Screening for cardiovascular disease in diabetes
– lesson from DIAD

The Detection of Ischemia in
Asymptomatic Diabetics (DIAD) Study

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Coronary artery disease (CAD) is a leading cause of morbidity and mortality in patients with diabetes. Myocardial ischemia may be silent in diabetic patients. The first presentation of CAD is often acute myocardial infarction or sudden death. CAD can be easily identified in a pre-clinical stage. Patients with silent ischemia will benefit from aggressive risk factor reduction, and, potentially, CAD-specific therapy such as medications or revascularization.
How to Screen for CAD in Diabetes

Introduction

- EKG exercise tolerance test
  ADA (‘98) – screen patient with high risk
  (abnormal resting EKG $\rightarrow$ Imaging study)
- Myocardial perfusion imaging (MPI)
  Exercise or pharmacological stress
- Stress echocardiography
- Electron beam computed tomography (EBCT)
  Coronary artery calcium (CAC)
The DIAD study

- **DIAD 1**
  
  Prevalence / predictors of silent MI in T2DM

- **DIAD 2**
  
  Progression / regression of CAD

- **DIAD 3**
  
  Cardiac event rates (vs. control group)
DIAD 1: Study Aims

Introduction

Hypotheses

Silent ischemia is highly prevalent.
Patients at highest risk can be identified for screening by risk factors (to find ‘enriched pool’).

To determine prospectively the prevalence and clinical predictors of inducible MI in asymptomatic patients with T2DM using myocardial perfusion imaging (Adenosine-Sestamibi SPECT)

Diabetes Care 2004;27:1954-61
Asymptomatic T2DM Patients

1123 Eligible Consented Patients (2000.7 - 2002.8)

Randomization

“Natural History”
562 Patients
No testing
5-y follow-up

“Screening”
561 Patients
MPI
5-y follow-up

DIAD 1 (2004)

DIAD 2 (2007: 3-y follow-up)

DIAD 3 (2009)
Inclusion Criteria

- Type 2 diabetes mellitus
- Age 50-75 years
- No history of CAD; no angina
- No clinical indication for stress testing
- Normal resting EKG

Methods

Diabetes Care 2004;27:1954-61
## Baseline Data in Screened Patients

### Results

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>60.7 ± 6.7 y</td>
</tr>
<tr>
<td>T2DM Duration</td>
<td>8.2 ± 7.1 y</td>
</tr>
<tr>
<td>A1C</td>
<td>7.2 ± 1.6%</td>
</tr>
<tr>
<td>BMI</td>
<td>31.1 ± 6.5kg/m²</td>
</tr>
<tr>
<td>LDL-C</td>
<td>114 ± 32mg/dL</td>
</tr>
<tr>
<td>TG</td>
<td>172 ± 118mg/dL</td>
</tr>
<tr>
<td>HDL-C</td>
<td>50 ± 15mg/dL</td>
</tr>
<tr>
<td>ASA use</td>
<td>44%</td>
</tr>
</tbody>
</table>

Diabetes Care 2004;27:1954-61
Myocardial SPECT Imaging

Results

Non-Perfusion abnormality

Perfusion abnormality

Mod-Large abnormality

Mild abnormality

Normal 409/522 (78%)

Abnormal 113/522 (22%)

83/113 (73%)

33/83 (40%)

50/83 (60%)

30/113 (27%)

Diabetes Care 2004;27:1954-61
Indications for cardiac testing in diabetic patient

ADA consensus (1998)

1. Typical or atypical cardiac symptoms
2. Resting EKG suggestive of ischemia or infarction
3. Peripheral or carotid occlusive arterial disease
4. Sedentary lifestyle, age >35 years, and plans to begin a vigorous exercise program

5. Two or more of the risk factors listed below (a–e) in addition to diabetes
   a) Cholesterol (Total >240, LDL >160, or HDL <35 mg/dl)
   b) BP >140/90 mmHg
   c) Smoking
   d) Family history of premature CAD
   e) Positive micro/macroalbuminuria

Diabetes Care 1998;21:1551-9
Prevalence of Silent Ischemia & Consensus Statement Risk Factors

<2 Risk factors

- Normal: 159/204 (78%)
- Abnormal: 45/204 (22%)

>2 Risk factors

- Normal: 240/306 (78%)
- Abnormal: 66/306 (22%)

VS.

Diabetes Care 2004;27:1954-61
Abnormal myocardial perfusion imaging (MPI)

- in 22% of asymptomatic T2D patients (1 in 5)

- Silent ischemia - not as common as previous report (50-60%)

- Markedly abnormal MPI in 6% of patients (1 in 16)

- Most of perfusion defects - small defect

(not suitable for revascularization)

Diabetes Care 2004;27:1954-61
In univariate analysis, routine clinical (BMI, BP, DM duration) and biochemical variables (A1c, lipids, hs-CRP) were NOT predictive.

In multivariate analysis, cardiac autonomic neuropathy (OR 5.6), DM duration (OR 5.2), and male gender (OR 2.5) were predictive of moderate-large defects.

A high-risk profile from routine risk factors couldn’t be constructed (except for gender & DM duration for moderate-large defects).

Diabetes Care 2004;27:1954-61
Hypothesis

In patients with T2DM, the prevalence and/or severity of myocardial ischemia increases over time.

Repeat Adenosine Sestamibi SPECT @ 3 years

Diabetes Care 2007;30:2892-8
The ‘DIAD 2’ Cohort

- Repeat SPECT - 68% (358/522)

- No Repeat SPECT – 32% (164/522)
  - Cardiac events: death (10), MI (2), revascularization (15)
  - New co-morbidity (10)
  - Refusal (87)
  - Lost to follow-up (17)
  - Katrina (21)
  - Non-interpretatable SPECT (2)

Diabetes Care 2007;30:2892-8
Changes

Index Screening
DIAD-1
(2000-2002)

‡ N = 358

Normal
287 (80%)

Abnormal
71 (20%)

Repeat Screening
DIAD-2
(2003-2005)

Normal
56 (79%)

Abnormal
15 (21%)

Resolution
of ischemia

N = 358

Normal
259 (90%)

Abnormal
28 (10%)

Patients with Events,
Revascularization Excluded

Diabetes Care 2007;30:2892-8
Exposure to 3 Medications Combined (Statin + ASA + ACEI)

Total Time Exposure (drug months)

- Resolution of Ischemia: 59 months
- New Ischemia: 45 months

p = 0.04

Diabetes Care 2007;30:2892-8
In the context of modern medical therapy, myocardial perfusion defects can and often do resolve in patients with T2DM.
DIAD 3: 5 Year Follow-Up

Hypothesis: Screening improves clinical outcomes by identifying disease early.

Primary Endpoint: Cardiac death + Non-fatal MI

<table>
<thead>
<tr>
<th></th>
<th>Cardiac death</th>
<th>Non-fatal MI</th>
<th>Primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>8</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>Non-screening</td>
<td>7</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>17</td>
<td>32</td>
</tr>
</tbody>
</table>

Event Rate: 3% (0.6%/year)

JAMA 2009;301:1547-55
Cardiac Death and Non-Fatal MI: Screening Group

- Negative predictive value: 401/409 (98.0%)
- Positive predictive value:
  - For any MPI abnormality: 7/113 (6.2%)
  - For moderate or large MPI defect: 4/33 (12.1%)

Log rank = 14.93, p = 0.005

JAMA 2009;301:1547-55
## Major Cardiac Event Predictors

<table>
<thead>
<tr>
<th>Variables</th>
<th>HR* (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male Gender</td>
<td>2.6 (1.1-6.3)</td>
<td>.03</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>3.2 (1.3-7.4)</td>
<td>.01</td>
</tr>
<tr>
<td>LDL-C per 10 mg/dl increase</td>
<td>1.16 (1.1-1.2)</td>
<td>.008</td>
</tr>
<tr>
<td>Serum Cr per 1 mg/dl increase</td>
<td>1.16 (1.1-1.2)</td>
<td>.0001</td>
</tr>
<tr>
<td>Abnormal HR response to standing</td>
<td>3.6 (1.7-7.6)</td>
<td>.001</td>
</tr>
<tr>
<td>Mod-large MPI defects</td>
<td>6.2 (2.1-18.3)</td>
<td>.001</td>
</tr>
<tr>
<td>Non-perfusion abnormalities</td>
<td>4.8 (1.1-20.8)</td>
<td>.04</td>
</tr>
</tbody>
</table>

*Cox Logistic Regression

JAMA 2009;301:1547-55
Cardiac Death and Non-Fatal MI Screening vs. No Screening

No Screening

Screening

Cumulative Incidence Cardiac Events

No. At Risk

JAMA 2009;301:1547-55
## All End Points at 5 Years

<table>
<thead>
<tr>
<th>Variables</th>
<th>No Screening (n=562)</th>
<th>Screening (n=561)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac death</td>
<td>7 (1.2%)</td>
<td>8 (1.4%)</td>
<td>NS</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>10 (1.8%)</td>
<td>7 (1.2%)</td>
<td>NS</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>3 (0.5%)</td>
<td>4 (0.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>Heart failure</td>
<td>7 (1.2%)</td>
<td>7 (1.2%)</td>
<td>NS</td>
</tr>
<tr>
<td>Stroke</td>
<td>5 (0.9%)</td>
<td>10 (1.8%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

JAMA 2009;301:1547-55
Lessons from DIAD 3

Although indiscriminate screening does identify a higher-risk group of patients, this approach does not appear to reduce cardiac events.
<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Middle-aged: 61±7 yrs</td>
<td>● Willing to participate in research</td>
</tr>
<tr>
<td>● DM duration: 8±7 yrs</td>
<td>● Self-referred</td>
</tr>
<tr>
<td>● BMI: 31±6 kg/m²</td>
<td>● No symptoms</td>
</tr>
<tr>
<td>● Insulin: 22%, OAD: 63%</td>
<td>● Normal rest EKG</td>
</tr>
<tr>
<td>● &gt; 2 Risk factors: 60%</td>
<td>● A1C: 7.1±1.5%</td>
</tr>
<tr>
<td>● No activity at all: 34%</td>
<td></td>
</tr>
<tr>
<td>● Unable to exercise: 50%</td>
<td></td>
</tr>
</tbody>
</table>

JAMA 2009;301:1547-55
## Outcomes by High-Risk Designation

**2010 ADA**

<table>
<thead>
<tr>
<th>Framingham Risk Score Intermediate/High Risk</th>
<th>No Screening (422)</th>
<th>Screening (418)</th>
<th>p</th>
<th>HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary CE</td>
<td>15 (3.6%)</td>
<td>13 (3.1%)</td>
<td>0.71</td>
<td>0.87 (0.41-1.83)</td>
</tr>
<tr>
<td>Secondary CE</td>
<td>13 (3.1%)</td>
<td>17 (4.1%)</td>
<td>0.79</td>
<td>1.14 (0.44-2.95)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>UKPDS Risk Engine Intermediate/High Risk</th>
<th>No Screening (289)</th>
<th>Screening (418)</th>
<th>p</th>
<th>HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary CE</td>
<td>11 (3.7%)</td>
<td>14 (4.8%)</td>
<td>0.51</td>
<td>1.30 (0.59-2.86)</td>
</tr>
<tr>
<td>Secondary CE</td>
<td>11 (3.7%)</td>
<td>12 (4.1%)</td>
<td>0.82</td>
<td>1.10 (0.30-2.62)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metabolic syndrome</th>
<th>No Screening (361)</th>
<th>Screening (352)</th>
<th>p</th>
<th>HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary CE</td>
<td>14 (3.5%)</td>
<td>10 (2.5%)</td>
<td>0.42</td>
<td>0.72 (0.32-1.62)</td>
</tr>
<tr>
<td>Secondary CE</td>
<td>12 (3.0%)</td>
<td>15 (3.8%)</td>
<td>0.77</td>
<td>1.16 (0.42-3.20)</td>
</tr>
</tbody>
</table>
Screening for Coronary Artery Disease in DM

1. Screening T2DM patients for silent ischemia with nuclear stress testing will detect ~1 in 5 patients with CAD (~1 in 16 having major abnormalities).

2. Ischemia appears to resolve in a significant number of patients. (Whether aggressive risk factor modification is responsible?)

3. Although stress testing does identify those at the highest risk for events, routine screening for CAD does NOT appear to favorably alter outcome rates, in the context of modern practice.
4. The overall cardiac event rates in DIAD were extremely favorable (0.6%/y)!

5. The DIAD population was not, at first glance, a ‘low-risk’ group. Post-hoc stratified analysis still finds no benefit to screening even the highest risk individuals.

6. While there may be some benefits to screening for some patients, routine screening cannot be recommended at this time.
Current Guidelines for CAD screening

- 1998 (consensus statement)
- 2007 (consensus statement): CAC by Clinical judgment

Cardiac CT- reserved for those in whom medical treatment goals cannot be met and for selected individuals in whom there is strong clinical suspicion of very-high-risk CAD

- Standards of Medical Care— 2010 (position statement)

CAD Screening in asymptomatic patients remains controversial - evaluate risk factors to stratify patients by 10-year risk, and treat risk factors accordingly. (B)
Current Guidelines for CAD screening

American Society of Nuclear Cardiology (2006)

Algorithm for screening to enrich target population

(EDITORIAL VIEW)

- 2 different aspects of CAD
  - CAC (atherosclerosis)
  - MPI (luminal obstruction)
Current Guidelines for CAD screening

- AHA (2006)- CAC (Class IIb) or CT angiography (Class III)
- AHA (2009) – Stress test before vigorous exercise (Class IIa)
- European Society of Cardiology (2010)
  - CAC → MPI → Angiography: (Class IIa)
  - Routine MPI: (Class III)
  - CT angiography : (Class III)
Identification and early Tx. of Silent MI

- Selective or Routine screening
- CAC, not CT angiography

Is early revascularization better?