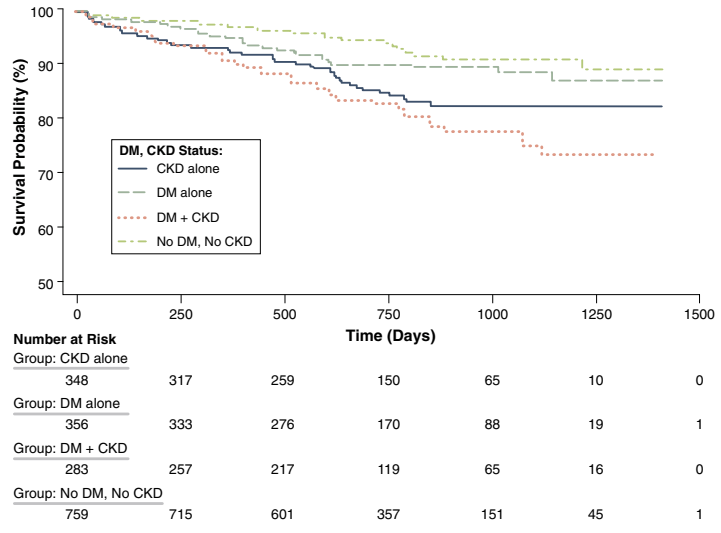

Figure 4. Kaplan Meier Survival Analysis for Freedom From CD/NFMI

Log-rank p value <0.0001 for comparisons between No DM No CKD and DM alone versus CKD alone and DM+CKD. The log-rank p test for No DM No CKD and DM only groups was not significant (log-rank p = 0.33). CD = cardiac death; NFMI = nonfatal myocardial infarction; other abbreviations as in Figure 1.

the study had statistically significant lower renal function (demonstrated by median eGFR) or greater number of perfusion defects (demonstrated by SSS and SDS values). The median SSS and SDS were higher in patients with CD compared with those without this end point (SSS 9.0 vs. 2.0, $p < 0.0001$; SDS 3.0 vs. 1.0, $p < 0.0001$). Patients with CD also had a lower median eGFR compared with those without CD (51.6 vs. 67.3, $p < 0.0001$). Kaplan Meier survival plot showing survival free from CD is shown in Figure 2. The survival probabilities for patients with CKD only and DM+CKD were significantly lower than for those with DM only and the no DM no CKD group (all log-rank $p < 0.01$). The log-rank p test for no DM no CKD and DM only groups was not significant (log-rank $p = 0.73$). Patients with both CKD and DM had a decrement in survival that was greater than the combined individual effects of DM and CKD, respectively, suggesting a negative synergistic effect of these 2 variables on survival ($p < 0.0001$). Similar trends were noted for ACM (Fig. 3) and CD/NFMI (Fig. 4).

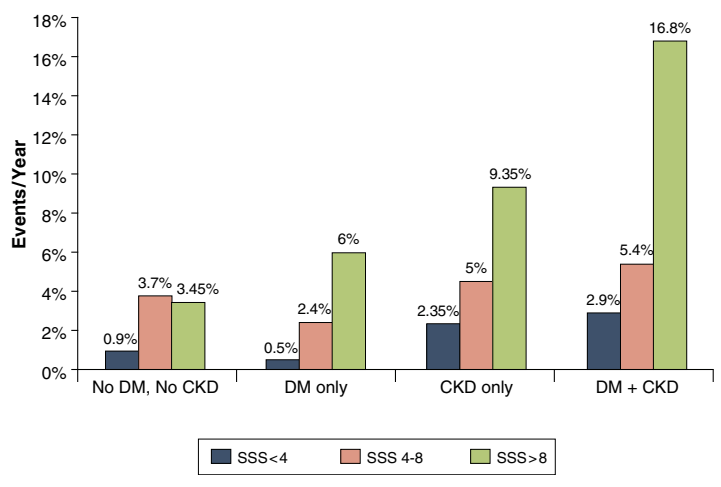

Figure 5. Annual CD Rate on the Basis of MPI and DM/CKD Status

There was a significant increase in CD rate with increasing severity of perfusion defects across all subgroups on the basis of DM and CKD status (all log-rank $p < 0.001$). The incidence of CD increased with increasing severity of SSS. MPA = myocardial perfusion abnormality; other abbreviations as in Figures 1 and 4.

Perfusion defects and outcomes. There was a significant increase in CD rate with increasing severity of perfusion defects across all subgroups on the basis of DM and CKD status (all log-rank $p < 0.001$) (Fig. 5). Patients in the mildly abnormal (SSS 4 to 8) and moderate to severely abnormal MPI (SSS ≥8) groups had statistically significant higher incidence of CD compared with normal MPI. This effect was further magnified among subgroups of CKD alone and DM+CKD compared with the DM alone and no DM no CKD groups. Regarding CD in particular, a normal myocardial perfusion study in patients without CKD (with or without DM) was associated with a low CD rate (0.9%/year). Conversely, the CD rate was 3 times higher for patients with normal scans but with CKD only (2.35%/year) and DM+CKD (2.9%/year) (Fig. 5). There was no significant interaction between disease status and SSS categories ($p = 0.35$).

Presence of ischemia and scar as determined by the severity of SDS and SRS was associated with higher risk of CD. The event rate increased with increasing severity of ischemia and scar across all subgroups on the basis of DM and CKD status. This effect appeared more pronounced in patients with CKD and DM and CKD (Figs. 6A and 6B). There was no significant interaction between disease status and ischemia (SDS) categories ($p = 0.73$). Similarly, there was no significant interaction between disease status and scar (SRS) categories ($p = 0.73$).

Predictors of cardiac outcomes by multivariable analysis. The results from the Cox proportional hazards model for the end point of CD are shown in Table 3. The presence of DM and CKD was a significant predictor of increased CD with a hazard ratio (HR) of 2.70 (95% confidence interval [CI]: 1.59 to 4.58, $p < 0.0001$). Other significant mul-

tivariable predictors of CD were age >65 (HR: 1.84, 95% CI: 1.21 to 2.80), hyperlipidemia (HR: 0.40, 95% CI: 0.27 to 0.59), EF <40% (HR: 4.05; 95% CI: 2.58 to 6.36), and SSS >4 (HR: 2.28, 95% CI: 1. 36 to 2.83). There was no significant interaction between the presence or absence of DM and CKD and all other covariates. The model fits well (p value for goodness-of-fit = 0.14; the Harrell's C statistic = 0.84).

An additional multivariable analysis model (result not shown) comprising patients with high-risk (moderate to severely abnormal MPI and EF <40%) showed that patients with DM+CKD had an HR of 3.17 (95% CI: 1.75 to 5.74) for CD compared with those high-risk patients without DM and CKD.

History of CAD and outcomes on the basis of DM/CKD status. Patients with a history of CAD had a significantly lower survival free of CD/NFMI as compared with those without history of CAD (6.7%/year vs. 3.6%/year; log-rank p < 0.0001). Event rates on the basis of CAD history with further stratification on the basis of DM/CKD status for the end points of CD, ACM, and CD/NFMI are shown in Table 4. Overall, the trends were similar to the entire cohort. Patients with DM/CKD had a 3- to 4-fold higher CD rate compared with those without DM or CKD, regardless of history of CAD. In either group, those with CKD had worse outcomes, regardless of DM status, compared with those without CKD (Fig. 7).

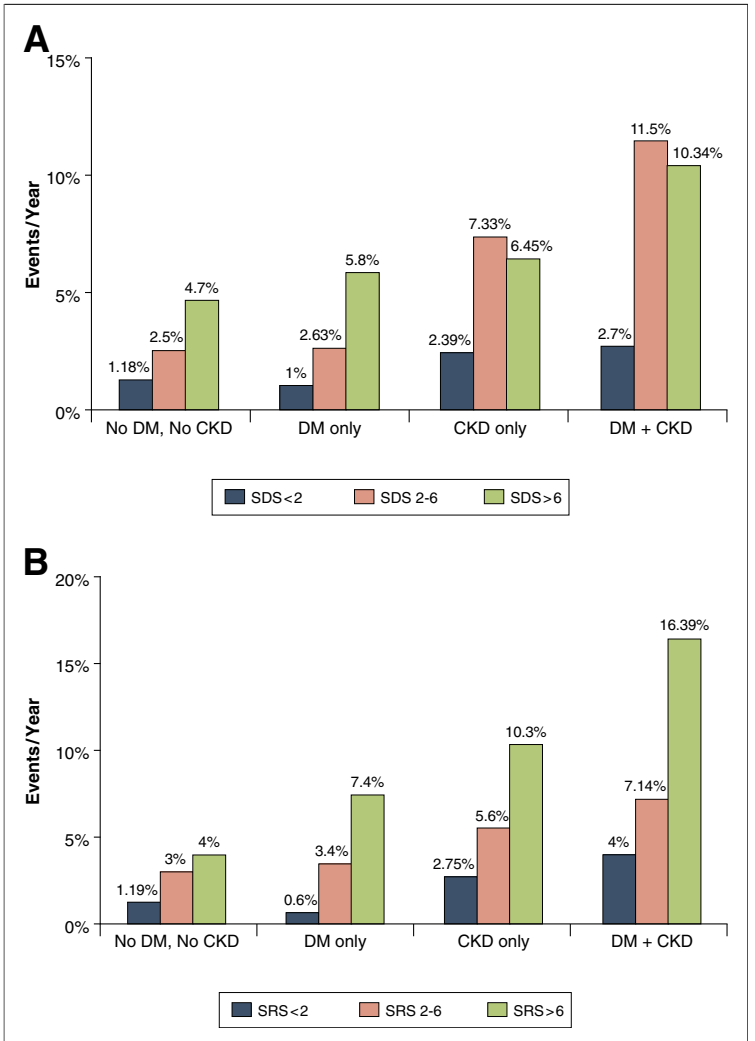

Figure 6. Annual CD on the Basis of Presence of Ischemia and Scar Stratified by DM/CKD Status

Presence of ischemia **(A)** and scar **(B)** as determined by the severity of SDS and SRS was associated with a higher risk of CD, this effect being significantly more pronounced in patients with CKD and DM and CKD (all log-rank p < 0.001). Abbreviations as in Figures 1 and 4.

DISCUSSION

Our study examined the impact of CKD and MPI on risk stratifying diabetic and nondiabetic patients for adverse cardiac events. After controlling for age, EF, CAD, hypertension, dyslipidemia, and previous MI, we found that diabetic persons with CKD had significantly higher predicted rates of CD compared with counterparts without CKD. This finding was in keeping with previous studies that demonstrated an increased risk of cardiovascular mortality and ACM in patients with renal insufficiency (23,24). However, we also found that the presence of CKD alone without DM was a powerful determinant of cardiac mortality, perhaps stronger than the presence of diabetes alone, because nondiabetic patients with CKD had a several-fold increased risk of CD compared with diabetic patients without CKD. The absence of CKD in diabetic patients might portend a lower risk, because diabetic patients without CKD had a low event rate in a relatively short term, almost comparable to patients without diabetes or CKD.

We also found that MPI provides effective risk stratification for cardiac events on the basis of diabetes and CKD status. Although the presence of a normal scan confers a lower risk in CKD patients with and without diabetes, the presence of CKD adversely effects the warranty period of a normal scan. Diabetic patients with CKD have a several-fold higher risk of death even in the presence of a normal scan, as do nondiabetic patients with CKD, but the risk is relatively lower. Lastly, the presence of DM and CKD strongly correlates with the presence and degree of perfusion defects, including

Table 3. Multivariable Analysis for CD Cox Proportional Hazards Model

Variable	HR	95% CI	p Value
DM/CKD category			
No DM No CKD	Referent		
DM only	1.03	0.54–1.97	0.93
CKD only	1.58	0.92–2.71	0.09
DM+CKD	2.70	1.59–4.58	<0.0001
Age >65	1.84	1.21–2.80	0.004
SOB	1.54	0.92–2.59	0.10
Angina	0.91	0.57–1.44	0.68
Hypertension	0.76	0.49–1.17	0.21
Hyperlipidemia	0.40	0.27–0.59	<0.0001
History of MI	0.96	0.62–1.49	0.87
EF <40%	4.05	2.58–6.36	<0.0001
Pharm stress test	1.72	0.98–3.00	0.06
SSS >4	2.28	1.36–3.83	0.002

CD = cardiac death; HR = hazard ratio; other abbreviations as in Tables 1 and 2.

a strong correlation with the presence of a high-risk scan.

The associations among cardiovascular disease, CKD, and increased cardiac mortality have been reported previously in the general population (25–27), in patients with known CAD undergoing PCI (28,29) and asymptomatic diabetic persons undergoing stress myocardial perfusion imaging (30), but our results also highlight the important point that diabetic persons are a heterogeneous group and that the absence of CKD in diabetic patients might portend a relatively benign short-term risk.

CKD as a cardiovascular risk factor. The connections between CKD and CVD are numerous. CKD is associated with many traditional risk factors for cardiovascular disease, including smoking, hypertension, dyslipidemia, physical inactivity, diabetes, and the metabolic syndrome (27,31–34). However, there are also several nontraditional risk factors for cardiovascular disease, including increased risk for left ventricular hypertrophy from volume and pressure overload, anemia causing increased cardiac output, altered bone mineral metabolism leading to hyperphosphatemia and increased vascular calcification, increased oxidative stress, and endothelial dysfunction. Because vascular disease is a systemic process affecting the rich renal vasculature, renal dysfunction measured by eGFR might serve as a convenient, quantifiable measure for atherosclerotic burden, a value aggregating the various disparate risk factors.

Implications in risk stratifying diabetic persons. With such a high burden for cardiovascular mortality in diabetic persons, noninvasive imaging has been proposed to risk stratify diabetic persons and identify those patients with a higher burden of atherosclerotic disease before a cardiac event. Although there are limited prospective data, there are a number of retrospective studies showing a benefit to noninvasive stress testing to risk stratify diabetic patients (35,36). Given the vast number of diabetic persons and the enormous cost for asymptomatic screening, there have been several attempts to identify high-risk diabetic persons who would most benefit from such an aggressive screening strategy.

Unfortunately, the use of 2 or more traditional cardiovascular risk factors has not predicted inducible ischemia on nuclear or echocardiographic myocardial perfusion imaging (37–39). Coronary artery calcium scores have also been proposed to identify patients with high likelihood of inducible ischemia on imaging (40,41) and have been prospectively studied in asymptomatic diabetic persons (39). Results of the DIAD trial showed that screening for silent ischemia with myocardial perfusion imaging testing in diabetic patients was not associated with a reduction in cardiovascular events (12). The DIAD cohort, however, had a very low cardiac event rate (average, 0.6%/year) translating into a 14% power to detect the originally anticipated difference between the groups. Although the low event rate precluded any multivariable analysis, age- and sex-adjusted analysis revealed microalbuminuria/proteinuria and serum creatinine to be predic-

Table 4. Annualized Event Rate on the Basis of History of CAD and DM/CKD Status

	No History of CAD (n = 1,015)	History of CAD (n = 732)	p Value
No DM No CKD			
CD	1.53%	1.9%	0.64
ACM	5%	3.8%	0.26
CD/NFMI	2.2%	4%	0.04
DM only			
CD	1.3%	2.8%	0.2
ACM	4%	5.4%	0.43
CD/NFMI	3.7%	5.4%	0.34
CKD only			
CD	4.4%	4.7%	0.9
ACM	8.8%	8.4%	0.9
CD/NFMI	5.1%	8.2%	0.1
DM+CKD			
CD	5.1%	9.2%	0.05
ACM	7.4%	9.6%	0.41
CD/NFMI	5.7%	12.6%	0.002

ACM = all-cause mortality; NFMI = nonfatal myocardial infarction; other abbreviations as in Tables 1 and 2.

tors of the primary outcomes. One major limitation of the DIAD study was stratification of the population on the basis of serum creatinine. Crude creatinine measurement is known to underestimate renal function (20,21).

Our study suggests that eGFR has a paramount role in identifying high-risk diabetic persons at highest risk for abnormal nuclear scans and CD. Furthermore, given the ubiquity of creatinine measurements in standard metabolic panels and the relative ease of calculating eGFR via the MDRD equation, this risk stratification tool would not require an additional test with the added cost and radiation risks.

Additionally, perfusion defects on MPI imaging provide substantial prognostic information in predicting adverse outcomes in both diabetic and nondiabetic patients. Together, both perfusion defects and eGFR are powerful risk predictors and provide additive and effective risk stratification in diabetic persons.

Study limitations. This study was a retrospective analysis with the inherent limitations of this design. Moreover, the study was conducted on a population of predominantly white male veterans with a baseline high prevalence of CKD and CAD risk factors. Other racial subsets were under-represented, precluding race-based analysis. For diabetic patients, data on medication regimen, hemoglobin A1C levels, proteinuria, and retinopathy were all unavailable, preventing the determination of whether level of glycemic control had any interaction with cardiac mortality. This study was conducted in a single center and followed patients for a mean of 2 years, preventing determination of long-term clinical outcomes. Perfusion defects were semiquantitatively assessed with a 20-segment model, which has the limitation of over-presenting the apex when compared with anatomic data compared with a 17-segment model. We used a 4-min adenosine infusion as compared with the standard 6-min adenosine infusion. The standard protocol includes 6 min of adenosine infusion; concern remains about suboptimal vasodilatation with a shorter duration of adenosine infusion. Although there are no randomized trials comparing 4-min versus 6-min adenosine infusion, a consensus statement from the American Society of Nuclear Cardiology agrees that "a shorter-duration adenosine infusion, lasting 4 min, has been found to be equally effective for the detection of CAD compared with the 6-min infusion" (42). Additionally, there could have been possible selection bias of sending patients with DM and CKD or CKD alone to stress imaging.

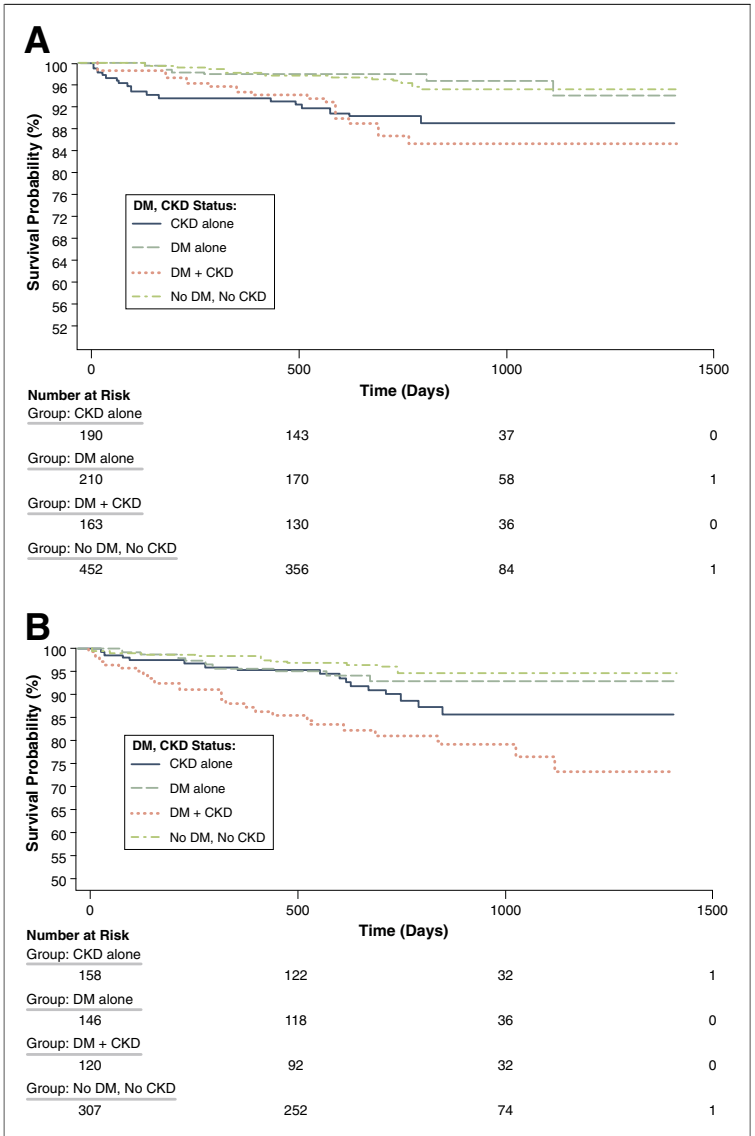

Figure 7. Kaplan Meier Survival Analysis for Freedom From CD on the Basis of DM/CKD Status in Patients Without and With History of CAD

Patients without **(A)** and with **(B)** history of CAD. Log-rank p value <0.0001 for comparisons between No DM No CKD and DM alone versus CKD alone and DM+CKD. The log-rank p test for No DM No CKD and DM only groups was not significant. Abbreviations as in Figures 1 and 4.

CONCLUSIONS

Chronic kidney disease defined by eGFR <60 ml/min/1.73 m^2 and myocardial perfusion defects are powerful prognostic indicators to help identify diabetic persons at high risk for both cardiac and ACM. Diabetic patients without CKD have a relatively good short-term outcome almost compa-

rable to nondiabetic patients. Hence the increased cardiovascular morbidity in diabetic persons might largely be due to underlying renal dysfunction. Thus, the use of eGFR might play an important role in identifying high-risk diabetic persons who would benefit most from myocardial perfusion imaging. Presence of a normal scan in diabetic persons with CKD or those with CKD alone is associated with a less benign prognosis. Further prospective studies are warranted to evaluate the impact of different cardiovascular prevention and management strategies in diabetic persons with CKD.

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