ORAL AND INJECTABLE (NON-INSULIN) PHARMACOLOGICAL AGENTS FOR TYPE 2 DIABETES

Joseph L. Evans, Ph.D., President, P & N Development Ventures, Saint Louis, MO USA
Email: jevansphd@earthlink.net

Börk Balkan, Ph.D., President, Baphyco, Madison, CT USA
Email: bork.balkan@gmail.com

Eunice Chuang, MD, Endocrinology Fellow, Department of Medicine, Division of Endocrinology & Metabolism, University of California San Francisco, San Francisco, CA USA
Email: eunice.chuang@ucsf.edu

Robert J. Rushakoff, M.D., Clinical Professor of Medicine, Department of Medicine, Medical Director for Inpatient Diabetes, Division of Endocrinology & Metabolism, University of California San Francisco, San Francisco, CA USA Email: robert.rushakoff@ucsf.edu

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ABSTRACT
Diabetes has reached epidemic proportions throughout the world and will continue to grow and remain the greatest global health challenge the world has ever known: 415 million people have diabetes (1 in 11 adults), and the number of people with the disease is predicted to rise beyond 642 million (55%; 1 in 10 adults) in less than 25 years. Individuals with type 1 and type 2 diabetes are at a significantly greater risk for developing microvascular and macrovascular diseases. In response to the enormity of the growing problem, efforts to identify and develop new pharmacological agents for type 2 diabetes have increased dramatically over the past 25 years. Currently in the US and most other world areas, there are nine classes of orally available pharmacological agents to treat type 2 diabetes: 1) sulfonylureas, 2) meglitinides, 3) metformin (a biguanide), 4) thiazolidinediones, 5) α-glucosidase inhibitors, 6) dipeptidyl peptidase IV (DPP-IV) inhibitors, 7) bile acid sequestrant, 8) dopamine agonist, and 9) sodium-glucose transport protein (SGLT2) inhibitors. A variety of fixed combination of 2 agents are also available. Besides the many options for insulin, there are also two classes of injectable medications: glucagon like peptide-1 (GLP-1) receptor agonists (incretin mimetics) and an amylin analogue. This chapter provides an overview and description of the existing oral and injectable (non-insulin) pharmacological agents for type 2 diabetes along with an up-to-date listing of those
agents currently in early and late-stage clinical development.

INTRODUCTION

Diabetes has reached epidemic proportions throughout the world and will continue to grow and remain the greatest global health challenge the world has ever known: 415 million people have diabetes (1 in 11 adults), and the number of people with the disease is predicted to rise beyond 642 million (55%; 1 in 10 adults) in less than 25 years ([http://www.diabetesatlas.org/resources/2015-atlas.html](http://www.diabetesatlas.org/resources/2015-atlas.html))(1-4). Approximately 90% of all individuals afflicted have type 2 diabetes, and about 1 in 2 remain undiagnosed. As shown in Figure 1, no world area is immune to this deadly disease. In absolute numbers, the greatest increase in individuals with diabetes will be seen in the Southeast Asia region (61.9 million), followed closely by the Western Pacific region (61.6 million)(Table 1)(1;2;5). In terms of percentage increase, diabetes in sub-Saharan Africa will increase a staggering 141%, while North Africa and the Middle East will experience a 104% increase. The countries with the most citizens affected is shown in Table 2; it should be obvious that many countries most seriously impacted are inadequately equipped, on many fronts, to wage this war. A particularly striking example of this unfortunate situation is India, a society that is transitioning from undernutrition to relative nutritional abundance. As this occurs in the context of decreased physical activity, the growing urbanization of its residents, and predicted aging population, the incidence of diabetes will continue to rise. Although diabetes in India is currently confined, mainly, to the more affluent sectors of society, the disease has begun to develop in the lower socioeconomic strata, which carries serious health and economic consequences (6).

The economic burden of diabetes is estimated to be about 12% of global healthcare expenditures, corresponding to about $800 billion. Drivers of this pandemic include increased global obesity which, in turn, is driven by increased standards of living, increased availability, affordability, and consumption of non-nutritive foods, and mass urbanization of the global population, in the context of an overall decrease in per capita physical activity (7;8).

Individuals with type 1 and type 2 diabetes are at a significantly greater risk for developing microvascular and macrovascular diseases. Those diabetics who cannot maintain adequate glycemic control (such as the failure to reach the recommended target level of HbA1c < 7%) are pre-disposed to develop neuropathy, retinopathy, nephropathy, cardiovascular disease, cerebrovascular disease, and premature death (9). Deaths from diabetes-associated complications (5 million) account for more deaths than combined deaths attributed to HIV/AIDS (1.5 million), tuberculosis (1.5 million), and malaria (0.6 million)(1). In response to the enormity of this medical catastrophe, there have been major initiatives on the part of global health organizations, national diabetes associations, and primary
caregivers to educate patients about the benefits of appropriate nutrition and physical activity (9). Since dietary modification and increased physical activity provide insufficient glucose control over the long-term course of the disease, many (most) individuals will require some type of medication for glycemic control and ultimately address their complication(s) (10). The purpose of this chapter is to provide to the healthcare practitioner an overview of the existing oral and injectable (non-insulin) pharmacological options indicated for type 2 diabetes. In addition, this chapter provides a comprehensive update of the most promising therapeutic options for type 2 diabetes that are in clinical or pre-clinical development.

![Figure 1. Estimated number of adults (20-79 years of age) with diabetes worldwide and per world area in 2015 and 2040 (projected). Source (with permission): International Diabetes Federation. *IDF Diabetes Atlas, 7th edition.* Brussels, Belgium: International Diabetes Federation, 2015; http://www.diabetesatlas.org (1).](image-url)
Table 1. Projected Increases 2015-2040 in Adults with Diabetes in Different World Areas

<table>
<thead>
<tr>
<th>World Area</th>
<th>Projected Increase in Individuals (20-79 years) with Diabetes, 2015-2040 (millions)</th>
<th>% Increase in Individuals (20-79 years) with Diabetes, 2015-2040</th>
</tr>
</thead>
<tbody>
<tr>
<td>South East Asia</td>
<td>61.9</td>
<td>79.1</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>61.6</td>
<td>40.2</td>
</tr>
<tr>
<td>Middle East and North Africa</td>
<td>36.7</td>
<td>103.7</td>
</tr>
<tr>
<td>Africa</td>
<td>20.0</td>
<td>140.9</td>
</tr>
<tr>
<td>South America and Central America</td>
<td>19.2</td>
<td>64.9</td>
</tr>
<tr>
<td>North America and Caribbean</td>
<td>16.2</td>
<td>36.6</td>
</tr>
<tr>
<td>Europe</td>
<td>11.3</td>
<td>18.9</td>
</tr>
</tbody>
</table>


Table 2. Top Ten Countries for Number of Adults with Diabetes, 2015-2040

<table>
<thead>
<tr>
<th>Rank</th>
<th>Country</th>
<th>Number of People with Diabetes, 2015</th>
<th>Country</th>
<th>Number of People with Diabetes (Projected), 2040</th>
<th>% Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>China</td>
<td>109.6</td>
<td>China</td>
<td>150.7</td>
<td>37.5</td>
</tr>
<tr>
<td>2</td>
<td>India</td>
<td>69.2</td>
<td>India</td>
<td>123.5</td>
<td>78.5</td>
</tr>
<tr>
<td>3</td>
<td>United States</td>
<td>29.3</td>
<td>United States</td>
<td>35.1</td>
<td>19.8</td>
</tr>
<tr>
<td>4</td>
<td>Brazil</td>
<td>14.3</td>
<td>Brazil</td>
<td>23.3</td>
<td>62.9</td>
</tr>
<tr>
<td>5</td>
<td>Russia</td>
<td>12.1</td>
<td>Mexico</td>
<td>20.6</td>
<td>79.1</td>
</tr>
<tr>
<td>6</td>
<td>Mexico</td>
<td>11.5</td>
<td>Indonesia</td>
<td>16.2</td>
<td>62.0</td>
</tr>
<tr>
<td>7</td>
<td>Indonesia</td>
<td>10.0</td>
<td>Egypt</td>
<td>15.1</td>
<td>93.6</td>
</tr>
<tr>
<td>8</td>
<td>Egypt</td>
<td>7.8</td>
<td>Pakistan</td>
<td>14.4</td>
<td>105.7</td>
</tr>
<tr>
<td>9</td>
<td>Japan</td>
<td>7.2</td>
<td>Bangladesh</td>
<td>13.6</td>
<td>91.6</td>
</tr>
<tr>
<td>10</td>
<td>Bangladesh</td>
<td>7.1</td>
<td>Russia</td>
<td>12.4</td>
<td>2.5</td>
</tr>
</tbody>
</table>
OVERVIEW OF INTERVENTIONS FOR TYPE 2 DIABETES

In response to the enormity of the growing problem, efforts to identify and develop new pharmacological agents for type 2 diabetes have increased dramatically over the past 25 years (11-13). These efforts have resulted in the successful introduction of new treatment options, and additional new therapies will likely gain regulatory approval in the US, Canada, European Union, Japan, and other global regions in the near future (see Emerging Treatments section below). Currently, there are nine classes of orally available pharmacological agents to treat type 2 diabetes: 1) sulfonylureas, 2) meglitinides, 3) metformin (a biguanide), 4) thiazolidinediones, 5) α-glucosidase inhibitors, 6) dipeptidyl peptidase IV (DPP-IV) inhibitors, 7) bile acid sequestrant, 8) dopamine agonist, and 9) sodium-glucose transport protein (SGLT2) inhibitors (Table 3). Medications from these distinct classes of pharmaceutical agents may be used as treatment by themselves or, more often, a combination of 2 or 3 drugs from multiple classes with multiple mechanisms of action is utilized (11). A variety of fixed combination of 2 agents are also available in the US and in many other countries (Table 4). These products may be useful and attractive to the patient, as they provide two drugs in a single tablet, likely offering convenience and increased compliance. In the US, they also enable patients to receive two medications for a single medical insurance co-payment. Besides the many options for insulin, there are also two classes of injectable medications currently used for the treatment of type 2 diabetes: glucagon like peptide-1 (GLP-1) receptor agonists (incretin mimetics) and an amylin analogue (Table 5).

Table 3. Currently Available (USA) Approved Oral Pharmacological Monotherapies to Treat Type 2 Diabetes

<table>
<thead>
<tr>
<th>General Class and Compound Name</th>
<th>Brand Name</th>
<th>Manufacturer</th>
<th>Generic Available (US market)</th>
<th>Daily Dose (mg)</th>
<th>Chemical Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Generation Sulfonylureas</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorpropamide</td>
<td>None</td>
<td>Generic</td>
<td>Yes</td>
<td>100-500 mg qd</td>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>Tolazamide</td>
<td>None</td>
<td>Generic</td>
<td>Yes</td>
<td>100-750 mg qd or divided tid</td>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>None</td>
<td>Generic</td>
<td>Yes</td>
<td>500-2000 mg qd or divided bid</td>
<td><img src="image" alt="Chemical Structure" /></td>
</tr>
<tr>
<td><strong>2nd Generation Sulfonylureas</strong></td>
<td><strong>Trade Name</strong></td>
<td><strong>Manufacturer</strong></td>
<td><strong>Availability</strong></td>
<td>Dosing</td>
<td></td>
</tr>
<tr>
<td>----------------------------------</td>
<td>----------------</td>
<td>-----------------</td>
<td>-----------------</td>
<td>--------</td>
<td></td>
</tr>
<tr>
<td>Glyburide (Glibenclamide)</td>
<td>Diabeta</td>
<td>Aventis</td>
<td>Yes</td>
<td>2.5-10 mg qd or divided bid</td>
<td></td>
</tr>
<tr>
<td>Glyburide (Glibenclamide)</td>
<td>Micronase</td>
<td>Pharmacia</td>
<td>Yes</td>
<td>2.5-10 mg qd or divided bid Same as above</td>
<td></td>
</tr>
<tr>
<td>Glyburide (Glibenclamide)</td>
<td>Glynase</td>
<td>Pharmacia</td>
<td>Yes</td>
<td>0.75-12 mg qd or divided bid Same as above</td>
<td></td>
</tr>
<tr>
<td>Glipizide</td>
<td>Glucotrol</td>
<td>Pfizer</td>
<td>Yes</td>
<td>10 mg qd or divided bid</td>
<td></td>
</tr>
<tr>
<td>Glipizide</td>
<td>Glucotrol XL</td>
<td>Pfizer</td>
<td>Yes</td>
<td>5-10 mg qd Same as above</td>
<td></td>
</tr>
<tr>
<td>Glimepiride</td>
<td>Amaryl</td>
<td>Aventis</td>
<td>Yes</td>
<td>1-4 mg qd</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Meglinides</strong></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Repaglinide</td>
<td>Prandin</td>
<td>Novo Nordisk</td>
<td>Yes</td>
<td>1.5-2 mg tid</td>
</tr>
<tr>
<td>Nateglinide</td>
<td>Starlix</td>
<td>Novartis</td>
<td>Yes</td>
<td>60-120 mg tid</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Biguanide</strong></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>Glucophage</td>
<td>Bristol-Myers Squibb</td>
<td>Yes</td>
<td>500-2500 mg qd-divided tid dosing Same as above</td>
</tr>
<tr>
<td>Metformin</td>
<td>Glucophage XR</td>
<td>Bristol-Myers Squibb</td>
<td>Yes</td>
<td>500-2500 mg qd-divided tid dosing Same as above</td>
</tr>
<tr>
<td>Metformin</td>
<td>Fortamet</td>
<td>Shionogi</td>
<td>No</td>
<td>500-2000 mg/day Same as above</td>
</tr>
<tr>
<td>Metformin</td>
<td>Glumetza</td>
<td>Valeant Pharmaceuticals</td>
<td>No</td>
<td>500-2000 mg/day Same as above</td>
</tr>
<tr>
<td>Metformin</td>
<td>Riomet</td>
<td>Ranbaxy Laboratories</td>
<td>No</td>
<td>500-2000 mg/day Same as above</td>
</tr>
<tr>
<td><strong>PPARγ Agonists (Thiazolidinedione; TZD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td><strong>Rosiglitazone</strong></td>
<td>Avandia</td>
<td>GlaxoSmithKline</td>
<td>No</td>
<td>4-8 mg qd</td>
</tr>
<tr>
<td><strong>Pioglitazone</strong></td>
<td>Actos</td>
<td>Takeda</td>
<td>Yes</td>
<td>15-45 mg qd</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Alpha-glucosidase inhibitors</strong></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acarbose</strong></td>
<td>Precose/Glucobay</td>
<td>Bayer</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Miglitol</strong></td>
<td>Glyset</td>
<td>Pharmacia</td>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Dipeptidyl peptidase-IV (DPP-IV) inhibitors</strong></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alogliptin</strong></td>
<td>Nesina</td>
<td>Takeda</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Linagliptin</strong></td>
<td>Tradjenta</td>
<td>Boehringer Ingelheim and Eli Lilly</td>
<td>No</td>
</tr>
<tr>
<td><strong>Saxagliptin</strong></td>
<td>Onglyza</td>
<td>Bristol-Myers Squibb and AstraZeneca</td>
<td>No</td>
</tr>
<tr>
<td><strong>Sitagliptin</strong></td>
<td>Januvia</td>
<td>Merck</td>
<td>No</td>
</tr>
</tbody>
</table>

<p>| <strong>Bile Acid Sequestrant</strong> |  |  |  |</p>
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Brand Name</th>
<th>Manufacturer</th>
<th>IND</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colesevelam</td>
<td>WelChol</td>
<td>Daiichi Sankyo</td>
<td>No</td>
<td>1875 mg bid</td>
</tr>
<tr>
<td><strong>Dopamine Agonist</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>Cycloset</td>
<td>Santarus (quick release formulation)</td>
<td>No</td>
<td>0.8-mg tabs - target range (1.6 - 4.8 mg)</td>
</tr>
<tr>
<td><strong>Sodium-glucose co-transporter-2 (SGLT2) inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>Invokana</td>
<td>Janssen</td>
<td>No</td>
<td>100-300 mg qd</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>Farxiga</td>
<td>AstraZeneca</td>
<td>No</td>
<td>10 mg qd</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>Jardiance</td>
<td>Boehringer Ingelheim and Eli Lilly</td>
<td>No</td>
<td>10-25 mg qd</td>
</tr>
</tbody>
</table>

NB 1: indicated for adults aged 18 and older with type 2 diabetes as an adjunct to diet and exercise to improve glycemic control; Brand name column contains hyperlinks to prescribing information.
## Table 4. Currently Available (USA) Approved Oral Pharmacological Fixed Combination Therapies to Treat Type 2 Diabetes

<table>
<thead>
<tr>
<th>Drug 1</th>
<th>Drug 2</th>
<th>Brand Name</th>
<th>Manufacturer</th>
<th>Available (US Market)</th>
<th>Available Doses (mg Drug 1/mg Drug 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glyburide</td>
<td>Metformin</td>
<td>Glucovance</td>
<td>Bristol-Myers Squibb</td>
<td>Yes</td>
<td>1.25/250; 2.5/500; 5/500 qd or bid</td>
</tr>
<tr>
<td>Glipizide</td>
<td>Metformin</td>
<td>Metaglip</td>
<td>Bristol-Myers Squibb</td>
<td>Yes</td>
<td>2.5/250; 2.5/500; 5/500 qd or bid</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>Pioglitazone</td>
<td>Duetact</td>
<td>Takeda</td>
<td>Yes</td>
<td>2/30; 4/30 qd</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>Rosiglitazone</td>
<td>Avandaryl</td>
<td>GlaxoSmithKline</td>
<td>No</td>
<td>1/4; 2/4; 4/4 qd</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>Metformin</td>
<td>Janumet</td>
<td>Merck</td>
<td>No</td>
<td>50/500; 50/1000 bid</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>Metformin</td>
<td>Kombiglyze XR</td>
<td>Bristol-Myers Squibb</td>
<td>No</td>
<td>5/500; 5/1000; 2.5/1000 qd</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Metformin</td>
<td>ACTOSplus Met; ACOSplus Met XR</td>
<td>Takeda</td>
<td>Yes</td>
<td>15/500; 15/850 qd, bid</td>
</tr>
<tr>
<td>Repaglinide</td>
<td>Metformin</td>
<td>PrandiMet</td>
<td>Novo Nordisk</td>
<td>Yes</td>
<td>1/500; 2/500 qd, bid</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>Metformin</td>
<td>Avandamet</td>
<td>GlaxoSmithKline</td>
<td>No</td>
<td>1/500; 2/500; 4/500; 2/1000; 4/1000 qd, bid</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>Metformin</td>
<td>Jentadueto</td>
<td>Boehringer Ingelheim</td>
<td>No</td>
<td>2.5/500; 2.5/850; 2.5/1000 qd</td>
</tr>
<tr>
<td>Alogliptin</td>
<td>Metformin</td>
<td>Kazano</td>
<td>Takeda</td>
<td>Yes</td>
<td>12.5/500; 12.5/1000 bid</td>
</tr>
<tr>
<td>Alogliptin</td>
<td>Pioglitazone</td>
<td>Oseni</td>
<td>Takeda</td>
<td>No</td>
<td>12.5/15; 12.5/30; 12.5/45; 25/15; 25/30; 25/45 qd</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>Metformin</td>
<td>Invokamet</td>
<td>Janssen</td>
<td>No</td>
<td>50/500; 50/1000; 150/500; 150/1000 qd, bid</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>Metformin</td>
<td>Xigduo XR</td>
<td>AstraZeneca</td>
<td>No</td>
<td>5/500; 5/1000; 10/500; 10/1000 qd</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>Linagliptin</td>
<td>Glyxambi</td>
<td>Boehringer Ingelheim &amp; Lily</td>
<td>No</td>
<td>10/5; 25/5 qd</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>Metformin</td>
<td>Synjardy</td>
<td>Boehringer Ingelheim &amp; Lily</td>
<td>No</td>
<td>5/500; 5/1000; 12.5/500; 12.5/1000 bid</td>
</tr>
</tbody>
</table>

NB 1: indicated for adults aged 18 and older with T2D as an adjunct to diet and exercise to improve glycemic control; Brand name column contains hyperlinks to prescribing information.
### Table 5. Currently Available (USA) Approved Injectable Pharmacological Therapies (Non-Insulin) to Treat Type 2 Diabetes

<table>
<thead>
<tr>
<th>General Class and Therapeutic Name</th>
<th>Brand Name</th>
<th>Manufacturer</th>
<th>Generic Available (US market)</th>
<th>Daily Dose (mg)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GLP-1 Receptor Agonist</strong> (Incretin Mimetic)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exenatide</td>
<td>Byetta</td>
<td>AstraZeneca</td>
<td>No</td>
<td>5 -10 mcg bid</td>
<td></td>
</tr>
<tr>
<td>Exenatide</td>
<td>Bydureon</td>
<td>AstraZeneca</td>
<td>No</td>
<td>2 mg once weekly</td>
<td></td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Victoza</td>
<td>Novo Nordisk</td>
<td>No</td>
<td>0.6-1.8 mg qd</td>
<td></td>
</tr>
<tr>
<td>Albiglutide</td>
<td>Tanzeum</td>
<td>GlaxoSmithKline</td>
<td>No</td>
<td>30-50 mg Once weekly</td>
<td></td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>Trulicity</td>
<td>Eli Lilly</td>
<td>No</td>
<td>0.75-1.5 mg Once weekly</td>
<td></td>
</tr>
<tr>
<td>Lixisenatide</td>
<td>Lyxumia</td>
<td>Sanofi</td>
<td>No</td>
<td>10-20 mcg qd</td>
<td>Approved throughout world; currently (2016) under review by US FDA</td>
</tr>
<tr>
<td><strong>Amylin Mimetic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pramlintide</td>
<td>Symlin</td>
<td>AstraZeneca</td>
<td>No</td>
<td>15-120 mcg tid</td>
<td>For patients with type 1 or 2 diabetes who use mealtime insulin but fail to attain target glycemic control</td>
</tr>
</tbody>
</table>

NB 1: Brand name column contains hyperlinks to prescribing information.
The actions of sulfonylureas and meglitinides involve the stimulation of insulin secretion; metformin suppresses hepatic glucose production; the thiazolidinedione class targets peripheral tissue insulin resistance; and the α-glucosidase inhibitors inhibit complex carbohydrate breakdown in the gut. A summary of their primary sites of action is given in Figure 2. There are no studies directly comparing the efficacy of all the oral agents. Data from multiple studies are provided in Tables 6 and 7, which summarize comparative efficacies when these drugs are used as monotherapy and in combination, respectively. A cost comparison (based on US pricing) of the medications is given in Table 8. Since several comprehensive reviews have focused on this topic (11-13), the overall objective of this chapter is to provide a concise, comparative overview of the available oral treatments, and to highlight some emerging approaches.

Figure 2. Sites of action of the current and potential future pharmacological therapies for the treatment of type 2 diabetes.
Table 6. Clinical Efficacy of Pharmacological Therapies to Treat Type 2 Diabetes When Used as Monotherapy or as Add-On Treatment

<table>
<thead>
<tr>
<th>General Class</th>
<th>↓ Fasting Plasma Glucose (mg/dl)</th>
<th>↓ HbA1c (%)</th>
<th>Insulin</th>
<th>Lipids</th>
<th>Body Weight</th>
<th>Major Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td>60-70</td>
<td>3.3-3.9</td>
<td>0.8-2.0</td>
<td>Increase</td>
<td>Increase</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>65-75</td>
<td>3.6-4.2</td>
<td>0.5-2.0</td>
<td>Increase</td>
<td>Increase</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Biguanide (Metformin)</td>
<td>50-70</td>
<td>2.8-3.9</td>
<td>1.5-2.0</td>
<td>Decrease</td>
<td>↓TG, ↓LDL, ↑HDL</td>
<td>GI disturbances, Lactic acidosis (rare)</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Flud retention, Decreased Hb, Congestive heart failure, Fractures</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>60-80</td>
<td>3.3-4.3</td>
<td>1.4-2.6</td>
<td>Decrease</td>
<td>↓TG, ↓LDL, ↑HDL</td>
<td>Increase</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a-Glucosidase inhibitors</td>
<td>25-30</td>
<td>1.9-2.2</td>
<td>0.5-0.7</td>
<td>No effect</td>
<td>No effect</td>
<td>GI disturbances</td>
</tr>
<tr>
<td>DDP-4 inhibitors</td>
<td>12-28</td>
<td>0.6-1.5</td>
<td>0.5-0.8</td>
<td>Increase</td>
<td>No effect</td>
<td>Risk of pancreatitis (not proven)</td>
</tr>
<tr>
<td>Bile Acid sequestrant</td>
<td>15</td>
<td>0.83</td>
<td>0.5</td>
<td>No effect</td>
<td>No effect</td>
<td>Risk of pancreatitis (not proven)</td>
</tr>
<tr>
<td>Dopamine Agonist</td>
<td>0-18</td>
<td>0-1.0</td>
<td>0.1-0.6</td>
<td>No effect</td>
<td>No effect</td>
<td>Risk of pancreatitis (not proven)</td>
</tr>
<tr>
<td>SGLT2 Inhibitors</td>
<td>19-35</td>
<td>1.1-1.9</td>
<td>0.7-1.0</td>
<td>No effect</td>
<td>-TG, ↓LDL, ↓HDL</td>
<td>Decrease</td>
</tr>
<tr>
<td>GLP-1R Agonists</td>
<td>9-28</td>
<td>0.5-1.5</td>
<td>0.7-0.9</td>
<td>Increase</td>
<td>No effect</td>
<td>Decrease</td>
</tr>
</tbody>
</table>

Note: Caution must be taken in comparing the results presented above. Head to head comparisons of these agents are limited. The patient cohorts studied were often different, with significantly different baseline HbA1c levels and background glucose lowering therapy. There is a strong correlation between baseline HbA1c and the magnitude of effectiveness of these agents (i.e. ability to decrease HbA1c). Significantly greater reductions in both fasting plasma glucose and
### Table 7. Clinical Efficacy of Pharmacological Therapies to Treat Type 2 Diabetes When Used in Combination

<table>
<thead>
<tr>
<th>Approved Combination</th>
<th>Baseline HbA1c (%)</th>
<th>Change from Baseline: HbA1c (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>SU + Metformin</td>
<td>8.8</td>
<td>-1.7</td>
<td>(15)</td>
</tr>
<tr>
<td>SU + Metformin</td>
<td>10.1</td>
<td>-1.0</td>
<td>(16)</td>
</tr>
<tr>
<td>SU + Metformin</td>
<td>11.0</td>
<td>-1.9</td>
<td>(17)</td>
</tr>
<tr>
<td>SU + Metformin</td>
<td>12.3</td>
<td>-3.3</td>
<td>(18)</td>
</tr>
<tr>
<td>SU + Metformin</td>
<td>10.8</td>
<td>-2.9</td>
<td>(19)</td>
</tr>
<tr>
<td>SU + TZD (Pio)</td>
<td>8.0</td>
<td>-1.3</td>
<td>(20)</td>
</tr>
<tr>
<td>SU + TZD (Rosi)</td>
<td>9.1</td>
<td>-0.9</td>
<td>(21)</td>
</tr>
<tr>
<td>SU + AGI (Acarbose)</td>
<td>7.4</td>
<td>-1.0</td>
<td>(22)</td>
</tr>
<tr>
<td>SU + AGI (Acarbose)</td>
<td>8.0</td>
<td>-0.9</td>
<td>(23)</td>
</tr>
<tr>
<td>SU + AGI (Acarbose)</td>
<td>9.0</td>
<td>-1.1</td>
<td>(24)</td>
</tr>
<tr>
<td>SU + AGI (Miglitol)</td>
<td>9.2</td>
<td>-0.5</td>
<td>(21)</td>
</tr>
<tr>
<td>Metformin + MEG (Rep)</td>
<td>8.3</td>
<td>-1.4</td>
<td>(25)</td>
</tr>
<tr>
<td>Metformin + MEG (Nat)</td>
<td>8.4</td>
<td>-1.5</td>
<td>(26)</td>
</tr>
<tr>
<td>Metformin + TZD (Pio)</td>
<td>8.0</td>
<td>-0.8</td>
<td>(21)</td>
</tr>
<tr>
<td>Metformin + TZD (Rosi)</td>
<td>8.9</td>
<td>-1.2</td>
<td>(21)</td>
</tr>
<tr>
<td>Metformin + AGI (Acarbose)</td>
<td>7.9</td>
<td>-0.8</td>
<td>(23)</td>
</tr>
<tr>
<td>Metformin + AGI (Acarbose)</td>
<td>8.5</td>
<td>-0.6</td>
<td>(27)</td>
</tr>
<tr>
<td>Metformin + SU + TZD (Tro)</td>
<td>9.6</td>
<td>-1.4</td>
<td>(28)</td>
</tr>
</tbody>
</table>

- **SU + Metformin** was added to patients failing on SU and metformin. Abbreviations: AGI, α-glucosidase inhibitor; DPP4I, dipeptidyl peptidase inhibitor; MEG, miglitinide; Nat, nateglinide; Pio, pioglitazone; Rep, repaglinide; Rosi, rosiglitazone; SU, sulfonylurea; Tro, troglitazone; TZD, thiazolidinedione

---

**Troglitazone (Rezulin®; this TZD is no longer available)** was added to patients failing on SU and metformin. Abbreviations: AGI, α-glucosidase inhibitor; DPP4I, dipeptidyl peptidase inhibitor; MEG, miglitinide; Nat, nateglinide; Pio, pioglitazone; Rep, repaglinide; Rosi, rosiglitazone; SU, sulfonylurea; Tro, troglitazone; TZD, thiazolidinedione

**b (S100 + M2000): Sitagliptin, 100 mg/day + metformin 2000 mg/day**

**c (S100 + M1000): Sitagliptin, 100 mg/day + metformin 1000 mg/day**

---

**HbA1c were observed in groups with higher baseline HbA1c. (see below) (14)**
(S2.5, S5, S10): Saxagliptin, 2, 5, or 10 mg/day, respectively added to stable dose of metformin (≥ 1,500 but not > 2,550 mg/day)

(A12.5, A25): Alogliptin, 12.5 or 25 mg/day, respectively, added to pioglitazone (30mg/day)
<table>
<thead>
<tr>
<th>General Class</th>
<th>Active Agent</th>
<th>Brand Name</th>
<th>Typical Daily Dose (mg)</th>
<th>Monthly Cost Range (USD)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td>Glyburide</td>
<td>Diabeta, Micronase</td>
<td>1.25-20</td>
<td>55-62</td>
<td>5 mg; 30 tablets;</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Glyburide</td>
<td>Generic</td>
<td>1.25-20</td>
<td>4-16</td>
<td>5 mg; 30 tablets</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Glyburide (micronized)</td>
<td>Glynase</td>
<td>1.5-12</td>
<td>109-117</td>
<td>6 mg; 30 tablets</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Glyburide (micronized)</td>
<td>Generic</td>
<td>1.5-12</td>
<td>4-22</td>
<td>6 mg; 30 tablets</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Glipizide</td>
<td>Glucotrol</td>
<td>5-20</td>
<td>39-45</td>
<td>5 mg; 30 tablets</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Glipizide</td>
<td>Generic</td>
<td>5-20</td>
<td>4-9</td>
<td>5 mg; 30 tablets</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Glipizide XL</td>
<td>Glucotrol XL</td>
<td>5-20</td>
<td>50-76</td>
<td>10 mg; 30 tablets</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Glipizide XL</td>
<td>Generic</td>
<td>5-20</td>
<td>10-23</td>
<td>10 mg; 30 tablets</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Glimepiride</td>
<td>Amaryl</td>
<td>1-4</td>
<td>127-141</td>
<td>4 mg; 30 tablets</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Glimepiride</td>
<td>generic</td>
<td>1-4</td>
<td>4-21</td>
<td>4 mg; 30 tablets</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>Repaglinide</td>
<td>Prandin</td>
<td>1.5-6</td>
<td>201-214</td>
<td>2 mg; 30 tablets</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>Repaglinide</td>
<td>Generic</td>
<td>1.5-6</td>
<td>14-90</td>
<td>2 mg; 30 tablets</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>Nateglinide</td>
<td>Starlix</td>
<td>180-360</td>
<td>94-101</td>
<td>60 mg; 30 tablets</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>Nateglinide</td>
<td>Generic</td>
<td>180-360</td>
<td>24-46</td>
<td>60 mg; 30 tablets</td>
</tr>
<tr>
<td>Biguanide</td>
<td>Metformin</td>
<td>Glucophage</td>
<td>500-2000</td>
<td>34-40</td>
<td>500 mg; 30 tablets</td>
</tr>
<tr>
<td>Biguanide</td>
<td>Metformin</td>
<td>generic</td>
<td>500-2000</td>
<td>4-10</td>
<td>500 mg; 30 tablets</td>
</tr>
<tr>
<td>Biguanide</td>
<td>Metformin XR</td>
<td>Glucophage XR</td>
<td>500-2000</td>
<td>34-40</td>
<td>500 mg; 30 tablets</td>
</tr>
<tr>
<td>Biguanide</td>
<td>Metformin XR</td>
<td>Generic</td>
<td>500-2000</td>
<td>4-11</td>
<td>500 mg; 30 tablets</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Rosiglitazone</td>
<td>Avandia</td>
<td>4-8</td>
<td>88-109</td>
<td>2 mg; 30 tablets</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Pioglitazone</td>
<td>Actos</td>
<td>15-45</td>
<td>532-600</td>
<td>30 mg; 30 tablets</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Pioglitazone</td>
<td>Generic</td>
<td>15-45</td>
<td>11-52</td>
<td>30 mg; 30 tablets</td>
</tr>
<tr>
<td>α-Glucosidase Inhibitors</td>
<td>Acarbose</td>
<td>Precose/ Glucobay</td>
<td>75-300</td>
<td>34-40</td>
<td>50 mg; 30 tablets</td>
</tr>
<tr>
<td>α-Glucosidase Inhibitors</td>
<td>Acarbose</td>
<td>Generic</td>
<td>75-300</td>
<td>13-28</td>
<td>50 mg; 30 tablets</td>
</tr>
<tr>
<td>α-Glucosidase Inhibitors</td>
<td>Migliitol</td>
<td>Glynset</td>
<td>75-300</td>
<td>70-76</td>
<td>50 mg; 30 tablets</td>
</tr>
<tr>
<td>α-Glucosidase Inhibitors</td>
<td>Migliitol</td>
<td>Generic</td>
<td>75-300</td>
<td>40-50</td>
<td>50 mg; 30 tablets</td>
</tr>
<tr>
<td>DDP-4 inhibitor</td>
<td>Sitagliptin</td>
<td>Januvia</td>
<td>100</td>
<td>371-416</td>
<td>100 mg; 30 tablets</td>
</tr>
<tr>
<td>DDP-4 inhibitor</td>
<td>Saxagliptin</td>
<td>Onglyza</td>
<td>2.5-5</td>
<td>371-416</td>
<td>5 mg; 30 tablets</td>
</tr>
<tr>
<td>DDP-4 inhibitor</td>
<td>Alogliptin</td>
<td>Nesina</td>
<td>25</td>
<td>371-393</td>
<td>25 mg; 30 tablets</td>
</tr>
<tr>
<td>DDP-4 inhibitor</td>
<td>Alogliptin</td>
<td>Generic</td>
<td>25</td>
<td>95-210</td>
<td>25 mg; 30 tablets</td>
</tr>
<tr>
<td>DDP-4 inhibitor</td>
<td>Linagliptin</td>
<td>Tradjenta</td>
<td>5</td>
<td>365-409</td>
<td>5 mg; 30 tablets</td>
</tr>
<tr>
<td>Bile Acid Sequestrant</td>
<td>Colesevelam</td>
<td>Welchol</td>
<td>3750</td>
<td>99-111</td>
<td>625 mg; 30 tablets</td>
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<tr>
<td>Dopamine Agonist</td>
<td>Bromocriptine</td>
<td>Cycloset</td>
<td>0.25-0.5</td>
<td>109-117</td>
<td>0.8 mg; 30 tablets</td>
</tr>
<tr>
<td>SGLT2 Inhibitor</td>
<td>Canagliflozin</td>
<td>Invokana</td>
<td>100-300</td>
<td>399-448</td>
<td>300 mg; 30 tablets</td>
</tr>
<tr>
<td>SGLT2 Inhibitor</td>
<td>Dapagliflozin</td>
<td>Farxiga</td>
<td>10</td>
<td>399-423</td>
<td>10 mg; 30 tablets</td>
</tr>
<tr>
<td>SGLT2 Inhibitor</td>
<td>Empagliflozin</td>
<td>Jardiance</td>
<td>10-25</td>
<td>391-408</td>
<td>25 mg; 30 tablets</td>
</tr>
<tr>
<td>GLP-1R agonist</td>
<td>Exenatide</td>
<td>Byetta</td>
<td>5-10 mcg SQ bid</td>
<td>567-622</td>
<td>10 mcg; 1 pen</td>
</tr>
<tr>
<td>GLP-1R agonist</td>
<td>Liraglutide</td>
<td>Victoza</td>
<td>1.2-1.8 mg SQ qd</td>
<td>700-793</td>
<td>18 mg/3ml; 3 pens</td>
</tr>
<tr>
<td>GLP-1R agonist</td>
<td>Albiglutide</td>
<td>Tanzeum</td>
<td>30-50 mg once weekly</td>
<td>447-474</td>
<td>30 mg; 4 syringes</td>
</tr>
<tr>
<td>GLP-1R agonist</td>
<td>Dulaglutide</td>
<td>Trulicity</td>
<td>0.75-1.5 mg once weekly</td>
<td>582-658</td>
<td>1.5 mg/0.5 ml; 4 pens</td>
</tr>
<tr>
<td>----------------</td>
<td>-------------</td>
<td>-----------</td>
<td>-------------------------</td>
<td>---------</td>
<td>------------------------</td>
</tr>
<tr>
<td>GLP-1R agonist</td>
<td>Lixisenatide</td>
<td>Lyxumia</td>
<td>10-20 mcg qd</td>
<td>Not yet available in US</td>
<td>Not yet available in US</td>
</tr>
<tr>
<td>Amylin</td>
<td>Pramlintide</td>
<td>Symlin</td>
<td>15-120 mcg tid</td>
<td>774-827</td>
<td>1.5 ml; 2 pens</td>
</tr>
</tbody>
</table>

**Combination Therapies**

<table>
<thead>
<tr>
<th>Available Doses (Mg Drug 1/mg Drug 2)</th>
<th>Glyburide</th>
<th>Metformin</th>
<th>Glucovance</th>
<th>1.25/250; 2.5/500; 5/500 qd or bid</th>
<th>44-50</th>
<th>5mg/500 mg; 30 tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glyburide</td>
<td>Metformin</td>
<td>Generic</td>
<td>1.25/250; 2.5/500; 5/500 qd or bid</td>
<td>4-20</td>
<td>5mg/500 mg; 30 tablets</td>
<td></td>
</tr>
<tr>
<td>Glipizide</td>
<td>Metformin</td>
<td>Generic</td>
<td>2.5/250; 2.5/500; 5/500 qd or bid</td>
<td>13-29</td>
<td>5mg/500 mg; 30 tablets</td>
<td></td>
</tr>
<tr>
<td>Glimepiride</td>
<td>Pioglitazone</td>
<td>Duetact</td>
<td>2/30; 4/30 qd</td>
<td>547-564</td>
<td>2 mg/30 mg; 30 tablets</td>
<td></td>
</tr>
<tr>
<td>Glimepiride</td>
<td>Pioglitazone</td>
<td>Generic</td>
<td>2/30; 4/30 qd</td>
<td>105-373</td>
<td>2 mg/30 mg; 30 tablets</td>
<td></td>
</tr>
<tr>
<td>Glimepiride</td>
<td>Rosiglitazone</td>
<td>Avandaryl</td>
<td>1/4; 2/4; 4/4 qd</td>
<td>238-254</td>
<td>2 mg/8 mg; 30 tablets</td>
<td></td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>Metformin</td>
<td>Janumet; Janumet XR</td>
<td>50/500; 50/1000 bid</td>
<td>190-208</td>
<td>50 mg/1000 mg; 30 tablets</td>
<td></td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>Metformin</td>
<td>Kombiglyze XR</td>
<td>5/500; 5/1000; 2.5/1000 qd</td>
<td>189-203</td>
<td>2.5 mg/1000 mg; 30 tablets</td>
<td></td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Metformin</td>
<td>ACTOSplus Met</td>
<td>15/500; 15/850 qd, bid</td>
<td>269-299</td>
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TREATMENT GOALS

It is well established that, in poorly-controlled individuals with diabetes, both macrovascular and especially microvascular complications are increased (34;35). Elevated post-prandial glucose is also associated with an increased risk for the development of macrovascular disease (36). In the United Kingdom Prospective Diabetes Study (UKPDS), a reduction of HbA1c significantly decreased the risk for the development of microvascular complications in patients with type 2 diabetes (35). Accordingly, recommendations for treatment goals have been proposed by several professional organizations.

The American Diabetes Association recommends an HbA1c of less than 7% for many non-pregnant adults (37). Providers might pursue the more stringent target of 6.5% for selected individuals, if this can be achieved without significant hypoglycemia or other adverse effects of treatment (37). In individuals with a history of severe hypoglycemia, limited life expectancy, advanced complications, extensive comorbidities, or long-standing diabetes, a less stringent goal of <8% is reasonable (37). Since there is some evidence that increased risk for the development of cardiovascular disease begins at concentrations of HbA1c in the normal range, the American Association of Clinical Endocrinologists recommends an HbA1c of 6.5% or less (38). These more aggressive goals may be tempered with the release of three large randomized prospective studies showing that lowering HbA1c below 7% did not reduce the risk of cardiovascular disease (39;40).

Though a majority of patients with diabetes are being treated, many are unable to achieve the currently recommended goal of HbA1c <6.5% (AACE) or HbA1c <7% (ADA). Bloomgarden et al reported results from a meta-regression analysis of 61 clinical trials evaluating the efficacy of the five major classes of oral anti-hyperglycemic agents (14). His results indicate that there is a strong correlation between baseline HbA1c and the magnitude of effectiveness of these agents (ie ability to decrease HbA1c). Significantly greater reductions in both fasting plasma glucose and HbA1c were observed in groups with higher baseline HbA1c. For those patients whose HbA1c was <8.0%, the reduction from therapy was only 0.1-0.2%. These results are presented graphically in Figure 3. Thus, expectations for the overall magnitude of effect from a given agent might be overly optimistic when treating patients whose baseline HbA1c is <7.5-8.0%. These observations certainly reinforce the need to use combination therapy (ie dual, triple, or even four agents) to achieve a recommended target for HbA1c. In addition, these results indicate that comparing efficacies among different anti-diabetic medications is challenging, when the baseline HbA1c is different in the studies being compared.
Figure 3. Relationship between baseline HbA1c and the observed reduction in HbA1c from baseline achieved following treatment with oral anti-hyperglycemic medication. Irrespective of drug class, the baseline glycemic control significantly influences the overall magnitude of efficacy. Data from Bloomgarden et al, Table 1 (14).
APPROVED INTERVENTIONS

Sulfonylureas

Introduction
Sulfonylureas, derived from sulfonic acid and urea, were initially developed in the 1950s, and have remained a cornerstone of therapy for type 2 diabetes (41). The combination of their proven efficacy in most patients, low incidence of adverse events, and low cost has contributed to their success and continued use. They are frequently classified as either 1st generation or 2nd generation agents. First generation sulfonylureas (acetohexomide, chlorpropamide, tolazamide, and tolbutamide) possess a lower binding affinity for the ATP-sensitive potassium channel, their molecular target (vide infra), and thus require higher doses to achieve efficacy, increasing the potential for adverse events. In addition, the plasma half-life of 1st generation sulfonylureas is extended (e.g. 5-36 h) compared to the 2nd generation agents. Chlorpropamide was once the most commonly used oral agent, but now it is rarely prescribed. Unique complications associated with chlorpropamide are hyponatremia (a key feature of syndrome of inappropriate anti-diuretic hormone secretion; SIADH) and an alcohol flushing reaction (disulfiram-antibuse reaction). In addition, tolbutamide, acetohexamide, and tolazamide generally require 2 or 3 doses per day and are rarely used.

Subsequently, 2nd generation sulfonylureas including glyburide (glibenclamide; glipizide and glimepiride) were introduced, and are now widely used. The 2nd generation sulfonylureas are much more potent compounds (~100-fold), possess a more rapid onset of action, and generally have shorter plasma half-lives and longer duration of action compared to the 1st generation agents.

Mechanism of Action
Sulfonylureas are insulin secretagogues, since they control blood glucose levels by directly stimulating first-phase insulin secretion in the pancreatic β cells. Through the concerted efforts of GLUT2 (the high Km glucose transporter) (42), glucokinase (the glucose sensor) (43), and glucose metabolism, these cells are responsible for sensing and secreting the appropriate amount of insulin in response to a glucose stimulus (44). Mitochondrial glucose metabolism leads to ATP generation and increases the intracellular ratio of ATP/ADP, which results in the closure of the ATP-sensitive potassium channel (K_{ATP}; a 140 kDa membrane protein) on the plasma membrane. Closure of this channel depolarizes the membrane and triggers the opening of voltage-sensitive calcium channels, leading to the rapid influx of calcium. Increased intracellular calcium causes an alteration in the cytoskeleton, and stimulates translocation of insulin-containing secretory granules to the plasma membrane and the exocytotic release of insulin.
The $K_{ATP}$ channel is comprised of two subunits, both of which are required for the channel to be functional. One subunit contains the cytoplasmic binding sites for both sulfonylureas and ATP, and is designated as the sulfonylurea receptor type 1 (SUR1). The other subunit is the potassium channel, which acts as the pore-forming subunit (45). Either an increase in the ATP/ADP ratio or ligand binding (by sulfonylureas, meglitinides) to SUR1 results in the closure of the $K_{ATP}$ channel and insulin secretion. Studies comparing sulfonylureas and non-sulfonylurea insulin secretagogues have identified several distinct binding sites on the SUR1 that cause channel closure. Some sites exhibit high affinity for glyburide and other sulfonylureas, while other sites exhibit high affinity for the non-sulfonylurea secretagogues (vide infra).

**Efficacy**

The overall clinical efficacy of sulfonylureas in patients with type 2 diabetes is related to the pre-treatment levels of fasting plasma glucose and HbA1c. The higher the fasting glucose level, the greater the effect will be. In patients with a pre-treatment glucose level of approximately 200 mg/dl (11.1 mmol/l), sulfonylureas typically will reduce glucose by 60-70 mg/dl (3.3-3.9 mmol/l) and HbA1c by 1.5-2% (Table 6). The most responsive patients are those who exhibit mild-to-moderate fasting hyperglycemia (<200-240 mg/dl; <12.2-13.3 mmol/l), along with adequate residual $\beta$-cell function (evidenced by elevated fasting C-peptide). When used at maximally effective doses, results from well-controlled clinical trials have not indicated a superiority of one 2nd generation sulfonylurea over another. Similarly, 2nd generation sulfonylureas exhibit similar clinical efficacy compared to the 1st generation agents. The principal advantage of glimepiride and Glucotrol XL compared to other agents is the once daily dosing regimen. Approximately 10-20% of patients will exhibit a poor initial response to sulfonylureas (primary failures). While these patients are typically those who have severe fasting hyperglycemia (>280 mg/dl; >15.5 mmol/l) and reduced fasting C-peptide levels, these tests are not specific enough to help decide on the usefulness of a sulfonylurea for an individual patient. In addition, treatment with sulfonylureas results in the eventual loss of therapeutic effectiveness (secondary failure) in the range of 3-10% per year (41).

**Side Effects**

The major side effect from sulfonylurea treatment is hypoglycemia. This side effect is really just an extension of the therapeutic objective. Mild hypoglycemic events occur in approximately 2-4% of patients and severe hypoglycemic reactions that require hospitalization occur at a frequency of 0.2-0.4 cases per 1000 patient-years of treatment (46). In light of this, initiation of treatment with sulfonylureas should be at the lowest recommended dose. An additional undesirable effect of sulfonylurea therapy (as is also the case with insulin therapy) is weight gain. In the UKPDS, sulfonylurea treatment caused
a net weight gain of 3 kg, which occurred during the first 3-4 years of treatment and then stabilized (47). In contrast, weight gain in response to insulin therapy increased progressively for the duration of the study. As mentioned above, chlorpropamide is associated with hyponatremia (SIADH) and an alcohol flushing reaction (disulfiram-antibuse reaction). All the agents can cause intrahepatic cholestasis. Rarely maculopapular or urticarial rashes occur. In renal failure, the dose of the sulfonylurea agent will require adjustment based on glucose monitoring. The half-life of insulin is extended in renal failure and thus there is an increased risk for hypoglycemia. This risk is typically manifest with fasting hypoglycemia.

**Meglitinides: Repaglinide and Nateglinide**

*Introduction*

The meglitinides are a novel class of non-sulfonylurea insulin secretagogues characterized by a very rapid onset and abbreviated duration of action. Repaglinide (Prandin®), a benzoic acid derivative introduced in 1998, was the first member of the meglitinide class. Nateglinide (Starlix®) is a derivative of the amino acid D-phenylalanine and was introduced to the market in 2001. Unlike sulfonylureas, repaglinide and nateglinide stimulate first-phase insulin release in a glucose-sensitive manner, theoretically reducing the risk of hypoglycemic events. The delivery of insulin as an early, transient pulse at the initiation of a meal affords several major physiological benefits (reviewed in (48;49)). These include the rapid suppression of hepatic glucose production, and reducing the stimulus for additional insulin that would be required subsequently to dispose of a larger glucose load. Thus, the rapid onset/short duration stimulation of insulin release by meglitinides enhances the control of prandial hyperglycemia, while reducing the risk for post-absorptive hypoglycemia and limiting exposure to hyperinsulinemia.

*Mechanism of Action*

Similar to sulfonylureas, meglitinides are insulin secretagogues, since they control blood glucose levels by directly stimulating first-phase insulin secretion in the pancreatic β cells. Receptor-binding studies performed in βTC-3 cells identified a high-affinity repaglinide (K_D = 3.6 nmol/l) site having lower affinity for glyburide (14.4 nmol/l), and one high-affinity glyburide (25 nmol/l) site having lower affinity for repaglinide (550 nmol/l)(50). Repaglinide is approximately 5 times more potent than glyburide in stimulating insulin secretion. Unlike glyburide (and other sulfonylureas), repaglinide does not stimulate insulin secretion in vitro in the absence of glucose. Rather, it enhances glucose-stimulated insulin secretion, especially at 180 mg/dl (10 mmol/l) glucose.

The mechanism of action of nateglinide also involves the binding to and closure of the K_ATP channel
resulting in membrane depolarization, an influx of calcium, and insulin exocytosis (51). The kinetics of interaction of nateglinide with the $K_{\text{ATP}}$ channel are distinct compared to both repaglinide and sulfonylureas, and accounts for its rapid insulinotropic effects. The onset of action of nateglinide is similar to that of glyburide but three-fold more rapid than that of repaglinide (48). When nateglinide is removed from the $K_{\text{ATP}}$ channel, its effect is reversed twice as quickly compared to glyburide, and five times more quickly than repaglinide. Thus, nateglinide initiates a more rapid release of insulin that is shorter in duration compared to repaglinide (48), despite having an in vivo pharmacokinetic profile that is similar (52;53).

**Efficacy**

The efficacy of repaglinide, when used as a monotherapy, is similar to sulfonylureas (54). Repaglinide treatment of patients with type 2 diabetes reduced fasting plasma glucose by approximately 60 mg/dl and HbA1c by 1.7% (55). In a double-blind placebo-controlled study, repaglinide had similar effects on lowering HbA1c (0.5-2%) and fasting plasma glucose (65-75 mg/dl; 3.6-4.2 mmol/l) compared to glyburide (56). Repaglinide is also efficacious when used in combination with either metformin or troglitazone (a thiazolidinedione withdrawn from the market). In patients treated with repaglinide and metformin, HbA1c was decreased from 8.3% to 6.9% and fasting plasma glucose by 40 mg/dl (2.2 mmol/l)(25). Although lowered, the changes observed in subjects treated with either repaglinide or metformin monotherapy were not significant for HbA1c (0.4 and 0.3% decrease, respectively), or fasting plasma glucose (9 mg/dl (0.5 mmol/l) increase and 5.4 mg/dl (0.3 mmol/l) decrease, respectively). Significant increases in body weight occurred in the both repaglinide and combined therapy groups.

The combination therapy of repaglinide and troglitazone showed a significant reduction in mean HbA1c values (1.7%) that were greater than with either type of monotherapy (57). Repaglinide monotherapy resulted in a reduction of HbA1c values that was significantly greater than troglitazone (0.8% vs. 0.4%). In addition, combination therapy was more effective in reducing fasting plasma glucose (80 mg/dl) than either repaglinide (43 mg/dl) or troglitazone (46 mg/dl) monotherapies. Repaglinide is also efficacious when used in combination with other available thiazolidinediones, rosiglitazone (Avandia) and pioglitazone (Actos) (58).

The efficacy of nateglinide when used as a monotherapy is similar to sulfonylureas and repaglinide (48;54). However, several therapeutically attractive features distinguish nateglinide from repaglinide and sulfonylureas. Nateglinide produces a more rapid post-prandial increase in insulin secretion, and its duration of response is shorter than that of glyburide (59;60). Thus, the risk of post-absorptive
hypoglycemia should be lower than with either sulfonylureas or repaglinide, but this has not been demonstrated in studies to date.

The efficacy of nateglinide treatment has been evaluated alone and in combination with metformin in patients with type 2 diabetes (26). In this randomized double-blind study, patients with an HbA1c level between 6.8 and 11.0% during a 4-week placebo run-in received treatment for 24 weeks with 120 mg nateglinide before meals (n = 179), 500 mg metformin three times a day (n = 178), combination therapy (n = 172), or placebo (n = 172). At the study conclusion, HbA1c and fasting plasma glucose were significantly reduced from baseline with nateglinide [0.5% and 12.6 mg/dl (0.7 mmol/l), respectively] and metformin [0.8% and 28.8 mg/dl (1.6 mmol/l), respectively], but was increased with placebo [0.5% and 7.2 mg/dl (0.4 mmol/l), respectively]. Combination therapy was additive [HbA1c, 1.4% and glucose, 43.2 mg/dl (2.4 mmol/l)]. Nateglinide also appears effective when used in combination with thiazolidinediones (49;58). In a direct comparison of repaglinide and nateglinide, the known pharmacodynamic differences in the drugs are evident on the clinical outcomes (61). The longer acting repaglinide has significant effects on fasting glucose levels while nateglinide does not (Figure 4). These clinical findings are important and can be incorporated into clinical decision making. For example, if the main issue for the patient is postprandial hyperglycemia, and fasting glucose are near normal, an agent that has limited effect on the fasting glucose would be beneficial.

Figure 4. Comparison of repaglinide and nateglinide. Data from (61).
**Side Effects**

In 1-year trials, the most common adverse events reported in repaglinide recipients (n = 1,228) were hypoglycemia (16%), upper respiratory tract infection (10%), rhinitis (7%), bronchitis (6%) and headache (9%). The overall incidence of hypoglycemia was similar to that recorded in patients receiving glibenclamide, glipizide or gliclazide (18%; n = 597); however, the incidence of serious hypoglycemia appears to be slightly higher in sulphonylurea recipients. Weight gain does occur in patients treated with repaglinide, but the magnitude is significantly less compared to treatment with glyburide. In patients switched from sulfonylureas to repaglinide, no weight gain was observed; in drug-naive patients, repaglinide-treatment increased body weight by approximately 3% (6 lb; 2.72 kg)(56;62).

The clinical trials of nateglinide carried out to date have found the drug to be safe and well tolerated. Dosage regimens ranging from 60 to 240 mg have been evaluated. The most common adverse effects are nausea, diarrhea, dizziness, and lightheadedness. The incidence of mild hypoglycemia is lower with nateglinide than for repaglinide and no reports of severe hypoglycemia, consistent with the mechanism of action of nateglinide. In the clinical studies carried out to date, there have been no reports of any increase body weight gain.

**Metformin**

*Introduction*

Metformin (dimethylbiguanide; Glucophage) is a synthetic analog of the natural product guanidine, whose history as a treatment for diabetes can be traced to medieval times (63;64). Since its initial clinical use and introduction as an approved therapy over 50 years ago, metformin has surpassed the sulfonylureas as the most widely prescribed oral agent for type 2 diabetes throughout the world because of its proven efficacy (as monotherapy and in combination with many other available agents) on glycemic control and insulin resistance, relative safety in most patients (see below), clean cardiovascular safety profile, absence of weight promoting activity, and its relative low cost (65-67).

The widespread acceptance of metformin evolved after the realization that lactic acidosis was not a major problem in individuals with normal renal function. Phenformin, a structurally analog of metformin, was previously withdrawn from the market in many countries due its propensity to induce lactic acidosis (68).

Metformin is recommended as a first-line therapy in newly diagnosed individuals (11). When used as a monotherapy, metformin decreases HbA1c by 1.5-2.0%, increases insulin sensitivity, does not promote weight gain, and has an acceptable side effect profile. If target HbA1c is not achieved after 3-
4 months, then metformin in combination with either a sulfonylurea, thiazolidinedione, DPP-4 inhibitor, SGLT-2 inhibitor, GLP-1 receptor agonist, or insulin (basal) is recommended (specific combination is dependent on a variety of patient and disease-specific factors)(11). In addition, there are a variety of fixed dose combination drugs that include metformin (Table 4). If target HbA1c is not achieved after 3-4 months on dual-therapy, then triple therapy using metformin in combination with two other medication classes (sulfonylurea, thiazolidinedione, DPP-4 inhibitor, SGLT-2 inhibitor, GLP-1 receptor agonist, or insulin) is recommended (specific combination is dependent on a variety of patient and disease-specific factors)(11). [See other relevant chapters in Endotext.org; chapters 14 and 17.1, along with reference (11), for details].

Mechanisms of Action
An elevated rate of basal hepatic glucose output is the primary determinant of elevated fasting blood glucose levels in patients with type 2 diabetes (69). A primary effect of metformin is the suppression of basal hepatic glucose production, thereby reducing fasting plasma glucose (70-72). Despite the large number of studies in vitro, in vivo, and in humans that have established this widely accepted mode of action, the relevant molecular targets of metformin action still await positive identification and validation. In fact, these last few years have been marked by renewed interest in identifying additional modes of action for metformin (68;73-76). Metformin does not stimulate insulin secretion; in contrast, metformin reduces fasting plasma insulin and improves whole-body insulin-stimulated glucose metabolism (insulin sensitivity) (70;72). While it is possible that the beneficial effect of metformin on insulin sensitivity is mediated directly, a more likely explanation is that it is secondary to a reduction in hyperglycemia, triglycerides, and free fatty acids.

In vitro and in vivo evidence has shown that metformin activates the AMP-activated protein kinase (AMPK) (77), a major cellular regulator of lipid and glucose metabolism (78;79). As a result, acetyl-CoA carboxylase activity is reduced, fatty acid oxidation induced (due to decreased malonyl-CoA), and the expression of lipogenic enzymes along with SREBP-1, a key lipogenic transcription factor, is suppressed (77;80). The use of a novel AMPK inhibitor indicated that AMPK activation was required for the inhibitory effect of metformin on glucose production in hepatocytes. In isolated rat skeletal muscle, metformin stimulated glucose uptake coincident with AMPK activation. Metformin does not activate AMPK directly, it does so indirectly (73). These results point to the activation of AMPK in hepatic and possibly other tissues as a major contributor to the beneficial effects of metformin. However, this mechanism has been challenged through 1) the use of LKB1 (the proximal upstream AMPK kinase) and AMPK knockout mice which remained metformin-responsive (81), along with 2) the finding that metformin increased hepatic AMP levels concomitant with the suppression of glucagon-
stimulated gluconeogenesis (82).

New evidence is available implicating the activation of a duodenal AMPK-dependent neuronal pathway in the acute anti-hyperglycemic effect of metformin, i.e., a gut-brain-liver axis (83). In this study conducted in insulin-resistant rats, infusion of metformin directly into the duodenal lumen resulted in suppression of hepatic glucose production (84). The effect was mediated by the AMPK-stimulation of GLP-1 release from, possibly, enteroendocrine L cells, and subsequent activation of GLP-1 receptors on the afferent vagal nerve. Such a signal could be relayed centrally and then to on to the liver resulting in the suppression of hepatic glucose production. In support of this novel mechanism, metformin effects were blocked by vagal denervation and GLP-1 receptor antagonist (exendin-9) and mimicked by a synthetic AMPK activator (A-769662).

The gastrointestinal tract plays a major role in regulation of postprandial glucose excursions and metabolism (85). There is emerging evidence that the primary glucose-lowering activity of metformin resides in its actions in the gut, and not the circulation. This pilot study was conducted in individuals with type 2 diabetes over 12-weeks (86;87). Using a novel delayed-release formulation of metformin designed to deliver the drug to the lower bowel, superior glycemic control compared to the identical dose of extended release metformin has recently been reported. In fact, the use of this formulation appeared to left-shift the dose response (i.e., enhance the potency of metformin) over the course of the study. These intriguing results will need to be confirmed in a larger study with a longer duration of intervention. Whether the gut-based activities of metformin involve alterations in the intestinal microbiome remains to be determined, but supporting evidence has recently been obtained (88).

**Efficacy**

A large number of well-controlled clinical studies have established that metformin monotherapy consistently reduces fasting plasma glucose by 60-70 mg/dl (3.3-3.9 mmol/l) and HbA1c by 1.5-2.0% (72;89;90). Thus, the efficacy of metformin is in the same range as that observed for monotherapy treatment with sulfonylureas. Similar to the sulfonylurea treatment, the overall magnitude of response to metformin is directly related to the starting fasting plasma glucose concentration. Metformin also reduces fasting plasma insulin, triglycerides, and free fatty acids (72). Unlike sulfonylurea treatment, metformin monotherapy is not associated with weight gain and even promotes a modest weight loss. When used in combination with other oral agents or insulin, weight gain is either not observed or blunted. Historically, patients with type 2 diabetes in the US had mean HbA1c of approximately 10% and fasting plasma glucose approximately 200-240 mg/dl. In patients of this sort, monotherapy with either metformin or a sulfonylurea generally decreased plasma glucose to <140 mg/dl (<7.8 mmol/l) in
about 25-30% of patients. In contrast, combined metformin and sulfonylurea therapy increased the percentage of patients who achieve this level of control to approximately 60-70% (72). When added to a sulfonylurea, the effects of both agents are additive, consistent with their different mechanisms of action. Interestingly, in patients that no longer responded to sulfonylurea treatment (secondary failures) and were removed from treatment, addition of metformin had minimal effects (15). Thus, in these patients, sulfonylurea treatment was still eliciting an effect, emphasizing the need to continue treatment with both agents.

The additive effect of metformin and sulfonylurea therapy is illustrated in **Figure 5**. As shown, there was no change in glucose levels when the sulfonylurea was changed to metformin. However, when the metformin was added, there was a dramatic decrease in plasma glucose. In fact, this pattern is seen in virtually all studies comparing two oral agents. This concept is illustrated in **Figure 6**. When a patient is on drug A and they are changed to drug B, no improvement in glucose control will be seen. However, if drug B is added to drug A, there is an improvement. This concept can often be extended by the addition of drug C, drug D, etc.

**Figure 5. Effect of metformin on fasting plasma glucose when given as add-on therapy to glyburide.** Data show the effects on fasting plasma glucose (mean change from baseline) in patients with type 2 diabetes continuing on glyburide therapy, switched to metformin, or given metformin as add-on therapy to glyburide. Data from (15).
Figure 6. Efficacy when oral agents are used as add-on therapy. When a patient is on drug A and they are changed to drug B, C, or D, often no improvement in glucose control will be seen. However, if drug B is added to drug A, there is an improvement. This concept can often be extended by the addition of drug C, drug D.

Benefits Beyond Glucose Control: Cardiovascular Disease

In a retrospective study on the effect of metformin-containing antidiabetic regimens on all-cause mortality in veterans with type 2 diabetes, there was a decreased hazard ratio for all-cause mortality for patients taking metformin whether they were also on other oral agents (0.77; P<0.01) or on insulin (0.62; P<0.04)(91). In the United Kingdom Prospective Diabetes Study, 10 years after the study was completed, if the subjects had been on treatment regimens that included metformin there was a reduction in any diabetes-related end point (21%, P=0.01), myocardial infarction (33%, P=0.005), and death from any cause (27%, P=0.002)(92). In the REACH Registry (Reduction of Atherothrombosis for Continued Health), 19,691 patients with diabetes and established atherothrombosis were assessed for the effect of metformin use in circumstances when the medication would historically be contraindicated. They found the mortality rates were 6.3% (95% confidence interval [CI], 5.2%-7.4%) with metformin and 9.8% (95% CI, 8.4%-11.2%) without metformin; the adjusted hazard ratio (HR) was 0.76 (0.65-0.89; P<0.001). Association with lower mortality was consistent among subgroups, noticeably in patients with a history of congestive heart failure (HR, 0.69; 95% CI, 0.54-0.90; P=0.006), patients older than 65 years (0.77; 0.62-0.95; P=0.02), and patients with an estimated creatinine clearance of 30 to 60 ml/min/1.73 m² (0.64; 95% CI, 0.48-0.86; P=0.003)(Note: to convert creatinine clearance to ml/s/m², multiply by 0.0167)(93).

Side Effects and Contraindications

The most common side effects of metformin are gastrointestinal disturbances (abdominal discomfort, diarrhea), which occur in approximately 20-30% of patients. These effects are generally transient, and can be minimized or avoided by careful dose titration. The incidence of lactic acidosis is rare and occurs with a frequency of 3 cases per 100,000 patient-years. It appears that metformin is not as unsafe as previously thought. Twenty-five percent of users have relative contraindication and yet lactic acidosis remains rare (94). In addition, the patients who do develop lactic acidosis usually have acute renal failure and previously had normal renal function (95).

Given metformin’s renal excretion, caution has been advised when prescribing it to those with or at high risk for renal insufficiency. Previously, the FDA package insert stated that metformin was contraindicated in males with a Cr ≥1.5 mg/dl, in females with a Cr ≥1.4 mg/dl, and anyone with abnormal creatinine clearance (Metformin hydrochloride tablets. Metformin Package Insert. Available at: http://www.fda.gov/ohrms/dockets/dailys/02/May02/053102/800471e6.pdf; accessed December 13,
While metformin accumulation, in the setting of renal insufficiency, may cause life-threatening lactic acidosis, clinical reviews found that metformin was not associated with an increased risk of lactic acidosis or increased lactate levels, even in those with renal dysfunction (estimated glomerular filtration rate [eGFR] 30-60 mL/min/1.73 m²)(96;97). Use of a novel assay for metformin levels has confirmed that metformin levels are not increased with eGFR levels as low as 30 ml/min per 1.73m² (98).

In addition, when lactic acidosis is found in patients taking metformin, the drug generally not responsible. These patients often have an underlying medical condition such as sepsis that is causing the lactic acidosis. Furthermore, those on metformin with an eGFR of 30 to 60 ml/min/1.73 m² have decreased mortality compared to those who are not on metformin (99). Therefore, there has been a move towards lowering the eGFR cutoff for metformin use from 60 to 30 ml/min/1.73 m². In 2012, the American Diabetes Association and the European Association for the Study of Diabetes released a position statement endorsing the United Kingdom’s National Institute for Health and Care Excellence guidelines that recommend using an eGFR cutoff of 30 ml/min/1.73 m², below which metformin is contraindicated and a dose reduction at 45 ml/min/1.73 m² (66).

While in one study published in 2015, metformin use was associated with a significantly increased all-cause mortality in patients with type 2 diabetes and stage 5 chronic kidney disease (100), this remains an outlier.

In response to a petition drive in the United states, the FDA updated guidelines on use of metformin in 2016. The key changes are as follows:

- Base assessment of renal function on eGFR, not serum creatinine.
- Obtain eGFR before starting metformin and annually; more frequently in those at risk for renal impairment (eg, the elderly).
- Metformin can be used when the eGFR is <60 mL/min but remains contraindicated in patients with an eGFR <30.
- Don’t start metformin in patients with an eGFR in the 30-45 range.
- If the eGFR falls <45 in someone on metformin, assess the overall benefits and risks before continuing treatment. Stop metformin if the eGFR falls <30.
- Hold metformin before iodinated contrast procedures if the eGFR is 30–60; also if there is any liver disease, alcoholism, or heart failure; or if intra-arterial contrast is used. Recheck the eGFR 48 hours after the procedure; restart metformin if renal function is stable.

In addition, in 2015, the American College of Radiology updated their Manual on Contrast Media with updates use of metformin in patients on metformin (101). These guidelines further the move towards not requiring metformin to be temporarily held after a contrast procedure.


**Category I.** (eGFR ≥30 ml/min/1.73 m²)

In patients with no evidence of AKI and with eGFR ≥30 mL/min/1.73 m², there is no need to discontinue metformin either prior to or following the intravenous administration of iodinated contrast media, nor is there an obligatory need to reassess the patient’s renal function following the test or procedure.

**Category II.** (eGFR <30 ml/min/1.73 m²)

In patients taking metformin who are known to have AKI or severe chronic kidney disease (stage IV or stage V; ie, eGFR <30 ml/min/1.73 m²), or are undergoing arterial catheter studies that might result in emboli (atheromatous or other) to the renal arteries, metformin should be temporarily discontinued at the time of or prior to the procedure, withheld for 48 hours subsequent to the procedure, and reinstituted only after renal function has been re-evaluated and found to be normal.

**Gadolinium-based contrast material**

It is not necessary to discontinue metformin prior to contrast medium administration when the amount of gadolinium-based contrast material administered is in the usual dose range of 0.1 to 0.3 mmol/kg body weight.

**Vitamin B12 deficiency**

Both short and long term use of metformin has been found to decrease vitamin B12 levels (decreased 4.2-47%) (15;102-106). Metformin is thought to induce malabsorption of vitamin B12 and intrinsic factor in the ileum, effects that can be reversed by increased calcium intake (107-109). Anemia may be minimal to severe (RR author observations). However, metformin-associated vitamin B12 deficiency may present without anemia and only as a peripheral neuropathy, possibly misdiagnosed as diabetic neuropathy. It has been speculated that exhaustion of vitamin B12 stores usually occurs after twelve to fifteen years of absolute and as metformin has been available in the United States for approximately fifteen years these clinical findings may now be coming to light (110).
**Thiazolidinediones: Pioglitazone and Rosiglitazone**

*Introduction*

Pioglitazone (Actos®) and rosiglitazone (Avandia®) are members of the thiazolidinedione class of insulin sensitizing compounds originally discovered and characterized for their glucose- and lipid-lowering activity (111;112). These compounds decrease insulin resistance and thereby enhance the biological response to endogenously produced insulin, as well as insulin administered by injection (113-115). Until September 23, 2010, each drug was approved for use in the US as monotherapy, therapy that results in a significant reduction in fasting plasma glucose by 60-80 mg/dl and in HbA1c by 1.4-2.6% (113). In addition, pioglitazone is approved for use in combination with insulin, metformin, or a sulfonylurea, and rosiglitazone is approved for use in combination with metformin or a sulfonylurea. Troglitazone (Rezulin®), another member of this chemical class, was withdrawn from US, European, and Japanese markets in 2000 due to idiosyncratic hepatic reaction leading to hepatic failure and death in some patients. Although there are some data from animal studies suggesting that hepatic toxicity might be characteristic of the thiazolidinedione class (116), current clinical evidence indicates that pioglitazone and rosiglitazone treatment do not result in liver toxicity (114;117-119). Higher required doses of troglitazone, due to lower potency, compared to other thiazolidinediones may have led to the higher incidence of hepatotoxicity.

As of September 2010, as a result of cardiovascular concerns (see below), rosiglitazone was removed from the European market and use in the United States was restricted by the FDA (120). Use of rosiglitazone was restricted to patients who could not use any other medication. In addition, the patient must be informed about the potential cardiovascular risks (120). As a consequence, prescription of rosiglitazone dropped by more than 90%. Recently, the cardiovascular safety concerns for rosiglitazone have been re-evaluated by an FDA advisory committee (121). Half of the panel members voiced support for easing the restrictions, while 7 out of 26 panel members voted to remove all restriction for prescription. **On Nov 25, 2013, the US Food and Drug Administration (FDA) lifted most restrictions on the prescribing and use of rosiglitazone drugs (Avandia, Avandamet, Avandaryl; GlaxoSmithKline) on the basis of data that demonstrated no elevated cardiovascular risk. All restrictions were removed in 2015.**

**Due to recent findings of possible risks of bladder cancer with continued use of pioglitazone, the FDA and the European regulatory authority (EMA) have restricted use in patients with bladder cancer or those who at risk for it.**

Thiazolidinediones, while highly effective at increasing insulin sensitivity and lowering HbA1c continue
to be troubled by safety concerns. Although pharmaceutical efforts have been directed towards the
development of safer compounds, no new drugs in this class have been approved. **Roche’s aleglitazar**
was the latest of a long list of PPAR activators that has been dropped from development, leaving only
a small number of PPAR drug candidates in development (122).

**Mechanism of Action**
The primary effects of pioglitazone and rosiglitazone are the reduction of insulin resistance and
improvement of insulin sensitivity, resulting in a reduction of fasting plasma glucose, insulin, and free
fatty acids (113;123-126). Unlike other existing anti-diabetic medications that possess a very rapid
onset of activity, pioglitazone and rosiglitazone exhibit a characteristic delay from 4-12 weeks in the
onset of their therapeutic benefits. This is likely related to their mode of action, which involves the
regulation of gene expression (123;127;128). Pioglitazone and rosiglitazone are selective agonists for
the peroxisome proliferator-activated receptor γ (PPARγ), a member of the super-family of nuclear
hormone receptors that function as ligand-activated transcription factors (129;130). The PPAR family,
which also includes PPARα and PPARδ, functions as receptors for fatty acids and their metabolites
(e.g. eicosanoids) and, consequently, plays a critical physiological role the regulation of glucose, fatty
acid, and cholesterol metabolism. PPARα is the receptor for the fibrate class of lipid-lowering drugs,
and PPARδ is the PPAR receptor involved in the regulation of high-density lipoprotein metabolism
(130;131).

The structure-activity relationship between PPARγ agonists and their glucose lowering activity *in vivo*
has been established (132). In the absence of ligand, PPARs bind as hetero-dimers with the 9-cis
retinoic acid receptor (RXR) and a multi-component co-repressor complex to a specific response
element (PPRE) within the promoter region of their target genes (130;133). Once PPAR is activated
by ligand, the co-repressor complex dissociates allowing the PPAR-RXR heterodimer to associate
with a multi-component co-activator complex resulting in an increased rate of gene transcription. The
target genes of PPARγ include those involved in the regulation of lipid and carbohydrate metabolism
(134-136).

It does not appear that rosiglitazone and pioglitazone improve insulin sensitivity and glucose disposal
by direct effects on either liver or muscle. PPARγ is expressed chiefly in adipose tissue, and its
expression in liver and skeletal muscle is low (137;138). Thus, it is more likely that the primary effects
of these drugs are on adipose tissue, followed by secondary benefits on other target tissues of insulin
(139). The ability of rosiglitazone and pioglitazone to decrease circulating free fatty acids could lead to
an improvement in insulin action in the periphery (123;124;140;141). More recently, PPARγ agonists
have been reported to increase the expression and circulating level of adiponectin (Acrp30), an adipocyte-derived protein with insulin sensitizing activity (142;143), in diabetic rodents (139) and in patients with type 2 diabetes (144). Recognition of the importance of PPARγ in the overall regulation of carbohydrate and lipid metabolism along with growing realization that the adipocyte is an endocrine organ (145;146) suggests that investigations in this area will intensify, and perhaps uncover additional mechanisms by which rosiglitazone and pioglitazone improve insulin sensitivity and glucose disposal.

**Efficacy**

**ROSIGLITAZONE:** The clinical efficacy of rosiglitazone and pioglitazone therapy has been extensively reviewed (113;114;118;147-151). Two 26-week, double blind, placebo-controlled clinical studies have established that rosiglitazone monotherapy reduces fasting plasma glucose and HbA1c in patients with type 2 diabetes (152;153). Treatment with rosiglitazone at 4 mg/day reduced fasting plasma glucose by approximately 30-45 mg/dl and HbA1c by 0.8-1.0%, compared with placebo. Treatment with rosiglitazone at 8 mg/day reduced fasting plasma glucose by approximately 45-65 mg/dl and HbA1c by 1.1-1.5%, compared with placebo (113;114;147). In patients with type 2 diabetes inadequately controlled with metformin, rosiglitazone produced a significant reduction in HbA1c compared to metformin treatment alone (154;155). In another study in which rosiglitazone was directly compared to a maximum stable dose of glyburide (15 mg/day), rosiglitazone reduced fasting plasma glucose by 25 mg/dl at 4 mg/day, and 40 mg/dl at 8 mg/day (147). The reduction in HbA1c was 0.7% for glyburide, 0.3% for rosiglitazone at 4 mg/day, and 0.5% for rosiglitazone at 8 mg/day.

**PIOGLITAZONE:** Double blind, placebo-controlled studies with pioglitazone as monotherapy, have established that this agent reduces fasting plasma glucose HbA1c in patients with type 2 diabetes (118;148;151;156). Patients treated with 15, 30, or 45 mg (once daily) pioglitazone had significant mean decreases in HbA1c (range -1.00 to -1.60% difference from placebo) and fasting plasma glucose (-39.1 to -65.3 mg/dl difference from placebo). The decreases in fasting plasma glucose were observed as early as the second week of therapy; maximal decreases occurred after 10-14 weeks and were maintained until the end of therapy (week 26). There was no evidence of drug-induced hepatotoxicity, or elevated alanine aminotransferase activity.

The efficacy and tolerability of pioglitazone in combination with metformin has been assessed in patients with type 2 diabetes (157). Patients receiving pioglitazone (30 mg) + metformin had statistically significant mean decreases in HbA1c (-0.83%) and fasting plasma glucose levels (-37.7 mg/dl) compared with placebo + metformin. Decreases in fasting plasma glucose levels occurred as early as the fourth week of therapy, the first time point at which fasting plasma glucose was measured. The pioglitazone + metformin group had significant mean percentage changes in levels of triglycerides (-18.2%) and high-density lipoprotein cholesterol (+8.7%) compared with placebo + metformin. Mean
percentage increases were noted in low-density lipoprotein cholesterol levels (7.7%, pioglitazone + metformin; 11.9%, placebo + metformin) and total cholesterol (4.1%, pioglitazone + metformin; 1.1%, placebo + metformin), with no significant differences between groups. In the extension study, patients treated with open-label pioglitazone + metformin for 72 weeks had mean changes from baseline of -1.36% in HbA1c and -63.0 mg/dl in fasting plasma glucose. In this study, there was no evidence of drug-induced hepatotoxicity.

The efficacy and tolerability of pioglitazone in combination with a sulfonylurea has been also assessed in patients with type 2 diabetes (20). Patients receiving pioglitazone (30 mg) + metformin had statistically significant mean decreases in HbA1c (-0.83%) and fasting plasma glucose levels (-37.7 mg/dl) compared with placebo + metformin. Decreases in fasting plasma glucose levels occurred as early as the fourth week of therapy, the first time point at which fasting plasma glucose was measured. The pioglitazone + metformin group had significant mean percentage changes in levels of triglycerides (-18.2%) and high-density lipoprotein cholesterol (+8.7%) compared with placebo + metformin. Mean percentage increases were noted in low-density lipoprotein cholesterol levels (7.7%, pioglitazone + metformin; 11.9%, placebo + metformin) and total cholesterol (4.1%, pioglitazone + metformin; 1.1%, placebo + metformin), with no significant differences between groups. In the extension study, patients treated with open-label pioglitazone + metformin for 72 weeks had mean changes from baseline of -1.36% in HbA1c and -63.0 mg/dl in fasting plasma glucose. In this study, there was no evidence of drug-induced hepatotoxicity.

The efficacy and tolerability of pioglitazone in combination with a sulfonylurea has been also assessed in patients with type 2 diabetes (125;158) and others (126). Twenty-three diabetic patients treated with a stable dose of sulfonylurea were randomly assigned to receive either placebo (n = 11) or pioglitazone (45 mg/day) (n = 12) for 16 weeks (158). Before and after 16 weeks of treatment, all subjects received a 75-g oral glucose tolerance test (OGTT) and peripheral insulin sensitivity was measured with a two-step euglycemic insulin clamp. After 16 weeks, pioglitazone treatment significantly decreased fasting plasma glucose, mean plasma glucose during OGTT, and HbA1c without changing fasting or glucose-stimulated insulin/C-peptide concentrations. Fasting plasma free fatty acid (FFA) and mean plasma FFA during OGTT also decreased significantly after pioglitazone treatment. Pioglitazone treatment significantly decreased endogenous glucose production, whereas insulin-stimulated total and non-oxidative glucose disposal was significantly increased indicative of an improvement in hepatic and peripheral (muscle) tissue sensitivity to insulin. Subsequent work has indicated that pioglitazone at doses of 30 and 45 mg/day (but not at doses of 7.5 or 15 mg/day) improves β-cell function along with whole-body insulin sensitivity (125).
Side Effects
The major side effects of this class of drugs are edema, weight gain, decreased hematocrit and hemoglobin, and elevated (but reversible) alanine aminotransferase activity. Unlike troglitazone, idiosyncratic hepatic reaction does not appear to be a problem with rosiglitazone or pioglitazone. The edema ranges from bothersome trace to anasarca. The mechanism of the edema production is not known. Clinically, diuretics have minimal effect on reducing the edema, though spironolactone may have more benefit than other diuretics (159). While there are no published studies on this subject, it does appear that the edema is dose dependent. Weight gain may be a modest 2-4 pounds to >20 lbs (160). Due to their mechanism of action, the risk of hypoglycemia with rosiglitazone or pioglitazone monotherapy is low. Mild to moderate hypoglycemia has been reported during combination therapy with sulfonylureas or insulin (21;113).

Cardiovascular Disease
A general listing of the cardiovascular effects of thiazolidinediones is shown below in Table 9.

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<thead>
<tr>
<th>Parameter</th>
<th>Effects</th>
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<tr>
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<td>↑ LDL cholesterol particle size</td>
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<td></td>
<td>↑ Lipoprotein a</td>
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<tr>
<td>Lipid profile</td>
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<td>↓/-- LDL/HDL ratio</td>
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<td></td>
<td>↓↑ Triglycerides</td>
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<tr>
<td>Coagulation and fibrinolysis</td>
<td>↓ Fibrinogen</td>
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<td>↓ Platelet aggregation</td>
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<td>Hemodynamic and vascular</td>
<td>↑ Intravascular volume</td>
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<td>parameters</td>
<td>↓ Blood pressure</td>
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<td></td>
<td>↓ Intima-media thickness</td>
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<td></td>
<td>↑ Endothelial function</td>
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<td></td>
<td>↓ Urine albumin excretion</td>
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</tbody>
</table>
In a meta-analysis reported by Nissen and Wolski (161), published literature and clinical trial registries were searched for cardiovascular end points such as myocardial infarction (MI) and death from cardiovascular causes. Data were combined by means of a fixed-effect model; forty-two trials were selected. In the rosiglitazone group, as compared with the control group, the odds ratio (OR) for MI was 1.43 (95% CI, 1.03-1.98; P = 0.03), and the OR for death from cardiovascular causes was 1.64 (95% CI, 0.98-2.74; P = 0.06). The authors concluded that rosiglitazone was associated with a significant increase in the risk of MI and with an increased risk of death from cardiovascular causes that had borderline significance. There were significant limitations to the study including lack of access to original data, which would have enabled time-to-event analysis, no confirmation of events, many studies had only zero or 1 report, and these trials were not designed to capture or adjudicate events. With correction of some of these limitations, another meta-analysis failed to show any statistical increased risk (162). Since that time there have been multiple meta-analyses looking at variations of the same data with variable results.

A meta-analysis of cardiovascular events using patient-level data from randomized trials comparing pioglitazone with a range of alternative regimens (163) determined that death, MI, or stroke occurred in 375 of 8,554 patients (4.4%) receiving pioglitazone and 450 of 7,896 patients (5.7%) receiving control therapy (HR, 0.82; 95% CI, 0.72-0.94; P = 0.005). The authors concluded that treatment with pioglitazone was associated with a significantly lower risk of death, MI, or stroke compared with any of the alternative regimens. Serious heart failure was increased in patients on pioglitazone, although without an associated increase in mortality (HR, 1.41; 95% CI, 1.14-1.76; P = 0.002).

There have been two prospective, randomized studies specifically looking at cardiovascular outcome and thiazolidinediones. The study looking at pioglitazone (PROactive study) failed to show a significant benefit of treatment on the primary composite end points (hazard ratio [HR], 0.90; 95% confidence interval [CI], 0.80-1.02; P = 0.095) (164). However, pioglitazone reduced risk for the main secondary end points, including death from any cause, nonfatal MI, and stroke (HR, 0.84; 95% CI, 0.72-0.98; P = 0.027). Addition of rosiglitazone to glucose-lowering therapy (RECORD Study) was confirmed to increase the risk of heart failure, but the data remained inconclusive about any possible effect on myocardial infarction. Rosiglitazone did not increase the risk of overall cardiovascular
morbidity or mortality compared with standard glucose-lowering drugs (165).

**Fractures**
In 2006, an increased risk of fractures was discovered in subjects receiving rosiglitazone participating in the ADOPT Study (A Diabetes Outcome and Progression Trial) (166). Since then there have been multiple reports on the association of thiazolidinediones and fractures with a meta-analysis of 10 randomized controlled trials (13,715 participants) and from 2 observational studies (31,679 participants) showed a significant increased risk of fractures in women (OR 2.23, 95% CI, 1.65-3.01; P<0.001), but not in men (167). There has been no explanation for the sex difference, but one may speculate that the age of the men in these studies is generally younger than one expects to see significant risk of fractures. Several studies have shown that bone mineral density declines with use of these medications (168;169).

**Bladder cancer**
Though controversial, pioglitazone has been reported to be associated with higher risks of bladder cancer (170;171). As a consequence, the FDA and the European regulatory authority have restricted use in patients with bladder cancer or those who at risk for it.

**α-Glucosidase Inhibitors**

**Introduction**
Acarbose (Precose, Glucobay) and miglitol (Glycet) are members of the α-glucosidase inhibitor class of oral anti-hyperglycemic compounds that function by blocking the enzymatic degradation of complex carbohydrates in the small intestine (172;173). These compounds lower post-prandial glucose and improve glycemic control without increasing the risk for weight gain or hypoglycemia. Each drug is approved for use in the US as monotherapy, which results in a significant reduction in fasting plasma glucose by 25-30 mg/dl, post-prandial glucose by 40-50 mg/dl, and HbA1c by 0.7-1.0% (89;172;173). In addition, acarbose is approved for use in combination with insulin, metformin, or a sulfonylurea, and miglitol is approved for use in combination with a sulfonylurea. The effects of these compounds on glycemic control are additive when used in combination, presumably since their mechanism of action is different. Neither drug is approved in the US for use in combination with a meglitinide or thiazolidinedione. α-Glucosidase inhibitors are suitable approaches for patients that have mild to moderate hyperglycemia, or those patients prone to hypoglycemia or at risk for lactic acidosis.

**Mechanism of Action**
α-Glucosidase inhibitors are competitive, reversible inhibitors of pancreatic α-amylase and membrane-
bound intestinal α-glucosidase hydrolase enzymes. Acarbose, the first α-glucosidase inhibitor discovered, is a nitrogen-containing pseudotetrasaccharide, while miglitol is a synthetic analog of 1-deoxyxojirimycin. The mechanism of action of these inhibitors is similar but not identical. They bind competitively to the oligosaccharide binding site of the α-glucosidase enzymes, thereby preventing enzymatic hydrolysis. Acarbose binding affinity for the α-glucosidase enzymes is: glycoamylase > sucrase > maltase > dextranase (172;174). Acarbose has little affinity for isomaltase and no affinity for the α-glucosidase enzymes, such as lactase (172). Miglitol is a more potent inhibitor of sucrase and maltase than acarbose, has no effect on α-amylase, but does inhibit intestinal isomaltase (172).

**Efficacy**
Clinical trials conducted to date have established that the anti-hyperglycemic effectiveness of acarbose and miglitol is less than 50% than that of either sulfonylureas or metformin. When used as monotherapy, acarbose primarily affects post-prandial glucose levels, which is reduced by 40-50 mg/dl after meal (89;172;173;175-177). In most studies, α-glucosidase inhibitors have no significant effects on either fasting insulin or whole body insulin sensitivity in patients with type 2 diabetes. However, there is some evidence that acarbose and voglibose, a structural analog of miglitol, reduces post-prandial hyperinsulinemia in glucose intolerant individuals (178;179). Some but not all studies have reported small decreases in fasting or post-prandial triglycerides (172). Since the mechanism of action of α-glucosidase inhibitors is different from other oral agents, their effects on glycemic control are additive when used in combination. As summarized by Lebovitz (172), addition of acarbose to sulfonylurea therapy decreases HbA1c by 0.85%; addition of acarbose to metformin therapy decreases HbA1c by 0.73%; and addition of acarbose to insulin therapy decreases HbA1c by 0.54%. As for monotherapy, the predominant improvement is on post-prandial hyperglycemia. Treatment with α-glucosidase inhibitors appears to have a lower rate of secondary failures characteristic of sulfonylurea and metformin therapy.

**Side Effects**
The major side effects of the α-glucosidase inhibitors are related to gastrointestinal disturbances (172;177). These occur in approximately 25-30% of diabetic patients, and include flatulence, diarrhea, bloating, and abdominal discomfort. These side effects can often be minimized by careful dose titration, and sometimes diminish with time. Acarbose is contraindicated in patients with inflammatory bowel disease, cirrhosis, or elevated plasma creatinine (>177 μmol/l). This class of drugs is associated with dose-dependent hepatotoxicity, and serum transaminase levels require monitoring for patients receiving high doses (>200 mg three times daily). Transaminase elevations, which are often asymptomatic, are reversible upon cessation of treatment. Hypoglycemia does not occur in patients on
α-glucosidase inhibitor monotherapy. If hypoglycemia occurs while a patient is taking an α-glucosidase inhibitor simultaneously with a sulfonylurea, insulin or a meglitinide, the recommended action is oral administration of pure glucose, dextrose or milk.

Overview of the Incretin Effect and the Incretins

The Incretin Effect

The incretin effect, defined by a significantly greater insulin stimulatory effect evoked after an oral glucose load than that evoked from an intravenous glucose infusion when plasma glucose concentrations are matched, was first described in the 1960s (180). This effect is shown below in Figure 7.

Figure 7. The difference between oral and intravenous glucose on insulin release. There is a significant increase in insulin with oral vs intravenous glucose: the incretin effect (180).

Although other hormones may take part in the incretin effect, the majority of the effect is thought to be due to glucose-dependent insulinotropic peptide (GIP) and glucagon like peptide-1 (GLP-1) (181-185). The physiological importance of GIP and GLP-1 in overall glucose metabolism has been demonstrated using receptor-knockout animal models (181-184), as well as with the use of receptor antagonists (185-187). Patients with type 2 diabetes have a significant reduction of the incretin effect, implying that these patients either have decreased concentration of the incretin hormones, or a resistance to their effects. GLP-1 concentrations are reduced in patients with type 2 diabetes in response to a meal, while GIP concentrations are either normal or increased, suggesting a resistance to the actions of GIP thus making GLP-1 a more logical target for therapeutic intervention (188;189).
GASTRIC INHIBITORY PEPTIDE / GLUCOSE-DEPENDENT INSULINOTROPIC PEPTIDE (GIP)
Brown and colleagues isolated the first incretin from cholecystokinin in 1971, and named it gastric inhibitory peptide (GIP) (190;191). After demonstrating its insulinotropic properties, Dupre renamed the peptide glucose-dependent insulinotropic peptide (GIP), thus preserving the acronym (192). Within minutes after ingestion of food, GIP is secreted from the K-cells located in the proximal region of the jejunum (193-195). GIP helps maintain normal glucose homeostasis in rodent models, and has an insulinotropic effect in response to hyperglycemia in both animals and humans (181;185;196). However, GIP does not inhibit glucagon secretion, and in fact may stimulate it during euglycemic states, and has no effect on gastric emptying (196-198). Furthermore, GIP concentrations in patients with type 2 diabetes are either normal, or slightly increased in response to a meal (189;196). In patients with type 2 diabetes, GIP infusion has not been able to reduce plasma glucose concentrations, due to a lack of amplification of late phase insulin response to glucose, compared to GLP-1 (196). Thus, GIP has not been considered a suitable candidate for therapeutic development for the treatment of type 2 diabetes (189).

GLUCAGON-LIKE PEPTIDE-1 (GLP-1)
GLP-1 is cleaved from the pro-glucagon molecule by the gut specific pro-hormone convertase enzymes 1 and 3 (199-201). Two forms of GLP-1 are secreted, GLP-1(7-37) and GLP-1 (7-36) amide (Figure 8)(202). The majority of circulating active GLP-1 appears to be GLP-1(7-36) amide (203;204). GLP-1 is stored in the L-cells of the ileum and colon, and is released at mealtime in response to neurohormonal signals and the presence of food in the gut (205-208).

GLP-1 exerts its effect on postprandial glucose concentrations through several mechanisms, including enhancing insulin secretion and suppressing postprandial glucagon secretion in a glucose-dependent manner (209;210). In addition, GLP-1 slows the rate of gastric emptying, which is often paradoxically accelerated in patients with diabetes (209;211). GLP-1 also acts as a postprandial satiety signal through neurohormonal networks that signal the brain to suppress appetite and food intake (204;212-214). Furthermore, GLP-1 also has direct effects on the β cells, as shown in studies done in animal models and cell lines, promoting cell proliferation and neogenesis, while preventing β-cell apoptosis (215). Additionally, GLP-1 can promote transformation of noninsulin-producing pancreatic cells into cells capable of synthesizing and secreting insulin (216-219).
Proglucagon mRNA Transcript:

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Pancreas: Glucagon, MPGF
Intestine: Glicentin, Oxyntomodulin, GLP-1, GLP-2, IP-2

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GRPP = Glicentin-Related Pancreatic Polypeptide
GLP-1 = Glucagon-Like Peptide-1
GLP-2 = Glucagon-Like Peptide-2
IP-1 = Intervening Peptide 1
IP-2 = Intervening Peptide 2
MPGF = Major Proglucagon Fragment

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**Figure 8. Processing of pro-glucagon-like peptide-1**

GLP-1 reportedly has effects on the liver, skeletal muscle as well as the adipose tissue, resulting in increased glycogen synthesis and peripheral insulin-stimulated glucose uptake (220-222). However, this effect is considered controversial, as there have been contradictory observations as well (223;224). GLP-1 receptors are also located in the heart, and have been associated with cardiovascular response to stress (219;224-226). Unfortunately, in spite of all the potentially beneficial effects of GLP-1 on glucose homeostasis, the therapeutic potential of naturally occurring GLP-1 is severely limited, due to its extremely short half-life of less than 2 minutes largely due to the degradation by the enzyme dipeptidyl peptidase IV (DPP-IV) (205;227-229).
Administration of exogenous GLP-1, as a continuous subcutaneous or intravenous infusion, has been shown to increase insulin secretion, and normalize both fasting and postprandial blood glucose concentrations. As shown in Figure 9, an infusion of GLP-1 in a hyperglycemic patient with type 2 diabetes will reduce the glucose level, increase insulin levels and suppress glucagon production (230).

![Graph showing glucose, insulin, and glucagon levels](image)

**Figure 9. Glucose-Dependent Effects of GLP-1 on Insulin and Glucagon Levels in Patients with Type 2 Diabetes.**

In one of the earliest studies with GLP-1, Gutniak et al showed that a continuous intravenous infusion of GLP-1 resulted in a reduction in the amount of insulin needed to maintain isoglycemia in patients with either type 1 or type 2 diabetes (231). A few years later, Zander et al, in a non-randomized parallel group study, showed that six weeks of continuous subcutaneous infusion of GLP-1 not only reduced fasting and postprandial plasma glucose concentrations, but also lowered HbA1c (-1.3%), and reduced body weight (~2 kg) (209). Juntti-Berggren et al reported the first randomized trial with the addition of subcutaneous infusion of GLP-1 to regular insulin therapy, and compared it with insulin therapy alone in 12 patients with type 2 diabetes (232). After initial intensive insulin therapy for 1 week, 8 patients were randomized to receive a subcutaneous infusion of GLP-1 along with injections of regular insulin with meals, and NPH insulin at bedtime, whereas 4 patients were randomized to regular insulin with meals and NPH insulin at bedtime. A significant reduction in postprandial glucose concentration was observed after one week of treatment in patients receiving subcutaneous infusion of GLP-1 added to insulin therapy, compared to insulin therapy alone. Furthermore, an additive lipid-
lowering effect was also observed in the GLP-1 infused patients (232).

In 2001, Larsen et al reported a randomized trial with continuous intravenous infusion of GLP-1 versus placebo infusion in 40 hospitalized patients with type 2 diabetes that was poorly controlled with sulfonylurea treatment (233). Sixty-three patients received an infusion of GLP-1 at 4 or 8 ng/kg/min for 16 or 24 h vs placebo for 7 days. Patients infused with GLP-1 showed a significant, dose-dependent, reduction in mean 24-hour plasma glucose concentrations compared with placebo. The fasting and nocturnal plasma glucose concentration was higher in the 16-h GLP-1 infused patients compared to the 24-h GLP-1-infused patients. GLP-1 infusion was also associated with a dose related increase in nausea, headache, and vomiting.

In another randomized study published in 2003, 16 elderly, insulin-naive patients with diabetes were divided in two groups of 8 patients each, and given either a continuous subcutaneous infusion of GLP-1 at an initial dose of 100 pmol/kg/h, titrated up to a maximum dose of 120 pmol/kg/h for 12 weeks, compared to controls treated with conventional therapy (234). Concomitant treatment with glucose lowering agents was discontinued for 1 week prior to study treatment in the group of patients infused with GLP-1, while the control group continued with their usual glucose lowering therapy without any dose changes. GLP-1 infusion was well tolerated, without significant side effects. Hypoglycemia occurred only once in the GLP-1 treatment group, while hypoglycemic events were frequent in the control group (87 events). No significant changes in HbA1c were observed, despite a discontinuation of oral hypoglycemic medications in the GLP-1 treated group. There was an enhanced glucose-induced insulin secretion, as well as an insulin-mediated glucose disposal, in the GLP-1 infused group compared to controls.

In 2004, Zander et al reported a randomized cross-over trial that evaluated the additive effect of continuous infusion of GLP-1 and pioglitazone in patients with type 2 diabetes (235). Eight patients with type 2 diabetes were given a saline infusion, continuous infusion of GLP-1 (4.8 pmol/kg/min), pioglitazone treatment (30 mg), and a combination treatment with GLP-1 infusion and pioglitazone, in a random order. During the studies with either saline or GLP-1 only infusions, the patients discontinued their normal medications for three weeks, with a 2-day washout period between the saline or GLP-1 infusions. During the studies with pioglitazone with or without GLP-1 infusion, all patients received 30 mg of pioglitazone for 12 weeks and then were randomly assigned to a 48-hour monotherapy period with either pioglitazone or a combination of GLP-1 with pioglitazone. A significant drop in fasting plasma glucose (FPG) concentrations in the GLP-1 only, pioglitazone only, and the combination of pioglitazone with GLP-1 group were observed compared to saline infusion group. FPG
was lower in combination therapy compared to monotherapy with either agent. Mean insulin concentrations were significantly higher with GLP-1 compared with pioglitazone. Glucagon concentrations were reduced in both GLP-1 treated arms compared to saline and pioglitazone treatments, and a sensation of appetite reduction was also noted in the GLP-1 treatment arms (235).

All these studies demonstrated the clinical potential of GLP-1 therapy in patients with type 2 diabetes. Unfortunately, for reasons of practicality, intravenous or subcutaneous continuous infusion of GLP-1 is not practical, as a long-term treatment of diabetes.

Two classes of agents have been developed to take advantage of the unique gluco-regulatory potential of GLP-1 (Figure 10):

1. The incretin mimetics (GLP-1 receptor agonists), such as exenatide (synthetic exendin-4, a peptide resistant to proteolytic cleavage by DPP-IV) or derivatives of GLP-1 (created by chemical modification of the native hormone, to render them resistant to rapid proteolytic cleavage by DPP-IV), targeting the pharmacological effects, and insufficient secretion of GLP-1 seen in type 2 diabetes, and
2. The DPP-IV inhibitors, compounds that increase the concentration of endogenous incretins, including GLP-1, by limiting the proteolytic cleavage by DPP-IV.

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**Figure 10. Pharmacologic effects of GLP-1.**

**GLP-1 Receptor Agonists (Incretin Mimetics)**

*EXENATIDE*: Exenatide (Byetta®) is a synthetic exendin-based GLP-1 analog that is approximately 53% homologous to native GLP-1. It is a synthetic version of exendin-4, a peptide originally identified
in the saliva of the Gila monster (*Heloderma suspectum*), and secreted upon ingestion of nutrients (210;236). It received regulatory approval in 2005. Exenatide is administered via a pre-filled subcutaneous injection device at a dose of 5 or 10 mcg twice daily, within 60 minutes before morning and evening. Current approved indications are as an add-on to metformin, sulfonylureas, thiazolidinedione, a combination of metformin and a sulfonylurea, or a combination of metformin and a thiazolidinedione. Exenatide was approved (US) as a monotherapy in 2009, and was based on a clinical study of patients with type 2 diabetes who were unable to achieve glycemic control through diet and exercise alone. Study findings showed that patients treated with 5 mcg or 10 mcg of exenatide as monotherapy reduced their HbA1C by 0.7% and 0.9%, respectively, and lost 6.0 pounds and 6.4 pounds, respectively (237).

**Mechanism of Action**

While exendin-4 has many of the properties of GLP-1, the two peptides are unique and are transcribed from distinct genes in the Gila monster. In humans and animal studies, exenatide enhances glucose-dependent insulin secretion, suppresses the elevated postprandial glucagon levels seen in type 2 diabetes, and slows the rate of gastric emptying (210;238;239) (which can be paradoxically accelerated in many people with diabetes) (210). In addition, both exenatide and GLP-1 have been reported to promote β-cell proliferation and neogenesis from ductal precursor in animal models (204;216-219;240). Data obtained in animal models also indicate that exenatide reduces food intake, promotes weight loss, and partially due to this weight loss has an insulin sensitizing effect (241;242). Moreover, exenatide has been shown to reduce food intake in healthy humans (243). Exenatide does not appear to be significantly degraded in the circulation, and is primarily cleared by the kidneys (244). After a subcutaneous injection, exenatide plasma concentrations increase in a dose-dependent manner (\( t_{\text{max}} \) of approximately 2 hours) and decay in a linear manner (\( t_{1/2} \) of 3.3 to 4.0 hours) (244).

Given the likely mechanism of action, the expected effect of the medication would be to lower postprandial glucose excursions. As shown in a study comparing the addition of either basal insulin or exenatide, exenatide suppresses the postprandial excursion while the basal insulin lowers fasting glucoses without any effect on postprandial levels. This is seen in **Figure 11** below.
Efficacy

Three large randomized, placebo-controlled clinical trials with subcutaneous administration of exenatide (bid), conducted in subjects with type 2 diabetes who were unable to achieve glycemic control with sulfonylureas and/or metformin, demonstrated that exenatide treatment resulted in mean reductions in HbA1c from baseline of ~1% accompanied by an average weight loss of 2 to 3 kg in those treated with 10 micrograms exenatide bid (246-248). In a 30-week study of exenatide 10 micrograms twice daily, used as monotherapy or in combination with one or two oral therapies, there was an HbA1c reduction of 1.5% from baseline (249). Exenatide was approved by the US FDA as a monotherapy (along with diet and exercise) for type 2 diabetes in 2009.

Side Effects

Mild-to-moderate nausea was the most commonly reported adverse event associated with exenatide, occurring with greatest frequency upon initiation, and generally subsiding with continued exposure to exenatide (246-248). Few new episodes of nausea were reported after 4 weeks of treatment. Furthermore, stepwise dose escalation was found to reduce the incidence of nausea and vomiting (250). There was no increase in the risk of hypoglycemia when exenatide was administered in combination with metformin, most likely due to the glucose-dependent actions of exenatide. However, the risk of hypoglycemia increased when exenatide was administered with a sulfonylurea, and this risk was greater when HbA1c was closer to normal, and the dose of sulfonylurea was not concomitantly reduced. The FDA had required addition of two warnings based on post-release reports. In 2008, the
A product label was updated to reflect FDA concern over reports of possible association of the drug with pancreatitis. A concern has been raised about several descriptions of acute pancreatitis, especially in diabetic patients, receiving incretin-based therapies (251;252). At this time (July, 2016), the FDA has not concluded that these drugs may cause or contribute to the development of pancreatic cancer. In November 2009, based on 78 reports of altered renal function, an alert on possible alteration in function was issued.

Approximately 45% of patients in these studies developed anti-exenatide antibodies; however, the presence of antibodies, and/or the magnitude of the antibody titer, were not associated with an individual patient’s magnitude of glycemic improvement, nor was there an association with incidence of adverse events (246-248).

• LIRAGLUTIDE

Liraglutide (Victoza™) is a once-daily GLP-1 receptor agonist with 97% amino acid sequence homology to endogenous human GLP-1 that was approved for clinical use by the FDA in January 2010. It is administered via a pre-filled subcutaneous injection device at a dose of 0.6 mg, 1.2 mg, or 1.8 mg, independently of meals. Current approved indications are as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Liraglutide is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise.

**Mechanism of Action**

Mechanism of action is as described above for the other GLP-1 receptor agonists.

**Efficacy**

Liraglutide at daily subcutaneous monotherapy doses of 1.2 and 1.8 mg as monotherapy decreased HbA1c levels from baseline by ~0.84% and ~1.14%, respectively, over 52 weeks, achieving significantly greater reductions than sulfonylurea therapy (decrease of ~0.51%) (253). In data from four clinical trials of liraglutide in combination with one or two oral therapies, there were significant reductions of HbA1c levels of ~1.0% to 1.5% for liraglutide (1.2 mg, vs placebo), and ~1.0% to 1.5% for 1.8 mg (vs placebo) (254-257). In these clinical trials of 26 to 52 weeks, liraglutide 1.2 to 1.8 mg/day produced weight reductions of ~1.0 to -3.2 kg.

**Side Effects**

In monotherapy or combination therapy trials, the rate of hypoglycemia ranged from 3% to 12%. There were no episodes requiring assistance from another person. When combined with a
sulfonylurea, the incidence ranged from 5% to 27% with six liraglutide-treated patients requiring assistance (254;255;257). Five-to-forty % of liraglutide-treated patients complained of nausea, but this generally subsided within the first 4 weeks of use (253;255-257).

Antibodies to liraglutide were found in 4% to 13% of subjects and did not appear to have any significant effect on the HbA1c-lowering efficacy of liraglutide (254;256;257). Recent findings of increased incidence of thyroid C-cell tumors in mice and rats treated with liraglutide have raised concern about possible similar effects in man (258). Further investigation showed that this effect was not seen in non-human primates, and that monitoring of patients for alterations in calcitonin levels has not pointed to any change associated with liraglutide therapy (259). **At this time the FDA recommends that patients with thyroid nodules or elevated levels of calcitonin be referred to an endocrinologist for further examination.**

**Cardiovascular outcomes and benefits**

There has been concern raised about the cardiovascular safety of anti-hyperglycemic therapies. Therefore, the FDA has mandated cardiovascular safety assessments of all new antidiabetic drugs. The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial was recently published (260). In this double-blind trial with over 9000 patients with type 2 diabetes and high cardiovascular risk with a median follow up of 3.8 years, there were better cardiovascular outcomes in the groups that received liraglutide. 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. There were fewer patients in the liraglutide group than in the placebo group to have experienced the primary outcome (608 of 4668 patients [13.0%] vs. 694 of 4672 [14.9%]; hazard ratio, 0.87). Fewer patients died from cardiovascular causes in the liraglutide group (219 patients [4.7%]) than in the placebo group (278 [6.0%]). 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%]). The number of patients who would need to be treated to prevent one event in 3 years was 66 in the analysis of the primary outcome and 98 in the analysis of death from any cause. Mean age of study subject was 64, mean duration of diabetes was 13 years, and mean glycosylated hemoglobin (HbA1c) was 8.7%. Placebo recipients were significantly more likely than liraglutide recipients to have insulin or sulfonylurea added during the trial (which might account for the 1% higher risk for severe hypoglycemia in the placebo group). The extent to which this outcome represents a direct beneficial effect of liraglutide (vs. detrimental effects of added antidiabetic drugs in the placebo group) is unclear. Editorialists' conclusions are reasonable: The results “appear encouraging, yet are not a ‘home run’” in diabetes management (261)(Brett AS Liraglutide and Cardiovascular Outcomes in Patients with Long
Benefits Beyond Glucose Control: Cardiovascular Disease
It was recently reported that liraglutide was linked to a reduction of major cardiovascular events and all-cause mortality, becoming only the second type 2 diabetes drug [the first was empagliflozin (Jardiance) (262)] to show cardiovascular benefit in a post-marketing trial (263). In the time-to-event analysis, the rate of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke among patients with type 2 diabetes mellitus was lower with liraglutide than with placebo.

ALBIGLUTIDE: Albiglutide (Tanzeum™) was approved by the US FDA in April 2014 as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm393289.htm. Approval of albiglutide was based on a series of individual phase III trials (Harmony 1-8) that included approximately 5,000 individuals.

Mechanism of Action
Mechanism of action is as described above for the other GLP-1 receptor agonists.

Efficacy
In an open-label 32-week study in 805 patients with type 2 diabetes inadequately controlled with oral drugs, Pratley and colleagues found that reductions in HbA1c with once-weekly albiglutide injections were clinically meaningful but less than those seen with daily liraglutide injections (0.78% vs 0.99%, respectively) (264). The dosage of albiglutide in the study was 30 mg once weekly titrated to 50 mg at week 6. The dosage of liraglutide was 0.6 mg once daily titrated to 1.2 mg at week 1 and 1.8 mg at week 2.

Side Effects
Patients who received albiglutide had fewer gastrointestinal events than those who received liraglutide (35.9% vs 49.9%) but had more injection-site reactions (12.9% vs 5.4%) and less weight loss (0.64 vs 2.19 kg).

Albiglutide has a Boxed Warning to warn that tumors of the thyroid gland (thyroid C-cell tumors) have been observed in rodent studies with some GLP-1 receptor agonists, but that it is unknown whether albiglutide causes thyroid C-cell tumors, including a type of thyroid cancer called medullary thyroid
carcinoma (MTC), in humans. **Albiglutide** should not be used in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (a disease where patients have tumors in more than one gland in their body and that predisposes them to MTC). The FDA is requiring the following post-marketing studies for **albiglutide**:

- a clinical trial to evaluate dosing, efficacy, and safety in pediatric patients
- a medullary thyroid carcinoma (MTC) case registry of at least 15 years’ duration to identify any increase in MTC incidence related to **albiglutide**
- a cardiovascular outcomes trial (CVOT) to evaluate the cardiovascular risk of **albiglutide** in patients with high baseline risk of cardiovascular disease.

**DULAGLUTIDE:** Dulaglutide (Trulicity™) was approved by the FDA in September 2014 as adjunctive therapy to diet and exercise to improve glycemic control in type 2 diabetes mellitus ([http://www.medscape.com/viewarticle/831969](http://www.medscape.com/viewarticle/831969)). It is administered as a once-weekly subcutaneous injection (265;266). Approval was based on six clinical trials (AWARD studies) involving a total of 3,342 patients who received dulaglutide as monotherapy, or as part of combination therapy. Dulaglutide was non-inferior to daily liraglutide as monotherapy, or as part of combination therapy. Dulaglutide was shown to be non-inferior as monotherapy compared with metformin in the AWARD-3 trial. Mean A1C reductions were dulaglutide 1.5 mg, 0.8%; dulaglutide 0.75 mg, 0.7%; compared with metformin 0.6%. AWARD-5 compared dulaglutide with sitagliptin in patients taking metformin (268). At the 52-week primary endpoint, mean A1C reductions were dulaglutide 1.5 mg, 1.1%; 0.75 mg, 0.9%; compared with sitagliptin 0.4%.

**Side Effects**
Adverse effects included nausea, diarrhea, vomiting, abdominal pain, and decreased appetite. Dulaglutide is not recommended for use as first-line pharmacologic treatment for type 2 diabetes, and
it is contraindicated in patients with personal or family history of medullary thyroid carcinoma or in those with multiple endocrine neoplasia syndrome type 2. The label includes a boxed warning that thyroid C-cell tumors have been observed in animal studies. The FDA is requiring Lilly to conduct the following post-marketing studies for dulaglutide:

- A clinical trial to evaluate dosing, efficacy, and safety in children.
- A study to assess potential effects on sexual maturation, reproduction, and central nervous system development and function in immature rats.
- An MTC case registry of at least 15 years' duration to identify any increase in medullary thyroid carcinoma (MTC) incidence with the drug.
- A clinical trial comparing dulaglutide with insulin glargine on glycemic control in patients with type 2 diabetes and moderate or severe renal impairment.
- A cardiovascular outcomes trial to evaluate the drug's cardiovascular risk profile in patients with high baseline risk for cardiovascular disease.

LIXISENATIDE: Lixisenatide (Lyxumia®) is a once daily prandial GLP-1 receptor agonist. It was approved in Europe in 2013 for the treatment of adults with type 2 diabetes mellitus to achieve glycemic control in combination with oral glucose-lowering agents and/or basal insulin when these, together with diet and exercise, do not provide adequate glycemic control. Lixisenatide is currently approved in over 60 countries throughout the world, including most EU countries, Japan, Brazil, Mexico, and many others. It is currently under review by the US FDA (as of 9/29/2015; http://www.news.sanofi.us/2015-09-29-Sanofi-New-Drug-Application-for-Lixisenatide-Accepted-for-Review-by-FDA). It is noteworthy that the New Drug Application dossier for lixisenatide was the first ever for an anti-diabetic agent to include cardiovascular outcome data. The study (ELIXA) showed that lixisenatide was non-inferior, although not superior, to placebo for cardiovascular safety (269). The US FDA advisory panel met on 5/25/2016 to discuss lixisenatide, and a positive decision regarding the acceptability of lixisenatide for the US market is expected later this year (2016).

Mechanism of Action
Mechanism of action is as described above for the other GLP-1 receptor agonists.

Efficacy
A study to assess efficacy and safety of lixisenatide monotherapy in type 2 diabetes found a once-daily dose of the drug improved glycemic control. Once-daily monotherapy significantly lowered postprandial glucose and was well tolerated by patients with type 2 diabetes (270). Once-daily
lixisenatide significantly improved HbA1c (mean baseline 8.0%) in both groups (least squares mean change vs. placebo: -0.54% (P < 0.0001). Significantly more lixisenatide patients achieved HbA1c <7.0% (52.2% 2-step, 46.5% 1-step) and <= 6.5% (31.9% 2-step, 25.4% 1-step) versus placebo (26.8% and 12.5%, respectively; P < 0.01). Lixisenatide led to marked significant improvements of 2-h postprandial glucose levels and blood glucose excursions measured during a standardized breakfast test. Mean decreases in body weight (approximately 2 kg) were observed in lixisenatide-treated groups.

Side Effects
The most common adverse event was gastrointestinal-nausea (lixisenatide 23% overall, placebo 4.1%) (270). Symptomatic hypoglycemia occurred in 1.7% of lixisenatide and 1.6% of placebo patients, with no severe episodes.

Dipeptidyl Peptidase-IV (DPP-IV) Inhibitors

Introduction
As described above, dipeptidyl peptidase IV (DPP-IV) inhibitors are compounds that increase the concentration of endogenous incretins, including GLP-1, by limiting the proteolytic cleavage by DPP-IV. As shown in Figure 8, GLP-1 is an insulinotropic hormone secreted by L-cells of the small intestine that stimulates insulin secretion in a glucose-specific manner, inhibits gastric emptying, suppresses glucagon secretion, and has central anorexic activity (229;271). Although it possesses multiple effective clinical activities, administration of GLP-1 is not an ideal approach since it cannot be administered orally. Furthermore, endogenous (and exogenously administered) GLP-1 has undesirable pharmacokinetics: after it is secreted, it is rapidly cleaved and inactivated [plasma half-life < 1 min (272)] by the enzyme DPP-IV. Thus, inhibition of DPP-IV has been suggested as a feasible alternative to elevate circulating GLP-1 levels, and overcome the limitations of GLP-1 administration (272-279).

The initial, orally active DPP-IV inhibitor, NVP-DPP728, was identified and characterized in vitro and in vivo (274;275;280-282). Inhibition of DPP-IV by NVP-DPP728 resulted in a significantly amplified early phase of the insulin response to an oral glucose load in obese fa/fa rats, and restoration of glucose excursions to normal (280). In contrast, DPP-IV inhibition produced only minor effects in lean FA/? rats. Inactivation of GLP-1 (7-36) amide was completely prevented by DPP-IV inhibition suggesting that the effects of this compound on oral glucose tolerance were mediated by increased circulating concentrations of GLP-1 (7-36) amide.
In DPP-IV(+) [but not in DPP-IV(-)] transgenic rats fed either standard chow or a high-fat diet, NVP-DPP728 significantly suppressed glucose excursions after glucose challenge by inhibiting the plasma DPP-IV activity, associated with the stimulation of early insulin secretion (281). NVP-DPP728 also improved the glucose tolerance after an oral glucose challenge by potentiating the early insulin response by inhibition of plasma DPP-IV activity in aged DPP-IV(+) Wistar and F344 rats (282). In contrast, NVP-DPP728 did not affect the glucose tolerance after an oral glucose challenge in aged DPP-IV(-)F344 rats (282). Taken together, these results indicate that treatment with NVP-DPP728 ameliorates glucose tolerance in vivo by the direct inhibition of plasma DPP-IV activity, and presumably the subsequent increase in endogenous GLP-1 action.

The clinical activity of this compound as a monotherapy was reported in patients at an early stage of type 2 diabetes (283). Compared with placebo, NVP-DPP728 at 100 mg (tid; n = 31) significantly reduced fasting glucose by 18 mg/dl (1.0 mmol/l), prandial glucose excursions by 21.6 mg/dl (1.2 mmol/l), and mean 24-h glucose levels by 18 mg/dl (1.0 mmol/l). Similar reductions were seen in the 150-mg (bid; n = 32) treatment group. Mean 24-h insulin was significantly reduced by 26 pmol/l in both groups. In the combined active treatment groups, HbA1c was significantly reduced from 7.4± 0.7% to 6.9± 0.7%. Laboratory safety and tolerability were good in all groups. These results provided clinical proof of concept that inhibition of DPP-IV is a feasible approach for the treatment of type 2 diabetes in the early stage of the disease.

*SITAGLIPTIN*: Sitagliptin (Januvia®) is a selective DPP-IV inhibitor that received regulatory approval in the US in 2006 (284).

*Mechanism of Action*

As described above, DPP-IV inhibitors are compounds that increase the concentration of endogenous incretins, including GLP-1, by limiting the proteolytic cleavage by DPP-IV. The clinical effect is to stimulate insulin secretion in a glucose-specific manner and suppress glucagon secretion.
Efficacy
In sitagliptin monotherapy studies, HbA1c was reduced from baseline by ~0.28% to 0.76% at 12 to 24 weeks (285-291). As an add-on agent, there were HbA1c reductions of 0.45% to 1.0% at 24 to 30 weeks (32;288;290;292-294). In the studies discussed above, there were no significant effects on weight reported.

Side Effects
As monotherapy, the incidence of hypoglycemia was reported to be between 0.5% to 2.2%, with no severe episodes (285-291). When used in combination with a sulfonylurea, hypoglycemia occurred in 12.2% of patients but no severe events were reported (292). Gastrointestinal events rarely occur. Headaches (incidence of 1.8% to 5.7%), nasopharyngitis (2.9% to 9.1%), and upper respiratory tract infection (0% to 8.8%) have been reported.

SAXAGLIPTIN:Saxagliptin (Onglyza®) is a selective DPP-IV inhibitor that received regulatory approval in the US in 2009.

Mechanism of Action
As described above, DPP-IV inhibitors are compounds that increase the concentration of endogenous incretins, including GLP-1, by limiting the proteolytic cleavage by DPP-IV. The clinical effect is to stimulate insulin secretion in a glucose-specific manner and suppress glucagon secretion.

Efficacy
When added to a sulfonylurea, saxagliptin at doses of 2.5 mg and 5 mg decreased HbA1c by 0.54% to 0.64%. The same doses decreased HbA1c by 0.66% to 0.94% when added to a thiazolidinedione (0.30% decrease seen with a thiazolidinedione plus placebo) (295;296).

Side Effects
At doses of 2.5 and 5 mg, saxagliptin was associated with a hypoglycemia incidence of 2.7% to 4.1% when combined with a thiazolidinedione, and 13.3% to 14.6% when combined with a sulfonylurea (295;296).
**LINagliptin**: Linagliptin (Tradjenta®) is a selective DPP-IV inhibitor that received regulatory approval in the US in 2011. Combination therapies of linagliptin with metformin (Jentadueto®) and with empagliflozin (Glyxambi®) have also been approved (see Table 4).

**Mechanism of Action**
As described above, DPP-IV inhibitors are compounds that increase the concentration of endogenous incretins, including GLP-1, by limiting the proteolytic cleavage by DPP-IV. The clinical effect is to stimulate insulin secretion in a glucose-specific manner and suppress glucagon secretion.

**Efficacy**
When given alone or added to metformin or combination of sulfonylurea and metformin in a pooled analysis of three 24-week Phase III trials, linagliptin at 5 mg qd decreased HbA1c by 1.2% in patients with HbA1c above 9.0% (vs 0.4% drop in HbA1c in placebo) (297).

**Side Effects**
At doses of 5 mg, linagliptin was associated with adverse events (61.9) at a similar rate to placebo (62.7%). Hypoglycemia incidence was rare (<1%) for linagliptin alone or in combination with metformin, but increased when combined with sulfonylurea (17.9% vs. placebo 8.3%)(297).

**ALOgliptin**: Alogliptin (Nesina®) is a selective DPP-IV inhibitor that received regulatory approval in the US in 2013. Combination therapies of alogliptin with metformin (Kazano®) and alogliptin with pioglitazone (Oseni®) have also been approved [http://www.takeda.com/news/2013/20130126_5626.html].

**Mechanism of Action**
As described above, DPP-IV inhibitors are compounds that increase the concentration of endogenous incretins, including GLP-1, by limiting the proteolytic cleavage by DPP-IV. The clinical effect is to stimulate insulin secretion in a glucose-specific manner and suppress glucagon secretion.

**Efficacy**
In a press release, the FDA cited results from 14 clinical trials involving 8500 patients. Alogliptin monotherapy resulted in reductions in HbA1c of ~0.4 % to 0.6% compared with placebo after 26 weeks of use. The combination of alogliptin with metformin resulted in additional reductions in HbA1c of 1.1 % over alogliptin and 0.5 % over metformin after 26 weeks of use. Alogliptin combined with pioglitazone resulted in a reduction in HbA1c of 0.4 % to 0.6 % over pioglitazone monotherapy and 0.4
% to 0.9 % compared to alogliptin monotherapy

**Side Effects**

Side effects of Alogliptin are low (runny nose, headache, upper respiratory tract infection). Combination therapies exhibited side effects of the individual drugs.

**Pancreatic Safety of Incretin-Based Agents (GLP-1R Agonists and DPP-IV Inhibitors)**

As a class, the DPP-IV inhibitors display low potential for side effects as noted in the individual drug reviews (298-300). A concern has been raised about several descriptions of acute pancreatitis, especially in diabetic patients, receiving DPP-IV inhibitors (251;252). Available data on these therapies have been reviewed by the FDA and presented at a NIH workshop in June 2013, and no evidence for concern for pancreatic disease that would require a change in use / restriction has been identified. It should be noted that, as a class, the DPP-IV inhibitors have been in use for only a relatively abbreviated duration, and data to be derived from studies of longer duration might present a changing perspective (301).

The pre-clinical and clinical literature contains conflicting reports regarding the use of incretin-based agents and an increased risk for the development of pancreatitis and pancreatic cancer (302). To address this issue and in an ongoing effort to ensure the safety of these products, both the US FDA and the European Medicines Agency (EMA) have independently reviewed (as of 2014) all available pre-clinical, clinical, and epidemiological data pertaining to agents that are incretin-based, i.e. that stimulate postprandial insulin secretion by potentiating incretin hormone pathways. Some of the datasets reviewed by the FDA included more than 250 toxicology studies conducted in over 18,000 healthy animals, along with more than 200 clinical trials involving approximately 41,000 subjects. With regard to the clinical trials reviewed by the FDA, there were more than 28,000 subjects who took an incretin-based agent: approximately 15,000 individuals were exposed to the agent for 24 weeks or more, and another 8,500 were exposed to the agent for 52 weeks or more. The EMA independently conducted similarly extensive reviews. The conclusion reached by each agency was that the assertions raised in the literature and media concerning a causal relationship between the use of incretin-based agents and pancreatitis or pancreatic cancer were inconsistent with current data (302). Importantly, neither the FDA nor the EMA have reached a final conclusion about a causal relationship, and will continue to regard pancreatitis as a risk associated with the use of incretin-based therapies until more data are available. Both agencies agree that the current information is reflected in product labeling, and that ongoing cardiovascular outcome studies will add to the existing knowledge base. In this regard, a large (> 970,000 subjects), population-based study reported that the use of incretin-
based drugs was not associated with an increased risk of pancreatic cancer compared with sulfonylureas (303). Although this potential adverse drug reaction will need to be monitored long term owing to the latency of the cancer, these findings provide some reassurance on the safety of incretin based drugs with respect to increasing the risk for pancreatic cancer.

**Bile Acid Sequestrant: Colesevelam**

*Introduction*

Colesevelam hydrochloride (WelChol®) is a non-absorbed, polymeric, lipid-lowering and glucose-lowering agent intended for oral administration. It is excreted primarily in the feces. Colesevelam hydrochloride is a high-capacity bile acid-binding molecule. It is poly(allylamine hydrochloride) cross-linked with epichlorohydrin and alkylated with 1-bromodecane and (6-bromohexyl)-trimethylammonium bromide.

*Mechanism of Action*

The actual glucose lowering mechanism of action remains under investigation. The proposed mechanisms of action include:

1. Decreased or slowed absorption of glucose and carbohydrates, reducing postprandial glucose excursions (304,305)
2. Alteration of nuclear receptors such as the liver X receptor (LXR) (306)
3. Alteration of GLP-1 levels (306)

*Efficacy*

Prior to FDA approval, three phase 3 clinical trials investigated the glucose-lowering efficacy of colesevelam when added to insulin-, metformin-, or sulfonylurea-based therapy, in patients with inadequately controlled type 2 diabetes (initial HbA1c, 7.5% to 9.5%) (306). Results showed that the addition of colesevelam to the existing, anti-diabetes therapy resulted in a significant placebo-corrected reduction in HbA1c (0.50%, 0.54%, and 0.54%, respectively, P<0.001 for all) (307-309).

*Side Effects*

As colesevelam is minimally absorbed from the gastrointestinal tract, few systemic adverse events occur after oral administration (310). A combination of 4 studies with enrollment of 1,129 subjects (567 patients receiving colesevelam; 562 patients receiving placebo) showed 8.6% colesevelam vs 2.0% placebo subjects complained of constipation. There were no differences in nasopharyngitis, dyspepsia, hypoglycemia, nausea, or hypertension.
Dopamine Agonist

Introduction
In 2009, bromocriptine mesylate a medication prescribed for many decades was approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. The version of this medication that was specifically approved in the US was a quick-release formulation developed by Vero Science, under the trade name Cycloset®. Bromocriptine is a centrally-acting dopamine D$_2$ receptor agonist that had been approved for the treatment of hyperprolactinemia-associated dysfunctions, acromegaly and Parkinson’s disease. The idea of using bromocriptine for the treatment of type 2 diabetes came while studying the metabolism of migrating birds, who develop seasonal insulin resistance in which dopamine plays a key role.

Mechanism of Action
Based on insulin-glucose clamp studies, the beneficial effect of bromocriptine on glucose homeostasis does not appear to be related to enhanced insulin-mediated glucose disposal or a reduction in basal endogenous glucose production. Potential unexplored mechanisms by which bromocriptine reduces the mean daylong plasma glucose levels include enhanced suppression of endogenous glucose production and/or increased splanchnic glucose uptake after glucose ingestion (311).

Efficacy
As shown in Figure 12, an early short placebo control study demonstrated a modest improvement in fasting glucose and HbA1c levels.
Figure 12. Time course of change from baseline in HbA1c and fasting plasma glucose (FPG) concentrations in bromocriptine and placebo-treated subjects (311).

In studies filed with the FDA but not yet published, for the specific preparation, Cycloset®, demonstrated minimal change in fasting glucose and HbA1c from baseline and modest improvement from placebo. These results are shown in Table 9.

Table 9. Changes in HbA1c and Fasting Glucose with the Bromocriptine Preparation Cycloset®.

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Change from Baseline</th>
<th>Change from Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>-0.1</td>
<td>-0.4</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>0</td>
<td>-23</td>
</tr>
<tr>
<td>Add to Sulphonylurea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>-0.25</td>
<td>-0.55</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>+7</td>
<td>-19</td>
</tr>
<tr>
<td>Add to metformin and sulphonylurea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>-0.5</td>
<td>-0.5</td>
</tr>
</tbody>
</table>
Side Effects
The most common adverse events associated with bromocriptine mesylate are nausea, fatigue, dizziness, vomiting and headache. Clinical trial data reveal that bromocriptine mesylate at doses up to 4.8 mg per day was not associated with a different rate of all-cause adverse events compared with placebo. However, the drug is known to be associated with nasal stuffiness, nausea, headache, constrictive pericarditis, neuroleptic malignant syndrome, and hypotension. The incidence of hypoglycemia was 6.9% among bromocriptine mesylate-treated patients compared with 5.3% of patients receiving placebo.

In the pooled CYCLOSET™ phase 3 clinical trials (CYCLOSET N = 2298; placebo N = 1266) data, adverse events leading to discontinuation occurred in 539 (24%) CYCLOSET-treated patients and 118 (9%) placebo-treated patients. This between-group difference was driven mostly by gastrointestinal adverse events, particularly nausea.

This drug is contraindicated in patients with known hypersensitivity to bromocriptine or ergot-related drugs. It is also contraindicated in patients with syncopal migraine. Bromocriptine increases the likelihood of a hypotensive episode among patients with syncopal migraine. It is also contraindicated in nursing women as it may inhibit lactation. There are post-marketing reports of stroke in these patients, although causality has not been proven.

Pramlintide
Introduction
The hormone amylin (Figure 13) is co-secreted with insulin by the pancreatic β cells in response to nutrient stimuli (312;313). Patients with type 1 diabetes may develop an absolute deficiency of both insulin and amylin (314), and those with type 2 diabetes have impaired beta-cell secretion amylin in response to a meal (315). Amylin suppresses post-prandial arginine-stimulated glucagon secretion (316) and slows gastric emptying time (317). Pramlintide (Symlin®) is a soluble synthetic analog of human amylin, allowing clinical application of this hormone.
Mechanism of Action

Pramlintide, an injectable synthetic analog of amylin, slows gastric emptying, attenuates post-prandial glucagon secretion, enhances satiety, and reduces food intake (318-320).

Efficacy

When added to pre-prandial insulin, pramlintide improves post-prandial glucose control and promotes weight loss in patients with both type 1 and type 2 diabetes (321-327). As shown in Figure 14, post-prandial glucose excursions are significantly blunted with the addition of pramlintide. Effects on HbA1c reduction are modest, with 52-week net reduction of 0.27% at 1 year (323). Similar reductions in HbA1c and weight have been reported in insulin-treated patients with type 2 diabetes (325;327).
Figure 14. Effect of pramlintide on post-prandial glucose (323).

Pramlintide has also been used as a pre-meal injection without concurrent pre-meal insulin in type 2 diabetes. In preliminary studies, when compared to patients receiving pre-prandial insulin (Figure 15), these patients were able to achieve similar glucose control with less hypoglycemia and without the weight gain seen with pre-prandial insulin (328).
Figure 15. Comparison of post-prandial insulin and pramlintide on glucose and body weight (328).

Side Effects
To date, there have not been any significant reports of toxicity to any major organs, significant elevations in laboratory tests, alterations in vital signs, electrocardiographic parameters, or physical exams. Overall, nausea, vomiting, and anorexia were the most frequently reported adverse drug events associated with pramlintide therapy. Rates of nausea were generally 16.5-25% (pramlintide) vs 9.5%-16% (placebo group). In patients with type 1 diabetes, these symptoms were mild to moderate and transient (within the first 4-8 weeks). The findings were similar in patients with type 1 diabetes and those with type 2 diabetes (327;329).
Sub-Type 2 Sodium-Glucose Transport Protein (SGLT2) Inhibitors: Canagliflozin, Dapagliflozin, and Empagliflozin

Introduction
SGLT2 are responsible for 90% of glucose re-absorption in the renal proximal tubules. They are a sub-type of sodium glucose transport proteins that, as the name suggests, allows for co-transport of sodium and glucose utilizing the energy of a sodium gradient to move glucose across a membrane. SGLT2 is a high capacity, low affinity transporter. It is able to effectively reabsorb glucose up to a blood glucose level of approximately 180 mg/dl. Hence, the appearance of sweet urine in untreated diabetics exceeding this blood glucose threshold. The renal threshold for glucose is further increased in type 2 diabetic subjects (330). Inhibition of SGLT2 will lower this threshold and will lead to urinary excretion of glucose at lower circulating glucose levels. The loss of glucose in the urine lowers the blood glucose level and also results in weight loss owing to caloric loss.

Traditionally, the SGLT inhibitor, phlorizin which is present in some plants, has been used in experimental diabetes to separate effects of hyperglycemia from other mechanisms affecting metabolism. In recent years, pharmaceutical companies, beginning with Tanabe, have targeted the SGLT2 transporter with selective inhibitors. The first SGLT2 inhibitor approved by the FDA in 2013 was canagliflozin. On January 8, 2014, the US FDA approved dapagliflozin for glycemic control, along with diet and exercise. In October, 2014, the FDA approved the combination product dapagliflozin and metformin called Xigduo XR®. A third SGLT2 inhibitor, empagliflozin (Jardiance®), was approved by the European Medicines Agency in May 2014, followed by approval by the FDA in August 2014. The FDA required four post-marketing studies: a cardiovascular outcomes trial, two studies in pediatric populations, and a toxicity study in animals related to the pediatric studies (see below).

In a study using empagliflozin, Ferrannini et al showed that in patients with type 2 diabetes, empagliflozin-induced glycosuria improved β-cell function and insulin sensitivity, despite the fall in insulin secretion and tissue glucose disposal and the rise in endogenous glucose production after one dose, thereby lowering fasting and postprandial glycemia (331). Interestingly, Bonner et al found that the inhibition of SGLT2 can induce glucagon secretion (332). SGLT2 transporters are present in pancreatic alpha cells and their inhibition triggers the release of glucagon.

FDA issued a Drug Safety Communication in May 2015 warning about the risk of ketoacidosis with SGLT2 inhibitors and alerting that the Agency would continue to evaluate this safety issue. A review of the FDA Adverse Event Reporting System (FAERS) database from March 2013 to May 2015 identified 73 cases of ketoacidosis in patients with type 1 or type 2 diabetes treated with SGLT2 inhibitors. In May 2015, the EMA (European Medicines Agency) reported 147 cases of ketoacidosis. The frequency
of ketoacidosis in clinical trials which led to the approval of these drugs was small (<0.1%) but occurred in 4-6% of patients when the inhibitor was added to insulin in patients with type 1 diabetes. There have been increasing reports of the disorder in surveillance of post-marketing use. In the majority of cases, there have been precipitating risk factors. The reduction in plasma insulin and glucose levels, induced by SGLT2 inhibitors, leads to decreased carbohydrate oxidation. In order to maintain energy homeostasis there is a shift in metabolism toward lipid oxidation fueled by increased lipolysis and circulating fatty acids. Conditions with more severe insulin deficiency or severe decrease in carbohydrate availability would exacerbate the degree of ketogenesis. Symptoms of ketoacidosis include nausea, vomiting, abdominal pain, tiredness, and trouble breathing. Patients should be educated about these symptoms and advised to stop their SGLT2 inhibitors and seek medical attention.

FDA also identified 19 cases of life-threatening blood infections (urosepsis) and kidney infections (pyelonephritis) that started as urinary tract infections with the SGLT2 inhibitors reported to FAERS (FDA Adverse Event Reporting System) from March 2013 through October 2014. All 19 patients were hospitalized, and a few required admission to an intensive care unit or dialysis in order to treat kidney failure. Patients should be counseled to contact their medical provider if they experience UTI symptoms.

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 (333). Furthermore, a roughly 30% increase in bone fractures was noted in patients receiving canagliflozin in a pooled analysis of eight clinical trials with mean duration 68 weeks (334). FDA has added a safety alert in September 2015 for canagliflozin related to the increased risk of bone fractures and decreased bone mineral density to the product labeling. SGLT2 inhibitors increase concentrations of phosphate in serum, probably via increased tubular reabsorption, which has the potential to adversely affect bone. Furthermore, SGLT2 inhibitors increase concentrations of PTH (334). Future mechanistic research might identify patients who are most susceptible to development of drug-induced bone fractures, and could suggest therapeutic approaches to minimize the risk.
Canagliflozin (Invokana®) is a 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. In August 2014, the US FDA approved canagliflozin in a fixed dose combination with metformin (Invokamet®).

**Mechanism of Action**
Canagliflozin is a selective SGLT2 inhibitor (257).

**Efficacy**
A dose ranging study with canagliflozin in type 2 diabetic patients insufficiently controlled by metformin therapy (HbA1c 7.6-8.0%) for 12 weeks resulted in a 0.7-0.92% reduction in HbA1c with doses ranging from 50-300mg qd compared to -0.22% HbA1c in placebo. Canagliflozin (300 mg, bid) resulted in a 0.95% reduction in HbA1c (335). Due to the loss of energy through glycosuria, a loss of body weight can be seen.

**Side Effects**
The most common side effects of canagliflozin are vaginal yeast infection (vulvovaginal candidiasis) and urinary tract infection. Because canagliflozin is associated with a diuretic effect, it can cause a reduction in intravascular volume leading to orthostatic or postural hypotension (a sudden fall in blood pressure when standing up). This may result in symptoms such as dizziness or fainting, and is most common in the first three months of therapy. Due to the mechanism of action of SGLT2 inhibitors, the potential for hypoglycemia is low. **The FDA has required a cardiovascular outcomes trial for canagliflozin.** While this study is not expected to be completed until 2017, some interesting trends emerged. Composite endpoint consisting of CV death, non-fatal myocardial infarct, nonfatal stroke, hospitalized unstable angina was elevated during the first 30 days of treatment (13 events in canagliflozin, 1 in placebo), while the ratio reversed as the trial continued. Whether this is a reflection of low number of subjects will have to become apparent with greater datasets.

In the ongoing **Canagliflozin Cardiovascular Assessment Study (CANVAS) clinical trial**, the trial’s independent data monitoring committee (IDMC) identified an increased risk of leg and foot amputations. The amputations occurred about twice as often in patients treated with canagliflozin compared to patients treated with placebo, which is an inactive treatment. An interim analysis showed that over a year’s time, the risks of amputation for patients in the trial were equivalent to:

- 7 out of every 1,000 patients treated with 100 mg daily of canagliflozin
• 5 out of every 1,000 patients treated with 300 mg daily of canagliflozin
• 3 out of every 1,000 patients treated with placebo

Patients in the CANVAS trial have been followed for an average of 4.5 years to date. The IDMC has recommended, based on an overall assessment, that the CANVAS trial continue. The IDMC has also reported that a second, similar trial evaluating canagliflozin, the CANVAS-R trial, has not shown the same risks of increased leg and foot amputations to date. Patients in the CANVAS-R trial have been followed for an average of 9 months. The FDA has not determined whether canagliflozin actually increases the risk of leg and foot amputations. They are currently investigating this new safety issue (as of 5/18/2016) and will provide an update when they have more information.

**DAPAGLIFLOZIN:** Dapagliflozin (Forxiga®) is a 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. In October 2014, the US FDA approved dapagliflozin in a fixed dose combination with metformin extended release (Xigduo XR®).

*Mechanism of Action*
Dapagliflozin is a selective SGLT2 inhibitor ([https://www.diabetesalliance.co.uk/hcp/forxiga/moa/](https://www.diabetesalliance.co.uk/hcp/forxiga/moa/)).

*Efficacy*
Safety and efficacy were established in 16 clinical trials of over 9,400 diabetes patients and showed patients had improvements in HbA1c with this drug. For a summary of these results, see the following link: [https://www.diabetesalliance.co.uk/hcp/forxiga/hba1c/](https://www.diabetesalliance.co.uk/hcp/forxiga/hba1c/), and the data below.

a) **Dapagliflozin (Forxiga™) plus metformin vs. sulphonylurea plus metformin**
As shown in **Figure 16**, dapagliflozin produced comparable reductions in HbA1c to a sulphonylurea (glipizide) when added to metformin (336). Dapagliflozin showed a sustained effect on glycemic control at 104 weeks compared to baseline. The primary endpoint shows that when added to metformin, HbA1c reductions were comparable between dapagliflozin (-0.52%) and glipizide (-0.52%) at 52 weeks (336).
Figure 16. Efficacy of dapagliflozin plus metformin compared to glipizide plus metformin.

b) Dapagliflozin vs placebo

Significant and sustained HbA1c reductions vs placebo when added-on to metformin (337;338). As shown in Figures 17 and 18, dapagliflozin produced significant reductions in HbA1c compared to placebo at the 24-week primary endpoint. Dapagliflozin produced significant reductions in HbA1c that were sustained over 102 weeks.

Figure 17. Efficacy of dapagliflozin plus metformin compared to placebo plus metformin.
The FDA is requiring six post-marketing studies for dapagliflozin (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm380829.htm):

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

The results of these trials have not yet been reported. However, a meta-analysis of the cardiovascular effects of dapagliflozin in patients with type 2 diabetes has been recently published (339). A total of 9,339 patients from 21 Phase 2b/Phase 3 clinical studies were included. The authors concluded that dapagliflozin was not associated with increased cardiovascular risk, and that there seemed to be an apparent benefit in the overall population, and in those individuals with a history of cardiovascular disease.

Side Effects
In clinical trials the most common side effects observed in patients treated with dapagliflozin were genital mycotic (fungal) infections and urinary tract infections.
Empagliflozin (Jardinace®) is the most recently approved member of the SGLT2 inhibitor class of anti-diabetic medications, receiving US FDA approval in August 2014. It is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes, in the dose range of 10-25 mg per day. Empagliflozin has >2,500-fold selectivity for SGLT2 vs SGLT1, greater than all the other SGLT2 inhibitors currently available in the US and Europe [ie canagliflozin (selectivity index of 414) and dapagliflozin (selectivity index of 1200)] (340;341). Empagliflozin has also been approved for use in the US (2015) in two separate fixed dose combination medications: in combination with the DPP-IV inhibitor linagliptin (Glyxambi®), and with metformin (Synjardy®)(see Table 4).

Mechanism of Action
Empagliflozin is a selective SGLT2 inhibitor (340).

Efficacy
A recent comprehensive review of the clinical pharmacology including efficacy of empagliflozin monotherapy and in combination is provided by Munir and Davis (340). A total of 986 patients with type 2 diabetes participated in a double-blind, placebo-controlled study to evaluate the efficacy and safety of empagliflozin monotherapy. Treatment-naïve patients with inadequately controlled type 2 diabetes entered an open-label placebo run-in for 2 weeks. At the end of the run-in period, patients who remained inadequately controlled and had an HbA1c between 7 and 10% were randomized to placebo, empagliflozin 10 mg, or empagliflozin 25 mg. At Week 24, treatment with empagliflozin 10 mg or 25 mg daily resulted in statistically significant reductions in HbA1c (P <0.0001), fasting plasma glucose (FPG), and body weight compared with placebo (Table 10).
Table 10. Effects of Empagliflozin Monotherapy vs Placebo on Glycemic Control at Week 24

<table>
<thead>
<tr>
<th></th>
<th>JARDIANE 10 mg N=224</th>
<th>JARDIANE 25 mg N=224</th>
<th>Placebo N=218</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HbA1c (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>7.9</td>
<td>7.9</td>
<td>7.9</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>-0.7</td>
<td>-0.8</td>
<td>0.1</td>
</tr>
<tr>
<td>Difference from placebo (adjusted mean) (97.5% CI)</td>
<td>-0.7 (-0.9, -0.6)</td>
<td>-0.9 (-1.8, -0.7)</td>
<td>--</td>
</tr>
<tr>
<td>Patients [n (%)] achieving HbA1c &lt;7%</td>
<td>72 (35%)</td>
<td>88 (44%)</td>
<td>25 (12%)</td>
</tr>
<tr>
<td><strong>FPG (mg/dL)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>153</td>
<td>153</td>
<td>153</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>-19</td>
<td>25</td>
<td>12</td>
</tr>
<tr>
<td>Difference from placebo (adjusted mean) (95% CI)</td>
<td>-31 (-37, -26)</td>
<td>-36 (-42, -31)</td>
<td>--</td>
</tr>
</tbody>
</table>

**Body Weight**

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Baseline (mean in kg)</td>
<td>78</td>
<td>78</td>
<td>78</td>
</tr>
<tr>
<td>% change from baseline (adjusted mean)</td>
<td>-2.8</td>
<td>-3.2</td>
<td>-0.4</td>
</tr>
<tr>
<td>Difference from placebo (adjusted mean) (95% CI)</td>
<td>-2.5 (-3.1, -1.9)</td>
<td>-2.8 (-3.4, -2.2)</td>
<td>--</td>
</tr>
</tbody>
</table>

*Modified intent to treat population. Last observation on study (LOCS) was used to impute missing data at Week 24. At Week 24, 94.9%, 94.4%, and 30.7% were imputed for patients randomized to JARDIANE 10 mg, JARDIANE 25 mg, and placebo, respectively. \( ^a \) ANCOVA derived p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, renal function, and region. Body weight and FPG: same model used as for HbA1c but additionally including baseline body weight/baseline FPG, respectively.)

**Source:** [http://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Jardiance/jardiance.pdf](http://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Jardiance/jardiance.pdf)

The FDA is requiring six post-marketing studies for empagliflozin

[http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm407637.htm](http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm407637.htm)

- Completion of an ongoing cardiovascular outcomes 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.

**Side Effects**

The following side effects / adverse reactions have been reported with the use of empagliflozin: hypotension, ketoacidosis, impairment in renal function, urosepsis and pyelonephritis, hypoglycemia with concomitant use with insulin and insulin secretagogues, genital mycotic infections, and increased low-density lipoprotein cholesterol (LDL-C) ([http://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Jardiance/jardiance.pdf](http://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Jardiance/jardiance.pdf))

**Cardiovascular outcomes and benefits**

While the benefit of strict glycemic control on reducing the microvascular complications of diabetes is well established (35), the impact of tight glycemic control on reducing the macrovascular complications is still unproven with the exception of metformin (342). In this regard, empagliflozin therapy is reported
to have beneficial effects on cardiovascular indices, including a reduction of blood pressure, arterial stiffness, and vascular resistance (343). More importantly, empagliflozin has recently been shown to exert a significant and clinically meaningful effect on accepted cardiovascular outcome measures in over 7,000 high-risk patients with established cardiovascular disease (262). Compared with placebo, empagliflozin significantly lowered the risk of death from cardiovascular causes [Hazard Ratio (HR) 0.62], death from any cause (HR 0.68), and hospitalization for heart failure (HR 0.65). At 12 weeks, the difference in HbA1c was −0.54% to −0.60% in the empagliflozin group vs placebo; at week 94, the difference was −0.42% to −0.47%; and at week 206, the difference decreased to −0.24% to −0.36%. Sub-group analyses showed that the greatest reduction in cardiovascular death was observed in individuals with HbA1c < 8.5%, and 65 years of age or older. Three comprehensive reviews of the effects of each SGLT2 inhibitor on cardiovascular outcomes are provided by Wu et al (344), Ghosh et al (345), and Inzucchi (341). The FDA advisory panel approved a cardiovascular benefit claim for empagliflozin in June 2016. The Endocrine and Metabolic Drug Advisory Committee (EMDAC) “drew nearly even on the question of whether a large post-market study offered “substantial evidence to establish that the drug reduced cardiovascular mortality in the population studied” according to MedPage Today (http://www.medpagetoday.com/cardiology/prevention/58822).

Renal outcomes and benefits
Empagliflozin has been shown to reduce intra-glomerular pressure and hyper-filtration in patients with type 1 diabetes (346;347), and it has been suggested that these effects may translate into improved renal outcomes. In the cardiovascular outcome trial for empagliflozin, pre-specified secondary outcomes were a composite microvascular outcome that included the first occurrence of any of the following: the initiation of retinal photocoagulation, vitreous hemorrhage, diabetes-related blindness, or incident or worsening nephropathy. The report of renal microvascular outcomes was recently published (348). The composite renal outcome of incident or worsening nephropathy occurred in significantly fewer empagliflozin patients than placebo patients (12.7% vs. 18.8%) with a hazard ratio in the empagliflozin group of 0.61. 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 relative risk reduction of 44%. Renal-replacement therapy was initiated in 13 of 4687 patients (0.3%) in the empagliflozin group and in 14 of 2333 patients (0.6%) in the placebo group, representing a 55% lower relative risk in the empagliflozin group. Among patients with no albuminuria at baseline, empagliflozin did not prevent development of microalbuminuria. Most of the renal benefit was driven by less progression to macroalbuminuria. Also, it is important to note that these were high-risk patients; all had previously diagnosed cardiovascular disease.
EMERGING APPROACHES

The development pipeline for new oral therapeutic agents for type 2 diabetes is encouraging and continues to expand. These intensive research and development efforts are in response to the increasing prevalence of the disease and related co-morbidities, realization by caregivers that successful glycemic control inevitably requires combination therapy for most patients, a growing understanding of the pathophysiology of the disease, and the identification and validation of new pharmacological targets. These targets include receptors and enzymes that: enhance glucose-stimulated insulin secretion, suppress hepatic glucose production, increase skeletal muscle glucose transport and utilization, increase insulin sensitivity and intracellular insulin signaling, reduce inflammation and cortisol, and modulate the microbiome. This section will highlight compounds in development that are directed at several molecular targets for approved anti-diabetic drugs, along with emerging approaches with mechanisms of action distinct from those of existing therapies. Extensive recent reviews on these topics are provided by Mittermayer et al (12) and Bailey et al (13).

Compounds in Development Possessing Mechanisms of Action Exhibited by Approved Drugs

There are a number of new compounds in late-stage clinical development possessing mechanisms of action identical to several approved agents. These agents are listed in Table 11.

• GLP-1 RECEPTOR AGONISTS (INCRETIN MIMETICS)
• Dipeptidyl peptidase-IV (DPP-IV) INHIBITORS
• SGTL2 INHIBITORS
<table>
<thead>
<tr>
<th>General Class and Compound Name</th>
<th>Compound Designation</th>
<th>Manufacturer</th>
<th>Most Recent Development Phase</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GLP-1 Receptor Agonist (Incretin Mimetic)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GLP-1 analog</td>
<td>NN9535</td>
<td>Novo Nordisk</td>
<td>3</td>
<td>Once weekly injectable</td>
</tr>
<tr>
<td>Exenatide, sc</td>
<td>ITCA 650</td>
<td>Intarcia</td>
<td>3</td>
<td>Continuous sc delivery of exenatide; once or twice yearly administration</td>
</tr>
<tr>
<td>GLP-1 analog, oral</td>
<td>NN9924</td>
<td>Novo Nordisk</td>
<td>2/3</td>
<td></td>
</tr>
<tr>
<td>GLP-1R agonist, oral</td>
<td>TTP273</td>
<td>vTv Therapeutics</td>
<td>2</td>
<td>Small molecule GLP-1R agonist</td>
</tr>
<tr>
<td>GLP-1R agonist (Efpeglenatide)</td>
<td>SAR439977</td>
<td>Sanofi</td>
<td>2</td>
<td>Long acting GLP-1 agonist</td>
</tr>
<tr>
<td>Exenatide, oral</td>
<td>ORMD-0901</td>
<td>Oramed</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>DPP-IV Inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trelagliptin, oral; once weekly</td>
<td>SYR-472</td>
<td>Takeda</td>
<td>3</td>
<td>Approved in Japan (2015); development status in other world areas unclear</td>
</tr>
<tr>
<td><strong>SGLT2 Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ertuglifozin</td>
<td>MK-8835 and PF-04971729</td>
<td>Merck/Pfizer</td>
<td>3</td>
<td>Phase 3 data to be presented at 2016 ADA meeting; also being developed in fixed combinations with metformin and sitagliptin</td>
</tr>
<tr>
<td>Bexagliflozin</td>
<td>EGT0001442</td>
<td>Theracos</td>
<td>1/2</td>
<td>To be compared to glymepride in combination with metformin in upcoming clinical trial</td>
</tr>
</tbody>
</table>

For the definition of Development Phase, see the following link: [https://www.takeda.com/research/pipeline/](https://www.takeda.com/research/pipeline/)
Compounds in Development with Novel Mechanisms of Action
There are a number of new compounds in early-stage clinical development possessing mechanisms of action distinct to those exhibited by currently approved agents. These agents are listed in Table 12.

- **DUAL GLP-1 / GLUCAGON RECEPTOR AGONISTS (INCRETIN MIMETIC)**

A number of gastrointestinal peptides are released in response to food, and these peptides affect energy homeostasis and food intake. Investigational agents have been designed to harness the effects of these gastrointestinal hormones individually or in combination. Oxyntomodulin (OXM) is a peptide generated by post-translational processing of preproglucagon in the gut and is secreted post-prandially from L-cells of the jejuno-ileum together with other pre-proglucagon-derived peptides including GLP-1 (349). In rodents, OXM reduces food intake and body weight, increases energy expenditure, and improves glucose metabolism (350-352). OXM activates both, the GLP-1 receptor (GLP-1R) and glucagon receptor (GCGR) in vitro, with 10- to 100-fold reduced potency compared with the cognate ligands GLP-1 and glucagon, respectively (353-355). Hence, the actions of OXM encompass the effects elicited by GLP-1 and glucagon, including reductions in a) food intake, b) gastric emptying, c) gastric acid secretion, d) β-cell apoptosis and increases in a) hepatic glucose production (counteracted by the simultaneous activation of GLP-1R), b) insulin secretion, c) somatostatin secretion (356;357). In a clinical trial in healthy volunteers (n=15), OXM, GLP-1, and glucagon decreased food intake but with no additional effect above that of the combination of GLP-1 and glucagon (358). Gastric emptying was reduced by all interventions except glucagon alone. Merck has sponsored a clinical trial evaluating OXM in individuals with type 2 diabetes. They reported a reduction in glucose levels following a single dose of OXM. ZP2929, a once-daily dual acting GLP-1 / GCGR peptide receptor agonist, is being developed for the treatment of diabetes and/or obesity, by Zealand Pharma (Copenhagen, Denmark) and was last reported to be in clinical Phase I (status updated 6/8/2016). TT401, a once-weekly dual acting GLP-1 / GCGR peptide receptor agonist, is being developed for the treatment of diabetes and/or obesity, by Transition Therapeutics in collaboration with Eli Lilly and was last reported to be in clinical Phase 2 (status updated 6/8/2016). Information about their interesting and promising clinical study results (2013 and 2016) are provided at the following links:

http://www.transitiontherapeutics.com/media/news.php

**DUAL GLP-1 / GIP RECEPTOR AGONISTS (INCRETIN MIMETIC)**

GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) are the primary hormones responsible for the incretin effect (see above). An experimental incretin mimetic has been reported that targets the
receptors for GLP-1 and GIP and has provided some interesting results (359). Most recently, Marcadia Biotech (subsequently acquired by Roche in 2010) has created a 40 amino acid pegylated peptide, MAR701, that stimulates both receptors. **Phase 1 data indicates that subcutaneous injections of MAR701 in healthy volunteers** augmented the insulin response to a graded glucose infusion, without affecting gastric emptying. No additional data are publically available for this agent, and it is assumed that commercial development has been terminated by Roche.

**SUB-TYPE 1 SODIUM-GLUCOSE TRANSPORT PROTEIN (SGLT1) INHIBITORS AND SGLT1/SGLT2 DUAL INHIBITORS**

In contrast to SGLT2 which is expressed almost exclusively in the kidney, SGLT1 is predominantly expressed in the lumen of the small intestine. It plays an important role in the absorption of both glucose and sodium. The function of SGLT1 in glucose absorption suggests that inhibitors could exert a beneficial impact on glycemia and energy balance. This rational has led to the active development of selective SGLT1 and dual SGLT1/SGLT2 inhibitors. A number of these compounds in development have shown efficacy on prandial glycemic excursions.

**PPAR AGONISTS**

The development of PPAR agonists seems to have lost all momentum and the interest of all but a few companies. A search of the portfolios and pipelines listed on company websites failed to produce any current development projects, at any stage, for glycemic control for individuals with type 2 diabetes, with the exception of two compounds: lobeglitazone (Duvie™) and chiglitazar (CS038). Lobeglitazone is a dual PPARα / PPARγ thiazolidinedione agonist that was approved for glycemic control in Korea in 2013 (Chong Kun Dang); post-market surveillance is ongoing through 2019. The recommended dose is 0.5 mg per day. There are a number of published studies reporting the safety, tolerability, pharmacokinetics, and clinical efficacy of this novel compound (24874)(360-362). An excellent presentation (Dr. Sin Gon Kim, Korea University College of Medicine; 2013) covering this new agent is provided at the following link: http://icdm2013.diabetes.or.kr/slide/Luncheon%20symposia%20Sin%20Gon%20Kim.pdf

The clinical efficacy regarding glycemic and lipid control appears similar to pioglitazone (15 mg qd), but with a better safety profile. The long-term cardiovascular safety is currently being monitored in the post-marketing studies. It is not known if there are plans to develop this compound in other markets.

Chiglitazar is classified as a pan-PPAR agonist, ie with affinity to PPARα, PPARγ, and PPARδ, and according the [Chipscreen Biosciences website](http://icdm2013.diabetes.or.kr/slide/Luncheon%20symposia%20Sin%20Gon%20Kim.pdf) appears to be active in their development pipeline. According to [Chipscreen Biosciences](http://icdm2013.diabetes.or.kr/slide/Luncheon%20symposia%20Sin%20Gon%20Kim.pdf), chiglitazar is a non-thiazolidinedione structure, with a selective
transcriptional activation profile distinct from other first-generation PPARγ agonists (Avandia™ and Actos™) (363). According to Chipscreen Biosciences, in a two-year carcinogenicity study, chigitazar did not induce carcinogenesis and significantly repressed breast tumors formation in rat. According to Chipscreen Biosciences, data from phase 2A and Phase 2B, with over 450 patients vs pioglitazone (Actos™), demonstrated similar clinical activity on decreasing Hb1Ac and fasting plasma glucose, and increasing HDL-cholesterol. The effects on decreasing triglycerides, total cholesterol, blood pressure, and LDL-cholesterol were better compared to pioglitazone. According to Chipscreen Biosciences, the studies indicated an excellent safety profile with no increase of body weight. It must be pointed out, that this information regarding the clinical data was derived from the company website, and no published information is available to support these clinical effects. In addition, no information on the cardiovascular safety was provided. It will be interesting to see the development fate of this interesting compound.

**INSULIN RECEPTOR ACTIVATORS**

In recent years, several reports have been published evaluating XMetA, a human, monoclonal antibody (Mab) that is an allosteric activator of the insulin receptor. This Mab binds the insulin receptor with high affinity and mimics the glucoregulatory actions of insulin, but not the mitogenic actions. Although no clinical trial data has been reported, the data from in vitro and pre-clinical models including primates are extremely encouraging (364-366). Xoma, the company that originally created this technology, licensed XMet A to Novo Nordisk for an upfront payment of $5 million, potential milestone payments of up to $290 million, and tiered royalties. Novo Nordisk will have worldwide rights to the XMetA program and will be solely responsible for the development and commercialization of antibodies and products.

The identification of small molecule activators of the insulin receptor was first reported about fifteen years ago. The original work in this area was pioneered by two groups (367-370). There is continuing interest in identifying small molecule activators of the insulin receptor (371-374). Although there is no indication that any compounds with this mechanism of action have entered the clinic, there remains cautious optimism regarding this approach.

**ANTI-INFLAMMATION TARGETS TO REDUCE CARDIOVASCULAR COMPLICATIONS**

Type 2 diabetes and obesity can be characterized as low-grade inflammatory states (375). Since the inflammatory processes encompass the key organs involved in the metabolic dysregulation in diabetes (eg β cells, liver, adipose tissue), attempts are being made to target the inflammation associated with type 2 diabetes. Since this approach does not, primarily, intend to improve glycemic or
lipid control, the full potential benefit along with side effects will only become understood once data from prolonged trials in large numbers if subjects becomes available.

Interleukins (IL) are cytokines that play central roles, both positive (pro-inflammatory) and negative (anti-inflammatory), in the inflammatory processes, and the increased production of some of these molecules can result in cell death. A number of IL-1 and IL-18 modulators are in clinical trials with the intent to evaluate safety along with the reduction of risk of cardiovascular events (376-378).

**FGF21 ANALOG**

Fibroblast growth factor 21 (FGF21) is a metabolic hormone predominantly produced by the liver, but is also expressed in adipocytes and the pancreas. It regulates glucose and lipid metabolism through pleiotropic actions in these tissues, and also in the brain (379;380). A recently published study evaluating the effects of an analog of FGF21 [LY2405319; (381)] in obese individuals with type 2 diabetes has found that this intervention exhibited clinically meaningful effects on several co-morbidities associated with type 2 diabetes (382;383). No further clinical trials appear to have been initiated since the original Phase 2 trial, raising doubts about the prospects for this approach.

**ANTAGONISM OF GLUCAGON RECEPTOR**

Glucagon is a hormone that counters many of the actions of insulin; in the context of insulin resistance and type 2 diabetes, glucagon drives hepatic glucose production. In poorly controlled individuals with type 2 diabetes, uncontrolled glucagon action can play a pivotal role increasing blood glucose levels. IONIS-GCGR_Rx is an anti-sense drug designed to reduce the amount of glucagon receptor (384;385). In a phase 2 study, patients with type 2 diabetes treated with ISIS-GCGR_Rx achieved statistically significant reductions in measures of glucose control. The absolute mean reductions in HbA1c were greater than 2 percentage points (P=0.001) and greater than 1 percentage point (P=0.001) in the 200 mg GCGR_Rx and 100 mg GCGR_Rx cohorts, respectively, compared to baseline after 13 weeks of treatment. Patients treated with ISIS-GCGR_Rx also experienced increased plasma GLP-1 levels. No further update regarding additional clinical trial data are available.

**ANTAGONISM OF GLUCOCORTOCOID RECEPTOR**

Glucocorticoid excess results in pro-diabetic consequences due to a variety of glucocorticoid-mediated actions on key target organs in metabolism along with effects in opposing insulin action. IONIS-GCCR_Rx is an anti-sense drug designed to reduce the amount of glucocorticoid receptor (386-388). According to the company’s website and listing of their pipeline projects, a phase 2 trial has been completed in subjects with type 2 diabetes. They reported that although some benefits were observed
in certain indices of glucose control and insulin sensitivity, there was no significant reduction in the primary outcome measure of plasma fructosamine. In light of the results with synthetic inhibitors directed to reduce cortisol production (see below), it appears that this particular approach may not be feasible for type 2 diabetes therapy.

**11β-HYDROXYSTEROID DEHYDROGENASE TYPE 1 (11β-HSD1) INHIBITORS**

Inhibition of the enzyme 11β-HSD1 has been explored as a novel approach for treatment of type two diabetes for over 15 years, with hundreds of compounds evaluated in many clinical trials. The 11β-HSD enzymes fall into two categories: type 1 and type 2. The 11β-HSD1 isoform is predominantly expressed in liver and adipose tissues along with the central nervous system, where it catalyzes the conversion of inactive cortisone into cortisol (active). The 11β-HSD2 isoform is predominantly expressed in the kidneys, where it catalyzes the reverse reaction cortisol, thereby reducing glucocorticoid action. As a class, the 11β-HSD1 inhibitors have been well tolerated and have improved glycemic control, lipid profiles, blood pressure, and even induced modest weight loss (389). However, the overall magnitude of effects compared to existing agents have been lower to justify their continued development for the primary indication of type 2 diabetes. Based on searches of websites of companies (Pfizer, Merck, Incyte) previously active in this area, it appears that all projects have been suspended or terminated.

**MICROBIOME MODULATORS**

In recent years, the intestinal microbiome has been identified as a major contributor to metabolism and other physiological processes in health and disease (390). Short-term clinical trials with dietary supplements have indicated a beneficial effect on the microbiome along with concomitant benefits on glucose tolerance and satiety (391). There are now numerous compounds in pharmaceutical clinical development that modulate the microbiome with the expressed intent of improving glycemic control (Table 12).

**Table 12. Compounds in Development with Novel Mechanisms of Action**

<table>
<thead>
<tr>
<th>General Class and Compound Name</th>
<th>Compound Designation</th>
<th>Manufacturer</th>
<th>Most Recent Development Phase a</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dual GLP-1 / Glucagon Receptor Agonists</td>
<td>TT401</td>
<td>Transition Therapeutics/Lily</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ZP2929</td>
<td>Zealand Pharma</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Code</td>
<td>Name</td>
<td>Company</td>
<td>Phase</td>
<td>Description</td>
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<td>------------------</td>
<td>-------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>SAR425899</td>
<td>SAR425899</td>
<td>Sanofi</td>
<td>1</td>
<td>Injectable peptide dual agonist</td>
</tr>
<tr>
<td>NN9709</td>
<td>NN9709</td>
<td>Novo Nordisk</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>SAR438335</td>
<td>SAR438335</td>
<td>Sanofi</td>
<td>1</td>
<td>Injectable peptide dual agonist</td>
</tr>
<tr>
<td>MAR701</td>
<td>MAR701</td>
<td>Roche</td>
<td>1</td>
<td>Development status unclear; does not appear on Roche website</td>
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<tr>
<td>SGLT1 Selective Inhibitors</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>GSK1614235</td>
<td>GSK1614235</td>
<td>GSK</td>
<td>1</td>
<td>Development status unclear; does not appear on GSK website</td>
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<tr>
<td>SGLT1/SGLT2 Dual Inhibitors</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sotagliflozin</td>
<td>LX4211 (SAR439954)</td>
<td>Lexicon/Sanofi</td>
<td>2b</td>
<td>(392)</td>
</tr>
<tr>
<td>PPAR Agonists</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Chigitazar</td>
<td>CS038</td>
<td>Chipscreen</td>
<td>3</td>
<td>Pan-PPARα/γ/δ agonist</td>
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<tr>
<td>Insulin Receptor Activators</td>
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<td></td>
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<td></td>
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<tr>
<td>XMetA</td>
<td>XMetA</td>
<td>Xoma/Novo Nordisk</td>
<td>Pre-clinical</td>
<td>Allosteric activating human monoclonal antibody against insulin receptor</td>
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<tr>
<td>Anti-Inflammation Targets</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canakinumab (Ilaris™)</td>
<td>Canakinumab</td>
<td>Novartis</td>
<td>2</td>
<td>Human monoclonal antibody against IL-1β(376)</td>
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<td>LY2189102</td>
<td>LY2189102</td>
<td>Eli Lilly</td>
<td>2</td>
<td>IL-1β neutralizing antibody(377)</td>
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<tr>
<td>AC-201</td>
<td>AC-201</td>
<td>TWi Pharmaceuticals</td>
<td>2</td>
<td>Orally available, small molecule inhibitor of IL-1B production and action</td>
</tr>
<tr>
<td>T2-18c3 (Xilonix™)</td>
<td>T2-18c3</td>
<td>X Biotech</td>
<td>2</td>
<td>IL-1α neutralizing antibody</td>
</tr>
<tr>
<td>GSK1070806</td>
<td>GSK1070806</td>
<td>Glaxo Smith Kline</td>
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<td>RG7992</td>
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<td>Roche/Genentech</td>
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<tr>
<td>Glucagon Receptor</td>
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<td>Roche/Genentech</td>
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</tr>
<tr>
<td>GCGR&lt;sub&gt;Rx&lt;/sub&gt;</td>
<td>GCGR&lt;sub&gt;Rx&lt;/sub&gt;</td>
<td>Ionis Pharma</td>
<td>2</td>
<td></td>
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<tr>
<td>Glucocorticoid Receptor</td>
<td>GCGR&lt;sub&gt;Rx&lt;/sub&gt;</td>
<td>Ionis Pharma</td>
<td>2</td>
<td></td>
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<tr>
<td>Microbiome (GI) Modulators</td>
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<tr>
<td>NM505</td>
<td>NM505 + Metformin</td>
<td>MicroBiome Therapeutics</td>
<td>2</td>
<td></td>
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<tr>
<td>NM504</td>
<td>NM504</td>
<td>MicroBiome Therapeutics</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

For the definition of Development Phase, see the following link: [https://www.takeda.com/research/pipeline/]  

Sotagliflozin is in Phase 3 development for type 1 diabetes

**PERSPECTIVES**

Despite the magnitude of the disease, the choice of oral anti-hyperglycemic drugs for type 2 diabetes was limited to sulfonylureas for over 40 years. The last 25 years have witnessed the introduction of multiple new classes of oral anti-hyperglycemic therapies (along with new injectable anti-hyperglycemics). Each possesses a distinct mechanism of action, which enables their use independently and, in many cases, as combination therapy. This is important since most patients with type 2 diabetes will require combination therapy to reach an acceptable level of glycemic control (89). However, despite these advances, there is still plenty of room and necessity for improvement.

It has long been recognized that obesity is a key factor in the risk for the development of type 2 diabetes. Two new therapies were approved by the US FDA in 2012 for the treatment of obesity. One, a combination of phentermine and topiramate extended-release (Qsymia®), is a combination of two
known drugs that both individually had modest weight loss properties that are increased when given together (393). The second, lorcaserin (Belviq®), is a serotonin 2C receptor agonist. It will be interesting to see how these therapies affect the often prevalent diabetes in obese patients.

The successful long-term management (and hopefully prevention) of type 2 diabetes and its related co-morbidities undoubtedly requires an aggressive, comprehensive approach. This includes intervention at the pre-diabetes stage (e.g. obesity, impaired glucose tolerance) including both changes in lifestyle (i.e. dietary modification and exercise), along with pharmacological intervention that might delay or even prevent the development of the disease and / or its complications. However, once the disease is established and beyond the control of lifestyle modifications, treatment must be initiated and carefully monitored using existing drugs that address the current understanding of the pathophysiology: impaired insulin secretion, increased hepatic glucose production, and peripheral tissue insulin resistance. It is anticipated that emerging agents will also have a beneficial impact on these processes, but with greater efficacy and safety due to a higher degree of selectivity for their molecular targets. In addition, new information regarding the biochemistry, cell biology, and pathophysiology of the disease process is rapidly providing additional exciting opportunities for target identification, validation and subsequent drug development. In the not too distant future, we will likely see specific strains of probiotic bacteria identified, characterized, and developed as prescription medications or medical devices.

The biological effects of emerging agents will not be limited to lowering blood glucose. Already, there are some new agents in clinical development that have been designed to afford a combination of benefits, including the reduction of both lipids and glucose. Other new therapies in development are attempting to address the significant inflammatory component of the disease. It seems likely that the failure of many existing therapies to address the inflammation component might be why tight glycemic control alone has experienced limited success at reducing the risk of macrovascular complications of diabetes. Targeting the risk factors for heart disease clearly requires serious attention and concomitant therapy. The complexity of type 2 diabetes and associated co-morbidities will continue to present a formidable challenge for successful pharmacological treatment. However, based on the growing sophistication of 21st Century research approaches (394-401) along with the realization of the consequences of failure (402;403), there is ample support for the optimistic viewpoint that the current selection of orally active treatment options will continue to expand.
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