Management of Cardiovascular Disease in Diabetes

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Western Diabetes Institute
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Diabetes: A Genetic Legacy

Then

Now
<table>
<thead>
<tr>
<th>Country/Territory</th>
<th>2010 Millions</th>
<th>Country/Territory</th>
<th>2030 Millions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 India</td>
<td>50.8</td>
<td>1 India</td>
<td>87.0</td>
</tr>
<tr>
<td>2 China</td>
<td>43.2</td>
<td>2 China</td>
<td>62.6</td>
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<tr>
<td>3 USA</td>
<td>26.8</td>
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</tr>
<tr>
<td>4 Russian Federation</td>
<td>9.6</td>
<td>4 Pakistan</td>
<td>13.8</td>
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<tr>
<td>5 Brazil</td>
<td>7.6</td>
<td>5 Brazil</td>
<td>12.7</td>
</tr>
<tr>
<td>6 Germany</td>
<td>7.5</td>
<td>6 Indonesia</td>
<td>12.0</td>
</tr>
<tr>
<td>7 Pakistan</td>
<td>7.1</td>
<td>7 Mexico</td>
<td>11.9</td>
</tr>
<tr>
<td>8 Japan</td>
<td>7.1</td>
<td>8 Bangladesh</td>
<td>10.4</td>
</tr>
<tr>
<td>9 Indonesia</td>
<td>7.0</td>
<td>9 Russian Federation</td>
<td>10.3</td>
</tr>
<tr>
<td>10 Mexico</td>
<td>6.8</td>
<td>10 Egypt</td>
<td>8.6</td>
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</tbody>
</table>
Complications of Diabetes: Contribution to Excess Healthcare Costs in a Managed Care Population

Total excess: $282.7 million

Contribution of macrovascular complications: 22.1% ($62.5 million)

Cardiovascular Risk in Patients With Diabetes
Clinical Impact of Diabetes Mellitus

Diabetes

- A 2- to 4-fold increase in cardiovascular mortality
- The leading cause of new cases of end stage renal disease
- The leading cause of new cases of blindness in working-aged adults
- The leading cause of nontraumatic lower extremity amputations

www.hypertensiononline.org
Patients With Diabetes: At High Risk for CV Mortality

The greatest cause of mortality in type 2 diabetes is atherosclerotic vascular disease and its sequelae.

Diabetic patients have:

- 2-Fold to 4-fold greater risk of CVD.
- Worse prognosis for survival.
- 3-Fold greater mortality from stroke.
- Greater risk of permanent brain damage with carotid emboli.

Increased Risk of CV Events Over 7 years in Type 2 Diabetics

- MI = no prior myocardial infarction
+ MI = prior myocardial infarction
CV = cardiovascular

* For diabetes vs. no diabetes and prior MI vs. no prior MI


www.hypertensiononline.org
5,163 men reported taking medication for diabetes and 342,815 men reported not taking medications for diabetes; average follow-up was 12 years.

Metabolic Syndrome: The Deadly Quartet

NIDDM

Obesity

Hypertension

Dyslipidemia

Insulin Resistance

Early Cardiovascular Disease

Macrovascular

Amputations

C.V.A

C.A.D.

Microvascular

Blindness

Renal failure

Cardiovascular Mortality Associated With Metabolic Syndrome (MS)

4,483 subjects aged 35-70 years were included. Metabolic syndrome was defined as per WHO criteria: the presence of at least two of the following risk factors: obesity, hypertension, dyslipidemia, or microalbuminuria.

HEART FAILURE: THE FREQUENT AND OFTEN FATAL COMPLICATION OF DIABETES
Heart Failure Is More Common in Patients With Type 2 Diabetes

Diabetes and Heart Failure: Current Knowledge

- Numerous trials (eg, SOLVD, HOPE and CHS) have identified diabetes as a major risk factor for development of heart failure.
- Diabetes can cause overt heart failure, independent of atherosclerosis or hypertension, via the development of a diabetic cardiomyopathy.
- There is indirect evidence that diabetes frequently causes abnormal heart function, even in the absence of other risk factors.
- Multiple mechanisms have been implicated in the causation of heart failure.

Epidemiology of Diabetic Heart Failure

• Framingham study
  – 2x diabetic males
  – 5x diabetic females
  – 4x young diabetic males
  – 8x young diabetic females

• US HMO prevalence
  – With diabetes, CHF developed at a rate of 3.33% per year

• Each 1% elevation in HbA$_{1c}$ leads to a 15% increase in frequency of CHF
Glycemic Control and Risk of Development of HF in Diabetes

![Bar chart showing the relationship between A1C (%) and risk of HF or death rate per 1,000 person-years.](image)

- A1C <7: 4.5
- 7 to <8: 5.8
- 8 to <9: 6.3
- 9 to <10: 8.3
- ≥10: 9.2

P = 0.001

HF = heart failure.

Diastolic Dysfunction
Heart Failure with Preserved EF%  

• Documented in young diabetic patients, most of whom have type 1 DM - 30% incidence on standard Echocardiography.

• With more rigorous Doppler methods, early diastolic dysfunction can be diagnosed.

• Diastolic dysfunction seen in 52% of diabetic patients in Olmstead County, Minnesota.

• Diastolic dysfunction seen in 60% of diabetic patients in Quebec, Canada.

• Discharge diagnosis of idiopathic cardiomyopathy more common in the diabetic patient.
Coronary Revascularization in the Diabetics
PRIMARY OUTCOME – DEATH / STROKE / MI

Logrank P = 0.005

5-Year Event Rates: 26.6% vs. 18.7%

<table>
<thead>
<tr>
<th>Years post-randomization</th>
<th>PCI/DES N953</th>
<th>CABG N943</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>848</td>
<td>814</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>40</td>
<td>44</td>
</tr>
</tbody>
</table>
Supported by NHLBI U01 grant #01HLO71988; presented at the Annual AHA meeting 2012
Conclusion

- In patients with diabetes and advanced coronary disease, **CABG** was of significant benefit as compared to **PCI**. MI & all cause mortality were independently decreased, while stroke was slightly increased.

- There was **no significant interaction** between the treatment effect of **CABG** on the primary endpoint according to **SYNTAX** score or any other prespecified subgroup.

- **CABG** surgery is the preferred method of revascularization for patients with diabetes & multi-vessel CAD.
Cost Effectiveness of CABG vs. PCI

Conclusions

• For patients with diabetes and multivessel CAD, CABG provides not only better long-term clinical outcomes than DES-PCI but these benefits are achieved at an overall cost that represents an attractive use of societal health care resources.

• These findings provide additional support for existing guidelines that recommend CABG for diabetic patients with multivessel CAD.
What is the Current Status of Managing Cardiovascular Complications
HOPE Study: Outcomes in Patients With Diabetes

Event rate (%)

- Combined: 25% RR, *P=0.0004*
- MI: 22% RR, *P=0.01*
- Stroke: 33% RR, *P=0.0074*
- CV death: 37% RR, *P=0.0001*
- Overt nephropathy: 24% RR, *P=0.027*

RR = risk reduction.

United Kingdom Prospective Diabetes Study (UKPDS): Results

Glucose Control

ACEI or BB for BP Control
(144/82 vs 154/87 mm Hg)

- Any Diabetes-Related Endpoint: -12% (P<.0001)
- Diabetes-Related Death: -10% (P=.34)
- Any Microvascular Endpoints: -25% (P<.01)

- Any Diabetes-Related Endpoint: -25% (P<.005)
- Diabetes-Related Death: -32% (P=.019)
- Stroke: -44% (P=.013)
- Microvascular Endpoints: -37% (P=.009)

1998;317:703-713.

UK Prospective Diabetes Study Group 38. BMJ. 1998;317:703-713.
Any Diabetes Related Endpoint

p < 0.0001

12% decrease per 10 mm Hg decrement in BP

# Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Microvasc</th>
<th>CVD</th>
<th>Mortality</th>
</tr>
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<tbody>
<tr>
<td>UKPDS</td>
<td>↓</td>
<td>↓</td>
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<tr>
<td>DCCT/EDIC*</td>
<td>↓</td>
<td>←→</td>
<td>←→</td>
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<tr>
<td>ACCORD</td>
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<td>↑</td>
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<tr>
<td>ADVANCE</td>
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<tr>
<td>VADT</td>
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<td>←→</td>
</tr>
</tbody>
</table>

Kendall DM, Bergenstal RM. © International Diabetes Center 2009


- **Green arrow**: Initial Trial
- **Blue arrow**: Long Term Follow-up
- **Red arrow**: *in T1DM
Problem of Hypoglycemia in Diabetics
Cumulative Incidence of CVD: Hypoglycemia Group vs Control

Hypoglycemia group: 30.65%
Control group: 17.48%

n=761 for both groups
P<0.0001
Cumulative Incidence of Microvascular Complications: Hypoglycemia Group vs Control

Hypoglycemia group: 34.46%
Control group: 22.03%

n=761 for both groups
P<0.0001

Patient Centered Glycemic Control

Most Intensive
6.0%

Highly Motivated, Adherent, Knowledgeable, Excellent Self-Care Capacities, & Comprehensive Support Systems

Psychosocioeconomic Considerations
Less motivated, Non-adherent, Limited insight, Poor Self-Care Capacities, & Weak Support Systems

Hypoglycemia Risk
Low
Moderate
High

Patient Age
40 45 50 55 60 65 70 75

Disease Duration
5 10 15 20

Other Comorbidities
None
Few/Mild
Multiple/Severe

Established Vascular Complications
None
Early Micro
Cardiovascular
Advanced Micro

What is new with lipid management?
TNT: Intensive Atorvastatin Treatment Reduces Cardiovascular Events in Patients With CHD and Diabetes

- **Atorvastatin 10 mg/day** (n=753)
- **Atorvastatin 80 mg/day** (n=748)

HR=0.75 (95% CI, 0.58-0.97)  
\( P=0.026 \)

*Composite of CHD death, nonfatal non-procedure-related MI, resuscitated cardiac arrest, and fatal or nonfatal stroke*

HPS2 –THRIVE Study – Niacin
(n= 12838 drug vs. n = 12835 placebo; Follow-up 3.9 years)

P = 0.29

Conclusions
Among high-risk patients who went through two run-in phases to demonstrate tolerability to study medication, extended-release niacin/ laropiprant did not reduce the frequency of major adverse events.

• HPS2-THRIVE Collaborative Group. Eur Heart J 2013;Feb 26:[Epub]
• (Heart Protection Study 2 results from 2013)
Niacin/Laropiprant Products to Be Suspended Worldwide

Lisa Nainggolan | Disclosures

Jan 11, 2013
ACCORD Lipid Trial - Conclusion (1)

• ACCORD Lipid does not support use of the combination of fenofibrate and simvastatin, compared to simvastatin alone, to reduce CVD events in the majority of patients with T2DM who are at high risk for CVD.

• Subgroup analyses suggesting heterogeneity in response to combination therapy by gender or by the presence of significant dyslipidemia require further investigation.
ORIGIN
Omega-3 Fatty Acid Trial: Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Omega-3 fatty acid (N=6,281)</th>
<th>Placebo (N=6,255)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite of CV death, or nonfatal MI, or nonfatal stroke</td>
<td>HR, 1.01 (95% CI, 0.93-1.10); P=0.81</td>
<td>HR, 0.98 (95% CI, 0.89-1.07); P=0.63</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>16.5 (1,034)</td>
<td>16.3 (1,017)</td>
</tr>
<tr>
<td></td>
<td>15.1 (951)</td>
<td>15.4 (964)</td>
</tr>
<tr>
<td>Arrhythmic death</td>
<td>4.6 (288)</td>
<td>4.1 (259)</td>
</tr>
</tbody>
</table>

ORIGIN = Outcome Reduction with Initial Glargine Intervention

Most LDL-C Reduction Occurs at Lower Doses of Statins

Daily Dose

Atorvastatin
10/20/40/80 mg
211 mg/dL*

Simvastatin
10/20/40 mg†
219 mg/dL*

Mean % Change From Baseline

-60%
-50%
-40%
-30%
-20%
-10%
0%

38%
46%
51%
54%

16% With 3 Titrations

28%
35%
41%

13%

* Mean baseline LDL-C.
† At the time of this study, the maximum dose for simvastatin was 40 mg.

Why Are So Few Patients Reaching Their LDL-C Goal?

- Many patients are never treated or do not follow their treatment program.

- Most LDL-C reduction with statins occurs with the starting dose.¹

- Each doubling of the statin dose lowers LDL-C about 6%.
  
  - Therefore, an additional 18% reduction would require doubling the dose 3 times.²

- Most patients taking statins do not have their dose increased.¹

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Statin Use and Risk for Diabetes: Results

When data from all studies combined, 9% increase (N=174) in additional cases of incident diabetes seen during follow-up among subjects receiving statin therapy vs those receiving placebo or standard care — in absolute terms, one additional case of diabetes per 255 (95% CI, 150–852) subjects receiving statin therapy for 4 years.

• No clear difference between statins observed with regard to diabetes risk

CI=confidence interval; CVD=cardiovascular disease; FPG=fasting plasma glucose; OR=odds ratio.

NEW TREATMENT GUIDELINES
### ADA Guidelines: Glycemic, Blood Pressure, and Lipid Control

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C</td>
<td>&lt;7.0%*</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>&lt;140/&lt;80 mm Hg†</td>
</tr>
<tr>
<td>Lipids</td>
<td>LDL-C: &lt;100 mg/dL (&lt;2.6 mmol/L)‡</td>
</tr>
<tr>
<td></td>
<td>Statin therapy for patients with MI history or aged &gt;40 years with other risk factors</td>
</tr>
</tbody>
</table>

*More or less stringent glycemic goals may be appropriate for individual patients. Individualize goals based on diabetes duration, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations.

†Lower systolic blood pressure goals may be appropriate based on individual patient characteristics and therapeutic response.

‡A lower LDL-C goal of <70 mg/dL, using a high dose of a statin, may be appropriate in persons with overt CVD.

CVD = cardiovascular disease; MI = myocardial infarction
Summary

• **There are many causes of vascular injury in diabetes**

• **Manage all cardiovascular risk factors**
  – Emphasize weight loss.
  – Control lipids and blood pressure to goal.
  – Control inflammation and clotting with aspirin.
  – Control glucose as early as possible, but avoid hypoglycemia.

• **Some lingering questions:**
  – How early is “early” with regard to control?
  – What is the right protection against oxidative stress?
Thank you for your attention.

Any ??