New Therapies for Diabetes: Getting to the Heart of the Matter

Vasantha Malladi
Consultant, Defined Health
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Section Overview

I. Massive Diabetes Epidemiology
II. Current SOC for Type 2 Diabetes
III. Advancing the SOC for T2D
IV. How Will the Emerging Battle for First-line Add-on to Metformin Shape Up?
V. What Will Be the Expected Pay Back For the New High Cost of Better Glycemic Control?
VI. Will Massive Increases in Rx Costs For T2d Be Accepted Without Big Payoffs In CVD Event Reduction?
VII. Beyond Glycemic Control
Our Disclaimer

The information in this presentation has been obtained from what are believed to be reliable sources and has been verified whenever possible. Nevertheless, we cannot guarantee the information contained herein as to accuracy or completeness.

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The contents of this presentation are not meant to be comprehensive, but to encourage a spirited dialogue. Feedback, comments and corrections are welcome.
I. Massive Epidemiology: Global prevalence of diabetes is currently at 250M & expected to reach over 400M by 2030

IDF Regions and global projections for the number of people with diabetes (20-79 years), 2010-2030
The number of cases in the US alone is forecasted to double from 24M in 2009 to 44M in 2034

Projected distribution of newly diagnosed, undiagnosed and established cases of diabetes 2009 to 2034

Spending on diabetes and related complications is projected to triple in the same period

• Note: This model does not account for utilization of novel branded anti-diabetic agents in future. Expressed in 2007 dollars

The World Economic Forum considers diabetes to be a major risk for global development
II. Current SOC for Type 2 Diabetes

Key Issues

- The standard of care for treatment of diabetes in the US has not changed meaningfully in over 15 years
  - Entrenched first- and second-line add on options are generic and inexpensive
  - But there is still significant unmet need in glycemic control
- Several branded drug classes have failed to gain sustained acceptance due to a variety of issues (tolerability, dosing, safety)
  - Newest classes of drugs approved, the incretin based therapies, made some inroads into the 2nd and 3rd add-on positions. However, these drugs are yet to take a majority share in the market.
Several classes of anti-diabetics marketed, yet >60% of patients still have poor glycemic control

- Current drugs were approved based on their HbA1C reducing efficacy
- But even with 7 different therapy classes and insulin analogs used in various combinations, the majority of diabetics exhibit progressive worsening of glycemic control (and end up needing daily insulin)
- Diabetics continue to have significantly higher mortality, CV morbidity and microvascular complications as a consequence

Schematic representation of current T2DM treatment paradigm

- 20% patients on 1 agent*
- 40% patients on 2 agents, 10% patients on 2+ agents
- 30% Insulin + combinations

*Schematic representation of current T2DM treatment paradigm

DH primary research.
There is little doubt that better glycemic control remains an important objective

- A1C increases by 1% every 2 years in most patients, requiring repeated and vigorous intervention
- Despite treatment, beta-cell function continued to deteriorate in association with progressively increasing hyperglycemia
- Cumulative incidence of monotherapy failure (FPG 180 mg/dl) at 5 years was: 15% - rosiglitazone, 21% - metformin, 34% - glyburide (ADOPT study)

Coefficient of β cell failure overtime in relation to A1C (from UKPDS)

Until we have the “Holy Grail” of glycemic control, there is a need for oral glycemic controllers

- The holy grail of diabetes management, short of a permanent cure, is a closed loop monitoring system that could take over all of the jobs that people taking insulin have to do -- calculating the impact of food and exercise on insulin levels, as well as adjust for the glucose naturally produced in the body.
- "Trying to mechanically reproduce the human pancreas is going to be very difficult," said Dr. Henry Anhalt, a pediatric endocrinologist and medical director at Animas.
- That's why Animas’ initial system is going to attempt to prevent serious highs and lows in blood sugar levels. "It's a step towards the perfection we're seeking," he said.

*JDRF website January 2010.*
Metformin is the gold standard first-line therapy for T2DM due to robust HbA1c reduction without worsening other metabolic risk factors

- Metformin was introduced in the US in 1994 and changed the SoC from solely insulin providing to increasing insulin sensitivity
- First-line SoC hasn’t changed since then due to lack of compelling evidence that any other agent could do better

IMS Health Incorporated, (IMS National Sales Perspectives, NPA Monthly Rx).
No other anti-diabetic agent has come close to replacing metformin as first-line option

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Key Advantages</th>
<th>Key Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>• Extensive experience, low cost and high potency.</td>
<td>• Upper and/or lower GI side-effects in 10-15% of pts.</td>
</tr>
<tr>
<td></td>
<td>• Relatively benign, no hypoglycemia as monotherapy, weight neutral, favorable on lipids.</td>
<td>• Contraindicated in patients with renal insufficiency.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Rare risk of lactic acidosis.</td>
</tr>
<tr>
<td>Secretagogues SFUs</td>
<td>• Extensive experience, low cost and high potency.</td>
<td>• Significant concerns regarding hypoglycemia and weight gain.</td>
</tr>
<tr>
<td>Secretagogues Glinides</td>
<td>• Rapid reduction of post-prandial hyperglycemia and potentially less risk of hypoglycemia.</td>
<td>• Modest potency &amp; higher cost compared to SFUs.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Risk of hypoglycemia still higher than other OADs.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• TID dosing.</td>
</tr>
<tr>
<td>TZDs</td>
<td>• High potency and no hypoglycemia as monotherapy.</td>
<td>• Weight gain and edema.</td>
</tr>
<tr>
<td></td>
<td>• Reduction in triglycerides (Actos) and increase in HDL.</td>
<td>• Increased risk of congestive heart failure.</td>
</tr>
<tr>
<td></td>
<td>• Benefits demonstrated in large post-marketing studies.</td>
<td>• Increased risk of fractures in women.</td>
</tr>
<tr>
<td>GLP-1 agonist</td>
<td>• 2-4% weight loss.</td>
<td>• SC injection.</td>
</tr>
<tr>
<td></td>
<td>• Lack of severe hypoglycemia in combination with metformin.</td>
<td>• Nausea in significant number of patients.</td>
</tr>
<tr>
<td></td>
<td>• Potential for beta cell preservation.</td>
<td>• Potential safety concerns such as risk of pancreatitis and cancer.</td>
</tr>
<tr>
<td>DPP-IV inhibitors</td>
<td>• Once a day oral and well tolerated.</td>
<td>• Modest efficacy.</td>
</tr>
<tr>
<td></td>
<td>• Weight neutral and no risk of hypoglycemia.</td>
<td></td>
</tr>
<tr>
<td>α-glucosidase inhibitors</td>
<td>• No risk of hypoglycemia.</td>
<td>• Modest efficacy.</td>
</tr>
<tr>
<td></td>
<td>• Weight neutral.</td>
<td>• Potentially severe GI tolerability issues (bloating, diarrhea and cramps).</td>
</tr>
</tbody>
</table>
Metformin – entrenched, effective and CHEAP!

- Even before going off patent, *Glucophage* daily cost was $2 or less per day; it’s now less than 50¢.

- If *Glucophage* were to be launched today at the price of *Januvia*, current US scripts of metformin alone would translate into a $12.6B market!
SFUs: No longer entrenched but also cheap

- SFUs are now off patent, and were inexpensive in any case by today’s standards of chronic daily branded therapy
- Although the SFU market share is declining due to increased awareness of hypoglycemia as a negative factor in long-term outcomes, SFUs still hold significant market share as second-line treatment option

IMS Health Incorporated, (IMS National Sales Perspectives, NPA Monthly Rx).
The need for improved glycemic controllers is clear

- Weight gain and hypoglycemia are common side-effects of older diabetes drugs. More recently cardiovascular risk associated with TZD class of drugs has received much attention.

<table>
<thead>
<tr>
<th>How the Diabetes Drugs Compare*</th>
<th>HbA1c Reduction (percentage points)</th>
<th>LDL Cholesterol Change (mg/dL)</th>
<th>HDL Cholesterol Change (mg/dL)</th>
<th>Triglyceride Change (mg/dL)</th>
<th>Risk of Hypoglycemia (% of people)</th>
<th>Weight Change (lbs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glyburide</td>
<td>▼ 1.3-1.8</td>
<td>◆</td>
<td>◆</td>
<td>▼ 10-20</td>
<td>10-22%</td>
<td>▲ 5-10</td>
</tr>
<tr>
<td>Glipizide</td>
<td>▼ 1.3-1.8</td>
<td>◆</td>
<td>◆</td>
<td>▼ 10-20</td>
<td>10-15%</td>
<td>▲ 5-10</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>▼ 1.3-1.8</td>
<td>◆</td>
<td>◆</td>
<td>▼ 10-20</td>
<td>9-14%</td>
<td>▲ 5-10</td>
</tr>
<tr>
<td>Metformin</td>
<td>▼ 0.9-1.4</td>
<td>▲ 5-7</td>
<td>◆</td>
<td>▼ 15-25</td>
<td>0-7%</td>
<td>◆</td>
</tr>
<tr>
<td>Pioglitazone (Actos)</td>
<td>▼ 0.8-1.2</td>
<td>▲ 8-12</td>
<td>▲ 5</td>
<td>▼ 35-45</td>
<td>0-3%</td>
<td>▲ 5-10</td>
</tr>
<tr>
<td>Rosiglitazone (Avandia)</td>
<td>▼ 0.9-1.4</td>
<td>▲ 12-15</td>
<td>▲ 3</td>
<td>▼ 10-20</td>
<td>4-11%</td>
<td>▲ 5-10</td>
</tr>
<tr>
<td>Repaglinide (Prandin)</td>
<td>▼ 0.8-2.0</td>
<td>◆</td>
<td>◆</td>
<td>▼ 10-15</td>
<td>11-32%</td>
<td>▲ 5-10</td>
</tr>
<tr>
<td>Nateglinide (Starlix)</td>
<td>▼ 0.3-0.8</td>
<td>IE</td>
<td>IE</td>
<td>IE</td>
<td>13%</td>
<td>IE</td>
</tr>
<tr>
<td>Acarbose (Precose)</td>
<td>▼ 0.6-0.9</td>
<td>◆</td>
<td>◆</td>
<td>▼ 10-15</td>
<td>0-5%</td>
<td>◆</td>
</tr>
<tr>
<td>Miglitol (Glyset)</td>
<td>▼ 0.4-0.9</td>
<td>IE</td>
<td>IE</td>
<td>IE</td>
<td>IE</td>
<td>IE</td>
</tr>
<tr>
<td>Sitagliptin (Januvia)</td>
<td>▼ 0.6-0.8</td>
<td>◆</td>
<td>◆</td>
<td>◆</td>
<td>Low</td>
<td>◆</td>
</tr>
</tbody>
</table>

Definitions: mg/dL=milligrams per deciliter of blood; HbA1c=hemoglobin A1c; LDL=low-density lipoprotein cholesterol; HDL= high-density lipoprotein cholesterol.

* Selected drugs and measures. For the complete table, see the full diabetes report at www.ConsumerReportsHealth.org/BestBuyDrugs.

A down arrow (▼) means a decrease or decline; an up arrow (▲) means increase; and a diamond (◆) means no meaningful effect or change. IE=insufficient evidence. Brand names are not given for drugs available as generics. Numbers are averages based on multiple studies.

© Consumers Union 2009
New incretin-based agents have had success taking share from TZDs & SFUs

- Safety concerns with SFUs (hypoglycemia, weight gain) and Avandia (CV) have borne well for the newer drugs like Januvia (DPP-IV inhibitor) and Byetta (GLP-1 analog)

- DPP-IV inhibitors are weight neutral and do not cause hypoglycemia
- GLP-1s have the added benefit of weight loss

Growth of GLP-1s and DPP-IV inhibitors is coming at the expense of SFU’s and TZD’s; SFU and TZD use is expected to decline, based on concerns about hypoglycemia (SFU's) and weight gain (and other TZD side effects such as heart failure and fracture risk).

Vol. 14, No. 6 July/August 2008 Journal of Managed Care Pharmacy.
III. Advancing the SOC for T2D

Key Issues:

• There is agreement that new diabetes treatments are needed and there is still significant unmet need
  – Good news is that new wave of innovation has produced attractive new classes of glycemic controllers, which are likely to be safe, convenient and not marred by weight gain (and some even promise weight loss)

• But, introduction of new branded agents will come with a huge increase in per patient drug costs in the context of massive increases in disease prevalence -- a treatment cost implosion
  – In addition to cost, polypharmacy concerns means some classes of drugs will need to replace others
Rampant therapeutic class innovation is anticipated this decade

<table>
<thead>
<tr>
<th>2 years</th>
<th>5 - 10 years</th>
<th>10+ years</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1 analogs</td>
<td>Selective PPAR Agonists</td>
<td>Glucokinase Stimulants</td>
</tr>
<tr>
<td>DPP-IV inhibitors</td>
<td>DGAT1 inhibitor</td>
<td>Glycogen Phosphorylase inhibitor</td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>RAGE antagonist</td>
<td>NPY-Y2 agonist</td>
</tr>
<tr>
<td>IL-1 antagonist</td>
<td></td>
<td>FGF-21 agonist</td>
</tr>
<tr>
<td>11 β HSD1 inhibitors</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Improved glycemic controllers in late-stage pipeline are weight neutral or induce weight loss

<table>
<thead>
<tr>
<th>Agent</th>
<th>Trial Details</th>
<th>$\Delta$ HbA1c</th>
<th>Safety and Tolerability</th>
<th>Metabolic Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Tx</td>
<td>Comp.</td>
<td></td>
</tr>
<tr>
<td>Liraglutide (vs exenatide)</td>
<td>Phase III n = 464</td>
<td>–1.1%</td>
<td>–0.8%</td>
<td>$\Delta$ Fasting BG: –28.8mg/dL, –10.8mg/dL, $\Delta$ Weight: –3.2kg, –2.9kg</td>
</tr>
<tr>
<td>LEAD-6</td>
<td>Phase III n = 250</td>
<td>–1.6%</td>
<td>–0.9</td>
<td>$\Delta$ Weight: –2.3kg(Tx), –1.4kg</td>
</tr>
<tr>
<td>Exenatide-LAR (vs Byetta)</td>
<td>Phase III n = 527</td>
<td>–0.6%</td>
<td>–0.1%</td>
<td></td>
</tr>
<tr>
<td>DURATION-5</td>
<td>Phase III n = 546</td>
<td>–0.67%</td>
<td>–0.70% –0.85%</td>
<td></td>
</tr>
<tr>
<td>Alogliptin (Metformin ±)</td>
<td>Phase III n = 133</td>
<td>* 8 w study</td>
<td>* 8 w study</td>
<td>$\Delta$ Fasting BG: –2.3, –1.6, –2.2 mmol/L; –2.3 control.</td>
</tr>
<tr>
<td>Dapagliflozin (2.5mg v 5mg v 10mg v Placebo + Metformin)</td>
<td>Phase III n = 546</td>
<td>–0.67%</td>
<td>–0.70% –0.85%</td>
<td></td>
</tr>
<tr>
<td>Taspoglutide Abstract: 10- OR ADA-2008</td>
<td>Phase II n = 133</td>
<td>* 8 w study</td>
<td>* 8 w study</td>
<td></td>
</tr>
</tbody>
</table>

Other selected pipeline agents: SGLT2 Inhibitors

**Novelty**
- Novel MOA works by increasing secretion of urinary glucose.
- Minimal hypoglycemia risk, weight loss and BP reductions observed in Phase III trial of first in class SGLT2 inhibitor Dapagliflozin
- Once a day oral pill
- Downside: modest HbA1C efficacy of lead SGLT2 agent and increased risk of genital infections

**Impact on future treatment algorithm**
- Best in class agent could be tough competitor to DPP-IV inhibitors if, HBA1c efficacy improves and/or infection risk is lower

**Estimated launch**
- First agent could be launched in ~2 year time frame

<table>
<thead>
<tr>
<th>Compound</th>
<th>Company</th>
<th>Phase</th>
<th>MOA</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dapagliflozin</td>
<td>AstraZeneca/BMS</td>
<td>III</td>
<td>SGLT2 Inhibitor</td>
<td>T2DM</td>
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<tr>
<td>Canagliflozin</td>
<td>Johnson &amp; Johnson</td>
<td>II</td>
<td>SGLT2 Inhibitor</td>
<td>T2DM and obesity</td>
</tr>
<tr>
<td>BI10773</td>
<td>Boehringer Ingelheim</td>
<td>II</td>
<td>SGLT2 Inhibitor</td>
<td>T2DM</td>
</tr>
<tr>
<td>LX4211</td>
<td>Lexicon Pharmaceuticals</td>
<td>II</td>
<td>SGLT2 Inhibitor</td>
<td>T2DM</td>
</tr>
<tr>
<td>Remogliflozin</td>
<td>GSK</td>
<td>II</td>
<td>SGLT2 Inhibitor</td>
<td>T2DM, T1DM</td>
</tr>
</tbody>
</table>

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Diabetes Insight Briefing
Other selected pipeline agents: 11 beta HSD1 Inhibitors

**Novelty**

- 11 beta HSD1 is a liver and adipose tissue specific enzyme involved in tissue specific cortisol synthesis which plays a role in development of insulin resistance and other components of metabolic syndrome
- Phase II data on first in class agent INCB 13739 shows HbA1c reduction similar to DPPIV inhibitors with modest weight loss and BP reduction and improvement in cholesterol profiles
- From a safety standpoint, key issues to watch are the levels of blood cortisol and potential endocrine effects resulting from 11betaHSD1 inhibition

**Impact on future treatment algorithm**

- Competitive oral glycemic controller with positive impact on cardio-metabolic risk

**Estimated launch**

- First agent could be launched in ~5 year time frame

<table>
<thead>
<tr>
<th>Compound</th>
<th>Company</th>
<th>Phase</th>
<th>MOA</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>INCB 13739</td>
<td>Incyte Corporation</td>
<td>II</td>
<td>11 beta HSD Inhibitor</td>
<td>T2DM</td>
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<tr>
<td>JTT654</td>
<td>Akros pharmaceuticals</td>
<td>I</td>
<td>11 beta HSD Inhibitor</td>
<td>T2DM</td>
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<tr>
<td>AZD 4017</td>
<td>AstraZeneca</td>
<td>I</td>
<td>11 beta HSD Inhibitor</td>
<td>T2DM</td>
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<tr>
<td>RG 4929</td>
<td>Roche</td>
<td>I</td>
<td>11 beta HSD Inhibitor</td>
<td>T2DM</td>
</tr>
</tbody>
</table>

DH secondary research.
Other selected pipeline agents: Glucokinase Stimulants

**Novelty**
- GK modulates blood glucose by inducing glucose-stimulated insulin release in the pancreas and by inducing glycogen formation and glucose breakdown in the liver.
- In pancreatic α-cells and in the intestinal endocrine cells, GK is assumed to be involved in the regulation of glucagon and of the incretin hormones, respectively.

**Impact on future treatment algorithm**
- Expected to promote superior glycemic control via 2 MOAs of increasing glucose uptake in liver and increasing insulin secretion in pancreas.
- Concerns would be risk of severe hypoglycemia due to overstimulation of pancreas.
- Preclinical data of TTP399 suggest a liver specific activity that does not cause severe hypoglycemia.

**Estimated launch**
- First agent could be launched in ~6-7 year time frame.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Company</th>
<th>Phase</th>
<th>MOA</th>
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<tr>
<td>AZD 6370</td>
<td>AZN</td>
<td>II</td>
<td>Glucokinase Stimulant</td>
<td>T2DM</td>
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<td>AZD 1656</td>
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<td>II</td>
<td>Glucokinase Stimulant</td>
<td>T2DM</td>
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<tr>
<td>R1511</td>
<td>Roche</td>
<td>I</td>
<td>Glucokinase Activator</td>
<td>T2DM</td>
</tr>
<tr>
<td>MK 0599</td>
<td>Merck</td>
<td>I</td>
<td>Glucokinase Activator</td>
<td>T2DM</td>
</tr>
<tr>
<td>ARRY 403</td>
<td>Array / Amgen</td>
<td>I</td>
<td>Glucokinase Stimulant</td>
<td>T2DM</td>
</tr>
</tbody>
</table>
Other selected pipeline agents: Diacylglycerol Acyltransferase (DGAT)-1 Inhibitors

**Novelty**
- DGAT-1 is one of two DGAT enzymes that catalyse the final step in triglyceride synthesis in mammals
- DGAT1-deficient mice show resistance to diet-induced obesity via increased energy expenditure. These mice have decreased levels of tissue triglycerides along with increased sensitivity to insulin and to leptin
- The inhibition of DGAT-1 therefore may be useful in the treatment of symptoms of insulin resistance and leptin resistance in human obesity

**Impact on future treatment algorithm**
- Insulin resistance reduction with triglyceride lowering without TZD like side effects

**Estimated launch**
- First agent could be launched in ~7-8 year time frame

<table>
<thead>
<tr>
<th>Compound</th>
<th>Company</th>
<th>Phase</th>
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<th>Indication</th>
</tr>
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<tbody>
<tr>
<td>PF 4620110</td>
<td>Pfizer</td>
<td>I</td>
<td>DGAT-1 Inhibitor</td>
<td>T2DM</td>
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<tr>
<td>LCQ 908</td>
<td>Novartis</td>
<td>II</td>
<td>DGAT-1 Inhibitor</td>
<td>T2DM</td>
</tr>
</tbody>
</table>

*DH secondary research.*
Other selected pipeline agents: G Protein Coupled Receptors

**Novelty**
- Several islet GPCRs are involved in the regulation of islet hormone secretion and are therefore potential targets for the treatment of islet dysfunction — the key defect in type 2 diabetes
- These therapies could offer effect of GLP-1 analogues with an oral dosing

**Impact on future treatment algorithm**
- Early stage agents with limited clinical experience

**Estimated launch**
- First agent could be launched in 7-10 years

<table>
<thead>
<tr>
<th>Compound</th>
<th>Company</th>
<th>Phase</th>
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<th>Indication</th>
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<tr>
<td>PSN821</td>
<td>Prosidion</td>
<td>I</td>
<td>G-Protein Coupled Receptor 119</td>
<td>T2DM</td>
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<td>MBX 2982</td>
<td>Metabolex</td>
<td>I</td>
<td>G-Protein Coupled Receptor 119</td>
<td>T2DM</td>
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<td>APD 597</td>
<td>Ortho-McNeil-Janssen, Arena</td>
<td>I</td>
<td>Glucose-Dependent Insulinotropic Receptor</td>
<td>T2DM</td>
</tr>
</tbody>
</table>
Other selected pipeline agents:
Fibroblast growth factor-21 agonist

Novelty
- FGF-21 is a hormone that is associated with hibernation, starvation and metabolism
- FGF-21 is a potent activator of glucose uptake on adipocytes, protects animals from diet-induced obesity when overexpressed in transgenic mice, and lowers blood glucose and triglyceride levels when therapeutically administered to diabetic rodents

Impact on future treatment algorithm
- Early-stage agents with limited clinical experience

Estimated launch
- First agent could be launched in 7-10 years

<table>
<thead>
<tr>
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<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>LP 10152</td>
<td>Lilly</td>
<td>I/II</td>
<td>FGF-21 Agonist</td>
<td>T2DM</td>
</tr>
</tbody>
</table>

DH secondary research.
Other selected pipeline agents: Glycogen Phosphorylase Inhibitor

**Novelty**
- Glycogen phosphorylase mediates the breakdown of glycogen to glucose in the liver and its inhibition would decrease hepatic glucose production, therefore providing a plausible target for treating diabetes
- GlaxoSmithKline has shown in preclinical studies that treatment with the compound resulted to a dose-dependent reduction in serum glucose level and increased liver glycogen levels
- A Phase I clinical trial of GSK 1362885 is under way in the US

**Impact on future treatment algorithm**
- Early-stage agents with limited clinical experience

**Estimated launch**
- First agent could be launched in 7-10 years

<table>
<thead>
<tr>
<th>Compound</th>
<th>Company</th>
<th>Phase</th>
<th>MOA</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSK 1362885</td>
<td>GSK</td>
<td>I</td>
<td>Glycogen Phosphorylase Inhibitor</td>
<td>T2DM</td>
</tr>
</tbody>
</table>
Key issue for pipeline classes: Where will they fit in the diabetes treatment algorithm?

- With the first spot taken by metformin, and the second spot more or less taken by SFUs or Januvia, achieving large patient share is going to be challenging for novel anti-diabetic agents poised to enter the Type II Diabetes market.

20% patients on 1 agent*

40% patients on 2 agents, 10% patients on 2+ agents

30% Insulin + combinations

Novel anti-diabetics will need to compete in these spaces

* DH primary & secondary research.
Key issue for pipeline classes: Where will they fit in the diabetes treatment algorithm?

- Metformin is not likely to cede first line position so all new classes will compete for first add on position. Second add-on drugs may still achieve commercial success but revenue forecasts plunge for third add-ons as this is at the limit of patient and payer tolerance and majority of pts requiring 3 drugs should likely be on insulin

DH prior research and analysis based on a survey of 25 endocrinologists.
Replacement of SFU in second-line with a branded agent will increase cost of therapy by 1200%!

WW Sales of Sulfonylurea Agents (2000-2014e) ($USD billions)

Increase in treatment cost based on cost of DPP-IV inhibitor in place of SFU therapy

SFU sales from Evaluate Pharma; ASP of Januvia Redbook.
While the debate rages over the cost of new cancer therapies...

Limits on Medicare's Ability to Control Rising Spending on Cancer Drugs

Peter B. Bach, M.D., M.A.P.P.

Fifteen years ago, the only commonly used cancer drug on the market that cost more than $2,500 per month was paclitaxel (Taxol, Bristol-Myers Squibb), which Chabner and Roberts labeled the first cancer "blockbuster." Today, cancer drugs that come on the market routinely cost many times that amount (Figure 1). Several established cancer drugs have recently seen price increases, which has added to the general upward trend in prices. Nitrogen mustard, a drug that has been used to treat cancer since 1949, saw its price for a course of treatment increase by a factor of 13 between the beginning and the end of 2006 (from $33 to $420).

NEJM V360:626-633, February 5, 2009, Number 6; http://content.nejm.org/cgi/content/full/360/6/626.
Diabetes drugs are predicted to drive spending growth at almost 3x the rate of cancer drugs!

- Rapid growth in epidemiology, increased use of new oral and injectable agents and limited first-time generic introductions are contributing to the increase in diabetes drug costs.

**Top Therapeutic Classes Contributing to Projected Drug Trend (2009-2011)**

- Therapeutic classes that are likely to drive the majority of spending growth between 2009 and 2011.
- Data are expressed as a percentage of the total projected increase in plan ingredient cost.

IV. How will the emerging battle for first line add-on to metformin shape up?

Two possible outcomes:
1. All out slugfest between large pharma over “share of voice”
IV. How will the emerging battle for first line add-on to metformin shape up?

Two possible outcomes:

2. Evidence-based guidelines so far lacking in T2DM emerge to form a more rational basis for selection of most appropriate drug class in selected patient types.

**Evidence based hypertension guidelines**

<table>
<thead>
<tr>
<th>Area of Concern</th>
<th>BP Target, mm Hg</th>
<th>Lifestyle Modification</th>
<th>Specific Drug Indications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>General CAD prevention</td>
<td>&lt;140/90</td>
<td>Yes</td>
<td>Any effective antihypertensive drug or combination</td>
<td>If SBP &gt;/=160 mm Hg or DBP &gt;/=100 mm Hg, then start with 2 drugs</td>
</tr>
<tr>
<td>High CAD risk</td>
<td>&lt;130/80</td>
<td>Yes</td>
<td>ACEI or ARB or CCB or thiazide diuretic or combination</td>
<td>If SBP &gt;/=160 mm Hg or DBP &gt;/=100 mm Hg, then start with 2 drugs</td>
</tr>
<tr>
<td>Stable angina</td>
<td>&lt;130/80</td>
<td>Yes</td>
<td>Beta-blocker and ACEI or ARB</td>
<td>If Beta-blocker contraindicated, or if side effects occur, can substitute diltiazem or verapamil (but not if bradycardia or LVD is present) Can add dihydropyridine CCB (not diltiazem or verapamil) to beta-blocker A thiazide diuretic can be added for BP control</td>
</tr>
<tr>
<td>UA/NSTEMI</td>
<td>&lt;130/80</td>
<td>Yes</td>
<td>Beta-blocker (if patient is hemodynamically stable) and ACEI or ARB</td>
<td>If Beta-blocker contraindicated, or if side effects occur, can substitute diltiazem or verapamil (but not if bradycardia or LVD is present) Can add dihydropyridine CCB (not diltiazem or verapamil) to beta-blocker A thiazide diuretic can be added for BP control</td>
</tr>
<tr>
<td>STEMI</td>
<td>&lt;130/80</td>
<td>Yes</td>
<td>Beta-blocker (if patient is hemodynamically stable) and ACEI or ARB</td>
<td>If Beta-blocker contraindicated, or if side effects occur, can substitute diltiazem or verapamil (but not if bradycardia or LVD is present) Can add dihydropyridine CCB (not diltiazem or verapamil) to beta-blocker A thiazide diuretic can be added for BP control</td>
</tr>
<tr>
<td>LVD</td>
<td>&lt;120/80</td>
<td>Yes</td>
<td>ACEI or ARB and Beta-blocker and aldosterone antagonist and thiazide or loop diuretic and hydralazine/isosorbide dinitrate (blacks)</td>
<td>Contraindicated: verapamil, diltiazem, clonidine, moxonidine, beta-blockers</td>
</tr>
</tbody>
</table>
V. What will be the expected pay back for the new high cost of better glycemic control?

- Evidence from large randomized trials suggests **microvascular complications** will be reduced
  - Nephropathy and CKD present reasonable opportunity for pharmacoeconomic justification of increased Rx treatment cost

- Evidence from large randomized trials suggests **macrovascular complications** will not be reduced
  - Lack of link between improved glycemic control and reduction of CVD, greatly weakens pharmacoeconomic argument as CVD drives majority of diabetes cost
Tight glycemic control has some impact on microvascular, but not macrovascular complications

### Impact of Intensive Therapy in Type 2 Diabetes: Summary of Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Microvascular</th>
<th>Macrovascular</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>UGDP</td>
<td>←</td>
<td>←</td>
<td>←*</td>
</tr>
<tr>
<td>UKPDS</td>
<td>↓</td>
<td>←</td>
<td>↓</td>
</tr>
<tr>
<td>DCCT/EDIC</td>
<td>↓</td>
<td>←</td>
<td>↓</td>
</tr>
<tr>
<td>ACCORD</td>
<td>?</td>
<td>←</td>
<td>↑</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>↓</td>
<td>←</td>
<td>←</td>
</tr>
<tr>
<td>VADT</td>
<td>←</td>
<td>←</td>
<td>←</td>
</tr>
</tbody>
</table>

© Defined Health, January 2010
Diabetes Insight Briefing
Renal damage is a predominant microvascular cost driver

- Diabetic nephropathy is now the most common cause of end-stage renal failure in the western world
- The main clinical associations that frequently precede overt diabetic nephropathy are hypertension and poor glycemic control

But the greater unmet need in diabetes is associated CVD

- People with diabetes mellitus have 2–8-fold increased cardiovascular mortality than people without diabetes
CVD complications generate the greatest % cost of chronic diabetes management

- Much of the morbidity and cost of diabetes management is attributable to long-term, diabetes-related complications, particularly cardiovascular disease (CVD).

*Graph showing cumulative costs over years for Macrovascular, Nephropathy, Retinopathy, and Neuropathy.*

*Taken from Caro et al. (2002).*
While tighter cholesterol and blood pressure control have clearly demonstrated a positive impact on heart disease, glycemic controllers have not shown similar impact.

Attributable declines in CHD deaths between 1980 and 2000

VI. Will a massive increase in Rx costs for T2DM be accepted without a big payoff in CVD event reduction?

- Payers will demand that glycemic controllers be associated with either additional metabolic benefits capable of translating into reduced CVD risk (e.g., weight loss, triglyceride reduction, increase in HDL, BP reductions, etc.)
- **Best case:** payers accept surrogate markers
- **Worst case:** morbidity and mortality reduction studies required for even initial acceptance
VII. Beyond glycemic control

• In addition to drugs offering metabolic profile improvement benefits, new classes targeting the cardiovascular risk of diabetes will be necessary
Diabetes and CVD: common risk factors and therapeutic targets

Similar features of Type 2 diabetes and atherosclerotic disease:
- common risk factors and mechanisms
- affect vascular homeostasis and glucose metabolism
- recent data suggests inflammation involved in both disorders and is a link between obesity, diabetes and/or CVD

- On the other hand, anti-diabetic agents, such as SGLT inhibitors and GLP1 receptor agonists may positively impact CVD outcomes by indirectly affecting shared risk factors such as hypertension, weight, etc.

Pioglitazone (Actos): the only anti-diabetic drug that has come close to showing positive outcomes

- The PROactive study was a randomized, double-blind, placebo-controlled outcomes study in 5238 patients with type 2 diabetes at high risk for cardiovascular events.
- Although the study did not meet primary efficacy endpoint which consisted of all-cause mortality, nonfatal myocardial infarction, stroke, acute coronary syndrome, and revascularization or amputation. **There was a 16% risk reduction of predetermined secondary endpoint of all-cause mortality, nonfatal MI (excluding silent MI), and stroke.**

Effect of Pioglitazone on cardiovascular outcomes in T2DM (PROActive)

Managing Dysglycemia in Cardiovascular Disease: Preventing Future Events, January 2010 CME, Heart.Org.
**CHICAGO study: Pioglitazone slowed progression of carotid atherosclerosis vs. glimepiride**

- The CHICAGO study was a randomized, double-blind, comparator-controlled trial, in 462 patients with Type 2 Diabetes. Patients were randomized to receive 72 weeks of treatment with pioglitazone, or glimepiride, titrated to the HbA1c target.

<table>
<thead>
<tr>
<th>End Point</th>
<th>Pioglitazone</th>
<th>Glimepiride</th>
<th>Difference (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point (mm)</td>
<td>-0.001</td>
<td>+0.012</td>
<td>-0.013 (-0.024 to 0.002)</td>
<td>.02</td>
</tr>
</tbody>
</table>

Similarly, pioglitazone slowed progression of maximum CIMT compared with glimepiride.

<table>
<thead>
<tr>
<th>End Point</th>
<th>Pioglitazone</th>
<th>Glimepiride</th>
<th>Difference (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression of maximum CIMT (mm)</td>
<td>+0.002</td>
<td>+0.026</td>
<td>-0.024 (-0.042 to 0.006)</td>
<td>.008</td>
</tr>
</tbody>
</table>

CIMT images captured by a single ultrasonographer at one center, read by a single reader blinded to treatment assignment using automated edge-detection technology.

The beneficial effect of treatment was similar across pre-specified subgroups based on age, sex, systolic blood pressure, duration of diabetes, HbA1c value, and statin use.

*Medscape.com.*
PERISCOPE study: similar results were observed

- In PERISCOPE, 543 patients with Type 2 Diabetes underwent coronary IVUS and then were randomized to receive either glimepiride (1-4 mg) or pioglitazone (15-45 mg) for 18 months, at which time IVUS studies were repeated.

<table>
<thead>
<tr>
<th>End point</th>
<th>Glimepiride</th>
<th>Pioglitazone</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherosclerosis (%)</td>
<td>+0.73</td>
<td>-0.16</td>
<td>.002</td>
</tr>
<tr>
<td>Fasting insulin (µU/mL)</td>
<td>1.33</td>
<td>-5.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>2.3</td>
<td>0.1</td>
<td>0.03</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>0.9</td>
<td>-0.9</td>
<td>0.003</td>
</tr>
<tr>
<td>HBA1c (%)</td>
<td>-0.36</td>
<td>-0.55</td>
<td>0.03</td>
</tr>
<tr>
<td>Fasting blood glucose</td>
<td>0.41</td>
<td>-8.5</td>
<td>0.003</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>3.3</td>
<td>-16.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>0.9</td>
<td>5.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>1.1</td>
<td>2.1</td>
<td>.69</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>-0.4</td>
<td>-1.0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Medscape.com.
More studies targeting anti-inflammatory and CV benefits

**ADA: Carotid Intima-Media Thickening Slowed with Pioglitazone**

By Kristina Fiore, Staff Writer, MedPage Today
Published: June 06, 2009
NEW ORLEANS, June 6 -- Pioglitazone appears to slow the rate progression, researchers said here.

**Drug Inhibits Restenosis in Diabetics After Stent**

Group receiving pioglitazone after bare-metal stent placement had lower restenosis rate.
Publish date: Jun 18, 2009
HealthDay

**Medscape Today**

From Diabetes
Pioglitazone Decreases Fasting and Postprandial Endogenous Glucose Production in Proportion to Decrease in Hepatic Triglyceride Content
Balasubramanian Ravikumar, Jean Gerrard; Chiara Dalla Man; Michael Claudio Cobelli; Roy Taylor
Posted: 09/30/2006; Diabetes. 2006;57(9):2288-2295. © 2006 American Diabetes Association

**Medscape Today**

From Journal of the American College of Cardiology
Anti-Inflammatory Effects of Pioglitazone and/or Simvastatin in High Cardiovascular-Risk Patients With Elevated High Sensitivity C-Reactive Protein: The PIOSTAT Study
Markolf Hanefeld, MD, PHD; Nikolaus Marx, MD; Andreas Pfützer, MD, PHD; Werner Baurecht, MSC; Georg Lübben, MD; Efstratios Karagiannis, MD; Ulf Ster, MD; Thomas Forst, MD
But TZDs will remain tainted with safety concerns of heart failure, weight gain and fracture risk

“We believe that from the patient's point of view it is this 16% reduction in death, MI, and stroke that really matters”

Prof John Dormandy, chair of the steering committee, PROActive study

Devils advocate

“From the patient's perspective, is it better to have healthy arteries in the heart than a failing heart?”

Professor Hannele Yki-Järvinen, MD, PhD, University of Helsinki, Finland

Medscape.com.
Selective partial PPAR Agonists

**Novelty**
- Potential for PPAR-like efficacy without harmful side effects

**Impact on future treatment algorithm**
- High if one of the agents could demonstrate cardiovascular benefit similar to pioglitazone

**Estimated launch**
- 5-7 years time frame

<table>
<thead>
<tr>
<th>Compound</th>
<th>Company</th>
<th>Phase</th>
<th>MOA</th>
<th>Indication</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>PN2034</td>
<td>Wellstat / Sanofi Aventis</td>
<td>II</td>
<td>non-TZD PPAR modulator</td>
<td>T2DM</td>
<td>Shown in rodent models to improve glycemic control and steatohepatitis with no weight gain</td>
</tr>
<tr>
<td>INT 131</td>
<td>InteKrin Therapeutics</td>
<td>II</td>
<td>PPARγ agonist</td>
<td>T2DM</td>
<td>Phase IIa results indicating superior profile to Actos</td>
</tr>
<tr>
<td>MSDC 0160</td>
<td>Metabolic Solutions</td>
<td>II</td>
<td>oral PPARγ-sparing insulin sensitizer</td>
<td>T2DM</td>
<td>MSDC 0160 is thought to decrease fat deposits in the abdomen</td>
</tr>
</tbody>
</table>
Role of inflammatory cytokines in diabetes and CVD

Role of pro-inflammatory cytokines in insulin resistance and atherogenesis

- Increasing adiposity activates inflammatory responses in fat and liver, with associated increases in production of cytokines and chemokines
- Immune cells, including monocytes and macrophages are recruited and/or activated, and together these cause local insulin resistance
- Portal delivery of abdominal fat-derived cytokines and lipids contributes to hepatic inflammation, insulin resistance and atherogenesis

Proposed role of pro-inflammatory cytokine IL-1 in beta cell destruction

- Beta cells producing interleukin-1β have been observed in pancreatic sections obtained from patients with Type 2 Diabetes
- IL-1 is hypothesized to be secreted as a result of glucotoxicity on beta cells and is a proposed mediator of islet cell apoptosis

IL-1 Antagonists in the pipeline

**Novelty**
- Encouraged by early clinical data generated from human trial of Anakira and Xoma-052 (both IL-1 antibodies) showing impact of HbA1c reduction and CRP level reduction, several other IL-1 antagonists

**Impact on future treatment algorithm**
- If they demonstrate improvement in CV risk in type II diabetics and succeed in once a month or less dosing, these agents could have significant potential despite inconvenient dosing.

**Estimated launch**
- 5-10 years time frame

<table>
<thead>
<tr>
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<th>Company</th>
<th>Phase</th>
<th>MOA</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>canakinumab</td>
<td>Novartis</td>
<td>II/III</td>
<td>IL-1β mAb</td>
<td>T2DM</td>
</tr>
<tr>
<td>LY 2189102</td>
<td>Lilly</td>
<td>II</td>
<td>IL-1β antibody</td>
<td>T2DM</td>
</tr>
<tr>
<td>CYT013</td>
<td>Cytos Biotech</td>
<td>I/IIa</td>
<td>IL-1β vaccine</td>
<td>T2DM</td>
</tr>
<tr>
<td>XOMA 052</td>
<td>XOMA</td>
<td>II (RA)</td>
<td>IL-1 beta antagonist</td>
<td>P1 – T2DM P2 – RA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>I (T2DM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VRS 826</td>
<td>Versartis</td>
<td>PC</td>
<td>IL-1ra-rPEG</td>
<td>T2D, RA</td>
</tr>
<tr>
<td>APG 101.10</td>
<td>Allostera</td>
<td>PC</td>
<td>IL-1 antagonist</td>
<td>T2D, Gout, RA</td>
</tr>
</tbody>
</table>

*DH secondary research.*
RAGE Antagonists

- Hyperglycaemia leads to the formation of advanced glycation end products (AGE), which irrevocably alter the diabetic vasculature, leading to vascular stiffening owing to extensive protein crosslinking.

- Extracellular AGE also bind and activate the signal transduction receptor RAGE (receptor of AGE). RAGE is a multi-ligand receptor that is a potent generator of accelerated vascular inflammation.

- The role of RAGE has been examined in both non-diabetic and diabetic mice deficient for the genes that encode Apo lipoprotein E and RAGE, and these studies have shown that RAGE has a pivotal role in atherosclerosis.

RAGE Pathway

**RAGE Antagonists**

**Novelty**
- First MOA to directly target glucose mediated damage to vasculature and resultant inflammation

**Impact on future treatment algorithm**
- Early stage agents with limited clinical experience

**Estimated launch**
- First agent could be launched in 8-10 years

<table>
<thead>
<tr>
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<th>MOA</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF04494700</td>
<td>Pfizer</td>
<td>II</td>
<td>Oral RAGE antagonist</td>
<td>Diabetic nephropathy, Alzheimer’s</td>
</tr>
</tbody>
</table>
Key Take-Aways

- **Multiple innovative treatment options** are in development in near & mid-term status

- **Improved therapies** will be welcomed by patients and physicians
  - The global disease burden of T2DM is enormous
  - Dysglycemia associated with T2DM remains poorly controlled

- **Commercial rewards for pharma are tempered** by several emerging barriers
  - Limits of polypharmacy will make the important first add-on position behind metformin highly competitive (between classes and intra-class)
  - Costs of new branded drugs represent dramatic increase over current SoC (generic and inexpensive)
  - Pharmacoeconomic justification & payer acceptance in regards to the various therapeutic classes; weak argument without proven impact on CVD (greatest cost driver)

- Focus should remain on mechanisms that can potentially **address the CVD burden** of diabetes
Defined Health's Therapeutic Insight will be a featured track at these 2010 EBD conferences:

**BIO-Europe Spring® 2010**
Barcelona, Spain
March 8–10, 2010

**BIOPharm America® 2010**
Boston, MA
September 15–17, 2010

http://www.definedhealth.com