Polypharmacy: Controversies and Updates in Type 2 Diabetes

USF Health: Office of Continuing Professional Development
Jose Barboza, Pharm.D., C.D.E.
Assistant Professor
University of South Florida College of Pharmacy

Disclosure

I, or an immediate family member, including spouse or partner, have no financial relationship(s) relevant to the content of this continuing education activity.

Objectives

• Assess the evidence behind the controversial topics with the treatment of type 2 diabetes (DM2)
• Discuss the efficacy of the newly approved medications for treating DM2
• Review the recent updates in the Standards of Care for DM2
Presentation Outline

- Controversial Topics
  - A. Do statins cause diabetes?
  - B. Should every patient with DM2 take an ACE inhibitor?

- New medications for diabetes: Focus on Efficacy
  - A. Alogliptin
  - B. Canagliflozin

- ADA Standards of Care 2013 Updates
  - A. New BP Goals for diabetics
  - B. Different A1C goals for different people

Statins: Risk of DM2

- Meta analysis of 13 trials (n=91,140)
  - 4278 patients developed diabetes (avg. 4 years)
    - 2,226 in the statin group
    - 2,052 in the control group
  - 9% increased risk of DM2 with statins
    - OR 1.09; CI:1.02-1.17
    - **NNH: 255** (CI: 150-852)


Risk of DM2 in High vs. Moderate Statin Doses

- Meta analysis of 5 trials (n=32,752)
- 2,749 patients developed DM2 (avg. 1.9 years)
  - Intensive statin dose: 1,449
  - Moderate statin dose: 1,300
  - **NNH: 498**
    - 12% increased risk, OR 1.12; CI: 1.04-1.22

  *JAMA. 2011 Jun 22;305(24):2556-64.*
Risk of CV: High vs. Moderate Statin Doses

- Cardiovascular events: 6,684 (avg. 1.9 years)
  - Intensive statin dose: 3,134
  - Moderate statin dose: 3,550
  - NNT: 155
    - 16% risk reduction, OR 1.84; CI: 0.75-0.94

JAMA. 2011 Jun 22;305(24):2556-64.

CV Benefit and DM Risk

- Analysis of JUPITER
  - JUPITER: RCT comparing rosuvastatin with placebo in primary prevention, n=17,603 (5 years)

<table>
<thead>
<tr>
<th>DM Risk Factors</th>
<th>≥1 (n=11,508)</th>
<th>0 (n=6,095)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of Developing DM</td>
<td>28%</td>
<td>0</td>
</tr>
<tr>
<td>Reduction in VTE</td>
<td>36%</td>
<td>53%</td>
</tr>
<tr>
<td>Reduction in total mortality</td>
<td>17%</td>
<td>22%</td>
</tr>
<tr>
<td>Reduction in primary endpoint</td>
<td>39%</td>
<td>52%</td>
</tr>
</tbody>
</table>


Question

Can statins cause diabetes?

A. Yes and they should no longer be used in practice
B. Yes, but the benefits outweigh the risks
C. No, there is no evidence to support that
D. No, statins decrease the risk for diabetes
Statins and Hyperglycemia: Summary

- **Increase of DM risk:** 9%¹
- **High dose vs. moderate Statin dose²**
  - NNH: 498 for DM
  - NNT: 155 for CV
- **DM risk factors³**
  - 0 DM RF: Limited increase in DM
  - ≥1 RF:
    - 28% increase in DM
    - 39% decrease in vascular events or deaths


ACEI and ARB use in Diabetes

- Diabetic nephropathy: Leading cause of ESRD
- **High blood glucose**
  - Glomerular hyperfiltration
  - Triggers:
    - Inflammation, oxidative damage, fibrosis, and RAAS
- **ACEIs and ARBs:**
  - Decrease the risk of ESRD in diabetics with macroalbuminuria¹, ²


ACEI and ARBs in Microalbuminuria

- **Microalbuminuria:**
  - 30 to 299 mg albumin/day
  - Associated with nephron damage and CV disease
  - Treatment with ACE inhibitors has shown decrease risk of microalbuminuria
Question

• Are ACE inhibitors or ARBs required to be used in all patients with diabetes?
  – A. Yes, they should be used at least in low doses
  – B. Yes, they must be used at full dose
  – C. No, unless there is evidence of HTN or renal disease
  – D. Never

ONTARGET Trial

• Telmisartan + ramipril vs. ramipril
• Primary endpoint: composite of dialysis, creatinine doubling, or death
• Result: Combination reduced progression to macroalbuminuria
• Result: Combination did not increase the risk of primary endpoint

Lancet 2008;372:547-53

Benefits of Decreasing Microalbuminuria?

<table>
<thead>
<tr>
<th>Trial</th>
<th>ADVANCE1</th>
<th>ACCOMPLISH2</th>
<th>ONTARGET3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medications</td>
<td>Perindopril + indapamide vs. placebo</td>
<td>HCTZ + benazepril vs. amlodipine + benazepril</td>
<td>Telmisartan + ramipril vs. ramipril</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>Prevent onset of microalbuminuria, macroalbuminuria</td>
<td>HCTZ+ benazepril reduced macroalbuminuria</td>
<td>Combo: Reduced progression to macroalbuminuria</td>
</tr>
<tr>
<td>Consideration</td>
<td>Combination did not prevent development of ESRD</td>
<td>Amlodipine + benazepril decreased cardiovascular events</td>
<td>Combination did not increased risk of primary endpoint</td>
</tr>
</tbody>
</table>

Is there a Potential Risk in Over-treating?

- **ALTITUDE**¹
  - ACEI/ARB vs. ACEI/ARB + telmisartan in high risk patients
    - Microalbuminuria, macroalbuminuria, and CV disease
    - Normotensive at baseline
  - Primary endpoint:
    - Reduce renal and CV morbidity and mortality in high risk DM patients (baseline controlled bp)
  - Combination: higher risk of non-fatal stroke, ESRD, renal death, hyperkalemia, and hypotension

- **ROADMAP**²
  - Olmesartan vs placebo
  - Primary outcome:
    - Time of first onset of macroalbuminuria
    - Olmesartan delayed onset of microalbuminuria
    - Increased fatal cardiovascular events with olmesartan


ACE inhibitors for Diabetics: Summary

- Use ACEIs/ARBs in:
  - HTN
  - Macroalbuminuria
- Consider ACEIs/ARBs in:
  - Microalbuminuria
- Lacking evidence to use ACEIs/ARBs in:
  - Normotensive without sign of kidney damage

Diabetes and ACE Inhibitors/ARBs

- ADA Standards of care 2013
  - Initiate pharmacological therapy to treat HTN (B)
  - Initiate ACEIs or ARBs in patients with urinary albumin excretion:
    - >300mg/day (A)
    - 30-299mg/day (C)
  - Normotensive, no sign of kidney damage:
    - No mention

Newly Approved Medications

• Nesina (alogliptin): January 2013
  – Kazano (alogliptin + metformin)
  – Oseni (alogliptin + pioglitazone)
• Invokana (canagliflozin): April 2013

Alogliptin: Nesina

• Mechanism:
  – GLP1 and GIP are hormones released in response to food consumption
    • stimulate insulin production from beta cells
    • Decrease glucagon release
    • Metabolized by dipeptidyl peptidase-4 (DPP4) enzyme
  – Inhibit DPP4 and allow increased levels of GLP1 and GIP
• Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes

Alogliptin: Dosing

• Dose: 25mg daily
• Treats: fasting plasma glucose
• CrCl ≥30 to <60ml/min: 12.5mg daily
• CrCl <30ml/min: 6.25mg daily
• Severe hepatic impairment: Not studied
• Geriatric: Less A1C reduction in ages >65
• Pregnancy category B
Alogliptin: Adverse Reactions/Precautions/Pharmacokinetics

- Adverse reactions:
  - Nasopharyngitis (4.4%), headache (4.2%), URI (4.2%)
- Precautions
  - Pancreatitis (0.2 vs. <0.1%), hepatic elevation (higher in comparators)
- Pharmacokinetics:
  - Limited drug interactions, not extensively metabolized
  - Minor CYP2D6 and 3A4 substrate
  - Time to peak: 1-2 hours
  - Half life: ~21 hours

Alogliptin Efficacy: A1C

- Monotherapy vs. Placebo
  - Alogliptin 25mg: -0.6%
  - Placebo: 0%
- Monotherapy and in combination: pioglitazone
  - Alogliptin 25mg: -1.0%
  - Pioglitazone 30mg: -1.2%
  - Alogliptin 25mg+pioglitazone 30mg: -1.7%

Canagliflozin: Invokana

- Mechanism: sodium-glucose co-transporter 2 (SGLT2) inhibitor
  - Kidneys filter and reabsorb BG
  - SGLT2: reabsorbs 90% of BG in the proximal convoluted tubules
  - Decreases re-absorption of filtered glucose
- Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes
Canagliflozin: Mechanism of Action

Canagliflozin: Dosing

- Dose: 100-300mg daily prior to first meal
  - Reduce postprandial BG levels
- eGFR: 45-59ml/min: Max dose 100mg daily
- eGFR: 30-45ml/min: Not recommended
- eGFR: <30ml/min: Contraindicated
- Severe hepatic impairment: not recommended
- Geriatric: Less A1C reduction in ages >65
- Pregnancy category C

Canagliflozin: Pharmacokinetics

- Metabolism:
  - Glucuronidation (UGT1A9 and UGH2B4) to active metabolites
  - CYP3A4 (~7%)
  - Half life: 10-13 hours
- Time to peak: 1-2 hours
- Drug interactions:
  - UGT inducers (rifampin), may increase digoxin levels (monitor), hypotension with antihypertensives, CYP3A4
Canagliflozin: Adverse Reactions/Precautions

- Adverse reactions:
  - Genital mycotic infection (4-11%), UTI (4-6%), increased urination (4.5-6%), thirst (2-3%), vulvovaginal pruritus (1.5-3%), hyperkalemia (3-5%), increase in LDL (4.5-8%), constipation (2%), nausea (2%)

- Precautions
  - Genital mycotic infection, hypotension, hyperkalemia, lipid abnormalities

Canagliflozin Efficacy: A1C and Weight

- Monotherapy:
  - 100mg: A1C -0.77%, Wt: -2.8kg
  - 300mg: A1C -1.03%, Wt: -3.9kg
  - Placebo: A1C +0.14%, Wt: -0.6kg

- Dual Therapy:
  - 100m + metformin: -0.82%, Wt: -4.2kg
  - 300mg + metformin: -0.93%, Wt: -4.7kg
  - Glimepiride (6-8mg) + metformin: -0.81%, Wt: +1.0kg

- Triple Therapy
  - Invokana+Met+SU: -1.03%, Wt: -2.5kg
  - Sitagliptin+Met+SU: -0.66%, Wt: +0.3kg

Question

Canagliflozin belongs to which of the following drug classes?
A. GLP-1 agonist
B. DPP4 inhibitor
C. SGLT2 inhibitor
D. Sulfonylurea
UKPDS: Tight BP Control

- UKPDS (8.4 years)
  - Median BP 144/82 vs. 154/87
  - Decreased risk of microvascular disease, stroke, and deaths related to diabetes

BMJ 2000;321:412–419

ACCORD: TIGHTER BP Control

- ACCORD
  - Type 2 diabetics and CVD for 5 years
  - Primary endpoint
    - Nonfatal MI, nonfatal stroke, CVD death

<table>
<thead>
<tr>
<th></th>
<th>Intensive</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP Goal (mmHg)</td>
<td>&lt;120</td>
<td>130-140</td>
</tr>
<tr>
<td>BP Achieved (mmHg)</td>
<td>119/64</td>
<td>133/70</td>
</tr>
<tr>
<td>Avg. Meds</td>
<td>3.4</td>
<td>2.1</td>
</tr>
</tbody>
</table>


ACCORD: TIGHTER BP Control

- Intensive group Results:
  - Primary endpoint: 0.88 (CI: 0.73-1.06, P=0.20)
  - Stroke and non fatal stroke: Decreased, NNT: 89
  - Increased syncope and hyperkalemia
  - Improved albuminuria, no differences in renal function

ADA Standards of Care 2013: BP Goal

- People with diabetes and hypertension should be treated to a systolic blood pressure goal of <140 mmHg. (B)
- Lower systolic targets, such as <130 mmHg, may be appropriate for certain individuals, such as younger patients, if it can be achieved without undue treatment burden. (C)
- Patients with diabetes should be treated to a diastolic blood pressure <80 mmHg. (B)


General Treatment Goals

<table>
<thead>
<tr>
<th>Organization</th>
<th>A1C (%)</th>
<th>Fasting Plasma Glucose (FPG, mg/dL)</th>
<th>2 hour post-prandial plasma glucose (PPG, mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA</td>
<td>&lt;7</td>
<td>70-130</td>
<td>&lt;180</td>
</tr>
<tr>
<td></td>
<td>6.5 in selected patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AACE</td>
<td>&lt;6.5</td>
<td>&lt;110</td>
<td>140</td>
</tr>
</tbody>
</table>


UK Prospective Diabetes Study (UKPDS)

- Multi-Centered Randomized Controlled Trial (RCT)
- 4239 newly diagnosed type 2 diabetics 25-65 years old with a median A1C of 9.1

Aims:
- To determine if intensive glucose control using sulfonylureas, insulin, or metformin will decrease diabetic complications

Endpoints:

Mean age: 53
- Male: 59%
- Study length (median): 10 years
- Conventional treatment group: Maintain FPG <270mg/dL
- Intensive treatment group: Maintain FPG <180mg/dL
Fasting plasma glucose between 6mmol/L (110mg/dL) and 13mmol/L (270mg/dL)

Main Randomisation
n=4209 (82%)

342 allocated to metformin

3867

Conventional Policy
30% (n=1138)

Intensive Policy
70% (n=2729)

Sulphonylurea
n=1573

Insulin
n=1156

HbA1c

cohort, median data

Conventional Insulin Chlorpropamide Glibenclamide

Years from randomisation

Aggregate Clinical Endpoints

<table>
<thead>
<tr>
<th>Relative Risk</th>
<th>Relative Risk &amp; 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>p</td>
</tr>
<tr>
<td>Any diabetes related endpoint</td>
<td>0.88</td>
</tr>
<tr>
<td>Diabetes related deaths</td>
<td>0.90</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>0.94</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.84</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.11</td>
</tr>
<tr>
<td>Microvascular</td>
<td>0.75</td>
</tr>
</tbody>
</table>
Metformin in Overweight Patients

- compared with conventional policy

- 32% risk reduction in any diabetes-related endpoints, p=0.023
- 42% risk reduction in diabetes-related deaths, p=0.017
- 36% risk reduction in all cause mortality, p=0.011
- 39% risk reduction in myocardial infarction, p=0.01

UKPDS 80, 10 Year Post-Follow Up

Insulin or Sulfonylurea vs. Conventional treatment

- Metformin vs. Conventional treatment

Insulin or Sulfonylurea vs. Conventional Treatment

- Any Diabetes-Related End Point: RRR: 9%
  - p=0.04

- Microvascular Disease: RRR: 24%
  - p<0.001

- Myocardial Infarction: RRR: 15%
  - p=0.03

- Death from any Cause: RRR: 13%
  - p=0.006
### Metformin vs. Conventional Treatment

<table>
<thead>
<tr>
<th>Year</th>
<th>Total</th>
<th>No. A1C</th>
<th>No. Events</th>
<th>Intensive</th>
<th>Standard</th>
<th>Intensive vs. Standard</th>
<th>RR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>368</td>
<td>180</td>
<td>60</td>
<td>124</td>
<td>56</td>
<td>0.20</td>
<td></td>
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**RRR:** 21%

### Metformin vs. Conventional Treatment

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<th>Standard</th>
<th>Intensive vs. Standard</th>
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</table>

**RRR:** 33%

### Metformin vs. Conventional Treatment

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<th>No. Events</th>
<th>Intensive</th>
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<td>56</td>
<td>0.20</td>
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</tbody>
</table>

**RRR:** 27%

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### Tight Glucose Control for Everyone?

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### Major Intensive vs. Standard Glucose Control Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>VADT</th>
<th>ADVANCE</th>
<th>ACCORD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>1,791</td>
<td>11,140</td>
<td>10,251</td>
</tr>
<tr>
<td>% females</td>
<td>F: 2.9%</td>
<td>F: 42%</td>
<td>F: 39%</td>
</tr>
<tr>
<td>Average age (years)</td>
<td>60</td>
<td>66</td>
<td>62</td>
</tr>
<tr>
<td>Median DM duration (years)</td>
<td>11.5</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Baseline A1C (median, %)</td>
<td>9.4</td>
<td>7.2</td>
<td>8.1</td>
</tr>
<tr>
<td>Intensive control target A1C (%)</td>
<td>Difference of 1.5 between groups</td>
<td>Intensive &lt;6.5</td>
<td>Intensive &lt;6 Standard 7.0-7.9</td>
</tr>
<tr>
<td>Median follow up (years)</td>
<td>5.6</td>
<td>5</td>
<td>3.5 (stopped early)</td>
</tr>
</tbody>
</table>

Results: Intensive vs. Standard Glucose Control Trials

<table>
<thead>
<tr>
<th></th>
<th>VADT1</th>
<th>ADVANCE2</th>
<th>ACCORD3</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C achieved (%)</td>
<td>6.9 vs. 8.4</td>
<td>6.5 vs. 7.3</td>
<td>6.4 vs. 7.5</td>
</tr>
<tr>
<td>Statistically significant differences?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macrovascular events</td>
<td>No 29.5% vs. 33.5%</td>
<td>No 10.0% vs. 10.6%</td>
<td>No 6.9% vs. 7.2%</td>
</tr>
<tr>
<td>Microvascular events</td>
<td>Yes for albuminuria 9.1% vs. 13.8%</td>
<td>Significantly decreased 9.4% vs. 10.9%</td>
<td>Not Measured</td>
</tr>
<tr>
<td>CV Death</td>
<td>No 2.1% vs. 1.7%</td>
<td>No 4.5% vs. 5.2%</td>
<td>Significantly increased 2.6% vs. 1.8%</td>
</tr>
<tr>
<td>Any Death</td>
<td>No 8.9% vs. 9.6%</td>
<td>Significantly increased 5% vs. 4%</td>
<td></td>
</tr>
</tbody>
</table>


Hypoglycemia

Limits glycemic control
Caused by Cognitive impairment, renal insufficiency, impaired blood glucose metabolism Clinical falls, functional decline, hypoglycemic coma, increased mortality

Risk Factors
- Alcohol intake
- Autonomic neuropathy
- Cognitive impairment
- Hepatic dysfunction
- Renal insufficiency
- Poor nutrition
- Recent hospitalization
- Adrenergic blocking agents
- Insulin or sulfonylureas
- Polypharmacy
- Sedative agents
- Tight glycemic control

Hypoglycemia requiring assistance (% per year)

<table>
<thead>
<tr>
<th></th>
<th>VADT</th>
<th>ADVANCE</th>
<th>ACCORD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.3 vs. 1.1</td>
<td>1.8 vs. 0.8</td>
<td>4.5 vs. 1.5</td>
</tr>
</tbody>
</table>


Question
Which of the following trials showed that initial tight glucose control glucose reduced long term mortality?

A. ADVANCE  
B. VADT  
C. UKPDS  
D. ACCORD
A1C Goals
Mortality and A1C

Recommended Glucose Control

Less stringent goals
CHCF/AGS, ADA, AACE
A1C <8%

Recommended for:
Severe hypoglycemia
Limited life expectancy
Advanced microvascular or macrovascular complications
Extensive co-morbid conditions
Long standing DM with unattainable treatment goals despite intensive efforts

Critically ill inpatients: Insulin infusion maintained between 140-180mg/dL.

DM2 Goals
A1C <6.5

- Short disease duration
- Long life expectancy
- No significant CVD
- Mild-moderate microvascular complications
- Ability to achieve goal
  - Low side effects
  - Without hypoglycemia

DM is a 71 year old female with a history of diabetes, NYHA Class-III heart failure, chronic kidney disease, osteoarthritis, neuropathy, and hypertension. She has a BMI of 17.6. Her most recent A1C was 7.5%, 2 months ago. What is(are) her most appropriate glycemic treatment goals?

1. Hemoglobin A1C <6.5%
2. Hemoglobin A1C <7%
3. Hemoglobin A1C <8%
4. Fasting plasma glucose <110 mg/dL
5. Fasting plasma glucose <130 mg/dL
6. Post prandial plasma glucose <140mg/dL

**Answers**

A. 2 and 5  
B. 3 and 6  
C. 1, 5, and 6  
D. 3 only  
E: More information is needed

**Cross References**