
*Projected.

Type 2 Diabetes is a CV Risk Factor
Additive Effects of Hypertension, Hypercholesterolemia, and Smoking

DOCUMENTED DEFECTS IN TYPE 2 DIABETES MELLITUS
(RIZZA RA: *DIABETES* 2010; 59:2697)

- Enhanced endogenous glucose production, and lack of postprandial suppression.
- Increased gluconeogenesis ? Increased glycogenolysis. Impaired insulin mediated hepatic glucose uptake
- Reduced hepatic glycogen synthesis presumably due to reduced hepatic glucokinase.
- Delayed insulin secretion
- Failure of suppression of Glucagon
What Drives the Concern

- Increased risk of mortality in both types of Diabetes
- Increased risk of mortality at FBG > 100 mgs/dl., and associated with a 6 year shorter life span in a 50 year old individual with DM
- Elevation of glycated hemoglobin correlate with mortality and CV events in a linear manner. 1% increase in HbA1c increase risk (20%-30%) for CV events or death.
- Elevated HbA1c ( >5%) may increase risk in non-diabetic patients.
<table>
<thead>
<tr>
<th>Year, Author</th>
<th>Journal</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1922, Levine SA</td>
<td><em>JAMA</em></td>
<td>High incidence of glycosuria in MI</td>
</tr>
<tr>
<td>1929, Levine SA</td>
<td><em>Medicine</em></td>
<td>Casual relationship between high glucose levels and coronary thrombosis</td>
</tr>
<tr>
<td>1931, Cruickshansk</td>
<td><em>BMJ</em></td>
<td>Vascular degeneration as common cause for both glycosuria and CHD</td>
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<tr>
<td>1976, Opie LH</td>
<td><em>Clin Endocrinol Metab</em></td>
<td>Glucose intolerance and the high circulating FFA are thought to be harmful to the ischaemic tissue</td>
</tr>
</tbody>
</table>
Relationship Between Glycemic Control and Coronary Heart Disease Events in Type 2 Diabetes Patients (Ages 65 to 74)

Pathophysiology

- Hyperglycemia induced disruption NO production through endothelial dysfunction.
- FFA induced impairment of vasodilation.
- Up regulation of TLR leading to excessive white cell-response leading to ischemic reperfusion injury.
- Enhanced Monocyte adhesion and differentiation - into macrophages and uptake od lipids to become –foam cells.
Obesity

- Adipocyte hypertrophy

Inflammation

- Innate immune activation
- Hepatic steatosis

Macrophages

- Decreased: Adiponectin

- Increased: Resistin, MCP-1

- Increased: IL-6, TNF-α, IL-1β

- Increased: PAI-1, RBP4

Artery

Muscle

Liver

Atherosclerosis

Insulin resistance
Plasma glucose concentration and vascular risks

- **Dysglycemia**
- **Diabetes**

Relative Risk

Plasma Glucose

- **CVD**
- **Microvascular**

Treatment

Prevention
Good Glycemic Control (Lower HbA$_{1c}$) Reduces Complications

<table>
<thead>
<tr>
<th></th>
<th>DCCT</th>
<th>Kumamoto</th>
<th>UKPDS</th>
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</thead>
<tbody>
<tr>
<td>HbA$_{1c}$</td>
<td>9 $\rightarrow$ 7%</td>
<td>9 $\rightarrow$ 7%</td>
<td>8 $\rightarrow$ 7%</td>
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<tr>
<td>Retinopathy</td>
<td>76%</td>
<td>69%</td>
<td>17-21%</td>
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<tr>
<td>Nephropathy</td>
<td>54%</td>
<td>70%</td>
<td>24-33%</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>60%</td>
<td>-</td>
<td>-</td>
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<tr>
<td><strong>Macrovascular disease</strong></td>
<td><strong>44%</strong>*</td>
<td>-</td>
<td><strong>16%</strong>*</td>
</tr>
</tbody>
</table>

* not statistically significant

Cardiovascular Events

Non-Fatal MI, Stroke or CVD Death

Risk reduction 57%
95% CI: 12, 79
Log-rank P = 0.018

Cumulative Incidence

Years from Study Entry

Number at Risk

Intensive: 705 686 640 118
Conventional: 721 694 637 96

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Cumulative Incidence of First of Any Event

Risk reduction 42%
95% CI: 19, 63
Log-rank P = 0.016

Number at Risk

<table>
<thead>
<tr>
<th>Years from Study Entry</th>
<th>Intensive</th>
<th>Conventional</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>705</td>
<td>683</td>
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<td>629</td>
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</table>

DCCT/EDIC

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UKPDS 80: “Legacy” effect of intensive glucose control on MI

N = 4209 with newly diagnosed T2DM

10-year post-trial follow-up, between-group A1C differences lost after 1 year SU/Insulin treatment resulted in persistent ↓24% in microvascular disease (P = 0.001)

*Log-rank P

The United Kingdom Prospective Diabetes Study (UKPDS): Post trial monitoring

## Legacy Effect of Earlier Glucose Control

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

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

*RRR = Relative Risk Reduction, P = Log Rank*

Multiple Targets for Diabetes Therapies

- Dietary Carbohydrates
- Intestine: $\alpha$-glucosidase inhibitors
- Kidney: ↑ glucose excretion
- SGLT2
- Liver: Metformin, TZDs, Dual PPAR
- Muscle: glucose uptake and utilization
- Pancreas: Insulin secretion
  - Sulfonylureas / meglitinides / d-phenylalanine deriv.
  - DPP-IV
  - GLP-1
- Fat: ↓ lipolysis
  - TZDs
  - Dual PPAR
- ↓ Blood Glucose
<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanism</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Cost</th>
</tr>
</thead>
</table>
| Biguanides | • Activates AMP-kinase  
          • ↓ Hepatic glucose production | • Extensive experience  
          • No hypoglycemia  
          • Weight neutral  
          • ? ↓ CVD | • Gastrointestinal  
          • Lactic acidosis  
          • B-12 deficiency  
          • Contraindications | Low |
| SUs / Meglitinides | • Closes KATP channels  
                    • ↑ Insulin secretion | • Extensive experience  
                    • ↓ Microvasc. risk | • Hypoglycemia  
                    • Weight gain  
                    • Low durability  
                    • ? Ischemic preconditioning | Low |
| TZDs | • PPAR-γ activator  
          • ↑ insulin sensitivity | • No hypoglycemia  
          • Durability  
          • ↓ TGs, ↑ HDL-C  
          • ? ↓ CVD (pio) | • Weight gain  
          • Edema / heart failure  
          • Bone fractures  
          • ? ↑ MI (rosi)  
          • ? Bladder ca (pio) | High |
| α-GIs | • Inhibits α-glucosidase  
          • Slows carbohydrate absorption | • No hypoglycemia  
          • Nonsystemic  
          • ↓ Post-prandial glucose  
          • ? ↓ CVD events | • Gastrointestinal  
          • Dosing frequency  
          • Modest ↓ A1c | Mod. |
<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanism</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP-4 inhibitors</td>
<td>• Inhibits DPP-4</td>
<td>• No hypoglycemia</td>
<td>• Modest ↓ A1c • ? Pancreatitis • Urticaria</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>• Increases GLP-1, GIP</td>
<td>• Well tolerated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GLP-1 receptor agonists</td>
<td>• Activates GLP-1 R</td>
<td>• Weight loss</td>
<td>• GI</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>• ↑ Insulin, ↓ glucagon</td>
<td>• No hypoglycemia</td>
<td>• ? Pancreatitis • Medullary cancer • Injectable</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• ↓ gastric emptying</td>
<td>• ? Beta cell mass</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• ↑ satiety</td>
<td>• ? CV protection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amylin mimetics</td>
<td>• Activates amylin receptor</td>
<td>• Weight loss</td>
<td>• GI <strong>/ insulin</strong> • Injectable • Hypo w/ insulin • Dosing frequency</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>• ↓ glucagon</td>
<td>• ↓ PPG</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• ↓ gastric emptying</td>
<td>• Modest ↓ A1c</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• ↑ satiety</td>
<td>• Injectable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>• Bind bile acids</td>
<td>• No hypoglycemia</td>
<td>• GI</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>• ↓ Hepatic glucose production</td>
<td>• Nonsystemic</td>
<td>• Modest ↓ A1c</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ↓ Post-prandial glucose</td>
<td>• Dosing frequency</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ↓ CVD events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dopamine-2 agonists</td>
<td>• Activates DA receptor</td>
<td>• No hypoglycemia</td>
<td>• Modest ↓ A1c • Dizziness/syncope • Nausea • Fatigue</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>• Modulates hypothalamic control of metabolism</td>
<td>• ? ↓ CVD events</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• ↑ insulin sensitivity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class</td>
<td>Mechanism</td>
<td>Advantages</td>
<td>Disadvantages</td>
<td>Cost</td>
</tr>
<tr>
<td>---------------</td>
<td>---------------------------------------------------------------------------</td>
<td>------------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>--------------</td>
</tr>
</tbody>
</table>
| Insulin       | • Activates insulin receptor  
• ↑ peripheral glucose uptake                                               | • Universally effective  
• Unlimited efficacy  
• Microvascular risk                                                      | • Hypoglycemia  
• Weight gain  
• ? Mitogenicity  
• Injectable  
• Training requirements  
• “Stigma”                                                        | Variable      |
| SGLT2 inhibitors | • Reduce renal glucose reabsorption                                       | • Globally Effective                    | • Increased frequency of UTI  
• Increase in Glucagon                                                        |              |
Failure to Achieve Goals

- Complex disease; Difficult lifestyle
- Natural progression of disease
- Low health literacy/ lower social strata
- Multiple medications – costs associated
- Lack of suppression of Glucagon
- Drug side effects
  - Weight gain
  - Hypoglycemia
  - GI side effects
  - Change in blood pressure
- Cardiovascular safety
- Restricted use (Elderly, CHF, Renal Impairment)
- Failure of health professionals
Major Trials Pertaining to CV Outcomes in Patients With Diabetes Mellitus Type -2

- ACCORD: Lowering HbA1c < 6 %
- ADVANCE: Lowering HbA1c < 6.5 %
- VADT: Lowering HbA1c to 1.5 % below standard therapy in older men
- UKPDS: Diet vs Medications
- DCCT: Intensified insulin therapy: HbA1c 7.4% vs 9.1% in Type1 DM
- DCCT-EDIC: 17 year Follow up of DCCT
- BARI 2D: Use of insulin provision vs Insulin sensitizers
- Heart 2D: Prandial vs Basal Insulin Therapy
- LOOK –AHEAD: Intensive Lifestyle Intervention
# 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>
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<tbody>
<tr>
<td>UKPDS</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
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<tr>
<td>DCCT / EDIC*</td>
<td>↓</td>
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<tr>
<td>ACCORD</td>
<td>↓</td>
<td>▼</td>
<td>↑</td>
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<tr>
<td>ADVANCE</td>
<td>↓</td>
<td>▼</td>
<td>▼</td>
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<tr>
<td>VADT</td>
<td>↓</td>
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</tr>
</tbody>
</table>

**Kendall DM, Bergenstal RM. © International Diabetes Center 2009**


* in T1DM
Metabolic Memory and Glycemic Legacy

UKPDS and VADT

Start of intensive therapy in UKPDS

Ideal course = early and sustained glycemic control

Start of intensive therapy in VADT

Drives risk of Complications

Risk of complications continues despite glycemic control

Survival as a function of HbA1c in people with Type 2 Diabetes: Retrospective Cohort Study Lancet 375:481, 2010

Figure 1. Adjusted hazard ratios for all-cause mortality by HbA1c deciles in people given oral combination and insulin-based therapies
What really works

– Treat Hyperglycemia to keep HbA1c < 8 %
– Choose right agent to treat Hyperglycemia and avoid over insulinization
– GLP-1 based therapies (?)
– Treat Dyslipidemia
  
  • 13% decline in mortality with 1 mmol reduction in LDL-C and 21% reduction in major vascular event in people with diabetes over a 4 year period.
– Treat Hypertension: sBP < 13 mm Hg
– Aspirin : Mostly secondary prevention
Healthy eating, weight control, increased physical activity

**Initial drug monotherapy**
- **Efficacy (**↓** HbA1c)**
- **Hypoglycemia**
- **Weight**
- **Side effects**
- **Costs**

**Two drug combinations**
- **Efficacy (**↓** HbA1c)**
- **Hypoglycemia**
- **Weight**
- **Major side effect(s)**
- **Costs**

**Healthy eating, weight control, increased physical activity**

**Metformin**
- High
- Low risk
- Neutral/loss
- GI / lactic acidosis
- Low

*If needed to reach individualized HbA1c target after ~3 months, proceed to 2-drug combination (order not meant to denote any specific preference):*

**Metformin +**
- **Sulfonylurea**
  - High
  - Moderate risk
  - Gain
  - Hypoglycemia
  - Low

**Metformin +**
- **Thiazolidinedione**
  - High
  - Low risk
  - Gain
  - Edema, HF, fx’s
  - High

**Metformin +**
- **DPP-4 Inhibitor**
  - Intermediate
  - Low risk
  - Neutral
  - Rare
  - High

**Metformin +**
- **GLP-1 receptor agonist**
  - High
  - Low risk
  - Loss
  - GI
  - High

**Metformin +**
- **Insulin (usually basal)**
  - Highest
  - High risk
  - Gain
  - Hypoglycemia
  - Variable

*If needed to reach individualized HbA1c target after ~3 months, proceed to 3-drug combination (order not meant to denote any specific preference):*

**Metformin +**
- **Sulfonylurea**
  - High
  - Moderate risk
  - Gain
  - Hypoglycemia
  - Low

**Metformin +**
- **Thiazolidinedione**
  - High
  - Low risk
  - Gain
  - Edema, HF, fx’s
  - High

**Metformin +**
- **DPP-4 Inhibitor**
  - Intermediate
  - Low risk
  - Neutral
  - Rare
  - High

**Metformin +**
- **GLP-1 receptor agonist**
  - High
  - Low risk
  - Loss
  - GI
  - High

**Metformin +**
- **Insulin (usually basal)**
  - Highest
  - High risk
  - Gain
  - Hypoglycemia
  - Variable

*If combination therapy that includes basal insulin has failed to achieve HbA1c target after 3-6 months, proceed to a more complex insulin strategy, usually in combination with 1-2 non-insulin agents:*

**Insulin**
- (multiple daily doses)
Approach to management of hyperglycemia:

- Patient attitude and expected treatment efforts:
  - More stringent: highly motivated, adherent, excellent self-care capacities
  - Less stringent: less motivated, non-adherent, poor self-care capacities

- Risks potentially associated with hypoglycemia, other adverse events:
  - Low
  - High

- Disease duration:
  - Newly diagnosed
  - Long-standing

- Life expectancy:
  - Long
  - Short

- Important comorbidities:
  - Absent
  - Few / mild
  - Severe

- Established vascular complications:
  - Absent
  - Few / mild
  - Severe

- Resources, support system:
  - Readily available
  - Limited

SOME REVELATIONS:

- **GOOD NEWS** (Diabetes Care 2012;35:1252)
  - Death rates among both U.S men and women with diabetes declined substantially between 1997 – 2006 reducing the absolute difference between adults with and without diabetes
  - Death rates declined by 40 %, and all cause mortality declined by 23 %
  - No difference in rate of decline in mortality between men and women
  - Discovery of a Glucose lowering neurocircuit connecting gut, brain and liver that directly reduces hepatic glucose production independent of involvement of insulin (Nature Medicine 2012;18:950)

- Intensive Glucose Control might not reduce the risk of clinical renal outcomes even while affecting surrogate markers (Arch Intern Med 2012;172(10):761)

- ARB’s not superior to ACE i's, and combination may be detrimental, as is addition of direct renin inhibitors

- Newer BP target for BP Control based KEEP Study (140/90 mm Hg) [Arch Intern Med 2012;172(1):41]; ACCORD study (N Engl J Med 2010;362:1575)
<table>
<thead>
<tr>
<th></th>
<th>Hypoglycemia</th>
<th>Wt. Gain</th>
<th>Edema</th>
<th>GII effects</th>
<th>Lactic Acidosis</th>
<th>Liver Toxicity</th>
<th>Use in Renal Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glyburide</td>
<td>4+</td>
<td>+</td>
<td>0</td>
<td>±</td>
<td>0</td>
<td>±</td>
<td>-</td>
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<tr>
<td>Gliclazide</td>
<td>2+</td>
<td>+</td>
<td>0</td>
<td>±</td>
<td>0</td>
<td>±</td>
<td>+</td>
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<td>Glimepiride</td>
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<td>+</td>
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<tr>
<td>Repaglinide</td>
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<td>+</td>
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<td>Metformin</td>
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<td>2+</td>
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<td>0</td>
<td>3</td>
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<td>+</td>
<td>0</td>
<td>0</td>
<td>±*</td>
<td>+</td>
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<tr>
<td>Pioglitazone</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>±*</td>
<td>+</td>
</tr>
</tbody>
</table>

* Liver enzyme monitoring recommended in product monographs

Adapted from Lebovitz H: Endocrinol & Metab Clinics of NA; 30 (4)909-933
Most Intensive  | Less Intensive  | Least Intensive
---|---|---
6.0%| 7.0%| 8.0%

Psychosocioeconomic considerations

Highly motivated, adherent, knowledgeable, excellent self-care capacities, and comprehensive support systems

Less motivated, nonadherent, limited insight, poor self-care capacities, and weak support systems

Hypoglycemia risk

Low  |  Moderate  |  High

Patient age, y

40 | 45 | 50 | 55 | 60 | 65 | 70 | 75

Disease duration, y

5 | 10 | 15 | 20

Other comorbid conditions

None | Few or mild | Multiple or severe

Established vascular complications

None | Cardiovascular disease | Early microvascular | Advanced microvascular