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HbA1c Predicts Diabetes but not Cardiovascular Disease in Non-Diabetic Women

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Abstract

Background—Hemoglobin A1c (HbA1c) is a marker of cumulative glycemic exposure over the preceding 2–3 month period. Whether mild elevations of this biomarker provide prognostic information for development of clinically evident type 2 diabetes and cardiovascular disease among individuals at usual risk for these disorders is uncertain.

Methods—We examined baseline HbA1c levels as a predictor of incident clinical diabetes and cardiovascular disease (non-fatal myocardial infarction, coronary revascularization procedure, ischemic stroke, or death from cardiovascular causes) in a prospective cohort study beginning in 1992 of 26,563 US female health professionals aged ≥ 45 years without diagnosed diabetes or vascular disease (median follow-up 10.1 years).

Results—During follow-up, 1238 cases of diabetes and 684 cardiovascular events occurred. In age-adjusted analyses using quintiles of HbA1c, a risk gradient was observed for both incident diabetes and cardiovascular disease. In multivariable-adjusted quintile analyses, HbA1c remained a strong predictor of diabetes but was no longer significantly associated with incident cardiovascular disease. In analyses of threshold effects, adjusted relative risks for incident diabetes in HbA1c categories of <5.0%, 5.0–5.4%, 5.5–5.9%, 6.0–6.4%, 6.5–6.9%, and ≥7.0% were 1.0, 2.9, 12.1, 29.3, 28.2, and 81.2. Risk associations persisted after additional adjustment for C-reactive protein and after excluding individuals developing diabetes within 2 and 5 years of follow-up.

Conclusions—These prospective findings suggest that HbA1c levels are elevated well in advance of the clinical development of type 2 diabetes supporting recent recommendations for lowering of diagnostic thresholds for glucose metabolic disorders. In contrast, the association of HbA1c with incident cardiovascular events is modest and largely attributable to coexistent traditional risk factors.

Hemoglobin glycation, estimated by percentage hemoglobin A1c (HbA1c), was first used clinically 30 years ago to assess degree of chronic hyperglycemia among diabetic patients [1] in whom values reflect weighted mean glucose levels over the preceding 3-month period.[2] Over the past three decades, elevated HbA1c has been firmly linked with long-term risk of microvascular complications and HbA1c assessment is now used ubiquitously for monitoring

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effective glycemic control as a cornerstone of diabetes care. With the introduction of reference method standardization, issues pertaining to high inter-laboratory and inter-assay analytic variability have been largely overcome such that in 2002, 98% of US laboratories surveyed used standardized methods.[3]

Given these favorable performance characteristics, recent investigative efforts have attempted to broaden the role of HbA1c as an index of cumulative glycemic exposure in diabetes and cardiovascular risk assessment among non-diabetic patients. Several studies have evaluated the ability of HbA1c levels to predict future type 2 diabetes in high-risk pre-diabetic individuals[4–7] and more recent data suggest that HbA1c may also be useful in detecting risk for incident cardiovascular events.[8–12] Importantly, whether a single HbA1c measurement can be used in this application remains uncertain and prospective population-based studies of individuals at low to average risk are rare.

In a prior nested case-control analysis,[13] we found that an elevated HbA1c level was a univariate predictor of incident cardiovascular events but this effect was not significant after adjustment for other cardiovascular risk factors. However, we did not examine non-linear threshold effects which may have prognostic significance as has been demonstrated in several prospective studies of plasma glucose and incident cardiovascular events [14–19] and at least one study of HbA1c and cardiovascular mortality.[8]

We therefore evaluated whether baseline HbA1c levels predict clinical diabetes and first cardiovascular events among otherwise healthy middle-aged and older American women, a population in which diabetes is a potent vascular risk factor and among whom data pertaining to this issue are sparse. We utilized both traditional quantile analysis and examined potential threshold effects with a focus on HbA1c levels currently considered to be well within the normal range.

METHODS

Study Population

The Women's Health Study (WHS)[20] is a recently completed randomized clinical trial of low-dose aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer. Between November 1992 and July 1995 a total of 39,876 US female health professionals aged 45 years and older without prior cardiovascular disease or cancer (except non-melanoma skin cancer) were enrolled and randomized into the study.

Before randomization, 28,345 participants provided blood specimens which were stored in liquid nitrogen until laboratory analysis. Of samples received, 27,882 were usable for HbA1c determination. We restricted the population to subjects without diagnosed diabetes and excluded women with missing baseline BMI (1.9%, n=517). All other major known diabetes and cardiovascular risk factors assessed had less than 1% missing data. The final study population comprised 26,563 women followed for a median of 10.1 years (range, 0.07–10.8 years).

Outcome Ascertainment

The status of type 2 diabetes was indicated at baseline by self-report, and women with a history of diagnosed diabetes were excluded. Thereafter, all participants were asked annually whether and when (month and year) they had been diagnosed with diabetes since completing the previous questionnaire. Two complementary methods for diabetes confirmation have been used.[21] First, as part of a nested case-control study[22] 406 consecutive cases of self-reported diabetes occurring between years 2 through 5 of follow-up were confirmed by telephone interview using American Diabetes Association (ADA) criteria.[23] Second, a random sample

of 147 women with self-reported diabetes was mailed a supplemental diabetes questionnaire. Among 136 respondents, 124 (91%) met ADA diagnostic criteria. Additionally, 113 of the 124 women gave permission to contact their primary care physician. Of 113 physicians approached, 97 responded and 90 provided adequate information to apply the ADA criteria. Among these 90, 89 (99%) were confirmed to have type 2 diabetes. Thus, we believe that self-reported type 2 diabetes is valid in the WHS.

Women with a self-reported history of diagnosed cardiovascular disease (myocardial infarction, coronary revascularization, angina, stroke, transient ischemic attack, and peripheral arterial surgery) were ineligible for randomization into the WHS. After randomization, all women were followed through annual mailed questionnaires for incident myocardial infarction, coronary revascularization, stroke, or death from cardiovascular causes. Medical records were obtained for all women reporting a cardiovascular endpoint. Records were reviewed in a blinded fashion by an endpoints committee of physicians. Myocardial infarction was confirmed if symptoms met World Health Organization criteria and if the event was associated with abnormal levels of cardiac enzymes or diagnostic electrocardiograms. Coronary revascularization was confirmed through review of procedural reports. A confirmed stroke was defined as a new neurologic deficit of sudden onset that persisted for at least 24 hours. Clinical information and radiographic reports were used to distinguish hemorrhagic from ischemic events. Death from cardiovascular was determined by autopsy or death certificates, medical records, and information obtained from family members.

Laboratory Analysis

HbA1c was estimated using the Tina-Quant turbidimetric inhibition immunoassay (Roche Diagnostics, Indianapolis, IN) on a Hitachi 911 autoanalyzer using packed red blood cells. The assay is specific for HbA1c, is standardized against the approved International Federation of Clinical Chemists (IFCC) reference method, and is traceable to the Diabetes Control and Complications Trial (DCCT) by use of a conversion factor. Values of HbA1c presented in this study are DCCT aligned. The reference range for healthy non-diabetic subjects is 4.8 to 5.9%. The coefficient of variation for HbA1c computed from blinded simultaneously analyzed quality controls was 7.2%.

EDTA specimens were analyzed for LDL- and HDL-cholesterol using direct measurement assays (Roche Diagnostics, Indianapolis, IN). C-reactive protein (CRP) was measured using a validated high-sensitivity assay (Denka Seiken, Niigata, Japan).

Statistical Analysis

Histograms of HbA1c levels were constructed according to 4 main groups: individuals remaining disease-free (N=24,725), developing cardiovascular disease only (N=600), diabetes only (N=1,154), or both cardiovascular disease and diabetes (N=84). The median, interquartile range (IQR), mean, and standard deviation (SD) were calculated. Differences in median HbA1c were tested using the Wilcoxon Rank Sum test. Cox proportional hazards models predicting incident diabetes and cardiovascular disease were constructed using HbA1c quintiles with the lowest quintile as referent. Tests of linear trends were computed using median values within each quintile. Models were first age-adjusted (5-year categories). Multivariable models further adjusted for ethnicity, smoking, history of hypertension, baseline anti-hypertensive therapy, BMI, diabetes in a first-degree relative (diabetes models) or parental history of myocardial infarction before age 60 (cardiovascular disease models), exercise frequency, alcohol consumption, use of menopausal hormone therapy (MHT), and measured LDL and HDL-cholesterol levels (see Table 1 footnote). Sensitivity analyses excluded diabetes cases diagnosed within 2 and 5 years of follow-up. We repeated our analysis of incident diabetes using only confirmed events.

In analyses examining alternate cutpoints of HbA1c, individuals were categorized into groups beginning at values below 5.0%, the population mean, in 0.5% increments up to a value ≥ 7.0%, the cutpoint corresponding to the optimal treatment target[24] and a level proposed as diagnostic of drug-requiring diabetes.[25] Kaplan-Meier survival curves were plotted and differences in event-free survival assessed using the log-rank test for multiple group comparisons.

All confidence intervals (CIs) are 2-tailed and calculated at the 0.05 level. Analyses were conducted using SAS statistical software version 8.01 (SAS Institute, Cary, NC).

RESULTS

The study population was predominantly non-Hispanic white (94.8%) having a mean age of 54.6 years (SD 7.1) and mean BMI of 25.8 kg/m^2 (SD 4.9). The baseline prevalence of hypertension, hyperlipidemia, current smoking, and current MHT use were as follows: 24.0%, 29.0%, 11.6%, and 43.8%. History of diabetes in a first-degree relative and parental history of MI before age 60 years and was reported by 24.8% and 11.5% of women, respectively. The median (IQR) and mean (SD) of levels of HbA1c at study initiation were 4.99% (4.83, 5.17) and 5.03% (0.37), respectively.

Overall, the age-specific rates of diagnosed diabetes for women in this study of initially healthy women were lower than among women in the US population-at-large as estimated by the National Health Interview Survey (NHIS)[26]. In 1999, the year corresponding to median follow-up of our cohort, the estimated incidence per 1000 population for women aged 45–64 and 65–79 years in the NHIS were 8.2 and 9.0, respectively. Among WHS participants in the same age groups, diabetes incidence rates were 4.8 and 5.1 per 1000 person-years, respectively. Among 74 women with baseline HbA1c levels ≥ 7.0%, 81.1% (n=60) developed diabetes during the period of observation. The median follow-up for this category was identical to the rest of the cohort (10.1 vs. 10.1 years, p=0.8).

Figure 1 shows the distribution of HbA1c values according to disease categories: individuals remaining event-free, developing cardiovascular disease only, diabetes only, or both. HbA1c values appeared normally distributed among individuals remaining event-free but were rightward skewed in other subpopulations. Median HbA1c values were significantly lower in women remaining event-free when compared to all other subgroups (p<0.001 for all two-group comparisons).

Table 1 provides event rates and results of statistical models according to HbA1c quintiles. A graded risk increase was present in both age-adjusted and multivariable-adjusted models predicting clinical diabetes. Multivariable-adjusted RRs were 1.0, 1.1, 1.7, 2.6, 8.6 (p-trend<0.001). Exclusion of diabetes cases occurring within the first 2 years (n=175) had minimal influence on risk estimates; multivariable-adjusted RRs were 1.0, 1.3, 1.8, 2.8, and 8.2; p-trend<0.001. Cardiovascular disease incidence rose across quintiles of HbA1c. Age-adjustment weakened this association. Age-adjusted RRs were 1.0, 0.9, 1.1, 1.0, and 1.2 (p-trend=0.046) with an apparent increase in risk confined to women in the highest quintile. Results were not statistically significant in models additionally adjusting for cardiovascular risk factors. When modeled as a linear continuous term, there was no significant increase in risk of cardiovascular disease associated with a 1% increase in HbA1c (RR 1.10, p=0.28).

To examine threshold effects, analyses were repeated according to clinically expedient cutpoints of 0.5% increments above 5.0%, with the highest category defined by values ≥ 7.0%. For diabetes an increase in risk was noted in each category above 5.0% in both age-adjusted and multivariable models and after exclusion of cases diagnosed within 2 years or even 5 years of follow-up. Results were unchanged when analyses were limited to confirmed cases (N=406) occurring during 5 years of follow-up (data not shown). Because HbA1c, rather than reflecting

ambient glucose levels, might indicate more widespread protein glycation[27] and associated inflammation which may precede the development of both diabetes and cardiovascular disease[28], we adjusted for baseline CRP and found similar results. In these analyses, the multivariable-adjusted RRs for incident diabetes across categories of HbA1c were 1.0, 2.9, 11.7, 27.8, 25.9, and 78.2 (95% CI for extreme categories: 57.3–106.8).

Figure 2 depicts Kaplan-Meier survival curves for diabetes according to HbA1c category. Event-free survival was significantly associated with baseline HbA1c (multi-group log-rank $p<0.001$). Importantly, curves appeared to diverge even among those with values of 5.0–5.4% and 5.5–5.9%.

For incident cardiovascular disease, the risk associated with HbA1c was weaker than for diabetes (Table 2). The age-adjusted relative risk increased above a level of 5.0%; the RRs were 1.1, 1.6, 2.3, 2.7, and 2.3 for HbA1c categories 5.0–5.4%, 5.5–5.9%, 6.0–6.4%, 6.5–6.9%, and ≥ 7.0% as compared to a value below 5.0%. Risk estimates were statistically significant only in those higher HbA1c categories with relatively large numbers of events. In multivariable analyses, effect estimates were attenuated and no longer statistically significant. In analyses additionally adjusting for baseline CRP, the multivariable RR according to HbA1c category were 1.0, 0.9, 1.1, 1.5, 1.5, and 1.5 (95% CI for extreme categories: 0.6–4.1).

COMMENT

In this large-scale prospective study of baseline HbA1c and 10-year incidence of type 2 diabetes and cardiovascular events in middle-aged and older American women, we found strong associations between asymptomatic glycemic exposure as quantified by HbA1c and incident diabetes. Our findings persisted in multivariable analysis after excluding early likely undiagnosed diabetes cases and in models assessing threshold effects. The risk gradient for incident diabetes was evident throughout the full range of baseline values even in categories minimally displaced from the population mean. Importantly, in this low-risk population, we observed an increased diabetes risk even among women with HbA1c levels between 5.0 and 5.5%, values falling within the normal reference range and not generally considered indicative of high risk in routine clinical practice. These findings support recent ADA recommendations to lower diagnostic thresholds for impaired fasting glucose.[29] In contrast, in our study population the strength of association between HbA1c and cardiovascular events appeared weak and did not persist after accounting for established cardiovascular risk factors suggesting that these factors rather than dysglycemia itself may be more important for development of vascular events.

Prior studies of HbA1c as a predictor of diabetes have been largely confined to high-risk populations. Findings from longitudinal studies of Pima Indians,[4, 6] Japanese[5] and Chinese[7] adults with baseline glucose intolerance or other diabetes risk factors suggest that in pre-diabetic individuals elevated HbA1c predicts progression to biochemical diabetes as determined by oral glucose tolerance testing. Among Pima Indians,[4] glucose intolerant individuals with an elevated HbA1c (≥ 6.03%), a cutpoint 2 SDs above the mean for healthy Caucasian volunteers, had a 7-fold sex-adjusted increase in diabetes risk. In a later report from the same cohort,[6] incorporation of HbA1c in a risk prediction algorithm allowed better identification of future diabetes than fasting or post-challenge glucose values. In this regard, a single measure of blood glucose has been shown to poorly characterize usual glycemia with large intraindividual variability, poor reproducibility, and potential for substantial misclassification.[30–32] In contrast, HbA1c reflects the integrated average of glucose levels weighted proportionately toward more recent values.[2] The test may be performed irrespective of prandial state, does not require glucose loading, and demonstrates good reproducibility on

repeated measurements in non-diabetic subjects over time.[33, 34] These favorable characteristics offer several practical advantages over other glycemic indicators.

Our findings demonstrate the potential prognostic importance of this biomarker at levels generally considered either normal or only mildly elevated in usual clinical care. We also chose to include individuals with HbA1c levels greater than 7.0% which was suggested to indicate biochemical diabetes in a meta-analysis comprising studies predominantly conducted in high-risk groups.[25] It is important to note that diagnostic thresholds derived from high-risk populations may not be generalizable to lower risk groups as screening characteristics vary with underlying glucose frequency distributions.[35, 36] In addition, while glycated hemoglobin levels are correlated with fasting and 2-hour blood glucose when glucose levels fall within the diabetic range, there is considerable overlap of HbA1c levels in milder forms of glucose intolerance.[37, 38] Furthermore, in our low-risk population approximately 20% of those with HbA1c levels ≥ 7.0% did not develop clinical diabetes over a 10-year period and would have been incorrectly classified as diabetic based on this threshold criterion alone.

With regard to incident cardiovascular disease, prior studies of smaller size have demonstrated variable results. In the Rancho Bernardo cohort of 1,239 older non-diabetic adults, baseline HbA1c but not fasting or post-challenge glucose predicted cardiovascular mortality in women but not in men. A threshold effect was noted, such that women in the highest (≥ 6.7%) versus lower four quintiles had a near 3-fold elevation in adjusted risk.[8] Subsequent reports from the Hoorn Study[9], Framingham Offspring Study,[11] and European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk)[12] found significant associations when HbA1c was assessed on a linear basis as per 1.4% (2 SD units), per 0.7% (interquartile range), and per 1% increments, respectively. In particular, in the EPIC-Norfolk study a 1% increment in HbA1c was associated with a 21% increase in cardiovascular risk after multivariable adjustment in both men and women. However, when subjects with prior diabetes and cardiovascular disease were excluded this association was diminished and not statistically significant (RR 1.16, CI 0.99–1.36; p=0.08). In the Hoorn Study, which also presented categorical analyses with and without adjustment for traditional risk factors, the age-adjusted risk in the highest versus lowest category (≥ 6.5% versus < 5.2%), was 3.8 (95% CI 1.6–8.0). However, after additional adjustment for gender, hypertension, dyslipidemia, and smoking, this effect was attenuated and no longer statistically significant (RR 1.8; 95% CI 0.8–4.2). In our prior nested case-control study in the WHS cohort[13], we similarly found that HbA1c levels were not predictive of cardiovascular events after adjustment for confounding effects of correlated cardiovascular risk factors.

Several limitations of our study merit further discussion. First, because our cohort comprised healthy predominantly non-Hispanic white women aged 45 years and older, our results may not be generalizable to other ethnic or racial groups, to men, or younger individuals who may otherwise be at risk for these disorders. Second, due to assay characteristics and specimen requirements, fasting glucose levels were not available. We were therefore unable to detect baseline mild unrecognized diabetes or lesser degrees of glucose intolerance. However, our results were similar in sensitivity analyses excluding individuals who developed clinical diabetes within 2 years and 5 years of follow-up. In addition, while type 2 diabetes may be unrecognized for many years in the general population, subjects in this study are health professionals who have regular access to medical care and therefore are less likely to remain undiagnosed. Nonetheless, given the likely inclusion of some subjects with undiagnosed diabetes and impaired glucose tolerance, our findings may not apply to those who are normoglycemic as assessed by more stringent metabolic criteria but importantly do apply to most clinic-based samples of asymptomatic individuals with no prior diagnosis of diabetes. Finally, we used a single baseline measurement of HbA1c. We therefore cannot evaluate the effects of changes in this parameter over time. However, glycated hemoglobin values have

been found to reliably categorize glycemic status in non-diabetic subjects during a period of at least 4 to 6 years[34] suggesting that exposure misclassification on this basis is likely to be small. Further, the distribution, mean and median values of HbA1c in our study are comparable to other referent populations with normal glucose tolerance.[25, 39]

In summary, we found that baseline HbA1c is an independent risk predictor for type 2 diabetes but not cardiovascular disease among healthy middle-aged and older women. We found evidence for a continuum of risk in the prediction of diabetes even at levels generally considered within the normal range. Although these data do not support the use of HbA1c as a single measure of diabetes risk, our results do suggest that the prognostic significance of elevated HbA1c may warrant a greater emphasis in primary prevention.

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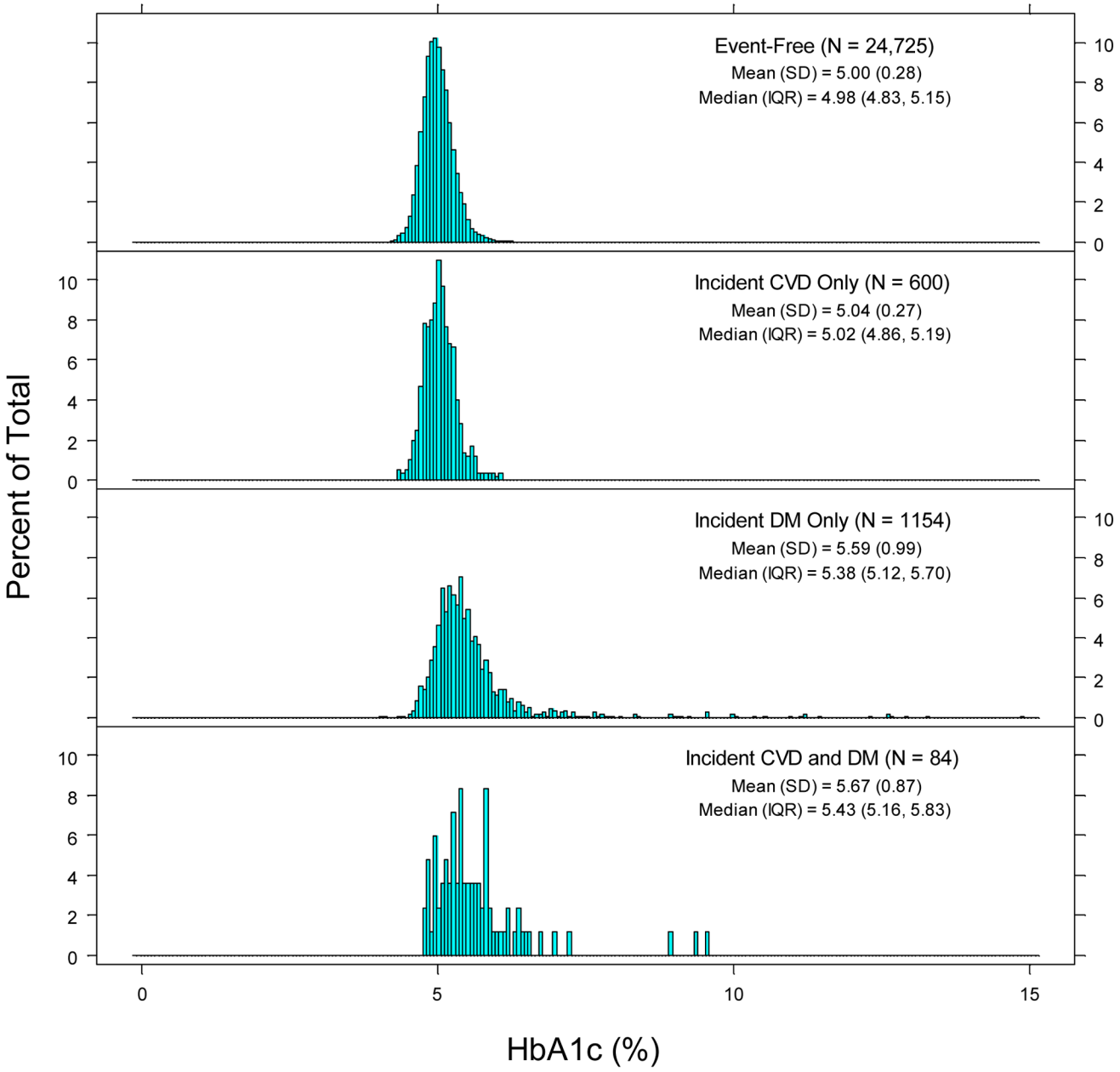

Figure 1.

Histograms of HbA1c distribution according to four main groups: individuals remaining disease-free (N=24,725), developing incident cardiovascular disease (CVD) only (N=600), incident diabetes mellitus (DM) only (N=1,154), or both cardiovascular disease and diabetes mellitus (N=84).

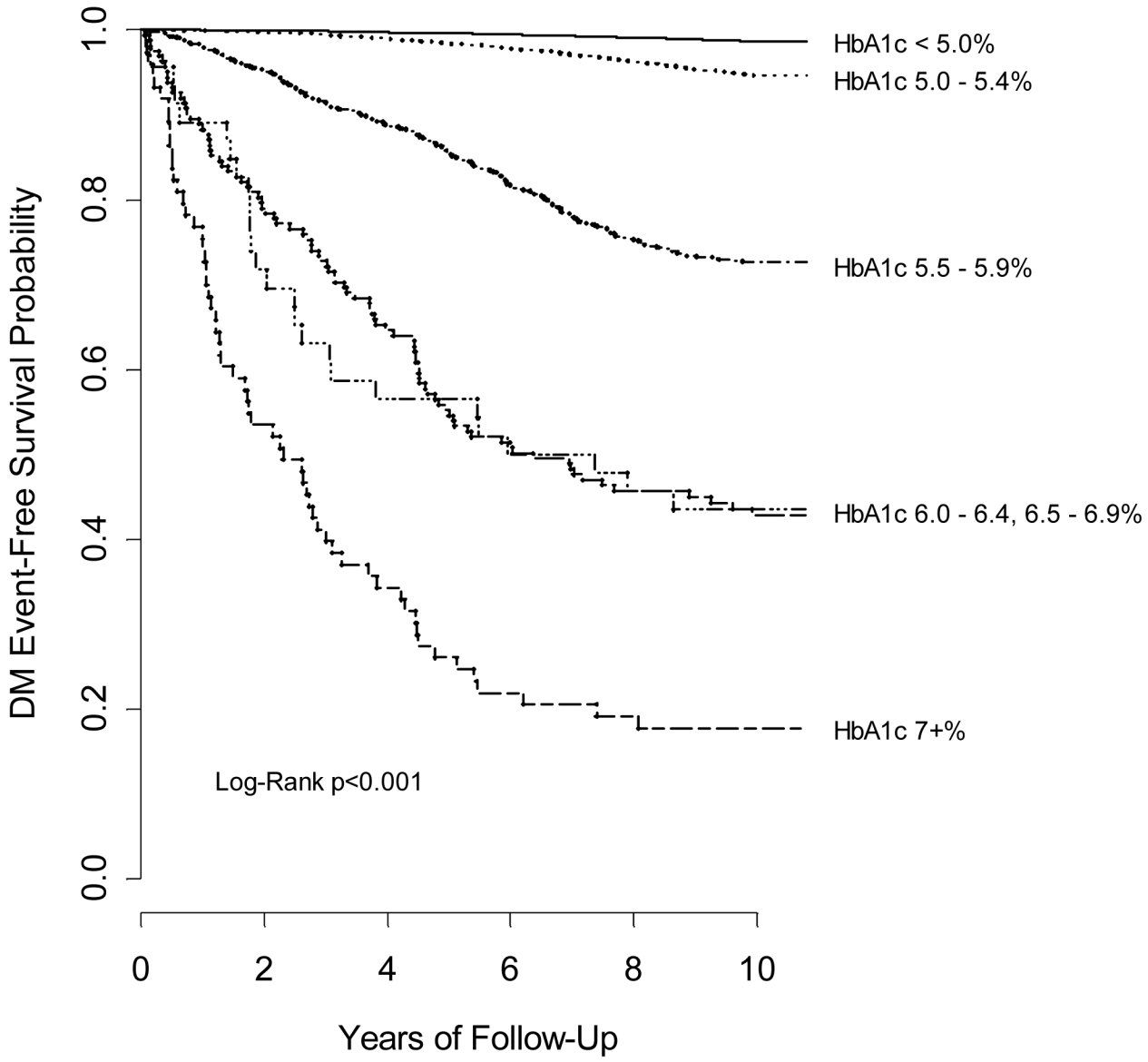

Figure 2.
Kaplan-Meier curves for 10-year diabetes incidence according to baseline HbA1c category.

Table 1

Relative risks (RRs) of diabetes and cardiovascular disease by HbA1c quintiles

	Hemoglobin A1c Quintiles					
	1 **< 4.8**	**2** **4.80 – 4.93**	**3** **4.94 – 5.06**	**4** **5.07 – 5.22**	**5** **> 5.22**	**P-Trend**
N	**5313**	**5313**	**5313**	**5311**	**5313**	
Incident diabetes mellitus						
Events	53	65	109	194	817	
Events/1000 person-years	1.0	1.2	2.1	3.8	17.0	
Age-adjusted RR (95% CI)	1.0	1.2 (0.9 –1.8)	2.1 (1.5 – 2.9)	3.7 (2.8 – 5.1)	17.2 (13.0 – 22.8)	<0.001
Multivariable-adjusted RR† (95% CI)	1.0	1.1 (0.8 – 1.6)	1.7 (1.2 – 2.3)	2.6 (1.9 – 3.5)	8.6 (6.5 – 11.6)	<0.001
Multivariable-adjusted RR‡ (95% CI)	1.0	1.3 (0.9 – 1.9)	1.8 (1.3 – 2.6)	2.8 (2.0 – 3.9)	8.2 (6.0 – 11.1)	<0.001
Incident cardiovascular events*						
Events	105	113	135	141	191	
Events/1000 person-years	2.0	2.2	2.6	2.7	3.7	
Age-adjusted RR (95% CI)	1.0	0.9 (0.7 – 1.2)	1.1 (0.8 – 1.4)	1.0 (0.8 – 1.3)	1.2 (1.0 – 1.6)	0.046
Multivariable-adjusted RR† (95% CI)	1.0	0.8 (0.6 – 1.1)	0.9 (0.7 – 1.2)	0.8 (0.6 – 1.0)	0.9 (0.7 – 1.2)	0.5

*Cardiovascular disease: MI, CABG/PTCA, ischemic stroke, and cardiovascular death

†Adjusted for age (5-year categories), ethnicity (Caucasian, African-American, Hispanic, Asian, American Indian, other, unknown), smoking (never, past, current), history of hypertension (no/yes self-report ≥ 140/90), baseline anti-hypertensive therapy (no/yes), BMI category (WHO category), family history of MI/DM (parental MI <60y, 1st degree relative DM), exercise (never, <1 time per week, 1–3 times per week, 4+ times per week), alcohol consumption (non-drinker, 1–3 per month, 1–6 per week, 1+ per day), MHT use, LDL (linear continuous), and HDL (linear continuous).

‡Adjusted as above after excluding women diagnosed with diabetes during the first two years of follow-up (N=175).

Table 2

Relative risks (RRs) for diabetes and cardiovascular disease by HbA1c category

	HbA1c Categories (0.5% Increments)					
	< 5.0	**5.0 – 5.4**	**5.5 – 5.9**	**6.0 – 6.4**	**6.5 – 6.9**	**≥ 7.0**
N (%)	**13567 (51.1)**	**11578 (43.6)**	**1136 (4.7)**	**162 (0.6)**	**46 (0.2)**	**74 (0.3)**
Incident diabetes						
Total Population						
Events	172	585	304	91	26	60
Events/1000 person-years	1.3	5.0	31.6	90.5	93.1	227.3
Age-adjusted RR (95% CI)	1.0	4.1 (3.5 – 4.9)	25.6 (21.1 – 30.8)	76.7 (59.4 – 99.1)	77.6 (51.4 – 117.4)	201.4 (149.7 – 271.1)
Multivariable-adjusted RR[†] (95% CI)	1.0	2.9 (2.4 – 3.4)	12.1 (10.0 – 14.8)	29.3 (22.4 – 38.3)	28.2 (18.5 – 43.0)	81.2 (59.5 – 110.9)
Excluding cases of diabetes occurring during (a) the first two and (b) the first five years of follow-up						
(a) Multivariable-adjusted RR[‡] (95% CI)	1.0	2.8 (2.4 – 3.4)	10.8 (8.8 – 13.3)	20.5 (14.9 – 28.2)	16.9 (9.5 – 30.0)	54.1 (35.3 – 82.9)
(b) Multivariable-adjusted RR[§] (95% CI)	1.0	3.0 (2.4 – 3.7)	9.4 (7.2 – 12.1)	12.5 (7.6 – 20.4)	11.8 (5.2 – 27.0)	29.2 (12.7 – 67.3)
Incident cardiovascular events[*]						
Total population						
Events	288	325	53	11	3	4
Events/1000 person-years	2.2	2.9	4.8	7.1	6.9	5.7
Age-adjusted RR (95% CI)	1.0	1.1 (0.9 – 1.3)	1.6 (1.2 – 2.1)	2.3 (1.3 – 4.3)	2.7 (0.9 – 8.5)	2.3 (0.8 – 6.1)
Multivariable-adjusted RR[†] (95% CI)	1.0	0.9 (0.8 – 1.1)	1.2 (0.9 – 1.6)	1.6 (0.9 – 3.0)	1.7 (0.5 – 5.3)	1.6 (0.6 – 4.5)

[*] Cardiovascular events: MI, CABG/PTCA, ischemic stroke, and cardiovascular death

[†] Adjusted for same covariates as listed in Table 1 footnote.

[‡] After excluding women diagnosed with diabetes during the first two years of follow-up (N=175).

[§] After excluding women diagnosed with diabetes during the first five years of follow-up (N=544).