Pharmacology Update: 14 Classes and Counting

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2/28/14
Number of people with DM by IDF Region, 2013

- **World**: 382M people living with diabetes, 46% undiagnosed
- **North America and Caribbean (NAC)**: 37M
- **South and Central America (SACA)**: 24M
- **Africa (AFR)**: 20M
- **Middle East and North Africa (MENA)**: 35M
- **South-East Asia (SEA)**: 72M
- **Europe (EUR)**: 56M
- **Western Pacific (WP)**: 138M
Undiagnosed DM

Proportion of cases of diabetes (20-79 years) that are undiagnosed, 2013
Expected Rise

WORLD 592M people living with diabetes in 2035

WORLD 382M

AFR ↑ 109.1%
MENA ↑ 96.2%
SEA ↑ 70.6%
SACA ↑ 59.8%
WP ↑ 46%
NAC ↑ 37.3%
EUR ↑ 22.4%

2013 2035
Top 10 countries of number of people with DM (20-79 years), 2013

- China: 98.4 million
- India: 65.1 million
- USA: 24.4 million
- Brazil: 11.9 million
- Russian Federation: 10.9 million
- Mexico: 8.7 million
- Indonesia: 8.5 million
- Germany: 7.6 million
- Egypt: 7.5 million
- Japan: 7.2 million
## Global Projections

<table>
<thead>
<tr>
<th>IDF REGION</th>
<th>2013 MILLIONS</th>
<th>2035 MILLIONS</th>
<th>INCREASE %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>19.8</td>
<td>41.4</td>
<td>109%</td>
</tr>
<tr>
<td>Middle East and North Africa</td>
<td>34.6</td>
<td>67.9</td>
<td>96%</td>
</tr>
<tr>
<td>South-East Asia</td>
<td>72.1</td>
<td>123</td>
<td>71%</td>
</tr>
<tr>
<td>South and Central America</td>
<td>24.1</td>
<td>38.5</td>
<td>60%</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>138.2</td>
<td>201.8</td>
<td>46%</td>
</tr>
<tr>
<td>North America and Caribbean</td>
<td>36.7</td>
<td>50.4</td>
<td>37%</td>
</tr>
<tr>
<td>Europe</td>
<td>56.3</td>
<td>68.9</td>
<td>22%</td>
</tr>
<tr>
<td><strong>World</strong></td>
<td><strong>381.8</strong></td>
<td><strong>591.9</strong></td>
<td><strong>55%</strong></td>
</tr>
</tbody>
</table>
Global Burden

- Diabetes caused 5.1 million deaths in 2013
- Every six seconds, a person dies from diabetes
- 450!
Epidemiology

Figure 2. Annual Number of U.S. Adults Aged 18–79 Years with Diagnosed Diabetes, 1980–2010

Source: National Diabetes Surveillance System, National Health Interview Survey data.
Overview of the Diabetes Epidemic in the United States

- 25.8 million people/8.3% of the population have diabetes\(^1\)
- 7.0 million people are undiagnosed\(^1\)
- 11.3% of adults aged ≥20 years have diabetes\(^1\)
  - ~1.9 million people aged ≥20 years were newly diagnosed in 2010
- Diabetes is the 7th leading cause of death in the U.S. \(^1\)
- Total estimated cost of diabetes in 2012 was $245 billion\(^2\)


\(^2\)American Diabetes Association, Diabetes Care DOI.10.2337/dc12-2625, published online 3/6/13 ahead of print
Pre-diabetes

• 33% of US adults have pre-diabetes
• More than 90% are UNaware of the condition
Pre-diabetes

- Progression to type 2 diabetes from pre-diabetes is not inevitable
- Diabetes Prevention Program (DPP) has shown that losing 5-7% of body weight and getting at least 150 min of moderate physical activity per week can prevent progression by 58%
Diseases Attributable to Obesity

Relative Risk of Developing Certain Diseases Over the Next Decade For Men With BMI >35

Relationship Between Weight Gain in Adulthood and Risk of Type 2 Diabetes Mellitus

American Association of Clinical Endocrinologists (AACE)

AACE Comprehensive Diabetes Management Algorithm 2013

Task Force
Pre-Diabetes

**Prediabetes Algorithm**

IGF (100–125) | IGT (140–199) | Metabolic Syndrome (NCEP 2001)

**Lifestyle Modification**
(Including Medically Assisted Weight Loss)

**Other CVD Risk Factors**
- CVD Risk Factor Modifications Algorithm
  - Dyslipidemia
  - Hypertension

**Anti-Obesity Therapies**
- Normal Glycemia
  - Progression

**Overt Diabetes**
- Proceed to Hyperglycemia Algorithm

**Anti-Hyperglycemic Therapies**
- FPG > 100 | 2 hour PG > 140
  - 1 Pre-DM Criterion
  - Multiple Pre-DM Criteria
    - Low Risk Medications
      - Metformin
      - Acarbose
    - TZD
    - GLP-1 RA
  - If glycemia not normalized, consider with caution
## Pre-Diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Relative Risk Reduction (%)</th>
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</thead>
<tbody>
<tr>
<td>Finnish DPS</td>
<td>Diet and Exercise</td>
<td>58</td>
</tr>
<tr>
<td>Diabetes Prevention Program</td>
<td>Diet and Exercise Metformin</td>
<td>58</td>
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<tr>
<td></td>
<td></td>
<td>31 (53% if obese)</td>
</tr>
<tr>
<td>STOP-NIDDM</td>
<td>Acarbose</td>
<td>36</td>
</tr>
<tr>
<td>TRIPOD</td>
<td>Troglitazone</td>
<td>56</td>
</tr>
<tr>
<td>DREAM</td>
<td>Rosiglitazone Ramipril</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NS</td>
</tr>
</tbody>
</table>
Beta Cell Mass is Decreased as Diabetes Progresses

Percentage of adults with diagnosed diabetes receiving treatment with insulin or oral medication, United States, 2007–2009

# 14 Classes of Drugs Available for Treatment of Type 2 Diabetes Mellitus

<table>
<thead>
<tr>
<th>#</th>
<th>Class</th>
<th>A1c Reduction (mg/dL)</th>
<th>Hypoglycemia</th>
<th>Weight Change</th>
<th>Dosing (times/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>Metformin</td>
<td>1.5-2.0</td>
<td>No</td>
<td>Neutral-Loss</td>
<td>2-3</td>
</tr>
<tr>
<td>02</td>
<td>GLP-1 agonists</td>
<td>0.5-1.5</td>
<td>No</td>
<td>Loss</td>
<td>1-2, QW Injected</td>
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<tr>
<td>03</td>
<td>DPP-IV inhibitors</td>
<td>0.6-0.8</td>
<td>No</td>
<td>Neutral</td>
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<tr>
<td>04</td>
<td>Amylin mimetics</td>
<td>0.5-1.0</td>
<td>No</td>
<td>Loss</td>
<td>3, Injected</td>
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<tr>
<td>05</td>
<td>Bromocriptine</td>
<td>0.4-0.6</td>
<td>No</td>
<td>Neutral</td>
<td>1</td>
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<tr>
<td>06</td>
<td>Sulfonylureas</td>
<td>1.5-2.0</td>
<td>Yes</td>
<td>Gain</td>
<td>1-2</td>
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<tr>
<td>07</td>
<td>Insulin, rapid acting</td>
<td>1.5-2.5</td>
<td>Yes</td>
<td>Gain</td>
<td>1-4, Injected</td>
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<tr>
<td>08</td>
<td>Insulin, long acting</td>
<td>1.5-2.5</td>
<td>Yes</td>
<td>Gain</td>
<td>1-2, Injected</td>
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<tr>
<td>09</td>
<td>Bile acid sequestrant</td>
<td>0.5</td>
<td>No</td>
<td>Neutral</td>
<td>1-2</td>
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<tr>
<td>10</td>
<td>Repaglinide</td>
<td>1.0-1.5</td>
<td>Yes</td>
<td>Gain</td>
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<tr>
<td>11</td>
<td>Nateglinide</td>
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<td>Rare</td>
<td>Gain</td>
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<td>12</td>
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<td>No</td>
<td>Neutral</td>
<td>3</td>
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<td>13</td>
<td>Thiazolidinediones</td>
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<td>No</td>
<td>Gain</td>
<td>1</td>
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<tr>
<td>14</td>
<td>SGLT2 Inhibitor</td>
<td>0.5-0.8</td>
<td>No</td>
<td>Neutral-Loss</td>
<td>1</td>
</tr>
</tbody>
</table>
Ominous Octet

Hyperglycemia in Type 2 Diabetes

- Neurotransmitter dysfunction
  - GLP-1 receptor agonists
  - Amylin
  - Bromocriptine
- Increased lipolysis and reduced glucose uptake
  - Thiazolidinediones
- Impaired insulin secretion
  - Sulfonylurea
  - Meglitinide
  - GLP-1 receptor agonists
  - DPP-4 inhibitors
- Increased glucagon secretion
  - GLP-1 receptor agonists
  - DPP-4 inhibitors
  - Amylin
- Increased hepatic glucose production
  - Metformin
  - Insulin
  - Thiazolidinediones
- Decreased incretin effect
  - Metformin
  - α-Glucosidase inhibitors
  - Colesevelam
- Increased glucose reabsorption
- Decreased glucose uptake
  - Metformin
  - Insulin
  - Thiazolidinediones

DeFronzo RA,[20]
Tahrani AA, et al.[25]
Sulfonylureas

- Secretagogues - stimulate release of insulin from pancreatic B cells.
  - Glyburide ($12)
  - Glipizide ($20)
  - Glimepiride ($15)
- A1c: 1-2%
- CHEAP
Caveats

- Hypoglycemia in elderly
- Weight gain
- Premature beta-cell exhaustion?
- The 3 drugs are not created equal
Glyburide

- Long half-life
- Active metabolite
- Higher risk of hypoglycemia
** Glycemic Control Algorithm **

**Lifestyle Modification**  
(Including Medically Assisted Weight Loss)

- **ENTRY A1c < 7.5%**
- **ENTRY A1c ≥ 7.5%**
- **ENTRY A1c > 9.0%**

**Monotherapy**
- Metformin
- GLP-1 RA
- DPP4-I
- AG-I
- SGLT-2
- TZD
- SU/GLN

If A1c > 6.5% in 3 months add second drug (Dual Therapy)

**Dual Therapy**
- GLP-1 RA
- DPP4-I
- SGLT-2
- TZD
- Basal insulin
- Colesevelam
- Ag-I
- SU/GLN

If not at goal in 3 months proceed to triple therapy

**Triple Therapy**
- GLP-1 RA
- DPP4-I
- SGLT-2
- TZD
- Basal insulin
- Colesevelam
- Bromocriptine QR
- AG-I
- SU/GLN

If not at goal in 3 months proceed to or intensify insulin therapy

**Progression of Disease**

**Legend**
- ✔ Few adverse events or possible benefits
- ⚠ Use with caution
• Retrospective Cohort (N= 91,521 DM 2)
• 24%-61 % excess risk for all cause mortality using SU compared to metformin
• “unfavorable risk profile of SU compared to MET”
Meglitinides

- Repaglinide
- Nateglinide
- A1c: 1-1.5%
**Glycemic Control Algorithm**

**Lifestyle Modification**
(Including Medically Assisted Weight Loss)

- **ENTRY A1c < 7.5%**
  - **MONOTHERAPY**
    - Metformin
    - GLP-1 RA
    - DPP4-I
    - AG-I
    - SGLT-2
    - TZD
    - SU/GLN
  - If A1c > 6.5% in 3 months add second drug (Dual Therapy)

- **ENTRY A1c ≥ 7.5%**
  - **DUAL THERAPY**
    - GLP-1 RA
    - DPP4-I
    - SGLT-2
    - TZD
    - Basal insulin
    - Colesevelam
    - Bromocriptine QR
    - AG-I
    - SU/GLN
  - If not at goal in 3 months proceed to triple therapy

- **ENTRY A1c > 9.0%**
  - **NO SYMPTOMS**
    - Dual Therapy
    - OR
    - Triple Therapy
  - **SYMPTOMS**
    - Insulin ± Other Agents
  - ADD OR INTENSIFY INSULIN

*Order of medications listed are a suggested hierarchy of usage
**Based upon phase 3 clinical trials data

**Progression of Disease**
Biguanide

• Metformin
  – Lactic Acidosis
  – Hold day of procedure, restart after 48 hrs

• A1c: 1-2%
Metformin and Sulfonylureas in Relation to Cancer Risk in Type II Diabetes Patients: A Meta-analysis using primary data of published studies

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\textsuperscript{b} Section of Endocrinology, Diabetes, and Nutrition, Boston Medical Center, Boston University School of Medicine, Boston, MA, USA
\textsuperscript{c} Division of Endocrinology, Diabetes & Metabolism, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA
\textsuperscript{d} Department of Internal Medicine, Boston Medical Center, Boston University School of Medicine, Boston, MA, USA

Grant Supports: National Institute of Diabetes and Digestive and Kidney Diseases
Metformin and SU cancer risks

- Meta-Analysis using PubMed involving RCTs, cohorts and case-control studies published through 2012
- 24 metformin studies were chosen
  - Reduced risk for the development of cancer in both cohort and case control but not RCT’s.
- 18 SU studies were chosen
  - Increase all-cancer risk in cohort studies but not case control or RCT’s
Study Conclusions

• “This analysis using pooled primary data demonstrates that metformin use reduces, while sulfonylurea use may be associated with an increased cancer risk in subjects with T2DM”
Metformin Is Associated With Survival Benefit in Cancer Patients With Concurrent Type 2 Diabetes: A Systematic Review and Meta-Analysis

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Metformin • Cancer • Diabetes • Survival • Meta-Analysis

Learning Objectives

Describe the influences of different types of glucose-lowering medications on therapeutic outcomes of cancer patients who received standard anticancer treatment.

Compare the survival associated with metformin treatment with survival in treatment with other glucose-lowering medications.
Meta-analysis of 20 publications (up to July 1, 2013) included 13,008 patients with cancer and concurrent DM 2.

- 6,343 patients received metformin alone or in combination with other glucose-lowering regimens
- 6,665 patients received non-metformin treatment such as insulin, sulfonylurea, thiazolidinedione, alpha-glucosidase inhibitor, dipeptidyl peptidase-4 inhibitors, amylin analogs, or glucagon-like peptide-1 analogs.
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Ethnicity</th>
<th>Country</th>
<th>n (met/non-met)</th>
<th>Cancer</th>
<th>OS</th>
<th>CSS</th>
<th>Median follow-up</th>
</tr>
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<tbody>
<tr>
<td>Sadeghi et al. [30]</td>
<td>2012</td>
<td>Mixed</td>
<td>USA</td>
<td>302 (117/185)</td>
<td>Pancreatic</td>
<td>Y</td>
<td>N</td>
<td>11.4 months</td>
</tr>
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<td>Mixed</td>
<td>UK</td>
<td>424 (208/216)</td>
<td>Colorectal</td>
<td>Y</td>
<td>N</td>
<td>70.7 months</td>
</tr>
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<td>Currie et al. [27]</td>
<td>2012</td>
<td>Mixed</td>
<td>UK</td>
<td>5016 (2843/2173)</td>
<td>Mixed</td>
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<td>N</td>
<td>19.2 months</td>
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<td>Romero et al. [32]</td>
<td>2012</td>
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<td>USA</td>
<td>44 (16/28)</td>
<td>Ovarian</td>
<td>Y</td>
<td>N</td>
<td>63 months</td>
</tr>
<tr>
<td>He et al. [33]</td>
<td>2012</td>
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<td>USA</td>
<td>154 (88/66)</td>
<td>Breast</td>
<td>Y</td>
<td>Y</td>
<td>47.6 months</td>
</tr>
<tr>
<td>Lee et al. [34]</td>
<td>2011</td>
<td>Asian</td>
<td>Korea</td>
<td>595 (258/337)</td>
<td>Colorectal</td>
<td>Y</td>
<td>Y</td>
<td>41 months</td>
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<td>Y</td>
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<td>Tan et al. [17]</td>
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<td>N</td>
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<tr>
<td>He et al. [36]</td>
<td>2011</td>
<td>Mixed</td>
<td>USA</td>
<td>233 (132/101)</td>
<td>Prostate</td>
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<td>N</td>
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<tr>
<td>Chen et al. [37]</td>
<td>2011</td>
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<td>Nakai et al. [38]</td>
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<td>Japan</td>
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<td>N</td>
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<tr>
<td>Spratt et al. [39]</td>
<td>2012</td>
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<td>USA</td>
<td>319 (157/162)</td>
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<td>Y</td>
<td>Y</td>
<td>8.7 years</td>
</tr>
<tr>
<td>Hou et al. [40]</td>
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<td>China</td>
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<tr>
<td>Kumar et al. [26]</td>
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<td>Ireland</td>
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<td>Cossor et al. [42]</td>
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<td>Y</td>
<td>4.1 years</td>
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<td>Kaushik et al. [28]</td>
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<td>USA</td>
<td>885 (323/562)</td>
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<td>Y</td>
<td>Y</td>
<td>5.1 years</td>
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<td>Canada</td>
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<td>Y</td>
<td>4.5 years</td>
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<td>Sandulache et al. [43]</td>
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<td>Larynx</td>
<td>Y</td>
<td>N</td>
<td>N/A</td>
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</tbody>
</table>

Abbreviations: CSS, cancer-specific survival; met, metformin; non-met, non-metformin; N/A, not available; NSCLC, non-small cell lung cancer; OS, overall survival; SCLC, small cell lung cancer.
Hazard ratios (HRs) of overall survival
<table>
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<tr>
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<th>Year</th>
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<td>41 months</td>
</tr>
<tr>
<td>Bayraktar et al. [35]</td>
<td>2012</td>
<td>Mixed</td>
<td>USA</td>
<td>130 (63/67)</td>
<td>Breast</td>
<td>Y</td>
<td>Y</td>
<td>62 months</td>
</tr>
<tr>
<td>Tan et al. [17]</td>
<td>2011</td>
<td>Asian</td>
<td>China</td>
<td>99 (39/60)</td>
<td>NSCLC</td>
<td>Y</td>
<td>N</td>
<td>N/A</td>
</tr>
<tr>
<td>He et al. [36]</td>
<td>2011</td>
<td>Mixed</td>
<td>USA</td>
<td>233 (132/101)</td>
<td>Prostate</td>
<td>Y</td>
<td>N</td>
<td>N/A</td>
</tr>
<tr>
<td>Chen et al. [37]</td>
<td>2011</td>
<td>Asian</td>
<td>Taiwan</td>
<td>53 (21/32)</td>
<td>Liver</td>
<td>Y</td>
<td>N</td>
<td>32.2 months</td>
</tr>
<tr>
<td>Nakai et al. [38]</td>
<td>2012</td>
<td>Asian</td>
<td>Japan</td>
<td>124 (8/116)</td>
<td>Pancreatic</td>
<td>Y</td>
<td>N</td>
<td>9.9 months</td>
</tr>
<tr>
<td>Mazzone et al. [16]</td>
<td>2012</td>
<td>Mixed</td>
<td>USA</td>
<td>522 (184/338)</td>
<td>NSCLC/SCLC</td>
<td>Y</td>
<td>N</td>
<td>N/A</td>
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<tr>
<td>Spratt et al. [39]</td>
<td>2012</td>
<td>Mixed</td>
<td>USA</td>
<td>319 (157/162)</td>
<td>Prostate</td>
<td>Y</td>
<td>Y</td>
<td>8.7 years</td>
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<tr>
<td>Hou et al. [40]</td>
<td>2013</td>
<td>Asian</td>
<td>China</td>
<td>1013 (419/594)</td>
<td>Breast</td>
<td>Y</td>
<td>N</td>
<td>68 months</td>
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<tr>
<td>Kumar et al. [26]</td>
<td>2012</td>
<td>Mixed</td>
<td>USA</td>
<td>164 (61/103)</td>
<td>Ovarian</td>
<td>N</td>
<td>Y</td>
<td>11 years</td>
</tr>
<tr>
<td>Spillance et al. [41]</td>
<td>2013</td>
<td>White</td>
<td>Ireland</td>
<td>315 (207/108)</td>
<td>Colorectal</td>
<td>Y</td>
<td>Y</td>
<td>N/A</td>
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<tr>
<td>Cossor et al. [42]</td>
<td>2013</td>
<td>Mixed</td>
<td>USA</td>
<td>212 (84/128)</td>
<td>Colorectal</td>
<td>Y</td>
<td>Y</td>
<td>4.1 years</td>
</tr>
<tr>
<td>Kaushik et al. [28]</td>
<td>2013</td>
<td>Mixed</td>
<td>USA</td>
<td>885 (323/562)</td>
<td>Prostate</td>
<td>Y</td>
<td>Y</td>
<td>5.1 years</td>
</tr>
<tr>
<td>Lega et al. [29]</td>
<td>2013</td>
<td>Mixed</td>
<td>Canada</td>
<td>2361 (1094/1267)</td>
<td>Breast</td>
<td>Y</td>
<td>Y</td>
<td>4.5 years</td>
</tr>
<tr>
<td>Sandulache et al. [43]</td>
<td>2013</td>
<td>Mixed</td>
<td>USA</td>
<td>43 (21/22)</td>
<td>Larynx</td>
<td>Y</td>
<td>N</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Abbreviations: CSS, cancer-specific survival; met, metformin; non-met, non-metformin; N/A, not available; NSCLC, non-small cell lung cancer; OS, overall survival; SCLC, small cell lung cancer.
Authors’ Conclusions

• “…metformin was associated with a significantly reduced risk for death in those with breast, prostate, pancreatic, colorectal, and other cancers, with the exception of lung cancer”…”

• “…these results suggest that metformin is the drug of choice in the treatment of patients with cancer and concurrent type 2 diabetes”
Alpha-glucosidase inhibitors

- Acarbose
- Miglitol

- A1c: 0.5%
Bile Acid Sequestrants

- Colesevelam
  - Decrease LDL but raise TG
  - 6 pills/day

- A1c: 0.5%
TZD

- Rosiglitazone
- Pioglitazone

- PPAR-gamma
- Weight gain/edema: Contraindicated in NYHA Class III-IV
  - Beta cell preservation
- ADA recommends pioglitazone only
- A1c: 1-1.5%
Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.
### Table 4. Rates of Myocardial Infarction and Death from Cardiovascular Causes.

<table>
<thead>
<tr>
<th>Study</th>
<th>Rosiglitazone Group</th>
<th>Control Group</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small trials combined</td>
<td>44/10,280 (0.43)</td>
<td>22/6105 (0.36)</td>
<td>1.45 (0.88–2.39)</td>
<td>0.15</td>
</tr>
<tr>
<td>DREAM</td>
<td>15/2,635 (0.57)</td>
<td>9/2634 (0.34)</td>
<td>1.65 (0.74–3.68)</td>
<td>0.22</td>
</tr>
<tr>
<td>ADOPT</td>
<td>27/1,456 (1.85)</td>
<td>41/2895 (1.44)</td>
<td>1.33 (0.80–2.21)</td>
<td>0.27</td>
</tr>
<tr>
<td>Overall</td>
<td>86/14,371</td>
<td>72/11,634</td>
<td>1.43 (1.03–1.98)</td>
<td>0.03</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small trials combined</td>
<td>25/6,557 (0.38)</td>
<td>7/3700 (0.19)</td>
<td>2.40 (1.17–4.91)</td>
<td>0.02</td>
</tr>
<tr>
<td>DREAM</td>
<td>12/2,365 (0.51)</td>
<td>10/2634 (0.38)</td>
<td>1.20 (0.52–2.78)</td>
<td>0.67</td>
</tr>
<tr>
<td>ADOPT</td>
<td>2/1,456 (0.14)</td>
<td>5/2854 (0.18)</td>
<td>0.80 (0.17–3.86)</td>
<td>0.78</td>
</tr>
<tr>
<td>Overall</td>
<td>39/10,378</td>
<td>22/9,188</td>
<td>1.64 (0.98–2.74)</td>
<td>0.06</td>
</tr>
</tbody>
</table>
Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial

Philip DHome, StuartJPocock, HenningBeck-Nielsen, PaulaSCurtis, RamonGomis, MarkolfHanefeld, NigelPJones, MichelKomajda, JohnJVMcMurray, for the RECORD Study Team

Summary

Background Rosiglitazone is an insulin sensitiser used in combination with metformin, a sulfonylurea, or both, for lowering blood glucose in people with type 2 diabetes. We assessed cardiovascular outcomes after addition of rosiglitazone... Lancet 2009; 373: 2125-35

- 4447 DM2 pts on metformin or SU monotherapy with mean A1c 7.9% randomized to rosiglitazone or to combination of metformin+SU
- Primary endpts: cardio hospitalization or death
RECORD Trial

HR 0.99 (95% CI 0.85–1.16)

Number at risk
- Rosiglitazone: 2220, 2086, 1981, 1883, 1795, 1720, 918
- Active control: 2227, 2101, 1995, 1895, 1798, 1697, 908
**RECORD Trial**

**A. All-cause death**
- Rosiglitazone
- Active control

Cumulative (%)

Number at risk
- Rosiglitazone: 2220, 2189, 2166, 2134, 2096, 2062, 1137, 1115
- Active control: 2227, 2198, 2174, 2142, 2104, 2070, 1141, 1119

HR 0.86 (95% CI 0.69-1.08)

**B. CV death**

Cumulative (%)

Number at risk
- Rosiglitazone: 2220, 2139, 2084, 2032, 1972, 1918, 1893, 1017
- Active control: 2227, 2148, 2085, 2025, 1965, 1893, 1851, 991

HR 0.84 (95% CI 0.50-1.18)

**C. Myocardial infarction**

Cumulative (%)

Number at risk
- Rosiglitazone: 2220, 2128, 2066, 2005, 1936, 1879, 1012, 996
- Active control: 2227, 2141, 2074, 2005, 1936, 1858, 996

HR 1.14 (95% CI 0.80-1.63)

**D. Stroke**

Cumulative (%)

Number at risk
- Rosiglitazone: 2220, 2132, 2070, 2098, 1947, 1891, 1024
- Active control: 2227, 2142, 2076, 2009, 1920, 1851, 991

HR 0.72 (95% CI 0.49-1.06)
The data is **inconclusive** about any possible effect on MI.

“Rosiglitazone does not increase the risk of overall cardiovascular morbidity or mortality compared to standard glucose-lowering drugs.”
FDA significantly restricts access to the diabetes drug Avandia

Credit: Getty Images

[09-23-2010] The U.S. Food and Drug Administration announced that it will significantly restrict the use of the diabetes drug Avandia (rosiglitazone) to patients with Type 2 diabetes who cannot control their diabetes on
June 03, 2013

FDA Questions Avandia Restrictions

The FDA has decided to revisit the once controversial case regarding Avandia (rosiglitazone; GlaxoSmithKline), and will ask upon an expert advisory panel whether the agency must reconsider the restrictions on Avandia.

Avandia is a thiazolidinedione indicated as adjunct to diet and exercise in type 2 diabetes, as monotherapy, or in combination with metformin and/or a sulfonylurea.

• 6/5-6/2013: expert advisory panel reconvene
Verdict 6/7/2013?

• Lessen Avandia Restrictions
  – 13 votes to modify restriction
  – 7 votes to remove REMS (Risk Evaluation Mitigation Strategy (REMS) program
  – 5 votes to continue REMS
  – 1 vote to withdraw
FDA NEWS RELEASE

For Immediate Release: Nov. 25, 2013
Media Inquiries: Morgan Liscinsky, 301-796-0397, morgan.liscinsky@hhs.fda.gov
Consumer Inquiries: 888-INFO-FDA, druginfo@fda.hhs.gov

FDA requires removal of certain restrictions on the diabetes drug Avandia
Nationally estimated number of prescriptions for rosiglitazone- and pioglitazone-containing products dispensed through U.S. retail pharmacies, years 1999-2012
Bromocriptine

- Approved May 2009
- Approve as adjunct to diet and exercise to improve glycemic control

- A1c lowering 0.6-0.9%
- Lower PPG, A1c
- Does not increase the risk of macrovascular events
Amylinomimetics

• Pramlintide
  – Amylin = natural peptide secreted with insulin
  – Suppress glucagon secretion, delay gastric emptying, promote satiety
  – Can be used in type 1 or 2
  – Injections with meals (tid) along with short acting insulins

• A1c: 0.4-0.6%
INCRETINS
Defects in Type 2 DM

Incretins

DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1; GIP=glucose-dependent insulino tropic polypeptide; HGP=hepatic glucose production.
DPP-IV inhibitors

- Oral medications for T2 DM as adjunct to diet and exercise
- Weight neutral
- A1c lowering of 0.6%

- 4 currently on the market
  - Sitaglipin
  - Saxagliptin
  - Linagliptin
  - Alogliptin

- Cardiovascular data for 2 DPP-IV inhibitors recently announced 9/2013
  - No harm and no benefits for high risk patients
Cardiovascular Safety Trials

- **SAVOR** - The **S**axagliptin **A**ssessment of **V**ascular **O**utcomes **R**ecorded in Patients with Diabetes Mellitus

- **EXAMINE** - **E**Xamination of **C**Ardiovascular **O**utcomes: Alogliptin **I**N vs. Standard of Care in Patients with Type 2 Diabetes Mellitus and Acute Coronary Syndrome
Hypothesis:

- Saxagliptin is **safe and reduces cardiovascular events** in T2 DM patients with established cardiovascular disease or multiple cardiac risk factors.
SAVOR

- 16,500 pts with DM 2 with established cardiovascular disease (78%) or multiple risk factors (22%)
  - Avg. DM duration: 11.9 years
  - Avg. A1c: 8.0%
  - Avg. age: 65 years
  - Standard of care meds: statins, HTN meds
  - DM: 70% metformin, 40% SU, 6% TZD, 40% insulin
SAVOR

- Patients were followed median 2 years
- A1c 7.9% placebo, 7.6% saxagliptin
• Results:
  – Saxagliptin was not inferior to the control group for cardiovascular safety
    • HR: 1.00 (0.89-1.12) MACE (major adverse cardiac events)
    • HR: 1.02 (0.94-1.11) for secondary endpoints: USA, HF, revascularization rates.
• Unexpected:
  – Increase in CHF requiring hospitalization in patients with saxagliptin
    • 3.5% saxagliptin vs. 2.8% placebo

• Checking BNP before using DPP-IV?
SAVOR

• No increased signal for pancreatitis or pancreatic cancer

“SAVOR demonstrated the good cardiovascular and non cardiovascular (infections, bone fractures, malignancies or pancreatitis) safety of Saxagliptin in diabetic people at high cardiovascular risk.”
EXAMINE

- Assess cardiovascular outcomes of alogliptin compared with placebo.
- 5380 pts with either AMI or USA requiring hospitalization within the last 90 days
- All received high levels of standard of care for Rx of T 2 DM and CV risk factors
- Followed for median 18 months
• Results?
  – The primary endpoint (CV death, nonfatal myocardial infarction and nonfatal stroke) occurred at similar rates in the alogliptin (11.3%) and placebo groups (11.8%)
• Secondary endpoints
  – CV death: 112 or 4.1% Alogliptin, 130 vs. 4.9% placebo
  – All cause mortality: 153 or 5.7% Alogliptin vs. 173 or 6.5% placebo
  – Hypoglycemia, malignancy, pancreatitis, dialysis similar.
    • No pancreatic cancer reported
“Among patients with type 2 diabetes who had had a recent acute coronary syndrome, the rates of major adverse cardiovascular events were not increased with the DPP-4 inhibitor alogliptin as compared with placebo”
GLP-1

- Approved to treat T 2 DM as adjunct to diet and exercise
- Twice daily, daily or weekly injections
- Weight loss potential
- A1c lowering 1-1.5%

- 3 currently on the market
  - Exenatide
  - Exenatide ER
  - Liraglutide
New Drug in Pipeline
SGLT-2 inhibitors

(a) Phlorizin
(b) Dapagliflozin
(c) Canagliflozin

TRENDS in Pharmacological Sciences
Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise

K. Stenlöf\textsuperscript{1}, W. T. Cefalu\textsuperscript{2,3}, K.-A. Kim\textsuperscript{4}, M. Alba\textsuperscript{5}, K. Usiskin\textsuperscript{5}, C. Tong\textsuperscript{5}, W. Canovatchel\textsuperscript{5} & G. Meininger\textsuperscript{5}

\textsuperscript{1}Clinical Trial Center, Sahlgrenska University Hospital, Gothenburg, Sweden
\textsuperscript{2}Pennington Biomedical Research Center, Baton Rouge, LA, USA
\textsuperscript{3}LSUHSC School of Medicine, New Orleans, LA, USA
\textsuperscript{4}Department of Internal Medicine, Dongguk University Ilsan Hospital, Dongguk University School of Medicine, Goyang, South Korea
\textsuperscript{5}Janssen Research & Development, LLC, Raritan, NJ, USA
A1c Reduction

![Graph showing A1c reduction over time for different treatment groups.](image-url)
Changes in A1c

Diabetes, Obesity and Metabolism 2013;15:372-382
Weight Changes

[Graph showing weight changes over time with PBO, CANA 100 mg, and CANA 300 mg conditions.]

Baseline (kg):
- PBO: 87.5
- CANA 100 mg: 85.9
- CANA 300 mg: 86.9

LS mean % change in body weight from baseline:
- PBO: -0.6% (-0.5 kg)
- CANA 100 mg: -2.8% (-2.5 kg)
- CANA 300 mg: -3.9% (-3.4 kg)

Time point (wk):
- 0
- 6
- 12
- 18
- 26

Statistical significance:
- -2.2% (-1.9 kg) p < 0.001 95% CI (-2.9, -1.6)
- -3.3% (-2.9 kg) p < 0.001 95% CI (-4.0, -2.6)
## Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Subjects, n (%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PBO (n = 192)</td>
<td>CANA 100 mg (n = 195)</td>
<td>CANA 300 mg (n = 197)</td>
</tr>
<tr>
<td>Any AE</td>
<td>101 (52.6)</td>
<td>119 (61.0)</td>
<td>118 (59.9)</td>
</tr>
<tr>
<td>AEs leading to discontinuation</td>
<td>2 (1.0)</td>
<td>6 (3.1)</td>
<td>4 (2.0)</td>
</tr>
<tr>
<td>AEs related to study drug†</td>
<td>18 (9.4)</td>
<td>34 (17.4)</td>
<td>50 (25.4)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>4 (2.1)</td>
<td>8 (4.1)</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Deaths‡</td>
<td>1 (0.5)</td>
<td>1 (0.5)</td>
<td>0</td>
</tr>
<tr>
<td>Selected AEs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UTI</td>
<td>8 (4.2)</td>
<td>14 (7.2)</td>
<td>10 (5.1)</td>
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<tr>
<td>Genital mycotic infection</td>
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<td></td>
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</tr>
<tr>
<td>Male§,¶</td>
<td>0</td>
<td>2 (2.5)</td>
<td>5 (5.6)</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>,**</td>
<td>4 (3.8)</td>
</tr>
<tr>
<td>Osmotic diuresis-related AEs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pollakiuria††</td>
<td>1 (0.5)</td>
<td>5 (2.6)</td>
<td>6 (3.0)</td>
</tr>
<tr>
<td>Polyuria‡‡</td>
<td>0</td>
<td>0</td>
<td>6 (3.0)</td>
</tr>
<tr>
<td>Volume-related AEs</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Postural dizziness</td>
<td>0</td>
<td>1 (0.5)</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>0</td>
<td>0</td>
<td>2 (1.0)</td>
</tr>
</tbody>
</table>
FDA NEWS RELEASE

For Immediate Release: Jan. 8, 2014
Media Inquiries: Morgan Liscinsky, 301-796-0397; morgan.liscinsky@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

FDA approves Farxiga to treat type 2 diabetes
The FDA is requiring six post-marketing studies for Dapagliflozin:

- a cardiovascular outcomes trial (CVOT) to evaluate the cardiovascular risk of Dapagliflozin in patients with high baseline risk of cardiovascular disease;
- a double-blind, randomized, controlled assessment of bladder cancer risk in patients enrolled in the CVOT;
- an animal study evaluating the role of Dapagliflozin-induced urinary flow/rate and composition changes on bladder tumor promotion in rodents;
- two clinical trials to assess the pharmacokinetics, efficacy, and safety in pediatric patients; and
- an enhanced pharmacovigilance program to monitor reports of liver abnormalities and pregnancy outcomes.
Dapagliflozin sensitiv

Aurora Mei
Teresa Van
Luke Nor

Diab
Plasma glucagon (pmol/l)

- **Baseline**
- **Acute dosing**
- **Chronic dosing**

Related Commentary, page 485 Clinical medicine
INSULIN
Long Acting Insulin

• Taken 1 or 2 times per day
  – Detemir
  – Glargine
  – Human NPH
Rapid Acting Insulin (Bolus Insulin)

- Lispro
- Glulisine
- Aspart
- Human Regular
Premix Insulins

Limitation - 2 Insulin Changes at Once

- 70/30
- 75/25
- 50/50

Newer designer insulins safer and more predictable. Most come in pen injectors which are easy to use and less cumbersome than vials/syringes.
Insulin Time Action Curves

- **Very Rapid (Aspart, Glulisine, Lispro)**
- **Short (Regular)**
- **Intermediate (NPH)**

The graph illustrates the insulin effect over time for different types of insulin: very rapid, short, and intermediate. The x-axis represents hours, and the y-axis represents insulin effect.
Insulin

• Think insulin when A1c > 9%
• Always start with basal (rarely exceptions)
• Start with 0.2 U/kg
• Can titrate every 2-3 days depending on am BS
• Recheck labs in 3 months. If still not adequate, consider prandial insulin
Insulin

• If prandial coverage is needed: 0.3-0.5 U/kg (50% basal, 50% prandial)
• Premixed if necessary
Algorithm for Adding/Intensifying Insulin

**START BASAL** (long-acting insulin)

- **A1c < 8%**
  - TDD: 0.1–0.2 U/kg

- **A1c > 8%**
  - TDD: 0.2–0.3 U/kg

**INTENSIFY** (prandial control)

- **Add GLP-1 RA or DPP4-i**
- **Add Prandial Insulin**
  - TDD: 0.3–0.5 U/kg
    - 50% Basal Analog
    - 50% Prandial Analog
    - Less desirable: NPH and regular insulin or premixed insulin

Glycemic Control Not at Goal**

**Insulin titration every 2–3 days to reach glycemic goal:**
- Fixed regimen: Increase TDD by 2 U
- Adjustable regimen:
  - FBG > 180 mg/dL: add 4 U
  - FBG 140–180 mg/dL: add 2 U
  - FBG 110–139 mg/dL: add 1 U
- If hypoglycemia, reduce TDD by:
  - BG < 70 mg/dL: 10% – 20%
  - BG < 40 mg/dL: 20% – 40%

Consider discontinuing or reducing sulfonylurea after basal insulin started (basal analogs preferred to NPH)

**Glycemic Goal:**
- For most patients with T2D, an A1c < 7%, fasting and premeal BG < 110 mg/dL in the absence of hypoglycemia.
- A1c and FBG targets may be adjusted based on patient’s age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk.

**Insulin titration every 2–3 days to reach glycemic goal:**
- Increase basal TDD as follows:
  - Fixed regimen: Increase TDD by 2 U
  - Adjustable regimen:
    - FBG > 180 mg/dL: add 4 U
    - FBG 140–180 mg/dL: add 2 U
    - FBG 100–139 mg/dL: add 1 U
- Increase prandial dose by 10% for any meal if the 2-hr postprandial or next premeal glucose is > 180 mg/dL
- Premixed: Increase TDD by 10% if fasting/premeal BG > 180 mg/dL
- If fasting AM hypoglycemia, reduce basal insulin
- If nighttime hypoglycemia, reduce basal and/or pre-supper or pre-evening snack short/rapid-acting insulin
- If between meal daytime hypoglycemia, reduce previous premeal short/rapid-acting insulin

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Thank God He Stopped Talking!!!