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Cardiac Outcomes After Screening for Asymptomatic Coronary Artery Disease in Patients With Type 2 Diabetes:

The DIAD Study: A Randomized Controlled Trial

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Abstract

Context—Coronary artery disease (CAD) is the major cause of mortality and morbidity in patients with type 2 diabetes. But the utility of screening patients with type 2 diabetes for asymptomatic CAD is controversial.

Objective—To assess whether routine screening for CAD identifies patients with type 2 diabetes as being at high cardiac risk and whether it affects their cardiac outcomes.

Design, Setting, and Patients—The Detection of Ischemia in Asymptomatic Diabetics (DIAD) study is a randomized controlled trial in which 1123 participants with type 2 diabetes and no symptoms of CAD were randomly assigned to be screened with adenosine-stress radionuclide myocardial perfusion imaging (MPI) or not to be screened. Participants were recruited from

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diabetes clinics and practices and prospectively followed up from August 2000 to September 2007.

Main Outcome Measure—Cardiac death or nonfatal myocardial infarction (MI).

Results—The cumulative cardiac event rate was 2.9% over a mean (SD) follow-up of 4.8 (0.9) years for an average of 0.6% per year. Seven nonfatal MIs and 8 cardiac deaths (2.7%) occurred among the screened group and 10 nonfatal MIs and 7 cardiac deaths (3.0%) among the not-screened group (hazard ratio [HR], 0.88; 95% confidence interval [CI], 0.44–1.88; *P*=.73). Of those in the screened group, 409 participants with normal results and 50 with small MPI defects had lower event rates than the 33 with moderate or large MPI defects; 0.4% per year vs 2.4% per year (HR, 6.3; 95% CI, 1.9–20.1; *P*=.001). Nevertheless, the positive predictive value of having moderate or large MPI defects was only 12%. The overall rate of coronary revascularization was low in both groups: 31 (5.5%) in the screened group and 44 (7.8%) in the unscreened group (HR, 0.71; 95% CI, 0.45–1.1; *P*=.14). During the course of study there was a significant and equivalent increase in primary medical prevention in both groups.

Conclusion—In this contemporary study population of patients with diabetes, the cardiac event rates were low and were not significantly reduced by MPI screening for myocardial ischemia over 4.8 years.

Almost 200 million people worldwide have type 2 diabetes.[1] Coronary artery disease (CAD) is a major health concern and the leading cause of death in individuals with type 2 diabetes.[2] CAD is often asymptomatic in these patients until the onset of myocardial infarction or sudden cardiac death.[3] Type 2 diabetes is also widely recognized as a CAD risk equivalent.[4]

The current standard of care for type 2 diabetes emphasizes the reduction of cardiovascular risk factors.[2,5] However, there has also been substantial interest in the early detection of asymptomatic CAD by screening of patients with type 2 diabetes.[6] Recent studies have shown that CAD can be detected noninvasively in a significant number of these individuals.[7–9] Inducible ischemia[7,10,11] and coronary artery calcium[9,11] each have been shown to be associated with worse cardiac outcomes. However, the potential of routine screening to alter treatment and to prevent cardiac events in persons without clinically apparent CAD is largely unknown.[6,12,13] Thus, although endorsed by some professional organizations,[6,14] screening of patients with type 2 diabetes and no symptoms of CAD remains highly controversial in the absence of prospective outcome studies supporting its utility.[6,12,13,15,16]

The Detection of Ischemia in Asymptomatic Diabetics (DIAD) study is a randomized controlled trial in which participants were randomly assigned either to be systematically screened with stress myocardial perfusion imaging (MPI) or not to be screened.[8] The aim of DIAD was to test the hypothesis that systematic screening would identify higher-risk individuals and beneficially affect their risk of myocardial infarction or cardiac death.

METHODS

The DIAD study prospectively assessed the prevalence, predictors, and outcomes of inducible ischemia in patients with type 2 diabetes without symptomatic or previously recognized CAD.[8] Inclusion criteria were that onset of type 2 diabetes occurred at age 30 years or older with no history of ketoacidosis and that patients were between the ages of 50 and 75 years at enrollment. Exclusion criteria included (1) angina pectoris or chest discomfort evaluated with a positive Rose questionnaire[8]; (2) stress test or coronary angiography within the prior 3 years; (3) history of myocardial infarction, heart failure, or coronary revascularization; (4) abnormal rest electrocardiographic results, ie, pathological Q waves, ischemic (≥1 mm depression) ST segments, deep negative T waves, or complete left bundle-branch block; (5) any clinical indication for stress testing; (6) active bronchospasm

precluding the use of adenosine; and (7) limited life expectancy due to cancer or end-stage renal or liver disease.[8]

Of 2764 patients screened, 1034 were excluded because they failed to satisfy the clinical inclusion criteria and 30 were excluded because of significant Q-waves on electrocardiogram (Figure 1). Of the 1700 eligible participants, 1123 (66%) consented to participate and were enrolled at 14 centers in the United States and Canada between July 2000 and August 2002.[8] The DIAD protocol was approved by the institutional review boards at each participating center. The study design and procedures were explained by a member of the local research team to potential participants. Those who agreed to participate subsequently provided written informed consent.

Medical history and demographics were obtained. Ethnic/racial origin was recorded as stated by the participants to confirm equal distribution in the randomized groups and to provide insight into the generalizability of the results. All participants had a physical examination, including assessment of diabetic neuropathy and cardiac autonomic dysfunction,[8,17] and underwent blood and urine laboratory testing.

After baseline testing, the participants were assigned a sequential identification number at each site and a corresponding sealed envelope was opened. Random permuted blocks (block size 6) were used to assign the randomization sequence 1:1 at each site.[8]

In total, 561 participants were randomized to screening with adenosine Tc-99m sestamibi MPI and 562 to no screening.[8]

Evaluation and Follow-up

Nuclear cardiologists at each site interpreted the stress MPI studies and communicated the results to the participants and their personal physicians.[8] Participants also received copies of their laboratory results, including hemoglobin A_{1c} and lipid levels. The screening MPI tests were also interpreted by an independent expert panel, with computer quantification of perfusion abnormalities as percent of the left ventricle at the core laboratory.[8] Nonperfusion abnormalities, including ischemic electrocardiographic changes, transient left ventricle dilation, or baseline left ventricle dysfunction, were also assessed.[8] The quality of images was deemed excellent or good in 509 (97%), poor in 13 (2%), and not interpretable in 1 (<1%). The panel's interpretations were used in analyzing risk for cardiac events but were not sent to the participants or their providers.

The DIAD study was not designed as a treatment trial and did not mandate coronary angiography or any specific treatment plan for patients with abnormal screening tests. The protocol design therefore reflects routine clinical practice, in which management decisions are made according to the best judgment of patients' medical providers. Thus, the DIAD study also assessed the value and effect of CAD screening on the overall medical management of participants.

Participants were asked about their health status, medications, intervening cardiac events, additional stress testing, coronary angiography, and revascularization at 6-month intervals.[8] Cardiac events were independently adjudicated by a committee, which was blinded to the randomization status.

Cardiac Events

The primary end point consisted of the composite of nonfatal myocardial infarction and cardiac death. Cardiac death included fatal myocardial infarction (within 30 days); death due

to heart failure or arrhythmia; or sudden cardiac death. Secondary end points included unstable angina, heart failure, stroke, and coronary revascularization.

Statistical Analysis

All analyses were conducted with SAS statistical software version 9.1 (SAS Institute Inc, Cary, North Carolina). Bivariate associations, according to losses to follow-up, randomization status, and factors associated with cardiac events, were first tested using *t* tests, Wilcoxon rank sum, χ^2, and Fisher exact analyses. All analyses were 2-sided. Changes in medications were assessed using the McNemar test and logistic regression. Actuarial survival analysis was used to assess cardiac events according to randomization status and then in the screening group with stratification by screening results. Cox proportional hazards regression was used to determine hazard ratios (HRs) comparing (1) events in screened vs non-screened participants; (2) events in participants with normal MPI vs non-perfusion, small or moderate or large perfusion defects, as well as those who were randomized to screening but who did not undergo MPI or who had an uninterpretable result (n=39); and (3) participants with and without a primary event in unadjusted and age- and sex-adjusted models.

The study was designed with an anticipated 5% to 10% cardiac event rate over a projected 5-year follow-up period. We estimated that 500 participants would be required in each group to have a power of 80% to detect a 20% difference between the 2 groups with a 2-sided α of .05.

RESULTS

Of the 561 participants randomized to screening, 522 underwent stress MPI and 39 did not. Of the latter, 22 refused, 16 were unable to schedule their MPI within the required 3-month time window, and the screening MPI of 1 participant was poor quality and not interpretable (Figure 1). These 39 participants without MPI were included in the analysis on an intention-to-screen basis. The total cohort of 1123 individuals was used in the analysis, with participants censored at the time of last follow-up (Figure 1). Table 1 shows the baseline characteristics of the participants in the screening and no-screening groups. The mean (SD) follow-up was 4.8 (0.9) years and median was 5 years. Follow-up was 97% complete at 3.5 years. Eighty-one participants, evenly distributed between groups, did not have complete follow-up visits, Notably, the prevalence of ischemia did not differ in screened participants with complete or incomplete follow-up. The last follow-up data were collected in September 2007.

Primary Outcomes

Table 2 and Figure 2A show cardiac events according to randomization status. Overall during the follow-up period, there were 32 cardiac events: 17 participants developed nonfatal MIs and 15 had cardiac deaths, of which 13 were sudden and unexpected. There were also 18 noncardiac deaths. The overall cumulative 5-year cardiac event rate was 2.9% and averaged 0.6% per year. When analyzed according to randomization, there were 15 events (7 nonfatal MIs; 8 cardiac deaths) in the screening group vs 17 events (10 nonfatal MIs; 7 cardiac deaths) in the no-screening group (HR, 0.88; 95% confidence interval [CI], 0.44–1.8; log-rank 0.12; *P*=.73).

Table 3 and Figure 2B show cardiac events in the screening group, which varied significantly according to the results of stress MPI (log-rank, 14.93; *P*=.005). Four hundred nine participants (78%) had normal test results and 50 (10%) had small MPI defects. Only 8 (2%) of 409 participants with normal MPI results and 1 (2%) of 50 participants with small

MPI defects had hard cardiac events, in contrast to 4 (12.1%) of 33 with moderate or large MPI defects (HR, 6.3; 95 CI, 1.9–20.1; *P*=.001). In addition, 2 (6.7%) of 30 participants with nonperfusion abnormalities had cardiac events (HR, 3.5; 95% CI, 0.8–16.7; *P*=.08). The mean (SD) MPI defect size was 4.1% (6.6%) of left ventricle in participants with cardiac events and 1.4% (2.2%) of left ventricle in participants without events (*P*=.12). The negative predictive value of having a normal MPI was 98% (401 of 409). The positive predictive value was only 6% (7 of 113) of patients for any MPI abnormality and 12% (4 of 33) of patients for moderate or large MPI defects.

Secondary Outcomes

Seven participants developed unstable angina, and 14 developed heart failure with a similar incidence in the 2 groups (Table 2). There were 15 strokes, with a trend toward more in the screened participants, but none of the strokes resulted from coronary angiography or revascularization.

Coronary Angiography and Revascularization

Coronary angiography was performed within 120 days after screening in 25 (4.4%)of561participants(Table 4), including in 5 (15%) of 33 with moderate or large defects. In comparison, only 3 (0.5%) of 562 participants in the no-screening group underwent angiography within 120 days after randomization (*P*<.001; Table 4). Nine of the 25 screened participants had significant CAD that was treated with revascularization (6 coronary artery bypass surgery and 3 percutaneous transluminal coronary angioplasty) vs 2 of 3 participants in the no-screening group. There were no procedural complications, but 1 of those screened experienced sudden cardiac death a year after undergoing CABG. Among the 28 participants with moderate or large defects on screening who did not undergo early angiography, only 3 had cardiac events over the ensuing 5 years, although an additional 6 ultimately underwent angiography. One of these latter participants had 3-vessel CAD, which was not amenable to surgery, and died a year later; 3 others had percutaneous transluminal coronary angioplasty.

Additional participants underwent coronary angiography and revascularization during the 5-year follow-up period because of unstable angina, chest pain, or perceived high risk. An additional 55 screened participants (10%) and 63 non-screened participants (11%) underwent angiography more than 120 days after randomization (Table 4). Also, 22 screened participants (4%) and 42 nonscreened participants(7%)underwent coronary revascularization more than120 days after randomization (Table 4).

Additional Testing

Participants in both groups were referred clinically for nonprotocol stress tests during follow-up, but this occurred more frequently in the unscreened group (*P*<.001; Table 4). Approximately one-fourth of tests were abnormal in both groups. By study design, all screened participants who had not experienced cardiac events or revascularization were also invited to return for stress MPI 3 years after entry; repeat tests were performed for 358 participants and overall showed significant improvement in MPI defects as previously reported.[18]

Medical Treatment

The use of statins, angiotensin-converting enzyme inhibitors, antihypertensive and antihyperglycemic medications, and aspirin for primary medical prevention increased significantly from baseline to 5 years later in the study (Table 4). However, the increased use of these medications was not different in screened and not-screened patients.

Predictors of Cardiac Events

Clinical factors associated with primary events are shown in Table 5. In unadjusted bivariate comparisons, as well as with adjustment for age and sex, we found that male sex, diabetes duration, microalbuminuria/proteinuria, serum creatinine, symptoms of peripheral neuropathy (numbness, pain), diminished peripheral sensation, cardiacautonomic dysfunction, peripheral vascular disease, elevated low-density lipoprotein levels, and family history of premature CAD were associated with development of a primary event. The low number of events precluded multivariate assessment; however, further exploratory analyses with combinations of these factors, suggested an independent role of male sex, serum creatinine, cardiac autonomic dysfunction, peripheral vascular disease, and low-density lipoprotein levels.

COMMENT

The DIAD study is the first large-scale prospective study to randomize type 2 diabetes patients with no symptoms of CAD to screening for inducible ischemia or no-screening and follow them up for clinical outcomes. Overall, cardiac event rates in this population were much lower than anticipated. Within this population of patients with asymptomatic type 2 diabetes, use of MPI screening had no discernable effect on subsequent cardiac events. The results also show that significant MPI abnormalities on screening were associated with a greater incidence of cardiac events, although the positive predictive value of such abnormalities was low and events also occurred in participants with normal screening tests.

The strategy of routine screening for CAD in patients with type 2 diabetes is based on the premise that testing could accurately identify a significant number of individuals at particularly high risk and lead to various interventions that prevent cardiac events. However, the results of the DIAD study would appear to refute this notion. Although type 2 diabetes is considered to be a CAD equivalent,[4] participants had a low cardiac event rate (average, 0.6% per year) and the identification of participants with abnormal screening results did not serve to eliminate their risk over 5 years of follow-up.

The overall cardiac event rate is 3- to 4-fold lower than those previously reported in retrospective analyses of patients with diabetes who had no symptoms of CAD but were referred to nuclear cardiologylaboratories.[7,19] However, such referred patients had a much higher incidence of peripheral arterial disease, renal insufficiency, and many were referred for preoperative evaluation.[7,19] Referred patients also have a 2- to 3-fold higher incidence of myocardial perfusion abnormalities than those in the DIAD study. These studies highlight the observation that patients referred for specific cardiac testing have a much higher risk than the overall population of patients with type 2 diabetes whose risk is better reflected by the DIAD study group. The event rate in DIAD is similar to that in prior research studies that screened for asymptomatic ischemia in type 2 diabetes.[20–22] For instance in the Milan study,[22] the overall event rates are quite comparable, probably reflecting the offsetting factors of healthier patients capable of exercise testing and the more intensive medical therapy in the DIAD study.

Comparison of the cardiac event rates (0.6% per year) with those reported recently in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial for the subgroup of patients with type 2 diabetes without previous cardiac events (1.4% per year) is also informative.[23] When one accounts for the inclusion of noncardiac vascular events in the ACCORD primary outcome definition and the selection of older patients with specific additional risk factors for cardiovascular disease, the event rates in ACCORD would appear favorable and compatible with those in DIAD.

The favorable cardiac outcomes among participants in the DIAD study likely reflect, in part, the impact of aggressive, guideline-driven management of cardiac risk factors, which is known to improve outcomes in patients with type 2 diabetes.[24] As such, the study reflects contemporary medical practice in which most participants had hemoglobin A_{1c} and lipid levels that were at or near the targeted range. Admittedly, a healthier cohort might have also been selected because prior stress testing was an exclusion criterion. Prior to study start, screening for CAD in patients with type 2 diabetes with 2 or more cardiac risk factors had been endorsed by an expert panel of the American Diabetes Association.[14] Although these recommendations were not evidence-based,[5,25] higher-risk individuals may have already been screened in clinical practice, excluding them from participation. We have also recently reported that DIAD patients frequently had resolution of inducible ischemia when rescreened 3 years after randomization,[18] which may partially explain their low overall cardiac event rate. This prior analysis did not include patients with intervening cardiac events or revascularization suggesting that the resolution of inducible ischemia was associated with more aggressive therapy of cardiovascular risk factors.[18]

DIAD study participants also had other characteristics that would predict at least an intermediate cardiac risk, including long-standing diabetes, older age, and obesity with more than 60% of participants having 2 or more additional cardiac risk factors at baseline. Moreover, half of the participants were unable to walk even at a slow rate on a flat treadmill during adenosine infusion.[8] The inability to exercise has been associated with higher cardiac risk in individuals with type 2 diabetes.[20]

Screening did identify participants, albeit a small number, who were at relatively greater risk than others, consistent with prior studies using stress MPI[7,9,19] and stress echocardiography in patients with diabetes.[10,26] DIAD study participants with moderate or large MPI defects had a 6-fold greater cardiac risk than those with normal studies or small defects. Nonperfusion abnormalities tended to convey an increased risk, as previously reported in symptomatic patients with suspected CAD.[27] However, even the group of 33 participants with moderate or large defects had an annual event rate of only 2.4% per year, which would fall only into an intermediate cardiac risk group (between 1% and 3% per year[28]). Thus, even moderate or large MPI defects had a positive predictive value of only 12%. Seventy-eight percent of participants had normal screening tests, which had a negative predictive value of 98%. However, even the low incidence of events after a normal MPI was somewhat problematic in this low-risk population, in that more than half of the cardiac events occurred in participants with a normal screening test.

Current clinical recommendations advise intensive cardiac risk factor modification in all patients with type 2 diabetes.[5,29] Thus, the validity of selective risk-factor intervention based on the results of screening, has been questioned.[29] In the DIAD study, the use of statins, angiotensin-converting enzyme inhibitors, aspirin, and other evidence-based medications was better than in the general population of patients with type 2 diabetes.[30] Medication use increased significantly during the course of study but did so comparably in the 2 groups (Table 4). These results suggest that ischemia detected by screening did not necessarily trigger more aggressive risk factor intervention in contemporary practice.

Screening for critical CAD to identify patients who might benefit from prophylactic revascularization also remains controversial.[6,14,29] In the DIAD study, management decisions were made according to the clinical judgment of treating physicians,[8] who referred only 4.4% of participants for coronary angiography within the first 120 days after screening, even though 22% had abnormal test results. Only 9 of these participants (1.6% of the screened group overall) underwent early revascularization, with 6 having CABG, indicating the severity of disease in this small group. Despite the small number of early

revascularization in the screened participants, the overall rate of revascularization was similar in the 2 groups. However, DIAD was not designed to address whether asymptomatic ischemiais best treated with revascularization, because treatment was not randomized and relatively few participants underwent revascularization. Some of these individuals also had CAD that was not amenable to intervention and revascularization did not fully prevent cardiac events, consistent with prior findings in the diabetic population.[31–34] Thus, it remains uncertain whether asymptomatic patients with type 2 diabetes benefit from revascularization after the identification of inducible ischemia, as was suggested in a prior retrospective database analysis[34] and a small randomized pilot study.[35] The on-going Bypass Angioplasty Revascularization Investigation(BARI)2DiabetesTrial may shed additional light on this issue.[36]

Limitations

The cardiac event rates were significantly lower than originally anticipated at the time of the design of the study and therefore the DIAD study does not have the power to exclude a small difference between the screened and unscreened participants. Based on the observed cardiac event rate, we would estimate that the study only had 14% power to detect a 20% difference between the 2 groups. A 3- to 4-fold larger study would be required to exclude such a difference,[13] and it is not clear that a reduction in cardiac events from 0.6% to 0.5% per year even if proved would justify cardiac screening.

Another potential limitation to consider is that nonprotocol stress tests were done during follow-up when clinically indicated in both groups. In addition, screening led to only a modest reduction in subsequent diagnostic testing. Testing was typically performed to evaluate potential cardiac symptoms but may have also been undertaken for risk stratification in some participants. In the no-screening group, such testing represents a crossover to a physician-directed screening strategy and theoretically might have counter-balanced a benefit of protocol-mandated systematic screening. However, because the DIAD study did not prohibit physician-directed cardiac evaluation, the results are more applicable to current day medicine in which patients are often evaluated for symptoms or preoperative risk stratification or when considered particularly high risk by their physicians.

Clinical Implications

In the light of our findings, routine screening for inducible ischemia in asymptomatic patients with type 2 diabetes cannot be advocated for 4 reasons. First, the yield of detecting significant inducible ischemia is relatively low.[8] Second, the overall cardiac event rate is low. Indeed, even our participants with moderate or large defects and the highest event rate would be conventionally assigned to an intermediate-risk category. Third, routine screening does not appear to affect overall outcome. Finally, routine screening of millions of asymptomatic diabetic patients would be prohibitively expensive.

However, rather than viewing this study, as a negative screening study, clinicians might consider the results as a positive message: patients with type 2 diabetes without symptoms to suggest CAD, receiving contemporary medical care, close follow-up, and appropriate diagnostic evaluation for symptoms of ischemia have relatively favorable outcomes in the current era.

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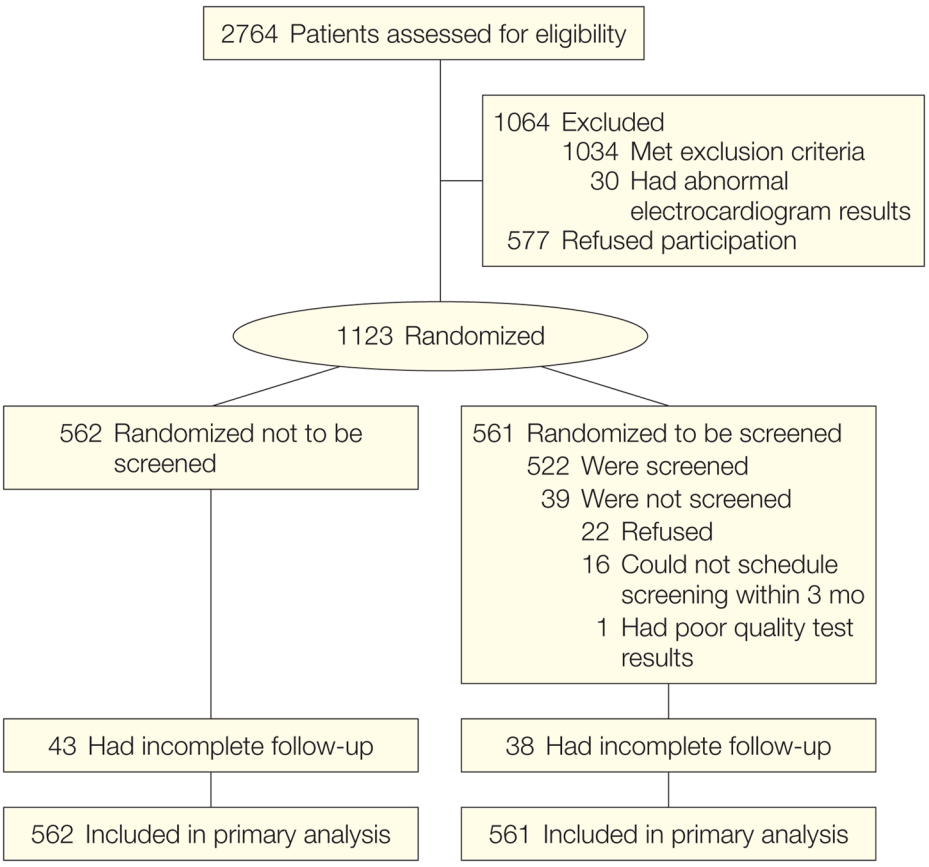

Figure 1.
Flow of Study Participants

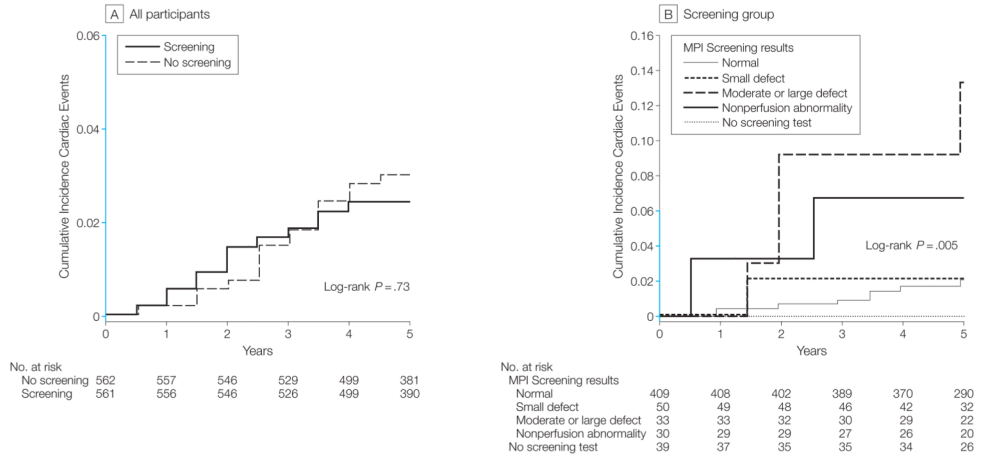

Figure 2. Cumulative Incidence of Cardiac Events in Participants With Type 2 Diabetes Without Symptomatic or Previously Diagnosed Coronary Artery Disease

A, Cumulative incidence of cardiac events in 561 participants randomized to systematic baseline screening with stress myocardial perfusion imaging (MPI) and 562 participants randomized to receive no screening. B, Cumulative incidence of cardiac events according to results of systematic screening with stress MPI: normal, small defect, moderate or large defect, and nonperfusion abnormality. No cardiac events occurred in participants who were randomized to but did not complete screening MPI. The y-axis scale in blue indicates range from 0 to 0.06.

Table 1

Baseline Characteristics According to Randomization

	No Screening (n = 562)	Screening (n = 561)
	Mean (SD)	
Age, y	60.8 (6.4)	60.7 (6.7)
Diabetes duration, y	8.9 (6.9)	8.2 (7.1)
Body mass index[a]	31.0 (6.1)	31.1 (6.5)
Hemoglobin A_{1C}, %	7.0 (1.5)	7.2 (1.6)
Serum creatinine, mg/dL	0.99 (0.33)	0.95 (0.29)
Clinical risk factors		
Cholesterol, mg/dL		
LDL	114 (33)	114 (32)
HDL	49 (15)	50 (15)
Triglycerides, mg/dL	168 (101)	172 (118)
Blood pressure, mm Hg		
Systolic	132 (16)	133 (17)
Diastolic	79 (8)	80 (9)
	No. (%) of Patients	
Male sex	311 (55)	290 (52)
Nonwhite race	129 (23)	122 (22)
Diabetes treatment		
Oral agents	356 (64)	346 (63)
Insulin	50 (9)	59 (11)
Insulin and oral agent	76 (13)	75 (13)
Diet only	80 (14)	81 (14)
Retinopathy	92 (16)	81 (14)
Microalbumin:creatinine ratio, μg/mg[c]		
<30	411 (75)	425 (78)
30–299	113 (20)	104 (19)
>300	27 (5)	19 (3)
Peripheral neuropathy		
Numbness	214 (38)	178 (32)

	No Screening (n = 562)	Screening (n = 561)
Pain	73 (13)	56 (10)
Tingling	158 (28)	156 (28)
Erectile dysfunction	149 (48)	140 (48)
Cardiac autonomic dysfunction, lowest quartile	125 (22)	120 (21)
Peripheral vascular disease	51 (9)	52 (9)
Current smoking	52 (9)	57 (10)
Family history of premature CAD[b]	98 (17)	117 (21)

Abbreviations: CAD, coronary artery disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

SI conversion factors: To convert HDL and LDL cholesterol from mg/dL to mmol/L multiply by 0.0259; serum creatinine from mg/dL to μmol/L, multiply by 88.4; triglycerides from mg/dL to mmol/L, multiply by 0.0113.

[a] Body mass index is calculated as weight in kilograms divided by height in meters squared.

[b] CAD in a parent or sibling who was diagnosed at age 50 years or younger.

[c] Data for 11 patients in the nonscreened and for 13 patients in the screened group were unavailable.

Table 2

Events in No-Screening vs Screening Group

	No. (%) of Patients			
	No Screening (n = 562)	Screening (n = 561)	HR (95% CI)[a]	Log-Rank *P* Value[b]
Primary events	17 (3.0)	15 (2.7)	0.88 (0.44–1.8)	.73
Myocardial infarction	10 (1.7)	7 (1.3)	0.82 (0.34–2.0)	.66
Cardiac death	7 (1.2)	8 (1.4)	1.1 (0.41–3.1)	.80
Secondary events	14 (2.5)[c]	21 (3.7)	1.5 (0.77–3.0)	.23
Unstable angina	3 (0.5)	4 (0.7)	1.3 (0.30–6.0)	.70
Heart failure	7 (1.2)	7 (1.2)	1.0 (0.35–2.9)	.99
Stroke	5 (0.9)	10 (1.8)	2.0 (0.69–5.9)	.20
Revascularizations	44 (7.8)[d]	31 (5.5)	0.71 (0.45–1.1)	.14
PTCA	27 (4.8)	15 (2.7)	0.90 (0.48–1.7)	.74
CABG surgery	20 (3.6)	16 (2.9)	0.81 (0.42–1.6)	.76
Death All cause	15 (2.7)	18 (3.2)	1.2 (0.69–2.4)	.60
Noncardiac	8 (1.4)	10 (1.8)	1.3 (0.49–3.2)	.63

Abbreviations: CABG, coronary artery bypass graft; CI, confidence interval; HR, hazards ratio; PTCA, percutaneous transluminal coronary angioplasty.

[a] Hazard ratios represent the ratio of screening vs no-screening participants from unadjusted Cox proportional hazards regression analysis.

[b] Log-rank *P* values are derived from unadjusted actuarial survival analysis.

[c] One patient had 2 secondary events.

[d] Three patients underwent both PTCA and CABG surgery.

Table 3

Events According to Findings of Screening Myocardial Perfusion Imaging (n = 522)

	No. (%) of Patients With Normal Imaging (n = 409)	Small Perfusion Defect (n = 50)		Moderate or Large Perfusion Defect (n = 33)		Nonperfusion Abnormality (n = 30)		
		No. (%)of Patients	HR (95% CI)[a]	No. (%)of Patients	HR (95% CI)[a]	No. (%)of Patients	HR (95% CI)[a]	*P* Value Log-Rank[c]
Percentage of patients	78	10		6		6		
Primary events	8 (2.0)	1 (2.0)	1.1 (0.1–8.5)	4 (12.1)	6.3 (1.9–20.1)	2 (6.7)	3.5 (0.8–16.7)	.005
Myocardial infarction	7 (1.7)	0	NA	0	NA	2 (6.7)	4.1 (0.8–19.6)	.14
Cardiac death	2 (0.5)	1 (2.0)	4.3 (0.4–47.4)	4 (12.1)	25.7 (4.7–140)	1 (3.3)	7.0 (0.6–77.8)	<.001
Secondary events	13 (3.2)	1 (2.0)	NA	3 (9.1)	3.0 (0.8–10.4)	4 (13.3)	4.6 (1.5–14.0)	.01
Unstable angina	1 (0.2)	0	NA	1 (3.0)	13.1 (0.8–210)	2 (6.7)	28.4 (2.6–313)	<.001
Heart failure	5 (1.2)	0	NA	0	NA	2 (6.7)	5.4 (1.1–27.9)	.08
Stroke	7 (1.7)	1 (2.0)	1.3 (0.2–10.4)	2 (6.1)	3.7 (0.8–17.7)	0	NA	.31
Revascularization	16 (3.9)	2 (4.0)	1.1 (0.2–4.6)	7 (21.2)	6.4 (2.6–15.6)	6 (20)	5.6 (2.2–14.4)	<.001
PTCA	9 (2.2)	1 (2.0)	0.2 (0.1–1.9)	3 (9.1)	0.7 (0.2–2.8)	2 (6.7)	2.1 (0.4–10.1)	.43
CABG surgery	7 (1.7)	1 (2.0)	1.2 (0.2–10)	4 (12.1)	7.9 (2.3–27)	4 (13.3)	8.3 (2.4–28.2)	<.001
Death All cause	9 (2.2)	2 (4.0)	1.9 (0.4–8.9)	5 (15.2)	7.2 (2.4–21.4)	1 (3.3)	1.6 (0.2–12.3)	.002
Noncardiac[b]	7 (1.7)	1 (2.0)	1.3 (0.2–10.2)	1 (3.0)	1.9 (0.2–15)	0	NA	.90

Abbreviations: CABG, coronary bypass graft; CI, confidence interval; HR, hazard ratio; MPI, myocardial perfusion imaging; NA, not applicable; PTCA, percutaneous transluminal coronary angioplasty.

[a] Hazard ratio of abnormal screening findings vs normal imaging.

[b] Thirty-nine patients who did not undergo screening according to protocol were included in the statistical analyses. None had any cardiac events, but 1 had noncardiac death.

[c] Log-rank of overall difference between groups.

Table 4

Follow-up and Medication Use

	No. (%) of Patients				
	No Screening (n = 562)		Screening (n = 561)		*P* Value
Additional cardiac testing					
Nonprotocol stress test	170 (30)		118 (21)		<.001
Abnormal nonprotocol stress test	45 (26)		28 (24)		.60
Coronary angiogram <120 d	3 (0.5)		25 (4.4)		<.001
Revascularization <120 d	2 (0.36)		9 (1.6)		.03
Total coronary angiograms	66 (12)[a]		80 (14)		.20
No. of vessels >70% stenosis					
0	22 (33)		40 (50)		.05
1	21 (32)		11 (14)		
2	13 (20)		19 (23)		
3	10 (15)		10 (12)		
	Baseline	5 Years	Baseline	5 Years	
Pharmacological treatment					
Insulin treatment	126 (22)	141 (29)[b]	134 (24)	171 (35)[b]	.54
Oral anti-hyperglycemic agents	482 (86)	444 (91)[b]	480 (86)	447 (92)[b]	.81
Lipid-lowering drugs	272 (48)	377 (78)	255 (45)	365 (76)[b]	.32
Statins	228 (41)	327 (67)[b]	209 (37)	324 (67)[b]	.25
Antihypertensive drugs	320 (57)	362 (75)	315 (56)	355 (74)[b]	.79
ACE or angiotensin receptor blockers	229 (41)	218 (45)[b]	206 (37)	210 (43)[b]	.17

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	No. (%) of Patients			
	No Screening (n = 562)		Screening (n = 561)	*P* Value
Aspirin	261 (46)	356 (73)[b]	241 (43)	364 (74)[b] .24

Abbreviation: ACE, angiotensin-converting enzyme.

[a] Twenty-seven (41%) of 66 coronary angiograms were performed after a nonprotocol stress test.

[b] $P < .05$ compared with baseline.

Table 5

Factors Associated With Primary Events

	Event (n = 32)	No Event (n = 1091)	Unadjusted, HR (95% CI), %	Age- and Sex-Adjusted, HR (95% CI), %[a]	*P* Value
	Mean (SD)				
Age, y	62.7 (5.9)	60.7 (6.6)	1.04 (0.99–1.10)	1.04 (0.99–1.10)	.09
Diabetes duration, y	12.0 (8.3)	8.4 (6.9)	1.05 (1.02–1.10)	1.05 (1.01–1.10)	.004
Body mass index[b]	28.7 (4.8)	31.2 (6.3)	0.93 (0.86–0.99)	0.94 (0.87–1.01)	.03
Hemoglobin A_{1C}, %	7.5 (1.5)	7.1 (1.5)	1.17 (0.98–1.40)	1.18 (0.99–1.42)	.11
Waist circumference, cm	41 (4.9)	41 (5.9)	0.99 (0.93–1.05)	0.99 (0.93–1.05)	.75
Hip circumference, cm	107 (10.4)	112 (14.5)	0.93 (0.87–1.00)	0.99 (0.93–1.05)	.02
Serum creatinine, mg/dL	1.24 (0.69)	0.96 (0.29)	1.14 (1.09–1.18)	1.13 (1.08–1.18)	.03
Cholesterol, mg/dL					
LDL	129 (41)	114 (32)	1.14 (1.04–1.24)	1.14 (1.04–1.24)	.01
HDL	47 (12)	50 (15)	1.00 (0.86–1.08)	1.00 (0.86–1.14)	.31
Triglycerides, mg/dL	203 (149)	169 (108)	1.01 (1.00–1.02)	1.00 (0.99–1.00)	.20
Antihypertensive drugs	19 (59)	616 (57)	1.12 (0.55–2.27)	1.15 (0.56–2.33)	.74
Blood pressure, mm Hg					
Systolic	134 (19)	131 (16)	1.01 (0.99–1.03)	1.01 (0.99–1.03)	.36
Diastolic	78 (7.7)	79 (8.4)	0.99 (0.95–1.03)	0.99 (0.95–1.03)	.59
	No. (%) of Patients				
Male sex	23 (72)	578 (53)	2.18 (1.01–4.72)	2.15 (1.00–4.66)	.03
Insulin treatment	11 (34)	249 (23)	1.82 (0.88–3.78)	1.77 (0.85–3.68)	.13
Retinopathy	6 (19)	167 (15)	1.32 (0.54–3.21)	1.22 (0.50–2.98)	.59

	Event (n = 32)	No Event (n = 1091)	Unadjusted, HR (95% CI), %	Age- and Sex-Adjusted, HR (95% CI), %[a]	*P* Value
Microalbumin:creatinine ratio, μg/mg					
<30	17 (59)	819 (77)			
30–299	7 (24)	210 (19)	4.78 (1.84–12.40)	4.59 (1.76–11.92)	.001
≥300	5 (17)	41 (4)			
Peripheral neuropathy					
Numbness	17 (53)	375 (34)	2.17 (1.09–4.35)	2.23 (1.11–4.48)	.03
Pain	7 (22)	122 (11)	2.22 (0.96–5.14)	2.36 (1.01–5.45)	.06
Tingling	11 (34)	303 (28)	1.36 (0.66–2.82)	1.44 (0.69–2.83)	.41
Absent vibration	9 (28)	317 (29)	0.98 (0.45–2.12)	0.85 (0.39–1.87)	.91
Absent sensation	9 (28)	127 (12)	2.99 (1.39–6.47)	2.83 (1.31–6.13)	.005
Absent reflex	10 (31)	348 (32)	0.96 (0.45–2.02)	0.87 (0.41–1.86)	.93
Autonomic neuropathy					
Bloating	6 (19)	160 (15)	1.35 (0.56–3.28)	1.55 (0.69–4.69)	.52
Dizziness	4 (13)	161 (15)	0.84 (0.29–2.39)	0.86 (0.30–2.48)	.72
Erectile dysfunction	14 (61)	275 (48)	1.69 (0.73–3.90)	1.45 (0.61–3.43)	.21
Cardiac autonomic dysfunction, lowest quartile[c]	17 (53)	228 (21)	4.28 (2.14–8.58)	4.33 (2.14–8.75)	<.001
Peripheral vascular disease	9 (28)	94 (9)	4.06 (1.88–8.77)	4.65 (2.14–10.1)	<.001
Current smoking	5 (16)	104 (10)	1.80 (0.69–4.69)	1.95 (0.74–5.12)	.25
Lipid-lowering drugs	15 (47)	512 (47)	0.98 (0.49–1.95)	0.95 (0.47–1.91)	.98
Aspirin use	16 (50)	486 (45)	1.25 (0.62–2.49)	1.18 (0.59–2.36)	.54
Family history of premature CAD	11 (34)	204 (19)	2.27 (1.09–4.70)	2.52 (1.21–5.26)	.03

Abbreviations: CAD, coronary artery disease; CI, confidence interval; HDL, high-density lipoprotein; HR, hazard ratio; LDL, low-density lipoprotein.

SI conversion factors: To convert HDL and LDL cholesterol from mg/dL to mmol/L, multiply by 0.0259; serum creatinine from mg/dL to μmol/L, multiply by 88.4; triglycerides from mg/dL to mmol/L, multiply by 0.0113.

[a] Units in the adjusted HRs are HDL, per 5 mg/dL; LDL, per 10 mg/dL; ratio waist:hip, per 0.01; serum creatinine, per 0.1 mg/dL; and blood pressure, per 1 mm Hg.

[b] Body mass index is calculated as weight in kilograms divided by height in meters squared.

[c] Change in heart rate during lying-to-standing test.