

Original Investigation

Glycated Hemoglobin Measurement and Prediction of Cardiovascular Disease

The Emerging Risk Factors Collaboration

IMPORTANCE The value of measuring levels of glycated hemoglobin (HbA_{1c}) for the prediction of first cardiovascular events is uncertain.

OBJECTIVE To determine whether adding information on HbA_{1c} values to conventional cardiovascular risk factors is associated with improvement in prediction of cardiovascular disease (CVD) risk.

DESIGN, SETTING, AND PARTICIPANTS Analysis of individual-participant data available from 73 prospective studies involving 294 998 participants without a known history of diabetes mellitus or CVD at the baseline assessment.

MAIN OUTCOMES AND MEASURES Measures of risk discrimination for CVD outcomes (eg, C-index) and reclassification (eg, net reclassification improvement) of participants across predicted 10-year risk categories of low (<5%), intermediate (5% to <7.5%), and high (≥7.5%) risk.

RESULTS During a median follow-up of 9.9 (interquartile range, 7.6-13.2) years, 20 840 incident fatal and nonfatal CVD outcomes (13 237 coronary heart disease and 7603 stroke outcomes) were recorded. In analyses adjusted for several conventional cardiovascular risk factors, there was an approximately J-shaped association between HbA_{1c} values and CVD risk. The association between HbA_{1c} values and CVD risk changed only slightly after adjustment for total cholesterol and triglyceride concentrations or estimated glomerular filtration rate, but this association attenuated somewhat after adjustment for concentrations of high-density lipoprotein cholesterol and C-reactive protein. The C-index for a CVD risk prediction model containing conventional cardiovascular risk factors alone was 0.7434 (95% CI, 0.7350 to 0.7517). The addition of information on HbA_{1c} was associated with a C-index change of 0.0018 (0.0003 to 0.0033) and a net reclassification improvement of 0.42 (−0.63 to 1.48) for the categories of predicted 10-year CVD risk. The improvement provided by HbA_{1c} assessment in prediction of CVD risk was equal to or better than estimated improvements for measurement of fasting, random, or postload plasma glucose levels.

CONCLUSIONS AND RELEVANCE In a study of individuals without known CVD or diabetes, additional assessment of HbA_{1c} values in the context of CVD risk assessment provided little incremental benefit for prediction of CVD risk.

 Supplemental content at jama.com

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To help achieve reductions in diabetes-specific microvascular complications, guidelines recommend screening people for diabetes mellitus by assessing glycemia measures, such as fasting blood glucose levels and levels of glycated hemoglobin (HbA_{1c}), a measure of glucose exposure over the previous 2 to 3 months.^{1,2} Furthermore, because higher levels of glycemia measures have also been associated with higher cardiovascular disease (CVD) incidence,^{3,4} it has been proposed that including information on glycemia measures in algorithms used to predict the risk of CVD might be associated with improvements in the ability to predict CVD.⁵⁻⁷

The 2010 American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines concluded that measurement of HbA_{1c} levels may be reasonable for CVD risk assessment in asymptomatic adults without a diagnosis of diabetes.⁸ In 2012 the Canadian Cardiovascular Society suggested that measurement of levels of fasting glucose, HbA_{1c}, or both might be of value for CVD risk stratification.⁹ The Reynolds Risk Score for prediction of CVD risk incorporates information on HbA_{1c}, although only for use in people known to have diabetes.¹⁰ However, measurement of glycemia measures was not recommended in the 2013 American College of Cardiology/American Heart Association Guideline on the Assessment of Cardiovascular Risk.¹¹

The current study aimed to determine whether adding information on HbA_{1c} levels to prognostic models containing conventional cardiovascular risk factors is associated with improvements in the prediction of first-onset CVD outcomes in middle-aged and older adults without a known history of diabetes. Additionally, we compared HbA_{1c} measurement with assessment of other frequently used glycemia measures, ie, fasting, random, or postload glucose levels.

Methods

Study Design

Details of the Emerging Risk Factors Collaboration have been published.¹²⁻¹⁴ The present study was designed and conducted by the collaboration's independent coordinating center and approved by the Cambridgeshire ethics review committee. Prospective cohort studies were included if they met all the following criteria: assayed HbA_{1c}, or fasting, random, or postload glucose level; had recorded baseline information for each participant on age, sex, smoking status, history of diabetes, systolic blood pressure, and levels of total and high-density lipoprotein (HDL) cholesterol (ie, conventional risk factors included in standard clinical risk scores⁸); were approximately population-based (ie, did not select participants on the basis of having previous disease); recorded cause-specific mortality, cardiovascular morbidity (nonfatal myocardial infarction or stroke), or both during follow-up using well-defined criteria; and recorded more than 1 year of follow-up. eTables 1-6 in Supplement and eAppendix 1 in Supplement provide study details, including criteria used in each study to define history of diabetes at the initial examination (ie based on self-reported information, medication usage, and/or on glycemia

measures [eTable 1 in Supplement]), assay methods, acronyms, and study references. In registering fatal outcomes, the majority of contributing studies used *International Classification of Diseases* coding to at least 3 digits, and ascertainment was based on death certificates, with 42 of 73 studies also involving medical records, autopsy findings, and other supplementary sources. Studies used a definition of myocardial infarction based on World Health Organization (or similar) criteria and a definition of stroke based on clinical and brain imaging features.

Statistical Analysis

Analyses excluded people with a known history of diabetes or CVD at baseline, as defined by each study. The primary outcome was first-onset CVD, defined as fatal or nonfatal coronary heart disease event or any stroke. Analyses involved a 2-stage approach, with estimates of association calculated separately within each study before pooling across studies by random-effects meta-analysis (in which the random effects concerned between-study variations in the associations of the exposure variables analyzed and CVD risk). Hazard ratios were calculated using Cox proportional hazard regression models stratified by sex, censoring deaths from non-CVD causes. The proportional hazards assumptions were tested as previously described and were satisfied.¹⁵ Participants contributed only their first outcome (whether nonfatal or death) recorded at 40 years or older (ie, deaths preceded by nonfatal coronary heart disease event or stroke were not included). To characterize shapes of associations, study-specific hazard ratios were calculated by overall predefined categories of each baseline glycemia measure, pooled on the log scale by multivariable random-effects meta-analysis and plotted against pooled mean levels within each category.¹⁵ Glycemia measurements were categorized using predefined groups approximately corresponding to 1-SD increments (HbA_{1c}: <4.5%, 4.5% to <5%, 5% to <5.5%, 5.5% to <6%, 6% to <6.5%, and ≥6.5%; fasting glucose [to convert mg/dL to mmol/L, multiply by 0.0555]: <76, 76 to <90, 90 to <105, 105 to <119, 119 to <133, and ≥133 mg/dL; random glucose: <68, 68 to <90, 90 to <112, 112 to <133, 133 to <155, and ≥155 mg/dL; postload glucose: <68, 68 to <108, 108 to <148, 148 to <187, 187 to <227, and ≥227 mg/dL). Confidence intervals (95%) were estimated using "floated" variances that assign an appropriate 95% CI to the log hazard ratio in every group, including the reference group, and enable valid comparisons to be made between any 2 exposure groups.¹⁶ Supplementary analyses used clinical cut points for glycemia measures defined by the American Diabetes Association.¹

We developed CVD risk prediction models containing several conventional risk factors (ie, age, sex, smoking status, systolic blood pressure, and total and HDL cholesterol) without or with a glycemia measure, and calculated improvements in predictive ability using measures of risk discrimination and reclassification.^{17,18} We used a 2-stage approach that allowed for the examination of between-study heterogeneity through calculation of the C-index, a measure of risk discrimination, and changes therein within each individual study before pooling results.¹⁸ Studies were weighted by numbers of CVD outcomes contributed. Supplementary

analyses excluded individuals with baseline diabetes defined according to glycemia measurements. Glycemia measurements were modeled using predefined categories as described above. Between-study heterogeneity in the risk discrimination measures and their changes was quantified using the I^2 statistic.¹⁹ χ^2 Tests were used to test for differences in changes in discrimination measures across subgroups, typically involving 2 to 4 categories. For participants in studies with at least 10 years of follow-up, we calculated measures of reclassification, which quantify the extent to which individuals are more appropriately classified into risk categories using a new vs old risk prediction model, using a 1-stage approach.¹⁸ We constructed reclassification tables using data from studies that had recorded both fatal and nonfatal CVD outcomes to examine movement of participants between 3 predicted 10-year CVD risk categories (low [$<5\%$]; intermediate [5% to $<7.5\%$]; and high [$\geq 7.5\%$])²⁰ on addition of a glycemia measure to conventional risk factors. Results were summarized using the net reclassification improvement, which is the sum of the percentage of events that move up and the percentage of nonevents that move down through the risk categories when using the new model.^{17,18} In further analyses, we also used reclassification measures not dependent on clinical risk categories (eg, integrated discrimination index, a measure that reflects the average improvement in predicted probabilities with the new vs old model, summed across events and nonevents).²¹

Analyses were performed using Stata version 12.0 (StataCorp), 2-sided P values, and 95% CIs.

Results

Data were available for 294 998 participants without a known history of diabetes or CVD at baseline in 73 prospective cohorts. Overall, the mean age of participants at baseline was 58 (SD, 9) years, 49% were women, and 86% lived in Europe or North America (Table and eTables 1-6 in Supplement). Baseline glycemia measures were distributed similarly across the contributing cohorts (eFigure 1 in Supplement). Mean levels were 5.37% (SD, 0.54) for HbA_{1c}, 96 (SD, 14) mg/dL for fasting glucose, 99 (SD, 21) mg/dL for random glucose, and 125 (SD, 41) mg/dL for postload glucose. Age- and sex-adjusted partial correlation coefficients with HbA_{1c} were 0.42 for fasting glucose, 0.32 for random glucose, and 0.35 for postload glucose (eFigure 2 in Supplement). In an analysis of serial measurements (median interval, 4 years) in up to 72 314 participants without a known history of diabetes or CVD at baseline, the age- and sex-adjusted regression dilution ratios were 0.65 (95% CI, 0.57-0.73) for HbA_{1c}, 0.70 (95% CI, 0.64-0.75) for fasting glucose, 0.46 (95% CI, 0.33-0.59) for random glucose, and 0.67 (95% CI, 0.61-0.72) for postload glucose (eFigure 3 in Supplement).

Associations With CVD Outcomes

During a median follow-up of 9.9 (interquartile range, 7.6-13.2) years, 20 840 incident fatal and nonfatal CVD outcomes (13 237 CHD and 7603 stroke outcomes) were recorded. In

analyses adjusted for several conventional CVD risk factors, there were approximately J-shaped associations between each glycemia measure we studied and CVD risk (Figure 1). Findings were similar in analyses that used fractional polynomials (eFigure 4 in Supplement). Hazard ratios for CVD changed only slightly after adjustment for total cholesterol levels, triglyceride levels, or estimated glomerular filtration rate, but attenuated somewhat after adjustment for HDL cholesterol levels or C-reactive protein concentrations (eTables 7-8 in Supplement). Although there was suggestive evidence of effect modification in some clinically relevant subgroups, cautious interpretation is required given the large number of comparisons made (eFigures 5-8 in Supplement). There was some evidence of heterogeneity according to assay characteristics for HbA_{1c} (with some evidence of higher hazard ratios in studies using values aligned to the Diabetes Control and Complications Trial; $P = .004$), but no effect modification was observed according to year of baseline survey or duration of follow-up (Figure 2 and eFigures 5-8 in Supplement). Results qualitatively similar to those described above were observed in analyses that were limited to participants with concomitant data on at least 2 glycemia measures; used fixed-effects models; used competing risk models; excluded the initial 5 years of follow-up; included fatal outcomes without censoring after previous nonfatal outcomes; and considered coronary heart disease and stroke separately.

Incremental CVD Prediction

Figure 3 and eTable 9 in Supplement show that there were small changes in the C-index and in the integrated discrimination index after adding information on levels of HbA_{1c}, fasting glucose, random glucose, or postload glucose to CVD risk prediction models containing age, sex, smoking, systolic blood pressure, and levels of total and HDL cholesterol. However, adding information on these glycemia measures did not yield significant improvements in net reclassification (eTable 9 in Supplement). There were no major differences in risk discrimination according to sex or in other clinically relevant subgroups (eFigures 9-12 in Supplement). Again, although there was no strong evidence of heterogeneity according to year of baseline survey or duration of follow-up, some evidence of heterogeneity was found according to the assay standards used for HbA_{1c} measurement ($P = .001$). In analyses limited to participants who had concomitant data on HbA_{1c} values and at least 1 other glycemia measure, the change in the C-index when 2 markers were used was broadly similar to the change when either marker was used alone (eFigure 13 in Supplement). Results similar to those observed overall were also found in analyses that used clinical categories of dysglycemia (eFigure 14 in Supplement); omitted participants with diabetes defined using baseline glycemia measurements (eFigure 15 in Supplement); omitted participants known to be taking medications that lowered lipid levels or blood pressure at study entry; omitted extreme low levels of glycemia measures; or were restricted to studies with at least 10 years of follow-up. There was no good evidence for small study effects (eFigures 16-23 in Supplement).

Table. Hazard Ratios for Incident Cardiovascular Disease (CVD) With Measured Baseline Levels of Risk Factors

	Participants With Information on							
	HbA _{1c} (24 Studies, 101 280 Participants, 4267 CVD Cases)		Fasting Glucose (50 Studies, 150 617 Participants, 13 511 CVD Cases)		Random Glucose (28 Studies, 107 364 Participants, 5855 CVD Cases)		Postload Glucose (23 Studies, 64 234 Participants, 7286 CVD Cases)	
	Mean (SD) or No. (%)	HR (95% CI) ^a	Mean (SD) or No. (%)	HR (95% CI) ^a	Mean (SD) or No. (%)	HR (95% CI) ^a	Mean (SD) or No. (%)	HR (95% CI) ^a
Age at baseline, mean (SD), y	60.2 (9.4)	2.00 (1.83-2.19)	57.5 (8.9)	1.94 (1.82-2.07)	59.5 (10.3)	2.35 (2.14-2.59)	60.0 (8.4)	1.87 (1.76-2.00)
Sex, No. (%)								
Men	34 581 (34.1)	NA ^b	84 077 (55.8)	NA ^b	60 438 (56.3)	NA ^b	33 239 (51.7)	NA ^b
Women	66 699 (65.9)	NA ^b	66 540 (44.2)	NA ^b	46 926 (43.7)	NA ^b	30 995 (48.3)	NA ^b
Smoking status, No. (%)								
Other	81 706 (80.7)	1 [Reference]	105 166 (69.8)	1 [Reference]	72 076 (67.1)	1 [Reference]	46 447 (72.3)	1 [Reference]
Current	19 574 (19.3)	2.11 (1.84-2.42)	45 451 (30.2)	1.74 (1.61-1.87)	35 288 (32.9)	1.81 (1.66-1.98)	17 787 (27.7)	1.69 (1.53-1.86)
Systolic blood pressure, mean (SD), mm Hg	133 (17)	1.32 (1.26-1.38)	135 (19)	1.33 (1.28-1.37)	136 (19)	1.38 (1.31-1.45)	135 (19)	1.35 (1.29-1.42)
Cholesterol, mean (SD), mg/dL								
Total	219 (41)	1.14 (1.09-1.19)	225 (41)	1.16 (1.14, 1.19)	224 (42)	1.24 (1.16-1.32)	227 (42)	1.18 (1.12-1.24)
HDL	55 (15)	0.85 (0.80-0.89)	53 (14)	0.85 (0.81-0.88)	52 (15)	0.85 (0.80-0.91)	52 (14)	0.84 (0.79-0.90)
HbA _{1c} , mean (SD), %	5.37 (0.54) ^c	1.43 (1.07-1.91) ^d						
Glucose, mean (SD), mg/dL								
Fasting			96 (14)	1.47 (1.32-1.64) ^e				
Random					99 (21)	1.96 (1.54-2.48) ^f		
Postload							125 (41)	1.19 (1.09-1.31) ^g

Abbreviations: HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein; HR, hazard ratio; NA, not available.

SI conversion factors: To convert total cholesterol and HDL values to mmol/L, multiply by 0.0259; glucose values to mmol/L, multiply by 0.0555.

^a Hazard ratios were calculated per 1-SD increment in the measured level or as compared with the relevant reference category. Where appropriate, hazard ratios were adjusted for age, sex, smoking status, systolic blood pressure, and levels of total and HDL cholesterol.

^b Hazard ratios according to sex are not available because these models were stratified by sex.

^c HbA_{1c} values can be converted to International Federation of Clinical Chemistry (IFCC) units in mmol/mol using the equation HbA_{1c} mmol/mol = [HbA_{1c} % - 2.15] × 10.929.

^d Hazard ratio compared values of 6.5 (48.0 mmol/mol) or greater vs less than 5.7 (38.8 mmol/mol). For this measure, 86 056 participants (86%) had values

less than 5.7% (38.8 mmol/mol), 11 521 (12%) had values between 5.7% and 6.4% (38.8-42.1 mmol/mol), and 2303 (2%) had values of 6.5% (48.0 mmol/mol) or greater.

^e Hazard ratio compared values of 126 mg/dL or greater vs less than 101 mg/dL. For this measure, 110 382 participants (74%) had values less than 101 mg/dL, 36 788 (24%) had values between 101 and 126 mg/dL, and 3447 (2%) had values of 126 mg/dL or greater.

^f Hazard ratio compared values of 200 mg/dL or greater vs less than 200 mg/dL. For this measure, 106 907 participants (99.6%) had values less than 200 mg/dL, and 457 (0.4%) had values of 200 mg/dL or greater.

^g Hazard ratio compared values of 200 mg/dL or greater vs less than 141 mg/dL. For this measure, 44 217 participants (69%) had values less than 141 mg/dL, 16 142 (25%) had values between 141 and 200 mg/dL, and 3875 (6%) had values of 200 mg/dL or greater.

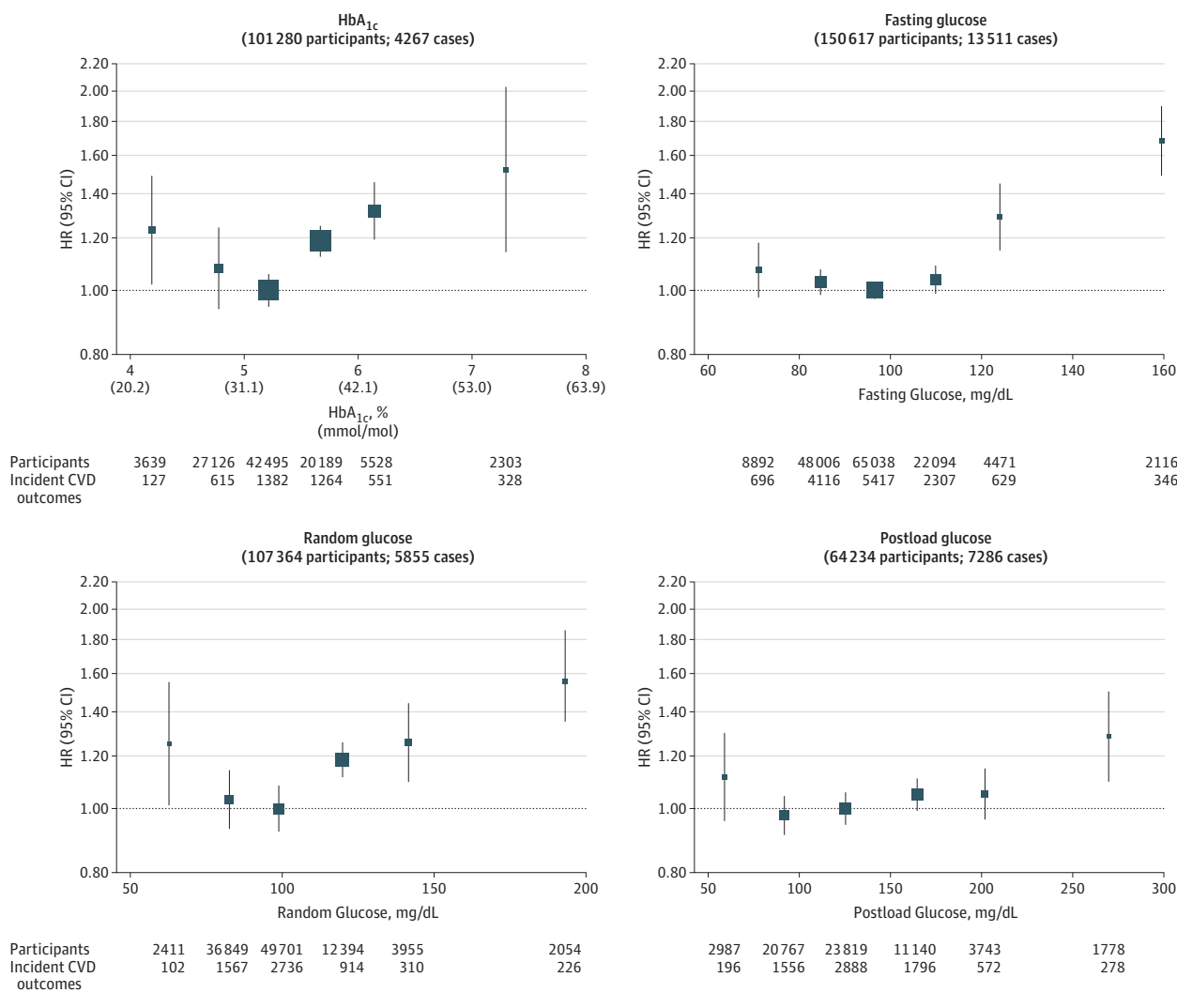
Discussion

Contrary to recommendations in some guidelines, the current analysis of individual-participant data in almost 300 000 people without known diabetes and CVD at baseline indicates that measurement of HbA_{1c} is not associated with clinically meaningful improvement in assessment of CVD risk. First, we found that adding information on levels of HbA_{1c} to conventional CVD risk factors was associated

with only slight improvement in risk discrimination, which aims to assess how well a statistical model can separate individuals who do and do not go on to develop CVD. Second, we found that adding information on HbA_{1c} was not associated with significant improvement in reclassification of participants across clinical risk categories currently recommended to inform decisions about the initiation of preventive treatment.²⁰

Third, our analysis provided a comparison of 4 glycemia measures, ie, HbA_{1c} levels and fasting, random, or postload

Figure 1. Hazard Ratios for Incident Cardiovascular Disease (CVD) Outcomes by Baseline Levels of Glycemia Measures



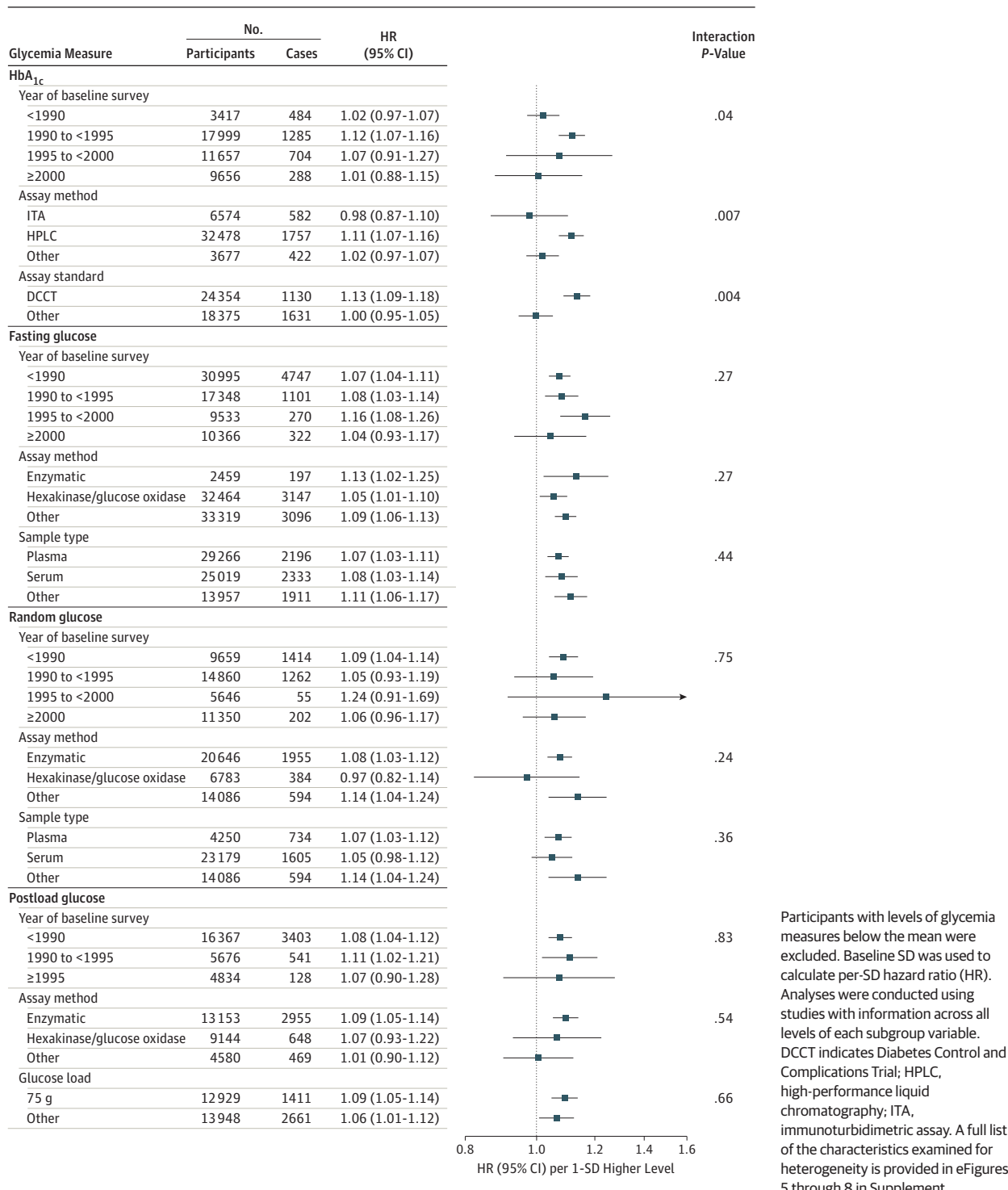
Analyses were adjusted for age, smoking status, systolic blood pressure, total cholesterol level, and high-density lipoprotein cholesterol level and stratified by sex and trial group where appropriate. Participants were classified into groups of (1) HbA_{1c}% (mmol/mol): <4.5 (<25.7), 4.5 to <5 (25.7-<31.1), 5 to <5.5 (31.1-<36.3) [reference category], 5.5 to <6 (36.6-<42.1), 6 to <6.5 (42.1-<48.0), and ≥6.5 (≥48.0); (2) fasting glucose (mg/dL): <76, 76 to <90, 90 to <105 [reference category], 105 to <119, 119 to <133, ≥133; (3) random glucose (mg/dL) <68, 68 to <90, 90 to <112 [reference category], 112 to <133, 133 to

<155, ≥155; (4) Postload glucose (mg/dL): <68, 68 to <108, 108 to <148 [reference category], 148 to <187, 187 to <227, ≥227. These categories approximately correspond to 1-SD increments for each factor. Incident CVD outcomes refer to first-onset CVD cases, defined as fatal or nonfatal coronary heart disease or any stroke. SI conversion factors: To convert glucose values to mmol/L, multiply by 0.0555. Sizes of boxes are proportional to the inverse of the variance.

plasma glucose levels. In contrast to some previous findings,^{3,22,23} we observed approximately J-shaped associations between each of these glycemia measures and CVD risk. The consistency of this finding is notable because the different glycemia measures we analyzed were only moderately correlated with one another and had differing degrees of reproducibility across glycemic measures. Indeed, in an analysis of serial measurements in up to 72 000 participants, we observed that the long-term reproducibility of fasting glucose measurements was at least as high as that for HbA_{1c} values and postload glucose levels. This result challenges suggestions that fasting glucose values are prone to greater long-term fluctuation than are these other glycemia measures.²⁴

Our observation of consistent J-shaped associations between various glycemia measures and CVD incidence should encourage further studies to test whether very low glycemia levels are markers of ill health, such as that caused by hepatic dysfunction or other comorbidities.^{25,26} Regarding comparison of glycemia measures to predict first-onset CVD outcomes, our results suggest that the improvement provided by HbA_{1c} assessment in prediction of CVD risk was at least equal to improvements estimated for assessment of fasting, random, or postload plasma glucose levels. This finding challenges suggestions that postload glucose levels predict CVD incidence more strongly than do other glycemia measures.²⁷ However, it was not possible to evaluate the value of assess-

Figure 2. Hazard Ratios for Incident Cardiovascular Disease for Glycemia Measures by Selected Study-Level Characteristics



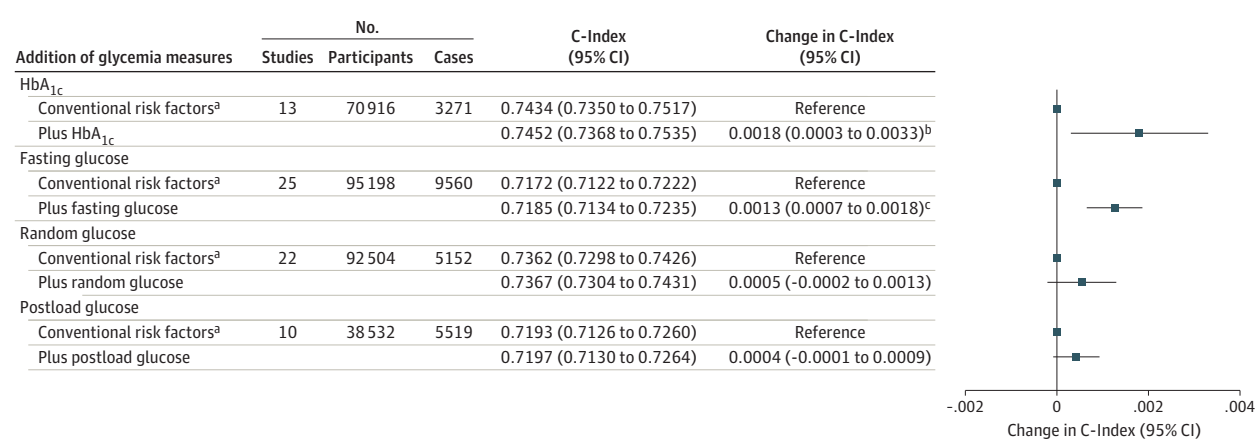
Participants with levels of glycemia measures below the mean were excluded. Baseline SD was used to calculate per-SD hazard ratio (HR). Analyses were conducted using studies with information across all levels of each subgroup variable. DCCT indicates Diabetes Control and Complications Trial; HPLC, high-performance liquid chromatography; ITA, immunoturbidimetric assay. A full list of the characteristics examined for heterogeneity is provided in eFigures 5 through 8 in Supplement.

ing several glycemia measures jointly, because few people in our study had the necessary concomitant data.

Because our study involved a large number of participants, it could provide precise estimates, even for analyses that involved categorization of glycemia measures. The generalizability of our findings was enhanced by inclusion of data from

73 prospective cohort studies in 20 countries and by the general consistency of the results across these studies. A further strength was the analysis of individual-participant data from studies with extended durations of follow-up. This feature enabled time-to-event analysis, analysis of subgroups, and a consistent approach to statistical analyses across the contribut-

Figure 3. Changes in Cardiovascular Disease Risk Discrimination After the Addition of Information on Glycemia Measures to Conventional Risk Factors



Incident cardiovascular disease outcomes refer to first-onset cardiovascular disease cases, defined as fatal or nonfatal coronary heart disease event or any stroke. Studies with missing self-reported diabetes information were excluded.

^a Conventional risk factors include age, sex (stratified), smoking status, systolic

blood pressure, and levels of total cholesterol and high-density lipoprotein cholesterol.

^b $P < .05$

^c $P < .001$.

ing studies. To further enhance the validity of risk estimates, we restricted analyses to people with information on a complete set of relevant risk factors.

It is important to note that our study did not address the value of assessing glycemia measures to screen for diabetes to reduce diabetes-specific microvascular complications, nor did it address etiologic and therapeutic questions. Our study had other limitations. We had incomplete information on medication use (eg, statins, antihypertensive drugs, or glucose-lowering drugs) during follow-up, which may have influenced our estimates of the effect of individual risk fac-

tors, or risk models, on outcomes. The reclassification measures used in our risk prediction analyses are intrinsically sensitive to choice of follow-up interval and clinical risk categories.²¹

Conclusions

In adults without a known history of diabetes or CVD, adding HbA_{1c} to conventional CVD risk factors was associated with little improvement in the prediction of CVD risk.

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Study concept and design: Di Angelantonio, Gao, Khan, Kondapally Seshasai, Sarwar, Khaw, Daimon, Goldbourt, Casiglia, Jukema, Sattar, Selvin, Danesh. **Acquisition, analysis, or interpretation of data:** All authors.

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