Cardiovascular Management of a Patient with Diabetes

Dr Jeremy Krebs
Clinical Leader Endocrinology and Diabetes
Wellington Hospital
Summary

• People with diabetes take a lot of medication
  • Compliance and Side Effects
• Most die from CVD
• Everyone is not created equal
  • Calculate individual CVD risk
• Primary vs Secondary Prevention

• If you decide to treat – GO HARD!
Summary

• Weight and Exercise

• Stop Smoking

• Glucose control
  – Legacy effect – Treat early
  – Avoid hypoglycaemia

• Blood Pressure
  – Aim 130/80mmHg
  – But not too low

• Lipids
  – Statin first line
  – Primary vs Secondary – consider your target
    • Maybe Fibrate if TG v high
    • Maybe Ezetimibe or Nicotinic acid

• Aspirin
  – Yes for secondary prevention
  – Probably not for primary unless high risk
MORTALITY FROM CORONARY HEART DISEASE IN SUBJECTS WITH TYPE 2 DIABETES AND IN NONDIABETIC SUBJECTS WITH AND WITHOUT PRIOR MYOCARDIAL INFARCTION

STEVEN M. HAFFNER, M.D., SEppo LEHTO, M.D., TAPANI RÖNNEMAA, M.D., KALEVI PYÖRÄLÄ, M.D., AND MARKKU LAAKSO, M.D.

Haffner S. NEJM 1998:339;229-34
<table>
<thead>
<tr>
<th>Study</th>
<th>Diabetes alone (No. of MI/No. of subjects)</th>
<th>Prior MI alone (No. of MI/No. of subjects)</th>
<th>Odds ratio (95% CI)</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al.</td>
<td>141/1460</td>
<td>59/283</td>
<td>0.41 (0.30 to 0.57)</td>
<td>2004</td>
</tr>
<tr>
<td>Evans et al.</td>
<td>113/1155</td>
<td>274/1347</td>
<td>0.42 (0.33 to 0.54)</td>
<td>2002</td>
</tr>
<tr>
<td>Haffner et al.</td>
<td>180/890</td>
<td>13/69</td>
<td>1.09 (0.58 to 2.04)</td>
<td>1998</td>
</tr>
<tr>
<td>Hu FB et al.</td>
<td>161/3705</td>
<td>61/1302</td>
<td>0.92 (0.68 to 1.25)</td>
<td>2001</td>
</tr>
<tr>
<td>Lotufo et al.</td>
<td>89/2317</td>
<td>445/5906</td>
<td>0.49 (0.39 to 0.62)</td>
<td>2001</td>
</tr>
<tr>
<td>Eberly et al.</td>
<td>171/1122</td>
<td>177/658</td>
<td>0.49 (0.39 to 0.62)</td>
<td>2003</td>
</tr>
<tr>
<td>Hu G et al.</td>
<td>159/962</td>
<td>373/1308</td>
<td>0.50 (0.40 to 0.61)</td>
<td>2005</td>
</tr>
<tr>
<td>Cho et al.</td>
<td>113/1285</td>
<td>364/2038</td>
<td>0.44 (0.35 to 0.55)</td>
<td>2002</td>
</tr>
<tr>
<td>Wannamathee et al.</td>
<td>36/202</td>
<td>140/517</td>
<td>0.58 (0.58 to 0.59)</td>
<td>2004</td>
</tr>
<tr>
<td>Natarajan et al.</td>
<td>35/178</td>
<td>92/300</td>
<td>0.55 (0.36 to 0.86)</td>
<td>2003</td>
</tr>
<tr>
<td>Vaccaro et al.</td>
<td>1087/4809</td>
<td>1468/4625</td>
<td>0.61 (0.56 to 0.67)</td>
<td>2004</td>
</tr>
<tr>
<td>Pajunen et al.</td>
<td>191/525</td>
<td>254/559</td>
<td>0.69 (0.54 to 0.88)</td>
<td>2005</td>
</tr>
<tr>
<td>Natarajan et al.</td>
<td>127/462</td>
<td>207/594</td>
<td>0.71 (0.54 to 0.92)</td>
<td>2005</td>
</tr>
<tr>
<td>Total</td>
<td>2603/19072</td>
<td>3927/19506</td>
<td>0.56 (0.53 to 0.60)</td>
<td></td>
</tr>
</tbody>
</table>

Random effects model: odds ratio = 0.56 (0.53, 0.60)
Fixed effects model: odds ratio = 0.56 (0.53, 0.60)
Test for heterogeneity: $I^2 = 75.0\%$

Favours diabetes as not a CHD risk equivalent
Favours diabetes as a CHD risk equivalent
All Things Are Not Created Equal
All Things Are Not Created Equal

• Mrs T 39yr
  – Type 2 diabetes 11 years
  – BMI 36 kg/m$^2$
  – Smoker
  – BP 148/84 mmHg
  – TC 4.9 mmol/l
  – TG 2.3 mmol/l
  – HDL 0.8 mmol/l
  – LDL 2.8 mmol/L
  – UACR 4.5

• Mr T 63yr
  – Type 2 diabetes 4 years
  – BMI 29 kg/m$^2$
  – BP 132/76 mmHg
  – TC 4.8 mmol/l
  – TG 0.9 mmol/l
  – HDL 1.4 mmol/L
  – LDL 2.8 mmol/L
  – UACR 1.8
Targets for CVD Risk Factors for Patients with Diabetes

Approach to setting treatment targets

- Setting treatment targets is an important component of diabetes management for all patients.
- Targets given for specific parameters are based on best available evidence but should be appropriate for the individual patient.

Treatment targets

Treatment targets to address risk factors:

- Should be appropriate for and agreed with the individual patient.
- Glycaemic control target: HbA1c 50–55 mmol/mol or as individually agreed.
- Blood pressure target: <130/80 mm Hg. Evidence suggests a BP target <120 mm Hg may be harmful. Care should be taken to estimate likely treatment response for patients when BP approaches the target of <130 mm Hg.
- Lipids target: triglycerides <1.7 mmol/L; total cholesterol <4.0 mmol/L.
### Table 8
Optimal levels (targets) for people with known cardiovascular disease, or cardiovascular risk >15% or diabetes

<table>
<thead>
<tr>
<th>Lipids</th>
<th>Known cardiovascular disease or cardiovascular risk &gt;15% or diabetes*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>&lt;4.0 mmol/L</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>&lt;2.0 mmol/L</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>≥1.0 mmol/L</td>
</tr>
<tr>
<td>TC:HDL ratio</td>
<td>&lt;4.0</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>&lt;1.7 mmol/L</td>
</tr>
</tbody>
</table>

**Blood pressure**

| BP                              | <130/80 mm Hg                                                        |

**Glycaemic control in people with diabetes**

| HbA1c                           | 50–55 mmol/mol or as individually agreed                            |

**Smoking cessation**

Smoking cessation should be strongly and repeatedly recommended at any level of CVD risk. All people who smoke should be advised to quit and offered treatment to help them stop completely. Reducing cigarette consumption is not a recommended treatment strategy.

*Content on diabetes has been updated to align with 2011 guidance on the management of people with type 2 diabetes (see Chapter 4 Management of type 2 diabetes).*
Smoking

- Baseline BMI vs Mortality
- 57 Prospective studies
- 894 576 individuals
- Mean age 46 yrs

Prospective Studies Collaboration. Lancet 2009 373;1083
Glucose Control
NZ Cohort Study (Get Checked) adjusted hazard ratio for CV events by HbA1c.

- $n=48444$
- $n=5667$ first events
- Median follow up 2.4yrs

HR 1.08 (1.06 – 1.10) per 1% HbA1c

UKPDS

HbA$_{1c}$

cross-sectional, median values

Conventional

Intensive

6.2% upper limit of normal range
UKPDS Glucose Control Study
Summary

12% for any diabetes related endpoint (p=0.029)
16% for myocardial infarction (p=0.052)
25% for microvascular endpoints (p=0.0099)
24% for cataract extraction (p=0.046)
21% for retinopathy at twelve years (p=0.015)
33% for albuminuria at twelve years (p=0.000054)
### Legacy Effect of Earlier Glucose Control

*After median 8.5 years post-trial follow-up*

<table>
<thead>
<tr>
<th>Aggregate Endpoint</th>
<th>1997</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any diabetes related endpoint</td>
<td>RRR: 12%</td>
<td>RRR: 9%</td>
</tr>
<tr>
<td></td>
<td>P: 0.029</td>
<td>P: 0.040</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>RRR: 25%</td>
<td>RRR: 24%</td>
</tr>
<tr>
<td></td>
<td>P: 0.0099</td>
<td>P: 0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>RRR: 16%</td>
<td>RRR: 15%</td>
</tr>
<tr>
<td></td>
<td>P: 0.052</td>
<td>P: 0.014</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>RRR: 6%</td>
<td>RRR: 13%</td>
</tr>
<tr>
<td></td>
<td>P: 0.44</td>
<td>P: 0.007</td>
</tr>
</tbody>
</table>

*RRR = Relative Risk Reduction, P = Log Rank*
Recent Trials of Glycaemic Control

- Advance, Accord
- 10 year post diagnosis, middle age
- Despite intensive HBA1c management have failed to show CVD benefit
ACCORD Study
The Action to Control Cardiovascular Risk in Diabetes Study Group

- N=10,000
  - 1/3 already on insulin
  - 1/3 prevalent CVD events
  - Mean Age 62
  - Diabetes for 10 years
  - HbA1c 8.3

*Strategy of (ultra) intensive glycaemic control aiming for HbA1c 6 (achieved 6.3)*
The mean difference during the trial was 1.1%
Accord June 2008

Primary Outcome: First occurrence of nonfatal MI, stroke or death from Cardiovascular cause

352 vs 371 events

HR 0.9 (0.78-1.04, p=0.16)
## Accord Study
### Primary and Secondary Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Intensive N (%)</th>
<th>Standard N (%)</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>352 (6.86)</td>
<td>371 (7.23)</td>
<td>0.90 (0.78-1.04)</td>
<td>0.16</td>
</tr>
<tr>
<td>Secondary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>257 (5.01)</td>
<td>203 (3.96)</td>
<td>1.22 (1.01-1.46)</td>
<td>0.04</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>186 (3.63)</td>
<td>235 (4.59)</td>
<td>0.76 (0.62-0.92)</td>
<td>0.004</td>
</tr>
<tr>
<td>Nonfatal Stroke</td>
<td>67 (1.31)</td>
<td>61 (1.19)</td>
<td>1.06 (0.75-1.50)</td>
<td>0.74</td>
</tr>
<tr>
<td>CVD Death</td>
<td>135 (2.63)</td>
<td>94 (1.83)</td>
<td>1.35 (1.04-1.76)</td>
<td>0.02</td>
</tr>
<tr>
<td>CHF</td>
<td>152 (2.96)</td>
<td>124 (2.42)</td>
<td>1.18 (0.93-1.49)</td>
<td>0.17</td>
</tr>
</tbody>
</table>
Incidence of Hypoglycaemia (first event) per Year

% of Participants

Incidence of Hypoglycaemia (first event) per Year

Year Post-randomization

1st 2nd 3rd 4th 5th 6th

Intensive Standard
Major Targeted Sites of Oral Drug Classes

- **Hepatic glucose overproduction**
  - Biguanides
  - TZDs
  - GLP-1 mimetics
  - DPP-4 inhibitors

- **Impaired insulin secretion**
  - Sulfonylureas
  - GLP-1 mimetics
  - DPP-4 inhibitors

- **Glucose level**
  - *↓*

- **Gut**
  - Glucose absorption
  - \(\alpha\)-Glucosidase inhibitors
  - Biguanides

- **Pancreas**
  - \(↓\) Insulin resistance

- **Liver**

- **Muscle and fat**
  - \(↓\) Insulin resistance
  - TZDs
  - Biguanides

DPP-4 = dipeptidyl peptidase 4; TZDs = thiazolidinediones.

Type 2 Diabetes Algorithm

Diet and Lifestyle

Metformin
- Oral agent
- Good evidence
- No hypos
- But weight gain, heart failure, fractures. ?IHD risk

SU
- Oral agent
- No hypos
- But GI side effects

Glitazone
- Weight neutral
- Oral agent
- No hypos

Acarbose
- Weight loss
- No hypos
- But Injectable

Sitagliptin

Exenatide

Insulin
- But weight gain, heart failure, fractures.
- But IHD risk
- Good evidence
- But hypos
Blood Pressure
UKPDS

Fig 2 Incidence rates (95% confidence interval) of myocardial infarction and microvascular end points by category of updated mean systolic blood pressure, adjusted for age, sex, and ethnic group expressed for white men aged 50-54 years at diagnosis and mean duration of diabetes of 10 years.
ACCORD BP trial

**Figure 1.** Mean Systolic Blood-Pressure Levels at Each Study Visit.
I bars indicate 95% confidence intervals.
Figure 2. Kaplan–Meier Analyses of Selected Outcomes.

Shown are the proportions of patients with events for the primary composite outcome (Panel A) and for the individual components of the primary outcome (Panels B, C, and D). The insets show close-up versions of the graphs in each panel.
Lipids
Dyslipidaemia in Diabetes

• Typical dyslipidaemia in type 2 diabetes
  – Elevated Triglycerides
  – Suppressed HDL cholesterol
  – Total and LDL cholesterol more variable

• So TREAT THE TG AND HDL
### FIELD Study

- **Fenofibrate vs Placebo**
- **N=9795 age 50-75yrs**
  - 2131 pre CVD
  - 7664 no CVD
- **Not on a statin**
  - (17% placebo and 8% fibrate group started)

### Primary Outcome
- **Death or nonfatal MI**
  - RR 0.89 (0.75-1.05)

---

**Total CV events. Death, MI, Stroke, Revascularisation**

**Lancet 2005: 366;1849-61**
Statins in Diabetes

• Secondary Prevention
  – Yes – Go for it!
    • Let the cardiologist zealots drive your LDL down!

• Primary Prevention
  – Yes – Maybe
    • Listen to your heart (and your Endocrinologist)
CARDS Study

- Primary prevention study
  - But! Retinopathy, albuminuria, smoking or hypertension
- 2838 patients 40-75yrs with diabetes
- Atorvastatin vs Placebo
- LDL<4.14
- TG<6.78

Colhoun H. Lancet 2004: 364;685
CARDS study

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>Atorvastatin 10 mg</th>
<th>Hazard ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td>127 (9.0%)</td>
<td>83 (5.8%)</td>
<td>0.63 (0.48–0.83)</td>
<td>0.001</td>
</tr>
<tr>
<td>Acute coronary events</td>
<td>77 (5.5%)</td>
<td>51 (3.6%)</td>
<td>0.64 (0.45–0.91)</td>
<td></td>
</tr>
<tr>
<td>Coronary revascularisation</td>
<td>34 (2.4%)</td>
<td>24 (1.7%)</td>
<td>0.69 (0.41–1.16)</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>39 (2.8%)</td>
<td>21 (1.5%)</td>
<td>0.52 (0.31–0.89)</td>
<td></td>
</tr>
<tr>
<td>Secondary endpoint</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>82 (5.8%)</td>
<td>61 (4.3%)</td>
<td>0.73 (0.52–1.01)</td>
<td>0.059</td>
</tr>
<tr>
<td>Any acute cardiovascular disease event</td>
<td>189 (13.4%)</td>
<td>134 (9.4%)</td>
<td>0.68 (0.55–0.85)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Colhoun H. Lancet 2004: 364;685
Statins in Diabetes

- Primary prevention studies

Large Subgroups with Diabetes

- ALLHAT
  - Pravastatin
  - NS reduction in death or MI

- HPS
  - Simvastatin
  - Sig reduction both 1° and 2°

- ASCOT
  - Atorvastatin
  - NS
LDL
How Low Do You Go?

Primary Prevention Trials

Secondary Prevention Trials
Add on to Statins

• Fibrates
  • Maybe if TG high

• Ezetimibe
  • Maybe if LDL still high
    – Lowers LDL well in combination
    – No outcome data

• Nicotinic Acid
  • Maybe if LDL high and HDL low
    – No outcome data
IMPROVE-IT Study

**Patients stabilized post-ACS ≤ 10 days**
LDL-C ≤ 125 mg/dL (or ≤ 100 mg/dL if prior statin)

**Double-blind**

ASA + Standard Medical Therapy

- Simvastatin 40 mg*
- Ezetimibe/ Simvastatin 10/40 mg*

*upltitrated to 80 mg if LDL-C >79

Follow-up visit day 30, every 4 months

Duration: Minimum 2 1/2 year follow-up (5250 events)

**Primary Endpoint:** CV Death, MI, Hospital Admission for UA, Revascularization (>30 days after randomization), or Stroke

**Table 1. Baseline characteristics of the first 10,000 patients enrolled**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median [interquartile range])</td>
<td>62 (55, 70)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>77</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>22</td>
</tr>
<tr>
<td>Prior MI (%)</td>
<td>17</td>
</tr>
<tr>
<td>Acute event</td>
<td></td>
</tr>
<tr>
<td>STEMI (%)</td>
<td>47</td>
</tr>
<tr>
<td>NSTEMI (%)</td>
<td>37</td>
</tr>
<tr>
<td>UA (%)</td>
<td>16</td>
</tr>
<tr>
<td>Preenrollment coronary angiography</td>
<td>91</td>
</tr>
<tr>
<td>Preenrollment PCI after ACS event</td>
<td>76</td>
</tr>
<tr>
<td>Baseline LDL-C (median [interquartile range]) (mg/dL)</td>
<td>97 (81, 112)</td>
</tr>
<tr>
<td>No prior lipid-lowering therapy</td>
<td>104 (89, 116)</td>
</tr>
<tr>
<td>Prior lipid-lowering therapy</td>
<td>80 (68, 90)</td>
</tr>
</tbody>
</table>
The Whole Package

“Control my diet, control my life style, control my carbs... What are you, some kind of freak?”

© 2004 Diabetes Health
Steno-2 Post Trial: Mortality of any cause

Cumulative incidence of death (%)

Years of follow-up

Log-rank P=0.015

Numbers at risk
Conventional 80 80 77 69 63 51 43 30
Intensive 80 78 75 72 65 62 57 39

Gaede et al. NEJM 2008
Steno-2 Post Trial: Any CVD events

Cumulative incidence of patients with a major CVD event during follow-up

Cumulative incidence of CVD events (%)

Numbers at risk
Conventional
Intensive
80  70  60  46  38  29  25  14
80  72  65  61  56  50  47  31

Gaede et al.  NEJM 2008
### Steno 2

Number of microalbuminuric patients with type 2 diabetes needed to treat for 13 years to prevent one...

<table>
<thead>
<tr>
<th>Event</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>5 patients</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>8 patients</td>
</tr>
<tr>
<td>Major cardiovascular event</td>
<td>3 patients</td>
</tr>
<tr>
<td>Progression to nephropathy</td>
<td>5 patients</td>
</tr>
<tr>
<td>Dialysis</td>
<td>16 patients</td>
</tr>
<tr>
<td>Laser treatment</td>
<td>7 patients</td>
</tr>
</tbody>
</table>

(from Gaede et al 2008 Steno 2, 13 year study)
Spot the Difference
Summary

- People with diabetes take a lot of medication
  - Compliance and Side Effects
- Most die from CVD
- Everyone is not created equal
  - Calculate individual CVD risk
- Primary vs Secondary Prevention
- If you decide to treat – GO HARD!
Summary

• Weight and Exercise

• Stop Smoking

• Glucose control
  – Legacy effect – Treat early
  – Avoid hypoglycaemia

• Blood Pressure
  – Aim 130/80mmHg
  – But not too low

• Lipids
  – Statin first line
  – Primary vs Secondary – consider your target
    • Maybe Fibrate if TG v high
    • Maybe Ezetimibe or Nicotinic acid

• Aspirin
  – Yes for secondary prevention
  – Probably not for primary unless high risk
UKPDS: Improving HbA$_{1c}$ Control
Reduced Diabetes-Related Complications

Relative Risk
N=3642

EVERY 1% reduction in HbA$_{1c}$

1%

Diabetes-related deaths
21%

Myocardial infarctions
14%

Microvascular complications
37%

Amputations or deaths from peripheral vascular disorders
43%

UKPDF=United Kingdom Prospective Diabetes Study.
Data adjusted for age, sex, and ethnic group, expressed for white men aged 50–54 years at diagnosis and with mean duration of diabetes of 10 years.
Management Goals for Diabetes

NZ Guidelines Group: Dec 2002

- Glycaemic control
  - HbA1c 6.5 - 7.5%

- Blood Pressure
  - <130/80 (125/75)

- Lipids
  - TC<4.0mmol/L (LDL<2.0, HDL>1.0)
  - TG<1.7mmol/L
MORTALITY FROM CORONARY HEART DISEASE IN SUBJECTS WITH TYPE 2 DIABETES AND IN NONDIABETIC SUBJECTS WITH AND WITHOUT PRIOR MYOCARDIAL INFARCTION

STEVEN M. HAFFNER, M.D., SEppo LEHTO, M.D., TAPANI RÖNNEMAA, M.D., KALEVI PYÖRÄLÄ, M.D., AND MARKKU LAAKSO, M.D.

Figure 1. Kaplan–Meier Estimates of the Probability of Death from Coronary Heart Disease in 1059 Subjects with Type 2 Diabetes and 1378 Nondiabetic Subjects with and without Prior Myocardial Infarction. MI denotes myocardial infarction. I bars indicate 95 percent confidence intervals.
Less than 50% of Adults With Type 2 Diabetes Have Achieved HbA$_{1c}$ Goals

US Population

- HbA$_{1c}$ level <7%: NHANES III (1988–1994) (n=1204) = 44.3%, NHANES 1999–2000 (n=370) = 37.0%
- Blood pressure <130/80 mmHg: NHANES III (1988–1994) (n=1204) = 29.0%, NHANES 1999–2000 (n=370) = 35.8%
- Total cholesterol <200 mg/dl: NHANES III (1988–1994) (n=1204) = 33.9%, NHANES 1999–2000 (n=370) = 48.2%

<table>
<thead>
<tr>
<th>Class</th>
<th>A1C Reduction</th>
<th>Severe Hypoglycemia</th>
<th>Weight Change</th>
<th>CVD Risk Factor Improvement</th>
<th>Dosing (times/day)</th>
<th>Diabetes Comorbidity Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>1.5</td>
<td>No</td>
<td>Neutral</td>
<td>Minimal</td>
<td>1-2</td>
<td>Kidney, liver</td>
</tr>
<tr>
<td>NPH, Glargine, Detemir</td>
<td>1.5 - 2.5</td>
<td>Yes</td>
<td>Gain</td>
<td>TG</td>
<td>1-2, Injected</td>
<td>None</td>
</tr>
<tr>
<td>R, Lispro, Aspart, Glulisine</td>
<td>1.5 - 2.5</td>
<td>Yes</td>
<td>Gain</td>
<td>TG</td>
<td>1-4, Injected</td>
<td>None</td>
</tr>
<tr>
<td>Glipizide ER, Glimepiride</td>
<td>1.5</td>
<td>Yes</td>
<td>Gain</td>
<td>None</td>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>0.5 - 1.4</td>
<td>No</td>
<td>Gain</td>
<td>Lipids, BP</td>
<td>1</td>
<td>CHF, liver</td>
</tr>
<tr>
<td>Repaglinide</td>
<td>1 - 1.5</td>
<td>Yes</td>
<td>Gain</td>
<td>None</td>
<td>3</td>
<td>None</td>
</tr>
<tr>
<td>Nateglinide</td>
<td>0.5 - 0.8</td>
<td>Rare</td>
<td>Gain</td>
<td>None</td>
<td>3</td>
<td>None</td>
</tr>
<tr>
<td>Acarbose, Miglitol</td>
<td>0.5 - 0.8</td>
<td>No</td>
<td>Neutral</td>
<td>Minimal</td>
<td>3</td>
<td>None</td>
</tr>
<tr>
<td>Pramlintide</td>
<td>0.5 – 0.9</td>
<td>No</td>
<td>Loss</td>
<td>w/ weight loss</td>
<td>3, Injected</td>
<td>None</td>
</tr>
<tr>
<td>Exenatide</td>
<td>0.5 - 1.0</td>
<td>No</td>
<td>Loss</td>
<td>w/ weight loss</td>
<td>2, Injected</td>
<td>Kidney</td>
</tr>
<tr>
<td>Sitagliptin-saxagliptin</td>
<td>0.6 - 0.8</td>
<td>No</td>
<td>Neutral</td>
<td>Minimal</td>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>Colesevelam</td>
<td>~0.5</td>
<td>No</td>
<td>Neutral</td>
<td>LDL</td>
<td>1-2</td>
<td>Severe TG's</td>
</tr>
</tbody>
</table>

Risks vs Benefits of Glucose Lowering Therapy

For intimal medial thickness, n = 454; P value < .001. For left ventricular mass index, n = 402; P value = .17. The “no change” category was defined as ± 0.01 mm for intimal medial thickness or ± 0.05 gm/m$^{2.7}$ for left ventricular mass index. P is for trend by each treatment group for intimal medial thickness and left ventricular mass index.
Hazard ratios for the primary end point by subgroup of achieved LDL cholesterol (adjusted for age, sex, baseline calculated LDL cholesterol, diabetes, and prior MI) in the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 trial.

![Graph showing hazard ratios for primary end point by LDL cholesterol subgroup](image)
Figure 1. Total cholesterol levels for hunter-gatherers, wild primates, and wild mammals generally range from about 70 to 140 mg/dl (corresponding to low-density lipoprotein levels of about 35 to 70 mg/dl [24,25]). The mean cholesterol levels of modern Westernized humans are almost twice these normal values (13).
Incidence rates of MI and microvascular endpoints by mean HbA$_{1c}$: UKPDS

Study population: white, Asian Indian, and Afro-Caribbean UKPDS patients (n = 4,585)
Adjusted for age, sex, and ethnic group

Error bars = 95% CI

<table>
<thead>
<tr>
<th>Study</th>
<th>Diabetes alone (No. of MI/No. of subjects)</th>
<th>Prior MI alone (No. of MI/No. of subjects)</th>
<th>Odds ratio (95% CI)</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al.</td>
<td>141/1460</td>
<td>59/283</td>
<td>0.41 (0.30 to 0.57)</td>
<td>2004</td>
</tr>
<tr>
<td>Haffner et al.</td>
<td>180/890</td>
<td>13/69</td>
<td>1.09 (0.58 to 2.04)</td>
<td>1998</td>
</tr>
<tr>
<td>Hu FB et al.</td>
<td>161/3705</td>
<td>61/1302</td>
<td>0.92 (0.68 to 1.25)</td>
<td>2001</td>
</tr>
<tr>
<td>Lotufo et al.</td>
<td>89/2317</td>
<td>445/5906</td>
<td>0.49 (0.39 to 0.62)</td>
<td>2001</td>
</tr>
<tr>
<td>Hu G et al.</td>
<td>159/962</td>
<td>373/1308</td>
<td>0.50 (0.40 to 0.61)</td>
<td>2005</td>
</tr>
<tr>
<td>Cho et al.</td>
<td>113/1285</td>
<td>364/2038</td>
<td>0.44 (0.35 to 0.55)</td>
<td>2002</td>
</tr>
<tr>
<td>Wannamathee et al.</td>
<td>36/202</td>
<td>140/517</td>
<td>0.58 (0.58 to 0.59)</td>
<td>2004</td>
</tr>
<tr>
<td>Natarajan et al.</td>
<td>35/178</td>
<td>92/300</td>
<td>0.55 (0.36 to 0.86)</td>
<td>2003</td>
</tr>
<tr>
<td>Vaccaro et al.</td>
<td>1087/4809</td>
<td>1468/4625</td>
<td>0.61 (0.56 to 0.67)</td>
<td>2004</td>
</tr>
<tr>
<td>Pajunen et al.</td>
<td>191/525</td>
<td>254/559</td>
<td>0.69 (0.54 to 0.88)</td>
<td>2005</td>
</tr>
<tr>
<td>Natarajan et al.</td>
<td>127/462</td>
<td>207/594</td>
<td>0.71 (0.54 to 0.92)</td>
<td>2005</td>
</tr>
<tr>
<td>Evans et al.</td>
<td>113/1155</td>
<td>274/1347</td>
<td>0.42 (0.33 to 0.54)</td>
<td>2002</td>
</tr>
<tr>
<td>Total</td>
<td>2432/17950</td>
<td>3750/18848</td>
<td>0.57 (0.54 to 0.61)</td>
<td></td>
</tr>
</tbody>
</table>

Random effects model: odds ratio = 0.57 (0.54, 0.61)
Fixed effects model: odds ratio = 0.57 (0.53, 0.60)
Test for heterogeneity: $I^2 = 74.2\%$

Bulugahapitiya U. Diabetic Med 2009:26;142-148
Success Comes From Using the Most Appropriate Tools