Type 2 Diabetes: An Evidence Based Pharmacotherapy Update

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Faculty Disclosure

• I do not have anything to declare as I do not speak for or consult for any pharmaceutical manufacturer.
Lifestyle Management Uplifted in 2017 ADA Diabetes Care Standards

- The ADA recommends limiting long periods of sitting as multiple studies have shown how it affects blood glucose management. They recommend that we all move every 30 minutes during prolonged periods of sitting by briefly standing, walking, or performing at other light physical activities.

- Recommend providing older adults with flexibility and balance training 2–3 times/week for older adults. Yoga and tai chi may be included based on individual preferences to increase flexibility, muscular strength, and balance.

- Most adults with type 1 C and type 2 B diabetes should engage in 150 min or more of moderate-to-vigorous intensity physical activity per week, spread over at least 3 days/week, with no more than 2 consecutive days without activity. Shorter durations (minimum 75 min/week) of vigorous-intensity or interval training may be sufficient for younger and more physically fit individuals.

- Adults with type 1 C and type 2 B diabetes should engage in 2–3 sessions/week of resistance exercise on nonconsecutive days.

- Structured exercise interventions of at least 8 weeks' duration have been shown to lower A1C by an average of 0.66% in people with type 2 diabetes, even without a significant change in BMI.

  - Diabetes Care 2017;40:S64-S74

Lifestyle Management Uplifted in 2017 ADA Diabetes Care Standards

- All individuals with diabetes should receive individualized medical nutrition therapy (MNT), preferably provided by a registered dietitian who is knowledgeable and skilled in providing diabetes-specific MNT.

- MNT delivered by a registered dietitian is associated with A1C decreases of 0.3–1% for people with type 1 diabetes and 0.5–2% for people with type 2 diabetes.

- As there is no single ideal dietary distribution of calories among carbohydrates, fats, and proteins for people with diabetes, macronutrient distribution should be individualized while keeping total calorie and metabolic goals in mind.

- A variety of eating patterns are acceptable for the management of type 2 diabetes and prediabetes including Mediterranean, DASH, and plant-based diets.

- Carbohydrate intake from whole grains, vegetables, fruits, legumes, and dairy products, with an emphasis on foods higher in fiber and lower in glycemic load, should be advised over other sources, especially those containing sugars.

- For many obese individuals with type 2 diabetes, weight loss.5% is needed to produce beneficial outcomes in glycemic control, lipids, and blood pressure, and sustained weight loss of >7% is optimal.

  - Diabetes Care 2017;40:S64-S74
Diabetes Aerobic and Resistance Exercise (DARE) trial

– 251 participants 39–70 years of age (mean age 54 y, 64% men) who had type 2 diabetes for >6 months, had baseline HbA1c levels of 6.6–9.9%, and who were previously inactive were randomized to one of four groups (aerobic exercise; resistance exercise; combined exercise or a control group for 6 months)

• Exercise groups received supervised training 3 times per week for 22 weeks
• Primary outcome was change in A1c at 6 months


Diabetes Aerobic and Resistance Exercise (DARE) trial

• Results at 6 months:
  – The aerobic exercise group had reduced A1c by 0.43% vs. an increase of 0.07% with the control group (difference of 0.51%, 95% CI -0.87 to -0.14)
  – The resistance exercise group had reduced A1c by 0.30% (difference of 0.38%, 95% CI -0.72 to -0.22)
  – The combined exercise group had reduced A1c by 0.90%
Standards of Medical Care in Diabetes 2015: Summary of Revisions

- The ADA now recommends a pre-meal blood glucose target of 80–130 mg/dL, rather than 70–130 mg/dL, to better reflect new data comparing actual average glucose levels with A1C targets.
- The type 2 diabetes management algorithm was updated to reflect all of the currently available therapies for diabetes management.
- The goal for diastolic blood pressure was changed from 80 mmHg to 90 mmHg for most people with diabetes and hypertension to better reflect evidence from randomized clinical trials. Lower diastolic targets may still be appropriate for certain individuals.

- Diabetes Care January 2015 vol. 38 no. Supplement 1 S4

ADA 2012 Clinical Practice Recommendations (Diabetes Care 2012;35: S11-S63)

- “Growing evidence suggests that there is an association between increase in sleep-time blood pressure and incidence of CVD events. A recent RCT of 448 participants with type 2 diabetes and hypertension demonstrated reduced cardiovascular events and mortality with median follow-up of 5.4 years if at least one antihypertensive medication was given at bedtime.”
- “Administer one or more antihypertensive medications at bedtime. (A)”
Influence of Time of Day of Blood Pressure–Lowering Treatment on Cardiovascular Risk in Hypertensive Patients with Type 2 Diabetes (Diabetes Care 2011; 34:1270-76)

- A prospective, randomized, single study center in Spain, open-label, blinded end point trial on 448 hypertensive patients with type 2 diabetes, 255 men/193 women, mean age 62.5 years, randomized to ingest all their prescribed hypertension medications upon awakening or 1 or more of them at bedtime.
- Ambulatory blood pressure was measured for 48 hrs at baseline and again annually or even more frequently (quarterly) after adjustments in treatment.
- The mean follow-up was 5.4 years.
- This was a subset of the original MAPEC Trial in 2156 hypertensive subjects from Spain (Chronobiology International 2010; 27(8): 1629–1651)

Influence of Time of Day of Blood Pressure–Lowering Treatment on Cardiovascular Risk in Hypertensive Patients with Type 2 Diabetes (Diabetes Care 2011; 34:1270-76)

- Results: patients ingesting one or more hypertension medications at bedtime showed a significantly lower cardiovascular risk (adjusted by age and sex) than subjects ingesting all medications upon awakening (hazard ratio 0.33 [95% CI 0.21–0.54]; P < 0.001).
- The difference between groups in the adjusted risk of major events (cardiovascular death, myocardial infarction, and stroke) was also statistically significant (0.25 [0.10–0.61]; P = 0.003).
- There was a significant 12% cardiovascular risk reduction per each 5 mmHg decrease in asleep systolic blood pressure during follow-up (P < 0.001).
Blood Pressure Goals ADA 2016

- Regarding blood pressure, the ADA continues to advise lowering to less than 140 mm Hg systolic and 90 mm Hg diastolic in people with diabetes.
- That guidance, first published in the 2013 Standards to align with the then newly released JNC8, has recently been called into question with new data from the Systolic Blood Pressure Intervention Trial (SPRINT) showing that a systolic target of less than 120 mm Hg might improve cardiovascular outcomes.
- The new document mentions SPRINT but also notes that patients with diabetes were excluded. "So, whether those cutoffs are appropriate for diabetes remains to be seen. But we felt it was an important enough trial, and there were some suggestive data in the past that lower levels were important, that we wanted to get that in," Dr Ratner explained.

Standards of Medical Care in Diabetes 2015: Summary of Revisions

- Recommendations for statin treatment and lipid monitoring were revised after consideration of 2013 American College of Cardiology/American Heart Association guidelines on the treatment of blood cholesterol. Treatment initiation (and initial statin dose) is now driven primarily by risk status rather than LDL cholesterol level.
- To reflect new evidence regarding the risks and benefits of tight glycemic control in children and adolescents with diabetes, the Standards now recommend a target A1C of <7.5% for all pediatric age-groups; however, individualization is still encouraged. The pre-meal goal is 90-130 mg/dl and the bedtime/overnight goal is 90-150 mg/dl.
- A new section was added to the Standards to provide recommendations related to pregnancy and diabetes, including recommendations regarding preconception counseling, medications, blood glucose targets, and monitoring.
  
  — Diabetes Care January 2015 vol. 38 no. Supplement 1 S4
A Fundamental Shift to a Patient-Centered Focus ADA 2016

• Throughout the entire document, there is a new emphasis on individual patient circumstances, needs, and desires, ADA chief scientific and medical officer Robert E Ratner, MD

• "The tone we've taken here is moving much more toward patient-centeredness. We focus on shared decision making, vulnerable populations, and setting goals that meet the needs of the individual. That's really a fundamental shift."

• To that end, the very first chapter addresses strategies for improving care, including "a patient-centered communication style," with treatment decisions "tailored to individual patient preferences, prognosis, and comorbidities."

– Diabetes Care. 2016 39 Suppl 1

Terminology Changes ADA 2016

• There are also some language changes for 2016. The word diabetic will no longer be used by the ADA when referring to people with diabetes, signifying that "We're not treating a disease. We're treating a patient," Dr Ratner said.

• “Diabetic" will still be used as an adjective, however, as in the case of another new term, "diabetic kidney disease," which replaces "nephropathy."

• Another linguistic shift is the use of "atherosclerotic cardiovascular disease (ASCVD)" as a more specific term than simple "CVD."

– Diabetes Care. 2016 39 Suppl 1
Diagnosis of Diabetes ADA 2016

• A revision in the discussion of diagnostic tests to make it clear that no one test is preferred over another.

• Following the 2015 US Preventive Services Task Force guidance, a recommendation to screen all adults for dysglycemia beginning at age 45 years, regardless of weight.
  – Diabetes Care. 2016 39 Suppl 1

Prevention or Delay of Type 2 Diabetes 2017

Recommendations:

• At least annual monitoring for the development of diabetes in those with prediabetes is suggested. E

• Patients with prediabetes should be referred to an intensive behavioral lifestyle intervention program modeled on the Diabetes Prevention Program to achieve and maintain 7% loss of initial body weight and increase moderate intensity physical activity (such as brisk walking) to at least 150 min/week. A

• Technology-assisted tools including Internet-based social networks, distance learning, DVD-based content, and mobile applications may be useful elements of effective lifestyle modification to prevent diabetes. B

• Given the cost-effectiveness of diabetes prevention, such intervention programs should be covered by third-party payers. B

• Metformin therapy for prevention of type 2 diabetes should be considered in those with prediabetes, especially for those with BMI >/=35 kg/m2, those aged <60 years, women with prior gestational diabetes mellitus, and/or those with rising A1C despite lifestyle intervention. A
  – Long-term use of metformin may be associated with biochemical vitamin B12 deficiency, and periodic measurement of vitamin B12 levels should be considered in metformin-treated patients, especially in those with anemia or peripheral neuropathy. B

  – Diabetes Care 2017;40(Suppl. 1):S44–S47
Aspirin and Lipids including Ezetimibe ADA 2016

- New in 2016 are evidence-based recommendations advising consideration of: low dose aspirin therapy for women aged 50 and older (a change from women >60 previously); antiplatelet use in patients younger than 50 with multiple risk factors; (ASCVD Risk >/=10%)
- The addition of ezetimibe (Zetia, Merck) to moderate-intensity statin therapy in select patients with diabetes, based on the recent IMPROVE-IT trial.
  - new recommendations for obtaining a fasting lipid profile in children starting at age 10 years.

### ADA and ACE Glycemic Goals

<table>
<thead>
<tr>
<th>Biochemical Index</th>
<th>ADA 2017</th>
<th>AACE/ACE</th>
</tr>
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<tbody>
<tr>
<td>Fasting/preprandial plasma glucose (mg/dL)</td>
<td>≤100</td>
<td>80–130</td>
</tr>
<tr>
<td>Postprandial plasma glucose (mg/dL)</td>
<td>&lt;140</td>
<td>&lt;180</td>
</tr>
<tr>
<td>Hemoglobin A1c (%)</td>
<td>&lt;6</td>
<td>&lt;7</td>
</tr>
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</table>

*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.*

AACE Comprehensive Diabetes Management Algorithm, Endoor Pract. 2016
Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Microvasc</th>
<th>CVD</th>
<th>Mortality</th>
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<tr>
<td>UKPDS</td>
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Kendall DM, Bergenstal RM. © International Diabetes Center 2009


ACCORD Glucose Arm

**Trial design:** Type 2 diabetic patients were randomized to intensive therapy (glycated hemoglobin <6%, n = 5,128) versus standard therapy (glycated hemoglobin 7%-7.9%, n = 5,123). Patients were followed for 3.5 years.

**Results**
- CV death, MI, or stroke: 6.9% vs. 7.2% (p = 0.16), respectively
- All-cause mortality: 5.0% vs. 4.0% (p = 0.04), respectively
- CV mortality: 2.6% vs. 1.8% (p = 0.02), respectively

**Conclusions**
- Intensive glucose lowering (mean glycated hemoglobin 6.4%) increased all-cause and CV mortality among type 2 diabetics
- National Heart, Lung, and Blood Institute stopped the trial 17 months early
- Other studies testing intensive glycemic control are ongoing


**Table:**

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</table>

* in T1DM
### Antihyperglycemic therapy in type 2 diabetes: general recommendations.

#### Start with Monotherapy unless:
- HbA1C greater than or equal to 9% consider Dual Therapy
- HbA1C greater than or equal to 8% and FPG greater than or equal to 200 mg/dL

#### Monotherapy
- **Metformin**
  - **EFFICACY**
    - High
  - **SUCCES**
    - High
  - **WEIGHT**
    - Neutral
  - **SIDE EFFECTS**
    - Weight loss
  - **COMMENTS**
    - Baseline weight loss

#### Dual Therapy
- **Metformin**
  - **EFFICACY**
    - Intermediate
  - **SUCCES**
    - Moderate
  - **WEIGHT**
    - Neutral
  - **SIDE EFFECTS**
    - Weight loss
  - **COMMENTS**
    - Initially, monotherapy with weight loss

#### Triple Therapy
- **Metformin**
  - **EFFICACY**
    - Low
  - **SUCCES**
    - Low
  - **WEIGHT**
    - High
  - **SIDE EFFECTS**
    - N/A
  - **COMMENTS**
    - May consider adding another agent

#### Combination Injectable Therapy
(See Figure 8.2)

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American Diabetes Association Dia Care 2017;40:564-574
UK Prospective Diabetes Study

Glucose Intervventional Trial

**Dietary Run-in**
- 744
  - Diet failure
  - FPG >15 mmol/l
- 5,102
  - Newly-diagnosed type 2 diabetes
- 149
  - Diet satisfactory
  - FPG <6 mmol/l

Mean age 54 years
(IQR 48–60)

**Randomisation 1977-1991**
- 2,729
  - Intensive
  - with sulfonylurea/insulin
- 1,138
  - (411 overweight)
  - Conventional
  - with diet
- 342
  - (all overweight)
  - Intensive
  - with metformin

**Trial end 1997**
- 5,102
  - Newly-diagnosed type 2 diabetes

UK Prospective Diabetes Study
Glucose Interventional Trial

<table>
<thead>
<tr>
<th>Outcome at 10 years</th>
<th>Diet/Met</th>
<th>Diet/Sulf/Insulin</th>
<th>Diet</th>
<th>RRR/ARR/NNT (Diet/Met vs. Diet)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any DM related endpoint</td>
<td>28.7%</td>
<td>36.8%</td>
<td>38.9%</td>
<td>26.2%/10.2%/10</td>
</tr>
<tr>
<td>Diabetes related death</td>
<td>8.2%</td>
<td>10.8%</td>
<td>13.4%</td>
<td>38.8%/5.2%/19</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>14.6%</td>
<td>20%</td>
<td>21.7%</td>
<td>32.7%/7.1%/14</td>
</tr>
<tr>
<td>MI</td>
<td>11.4%</td>
<td>14.6%</td>
<td>17.8%</td>
<td>36%6.4%/16</td>
</tr>
<tr>
<td>Stroke</td>
<td>3.5%</td>
<td>6.3%</td>
<td>5.6%</td>
<td>44.4%/2.8%/36</td>
</tr>
<tr>
<td>Micro-vascular events</td>
<td>7.0%</td>
<td>7.8%</td>
<td>9.2%</td>
<td>N/S</td>
</tr>
</tbody>
</table>

Lancet, 1998;352: 854 - 865

Long-term Effects of Metformin on Metabolism and Microvascular and Macrovascular Disease in Patients With Type 2 Diabetes Mellitus Treated with Insulin Arch Intern Med. 2009;169(6):616-625

- 390 patients treated with insulin in the outpatient clinics of 3 hospitals in a randomized, placebo-controlled trial with a follow-up period of 4.3 years. Either metformin hydrochloride, 850 mg, or placebo (1-3 times daily) was added to insulin therapy.

- The primary end point was an aggregate of microvascular and macrovascular morbidity and mortality. The secondary end points were microvascular and macrovascular morbidity and mortality independently.

“Hyperinsulinemia the Outcome of its Metabolic Effects (HOME)”
Long-term Effects of Metformin on Metabolism and Microvascular and Macrovascular Disease in Patients With Type 2 Diabetes Mellitus Treated with Insulin *Arch Intern Med.* 2009;169(6):616-625

**Results:**

- Metformin treatment prevented weight gain (mean weight gain, $-3.07$ kg [range, $-3.85$ to $-2.28$ kg]; *P* = 0.001).
- Improved glycemic control (mean reduction in HbA1c level, 0.4% percentage point [95% CI, 0.55-0.25]; *P* = 0.001), despite the aim of similar glycemic control in both groups,
- **Reduced insulin requirements** (mean reduction, 19.63 IU/d [95% CI, 24.91-14.36 IU/d]; *P* = 0.001).
- Metformin was not associated with an improvement in the primary end point.
- It was, however, associated with an improvement in the secondary, macrovascular end point (hazard ratio, 0.61 [95% CI, 0.40-0.94; *P* = .02]), which was partly explained by the difference in weight.
- The number needed to treat to prevent 1 macrovascular end point was 16.1 (95% CI, 9.2-66.6).
- These sustained beneficial effects support the policy to continue metformin treatment after the introduction of insulin in any patient with DM2, unless contraindicated.

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**FDA Updates Metformin Dosing Information 4-8-2016**

- We are also **requiring manufacturers to revise the labeling to recommend that the measure of kidney function used to determine whether a patient can receive metformin be changed from one based on a single laboratory parameter (blood creatinine concentration) to one that provides a better estimate of renal function (i.e., glomerular filtration rate estimating equation (eGFR)).** This is because in addition to blood creatinine concentration, the glomerular filtration rate takes into account additional parameters that are important, such as the patient’s age, gender, race and/or weight.
FDA Updates Metformin Dosing Information 4-8-2016

- The labeling recommendations on how and when kidney function is measured in patients receiving metformin will include the following information:
  - Before starting metformin, obtain the patient’s eGFR.
  - Metformin is contraindicated in patients with an eGFR below 30 mL/minute/1.73 m².
  - Starting metformin in patients with an eGFR between 30-45 mL/minute/1.73 m² is not recommended.
  - Obtain an eGFR at least annually in all patients taking metformin. In patients at increased risk for the development of renal impairment such as the elderly, renal function should be assessed more frequently.
  - In patients taking metformin whose eGFR later falls below 45 mL/minute/1.73 m², assess the benefits and risks of continuing treatment. Discontinue metformin if the patient’s eGFR later falls below 30 mL/minute/1.73 m².
  - Discontinue metformin at the time of or before an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/minute/1.73 m²; in patients with a history of liver disease, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart metformin if renal function is stable.


Proposed Recommendations for Use of Metformin Based on e-GFR

<table>
<thead>
<tr>
<th>eGFR (ml/min per 1.73m²)</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60</td>
<td>No renal contraindication to metformin</td>
</tr>
<tr>
<td>&gt;45</td>
<td>Continue use Increase monitoring of renal function (every 3–6 months)</td>
</tr>
<tr>
<td>&lt;45 and &gt;30</td>
<td>Prescribe metformin with caution Use lower dose (e.g., 50%, or half-maximal dose) Closely monitor renal function (every 3-6 months) Do not start new patients on metformin</td>
</tr>
<tr>
<td>&lt;30</td>
<td>Stop metformin</td>
</tr>
</tbody>
</table>

Consistent with the National Institute for Health and Clinical Excellence guidelines in the U.K. and those endorsed by the Canadian Diabetes Association and the Australian Diabetes Society.
**Metformin Pricing?**

- Glucophage AB 1000 mg/60: $136.00 (BMS)
- Generic Glucophage AB 1000 mg/60: $0.00-12.00
- Glucophage XR 750 mg/60: $203.00
- Generic Glucophage XR 750 mg/60: $4.00-12.00
- Glumetza AB 3 1000 mg/60: $7,104.00 (Santarus)
- Generic Glumetza AB 3 1000 mg/60: $6,137.00
- Fortamet AB 2 1000 mg/60: $672.00 (Andrx)
- Generic Fortamet AB 2 1000 mg/60: $672.00
  - GoodRx.com 2-2-2017

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**FDA Removes Restrictions on Rosiglitazone - Avandia**

- Potential risks listed in the current FDA approved label for pioglitazone and rosiglitazone;
  - Significant weight gain and edema
  - Heart failure (NNH=34 at 3 yrs) in PROactive
  - Upper and lower extremity fractures ~ twice the risk as comparators including PROactive after only 1 year of use
  - Diabetes related macular edema ~ twice the risk in multiple retrospective data sets and increased more when used in combination with insulin
  - Potential for bladder cancer in males with pioglitazone (~40% increase?)
Insulin Glargine – Basaglar by Lilly and BI

- Dec 16, 2015 FDA approved Basaglar (insulin glargine) but not launched until after Dec 2016 based upon court action. The first insulin product approved through an abbreviated approval pathway under the FDA 505(b) (2) application which did rely partly on the safety and effectiveness of Lantus (insulin glargine by Sanofi).
- Lilly just announced the price will be 15% lower than Lantus

The FDA determined that Basaglar was sufficiently similar to Lantus and in addition Basaglar was studied in two large trials (543 Type 1 and 744 Type 2 patients with diabetes). Like Lantus FDA approved for patients age 6 and up.

Basaglar is considered a “follow-on” NOT FDA approved as a “Biosimilar” product. (There is no reference listed drug for Lantus under the Public Health Services Act) Requires prescriber approval. CVS/Caremark is now excluding Lantus as of 2017

Insulin Degludec- Tresiba by Novo Nordisk

- September 25, 2015 FDA approved Tresiba (insulin degludec) a once-daily new-generation basal insulin analogue with a half-life of 25 hours and a duration of action of at least 42 hours. (expected launch date early 2016)
  - indicated for use alone, or in combination with oral antidiabetic medicines or bolus insulin, and is approved for glycemic control in adults with type 1 and type 2 diabetes.
  - Will only be available in the Flex Touch Pen in both U 100 and U 200/ml 3 ml pens which can be administered at anytime during the day
Insulin Degludec- Tresiba

- U-100 FlexTouch - 3 mL 100 units/mL - 300 Units/pen – max dose 80 Units in 1 Unit increments – available 5 pens/pack ~$450.00
- U-200 FlexTouch - 3 mL 200 units/mL - 600 Units/pen – max dose 160 Units in 2 Unit increments - available 3 pens/pack ~$550.00

- Keep under refrigeration (NOT frozen) but stable for 56 days (8 weeks) at room temperature once taken out of refrigeration.

Insulin Degludec- Tresiba

- The Institute for Clinical and Economic Review (ICER) has released a new draft report titled Insulin Degludec for the Treatment of Diabetes: Effectiveness, Value, and Value-Based Price Benchmarks
Insulin Degludec- Tresiba

• ICER's analyses concluded that the evidence for the net health benefit of insulin degludec provides moderate certainty of equivalent glycemic control with a 25-35% reduction in nocturnal hypoglycemia in comparison to other long-acting insulins like insulin glargine (Lantus®, Sanofi-Aventis) and insulin detemir (Levemir®, Novo Nordisk).

• The draft ICER value-based price benchmark for insulin degludec is $7,006 to $7,154 per year. This represents an 8-10% discount from the average cost per year, which is well within the range of typical discounts available to payers.

Insulin Degludec/Aspart 70/30 – Ryzodeg by Novo Nordisk

• The FDA also approved Ryzodeg 70/30 contains insulin degludec in a soluble co-formulation with insulin aspart, and can be administered once or twice daily with any main meal.
Toujeo – Insulin glargine U-300  
by Sanofi

- Feb 25, 2015 FDA approved a new higher concentration U-300 insulin glargine - Toujeo available in the Solostar pen device only with 1.5ml (450U)/pen in boxes of 3 ($363.00) or 5 ($618.00) pens
- When compared head to head in multiple 26 weeks studies the efficacy was similar (noninferior) but the daily doses of Toujeo (U-300) were typically 10-20% higher than with Lantus (U-100)
- The data also suggest that the duration of action is slightly longer with a tail of ~30 hours.

Insulin Lispro - Humalog U-200  
KwikPen by Lilly

- The first concentrated mealtime insulin analog to receive FDA approval, the Humalog U-200 KwikPen delivers the same dose as Lilly’s Humalog U-100 KwikPen in half the volume.  
  Compared with the 300 units of insulin held by the U-100 formulation, the U-200 KwikPen holds 600 units
  - The FDA based its approval on data that demonstrated the bioequivalence of Humalog U-200 relative to Humalog U-100 in a pharmacokinetic/pharmacodynamic study.

Be careful in calculating the days supply with both of these new more concentrated insulins and be glad that they are not available in a vial!  
Boxes of 2 pens ~$425.00
Humulin R U-500 KwikPen by Lilly

- Humulin R U-500 (500 units per mL) is available in a colorless solution as a 3ml pen
  - 20mL vial (containing 10,000 units of insulin)
  - Cost ~ $1350.00/20cc vial
  - GoodRx.com

- As of July 2016 the FDA has also approved a dedicated U-500 insulin syringe to only use with U-500 Regular Insulin vial.

- 3mL Humulin R U-500 KwikPen (prefilled, 1,500 units of insulin 5 U increments) boxes of 2 pens (FDA approved 12/2015) Cost ~ $571.00

Store at room temperature, below 86°F (30°C) and the pen must be discarded after 28 days and the vial after 40 days.

Insulin Price Increases?

- Robert A. Gabbay, MD, PhD, FACP, of Joslin Diabetes Center, discusses rising insulin prices in his editor-in-chief letter in the 9/2016 issue of Evidence-Based Diabetes Management. Which do you think is the more likely response to price increases of about 3 fold in the last 10 years?

- Rising insulin prices will be addressed as part of a broader effort to deal with drug costs in the next presidential administration (57%)
- Insulin prices have reached a crisis point and must be addressed now because the lives and health of people with diabetes are at risk (43%)
American Diabetes Association Issues Resolution and Launches Petition Calling for Access to Affordable Insulin

- November 17, 2016 he American Diabetes Association issued a resolution and the launch of a petition calling on all entities in the insulin supply chain to increase transparency and to ensure that no person with diabetes is denied affordable access to insulin. The Association is also calling on Congress to hold hearings with all entities in the insulin supply chain to identify the reasons for the dramatic increases in insulin prices and to take action to ensure affordable access to insulin for all who need it.


Liraglutide – Victoza by Novo-Nordisk

- A human analog of the glucagon-like peptide-1 (GLP-1) with 97% amino acid sequence homology to endogenous human GLP-1.
  - T1/2 ~11-15 hrs
  - 1.2 mg dose (2 pens/mo)
    - $536.00 GoodRx.com
  - 1.8 mg dose (3 pens/mo)
    - $800.00 GoodRx.com
- Adjunct to diet and exercise for Type 2 DM but not first line and no data in combo with prandial insulin
Liraglutide with or without oral antidiabetic drug therapy in type 2 diabetes: an overview of the LEAD 1–5 studies
Diabetes, Obesity and Metabolism, 11 (Suppl. 3), 2009, 26–34

LEADER was a multicenter, international, randomized, double-blind, placebo-controlled trial investigating the long-term effects of liraglutide (1.2 and 1.8 mg) compared to placebo, both in addition to standard of care, in people with type 2 diabetes at high risk of cardiovascular events. The trial was initiated in September 2010 and randomized 9,340 people with type 2 diabetes from 32 countries that were followed for 3.5-5 years. The primary endpoint was the first occurrence of a composite cardiovascular outcome comprising cardiovascular death, non-fatal myocardial infarction or non-fatal stroke.
LEADER CV Safety Trial with Liraglutide

- 9340 patients with type 2 diabetes and high cardiovascular risk to receive liraglutide or placebo. The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.
  - The median follow-up was 3.8 years.
- The primary outcome occurred in significantly fewer patients in the liraglutide group (608 of 4668 patients [13.0%]) than in the placebo group (694 of 4672 [14.9%]) (HR 0.87; 95% CI, 0.78 to 0.97; P<0.001 for noninferiority; P = 0.01 for superiority) ARR 1.9%, NNT=53

LEADER CV Safety Trial with Liraglutide

- Death from cardio-vascular causes in the liraglutide group (219 patients [4.7%]) than in the placebo group (278 [6.0%]) (hazard ratio, 0.78; 95% CI, 0.66 to 0.93; P = 0.007). ARR 1.3%, NNT 77
- The rate of death from any cause was lower in the liraglutide group (381 patients [8.2%]) than in the placebo group (447 [9.6%]) (HR 0.85; 95% CI, 0.74 to 0.97; P = 0.02). ARR 1.4%, NNT=72
LEADER CV Safety Trial with Liraglutide

• The rates of nonfatal myocardial infarction (HR 0.88), nonfatal stroke (HR 0.89), and hospitalization for heart failure (HR 0.87) were all nonsignificantly lower in the liraglutide group than in the placebo group.

LEADER CV Safety Trial with Liraglutide

• Microvascular Outcomes: The incidence of a composite outcome of renal or retinal microvascular events was lower in the liraglutide group than in the placebo group (HR 0.84; 95% CI, 0.73 to 0.97; P = 0.02)
  – The difference that was driven by a lower rate of nephropathy events in the liraglutide group (1.5 vs. 1.9 events per 100 patient-years of observation; HR 0.78; 95% CI, 0.67 to 0.92; P = 0.003)
  – The incidence of retinopathy events was nonsignificantly higher in the liraglutide group than in the placebo group (0.6 vs. 0.5 events per 100 patient-years; HR 1.15; 95% CI, 0.87 to 1.52; P = 0.33).
LEADER CV Safety Trial with Liraglutide

- The most common adverse events leading to the discontinuation of liraglutide were gastrointestinal events. The incidence of pancreatitis was non-significantly lower in the liraglutide group (18 vs. 23) than in the placebo group.
  - Pancreatic carcinoma 13 (0.3) with liraglutide vs. 5 (0.1) with placebo p=0.06
  - Medullary thyroid carcinoma 0 with liraglutide vs. 1 (<0.1) with placebo p=0.32

Dulaglutide – Trulicity

- Available in 0.75-mg and 1.5-mg single-dose pens which do not require mixing, measuring or needle attachment and can be administered any time of day.
  - Insert states that for added comfort patients may want to take the pen out of the refrigerator for ~30 min prior to administration (DO NOT microwave or run under hot water)
- Box of 4 pens (either dose) ~$672.00 retail (GoodRx.com)
Dulaglutide – Trulicity

• The AWARD-6 study, once-weekly dulaglutide 1.5 mg achieved the primary endpoint of non-inferiority to once-daily liraglutide 1.8 mg, as measured by the reduction of hemoglobin A1c (HbA1c) from baseline at 26 weeks in 599 patients. (to date the only GLP-1 agonist to demonstrate non-inferiority to liraglutide to date)

Dulaglutide – Trulicity

• At the primary endpoint of 26 weeks, once-weekly dulaglutide 1.5 mg and once-daily liraglutide 1.8 mg significantly reduced HbA1c levels from baseline (-1.42 percent and -1.36 percent, respectively), with dulaglutide demonstrating non-inferiority compared to liraglutide. A similar majority of patients in both treatment groups (68 percent) reached the American Diabetes Association's recommended HbA1c target of less than 7 percent. Patients treated with once-weekly dulaglutide and once-daily liraglutide showed significant weight reductions from baseline (-2.9 kg, -3.6 kg, respectively). This weight reduction was statistically greater in the liraglutide treatment arm.  
  — The Lancet, Early Online Publication, 11 July 2014  
  doi:10.1016/S0140-6736(14)60976-4
Dulaglutide – Trulicity

• FDA Box Warning: (Same as for all members of the GLP-1 class of medications)
  – “Thyroid C-cell tumors have been observed in rodent studies with glucagon-like peptide-1 (GLP-1) receptor agonists at clinically relevant exposures. It is unknown whether Trulicity causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans.”
  – symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness).

• Additional Warnings and Precautions;
  – In clinical trials, acute pancreatitis has been reported in association with dulaglutide.
    • Consider other antidiabetic therapies in patients with a history of pancreatitis.

GLP-1 Agonists and Gallbladder Disease?

• Based upon a population based cohort study in more than 71,000 pts there was about a 2 fold increase in the risk of gallbladder disease and cholecystectomy limited to the first 180 days, A proposed plausible mechanism is related to the weight loss seen with this class of agents which has been shown to increase saturation of cholesterol in the bile a risk factor for this outcome. The lack of association after 180 days also might support this hypothesis and the lack of association with DPP-4's which do not cause weight loss is also supportive of the potential mechanism.
Xultophy (IDegLira) by Novo/Nordisk (combination of insulin degludec/Tresiba plus liraglutide/Victoza)

- Liraglutide - Victoza: 1.2 mg dose (2 pens/mo) $497.00
  GoodRx.com
- 1.8 mg dose (3 pens/mo) $743.00
  GoodRx.com
- Insulin Degludec- Tresiba U-100 FlexTouch - 3 mL 100 units/mL - 300 Units/pen – max dose 80 Units in 1 Unit increments – available 5 pens/pack ~$450.00
- ? Rumor that the combo price will be about 20% less than the two separately? ~ $1,000.00/mo

Converting to Xultophy 100/3.6 from liraglutide

- A 26-week randomized, open-label, treat-to-target (FPG goal of 72 to 90 mg/dL) trial in 348 patients not at goal on liraglutide and metformin alone or in combination with pioglitazone, sulfonylurea or both.
- The starting dose of Xultophy 100/3.6 was 16 units (16 units insulin degludec/0.58 mg liraglutide) and the average starting dose of liraglutide was 1.7 mg. Xultophy 100/3.6 was titrated twice weekly to target a fasting plasma glucose goal of <90 mg/dL. The end of trial dose of Xultophy was 44 units (44 units insulin degludec/1.58 mg liraglutide)
Converting to Xultophy 100/3.6 from liraglutide

• The primary endpoint, change in HbA1c, was tested for superiority of Xultophy 100/3.6 to unchanged liraglutide therapy.
• At the end of 26 weeks, there was a reduction in HbA1c from baseline of 1.31% for Xultophy 100/3.6 and 0.36% for liraglutide. A1c at baseline was 7.8% in both groups and 26 weeks was 6.4% with Xultophy and 7.4% with liraglutide.
• % of patients who achieved A1c less than 7.0% was 74.6% with Xultophy vs. 30.2% with liraglutide
  – FPG (mg/dl) baseline 161 and 169 mg/dl Xultrophy vs. liraglutide and at 26 weeks (LS Mean) 112 mg/dl vs. 153 mg/dl Xultophy vs. liraglutide

Converting to Xultophy 100/3.6 from basal insulin degludec

• A 26 week randomized double-blind, trial in 398 patients with type 2 diabetes mellitus inadequately controlled on basal insulin and metformin alone or in combination with sulfonylurea/glinides. Basal insulin and sulfonylurea/glinides were discontinued at randomization.
• The starting dose of Xultophy 100/3.6 and insulin degludec was 16 units (16 units insulin degludec/0.58 mg liraglutide) and 16 units, respectively. Patients could not increase their dose by more than 4 units per week and the prespecified maximum dose of insulin degludec was limited to 50 units
• The mean final dose of Xultophy 100/3.6 and insulin degludec was 46 units (the Xultophy group was also getting 1.66mg/day of liraglutide)
Converting to Xultophy 100/3.6 from basal insulin degludec

- At the end of 26 weeks, the reduction in HbA1c from baseline (8.7-8.8%) of 1.94% for Xultophy 100/3.6 and 1.05% for insulin degludec limited to 50 units daily were observed. The 26 week A1c (LS Mean) was 6.9% vs 7.7% with Xultophy vs insulin degludec.
- % of patients who achieved A1c less than 7.0% was 57.3% with Xultophy vs. 22.6% with insulin degludec.
- FPG (mg/dl) (LS Mean) went from 175 mg/dl at baseline to 110 mg/dl with Xultophy vs. 172 mg/dl at baseline to 118 mg/dl with insulin degludec

Converting to Xultophy 100/3.6 from basal insulin glargine

- A 26-week randomized, open-label, two-arm parallel trial in 557 patients with type 2 diabetes mellitus inadequately controlled on insulin glargine U-100 and metformin.
- Xultophy 100/3.6 and insulin glargine were to be titrated twice weekly to target a fasting plasma glucose goal of <90 mg/dL. The starting dose of Xultophy 100/3.6 was 16 units (16 units insulin degludec/0.58 mg liraglutide). The average starting dose of insulin glargine U-100 was 32 units. Patients could not increase the dose of the two products by more than 4 units per week and there was no maximum dose of insulin glargine.
- At 26 weeks the final dose of Xultophy was 41 units of insulin degludec and 1.48 mg of liraglutide and 66 units of insulin glargine
Converting to Xultophy 100/3.6 from basal insulin glargine

- After 26 weeks, treatment with Xultophy 100/3.6 resulted in a reduction in HbA1c from a baseline of 8.4% to 6.6% a difference of 1.67% and from a baseline of 8.2% to 7.1% a difference of 1.16% for insulin glargine U-100.
- % of patients achieving an A1c of less than 7.0% was 68.3% with Xultophy and 46.2% with insulin glargine.
- FBS (mg/dl) (LS Mean) was reduced from 161 at baseline to 110mg/dl with Xultophy and from 160 mg/dl to 110 mg/dl with insulin glargine.

Xultophy risk of severe hypoglycemia in controlled trials

- Severe hypoglycemia were defined as an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions’
- No clinically important differences in risk of severe hypoglycemia between Xultophy 100/3.6 and comparators were observed in clinical trials
Lixisenatide – Adlyxin by Sanofi

- FDA approved 7-27-2016 a once a day GLP-1 receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
  - Injection: 50 mcg/mL in 3 mL in green prefilled pen (for 14 pre-set doses; 10 mcg per dose)
  - Injection: 100 mcg/mL in 3 mL in burgundy prefilled pen (for 14 pre-set doses; 20 mcg per dose)
    - Cost: ~$600.00/ 2 pens (28 day supply)
  - Initiate at 10 mcg once daily for 14 days. On Day 15, increase dosage to 20 mcg once daily
    - Administer once daily within one hour before the first meal of the day

Lixisenatide – Adlyxin

Replace the cap to protect from light

You must activate the pen one time before the first use and not again or you will loose doses, the orange window should only appear prior to the first dose which is discarded and thereafter remain white

An insulin needle must be attached to deliver any dose including the discarded initial dose
Lixisenatide – Adlyxin

- Immunogenicity: In the pool of 9 placebo-controlled studies, **70% of patients exposed to lixisenatide tested positive for anti-lixisenatide antibodies during the trials.**
  - In the subset of patients (2.4%) with the highest antibody concentrations (>100 nmol/L), an attenuated glycemic response was observed.
  - A higher incidence of allergic reactions and injection site reactions occurred in antibody positive patients.
  - Allergic reactions (such as anaphylactic reaction, angioedema and urticaria) were observed in 0.4% of lixisenatide patients vs. 0.2% with placebo.

Lixisenatide vs. Liraglutide

- **26-week**, randomized, parallel-group, open-label trial, **404 patients were randomized 1:1 to liraglutide 1.8 mg or lixisenatide 20 µg as add-on to metformin.** Liraglutide was administered once daily at any time of the day. Lixisenatide was administered once daily within 1 h prior to the morning or evening meal.
  - Diabetes Care 2016 Sep; 39(9): 1501-1509.
Lixisenatide vs. Liraglutide

• At week 26, liraglutide reduced HbA1c (primary end point) more than lixisenatide (estimated treatment difference $-0.62\%$ [95% CI $-0.8$; $-0.4$]; $P < 0.0001$), with more patients reaching HbA1c <7% and ≤6.5% versus lixisenatide (74.2% and 54.6% for liraglutide vs. 45.5% and 26.2% for lixisenatide; $P < 0.0001$ for both).

• Both drugs promoted similar body weight decrease ($-4.3$ kg for liraglutide, $-3.7$ kg for lixisenatide; $P = 0.23$).

  — Diabetes Care 2016 Sep; 39(9): 1501-1509.

ELIXA – a cardiovascular safety outcomes trial of lixisenatide

• Lixisenatide (Adlyxin) was FDA approved 7/28/2016

• March 2015, Sanofi announced top-line results of the ELIXA outcome study, a Phase IIIb cardiovascular safety outcomes trial of lixisenatide (Adlyxin®) compared to placebo in 6,000 a high-risk (post ACS) population of adults with Type 2 diabetes for the evaluation of cardiovascular safety.

  — First CV safety trial for any of the GLP-1 Agonists to report out.

• The results from the study showed that lixisenatide was non-inferior, although not superior, to placebo for cardiovascular safety, and establish that there is no additional cardiovascular risk, in a high-risk patient, associated with treatment with lixisenatide, helping to support the existing consensus around the therapeutic benefits of lixisenatide.

  — Results presented at ADA in Boston on June 9, 2015
ELIXA: No Cardiovascular Risks or Benefits With Lixisenatide Vs Placebo

Primary composite endpoint: CV death, nonfatal MI, nonfatal stroke, hospitalization for UA

- Lixisenatide: 13.4%
- Placebo: 13.2%

HR=1.02
95% CI, 0.89-1.17

About ELIXA
- First events-driven CV outcomes study to provide data for a GLP-1 receptor agonist
- Randomized, double-blind, placebo-controlled trial
- N=6,068 subjects with type 2 diabetes and recent ACS event
- Randomization:
  - Lixisenatide 10 mcg/d*
  - Placebo

*Up or down-dilated to maximum 20 mcg/d

ELIXA=Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With Lixisenatide

Pfeffer MA, et al. Presented at the American Diabetes Association 75th Scientific Sessions, June 6-9, 2015, Boston, Massachusetts

ELIXA: Cardiovascular Outcomes for Lixisenatide Vs Placebo

No increased risk for lixisenatide vs placebo for:

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Lixisenatide</th>
<th>Placebo</th>
</tr>
</thead>
</table>
| Primary composite outcome: CV death, nonfatal MI, nonfatal stroke, hospitalization for UA | 13.4% | 13.2%
| HR=1.02 | (95% CI: 0.89-1.17) |
| Primary outcome plus hospitalization for heart failure | HR=0.97 (95% CI: 0.85-1.10) |
| Hospitalization for heart failure | HR=0.96 (95% CI: 0.75-1.23) |
| All-cause mortality | HR=0.94 (95% CI: 0.78-1.13) |
Soliqua™ 100/33 (insulin glargine & lixisenatide injection) 100 Units/mL & 33 mcg/mL

• Soliqua 100/33 will be delivered in a single pre-filled pen for once-daily dosing covering 15 to 60 Units of insulin glargine 100 Units/mL and 5 to 20 mcg of lixisenatide using SoloStar technology, Soliqua 100/33 will be available in U.S. retail pharmacies in January 2017.

Price ~$680.00/5 pens GoodRx.com 1-25-2017

Combination of Insulin Glargine Plus Lixisenatide in Type 2 Diabetes Inadequately Controlled on Basal Insulin and Metformin

• 736 basal insulin-treated patients (mean diabetes duration 12 years, BMI 31 kg/m2) were randomized 1:1 to open-label, once-daily iGlarLixi or iGlar, both titrated to fasting plasma glucose <100 mg/dL up to a maximum dose of 60 units/day. The primary outcome was change in HbA1c levels at 30 weeks.
• HbA1c decreased from 8.5% to 8.1% during the run-in period. After randomization, iGlarLixi showed greater reductions in HbA1c from baseline compared with iGlar (−1.1% vs. −0.6%, P < 0.0001), reaching a mean final HbA1c of 6.9 compared with 7.5% for iGlar.
• HbA1c <7.0% was achieved in 55% of iGlarLixi patients compared with 30% on iGlar.
• Mean body weight decreased by 0.7 kg with iGlarLixi and increased by 0.7 kg with iGlar (1.4 kg difference, P < 0.0001).
• Documented symptomatic hypoglycemia (≤70 mg/dL) was comparable between groups. Mild gastrointestinal adverse effects were very low but more frequent with iGlarLixi.

Soliqua™ 100/33 (insulin glargine & lixisenatide injection) 100 Units/mL & 33 mcg/mL

Dosage and Administration:
• Discontinue therapy with lixisenatide or basal insulin prior to initiation of Soliqua 100/33.
• In patients inadequately controlled on less than 30 units of basal insulin or on lixisenatide, the starting dosage is 15 units (15 units insulin glargine/5 mcg lixisenatide) given subcutaneously once daily.
• In patients inadequately controlled on 30 to 60 units of basal insulin, the starting dosage is 30 units (30 units insulin glargine/10 mcg lixisenatide) given subcutaneously once daily.
• Inject once a day within the hour prior to the first meal of the day.
• Maximum daily dosage is 60 units (60 units of insulin glargine and 20 mcg of lixisenatide).
• Soliqua 100/33 Pen delivers doses from 15 to 60 units with each injection.

Soliqua™ 100/33 (insulin glargine & lixisenatide injection) 100 Units/mL & 33 mcg/mL

• Soliqua 100/33 will be delivered in a single pre-filled pen for once-daily dosing covering 15 to 60 Units of insulin glargine 100 Units/mL and 5 to 20 mcg of lixisenatide using SoloStar technology, Soliqua 100/33 will be available in U.S. retail pharmacies in January 2017.
## TECOS Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Sitagliptin (n=7382)</th>
<th>Placebo (n=7339)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Outcome</td>
<td>11.4%</td>
<td>11.6%</td>
<td>0.98 (0.89-1.08)</td>
</tr>
<tr>
<td>CV Death, non-fatal MI, non-fatal CVA</td>
<td>10.2%</td>
<td>10.2%</td>
<td>0.99 (0.89-1.10)</td>
</tr>
<tr>
<td>CV Death</td>
<td>5.2%</td>
<td>5.0%</td>
<td>1.03 (0.89-1.19)</td>
</tr>
<tr>
<td>Hospitalization unstable angina</td>
<td>1.6%</td>
<td>1.8%</td>
<td>0.90 (0.70-1.16)</td>
</tr>
<tr>
<td>Fatal or non-fatal MI</td>
<td>4.1%</td>
<td>4.3%</td>
<td>0.95 (0.81-1.11)</td>
</tr>
<tr>
<td>Fatal or non-fatal CVA</td>
<td>2.4%</td>
<td>2.5%</td>
<td>0.97 (0.79-1.19)</td>
</tr>
<tr>
<td>Hospitalization for HF</td>
<td>3.1%</td>
<td>3.1%</td>
<td>1.00 (0.83-1.20)</td>
</tr>
<tr>
<td>Hospitalization for HF or CV Death</td>
<td>7.3%</td>
<td>7.2%</td>
<td>1.02 (0.90-1.15)</td>
</tr>
</tbody>
</table>

NEJM: on-line June 8, 2015

## FDA Safety Alert: DPP-4 Inhibitors and Potential for Severe Joint Pain

- **8-28-15** FDA is warning that the type 2 diabetes medicines sitagliptin, saxagliptin, linagliptin, and alogliptin may cause joint pain that can be severe and disabling.
- The FDA found 33 patients and all experienced arthralgia that resulted in a substantial reduction in their prior level of activity, including 10 patients who were hospitalized due to disabling joint pain.
FDA Safety Alert: DPP-4 Inhibitors and Potential for Severe Joint Pain

- In 22 cases, symptoms appeared within 1 month of initiation of treatment with a DPP-4 inhibitor. In 20 of the 33 cases, the DPP-4 inhibitor was suspected as a possible cause of arthralgia and was discontinued within a month following the onset of symptoms. However, 8 of the remaining 13 cases reported a period of 44 days to 1 year between the onset of symptoms and discontinuation of the DPP-4 inhibitor. In 23 of the 33 cases, symptoms resolved less than 1 month after discontinuation of the drug.
  - eight of the 33 cases documented a positive rechallenge with the same or other drug in the class

FDA Safety Alert: DPP-4 Inhibitors and Potential for Severe Joint Pain

- Ten of the 33 cases reported fever and chills, rash, and swelling, which are suggestive of an immunological reaction. Of the 13 cases with available results of laboratory assays for systemic autoimmune disorders, 8 reported a negative or normal test result. Five cases reported positive test results: antinuclear antibody (n=2), erythrocyte sedimentation rate (n=1), C-reactive protein (n=1), and antinuclear cytoplasmic antibody (n=1). However, none of these tests are specific for a particular autoimmune condition that can cause severe joint pain.
Canagliflozin vs. Dapagliflozin: results of a randomized, double-blind, crossover study
(Diabetes, Obesity and Metabolism 2015; 17: 188-97)

- Canagliflozin 300 mg and dapagliflozin 10 mg had similar effects on UGE and RTG for 4 h after dosing, but canagliflozin was associated with higher UGE and greater RTG reductions for the remainder of the day. Mean 24-h UGE was ~25% higher with canagliflozin than with dapagliflozin (51.4 vs. 40.8 g),

- Conclusions: In healthy participants, canagliflozin 300 mg provided greater 24-h UGE, a lower RTG and smaller PPG excursions than dapagliflozin 10 mg.

Empagliflozin – Jardiance by Boehringer Ingelheim and Lilly

- August 1, 2014 FDA approved sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

- The FDA is requiring four post marketing studies:
  - Completion of an ongoing 7,000 pt. cardiovascular outcomes trial (EMPA-REG Outcome Trial)
  - A pediatric pharmacokinetic/pharmacodynamic study.
  - A pediatric safety and efficacy study. As part of the safety and efficacy study, the effect on bone health and development will be evaluated.
  - A nonclinical (animal) juvenile toxicity study with a particular focus on renal development, bone development, and growth.
Empagliflozin – Jardiance

- EMPA-REG OUTCOME was a multicenter, randomized, double-blind, placebo-controlled trial in more than 7,000 individuals from 42 countries for a median duration of 3.1 years. The study evaluated the effect of empagliflozin (10mg or 25mg once daily) added to standard of care compared with placebo added to standard of care on CV events in adults with T2D at high risk of CV events and with less than optimized blood glucose control. The study was designed to first test for non-inferiority and then for superiority.
  - Standard of care was comprised of glucose lowering agents and cardiovascular drugs (including antihypertensive and lipid lowering agents).

EMPA-REG OUTCOME Trial

- The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke occurred in 490 of 4687 patients (10.5%) in the pooled empagliflozin group and in 282 of 2333 patients (12.1%) in the placebo group (hazard ratio in the empagliflozin group, 0.86; 95.02% confidence interval, 0.74 to 0.99; P=0.04 for superiority).
  - ARR = 1.6%, NNT 63
  - No significant differences in rates of MI or CVA
  - No significant difference with 10 vs. 25 mg doses.
  - Death from cardiovascular causes (3.7%, vs. 5.9% in the placebo group; 38% relative risk reduction; ARR = 2.2%, NNT 46

- NEJM on-line 9-17-2015
**EMPA-REG OUTCOME Trial**

- Hospitalization for heart failure (2.7% and 4.1%, respectively; 35% relative risk reduction)
- Death from any cause (5.7% and 8.3%, respectively; 32% relative risk reduction).
- Among patients receiving empagliflozin, there was an increased rate of genital infection (1 in 20 or 5%) but no increase in other adverse events.
  -- NEJM on-line 9-17-2015

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**EMPA-REG OUTCOME Trial**

- Unanswered questions:
  -- What might explain the CV benefit seen in this short term trial when it has not been seen previously and both groups of patients were treated with evidence-based therapies to reduce CV risk (IE statins, RAST blockers, BB and aspirin)?
  - Hypothesis? Dr. Gerstein, McMaster University. speculates that the strikingly early separation of the event curves suggests that the effect of the study drug was likely not mediated through glucose or blood pressure. Instead, he felt that the osmotic diuretic aspect to this agent may have resulted in a better hemodynamic status, perhaps treating early heart failure or preventing heart failure.
  -- Yale CME 2015 EASD Newsletter - Issue three
EMPA-REG OUTCOME Trial

• The proportions of patients with confirmed hypoglycemic adverse events, acute renal failure, diabetic ketoacidosis, thromboembolic events, bone fracture, and events consistent with volume depletion were similar in the two study groups. Urosepsis was reported in 0.4% of patients in the empagliflozin group and 0.1% of those in the placebo group, but there was no imbalance in overall rates of urinary tract infection, complicated urinary tract infection, or pyelonephritis.

• About 25% of empagliflozin treated patients discontinued therapy during the trial.

— NEJM on-line 9-17-2015

Empagliflozin – Jardiance

• December 2, 2016 the FDA approved a new indication for Jardiance (empagliflozin) to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and cardiovascular disease.
EMPA-REG OUTCOME Trial: Renal Data

- 7020 patients with type 2 diabetes with a history of CV disease and an estimated glomerular filtration rate of at least 30 ml per minute per 1.73 m² of body-surface area were assigned to receive either empagliflozin (at a dose of 10 mg or 25 mg) or placebo once daily. Prespecified renal outcomes included incident or worsening nephropathy (progression to macroalbuminuria, doubling of the serum creatinine level, initiation of renal-replacement therapy, or death from renal disease) and incident albuminuria.
  – NEJM on-line June 14, 2016 and presented at ADA Meeting

EMPA-REG OUTCOME Trial: Renal Data

Microvascular Outcome

- The prespecified composite microvascular outcome in the overall trial population occurred in 577 of 4132 patients (14.0%) in the empagliflozin group and in 424 of 2068 patients (20.5%) in the placebo group, a significant RRR 38% ARR 6.5%, NNT=16
  – the overall result for this composite microvascular outcome was driven entirely by the renal component NEJM on-line June 14, 2016
EMPA-REG OUTCOME Trial: Renal Data

- The benefit was primarily driven by the reduction in progression to macroalbuminuria, which occurred in 459 of 4091 patients taking empagliflozin compared with 330 of 2033 patients on placebo (11.2% vs 16.2%; HR, 0.62; P < .001). ARR 5.0%, NNT =20

- A doubling of the serum creatinine level occurred in 70 of 4645 patients (1.5%) in the empagliflozin group and in 60 of 2323 (2.6%) in the placebo group, a significant RRR 44%, ARR 1.1%, NNT=91

- Kidney dialysis was also reduced by 55% among those taking empagliflozin, although the absolute numbers affected were small 0.3% vs. 0.6% (HR, 0.45; P = .0409). NEJM on-line June 14, 2016

EMPA-REG OUTCOME Trial: Renal Data

- There were three deaths from renal disease in the empagliflozin group (0.1%) and none in the placebo group.

- There was no significant between-group difference in the rate of incident albuminuria, which occurred in 1430 of 2779 patients (51.5%) in the empagliflozin group and in 703 of 1374 (51.2%) in the placebo group.

  — NEJM on-line June 14, 2016
FDA Drug Safety Update – 6-14-2016

• FDA has strengthened the existing warning about the risk of acute kidney injury for the type 2 diabetes medicines canagliflozin (Invokana, Invokamet) and dapagliflozin (Farxiga, Xigduo XR).
  – from March 29, 2013, to October 19, 2015, the FDA identified 101 cases of acute kidney injury with sufficient detail to confirm the diagnosis and demonstrate a temporal relationship with canagliflozin (73 patients) and dapagliflozin (28 patients). Hospitalization for evaluation and management of acute kidney injury was necessary in 96 of the 101 cases, 22 were admitted to the ICU. The time to onset of acute kidney injury occurred within one month or less of initiating the drug.

FDA Drug Safety Update – 6-14-2016

• In the 78 cases reporting drug discontinuation, 56 cases reported improvement, demonstrating reversibility of this adverse event in a majority of cases.
• 15 patients received dialysis
• 11 patients did not recover, which included the 4 deaths (2 were cardiac related).
Empagliflozin – Jardiance

- In patients with type 2 diabetes, **urinary glucose excretion increased** immediately following a dose of empagliflozin and was maintained at the end of a 4-week treatment period averaging at approximately 64 grams per day with 10 mg empagliflozin and 78 grams per day with 25 mg once daily.

- In a 5-day study, **mean 24-hour urine volume increase from baseline was 341 mL on day 1 and 135 mL on day 5 of empagliflozin 25 mg once daily treatment.**

### Empagliflozin– Jardiance

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Empagliflozin</th>
<th>N</th>
<th>A1C (%)</th>
<th>FPG (mg/dl)</th>
<th>Weight (Kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy</td>
<td>10mg</td>
<td>224</td>
<td>-0.7</td>
<td>-31</td>
<td>-2.5</td>
</tr>
<tr>
<td></td>
<td>25mg</td>
<td>224</td>
<td>-0.7</td>
<td>-36</td>
<td>-2.8</td>
</tr>
<tr>
<td>Add to metformin</td>
<td>10mg</td>
<td>217</td>
<td>-0.6</td>
<td>-26</td>
<td>-2.5</td>
</tr>
<tr>
<td></td>
<td>25mg</td>
<td>213</td>
<td>-0.6</td>
<td>-29</td>
<td>-2.9</td>
</tr>
<tr>
<td>Add to metformin and glimepiride</td>
<td>10mg</td>
<td>225</td>
<td>-0.6</td>
<td>-29</td>
<td>-2.9</td>
</tr>
<tr>
<td></td>
<td>25mg</td>
<td>216</td>
<td>-0.6</td>
<td>-29</td>
<td>-3.2</td>
</tr>
<tr>
<td>Add to pioglitazone</td>
<td>10mg</td>
<td>165</td>
<td>-0.5</td>
<td>-23</td>
<td>-2.6</td>
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<tr>
<td></td>
<td>25mg</td>
<td>168</td>
<td>-0.6</td>
<td>-28</td>
<td>-2.4</td>
</tr>
<tr>
<td>Add to insulin (78wks)</td>
<td>10mg</td>
<td>169</td>
<td>-0.5</td>
<td>-12.9</td>
<td>-3.0</td>
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<tr>
<td></td>
<td>25mg</td>
<td>155</td>
<td>-0.7</td>
<td>-17.9</td>
<td>-3.0</td>
</tr>
</tbody>
</table>
## Empagliflozin– Jardiance

### Adverse Effects from Controlled Trials

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo N=995</th>
<th>Empagliflozin 10 mg N=999</th>
<th>Empagliflozin 25 mg N=977</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract infection</td>
<td>7.6%</td>
<td>9.3%</td>
<td>7.6%</td>
</tr>
<tr>
<td>Female genital mycotic infections (N= 420-481)</td>
<td>1.5%</td>
<td>5.4%</td>
<td>6.1%</td>
</tr>
<tr>
<td>Upper respiratory tract infections</td>
<td>3.8%</td>
<td>3.1%</td>
<td>4.0%</td>
</tr>
<tr>
<td>Increased urination</td>
<td>1.0%</td>
<td>3.4%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>3.4%</td>
<td>3.9%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2.2%</td>
<td>2.4%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Male genital mycotic infections (N=514-557)</td>
<td>0.4%</td>
<td>3.1%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.4%</td>
<td>2.3%</td>
<td>1.1%</td>
</tr>
</tbody>
</table>

## Empagliflozin– Jardiance

### Renal Effects:

- Empagliflozin may increase serum creatinine and decrease eGFR (the risk of impaired renal function is increased in elderly patients and patients with moderate renal impairment).

- The glucose lowering benefit of 25 mg decreased in patients with worsening renal function. The risks of renal impairment, volume depletion adverse reactions and urinary tract infection-related adverse reactions increased with worsening renal function.
Empagliflozin – Jardiance

- The recommended dose is 10 mg once daily in the morning, taken with or without food. In patients tolerating empagliflozin, the dose may be increased to 25 mg.
  - In patients with volume depletion, correcting this condition prior to initiation of empagliflozin is recommended.
  - Empagliflozin should not be initiated in patients with an eGFR less than 45 mL/min/1.73 m2 and should be discontinued if eGFR is persistently less than 45 mL/min/1.73 m2.
  - Cost ~ $464.00/30 tabs both strengths GoodRx.com

Empagliflozin/Linagliptin-Glyxambi (Boehringer Ingelheim/Eli Lilly)

- 2-2-2015 the FDA approved the empagliflozin/linagliptin combination Glyxambi (Boehringer Ingelheim/Eli Lilly) as adjunctive treatment to diet and exercise for adults with type 2 diabetes.
- The once-daily tablet is the first in the US to combine a sodium glucose cotransporter 2 (SGLT2) inhibitor (empagliflozin) with a dipeptidyl peptidase-4 (DPP-4) inhibitor (linagliptin). The tablets contain 10 or 25 mg of empagliflozin and 5 mg of linagliptin.
  - Cost: $563.00/30 GoodRx.com
Empagliflozin/Linagliptin-Glyxambi

• The Phase III trial enrolled 686 adults with type 2 diabetes who had baseline hemoglobin A1c (HbA1c) levels between 7.0% and 10.5% despite taking high-dose metformin (mean daily dose 1889 mg).
  – Results at 24 weeks, those receiving empagliflozin/linagliptin achieved mean HbA1c levels of 6.9% with the 10/5 mg dose and 6.7% with the 25/5 mg dose, compared with 7.3% and 7.4% with empagliflozin 10 and 25 mg, respectively, and 7.3% with linagliptin 5 mg. (difference of 0.4 to 0.7%)
  • Diabetes Care 1-12-2015 on-line

Empaglifozin/Metformin – Synjardy by BI/Lilly

• 8-31-2015 the FDA has approved a new combination of empagliflozin and metformin for the treatment for patients with Type 2 DM.
• Available in 5/500 mg; 5/1000 mg as well as 12.5/500 mg and 12.5/1000 mg tabs for twice a day dosing.
• Cost: $464.00/60 tabs GoodRx.com
Empagliflozin/Metformin – Synjardy

• In a 24 week trial in 637 patients on metformin at least 1500 mg/day randomized to empagliflozin 10 or 25 mg/day vs. placebo, the reductions in A1c placebo subtracted were -0.6 with both doses with a mean baseline A1c of 7.9% as well as a reduction in FPG of 26 and 29 mg/dl. The weight loss was -2.0 Kg and -2.5 Kg with the two doses of empagliflozin vs. metformin plus placebo. Systolic BP was also reduced by – 4.1 mmHg and – 4.8 mmHg vs. metformin plus placebo.

SGLT-2 Inhibitors and Bone Fractures?

• In a study in people with moderate renal impairment, 9.4% (8/85) of patients treated with 10 mg and 6.0% (5/83) of patients treated with 5 mg dapagliflozin had bone fractures over 104 weeks of follow-up, whereas no fractures were reported in patients receiving placebo.

• A pooled analysis of 8 trials with canagliflozin with a mean duration of 68 weeks suggested an ~ 30% increase in fractures

– The Lancet Diabetes and Endocrinology 2015; 3:8-10
SGLT-2 Inhibitors and Bone Fractures?

• It has also been reported that 300 mg of canagliflozin reduced bone mineral density in both the total hip and lumbar spine.

• SGLT-2 inhibitors increase serum phosphate levels and may also increase serum PTH levels (7-9%) but up to 50% in a significant number of patients. 1-25 dihydroxyvitamin D levels are also decreased by about 12% in patients on canagliflozin. The mechanism is not well established but it does require further study.

  – The Lancet Diabetes and Endocrinology 2015; 3:8-10

FDA Safety Announcement

• [5-15-2015] The FDA is warning that the SGLT-2 inhibitors: canagliflozin, dapagliflozin, and empagliflozin may lead to ketoacidosis, a serious condition where the body produces high levels of blood acids called ketones that may require hospitalization.

• Patients should pay close attention for any signs of ketoacidosis and seek medical attention immediately if they experience symptoms such as difficulty breathing, nausea, vomiting, abdominal pain, confusion, and unusual fatigue or sleepiness.
FDA Safety Announcement

• From March 2013 (approval of the first drug in the class) through June 6, 2014, and identified 20 cases of diabetic ketoacidosis (DKA), ketoacidosis, or ketosis were reported.
  – The median time to onset of symptoms following initiation of drug therapy was 2 weeks (range 1 to 175 days). DKA case presentations were atypical in that glucose levels were only mildly elevated at less than 200 mg/dL in some reports.
  – The FDA is continuing to investigate this safety issue.

Canagliflozin in Type 1 Diabetes

• 18-week, randomized, double-blind, phase 2 study, Type 1 patients (N = 351; HbA1c 7.0–9.0%) on multiple daily insulin injections or continuous subcutaneous insulin infusion received canagliflozin 100 or 300 mg or placebo once daily.
  • At week 18, the incidence of any ketone-related AE with canagliflozin 100 and 300 mg was 5.1% (n = 6 of 117) and 9.4% (n = 11 of 117), respectively; no patients in the placebo group experienced a ketone-related AE. The incidence of serious AEs of DKA was 4.3% (n = 5 of 117) with canagliflozin 100 mg and 6.0% (n = 7 of 117) with canagliflozin 300 mg
SGLT-2 Inhibitors and Amputations?

• 4-15-2016 The European Medicines Agency (EMA) has begun a review of the sodium glucose cotransporter 2 (SGLT2) inhibitor canagliflozin (Invokana, Janssen), used to treat type 2 diabetes, after an increase in amputations, mostly of the toe, was observed in a large ongoing clinical trial of the drug.

• Cases of lower-limb amputation occurred in both the active drug and placebo groups in the Canagliflozin Cardiovascular Assessment Study (CANVAS), which is the cardiovascular-outcomes trial for this agent and is randomizing just over 4000 type 2 diabetes patients to canagliflozin 100 mg or 300 mg daily or to placebo, slated for completion in 2017.

SGLT-2 Inhibitors and Amputations?

• The incidence of lower-limb amputation in CANVAS is currently seven in 1000 patient-years with canagliflozin 100 mg daily and five in 1000 patient-years with canagliflozin 300 mg daily, compared with three in 1000 patient-years with placebo, EMA indicates. Patients in the study have so far been followed up for an average of 4.5 years.

• In CANVAS-R, a study on the effects of canagliflozin on renal end points in adults with type 2 diabetes, the incidence of lower-limb amputation is seven in 1000 patient-years with canagliflozin and five in 1000 patient-years with placebo. This difference is not statistically significant. Patients in this study have so far been followed up for an average of 0.75 years.
SGLT-2 Inhibitors and Amputations?

• The independent data monitoring committee for CANVAS and CANVAS-R has recommended that the trials should continue.

• The Pharmacovigilance Risk Assessment Committee (PRAC) will also ask for data on other medicines in the SGLT2 inhibitor class, which include dapagliflozin (Farxiga, AstraZeneca) and empagliflozin (Jardiance, Lilly/Boehringer Ingelheim).

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STENO Type 2 DM Trial

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Intensive</th>
<th>Standard</th>
<th>RRR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephropathy</td>
<td>11%</td>
<td>25%</td>
<td>56%</td>
<td>7</td>
</tr>
<tr>
<td>Retinopathy progression</td>
<td>26%</td>
<td>43%</td>
<td>49%</td>
<td>6</td>
</tr>
<tr>
<td>Blindness in 1 eye</td>
<td>1%</td>
<td>9%</td>
<td>85%</td>
<td>13</td>
</tr>
<tr>
<td>Progression of autonomic neuropathy</td>
<td>11%</td>
<td>29%</td>
<td>62%</td>
<td>6</td>
</tr>
<tr>
<td>Combined death and macrovascular events</td>
<td>34%</td>
<td>54%</td>
<td>37%</td>
<td>5</td>
</tr>
</tbody>
</table>
STENO 2 Trial after 21 Years

• The original intervention (mean treatment duration 7.8 years) involved 160 patients with type 2 diabetes and microalbuminuria who were randomly assigned (using sealed envelopes) to receive either conventional therapy or intensified, multifactorial treatment including both behavioral and pharmacological approaches.

• After 7.8 years the study continued as an observational follow-up with all patients receiving treatment as for the original intensive-therapy group.

  – Diabetologia 2016 DOI 10.1007/s00125-016-4065-6
STENO 2 Trial after 21 Years

• The primary endpoint of this follow-up 21.2 years after intervention start was difference in median survival time between the original treatment groups with and without incident cardiovascular disease.

• The patients in the intensive therapy group survived for a median of 7.9 years longer than the conventional-therapy group patients. Median time before first cardiovascular event after randomization was 8.1 years longer in the intensive-therapy group (p= 0.001).

• The hazard for all microvascular complications was decreased in the intensive-therapy group in the range 0.52 to 0.67, except for peripheral neuropathy (HR 1.12).

  — Diabetologia 2016 DOI 10.1007/s00125-016-4065-6

G5 Mobile Continuous Glucose Monitoring System by Dexcom

• December 20, 2016: The U.S. Food and Drug Administration today expanded the approved use of Dexcom’s G5 Mobile Continuous Glucose Monitoring System to allow for replacement of fingerstick blood glucose (sugar) testing for diabetes treatment decisions in people 2 years of age and older with diabetes. This is the first FDA-approved continuous glucose monitoring system that can be used to make diabetes treatment decisions without confirmation with a traditional fingerstick test. The system was previously approved to complement, not replace, fingerstick testing for diabetes treatment decisions.

  — FDA News Release 12-20-2016
G5 Mobile Continuous Glucose Monitoring System

• The G5 Mobile Continuous Glucose Monitoring System uses a small sensor wire inserted just below the skin that continuously measures and monitors glucose levels. Real-time results are sent wirelessly every five minutes to a dedicated receiver and a compatible mobile device (e.g., smart phone or tablet) running a mobile app. Alarms and alerts indicate glucose levels above or below user-set thresholds. The system measures glucose in fluid under the skin and must be calibrated at least two times per day using blood obtained from fingerstick tests.
• Users are warned that the system must be calibrated using a fingerstick blood sample at least once every 12 hours and that taking any medications containing acetaminophen while wearing the system may falsely raise glucose readings.
   — FDA News Release 12-20-2016

G5 Mobile Continuous Glucose Monitoring System

Consists of 3 parts:
• Small Sensor That Measures Glucose Levels Just Underneath The Skin.
• Transmitter That Is Fastened On Top Of The Sensor And Sends Data Wirelessly To Your Compatible Smart Device Or Your Receiver.
• A Display Device Which Can Be A Compatible Smart Device With The Dexcom G5® Mobile App Or The Dexcom G5® Mobile Receiver.
• Cost is about $1,200.00 and sensors which are good for up to 7 days cost ~$300.00/4 sensors
G5 Mobile Continuous Glucose Monitoring System

Sensor

Sensor Inserting Device