Detection of Coronary Artery Disease in Asymptomatic Diabetic Patients

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Cardiologie & Urgences Cardiologiques
CHU de Grenoble
Disclosure Statement of Financial Interest

I currently have, or have had over the last two years, an affiliation or financial interests or interests of any order with a company or I receive compensation or fees or research grants with a commercial company:

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<th>Affiliation/Financial Relationship</th>
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None regarding the present communication
1. Cardiac risk of asymptomatic diabetic patients in 2017?

2. Prognostic value of silent ischemia?

3. Is revascularisation of silent ischemia of benefit?

4. New strategy of screening?
1. Cardiac risk of asymptomatic diabetic patients in 2017?

2. Prognostic value of silent ischemia?

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4. New strategy of screening?
Figure 1. Kaplan–Meier Estimates of the Probability of Death from Coronary Heart Disease in 1059 Subjects with Type 2 Diabetes and 1378 Nondiabetic Subjects with and without Prior Myocardial Infarction. MI denotes myocardial infarction. I bars indicate 95 percent confidence intervals.
Cardiac risk in type 2 diabetic patients

Diabetes + CHD
Diabetes - severe
Diabetes - non severe

Mondesir FL et al Am Heart J 2016;181:43-5
Patient selection is the major issue: The DIAD Study

2764 Patients assessed for eligibility

1064 Excluded
  1034 Met exclusion criteria
  30 Had abnormal electrocardiogram results
  577 Refused participation

1123 Randomized

562 Randomized not to be screened

562 Included in primary analysis

43 Had incomplete follow-up

561 Randomized to be screened

522 Were screened

39 Were not screened

22 Refused

16 Could not schedule screening within 3 mo

1 Had poor quality test results

38 Had incomplete follow-up

561 Included in primary analysis

Death + non Fatal MI

Cumulative incidence of cardiac events

Log-rank P = .73

LH Young & al. JAMA. 2009;301:1547-1555
DIAD: Story of a missed target...

- **No patient pre-screening**
  - Inclusion criteria: type 2 diabetic patients aged 50 to 75 years
  - HbA1c 7.2% - Nephropathy: 5% - Associated vascular disease: 9%

- **Low risk patients → low MACE rate**
  - 0.6% / yr versus ± 2.0% /yr in most studies

- **Low efficiency of SMI detection**
  - 409 normal tests = 83%
  - 50 mild MPI defects = 10%
  - 33 moderate to severe defects = 7%

- **No pre-defined therapeutic strategy according to MPI data**

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LH Young & al. JAMA. 2009;301:1547-1555
Prevalence of SMI in diabetes according to pre-screening

- **Low pretest CV risk**
- **Intermediate pretest CV risk**
- **High pretest CV risk**

<table>
<thead>
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<th>Year</th>
<th>CV Risk</th>
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- **Intermediate pretest CV risk**

- **High pretest CV risk**

- **Overall**

- **Low pretest CV risk**
- **Intermediate pretest CV risk**
- **High pretest CV risk**

DIAD
Impact of conventional risk factors


Incremental prognostic value of stress myocardial perfusion imaging in asymptomatic diabetic patients

Figure 2. Distribution of the prevalence of silent myocardial ischemia stratified by number of coronary artery disease risk factors and 10-year coronary heart disease risk.
Detection of asymptomatic ischemia is more likely to be of benefit in selected high risk subset of patients (IIB)

- Patients > 60 yrs with type 2 diabetes > 10 yrs and associated CV risk factors and micro / macrovascular disease
- Patients with poor (<4 Mets) or unappreciable functional capacity and high ESC risk score undergoing high risk non cardiac surgery
- Asymptomatic adults with diabetes or a strong family history of CHD or when previous risk assessment testing suggests high risk of CHD
- Asymptomatic intermediate risk sedentary adults considering starting a vigorous exercise program → ECG
Who are high risk diabetic patients?

- Type 2 DM > 60 yrs and > 10 yrs of evolution
- With organ damage
  - Moderate to severe diabetic retinopathy
  - Macroproteinuria and/or renal failure
  - Peripheral vascular disease
- Insulin treated
- High level of associated risk factors
- Type 1 diabetic patient > 40 yrs and > 15 yrs of evolution and CVRF
1. Cardiac risk of asymptomatic diabetic patients in 2017?

2. Prognostic value of silent ischemia?

3. Is revascularisation of silent ischemia of benefit?

4. New strategy of screening?
Studies demonstrating the prognostic value of SMI in diabetes

<table>
<thead>
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25+ years of experience
25000+ patients
Up to 20 year follow-up
Prognostic value of SMI in diabetes

Death + Non fatal MI + Stroke


Valensi & al. Diabetes Care 2005;28:2722-2727
Prognostic value of SMI in diabetes

MACCES

<table>
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<th>Study or Subgroup</th>
<th>Risk Ratio</th>
<th>M-H, Fixed, 95% CI</th>
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<td>Total (95% CI)</td>
<td>3.48</td>
<td>[2.59, 4.68]</td>
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Cardiac Death

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<tr>
<td>Total (95% CI)</td>
<td>4.60</td>
<td>[1.78, 11.84]</td>
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Conclusion: In asymptomatic diabetic patients, post-stress LVEF and stress induced ischemia by gated MPS influence the temporal characteristic of the patient’s risk at long-term follow-up.

1. Cardiac risk of asymptomatic diabetic patients in 2017?

2. Prognostic value of silent ischemia?

3. Is revascularisation of silent ischemia of benefit?

4. New strategy of screening
Ischemia guided therapy is the gold standard

## Revascularization in Silent Myocardial Ischemia


### Table: Risk of Mortality and Death + MI

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<td>ACIP (2007)</td>
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<td>COURAGE (2007)</td>
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<td>0.77 (0.45–1.32)</td>
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<td>Total</td>
<td>45/423</td>
<td>0.47 (0.26–0.85)*</td>
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<td><strong>Death</strong></td>
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### Risk Ratio

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<td><strong>TOTAL</strong></td>
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<td><strong>Mortality</strong></td>
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PCI + OMT better than OMT
Revascularisation in high risk asymptomatic patients

Improved Survival in Asymptomatic Diabetic Patients With High-Risk Spect Imaging Treated With Coronary Artery Bypass Grafting

Paul Sorajja, MD; Panithaya Chareonthaitawee, MD; Navin Rajagopalan, MD; Todd D. Miller, MD, FAHA; Robert L. Frye, MD, FAHA; David O. Hodge, MS; Raymond J. Gibbons, MD, FAHA

N=826 diabétiques asymptomatiques

Figure 2. Survival of patients with high-risk perfusion abnormalities (SSS ≥47).

Figure 4. Survival of asymptomatic diabetic patients without high-risk perfusion abnormalities (SSS=48 to 55).
Patient management strategies that focus on ischemia resolution can be useful to guide the efficacy of near-term therapeutic approaches.
BARI 2D study – High risk scan patients

Death, myocardial infarction, or stroke

A strategy of prompt CABG significantly reduces the rate of death/myocardial infarction MI/stroke in diabetic patients with extensive coronary artery disease or impaired left ventricular function.

SMI guided strategy

Low risk
High risk ischemia guided
High risk liberal

MACEs free survival

N = 667
Logrank P value after adjustment on CRS:
Group I vs. II  P = 0.0001
Group I vs. III  P = NS
Group II vs. III  P = 0.0001

F-UP (Months)
1. Cardiac risk of asymptomatic diabetic patients in 2017?

2. Prognostic value of silent ischemia?

3. Is revascularisarion of silent ischemia of benefit?

4. New strategy of screening?
Patient selection is the major concern

- Detection of asymptomatic ischemia is more likely to be of benefit in selected high risk subset of patients (IIB)

  - Patients > 60 yrs with type 2 diabetes > 10 yrs and associated CV risk factors and micro / macrovascular disease

  - Patients with poor (<4 Mets) or unappreciable functional capacity and high ESC risk score undergoing high risk non cardiac surgery

  - Asymptomatic adults with diabetes or a strong family history of CHD or when previous risk assessment testing suggests high risk of CHD

  - Asymptomatic intermediate risk sedentary adults considering starting a vigorous exercise program → ECG
Figure 3. Kaplan–Meier survival curves in diabetic and nondiabetic individuals according to coronary artery calcium (CAC) scores.
Coronary Calcium Score

- 1123 diabetic patients with 7.4 yr-F-Up after CAC-score
- 8% cardiovascular-death $\rightarrow \pm 1\%$/year

**Figure 2**—Receiver operating characteristic curve analysis depicting AUC with and without CAC to predict CVD mortality. (A high-quality color representation of this figure is available in the online issue.)

Agarwal & al. Diabetes Care 2013. 36:972–977
Coronary Calcium Score

p trend for CVD Mortality < 0.0001

Incidence of Cardiovascular Mortality

14%  86%  16%

1%  4%  5%  6%

14%

ODDS RATIO (LOG SCALE)

2.93; p=0.13  3.17; p=0.13  4.41; p=0.03  11.2; p=0.0001

1.00 (Ref)

0-9 (n=156)  10-99 (n=235)  100-299 (n=132)  300-999 (n=195)  1000+ (n=401)

Coronary Artery Calcium Score (Agatston Units)

Agarwal & al. Diabetes Care 2013. 36:972–977
Toward an alternative strategy?

Low to moderate CV risk:
- Treat to target

High to very-high CV risk:
- Ischemia test
  - < 10% LV: Treat to target -> Medical Rx
  - > 10-15% LV: Treat to target -> Coronary angio

Medical Rx

Revascularization Medical RX
Toward an alternative strategy?

Low to moderate CV risk
- CAC
  - ≤ ??? Agaston
    - Treat to target
  - > ??? Agaston

High to very-high CV risk
- Ischemia test
  - < 10% LV
    - Treat to target
  - > 10-15% LV
    - Medical Rx
    - Coronary angio

Revascularization Medical Rx

Budoff MJ JACC 2016
We should care about and search for silent ischemia because

- Its prevalence is high in selected high-risk population

- It is a powerful predictor of future major and minor CV events in asymptomatic as in symptomatic patients

- There are strong clues that reduction of silent ischemia by OMT and myocardial revascularization if extensive improves outcome

- It is therefore common sense based – if not yet evidence based
Short term prognosis value of the presence and extent of ischemia

Long term prognosis value of the presence and extent of ischemia


MACE free Survival

Logrank-test P < 0.0001

# patients
Normal scan
1-2 abn. seg.
≥ 3 abn seg

0 1 2 3 4 5 6 7 (yrs)

388 385 379 367 351 339 205 93
554 539 523 502 480 462 309 158
195 186 176 166 160 148 97 47

Normal
Mild/moderate
Severe
Angina is a matter of feeling…

Presence of angina according to pain thresholds

Figure 7. Dental pulp stimulation testing in patients with (open bars) and without (solid bars) symptoms during coronary intervention. Asymptomatic patients had significantly higher mean dental pain threshold, lower mean threshold reaction and lower mean maximal reaction, than symptomatic patients. Reproduced from Falcone et al54 with permission.
Quels patients ?

- Tout diabétique avec atteinte macrovasculaire ou rénale avérée
  - AOMI clinique
  - Sténose carotidienne / AVC
  - Proteinurie
  - Insuffisance rénale

- Diabétique de type 2 avec ≥ 2 FRCV associés et
  - atteinte microvasculaire latente (microalbuminurie)
  - âge ≥ 60 ans
  - > 10 ans d’évolution du diabète

(Diabétique de Type 1 avec 2 ou plus FRCV, avec diabète ≥ 15 ans et âgé ≥ 45 ans)
Figure 2 Survival curve for the main composite end-point (time to death from all causes, non-fatal myocardial infarction, non-fatal stroke, or heart failure requiring hospitalization or emergency service intervention).
DYNAMIT: Story of misused tests…

- Accurate screening of patients high risk diabetic patients
  > 2 cardiovascular risk factors or markers
  HbA1c 8.7% - Nephropathy: 42% - CV disease: 14%

- MACE rate as expected
  1.8% / yr in DYNAMIT

- Acceptable efficiency of SMI detection: 21%

- Miss-use of functional tests
  Only 31.0% underwent MPI
  Results were definitely “abnormal or uncertain” in 68 pts

- Not powered to allow any conclusion
  Study stopped > 631 inclusions for an expected population of 3000 pts
  (RRR 22% - $\alpha = 0.20$ – $\beta = 0.05$ )
Cardiac risk in type 2 diabetic patients
Long-Term Survival Benefit of Coronary Revascularization in Patients Undergoing Stress Myocardial Perfusion Imaging

Mario Petretta, MD; Wanda Acampa, MD, PhD; Stefania Daniele, PhD; Emilia Zampella, MD; Roberta Assante, MD; Carmela Nappi, MD; Marco Salvatore, MD; Alberto Cuocolo, MD