Pharmacologic Advances in the Management of Type 2 Diabetes 2016

April 22, 2016
Scripps Research Institute
Susan Jane Boston, M.D.
Financial Disclosure Statement

“I do not have any financial relationships relative to the content of this program.”
OUTLINE

• Drugs available to treat DM2
• Treatment algorithms
• In depth look at GLP1s, DPP4s, SGLT2s
• Medication risks/warnings
• Cardiovascular benefit of DM drugs
• Insulin landscape
• Patient cases
World Health Day 2016: Beat diabetes

World Health Day 2016: Action needed to halt rise in diabetes

6 April 2016 – The number of people living with diabetes has nearly quadrupled since 1980 to 422 million adults, with most living in developing countries. WHO is marking World Health Day, 7 April, by calling for action on diabetes. In its first "Global report on diabetes", WHO highlights the need to step up prevention and treatment of the disease.

WHO Director-General launches diabetes report
Read the Global report on diabetes
Read the news release
Half-Century of HTN & T2DM Medications in U.S.
Half-Century of HTN & T2DM Medications in U.S.
The Complex Pathogenesis of T2DM

- Peripheral glucose uptake
- Hepatic glucose production
- Pancreatic insulin secretion
- Pancreatic glucagon secretion
- Gut carbohydrate delivery & absorption
- Incretin effect
- HYPERGLYCEMIA

Adapted from: Inzucchi SE, Sherwin RS in: Cecil Medicine 2011
# Glycemic Targets

| Table 6.2—Summary of glycemic recommendations for nonpregnant adults with diabetes |
|---------------------------------|---------------------------------|
| A1C                             | <7.0%*                          |
| Preprandial capillary plasma glucose | 80–130 mg/dL* (4.4–7.2 mmol/L) |
| Peak postprandial capillary plasma glucose† | <180 mg/dL* (<10.0 mmol/L) |

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

†Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes.
<table>
<thead>
<tr>
<th>Highly Motivated, Adherent, Knowledgeable, Excellent Self-Care Capacities, &amp; Comprehensive Support Systems</th>
<th>Less motivated, Non-adherent, Limited insight, Poor Self-Care Capacities, &amp; Weak Support Systems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Age (40, 45, 50, 55, 60, 65, 70, 75)</td>
<td>Hypoglycemia Risk (Low, Moderate, High)</td>
</tr>
<tr>
<td>Disease Duration (5, 10, 15, 20)</td>
<td>Other Comorbidities (None, Few/Mild, Multiple/Severe)</td>
</tr>
<tr>
<td>Established Vascular Complications (None, Early Micro, Cardiovascular, Advanced Micro)</td>
<td>Psychosocioeconomic Considerations</td>
</tr>
</tbody>
</table>

Biguanides

- **Metformin**
- **Mechanism**: Activates AMP-kinase
- **Primary action**: Decrease hepatic glucose production
- **Advantages**: Extensive experience, no HYPOs, weight loss
- **Disadvantages**: GI, B12 deficiency, lactic acidosis (CKD/CHF/liver disease)
- **Costs**: LOW
Sulfonylureas

- Glyburide, Glipizide, Glimepiride
- **Mechanism**: Closes K ATP channels on Bcell plasma membrane
- **Primary action**: Increase insulin secretion
- **Advantages**: Extensive experience
- **Disadvantages**: HYPOglyemia, weight gain
- **Costs**: LOW
Meglitinides

- Repaglinide, Nateglinide
- **Mechanism:** Closes K ATP channels on Bcell plasma membrane
- **Primary action:** Increase insulin secretion
- **Advantages:** Decrease postprandial excursions, flexible dosing
- **Disadvantages:** HYPOglyemia, weight gain, frequent dosing
- **Costs:** MODERATE
TZDs

- Pioglitazone, Rosiglitazone
- **Mechanism:** Activates PPAR-gamma
- **Primary action:** Increase insulin sensitivity
- **Advantages:** No HYPOs, durability, inc HDL/dec TGs, reduced CVD events?
- **Disadvantages:** Weight gain, edema, HF, fractures, inc LDL, inc MI?
- **Costs:** LOW

Diabetes Care, Vol 39, Supplement 1, Jan 2016
Alpha-Glucosidase Inhibitors

- Acarbose, Miglitol
- **Mechanism**: Inhibits intestinal alpha glucosidase
- **Primary action**: Slow intestinal CHO digestion/absorption
- **Advantages**: No HYPOs, dec postprandial excursions, non-systemic
- **Disadvantages**: Modest ha1c lowering, GI SEs, frequent dosing
- **Costs**: LOW-MODERATE
DPP4 Inhibitors

- Sitagliptin, Saxagliptin, Linagliptin, Alogliptin
- **Mechanism:** Inhibits DPP4, increasing postprandial incretins (GIP/GLP1)
- **Primary action:** Increase insulin secretion, dec glucagon secretion
- **Advantages:** No HYPOs, well tolerated
- **Disadvantages:** angioedema/urticaria, pancreatitis, inc HF hospitalizations
- **Costs:** HIGH
Bile Acid Sequestrants

- Colesevelam
- **Mechanism**: Intestinal BA binding, increase hepatic BA production
- **Primary action**: Decreased hepatic glucose production, inc incretins
- **Advantages**: No HYPOs, dec LDL
- **Disadvantages**: Modest ha1c lowering, constipation, inc TGs, medication binding
- **Costs**: HIGH
Dopamine 2 Agonists

- Bromocriptine-quick release
- **Mechanism**: Activates DA receptors
- **Primary action**: Modulates hypothalamic regulation of metabolism, inc insulin sensitivity
- **Advantages**: No HYPOs, dec CVD events
- **Disadvantages**: Modest ha1c lowering, dizziness/syncope/nausea/fatigue, rhinitis
- **Costs**: HIGH

*Diabetes Care, Vol 39, Supplement 1, Jan 2016*
SGLT2 inhibitors

- Canagliflozin, Dapagliflozin, Empagliflozin
- **Mechanism**: Inhibits SGLT2 in kidney
- **Primary action**: Blocks renal glucose absorption, promotes glucosuria
- **Advantages**: No HYPOs, weight loss, lower BP, effective at all DM stages, lower CVD event rate and mortality
- **Disadvantages**: GU infections, polyuria, hypotension, inc LDL, inc creatinine, DKA
- **Costs**: HIGH
GLP1 Receptor Agonists

- Exenatide/ER, Liraglutide, Albiglutide, Dulaglutide
- **Mechanism:** Activates GLP1 receptors
- **Primary action:** Inc insulin secretion, dec glucagon secretion, slowed gastric emptying, inc satiety
- **Advantages:** No HYPOs, weight loss, dec PP excursion, dec CV risk
- **Disadvantages:** GI SEs, inc HR, pancreatitis, MTC, injectable/training
- **Costs:** HIGH

Diabetes Care, Vol 39, Supplement 1, Jan 2016
Amylin mimetics

- Pramlintide
- **Mechanism:** Activates amylin receptors
- **Primary action:** Decreased glucagon secretion, slowed gastric emptying, increased satiety
- **Advantages:** Decreased postprandial excursions, decreased weight
- **Disadvantages:** Modest HbA1c effect, GI SEs, HYPOs, injected/training, frequent dosing
- **Costs:** HIGH
Insulins

- MANY
- **Mechanism:** Activates insulin receptors
- **Primary action:** Inc glucose disposal, dec hepatic glucose production, suppresses ketogenesis
- **Advantages:** Universal response, unlimited efficacy, dec microvascular risk
- **Disadvantages:** HYPOs, weight gain, mitogenic?, injectable/training, patient resistance
- **Costs:** MODERATE-HIGH

Diabetes Care, Vol 39, Supplement 1, Jan 2016
GLYCEMIC CONTROL ALGORITHM

LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

Entry A1C < 7.5%
- Metformin
- GLP-1 RA
- SGLT-2i
- DPP-4i
- TZD
- AGi
- SU/GLN

If not at goal in 3 months proceed to Dual Therapy

Entry A1C ≥ 7.5%
- GLP-1 RA
- SGLT-2i
- DPP-4i
- TZD
- Basal Insulin
- Colesevelam
- Bromocriptine QR
- AGi
- SU/GLN

MET or other 1st-line agent + 2nd-line agent

If not at goal in 3 months proceed to Triple Therapy

Entry A1C > 9.0%
- GLP-1 RA
- SGLT-2i
- DPP-4i
- TZD
- Basal Insulin
- Colesevelam
- Bromocriptine QR
- AGi
- SU/GLN

MET or other 1st-line agent + 2nd-line agent

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

Entry A1C > 9.0%
- DUAL Therapy
- OR
- TRIPLE Therapy
- INSULIN ± Other Agents

SYMPTOMS
NO
- DUAL Therapy
- OR
- TRIPLE Therapy
YES
- ADD OR INTENSIFY INSULIN
  - Refer to Insulin Algorithm

LEGEND
- Few adverse events and/or possible benefits
- Use with caution

PROGRESSION OF DISEASE

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ADA/EASD Position Statement: Managing Hyperglycemia in Type 2 Diabetes

Recommendations for Antihyperglycemic Therapy in Type 2 Diabetes

Lifestyle changes: healthy eating, weight control, increased physical activity, diabetes education

Monotherapy
- Metformin (MET)

Dual therapy
- MET + SU
- MET + TZD
- MET + GLP-1 RA
- MET + DPP-4 inhibitor
- MET + SGLT2 inhibitor
- MET + Insulin (basal)

If A1C target not achieved after 3 months of monotherapy, proceed to dual therapy.

If A1C target not achieved after 3 months of dual therapy, proceed to triple therapy.

Triple therapy
- MET + SU
- MET + TZD
- MET + GLP-1 RA
- MET + DPP-4 inhibitor
- MET + SGLT2
- MET + Insulin (basal)

If A1C target not achieved after 3 months of triple therapy and patient (1) on oral combination, move to injectable; (2) on GLP-1, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1 or mealtime insulin.

Refractory patients: consider adding TZD or SGLT2.

Combination injectable therapy
- Basal insulin + Mealtime insulin or GLP-1
Healthy eating, weight control, increased physical activity, and diabetes education

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy*</td>
<td>high</td>
</tr>
<tr>
<td>Hypo risk</td>
<td>low risk</td>
</tr>
<tr>
<td>Weight</td>
<td>neutral / loss</td>
</tr>
<tr>
<td>Side effects</td>
<td>GI / lactic acidosis</td>
</tr>
<tr>
<td>Costs*</td>
<td>low</td>
</tr>
</tbody>
</table>

If A1C target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

<table>
<thead>
<tr>
<th>Metformin</th>
<th>Glyburide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazolidinedione</td>
<td>high</td>
</tr>
<tr>
<td>Metformin</td>
<td>DPP-4 inhibitor</td>
</tr>
<tr>
<td>Intermediate</td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>SGLT2 inhibitor</td>
</tr>
<tr>
<td>Intermediate</td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>GLP-1 receptor agonist</td>
</tr>
<tr>
<td>high</td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>Insulin (basal)</td>
</tr>
<tr>
<td>highest</td>
<td></td>
</tr>
</tbody>
</table>

If A1C target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

<table>
<thead>
<tr>
<th>Metformin</th>
<th>Sulfonylurea</th>
</tr>
</thead>
<tbody>
<tr>
<td>TZD</td>
<td></td>
</tr>
<tr>
<td>or</td>
<td></td>
</tr>
<tr>
<td>DPP-4-i</td>
<td></td>
</tr>
<tr>
<td>or</td>
<td></td>
</tr>
<tr>
<td>SGLT2-i</td>
<td></td>
</tr>
<tr>
<td>or</td>
<td></td>
</tr>
<tr>
<td>GLP-1-RA</td>
<td></td>
</tr>
<tr>
<td>or</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td></td>
</tr>
<tr>
<td>or</td>
<td></td>
</tr>
<tr>
<td>DPP-4-i</td>
<td></td>
</tr>
<tr>
<td>or</td>
<td></td>
</tr>
<tr>
<td>SGLT2-i</td>
<td></td>
</tr>
<tr>
<td>or</td>
<td></td>
</tr>
<tr>
<td>GLP-1-RA</td>
<td></td>
</tr>
<tr>
<td>or</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td></td>
</tr>
<tr>
<td>or</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td></td>
</tr>
</tbody>
</table>

If A1C target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-i:

<table>
<thead>
<tr>
<th>Metformin</th>
<th>Basal insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mealtime insulin</td>
<td></td>
</tr>
<tr>
<td>or</td>
<td></td>
</tr>
<tr>
<td>GLP-1-RA</td>
<td></td>
</tr>
</tbody>
</table>
“Lizard Spit”

- Exendin-4, a protein naturally secreted in the saliva and concentrated in the tail of the Gila monster.
  - Shares homology and function with mammalian GLP-1
  - Resistance to degradation by DPP-IV (allowing for a longer pharmacological half life).
  - Subsequent clinical testing showed desirable glucagon and appetite-suppressant effects.
Exendin-4
-First isolated by Dr. John Eng in 1992 while working at the Veterans Administration Medical Center, in The Bronx, NY

-Synthetic form=Exenatide (Byetta) approved in 2005
The Incretin System: Key Regulator of Post-Prandial Glucose Metabolism

- Gastric emptying
- Peripheral glucose uptake
- Hepatic glucose production
- Insulin secretion
- GLP-1
- GIP
- Glucagon secretion
- DPP-4

- Insulin secretion
- Glucagon secretion
- Hepatic glucose production
- Peripheral glucose uptake
Glucagon-Like-Peptide-1 Agonists

GLP-1 is an important component in glycemic regulation

The actions of GLP-1 are dependent on food intake, and GLP-1 is short-lived

1. Stimulates glucose-dependent insulin secretion
2. Improves first-phase insulin response
3.Suppresses postprandial glucagon secretion, which decreases hepatic glucose production
4. Slows gastric emptying
5. Reduces food intake

*This effect is postulated to be mediated through the central nervous system.
GLP1 agonists

- Byetta (exenatide), 4/2005
  - Bydureon , 2/2012, pen 3/2014
- Victoza (liraglutide), 1/2010
- Tanzeum (albiglutide), 4/2014
- Trulicity (dulaglutide), 9/2014
- Saxenda (liraglutide 3.0mg), approved 12/23/14 for weight loss
GLP1 Comparisons

- Daily injections: Victoza
- Once weekly: Bydureon, Tanzeum, Trulicity
- Renal safety: Tanzeum, Trulicity
- Improved GI profile: Tanzeum, Trulicity
  - Less weight loss seen compared to Victoza
- Class warnings: pancreatitis, medullary thyroid cancer
- Ha1c lowering 1-1.5% on average
Dipeptidyl Peptidase-4 inhibitors
DPP4 inhibitors

- Januvia (sitagliptin), 10/2006
- Onglyza (saxagliptin), 7/2009
- Tradjenta (linagliptin), 5/2011
- Nesina (alogliptin), 1/2013

SNAP SHOT:
- HbA1c lowering 0.5-0.8%
- Weight neutral
- Once daily oral medication
- Linagliptin does NOT need adjustment for renal insufficiency
The Kidney’s Role in Normal Glucose Homeostasis^{1,2}

**Glucose input ~250 g/day:**
- Dietary intake ~180 g/day
- Glucose production ~70 g/day
  - Gluconeogenesis
  - Glycogenolysis

**Glucose uptake ~250 g/day:**
- Brain ~125 g/day
- Rest of the body ~125 g/day

Net balance ~0 g/day

Glucose filtered ~180g/day = Glucose reabsorbed ~180g/day

Glucose is filtered in the glomerulus. Loop of Henle. Collecting Duct. Urine.

SGLT1: sodium-glucose co-transporter

- 180 g/day/1.73 m² is filtered glucose load
- SGLT2 transports 90% of filtered glucose out of the tubular lumen
- SGLT1 transports the remaining 10% of filtered glucose
  - SGLT1 is the primary SGLT in the small intestine

Glucose reabsorbed into systemic circulation.

No detectable glucose in urine.

SGLT, sodium-glucose co-transporter

SGLT-2 inhibitors Lower Renal Threshold for Glucose Excretion (RT\textsubscript{G})

T2DM, type 2 diabetes mellitus.

Adapted with permission from Abdul-Ghani MA, DeFronzo RA.
3. Invokana™ (canagliflozin) prescribing information.
SGLT-2 Inhibitors

**PRO:** Low risk of HYPOglycemia

**CON:** 10-15% risk of mycotic genital infections
4. Dosage Adjustments for Renal Insufficiency

<table>
<thead>
<tr>
<th>eGFR mL/min/1.73m²</th>
<th>Canagliflozin</th>
<th>Dapagliflozin</th>
<th>Empagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 60</td>
<td>No dosage adjustment 100 to 300 mg/d</td>
<td>No dosage adjustment 5 to 10 mg/d</td>
<td>No dosage adjustment 10 to 25 mg/d</td>
</tr>
<tr>
<td>45 to 60</td>
<td>100 mg/d</td>
<td>Not recommended eGFR &lt;60</td>
<td>10 mg/d</td>
</tr>
<tr>
<td>30 to 45</td>
<td>Not recommended eGFR &lt;45</td>
<td>N/A</td>
<td>Not recommended eGFR &lt;45</td>
</tr>
<tr>
<td>&lt;30</td>
<td>Contraindicated</td>
<td>Contraindicated</td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>
SLGT2 inhibitors

- Invokana (canagliflozin), 3/2013
- Farxiga (dapagliflozin), 1/2014
- Jardiance (empagliflozin), 8/2014

SNAP SHOT:
- HbA1c lowering 0.6-1.0%
- Weight lowering
- Once daily oral medication
- Do not use in GFR <45
- Risk of UTI/yeast infections
“Personalizing” Type 2 Diabetes Therapy

Anticipation of Drug Efficacy
- Post-prandial BGs...GLP1s
- High fasting BGs...basal insulin
- Very insulin resistant...pio

Concerns of ‘Adverse Effects’
- Self-pay...NO GLP1s, SGLT2s
- GI sx...NO metformin
- HYPOs...NO SU

Desire for Added Benefits
- Needs weight loss...GLP1s, SGLT2s
- LDL/no statin...colesevelam
- LFTs/steatosis...pio

MEDICATION CHOICE?
Pharmacy

"Each capsule contains your medication, plus a treatment for each of its side effects."
Symptom onset 1 day to years after start of DPP-4 inhibitor.

Symptom resolution in <1month after medication discontinuation.

Some with symptom return on same or alternate DPP-4 restart.
Fractures occur more frequently, can occur as early as 12 weeks after start, with minor trauma.

Decreased BMD at spine and hip.
73 cases of ketoacidosis in patients with type 1 or type 2 diabetes.

19 cases of urosepsis and pyelonephritis that started as urinary tract infections.
More patients were hospitalized for heart failure compared to placebo.

- Saxagliptin trial, 3.5% vs. 2.8% placebo.
- Alogliptin trial, 3.9% vs. 3.3% placebo.
"There is your prescription, Mrs. Hickford, and here is the pamphlet of side effects."
• Prior: Unsafe in creatinine >1.5mg/dL (M) or >1.4mg/dL (F).
• Current: Unsafe in eGFR <30mL/min and do not start if eGFR 30-45mL/min.
Could diabetes drugs have a cardiovascular benefit?

- EMPA-REG: empagliflozin, Sept 2015
- LEADER: liraglutide, March 2016
- IRIS: pioglitazone, April 2016

Zinman et al, NEJM Nov 2015; 373: 2117-2128
Kernan et al, NEJM April 2016; 374: 1321-1331
Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

N Engl J Med
Volume 373(22):2117-2128
November 26, 2015
Cardiovascular Outcomes and Death from Any Cause

A Primary Outcome

Hazard ratio, 0.86 (95% CI, 0.74–0.99) 
P=0.04 for superiority

B Death from Cardiovascular Causes

Hazard ratio, 0.62 (95% CI, 0.49–0.77) 
P<0.001

C Death from Any Cause

Hazard ratio, 0.68 (95% CI, 0.57–0.82) 
P<0.001

D Hospitalization for Heart Failure

Hazard ratio, 0.65 (95% CI, 0.50–0.85) 
P=0.002

### Table 1. Primary and Secondary Cardiovascular Outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo (N=2333)</th>
<th>Empagliflozin (N=4687)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke: primary outcome*</td>
<td>282 (12.1)</td>
<td>490 (10.5)</td>
<td>0.86 (0.74–0.99)</td>
<td></td>
</tr>
<tr>
<td>Noninferiority</td>
<td></td>
<td></td>
<td>&lt;0.001†</td>
<td></td>
</tr>
<tr>
<td>Superiority</td>
<td></td>
<td></td>
<td>0.04†</td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina: key secondary outcome*</td>
<td>333 (14.3)</td>
<td>599 (12.8)</td>
<td>0.89 (0.78–1.01)</td>
<td></td>
</tr>
<tr>
<td>Noninferiority</td>
<td></td>
<td></td>
<td>&lt;0.001†</td>
<td></td>
</tr>
<tr>
<td>Superiority</td>
<td></td>
<td></td>
<td>0.08†</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>From any cause</td>
<td>194 (8.3)</td>
<td>269 (5.7)</td>
<td>0.68 (0.57–0.82)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>From cardiovascular causes</td>
<td>137 (5.9)</td>
<td>172 (3.7)</td>
<td>0.62 (0.49–0.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fatal or nonfatal myocardial infarction excluding silent myocardial infarction</td>
<td>126 (5.4)</td>
<td>223 (4.8)</td>
<td>0.87 (0.70–1.09)</td>
<td>0.23</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction excluding silent myocardial infarction</td>
<td>121 (5.2)</td>
<td>213 (4.5)</td>
<td>0.87 (0.70–1.09)</td>
<td>0.22</td>
</tr>
<tr>
<td>Silent myocardial infarction‡</td>
<td>15 (1.2)</td>
<td>38 (1.6)</td>
<td>1.28 (0.70–2.33)</td>
<td>0.42</td>
</tr>
<tr>
<td>Hospitalization for unstable angina</td>
<td>66 (2.8)</td>
<td>133 (2.8)</td>
<td>1.09 (0.74–1.34)</td>
<td>0.97</td>
</tr>
<tr>
<td>Coronary revascularization procedure</td>
<td>186 (8.0)</td>
<td>329 (7.0)</td>
<td>0.86 (0.72–1.04)</td>
<td>0.11</td>
</tr>
<tr>
<td>Fatal or nonfatal stroke</td>
<td>69 (3.0)</td>
<td>164 (3.5)</td>
<td>1.18 (0.89–1.56)</td>
<td>0.26</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>60 (2.6)</td>
<td>150 (3.2)</td>
<td>1.24 (0.92–1.67)</td>
<td>0.16</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>23 (1.0)</td>
<td>39 (0.8)</td>
<td>0.85 (0.51–1.42)</td>
<td>0.54</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>95 (4.1)</td>
<td>126 (2.7)</td>
<td>0.65 (0.50–0.85)</td>
<td>0.002</td>
</tr>
<tr>
<td>Hospitalization for heart failure or death from cardiovascular causes excluding fatal stroke</td>
<td>198 (8.5)</td>
<td>265 (5.7)</td>
<td>0.66 (0.55–0.79)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Data were analyzed with the use of a four-step hierarchical-testing strategy for the pooled empagliflozin group versus the placebo group in the following order: noninferiority for the primary outcome; noninferiority for the key secondary outcome; superiority for the primary outcome, and superiority for the key secondary outcome. Each successive hypothesis could be tested, provided that those preceding it met the designated level of significance. Data are based on Cox regression analyses in patients who received at least one dose of a study drug. † One-sided P values are shown for tests of noninferiority, and two-sided P values are shown for tests of superiority. ‡ Silent myocardial infarction was analyzed in 2378 patients in the empagliflozin group and 1211 patients in the placebo group.
<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (N = 2333)</th>
<th>Empagliflozin, 10 mg (N = 2345)</th>
<th>Empagliflozin, 25 mg (N = 2342)</th>
<th>Pooled Empagliflozin (N = 4687)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>2139 (91.7)</td>
<td>2112 (90.1)</td>
<td>2118 (90.4)</td>
<td>4230 (90.2)</td>
</tr>
<tr>
<td>Severe adverse event</td>
<td>592 (25.4)</td>
<td>536 (22.9)</td>
<td>564 (24.1)</td>
<td>1100 (23.5)</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>592 (25.4)</td>
<td>536 (22.9)</td>
<td>564 (24.1)</td>
<td>1100 (23.5)</td>
</tr>
<tr>
<td>Death</td>
<td>119 (5.1)</td>
<td>97 (4.1)</td>
<td>79 (3.4)</td>
<td>176 (3.8)</td>
</tr>
<tr>
<td>Adverse event leading to discontinuation of a study drug</td>
<td>453 (19.4)</td>
<td>416 (17.7)</td>
<td>397 (17.0)</td>
<td>813 (17.3)</td>
</tr>
<tr>
<td>Confirmed hypoglycemic adverse event</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>650 (27.9)</td>
<td>656 (28.0)</td>
<td>647 (27.6)</td>
<td>1303 (27.8)</td>
</tr>
<tr>
<td>Requiring assistance</td>
<td>36 (1.5)</td>
<td>33 (1.4)</td>
<td>30 (1.3)</td>
<td>63 (1.3)</td>
</tr>
<tr>
<td>Event consistent with urinary tract infection</td>
<td></td>
<td>423 (18.1)</td>
<td>426 (18.2)</td>
<td>416 (17.8)</td>
</tr>
<tr>
<td>Male patients</td>
<td>158 (9.4)</td>
<td>180 (10.9)</td>
<td>170 (10.1)</td>
<td>350 (10.5)</td>
</tr>
<tr>
<td>Female patients</td>
<td>265 (40.6)</td>
<td>246 (35.5)</td>
<td>246 (37.3)</td>
<td>492 (36.4)</td>
</tr>
<tr>
<td>Complicated urinary tract infection**</td>
<td>41 (1.8)</td>
<td>34 (1.4)</td>
<td>48 (2.0)</td>
<td>82 (1.7)</td>
</tr>
<tr>
<td>Event consistent with genital infection††</td>
<td>42 (1.8)</td>
<td>153 (6.5)</td>
<td>148 (6.3)</td>
<td>301 (6.4)</td>
</tr>
<tr>
<td>Male patients</td>
<td>25 (1.5)</td>
<td>89 (5.4)</td>
<td>77 (4.6)</td>
<td>166 (5.0)</td>
</tr>
<tr>
<td>Female patients</td>
<td>17 (2.6)</td>
<td>64 (9.2)</td>
<td>71 (10.8)</td>
<td>135 (10.0)</td>
</tr>
<tr>
<td>Event consistent with volume depletion‡‡</td>
<td>115 (4.9)</td>
<td>115 (4.9)</td>
<td>124 (5.3)</td>
<td>239 (5.1)</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>155 (6.6)</td>
<td>121 (5.2)</td>
<td>125 (5.3)</td>
<td>246 (5.2)</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>37 (1.6)</td>
<td>26 (1.1)</td>
<td>19 (0.8)</td>
<td>45 (1.0)</td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
<td>1 (&lt;0.1)</td>
<td>3 (0.1)</td>
<td>1 (&lt;0.1)</td>
<td>4 (0.1)</td>
</tr>
<tr>
<td>Thromboembolic event</td>
<td>20 (0.9)</td>
<td>9 (0.4)</td>
<td>21 (0.9)</td>
<td>30 (0.6)</td>
</tr>
<tr>
<td>Bone fracture</td>
<td>91 (3.9)</td>
<td>92 (3.9)</td>
<td>87 (3.7)</td>
<td>179 (3.8)</td>
</tr>
</tbody>
</table>
Original Article

Pioglitazone after Ischemic Stroke or Transient Ischemic Attack

Walter N. Kernan, M.D., Catherine M. Viscoli, Ph.D., Karen L. Furie, M.D., M.P.H., Lawrence H. Young, M.D., Silvio E. Inzucchi, M.D., Mark Gorman, M.D., Peter D. Guarino, Ph.D., Anne M. Lovejoy, P.A.-C., Peter N. Peduzzi, Ph.D., Robin Conwit, M.D., Lawrence M. Brass, M.D., Gregory G. Schwartz, M.D., Ph.D., Harold P. Adams, Jr., M.D., Leo Berger, M.D., Antonio Carolei, M.D., Wayne Clark, M.D., Bruce Coull, M.D., Gary A. Ford, M.B., B.Chir., Dawn Kleindorfer, M.D., John R. O’Leary, M.A., Mark W. Parsons, M.D., Peter Ringleb, M.D., Souvik Sen, M.D., J. David Spence, M.D., David Tanne, M.D., David Wang, M.D., Toni R. Winder, M.D., for the IRIS Trial Investigators

N Engl J Med
Volume 374(14):1321-1331
April 7, 2016
Primary Outcome.


![Graph showing cumulative probability of event-free survival for Pioglitazone and Placebo]

- **Cumulative Probability of Event-free Survival**
- **Years since Randomization**
- **No. at Risk**
  - Pioglitazone: 1939, 1793, 1701, 1491, 1196, 481
  - Placebo: 1937, 1778, 1690, 1476, 1182, 459

**Hazard ratio, 0.76 (95% CI, 0.62–0.93)**

**P=0.007**
## Primary and Secondary Outcomes

**Table 2. Primary and Secondary Outcomes.**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pioglitazone (N=1939)</th>
<th>Placebo (N=1937)</th>
<th>Hazard Ratio (95% CI) (^\dagger)</th>
<th>Adjusted P Value (^\dagger)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke or myocardial infarction(\dagger)</td>
<td>175 (9.0)</td>
<td>228 (11.8)</td>
<td>0.76 (0.62–0.93)</td>
<td>0.007</td>
</tr>
<tr>
<td>Stroke</td>
<td>123 (6.3)</td>
<td>150 (7.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal</td>
<td>9 (0.5)</td>
<td>13 (0.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal</td>
<td>114 (5.9)</td>
<td>137 (7.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>52 (2.7)</td>
<td>78 (4.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal</td>
<td>7 (0.4)</td>
<td>14 (0.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal</td>
<td>45 (2.3)</td>
<td>64 (3.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Secondary outcome(\dagger)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>127 (6.5)</td>
<td>154 (8.0)</td>
<td>0.82 (0.61–1.10)</td>
<td>0.19</td>
</tr>
<tr>
<td>Acute coronary syndrome: myocardial infarction or unstable angina</td>
<td>96 (5.0)</td>
<td>128 (6.6)</td>
<td>0.75 (0.52–1.07)</td>
<td>0.11</td>
</tr>
<tr>
<td>Stroke, myocardial infarction, or serious heart failure(\dagger)</td>
<td>206 (10.6)</td>
<td>249 (12.9)</td>
<td>0.82 (0.65–1.05)</td>
<td>0.11</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>73 (3.8)</td>
<td>149 (7.7)</td>
<td>0.48 (0.33–0.69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>136 (7.0)</td>
<td>146 (7.5)</td>
<td>0.93 (0.73–1.17)</td>
<td>0.52</td>
</tr>
</tbody>
</table>

* Hazard ratios were calculated by means of a Cox regression model with corresponding 95% confidence intervals. The confidence interval for the primary outcome was adjusted for interim monitoring; confidence intervals for the secondary outcomes were adjusted for multiple comparisons.

\(^\dagger\) The P value for the primary outcome was adjusted for interim monitoring. P values for the five secondary outcomes were adjusted for multiple comparisons by the Hochberg procedure using an overall familywise type I error of 5%.

\(^\dagger\) Only the first event, stroke or myocardial infarction, was counted for each patient.

\(\dagger\) In the composite categories, only the first event was counted for each patient (e.g., a patient with myocardial infarction followed by unstable angina would be counted only as having a myocardial infarction in the category for acute coronary syndrome). More strokes are listed as occurring as a secondary outcome than a primary outcome because the secondary outcome included strokes occurring after myocardial infarction.

\(\dagger\) Serious heart failure was defined as an episode resulting in hospitalization or death.
### Table 3. Adverse Events, According to Severity.*

<table>
<thead>
<tr>
<th>Event</th>
<th>Pioglitazone (N = 1939)</th>
<th>Placebo (N = 1937)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serious adverse event</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization</td>
<td>908 (46.8)</td>
<td>946 (48.8)</td>
<td>0.21</td>
</tr>
<tr>
<td>Death</td>
<td>136 (7.0)</td>
<td>146 (7.5)</td>
<td>0.53</td>
</tr>
<tr>
<td><strong>Incident cancer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>133 (6.9)</td>
<td>150 (7.7)</td>
<td>0.29</td>
</tr>
<tr>
<td>Prostate</td>
<td>28 (1.4)</td>
<td>25 (1.3)</td>
<td>0.68</td>
</tr>
<tr>
<td>Breast</td>
<td>10 (0.5)</td>
<td>16 (0.8)</td>
<td>0.24</td>
</tr>
<tr>
<td>Lung</td>
<td>13 (0.7)</td>
<td>11 (0.6)</td>
<td>0.68</td>
</tr>
<tr>
<td>Bladder</td>
<td>12 (0.6)</td>
<td>8 (0.4)</td>
<td>0.37</td>
</tr>
<tr>
<td>Other</td>
<td>75 (3.9)</td>
<td>93 (4.8)</td>
<td>0.15</td>
</tr>
<tr>
<td>Bone fracture†</td>
<td>99 (5.1)</td>
<td>62 (3.2)</td>
<td>0.003</td>
</tr>
<tr>
<td>Heart failure‡</td>
<td>51 (2.6)</td>
<td>42 (2.2)</td>
<td>0.35</td>
</tr>
<tr>
<td>Other§</td>
<td>2 (0.1)</td>
<td>1 (0.1)</td>
<td>0.50</td>
</tr>
<tr>
<td><strong>Other adverse event</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone fracture¶</td>
<td>133 (6.9)</td>
<td>94 (4.9)</td>
<td>0.008</td>
</tr>
<tr>
<td>Heart failure¶</td>
<td>29 (1.5)</td>
<td>32 (1.7)</td>
<td>0.70</td>
</tr>
<tr>
<td>Weight gain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;4.5 kg</td>
<td>1013 (52.2)</td>
<td>653 (33.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;13.6 kg</td>
<td>221 (11.4)</td>
<td>88 (4.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Edema</td>
<td>691 (35.6)</td>
<td>483 (24.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>342 (17.6)</td>
<td>292 (15.1)</td>
<td>0.03</td>
</tr>
<tr>
<td>Alanine aminotransferase &gt;ULN</td>
<td>26 (1.3)</td>
<td>59 (3.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Macular edema</td>
<td>3 (0.2)</td>
<td>2 (0.1)</td>
<td>0.66</td>
</tr>
</tbody>
</table>
TECH & SCIENCE

THE DIABETES DRUG THAT COULD BE AN ANTI-AGING MIRACLE

BY ALISSA FLECK ON 12/12/15 AT 1:12 PM
Can diabetes drug Metformin extend your life?

- Improved survival
- Anti-cancer benefits
- Cardiovascular benefit
- Cognitive benefits
- Reduce pre-diabetes progression
Diabetes, Obesity and Metabolism 16: 1165-1173, 2014

(a) Cumulative Survival

Time to death (years)

Cumulative Survival

0.75
0.80
0.85
0.90
0.95
1.00

0
1
2
3
4
5
6

p = 0.037

(b) Cumulative survival

Time to death (years)

Cumulative survival

0.75
0.80
0.85
0.90
0.95
1.00

0
1
2
3
4
5
6

p < 0.001

(c) Cumulative survival

Time to death (years)

Cumulative survival

0.75
0.80
0.85
0.90
0.95
1.00

0
1
2
3
4
5
6

Metformin monotherapy
Suphonylurea monotherapy
Controls (matched with metformin)
Controls (matched with sulphonylurea)
Diabetes, metformin and incidence of and death from invasive cancer in postmenopausal women: Results from the women’s health initiative

Zhihong Gong1, Aaron K. Aragaki2, Rowan T. Chlebowski3, JoAnn E. Manson4, Thomas E. Rohan1, Chu Chen2, Mara Z. Vitonis4, Lesley F. Tinker5, Erin S. LeBlanc7, Lewis H. Kuller6, Lifang Hou5, Michael J. LaMonte10, Juhua Luo11 and Jean Wactawski-Wende10

- 45% higher odds of dying from cancer if diabetic compared to non-diabetic
- Women with cancer and DM2 on metformin had the same risk of dying as non-diabetic women

### Table. Weighted Characteristics of Treated Patients With Diabetes in the Medical Expenditure Panel Survey (MEPS), 2002-2013

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>MEPS Survey Years</th>
<th>2002-2004 (n = 5799)</th>
<th>2005-2007 (n = 6486)</th>
<th>2008-2010 (n = 7237)</th>
<th>2011-2013 (n = 8356)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated diabetes, % (95% CI)</td>
<td></td>
<td>5.2 (4.9-5.4)</td>
<td>6.2 (5.5-6.5)</td>
<td>7.1 (6.8-7.4)</td>
<td>7.7 (7.4-8.0)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td></td>
<td>60.2 (15.0)</td>
<td>60.3 (14.6)</td>
<td>60.3 (14.8)</td>
<td>60.7 (14.6)</td>
</tr>
<tr>
<td>Men, No. (%)</td>
<td></td>
<td>2496 (47.7)</td>
<td>2850 (48.3)</td>
<td>3182 (47.9)</td>
<td>3845 (50.0)</td>
</tr>
<tr>
<td>Race, No. (%)</td>
<td></td>
<td>2951 (65.3)</td>
<td>3209 (65.0)</td>
<td>3089 (64.9)</td>
<td>3210 (62.0)</td>
</tr>
<tr>
<td>White</td>
<td></td>
<td>1202 (16.2)</td>
<td>1350 (15.1)</td>
<td>1805 (15.0)</td>
<td>2197 (15.5)</td>
</tr>
<tr>
<td>Black</td>
<td></td>
<td>1334 (12.5)</td>
<td>1533 (13.5)</td>
<td>1699 (12.9)</td>
<td>2202 (15.1)</td>
</tr>
<tr>
<td>Hispanic</td>
<td></td>
<td>312 (6.1)</td>
<td>394 (6.5)</td>
<td>644 (7.2)</td>
<td>747 (7.4)</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of medications, % (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td></td>
<td>28.1 (26.2-29.8)</td>
<td>24.1 (22.4-25.8)</td>
<td>25.3 (23.7-27.0)</td>
<td>29.2 (27.6-30.8)</td>
</tr>
<tr>
<td>Metformin</td>
<td></td>
<td>36.1 (34.2-38.0)</td>
<td>43.6 (41.6-45.5)</td>
<td>47.3 (45.4-49.2)</td>
<td>51.5 (49.8-53.1)</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td></td>
<td>38.2 (36.2-40.1)</td>
<td>35.1 (33.2-36.9)</td>
<td>30.7 (28.9-32.4)</td>
<td>27.5 (25.8-29.3)</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td></td>
<td>21.1 (19.5-22.7)</td>
<td>23.2 (21.5-24.9)</td>
<td>13.0 (11.6-14.3)</td>
<td>5.8 (5.0-6.6)</td>
</tr>
<tr>
<td>o-Glucosidase inhibitors and sulfonylurea secretagogues</td>
<td></td>
<td>2.6 (2.0-3.2)</td>
<td>2.8 (2.2-3.4)</td>
<td>1.4 (1.0-1.8)</td>
<td>0.7 (0.5-1.0)</td>
</tr>
<tr>
<td>DPP-4 Inhibitors</td>
<td></td>
<td>1.2 (0.8-1.5)</td>
<td>5.6 (4.7-6.5)</td>
<td>7.7 (6.8-8.7)</td>
<td></td>
</tr>
<tr>
<td>Combinations</td>
<td></td>
<td>6.8 (5.8-7.7)</td>
<td>8.9 (7.8-9.9)</td>
<td>8.0 (7.0-9.0)</td>
<td>6.0 (5.1-6.9)</td>
</tr>
<tr>
<td>All orals</td>
<td></td>
<td>68.9 (66.9-70.8)</td>
<td>72.6 (70.9-74.4)</td>
<td>70.8 (69.2-72.5)</td>
<td>69.5 (67.9-71.1)</td>
</tr>
<tr>
<td>Amylin analogs</td>
<td></td>
<td>0.1 (0-0.1)</td>
<td>0.2 (0.1-0.4)</td>
<td>0.2 (0.1-0.4)</td>
<td>0.1 (0-0.2)</td>
</tr>
<tr>
<td>GLP-1 receptor agonists</td>
<td></td>
<td>2.2 (1.6-2.8)</td>
<td>2.7 (2.1-3.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All noninsulin injectables</td>
<td></td>
<td>2.4 (1.8-3.1)</td>
<td>2.8 (2.1-3.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quantity of medications (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin, mL</td>
<td></td>
<td>171 (160-181)</td>
<td>150 (137-164)</td>
<td>205 (191-218)</td>
<td>206 (193-220)</td>
</tr>
<tr>
<td>All orals, tablets</td>
<td></td>
<td>611 (580-641)</td>
<td>632 (607-657)</td>
<td>775 (746-804)</td>
<td>800 (772-828)</td>
</tr>
<tr>
<td>All noninsulin injections, mL</td>
<td></td>
<td>21 (16-25)</td>
<td>36 (30-42)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1.

a The reported statistics were based on a pooled sample across 3 waves of MEPS.

b Percentage of all survey respondents. People treated for diabetes were identified using 3-digit International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis codes.

c Race was included as part of the descriptive analysis. As defined by MEPS, classification by race and ethnicity was mutually exclusive and based on information reported for each family member. All persons whose main national origin or ancestry was reported as Hispanic, regardless of racial background, were classified as Hispanic.

d Included metformin, sulfonylureas, thiazolidinediones, o-glucosidase inhibitors, and nonsulfonylurea secretagogues, combinations, and DPP-4 inhibitors.

e Included amylin analogs and GLP-1 receptor agonists from 2008.

f Quantities of medication used were means per patient per year, conditional on some recorded use of the drug over the given period.
Cost of insulin up $231.48 > $736.09

Price of insulin per mL up 197%

Cost greater than all other DM meds combined

Medications were classified as follows: insulin (human and analog); newer oral therapies (thiazolidinediones, dipeptidyl peptidase-4 inhibitors, and combinations); older oral therapies (metformin, sulfonylureas, α-galactosidase inhibitors, and nonsulfonylurea secretagogues); noninsulin-based injectable therapies (glucagon-like peptide-1 receptor agonists and amylin analogs).
• Eli Lily, Sanofi and NovoNordisk hold patents to manufacture insulin
• No generics or “biosimilars” yet

New insulins

- **Novo-Nordisk**
  - Tresiba U-100 and U-200
  - Ryzodeg 70/30 (degludec/aspart)
  - Ultra rapid/NovoRapid (phase 3)

- **Lilly**
  - U-500 Humulin R pen
  - Basaglar (glargine biosimilar)
  - Ultra rapid (phase 1)

- **Sanofi**
  - Toujeo U-300
  - Lispro biosimilar (phase 3)
Are newer insulins worth the cost?

**PRO**
- Only 30% of DM2 on insulin at goal ha1c
- Lower risk of Nocturnal HYPOglycemia
- Less weight gain
- Longer, smoother, more predictable response
- Convenient, more flexible dosing

**CON**
- Nocturnal HYPO 20x lower in DM2 vs. DM1
- Prandial insulin less important in DM2
- Small difference in Ha1c (<0.1%)
Afreeza

Approved 6/2014

- **PROS:**
  - More rapid onset/duration mimics native insulin secretion
  - Less weight gain, less HYPOs
  - Avoid injections
  - Approved for DM1 and DM2

- **CONS:**
  - Throat pain, irritation
  - Do not use with asthma/COPD
  - Do not use in smokers or recent smokers
  - Long term pulmonary safety data?

Source: Mannkind

Afreeza Approved 6/2014
2. Insulin Aspart, 0.2 U/kg. Regular Human Insulin, 0.2 U/kg units. Subcutaneous injection in abdomen. Adapted from Mudaliar SR et al. Diabetes Care. 1999;22:1501-1506.
MNKD: Afrezza Launch Will Propel MannKind Stock

MNKD stock is still a screaming buy as Afrezza launch nears

By John Divine, InvestorPlace Assistant Editor | Jan 23, 2015, 2:00 pm EST

MannKind Corporation (NASDAQ:MNKD) stock is primed to take off higher as the much-awaited launch of its inhalable insulin drug, Afrezza, approaches.

MNKD stock and its $2.3 billion market capitalization hang in the balance, as its fate could
Patient Cases
Weight

Date

Lbs

250
245
240
235
230
225
220
215
210
205
200
195
190
185
180
175
170
165
160
01/16/2014 03/31/2014 06/13/2014 08/26/2014 11/08/2014 01/21/2015 04/05/2015 06/18/2015 08/31/2015 11/13/2015 01/26/2016
NB

9/5/15

4/18/16
Cleveland Clinic
Every life deserves world class care.