Should There Be a New Paradigm for Glycemic Management of Type 2 Diabetes?

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The Treatment Paradigm for Type 2 Diabetes and Outcomes

- Review the treatment ‘paradigm’ used for treating type 2 diabetes over the last decade
- Review the efficacy and side effects of monotherapy and sequential oral therapies for type 2 diabetes
- Discuss possible mechanisms and theories for apparent lack of effect of glycemic control on cardiovascular risk seen in most recent studies
- Propose new ‘paradigm’ for the treatment of type 2 diabetes and discuss questions that need answers in the quest to achieve sustained glucose control and reduce CV risk
## Therapies for Type 2 DM in 2009
(Pathophysiologic Effects of Drugs for the Treatment of Type 2 DM)

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Insulin Deficiency</th>
<th>Insulin Resistance</th>
<th>Excessive Hepatic Glucose Production</th>
<th>Inappropriate Elevated Glucagon Secretion</th>
<th>Gastric Emptying Dysregulation</th>
<th>Body Weight Dysregulation</th>
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<tbody>
<tr>
<td>Biguanides</td>
<td>None</td>
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<td>Neutral</td>
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<td>None</td>
<td>Increase</td>
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<tr>
<td>α-glucosidase inhibitors</td>
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<td>None</td>
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<td>Neutral</td>
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<td>Sulfonylureas</td>
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<tr>
<td>Meglitinides</td>
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<td>Insulin</td>
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<tr>
<td>Amylinomimetics</td>
<td>None</td>
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<td>None</td>
<td>Beneficial</td>
<td>Beneficial</td>
<td>Decrease</td>
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<tr>
<td>Incretin mimetics</td>
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<td>None</td>
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<td>Decrease</td>
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<tr>
<td>DPP-IV inhibitors</td>
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<td>None</td>
<td>None</td>
<td>Beneficial</td>
<td>Unknown</td>
<td>Neutral</td>
</tr>
</tbody>
</table>
The ‘Octuplet’ of Defects in Type 2 Diabetes

- Brain
- Liver
- Muscle
- GI tract
- Adipocytes
- Insulin Deficiency
- Glucagon Excess
- Kidney
Diagnosis

Lifestyle Intervention and Metformin

A1c ≥ 7%

- No
- Yes

Add Basal Insulin

- Most effective

Add Sulfonylurea

- Least expensive

Add TZD

- No hypoglycemia

A1c ≥ 7%

- No
- Yes

Intensify Insulin

Add TZD

Add Basal Insulin

Add Sulfonylurea

Add GLP-1 agonist
Add DPP-4 inhibitor

THE ORIGINAL RECIPE

Intensive Insulin + Metformin +/- TZD
Trends in $A_1C$ Among US Adults With Diagnosed Diabetes: Percentage of $A_1C < 7\%$

At diagnosis: Lifestyle + Metformin

Tier 1: Well-validated core therapies

STEP 1:
- Lifestyle + metformin + Basal insulin

STEP 2:
- Lifestyle + metformin + Sulfonylurea
- Lifestyle + metformin + Basal insulin

STEP 3:
- Lifestyle + metformin + Intensive insulin

Tier 2: Less well validated therapies

- Lifestyle + metformin + Pioglitazone
  - No hypoglycemia
  - Edema/CHF
  - Bone loss

- Lifestyle + metformin + GLP-1 agonist
  - No hypoglycemia
  - Weight loss
  - Nausea/vomitting

- Lifestyle + metformin + Pioglitazone + Sulfonylurea
- Lifestyle + metformin + Basal insulin

EXTRA CRISPY RECIPE
The ‘Recipe’ of Sequential Therapy in Type 2 DM

Adapted from Campbell IW. Br J Cardiol 2000;7:625-631
The Treatment Paradigm for Type 2 Diabetes and Outcomes

✓ Review the treatment ‘paradigm’ used for treating type 2 diabetes over the last decade

✓ Review the efficacy and side effects of monotherapy and sequential oral therapies for type 2 diabetes

✓ Discuss possible mechanisms and theories for apparent lack of effect of glycemic control on cardiovascular risk seen in most recent studies

✓ Propose new ‘paradigm’ for the treatment of type 2 diabetes and discuss questions that need answers in the quest to achieve sustained glucose control and reduce CV risk
A Diabetes Outcome Progression Trial
ADOPT Objective

Compare the durability of glycaemic control using rosiglitazone versus metformin or glyburide as initial monotherapy in patients with recently diagnosed type 2 diabetes mellitus
Inclusion Criteria

- Type 2 diabetes mellitus ≤3 years
- Drug naïve
- Male and female
- Aged 30–75 yr inclusive
- Fasting plasma glucose
  - 126–180 mg/dl (7–10 mmol/l) after 4-week run-in and prior to randomisation
HbA1c Over Time

Rosiglitazone vs Metformin
-0.13 (-0.22 to -0.05), P=0.002

Rosiglitazone vs Glyburide
-0.42 (-0.50 to -0.33), P<0.001

Time (years)

%
Weight Over Time

Rosiglitazone vs Metformin
6.9 (6.3 to 7.4), P<0.001

Rosiglitazone vs Glyburide
2.5 (2.0 to 3.1), P<0.001

- Rosiglitazone
- Glyburide
- Metformin
Hip Circumference Over Time

Rosiglitazone vs Metformin
5.3 (4.4 to 6.3), P<0.001

Rosiglitazone vs Glyburide
2.4 (1.4 to 3.4), P<0.001

Rosiglitazone

Glyburide

Metformin

Time (years)
## Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Rosiglitazone</th>
<th>Metformin</th>
<th>Glyburide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight gain (kg)</td>
<td>4.8</td>
<td>- 2.1</td>
<td>2.3</td>
</tr>
<tr>
<td>Hypoglycemia (%)</td>
<td>10</td>
<td>12</td>
<td>39</td>
</tr>
<tr>
<td>Edema (%)</td>
<td>14</td>
<td>7</td>
<td>9</td>
</tr>
</tbody>
</table>
Monotherapy Fails in Type 2 DM - UKPDS

Within 3 years of diagnosis 50% of patients with type 2 diabetes will require multiple therapies (≥1 oral agent, including a combination of oral agents with insulin)

The ‘Recipe’ of Sequential Therapy in Type 2 DM

Adapted from Campbell IW. Br J Cardiol 2000;7:625-631
Glycemic Control Continues to Deteriorate After Sulfonylureas Are Added to Metformin Among Patients With Type 2 Diabetes

- Failing metformin
  - N= 2,220
  - Duration DM= 3.8 y

- Sulfonylurea added
  - A₁c ≈ 8.8%

- A₁c nadir 7.3%
  - at 6-12 months

‘Velocity’ of rise in A₁c comparable to monotherapy after 6 months

Typical delay when oral drugs are failing

982 patients on sulfonylurea and/or metformin and sub-optimally controlled

Time HbA₁c >8% before any change = 26 months

Last HbA₁c before change = 9.6%

Glycemic Control Continues to Deteriorate After Sulfonylureas Are Added to Metformin Among Patients With Type 2 Diabetes

Glycemic Control Continues to Deteriorate After Sulfonylureas Are Added to Metformin Among Patients With Type 2 Diabetes

Pre-SU A1c:
- ≥ 10%
- 9.0-9.9%
- 8.0-8.9%
- 4.0-7.9%

Earlier and More Aggressive Intervention May Improve Patients’ Chances of Reaching Goal

Mean A1C of patients

OAD=oral antidiabetic agent.

PRESERVE-β
Two-year efficacy and safety of initial combination therapy with nateglinide or glyburide plus metformin

Baseline $A_1c \approx 8.3\%$

UKPDS & ADOPT monotherapy

Nateg/Met (n=208) $A_1c \approx 6.9\%$

Glyb/Met (n=198) $A_1c \approx 6.8\%$

PRESERVE-β
Two-year efficacy and safety of initial combination therapy with nateglinide or glyburide plus metformin

✓ Trajectory of $A_1c$ deterioration typically 0.05%/month or 0.5-0.6%/year in monotherapy or add-on studies from nadir to endpoint

✓ Trajectory of $A_1c$ deterioration reduced by 50% with initial combination therapy

✓ Hypoglycemia: 18% on metformin/glyburide
8% on metformin/nateglinide

Initial Combination Therapy With Sitagliptin Plus Metformin

Screening period

Diet and exercise run-in period

Single-blind placebo run-in period

Eligible if A1C 7.5%–11%

Week 1

Week 24

Week 54

Week 104

24-week phase\(^1\) with 30-week continuation phase\(^2\)

50-week extension study \(^3\)

Sitagliptin 100 mg qd

Metformin 500 mg bid

Metformin 1,000 mg bid

Sitagliptin 50 mg bid + metformin 500 mg bid

Sitagliptin 50 mg bid + metformin 1,000 mg bid

Placebo

FPG criteria to week 24

A1C >8% to week 54

A1C >7.5% to week 104

6–12 weeks

Glycemic rescue criteria

Week –2

Day 1

bid=twice a day; FPG=fasting plasma glucose; OHA=oral antihyperglycemic agent; qd=daily; R=randomization; T2DM=type 2 diabetes mellitus.

3. Data available on request from Merck & Co., Inc. Please specify 20852883(2)-JAN.
Initial Combination Therapy With Sitagliptin Plus Metformin Study: A₁C Results at 24 Weeks

- Placebo
- Sitagliptin 100 mg qd
- Metformin 500 mg bid
- Sitagliptin 50 mg bid + metformin 500 mg bid
- Metformin 1,000 mg bid
- Sitagliptin 50 mg bid + metformin 1,000 mg bid

Mean baseline A₁C = 8.8%

Mean baseline A₁C = 8.8%

Week 0 6 12 18 24

LSM A₁C Change From Baseline, %

-0.5
-1.0
-1.5
-2.0

bid=twice a day; LSM=least-squares mean; qd=once a day.
Initial Combination Therapy With Sitagliptin Plus Metformin Study: A₁C Results at 24 Weeks

LSM A₁C Change From Baseline, %

24-Week placebo-adjusted results
Mean baseline A₁C = 8.8%

-0.8<sup>a</sup> n=175
-1.0<sup>a</sup> n=178
-1.3<sup>a</sup> n=177
-1.6<sup>a</sup> n=183
-2.1<sup>a</sup> n=178

Placebo group results at 24 weeks: +0.2%

- Sitagliptin 100 mg qd
- Metformin 500 mg bid
- Metformin 1,000 mg bid
- Sitagliptin 50 mg bid + metformin 500 mg bid
- Sitagliptin 50 mg bid + metformin 1,000 mg bid

bid=twice a day; LSM=least-squares mean; qd=once a day.

<sup>a</sup><i>P</i>≤.001 vs placebo.

<sup>b</sup>LSM change from baseline without adjustment for placebo.

Initial Combination Therapy With Sitagliptin Plus Metformin Study: FPG and PPG Results at 24 Weeks

**FPG**

Mean baseline level: 197–205 mg/dL

- Sitagliptin 100 mg qd
  - LSM FPG Change, mg/dL: -23a
  - n=178
- Metformin 500 mg bid
  - LSM FPG Change, mg/dL: -33a
  - n=179
- Sitagliptin 50 mg bid + metformin 500 mg bid
  - LSM FPG Change, mg/dL: -35a
  - n=179
- Sitagliptin 100 mg bid + metformin 1,000 mg bid
  - LSM FPG Change, mg/dL: -53a
  - n=183
- Metformin 1,000 mg bid
  - LSM FPG Change, mg/dL: -70a
  - n=180

Placebo group results: +6 mg/dL

**2-hour PPG**

Mean baseline level: 283–293 mg/dL

- Sitagliptin 100 mg qd
  - LSM PPG Change, mg/dL: -52a
  - n=136
- Metformin 500 mg bid
  - LSM PPG Change, mg/dL: -54a
  - n=141
- Sitagliptin 50 mg bid + metformin 500 mg bid
  - LSM PPG Change, mg/dL: -78a
  - n=138
- Sitagliptin 50 mg bid + metformin 1,000 mg bid
  - LSM PPG Change, mg/dL: -93a
  - n=147
- Metformin 1,000 mg bid
  - LSM PPG Change, mg/dL: -117a
  - n=152

Placebo group results: +0.3 mg/dL

bid=twice a day; FPG=fasting plasma glucose;
LSM=least-squares mean; PPG=postprandial glucose; qd=once a day.
aLSM adjusted for baseline value.
bDifference from placebo.
cNot placebo-adjusted.
Initial Combination Therapy With Sitagliptin Plus Metformin Study: Percentage of Patients Achieving Target A1C Goals at 24 Weeks

- Sitagliptin 50 mg bid + metformin 1,000 mg bid
- Metformin 1,000 mg bid
- Sitagliptin 100 mg qd
- Sitagliptin 50 mg bid + metformin 500 mg bid
- Metformin 500 mg bid
- Placebo

Mean Baseline A1C = 8.8%

bid=twice a day; qd=once a day.

*P<0.01 vs monotherapy.

Goldstein B et al. *Diabetes Care*. 2007;30(8):1979–1987. Please note: Dr. Goldstein is currently a Merck employee but was not at the time this study was conducted or when the publication was written.
Initial Combination Therapy With Sitagliptin Plus Metformin Study: Change in Body Weight at 24 Weeks

- Sitagliptin 50 mg + metformin 1,000 mg bid
- Metformin 1,000 mg bid
- Sitagliptin 100 mg qd
- Sitagliptin 50 mg + metformin 500 mg bid
- Metformin 500 mg bid
- Placebo

![Graph showing change in body weight at 24 weeks for different treatment groups.]

LSM Weight Change From Baseline, kg

- n=167
- n=175
- n=179
- n=175
- n=184
- n=178

bid=twice a day; LSM=least squares mean; qd=once daily.

2. Data available on request from Merck & Co., Inc. Please specify 20751298(1)-JAN.
## Initial Combination Therapy With Sitagliptin Plus Metformin Study: Adverse Experience Profiles at 24 Weeks

### Summary of Adverse Experiences

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Sitagliptin 100 mg qd</th>
<th>Metformin 500 mg bid</th>
<th>Metformin 1,000 mg bid</th>
<th>Sitagliptin 50 mg + metformin 500 mg bid</th>
<th>Sitagliptin 50 mg + metformin 1,000 mg bid</th>
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<tr>
<td>n</td>
<td>176</td>
<td>179</td>
<td>182</td>
<td>182</td>
<td>190</td>
<td>182</td>
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<tr>
<td>≥1 AE, %</td>
<td>50.6</td>
<td>53.6</td>
<td>55.5</td>
<td>62.1</td>
<td>57.9</td>
<td>57.7</td>
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<tr>
<td>Drug-related AEs, %</td>
<td>9.7</td>
<td>6.7</td>
<td>11.5</td>
<td>16.5</td>
<td>12.6</td>
<td>15.4</td>
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<tr>
<td>Serious AEs, %</td>
<td>5.7</td>
<td>5.0</td>
<td>2.2</td>
<td>1.1</td>
<td>3.2</td>
<td>0.5</td>
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<tr>
<td>Hypoglycemia, %</td>
<td>0.6</td>
<td>0.6</td>
<td>0.5</td>
<td>1.1</td>
<td>1.1</td>
<td>2.2</td>
</tr>
<tr>
<td>All gastrointestinal AEs, %</td>
<td>10.8</td>
<td>15.1</td>
<td>15.9</td>
<td>25.3</td>
<td>17.9</td>
<td>24.7</td>
</tr>
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</table>

AE=adverse experience; bid=twice a day.
Initial Combination Therapy With Sitagliptin Plus Metformin Study: A1C Results at 104 Weeks (Extension Study)

APT Population (Extension Study)

- Sitagliptin 100 mg qd (n=50)
- Metformin 500 mg bid (n=64)
- Sitagliptin 50 mg bid + metformin 1,000 mg bid (n=105)
- Metformin 1,000 mg bid (n=87)
- Sitagliptin 50 mg bid + metformin 500 mg bid (n=96)

Mean baseline A1C = 8.5%–8.7%

APT=all-patients-treated; bid=twice a day; LSM=least-squares mean; qd=daily.

*Values represented are rounded. Actual values are 1.15 for sitagliptin 100 mg qd and 1.06 for metformin 500 mg bid.

Data available on request from Merck & Co., Inc. Please specify 20852883(2)-JAN.
APE Road Map to Achieve Glycemic Goals in Treatment-Naive Patients With Type 2 Diabetes

**Initial Glycemic Goals**

- A1C, % (FPG, PPG, and A1C)

**Intervention**

- **Initial Therapy**
  - Preferred
  - Metformin
  - TZD
  - AGI
  - DPP-4 inhibitor

- **Assess FPG and PPG**

**Continuous Titration of Medication (2-3 months)**

- **Lifestyle Modification**
- **Combine Therapies**
  - Prandial insulin
  - Metformin
  - SU
  - TZD

- **Adjust medication to maximal effective dose to meet ACE glycemic goals**

- **If ≤6.5% A1C Goal Not Achieved**
  - Intensify Lifestyle Modification
  - Intensify or combine medications including:
    - incretin mimetic
    - SU, TZD

- **If ≥6.5% A1C Goal Not Achieved**
  - Continuous Titration of Medication

---

ACE=American College of Endocrinology; AGI=alpha-glucosidase inhibitor; DPP-4=dipeptidyl peptidase-4; FPG=fasting plasma glucose; met=metformin; PPG=postprandial glucose; SU=sulfonylurea; TZD=thiazolidinedione.

**Target:**

- PPG and FPG

**Alternatives**

- Glinides
- SU (low dose)
- Prandial insulin
d,e
- Premixed insulin
e
- Basal insulin
- Basal insulin analog

**Monitor/adjust medication to maximal effective dose to meet ACE glycemic goals†**

---

*A ACE glycemic goals: A1C < 6.5%; FPG <110 mg/dL; 2-hour PPG <140 mg/dL.

*b Preferred first agent in most patients.

*c According to the US Food and Drug Administration, rosiglitazone not recommended with insulin.

*d Analog preparations preferred.

*e Rapid-acting insulin analog (available as lispro, aspart, and glulisine) or regular insulin.

*f Indicated for patients not at goal despite SU and/or metformin or TZD therapy; incretin mimetic is not indicated for insulin-using patients.

**Available as glargine and detemir.**

Can We Preserve $\beta$-Cell Function in Type 2 Diabetes?
β-Cell Decline is Progressive

The insulin secretion/insulin resistance (disposition) index = ΔI/ΔG / IR

HbA1c Over Time

Rosiglitazone vs Metformin
-0.13 (-0.22 to -0.05), P=0.002

Rosiglitazone vs Glyburide
-0.42 (-0.50 to -0.33), P<0.001
Can We Preserve $\beta$-Cell Function in Type 2 Diabetes?

Rosiglitazone vs Metformin
5.8%, $P=0.003$

Rosiglitazone vs Glyburide
−0.8%, $P=0.67$

HOMA %B

0 1 2 3 4 5

Time (years)
Lack of Sustained Glycemic Control with Sulfonylurea Therapy
Exenatide Improved HOMA-B From Baseline Through 3 Years

Patients received MET or SFU; n = 92.
Mean (+ SE); \( P < 0.0001 \) from baseline after 3 years of exenatide
Data on file, Amylin Pharmaceuticals, Inc.
Buse JB, et al. Presented at ADA, 67th Scientific Sessions; 2007; Chicago, IL (abstract 0283-OR)
Can We Preserve $\beta$-Cell Function in Type 2 Diabetes?

Demonstrable improvements in insulin secretion/insulin resistance (disposition) index = $\Delta I/\Delta G / IR$

- ACT NOW (Actos Now for Prevention of Diabetes) @ 2.6 years:
  - 81% reduction in time to diabetes vs. placebo ($p<0.00001$)
  - Improvement in disposition index vs. placebo ($p<0.05$)

- Exenatide for adjunctive treatment of diabetes for 3 years:
  - Significant improvement in HOMA-B and $\Delta I/\Delta G$
  - Sustained hemoglobin $A_1c$ control and 5.3 kg sustained weight loss

DeFronzo RA, et al. Late-breaking abstract presented at 68th Scientific Session of ADA, 6-10 June 2008, San Francisco, CA

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## Oral Medications for Diabetes Mellitus and Weight Change

<table>
<thead>
<tr>
<th>Medication</th>
<th>Weight: Positive change (lb/yr)</th>
<th>Weight: Negative change (lb/yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td>1 – 3</td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td></td>
<td>0 – 6</td>
</tr>
<tr>
<td>α-glucosidase inhibitors</td>
<td></td>
<td>0 – 10</td>
</tr>
<tr>
<td>TZD’s</td>
<td>1 – 13</td>
<td></td>
</tr>
<tr>
<td>Glinides</td>
<td>1 – 3</td>
<td></td>
</tr>
<tr>
<td>Exenatide*</td>
<td></td>
<td>1.75 (15-month RCT)</td>
</tr>
<tr>
<td>Sitagliptin†</td>
<td>0 (24-week RCT)</td>
<td>0 (24-week RCT)</td>
</tr>
<tr>
<td>Pramlintide‡</td>
<td></td>
<td>3.7 (16-week RCT)</td>
</tr>
</tbody>
</table>

TZD=thiazolidinedione; RCT=randomized controlled trial
†Diabetes Care 2006;29:2632–2637.
‡J Clin Endocrinol Metab 2007;92:2977–2983.
Rosiglitazone added to glyburide & metformin for 24 weeks:

- Hemoglobin A$_1$c improved by 1.0% vs. placebo (p<0.001)
- Hypoglycemia significantly increased at 22%
- Average weight gain 3 kg

Triple oral therapy in DM2

Sulfonylurea (glimepiride) added to TZD & metformin for 30 weeks:

- Hemoglobin A1c improved 1.3%
- Average weight gain 3.76 kg
- Hypoglycemia significantly increased at 51%

Roberts L, et al. *Clinical Therapeutics* 2005;27:1535-1547
Similar 1-1.5% $A_1c$ reduction if sulfonylurea added to TZD/metformin versus TZD added to SU/metformin

↓

Weight gain

More hypoglycemia
The Treatment Paradigm for Type 2 Diabetes and Outcomes

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Glycemic Control & CV Outcomes: UKPDS
## Glycemic Control & CV Outcomes: ACCORD vs. ADVANCE vs. VADT

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ACCORD</th>
<th>ADVANCE</th>
<th>VADT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome (intensive vs. standard)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median HbA₁c at end (%)</td>
<td>6.4 vs. 7.5</td>
<td>6.3 vs. 7.0</td>
<td>6.9 vs. 8.5</td>
</tr>
<tr>
<td>On TZD at study end (%)</td>
<td>91 vs. 58</td>
<td>17 vs. 11</td>
<td>53 vs. 42</td>
</tr>
<tr>
<td>On insulin at study end (%)</td>
<td>77 vs. 55</td>
<td>40 vs. 24</td>
<td>89 vs. 74</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR for mortality</td>
<td>1.22*</td>
<td>0.93</td>
<td>1.07</td>
</tr>
<tr>
<td>Major/severe hypoglycemia (%)</td>
<td>16.2 vs. 5.1</td>
<td>2.7 vs. 1.5</td>
<td>21.2 vs. 9.9</td>
</tr>
<tr>
<td>Weight gain (kg)</td>
<td>3.5 vs. 0.4</td>
<td>0.0 vs. -1.0</td>
<td>8.2 vs. 3.4</td>
</tr>
<tr>
<td>Weight gain &gt; 10 kg (%)</td>
<td>28 vs. 14</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>BMI change</td>
<td></td>
<td></td>
<td>2.5 vs. 1.1</td>
</tr>
</tbody>
</table>
**Glycemic Control & CV Outcomes: ACCORD vs. ADVANCE vs. VADT**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ACCORD</th>
<th>ADVANCE</th>
<th>VADT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median duration (yr)</td>
<td>3.4</td>
<td>5.0</td>
<td>5.6</td>
</tr>
<tr>
<td>Medical treatment at completion (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>77 vs. 55</td>
<td>41 vs. 24</td>
<td>89 vs. 74</td>
</tr>
<tr>
<td>Metformin</td>
<td>95 vs. 87</td>
<td>74 vs. 67</td>
<td></td>
</tr>
<tr>
<td>Secretagogue</td>
<td>87 vs. 74</td>
<td>94 vs. 62</td>
<td></td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>92 vs. 58</td>
<td>17 vs. 11</td>
<td>53 vs. 42</td>
</tr>
<tr>
<td>Incretin</td>
<td>18 vs. 5</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Statin</td>
<td>88 vs. 88</td>
<td>46 vs. 48</td>
<td>86 vs. 83</td>
</tr>
<tr>
<td>Any antihypertensive drug</td>
<td>91 vs. 92</td>
<td>89 vs. 88</td>
<td></td>
</tr>
<tr>
<td>ACE-inhibitor</td>
<td>70 vs. 72</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>76 vs. 76</td>
<td>57 vs. 55</td>
<td>88 vs. 86</td>
</tr>
</tbody>
</table>
Glycemic Control & CV Outcomes: VADT

✓ Incidences of severe hypoglycemia (very low glucose levels with change in consciousness) in ≈21% of participants in the intensive group and ≈9% of those in the standard treatment group

✓ Increase in mortality in intensive-treatment group was accounted for by an increase in sudden death:
  - Having recent severe hypoglycemia episode associated with fourfold increase in CV death
Glycemic Control and Cardiovascular Risk

✓ What effect do weight gain and waist circumference/visceral adiposity have on cardiovascular risk?
Increased Mortality Risk with ↑ BMI

The Surgeon General's Call to Action to Prevent Overweight and Obesity & NIH, NEJM, 1995.
Central Adiposity and CHD Risk in Type 2 Diabetes

‘The Metabolic Cesspool’

Visceral adipocytes

Pro-thrombosis
- PAI-1

Central Fat Deposition
- 11-β-HSD₁

Inflammation
- TNF-α
  - IL-6

Hypertension
- Angiotensinogen
  - Angiotensin II

Insulin Resistance & β-cell Dysfunction
- ↑ Resistin
- ↓ Adiponectin
- Free Fatty Acids

Hepatic CRP

CNS ‘leptin resistance’
43 lean, healthy volunteers (average age 29 years) randomized to 9 pounds (4 kg) of weight gain vs. weight maintenance.

Endothelial function measured by flow-mediated dilation (FMD) of the brachial artery measured after 8 weeks of weight gain and at 16 weeks after weight was lost:

- Brachial artery FMD remained unchanged in weight maintainers.

- FMD decreased in fat-gainers (FMD=9.1 ± 3 vs. 7.6 ± 3.2, p=0.003) but recovered to baseline after subjects shed the gained weight.

- Visceral fat gain, but not subcutaneous fat gain was significantly correlated with the decrease in brachial artery FMD (p=0.004 and p=0.15, respectively).

Weight Gain and Endothelial Dysfunction

43 lean, healthy volunteers (average age 29 years) randomized to 9 pounds (4 kg) of weight gain vs. weight maintenance

Conclusions: In lean healthy young subjects, modest weight gain results in impaired endothelial function, even in the absence of changes in blood pressure.

Endothelial function recovers after weight loss.

Visceral rather than subcutaneous fat predicts endothelial dysfunction.

Exenatide Sustained A1C Reduction 3-Year Completers

Mean (SE) P < 0.0001 from baseline to 30 weeks and baseline to 3 years

Data on file, Amylin Pharmaceuticals, Inc.

Buse JB, et al. Presented at ADA, 67th Scientific Sessions; 2007; Chicago, IL (abstract 0283)

Exenatide Sustained A1C Reduction 3-Year Completers

Baseline A1C 8.2%

-1.1 ± 0.1%

46%

% achieving A1C ≤7%

-1.0 ± 0.1%

54%

46%

0 26 52 78 104 130 156

Time (wk)

A1C (%)
Exenatide Continues to Reduce Weight 3-Year Completers

Baseline Weight
99 kg

-5.3 ± 0.4 kg

Change in body weight (kg)

Time (wk)
Evolution of HOMA Indices after 6 Months Exenatide Therapy in Type 2 Diabetes Patients

33 patients (mean age 59 years) with HbA$_1c$ > 7.5% on maximum doses of metformin and sulfonylurea

- 34% absolute increase in insulin sensitivity (p=0.003)
- 4 kg weight reduction (p=0.001)
- 2 cm waist circumference reduction (p=0.023)

Improvement in CV Risk Factors With 3.5 years of Exenatide

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline (Mean ± SD)</th>
<th>Δ Baseline (Mean ± SE)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>225±142</td>
<td>-44.4±12.1</td>
<td>-68.3 to -20.5</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>184±37</td>
<td>-10.8±3.1</td>
<td>-17.0 to -4.6</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>39±10</td>
<td>8.5±0.6</td>
<td>7.2 to 9.7</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>114±33</td>
<td>-11.8±2.9</td>
<td>-17.5 to -6.1</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>129±13</td>
<td>-3.5±1.2</td>
<td>-5.9 to -1.0</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>79±8</td>
<td>-3.3±0.8</td>
<td>-4.9 to -1.7</td>
</tr>
</tbody>
</table>

3.5-y completers, N = 151
The effect of GLP-1 on cardiac ejection fraction and wall motion in patients with acute myocardial infarction

Bromocriptine Mesylate (Cycloset®) for Type 2 DM

3,723 patients with type 2 diabetes randomized across 4 double-blind, placebo-controlled trials

- Bromocriptine mesylate vs. placebo:
  - Typically 0.5-0.6% reduction in HbA1c
  - 0.3 kg to 0.9 kg weight gain
  - 1.4% to 3.6% more frequent hypoglycemia

- 42% reduction in combined endpoint of MI, stroke, hospitalization for unstable angina, CHF, and revascularization surgery (p<0.036) in 52-week safety study
Glycemic Control and Cardiovascular Risk

Could hypoglycemia (both reported and ‘silent’) contribute significantly to mortality?
Hypoglycemia

Biochemical Definition = Glucose $\leq 70$ mg/dL

Minor hypoglycemia = Patient can self-treat

Severe hypoglycemia: Patient requires assistance
  – With or without coma and/or seizure

Hypoglycemia

Severe hypoglycemia requiring emergency rx:

- 7.1% annual rate DM 1
- 7.3% annual rate DM 2 on insulin

Hypoglycemia—Physiologic Response

- Glucagon – most important counterregulatory hormone with respect to effect on normalization of blood glucose level

- Epinephrine (norepinephrine) – decreases insulin production and decreases glucose uptake in peripheral tissues. Also stimulates hepatic glucose production

  ▶ vasoconstriction

  ▶ platelet aggregation

Hypoglycemia – Deleterious Impact

Drug-induced hypoglycemic Coma in 102 Diabetic Patients (92 type 2 DM, 10 type 1 DM)

Mortality ≈ 5%

Acute MI ≈ 2%

CVA ≈ 1%

Hypoglycemia – Deleterious Impact

72-hours of continuous glucose monitoring (CGM) and holter-monitoring
(21 patients with type 2 diabetes, existing CAD, and on insulin)

54 episodes of < 70 mg/dl
✓ 18% of time = angina
✓ 8% of time ECG changes

Glycemic Control and Cardiovascular Risk

- Benefits of early and aggressive therapy may not become evident for 5-15 years
Glycemic Control & CV Outcomes: ADVANCE

Major Macrovascular Events (%)

Months of Follow-up

Glycemic Control & CV Outcomes: ADVANCE

Death from Any Cause (%)

Glycemic Control & CV Outcomes: STENO-2

✓ Design: 160 men and women with type 2 DM

Persistent microalbuminuria

Randomized to intensive multi-factorial intervention (tight glucose regulation, ARBs, aspirin and lipid-lowering agents) and behavioral modification interventions

Mean treatment period 7.8 years

Additional observation for mean 5.5 years

Glycemic Control & CV Outcomes: STENO-2

Cumulative Index of Death (%)

Years

P = 0.02

Conventional therapy

Intensive therapy

The Treatment Paradigm for Type 2 Diabetes and Outcomes

✓ Review the treatment ‘paradigm’ used for treating type 2 diabetes over the last decade

✓ Review the efficacy and side effects of monotherapy and sequential oral therapies for type 2 diabetes

✓ Discuss possible mechanisms and theories for apparent lack of effect of glycemic control on cardiovascular risk seen in most recent studies

✓ Propose new ‘paradigm’ for the treatment of type 2 diabetes and discuss questions that need answers in the quest to achieve sustained glucose control and reduce CV risk
A New Treatment Paradigm for Glycemic Management of Type 2 DM

1. Early use of initial combination therapy (2 to 3 drugs in all patients with metformin and incretin-based therapy as ‘core’?)

2. Strongly consider use of therapies that minimize weight gain and hypoglycemia and may provide β-cell preserving effects

3. Do not sacrifice glycemic control, especially if can be achieved with minimal weight gain and hypoglycemia

4. Earlier use of insulin therapy (hemoglobin A$_1$c $\geq$ 9%)

5. Aggressive cardiovascular risk factors management
Cost-effectiveness of sitagliptin-based treatment regimens in European patients with type 2 diabetes and HbA$_1c$ above target on metformin monotherapy

An event simulation model using the UKPDS Outcomes Model risk equations for predicting risks of diabetes-related complications:

Lifetime costs and benefits projected to be dominant (cost saving with improved health outcomes) with the addition of *sitagliptin* to metformin vs. adding *rosiglitazone* and at least cost-effective vs. adding *sulfonylurea*

Sorry, not in my job description…