Macrovascular Disease in Diabetes

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Conflicts

CPC Clinical Research (University-based Academic Research Center) receives grant support from numerous industry sponsors and NIH. William Hiatt is a member of the FDA Division of Metabolism and Endocrinology Advisory Committee. I have no other conflicts and do not receive funds personally from any industry sponsor.
Pathophysiology of Cardiovascular Disease in Diabetes

Hyperglycemia and vascular injury

- Activation of protein kinase C (PKC)
- Reduced NO availability and accumulation of reactive oxygen species (ROS) from mitochondria
- Formation of endothelin-1 (vasoconsriction) and thromboxane (platelet activation)
- Release of inflammatory cytokines

Eur Heart J 2013;34:2436-43
Mechanisms of Hyperglycemia-Induced Vascular Injury

Eur Heart J 2013;34:2436-43
Pathophysiology of Cardiovascular Disease in Diabetes

Insulin resistance and atherothrombosis

• Obesity and insulin resistance lead to:
• FFA’s binding to Toll-like receptor (TLR) which activates NF-κB triggering tissue inflammation (IL-6 and TNF-α)
• Promotes endothelial dysfunction and platelet aggregation
Diabetes and Atherothrombosis

- Obesity
  - ↑FFA
  - ↓TLR
  - ↑IKK-β
  - ↑NFκB
  - ↑TNF-α
  - ↓GLUT-4
  - ↓IRS-1/Akt

- Type 2 Diabetes
  - ↑JNK/PKC

- Insulin resistance

- Endothelium
  - ↓PI3/Akt
  - ↑FFA oxidation
  - ↑ROS
  - ↑AGEs
  - ↑PKC
  - ↓GlcNAc
  - ↓PGI2 synthase
  - ↓eNOS activity
  - ↓NO
  - Endothelial dysfunction

- Platelets
  - ↓IRS-1/PI3K
  - ↓Ca2+
  - Platelet aggregation

Atherothrombosis
Pathophysiology of Cardiovascular Disease in Diabetes

MicroRNA (miRNA)
• Small non-coding RNA’s that regulate post-transcriptional gene expression
• Drive complex signaling controlling the expression of genes that regulate cell differentiation, migration and survival
MicroRNA

Diabetes

↑ miR-320
- VEGF/IGF-1
- Angiogenesis

↑ miR-221
- c-kit
- EPCs Proliferation Migration Homing

↓ miR-222
- P27KIP1/P57KIP2
- AGEs
- Angiogenesis Endothelial dysfunction

↑ miR-503
- CCNE/cdc25A

↓ miR-126
- Spred-1
- EPCs function Angiogenesis

↓ Vascular Repair

↓ Diabetic Vascular Disease
Pathophysiology of Cardiovascular Disease in Diabetes

Thrombosis and coagulation

- Hyperglycemia and insulin resistance are pro-thrombotic
- Increase in tissue factor, thrombin, fibrin and PAI-1
- Decrease in tissue plasminogen activator
Diabetes, Coagulation and Platelets

- Hyperglycemia
- Inflammation
- Insulin Resistance

- Endothelial Damage
- Fibrinogen
- Fibrin
- TF
- Thrombin
- t-PA
- PAI-1
- MP
- IIb/IIIa
- IIb/IIIa
- vWF
- EC
- Collagen

- Platelets
- Calcium
Treating CVD Risk in Diabetes

Dyslipidemia
- Adipocytes
  - ↑ FFA's
  - ↑ Triglycerides
  - ↓ HDL
  - ↑ oxLDL

Hyperglycaemia and Insulin Resistance
- Hepatic Output
  - ↑ Insulin
  - ↑ Glucose

Statins
- Hypertension
  - ACE-Is
  - Beta Blockers
  - ARBs
  - CaCBs

Insulin Sulphonylureas
  - Metformin

ASA
  - Clopidogrel

Platelet Activation
AHA Heart and Stroke Statistics

Circulation 2012:
Lifestyle Interventions

5145 overweight or obese patients with type 2 diabetes
Median follow-up 9.6 years
Primary outcome = composite of CV death, nonfatal MI, nonfatal stroke, or hospitalization for angina
Results:
• Better weight loss, A1c and fitness
• CV events HR 0.95 (95% CI 0.83-1.09)

NEJM 2013;369:145-54
Bariatric Surgery and Diabetes

Decreased incidence of diabetes

Improved control in established diabetes

NEJM 2012;367:695-704
NEJM 2014;370:2002-13
UK PROSPECTIVE DIABETES STUDY
Intensive Glycemic Control

4209 type 2 diabetes mellitus followed 10 years
  - 1138 conventional (diet)
  - 2729 intensive (sulphonylurea or insulin)
  - 342 metformin (obese subjects)

Hemoglobin A$_{1c}$
  - 7.9% conventional group
  - 7.0% intensive group
  - 7.4% metformin group

**UK PROSPECTIVE DIABETES STUDY**

<table>
<thead>
<tr>
<th>Event</th>
<th>Intensive RR (95% CI)</th>
<th>Metformin RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any DM endpoint</td>
<td>0.88 (0.79-0.99)*</td>
<td>0.68 (0.53-0.87)*</td>
</tr>
<tr>
<td>Microvascular</td>
<td>0.75 (0.60-0.93)*</td>
<td>0.71 (0.43-1.19)</td>
</tr>
<tr>
<td>Diabetes death</td>
<td>0.90 (0.73-1.11)</td>
<td>0.58 (0.37-0.91)*</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>0.94 (0.80-1.10)</td>
<td>0.64 (0.45-0.91)*</td>
</tr>
<tr>
<td>Myocardial infarct</td>
<td>0.84 (0.71-1.00)</td>
<td>0.61 (0.41-0.89)*</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.11 (0.81-1.51)</td>
<td>0.59 (0.29-1.18)</td>
</tr>
<tr>
<td>PAD death or amp</td>
<td>0.65 (0.36-1.18)</td>
<td>0.74 (0.26-2.09)</td>
</tr>
<tr>
<td>Microvascular</td>
<td>0.75 (0.60-0.93)*</td>
<td>0.71 (0.43-1.19)</td>
</tr>
</tbody>
</table>

**Statin Benefit in Diabetes**

![Graph showing the benefits of statins in diabetes](chart.png)

**Table C: More Statin vs. Less Statin and Statin vs. Control (26 trials)**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Statin or More Statin</th>
<th>Control or Less Statin</th>
<th>Relative Risk per 1 mmol/liter (39 mg/dl) Reduction in LDL Cholesterol (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vascular Events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major vascular event</td>
<td></td>
<td></td>
<td>0.77 (0.58–1.01)</td>
</tr>
<tr>
<td>Patients with type 1 diabetes</td>
<td>145 (4.5)</td>
<td>192 (6.0)</td>
<td></td>
</tr>
<tr>
<td>Patients with type 2 diabetes</td>
<td>2494 (4.2)</td>
<td>2920 (5.1)</td>
<td>0.80 (0.74–0.86)</td>
</tr>
<tr>
<td>Patients without diabetes</td>
<td>8272 (3.2)</td>
<td>10,163 (4.0)</td>
<td>0.78 (0.75–0.81)</td>
</tr>
<tr>
<td>Any major vascular event</td>
<td>10,973 (3.2)</td>
<td>13,350 (4.0)</td>
<td>0.78 (0.76–0.80)</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cause-specific mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cardiac</td>
<td>3333 (0.9)</td>
<td>3384 (1.1)</td>
<td>0.84 (0.80–0.88)</td>
</tr>
<tr>
<td>Stroke</td>
<td>483 (0.1)</td>
<td>501 (0.1)</td>
<td>0.96 (0.84–1.09)</td>
</tr>
<tr>
<td>Any vascular</td>
<td>4220 (1.2)</td>
<td>4794 (1.3)</td>
<td>0.86 (0.82–0.90)</td>
</tr>
<tr>
<td>Any nonvascular</td>
<td>2943 (0.8)</td>
<td>2994 (0.8)</td>
<td>0.97 (0.92–1.03)</td>
</tr>
<tr>
<td>All-cause mortality (any death)</td>
<td>7642 (2.1)</td>
<td>8327 (2.3)</td>
<td>0.90 (0.87–0.93)</td>
</tr>
</tbody>
</table>

Lancet 2010;376:1670-81
Statin Risk and Diabetes

Statin risk of causing new onset diabetes

- Meta-analysis of 6 statin trials (57,593 patients)
  - 13% relative risk increase of incident diabetes
- Meta-analysis of 13 trials (91,140 patients)
  - Odds Ratio 1.09
  - In 255 patients treated 4 years = 1 new case of diabetes and 5.4 fewer vascular events
- Diabetes risk dose-dependent (odds ratio 12% compared with low dose) but 16% greater reduction in vascular events
- Therefore - benefit >> risk

Diabetes Care 2009;32:1924-9
Lancet 2010;375:735-42
JAMA 2011;305:2556-64
Cardiovascular Therapies for Diabetes

**Hyperglycemia**
+ Metformin to lower Hgb A1c to <7% in the prevention of CVD
  Θ Target Hgb A1c of 6–6.5% is harmful compared with 7%
  UKPDS, ACCORD, ADVANCE

**Hypertension**
+ Blood pressure should be reduced to <140/90 mmHg
+ Patients with CHD, CVD, or PAD should receive an ACE/ARB
  ALLHAT, HOPE, VALUE, ONTARGET
  Θ Blood pressure lowered < 120/80 mmHg is harmful
  Θ Avoid alpha adrenergic blockers
  ACCORD-BP, ALLHAT

**Dyslipidemia**
+ All patients should be treated with statins
  HPS CARDS
  Θ Fibrates or long-acting niacin not useful
  ACCORD-Lipid, AIM-HIGH
  ± benefit of fibrates in HDL <34 mg/dL, TG > 204 mg/dL
  SACKS, FIELD

**Antiplatelet therapy**
+ Aspirin is effective in secondary prevention for CVD
+ P2Y12 inhibitors plus aspirin in ACS is established
+ P2Y12 inhibitors are superior to aspirin as monotherapy in PAD
  CURE, TRITON, CAPRIE
  Θ Aspirin for primary prevention of CVD is not established
  JPAD, POPADAD