DPP4 Inhibitors vs. Sulfonylureas: Choosing an Oral Agent to Treat Type 2 Diabetes Inadequately Controlled with Metformin

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Learning Objectives:
1. Describe the role of individualized HbA1c treatment goals
2. Describe the pathophysiology of the DM and hypoglycemia
3. Explain the mechanism of action of DPP4s and Sulfonylureas
4. Evaluate the literature concerning the efficacy of DPP4 inhibitors vs sulfonylureas when added to metformin
5. Discuss the role of DPP4s and sulfonylureas in the treatment of Type 2 Diabetes
BACKGROUND

1-6, 20

- Diabetes Mellitus-Type 2
  - Epidemiology
    - Type II diabetes affects 25.8 million Americans
      - 8.3% of the US population
    - Based on fasting glucose or hemoglobin A1c levels, 35% of US adults >20 years have pre-diabetes (~79 million Americans)
      - 50% of US Adults >65 years have pre-diabetes
  - Impact
    - The US national economic burden of pre-diabetes and diabetes reached 218 billion in 2007
      - $153 Billion in higher medical costs and $65 billion in reduced productivity
  - Complications
    - Retinopathy
      - Leading cause of blindness in patients aged 20-74
    - Nephropathy
      - Leading cause of kidney failure
    - Neuropathy
      - >60% of non-traumatic lower limb amputations occur in patients with diabetes
    - Macro vascular
      - Adults with diabetes have heart disease death rates 2-4 times higher than those without diabetes
  - Treatment goals:
    - ACCORD/ADVANCE/VADT:
      - ACCORD and VADT HbA1c<6%
      - ADVANCE HbA1c ≤6.5%
      - No statistically significant reduction in cardiovascular endpoints
      - ACCORD: 22% increase in total mortality associated with intensive approach
      - Hypoglycemia significantly higher in intensive group
      - Unclear what was responsible for change in outcomes (hypoglycemia, weight gain, TZDs, complexity of therapy, etc)
    - Target range for glycemic control should be individualized based on risk/benefit ratio
      - Lower HbA1c goals: short disease duration, long life expectancy, no significant cardiovascular disease, patient motivation
      - Higher HbA1c goals: History of severe hypoglycemia, limited life expectancy, advanced complications, extensive comorbid conditions, and in those in whom the target is difficult to attain despite maximal efforts.
    - ADA/EASD 2012 Position Statement
      - HbA1c <7%, fasting and premeal <130 mg/dL, postprandial glucose <180mg/dL
    - More stringent HbA1c targets (6.0-6.5%) vs. Less stringent HbA1c targets (7.5-8.0%)
    - VA/DOD 2010
      - HbA1c <7%
      - Less stringent HbA1c targets (7-8% or 8-9%) may be considered
    - AACE/ACE Consensus Statement 2009
      - HbA1c ≤6.5%
      - Less stringent HbA1c targets may be considered
Hypoglycemia

- Epidemiology
  - It is difficult to ascertain the true incidence of hypoglycemia due to lack of a standardized definition and because it is not commonly reported/document.
  - Most commonly implicated medications in Emergency hospitalizations for adverse drug reactions:
    - Warfarin 33.3% Hospitalized: 46.2%
    - Insulin 13.9% Hospitalized: 40.6%
    - Anti-platelet 13.3% Hospitalized: 41.5%
    - Oral hypoglycemic 10.7% Hospitalized: 51.8%
    - Opiods 4.8% Hospitalized: 32.4%

- Impact
  - Increased costs
  - Increased morbidity and mortality—(ACCORD?)
  - Decreased patient compliance

- Complications
  - Autonomic dysfunction/Hypoglycemic unawareness
  - Dysrhythmias
  - Accident/Falls
  - Brain Dysfunction

- Patients at risk for hypoglycemia
  - Elderly, renal impairment, cognitive impairment, mental health issues, long duration of diabetes, impaired counter-regulatory system, the use of insulin/insulin secretagogues, incorrect use of medications, missed/irregular meals, exercise

- Clinical Definition
  - Documented Symptomatic Hypoglycemia
    - Typical symptoms of hypoglycemia + plasma glucose concentration <70 mg/dL
    - Probably Symptomatic: without a test of plasma glucose
  - Asymptomatic Hypoglycemia
    - No symptoms + plasma glucose concentration <70 mg/dL
    - Antecedent plasma glucose concentration <70 ml/dL reduce sympathoadrenal responses to subsequent hypoglycemia
  - Relative hypoglycemia
    - Typical symptoms + plasma glucose concentrations >70 ml/dL
    - May occurs in patients with chronically poor glycemic control
  - Severe Hypoglycemia
    - Requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions
  - Meaningful reduction in hypoglycemia:
    - 10-20% reduction in severe hypoglycemia
    - >30% in documented hypoglycemia
• Diabetes Mellitus-Type 2
  o Insufficient insulin action to maintain plasma glucose levels in normal range
    ▪ Insulin resistance at key target tissues (liver, skeletal muscles, and adipose tissue)
    ▪ Relative lack of insulin (beta cell function)
  o Impaired beta cell function
    ▪ Beta cell sensitivity to glucose, insulinotropic GI hormones, and neural signaling is impaired
    ▪ The absolute mass of beta cells is reduced in type 2 diabetes
      ▪ Estimated loss of 50-80% of beta cells in early type 2 diabetes
    ▪ Gradual loss of beta cell mass over time
    ▪ Proinsulin, the precursor to insulin, is inefficiently processed in the diabetic islet
      ▪ Circulating insulin as proinsulin: Healthy subjects 2-4% vs. Diabetic 10-20%
    ▪ Decrease in fasting insulin → Increase hepatic glucose production → Elevated fasting glucose
      ▪ When fasting plasma glucose >140 mg/dL → the B-cell is unable to maintain it elevated rate of insulin secretion
    ▪ Decreased postprandial insulin secretion us due to:
      ▪ Impaired beta cell function
      ▪ Reduced stimulus for insulin secretion from gut hormones (incretin)
  o Incretin effect
    ▪ In healthy adults 73% more insulin is released in response to oral glucose vs. IV glucose
    ▪ Diabetics respond to this same challenge with an increase in insulin secretion that is 50% less than non-diabetics
    ▪ GLP-1 and GIP are responsible for over 90% of the increased insulin secretion seen in response to oral glucose. Diabetics remain sensitive to GLP-1 while they are often resistant to GIP
    ▪ GLP-1 insulinotropic effect is glucose dependent (requires glucose >90mg/dL)
    ▪ GLP-1 stimulates insulin secretion, suppresses glucagon secretion, slows gastric emptying, and increases satiety
    ▪ The half-life of both GLP-1 and GIP is short (<10 minutes). They are rapidly inactivated by DPP4.
• Hypoglycemia
  o Glucose counter regulatory mechanisms
    1.) Reduction in insulin secretion
    2a.) Increase in glycogen secretion (may become deficient in DM of long duration)
    2b.) Epinephrine (deficient → autonomic neuropathy → severe hypoglycemia risk increases)
    3.) Increased cortisol and growth hormone (prolonged hypoglycemia)
  o Signs/Symptoms
    ▪ Neurogenic
      • Sweating, hunger, paresthesias, palpitations, tremor, and anxiety
    ▪ Neuoglycopenic:
      • Confusion, weakness, difficulty concentrating, drowsiness, dizziness, blurred vision, loss of consciousness
    ▪ Severe: convulsions, coma, and death
ORAL ANTI-DIABETIC AGENTS\textsuperscript{4,5,6,10}

- **Biguanides (Metformin)**
  - Medications in this class: metformin
  - Mechanism/Effect:
    - Increases the activity of AMP-dependent protein kinase (AMPK)
    - AMPK stimulates fatty acid oxidation, glucose uptake, and nonoxidative metabolism, and reduces lipogenesis and gluconeogenesis
    - Net effect: Decreased hepatic glucose production, increased insulin sensitivity, increased glycogen storage in the muscles, and lower plasma glucose
  - Estimated A1c Lowering Effect: 1-2%
  - Advantages: Extensive clinical experience, low incidence of hypoglycemia, no weight gain, low cost,
  - Disadvantages: Gastrointestinal side effects, lactic acidosis, contraindications (CKD)

- **Sulfonylureas**
  - Pharmacology: please see Appendix A
  - Medications in this class: glipizide, glyburide, glimepiride
  - Mechanism/Effect:
    - Inhibit the activity of the B-cell KATP channel causing cell membrane depolarization
    - Net effect: increase in insulin secretion
    - May also decrease hepatic clearance of insulin
  - Estimated A1c Lowering Effect: 1-2%
  - Advantages: extensive experience, low cost
  - Disadvantages: hypoglycemia, weight gain, low durability, blunts myocardial ischemic preconditioning

- **DPP4-Inhibitors**
  - Pharmacology: please see Appendix A
  - Medications in this class: sitagliptin, saxagliptin, linagliptin
  - Mechanism/Effect:
    - Inhibits the DPP-4 enzyme which is responsible for the inactivation of GLP-1 and GIP
    - Two fold increase in plasma concentrations of GIP and GLP-1
  - Results in an increase in insulin secretion and an inhibition of glucagon secretion (glucose-dependent)
  - Estimated A1c Lowering Effect: 0.5-1%
  - Advantages: No hypoglycemia, well tolerated
  - Disadvantages: generally modest HbA1c efficacy, urticaria/angioedema, high cost, pancreatitis?

- **Ideal agent?**
  - ADA/EASD 2012:
    - The aims of controlling glycemia are to avoid acute osmotic symptoms of hyperglycemia, to avoid instability in blood glucose over time, and to prevent/delay the development of diabetes complications without adversely affecting quality of life.
  - AACE/ACE 2009:
    - We prioritize choices of medications according to safety, risk of hypoglycemia, efficacy, simplicity, anticipated degree of patient adherence, and cost of medications
    - The most important guiding principle of our current algorithm is the recognition of the importance of avoiding hypoglycemia
  - VA/DOD 2010:
    - When selecting an agent, consideration must be given to efficacy, contraindications, drug interactions, and side effects. Educate patient about treatment options and arrive at a shared treatment plan with consideration for patient preferences.
### REVIEW OF TYPE 2 DM TREATMENT RECOMMENDATIONS

1. ADA 2012
   - If noninsulin monotherapy at maximal tolerated dose does not achieve or maintain the A1C target over 3–6 months, add a second oral agent, a GLP-1 receptor agonist, or insulin.

2. AACE/ACE 2009
   - **HbA1c 6.5%-7.5%**
     - **Monotherapy**
       - Metformin or TZD, DPP-4, AGIs
     - **Dual Therapy**
       - (Metformin or TZDs) +
         1. Incretin mimicetic
         2. DPP-4 Inhibitor
         3. Insulin secretagogue
     - **Triple Therapy**
       1. Metformin + GLP-1 agonist + TZD
       2. Metformin + GLP-1 agonist + glinide
       3. Metformin + GLP-1 agonist + sulfonylurea
       4. Metformin +DPP-4 Inhibitor + TZD
       5. Metformin + DPP-4 inhibitor+ glinide
       6. Metformin + DPP-4 inhibitor + sulfonylurea
   - **HbA1c 7.6-9%**
     - **Monotherapy**
       - Monotherapy is unlikely to be successful in this group. Bypass.
     - **Dual Therapy**
       1. Metformin + GLP-1 Agonist
       2. Metformin + DPP-4 Inhibitor
       3. Metformin + TZD
       4. Metformin + sulfonylurea
       5. Metformin + glinide
     - **Triple Therapy**
       1. Metformin + GLP-1 agonist + TZD
       2. Metformin + DPP-4 inhibitor + TZD
       3. Metformin + GLP-1 agonist + sulfonylurea
       4. Metformin +DPP-4 Inhibitor + TZD
       5. Metformin + TZD + Sulfonylurea

3. ADA/EASD 2012
   - If monotherapy alone does not achieve/maintain an HbA1c target over 3 months, the next step would be to add a second oral agent, a GLP-1 receptor agonist, or basal insulin

4. VA/DOD 2010
   - Metformin + sulfonylurea is the preferred oral combination for patients who no longer have adequate glycemic control on monotherapy with either drug
   - Other combinations (TZDs, AGI, meglitinides, DPP-4 inhibitors, and GLP-1 agonists) can be considered for patients unable to use metformin or a sulfonylurea due to contraindications, adverse events, or risk for adverse events
   - Addition of bedtime NPH or daily long acting insulin analog to metformin or sulfonylurea should be considered, particularly if the desired HBA1c is not likely to be achieved by use of combination oral therapy
LITERATURE EVALUATION

Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Sitagliptin vs. Glipizide 52 weeks</th>
<th>Sitagliptin vs. Glipizide 104 weeks (PP)</th>
<th>Saxagliptin vs. Glipizide</th>
<th>Linagliptin vs. Glimepiride</th>
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<tbody>
<tr>
<td>Average Age (years)</td>
<td>57</td>
<td>57</td>
<td>57.6</td>
<td>60</td>
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<tr>
<td>Duration of Diabetes (years)</td>
<td>6.5</td>
<td>5.8</td>
<td>5.4</td>
<td>≤1 year: 7%</td>
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<td>&gt;1 and &lt;5 years: 40%</td>
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<td>&gt;5 years: 53%</td>
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<td>Mean HbA1c (%)</td>
<td>7.7</td>
<td>7.3</td>
<td>7.7</td>
<td>7.7</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>31</td>
<td>31</td>
<td>31.4</td>
<td>30</td>
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</tbody>
</table>

Article Title/Citation | Sitagliptin vs. glipizide 52 + 104 weeks
Study Objectives/Purpose | To evaluate the 2 year safety and efficacy of adding sitagliptin or glipizide to ongoing metformin in patients with type 2 diabetes
Study Design and Methodology
- Multi-national, randomized, parallel-group, non-inferiority study with an active controlled, double-blind treatment period
- N: 1172: Sitagliptin (n=588) and glipizide (n=584)
  - APT Cohort: Sitagliptin (n=576) and Glipizide (n=559)
  - PP Cohort: Sitagliptin (n=248) and Glipizide (256)
Inclusion Criteria
- Type II DM, Age 18-78 years old
- Not on OHA, Any OHA monotherapy, or metformin in combination with any other OHA
Exclusion Criteria
- Type I DM
- Insulin use within 8 weeks of screening
- Renal function impairment inconsistent with metformin
- FBG > 270mg/dl
Interventions
- Patient’s already on metformin >1500mg/day + HbA1C between ≥6.5 and <10 entered a 2 week placebo run in period then were eligible to be randomized
- Patient not currently on an OHA, patients on an OHA other than metformin monotherapy >1500mg/day, or patients on metformin in combination with another OHA entered into a metformin monotherapy titration for <8wks. If patient’s HbA1C ≥6.5 and <10 entered a 2 week placebo run in period then were eligible to be randomized
- Treatment Groups (Randomized 1:1)
  - Metformin + Sitagliptin 100mg once daily
  - Metformin + Glipizide 5mg/day titrated to a max dose of 20mg/day
    - Titrated in 3 week intervals if all premeal glucose values >110mg/dl
    - Uptitration could be withheld at the investigators discretion if the patient was at risk for hypoglycemia
    - At any point in the study glipizide could be down titrated to avoid hypoglycemia
- Patient’s discontinued if they failed to meet the following criteria:
  - Randomization through week 6: FPG>270mg/dL, Week 6-12: FPG>240 mg/dL, Week 12-18: FPG>220mg/dL, Week 18-30: FPG>200 mg/dL, Week 30-52: HbA1c>8.0%, Week 52-104: HbA1c>7.5%
## Outcomes
- **Primary**
  - Reduction in HbA1c from baseline at week 52 in PP cohort (non-inferior)
- **Secondary**:
  - Reduction in HbA1c from baseline at week 104 in PP cohort
  - % of patients treated who experienced hypoglycemia + episodes
  - Weight Gain
  - Rise in HbA1c (Coefficient of Durability)

## Statistical Analysis
- Non-inferiority margin: δ=0.3%
- For efficacy endpoints the ANCOVA model was used to compare the treatment groups
- To support the findings in the analysis of the PP population additional efficacy analyses were performed on key endpoints the APT cohort

## Results
- **Primary outcome**:
  - Reduction in HbA1c from baseline at week 52: -0.67% in both groups. The mean difference was 0.08% satisfying the non-inferiority margin of 0.3%
- **Secondary** (Week 104):
  - Reduction in HbA1c from baseline at week 104: -0.51% in the glipizide group and -0.54% in the sitagliptin group. Difference: -0.03 (95% CI -0.13, 0.07)
  - Rise in HbA1c from week 24-104:
    - Sitagliptin 0.16%/yr vs. glipizide 0.26%/yr. Difference: -0.1%/yr (95%CI -0.16, -0.05)
  - Weight Gain:
    - Week 104: Sitagliptin -1.6kg vs. Glipizide 0.7kg. Difference: -2.3kg (95%CI -3,-1.6)
- Hypoglycemia:
  - 199 (34.1%) glipizide treated patients-805 episodes
  - 31(5.3%) sitagliptin treated patients- 57 episodes
  - % Difference: -28.8% (95% CI -33,-24.5)
  - 9 glipizide(1.5%) and 1 (0.2%) required medical assistance
- **Confirmatory Analysis (APT Cohort)**
  - Reduction in HbA1c from baseline at week 104: -0.33% sitagliptin and -0.35% glipizide. Difference: 0.01% (95%CI -0.08,0.1)

## Authors Conclusions
- Sitagliptin was non-inferior to glipizide in HbA1c lowering efficacy at 52 weeks in the PP population.
- Sitagliptin and glipizide provided similar reduction reductions in HbA1c at 104 weeks
- Durability (defined as the slope of change in HbA1c over time) was greater with sitagliptin, suggesting a more durable glycemic response for sitagliptin treated patients
- Sitagliptin was associated with weight loss, whereas glipizide was associated with weight gain
- Glipizide was associated with a 14-fold higher number of hypoglycemic episodes relative to sitagliptin over the course of 104 weeks
- The APT results were consistent with and supported the HbA1c reduction from the PP analysis

## Comments
- Small sample size
- Patients included in the study had relatively short duration of diabetes and a relatively low baseline A1c
- Follow up time may be too short to truly assess the long term durability of the agents
- Primary endpoint confirmed with APT group
<table>
<thead>
<tr>
<th>Article Title/Citation</th>
<th>Saxagliptin vs. glipizide 52 weeks&lt;sup&gt;1b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Objectives/ Purpose</td>
<td>To assess the efficacy and safety of saxagliptin vs. glipizide as add on therapy to metformin in patients with type 2 diabetes mellitus and inadequate glycemic control on metformin alone</td>
</tr>
</tbody>
</table>
| Study Design and Methodology | - International, multi-center, randomized, parallel-group, active controlled, double blind, non-inferiority trial  
- N: 858: Saxagliptin (n=428) and glipizide (n=430)  
  - PP Analysis Set: Sitagliptin (n=312) and Glipizide (321) |
| Inclusion Criteria | - >18 years old with T2DM and HBA1c >6.5-10%  
- On a stable dose of metformin monotherapy ≥1500mg for at least 8 week prior to enrollment |
| Exclusion Criteria | - Type I DM, History of diabetic ketoacidosis or hyperosmolar non-ketotic coma, Insulin use within 1 year of enrolment, Treatment with a TZD within 12 weeks prior to enrolment, Treatment with systemic glucocorticoids other than replacement therapy, Previous DPP-4 Inhibitor treatment, Donation of blood, plasma, or platelets within 3 months prior to enrolment, CHF NYHA class III or IV and/or known LVEF<40%, Significant CV history within the past 6 months (MI, CABG, Valve, TIA, CVA, etc), History of hemoglobinopathies, Significant alcohol or drug abuse with the year prior to enrolment, Treatment with HIV/Antiviral drugs or CYP450 3A4 inducers, Scr >1.4 in men; Scr >1.5 in women, LFTs >2x ULN |
| Interventions | - Eligible patients enrolled in a 2 week, single-blind, placebo-controlled lead in period  
- Following the lead-in period, eligible patients were randomized 1:1  
- Treatment Groups  
  - Metformin + Saxagliptin 5mg once daily  
  - Metformin + Glipizide 5mg/day titrated to a max dose of 20mg/day  
  - Titrated to an optimal effect (FBG≤110) or the highest tolerated  
  - Titrated in 3 week intervals during an 18 week titration period  
  - At any point in the study glipizide could be down titrated to avoid hypoglycemia.  
- Patient’s discontinued if they failed to meet the following criteria:  
  - Patients with FPG>270mg/dL, >240mg/dL, >220 mg/dL, or >200 mg/dL at weeks 3, 12, 18, or 24 respectively  
  - HbA1c>8% at week 30 or 39 |
| Outcomes | - Primary  
  - Change from baseline to week 52 HbA1c (non-inferior)  
- Key secondary endpoints  
  - Mean slope of regression of change from week 24-52 in HbA1c  
  - Change from baseline body weight  
  - Proportion of patients reporting >1 event of hypoglycemia over 52 weeks |
| Statistical Analysis | - The primary and key secondary efficacy analyses involving HbA1c was conducted using the PP analysis set.  
- The full analysis set was used for confirmatory analysis.  
- Saxagliptin was considered non-inferior to glipizide if the upper limit of the 95% CI of the difference in change in HbA1c from baseline to week 52 between the two groups was <0.35% |
| Results | - Primary:  
  - HbA1c reduction from baseline at 52 weeks was -0.74% for saxagliptin and -0.80% for glipizide. Difference = was 0.06% (95% CI, -0.05 to 0.16%)  
- Confirmatory analysis of the full analysis set yielded consistent results  
- Change from baseline HbA1c: Saxagliptin -0.57% and Glipizide -0.66% |
<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Conclusions</th>
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<tbody>
<tr>
<td></td>
<td>The HbA1c reduction at week 52 with saxagliptin + metformin was non-inferior to glipizide + metformin</td>
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<td>Saxagliptin+metformin showed a smaller rise per week in HbA1c than glipizide+metformin, indicating a longer period of sustained glycemic control with saxagliptin treatment</td>
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<td>Saxagliptin led to a decrease in body weight while glipizide led to an increase in body weight</td>
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<td>Saxagliptin resulted in a statistically significant lower proportion of patients with hypoglycemia than glipizide</td>
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<table>
<thead>
<tr>
<th>Comments</th>
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<tbody>
<tr>
<td>Baseline patient characteristics and HbA1c reduction similar to previous study</td>
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<tr>
<td>Small sample size</td>
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<td>Patients included in the study had relatively short duration of diabetes and a relatively low baseline A1c</td>
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<td>Follow up time may be too short to truly assess the long term durability of the agents</td>
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<td>Primary endpoint confirmed with full analysis set</td>
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<thead>
<tr>
<th>Article Title/Citation</th>
<th>Linagliptin vs. glimepiride 104 weeks&lt;sup&gt;17&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>Study Objectives/Purpose</td>
<td>To assess the efficacy and safety of linagliptin vs. glimepiride as add on therapy to metformin in patients with type 2 diabetes mellitus and inadequate glycemic control on metformin alone</td>
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<tr>
<td>Study Design and Methodology</td>
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<tr>
<td></td>
<td>Multi-national, randomized, parallel-group, active controlled, non-inferiority trial</td>
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<td>N: 1551: Linagliptin(n=776) and glimepiride (n=775)</td>
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<td>Full analysis set: Linagliptin(764) and Glimepiride (755)</td>
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<td>PP set: Linagliptin(447) and Glimepiride (458)</td>
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<td>Inclusion Criteria</td>
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<td>18-80 years</td>
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<td>Type II DM</td>
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<td>Metformin ≥1500mg/day alone or with one other oral anti-diabetic drug</td>
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<td>Metformin monotherapy: HbA1c 6.5%-10%</td>
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<td>Metformin + one additional oral antidiabetic: HbA1c 6-9%</td>
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<td>BMI ≤40 kg/m2</td>
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<td>Exclusion Criteria</td>
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<td>Myocardial infarction, stroke, or TIA in 6 months before screening</td>
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<td>Impaired hepatic function at screening</td>
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<td>Treatment with rosiglitazone, pioglitazone, a GLP-1 agonist, insulin or an anti-obesity drug in the 3 months before screening.</td>
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<tr>
<td>Interventions</td>
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<td>Patients receiving metformin monotherapy entered a 2 week placebo run in period then were eligible to be randomized</td>
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<td>Patients receiving metformin + one additional oral antidiabetic drug entered a 6 week washout period followed by the 2 week open lab placebo run in period.</td>
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<td>By the start of the placebo run in period the HbA1c inclusion criteria was 6.5%-10% for all participants</td>
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<tr>
<td><strong>Outcomes</strong></td>
<td><strong>Primary Efficacy:</strong></td>
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<td>Change in HbA1c from baseline to week 104</td>
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<td>Key secondary endpoints</td>
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<td>Occurrence of hypoglycemic episodes up to 104 weeks</td>
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<td>Change in bodyweight from baseline to week 104</td>
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<td>CV events</td>
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<thead>
<tr>
<th><strong>Statistical Analysis</strong></th>
<th><strong>Primary:</strong></th>
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<tr>
<td></td>
<td>After 2 years linagliptin was non-inferior to glimepiride in reducing HbA1c. In full analysis set the mean change from baseline HbA1c was -0.16% with linagliptin and -0.36% with glimepiride. Difference=0.2% (97.5%CI 0.09-0.3);p=0.0004, p&lt;0.0125(one sided))</td>
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<td>Sensitivity Analysis with PP set</td>
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<tr>
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<td>HbA1c change from baseline: linagliptin -0.35% and glimepiride -0.53%. Difference=0.17% (97.5% CI 0.07-0.28; p=0.0001, p&lt;0.0125(one sided))</td>
</tr>
<tr>
<td></td>
<td>Key secondary:</td>
</tr>
<tr>
<td></td>
<td>Overall incidence of hypoglycemia was 4.8x lower with linagliptin that with glimepiride (58[7%] of 776 vs. 280[36%] of 775 patients;p&lt;0.0001)</td>
</tr>
<tr>
<td></td>
<td>Bodyweight decreased with linagliptin -1.4kg but increased with glimepiride 1.3kg. Difference=-2.7kg(97.5%CI -3.2 to -2.2,p&lt;0.0001)</td>
</tr>
<tr>
<td></td>
<td>Other secondary:</td>
</tr>
<tr>
<td></td>
<td>Major cardiovascular events: Linagliptin 12/776(2%) and Glimepiride 26/775(3%). RR=0.46 (95%CI 0.23-0.91; p=0.0213)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Authors Conclusions</strong></th>
<th>Linagliptin was non-inferior to glimepiride in lowering HbA1c</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Linagliptin was associated with significantly less hypoglycemia and weight loss</td>
</tr>
<tr>
<td></td>
<td>Linagliptin was associated with significantly fewer cardiovascular events compared with glimepiride</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th><strong>Comments</strong></th>
<th>Small sample size</th>
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<tbody>
<tr>
<td></td>
<td>Patients included in the study had relatively short duration of diabetes and a relatively low baseline A1c</td>
</tr>
<tr>
<td></td>
<td>Follow up time may be too short to truly assess the long term durability of the agents and cardiovascular safety</td>
</tr>
<tr>
<td></td>
<td>Primary endpoint was tested with the non-completion group</td>
</tr>
</tbody>
</table>
Other Studies:

- Effect of Noninsulin Antidiabetic Drugs added to Metformin Therapy on Glycemic control, weight gain, and hypoglycemia in Type 2 Diabetes; JAMA 2010
  - Systematic literature search 1950-2010 in MEDLINE and Cochrane
  - Randomized control trials with at least 3 months duration, evaluating noninsulin antidiabetic drugs added to metformin in patients experiencing an inadequate response to metformin
  - 27 randomized controlled trials (n=11,198), Age range: 53-62, mean trial duration: 32 weeks, and baseline HbA1c: 6.4-9.3%
  - The different classes of drugs were associated with similar HbA1c reduction (0.64%-0.97%) compared with placebo—Sulfonylureas -0.79% and DPP-4 Inhibitors -0.78%.
  - Weight gain: TZDs, sulfonylureas, glinides
  - Hypoglycemia: sulfonylureas and glinides

### SUMMARY

- When added to metformin therapy, noninsulin anti-diabetic drugs provide similar HbA1c reduction
- Hypoglycemia can lead to increased morbidity/mortality, increased costs, and decreased patient compliance
- Patients HbA1c goals should be individualized, taking into account duration of disease, life expectancy, risk of hypoglycemia, comorbid conditions, and advanced complications.
- Based on the current diabetes treatment guidelines, no one oral anti-diabetic agent is unanimously recommended over another to add to metformin
- The attributes clinicians should take into account when choosing an anti-diabetic agent are:
  - Effectiveness, simplicity, safety, cost, and durability.

<table>
<thead>
<tr>
<th></th>
<th>DPP4 Inhibitor + Metformin</th>
<th>Sulfonylurea + Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c Reduction</td>
<td>Equally effective</td>
<td>Equally effective</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Significantly less</td>
<td>More</td>
</tr>
<tr>
<td>Weight</td>
<td>Weight loss</td>
<td>Weight gain</td>
</tr>
<tr>
<td>Durability</td>
<td>Slower increase in HbA1c</td>
<td>Faster increase in HbA1c</td>
</tr>
</tbody>
</table>

### RECOMMENDATIONS

**Adding a 2nd Oral Agent to Metformin**

- Patients at high risk of hypoglycemia requiring an HbA1c reduction of 0.5-1% should be treated with the combination of a DPP4 inhibitor & metformin rather than the combination of a sulfonylurea & metformin
- Patients with a relatively short duration of diabetes (~5 years) and a low baseline HbA1c (7-8%) should be treated with a DPP4 inhibitor & metformin rather than the combination of a sulfonylurea & metformin
- More evidence is needed to assess the long term complications of hypoglycemia
- More evidence is needed to assess the long term durability of DPP4 Inhibitors
- More evidence is needed to assess whether patients taking sulfonylureas are at increased risk for cardiovascular events compared to DPP4 inhibitors.
## Appendix A

### Sulfonylureas

**Mechanism of Action**
Stimulates insulin secretion from pancreas (not glucose dependent)

**Drugs**
- Glipizide
- Glimepiride
- Glyburide
- Sitagliptin
- Saxagliptin
- Linagliptin

**Initial Dose**
- Glipizide: 5mg daily
- Glimepiride: 1-2 mg daily
- Glyburide: 2.5-5mg daily
- Sitagliptin: 100mg daily
- Saxagliptin: 2.5-5mg daily
- Linagliptin: 5mg daily

**Max Dose**
- Glipizide: 40mg daily
- Glimepiride: 8mg daily
- Glyburide: 20mg daily
- Sitagliptin: 100mg daily
- Saxagliptin: 5mg daily
- Linagliptin: 5mg daily

**Renal Dose Adjustment**
- GFR<50: Reduce dose by 50%
- CrCl<22: Initial dose 1mg
- CrCl<50: Not recommended
- CrCl 30-50: 50mg daily
- CrCl<30: 25mg daily
- CrCl<50: 2.5mg daily
- None

**Hepatic Dose Adjustment**
- Initial 2.5mg
- None listed
- Avoid in severe disease
- Not studied in severe disease
- None
- None

**Geriatric Dose Adjustment**
- Initial 2.5mg
- Initial 1mg
- Initial 1.25-2.5mg
- None
- None
- None

**Metabolism**
- Hepatic via 2C9 (no active metabolites)
- Hepatic via 2C9 (active metabolites)
- Hepatic via 2C9 (active metabolites)
- Minimal hepatic. Substrate of P-Gp.
- Hepatic via 3A4/5 (active metabolites)
- Not extensively metabolized. 3A4. P-Gp.

**Half-life**
- 2-5 hours
- 5-9 hours
- Reg: 10 hrs Micr: 4 hours
- 12 hours
- 2.5 hours Metabolite: 3.1 hours
- 12 hours

**Duration of Action**
- 12-24 hours
- 24 hours
- ≤24 hours
- Not listed
- 24 hours
- Not listed

**Time to peak**
- IR: 1-3 hrs ER: 6-12 hrs
- 2-3 hours
- 2-4 hours
- 1-4 hours
- 2 hours Metabolite: 4 hours
- 1.5 hours

**Major Drug Interactions (D or X)**
- Strong 2C9 Inhibitors
- Strong 2C9 Inhibitors
- X: Bosentan
- Strong 2C9 Inhibitors
- None
- Strong 3A4 Inhibitors
- Strong 3A4 inducers P-GP inducers and inhibitors

**Common Side Effects**
- Hypoglycemia
- Weight gain
- <10% GI
- Nasopharyngitis
- <10% GI
- Headache
- UTI
- <10% Headache
- Arthralgia
- Nasopharyngitis

**Contraindications**
- Type 1 DM
- Hypersensitivity to sulfonylureas or sulfonamides
- Hypersensitivity to the product or its components

**Warnings**
- G6PD Deficiency-Hemolytic Anemia
- Secondary failure: loss of efficacy
- Hypoglycemia
- Pancreatitis
- Angioedema, Anaphylaxis, SJS
- Caution: use of concomitant insulin or Insulin secretagogues

**Cost**
- Glipizide: 10mg (90): $19.50
- Glimepiride: 4mg (30): $14.99
- Glyburide: 5mg (30): $18.99
- Sitagliptin: 100mg (30): $235
- Saxagliptin: ??
- Linagliptin: ??
APPENDIX B

Approach to management of hyperglycemia:

- **More stringent**
  - Patient attitude and expected treatment efforts: Highly motivated, adherent, excellent self-care capacities
  - Risks potentially associated with hypoglycemia, other adverse events: Low
  - Disease duration: Newly diagnosed
  - Life expectancy: Long
  - Important comorbidities: Absent
  - Established vascular complications: Absent
  - Resources, support system: Readily available

- **Less stringent**
  - Patient attitude and expected treatment efforts: Less motivated, non-adherent, poor self-care capacities
  - Risks potentially associated with hypoglycemia, other adverse events: High
  - Disease duration: Long-standing
  - Life expectancy: Short
  - Important comorbidities: Few / mild
  - Established vascular complications: Few / mild
  - Resources, support system: Limited

APPENDIX C

<table>
<thead>
<tr>
<th>Medication</th>
<th>Annual National Estimate of Hospitalizations (N=99,628)</th>
<th>Proportion of Emergency Department Visits Resulting in Hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no.</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>Most commonly implicated medicines†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>33,171</td>
<td>33.3 (28.0–38.5)</td>
</tr>
<tr>
<td>Insulins</td>
<td>13,854</td>
<td>13.9 (9.8–18.0)</td>
</tr>
<tr>
<td>Oral antiplatelet agents</td>
<td>13,263‡</td>
<td>13.3 (7.5–19.1)</td>
</tr>
<tr>
<td>Oral hypoglycemic agents</td>
<td>10,656</td>
<td>10.7 (8.1–13.3)</td>
</tr>
<tr>
<td>Opioid analgesics</td>
<td>4,778</td>
<td>4.8 (3.5–6.1)</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>4,205</td>
<td>4.2 (2.9–5.5)</td>
</tr>
</tbody>
</table>