Cardiovascular Disease and Diabetes – Management of Chronic Coronary Disease

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Diabetes and Management of Chronic CAD

**Objectives**

- Prevention
- Stabilize $\rightarrow$ 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

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

Haffner S et al. NEJM 1998;339:229
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

P Moreno et al. Circulation 2000; 102:2180
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\(^1\))
  - 22% Type 2 DM (age 50-75) + pharmacologic stress test; large defects in 5%
- In retrospective series\(^2\)
  - 40-60% of asymptomatic Type 2 DM patients had abnormal stress tests
  - High-risk findings in 20%

2. Rajagopalen 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 → Risk Factors

Risk Factors → 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>Sulfonylurea/Insulin</td>
<td>UKPDS</td>
<td>-16% (NS)</td>
</tr>
<tr>
<td>Metformin/Sulfonylurea</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 Type 1 DM</td>
<td>DCCT</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%

- N=10,251
- Mean FU 3.5 Y

<table>
<thead>
<tr>
<th></th>
<th>Intense</th>
<th>Standard</th>
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</thead>
<tbody>
<tr>
<td>CV Event</td>
<td>6.6%</td>
<td>9.1%</td>
</tr>
<tr>
<td>Death</td>
<td>3.6%</td>
<td>5.4%</td>
</tr>
</tbody>
</table>

HR 0.90 (0.78-1.04)

### ADVANCE

**Goal:** HBA1C <6.5%

- N=11,140
- Mean FU 5Y

<table>
<thead>
<tr>
<th></th>
<th>Intense</th>
<th>Standard</th>
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<tbody>
<tr>
<td>CV Event</td>
<td>5.8%</td>
<td>9.5%</td>
</tr>
<tr>
<td>Death</td>
<td>2.7%</td>
<td>4.4%</td>
</tr>
</tbody>
</table>

HR 0.94 (0.84-1.06)

**References**

ACCORD NEJM 2008;358:2545

ADVANCE NEJM 2008;358:2560
# BARI 2D – Glycemic Control Strategy

<table>
<thead>
<tr>
<th>Drug Therapy</th>
<th>Insulin-Provision N=967</th>
<th>Insulin-Sensitization N=977</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Therapy</td>
<td>Insulin (61%)</td>
<td>Metformin (75%)</td>
</tr>
<tr>
<td></td>
<td>Sulfonylurea (52%)</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>

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.

A 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

P=0.04
P=0.02
P=0.03

Mean FU = 4.3 years

A Patel et al Lancet 2007; 370:829
Role of Intensive Therapy

What is the BP target?

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
Targeting Diabetic Dyslipidemia

Is there benefit beyond statin therapy?

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
- 1° endpoint = CV death, MI or stroke

1° EP + Revasc or CHF

Fibrate Placebo P int
Men 11.2 13.3 0.01
Women 9.0 6.6
↑ Trig* 12.4 17.3 0.057
↓ HDL
Others 10.1 10.1

* 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

Coronary angiography was performed in patients with type 2 diabetes referred for evaluation for coronary artery disease.

2368 Were enrolled

763 Were selected for CABG stratum
- 385 Were randomly assigned to medical therapy
  - 194 Were randomly assigned to insulin provision
  - 191 Were randomly assigned to insulin sensitization
- 378 Were randomly assigned to revascularization
  - 190 Were randomly assigned to insulin provision
  - 190 Were randomly assigned to insulin sensitization

1605 Were selected for PCI stratum
- 807 Were randomly assigned to medical therapy
  - 399 Were randomly assigned to insulin provision
  - 408 Were randomly assigned to insulin sensitization
- 798 Were randomly assigned to revascularization
  - 402 Were randomly assigned to insulin provision
  - 396 Were randomly assigned to insulin sensitization

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

Overall Results PCI Stratum

42% of medical therapy group underwent revascularization during follow-up.

43% of medical therapy group underwent revascularization during follow-up.
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)

BARI 2D Inv. NEJM 2009;360:2503-15
PCI versus Medical Therapy

The COURAGE Trial


BARI 2D

BARI 2D Inv. NEJM 2009;360:2503-15
Ischemia Reduction in COURAGE

Impact on Death or MI

Nuclear Substudy

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

RR=0.47, 95% CI 0.23-0.95

p=0.037

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

PCI vs OMT for ischemia reduction

- Ischemia Reduction ≥5%
- PCI + OMT: 33.3% with +68% increase
- OMT: 19.8%

p = 0.004

N = 159

N = 155

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

N=888 randomized

FFR $\leq 0.80$: 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
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 3.8 yrs)

**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-Procedue
- Cost-Effectiveness
- Quality of Life at 30 Days, 6 Months, 1, 2 & 3 Years

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

Primary Endpoint

All-Cause Mortality

P=0.005 by log-rank test
5-Yr event rate: 26.6% vs. 18.7%

P=0.049 by log-rank test
5-Yr event rate: 16.3% vs. 10.9%
BARI RCT: 
Relationship between IMA graft and Mortality

Non-Diabetics

Treated Diabetics

CABG +IMA | CABG SVG only | PTCA
---|---|---
4.6% | 5.4% | 4.8%

CABG +IMA | CABG SVG only | PTCA
---|---|---
2.8% | 18.2% | 20.6%
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
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.