De-escalating Drug Therapy in Type 2 Diabetes

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Disclosure/Conflict of Interest

I, Pamela L. Stamm, have no actual or potential conflict of interest in relation to this program.
Objectives

- Individualize A1C goals for given patients
- Select patients who are candidates for de-escalation of diabetes pharmacotherapy
- Select diabetes therapies to de-escalate while maximizing benefits and minimizing risks of therapy
- Describe a population management strategy for identification of patients potentially eligible for de-escalation of diabetes therapy
Organizations Recommending Relaxed A1C Goals

- American Diabetes Association (ADA)
- European Association for the Study of Diabetes (EASD)
- American Association of Clinical Endocrinologists (AACE)
- American Geriatric Society (AGS)
- Kidney Disease: Improving Global Outcomes (KDIGO)
- International Association of Gerontology and Geriatrics (IAGG)
- European Diabetes Working Party for Older People (EDWPOP)
- International Task Force of Experts in Diabetes (ITFED)
- National Institute of Clinical Excellence (NICE)
- International Diabetes Federation (IDF)
Battle of the A1Cs

**BENEFITS**
- UKPDS (Type 2, New)
- UKPDS extension
- Kumomato (Type 2, New)

**RISKS**
- ADVANCE (Type 2, experienced)
- ACCORD (Type 2, experienced)
- VADT (Type 2, experienced)

What did the Early Trials Show Us?

UKPDS

# Summary of Outcomes

<table>
<thead>
<tr>
<th></th>
<th>UKPDS</th>
<th>ADVANCE</th>
<th>ACCORD</th>
<th>VADT</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM Duration (y)</td>
<td>New</td>
<td>8</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Age (y)</td>
<td>54</td>
<td>66</td>
<td>62</td>
<td>60</td>
</tr>
<tr>
<td>A1C Achieved</td>
<td>7 vs 7.9</td>
<td>6.5 vs 7.4</td>
<td>6.4 vs 7.5</td>
<td>6.9 vs 8.4</td>
</tr>
<tr>
<td>Trial Duration (y)</td>
<td>Mdn 8.5</td>
<td>5</td>
<td>3.5</td>
<td>6</td>
</tr>
<tr>
<td>Albuminuria*</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>↓</td>
<td>NS</td>
<td>↓</td>
<td>NS</td>
</tr>
<tr>
<td>Visual Deterioration</td>
<td>↓</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>↓</td>
<td>NS</td>
<td>↓</td>
<td>NS</td>
</tr>
<tr>
<td>Macrovascular Disease</td>
<td>Metformin, extension</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Mortality</td>
<td>↓</td>
<td>NS</td>
<td>↑</td>
<td>NS</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>
Risk of Complications According to A1C

Lifetime Risk of Complications

- ESRD: 1.7%
- Blindness: 1.2%
- CV Death: 64.8%

55 yoa at diagnosis, A1C of 9 for lifespan

## Tight vs Standard Therapy on Doubling Serum Creatinine

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Intensive Therapy</th>
<th>Standard Therapy</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>ACCORD³,¹⁴</td>
<td>392</td>
<td>5041</td>
<td>357</td>
<td>5035</td>
</tr>
<tr>
<td>ADVANCE¹²</td>
<td>67</td>
<td>5571</td>
<td>61</td>
<td>5569</td>
</tr>
<tr>
<td>UKPDS 33¹⁶</td>
<td>7</td>
<td>2150</td>
<td>7</td>
<td>895</td>
</tr>
<tr>
<td>VADT¹¹</td>
<td>78</td>
<td>882</td>
<td>78</td>
<td>884</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>13644</strong></td>
<td></td>
<td><strong>12383</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td><strong>544</strong></td>
<td></td>
<td><strong>503</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 0.00; \chi^2 = 3.46; \ P = .33; \ I^2 = 13\%$

Test for overall effect: $z = 0.76; \ P = .44$

Coca SG, et al., JAMA 2012;172(10);761-69.
Tight vs Standard Therapy on ESRD

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Intensive Therapy</th>
<th>Standard Therapy</th>
<th>Risk Ratio M-H, Random (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>ACCORD8,14</td>
<td>138</td>
<td>5119</td>
<td>151</td>
</tr>
<tr>
<td>ADVANCE12</td>
<td>11</td>
<td>5571</td>
<td>31</td>
</tr>
<tr>
<td>UKPDS 3316</td>
<td>16</td>
<td>2729</td>
<td>9</td>
</tr>
<tr>
<td>UKPDS 3417</td>
<td>2</td>
<td>342</td>
<td>2</td>
</tr>
<tr>
<td>VADT11</td>
<td>7</td>
<td>882</td>
<td>11</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>14643</td>
<td></td>
<td>13117</td>
</tr>
</tbody>
</table>

Total events 174

Heterogeneity: $\tau^2=0.09$; $\chi^2=7.08$; $P=.13$; $I^2=43\%$

Test for overall effect: $z=1.72$; $P=.09$
ADVANCE Renal Outcomes (n=11,140  median 5 yrs)

Advance Renal Outcomes & NNT (n=11,140 median 5 yrs)

Table 3 | NNT over 5 years to prevent one ESRD event overall

<table>
<thead>
<tr>
<th>Participant population</th>
<th>Participants (%)</th>
<th>Standard (%)</th>
<th>Intensive (%)</th>
<th>NNT to prevent one ESRD event over 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>11,140 (100)</td>
<td>0.075</td>
<td>0.026</td>
<td>410</td>
</tr>
<tr>
<td>Albuminuria (micro or macro)</td>
<td>3261 (29.3)</td>
<td>0.17</td>
<td>0.039</td>
<td>152</td>
</tr>
<tr>
<td>Macroalbuminuria</td>
<td>404 (3.6)</td>
<td>0.61</td>
<td>0.12</td>
<td>41</td>
</tr>
<tr>
<td>eGFR &lt;60</td>
<td>2148 (19.3)</td>
<td>0.20</td>
<td>0.061</td>
<td>147</td>
</tr>
<tr>
<td>eGFR &lt;60 and albuminuria</td>
<td>776 (7.0)</td>
<td>0.29</td>
<td>0.056</td>
<td>85</td>
</tr>
</tbody>
</table>

Benefits of Other Treatments on Outcomes

-8
-6
-4
-2
0
-2
-4
-6
-8

BP Control
Glycemic Control

Absolute Risk Reduction per 1000 patient years

J Curve of Diabetes Duration and Benefit vs Risk

### Risk of CV event according to comorbidity level

<table>
<thead>
<tr>
<th>TIBI score</th>
<th>A1C $\leq 6.5%$</th>
<th>A1C $&gt;6.5%$</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low – mod comorbidity</td>
<td>2.2</td>
<td>3.8</td>
<td>0.6 (0.42-85)</td>
</tr>
<tr>
<td>High comorbidity</td>
<td>4.9</td>
<td>5.2</td>
<td>0.92 (0.68-1.25)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TIBI score</th>
<th>A1C $\leq 7.0%$</th>
<th>A1C $&gt;7.0%$</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low – mod comorbidity</td>
<td>2.4</td>
<td>4.1</td>
<td>0.61 (0.44-0.83)</td>
</tr>
<tr>
<td>High comorbidity</td>
<td>4.8</td>
<td>5.4</td>
<td>0.86 (0.64-1.14)</td>
</tr>
</tbody>
</table>

Is there a J-Curve by Treatment?

All cause mortality

Metformin and SFU

Insulin

Medication Utilization for T2DM Treatment (%)

Proportion of Patients Taking Each Medication

- No medication: 18%
- Oral: 50%
- Insulin: 18%
- Combination: 13%
Medications and Risk of Hypoglycemia

- Insulin
- Sulfonlyurea
- Meglitinides
- TZD
- GLP-1 Mimetics
- SGLT-2 Inhibitors
- Alpha-glucosidase inhibitors
- Metformin
Medications Implicated in Emergent Hospitalizations Among Older Adults

Series 1

- Insulin
- Sulfonylureas
Consequences of Hypoglycemia
## VADT Hypoglycemic Episodes

**Table 2. Hypoglycemic Episodes.***

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standard Therapy (N = 899)</th>
<th>Intensive Therapy (N = 892)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no./100 patient-yr</td>
<td></td>
</tr>
<tr>
<td>Episodes with impaired consciousness</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Episodes with complete loss of consciousness</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Nocturnal episodes</td>
<td>44</td>
<td>152</td>
</tr>
<tr>
<td>Total episodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With symptoms</td>
<td>383</td>
<td>1333</td>
</tr>
<tr>
<td>Without symptoms</td>
<td>49</td>
<td>233</td>
</tr>
<tr>
<td>Relieved by food or sugar intake</td>
<td>421</td>
<td>1516</td>
</tr>
<tr>
<td>Measurement of blood glucose during episode</td>
<td>348</td>
<td>1392</td>
</tr>
<tr>
<td>With documented blood glucose &lt;50 mg/dl (2.8 mmol/liter)</td>
<td>52</td>
<td>203</td>
</tr>
</tbody>
</table>

* p value <.001 for all differences between groups

Consequences of Hypoglycemia

Inpatient consequences (severe hypoglycemia)
- Inpatient death
- Increased length of stay
- Increased risk of death in 1 year

Outpatient consequences
- Quality of life
- Chronic mood disorders (depression and anxiety)
- Impact sleep
- Impact independence
- Reduced job productivity
- Injury
Risk Factors for Hypoglycemia

- Advancing age
- Cognitive decline
- Functional decline
- Polypharmacy
- Drug interactions
- Low socioeconomic status
- Low health literacy
- Insulin
- Sulfonylurea, glinide

- Depression
- Reduced appetite
- Renal impairment
- Hepatic impairment
- Recent hospitalization
- Hypoglycemia unawareness
- H/o severe hypoglycemia
- More intensive control
When is it Hypoglycemia?

- Traditionally BG < 70 mg/dL with or without symptoms
- < 70mg/dL intended as an “alert value” not a level at which all patients are hypoglycemic
- Symptoms typically occur at the threshold for counterregulatory hormone release
Hypoglycemia: Normal Threshold

- 58 → Counterregulatory hormone release; Symptom onset
- 50 → Cognitive dysfunction
- 27 → Severe cognitive dysfunction

Age and Asymptomatic Hypoglycemia

Arterial Blood Glucose (mg/dL)

Younger men 64.8 mg/dL
Older men 54.8 mg/dL
Younger men 46.8 mg/dL

Hypoglycemia: Moving Threshold for Counterregulatory Hormone Response

Classifying Hypoglycemia

- Probable symptomatic
- Documented symptomatic
- Severe
- Asymptomatic
- Pseudo-hypoglycemia (relative hypoglycemia)
Comparing oral diabetes drugs

- Acarbose, GLP 1 Inh, DPP 4 Inh, TZD, Metformin
- SGLT2 Inh
- Meglitandine
  (nateglinide < repaglinide)
- Sulfonylurea
  (glyburide, glipizide > glimepiride)

Comparing Insulins

Human Insulins (regular, NPH)

Analog Insulins
(glargine, detemir, degludec, aspart, lispro, gluisine)

## Considerations for A1C Selection

<table>
<thead>
<tr>
<th>Tight Control</th>
<th>Less Intensive Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>(&lt; 7%)</td>
<td>(7.5 - 9 %)</td>
</tr>
</tbody>
</table>

- **Tight Control (< 7%)**
  - Young
  - Short duration of diabetes
  - Low risk of hypoglycemia
  - Motivated patient
  - Good support system

- **Less Intensive Control (7.5 - 9 %)**
  - Older
  - Longer duration of diabetes
  - Higher risk of hypoglycemia
  - History of Severe hypoglycemia
  - Hypoglycemia Unawareness
  - Person in whom outcome of severe hypoglycemia could be disastrous
  - Certain co-morbidities
    - Limited life expectancy
    - Significant microvascular disease
  - Amotivated
  - Poor resources or support system
<table>
<thead>
<tr>
<th>Mean BG mg/dL</th>
<th>7-7.49</th>
<th>7.5-7.99</th>
<th>8-8.5</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBG</td>
<td>152</td>
<td>167</td>
<td>178</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(143-162)</td>
<td>(157-177)</td>
<td>(164-192)</td>
<td></td>
</tr>
<tr>
<td>PrePrandial</td>
<td>152</td>
<td>155</td>
<td>179</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(147-157)</td>
<td>(148-161)</td>
<td>(167-191)</td>
<td></td>
</tr>
<tr>
<td>PostPrandial</td>
<td>176</td>
<td>189</td>
<td>206</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(170-183)</td>
<td>(180-197)</td>
<td>(195-217)</td>
<td></td>
</tr>
<tr>
<td>Bedtime</td>
<td>177</td>
<td>175</td>
<td>222</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(166-188)</td>
<td>(163-188)</td>
<td>(197-248)</td>
<td></td>
</tr>
<tr>
<td>Plasma Glucose</td>
<td></td>
<td></td>
<td></td>
<td>212</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(170-249)</td>
</tr>
</tbody>
</table>

A1C According to Health Status (NHANES 2001-2010)
Population Strategies for De-Escalation

- Consider the risk factors discussed today. Take 2 minutes to write down some strategies you could implement in your practice to begin to identify patients who could undergo de-escalation of their therapy.

- Share those strategies with your neighbor (2 minutes).
Population Strategies

- A1C report
  - Cross reference by other risk factors
- Drug specific report
  - Sulfonylurea, insulin, meglitnide
Mr. Yardy

- 68 yo male
- PMH: T2DM ('02), PVD, Neuropathy, Retinopathy
- Works in yard daily, eats lunch late, wife tries to get pt to check but he still forgets, frequent midday lows
- Targets 60 g carbs per meal daily
- A1C: 7.0
- FBG: 110-120
- DM Medications:
  - Glargine 34 units daily
  - Aspart 10-10-14 units before meals
- eGFR 50
- SCr 1.6
Questions to Discuss with a Partner

- Tight or relaxed A1C?
- What is the justification for your recommendation?
- Which goal would you select?
- What pre and postprandial goals align with the A1C goal?
- Should this patient’s therapy be modified?
- How?
- Why?
Case 4: Mr. Kopeski

- 65 year old male in independent living
- PMH: DM 5 yrs, HTN
- Maximum metformin and glipizide
- FSBG:160-180; Recent A1C: 8.5
- No hypoglycemia
Questions to Discuss with a Partner

- Tight or relaxed A1C?
- What is the justification for your recommendation?
- Which goal would you select?
- What pre and postprandial goals align with the A1C goal?
- Should this patient’s therapy be modified?
- How?
- Why?
Mr. Lowe

- 68 yo male
- PMH: T2DM ('97), HTN, MI ('12)
- Ambulates well - walks 30 min. daily
- Targets 60 g carbs per meal daily
- A1C: 6.2
- FBG: 110-120
- DM Medications:
  - Glargine 40 units daily
  - Metformin 1g BID
  - Glipizide XL 20mg daily
Mr. Lowe

- 68 yo male
- PMH: T2DM (‘97), HTN, MI (‘12)
- Ambulates well - walks 30 min. daily
- Targets 60 g carbs per meal daily
- A1C: 6.2
- FBG: 110-120
- DM Medications:
  - Glargine 40 units daily
  - Metformin 1g BID
  - Glipizide XL 20mg daily
Questions to Discuss with a Partner

- Tight or relaxed A1C?
- What is the justification for your recommendation?
- Which goal would you select?
- What pre and postprandial goals align with the A1C goal?
- Should this patient’s therapy be modified?
- How?
- Why?
Mrs. Nomer

- 73 yo female
- PMH: T2DM ('05), HTN, CVA ('14)
- Does not ambulates well, neuropathy
- Targets 45 g carbs per meal daily
- A1C: 7.3
- FBG: 74-100; Pre-supper: 160-180; HS: 180-220
- DM Medications:
  - Glargine 80 units daily
  - Metformin 1g BID
- eGFR 55
- Cr 1.0
- Wt 64 kg
Questions to Discuss with a Partner

- Tight or relaxed A1C?
- What is the justification for your recommendation?
- Which goal would you select?
- What pre and postprandial goals align with the A1C goal?
- Should this patient’s therapy be modified?
- How?
- Why?
Mr. Ford

- 80 yo male
- PMH: T2DM (‘97), CKD Stage 4, CAD, COPD, HTN, dyslipidemia, neuropathy, just start chemotherapy for colon cancer without metastasis, takes steroids on 1st day of chemo every 2 weeks
- Ambulates with a walker
- Appetite is highly variable, good days and bad
- A1C: 6.4
- FBG: typical 110-120, goes low when feels like working on cars
- DM Medications:
  - Gargine 40 units daily
  - Glipizide 10 mg BID 30 minutes before meals
  - Metformin 1g BID

- eGFR 28
- Cr 2.2
- 98 kg
Questions to Discuss with a Partner

- Tight or relaxed A1C?
- What is the justification for your recommendation?
- Which goal would you select?
- What pre and postprandial goals align with the A1C goal?
- Should this patient’s therapy be modified?
- How?
- Why?
Ms. Sports

- 82 yo female w/ T2DM
- Metformin 1g BID
- Liraglutide 1.2mg daily
- Glimepiride 4mg BID
- Degludec 70 units QHS
- A1C 7.5%
- Pre-meal readings:

<table>
<thead>
<tr>
<th></th>
<th>Breakfast</th>
<th>Lunch</th>
<th>Midday Snack</th>
<th>Supper</th>
<th>Bedtime</th>
</tr>
</thead>
<tbody>
<tr>
<td>120</td>
<td>120</td>
<td>Y</td>
<td>175</td>
<td>270</td>
<td></td>
</tr>
<tr>
<td>115</td>
<td>45</td>
<td>Y</td>
<td>180</td>
<td>264</td>
<td></td>
</tr>
<tr>
<td>105</td>
<td>110</td>
<td>Y</td>
<td>180</td>
<td>248</td>
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</tr>
<tr>
<td>112</td>
<td>62</td>
<td>Y</td>
<td>174</td>
<td>300</td>
<td></td>
</tr>
</tbody>
</table>
Questions to Discuss with a Partner

- Tight or relaxed A1C?
- What is the justification for your recommendation?
- Which goal would you select?
- What pre and postprandial goals align with the A1C goal?
- Should this patient’s therapy be modified?
- How?
- Why?
Key Take Aways

- A1C should be individualized
- Evaluate risk vs. benefit of tight control
- Consider modifying pre-prandial and post-prandial BG goals accordingly
- Minimize use of insulin, sulfonylureas, and meglitriandes in high risk patients
- Consider implementation of population and patient level strategies to de-escalate therapy