Hartinfarct en óók nog eens diabetes

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Disclosure

• In the past 48 months, I have received research grants from and was speaker on (CME accredited) meetings sponsored by:
  Astellas, Astra-Zeneca, Bayer, Biotronik, Boston Scientific, Bristol Myers Squibb, Cordis, Daiichi Sankyo, Lilly, Genzyme, Medtronic, Merck-Schering-Plough, Pfizer, Orbus Neich, Novartis, Roche, Servier, The Medicines Company, the Netherlands Heart Foundation, the Interuniversity Cardiology Institute of the Netherlands (ICIN) and the European Community Framework KP7 Programme

Atherosclerosis Is Common in Newly Diagnosed Diabetes Mellitus

• Cardiovascular diseases are common causes of morbidity and mortality in people with diabetes
• >50% of patients with newly diagnosed type 2 diabetes show evidence of cardiovascular disease
• Atherosclerosis is a major cause of death among patients with diabetes mellitus
  – 75% from coronary atherosclerosis
  – 25% from cerebral or peripheral vascular disease
• >75% of hospitalizations for individuals with diabetes are for atherosclerotic disease


Two-Thirds of People with Diabetes Die of Cardiovascular Disease

• Among people with diabetes, macrovascular complications, including CHD, stroke, and peripheral vascular disease, are the leading causes of morbidity and mortality.

Causes of mortality in people with diabetes


Mortality Following First MI in People with and without Diabetes

• Many patients with diabetes will not survive their first MI

<table>
<thead>
<tr>
<th></th>
<th>Mortality rate (n=890)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>44% (n=437)</td>
</tr>
<tr>
<td>Women</td>
<td>33% (n=2699)</td>
</tr>
</tbody>
</table>

Adapted from Amos AF et al Diabetes Care 1998;21:69-75.

People with Diabetes Have MI Risk Levels Comparable to People with Prior MI

• Patients with diabetes without previous MI have as high of a risk of MI as nondiabetic patients with previous MI.
• These data provide a rationale for treating cardiovascular risk factors in diabetic patients as aggressively as in nondiabetic patients with prior MI.

Factors Enhance Each Other!

Smoking 1.6x Hypertension 3x
6x 16x
9x 4x
Hypercholesterolemia

Atherosclerosis (=Dichtslibbing) = Problem

In adjunction to optimal medical therapy and lifestyle modification in patients with DM?

What is the best revascularisation therapy??

Arterial and Venous Bypasses

Stent implantation
PCI / Restenosis background

• Percutaneous Coronary Intervention (PCI) is a safe and effective treatment of atherosclerotic coronary artery disease
• Restenosis remains an important complication after PCI

Therapeutic strategy in DM patients

BARI 2D Study: Medical therapy vs. CABG vs. PCI

Patient: 2,368 DM patients
Intervention: OMT (n=807) vs. PCI (n=798)
Comparison: OMT (n=385) vs. CABG (n=378)
Outcomes: 5-year incidence of death, MI, stroke

Therapeutic strategy in DM patients

CARDia trial: CABG vs. PCI

Patient: 510 DM patients, multi/complex single-vessel
Intervention: PCI (n=248)
Comparison: CABG (n=242)
Outcomes: 1-year incidence of death, MI, stroke, revasc.

Events | PCI vs. CABG HR (95% CI) | p Value
--- | --- | ---
1. Death | 0.98 (0.37-2.61) | 0.97
2. Nonfatal MI (total) | 1.77 (0.92-3.40) | 0.088
3. Nonfatal stroke | 0.14 (0.02-1.14) | 0.066
Composite outcome (1+2+3) | 1.25 (0.75-2.09) | 0.393
4. Revascularization | 6.18 (2.40-15.94) | <0.001
Composite outcome (1+2+3+4) | 1.77 (1.11-2.82) | 0.016
5. TIMI bleeding | 0.19 (0.05-0.67) | 0.009

Therapeutic strategy in DM patients

1YR outcomes of the SYNTAX trial: CABG vs. PCI

Patient: 1,800 patients (452 DM) with LM and/or 3VD
Intervention: DM : PES (n=231) vs. CABG (n=221)
Non-DM : PES (n=672) vs. CABG (n=676)
Outcomes: 1-year MACED (Death, Stroke, MI, Repeated Revasc.)

3YR outcomes of the SYNTAX trial: CABG vs. PCI

Patient: 1,800 patients (452 DM) with LM and/or 3VD
Intervention: PES (n=231)
Comparison: CABG (n=221)
Outcomes: 3-yr MACE (Death, Stroke, MI, Revasc.)

ESC 2010 CONGRESS PAPER:
“debate on CABG vs PCI in DM goes on”
Conclusions: Revascularisation in Patients with Diabetes mellitus

PCI is getting better (but so does CABG), but is not (yet) good enough in complex lesions/multivessel disease in patients with DM.

Update 2008 ESC guideline:

**Recommendation**

- Treatment decisions regarding revascularisation in patients with diabetes should favour coronary artery bypass surgery over percutaneous intervention.
- Glycoprotein IIb/IIIa inhibitors are indicated in elective PCI in a diabetic patient.
- When PCI with stent implantation is performed in a diabetic patient, drug-eluting stents (DES) should be used.

**Intensive glycemic control**

- UKPDS trial benefits on microvascular complications
- Observational studies improved CV outcomes
- less stenosis associated with lower HbA1c
What do the intervention studies teach us?

UKPDS, EXAMINE, HPS, CARDS

United Kingdom Prospective Diabetes Study (UKPDS): Results

<table>
<thead>
<tr>
<th>Intensive glucose control</th>
<th>RR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrovacular endpoints</td>
<td>12%</td>
<td>0.029</td>
</tr>
<tr>
<td>Microvascular endpoints</td>
<td>25%</td>
<td>0.010</td>
</tr>
</tbody>
</table>

Blood pressure Tx risk reduction:
- Macrovascular endpoints: 32% 0.019
- (CVA): 44% 0.013
- Microvascular endpoints: 37% 0.009


Risk factors for CAD in DM type 2

<table>
<thead>
<tr>
<th>% risk increase</th>
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<tbody>
<tr>
<td>HbA1C per 1 %</td>
</tr>
<tr>
<td>Systolic blood pressure per 10 mm Hg.</td>
</tr>
<tr>
<td>HDL-cholesterol per 0.1 mmol/l</td>
</tr>
<tr>
<td>LDL-cholesterol per 1 mmol/l</td>
</tr>
</tbody>
</table>

UKPDS BMJ 1998

What is most important in patients with CAD en DM?

‘Veel dokters hebben last van het HbA1c-fetisjisme’

Medisch Contact 2013;68:1134-5.

Metformin is your friend in DM/CAD, how are the other guys doing?

Mortality and cardiovascular risk associated with different insulin secretagogues compared with metformin in type 2 diabetes, with or without a previous myocardial infarction: a nationwide study

Tina Kim Schramm1*, Gunnar Hiknør Gröndal1, Aksel Vrang1, Jepsen Nørgaard Rasmussen1, Frédrik Folke4, Morten Lash Hansen4, Emil Lohrup Fostel1, Lars Kober1, Mette Lykke Nørgaard4, Mette Madsen4, Peter R. Hansen1, and Christian Torg-Pedersen1

Mortality with the most used SSIS, including glimepiride, glibenclamide, gliclazide, and tolbutamide, seems to be associated with increased mortality and cardiovascular risk compared with metformin. Glimepiride and repaglidi are associated with a lower risk than other SSIS.

ORIGINAL ARTICLE

Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus


New Engl J Med 2013, on line
**Good and less good news**

- Glitins for glucose lowering seem safe in cardiac patients
- Caveat: beware of heart failure (symptoms)
- No (5yr) benefit on cardiovascular endpoints

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**Second coronary prevention in DM**

- **High-intensity statin**
  - Heart Protection Study
    - 37% ↓ in CHD death/MI
- **ACE inhibitor**
  - HOPE diabetic substudy
    - 25% ↓ in CV-death/stroke (p<0.001)
    - 37% ↓ in CV-death over 5yr f/u (p<0.001)
- **Intensive glycemic control**
  - UKPDS trial
    - Benefits on microvascular complications
    - Observational studies
      - Improved CV outcomes
      - Less stenosis associated with lower HbA1c

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**Lipoprotein profile in Diabetes**

- High Triglycerides
- Low HDL-c
- "Normal" LDL-c
- Small dense LDL-c

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"Normal" LDL-C Levels in People with Diabetes Can Be Misleading...
Small, Dense LDL-C Particles Are More Atherogenic

- No diabetes
  - LDL particles
- Diabetes
  - LDL particles

- "Normal" LDL-C level
  - Number of LDL particles
  - Concentration of apoB

- Small, dense LDL with more apoB

CHD risk
Heart Protection Study
Diabetes Sub-Study

• Almost 6000 men and women, aged 40–80 with DM – 1981 persons with history of CHD – 3982 persons with no history of CHD
• People randomized to simvastatin 40 mg or placebo
• Mean duration of follow-up 5 years
• Objective—to evaluate the long-term benefits of simvastatin and/or antioxidants in people with DM with or without CHD regardless of cholesterol level
• Primary endpoints—first major coronary events* and first major vascular events**
• Statin not considered clearly indicated or contraindicated by patients’ primary physicians

Adapted from Heart Protection Study Collaborative Group

Impact of Simvastatin in Patients with Diabetes
Major Coronary Events, Stroke, and Revascularization

Impact of Simvastatin in Patients with Diabetes
With Low LDL-C

CARDS — The Collaborative Atorvastatin Diabetes Study

Study Design

Patient population:
- Enrolled at 132 sites in the UK and Ireland
- Type 2 diabetes with no previous MI or CHD
- ≥1 other CHD risk factor plus LDL-C ≥160 mg/dL and TG ≥600 mg/dL
- Aged 40-75 years

Atorvastatin 10 mg/day
Placebo

 Completion date:
- Terminated early in 2003 due to significant benefit observed in atorvastatin arm

A Brilliant Job?
Do The RIGHT Things Right!


Adapted from Major Protection Study Collaborative Group Lancet 2004;364:685–96.
A Brilliant Job?
Do The RIGHT Things Right!

Influence of DM on CAD

High co-morbidity PVD, CRF
Worse long-term clinical outcomes Death, MI, Stroke
Excessive restenosis Intimal hyperplasia, negative remodeling
High periprocedural complication

加速的动脉粥样硬化 Progression of disease, small vessel diffuse
死亡, MI, 中风 Death, MI, Stroke

Conclusions
Diabetes and the Heart

- Diabetes en CHZ: ‘a bad combination’
- Revascularisatie bij complexe CHZ: PCI verbetert (maar dat geldt ook voorCABG), CABG verdient de voorkeur bij complexe laesies /multivessel disease bij patiënten met DM.
- Glucose regulatie is belangrijk, maar LDL cholesterol verlaging/statine behandeling is minstens zo belangrijk!