Cardiovascular Disease and Diabetes – Management of Chronic Coronary Disease

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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

Diabetes Mellitus is a CHD Equivalent

DM without prior MI versus non DM
  • 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

P Moreno et al. Circulation 2000;102:2189

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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. Quinninnes et al. Ann Int Med 2004; 141:780
K. Mathur et al. JACC 2001;37:1344
M Mathur et al. JACC 2003;36:115

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
G.L. Booth et al. Lancet 2006;368:29

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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. 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.

Diabetes Care 2013;Suppl 1:S32

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.
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

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

Libby P and Plutzky J. Circulation 2002;106:2762

BARI 2D – Glycemic Control Strategy

<table>
<thead>
<tr>
<th>Drug Therapy</th>
<th>Insulin-Provision N=967</th>
<th>Insulin-Sensitization N=977</th>
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<tbody>
<tr>
<td></td>
<td>HbA1C (3 years) 7.5%</td>
<td>HbA1C (3 years) 7.0%</td>
</tr>
<tr>
<td></td>
<td>HbA1C (5 yrs) 12.1%</td>
<td>HbA1C (5 yrs) 11.8%</td>
</tr>
<tr>
<td></td>
<td>Major CV events (5 yrs) 24.6%</td>
<td>Major CV events (5 yrs) 22.3%</td>
</tr>
</tbody>
</table>

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

Audience Response Question 1

Which of the following is true regarding the development of cardiovascular complications of diabetes?

A: Patients with diabetes have increased prevalence of traditional risk factors for heart disease
B: Traditional risk factors have a greater impact on the risk for heart disease in patients with diabetes
C: Diabetes has a direct effect on development and progression of heart disease unrelated to other traditional risk factors
D: All of the above

Correct answer = D
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 33.1/1000 pt years at SBP >160 and 18.4/1000 pt years at SBP <120.

Role of Intensive Therapy

What is the BP target?

- Fixed dose perindopril + indapamide versus placebo
- Other agents including ACE-I (40% in placebo group) continued
- Rx not guided by BP goal, but lower in intense group (134.5/74 vs 140/76, p<0.0001)
- 1st Endpoint composite of macro- and microvascular complications

Fenofibrate vs Placebo

<table>
<thead>
<tr>
<th>Subgroups (5 year rates)</th>
<th>Subgroups (5 year rates)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>10.3</td>
<td>6.6</td>
</tr>
<tr>
<td>Test LDL</td>
<td>Test HDL</td>
</tr>
<tr>
<td>17.3</td>
<td>17.3</td>
</tr>
<tr>
<td>Others</td>
<td>Others</td>
</tr>
<tr>
<td>10.1</td>
<td>10.3</td>
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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

Death, MI, Stroke at 5 Years

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 (21.6 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)

The COURAGE Trial

- 3011 patients, 1:1 vs. 3 months of optimal medical therapy
- 22% vs. 26% vs. 25% of patients at 5 years

BARI 2D

- Death, MI, Stroke at 5 Years

- CABG vs. Medical Therapy

- Reduced risk of MI (10.0 vs 17.6%, p=0.003)
- Reduced risk of Death/MI (21.6 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)
Ischemia Reduction in COURAGE
Impact on Death or MI

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

<table>
<thead>
<tr>
<th>Ischemia Reduction</th>
<th>No Ischemia Reduction</th>
</tr>
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<tbody>
<tr>
<td>N=82</td>
<td>N=232</td>
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<tr>
<td>Ischemia Reduction</td>
<td>15.4</td>
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<tr>
<td>RR=0.47, 95% CI 2.23-0.95</td>
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Impact on Death or MI

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<td>p=0.037</td>
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COURAGE Nuclear Substudy
PCI vs OMT for ischemia reduction

<table>
<thead>
<tr>
<th>Ischemia Reduction</th>
<th>PCI + OMT</th>
<th>OMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=159</td>
<td>33.3</td>
<td></td>
</tr>
<tr>
<td>P=0.004</td>
<td></td>
<td></td>
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<tr>
<td>N=155</td>
<td>19.8</td>
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Ischemia Reduction >5% No Ischemia Reduction

Death or MI %

RR=0.47, 95% CI 0.23-0.95
p=0.037

N=82 N=232

L Shaw et al. Circulation 2008;117:1283-91

Ischemia Reduction ≥5%

PCI vs OMT

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N=159 N=155

L Shaw et al. Circulation 2008;117:1283-91

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
  + (54%) vs 10.1%, p=0.001
  + trap (21%) or ECG (27%) in 48% of urgent revascs
- Not blinded

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

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>
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<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>
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<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>276</td>
<td>1.49</td>
</tr>
<tr>
<td>ARTS (8)</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

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**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 %, α = .05.

**FREEDOM Results**

**Primary Endpoint**

M.Farkouh et al. NEJM 2012; 11/4/12

<table>
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<th>Non-Diabetics</th>
<th>Treated Diabetics</th>
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<td>CABG +IMA</td>
<td>4.6%</td>
<td>3.4%</td>
</tr>
<tr>
<td>CABG SVG only</td>
<td>9.4%</td>
<td>16.2%</td>
</tr>
<tr>
<td>PTCA</td>
<td>4.8%</td>
<td>20.6%</td>
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**All-Cause Mortality**

M.Farkouh et al. NEJM 2012; 11/4/12

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<tr>
<td>PTCA</td>
<td>30%</td>
<td>30%</td>
</tr>
</tbody>
</table>

**Audience Response Question 2**

Which of the following is true regarding revascularization therapy for patients with diabetes and chronic CAD?

A. All patients require revascularization.

B. Stenting and coronary artery bypass surgery have similar outcomes for multivessel CAD requiring revascularization.

C. Among patients with diabetes and multivessel CAD coronary bypass surgery is superior to stenting only due to lower risk for repeat revascularization procedures.

D. Among patients with diabetes and CAD who are candidates for coronary stenting, initial medical therapy alone is associated with similar risk for death, MI, or stroke over 5 year follow-up.

Correct answer = D

**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

- **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

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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.