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Contributors to Mortality in High-Risk Diabetic Patients in the Diabetes Heart Study

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OBJECTIVE

Not all individuals with type 2 diabetes and high coronary artery calcified plaque (CAC) experience the same risk for adverse outcomes. This study examined a subset of high-risk individuals based on CAC >1,000 mg (using a total mass score) and evaluated whether differences in a range of modifiable cardiovascular disease (CVD) risk factors provided further insights into risk for mortality.

RESEARCH DESIGN AND METHODS

We assessed contributors to all-cause mortality among 371 European American individuals with type 2 diabetes and CAC >1,000 from the Diabetes Heart Study (DHS) after 8.2 ± 3.0 years (mean ± SD) of follow-up. Differences in known CVD risk factors, including modifiable CVD risk factors, were compared between living (n = 218) and deceased (n = 153) participants. Cox proportional hazards regression models were used to quantify risk for all-cause mortality.

RESULTS

Deceased participants had a longer duration of type 2 diabetes (P = 0.02) and reduced use of cholesterol-lowering medications (P = 0.004). Adjusted analyses revealed that vascular calcified plaque scores were associated with increased risk for mortality (hazard ratio 1.31–1.63; $3.89 \times 10^{-5} < P < 0.03$). Higher HbA_{1c}, lipids, and C-reactive protein and reduced kidney function also were associated with a 1.1- to 1.5-fold increased risk for mortality ($3.45 \times 10^{-6} < P < 0.03$) after adjusting for confounding factors.

CONCLUSIONS

Even in this high-risk group, vascular calcification and known CVD risk factors provide useful information for ongoing assessment. The use of cholesterol-lowering medication seemed to be protective for mortality.

Rates of cardiovascular disease (CVD) are two- to fourfold greater in individuals with type 2 diabetes compared with nondiabetic individuals, and up to 65% of all-cause mortality among individuals with type 2 diabetes is attributed to CVD (1,2). However, the risk profile is not uniform for all individuals affected by diabetes (3–5). Coronary artery calcified plaque (CAC), determined using computed tomography, is a measure of CVD burden (6,7). CAC scores have been shown to be an independent predictor of CVD outcomes and mortality in population-based studies (8–10) and a powerful predictor of all-cause and CVD mortality in individuals affected by type 2 diabetes (4,11–15).

In the Diabetes Heart Study (DHS), individuals with CAC >1,000 were found to have greater than 6-fold (16) and 11-fold (17) increased risk for all-cause mortality

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and CVD mortality, respectively, after 7 years of follow-up. With this high risk for adverse outcomes, it is noteworthy that >50% of the DHS sample with CAC >1,000 have lived with this CVD burden for (now) an average of over 12 years. This suggests that outcomes vary in the type 2 diabetic patient population, even among individuals with the highest risk. This study examined the subset of DHS participants with CAC >1,000 and evaluated whether differences in a range of clinical factors and measurements, including modifiable CVD risk factors, provided further insights into risk for mortality.

RESEARCH DESIGN AND METHODS

Study Design and Sample

The study design, including ascertainment and recruitment procedures for the DHS, has been previously described in detail (18,19). This investigation focused on 371 high-risk participants (from 260 families) from a total of 1,220 individuals who completed the baseline examination. Participants self-identified as European American and had type 2 diabetes and baseline CAC >1,000 at enrollment in the DHS cohort. Type 2 diabetes was clinically defined as diabetes developing after the age of 35 years and treated initially with diet and exercise and/or oral antihyperglycemic medications. Individuals reporting treatment with insulin alone for more than the first year following diagnosis were excluded from the study. Diagnoses were confirmed by baseline measurement of fasting blood glucose and glycosylated hemoglobin (HbA_{1c}).

Study protocols were approved by the institutional review board at Wake Forest School of Medicine, and all participants provided written informed consent. Participant examinations were conducted in the General Clinical Research Center of the Wake Forest Baptist Medical Center and included anthropometric measures, resting blood pressure, electrocardiography, and fasting blood sampling for laboratory analyses including fasting glucose, HbA_{1c}, lipids, C-reactive protein (CRP), serum albumin, and creatinine concentrations. Estimated glomerular filtration rate (eGFR) was calculated using the four-variable Modification of Diet in Renal Disease equation (20). A spot urine collection was obtained to determine urine albumin-to-creatinine ratio (UACR). The examinations included interviews to record medical history, health behaviors, and medication use. Participants were encouraged to bring prescribed medications to the study visit for accurate recording. For the purposes of this analysis, oral hypoglycemic medications included those from the biguanide, thiazolidinedione, sulfonylurea, and meglitinide classes. Cholesterol-lowering medications included statins, fibric acid derivatives, bile acid sequestrants, and niacin.

Subclinical CVD was assessed by measuring calcified plaque in the coronary (CAC), carotid (CarCP), and abdominal aortic (AACP) vascular beds using fast-gated helical computed tomography scanners; calcium scores were calculated using a previously described method (19–22) and are reported as total calcium mass (mg). To assess vascular calcification from a more global perspective, a multibed vascular calcification score was derived from the sum of the available calcified plaque scores from the three vascular beds (multibed score). To account for the differences in the absolute values between the three vascular beds, the distributions of each first were standardized and then fitted to a minimum value of zero before the sum of all three beds was obtained. Finally, carotid intima-media thickness (IMT) was measured using high-resolution B-mode ultrasonography, as described previously (23).

Prevalent CVD was determined based on individuals' self-reported history of CVD events (angina, myocardial infarction, stroke) and/or interventions (coronary angioplasty/stenting, coronary artery bypass grafting, carotid endarterectomy). Individuals were classified as hypertensive if they were prescribed antihypertensive medication or if blood pressure measurements exceeded 140 mmHg (systolic) or 90 mmHg (diastolic) and were classified as dyslipidemic based on the criteria established in the *Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults* (24).

Vital Status

Vital status was determined for all participants, using the National Social Security Death Index, maintained by the U.S. Social Security Administration, to identify any participants deceased since their last contact with the research team. For participants confirmed as deceased, length of follow-up was determined from the date of the initial study visit to the date of death. For all other participants, the length of follow-up was determined from the date of the initial study visit to the end of 2012.

Statistical Analysis

Summary statistics for key demographic and outcome measures were determined. For dichotomous/ordinal measures, these are presented as counts and percentages and for continuous measures, as mean ± SD. To better control for heterogeneity of variance, continuous variables were transformed as appropriate to approximate normality before inclusion in statistical models. Analyses were performed using a Cox proportional hazards regression to appropriately account for time-to-event effects. Sandwich-based variance estimation was used in the Cox proportional hazards model because of the inclusion of related individuals in this study. Risk for mortality was quantified for each SD change in the predictor (continuous variables) or change in group assignment (dichotomous variables). An exploratory analysis examining differences in key demographic measures and known CVD risk factors between living and deceased groups was performed initially. Proportional hazards models then were adjusted for potential confounders: *1*) age and sex (model 1) and *2*) age, sex, and other relevant confounders (model 2), which included medication use relevant to specific traits (i.e., HbA_{1c}, blood lipids, and kidney function) and, in the case of the subclinical CVD measures, other known CVD risk factors including dyslipidemia, smoking, duration of diabetes, CRP, and UACR, which have been shown previously to be independent predictors of mortality in the DHS (25,26). For these adjusted models, continuous variables were standardized for analysis of associations with outcome to compare their relative importance. Analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC). $P < 0.05$ was accepted as statistically significant.

RESULTS

The goal of this analysis was to identify clinical and other characteristics that influence risk for all-cause mortality in high-risk (baseline CAC >1,000) DHS participants. Prior analysis clearly defines this subgroup of the DHS cohort to be at the highest risk for adverse outcomes (16,17). As anticipated, a predominance of traditional CVD risk factors, including older age, male sex, elevated BMI, and high rates of dyslipidemia and hypertension, was evident in this high-risk subgroup (Table 1). These participants were followed for 8.2 ± 3.0 years (mean ± SD), over which time 41% died. The mortality rate seemed to be consistent over the follow-up period.

Differences between these high-risk living and deceased participants were evaluated initially using generalized estimating equations. With the exception of age, other demographic features (sex, BMI, smoking status) were not significantly different between living and deceased participants (Table 1). Prior self-reported prevalent CVD was not significantly different. In contrast, deceased participants had a tendency for longer duration of type 2 diabetes at recruitment, and significant differences in HbA_{1c}, total cholesterol, LDL cholesterol, measures of kidney function, and CRP also were noted (Table 1). Measures of hypertension and fasting glucose did not demonstrate significant differences. All measures of subclinical CVD, including vascular calcified plaque in the three vascular beds (CAC, CarCP, and AACP) and carotid IMT, were also significantly higher in the deceased group (Table 1). Use of cholesterol-lowering medication at baseline was significantly less among the deceased participants (P = 0.004). Other medication use did not differ between the living and deceased groups (Table 1).

Observing these simple differences in the risk factor profiles between living and deceased groups, adjusted Cox proportional hazards models were used to quantify risk for adverse outcomes after accounting for relevant confounding factors. Among this group with a high

Table 1—Comparison of demographic and laboratory measures between living and deceased DHS participants with type 2 diabetes and CAC scores >1,000 (n = 371)

	Patients				
	All (n = 371)	Living (n = 218)	Deceased (n = 153)	HR (95% CI)	P value*
Demographic information					
Age (years)	65.5 ± 8.2	63.7 ± 7.6	68.2 ± 8.2	1.06 (1.04–1.09)	1.72×10^{-7}
Male sex (%)	70.1	70.6	69.3	1.08 (0.74–1.56)	0.70
BMI (kg/m^2)	32.0 ± 6.3	32.3 ± 5.8	31.5 ± 6.9	0.73 (0.50–1.07)	0.11
Current smoking (%)	14.6	12.4	17.6	1.38 (0.85–2.21)	0.19
Pack-years (among smokers)	41.9 ± 32.1	39.5 ± 31.3	44.9 ± 32.8	1.00 (0.99–1.01)	0.68
Duration of diabetes (years)	12.6 ± 8.0	11.6 ± 7.0	13.9 ± 9.0	1.02 (1.00–1.04)	0.02
Self-reported prior CVD (%)	68.5	68.3	68.6	0.94 (0.64–1.39)	0.76
Laboratory measures					
Pulse pressure (mmHg)	70 ± 17	69 ± 16	71 ± 18	1.01 (1.00–1.02	0.11
Blood pressure (mmHg)					
Systolic	141 ± 21	141 ± 18	141 ± 24	1.01 (1.00–1.02)	0.34
Diastolic	71 ± 11	72 ± 10	70 ± 12	0.99 (0.97–1.01)	0.35
Glucose (mg/dL)	148 ± 56	148 ± 53	147 ± 61	0.76 (0.45–1.28)	0.30
HbA_{1c} (%)	7.6 ± 1.5	7.4 ± 1.3	7.8 ± 1.8	1.99 (0.66–5.97)	0.22
HbA_{1c} (mmol/mol)	59.4 ± 16.8	57.5 ± 14.2	62.2 ± 19.6	1.55 (0.70–3.47)	0.22
Cholesterol (mg/dL)	179 ± 42	174 ± 42	186 ± 42	2.24 (1.09–4.60)	0.03
LDL (mg/dL)	99 ± 32	95 ± 31	105 ± 32	1.01 (1.00–1.01)	0.01
HDL (mg/dL)	40 ± 11	40 ± 10	41 ± 12	1.11 (0.88–1.41)	0.37
Triglycerides (mg/dL)	207 ± 135	200 ± 126	278 ± 146	1.05 (0.73–1.51)	0.80
UACR (mg/g)	143.3 ± 413.8	106.9 ± 389.3	195.8 ± 442.9	1.24 (1.12–1.37)	3.89×10^{-5}
eGFR	65.5 ± 19.3	67.8 ± 17.3	62.1 ± 21.4	4.78 (2.38–9.62)	1.18×10^{-5}
CRP (mg/L)	5.7 ± 10.2	4.5 ± 8.1	7.5 ± 12.6	2.14 (1.33–3.43)	0.002
Subclinical CVD					
CAC	4,489 ± 4,204	4,088 ± 4,421	5,051 ± 3,816	1.44 (1.14–1.81)	0.002
CarCP	657 ± 913	506 ± 790	871 ± 1,028	1.29 (1.17–1.42)	2.79×10^{-7}
AACP	22,457 ± 19,458	19,410 ± 18,410	28,101 ± 20,171	1.01 (1.00–1.01)	4.82×10^{-6}
Derived multibed score	3.89 ± 3.03	3.34 ± 2.93	4.91 ± 2.98	2.31 (1.67–3.19)	3.43×10^{-7}
Carotid IMT	0.726 ± 0.151	0.704 ± 0.146	0.757 ± 0.154	1.30 (1.12–1.51)	0.0008
Medication use† (%)					
Cholesterol-lowering drug	60.6	67.9	50.3	1.68 (1.19–2.39)	0.004
Antihypertensive	84.9	84.9	85.0	1.05 (0.65–1.68)	0.85
ACE/angiotensin receptor blocker	67.1	69.2	64.1	1.31 (0.92–1.87)	0.14
Insulin	34.5	33.5	35.9	0.90 (0.62–1.30)	0.57
Oral hypoglycemics	79.2	79.8	78.4	0.98 (0.64–1.50)	0.92

Data are mean ± SD unless otherwise indicated. Hazard ratios (HRs) are for an SD change in the predictor (continuous variables) or change in group assignment (dichotomous variables). *P values for difference between living and deceased groups were assessed using Cox proportional hazards models with sandwich-based variance estimation and appropriately transformed continuous variables. †Medication use HRs are presented to reflect risk for mortality among those individuals not using the designated medication classes.

burden of CAC, a number of indices continued to significantly predict outcome following adjustment for other CVD risk factors (including age, sex, and medication use) (Table 2). Higher cholesterol and LDL concentrations were associated with an increased risk (~1.3-fold) for mortality (Table 2). Slightly larger increases in risk for mortality were observed with changes in kidney function (1.3- to 1.4-fold) and elevated CRP (~1.4-fold) (Table 2). Among the measures of subclinical CVD, the derived multibed score was associated with an approximate 1.4-fold increase in risk for mortality and carotid IMT was associated with the smallest increase in risk (~1.15-fold) (Table 2). Last, use of cholesterol-lowering medication was less common among the deceased participants; those reporting no use of cholesterol-lowering medication at baseline were at a 1.4-fold increased risk of mortality (Table 2). Results were essentially unchanged following additional adjustments for relevant medication use (i.e., relevant to measures of blood lipids and kidney function) and, in the case of the subclinical CVD measures, other known CVD risk factors (Table 2).

CONCLUSIONS

This study, which focused on individuals affected by type 2 diabetes with high CAC scores, examined the association of CVD risk factors with adverse outcomes. In our prior work we showed that type 2 diabetes–affected individuals with CAC >1,000 have a substantially increased risk of mortality compared with other type 2 diabetes–affected individuals with lower CAC scores (16,17). Other investigators also documented high risk for adverse outcomes with very high CAC scores (9,12–14,27). Thus, in a class of patients—all of whom are presumed to be at high risk—there are individuals at even greater risk. Importantly, these results confirm that, even among this high-risk group, heterogeneity in known CVD risk factors and associations with adverse outcomes are still observed and support their ongoing consideration as useful tools for individual risk assessment. Finally, the data presented here suggest that use of cholesterol-lowering medication was strongly associated with protection, supporting the known beneficial effects of cholesterol management on CVD risk (28,29).

Some of the observed differences between living and deceased individuals with CAC >1,000 in the DHS are not surprising given that we previously reported the relationships of both CRP (26) and measures of kidney function and albuminuria (25) with mortality in the entire DHS cohort. Also of note was the fact that, despite the considerable burden of subclinical disease in these individuals (as measured by CAC), measures of vascular calcification remained predictive of outcome. Interestingly, the derived multibed score showed a particularly strong association with mortality, suggesting that consideration of vascular calcification as a more global phenomenon may more fully reflect the extent of subclinical disease and attendant risk. That measures of calcified plaque remained predictive of outcome even when selecting individuals from the extreme of the distribution provides further evidence supporting the relationships between these measures of subclinical CVD and adverse outcome in individuals with type 2 diabetes.

While other medication classes failed to differ between living and deceased participants, the use of cholesterol-lowering drugs was significantly lower in deceased individuals and cholesterol and LDL were significantly higher. This observation supports the importance of widespread prescription of cholesterol-lowering medications among individuals with type 2 diabetes and existing high CVD risk. Interestingly, despite recent evidence supporting improved outcome with statin use in type 2 diabetes–affected individuals (30), rates of reported use of cholesterol-lowering medications from other large cohort studies include the Multi-Ethnic Study of Atherosclerosis (use in 20–30% of type 2 diabetes–affected participants)

Table 2—Association between key demographic characteristics and known CVD risk factors and outcome among DHS participants with CAC >1,000

	Model 1*		Model 2†		
Characteristics	HR (95% CI)	*P* value	HR (95% CI)	*P* value	Additional confounders
Duration of diabetes (years)‡	1.18 (1.01–1.39)	0.04	—	—	—
HbA_{1c} (%)	1.36 (1.16–1.60)	0.0002	1.36 (1.15–1.61)	0.0004	Insulin, oral hypoglycemic medications
Cholesterol (mg/dL)	1.30 (1.10–1.55)	0.0009	1.27 (1.07–1.49)	0.006	Cholesterol-lowering medication
LDL (mg/dL)	1.26 (1.08–1.46)	0.003	1.21 (1.02–1.44)	0.03	Cholesterol-lowering medication
UACR (mg/g)	1.36 (1.17–1.58)	6.39×10^{-5}	1.37 (1.17–1.60)	9.22×10^{-5}	ACE/ARB medications
eGFR	1.35 (1.11–1.64)	0.003	1.35 (1.11–1.64)	0.003	ACE/ARB medications
CRP (mg/L)	1.44 (1.21–1.70)	2.75×10^{-5}	1.44 (1.21–1.70)	3.45×10^{-6}	BMI
CAC	1.23 (1.05–1.45)	0.01	1.29 (1.08–1.55)	0.006	Duration of diabetes, current smoking, dyslipidemia, CRP, UACR
CarCP	1.38 (1.16–1.64)	0.0002	1.63 (1.29–2.06)	3.89×10^{-5}	
AACP	1.21 (0.99–1.48)	0.06	1.31 (1.03–1.67)	0.03	
Carotid IMT	1.15 (0.98–1.34)	0.09	1.07 (0.90–1.26)	0.44	
Derived multibed score	1.39 (1.15–1.69)	0.0008	1.55 (1.25–1.93)	8.02×10^{-5}	
No cholesterol-lowering medication	1.44 (1.05–1.96)	0.02	—	—	—

Hazard ratios (HRs) are for an SD change in the predictor (continuous variables) or change in group assignment (dichotomous variables). *Model 1 was adjusted for age and sex; all continuous variables were standardized to compare effects relative to each other. †Model 2 was adjusted for age, sex, and other relevant confounders, as appropriate. ‡Adjusted for sex only. ARB, angiotensin receptor blocker.

(31), the Framingham Offspring Cohort (use in 25% of type 2 diabetes–affected participants) (32), and the Cardiovascular Health Study (use in 25% of type 2 diabetes–affected participants) (33). These data suggest that cholesterol-lowering medications may be used less than recommended and need to be more aggressively targeted as a critical modifiable risk factor. That said, the American Diabetes Association Standards of Medical Care in Diabetes have changed since recruitment to the DHS commenced, and since 2008 they have included recommendations for statin prescription to all type 2 diabetes–affected individuals, regardless of baseline LDL, in whom more than one CVD risk factor exists (34). Data pertaining to changes in medication use during the follow-up period are not available for the DHS cohort, and it remains unclear whether a reanalysis in the remaining DHS sample based on contemporary medication use would produce the same result as that described here.

Discussion of the findings from this study would be incomplete without acknowledging additional limitations. Although the relationships between risk factors and outcome in this high-risk cohort offer useful information in the context of risk assessment, causality cannot be automatically assumed, and other factors such as propensity for plaque rupture or thrombosis are highly important. Indeed, the fact that 60% of this high-risk sample is living after, on average, more than 8 years of follow-up emphasizes the need for greater insights into the seemingly episodic events that lead to death. Further, it is unclear whether similar observations will be made in other ethnic groups because the individuals included in this analysis were exclusively European American.

In conclusion, the findings described here suggest that even among individuals with type 2 diabetes and high burden of subclinical CVD, modifiable risk factors exist that could be targeted for early and continued intervention to reduce the risk of adverse outcomes. Regression of calcified plaque is not likely, and this measure is unlikely to be appropriate for assessing the effectiveness of intervention approaches. Given the multifactorial nature of CVD and the complex pathophysiological mechanisms underpinning the disease, however, numerous multiple risk reduction strategies are necessary. Early and active intervention to try to avoid accumulation of calcified plaque to this extent is especially relevant given the high mortality in the group with CAC $>$1,000.

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