ORIGINAL ARTICLE

Coronary risk equivalence of diabetes assessed by SPECT-MPI

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Background. **Several publications and guidelines designate diabetes mellitus (DM) as a coronary artery disease (CAD) risk equivalent. The aim of this investigation was to examine DM cardiac risk equivalence from the perspective of stress SPECT myocardial perfusion imaging (MPI).**

Methods and Results. **We examined cardiovascular outcomes (cardiac death or nonfatal MI) of 17,499 patients referred for stress SPECT-MPI. Patients were stratified into four categories: non-DM without CAD, non-DM with CAD, DM without CAD, and DM with CAD, and normal or abnormal perfusion. Cardiac events occurred in 872 (5%), with event-free survival best among non-DM without CAD, worst in DM with CAD, and intermediate in DM without CAD, and non-DM with CAD. After multivariate adjustment, risk remained comparable between DM without CAD and non-DM with CAD [AHR 1.0 (95% CI 0.84–1.28), *P* =0.74]. Annualized event rates for normal subjects were 1.4% and 1.6% for non-DM with CAD and DM without CAD, respectively (*P* = 0.48) and 3.5% (*P* = 0.95) for both abnormal groups. After multivariate adjustment, outcomes were comparable within normal [AHR 1.4 (95% CI 0.98–1.96) *P* = 0.06] and abnormal [AHR 1.1 (95% CI 0.83–1.50) *P* = 0.49] MPI.**

Conclusions. **Diabetic patients without CAD have comparable risk of cardiovascular events as non-diabetic patients with CAD after stratification by MPI results. These findings support diabetes as a CAD equivalent and suggest that MPI provides additional prognostic information in such patients. (J Nucl Cardiol 2019;26:1093–102.)**

Key Words: diabetes mellitus • coronary artery disease equivalent • myocardial perfusion imaging

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Abbreviations

CAD	Coronary artery disease
DM	Diabetes mellitus
SPECT-MPI	Single photon emission computed tomography myocardial perfusion imaging
SSS	Summed stress score
MET	Metabolic equivalent
AHR	Adjusted hazard ratio
MI	Myocardial infarction
ACC/AHA	American College of Cardiology/ American Heart Association
ACE	Angiotensin converting enzyme
mCi	Millicurie

See related editorial, pp. 1103–1106

INTRODUCTION

Diabetes mellitus (DM) is a global epidemic with over 300 million diagnosed, with the greatest prevalence in North America.[1] Patients with DM are at greater risk for adverse cardiovascular outcomes, with up to fourfold higher risk of developing coronary artery disease (CAD) compared to their non-diabetic counterparts.[2,3] Initial reports demonstrated ''risk equivalency'' for myocardial infarction (MI) among patients with Type 2 DM without prior MI and non-diabetic patients with prior MI.[4] Guidelines by national and international professional societies continue to recommend aggressive treatment targets for diabetic patients similar to patients with a history of CAD alone.[5,6]

The concept of risk equivalency has widespread diagnostic and treatment implications. Multiple investigations have since either supported[7–12] or contradicted[13–20] the validity of diabetes as a CAD risk equivalent. Myocardial perfusion imaging (MPI) is a contemporary noninvasive tool used for diagnosis and risk stratification of CAD in diabetic patients. The aim of this study was to investigate cardiac risk and prognostic association of normal or abnormal MPI result among a large contemporary cohort of diabetic and non-diabetic patients with and without CAD referred for single photon emission computed tomography myocardial perfusion imaging (SPECT-MPI).

METHODS

Study Population

Our study population comprised of all patients referred for SPECT-MPI in the Nuclear Cardiology Laboratory at Hartford Hospital between January 2, 1996 and December 30, 2006. This investigation was a retrospective analysis of data extracted from a prospectively collected database. Data were gathered on concomitant co-morbidities, medications, stress metrics, and perfusion results. The study was approved by and conducted within guidelines established by the Institutional Review Board at Hartford Hospital.

The presence of DM was self-identified by patients or during physician interview corresponding to ADA guidelines at the time of the stress test. CAD was self-reported or determined by review of an electronic hospital medical record with a history of prior MI or coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting) procedure.

Stress Protocols

Patients were scheduled for a specific stress modality based upon the patient's perceived exercise ability and ordering physician's discretion. Exercise was performed using symptom-limited treadmill testing employing the standard or modified Bruce protocol, according to the ACC/AHA.[21] Vasodilator stress with standard infusion of dipyridamole or adenosine was performed solely (for those patients unable to perform any exercise) or in combination with exercise (for those unable to perform adequate exercise). Dobutamine stress was performed for patients unable to exercise with contraindications to vasodilator stress testing.

Image Acquisition and Processing

Radiopharmaceutical dosing, electrocardiogram-gated SPECT image acquisition protocols, and processing were performed within the American Society of Nuclear Cardiology guidelines.[22] Our study consisted primarily of patients (90.9%) who underwent either a one or two-day rest/stress protocol. A minority of patients (9.1%) with normal perfusion and function on stress MPI did not undergo rest imaging. For patients undergoing a one-day rest/stress protocol, 10–15 mCi of Tc-99m sestamibi or Tc99m tetrofosmin was injected for rest and 30–45 mCi for stress imaging based on body weight. For patients undergoing a two-day study, 25–40 mCi of Tc-99m sestamibi or Tc99m tetrofosmin was injected for each imaging study. Attenuation corrected data were not used.

Image Interpretation

Myocardial perfusion images were interpreted during daily clinical reading sessions by a consensus of at least two experienced readers blinded to patient identity, clinical history, and type of stress, using ASNC standard 17 segment model.[23] Each segment was scored on a scale of 0–4 (0 = normal photon activity to 4 = absent photon activity). The segmental scores were added to obtain a summed stress score (SSS), with SSS $<$ 4 classified as normal and SSS $\geq$ 4 considered abnormal.

Follow-Up

Cardiac events consisted of cardiac death and nonfatal MI. Patient follow-up was obtained by mailed questionnaires after each stress SPECT-MPI. If there was no response or if more information was needed, scripted telephone interviews were attempted to obtain necessary data. Additional follow-up was obtained using hospital records, the Social Security Death Index, and death certificates by an investigator blinded to the clinical, stress testing, and SPECT data.

Statistical Analysis

Continuous variables were presented as means with standard deviations and were compared using a Student's *t*-test or ANOVA test where appropriate. Dichotomous variables were presented as percentages and compared using the X2 or Fisher's exact test where appropriate. Annualized event rates were calculated as the number of first events divided by the sum of each individual follow-up period in years. Multivariable Cox proportional hazard models were constructed to determine whether the presence of diabetes with or without CAD was predictive of time to the composite outcome of cardiac death or nonfatal MI and to control for potential confounders. All baseline variables demonstrating a significant association upon univariate analysis ($P < 0.2$ for inclusion) between the occurrence of the endpoint (dependent variable of cardiac death or nonfatal MI) and treatment and comorbidity characteristics (independent variables) were entered into the multivariable model. Previously identified independent predictors of mortality were included in the model regardless of their strength of univariate correlation. The model was adjusted for age, gender, tobacco use, stress modality, history of CAD, DM, hypertension, hyperlipidemia, and SSS. In the multivariable model, variables were selected by stepwise forward conditional method, and a $P \leq 0.05$ was considered statistically significant. Kaplan-Meier cardiac event-free survival rates during the follow-up period were computed to compare survival among the diabetic and non-diabetic subjects with and without CAD using the log-rank statistic, from the time of first MPI and censored at five years or at the first composite event. Adjusted hazard ratios (AHRs) and 95% confidence intervals (CIs) were calculated for all independent predictors. All analyses were performed with SPSS 15.0 (IBM SPSS., New York).

RESULTS

Study Population

The study population consisted of 19,798 consecutive subjects who underwent SPECT-MPI. Of these, 2,299 (11.5%) had incomplete data regarding cardiovascular outcomes. We identified 17,499 subjects available for final analyses which were stratified based on CAD and DM status at the time of SPECT-MPI: non-diabetic patients without CAD (n = 9,133), non-diabetic patients with CAD (n = 3,906), diabetic patients without CAD (n = 2,768), and diabetic patients with CAD (n = 1,692). These 4 groups were further subdivided based on stress SPECT-MPI results (normal SSS $<$ 4; abnormal SSS $\geq$ 4). The 2,299 subjects not included in the analysis were generally younger, consisted of more men with slightly higher mean SSS, and exhibited similar incidence of diabetes, coronary artery bypass graft procedure, hypertension, use of angiotensin converting enzyme (ACE) inhibitors, aspirin, lipid lowering agents, and mean body mass index compared to subjects with known cardiovascular outcomes. Baseline characteristics within the study population and DM/CAD stratification cohorts are listed in Table 1. Overall, the study population had a mean age of 62 ± 14 years, was equally distributed in gender, and demonstrated 32% and 19% incidences of CAD and DM, respectively. Fifty percent underwent exercise stress testing with 32% demonstrating an abnormal (SSS $\geq$ 4) MPI result. Diabetic subjects without CAD compared with non-diabetic subjects with CAD were younger, more often women, had greater incidence of tobacco use, hypertension, a higher body mass index, greater incidence of ACE inhibitor use, and less often treated with beta blocker, lipid lowering agent, and aspirin. Diabetic subjects without CAD demonstrated a statistically significant lower SSS compared with non-diabetic subjects with CAD [mean 2.9 (range 0–46) vs. mean 7.1 (range 0–52), $P < 0.001$].

Cardiac Outcomes

Over a mean follow-up duration of 2.4 ±1.5 years, the overall incidence of the composite outcome (cardiac death or nonfatal MI) was 5.0% (872/17,499). Of the 872 cardiac events, 541 (63%), and 330 (37%) were identified as cardiac death and nonfatal MI, respectively (Table 2). The overall incidence of adverse cardiac events was lower among diabetic subjects without CAD compared with non-diabetic subjects with CAD (5.5% vs. 7.1%; $P < 0.001$). Similarly, the annualized cardiac event rate was significantly lower among diabetic subjects without CAD compared with non-diabetic subjects with CAD (2.3% vs. 3.0% respectively, P = 0.002).

Kaplan-Meier analysis was performed to examine cardiac events over the follow-up period, Figure 1. Compared with non-diabetic subjects without CAD, a statistically significant increased risk of cardiac death or nonfatal MI was observed among non-diabetic subjects with CAD [AHR 1.9 (95% CI 1.58–2.35) $P < 0.001$], and diabetic subjects without CAD [AHR 1.9 (95% CI 1.49–2.31) $P < 0.001$], with the greatest risk increase being observed among diabetic subjects with CAD [AHR 3.7 (95% CI 3.02–4.50) $P < 0.001$]. Diabetic subjects without CAD demonstrated a similar risk of adverse cardiac outcomes compared with non-diabetic subjects with CAD [AHR 1.0 (95% CI 0.84–1.28), P =

Table 1. Demographics of study population based on diabetes and CAD status

Characteristics	Study population *N* = 17,499 (100%)	Non-diabetic subjects *N* = 13,039 (75%)		Diabetic subjects *N* = 4,460 (25%)		*P value	*P* value all groups
		Without CAD *N* = 9,133 (52%)	With CAD* *N* = 3,906 (22%)	Without CAD* *N* = 2,768 (16%)	With CAD *N* = 1,692 (10%)		
Age, years (mean ± SD)	62 ± 14	60 ± 14	67 ± 12	61 ± 13	66 ± 12	< 0.001	< 0.001
Female	8,695 (50)	5,223 (57)	1,270 (33)	1,535 (56)	667 (39)	< 0.001	< 0.001
Coronary artery disease	5,598 (32)	-	3,906 (100)	-	1,692 (100)	-	< 0.001
Myocardial infarction history	3,295 (19)	-	2,285 (59)	-	1,010 (60)	-	< 0.001
Coronary artery bypass surgery history	1,977 (11)	-	1,321 (34)	-	656 (39)	-	< 0.001
Percutaneous intervention history	2,035 (12)	-	1,505 (39)	-	530 (31)	-	< 0.001
Hypertension	10,345 (59)	4,464 (49)	2,537 (65)	2,034 (74)	1,310 (78)	< 0.001	< 0.001
Hyperlipidemia	8,418 (48)	3,311 (36)	2,586 (66)	1,440 (52)	1,081 (64)	< 0.001	< 0.001
Tobacco use	6,624 (36)	3,042 (33)	1,574 (40)	976 (35)	632 (38)	< 0.001	< 0.001
Family history of CAD	6,299 (36)	3,266 (36)	1,601(41)	854 (31)	578 (34)	< 0.001	< 0.001
Beta blocker use	6,976 (40)	2,470 (27)	2,535 (65)	888 (32)	1,083(64)	< 0.001	< 0.001
Angiotensin converting enzyme inhibitor use	5,033 (29)	1,761 (19)	1,228 (32)	1,250 (45)	794 (47)	< 0.001	< 0.001
Aspirin use	7,718 (44)	2,929 (32)	2,672 (69)	1,073 (39)	1,044 (62)	< 0.001	< 0.001
Lipid lowering agent	6,412 (37)	2,095 (23)	2,229 (57)	1,131 (41)	957 (57)	< 0.001	< 0.001
Body mass index	29.1 ±9	28.5 ±9	27.6 ±9	32.3 ±10	30.1 ±10	< 0.001	< 0.001
Insulin use	1729 (10)	-	-	1,018 (39)	711 (47)	-	< 0.001
Exercise stress	8,388 (50)	5,104 (56)	1,844 (47)	971 (35)	469 (28)	< 0.001	< 0.001
LV ejection fraction (mean ± SD)	59 ±13	63 ±10	53 ±14	60 ±14	50 ±15	< 0.001	< 0.001
SSS, mean (range)	3.8 (0–52)	1.8 (0–40)	7.1 (0–52)	2.9 (0–46)	9.0 (0–52)	< 0.001	< 0.001
Abnormal myocardial perfusion imaging, SSS $\geq$ 4	5540 (32)	1493 (16)	2189 (56)	736 (27)	1122 (67)	< 0.001	< 0.001
Follow-up duration, years (mean)	2.4 ±1.5	2.3 ±1.4	2.7 ±1.6	2.5 ±1.5	2.7 ±1.6	< 0.001	< 0.001

SD standard deviation, *CAD* coronary artery disease, *SSS* summed stress score
**P* value refers to non-diabetics with CAD and diabetics without CAD

Table 2. Cardiac events in relation to diabetes and CAD status

	Non-diabetic subjects *N* = 13,039		Diabetic subjects *N* = 4,460			
Outcomes	**Without CAD *N* = 9,133 %**	**With CAD* *N* = 3,906 %**	**Without CAD* *N* = 2,768 %**	**With CAD *N* = 1,692 %**	***P* value**	***P* value all groups**
Cardiac death	115 (1.3)	169 (4.3)	95 (3.4)	162 (9.6)	0.022	< 0.001
Nonfatal MI	83 (0.9)	108 (2.8)	56 (2.0)	83 (4.9)	< 0.001	< 0.001
Composite outcome, cardiac death or nonfatal MI	199 (2.2)	277 (7.1)	151 (5.5)	245 (14.5)	< 0.001	< 0.001
Annualized event rate of composite outcome	1.2	3.0	2.3	6.0	0.002	< 0.001

CAD coronary artery disease, *MI* myocardial infarction

0.742]. Independent predictors of cardiac death or nonfatal MI are listed in Table 3.

SPECT Myocardial Perfusion Imaging Outcomes

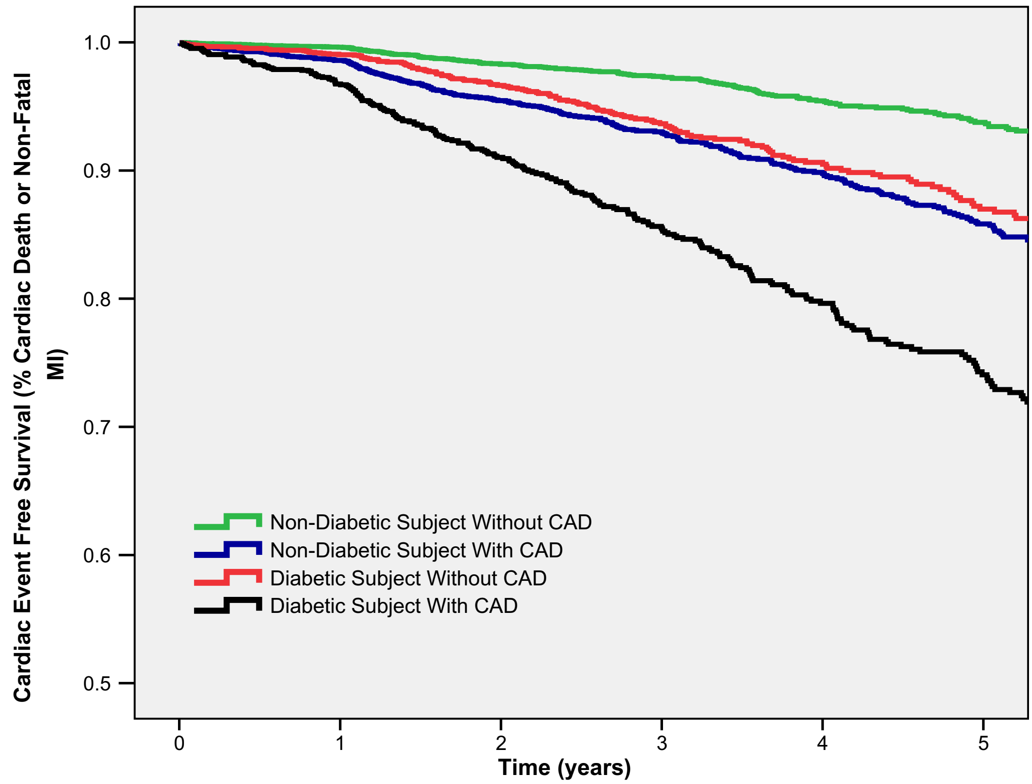
Analyses were conducted to determine the prognostic association of a normal (SSS < 4) or abnormal (SSS $\geq$ 4) myocardial perfusion imaging result among the DM/CAD stratification groups. The annualized event rates increased within each group with the presence of an abnormal perfusion result as compared to a normal perfusion result (Figure 2, $P < 0.05$ for all comparisons). Diabetic subjects without CAD demonstrated a similar incidence of an adverse cardiac outcome compared to non-diabetic subjects with CAD both among subjects with a normal (1.6% vs. 1.4%, P = 0.477) or abnormal (3.5% vs. 3.5%, P = 0.949) MPI result. Kaplan-Meier analyses demonstrated a similar risk of outcomes between diabetic subjects without CAD and non-diabetic subjects with CAD based on normal (SSS < 4) or abnormal (SSS $\geq$ 4) MPI results, Figure 3. Similarly, there was no statistically significant difference of outcomes between diabetic subjects without CAD and non-diabetic subjects with CAD upon multivariable analysis both among cohorts with a normal [SSS <4 AHR 1.4 (95% CI 0.98–1.96) P = 0.063] and abnormal [SSS $\geq$ 4 AHR 1.1 (95% CI 0.83–1.50) P = 0.489] MPI result.

DISCUSSION

The recognition of diabetes as a CAD risk equivalent has been based upon data such as Haffner et al who demonstrated that diabetic patients without CAD were at similar risk of MI as their non-diabetic counterparts with known CAD[4]. Since that landmark article, multiple investigations have either supported[7–12] or challenged[13–20] the concept of DM-CAD risk equivalency. SPECT-MPI has also been useful in risk assessment in diabetic patients[24–26] but has not been examined in this context. Thus, we evaluated cardiovascular outcomes of diabetic and non-diabetic patients with and without known CAD referred for SPECT-MPI. In a large series of over 17,000 patients, we found cardiac risk to be comparable between non-diabetic patients with CAD and diabetic patients without known CAD, similar to Haffner et al.[4] Further classification by nuclear imaging results confirmed the similarity between these two groups. Our findings reinforce the concept of ''CAD risk equivalence'' in diabetic patients.

Prognostic Association of SPECT-MPI among Diabetic Patients without CAD

An important finding from the present study was that SPECT-MPI identifies a high risk cohort of diabetic patients without CAD in which the risk of adverse outcomes was similar to non-diabetic patients with CAD. Surrogate markers of CAD are attractive options to analyze the DM-CAD association. In this context, Haffner[27] and Lee[13] provided compelling evidence of the association of diabetes and atherosclerotic vascular disease among patients enrolled in the IRAS (Insulin Resistance Atherosclerosis Study) and ARIC (Atherosclerosis Risk In Communities) studies. Diabetic subjects without CAD demonstrated a similar carotid intima-media thickness compared to non-diabetic subjects with CAD.[13,27] Moreover, Liao and colleagues



No. at risk	0	1	2	3	4	5
Non-Diabetic Without CAD	9133	8657	4099	2624	1494	878
Non-Diabetic With CAD	3906	3635	2159	1526	1074	781
Diabetic Without CAD	2768	2572	1432	980	597	379
Diabetic With CAD	1692	1523	952	681	466	316

Figure 1. Cardiac event-free survival in diabetic and non-diabetic subjects with and without CAD—subjects without CAD or DM had the best prognosis, while subjects with both CAD and DM had the worst prognosis. Diabetic subjects without CAD and non-diabetic subjects with CAD both displayed a similar increased risk for an adverse cardiac outcome [AHR 1.0 (95% CI 0.84–1.28), $P = 0.742$].

Table 3. Independent predictors of cardiac death or nonfatal myocardial infarction

Characteristics	*P* value	Wald score	Adjusted hazard ratio	95% Confidence interval
Female	0.002	9.823	0.793	0.686-0.917
Age	< 0.001	158.917	1.041	1.034-1.047
Coronary artery disease	< 0.001	18.132	1.399	1.199-1.633
Diabetes mellitus	< 0.001	72.585	1.820	1.586-2.089
Hyperlipidemia	< 0.001	15.313	0.757	0.659-0.870
Tobacco use	0.003	8.628	1.236	1.073-1.424
Exercise stress	< 0.001	73.696	0.471	0.396-0.559
Summed stress score	< 0.001	202.078	1.056	1.048-1.064

recently demonstrated that vascular endothelial function in patients with CAD was comparable to patients with diabetes.[28] In the aggregate, these studies suggest an increased atherosclerotic burden among diabetic individuals and support aggressive risk factor modification to prevent CAD development and progression.

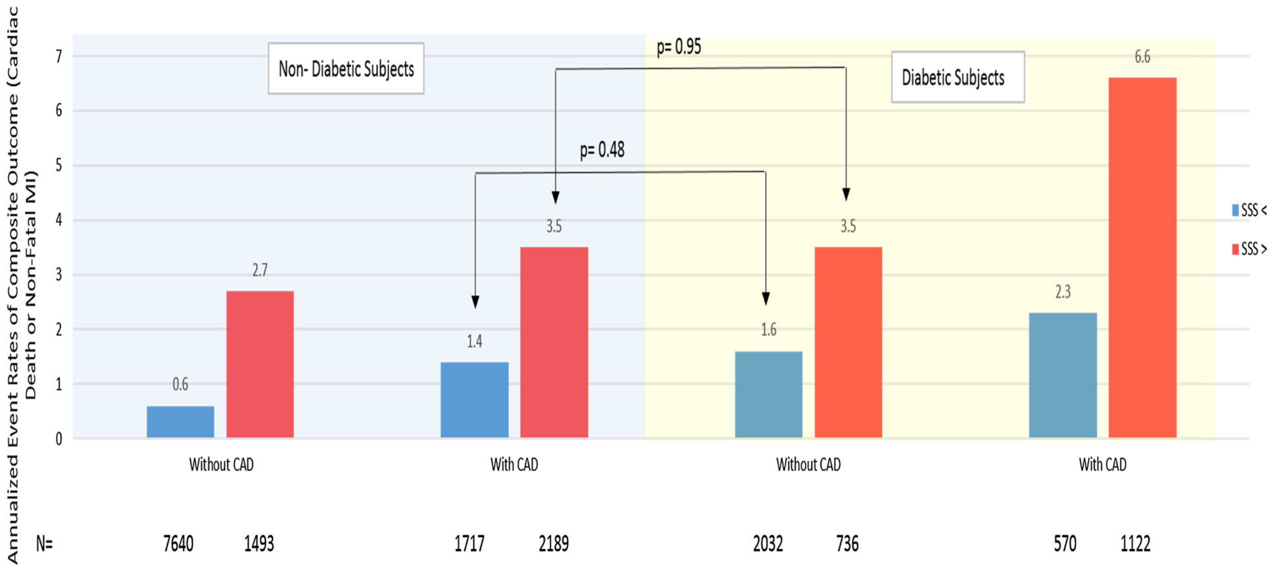


Figure 2. Annualized cardiac event rates stratified by DM/CAD status and perfusion imaging—independently having DM, CAD, or an abnormal MPI resulted in increased hazard of having an adverse cardiac event. Subjects with both DM and CAD displayed additive risk of the composite outcome. Annualized event rates were similar between non-diabetic subjects with CAD and diabetic subjects without CAD with normal (1.4 vs. 1.6, $P = 0.477$) or abnormal (3.5 vs. 3.5, $P = 0.949$) MPI.

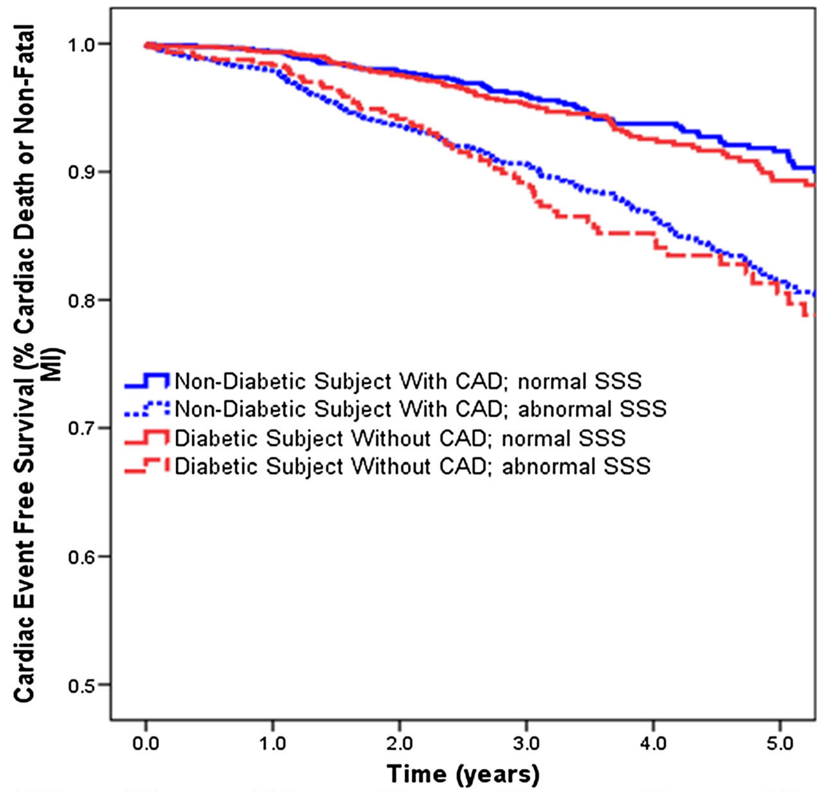
Diabetes Heterogeneity

Observations within the demographic profile of our population revealed a mean age of 62, which demonstrate a clustering of coronary risk factors and is representative of a typical referral population. Notwithstanding, heterogeneity within diabetic patients including disease severity and disease duration are important factors when determining global or cardiovascular risk.[8] In a previous study from our group, Barmpouletos and colleagues demonstrated that insulin use or diabetes duration of greater than 10 years identified a greater risk cohort for cardiac death or nonfatal MI particularly among patients with an abnormal moderate to high risk perfusion result.[24] These data suggest that diabetes factors such as insulin use, and duration of disease should heighten the concern for the cardiovascular risk of abnormal perfusion results. The Detection of Ischemia in Asymptomatic Diabetics study demonstrated that screening SPECT-MPI abnormalities were predictive of worsened outcomes even among asymptomatic diabetic patients with moderate to large perfusion defects[25].

An inverse association between cardiorespiratory fitness and mortality is well established among a broad spectrum of patients with and without cardiovascular disease.[29–31] In general, a one metabolic equivalent (MET) increase in exercise capacity has been associated with an average 13% risk reduction in cardiac death and all-cause mortality with the greatest benefit and longevity among individuals attaining an exercise capacity greater than 11-METs.[32] Within our population, exercise ability was among the strongest independent predictors of lower cardiovascular events, with a greater than 50 percent risk reduction of cardiovascular outcomes. Exercise ability among diabetic patients at the time of stress testing is associated with improved survival compared to diabetic patients undergoing vasodilator stress,[26] with a 30–80% survival benefit among diabetic patients achieving 4-METs exercise capacity.[33] In addition, Ghatak and colleagues observed that the prognosis of diabetic patients undergoing an exercise stress test SPECT-MPI was strikingly lower than diabetic patients undergoing pharmacologic stress and was more similar to non-diabetic patients also undergoing exercise SPECT-MPI.[26] In the aggregate, these previous studies demonstrate that other factors in diabetic patients should be considered such as exercise capacity, medication use, and disease duration.

NEW KNOWLEDGE GAINED

The concept of CAD equivalence is instrumental in promoting awareness that diabetic patients are at increased risk of cardiac death and MI compared to their non-diabetic counterparts. Since Haffner's landmark study,[4] multiple investigators have either supported[7–12] or contradicted[13–18] the validity of



No. at risk	0.0	1.0	2.0	3.0	4.0	5.0
Non-Diabetic With CAD, nml SSS	1711	1612	951	677	489	367
Diabetic Without CAD, nml SSS	2041	1903	1080	735	444	277
Non-Diabetic With CAD, abnml SSS	2194	2018	1205	848	584	413
Diabetic Without CAD, abnml SSS	735	667	350	244	152	101

Figure 3. Cardiac event-free survival rates based on MPI—subjects with abnormal MPI had an incremental increase in risk of cardiac events compared with normal MPI results. There was a similar risk of cardiac events among patients based on myocardial perfusion data between diabetic subjects without CAD and non-diabetic subjects with CAD. *CAD* coronary artery disease, *DM* diabetes mellitus, *SSS* summed stress score, *MPI* myocardial perfusion imaging, *AHR* adjusted hazard ratio.

diabetes as a CAD risk equivalent. After reviewing the body of literature and incorporating our findings, it is likely that the discordance amongst these studies are attributable to the heterogeneity of diabetic patients, whether it be through factors such as disease severity, disease duration, or functional capacity. In the current era, this study contributes to the present knowledge that SPECT-MPI can identify the substantial heterogeneity of CAD risk that exists in patients with DM and suggests the value of early assessment of that risk with SPECT MPI to improve outcomes with more intensive preventive therapy or revascularization.

LIMITATIONS

Cohort trials have inherent limitations that reduce internal validity compared with randomized trials. While we employed methods to minimize variability and adjust for known confounders, patient management was at the discretion of the referring physicians and not part of the study. We were unable to examine metabolic data or the presence of organ dysfunction to further quantify diabetes disease severity. In addition, we were unable to determine diabetes disease duration in all of the subjects and exclude patients with Type 1 diabetes.

CONCLUSIONS

Based upon diabetes and CAD status, we find patients with CAD and no diabetes to be at comparable risk to patients with diabetes and no CAD after SPECT-MPI. SPECT imaging highlights the heterogeneity within diabetic patients and can help identify patients who are at comparable risk to those who have CAD alone. Our findings support the concept of CAD risk equivalency among patients with diabetes mellitus without CAD as well as that MPI provides additional prognostic information.

Disclosure

This evaluation was not funded, and the authors have no conflicts of interest to disclose.

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