Percutaneous coronary intervention in patients with diabetes mellitus

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The prevalence is increasing:

- within the next 25 years, the worldwide prevalence is estimated to double

Wild et al Diabetes Care 2004;27:1047-53
The global burden of diabetes

Patients with DM have a 2-4x increased risk of cardiovascular disease and a significantly shorter life expectancy.

Cardiovascular disease is responsible for 75-80% deaths in diabetic patients.

Source: International Diabetes Federation
Complex coronary disease

- Multivasel disease
- Diffuse disease
- Small vessel disease
- Distal disease
- Calcification
- Impaired left ventricular function
Pathophysiology

• **Atherogenic dyslipidemia**
  – high triglyceride levels: enhanced thrombogenicity, remnant triglyceride-rich lipoproteins
  – small dense LDL particles: increased penetration of arterial intima, enhanced proteoglycan binding, increased oxidation potential
  – low HDL cholesterol: reduced antioxidant and anti-inflammatory activity

• **Impaired endothelial function** - decreased nitric oxide, increased endothelin-1 and angiotensin II increases vascular tone and smooth muscle cell migration and growth
Pathophysiology

• **Prothrombotic milieu** –
  
  – increased platelet activation:
    * (increased number of circulating platelets, decreased platelet cAMP, increased GP IIb/IIIa receptor density, increased vitronectin circulating fibrinogen and thrombin / antithrombin II complexes, increased P-selectin)
  
  – coagulation cascade activation:
    * (increased fibrinogen, increased von Willebrand factor, increased FPA (increased thrombin activity), decreased activity of AT III, decreased sulfation of endogenous heparin)
  
  – impaired fibrinolysis:
    * (increased plasminogen activator inhibitor-1 synthesis, (directly increased by insulin & IGF-1, decreased concentration of alpha-2 antiplasmin)
Prognosis of patients with DM and coronary artery disease

• 5-year survival curves for 3320 patients (24% diabetic) treated at Duke Medical Center, for multivessel disease
MACE following PCI in diabetic patients

- Diabetic patients have higher rates of MACE
- Diabetes increases restenosis
  - Increased rates if on insulin therapy
- Diabetes is an independent predictor of TLR

Gilbert et al Diabetes Care 2004;27:990-994, Cutlip et al JACC 2002;40:2082-9,
Lemos et al Circulation 2004;109:1366-1370
Worse prognosis in ACS

- GRACE registry: prospective multicenter study of patients with ACS
  - diabetic versus non-diabetic pts

<table>
<thead>
<tr>
<th>In-hospital outcomes</th>
<th>STEMI</th>
<th></th>
<th>NSTEMI</th>
<th></th>
<th>Unstable angina</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DM</td>
<td>Non-DM</td>
<td>DM</td>
<td>Non-DM</td>
<td>DM</td>
</tr>
<tr>
<td>n</td>
<td>1141</td>
<td>4262</td>
<td>1271</td>
<td>3454</td>
<td>1489</td>
</tr>
<tr>
<td>Death</td>
<td>1.48 (1.03-2.13)</td>
<td>1.14 (0.85-1.52)</td>
<td>1.41 (1.02-1.95)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>1.08 (0.76-1.53)</td>
<td>1.09 (0.79-1.50)</td>
<td>1.33 (0.88-2.02)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>1.74 (1.43-2.11)</td>
<td>1.88 (1.60-2.21)</td>
<td>1.80 (1.50-2.18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal failure</td>
<td>1.50 (1.00-2.23)</td>
<td>1.72 (1.32-2.25)</td>
<td>2.12 (1.45-3.08)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Franklin et al Arch Int Med 2004;164:1457-1463
Worse prognosis with AMI

- VALIANT study of 14,703 patients with AMI
  - Known DM (n=3,400, 23%)
  - Newely diagnosed DM (n=580, 4%)
  - No DM (n=10,719)

Survival at 1 year by diabetic status

- p<0.001 for previous DM vs no DM
- p<0.001 for new DM vs no DM
- p=0.43 for previous DM vs new DM

Aguilar et al. Circulation 2004;110:1572-78
Prognosis of patients with DM and coronary artery disease

- Long-term survival rates of 604 diabetic patients following successful balloon angioplasty
- Stratified according to the results of follow-up angiography at 6-months

Van Belle et al Circulation 2001
DIABETES trial: in-segment restenosis rate at 9-months

- **Overall NIDDM IDDM SES (n=80)**
  - SES (n=80)
  - BMS (n=80)

- **p<0.001**
- **p=0.001**
- **p=0.001**

SES tended to have shorter length of restenosis

Occlusive restenosis occurred in 5.5% BMS versus 0.9% SES, (p=0.07)

Sabate et al Circulation 2005;112:2175-2183
## DIABETES trial: clinical outcomes at 9-months

<table>
<thead>
<tr>
<th>Event</th>
<th>SES (n=80)</th>
<th>BMS (n=80)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, n (%)</td>
<td>1 (1.3)</td>
<td>2 (2.5)</td>
<td>ns</td>
</tr>
<tr>
<td>Q-MI, n (%)</td>
<td>1 (1.3)</td>
<td>0</td>
<td>ns</td>
</tr>
<tr>
<td>Non-Q MI, n (%)</td>
<td>1 (1.3)</td>
<td>5 (6.3)</td>
<td>ns</td>
</tr>
<tr>
<td>TLR, n (%)</td>
<td>5 (6.3)</td>
<td>25 (31.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MACE, n (%)</td>
<td>8 (10.0)</td>
<td>29 (36.3)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Sabate et al Circulation 2005;112:2175-2183
TAXUS™ Stent in diabetics

TAXUS 4 yr meta-analysis: All Diabetics
TAXUS II¹ (4 yr), IV² (4 yr), V³ (2yr), VI⁴ (3 yr) studies (N=814)

<table>
<thead>
<tr>
<th>Events (%)</th>
<th>Stent Thrombosis</th>
<th>All Death</th>
<th>Cardiac Death</th>
<th>QWMI</th>
<th>TLR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bare Metal Stent (N=415)</td>
<td>1.2%</td>
<td>11.0%</td>
<td>3.8%</td>
<td>1.7%</td>
<td>25.5%</td>
</tr>
<tr>
<td>TAXUS Stent (N=399)</td>
<td>1.4%</td>
<td>9.1%</td>
<td>4.6%</td>
<td>0.5%</td>
<td>13.1%</td>
</tr>
</tbody>
</table>

p=0.80  p=0.58  p=0.75  p=0.18  p<0.0001

Prothrombotic milieu: increased risk of stent thrombosis

- Independent predictors of stent thrombosis
- 2229 pts undergoing “real world” DES implantation

<table>
<thead>
<tr>
<th>Predictor</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature APT discontinuation</td>
<td>89.78 (29.90-269.60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Renal failure</td>
<td>6.49 (2.60-16.15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bifurcation lesion</td>
<td>6.42 (2.93-14.07)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3.71 (1.74-7.89)</td>
<td>0.001</td>
</tr>
<tr>
<td>LV EF per 10% decrease</td>
<td>1.09 (1.05-1.13)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Iakovou et al JAMA 2005;293:2126-2130
• 8,146 patients treated with DES implantation (SES, n=3823, PES n=4323)
• Angiographically confirmed stent thrombosis occurred in 152 patients (cumulative incidence at 3 years 2.9%)
• Independent predictors of stent thrombosis
  – ACS at presentation (HR 2.28, 95% CI 1.29-4.03)
  – Diabetes (HR 2.03, 95% CI 1.07-3.83)

Daemon et al The Lancet 2007;369:667-678
Anti-platelet therapy

• Diabetic platelets are different!
  – Platelets have reduced membrane fluidity perhaps reflecting glycation of membrane proteins, and also related to increased intracellular calcium mobilization
  – Arachidonic acid metabolism is increased, leading to enhanced thromboxane A2 production
  – Reduced intracellular magnesium concentration – consistent with increased platelet hyperaggregability and adhesiveness
  – Diabetic platelets produce less NO (platelets contain less NO synthase) and prostacyclin, which normally inhibit platelet-endothelium interactions and promote endothelium-mediated vasodilation
  – Platelets have increased expression of activation-dependent adhesion molecules eg GPIIb/IIIa, thrombospondin, and P-selectin
  – Patients with DM have a greater rate of platelet turnover

Colwell et al Diabetes Care 2003 26:2181-88
GPIIb/IIIa inhibitor use in diabetic patients with ACS

- 6,458 diabetic patients
  - GPIIb/IIIa inhibitor use reduced 30-day mortality (4.6% versus 6.2% (OR 0.74; 95% CI 0.59-0.92, p=0.007))
  - 1,279 diabetic patients had PCI during index admission, in this subgroup, GPIIb/IIIa inhibitor use reduced 30-day mortality (1.2% versus 4.0% (OR 0.30; 95% CI 0.14-0.69, p=0.002))

Roffi et al Circulation 2001;104:2767-2771
GPIIb/IIIa inhibitor use in DM: abciximab

- Pooled data from EPIC, EPILOG, and EPISTENT
- Abciximab versus placebo in patients undergoing elective or urgent PCI
- 1,462 patients with DM

Abciximab reduced mortality from 4.5% to 2.5%, p=0.03

Bhatt et al JACC 2000;35:922-8
OPTIMUS

- Type 2 diabetics (n=40) with CAD and previous PCI, with a suboptimal response to clopidogrel
- Randomised to 150mg od versus 75mg od clopidogrel, with assessment of platelet function
- Inhibition of late platelet aggregation between baseline and at 30 days, assessed after 30µmol/L and 5 µmol/L ADP

ACUITY

ACS: Unstable angina or NSTEMI, N=13,819
Chest pain >10’ within 24 hours, plus
  Biomarker +, or
Dynamic ECG changes, or
Documented CAD or all other TIMI risk criteria

Enoxaparin or UFH + IIb/IIIa inhibitor
Bivalirudin + IIb/IIIa inhibitor
Bivalirudin provisional IIb/IIIa inhibitor

ASA
Clopidogrel per local practice

Prior UFH, LMWH (1 dose), eptifibatide and tirofiban were allowed

Cath within 72 hours
PCI, CABG or medical management

30 day endpoints
Death, MI, IUR, ACUITY major bleeding
(net clinical outcome)

Feit et al, presented at TCT 2006
ACUITY diabetic subgroup: 30-day results

- Heparin + GPIIb/IIIa (n=703)
- Bivalirudin + GPIIb/IIIa (n=713)
- Bivalirudin alone (n=721)

30-day results:
- Net clinical outcome: p=0.08
- Composite ischaemia: p=0.42
- Major bleeding: p=0.003
Characteristics of the diabetic patient

We must take a holistic approach to the management of patients with diabetes mellitus.
The importance of glycemic control

- 160 patients with DM randomised to conventional therapy vs intensive therapy of cardiovascular risk factors
  - Bp
  - Lipids
  - Diet
  - HbA1c

- Primary endpoint was composite of death, MI, stroke, revascularisation, amputation

Gaede et al NEJM 2003;348:383-93
Optimal glycaemic control is associated with less TVR

- 239 patients undergoing elective PCI
- HbA1c ≤7% versus HbA1C >7%
- HbA1c was an independent predictor of TVR

Corpus et al JACC 2004;43:8-14
Fluvastatin after PCI: LIPS study

- DM n=202, no DM n=1475
- Fluvastatin 80mg od versus placebo
- MACE: death, MI, reintervention

- Diabetes increased the rate of MACE almost 2-fold in patients treated with placebo (RR 1.78, 95% CI:1.20-2.64, p=0.0045)

- However, in diabetic patients, fluvastatin reduced the risk of MACE by 51% (p=0.009)

Arampatzis et al AHJ 2005;149:329-35
BARI 2D-trial (sponsored by NHLBI)

- Revascularization versus no revascularization in insulin versus non-insulin-treated diabetic patients with mild / moderate symptoms

2,600 patients with type 2 DM and CAD

Coronary revascularisation hypothesis

Method of glycemic control hypothesis

Initial elective PCI/CABG*

Medical therapy alone*

Insulin provision

Insulin sensitisation

*Aggressive medical therapy in both arms

*Target HbA1c <7.5%

Primary endpoint – 5-year mortality
The CARDia Trial

- Multi-centre, randomised, prospective study of revascularization in diabetics in the UK
- Multivessel disease or complex single vessel disease
- DES (with abciximab) versus CABG (use of LIMA, on or off pump)
- Evaluation of 600 patients (so far recruited approx 90%)
- Primary endpoint: composite of death, AMI, or stroke at 1 year
FREEDOM trial (sponsored by NHLBI)

DES versus CABG in diabetics with multivessel disease

PI: Valentin Fuster

Eligibility: DM patients with ≥2 vessel disease suitable for stent or surgery
Exclude: AMI and / or cardiogenic shock

2400 patients randomised 1:1

DES Cypher or Taxus with abciximab

CABG

Primary endpoint: 3 yr composite of death, AMI, or stroke

Medical therapy: HbA$_{1c}$ <7.0%
target BP <130/80mmHg
target LDL <70mg/dL

All patients to receive both aspirin and clopidogrel for 1 year
Conclusions

• Outcomes in diabetic patients are worse whether treated by PCI or CABG compared with non-diabetics
  – More complex disease
  – Less complete revascularization
  – Increased lesion progression

• DES are effective in DM, however DM remains an independent predictor of MACE and TLR

• Remember to optimise medical therapy
  – Pre-procedure eg renal function, clopidogrel loading
  – Peri-procedure eg GPIIb/IIIa inhibitor / bivalirudin
  – Post-procedure eg glycemic control, BP control