Fasting and Postchallenge Glycemia and Cardiovascular Disease Risk

The Framingham Offspring Study

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OBJECTIVE — To test the hypothesis that fasting hyperglycemia (FHG) and 2-h postchallenge glycemia (2hPG) independently increase the risk for cardiovascular disease (CVD).

RESEARCH DESIGN AND METHODS — During 1991–1995, we examined 3,370 subjects from the Framingham Offspring Study who were free from clinical CVD (coronary heart disease, stroke, or intermittent claudication) or medication-treated diabetes, and we followed them for 4 years for incident CVD events. We used proportional-hazards regression to assess the risk associated with FHG (fasting plasma glucose ≥7.0 mmol/l) and 2hPG, independent of the risk predicted by standard CVD risk factors.

RESULTS — Mean subject age was 54 years, 54% were women, and previously undiagnosed diabetes was present in 3.2% by FHG and 4.9% (164) by FHG or a 2hPG ≥11.1 mmol/l. Of these 164 subjects, 55 (33.5%) had 2hPG ≥11.1 without FHG, but these 55 subjects represented only 1.7% of the 3,261 subjects without FHG. During 12,242 person-years of follow-up, there were 118 CVD events. In separate sex- and CVD risk–adjusted models, relative risk (RR) for CVD with fasting plasma glucose ≥7.0 mmol/l was 2.8 (95% CI 1.6–5.0); RR for CVD per 2.1 mmol/l increase in 2hPG was 1.2 (1.1–1.3). When modeled together, the RR for FHG decreased to 1.5 (0.7–3.6), whereas the RR for 2hPG remained significant (1.1, 1.02–1.3). The *c*-statistic for a model including CVD risk factors alone was 0.744; with addition of FHG, it was 0.746, and with FHG and 2hPG, it was 0.752.

CONCLUSIONS — Postchallenge hyperglycemia is an independent risk factor for CVD, but the marginal predictive value of 2hPG beyond knowledge of standard CVD risk factors is small.

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Observational data have established hyperglycemia as a risk factor for cardiovascular disease (CVD), including coronary heart disease (CHD), stroke, and intermittent claudication. Increased risk is continuous and graded across the distributions of fasting plasma glucose (FPG), levels of plasma glucose after an oral glucose challenge, and average levels of glycemia as measured by HbA_{1c} (1–3). Both fasting and 2-h postchallenge glucose levels contribute to average glycemia, but the relative contributions of fasting and postchallenge hyperglycemia to CVD risk remain uncertain (4). This issue is important to resolve because recent U.S. diabetes diagnostic criteria have abandoned postchallenge glycemia and have relied predominantly on FPG levels to establish the diagnosis (5). Elsewhere, an oral glucose tolerance test (OGTT) is still recommended for adequate diabetes diagnosis (6). In addition, new diabetes therapies focused on reducing postprandial hyperglycemia have become available and may benefit glycemic control and CVD risk factor levels (7–9).

Diagnostic criteria for diabetes are intended to define glycemic levels above which the specific complications of diabetes begin to increase. Elevated FPG levels reliably identify elevated risk for retinopathy, but several large population-based studies have shown that a diabetes diagnosis based on FPG levels has limitations. Fasting glucose criteria underestimate the prevalence of diabetes and overlook a substantial fraction of subjects at increased risk for CVD on the basis of elevated postchallenge levels (10–15). Whether CVD risk associated with elevated postchallenge glycemia is independent of associated elevations in fasting hyperglycemia has not been well defined. In this study, we tested the hypothesis that fasting, postchallenge, and average hyperglycemia (assessed by HbA_{1c}) independently increase the risk for incident CVD among subjects of the population-based Framingham Offspring Study.

RESEARCH DESIGN AND METHODS

Study subjects

Study subjects were participants in the Framingham Offspring Study, a community-based observational study of risk factors for CVD (16). From January 1991 through June 1995 (examination cycle 5), participants fasted overnight, provided written informed consent, underwent a standardized clinical examination, and those without diagnosed diabetes had an

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Abbreviations: 2hPG, 2-h postchallenge glucose; CHD, coronary heart disease; CVD, cardiovascular disease; FPG, fasting plasma glucose; IQR, interquartile range; OGTT, oral glucose tolerance test; ROC, receiver operating curve; RR, relative risk.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

See Point-Counterpoint, p. 1879.

OGTT. Of 3,799 participants, we excluded 402 subjects with previously diagnosed medication-treated diabetes, prevalent CVD, or missing glucose or Framingham Risk Score data, which left 3,370 subjects in this analysis. Because HbA_{1c} collection began late during examination 5, only 2,435 subjects contributed HbA_{1c} levels.

Table 1—*Subject characteristics*

n	3,370
Age (years)	54
Age range (years)	26–82
Age ≥65 years (%)	18.1
Women (%)	54.0
FPG [mmol/l (mg/dl)]	5.4 (97)
2h PG [mmol/l (mg/dl)]	6.3 (113)
HbA_{1c} (% of total hemoglobin)	5.33
Untreated Previously Undiagnosed Diabetes	
By 1997 American Diabetes Association* (%)	3.2
By 1999 World Health Organization† (%)	4.9
CVD	
Events	118
Person-years	12,241
Incidence rate/1,000 person-years	9.6
Cumulative incidence (%)	12.9

CVD includes fatal and nonfatal myocardial infarction, stroke or transient ischemic attack, and intermittent claudication. *FPG ≥7.0 mmol/l (126 mg/dl); †FPG ≥70 mmol/l or 2hPG ≥11.1 mmol/l (200 mg/dl).

Clinical examination and laboratory methods

FPG was measured in fresh specimens with a hexokinase reagent kit (A-gent glucose test; Abbott, South Pasadena, CA). Glucose assays were run in duplicate; the intra-assay coefficient of variation was <3%. HbA_{1c} was measured by high-performance liquid chromatography after an overnight dialysis against normal saline to remove the labile fraction. The mean (SD) for this assay among nondiabetic subjects in this population was 5.22% (0.6), and the inter- and intra-assay coefficients of variation were <2.5%. The assay was standardized against the glycosylated hemoglobin assay used in the Diabetes Control and Complications Trial (17). Total cholesterol levels were measured enzymatically, and the HDL cholesterol fraction was measured after precipitation of LDLs and VLDLs with dextran sulfate-magnesium (18). The Framingham laboratory participates in the lipoprotein cholesterol laboratory standardization program administered by the Centers for Disease Control and Prevention in Atlanta, Georgia. Blood pressure was assessed as the average of two measurements taken after subjects had been seated for at least 5 min. Subjects reporting smoking at least one cigarette per day during the year before the examination were classified as current smokers.

Definitions of hyperglycemia

We used the magnitude of the interquartile range (IQR) as a unit of exposure for continuously distributed glycemic measures in predicting CVD risk. For instance, the 25th percentile of the FPG distribution was 5.0 mmol/l (89 mg/dl), the 75th percentile was 5.7 mmol/l (102 mg/dl), and the magnitude of the IQR was 0.7 mmol/l (13 mg/dl). Thus, risk associated with a 0.7 mmol/l increase in the FPG level indicated risk associated an increase from the 25th to 75th percentile of the FPG population distribution. Use of the IQR allowed standardized comparison of CVD risk across glycemic measures. The 25th percentile of the 2-h postchallenge glucose (2hPG) distribution was 4.8 mmol/l (87 mg/dl), the 75th percentile was 6.9 mmol/l (125 mg/dl), and the magnitude of this range was 2.1 mmol/l (38 mg/dl). The 25th percentile of the HbA_{1c} distribution was 4.90% (of total hemoglobin), the 75th percentile was 5.61%, and the magnitude of this range was 0.71%.

We also categorized hyperglycemia using the 1997 American Diabetes Association criteria to define diabetic fasting hyperglycemia (FPG ≥7.0 mmol/l or 126 mg/dl) and the 1999 World Health Organization criteria to define diabetes on the basis of both fasting hyperglycemia and 2-h postchallenge hyperglycemia (2hPG ≥11.1 mmol/l or 200 mg/dl) (5,6). We defined isolated postchallenge hyperglycemia as normal fasting glycemia (FPG <7.0 mmol/l) but postchallenge hyperglycemia (2hPG ≥11.1 mmol/l).

CVD assessment and follow-up

Incident CVD, including CHD [fatal and nonfatal myocardial infarction]), stroke or transient ischemic attack, and intermittent claudication, was assessed using standard Framingham Heart Study criteria (19). Subjects free from CVD at the fifth (baseline) examination were followed for 4 years to the sixth examination cycle (1995–1999). Person-years of follow-up were accrued from baseline to the date of first event or censored at the date of the sixth examination if free of a CVD event. In this article, we report results for aggregate CVD outcomes; results when the analysis was restricted to the 76 CHD outcomes were similar.

Statistical analysis

We compared baseline subject characteristics using *t* tests, χ^2 tests, and Pearson correlation coefficients. We used Cox proportional-hazards regression models to assess the association of glycemic exposures with incident CVD. Models were adjusted for sex, or sex and Framingham Risk Scores to account for the effect of standard CVD risk factors. The independent effects of age, total and HDL cholesterol, systolic and diastolic blood pressure, diabetes, and smoking are accounted for by assigning the Framingham Risk Score (20). All subjects in this analysis were assigned a zero value for the diabetes covariate because subjects with diagnosed treated diabetes were excluded at baseline. Alternative models used these risk factors as individual covariates to control for effects of standard CVD risk factors; results were similar, and only models adjusted for the Risk Score are presented. In all analyses, nested regression models included terms for sex, Risk Score, and one or more of FPG, 2hPG, and HbA_{1c}. We assessed possible collinearity among glycemic measures by estimating Pearson correlations between their levels and by examining effects on risk estimates when one or more were included together in predicting models. In-

Table 2—*Sex and Framingham Risk Score–adjusted RRs for CVD associated with levels of fasting, 2-h postchallenge, and average glycemia*

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
FPG (per 0.7 mmol/l [13 mg/dl] increase)						
RR	1.088			0.868	1.024	
95% CI	1.02–1.16			0.76–0.998	0.92–1.14	
P	0.008			0.046	0.7	
2hPG (per 2.1 mmol/l [38 mg/dl] increase)						
RR		1.182		1.42		1.232
95% CI		1.10–1.27		1.17–1.72		1.07–1.43
P		0.0001		0.0004		0.005
HbA_{1c} (per 0.71% hemoglobin increase)						
RR			1.151		1.115	0.929
95% CI			1.02–1.30		0.92–1.35	0.77–1.13
P			0.03		0.3	0.5
c-statistic	0.752	0.749	0.740	0.741	0.745	0.741

teractions by sex or age on associations of glycemic covariates with CVD were tested using first-order multiplicative interaction terms. The 4-year predictive capability of models was assessed with the *c*-statistic, analogous to the area under the receiver operating curve (ROC) curve. We used SAS for analyses and defined statistical significance as $P < 0.05$ (21).

RESULTS — The predominantly Caucasian study subjects were of a wide age range, and about half were women (Table 1). Of the 3,370 subjects, 109 (3.2%) had previously undiagnosed diabetes defined solely by fasting hyperglycemia. Only 28 subjects (0.8%) had fasting hyperglycemia but normal 2hPG levels. Of the 3,261 subjects without fasting hyperglycemia, 55 (1.7%) had diabetes defined by isolated postchallenge hyperglycemia. Overall, 164 (4.9%) had diabetes defined by fasting or postchallenge hyperglycemia; of these, 55 (33.5%) had isolated postchallenge hyperglycemia. The prevalence of isolated postchallenge hyperglycemia was slightly higher comparing women with men without fasting hyperglycemia (1.9% in women vs. 1.4% in men, $P = 0.07$) or among individuals with diabetes defined by fasting or 2hPG criteria (41.5 vs. 25.6%, $P = 0.05$). The prevalence of isolated postchallenge hyperglycemia was also higher comparing older with younger subjects without fasting hyperglycemia (4.6% in subjects ≥65 years of age vs. 1.0% in subjects <65 years of age, $P = 0.001$) or among individuals with diabetes defined by fasting or 2hPG criteria (43.8 vs. 27.0%, $P = 0.07$). The Pearson correlation coefficient for FPG with 2hPG was 0.73 and with HbA_{1c} was 0.54; the correlation between 2hPG and HbA_{1c} was 0.48 (all $P < 0.0001$). These correlations were similar when stratified by men versus women or older versus younger subjects.

During the 4 years of follow-up, there were 118 CVD events. Elevated levels of all three glycemic exposures individually increased risk for incident CVD. The sex-adjusted relative risk (RR) for fasting glucose was 1.13 per 0.7 mmol/l increase (95% CI 1.07–1.20), for 2hPG was 1.26 (1.17–1.34) per 2.1 mmol/l increase, and for HbA_{1c} was 1.24 (1.11–1.39) per 0.7% increase. These effects were attenuated but remained significant after adjustment for established CVD risk factors (models 1–3, Table 2). When included in the same prediction model, 2hPG remained a significant risk factor for CVD, whereas FPG had a weak protective effect of borderline significance (model 4, Table 2). Neither FPG nor HbA_{1c} was a significant predictor of CVD when included in the same model (model 5, Table 2). Postchallenge hyperglycemia but not HbA_{1c} remained a significant predictor of CVD when modeled together (model 6, Table 2). However, addition of glycemic categories did not substantially improve prediction of CVD beyond knowledge of standard CVD risk factors alone. The *c*-statistic (reflecting the predictive capability of prediction models, with larger values being better) for the sex-adjusted Framingham Risk Score alone predicting CVD was 0.744, and for models including glycemic exposures, it ranged from 0.741 to 0.752 (Table 2).

We also modeled the CVD risk-adjusted joint effects of fasting and postchallenge hyperglycemia using fasting hyperglycemia as a separate categorical variable (diabetes, yes or no) rather than as a continuous exposure. This approach explored whether postchallenge hyperglycemia increases risk for CVD when diabetes status is already known, on the basis of a FPG level ≥7.0 mmol/l. In a sex and CVD risk factor–adjusted model, the RR for CVD for FPG ≥7.0 mmol/l was 2.81 (95% CI 1.57–5.01; *c*-statistic 0.746). After additional adjustment for 2hPG, the RR associated with FPG ≥7.0 mmol/l declined by 46% and became nonsignificant (RR 1.52, 95% CI 0.65–3.55), whereas 2hPG remained a significant predictor, increasing RR for CVD by 1.14 (95% CI 1.02–1.27; *c*-statistic 0.752) per 2.1 mmol/l increase (Fig. 1, left-hand pair of bars). There was no interaction by sex on the effect of fasting diabetes and 2hPG on risk of CVD ($P = 0.3$ for first-order interactions), but with younger versus older age, there was a significant interaction ($P = 0.02$). Among subjects <65 years old, diabetic fasting hyperglycemia increased RR risk for CVD by 3.13 (95% CI 1.14–8.62), whereas postchallenge hyperglycemia was not a significant predictor (Fig. 1, center pair of bars). Among subjects 65 years and older, diabetic fasting hyperglycemia was not a significant predictor, whereas 2hPG increased risk for CVD by 1.35 (1.09–1.68) per 2.1 mmol/l increase (Fig. 1, right-hand pair of bars).

CONCLUSIONS — In this study, we found that fasting, postchallenge, and average hyperglycemia (assessed by HbA_{1c})

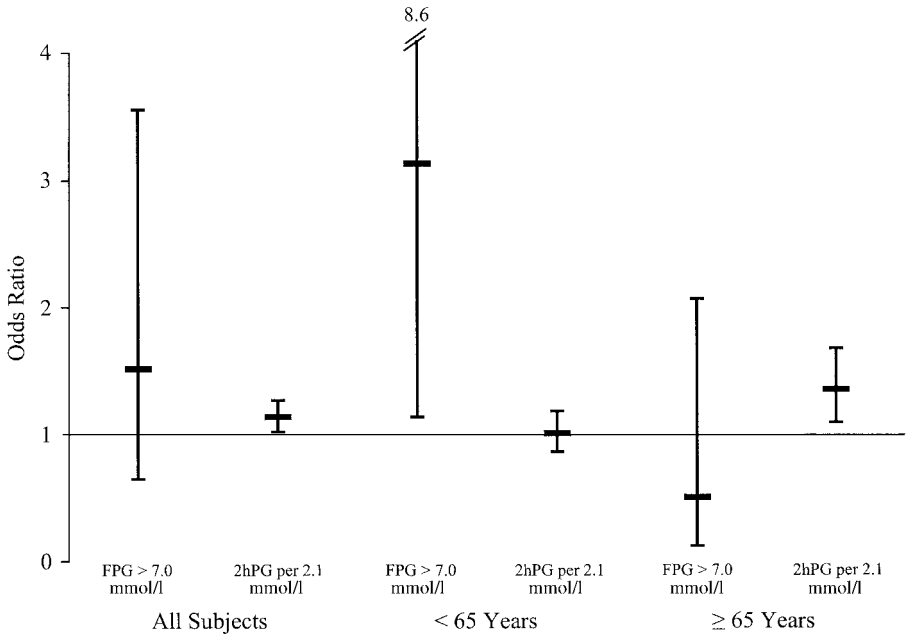

Figure 1—*Joint RRs and 95% CIs for CVD associated with diabetic fasting hyperglycemia (FPG >7.0 mmol/l) and postchallenge hyperglycemia (risk per 2.1 mmol/l increase) among all study subjects (left-hand pair of bars) and stratified by age <65 years (center pair of bars) or ≥65 years (right-hand pair of bars). Models included terms for both fasting and postchallenge glycemic covariates and were adjusted for sex and standard CVD risk factors; RRs for age strata were derived from separate models for older and younger subjects.*

all individually increased risk for incident CVD events, even after accounting for standard nonglycemic CVD risk factors. These observations confirm similar observations from several other studies (3,13,15,22–24), including the original Framingham Heart Study cohort (25). Some prior studies have also suggested that measurement of postchallenge glycemia identified individuals at increased risk for CVD beyond the risk associated with fasting glycemic assessment alone (13,14,26). In particular, the DECODE (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe) Study Group found that after adjustment for standard CVD risk factors, the FPG level did not independently increase risk for CVD mortality (RR for FPG ≥7.0 mmol/l, 1.20, 95% CI 0.88–1.64), but the 2hPG level was a significant independent predictor (RR for 2hPG ≥11.1 mmol/l, 1.4, 1.02–1.92) (15). In the present study, we extend these observations, demonstrating that glycemic levels 2 h after oral glucose challenge increase risk for CVD events independent of standard CVD risk factors and levels of fasting or average hyperglycemia. For each 2.1 mmol/l increase in the 2hPG level (equivalent to an increase from the 25th to 75th percentile of the 2hPG distribution), the RR for incident CVD events increased by 12–42%, depending upon the manner in which FPG and HbA_{1c} were handled in the model. Neither fasting hyperglycemia nor HbA_{1c} independently predicted CVD after accounting for postchallenge hyperglycemia. Recent data from the Cardiovascular Health Study confirm the independent association of postchallenge hyperglycemia with CVD: among elderly nondiabetic and untreated diabetic subjects, the risk factor– and 2hPG-adjusted FPG level did not independently increase risk for CVD events (RR for FPG ≥112 mg/dl, 1.09, 95% CI 0.84–1.41), but the risk factor– and FPG-adjusted 2hPG level was a significant independent predictor (RR for 2hPG ≥182 mg/dl, 1.58, 1.23–2.02) (24).

However, despite its apparent importance as an independent predictor of CVD events, postchallenge hyperglycemia was relatively scarce (<2%) among subjects without diabetic fasting hyperglycemia in this population. The marginal predictive capacity of postchallenge hyperglycemia was small (no more than 0.06 additional area under the ROC curve) in models already including standard CVD risk factors and fasting hyperglycemia. Although abandonment of the OGTT for screening and diagnosis has raised serious concerns (4,6), our observations suggest that eliminating the OGTT for the screening and diagnosis of diabetes would have a minimal effect in terms of identifying CVD risk. On the other hand, isolated postchallenge hyperglycemia was common in individuals with diabetes from either fasting or postchallenge glycemic criteria, where about one-third of subjects had 2hPG ≥11.1 mmol/l as their only diagnostic abnormality. The pattern of low rates of isolated postchallenge hyperglycemia in nondiabetic groups but high rates in diabetic groups has been observed in other populations (10,11,27). However, although postchallenge hyperglycemia may be relatively more prevalent in type 2 diabetes, it is important to remember that the response to the supraphysiologic OGTT is not equivalent to lesser glycemic surges typical of the postprandial state. It remains to be demonstrated that postchallenge hyperglycemia confers similar risk compared with the response to lesser calorie challenges from typical meals (4), or whether therapy focused on reduction of postprandial hyperglycemia translates into reduced diabetic complications beyond benefits expected from lowering HbA_{1c} (28) or nonglycemic risk factors (29,30).

The presumption that hyperglycemia contributes to CVD risk by the same mechanisms regardless of whether glycemia is elevated in the fasting, average, or postchallenge state needs to be scrutinized on the basis of these data. The finding of independent risk for CVD with postchallenge hyperglycemia implies that subjects with this condition may have unique or more exaggerated underlying atherogenic metabolic abnormalities than subjects without postchallenge hyperglycemia. A greater degree of insulin resistance in these subjects is one likely possibility accounting for the observed excess risk. Whereas fasting hyperglycemia results from impaired first-phase insulin secretion and excessive endogenous glucose output in the setting of tissue insulin resistance, postchallenge hyperglycemia is primarily a function of insulin resistance and is relatively inadequate but still exaggerated hyperinsulinemia (31,32). Prediabetic subjects with insulin resistance have substantially more ad-

verse CVD risk profiles than individuals at risk for diabetes on the basis of impaired β-cell function (33,34). Postchallenge hyperinsulinemia (35) is associated with an impaired fibrinolytic state that favors acute thrombosis and enhanced risk for acute CVD events (36). Nonetheless, although these physiological observations provide a biologic basis that accounts for the effects of hyperglycemia on CVD, the direct effect of glucose on atherosclerosis remains controversial. Observational data support an association, whereas experimental data do not (28,37). Further clinical trial data are needed to untangle the relative benefits of control of hyperglycemia versus control of standard risk factors to reduce CVD events.

In this population, age modified effects of hyperglycemia on risk for CVD. In older subjects, postchallenge hyperglycemia appeared to be a stronger CVD risk factor, but in subjects younger than 65 years of age, fasting hyperglycemia was the stronger risk factor. If the reasoning outlined above is correct, this implies that the glycemic reflection of insulin resistance shifts from primarily fasting hyperglycemia in younger subjects to primarily postchallenge hyperglycemia in older subjects, but this hypothesis remains to be tested. We also found that isolated postchallenge hyperglycemia was substantially more common in older subjects than in younger subjects. It is well known that risk for type 2 diabetes increases with age, with postchallenge hyperglycemia becoming the predominant diagnostic abnormality in older subjects (11,14). From a prevention perspective, these findings imply that screening for diabetes with FPG will identify the vast majority of at-risk younger individuals but will miss a much larger proportion of older at-risk individuals.

This analysis has several limitations. Glycemic measures are correlated, potentially introducing collinearity into prediction models that include more than one glycemic term. That these variables are measuring similar phenomena may account in part for the lack of independent effects of HbA_{1c} or FPG when modeled together or with 2hPG. Yet, if collinearity were the only explanation for attenuation of risk estimates, one would expect the risk associated with 2hPG to also have been substantially diminished in multivariable risk models. Postchallenge hyperglycemia remains a consistent independent risk factor for CVD, regardless of model used, and argues for a true independent effect. We only assessed glycemic status once; intra-individual variability in these measures may have misclassified subjects, but this problem would produce an underestimate of the effects of glycemia on CVD. Our analysis does not address whether there is a threshold below which any measure of glycemia ceases to confer increased risk for CVD, and results may only be generalizable to Caucasian subjects of mixed European ancestry.

In summary, we found that elevated glucose levels 2 h after oral challenge increased RR for incident CVD by up to 40%, independent of elevated levels of nonglycemic risk factors or fasting or average hyperglycemia. This finding extends the observation that diabetes diagnostic criteria that incorporate 2hPG levels identify additional individuals at an increased risk for CVD events. Although isolated postchallenge hyperglycemia is uncommon among subjects with fasting glucose levels below the diabetes diagnostic threshold, it is more common among older subjects and subjects with diabetes by either fasting or postchallenge glycemic criteria. Diabetes screening programs relying on fasting glucose alone will identify most younger subjects at risk for the metabolic complications of hyperglycemia, but administration of an OGTT may be needed to identify older diabetic subjects or subjects whose only evidence of diabetes is postchallenge hyperglycemia. In any case, measurement of glycemic levels among subjects not known to have diabetes contributes only a small marginal amount of additional prognostic information. Measurement of standard nonglycemic risk factors remains the best way to identify the majority of subjects who will benefit from interventions to reduce CVD risk.

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