Diabetes og kardiovaskulær sykdom

Emnekurs i Diabetes 24.09.14
Hildegunn Aarsetøy
Hvor stor er risikoen?

Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction.

7 års insident-rate for MI:
Uten diabetes mellitus
  Uten infarkt: 3,5 %
  Med infarkt: 18,8 %
Diabetes mellitus
  Uten infarkt: 20,2 %
  Med infarkt: 45,0 %

Atherosklerosis Risk In Communities (ARIC) Study

Cardiovascular Events in Diabetic and Nondiabetic Adults With or Without History of Myocardial Infarction.
Lee CD et al.
Hazard ratios (HRs) for vascular outcomes in people with versus those without diabetes at baseline. Analyses were based on 530,083 participants. HRs were adjusted for age, smoking status, body-mass index, and systolic blood pressure.

### A Coronary heart disease

<table>
<thead>
<tr>
<th></th>
<th>Number of cases</th>
<th>HR (95% CI)</th>
<th>Interaction p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>20,218</td>
<td>1.83 (1.73-2.06)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female</td>
<td>223,550</td>
<td>2.59 (2.39-2.80)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Age at survey</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-59 years</td>
<td>410,833</td>
<td>2.51 (2.25-2.81)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>60-69 years</td>
<td>75,785</td>
<td>2.01 (1.80-2.26)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>70+ years</td>
<td>43,465</td>
<td>1.78 (1.54-2.05)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Smoking status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>343,864</td>
<td>2.35 (2.21-2.61)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Current</td>
<td>128,019</td>
<td>1.62 (1.56-2.07)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bottom third</td>
<td>176,274</td>
<td>2.30 (2.00-2.64)</td>
<td>0.0143</td>
</tr>
<tr>
<td>Middle third</td>
<td>176,323</td>
<td>2.17 (2.05-2.34)</td>
<td>0.0483</td>
</tr>
<tr>
<td>Top third</td>
<td>177,477</td>
<td>1.98 (1.76-2.23)</td>
<td>0.0015</td>
</tr>
<tr>
<td><strong>Systolic blood pressure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bottom third</td>
<td>183,314</td>
<td>2.85 (2.36-3.42)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Middle third</td>
<td>252,622</td>
<td>2.31 (2.05-2.60)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Top third</td>
<td>154,147</td>
<td>1.97 (1.78-2.18)</td>
<td>0.0037</td>
</tr>
</tbody>
</table>

### B Ischaemic stroke

<table>
<thead>
<tr>
<th></th>
<th>Number of cases</th>
<th>HR (95% CI)</th>
<th>Interaction p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>21,93</td>
<td>2.16 (1.84-2.61)</td>
<td>0.0079</td>
</tr>
<tr>
<td>Female</td>
<td>125,571</td>
<td>1.60 (1.35-1.89)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Age at survey</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-59 years</td>
<td>234,263</td>
<td>2.06 (1.64-2.58)</td>
<td>0.0001</td>
</tr>
<tr>
<td>60-69 years</td>
<td>38,140</td>
<td>2.06 (1.44-2.93)</td>
<td>0.0001</td>
</tr>
<tr>
<td>70+ years</td>
<td>21,359</td>
<td>1.89 (1.40-2.57)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Smoking status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>191,125</td>
<td>2.58 (2.53-3.05)</td>
<td>0.1355</td>
</tr>
<tr>
<td>Current</td>
<td>102,657</td>
<td>1.98 (1.76-2.22)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bottom third</td>
<td>110,044</td>
<td>2.50 (2.05-2.99)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Middle third</td>
<td>97,478</td>
<td>2.28 (1.85-2.80)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Top third</td>
<td>85,240</td>
<td>2.50 (2.03-3.08)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Systolic blood pressure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bottom third</td>
<td>113,109</td>
<td>3.03 (2.39-4.04)</td>
<td>0.7275</td>
</tr>
<tr>
<td>Middle third</td>
<td>106,965</td>
<td>2.79 (2.23-3.49)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Top third</td>
<td>73,597</td>
<td>2.49 (2.02-3.10)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
10 års risiko > 20 % (høyrisiko) for MI, slag, død eller revaskularisering:
Menn 41 år
Kvinner 48 år
Detection of Coronary Artery Disease in Asymptomatic Patients with Type 2 Diabetes Mellitus.
Scognamiglio R et al. Circulation 2006; 47: 65-71
Asymptomatisk CAD og risikostratifisering

Risk stratification in uncomplicated type 2 diabetes: prospective evaluation of the combined use of coronary artery calcium imaging and selective myocardial perfusion scintigraphy.
Angiographic study of coronary artery disease in diabetic patients in comparison with nondiabetic patients.
Melidonis A et al. Angiology 1999; 50: 997

Figure 1.  Angiographic disease severity in diabetics and controls.

Figure 2.  Distribution of CAD in the coronary vessels.
Hvorfor har diabetikere økt risiko for CVD?

Oftere flere samtidige risikofaktorer:
- Kjønn; kvinne > mann
- Overvekt
- Røyking
- Familiehistorie
- Hypertensjon
- Dyslipidemi

Diabetes relaterte faktorer:
- Hyperglykemi
- Insulinresistens
- Økte nivåer av FFA
  - AGE
  - Økt oksidativt stress/frie radikaler
- Abnorme lipoprotein
- Økt inflammasjon
- Redusert fibrinolyse
- Økt aktivering av blodplater
Insulin resistance and the endothelium

Willa A Hsueh, Christopher J Lyon, Manuel J Quiñones.
Forebygging

• Livsstilsintervensjon?
  - Vektnedgang
  - Økt mosjon
  - Røykeslutt

• Medikamentell behandling
  - Glykemisk kontroll
  - BT-behandling
  - Lipidsenkende behandling
  - ASA?
Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes
The Look AHEAD Research Group

INKLUSJONSKRITERIER:
• 45-75 år
• BMI > 25
• HbAc < 11 %
• BT < 160/100
• Triglyserider < 6,7 mmol/L
• Alle medikamenter tillatt
• Med/uten kjent CVD

INTERVENSJONSGRUPPE (n=2570):
• 1200-1800 kcal/dag
• Minimum 175 min moderat-intensiv fysisk aktivitet/uke
• MÅL: Vektreduksjon ≥ 7 %

KONTROLLGRUPPE (n=2575):
Generell undervisning om diabetes, kost og mosjon

Changes in Weight, Physical Fitness, Waist Circumference, and Glycated Hemoglobin Levels during 10 Years of Follow-up.

Cumulative Hazard Curves for the Primary Composite End Point.

Medikamentell behandling
Glykemisk kontroll

Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study

Stratton I M et al. BMJ 2000;321:405-412
Glycosylated Hemoglobin and Cardiovascular Disease in Diabetes Mellitus

Kan CVD forebygges ved god blodsukkerkontroll?

Intensive Diabetes Treatment and Cardiovascular Disease in Patients with Type 1 Diabetes (DCCT/ EDIC-study)

**DCCT (Diabetes Control and Complications Trial):**
- 1983-1993
- 1441 DM1 pasienter
- Alder 13-40 år
- Fravær av CVD eller andre risikofaktorer
- Intensiv glykemisk kontroll: HbA1c < 6,05 %, F-glu 3,9-6,7 mmol/L Postprandialt < 10
- Konvensjonell beh.

**EDIC (Epidemiology of Diabetes Interventions and Complications):**
- 1993-2004
- N=1394
- HbA1c 1993:
  - Intensiv gruppe 7,4 %
  - Kontrollgruppe 9,1 %
- HbA1c 2004:
  - Intensiv gruppe 7,9 %
  - Kontrollgruppe 7,8 %
Blodsukker kontroll ved DM2

The Action to Control Cardiovascular Risk in Diabetes Study Group (ACCORD)

Median HbA1c Levels at Each Study Visit.

The Action to Control Cardiovascular Risk in Diabetes Study Group (ACCORD)

### Primary Outcome

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>No. of Events</th>
<th>Hazard Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>10,251</td>
<td>723</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous cardiovascular event</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>6,643</td>
<td>330</td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>Yes</td>
<td>3,608</td>
<td>393</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>3,952</td>
<td>212</td>
<td></td>
<td>0.74</td>
</tr>
<tr>
<td>Male</td>
<td>6,299</td>
<td>511</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>6,779</td>
<td>383</td>
<td></td>
<td>0.65</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>3,472</td>
<td>340</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycated hemoglobin at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤8.0%</td>
<td>4,868</td>
<td>284</td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>&gt;8.0%</td>
<td>5,360</td>
<td>438</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonwhite</td>
<td>3,647</td>
<td>222</td>
<td></td>
<td>0.29</td>
</tr>
<tr>
<td>White</td>
<td>6,604</td>
<td>501</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS)

- Nydiagnostisert DM2
- Alder 25 – 65 år
- Fravær av CVD eller andre komplikasjoner v/inkl.
- Intensiv gruppe f-glu < 6 mmol/L
- Kontroll: f-glu < 15 mmol/L (kost)

C Myocardial Infarction

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Years since Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional therapy</td>
<td>1138 1013  857  578  221  20</td>
</tr>
<tr>
<td>Sulfonylurea–insulin</td>
<td>2729 2488 2097 1459 577  66</td>
</tr>
</tbody>
</table>

Medikamentell behandling
Metformin

Improved endothelial function with metformin in type 2 diabetes mellitus

Endothelium-dependent blood flow responses before and after treatment with metformin. Doses are 3, 10 and 30 μg/min.

*p = 0.0027 by two-way analysis of variance, comparing treatment effects in the two groups. ACh = acetylcholine; FBF = forearm blood flow.

Mather KJ et al. J Am Coll Cardiol 2001; 37: 1344 - 1350
Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom prospective diabetes study (UKPDS)

Turner RC et al. BMJ 1998; 31: 823
Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial

Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis

Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus (ACCORD Lipid)

Lipid Values

Simvastatin with or without Ezetimibe in Familial Hypercholesterolemia

Lipidsenkende tiltak utover medikamentell behandling

Endring av livsstil:
- Redusert inntak av mettet fett og transfett
- Vektreduksjon
- Økt fysisk aktivitet
- Røykeslutt

Kan redusere LDL-kolestrolet med 10 %

Forbedring av glykemisk kontroll:

Arch Intern Med. 2000;160(18):2756-2762
Anbefalinger for lipidsenkende behandling

• Alle pasienter med kjent CVD bør behandles med et statin
• Pasienter uten CVD bør behandles med statin dersom:
  - > 40 år og LDL-kolestrol > 3,5 mmol/l
    (kan fravikes ved fravær av andre risikofaktorer)
  - > 40 år og multiple risikofaktorer for CVD
  - < 40 år og samtidig høy risiko (nefropati, retinopati,
    heriditet, høy HbA1c, røyking)
• Behandlingsmål uten CVD: LDL < 2,5 mmol/l
  med CVD: LDL < 1,8 mmol/l
• Ved triglycerider > 10 mmol/l tillegg av fibrater
• Ingen dokumentasjon for oppstart etter fylte 80 år
Medikamentell behandling

ASA

• Anbefales ikke som ledd i primær profylakse

Oppsummering

• Diabetes gir 2-4 ganger økt risiko for kardiovaskulær sykdom
• «Coronary heart disease equivalent»?

• Viktig med god forebygging fra sykdomsdebut
• Røykeslutt
• Livsstilsendring?
• HbA1c < 7 %
  - spesielt viktig ved primær prevensjon og kort sykdomsvarighet
  - effekten av god regulering kan vedvare over lang tid
  - individuell vurdering

• Tilstrekkelig blodtrykksbehandling
• Statiner ved indikasjon
TAKK FOR OPPMERKSOMHETEN!