Five-Year Outcomes in High-Risk Participants in the Detection of Ischemia in Asymptomatic Diabetics (DIAD) Study

A post hoc analysis

Shanti Bansal, md[1]
Frans J.Th. Wackers, md[1]
Silvio E. Inzucchi, md[2]
Deborah A. Chyun, phd[3]
Janice A. Davey, msn[1]
Lawrence H. Staib, phd[4]
Lawrence H. Young, md[1]
for the DIAD Study Investigators*

OBJECTIVE — To estimate baseline cardiovascular risk of 1,123 participants in the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study and to assess cardiac event rates and the effect of screening on outcomes in these higher-risk participants.

RESEARCH DESIGN AND METHODS — Baseline cardiovascular risk was assessed using four established methods: Framingham score, UK Prospective Diabetes Study (UKPDS) risk engine, criteria of the French-Speaking Association for the Study of Diabetes and Metabolic Diseases, and the presence or absence of metabolic syndrome. Cardiac events (cardiac death or nonfatal myocardial infarction) were assessed during the 4.8-year follow-up in participants with intermediate/high cardiovascular risk.

RESULTS — By various risk-stratification approaches, 53–75% of participants were defined as having intermediate or high cardiovascular risk. The prevalence of inducible ischemia on screening in these individuals ranged from 21 to 24%, similar to lower-risk participants (19–23%). Cardiac event rates were greater in intermediate-/high-risk versus low-risk groups, but this was only significant for the UKPDS risk engine (4.2 vs. 1.2%, $P = 0.002$). The annual cardiac event rate was <1% in all risk groups, except in the high-risk UKPDS group (~2% per year). In intermediate-/high-risk participants randomized to screening versus no screening, 4.8-year cardiac event rates were similar (2.5–4.8% vs. 3.1–3.7%).

CONCLUSIONS — A substantial portion of the DIAD population was defined as having intermediate/high baseline cardiovascular risk. Nevertheless, their annual cardiac event rate was low and not altered by routine screening for inducible ischemia.

Diabetes Care 34:204–209, 2011

In the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study, 1,123 asymptomatic individuals with type 2 diabetes were randomized to either screening with stress myocardial perfusion imaging (MPI) or no screening. The prevalence of inducible ischemia was assessed and the hypothesis that screening would have a favorable effect on outcome was tested. The results of the DIAD study have been published (1–3). The prevalence of abnormal MPI was not only lower than anticipated at 22% of participants, but, in addition, only 6% of participants had clinically significant inducible ischemia and another 6% had adenosine-induced ischemic electrocardiogram changes (1). The cumulative 4.8-year cardiac event rate (cardiac death and nonfatal myocardial infarction) was low (2.9% overall or 0.6% per year) (3). Moreover, there was no significant difference in cardiac outcomes between participants who were randomized to screening versus no screening. These favorable outcomes were unexpected when compared with historical outcomes data in patients with type 2 diabetes (4,5). One possible explanation for these findings could be that the DIAD population was at relatively low baseline cardiovascular risk and therefore not representative of the general type 2 diabetic population.

To place the DIAD cohort into clear perspective, a post hoc analysis of baseline cardiovascular risk was performed using four well-known risk-stratification approaches, including the Framingham risk score (6), the UK Prospective Diabetes Study (UKPDS) risk engine (7), high-risk criteria as defined by the French-Speaking Association for the Study of Diabetes and Metabolic Diseases (ALFEDIAM) and the French Society of Cardiology (SFC) (8), and the presence of metabolic syndrome as defined by the International Diabetes Federation Taskforce (9). The prevalence of abnormal screening, cardiac event rates and the effect of screening on outcomes were analyzed in participants stratified as having intermediate/high cardiovascular risk (Fig. 1).

RESEARCH DESIGN AND METHODS

— Methods of recruitment and randomization as well as the demographics of the DIAD study have been published (1). Participants were recruited from 14 diabetes clinics in the U.S. and Canada. Inclusion criteria were type 2 diabetes, age 50–75 years, and no symptoms or clinical signs suggestive of coronary artery disease (CAD). Exclusion criteria included angina pectoris; stress test or coronary angiography within the previous 3 years; history of myocardial infarction, heart failure, or coronary re-

From the [1]Section of Cardiovascular Medicine, Yale University School of Medicine, New Haven, Connecticut; the [2]Section of Endocrinology, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut; the [3]College of Nursing at the College of Dentistry, New York University, New York, New York; and the [4]Division of Bioimaging Sciences, Department of Diagnostic Radiology, Yale University School of Medicine, New Haven, Connecticut.
Corresponding author: Frans J.Th. Wackers, frans.wackers@yale.edu.
Received 22 June 2010 and accepted 2 October 2010. Published ahead of print at http://care.diabetesjournals.org on 7 October 2010. DOI: 10.2337/dc10-1194. Clinical trial reg. no. NCT00769275, clinicaltrials.gov.
*A complete listing of the DIAD Study Investigators is available in an online appendix at http://care.diabetesjournals.org/cgi/content/full/dc10-1194/DC1.

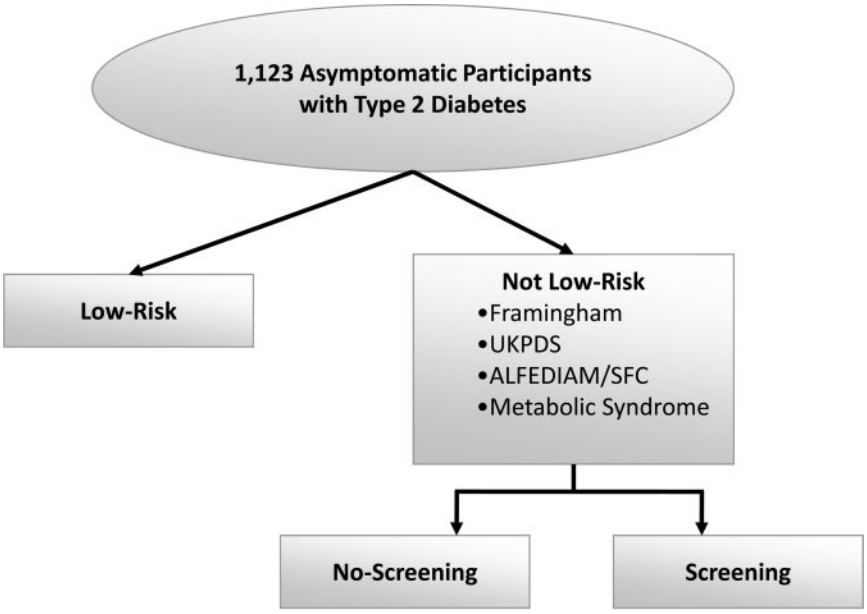

Figure 1—*Flow diagram of the post hoc analysis of the DIAD data. Cardiac outcomes were reanalyzed in the not-low-risk participants who were randomized to no screening versus screening.*

vascularization; abnormal rest electrocardiogram; any current clinical indication for stress testing; active bronchospasm; and limited life expectancy due to comorbidity.

The participants were randomized to screening with an adenosine vasodilator Tc-99m-Sestamibi MPI ($n = 561$) or no screening ($n = 562$) (1). After randomization, treatment was at the discretion of the participant's physician. The protocol was approved by the institutional review boards. Details of the stress testing and MPI interpretation have been described (1,2). All participants had follow-up for 5 years (3).

Post hoc risk stratification

The DIAD participants were risk-stratified as follows:

1) Framingham risk score: On the basis of age, sex, lipid levels, blood pressure, smoking, and presence of diabetes, the participants were categorized as having either a low (<10%), intermediate (10–20%), or high (>20%) 10-year risk for symptomatic CAD (6). Participants with intermediate or high Framingham risk scores were defined as having a higher risk and were compared with the low-risk group.

2) UKPDS risk engine: On the basis of age, sex, duration of diabetes, smoking, systolic blood pressure, total cholesterol, HDL, ethnicity, and A1C, the participants were classified into three UKPDS risk categories: low (<14%), intermediate (15–30%), or high (>30%) 10-year risk for CAD (7). Participants with an intermediate or high UKPDS risk score were defined as having a higher risk and were compared with the low-risk group.

3) ALFEDIAM/SFC high-risk criteria: The ALFEDIAM recommended screening for inducible myocardial ischemia in patients with type 2 diabetes (8) with one of the following: age >60 years; duration of diabetes >10 years and at least two other cardiovascular risk factors; peripheral arterial disease; and proteinuria and microalbuminuria with at least two other cardiovascular risk factors. Participants meeting one of these criteria were defined as the higher-risk cohort.

4) Metabolic syndrome: Metabolic syndrome was defined by at least three of five criteria defined by the International Diabetes Federation Taskforce (9) and was considered to represent higher cardiovascular risk (10,11). The criteria included waist circumference ≥102 cm (for men) or ≥88 cm (for women), triglycerides ≥150 mg/dl, HDL <40 mg/dl (for men) or <50 mg/dl (for women), systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg, and fasting glucose ≥100 mg/dl. Participants with metabolic syndrome were defined as having a higher risk; their outcome was compared with the cohort without metabolic syndrome.

Statistical analysis

The participants were risk stratified based on clinical variables documented at enrollment into the study. Because it is generally agreed that low-risk patients should not undergo specialized cardiac testing (12), only participants defined as having an intermediate/high risk were analyzed for outcomes according to randomization. Primary end points were nonfatal myocardial infarction and cardiac death. Secondary end points included unstable angina, heart failure, stroke, and coronary revascularization (3). The rate of coronary revascularization was analyzed separately. Of 561 participants randomized to screening, 522 underwent screening and 39 did not. The latter participants were analyzed on an intention-to-screen basis.

Statistical analysis was performed with Minitab 15 statistical software (Minitab, State College, PA). Cardiac outcomes were compared in low-risk versus intermediate-/high-risk groups and in intermediate-/high-risk participants randomized to screening versus no screening. The Fisher exact test was used to compare the prevalence of abnormal MPI. The log-rank test was used for comparing cardiac outcomes between groups. Cox proportional hazards regression was computed using COXPH in R (www.r-project.org) in order to determine hazard ratios (HRs) comparing events in low-risk versus intermediate-/high-risk groups and in screened versus not screened high-/intermediate-risk participants.

RESULTS

Framingham risk score

Overall, 283 (25%) participants would be defined as having low risk, and 840 (75%) as having intermediate (542 [48%]) or high (298 [27%]) cardiovascular risk (Table 1). Of 522 screened participants, 387 (74%) were defined as having intermediate/high risk. The prevalence of abnormal MPI in the screened intermediate-/high-risk versus screened low-risk groups was similar (21 vs. 23%, $P = 0.72$) (Table 2). Primary and secondary cardiac events and coronary revascularizations are shown in Table 1. Overall, primary cardiac events trended to be higher in the intermediate-/high-risk group versus the low-risk group (28 [3.3%] vs. 4 [1.4%], $P = 0.09$). However, primary cardiac event rates in 418 intermediate-/high-risk participants randomized to screening and in the 422 intermediate-/high-risk participants random-

Table 1—*Cardiac events in risk groups according to various risk stratification schemes*

	Low risk	Intermediate risk	High risk	Intermediate/ high risk	*P**	HR (95% CI)
Framingham score						
n	283	542	298	840		
Primary cardiac events	4 (1.4)	14 (2.6)	14 (4.7)	28 (3.3)	0.09	2.4 (0.84–6.85)
Secondary cardiac events	5 (1.8)	15 (2.8)	15 (5.0)	30 (3.6)	0.12	2.07 (0.80–5.34)
Revascularizations	9 (3.2)	40 (7.4)	26 (8.7)	66 (7.9)	0.006	2.57 (1.28–5.16)
UKPDS risk engine						
n	515	447	142	589		
Primary cardiac events	6 (1.2)	11 (2.5)	14 (9.9)	25 (4.2)	0.002	3.65 (1.50–8.90)
Secondary cardiac events	12 (2.3)	16 (3.6)	7 (4.9)	23 (3.9)	0.13	1.70 (0.84–3.41)
Revascularizations	18 (3.5)	39 (8.7)	17 (12.0)	56 (9.5)	0.0001	2.80 (1.65–4.77)
ALFEDIAM/SFC criteria						
n	410		713			
Primary cardiac events	8 (2.0)		24 (3.4)		0.19	1.71 (0.77–3.80)
Secondary cardiac events	5 (1.2)		30 (4.2)		0.01	3.46 (1.34–8.91)
Revascularizations	22 (5.4)		53 (7.4)		0.21	1.38 (0.84–2.26)
Metabolic syndrome	No			Yes		
n	319			804		
Primary cardiac events	8 (2.5)			24 (3.0)	0.67	1.19 (0.54–2.65)
Secondary cardiac events	8 (2.5)			27 (3.4)	0.46	1.35 (0.61–2.96)
Revascularizations	21 (6.6)			54 (6.7)	0.9	1.03 (0.62–1.71)

Data are *n* (%), unless otherwise indicated. **P* values are shown for low risk versus intermediate/high risk for Framingham and UKPDS; low risk versus high risk for ALFEDIAM/SFC; no versus yes for metabolic syndrome.

ized to no screening were similar (3.1 and 3.6%; log rank $P = 0.71$) Table 3).

UKPDS risk engine

Because of missing data, 19 participants could not be categorized by the UKPDS risk engine. Of the remaining 1,104 participants, 515 (47%) were categorized as low risk and 589 (53%) as intermediate (447 [40.5%]) or high (142 [13%]) risk (Table 1). Of those screened, 276 (53%) were at intermediate/high risk (Table 2). The prevalence of abnormal MPI in intermediate-/high-risk and low-risk participants was not different (24 vs. 19%, $P = 0.2$) (Table 2). However, the incidence of primary cardiac events was higher in the intermediate-/high-risk group compared with the low-risk group (25 [4.2%] vs. 6 [1.2%], $P = 0.002$) (Table 1). Primary cardiac event rates were similar in 291 intermediate-/high-risk participants randomized to screening and in 298 intermediate-/high-risk participants randomized to no screening (4.8 vs. 3.7%, log rank $P = 0.51$) (Table 3).

ALFEDIAM/SFC high-risk criteria

Of 1,123 participants, 713 (63%) met ALFEDIAM/SFC high-risk criteria (Table 1). Of 522 screened participants, 326 (62%) were high risk (Table 2). The prevalence of abnormal MPI in high-risk and low-risk participants was not different (23 vs. 19%, $P = 0.27$) (Table 2). The incidence of primary cardiac events was not different in the high- and low-risk groups (24 [3.4%] vs. 8 [2.0%], $P = 0.19$) (Table 1), but secondary event rates were higher in the high-risk than in the low-

Table 2—*Results of stress MPI in 522 participants randomized to screening, grouped according to various risk stratification schemes*

	Total normal MPI	Total abnormal MPI	Non-MPI abnormalities	Small defect	Moderate/large defect
Framingham score					
Low risk ($n = 135$)	104 (77.0)	31 (23.0)	9 (6.7)	14 (10.4)	8 (5.9)
Intermediate/high risk ($n = 387$)	305 (78.8)	82 (21.2), $P = 0.72$	21 (5.4)	36 (9.3)	25 (6.5)
UKPDS risk engine					
Low risk ($n = 241$)	195 (80.9)	46 (19.1)	14 (5.8)	20 (8.3)	12 (5.0)
Intermediate/high risk ($n = 276$)	210 (76.1)	66 (23.9), $P = 0.2$	16 (5.8)	30 (10.9)	20 (7.3)
ALFEDIAM/SFC criteria					
Low risk ($n = 196$)	159 (81.1)	37 (18.9)	6 (3.1)	17 (8.7)	14 (7.1)
High risk ($n = 326$)	250 (76.7)	76 (23.3), $P = 0.27$	24 (7.4)	33 (10.1)	19 (5.8)
Metabolic syndrome					
No ($n = 157$)	120 (76.4)	37 (23.6)	11 (7.0)	18 (11.5)	8 (5.1)
Yes ($n = 365$)	289 (79.2)	76 (20.8), $P = 0.49$	19 (5.2)	32 (8.8)	25 (6.9)

Data are *n* (%). A total of 19 participants not categorized due to missing data. *P* values reflect comparison of total abnormal MPI in two risk groups (see text). Non-MPI abnormalities = ischemic electrocardiogram changes during adenosine infusion, transient ischemic dilation, or baseline left ventricular dysfunction.

Table 3—*Cardiac events in intermediate-/high-risk participants randomized to no screening versus screening*

	Framingham score: intermediate/high risk (n = 840)			
	No screening (n = 422)	Screening (n = 418)	P	HR (95% CI)
Primary cardiac events	15 (3.6)	13 (3.1)	0.71	0.87 (0.41–1.83)
Secondary cardiac events	13 (3.1)	17 (4.1)	0.45	1.32 (0.64–2.72)
Revascularizations	41 (9.7)	25 (6.0)	0.05	0.61 (0.37–1.01)
	UKPDS risk engine: intermediate/high risk (n = 589)			
	No screening (n = 298)	Screening (n = 291)		
Primary cardiac events	11 (3.7)	14 (4.8)	0.51	1.30 (0.59–2.86)
Secondary cardiac events	11 (3.7)	12 (4.1)	0.79	1.12 (0.49–2.53)
Revascularizations	31 (10.4)	25 (8.6)	0.48	0.83 (0.49–1.4)
	ALFEDIAM/SFC criteria: high risk (n = 713)			
	No screening (n = 361)	Screening (n = 352)		
Primary cardiac events	11 (3.1)	13 (3.7)	0.61	1.23 (0.55–2.75)
Secondary cardiac events	12 (3.3)	18 (5.1)	0.21	1.59 (0.77–3.31)
Revascularizations	31 (8.6)	22 (6.3)	0.27	0.74 (0.43–1.27)
	Metabolic syndrome: yes (n = 804)			
	No screening (n = 406)	Screening (n = 398)		
Primary cardiac events	14 (3.5)	10 (2.5)	0.42	0.72 (0.32–1.62)
Secondary cardiac events	12 (3.0)	15 (3.8)	0.55	1.26 (0.59–2.70)
Revascularizations	31 (7.6)	23 (5.8)	0.31	0.76 (0.44–1.3)

Data are n (%), unless otherwise indicated.

risk group (30 [4.2%] vs. 5 [1.2%], P = 0.01) (Table 1). However, the primary cardiac event rates were similar in 352 high-risk participants randomized to screening and 361 high-risk participants randomized to no screening (3.7 vs. 3.1%, log rank P = 0.61) (Table 3).

Metabolic syndrome

Of all participants, 804 (72%) had metabolic syndrome (Table 1). Of 522 screened participants, 365 (70%) had metabolic syndrome (Table 2). The prevalence of abnormal MPI in participants with versus without metabolic syndrome was not different (21 vs. 24%, P = 0.49) (Table 2). Overall, primary cardiac event rates were similar in both groups (metabolic syndrome 24 [3.0%] vs. no metabolic syndrome 8 [2.5%], P = 0.67) (Table 1). Primary cardiac event rates in 398 participants with metabolic syndrome randomized to screening and in 406 participants with metabolic syndrome randomized to no screening were similar (2.5 vs. 3.5%, log rank P = 0.42) (Table 3).

CONCLUSIONS — This post hoc analysis provides an important perspective on the results of the DIAD study (3) by demonstrating that the majority of participants were categorized as being either at intermediate or high cardiovascular risk according to four commonly used cardiac risk-stratification schemes. The UKPDS risk engine, specifically designed for type 2 diabetic patients, appeared to best predict the occurrence of cardiac events in DIAD participants. In contrast, risk stratification did not predict the results of screening-stress MPI. The study was not powered to determine the effect of screening on outcomes in the subgroup of DIAD participants categorized as having higher risk; such analysis would have required a three- to fourfold larger sample size. However, screening had no apparent benefit on outcomes in the subgroups as defined by these four separate stratification schemes.

This analysis expands upon our previous finding that the overall cardiac event rate in asymptomatic patients with type 2 diabetes is lower in the current era than might be predicted based on historical data. Specifically, it shows that the purportedly higher-risk subgroups actually had lower event rates than were predicted by either the Framingham or UKPDS scores. The average annual risk of participants in the combined intermediate-/high-risk Framingham group was lower (0.6% per year) than predicted (1–2% per year for intermediate risk and >2% per year for high risk). Similarly, in the combined intermediate-/high-risk UKPDS groups, the risk was also lower (0.8% per year) than predicted (intermediate 1.5–3% per year and high risk >3% per year). Thus, even these higher-risk participants had observed cardiac event rates that would traditionally been considered to be low risk. Only a small subgroup of 142 high-risk participants defined by the UKPDS risk engine had an event rate of ~2% per year (Table 1), which might have warranted more aggressive risk-reduction strategies. Although 14 of these high-risk participants had primary cardiac events, it is important to note that the majority of events (17 of 31) occurred in participants who were not categorized as high risk according to the UKPDS engine (Table 1).

The observation that cardiac event rates in the DIAD were lower than predicted by either the Framingham score or the UKPDS risk engine likely reflects the fact that these scoring schemes are based

on clinical data collected in the 1970s to 1990s (13,14). In the intervening years, the awareness of cardiovascular risk in type 2 diabetes has grown (15), and primary cardiac prevention measures have been widely endorsed and implemented (16). In the DIAD study, the majority of participants were aggressively treated with statins, ACE inhibitors, and aspirin (3). One might hypothesize that these interventions prevented cardiac events in the higher-risk DIAD participants. Rather than concluding from this analysis that diabetes does not confer significant cardiac risk, it is more appropriate to emphasize the potential benefit of contemporary medical therapy on the outcomes of these patients.

Our findings have important implications for the utilization of cardiac screening in asymptomatic diabetic patients. The 2009 *Appropriate Use Criteria for Cardiac Radionuclide Imaging*, issued by a consortium of professional societies (12), considered asymptomatic diabetic patients to be a special group in whom screening was appropriate based on their historically high risk for cardiovascular complications, equivalent to that of patients with established CAD (16,17). The results of the present analysis raise questions about the appropriateness of screening asymptomatic patients with diabetes who are treated with contemporary risk factor–modifying therapies. They further suggest that existing guidelines warrant revision.

One interesting observation in the current analysis is that none of the stratification schemes predicted abnormalities on screening-stress MPI. Neither the presence nor severity of MPI abnormalities was greater in the higher-risk patients. The reasons for this finding are uncertain, but this lack of correlation reduces the potential impact of screening strategies based on existing clinical risk stratification. For example, since the UKPDS risk engine predicts outcome but not MPI screening results, there would be patients who might screen negative but still would be at risk for events. In the DIAD study, although moderate/large MPI abnormalities were predictive of cardiac events, numerically more than half of the events occurred in the larger cohort of patients with negative screening (3).

We did not observe an effect of screening on cardiac events in any of the intermediate-/high-risk subgroups. Thus, these results buttress the original conclusion of the DIAD study that screening for inducible ischemia cannot be currently advocated in asymptomatic patients with type 2 diabetes. However, because of the limited number of subjects, we cannot exclude the possibility that a larger study specifically screening a high-risk subgroup might come to a different conclusion in support of screening.

It is important to point out that this post hoc analysis has inherent limitations. Most notably, the DIAD study was designed to include asymptomatic patients with diabetes regardless of additional clinical risk factors (1). Because of the relatively small number of participants at higher cardiovascular risk, the subgroup analyses have insufficient power to make definitive statistical conclusions as to whether screening leads to strategies that improve cardiac outcomes. Furthermore, the DIAD cohort was representative of the North American population mix that received aggressive primary cardiac prevention. Thus, generalization to other countries with different ethnicities and different approaches to diabetes care might not be appropriate.

In conclusion, a substantial portion of the DIAD population would be defined by commonly used risk-stratification schemes as being at intermediate/high cardiovascular risk. Nevertheless, even in these higher-risk participants, the annual cardiac event rates were low and outcome was not affected by routine screening for inducible ischemia. Current guidelines for routine cardiovascular screening in asymptomatic patients with diabetes require reconsideration.

Acknowledgments— This work was performed with the support of the general clinical research centers at Yale University (National Institutes of Health [NIH] M01-RR-00125), the University of Rochester (NIH 5M01-RR-00847), and Tulane University (NIH 6M01-RR-05096). The DIAD study was supported by grants from Bristol-Myers Squibb Medical Imaging (North Billerica, MA) and Astellas Pharma (Deerfield, IL), who also provided technetium-99m Sestamibi (Cardiolite) and adenosine (Adenoscan) for study patients.

No potential conflicts of interest relevant to this article were reported.

The DIAD study is an investigator-initiated study. The industrial sponsors had no role in the design or conduct of the study; in the collection, analysis, or interpretation of data; or in the preparation of the manuscript.

S.B., F.J.T.W., S.E.I., L.H.Y., D.A.C., and L.H.S. had full access to all data of the DIAD study and take responsibility for the integrity of data and accuracy of the data analysis. S.B., F.J.T.W., L.H.Y., D.A.C., and S.E.I. contributed to the study concept and design. The DIAD Study Investigators (see online appendix, available at http://care.diabetesjournals.org/cgi/content/full/dc10-1194/DC1) contributed to the recruitment of participants and acquisition of data. F.J.T.W., S.B., L.H.S., S.E.I., L.H.Y., and D.A.C. contributed to the analysis and interpretation of data. S.B., F.J.T.W., S.E.I., and L.H.Y. contributed to drafting of the manuscript. F.J.T.W., S.B., S.E.I., L.H.Y., L.H.S., J.A.D., and D.A.C. contributed to the critical revision of the manuscript for important intellectual content.

References

1. Wackers FJ, Young LH, Inzucchi SE, Chyun DA, Davey JA, Barrett EJ, Taillefer R, Wittlin SD, Heller GV, Filipchuk N, Engel S, Ratner RE, Iskandrian AE. The Detection of Ischemia in Asymptomatic Diabetics Investigators: detection of silent myocardial ischemia in asymptomatic diabetic subjects: the DIAD study. Diabetes Care 2004;27:1954–1961
2. Wackers FJ, Chyun DA, Young LH, Heller GV, Iskandrian AE, Davey JA, Barrett EJ, Taillefer R, Wittlin SD, Filipchuk N, Ratner RE, Inzucchi SE. Resolution of asymptomatic myocardial ischemia in patients with type 2 diabetes in the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study. Diabetes Care 2007; 30:2892–2898
3. Young LH, Wackers FJ, Chyun DA, Davey JA, Barrett EJ, Taillefer R, Heller GV, Iskandrian AE, Wittlin SD, Filipchuk N, Ratner RE, Inzucchi SE. Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with type 2 diabetes: the DIAD study: a randomized controlled trial. JAMA 2009;301: 1547–1555
4. Fox CS, Coady S, Sorlie PD, D'Agostino RB, Pencina MJ, Vasan RS, Meigs JB, Levy D, Savage PJ. Increasing cardiovascular disease burden due to diabetes mellitus: the Framingham Heart Study. Circulation 2007;115:1544–1550
5. Stratton IM, Adler AI, Neil HA, Matthews DR, Maley SE, Cull CA, Hadden D, Turner RC, Holman RR. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. Br Med J 2000;321:405–412
6. Wilson PWF, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation 1998; 97:1837–1847
7. Stevens R, Kothari V, Adler AI, Stratten IM, Holman RR. UKPDS 56: the UKPDS risk engine: a model for the risk of coronary heart disease in type 2 diabetes. Clin Sci 2001;101:671–679
8. Puel J, Valensi P, Vanzetto G, Lassmann-

Vague V, Monin JL, Moulin P, Ziccarelli CH, Mayaudon H, Ovize M, Bernard S, Van Belle E, Halimi S. Identification of myocardial ischemia in the diabetic patient: joint ALFEDIAM and SFC recommendations. Diabetes Metab 2004;30: 3S3–3S18

9. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart J-C, James WPT, Loria CM, Smith SC Jr. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity Circulation 2009; 120:1640–1645
10. Gami A, Witt B, Howard D, Erwin P, Gami L, Somers V, Montori V. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. J Am Coll Cardiol 2007;49:403–414
11. Saely CH, Aczel S, Marte T, Langer P, Hoefle G, Drexel H. The metabolic syndrome, insulin resistance, and cardiovascular risk in diabetic and nondiabetic patients. J Clin End Metab 2005; 90:5698–5703
12. Hendel RC, Berman DS, Di Carli MF, Heidenreich PA, Henkin RE, Pellikka PA, Pohost GM, Williams KA. ACCF/ASNC/ACR/AHA/ASE/SCCT/SCMR/SNM 2009 appropriate use criteria for cardiac radionuclide imaging: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the American Society of Nuclear Cardiology, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the Society of Cardiovascular Computed Tomography, the Society for Cardiovascular Magnetic Resonance, and the Society of Nuclear Medicine. J Am Coll Cardiol 2009;53: 2201–2229
13. Kannel WB, McGee DL. Diabetes and cardiovascular risk factors: the Framingham Study. Circulation 1979;59:8–13
14. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352: 837–853
15. Grundy SM, Benjamin IJ, Burke GL, Chait A, Eckel RH, Howard BV, Mitch W, Smith SC, Jr, Sowers JR. Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. Circulation 1999;100:1134–1146
16. Grundy SM, Howard B, Smith S Jr, Eckel R, Redberg R, Bonow RO. Prevention Conference VI: diabetes and cardiovascular disease: executive summary: conference proceeding for healthcare professionals from a special writing group of the American Heart Association. Circulation 2002; 105:2231–2239
17. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339:229–234