A Diabetes Update: Hypoglycemic Safety

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https://www.youtube.com/watch?v=FqQ-JuRDkl8
Learning Objectives

• Review the evidence supporting ‘tight’ glycemic control

• Review the risks vs benefits of targeting therapy for A1C <7%

• Discuss clinical initiatives to reduce hypoglycemia associated with diabetes therapy
Polling Question

True or False: For most patients with diabetes, an A1c goal of <7% is recommended
Challenges in Reducing Over-treatment

Survey conducted by Caverly, TJ et al

Response to a vignette of a 77y/o with long standing DM, severe kidney disease, A1c 6.5%, taking glipizide 10mg BID.

<table>
<thead>
<tr>
<th></th>
<th>D/SD</th>
<th>A/SA</th>
</tr>
</thead>
<tbody>
<tr>
<td>I think this patient would benefit if A1c maintained below 7%</td>
<td>61.4%</td>
<td>39.6%</td>
</tr>
<tr>
<td>I worry that this patient would be harmed if his A1c is maintained below 7%</td>
<td>44.9%</td>
<td>55.1%</td>
</tr>
<tr>
<td>I would worry that reducing his medication would lead to an A1c that falls outside current performance measures</td>
<td>57.9%</td>
<td>42.1%</td>
</tr>
<tr>
<td>It would be helpful to have a clinical decision support tool that would help me determine whether this patient would benefit from reducing his medications.</td>
<td>30.8%</td>
<td>69.2%</td>
</tr>
<tr>
<td>It would be helpful to have patient education materials to discuss reducing diabetes medication</td>
<td>14.6%</td>
<td>85.4%</td>
</tr>
</tbody>
</table>
DCCT: Risks of Sustained Progression of Retinopathy and Severe Hypoglycemia in Type 1 Diabetic Patients by HbA1c Level

United Kingdom Prospective Diabetes Study (UKPDS)

A1C (%)

Conventional Group

Intensive Group

Years


Glycemic control early in diabetes has a lasting benefit, including for CVD risk

Interpreted as everyone should have A1c goal <7%, and national guidelines followed suit
- Only included healthy, newly diagnosed patients <65 years old
Outpatient Intensive Glucose Control

HbA1c: Advantages

Biology
1. Reflects chronic glycemia (~8-12 weeks)
2. Independent of acute factors e.g., stress, exercise
3. Very low intra-individual variability (CV ~1%)

Analysis
1. Fasting not necessary
2. Blood may be collected any time of the day
3. Sample is stable
4. Assay is standardized across instruments
5. Accuracy of test is monitored
<table>
<thead>
<tr>
<th>Disease or condition</th>
<th>Effect on HbA1c level</th>
<th>Potential mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid erythrocyte turnover</td>
<td>Falsely low</td>
<td>Unstable erythrocyte pool</td>
</tr>
<tr>
<td>Homolytic states</td>
<td>Falsely low</td>
<td>Unstable erythrocyte pool</td>
</tr>
<tr>
<td>Iron deficiency anemia</td>
<td>Falsely high</td>
<td>Unknown</td>
</tr>
<tr>
<td>Hemoglobin SS, SC or CC disease</td>
<td>Falsely low</td>
<td>Unstable erythrocyte pool</td>
</tr>
<tr>
<td>Variant hemoglobin trait</td>
<td>Variable</td>
<td>Assay interference</td>
</tr>
<tr>
<td>Fetal hemoglobin</td>
<td>Variable</td>
<td>Assay interference</td>
</tr>
<tr>
<td>Blood transfusions</td>
<td>Falsely low</td>
<td>Unstable erythrocyte pool</td>
</tr>
<tr>
<td>Aging</td>
<td>Falsely high</td>
<td>Unknown</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>Falsely low</td>
<td>Unknown</td>
</tr>
<tr>
<td>Uremia</td>
<td>Falsely low</td>
<td>Carbamylated hemoglobin</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>Falsely low</td>
<td>Multiple</td>
</tr>
<tr>
<td>HIV infection</td>
<td>Falsely low</td>
<td>Occult hemolysis</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Falsely low</td>
<td>Hemolysis?</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Variable</td>
<td>Assay interference</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>Variable</td>
<td>Assay interference</td>
</tr>
<tr>
<td>Aspirin use (large doses)</td>
<td>Variable</td>
<td>Acetylated hemoglobin</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>Variable</td>
<td>Interference with glycation</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Falsely low</td>
<td>Interference with glycation</td>
</tr>
<tr>
<td>Alcohol excess</td>
<td>Variable</td>
<td>Assay interference</td>
</tr>
<tr>
<td>Opiate use</td>
<td>Variable</td>
<td>Assay interference</td>
</tr>
</tbody>
</table>
Factors That May Influence Interpretation of HbA1c

1. Physiological e.g., age, race
2. Chronic kidney disease
3. Iron deficiency anemia
4. Erythrocyte lifespan
5. Glycation “phenotypes”
6. Drugs e.g., dapsone, antiretroviral
A1c Variability

- A1c test result is within a range; it is not an absolute lab value
Hemoglobin A1c and Risk of Retinopathy

Retinopathy risk vs. HbA1c

GOOD CARE  BAD CARE

United Kingdom Prospective Diabetes Study, Lancet, 1998
Tight control OK for *young* patients, not older
Who isn’t a little afraid of hypoglycemia?

Serious Sequelae:

- Tachycardia
- Bradyarrhythmias
- ST Depression
- T-wave Flattening
- QT Prolongation
- Hypokalemia
- Severe Hypertension
- Falls
- Death

Prevalence of Hypoglycemia

- In 2011, ~282,000 ED visits for adults aged 18+ had hypoglycemia as the first-listed diagnosis and diabetes as another diagnosis.¹
- A population-based study of patients with type 2 diabetes aged > 65 years reported incidence of serious hypoglycemia: ²
  - 1.23 episodes per 100 person-years with sulfonylurea treatment
  - 2.76 episodes per 100 person-years with insulin treatment

Modest hypoglycemia is frequent and often asymptomatic in type 2 diabetes

Chow et al

- Performed 5 days of continuous glucose monitoring in 25 T2DM
- HG defined as sustained CGM glucose $\leq 3.5$ mmol/l (63 mg/dl) for $\geq 20$ min
- Recorded 134 hrs of HG

<table>
<thead>
<tr>
<th></th>
<th>Daytime episodes</th>
<th>Nocturnal episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>$62 \pm 42$ min</td>
<td>$170 \pm 112$ min</td>
</tr>
<tr>
<td>Nadir</td>
<td>$2.8 \pm 0.5$ mmol/l (50 $\pm 0.9$ mg/dl)</td>
<td>$1.9 \pm 0.7$ mmol/l (34 $\pm 13$ mg/dl)</td>
</tr>
</tbody>
</table>

Only 3/34 episodes were symptomatic

> 90 % of episodes occurred without symptoms

Avoid using medications to achieve A1c <7.5% in most adults >65 years old; moderate control is generally better.

No evidence that using medications to achieve tight glycemic control in older adults with Type 2 diabetes is beneficial.
Risk Factors for Hypoglycemia

- Intensive glucose control / A1C targets
- Advanced age and/or cognitive decline
- Low health literacy and numeracy
- Social determinants including food insecurity
- Insulin and/or sulfonylurea medication therapy
- Low economic status
- Prior hypoglycemic event
- Hypoglycemia unawareness
- Liver / kidney disease
Risk of Hypoglycemia in Older Veterans with Dementia and Cognitive Impairment

<table>
<thead>
<tr>
<th>Frequency of Hypoglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia</td>
</tr>
<tr>
<td>Cognitive Impairment</td>
</tr>
<tr>
<td>Neither</td>
</tr>
</tbody>
</table>

30% patients with dementia or cognitive impairment are on insulin

Health Literacy Issues – US Adults

• **77 million** have basic or below basic health literacy.¹

• Only **12%** had proficient health literacy.¹

• Association between limited health literacy and numeracy and poor diabetes outcomes.²

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Causes of Severe Hypoglycemia

Figure 2. Causes identified by patients for the severe hypoglycaemic events and number of patients (as % of group) reporting them. White bar = total of all countries (type 1, 319; type 2, 320); black bar = UK (type 1, 101; type 2, 100), grey bar = Germany (type 1, 94; type 2, 120), dotted bar = Spain (type 1, 124; type 2, 100).

Food Insecurity by Day

### At Risk Populations

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>32.8%</td>
<td>Low-income households with incomes below 185% of the poverty threshold</td>
</tr>
<tr>
<td>30.3%</td>
<td>Households with children headed by a single woman</td>
</tr>
<tr>
<td>22.4%</td>
<td>Households with children headed by single man</td>
</tr>
<tr>
<td>21.5%</td>
<td>Black, non-Hispanic households</td>
</tr>
<tr>
<td>19.1%</td>
<td>Hispanic households</td>
</tr>
<tr>
<td>14-16.9%</td>
<td>Households with children under age 6; All households with children; <strong>Women</strong> living alone; <strong>Men</strong> living alone</td>
</tr>
</tbody>
</table>

## Behaviors Leading to Hypoglycemia

<table>
<thead>
<tr>
<th>Behaviors</th>
<th>Intensive Glycemia % (n)</th>
<th>Standard Glycemia % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>14% (79)</td>
<td>11% (20)</td>
</tr>
<tr>
<td><strong>Food Related</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed or missed meal</td>
<td>31% (167)</td>
<td>44% (81)</td>
</tr>
<tr>
<td>Ate less carbohydrate</td>
<td>26% (144)</td>
<td>25% (47)</td>
</tr>
<tr>
<td>Unexpected, vigorous exercise</td>
<td>15% (80)</td>
<td>12% (23)</td>
</tr>
<tr>
<td>Took more insulin than prescribed</td>
<td>5% (30)</td>
<td>7% (13)</td>
</tr>
<tr>
<td>Ingested alcohol</td>
<td>3% (18)</td>
<td>2% (4)</td>
</tr>
</tbody>
</table>

Bonds et al. *BMC Endocrine Disorders* 2012, 12:5
Shared Decision Making with the patient when choosing INDIVIDUALIZED goals of therapy is key.

**Looser Glycemic Targets:**
- A1c 7.5 – 8%
- Hypoglycemia prone
- Limited life expectancy
- Advanced complications
- Extensive co-morbid conditions
- Target difficult to attain

**Glycemic Target:**
- A1c <7.5%

For patients with life expectancy >10-15 years and no contraindications to therapy, incidence of microvascular disease.

**Tighter Glycemic Targets:**
- A1c <7%
- Short disease duration
- Long life expectancy
- No significant CVD
- If can be achieved without hypoglycemia
Patient Case #1

86 year old patient with DM1 continual hypoglycemia episodes & unawareness A1c 7.0%.
## Risk of Hypoglycemia

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>Moderate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanide (metformin)</td>
<td>Sulfonylureas (Glyburide, Glipizide, Glimepiride)</td>
<td>Insulin</td>
</tr>
<tr>
<td>TZDs (Pioglitazone, Rosiglitazone)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DPP-4 Inhibitors (Sitagliptin, Saxagliptin, Linagliptin, Alogliptin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGLT-2 Inhibitors (Canagliflozin, Dapagliflozin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GLP-1 Agonists (Exenatide, Liraglutide, Albiglutide, Lixesenaside, Dulaglutide)</td>
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<td></td>
</tr>
</tbody>
</table>

TZD: Thiazolidinedione; DPP-4: Dipeptidyl peptidase-4; SGLT-2: Sodium-glucose co-transporter 2; GLP-1: Glucagon-like peptide-1
Clinical Pearls

• Metformin
  – A1c lowering of 1-2%
  – New/less strict FDA labeling for reduced kidney function

• Sulfonylureas
  – A1c lowering of 1-2%
  – Caution in patient with erratic eating habits; must take 30 minutes before meal
  – Avoid in patients already on insulin

Clinical Pearls

• Insulin
  – Highest risk for hypoglycemia of all meds; greatest A1c lowering effect
  – Pre-mixed insulins are more convenient but allow for less individualizing and often more hypoglycemia
  – Consider earlier in therapy based on A1c goals

Patient Case #2

62 year old with h/o alcoholic cirrhosis and DM2 (x1 year). A1c 8.5% with relative morning hypoglycemia and loose stools.

On Metformin 1000mg BID and Insulin Glargine 15 units QPM.
CMS Quality Measure Development Plan (2016)

Merit-based Incentive Payment System (MIPS)

Documentation of an individualized glycemic treatment goal

Takes into account patient-specific factors

Reassessed at least annually
VHA Choosing Wisely®
Hypoglycemia Safety Initiative

- In concert with ABIM’s Choosing Wisely® Initiative
- Supported by VA/DoD DM guidelines since 1997; more recently by DHHS and CMMS
- A voluntary program to improve patient-centered care and reduce the risk of hypoglycemia across the VHA nation-wide
CW-HSI Methods

• Identify high-risk cohort
  - HbA1c < 7%
  - Insulin or Sulfonylurea
  - Age ≥ 75 or Dementia / Cognitive Impairment or SCr > 1.7 mg/dL

• Integrated Approach
  - Multi-Disciplinary Education
  - EMR Tools
  - Online Panel Reports
Evaluation
Over **9,300 patients** have been **evaluated** using the EMR template

**Evaluation rate** for high-risk patients assigned to primary care is **87%**

Occurrence
Hypoglycemia has been reported by **25%** of those evaluated

Action
Of all patients evaluated, **95%** have **documented** shared decision making

Of those reporting hypoglycemia, **56%** have made a **shared decision** with their provider to **relax treatment**
Patient Case #3

- 73yo carpenter with T2DM >20 years, widowed 2012.
- BMI 20.7 (BMI target for age >23)
- CKD stage 3 with eGFR 32
- Taking Insulin Glargine Q bedtime & Aspart with meals
- Recent ER visit; cut finger off while helping family member with a project. Did not want to stop for lunch
Risk Stratification Tool & Action Steps

Identify risk factors and patient preferences:
- Cognitive Impairment/dementia
- Clinically significant Chronic Kidney Disease
- Social factors (homelessness, lives alone/socially isolated)
- History of or risk for falls
- Difficulty in self-management (poor dexterity, mental health issues)
- Food insufficiency (Do you ever skip meals? Do you ever go to bed hungry?)
- Patient fears and quality of life

Determine prior hypoglycemic events:
- Hypoglycemia requiring paramedics, emergency dept visit or Inpatient evaluation/care
- Any episode(s) of hypoglycemia requiring bystander assistance
- Self reported hypoglycemia
- No prior events but high risk and/or patient fears and concerns
- No major Issues identified

Develop an individualized action plan:
- Case management, Specialty care if available, Urgent review of medication regimen
- Urgent review of medication regimen, self-management, target goals, patient education to identify cause of lows and course of action
- Review of medication regimen, self-management, target goals, patient education to identify cause of lows and course of action
- Telephone/remote monitoring; individualized risk reduction strategies/education, discuss patient goals and preferences
- Routine management and continued surveillance

Developed in Collaboration with the Federal Interagency Workgroup – Diabetes Agents (DHHS, Office of Disease Prevention and Health Promotion).
Be Proactive!

How can you work to identify patients at high risk?

https://www.youtube.com/watch?v=FqQ-JuRDkl8