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Diabetes Mellitus

Subclinical Cardiovascular Disease and Risk of Incident Cardiovascular Disease and All-Cause Mortality

Lewis H. Kuller, Priscilla Velentgas, Joshua Barzilay, Norman J. Beauchamp,
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Abstract—Previously diagnosed diabetes mellitus, newly diagnosed diabetes mellitus, and impaired glucose tolerance are important determinants of the risk of clinical cardiovascular disease (CVD). We have evaluated the relation of patients with subclinical CVD, diabetes, and impaired glucose tolerance and “normal” subjects and the risk of clinical CVD in the Cardiovascular Health Study. Diabetes (1343), impaired glucose tolerance (1433), and normal (2421) were defined by World Health Organization criteria at baseline in 1989 to 1990. The average follow-up was 6.4 years (mean age 73 years). Diabetics had a higher prevalence of clinical and subclinical CVD at baseline. Compared with diabetes in the absence of subclinical disease, the presence of subclinical CVD and diabetes was associated with significant increased adjusted relative risk of death (1.5, CI 0.93 to 2.41), relative risk of incident coronary heart disease (1.99, CI 1.25 to 3.19), and incident myocardial infarction (1.93, CI 0.96 to 3.91). The risk of clinical events was greater for participants with a history of diabetes compared with newly diagnosed diabetics at baseline. Compared with nondiabetic nonhypertensive subjects without subclinical disease, patients with a combination of diabetes, hypertension, and subclinical disease had a 12-fold increased risk of stroke. Fasting blood glucose levels were a weak predictor of incident coronary heart disease as were most other risk factors. Subclinical CVD was the primary determinant of clinical CVD among diabetics in the Cardiovascular Health Study. (*Arterioscler Thromb Vasc Biol.* 2000;20:823-829.)

Key Words: diabetes ■ atherosclerosis ■ subclinical disease ■ stroke ■ heart attack

Previously diagnosed diabetes mellitus (DM), newly diagnosed DM, and impaired glucose tolerance (IGT) are important determinants of the risk of clinical cardiovascular disease (CVD).^{1,2}

The basis for excess risk of CVD among diabetics has not been completely determined. First, there is a high prevalence of atherosclerosis among diabetic compared with nondiabetic individuals.³ Second, diabetics are at increased risk for thrombosis formation, decreased fibrinolysis, and enhanced inflammatory response.⁴ Third, glycosylation of proteins may also affect arterial wall physiology and risk of disease.⁵

There is a high prevalence of subclinical atherosclerosis among older diabetic and nondiabetic individuals.⁶⁻⁹ Markers of subclinical disease are associated with an increased risk of cardiovascular morbidity and mortality.^{10,11} Haffner et al¹² have suggested that the higher prevalence of atherosclerosis among diabetics begins before the onset of clinical diabetes.

In the Cardiovascular Health Study (CHS), we have previously reported that participants with diabetes had an increased risk of incident myocardial infarction (MI),¹³ stroke,¹⁴ and congestive heart failure (CHF).¹⁵ We have

previously reported that participants with diabetes and IGT by World Health Organization (WHO) criteria had a higher prevalence of measures of subclinical disease than did “normal” subjects in the CHS.¹⁶ We have evaluated the prevalence of diabetes in the CHS on the basis of either the new American Diabetes Association (ADA) or WHO criteria. Diabetes prevalence was based on WHO compared with ADA criteria.¹⁷ The attributable risk of MI, stroke, or death was greater on the basis of WHO criteria rather than ADA criteria.¹⁷ This analysis, however, did not include measures of subclinical disease.

The CHS provides a unique opportunity to test the hypothesis that the excess risk of CVD among older diabetics (>65 years) was primarily due to their higher prevalence of subclinical atherosclerosis. We have also tested whether the presence of subclinical CVD subsumes the role of many of the traditional cardiovascular risk factors that are involved in the pathogenesis of clinical CVD.

Methods

Detailed descriptions of the CHS have been published.¹⁸ The original cohort was recruited from 4 communities in the United States from

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a defined sample of Medicare beneficiaries aged >65 years. There were 5201 participants in the original sample: 2955 women and 2246 men. The initial sample was recruited in 1989 to 1990. In 1992 to 1993, a new cohort of 248 black men and 428 black women was added to the study and was combined with 153 black women and 91 black men in the original sample. The new "black cohort" was recruited in the same manner as the original cohort and has similar risk factors and prevalence of subclinical disease as the original "black" sample.⁶ Baseline examination included a home interview and physical examination in the clinic.

Prevalent CVD was defined at baseline of the study by self-report and subsequent validation from clinical records, history, and the like.^{6,16,18–20} Subclinical disease in the CHS was previously defined as any of the following for participants who did not have prevalent clinical disease at baseline: an ankle-arm index ≤ 0.9 , internal carotid artery wall thickness >80th percentile, common carotid artery wall thickness >80th percentile, carotid stenosis >25%, major ECG abnormalities (based on the Minnesota code), and a Rose Questionnaire positive for claudication or angina pectoris in the absence of clinical diagnosis of angina pectoris or claudication.^{6,16}

Participants with evidence of silent MI based on Minnesota Code Q waves at baseline examination were included with clinical and not subclinical disease. Major ECG abnormalities based on the Minnesota Code have previously been reported to be associated with a substantial excess risk of clinical CVD, morbidity, and mortality and could be classified as "clinical disease," although the participants are not normally treated for these ECG abnormalities.²¹ In a prior study, we have shown that exclusion of major ECG abnormalities from the category of subclinical disease does not affect the association of subclinical disease compared with the absence of subclinical disease and the subsequent risk of coronary heart disease.¹⁰ The echocardiogram abnormalities were not included in the definition of subclinical disease in the present study because they were not included at the baseline examination (1992 to 1993) for the "new" black sample.⁶

The participants with subclinical disease at baseline were not being treated for CVD, nor did they have any clinical diagnosis of CVD. The combination of the various measures of subclinical disease was developed because of the high correlation of the various measures of subclinical disease.

At the baseline clinic visit, a blood sample was obtained on study participants after a 9-hour fast. Blood was collected early during the study visit and then 2 hours after the participants drank a 75-g oral glucose load.²² Known diabetic participants using insulin or oral hypoglycemic agents were excluded from the 2-hour glucose challenge. The new black sample did not have an oral glucose tolerance test at the time of their baseline examination in 1992 to 1993 and are included in the diabetes group on the basis of their history of diabetes or new diabetes as indicated by fasting blood glucose levels. The fasting blood glucose and the 2-hour glucose measurements were performed with a Kodak Ektacham 700 Analyzer (Eastman Kodak Corp).²²

The CHS criteria for diagnosis of diabetes was based on WHO criteria: a fasting blood glucose level ≥ 140 mg% or a 2-hour glucose level after a 75-g glucose challenge of >200 mg%. IGT was considered a fasting glucose level ≤ 140 mg% and a 2-hour glucose level ≥ 140 mg but <200 mg%; normal was considered fasting glucose and 2-hour oral glucose levels of <140 mg% and no history of diabetes or self-reported use of oral hypoglycemic agents or insulin.²³ We have also compared the association of subclinical disease with clinical disease among newly diagnosed diabetics on the basis of new ADA²³ (fasting glucose ≥ 126 mg%) and WHO^{24,25} criteria. Microvascular disease, such as microalbuminuria and retinopathy, were not measured until later in the study and are not included in the analysis.

The 7 primary end points for the CHS²⁶ were MI, angina pectoris, CHF, peripheral vascular disease, stroke, transient ischemic attack, and all-cause mortality. Event ascertainment followed a detailed protocol at each of the field centers.²⁶ Events were reviewed independent of CHS records and of the results of measurement of subclinical disease.

Most analyses reported in the present study are limited in focus to those CHS participants without clinical CVD at the time of study entry. Median follow-up time was 6.5 years.

The follow-up of CHS participants has been excellent at 10 years: 95% of the CHS cohort alive are in the follow-up, and only 4% have refused further evaluation.

Statistical Methods

Associations of cardiovascular and total deaths and cardiovascular event outcomes with diabetes status and subclinical disease were assessed by using Cox proportional hazards regression procedures.²⁷ All relative risks presented were adjusted for age, sex, and race (black and nonblack). Stepwise Cox regression procedures were used to identify statistically significant ($P < 0.05$) predictors of death, CVD death, incident CHD, and MI only among diabetic participants from a set of known CVD risk factors, including subclinical CVD, past or present cigarette smoking, hypertension (defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg or use of any antihypertensive medication), C-reactive protein (log-transformed), LDL cholesterol, HDL cholesterol, triglycerides, body mass index, waist circumference, fibrinogen, creatinine, and fasting glucose. These analyses also included adjustment for age, sex, and race. In addition to these stepwise regression models, Cox regression models containing all of the above-mentioned CVD risk factors and time to event were used to obtain fully adjusted estimates for the relative risk of CVD among diabetic participants associated with each risk factor.

Results

Characteristics of the Population

The overall prevalence of diabetes (25%) was slightly higher for black women (29%) than for black men (26%), white men (24%), and white women 22% (Table 1). Fasting glucose and 2-hour glucose levels were similar by age group within categories of normal, IGT, and DM. There were 1343 with diabetes at baseline, of which 502 (38%) were on pharmacological therapy, including 362 (27%) on oral hypoglycemic agents, 128 (10%) on insulin, and 12 (1%) on both oral hypoglycemic agents and insulin. The duration of diabetes, always difficult to ascertain, was not determined at the baseline examination in the CHS. Diabetic participants had a higher prevalence of both clinical and subclinical CVD at baseline ($P = 0.001$, Table 1). Diabetic participants also had a higher prevalence of hypertension by history; elevated systolic blood pressure, body mass index, waist circumference, C-reactive protein, triglyceride, and fibrinogen levels; and lower HDL cholesterol (Table 1). The associations were similar for men and women.

Among diabetic participants only, newly diagnosed or with a history of diabetes at baseline, those with subclinical or clinical disease were older, more likely to be men, more likely to be hypertensive, and more likely to have higher systolic blood pressure levels, higher fibrinogen levels, higher blood creatinine levels, and lower HDL cholesterol levels than those without any evidence of either subclinical or clinical CVD at baseline (Table I; Tables I through IV can be found online only at <http://atvb.ahajournals.org/cgi/content/full/20/3/823/DC1>).

Incidence of CVD and Mortality

The all-cause mortality rate per 1000 person years was strongly associated ($P = 0.001$) with diabetes or IGT and the prevalence of clinical or subclinical disease (Figure 1). The relative risk of death (adjusted for age, race, and sex) associated with the presence of diabetes and clinical disease was 5.3 (CI 3.9 to 7.2), and that associated with subclinical disease was 3.2 (CI 2.1 to 5.1) compared with the risk of

TABLE 1. CHS Baseline Characteristics According to WHO Diabetes Status

	Normal (n=2421)	IGT (n=1433)	Diabetic Participants (n=1343)	P (n=5197)
Age, y	73.4	73.3	73.0	<0.001
Sex: female, %	56.7	57.5	55.5	0.554
Race: black,* %	4.2	3.3	18.5	...
CVD at baseline				
Clinical, %	25.5	30.7	40.3	<0.001
Subclinical, %	40.4	41.9	43.8	...
Components of subclinical disease				
Ankle-arm index < -0.9	9.5	11.2	19.3	<0.001
Maximum internal carotid >80th percentile	17.0	21.7	24.4	<0.001
Maximum common carotid >80th percentile	15.5	19.3	26.8	<0.001
Maximum stenosis >25%	43.4	50.4	55.7	<0.001
Any major ECG abnormality	23.9	28.8	36.9	<0.001
Rose claudication: yes	1.8	1.6	2.8	0.065
Rose angina: yes	5.2	5.9	8.2	0.001
Smoking				
Current, %	13.7	9.2	10.1	0.001
Former, %	42.9	41.0	42.8	...
Hypertension,† %	54.3	66.6	78.9	<0.001
Systolic blood pressure, mm Hg	132.5	137.4	140.6	<0.001
Diastolic blood pressure, mm Hg	69.9	70.8	70.4	0.028
Body mass index, kg/m ²	25.5	26.8	28.2	<0.001
Waist circumference, cm	91.2	94.8	99.2	<0.001
C-Reactive protein, mg/dL	2.82	3.46	4.97	<0.001
HDL cholesterol, mg/dL	56.3	53.0	49.6	<0.001
LDL-cholesterol, mg/dL	130.2	131.7	127.1	0.003
Triglycerides, mg/dL	125.5	148.2	167.4	<0.001
Fibrinogen, mg/dL	314.5	323.1	333.1	<0.001
Creatinine, mg/dL	1.05	1.08	1.08	0.065

Data are for 5197 CHS participants with complete information on WHO diabetes status. Fasting and 2-hour glucose tolerance test results were required to be classified as IGT or normal; thus, members of the new minority cohort are not included in these groups. Self-reported history of diabetes, use of diabetes medications (insulin or oral hypoglycemics), and fasting glucose or 2-hour glucose tolerance tests were used to classify participants as diabetic; this group includes minority cohort members with history of diabetes, use of diabetes medications, or fasting glucose level >140.

*Differences in race according to diabetes status are mostly attributable to unavailability of 2-hour oral glucose test results for the minority cohort, preventing their inclusion in the normal and IGT groups, but not the diabetic group as described above.

†Hypertension is defined as systolic blood pressure \geq 140 mm Hg or diastolic blood pressure \geq 90 mm Hg or current use of any antihypertensive medications.

death associated with neither diabetes nor subclinical disease (Table II, online).

The incidence of CHD (including MI and angina) cases over the 6.4-year follow-up was higher in diabetic participants and those with IGT. However, the increase in incident disease risk was largely confined to those with prevalent subclinical CVD at baseline (Figure 2). The relative risk for diabetes and subclinical disease was 2.5 (CI 1.9 to 3.4), and that for diabetes with no subclinical disease was 1.3 (CI -0.8 to 2.0) compared with the relative risk associated with no diabetes and no subclinical disease (Table II, online).

The risk for incident stroke (fatal and nonfatal, Figure 2) was elevated for diabetic participants with (relative risk 4.1,

CI 2.6 to 6.7) and without (relative risk 2.5, CI 1.3 to 4.8) subclinical disease at baseline. Only those with IGT with prevalent subclinical CVD at baseline had increased risk of stroke (relative risk 2.3, CI 1.4 to 3.8). A similar pattern was seen for CHF (Table II, online).

The hypertensives (64% of the CHS cohort) had much higher rates of stroke and CHF. The risk of stroke was only 2.2 per 1000 person years for participants without a history of hypertension or diabetes and no subclinical disease, and the risk of stroke was 25 per 1000 person years (n=57 strokes) for diabetics and hypertension with subclinical disease, a 12-fold difference. Approximately 25% of all strokes in the CHS study occurred among the high-risk group, those with

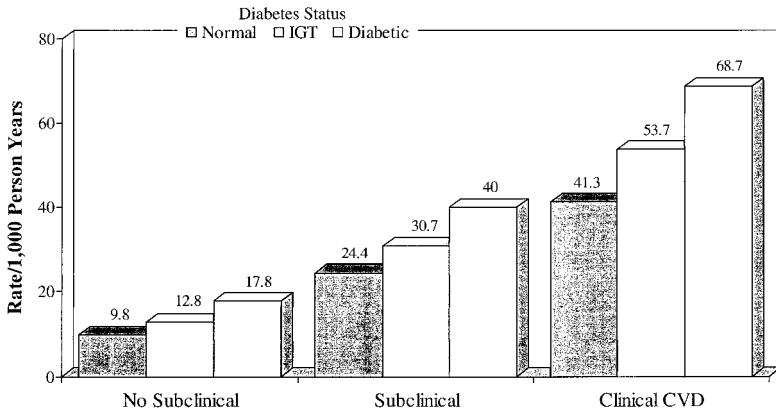


Figure 1. Diabetes status and presence of sub-clinical/clinical CVD at baseline and incidence of specific events among men and women in the CHS (outcome: death).

diabetes, hypertension, and subclinical disease, which constituted 449 (8.6%) of the total sample of 5197 participants.

We further analyzed the data comparing risk within the diabetic group, the IGT group, and the group with neither diabetes nor IGT. The age-, sex-, and race-adjusted relative risk values for incident CHD were as follows: no subclinical disease was taken to have a value of 1; in the diabetic category, subclinical disease was 2.2 (CI 1.4 to 3.3), incident stroke was 1.8 (CI 1.0 to 3.2), and CHF was 1.4 (CI 0.8 to 2.3); in the IGT category, incident CHD was 1.8 (CI 1.2 to 2.8), stroke was 1.8 (CI 1.0 to 3.5), and CHF was 1.9 (CI 1.1 to 3.4); and in the category with neither diabetes nor IGT (no subclinical versus subclinical), incident CHD was 1.4 (CI 1.0 to 1.8), stroke was 1.7 (CI 1.0 to 2.8), and CHF was 1.3 (CI 0.9 to 2.0).

New Diabetics and Prevalent Diabetics

We further studied whether the increase in incident CVD among diabetics was related to whether diabetes was newly diagnosed or prevalent at baseline. The diabetic participants were stratified into those with known (prevalent) DM and those with newly diagnosed DM (Figure 3; Table III, online). There were 214 (74%) of 397 prevalent diabetics and 294 (73%) of 405 new diabetics with subclinical CVD at baseline. In all CVD categories, incident disease was higher for those with prevalent DM than for those with newly diagnosed DM. For those with prevalent DM, incident CVD event risk increased whether or not subclinical CVD was present at baseline. On the other hand, for those with newly diagnosed DM, risk of incident CVD increased only in the presence of prevalent subclinical CVD (relative risk 2.0, CI 1.4 to 2.9),

but no subclinical disease had a relative risk of only 1.0 (CI 0.5 to 1.9).

The analyses presented so far were based on the WHO criteria for diabetes. We also evaluated the relation between subclinical disease and risk of clinical CVD among newly diagnosed diabetic participants at the baseline by using the new ADA criteria. For deaths, the rate was 46.1 per 1000 person years, and relative risk adjusted for age, sex, and race was 3.2 for diabetes and subclinical disease on the basis of the ADA criteria; for WHO criteria, the rate was 37.9 per 1000 person years (relative risk 2.7). Similarly, for total CHD, the rate was 33.9 per 1000 person years on the basis of the ADA criteria (relative risk 2.2) and 32.1 per 1000 person years (relative risk 2.0) on the basis of the WHO criteria for a combination of diabetes and subclinical disease versus no subclinical disease and no diabetes.

Men and Women

The relations between incident events (known and newly diagnosed), diabetes, and subclinical disease were similar for men and women (Table IV, online). Rates were generally higher for men than for women within each category of diabetes and subclinical disease.

Time to Event and Disease Risk

The associations of subclinical disease with risk of clinical disease could be time dependent from measurement of subclinical disease to the event. The statistical tests for the interaction of exposure status with time to event were borderline significant ($P=0.08$) for total mortality and inci-

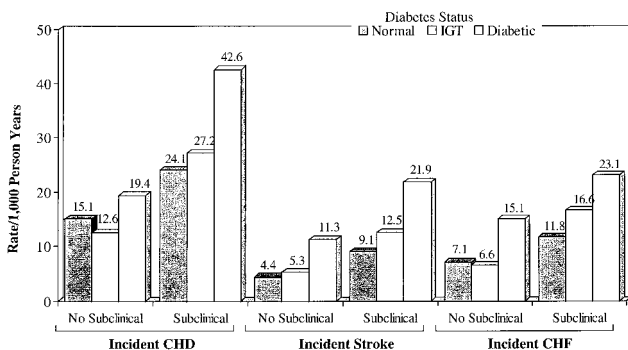


Figure 2. Diabetes status and presence of subclinical/clinical CVD at baseline and incidence of specific events among men and women in the CHS.

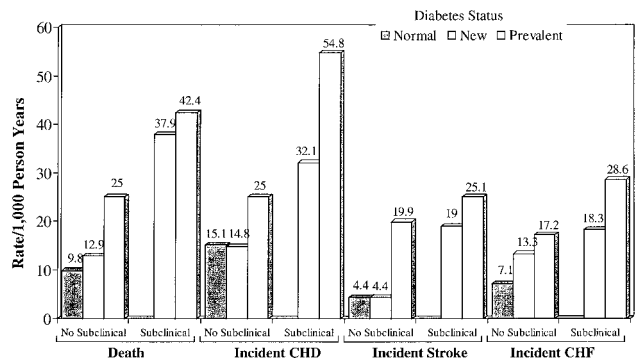


Figure 3. Prevalent or new diabetes status and presence of subclinical CVD at baseline and incidence of specific events among men and women in the CHS.

TABLE 2. Multivariate Associations of Subclinical Disease With Clinical End Points: Diabetic Participants Without History of Clinical Disease at Baseline

Variables	Interval	Outcome			
		Total Mortality	CVD Mortality	Incident MI	Incident CHD
Age	5 y	1.67 (1.42–1.98)	1.44 (1.10–1.89)	1.27 (0.98–1.65)	...
Sex (male)		1.83 (0.92–3.64)	...
Subclinical disease		1.50 (0.93–2.41)	2.51 (1.05–6.01)	1.93 (0.96–3.91)	1.99 (1.25–3.19)
Cigarette smoking		2.89 (1.73–4.79)
Past history of cigarette smoking		1.33 (0.90–1.98)
Creatinine	1 mg/dL	1.82 (1.05–3.15)	2.15 (1.03–4.52)
Fasting glucose	20 mg/dL	1.09 (1.04–1.14)	1.06 (1.00–1.12)
Diastolic blood pressure	10 mm Hg	...	1.18 (0.90–1.54)	1.38 (1.06–1.80)	1.18 (0.99–1.41)
Triglycerides	20 mg/dL	1.06 (0.98–1.15)	1.07 (1.01–1.13)

Risk factors shown are significant at $P=0.05$ only. Variables included in model were age, sex, race, subclinical disease, past and current smoking, hypertension, systolic and diastolic blood pressure, LDL cholesterol, HDL cholesterol, triglycerides, body mass index, waist circumference, fasting glucose, creatinine, C-reactive protein, and fibrinogen. Values in parentheses are CIs.

dent stroke ($P=0.07$) but not for incident CHD ($P=0.30$); risk was slightly higher earlier in the follow-up.

Multivariate Analysis

Multivariate Cox regression analysis was performed. Subclinical disease was a strong independent risk factor for CVD mortality among diabetic participants (fully adjusted relative risk 2.51, CI 1.05 to 6.01; Table 2). Creatinine and diastolic blood pressure were the only other significant independent risk factors for CVD mortality in the stepwise regression analysis. The fasting glucose level among the diabetic participants was not a significant predictor of CVD mortality, with an adjusted relative risk of 1.04 (CI 0.95 to 1.14). The relative risk of subclinical disease and total mortality (Table 2) was weaker (relative risk 1.50, CI 0.93 to 2.41) than for CVD mortality. Cigarette smoking, creatinine levels, and fasting glucose were predictors of total mortality.

A similar multivariate analysis was performed for incident MI and for incident CHD (Table 2). Subclinical disease was a significant predictor of incident MI (relative risk 1.93, CI 0.96 to 3.91). Subclinical disease and total incident CHD (adjusted relative risk 1.99, CI 1.25 to 3.19), which included both MI and angina pectoris. Diastolic blood pressure, triglyceride, and fasting glucose levels were also significantly associated with total incident CHD. There was no association of LDL cholesterol, HDL cholesterol, body mass index, waist circumference, fibrinogen, systolic blood pressure, and any of the 4 outcomes in the multivariate models shown in Table 2. We also performed the same multivariate analysis excluding the subclinical disease measures. The coefficients were similar with subclinical disease included or excluded. The coefficients for LDL cholesterol and total CHD risk increased to 1.10 (CI 1.00 to 1.20, $P<0.05$) from 1.08 (CI 0.98 to 1.18, $P=NS$).

The relative risk for incident CHD and subclinical disease adjusting only for age, sex, and race was 2.2; after adjustment for all risk factors above, relative risk was 1.99, a nonsignificant change.

Discussion

The results of the present study have important implications for understanding the risks and potential prevention of mac-

rovascular disease among older diabetics, patients with IGT, and “normal participants.” The prevalence of measures of subclinical vascular disease are very high among participants without clinical CVD. The high prevalence of subclinical disease was similar among newly diagnosed diabetics on the basis of either the WHO or the new ADA criteria.

The time of onset of clinical diabetes is not known for the newly diagnosed diabetics at baseline. Previous studies have noted a high prevalence of microvascular disease at the time of the diagnosis of non-insulin-dependent DM and have tried to estimate the duration of diabetes before clinical diagnosis.²⁸ IGT is an important determinant of the risk of diabetes. In the CHS study, the prevalence of subclinical disease among participants with IGT was 60% and 54% for the normal participants. These results suggest that subclinical disease may have developed before the onset of clinical diabetes, assuming that a high percentage of the participants with IGT will ultimately develop clinical diabetes, which is consistent with other studies.²⁹

The fasting blood glucose levels were a weak predictor of outcomes in the study. Most of the other traditional cardiovascular risk factors were also not significant predictors of the risk of CVD among the diabetics after adjusting for the extent of subclinical disease. The traditional cardiovascular risk factors are the primary determinants of the prevalence of subclinical disease.¹⁶ We have previously demonstrated that elevated LDL cholesterol, lower HDL cholesterol, and elevated triglyceride levels, along with cigarette smoking and elevated systolic blood pressure, are important determinants of subclinical CVD.¹⁶ Once subclinical CVD has developed, these risk factors may have a smaller association with clinical disease, especially lipid levels. However, modifications of these risk factors may still reduce the risk of clinical disease by modifying the amount or characteristics of subclinical disease or plaque stability and thrombosis.^{30–43}

Neither the CHS nor any of the prior studies can document that subclinical atherosclerosis developed before diabetes or even insulin resistance. Longitudinal studies with long follow-ups and measures of subclinical disease, insulin resistance, and glucose metabolism would be required. The strong association of subclinical disease with the risk of clinical

CVD among diabetics does not preclude the importance of measures of microvascular disease, such as small-vessel disease, microcirculation, and autonomic neuropathy, to clinical CVD.

In summary, the primary determinant of the risk of clinical CVD among older diabetics (prevalent and newly diagnosed) is the presence of subclinical disease. IGT is a risk factor for clinical CVD, primarily among participants who also exhibited subclinical disease. The prevalence of subclinical disease is very high among older diabetics, even though they were newly diagnosed at entry to the CHS. The measurement of subclinical disease may enhance risk stratification among diabetic patients.

Appendix: Participating Institutions and Principal Staff

From Forsyth County, NC, Bowman Gray School of Medicine of Wake Forest University: Gregory L. Burke, Sharon Jackson, Alan Elster, Walter H. Ettinger, Curt D. Furberg, Gerardo Heiss, Dalane Kitzman, Margie Lamb, David S. Lefkowitz, Mary F. Lyles, Cathy Nunn, Ward Riley, John Chen, and Beverly Tucker; from Forsyth County, NC, Bowman Gray School of Medicine, EKG Reading Center: Farida Rautaharju and Pentti Rautaharju; from Sacramento County, Calif, University of California, Davis: William Bommer, Charles Bernick, Andrew Duxbury, Mary Haan, Calvin Hirsch, Lawrence Laslett, Marshall Lee, John Robbins, and Richard White; from Washington County, Md, The Johns Hopkins University: M. Jan Busby-Whitehead, Joyce Chabot, George W. Comstock, Adrian Dobs, Linda P. Fried, Joel G. Hill, Steven J. Kittner, Shiriki Kumanyika, David Levine, Joao A. Lima, Neil R. Powe, Thomas R. Price, Jeff Williamson, Moyses Szklo, and Melvyn Tockman; from Washington County, Md, MRI Reading Center, The Johns Hopkins University: R. Nick Bryan, Norman Beauchamp, Carolyn C. Meltzer, Naiyer Iman, Douglas Fellows, Melanie Hawkins, Patrice Holtz, Michael Kraut, Grace Lee, Larry Schertz, Cynthia Quinn, Earl P. Steinberg, Scott Wells, Linda Wilkins, and Nancy C. Yue; from Allegheny County, Pa, University of Pittsburgh: Diane G. Ives, Charles A. Jungreis, Laurie Knepper, Lewis H. Kuller, Elaine Meilahn, Peg Meyer, Roberta Moyer, Anne Newman, Richard Schulz, Vivienne E. Smith, and Sidney K. Wolfson; from Echocardiography Reading Center (Baseline), University of California, Irvine: Hoda Anton-Culver, Julius M. Gardin, Margaret Knoll, Tom Kurosaki, and Nathan Wong; from Washington, DC, Echocardiography Reading Center (Follow-Up), Georgetown Medical Center: John Gottdiener, Eva Hausner, Stephen Kraus, Judy Gay, Sue Livengood, Mary Ann Yohe, and Retha Webb; from Ultrasound Reading Center, Tufts New England Medical Center: Daniel H. O'Leary, Joseph F. Polak, and Laurie Funk; from Central Blood Analysis Laboratory, University of Vermont, Burlington: Edwin Bovill, Elaine Cornell, Mary Cushman, and Russell P. Tracy; from Respiratory Sciences, University of Arizona, Tucson: Paul Enright; from Coordinating Center, University of Washington, Seattle: Alice Arnold, Annette L. Fitzpatrick, Bonnie K. Lind, Richard A. Kronmal, Bruce M. Psaty, David S. Siscovick, Lynn Shemanski, Will Longstreth, Patricia W. Wahl, David Yanez, Paula Diehr, Maryann McBurnie, Chuck Spiekerman, Scott Emerson, Cathy Tangen, and Priscilla Velentgas; and from Bethesda, Md, National Heart, Lung, and Blood Institute Project Office: Robin Boineau, Teri A. Manolio, Peter J. Savage, and Patricia Smith.

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