Diabetes and Cardiovascular Disease – Risk and Management

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Diabetes and Management of Chronic CAD

Objectives

• Prevention
• Stabilize -> Prevent Acute Coronary Syndromes
• Reduce Symptoms
• Reduce Progression and Late Complications
  – Heart Failure
  – Cardiovascular Death

Prevalence

Diabetes – A Cardiovascular Disease

• Framingham Heart Study – Diabetes increased risk for CHD 2 times in men and 3 times in women.
• MRFIT study – 12 year risk for cardiovascular death 9.7% for diabetes versus 2.6% without diabetes
• Emerging Risk Factors Collaboration – Meta-analysis of 102 studies with over 500,000 subjects.
  – Diabetes associated with doubling of risk for cardiovascular disease, cardiovascular death and MI

W Kannel et al. Circulation 1979;59:8
ERFC Lancet 2010;375:2215
Diabetes Mellitus is a CHD Equivalent

Haffner S et al. NEJM 1998;339:229

DM without prior MI versus non DM with prior MI:
• Future MI (20% vs 19%)
• Coronary Death (15% vs 16%)

Hallmarks of Diabetic Coronary Artery Disease

Compared to patients without diabetes -
• Increased atherosclerotic burden
  – Diffuse disease
  – Multi-vessel involvement
  – Increased disease progression
• Increased risk for acute MI and death
• Poor response to medical and revascularization therapies

Diabetes and Plaque Composition

• Increased unstable plaque histology based on atherectomy specimens
  – Increased lipid rich atheroma
  – Increased macrophage infiltration
  – Increased thrombus

Plaque vulnerability ➔ Myocardial Infarction

Diabetes and Coronary Thrombosis

- Increased platelet activation and aggregation
- Platelet hyperreactivity mediated in part by hyperglycemia
- Elevated fibrinogen and enhanced binding to platelet GP IIb/IIIa receptor
- Decreased fibrinolytic activity – increased levels and binding of plasminogen activator inhibitor (PAI-1)

M Quinones et al. Ann Int Med 2004; 140:700
K Mather et al. JACC 2001;37:1344
M Mullen et al. JACC 2000;36:410

Diabetes and CAD in Women

- Diabetes is an independent predictor of MI and coronary death in women.
- The increased risk for coronary disease among patients with diabetes is greater for women (3 fold vs 2 fold).
- Diabetes eliminates the age gap in development of cardiovascular disease between men and women (age of high-risk for women with diabetes = 48 years).

R Huxley et al. BMJ 2006; 332:73
GL Booth et al. Lancet 2006;368:29

Screen Asymptomatic DM Patients?

- DIAD (Detection of Silent Myocardial Ischemia in Asymptomatic Diabetic Subjects)
  - 22% Type 2 DM (age 50-75) + pharmacologic stress test; large defects in 5%
- In retrospective series
  - 40-60% of asymptomatic Type 2 DM patients had abnormal stress tests
  - High-risk findings in 20%

2. Rajagopalan N et al. JACC 2005;45:43
Limitations of Routine Screening

- 10-15% false positives and false negatives
- Risk of angiography and revascularization procedures
- Unproven benefit of treatment beyond risk factor control
- Failure to prevent events over time – DIAD showed no difference in cardiac events among patients randomized to screening.¹

¹ LH Young et al. *JAMA* 2009;301:1547–1555

Screen Asymptomatic DM Patients?

Updated ADA Recommendations

- Typical or atypical symptoms
- Abnormal resting ECG
- Prior recommendation for screening of patients with 2 or more other CAD risk factors and prior to exercise program removed.

Screen Asymptomatic DM Patients?

Our Approach

- Careful search for atypical symptoms (nausea, fatigue, dyspnea)
- Lower threshold for patients with autonomic neuropathy
- Non-imaging ETT may be of value to assess functional status and exclude symptoms (in some patients), especially prior to exercise program.
Step 1- Prevention
Diabetes and Pathways to Heart Disease

Risk Factors

Diabetes
Coronary Heart Disease

Glycemic Control
Failure to Prevent Macrovascular Complications

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Trial Name</th>
<th>Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Hypoglycemics</td>
<td>UGDP</td>
<td>Tolbutamide ↑ CV risk; No difference other groups</td>
</tr>
<tr>
<td>Sulfonurea/Insulin</td>
<td>UKPDS</td>
<td>-16% (NS)</td>
</tr>
<tr>
<td>Metformin/Sulfonurea</td>
<td>UKPDS</td>
<td>+96% (DM-related mortality)</td>
</tr>
<tr>
<td>Metformin (overweight)</td>
<td>UKPDS</td>
<td>-39% (p&lt;0.05)</td>
</tr>
<tr>
<td>Insulin</td>
<td>DCCT Type 1 DM</td>
<td>+42% (p=0.02)</td>
</tr>
</tbody>
</table>

Adapted from Libby and Plutzky. Circulation 2002;106:2762

Why Does Intensive Glycemic Control Not Reduce Diabetic Cardiovascular Disease?

- Complex multifactorial process that is only partially related to direct effects of hyperglycemia
- Tardy initiation of therapy after inflammatory and oxidative pathogenic pathways well developed
- “Intensive” therapy is still inadequate
- Most therapies increase insulin supply (sulfonylureas, insulin) versus insulin sensitizing.

Libby P and Plutzky J. Circulation 2002;106:2760
**Intensive Glucose Control and CV Events**

**ACCORD and ADVANCE**

**ACCORD**
- Goal: HbA1C <6.0%
- Intense: Mean FU 3.5 Y
  - N=10,251
  - HR 0.90 (0.78-1.46) for CV Event Death

**ADVANCE**
- Goal: HbA1C <6.5%
- Intense: Mean FU 5Y
  - N=11,140
  - HR 0.84 (0.81-1.00) for CV Event Death

**BARI 2D – Glycemic Control Strategy**

<table>
<thead>
<tr>
<th>Drug Therapy</th>
<th>Insulin-Provision</th>
<th>Insulin-Sensitization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=987</td>
<td>N=977</td>
</tr>
<tr>
<td>Insulin (61%)</td>
<td>Sulfonylurine (52%)</td>
<td>Metformin (72%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TZD (62%)</td>
</tr>
<tr>
<td>HbA1C (3 years)</td>
<td>7.5%</td>
<td>7.0% (p&lt;0.001)</td>
</tr>
<tr>
<td>Death (5 yrs)</td>
<td>12.1%</td>
<td>11.8%</td>
</tr>
<tr>
<td>Major CV events (5 yrs)</td>
<td>24.6%</td>
<td>22.3%</td>
</tr>
</tbody>
</table>

**Diabetes and Coronary Disease**

**The Role of Hypertension**

- Hypertension present at diagnosis in many patients with Type 2 diabetes
- Each 10 mmHg decrease in SBP associated with 12% decrease in cardiovascular risk
- MI risk 3.1/1000 pt years at SBP >160 and 18.4/1000 pt years at SBP <120.

Source: Adler et al. BMJ 2000;321:412
Role of Intensive Therapy

What is the BP target?

ADVANCE (N=11,140, Type 2 DM at high CV risk)

- Fixed dose perindopril + indapamide versus placebo
- Other agents including ACE-I (45% in placebo group) continued
- Rx not guided by BP goal, but lower in intense group (134.5/74 vs 140/76, p<0.0001)
- 1° Endpoint composite of macro- and microvascular complications


ACCORD - Hypertension (N=4733, Type 2 DM, high CV risk)

- Goal BP <120 vs <140 mmHg
- Mean attained SBP (119.3 vs 133.5)
- 1° Endpoint composite: CV death, MI or stroke
- Fewer strokes for intensive Rx (0.3 vs 0.5%, p=0.01)
- Drug-related SAEs increased for intensive Rx (3.3 vs 1.3%, p<0.001)


LDL-C Levels and Relative Risk for CHD: How Low to Go?

Targeting Diabetic Dyslipidemia

Is there benefit beyond statin therapy?

- **Niacin**
  - AIM-High trial - extended release niacin in pts with controlled LDL but low HDL and high triglycerides stopped early due to lack of benefit.

- **Fibrates**
  - FIELD trial: Fenofibrate vs Placebo in 9775 patients with Type 2 DM and mild dyslipidemia not on statins
  - No benefit in primary endpoint of CV death or MI
  - Despite blinding there was increased statin use in placebo group.

**FIELD Inv.** Lancet 2005;366:1849-61

**ACCORD-LIPID Substudy (N = 5518, Type 2 DM)**

- LDL 60-180 mg/dl; HDL <55 mg/dl women/blacks; <50 white men
- Open label simvastatin per guidelines
- 1st endpoint = CV death, MI or stroke

<table>
<thead>
<tr>
<th>Subgroups (5 year rates)</th>
<th>Fibrate</th>
<th>Placebo</th>
<th>P int</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>11.2</td>
<td>13.3</td>
<td>0.01</td>
</tr>
<tr>
<td>Women</td>
<td>9.0</td>
<td>6.6</td>
<td>0.6</td>
</tr>
<tr>
<td>1° EP + Revasc or CHF</td>
<td>12.4</td>
<td>17.3</td>
<td>0.055</td>
</tr>
<tr>
<td>Others</td>
<td>10.1</td>
<td>10.1</td>
<td></td>
</tr>
</tbody>
</table>


*Trig >204 and HDL<34

**Medical Therapy of CAD**

- Risk factor management to targets
  - BP <140/80 (New ADA recommendation)
  - LDL <100 mg/dl (<70 in patients with known CAD)
  - HBA1C <7.0%
- Anti-platelet therapy
- Anti-ischemic
  - Beta blockers
  - Calcium channel blockers
  - Long acting nitrates
  - Ranolazine

At least 2 agents to consider adequate trial medical therapy
Anti-Platelet Therapy

- Aspirin 75-162 mg daily if:
  - Known CAD (secondary prevention)
  - High CAD risk (10-year risk >10%)
    - Includes most men > 50 and women > 60 years old
  - Intermediate CAD risk (10-year risk 5-10%) with multiple other risk factors
  - Consider primary prevention at younger age
  - Consider clopidogrel 75 mg/day alternative if aspirin allergic

Medical Rx vs Revascularization
Impact of Diabetes - BARI 2D

BARI 2D Inv. NEJM 2009;360:2503-15

Overall Results

PCI Stratum

BARI 2D Inv. NEJM 2009;360:2503-15

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Medical Therapy versus CABG
BARI-2D – CABG Stratum

Death, MI, Stroke at 5 Years

CABG vs. Medical Therapy
- MI (10.0 vs 17.6%, p=0.003)
- Death/MI (21. vs 29.2%, p=0.01)
- Reduction in MI significant only in insulin sensitization group (6.3 vs 19.0%, p<0.001) but not insulin provision group (13.5 vs 16.2%, p=0.40)

PCI versus Medical Therapy

The COURAGE Trial

Ischemia Reduction in COURAGE
Impact on Death or MI

Nuclear Substudy
34% Pts with baseline mod/severe ischemia (>10%)

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**COURAGE Nuclear Substudy**

*PCI vs OMT for ischemia reduction*

![Graph showing ischemia reduction rates for PCI + OMT (33.3%) vs OMT (19.8%).]

- PCI + OMT: 33.3%
- OMT: 19.8%
- p=0.004


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**FAME II Trial**

*FFR ≤ 0.80: PCI vs Med Rx*

- FFR > 0.80: Med Rx Registry

Primary Endpoint:
- Death, MI, urgent revascularization

Critique:
- Terminated early by DSMB
- EP driven by urgent revasc
- (1.6% vs 11.1%, p<0.001)
- + trop (21%) or ECG (27%) in 48% of urgent revascs
- Not blinded

B. De Bruyne et al. *NEJM* 2012;367:991-1001

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**Revascularization Treatment Options**

*Percutaneous Coronary Intervention (PCI) vs CABG*

- **Acute Coronary Syndrome**
  - Revascularization benefit in most patients
  - PCI usually preferred if feasible
- **Stable CAD**
  - Single vessel (non proximal LAD) > PCI preferred
  - Proximal LAD
    - Most prefer PCI unless diffuse or complex disease
    - Limited comparative effectiveness data
- **Multi-vessel CAD**
**Diabetic Patients With Multivessel CAD**

*CABG Versus PTCA or BMS*

<table>
<thead>
<tr>
<th>Study (yrs fu)</th>
<th>Type of Study</th>
<th>N</th>
<th>Mortality Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>BARI (8)</td>
<td>RCT</td>
<td>353</td>
<td>1.87*</td>
</tr>
<tr>
<td>EAST (8)</td>
<td>RCT</td>
<td>90</td>
<td>1.56</td>
</tr>
<tr>
<td>Duke databank (5)</td>
<td>Obs</td>
<td>770</td>
<td>1.27</td>
</tr>
<tr>
<td>Emory databank (6)</td>
<td>Obs</td>
<td>889</td>
<td>1.35*</td>
</tr>
<tr>
<td>NNE (2)</td>
<td>Obs</td>
<td>2766</td>
<td>1.49*</td>
</tr>
<tr>
<td>ARTS (5)</td>
<td>RCT</td>
<td>210</td>
<td>1.61</td>
</tr>
</tbody>
</table>

*P<0.05

**FREEDOM Design (1)**

Eligibility: DM patients with MV-CAD eligible for stent or surgery
Exclude: Patients with acute STEMI

Randomized 1:1

- MV-Stenting With Drug-eluting (94% SES or PES)
- CABG With or Without CPB

All concomitant Meds shown to be beneficial were encouraged, including: clopidogrel, ACE inhib., ARBs, b-blockers, statins

**FREEDOM Trial Design (2)**

Design: Superiority trial of 7 yrs (minim. 2 yrs, median 3.8yrs)

Sample Size: N= 1900 (953 PCI / DES vs. 947 CABG; 131 ctrs)

Primary Outcome: Composite of earliest occurring of:
- All cause mortality, Non-fatal MI, and Non-fatal Stroke

Secondary Outcomes:
- MACCE (Death, MI, Stroke, Repeat Revasc.) at 1 Year
- Survival at 1, 2, 3 Years
- MACCE Components at 30 Days Post-Procedure
- Cost-Effectiveness
- Quality of Life at 30 Days, 6 Months, 1, 2 & 3 Years

Original Power: Target N=2400, Power ≥ 85% to detect at least an 18% reduction from 4-year rates ranging from 30-38 %, a = .05.
**FREEDOM Results**

**Primary Endpoint**

<table>
<thead>
<tr>
<th>CABG + IMA</th>
<th>CABG SVG only</th>
<th>PTCA</th>
<th>M.A. Farkouh et al. NEJM 2012; 11/4/12</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.6%</td>
<td>5.4%</td>
<td>4.8%</td>
<td></td>
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</table>

**All-Cause Mortality**

<table>
<thead>
<tr>
<th>CABG + IMA</th>
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<th>PTCA</th>
<th>M.A. Farkouh et al. NEJM 2012; 11/4/12</th>
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</thead>
<tbody>
<tr>
<td>2.8%</td>
<td>18.2%</td>
<td>20.5%</td>
<td></td>
</tr>
</tbody>
</table>

**BARI RCT:**

**Relationship between IMA graft and Mortality**

**Assessment and Treatment of CAD**

**Proposed Algorithm**

- Aggressive management of risk factors
- Stress testing if any symptoms, including atypical features – fatigue, breathlessness common
- If + moderate or severe ischemia or high risk stress test (early + or drop in BP) proceed to coronary angiography
- If mild-to-moderate disease by angiography or low risk stress test use anti-ischemic medical Rx as first option
Assessment and Treatment of CAD

Proposed Algorithm

- Revascularization Strategy
  - For patients who fail medical therapy or who have high risk stress test or clinical history
  - Stenting versus CABG
    - Stenting reasonable for 1-2 vessel disease not involving proximal LAD
    - If proximal LAD involved consider CABG instead if good surgical candidate
    - If 3 vessel CAD, CABG preferred unless higher than acceptable risk

Conclusions

- CAD is prevalent among both men and women with diabetes – earlier age at onset and higher risk for death/MI.
- Aggressive risk factor management is the cornerstone of therapy for chronic CAD.
- Screening functional test may be helpful in the presence of any symptoms, including those that are atypical.
- Medical management is the preferred initial strategy in most patients with diabetes and chronic CAD.
- For patients with multi-vessel CAD who warrant revascularization, CABG is preferred over stenting and possibly over initial medical therapy.