# 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

Choosing Wisely®
An initiative of the ABIM Foundation

ODPHP

American Geriatrics Society
AGS Geriatrics Healthcare Professionals
Leading Change. Improving Care for Older Adults.
Five Things Physicians and Patients Should Question

VA | U.S. Department of Veterans Affairs

# Polling Question

True or False: For most patients with diabetes, an A1c goal of <7% is recommended

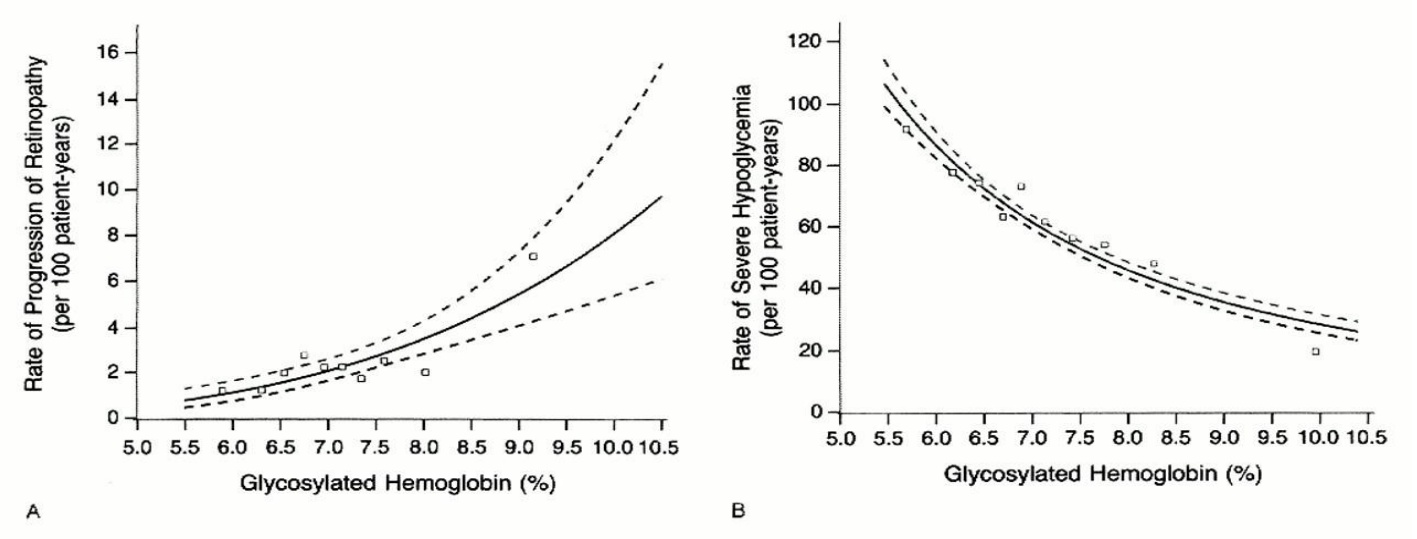
# Challenges in Reducing Over-treatment

Survey conducted by Caverly, TJ et al

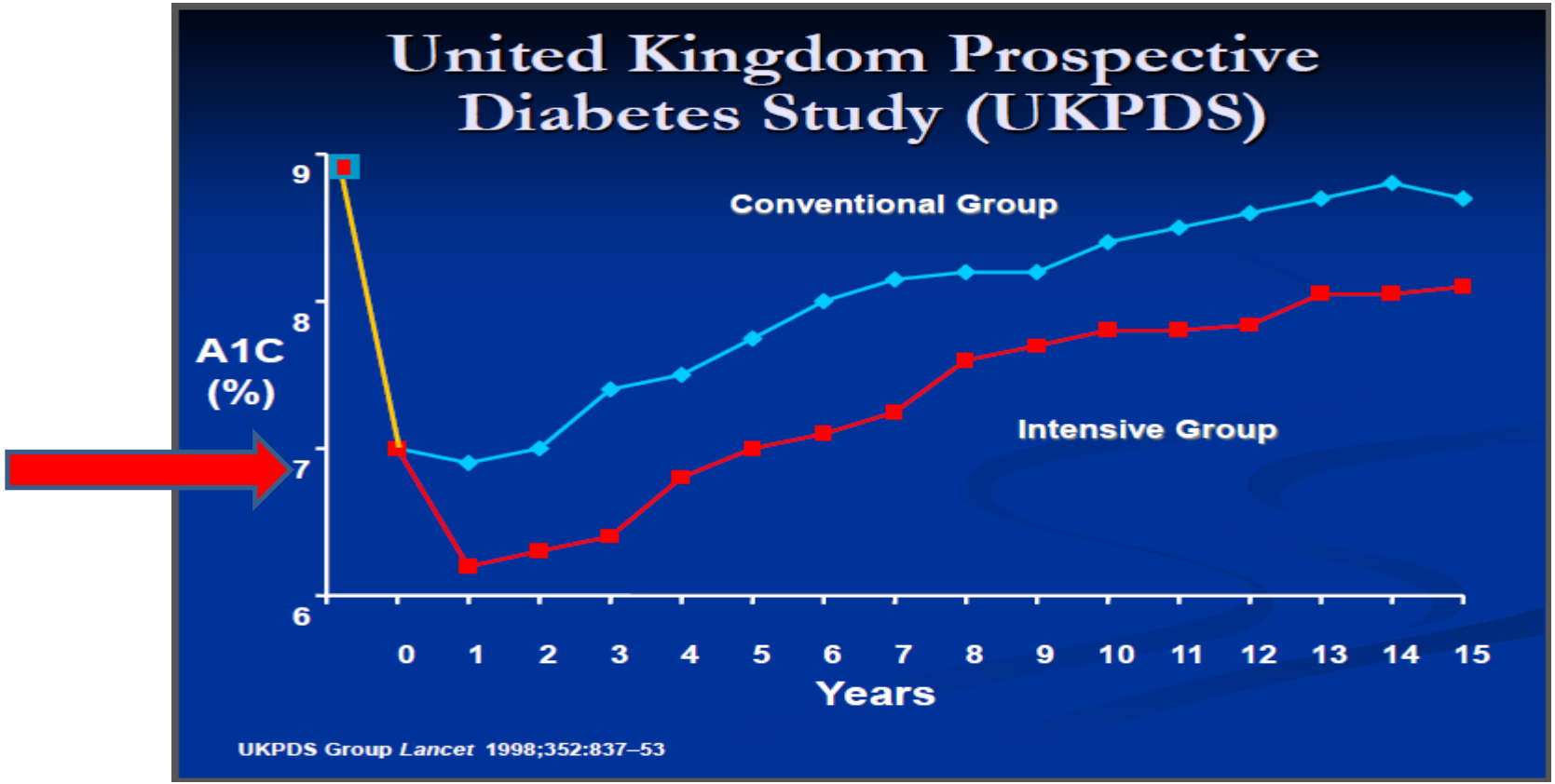
Response to a vignette of a 77y/o with long standing DM, severe kidney disease, A1c 6.5%, taking glipizide 10mg BID.

| | D/SD | A/SA |
|---|---|---|
| I think this patient would benefit if A1c maintained below 7% | 61.4% | **39.6%** |
| I worry that this patient would be harmed if his A1c is maintained below 7% | **44.9%** | 55.1% |
| I would worry that reducing his medication would lead to an A1c that falls outside current performance measures | 57.9% | **42.1%** |
| 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. | **30.8%** | 69.2% |
| It would be helpful to have patient education materials to discuss reducing diabetes medication | **14.6%** | 85.4% |

# DCCT: Risks of Sustained Progression of Retinopathy and Severe Hypoglycemia in Type 1 Diabetic Patients by HbA1c Level




*DCCT. N Engl J Med 329:977-986, 1993*



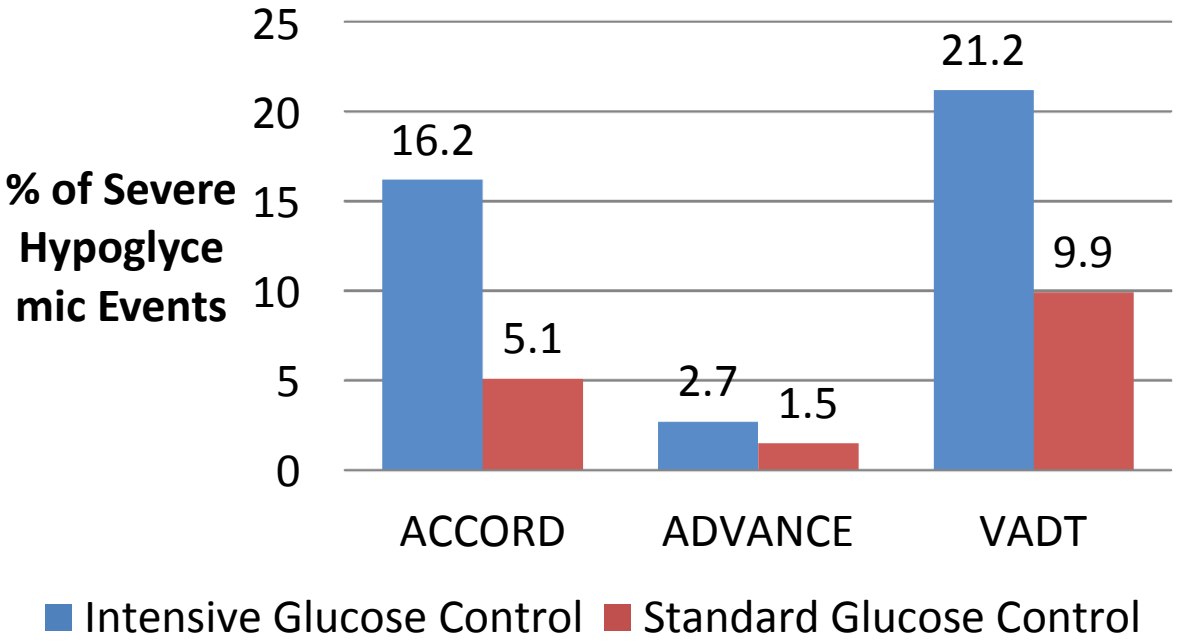

UKPDS Group *Lancet* 1998;352:837-853

# UKPDS

- 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**

UKPDS Group *Lancet* 1998;352:837-853

# Outpatient Intensive Glucose Control




Frier BM, Schernthaner G, Heller SR. Hypoglycemia and cardiovascular risks. Diabetes Care 2011;34(suppl 2):S132–S137.

# 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

Sacks *Diabetes* 2013; 62:41

# Non-glycemic Factors That May Alter HbA1c

| Disease or condition | Effect on $HbA_{1c}$ level | Potential mechanism |
|---|---|---|
| Rapid erythrocyte turnover | Falsely low | Unstable erythrocyte pool |
| Hemolytic states | Falsely low | Unstable erythrocyte pool |
| Iron deficiency anemia | Falsely high | Unknown |
| Hemoglobin SS, SC or CC disease | Falsely low | Unstable erythrocyte pool |
| Variant hemoglobin trait | Variable | Assay interference |
| Fetal hemoglobin | Variable | Assay interference |
| Blood transfusions | Falsely low | Unstable erythrocyte pool |
| Aging | Falsely high | Unknown |
| Cirrhosis | Falsely low | Unknown |
| Uremia | Falsely low | Carbamylated hemoglobin |
| Hemodialysis | Falsely low | Multiple |
| HIV infection | Falsely low | Occult hemolysis |
| Pregnancy | Falsely low | Hemodilution? |
| Dyslipidemia | Variable | Assay interference |
| Hyperbilirubinemia | Variable | Assay interference |
| Aspirin use (large doses) | Variable | Acetylated hemoglobin |
| Vitamin C | Variable | Interference with glycation |
| Vitamin E | Falsely low | Interference with glycation |
| Alcohol excess | Variable | Assay interference |
| Opiate use | Variable | Assay interference |

***Sacks Nat Rev Endocrinol* 2010; 6:589**

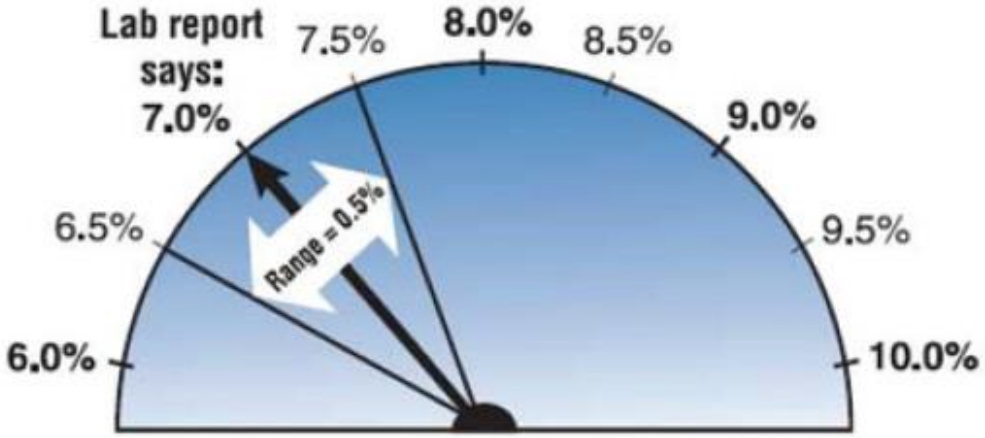
# Factors That May Influence Interpretation of HbA1c

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

***Sacks Diabetes Care* 2016; 39:1299**

# A1c Variability

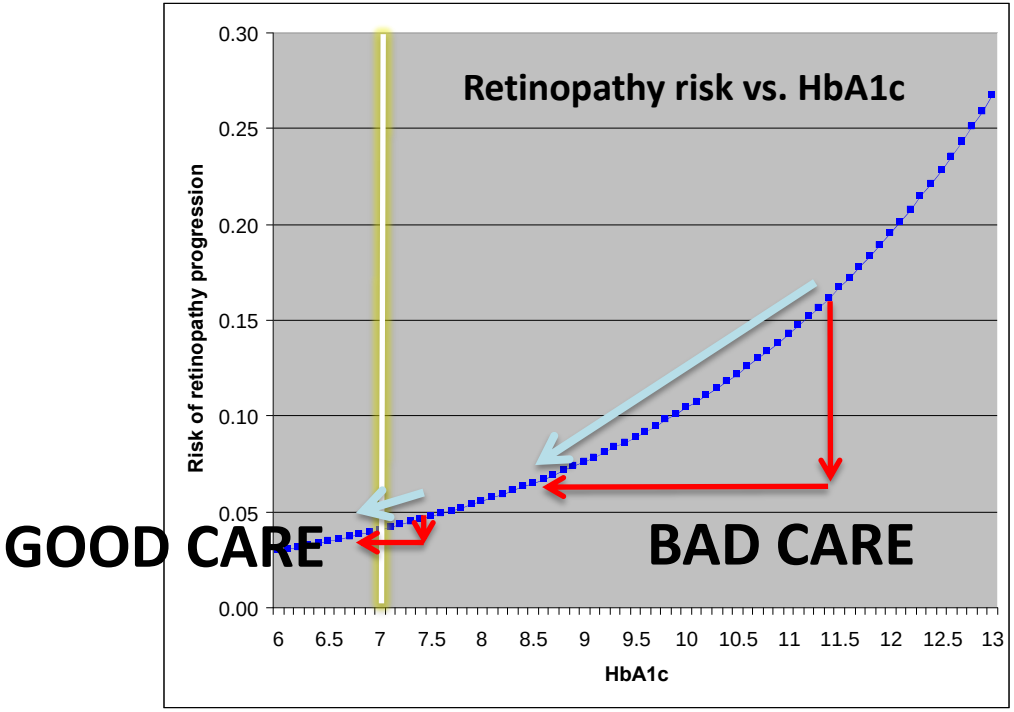
- A1c test result is within a range; it is **not** an absolute lab value




*Courtesy of David Aron, M.D., Louis Stokes Department of Veterans Affairs Medical Center, Cleveland, OH*

The A1c Test & Diabetes. (2014, September). Retrieved from https://www.niddk.nih.gov/health-information/diabetes/overview/tests-diagnosis/a1c-test

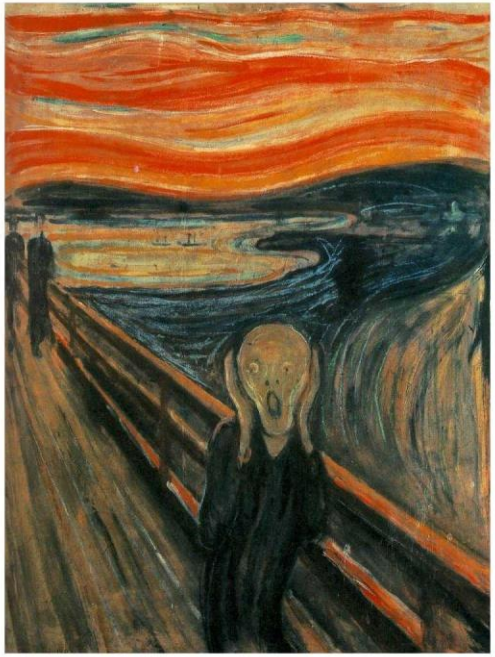
# Hemoglobin A1c and Risk of Retinopathy




*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

Sanon, V. P., et al. Clin Cardiol. 2014

# 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


1. Centers for Disease Control and Prevention. National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014. Atlanta, GA: U.S. Department of Health and Human Services; 2014.
2. Zammitt NN, Frier BM. Hypoglycemia in Type 2 Diabetes. Diabetes Care. 2005;28(12).

# 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 ≤ 3.5 mmol/l (63 mg/dl) for ≥ 20 min**
- **Recorded 134 hrs of HG**

| | Daytime episodes | Nocturnal episodes |
|---|---|---|
| **Duration** | **62 ± 42 min** | **170 ± 112 min** |
| **Nadir** | **2.8 ± 0.5 mmol/l (50 ± 0.9 mg/dl)** | **1.9 ± 0.7 mmol/l (34 ± 13 mg/dl)** |

**Only 3/34 episodes were symptomatic**
**> 90 % of episodes occurred without symptoms**

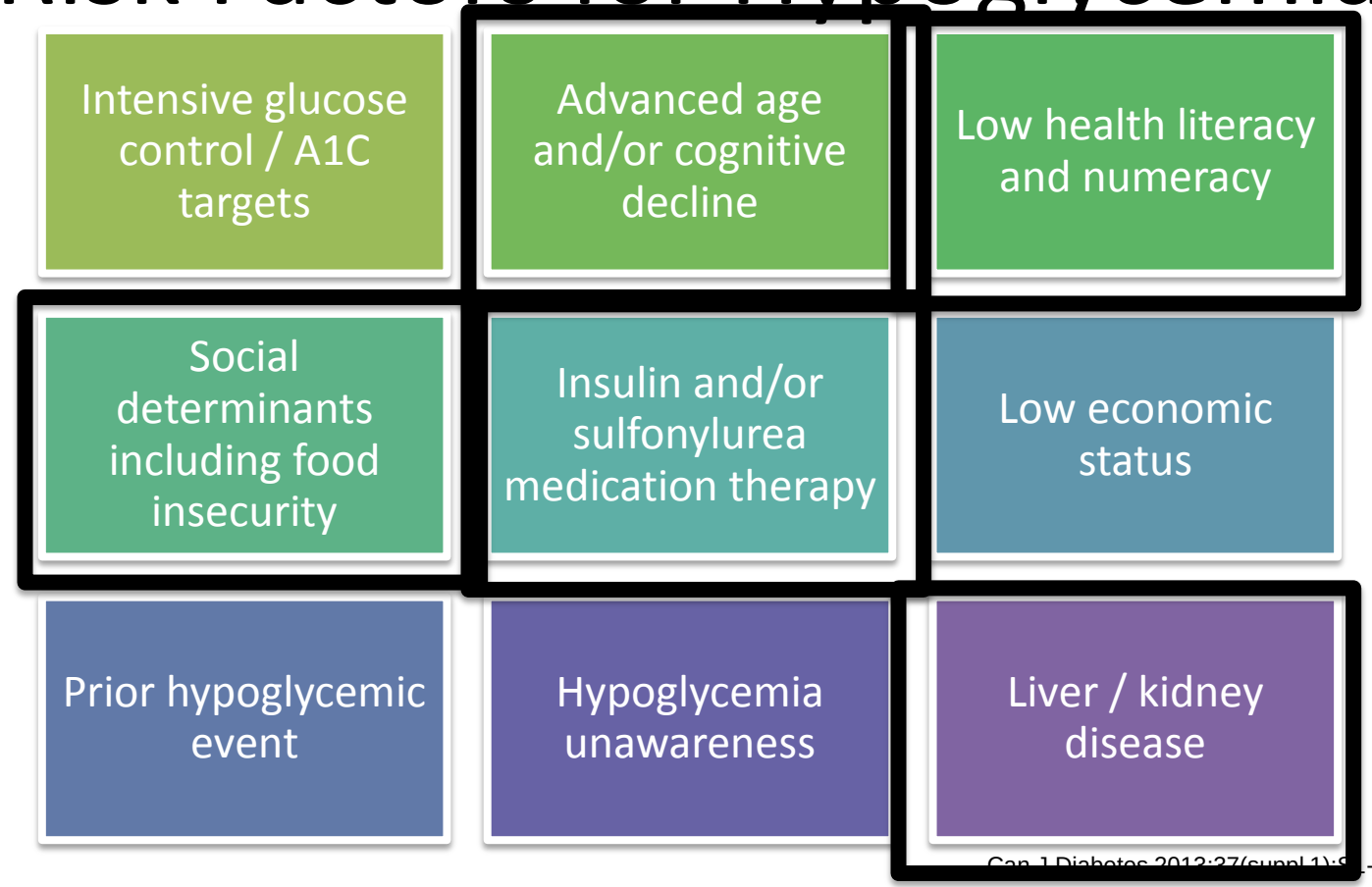
Chow et al. Diabetes 63: 1738. 2014.

# American Geriatric Society

- 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

J Am Geriatr Soc. 2013 Nov;61(11):2020-6. doi: 10.1111/jgs.12514

# Risk Factors for Hypoglycemia




Can J Diabetes 2013;37(suppl 1):S1-S212.

# Risk of Hypoglycemia in Older Veterans with Dementia and Cognitive Impairment

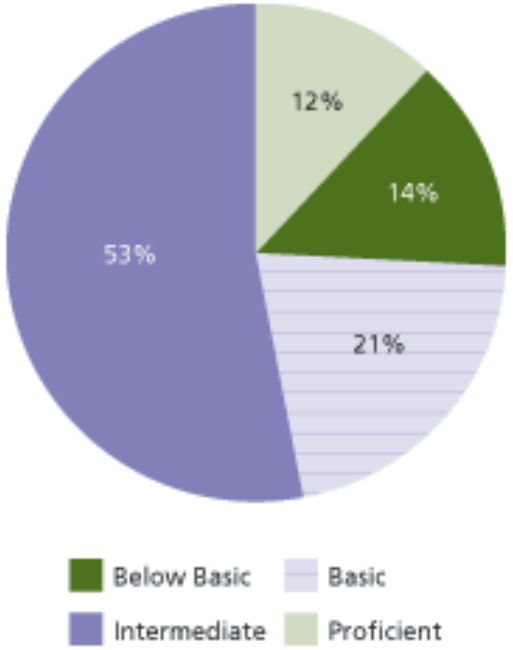
| Frequency of Hypoglycemia | |
|---|---|
| Dementia | 14.1% |
| Cognitive Impairment | 10.4% |
| Neither | 6.3% |

**30% patients with dementia or cognitive impairment are on insulin**

Feil DG, Rajan M, Soroka O, Tseng CL, Miller DR , Pogach LM. (2011). Risk of Hypoglycemia in Older Veterans with Dementia and Cognitive Impairment: Implications for Practice and Policy. J Am Geriatr Soc, 59: 2263–2272.

# 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]





1. America's Health Literacy: An Issue Brief From the U.S. Department of Health and Human Services. 2008.
2. White RO, et al. Addressing Health Literacy and Numeracy to Improve Diabetes Education and Care. Diabetes Spectrum Oct 2010, 23 (4) 238-243.

# Causes of Severe Hypoglycemia

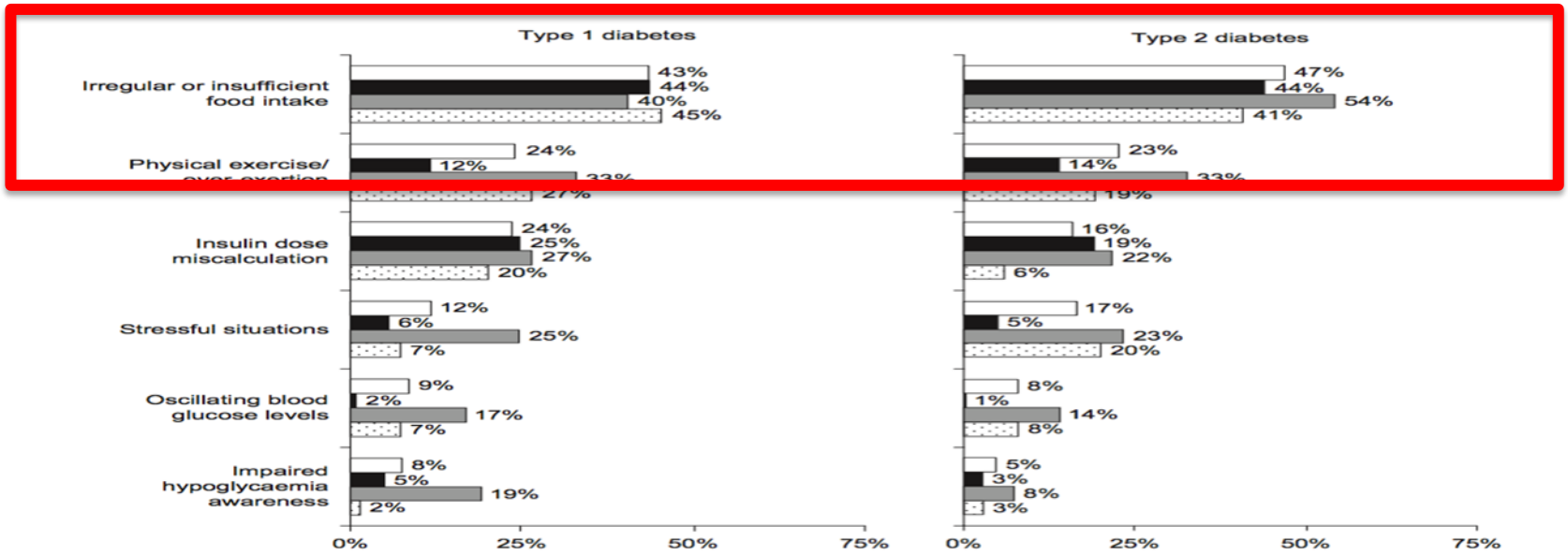
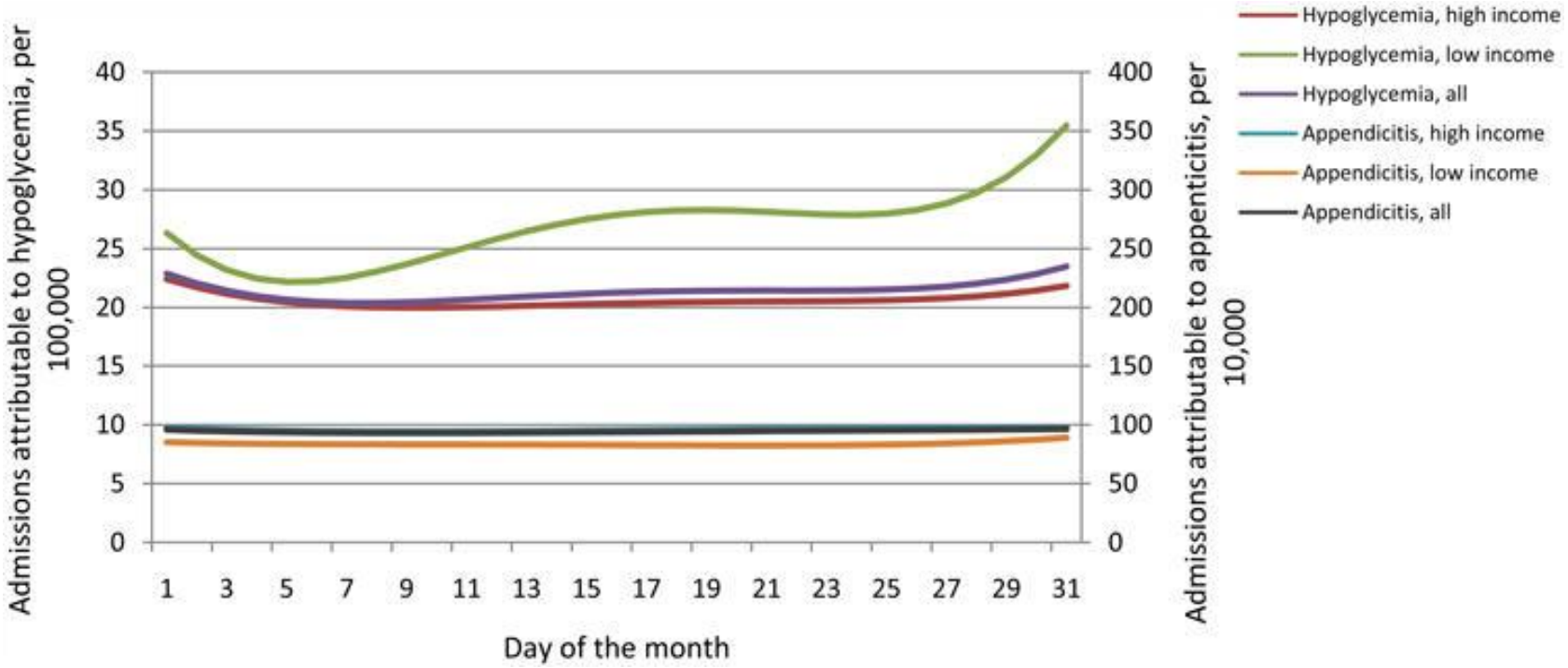



**Figure 2.** Causes identified by patients for the severe hypoglycaemic events and number of patients (as % of group) reporting them. White bar = total of all countries (type 1, 319; type 2, 320); black bar = UK (type 1, 101; type 2, 100), grey bar = Germany (type 1, 94; type 2, 120), dotted bar = Spain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

*J Med Econ.* 2009;12(4):269-80.

# Food Insecurity by Day




Seligman HK, et al. Health Affairs. 2014; 33(1): 116–123.

# At Risk Populations

| | |
|---|---|
| 32.8% | • **Low-income households with incomes below 185% of the poverty threshold** |
| 30.3% | • **Households with children headed by a single woman** |
| 22.4% | • Households with children headed by single man |
| 21.5% | • Black, non-Hispanic households |
| 19.1% | • Hispanic households |
| 14-16.9% | • Households with children under age 6; All households with children; **Women** living alone ; **Men living alone** |

Coleman-Jensen A, Rabbitt MP, Gregory CA, et al. United States Department of Agriculture; Economic Research Report No. (ERR-215) 44 pp, September 2016.

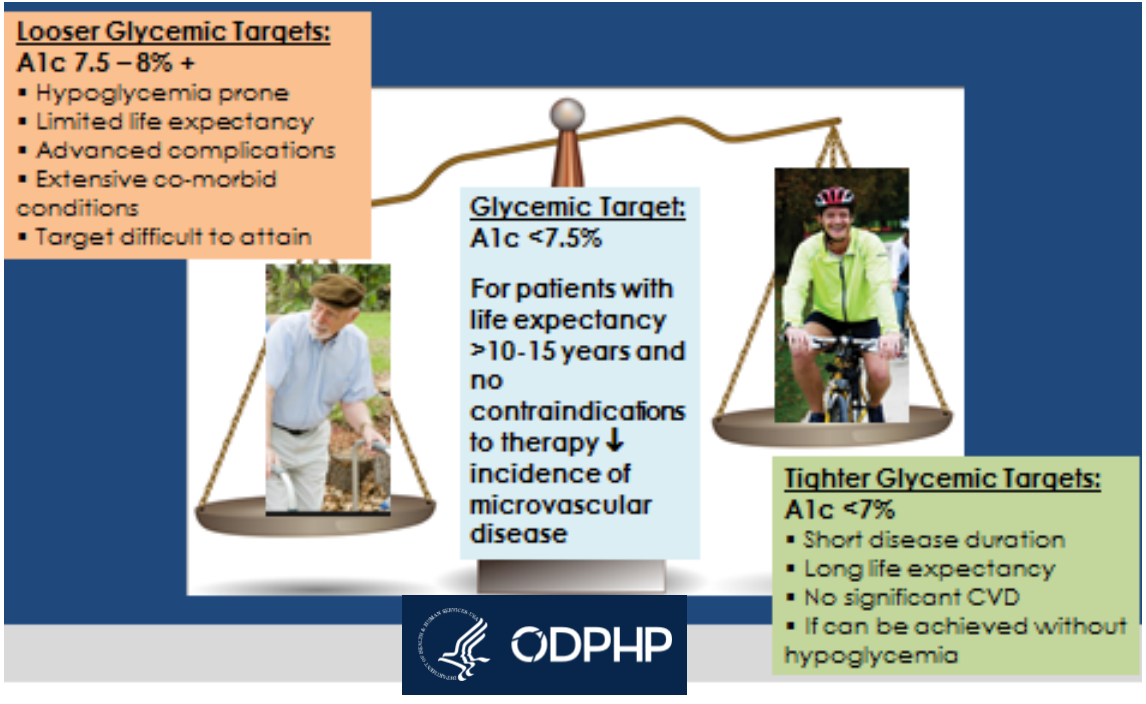
# Behaviors Leading to Hypoglycemia

| | Intensive Glycemia % (n) | Standard Glycemia % (n) |
|---|---|---|
| None | 14% (79) | 11% (20) |
| **Food Related** | **48% (263)** | **58% (107)** |
| **Delayed or missed meal** | **31% (167)** | **44% (81)** |
| **Ate less carbohydrate** | **26% (144)** | **25% (47)** |
| Unexpected, vigorous exercise | 15% (80) | 12% (23) |
| Took more insulin than prescribed | 5% (30) | 7% (13) |
| Ingested alcohol | 3% (18) | 2% (4) |

Bonds et al. *BMC Endocrine Disorders* 2012, 12:5

# Shared Decision Making

Shared Decision Making with the patient when choosing INDIVIDUALIZED goals of therapy is key



# Patient Case #1

86 year old patient with DM1 continual hypoglycemia episodes & unawareness A1c 7.0%.

# Risk of Hypoglycemia

| Low Risk | Moderate Risk | High Risk |
|---|---|---|
| Biguanide (metformin) | Sulfonylureas (Glyburide, Glipizide, Glimepiride) | Insulin |
| TZDs (Pioglitazone, Rosiglitazone) | | |
| DPP-4 Inhibitors (Sitagliptin, Saxagliptin, Linagliptin, Alogliptin) | | |
| SGLT-2 Inhibitors (Canagliflozin, Dapagliflozin) | | |
| GLP-1 Agonists (Exenatide, Liraglutide, Albiglutide, Lixesenaside, Dulaglutide) | | |

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

Diabetes Care 2017;40(Suppl. 1):S64 –S74

# 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

Cross, Brian L, et al. Diabetes Mellitus. In: Bainbridge JL, Branham, A, Coyle EA et al. Updates in Therapeutics®: Ambulatory Care Pharmacy Preparatory Review and Recertification Course, 2015 ed. Lenexa, KS: American College of Clinical Pharmacy, 2017:1-3 – 1-31.

# 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

Cross, Brian L, et al. Diabetes Mellitus. In: Bainbridge JL, Branham, A, Coyle EA et al. Updates in Therapeutics®: Ambulatory Care Pharmacy Preparatory Review and Recertification Course, 2015 ed. Lenexa, KS: American College of Clinical Pharmacy, 2017:1-3 – 1-31.

# 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

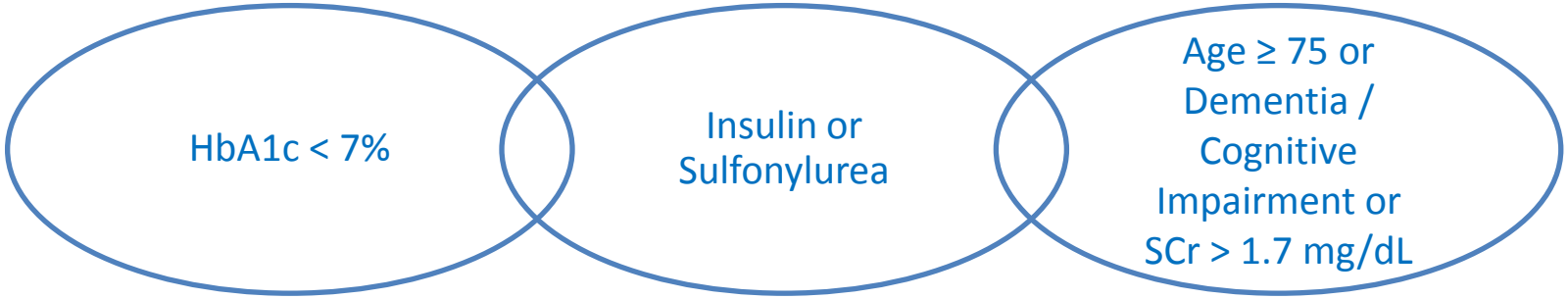
Reassessed at least annually

# 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

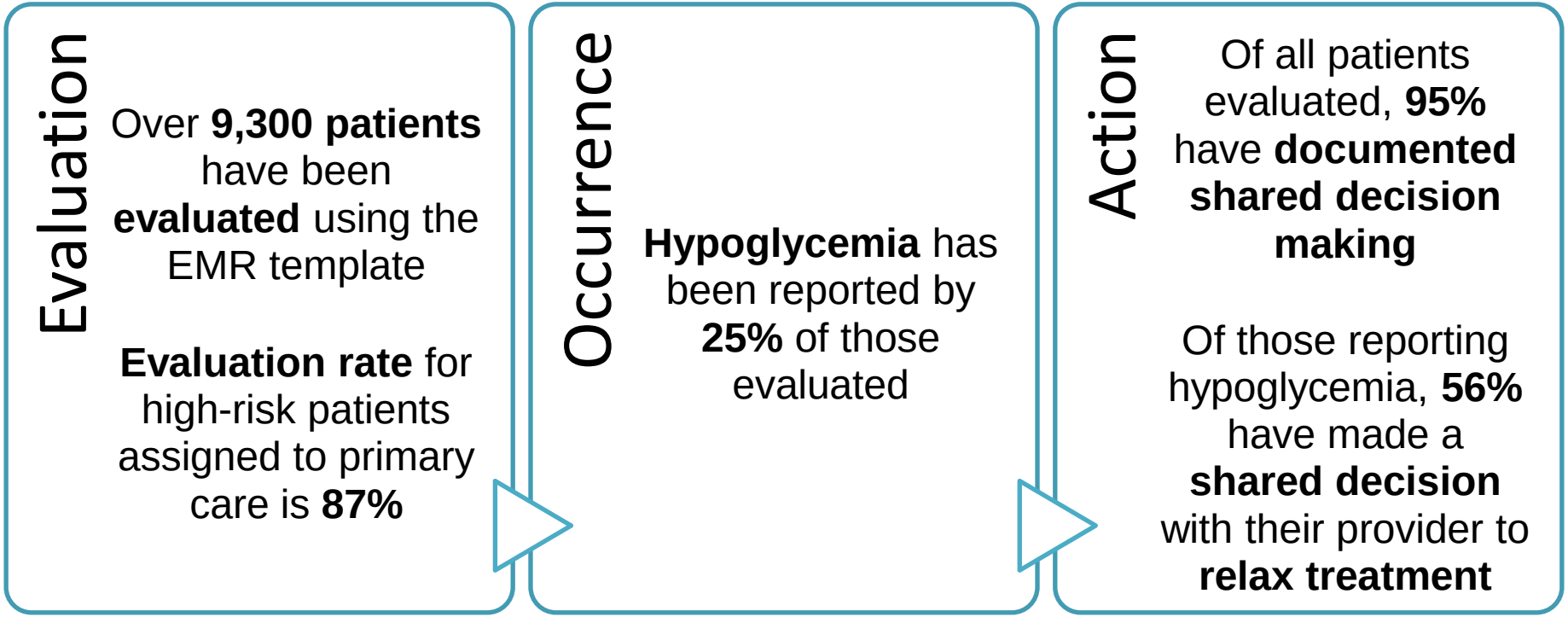
# CW-HSI Methods

- Identify high-risk cohort




- Integrated Approach

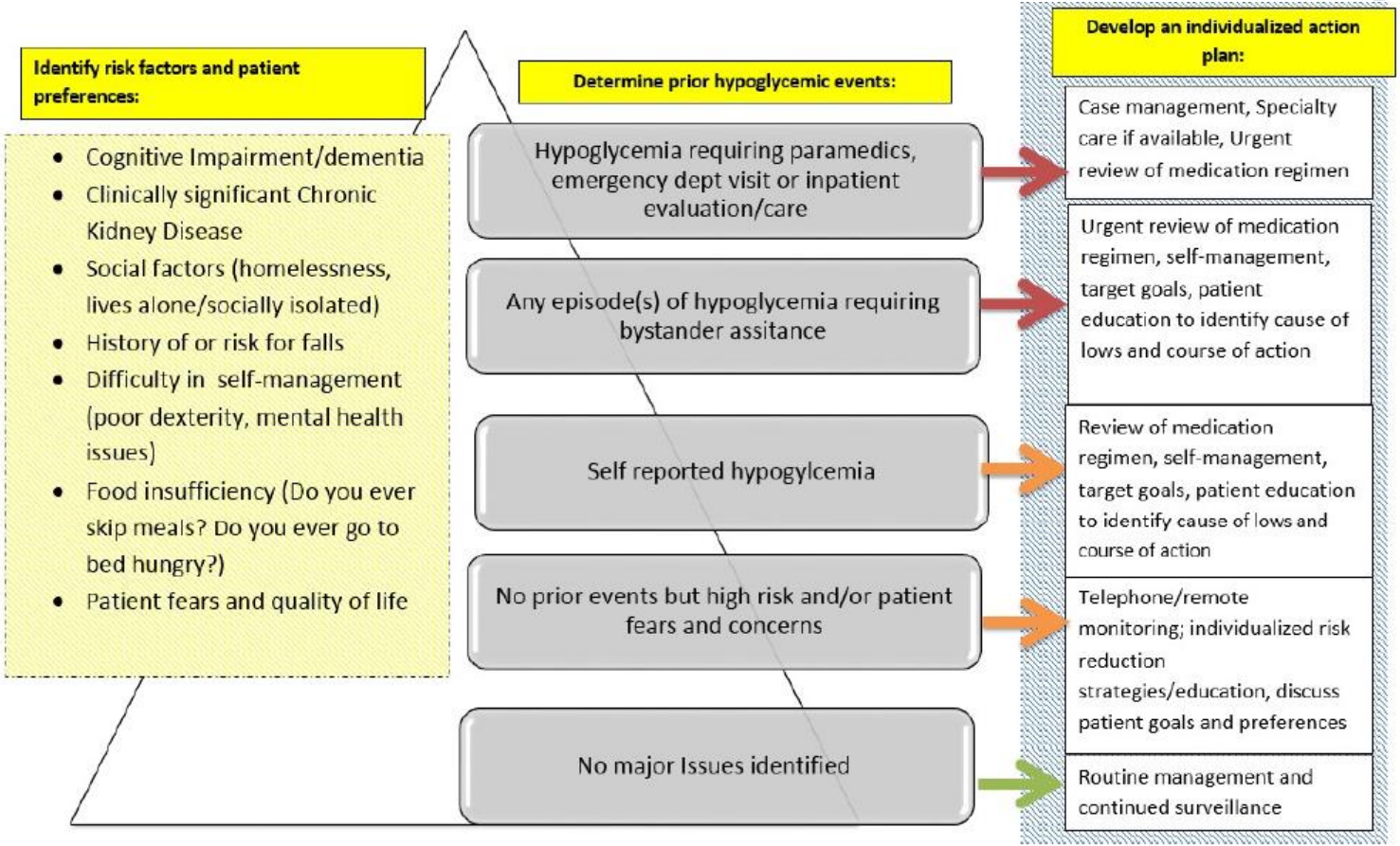
# CW-HSI Pilot Findings



# 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




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**