Clinical trials have, for the most part, excluded older, sicker patients and, as a result, medical decision making in older adults is currently not evidence based. The major randomized controlled trials in type 2 diabetes that form the evidence base for glycemic control had exclusion criteria that, based on age alone, would exclude up to 39% of the real-world U.S. population with type 2 diabetes. The UKPDS explicitly excluded patients ≥65 years at the time of enrollment. ACCORD, ADVANCE, and VADT enrolled patients in their 60s and 70s but applied numerous exclusion criteria (e.g., history of severe hypoglycemia, unwillingness to use insulin, and creatinine>1.5 mg/dl) that barred many older adults with diabetes. ACCORD had to discontinue enrollment of patients ≥80 years because of high rates of hypoglycemia. Ongoing trials continue to exclude patients with common comorbidities or long duration of diabetes. GRADE, a comparative effectiveness trial of second-line medications, excludes patients with existing conditions (creatinine>1.4, active ischemic heart disease, congestive heart failure [Class III/IV]) or duration of diabetes >10 years. More recent trials of the SGLT-2 inhibitors excluded patients with eGFR<30, history of cancer, and/or history of severe hypoglycemia.

In the absence of directly available trial data, data from real-world practice has provided invaluable insights into the care of the heterogeneous population older patients. Notably, such data has been used to characterize the high level of comorbidity in the geriatric diabetes population and helped to identify naturally occurring classes or subgroups of older patients. Real-world data has also provided important contemporary natural history of disease data that reveal baseline rates of complications that are strikingly different from older epidemiologic studies; rates of hospitalization for severe hypoglycemia now exceed those of severe hyperglycemia and rival rates of major cardiovascular events. This evidence has shaped contemporary care guidelines for geriatric diabetes that now all emphasize the need to stratify goals of diabetes care by health status and the primacy of avoiding hypoglycemia. Interestingly, real-world data has also been examined to assess the quality of diabetes care based on these newer guidelines and revealed that the intensity of diabetes care (glycemic level achieved and use of medications such as insulin) is essentially the same across categories of health status. This has opened up new lines of inquiry regarding the interventions designed to encourage the personalization of diabetes care.
References

Data from Real-World Practice and the Care of Older People with Diabetes

Elbert S. Huang, MD MPH FACP

ADA Research Symposium
Washington, D.C.
November 16, 2018

Outline

• Glycemic control and medications in clinical trials
• Data from real-world practice
• Evolution of diabetes care guidelines
• Why do we appear not to personalize care
• Interventions to improve medical decisions, care, and outcomes
The Clinical Trial is Open. Older People Need Not Apply.

Glycemic Control and Medications in Clinical Trials
### United Kingdom Prospective Diabetes Study

#### Intervention Trial
- Median follow-up: 10.0 years
- RR = 0.88 (0.79 - 0.99)
- P = 0.029

#### Intervention Trial + Post-trial monitoring
- Median follow-up: 16.8 years
- RR = 0.91 (0.83 - 0.99)
- p = 0.040


### Late 2000s Glycemic Control Trials

<table>
<thead>
<tr>
<th></th>
<th>ACCORD</th>
<th>ADVANCE</th>
<th>VADT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean</strong></td>
<td>62.2</td>
<td>66</td>
<td>60.4</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>10 yrs (median)</td>
<td>8 yrs (mean)</td>
<td>11.5 yrs (mean)</td>
</tr>
<tr>
<td><strong>A1C Achieved</strong></td>
<td>7.5% vs. 6.4%</td>
<td>7.3% vs. 6.5%</td>
<td>8.4% vs. 6.9%</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>1.22, CI (1.01-1.46)</td>
<td>0.93, CI (0.83-1.06)</td>
<td>1.07, CI (0.81, 1.42)</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td>Non-fatal and fatal cardiovascular disease 0.90 (0.78-1.04)</td>
<td>Macrovascular 0.94 (0.84-1.06)</td>
<td>Cardiovascular events 0.88 (0.74-1.05)</td>
</tr>
<tr>
<td></td>
<td>Non-fatal myocardial infarction 0.76 (0.62-0.92)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Microvascular</strong></td>
<td>0.86 (0.77-0.97)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Glycemic Control Trials and Patients over 80

• ACCORD
  – Initially enrolled patients over 80 but stopped after observing high rates of hypoglycemia

• Japan Elderly Diabetes Intervention Trial
  – Attempted to evaluate a multiple risk factor intervention in patients 65-85 (N=1173)
  – Unable to achieve separation in A1C
  – Attributed to fear of inducing hypoglycemia

Trials and Generalizability <2010

• UKPDS inclusion criteria
  – Newly diagnosed diabetes
  – 26-65 years of age at baseline

• Applying UKPDS exclusions, 49% of patients with new onset diabetes would be excluded

• Among 7 major trials of glucose lowering, 39% of type 2 population would be excluded

• Sample exclusion criteria
  – History of severe hypoglycemia
  – Unwillingness to use insulin
  – Creatinine>1.5 mg/dl

EMPA-REG OUTCOME (SGLT-2 Inhibitor)

A. Primary Outcome

B. Death from Cardiovascular Causes

C. Death from Any Cause

D. Hospitalisation for Heart Failure

NEJM 2015; 373: 2117

CVD-REAL Nordic – SGLT2 in Real-World Practice

Figure 2: Pooled Kaplan-Meier curves and hazard ratios comparing new users of SGLT2 inhibitors and new users of other glucose-lowering drugs for cardiovascular mortality and major adverse cardiovascular events. Groups were matched 1:1 by propensity score. SGLT2 = sodium-glucose co-transporter-2, HR = hazard ratio.

Trials and Generalizability >2010

• More recent drug-placebo trials include patients in 60s and 70s with ↑CVD risk but…

• SGLT2 Trial Exclusion Criteria:
  – eGFR<30
  – History of cancer
  – History of severe hypoglycemia

• GRADE Trial Exclusion Criteria:
  – Creatinine>1.4 mg/dl
  – Active ischemic heart disease
  – Congestive heart failure (Class III/IV)
  – Duration of diabetes>10 years

Older Adults with Diabetes in Real-World Clinical Practice
Classifying Older Adults with Diabetes by Comorbid Conditions (NSHAP)


Class 1: 9%  
Class 2: 17%  
Class 3: 33%

Table 3. Sex- and Race-Adjusted Incidence of Diabetes Complications in Older Adults With Longer Duration of Type 2 Diabetes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Events per 1000 Person-years (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age 60-69 y</td>
<td>Age 70-79 y</td>
</tr>
<tr>
<td>Acute hyperglycemic event</td>
<td>1.85 (1.44-2.37)</td>
<td>1.76 (1.36-2.27)</td>
</tr>
<tr>
<td>Acute hypoglycemic event</td>
<td>9.62 (8.70-10.64)</td>
<td>15.88 (14.56-17.32)</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>7.92 (7.08-8.84)</td>
<td>7.64 (6.83-8.54)</td>
</tr>
<tr>
<td>Eye disease</td>
<td>20.26 (18.41-22.30)</td>
<td>14.97 (13.45-16.66)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>4.02 (3.47-4.57)</td>
<td>4.90 (4.25-5.64)</td>
</tr>
<tr>
<td>Lower limb amputation</td>
<td>3.94 (3.38-4.60)</td>
<td>4.26 (3.66-4.95)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>15.15 (13.69-16.61)</td>
<td>18.98 (17.50-20.59)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>13.83 (12.62-15.15)</td>
<td>23.86 (22.10-25.76)</td>
</tr>
<tr>
<td>Mortality</td>
<td>33.21 (31.55-34.95)</td>
<td>65.87 (63.28-68.56)</td>
</tr>
</tbody>
</table>

* Duration of diabetes was 10 years or more.
* Information was obtained from Kaiser Permanente Northern California database, 2004-2010.
A1C-Mortality Relationship in UK Diabetes Population

### Glycemic Control and Mortality Risk in the Elderly (Diabetes and Aging Study)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Baseline Glycosylated Hemoglobin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;6.0</td>
</tr>
<tr>
<td>60-69</td>
<td>HR</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
</tr>
<tr>
<td>70-79</td>
<td>HR</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
</tr>
<tr>
<td>80+</td>
<td>HR</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
</tr>
</tbody>
</table>


---

### Simulation Model of Diabetes Complications

Assign initial patient characteristics → Simulate natural history of diabetes progression according to patient characteristics → Advance in disease progression one year → Alive → Select next patient → Mortality Module → Dead

- Retinopathy Module
- Nephropathy Module
- Neuropathy Module
- Coronary Heart Disease Module
- Stroke Module
Results of Simulated Trials (UKPDS) in Older, Sicker Patients


From: Development and Validation of a Tool to Identify Patients With Type 2 Diabetes at High Risk of Hypoglycemia-Related Emergency Department or Hospital Use


### Tool Inputs

- How many times has the patient ever had hypoglycemia-related utilization in an ED (primary diagnosis of hypoglycemia*) or hospital (principal diagnosis of hypoglycemia*)? (0, 1-2, ≥3 times)?
- How many times has the patient gone to an ED for any reason in the prior 12 months (<2, ≥2 times)?
- Does the patient use insulin (yes/no)?
- Does the patient use sulfonylurea (yes/no)?
- Does the patient have severe or end-stage kidney disease (CKD stage 4 or 5) (yes/no)?
- Is the patient <77 years old (yes/no)?

### Instructions

The 6 inputs above are used to identify one of the mutually exclusive exposure groups and the corresponding risk category (high, low, or intermediate) for hypoglycemia-related ED or hospital utilization in the following 12 months. The first 5 options are defined by unique combinations of predictor variables, while the sixth option is indicated only after ruling out the first 5 options.

<table>
<thead>
<tr>
<th>Input Description</th>
<th>Risk Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥3 Prior hypoglycemia-related ED or hospital utilization</td>
<td>High risk (&gt;5%)</td>
</tr>
<tr>
<td>1-2 Prior hypoglycemia-related ED or hospital utilization AND Insulin use</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Input Description</th>
<th>Risk Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prior hypoglycemia-related ED or hospital utilization AND No insulin AND No sulfonylurea use</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Input Description</th>
<th>Risk Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prior hypoglycemia-related ED or hospital utilization AND No insulin AND Uses sulfonylurea AND Age &gt; 77 years AND Does not have severe or end-stage kidney disease</td>
<td>Low risk (&lt;1%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Input Description</th>
<th>Risk Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prior hypoglycemia-related ED or hospital utilization AND Uses insulin AND Age &gt; 77 years AND &gt;2 ED visits in prior year</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Input Description</th>
<th>Risk Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>All other risk factor combinations</td>
<td>Intermediate risk (1%-5%)</td>
</tr>
</tbody>
</table>
**General Population Diabetes Care Goals**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Recommended Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose control (A1C)</td>
<td>&lt;7.0%</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>&lt;130/80 mm Hg</td>
</tr>
<tr>
<td>Cholesterol (LDL cholesterol)</td>
<td>&lt;100 mg/dl</td>
</tr>
</tbody>
</table>
### Comparison of Guidelines

<table>
<thead>
<tr>
<th>Description of patient stratum</th>
<th>European Diabetes Working Party for Older People</th>
<th>American Geriatrics Society</th>
<th>Department of Veterans Affairs</th>
<th>American Diabetes Association</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A1C goal</strong></td>
<td><strong>A1C goal</strong></td>
<td><strong>A1C goal</strong></td>
<td><strong>A1C goal</strong></td>
<td><strong>A1C goal</strong></td>
</tr>
<tr>
<td>Without major comorbidities</td>
<td>7.0-7.5%</td>
<td>Healthy</td>
<td>7.0-7.5%</td>
<td>&lt;7.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>None or very mild</td>
<td></td>
<td>Healthy (few co-existing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>microvascular complications;</td>
<td></td>
<td>chronic illnesses; intact</td>
</tr>
<tr>
<td></td>
<td></td>
<td>life expectancy of 10-15</td>
<td></td>
<td>cognitive and functional</td>
</tr>
<tr>
<td></td>
<td></td>
<td>years</td>
<td></td>
<td>status)</td>
</tr>
<tr>
<td>Frail patients (dependent;</td>
<td>7.6-8.5%</td>
<td>Moderate</td>
<td>7.5-8.0%</td>
<td>&lt;8.0%</td>
</tr>
<tr>
<td>multi-system disease; care</td>
<td></td>
<td>comorbidities</td>
<td></td>
<td>Complex/intermediate (</td>
</tr>
<tr>
<td>home residency, including</td>
<td></td>
<td></td>
<td></td>
<td>examples: multiple</td>
</tr>
<tr>
<td>those with dementia)</td>
<td></td>
<td></td>
<td></td>
<td>co-existing chronic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>illnesses*, ≥2 instrumental</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ADL impairments, or mild-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>moderate cognitive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>impairment)</td>
</tr>
<tr>
<td>Multiple comorbidities</td>
<td>8.0-9.0%</td>
<td>Advanced</td>
<td>8.0-9.0%</td>
<td>&lt;8.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>microvascular complications</td>
<td></td>
<td>Very complex/poor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>and/or major comorbid</td>
<td></td>
<td>health (examples: long</td>
</tr>
<tr>
<td></td>
<td></td>
<td>illness; life expectancy</td>
<td></td>
<td>term care, end stage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;5 years</td>
<td></td>
<td>chronic illnesses†, moderate-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>severe cognitive impairment,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥2 ADL dependencies)</td>
</tr>
</tbody>
</table>

**WHY DO WE APPEAR TO NOT PERSONALIZE DIABETES CARE?**
From: Potential Overtreatment of Diabetes Mellitus in Older Adults With Tight Glycemic Control


The JAMA Network

---

The JAMA Network

From: Potential Overtreatment of Diabetes Mellitus in Older Adults With Tight Glycemic Control


---
Barriers to Personalized Diabetes Care

Clinician

Patient

Health Care Delivery Systems

INTERVENTIONS TO IMPROVE PERSONALIZED MEDICAL DECISIONS AND CARE
How can we overcome barriers

<table>
<thead>
<tr>
<th>Barrier</th>
<th>Possible Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychological</td>
<td>Show provider’s data, compare to peers</td>
</tr>
<tr>
<td></td>
<td>Show wider range of alternative options</td>
</tr>
<tr>
<td></td>
<td>Periodic reminders to change options</td>
</tr>
<tr>
<td>System</td>
<td>Revise guidelines to reflect new evidence base for personalization</td>
</tr>
<tr>
<td></td>
<td>Revise performance measures</td>
</tr>
<tr>
<td>Lack of time or support</td>
<td>Generate and present data needed for personalization</td>
</tr>
<tr>
<td></td>
<td>Engage patients to collect data needed for preference-sensitive decisions</td>
</tr>
</tbody>
</table>

Conceptual Framework for Personalized Decision Support

Clinical Decisions: Risk Factor Goals

Clinical Decisions: Treatment Selection

Clinical Factors

Patient Preferences

Philosophical differences in intervention approach

<table>
<thead>
<tr>
<th>Goal</th>
<th>Intervention Format</th>
</tr>
</thead>
</table>
| Shared Decision Making | • Information sharing between patient (preferences) and provider (risks and benefits)  
  • Deliberation  
  • Decision-Making | Decision Aid |
| Decision Support | • Nudge subject towards a decision that one has already decided is the right one | Restricted choice sets  
  Accountable justifications  
  Peer comparison  
  Financial incentives |


University of Chicago-
Personalized Decision Support

- **Shared decision making and prognostic modeling**
- **Short-Term Goal**
  - Provide data needed to support personalization of A1C target
- **Long-Term Goal**
  - Intensive A1C target for healthy older patients  
  - Less intensive A1C targets for sicker older patients
- **Components:**
  - Patient education  
  - Personalized prognostic estimates (simulation model)  
  - Screening for geriatric syndromes  
  - Patient preference elicitation  
  - Feed information to doctors in 2-pages

What is an A-1-C Test?

- The A-1-C test is a blood test that allows doctors to see how many hemoglobins have sugar attached to them.

- The A-1-C test shows how high or low your daily blood sugars have been the past few months.

**PROBABILITY OF COMPLICATIONS**

The following tables look at your risk of developing amputation and blindness based on how you control your sugar. Talk to your doctor about what these tables mean and how it can affect your treatment.

<table>
<thead>
<tr>
<th>If your Target A1C is:</th>
<th>How many people like me will have an amputation?</th>
</tr>
</thead>
<tbody>
<tr>
<td>7%</td>
<td>44 out of 1000</td>
</tr>
<tr>
<td>8%</td>
<td>60 out of 1000</td>
</tr>
<tr>
<td>9%</td>
<td>65 out of 1000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>If your Target A1C is:</th>
<th>How many people like me will have blindness?</th>
</tr>
</thead>
<tbody>
<tr>
<td>7%</td>
<td>43 out of 1000</td>
</tr>
<tr>
<td>8%</td>
<td>52 out of 1000</td>
</tr>
<tr>
<td>9%</td>
<td>55 out of 1000</td>
</tr>
</tbody>
</table>

The following table looks at your risk of developing a heart attack for an A-1-c test level of 7.7.5%. In older adults, it is uncertain if lowering sugars will help lower the risk of heart disease.

<table>
<thead>
<tr>
<th>How many people like me will have a Heart Attack?</th>
</tr>
</thead>
<tbody>
<tr>
<td>248 out of 1000</td>
</tr>
</tbody>
</table>
Clinical Trial Conclusions

• Decision support tool significantly reduced patients’ informed subscale of decisional conflict scores
• Other findings not statistically significant but promising
  – Intervention patients had more communication about A1C goals during clinic visits
  – More awareness of their personal A1C goal
  – More changes in goal selection by their physicians
• Intervention acceptable to patients
Unanswered Questions

- How do we personalize selection of glucose lowering agents?
- Does eliciting patients’ preferences make a difference in outcomes?
- Does risk stratification make a difference in outcomes?
- What are the clinical consequences of a comprehensive model of care that actively personalizes diabetes goals and treatments in older patients?
- What are alternative implementation approaches to personalizing diabetes care?

Overall Conclusions

- Real-world data from clinical practice
  - Subgroups of patients
  - Natural history of disease
  - Observational drug comparison studies
  - Prediction models
- We don’t appear to personalize diabetes care
- Advances in computing and electronic medical records may allow us to deliver personalized recommendations more easily
  - Prediction, Pharmacogenomics, Preferences
Patient Feedback

“Thank you for your article in this week’s JAMA. In my 79th year, I still try to keep up with medicine and was shocked to find myself included in the very old age group. Having T2D, very mild without complications, I am pleased to note that my physician said she will allow my A1C to go as high as 7.0% without further ado.

Evidence based medicine is a wonderful thing! Thanks for your article from a very old physician.”

Funders

• NIDDK K24 DK105340
• NIDDK R01 DK081796
• NIA R56 AG051683
• NIA R01 AG030481
• Centers for Disease Control and Prevention U36 CCU319276
• American Diabetes Association (1-08-CR-25)
• The Retirement Research Foundation (2007-250)
• NIA K23 AG021963
• NIDDK P30 DK092949
• NIDDK P60 DK20595
Collaborators

University of Chicago
- Aviva Nathan
- Jennifer Cooper
- Priya John
- Sydney Brown
- Harry Zhang
- Niren Gandra
- Neda Laiteerapong
- William Dale
- Marshall Chin
- David Meltzer
- James Invenniuk
- Edward Laumann

Kaiser Division of Research
- Jennifer Liu
- Margaret Warton
- Rachel Whitmer
- Howard Moffet
- Andy Karter

UCSF
- Sei Lee
- Ken Covinsky
- Rebecca Sudore
- Dean Schillinger
- Nancy Adler

ACCESS
- Mickey Eder

Shared Decision Making Resources
- Nananda Col

Thank You

ehuang@medicine.bsd.uchicago.edu
http://chronicdisease.uchicago.edu
Twitter: @ChronicDiseaseU