Early Combination Therapy in the Treatment of Type 2 Diabetes

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**Planning Committee & Non-faculty Contributors**  
Additional non-faculty contributors and others involved in the planning, development, and editing/review of the content have no relevant financial relationships to disclose in the last 12 months.
Program Overview
This symposium will present nurse practitioners and physician assistants with the current guideline recommendations for the treatment of type 2 diabetes. The program will review the benefits and risks of various classes of antihyperglycemic agents including SGLT-2 inhibitors, discuss considerations for early combination therapy, and strategies for reducing clinical inertia.

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Target Audience
This CME initiative will target nurse practitioners and physician assistants.

Learning Objectives
• Review current guideline recommendations for the initiation and intensification of therapy in patient with type 2 diabetes
• Discuss the benefits and risks of various classes of antihyperglycemic agents
• Discuss clinical considerations for early combination therapy
• Implement strategies to reduce clinical inertia in the treatment of patients with type 2 diabetes

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• Participate in the activity
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• Complete Final Evaluation

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Early Combination Therapy in the Treatment of Type 2 Diabetes

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Associate Director of Diabetes Research Center
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Objectives

• Review current guidelines recommendation for the initiation and intensification of therapy in patients with type 2 diabetes
• Discuss the benefits and risk of various classes of antihyperglycemic agents
• Discuss clinical consideration for early combination therapy
• Implement strategies to reduce clinical inertia in the treatment of patients with type 2 diabetes

Patient Case: Newly Diagnosed Type 2 DM

• Peter is a 51 year-old Caucasian male. He had routine lab work and physical 2 weeks ago. FPG of 267 mg/dL was noted. Repeat lab ordered for today’s visit. He states that he hasn’t lost any weight nor have felt thirsty or been going to the restroom more frequently.
• Allergies: Sulfa- severe rash- hospitalized when 12 years old.
• PMH: 1. Dyslipidemia 2. HTN 3. Obesity
• Past Surgical History: Cholecystectomy 24 year ago and right ulna fracture with plate and screw at 17 years old.

Patient Case: Background

• Family History: T2DM – both parents, 1 brother, and 1 sister; CKD – mother, not on dialysis; Father – MI at age 52; all have HTN
• Social Hx: Married for 25 years, works as insurance adjuster, 2 children, ages 22 and 19 years old – both healthy
• Chews tobacco, has tried quitting “at least 20 times”
• Alcohol – 0-3 beers or glasses of wine only on a weekend, no drugs
• “I’m not a big fan of drugs, I was hospitalized when 12 years old due to a drug. Can I get control without?”
• Diet: Family eats very healthy thanks to wife – not high carbohydrates, rare sugar drinks, likes cheesecake. When “on the road” eats very unhealthy.

Patient Case: Medications and Labs

• Current medications
  – Lisinopril 10 mg PO daily, amlodipine 5 mg PO daily, and atorvastatin 20 mg PO daily
• Physical exam: BMI 35 kg/m² BP 132/80 mmHg HR 74 BPM
• Laboratory:
  – A1C 8.8% FPG 266 mg/dL Random microalbumin/creatinine 12 mg/g
  – UA-normal except for +3 urine CBC-WNL
  – TC-201 mg/dL LDL-114 mg/dL HDL-39 mg/dL TG-242 mg/dL
  – Scr 0.7 (eGFR = 123 mL/min/1.73m²)

Guideline Recommended Glycemic Goals*

<table>
<thead>
<tr>
<th>AACE1</th>
<th>ADA2</th>
<th>ACP3</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C (%)</td>
<td>58.5 if no serious illness or low hypo risk</td>
<td>&lt;6.5% for select patients &lt;7% for most patients &lt;8% if previous severe hypoglycemia or multiple comorbidities</td>
</tr>
<tr>
<td>FPG</td>
<td>&lt;110 mg/dL</td>
<td>80-130 mg/dL</td>
</tr>
<tr>
<td>PPG</td>
<td>&lt;140 mg/dL²</td>
<td>&lt;180 mg/dL³</td>
</tr>
</tbody>
</table>

ACP recommendations are controversial and are a departure from all major guideline recommendations including Canadian, European, and NICE

*FPG = fasting plasma glucose; PPG = postprandial glucose
Diabetic Complications Progress with Increasing A1C*

*Based on the Diabetes Control and Complications Trial (DCCT) data.


Relative risk of complications

6 8 10 12

10 11 12 13

Percentage of A1C level (%)

Retinopathy  Neuritis  Nephropathy

Intensive Glycemic Control in T2DM Reduces Risk of Complications (UKPDS)

Risk Reduction with 1% Decline in A1C* (7.9% vs 7.0%)

45 30 15 0

RRR  (%)

Microvascular Disease  PVD  MI  Stroke  Heart Failure  Cataract Extraction  Death Related to Diabetes

Microvascular  Macrovascular  Mortality

UKPDS  ACCORD  ADVANCE  VADT

Observational Follow-up


Microvascular  Mcrovascular  Mortality

ACCORD  ADVANCE  VADT  UKPDS

Number of subjects 10,251 11,140 1,791 4,209

Gender (% males) 62 58 97 61

Age (yrs) 62 66 60 53

Diabetes duration (yrs) 10 8 11.5 0

Baseline A1C (% 8.1 7.5 9.4 7.1

CV events (%) ~35 ~32 ~40 ~35

Insulin use (%) ~35 ~1.5 ~50 ~15

CV = cardiovascular; T2DM = type 2 diabetes.

ACCORD  ADVANCE  VADT  UKPDS

Approach to the Management of Hyperglycemia

• Intensification approach should be individualized

Recommended for our patient RA

2018 ADA Guideline Recommendations

At Diagnosis, initiate lifestyle management, set A1C target, and initiate therapy based on A1C

A1C ≥ 9%

A1C 6.0–7.0% 8.0–9.0%

Less stringent  More stringent  A1C 7%  Less stringent

High

Low

A1C < 9%

Refer to Insulin Algorithm

A1C ≥ 9%, HbA1c ≥ 8.1%,

Consider Start Therapy

Consider Oral Therapy

Consider Monotherapy
### 2018 AACE/ACE Guideline Recommendations

**Early A1C < 9.0%**

- **Metformin** or other first-line agent + second-line agent

  - **GLP-1 RA**
  - **SGLT-2 i**
  - **TZD**
  - Basil Insulin
  - **DPP-4 i**
  - **AGI**
  - **SU/GLN**

**Entry A1C > 9.0%**

- **Yes**

  - **Metformin** or other first-line agent + second-line agent

    - **GLP-1 RA**
    - **SGLT-2 i**
    - **DPP-4 i**
    - **TZD**
    - Basil Insulin
    - **Colesevelam**
    - **Bromocriptine QR**
    - **AGI**
    - **SU/GLN**

**Entry A1C ≥ 7.5%**

- **If not at goal in 3 months, proceed to Triple Therapy**

**Entry A1C < 7.5%**

- **Triple Therapy**
  - **Metformin**
  - **GLP-1 RA**
  - **SGLT-2 i**
  - **DPP-4 i**
  - **AGI**
  - **TZD**
  - **SU/GLN**

**ADD or Intensify Insulin**

- Refer to Insulin Algorithm

**Few adverse events or possible benefits**

- Use with caution

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### ADA and AACE/ACE Recommendations for Peter

**American Diabetes Association**

- **Recommendations if:**
  - A1C < 9.0%
  - Monotherapy
  - A1C ≥ 9.0%
  - Dual therapy
  - A1C ≥ 10%, blood glucose ≥300 mg/dL, or patient is symptomatic
  - Combination injectable therapy

**AACE/ACE**

- **Recommendations if:**
  - A1C ≥ 7.5%
  - Dual therapy
  - A1C > 9.0% and No Symptoms
  - Dual or Triple Therapy
  - A1C > 9.0% + Symptomatic
  - Insulin (± other drugs)

**Patient Case: Continued**

- You discuss the treatment options with Peter and decided to start him on metformin 500 mg BID and titrate to 1000 mg BID.
- At 3 month checkup his A1C was 7.5%. You discussed with him about possibly adding another drug. He asked for more time so that he can try exercising more and improve his diet to see if it would help. You agree.
- He had missed an appointment and returns for a follow-up visit 9 months later and his A1C was 7.4%. Since his A1C improved with his exercise and diet, a decision was made for him to continue.
- He returns 6 months later for another checkup and his A1C was 7.7%.

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### Clinical Inertia

**Common in Real-World Treatment of Type 2 Diabetes**

Retrospective cohort study of 81,573 T2DM patients in the United Kingdom using the Clinical Practice Research Datalink database between January 2004 and December 2006, with follow-up until April 2011

<table>
<thead>
<tr>
<th># of OADs</th>
<th>A1C at Insulin Initiation</th>
<th>Median Time to Intensification with Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8.7%</td>
<td>7.1 years</td>
</tr>
<tr>
<td>2</td>
<td>9.1%</td>
<td>6.1 years</td>
</tr>
</tbody>
</table>

OADs = oral antidiabetic drugs

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### Common Causes of Clinical Inertia

- **Provider**
  - Clear goals not specified
  - Intervention not prescribed or implemented
  - Ineffective treatment
  - Patient “sidetracks” visit
  - Ineffective communication with patient
- **Patient**
  - Denial having disease or that it is serious
  - Low health-literacy
  - Cost
  - Burden of therapy (too many medications)
  - Lifestyle issues and unwilling to highly prioritize health
  - Absence of issues with disease makes them less likely to act
- **System**
  - Lack of decision planning
  - No follow-up decision support
  - No active outreach to patients
  - No team-based approach to care
- **Medications**
  - Impossible to get to goal with chosen therapy
  - Side effects
  - Cost
  - Ease-of-use
  - Communication
  - Misunderstanding that T2DM is a progressive disease, which will require combination therapy

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### Provider Clinical Inertia

- **Primary reasons providers fail to intensify treatment**
  - Overestimation of care provided
    - i.e., providers overestimate their adherence to guidelines and the care they provide
  - Citing “soft” reasons to avoid intensification of treatment
    - i.e., perception that the overall care of their patient is improving, nonadherence among patients, and concerns about results from recent large CV trials
  - Lack of training

Clinical Impact of Clinical Inertia

- Retrospective cohort study using UK Clinical Practice Research Datalink
- 105,477 newly diagnosed type 2 diabetes from 1990 with follow-up data available until 2012
- Mean A1C 8.1% at diagnosis, 11% had history of cardiovascular disease, and 7.1% experienced at least one CV event during 5.3 years of median follow-up
- One year delay in receiving intensified therapy (goal A1C < 7.0%) was associated with significantly increased risk of MI by 67%, stroke by 51%, HF by 64%, and composite CVE by 62%

T2DM Patients Experience Progressive Deterioration in Glycemic Control Over Time

- β-Cell Function
- UKPDS A1C Level

Requirement for Multiple Therapies in T2DM to Maintain Glycemic Control

- Percentage of patients needing >1 drug to achieve glycemic control

Initial Triple Therapy with Metformin, Pioglitazone, and Exenatide BID vs. Conventional Stepwise Therapy

- 221 T2DM patients were randomized in an open-label study to receive intensive triple therapy or conventional stepwise therapy

Advantages and Disadvantages of Antihyperglycemic Agents

- Sulfonylureas
  - Glyburide, glipizide, glimepiride
  - Advantages
    - High efficacy; low cost
  - Disadvantages
    - High hypoglycemia risk; weight gain
    - Glyburide not recommended in patients with renal disease

- DPP-4 inhibitors
  - Alogliptin, linagliptin, saxagliptin, sitagliptin
  - Advantages
    - No hypoglycemia risk; no weight gain; well tolerated
  - Disadvantages
    - Intermediate efficacy; may worsen heart failure (alogliptin, saxagliptin); reduce dose in renal disease (alogliptin, saxagliptin, sitagliptin)
**Advantages and Disadvantages of Antihyperglycemic Agents (Continued)**

**GLP-1 RAs**
- Dulaglutide, exenatide, lixisenatide, semaglutide
- **Advantages**
  - High efficacy; no hypoglycemia risk; weight loss; CV and renal benefit
  - GLP-1 RAs (lixisenatide, exenatide ER)
- **Disadvantages**
  - Injection; not recommended in patients with eGFR <30 mL/min; GI side effects common

**Insulin**
- Human insulin (i.e., NPH), analog insulin (i.e., glargine, detemir)
- **Advantages**
  - Lowest cost; potential CV benefit
  - Highest efficacy; can use in pregnancy and renal failure; proven CV safety (insulin glargine, degludec)
- **Disadvantages**
  - Weight gain; increase hypoglycemia risk.

**SGLT-2 inhibitors**
- Canagliflozin, dapagliflozin, empagliflozin, etodolac
- **Advantages**
  - No hypoglycemia risk; weight loss, proven CV, CHF, and renal benefit (canagliflozin, empagliflozin)
  - Intermediate efficacy, GU infections; contraindicated in renal dysfunction
  - Risk of amputations & bone fractures (canagliflozin); risk of DKA
- **Disadvantages**
  - Risk of amputations were seen in the study, leading to Black Box Warning in label
  - 40% reduction in eGFR, renal replacement therapy, or renal death
  - Increase risk of amputations & bone fractures (canagliflozin)

**TZDs**
- Pioglitazone
- **Advantages**
  - High efficacy; no hypoglycemia risk; low cost; potential CV benefit
- **Disadvantages**
  - Weight gain; increase fracture risk; exacerbate heart failure; edema

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**LEADER Study: Results**

9,340 T2DM patients with established or at high CV risk were randomized to liraglutide or placebo and followed for a median of 3.5 years

**Primary composite endpoint**
- 0.76 (0.67-0.86)

**Hazard ratio (95% CI)**

**P value**

0.00 0.50 1.00 1.50

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**EMPA-REG OUTCOME Study: Results**

7,020 T2DM patients with established CVD were randomized to empagliflozin or placebo and followed over 3.1 years

**Hazard ratio (95% CI)**

**P value**

0.00 0.50 1.00 1.50

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**SAVOR-TIMI 53, EXAMINE, and TECOS: Hospitalization for Heart Failure**

<table>
<thead>
<tr>
<th>Study Drug</th>
<th>Placebo</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAVOR-TIMI (sitagliptin vs placebo)</td>
<td>249/310</td>
<td>1.27</td>
<td>1.01, 1.51</td>
<td>0.009*</td>
</tr>
<tr>
<td>EXAMINE (lixisenatide vs placebo)</td>
<td>103/270</td>
<td>1.19</td>
<td>0.98, 1.45</td>
<td>0.238</td>
</tr>
<tr>
<td>TECOS (sitagliptin vs placebo)</td>
<td>228/732</td>
<td>1.00</td>
<td>0.83, 1.20</td>
<td>0.983</td>
</tr>
</tbody>
</table>

*Statistically significant increase in hospitalizations for heart failure associated with saxagliptin use in SAVOR-TIMI

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**Advantages and Disadvantages of Antihyperglycemic Agents (Continued)**

**Zinman B, et al.**


**Canagliflozin or placebo and followed for a median of 2.4 years**

**Hazard ratio (95% CI)**

**P value**

0.00 0.50 1.00 1.50

---

Patient Case: Continued

- After discussing the treatment options with Peter, you decided to add a DPP-4 inhibitor. Since he is already taking metformin, you suggested prescribing to him a single pill for the combination.
- He agrees and is looking forward to improving his glucose control.

Earlier Use of Combination Therapy May Improve Glycemic Control Compared With Conventional Therapy

![Graph showing early combination approach vs. conventional therapy]

- Early combination approach
- A1C vs. Duration of diabetes

Factors to Consider in Choosing Early Combination Therapy over Monotherapy

- Would clinical inertia be reduced?
- Is it pathophysiologically sound and is there complimentary mechanisms of action?
- Would patient be unlikely to get to goal with monotherapy?
- Would there be a possible delay in deterioration of glycemic control?
- Are the costs appropriate? Is there a cost advantage to the patient?
- Is the risk-to-benefit ratio acceptable?
- Would it improve unmet clinical needs, such as weight gain, hypoglycemia, CVD, and/or renal outcomes?
- Would adherence/compliance be improved?

Fixed-Dose Combination Therapy

- Complementary mechanisms of action
- Address multiple defects underlying T2DM
- Simplify administration and reduce medication burden
- May reduce costs
- Improve adherence
- Reduce clinical inertia
- Lower dose of individual components
Fixed-Dose Combinations for Treatment of T2DM

<table>
<thead>
<tr>
<th>Class</th>
<th>Combinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin/Sulfonylurea</td>
<td>MET/glyburide; MET/gliclizide; MET/glimepiride</td>
</tr>
<tr>
<td>Metformin/TZD</td>
<td>MET/pioglitazone; MET/roziglitazone</td>
</tr>
<tr>
<td>Metformin/DPP-4 inhibitor</td>
<td>MET/taiogliflozin; MET/memagliflozin; MET/tolagliflozin; MET/deglyliflozin</td>
</tr>
<tr>
<td>Metformin/SGLT-2 inhibitor</td>
<td>MET/canagliflozin; MET/empagliflozin; MET/ertugliflozin; MET/dapagliflozin</td>
</tr>
<tr>
<td>Metformin/glinide</td>
<td>MET/repaglinide</td>
</tr>
<tr>
<td>SGLT-2 inhibitor/DPP-4</td>
<td>Empagliflozin/linagliptin; Ertugliflozin/sitagliptin</td>
</tr>
<tr>
<td>TZD/Sulfonylurea</td>
<td>Pioglitazone/glimepiride; Rosiglitazone/glimepiride</td>
</tr>
</tbody>
</table>

Novel Combinations

• SGLT-2 inhibitor and DPP-4 inhibitor
  – Complimentary MOA
  – Low risk of hypoglycemia and weight gain

Efficacy of SGLT-2/DPP-4 Inhibitor Combination Therapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean Change From Baseline in A1C at Week 24, %</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empa 25 mg/linagliptin 5 mg</td>
<td>-1.08</td>
<td>&lt;0.001 vs. Lina 5 mg</td>
</tr>
<tr>
<td>Empa 10 mg/linagliptin 5 mg</td>
<td>-1.34</td>
<td>&lt;0.001 vs Empa 10 mg &amp; Lina 5 mg</td>
</tr>
<tr>
<td>Empagliflozin 25 mg</td>
<td>-0.95</td>
<td>-</td>
</tr>
<tr>
<td>Empagliflozin 10 mg</td>
<td>-0.83</td>
<td>-</td>
</tr>
<tr>
<td>Empagliflozin 5 mg</td>
<td>-0.67</td>
<td>-</td>
</tr>
<tr>
<td>Dapa 10 mg/saxagliptin 5 mg</td>
<td>-1.47</td>
<td>&lt;0.0001 vs Saxa + MET 5.0166 vs. Dapa + MET</td>
</tr>
<tr>
<td>Saxagliptin 5 mg + MET</td>
<td>-0.88</td>
<td>-</td>
</tr>
<tr>
<td>Dapagliflozin 10 mg + MET</td>
<td>-1.20</td>
<td>-</td>
</tr>
</tbody>
</table>

SGLT-2/DPP-4 Inhibitor Combination vs. Individual Agents in T2DM Patients Uncontrolled on Metformin

<table>
<thead>
<tr>
<th>Time</th>
<th>Empa 5 mg</th>
<th>Empa 10 mg</th>
<th>Empa 25 mg</th>
<th>Sitagliptin 100 mg</th>
<th>Ertug 5 mg + Sita 100 mg</th>
<th>Ertug 15 mg + Sita 100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>W1</td>
<td>1.4</td>
<td>2.8</td>
<td>3.2</td>
<td>3.2</td>
<td>3.4</td>
<td>3.8</td>
</tr>
<tr>
<td>W2</td>
<td>1.6</td>
<td>3.0</td>
<td>3.4</td>
<td>3.4</td>
<td>3.6</td>
<td>3.8</td>
</tr>
<tr>
<td>W3</td>
<td>1.8</td>
<td>3.2</td>
<td>3.6</td>
<td>3.6</td>
<td>3.8</td>
<td>4.0</td>
</tr>
<tr>
<td>W4</td>
<td>2.0</td>
<td>3.4</td>
<td>3.8</td>
<td>3.8</td>
<td>4.0</td>
<td>4.2</td>
</tr>
<tr>
<td>W5</td>
<td>2.2</td>
<td>3.6</td>
<td>4.0</td>
<td>4.0</td>
<td>4.2</td>
<td>4.4</td>
</tr>
</tbody>
</table>

Considerations for Add-on Medication Selection

| Add another agent best suited to the individual by prioritizing patient characteristics. |
|-----------------------------------------------|-----------------------------------------------------------------------------------|
| CLINICAL CONSIDERATIONS                      | CHOICE OF AGENT                                                                  |
| PRIORITY                                      | Antihyperglycemic agent with demonstrated CV benefit (empa, lira, cana)           |
| No clinical cardiovascular disease            | DPP-4 inhibitor, GLP-1 receptor agonist or SGLT2 inhibitor                         |
| Avulsion of hypoglycemia and/or weight gain   |                                                                                   |
| with adequate glycemic efficacy               |                                                                                   |
| Other considerations:                        |                                                                                   |
| Degree of hypoglycemia                       |                                                                                   |
| Risk of hypoglycemia                         |                                                                                   |
| Overweight or obesity                        |                                                                                   |
| CV disease or multiple risk factors           |                                                                                   |
| Comorbidities (renal, CHP, hepatic)          |                                                                                   |
| Preferences & access to treatment planning   |                                                                                   |
| Pregnancy                                     |                                                                                   |

Key Takeaways

• A1C goals need to be individualized
  – <7% for most patients and less stringent in patients with significant comorbidities or advanced age
• Clinical inertia is common in patients with T2DM
  – Early combination therapy is proven to increase the number of patients who attain glycemic goal and reduce clinical inertia
• Individualize addition of diabetes medications based on glycemic goal and important clinical and patient considerations
  – Comorbidities, ease-of-use, cost, etc...
  – SGLT2 inhibitors or GLP-1 RA’s should be used in patients with established CAD or renal disease
