Resolution of Asymptomatic Myocardial Ischemia in Patients With Type 2 Diabetes in the Detection of Ischemia in Asymptomatic Diabetics (DIAD) Study

FRANS J. TH. WACKERS, MD[1]
DEBORAH A. CHYUN, PHD[2]
LAWRENCE H. YOUNG, MD[1]
GARY V. HELLER, MD[3]
AMI E. ISKANDRIAN, MD[4]
JANICE A. DAVEY, MSN[1]
EUGENE J. BARRETT, MD[5]
RAYMOND TAILLEFER, MD[6]
STEVEN D. WITTLIN, MD[7]
NEIL FILIPCHUK, MD[8]
ROBERT E. RATNER, MD[9]
SILVIO E. INZUCCHI, MD[1]
FOR THE DETECTION OF ISCHEMIA IN ASYMPTOMATIC DIABETICS (DIAD) INVESTIGATORS*

OBJECTIVE — The purpose of this study was to assess whether the prevalence of inducible myocardial ischemia increases over time in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — Participants enrolled in the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study underwent repeat adenosine-stress myocardial perfusion imaging 3 years after initial evaluation. Patients with intervening cardiac events or revascularization and those who were unable or unwilling to repeat stress imaging were excluded.

RESULTS — Of the initial 522 DIAD patients, 358 had repeat stress imaging (DIAD-2), of whom 71 (20%) had ischemia at enrollment (DIAD-1). Of 287 patients with normal DIAD-1 studies, 259 (90%) remained normal in DIAD-2, whereas 28 (10%) developed new ischemia in DIAD-2. Of the 71 patients with abnormal DIAD-1 studies, 56 (79%) demonstrated resolution of ischemia, whereas 15 (21%) remained abnormal. During this 3-year interval, medical treatment was intensified, with more patients using statins, aspirin, and ACE inhibitors than at baseline. Patients with resolution of ischemia had significantly greater increases in these medications than patients who developed new ischemia ($P = 0.04$).

CONCLUSIONS — Thus, the majority of asymptomatic patients with type 2 diabetes demonstrated resolution of ischemia upon repeat stress imaging after 3 years. This resolution was associated with more intensive treatment of cardiovascular risk factors.

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From the [1]Department of Internal Medicine, Section of Cardiovascular Medicine, Yale University School of Medicine, New Haven, Connecticut; the [2]Yale University School of Nursing, New Haven, Connecticut; the [3]Hartford Hospital, Hartford, Connecticut; the [4]University of Alabama, Birmingham, Alabama; the [5]University of Virginia, Charlottesville, Virginia; the [6]University of Montreal, Montreal, Quebec, Canada; the [7]University of Rochester, Rochester, New York; [8]Cardiology Consultants, Calgary, Alberta, Canada; and [9]Medstar Research Institute, Washington, DC.

Address correspondence and reprint requests to Frans J.Th. Wackers, MD, Yale University School of Medicine, Section of Cardiovascular Medicine, 333 Cedar St. Fitkin-3, New Haven, CT 06520. E-mail: frans.wackers@yale.edu.

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*A complete listing of the DIAD Study Investigators is listed in the APPENDIX.

Abbreviations: CAD, coronary artery disease; DIAD, Detection of Ischemia in Asymptomatic Diabetics; ECG, electrocardiogram; SPECT, single photon emission computerized tomography.

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

The Detection of Ischemia in Asymptomatic Diabetics (DIAD) study was designed to assess the prevalence of silent myocardial ischemia and the 5-year cardiac event rate in asymptomatic patients with type 2 diabetes. We have previously reported that inducible ischemia was detected in 22% of patients and could not be predicted by either traditional or novel risk factors for coronary artery disease (CAD) but was associated with cardiac autonomic dysfunction (1). Because type 2 diabetes is a powerful risk factor for CAD progression (2), we hypothesized that the prevalence of ischemia would increase over time. Thus, the DIAD-2 study was designed to reassess the prevalence of inducible ischemia after 3 years.

RESEARCH DESIGN AND METHODS

— Inclusion and exclusion criteria for the DIAD study have been published previously (1). In brief, patients eligible for the DIAD study had type 2 diabetes, a normal resting electrocardiogram (ECG), and no symptoms, signs, or prior history of CAD. A total of 1,123 patients were enrolled from diabetes clinics between July 2000 and August 2002. Of these, 561 patients were randomly assigned to adenosine-stress single photon emission computerized tomography (SPECT) myocardial perfusion imaging with ^{99m}Tc-sestamibi. Of these randomly assigned patients, 522 underwent imaging and 113 (22%) had evidence of inducible ischemia (1). These results will be referred to as DIAD-1. Of importance, ischemia detected in DIAD-1 was treated at the discretion of the patients' primary caregiver.

According to protocol, all patients initially randomly assigned to stress imaging were invited to have repeat imaging after 3 years (with a window of up to 6 months) of their DIAD-1 imaging, unless major intervening cardiac events (death or nonfatal myocardial infarction) or revascularization had occurred. A total of 162 patients did not undergo repeat imaging because of intervening death (n = 10), nonfatal myocardial infarction (n =

2), coronary bypass surgery ($n = 9$), percutaneous coronary intervention ($n = 6$), new severe comorbidities that made stress imaging unfeasible ($n = 10$), patient refusal ($n = 87$), loss to follow-up ($n = 17$), or logistic issues resulting from Hurricane Katrina at our New Orleans site ($n = 21$). Two additional patients had imaging studies that were not interpretable. Thus, a total of 164 patients were not included because they lacked acceptable paired stress imaging studies.

The remaining 358 patients will be referred to as the DIAD-2 cohort. Seventy-one (20%) had ischemia on DIAD-1 stress imaging, similar to the overall 22% prevalence of ischemia observed in 522 DIAD-1 patients.

Vasodilator stress SPECT myocardial perfusion imaging

ECG-gated adenosine-^{99m}Tc-sestamibi SPECT imaging was performed in an manner identical to that for DIAD-1 (1). No attenuation correction was applied to images. Vasodilator stress was performed by intravenous infusion of adenosine (140 $\mu g \cdot kg^{-1} \cdot min^{-1}$) (3) to ensure comparable stress in all patients. Simultaneous low-level treadmill exercise (Bruce stage 1) was performed by 255 (71%) patients during DIAD-2 and by 205 (57%) patients in DIAD-1 (NS). During adenosine infusion, a 12-lead ECG, heart rate, and blood pressure were recorded each minute.

Image analysis

Unprocessed ECG-gated SPECT images were sent to the Yale University Radionuclide Core Laboratory for processing and quantitative analysis using WLCQ software (4). Myocardial perfusion defects were quantified and expressed as a percentage of the left ventricle relative to a normal database. The left ventricular ejection fraction was derived from ECG-gated images (5). To assess reproducibility of quantification in the DIAD population, all abnormal DIAD-2 studies and a random selection of normal DIAD-2 studies, totaling 130 in all, were processed independently on two separate occasions.

The same panel of expert readers (A.E.I., G.V.H., and F.J.W.) that interpreted the DIAD-1 images in 2002 interpreted the DIAD-2 images in 2006. The readers were blinded to the patient's identity and adenosine ECG responses and had no access to the DIAD-1 images or their interpretations. All DIAD-2 images were read by consensus, based on visual analysis and defect quantification. DIAD-2 images were reviewed in random order and mixed with 20 non-DIAD studies, unknown to the panel, to prevent interpretation bias. Image quality was scored subjectively as excellent, good, poor, or not interpretable. Images were interpreted as normal or abnormal. Images with obvious or probable diaphragmatic or breast attenuation artifacts were scored as normal. Myocardial perfusion abnormalities were described as reversible (ischemia), fixed (scar), or mixed (scar plus ischemia). The size of visually identified myocardial perfusion abnormalities was additionally categorized on the basis of computer quantification as small (0 to <5% of left ventricle), moderate (≥5 and <10%), or large (≥10%) (1,4). This computer analysis incorporates both the extent and severity of perfusion abnormalities. Images revealing increased radiotracer lung uptake, transient ischemic left ventricular dilation after stress, and resting left ventricular dysfunction (ejection fraction <45%) without associated perfusion defects were categorized as nonperfusion abnormalities. Flat or downsloping ST-segment depression ≥1 mm at 80 ms after the J-point in two or more leads on the ECG during adenosine infusion was also interpreted as an abnormal test result (6).

In addition to the consensus interpretation by the expert readers, paired DIAD-1 and DIAD-2 images were analyzed based on computerized quantification. The reproducibility of computer quantification of defect size was established previously to be within 3% of the left ventricle (7). Thus, studies with a stress defect size ≤3% were considered normal, and studies with larger stress defects were deemed abnormal. All DIAD-1 and DIAD-2 SPECT images, identified as having attenuation artifacts by the panel readers, were categorized for this quantitative analysis as normal, regardless of computerized defect size. The separate interpretations of DIAD-1 and DIAD-2 studies by the panel were compared with the paired computerized quantitative image analysis.

Analysis

All data were imported into statistical analysis software for analysis (8). Differences between subjects undergoing and not undergoing repeat imaging were assessed using *t* tests and χ^2 analysis. McNemar's test was used to compare changes in medications from baseline to 36 months. Reproducibility of defect quantification was evaluated by Bland-Altman analysis (9).

On the basis of the interpretation of DIAD-1 and DIAD-2 images, patients were categorized as normal-normal, normal-abnormal, abnormal-abnormal, and abnormal-normal. The abnormal-normal category suggested resolution of ischemia, whereas the category normal-abnormal indicated development of new ischemia.

To determine whether changes of medical therapy occurred during the course of the study, the use of preventive cardiac medications (statins, aspirin, and ACE inhibitors) was analyzed. First, the numbers of patients taking these medications at the time of DIAD-1 imaging (baseline) and at each 6-month time point including the time of DIAD-2 imaging (36 months) were determined, using mixed modeling procedures. Second, the mean duration of exposure to statins, aspirin, or ACE inhibitors, alone and in combination, during the 3-year interval was calculated and assessed with ANOVA using linear contrasts to determine differences between those with resolution of ischemia and new ischemia. Third, the total months of exposure to drugs were summed, e.g., a patient taking a statin, aspirin, and an ACE inhibitor for 36 months would have a total exposure of 108 drug-months. Finally, factors associated with the development of new ischemia in the 287 patients with normal imaging at baseline were assessed with bivariate measures followed by multivariate relative risk regression.

RESULTS — Table 1 shows baseline demographics, characteristics, and original myocardial perfusion imaging findings for the 522 DIAD patients who underwent initial imaging as well as for the 358 patients with and 164 patients without repeat imaging. Patients who had repeat imaging were less often African American; had lower A1C; had less peripheral neuropathy, erectile dysfunction, and diabetic retinopathy; and were less likely to be taking oral hypoglycemic medication, particularly sulfonylureas. However, the prevalence of ischemia at initial imaging was similar in the DIAD-2 cohort (20%) and the total DIAD-1 cohort of 522 patients (22%). In addition, the prevalence of ischemia at initial imaging in the 164 patients who did not have repeat imaging was similar (26%) to that in

Table 1—*Baseline characteristics of the original DIAD-1 cohort and patients with (DIAD-2) and without repeat adenosine ^{99m}Tc-sestamibi SPECT imaging*

	Original adenosine SPECT (DIAD-1)	Repeat adenosine SPECT (DIAD-2)	No repeat adenosine SPECT	*P*
n	522	358	164	
Demographics				
Age (years)	60.7 ± 6.8	60.6 ± 6.7	60.9 ± 6.9	0.67
Sex				
Male	277 (53)	196 (56)	81 (49)	
Female	245 (47)	162 (44)	83 (51)	0.25
Race				
White	419 (80)	305 (85)	114 (70)	
Black	79 (15)	36 (10)	43 (26)	
Other	24 (5)	17 (5)	7 (4)	<0.0001
BMI (kg/m^2)	31.1 ± 6.6	31.0 ± 6.4	31.1 ± 6.9	0.99
Diabetes duration (years)	8.2 ± 7.1	8.0 ± 7.0	8.6 ± 7.3	0.36
A1C (%)	7.1 ± 1.5	7.0 ± 1.4	7.4 ± 1.7	0.005
Treatment				
Insulin	52 (10)	35 (10)	17 (10)	
Insulin + oral agent	67 (12)	46 (13)	21 (13)	
Diet only	77 (15)	64 (18)	13 (8)	
Oral agent	326 (63)	213 (59)	113 (69)	0.04
Metformin	286 (55)	190 (53)	96 (59)	0.24
Sulfonylurea	207 (40)	126 (35)	81 (49)	0.002
Thiazolidinedione	106 (20)	75 (21)	31 (19)	0.59
Peripheral neuropathy symptoms/signs				
Numbness	163 (31)	101 (28)	62 (38)	0.03
Pain	51 (10)	32 (9)	19 (12)	0.34
Tingling	141 (27)	92 (26)	49 (30)	0.32
Absent vibration	145 (28)	90 (25)	55 (34)	0.05
Absent sensation	59 (11)	36 (10)	23 (14)	0.18
Absent reflex	161 (31)	116 (32)	45 (27)	0.25
Autonomic neuropathy symptoms				
Bloating	85 (16)	55 (15)	30 (18)	0.40
Dizziness	89 (17)	54 (15)	35 (21)	0.08
Erectile dysfunction	134 (48)	87 (44)	81 (58)	0.03
Abnormal Valsalva ratio	99 (19)	60 (17)	39 (24)	0.06
Peripheral vascular disease	47 (9)	29 (8)	18 (11)	0.29
Smoking				
Never/past	471 (90)	327 (91)	144 (88)	
Current	51 (10)	31 (9)	20 (12)	0.33
Lipid treatment	242 (47)	169 (47)	73 (45)	0.57
LDL (mg/dl)	113 ± 32	114 ± 31	111 ± 34	0.36
Triglycerides (mg/dl)	170 ± 118	169 ± 115	173 ± 125	0.74
Hypertension treatment	291 (56)	193 (54)	98 (60)	0.21
Systolic blood pressure (mmHg)	131 ± 17	132 ± 17	131 ± 17	0.57
Diastolic blood pressure (mmHg)	79 ± 8	79 ± 9	78 ± 8	0.16
Aspirin use	229 (44)	151 (42)	78 (48)	0.25
Family history CAD	110 (21)	70 (20)	40 (24)	0.21
Retinopathy	73 (14)	41 (11)	32 (20)	<0.0001
Albuminuria	112 (22)	70 (20)	42 (26)	0.10
Adenosine ^{99m}Tc SPECT imaging results (DIAD-1)				
Normal	409 (78)	287 (80)	122 (74)	0.12
Abnormal	113 (22)	71 (20)	42 (26)	
Perfusion abnormalities	83 (16)	54 (15)	29 (17)	
Small defects	50 (10)	38 (11)	12 (7)	
Moderate/large defects	33 (6)	16 (4)	17 (10)	
Nonperfusion abnormalities	30 (6)	17 (5)	13 (9)	
Abnormal ECG	21 (4)	11 (3)	10 (7)	
Transient ischemic dilation	4 (1)	4 (1)	0 (0)	
Left ventricular dysfunction	5 (1)	2 (1)	3 (2)	

Data are means ± SD or *n* (%).

Table 2—*Results of repeat adenosine ^{99m}Tc-sestamibi SPECT imaging*

	DIAD-2 adenosine SPECT	
	Blinded panel read	Computer quantification
n	358	358
Normal	315 (88)	321 (90)
Abnormal	43 (12)	36 (10)
Regional perfusion abnormalities	24 (7)*	18 (5)
Small	11 (3)†	4 (1)
Moderate/large	13 (4)‡	14 (4)
Nonperfusion abnormalities	19 (5)§	
Positive ECG	15 (4)‖	
Transient dilation	2 (0.5)¶	
Left ventricular dysfunction	2 (0.5)**	
DIAD-1 vs. DIAD-2 categorization		
Normal-normal	259 (72)	274 (77)
Normal-abnormal	28 (8)	25 (7)
Abnormal-abnormal	15 (4)	12 (3)
Abnormal-normal	56 (16)	47 (13)

Data are *n* (%). New abnormalities in DIAD-2 analysis: *18; †9; ‡9; §12; ‖9; ¶2; **1.

the 358 patients with repeat imaging (20%, $P = 0.12$).

DIAD-2 myocardial perfusion imaging

DIAD-2 image quality was deemed good to excellent in 319 (89%) and poor in 39 (11%) patients. The expert readers identified seven attenuation artifacts that they interpreted as normal, whereas during DIAD-1 imaging, 16 artifacts were identified in the same cohort of patients. Table 2 shows the results of the interpretation of DIAD-2 images by the panel of expert readers as well as by computerized quantitative analysis. The readers interpreted 43 (12%) of 358 DIAD-2 studies as abnormal, which was significantly less ($P = 0.008$) than the prevalence of ischemia in DIAD-1 studies, i.e., 71 of 358 (20%).

Of the 43 abnormal DIAD-2 SPECT studies, 24 demonstrated regional myocardial perfusion abnormalities and 19 were nonperfusion abnormalities. Among the 43 patients with abnormal results, 15 were also abnormal in DIAD-1 studies, whereas the other 28 were new abnormalities. Figure 1 shows the changes in stress-inducible myocardial ischemia over time. Table 2 also shows categorizations of paired imaging findings. Of 287 normal studies in DIAD-1, 259 (90%) remained normal in DIAD-2, whereas 28 studies (10%) showed evidence of new inducible myocardial ischemia. Of the 71 abnormal studies in DIAD-1, 15 (21%) remained abnormal, whereas 56 studies (79%) became normal and had apparent resolution of inducible ischemia. Of the 71 abnormal DIAD-1 studies, 54 demonstrated regional perfusion abnormalities, of which 43 (80%) normalized in DIAD-2. Resolution occurred in 11 of 16 studies (69%) with moderate/large defects and in 32 of 38 studies (84%) with small defects. Of 17 nonperfusion abnormalities (mainly ischemic ECG ST segment changes during adenosine infusion) in DIAD-1, 13 (76%) resolved.

Analysis based on computer quantification (Table 2) showed results and categorization that were very similar to those by the panel. Bland-Altman analysis of 43 abnormal and 87 normal DIAD-2 studies showed excellent reproducibility (0.98, $y = 0.97 \times 0.05$) of computer quantification over the entire range of perfusion abnormalities. The mean difference ± SD was −0.02 ± 0.52% of the left ventricle, respectively. The 95% limit of agreement for defect size was ±1% (2 SD).

Medical therapy and inducible ischemia

Over the 3 years after initial stress imaging, there was a significant increase in the use of cardiac medication by the DIAD patients. At the time of DIAD-1 imaging, only 151 (42%) patients were taking aspirin, 136 (38%) were taking statins, and 120 (34%) were taking ACE inhibitors. Thirty-six months later, at the time of DIAD-2 imaging, the use of these medications increased to 248 (69%, $P < 0.0001$

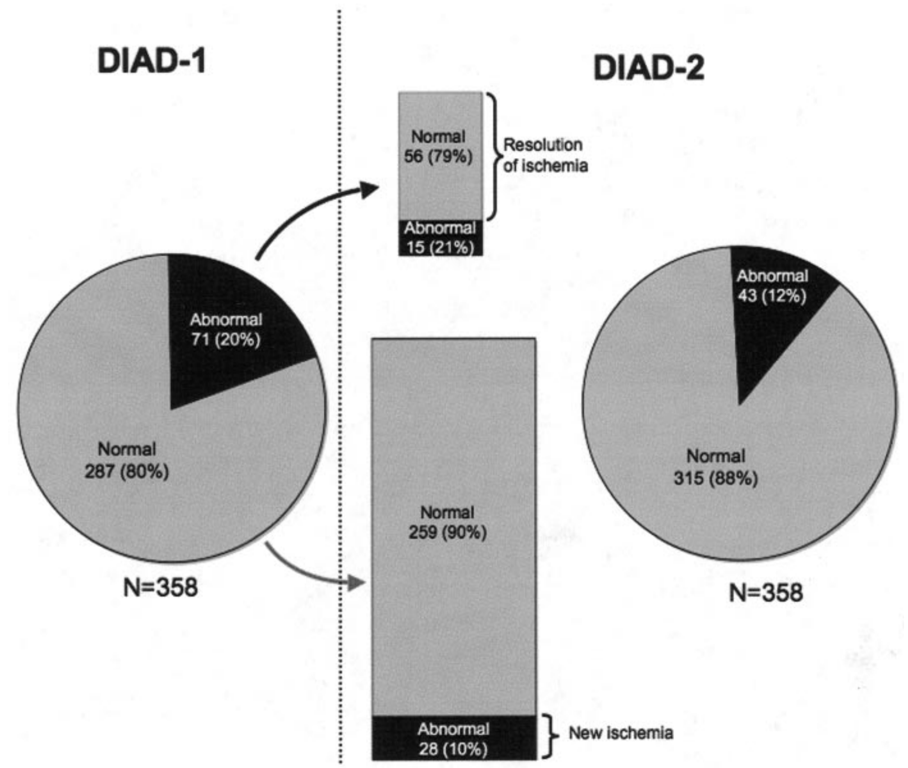

Figure 1—*Changes in stress-induced myocardial ischemia in the DIAD study over time. At enrollment into the study (DIAD-1), the prevalence of ischemia in 358 patients was 20%. At repeat stress imaging 3 years later (DIAD-2), only 12% of patients had inducible myocardial ischemia. This result was due to resolution of ischemia in 79% of 71 patients who initially had abnormal studies, whereas 10% of 287 patients with initially normal studies developed new ischemia.*

compared with baseline), 212 (59%, $P < 0.0001$), and 149 (42%, $P = 0.002$) patients, respectively.

Medication use was analyzed according to the results of repeat imaging studies. Aspirin use increased in all patients; however, significantly more patients with resolution of ischemia (abnormal-normal) were taking aspirin during follow-up ($P = 0.04$). Statin use also increased over time, but no statistical differences were apparent between groups. The use of ACE inhibitors remained about the same over time, with patients categorized as abnormal-abnormal having consistently low usage. Combined time of exposure to cardiac medications (aspirin, statins, and ACE inhibitors) over the intervening 36 months was greater in patients with resolution of ischemia than in those with new ischemia (59 ± 31 vs. 45 ± 28 total drug months, $P = 0.04$).

Patients with new ischemia had a significantly higher ($P = 0.005$) incidence of peripheral vascular disease than those with resolution of ischemia, but otherwise demographic and clinical variables, including conventional risk factors, were similar. In multivariate analyses, peripheral vascular disease (relative risk 3.4 [95% CI 1.45–8.11]; $P = 0.005$) and elevated LDL cholesterol levels (2.37 [0.82–6.9]; $P = 0.11$) were associated with risk of new ischemia.

CONCLUSIONS — This study is the first to evaluate changes in inducible myocardial ischemia over time in patients with type 2 diabetes without symptomatic or known CAD. The most striking and unexpected finding of this study is that inducible ischemia resolved in 79% of patients who had perfusion abnormalities at the start of the DIAD study and who underwent repeat imaging 3 years later. This result was unanticipated because type 2 diabetes is an important aggravating risk factor for CAD and CAD progression (2). Although new ischemia occurred as well, it developed in a relatively small proportion (10%) of patients.

The observed resolution of ischemia on SPECT imaging was associated with intensification of treatment with cardiac medications. At the time of repeat imaging, a significantly greater number of patients were taking statins, aspirin, and ACE inhibitors than at the beginning of the DIAD study. More aggressive treatment of cardiac risk factors might have been driven by increasingly stringent practice guidelines that had an impact on the care of patients with type 2 diabetes (10). However, the DIAD study was not designed as a treatment trial, and the association of resolution of ischemia and intensification of medical treatment does not prove a causal relationship between the two. Although this observation should be interpreted with caution, it is of interest in view of previous studies that have shown the beneficial effect of aggressive lipid-lowering treatment on myocardial perfusion imaging abnormalities. Schwartz et al. (11) showed that myocardial perfusion abnormalities improved in 48% of dyslipidemic patients after 6 months of treatment with pravastatin. Similarly, Sdringola et al. (12) observed marked decreases in the size and severity of myocardial perfusion abnormalities, as well as in cardiac events after intensive lifestyle changes and pharmacological antilipid treatment (12).

Myocardial ischemia in patients with diabetes

Stress-induced myocardial perfusion defects in patients with diabetes may be caused by obstructive epicardial CAD, microvascular disease, or endothelial dysfunction. In DIAD-1, most myocardial perfusion abnormalities were relatively small, and only 40% were moderate/large in size (1). It is therefore conceivable that microvascular disease was partly responsible for the previously observed abnormalities. Statins have pleiotropic effects beyond their lipid-lowering effects and may improve endothelial dysfunction and stabilize atherosclerotic plaques through anti-inflammatory actions (13,14). Similarly, aspirin and ACE inhibitors may also have direct beneficial effects on vascular remodeling (15–17). Although small myocardial perfusion abnormalities might also be due to microvascular disease, endothelial dysfunction, or in some instances unrecognized imaging artifacts, moderate and large perfusion abnormalities are most often caused by obstructive CAD. They are of great clinical concern because they are associated with a high incidence of future cardiac events and often trigger invasive evaluation (18). Thus, the observed improvement of moderate or large perfusion abnormalities is a significant finding in this study. Moreover, ECG changes during adenosine infusion, another manifestation of ischemia with prognostic significance in symptomatic patients with CAD (6,19), resolved in some patients as well. Although these findings are consistent with the conclusion that inducible ischemia improved over time, they do not address whether there was, in fact, regression of coronary atherosclerosis or improvement in collateral flow or endothelial dysfunction. Serial coronary angiography or intracoronary ultrasonography would be needed to make this assessment and were not required elements of the DIAD protocol.

Limitations

Not all DIAD-1 patients randomly assigned to SPECT imaging underwent repeat imaging. Patients who had cardiac events or coronary revascularizations were excluded from DIAD-2 imaging. There were also additional patients who did not have repeat imaging for a variety of reasons. Although the patients without repeat imaging had a similar prevalence of ischemia at baseline, they had a higher cardiovascular risk from a clinical perspective. Because of this selection bias, the overall prevalence of progression of ischemia may have been underestimated in our study. Nonetheless, the current observations are of clinical interest in suggesting that ischemia can be improved by optimizing medical therapy in a substantial number of patients with type 2 diabetes.

Potential limitations of stress myocardial perfusion imaging should also be considered in interpreting our findings. Exercise myocardial perfusion imaging with SPECT is generally highly reproducible in patients with stable CAD (20,21), but variations in the amount of exercise can have an impact on the results. However, one would expect a high level of reproducibility in DIAD, because all patients underwent pharmacological stress with adenosine and the numbers of patients performing additional low-level exercise were similar in DIAD-2 and in DIAD-1. Inter- and intraobserver variability in the processing or interpretation of SPECT images might also have an impact on the reproducibility of findings (22). The DIAD-2 images were interpreted separately 3–4 years after the DIAD-1 images, raising the possibility that the interpretative approach of the readers might have changed over time. Paired computer analysis of DIAD-1 and DIAD-2 studies (Table 2) showed excellent concordance with the expert panel interpretation and thus provided substantial support for the lower prevalence of inducible ischemia on follow-up studies.

Clinical implications

Unexpected resolution of ischemia occurred in the majority of patients with type 2 diabetes without symptomatic CAD, potentially because of more aggressive medical treatment of cardiovascular risk factors. This analysis highlights the importance of studying whether a strategy of screening for inducible ischemia has an impact on clinical outcomes in such patients. It is unclear whether the observed resolution of ischemia and associated intensification of medical treatment were causally related to initial screening. The ongoing 5-year follow-up of all 1,123 DIAD patients will help to address this issue. The results will be of particular interest in view of recent randomized trials, which showed that optimized medical therapy resulted in outcomes similar to those with coronary revascularization in stable CAD (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation [COURAGE]) and after acute myocardial infarction (Adenosine Sestamibi Post Infarction Evaluation [INSPIRE]) (23,24). The ongoing Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial, in which asymptomatic or mildly symptomatic patients with diabetes were randomly assigned to intensive medical treatment with or without coronary revascularization, will also provide guidance in terms of how best to manage these patients (25). It is hoped that these clinical studies will provide data that will help to formulate evidence-based guidelines for the evaluation and management of the large number of patients with type 2 diabetes and asymptomatic CAD.

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APPENDIX

DIAD Study Investigators

Principal Investigators: Frans J. Th. Wackers, MD; Lawrence H. Young, MD; Silvio E. Inzucchi, MD (Yale University School of Medicine, New Haven, CT); Deborah A. Chyun, RN, MSN, PhD (Yale University School of Nursing, New Haven CT).

Study Coordinator: Janice A. Davey, APRN, MSN (Yale University School of Medicine, New Haven, CT).

Clinical Centers: University of Montreal: Raymond Taillefer, MD, Sylvain Prévost, MD, Carole Benjamin, CNMT, and Andre Gagnon, CNMT; MedStar Research Institute: Robert Ratner, MD, Maureen Passaro, MD, Evelyn Robinson, RN, and Amy Smith, BA; Hartford Hospital: Gary Heller, MD, Neil Gray, MD, and Deborah Katten, RN, MPH; Tulane University: Vivian Fonseca, MD, Richard Campeau, MD, Rhonda Fontenot, RN, and Sunil Asnani, MD; University of Alabama: Ami Iskandrian, MD, Fernando Ovalle, MD, Mary Beth Schaaf, RN, and Misty Collins, RN; University of Virginia: Eugene Barrett, MD, George Beller, MD, Wendie Price, RN, and Denny Watson, PhD; Soundview Research Associates: Samuel Engel, MD, Mindy Sotsky, MD, and Jean Ritacco, RN; University of Rochester: Steven Wittlin, MD, Ronald Schwartz, MD, and Mary Kelly, RN; University of North Carolina: Jean Dostou, MD, John Buse, MD, Joe Largay, PA-C, Michele Duclos, MPH, and Cristina Metz, BS; Midwest Cardiology Research Foundation: Dennis A. Calnon, MD, Connie Zimmerman, ARRT; Maine Cardiology Associates: Mylan C. Cohen, MD, MPH; Cardiology Consultants: Neil Filipchuk, MD, and Marie Small, RN; Kansas City Cardiology: Timothy Blackburn, MD, Eric Hockstad, MD, Terry Plesser, RN, and Denetta Nelson, MA.

Yale University Radionuclide Core Laboratory and Data Coordinating Center: Donna Natale, CNMT, and Roberta O'Brien.

Advisory Board and Data Safety and Monitoring Board: Barry L. Zaret, MD, Robert S. Sherwin, MD, and Ralph I. Horwitz, MD.

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