Clinical Considerations: Optimizing Treatment for Patients with T2DM

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Case Study #1:

Clinical Implications of Hypoglycemia: Assessing Risk

Case Study #1

- **INTRODUCTION**: GRL is a 68-year-old woman with T2DM; found unconscious; blood glucose level is 38 mg/dL; took 2 extra doses off her diabetic medication before breakfast; last memory is around 8:30AM

- **PAST MEDICAL HISTORY**:
  - 9-year history of T2DM
  - Unreported mild episodes of hypoglycemia during the past year (self-treated)
  - 4-year history of atrial fibrillation (AF)
  - Depression and weight gain since the death of her husband last year

Case Study #1 (cont'd)

- **FAMILY HISTORY:** Father died at age 72 of a heart attack; mother died at 84 of no specific reason; both had a history of T2DM and HTN

- **SOCIAL HISTORY:** Routinely eats breakfast around 7AM; lunch at noon at a restaurant 3 X/week with friends (does not always eat lunch when home); dinner is usually at 5PM; frequently snacks in mid-morning when feeling dizzy and anxious; drinks 1 glass of red wine before dinner; denies smoking or substance abuse.

Case Study #1 (cont'd)

PHYSICAL EXAM: Height, 5'3" (160 cm); weight, 147 pounds (66.8 kg); BMI, 26.0 kg/m².

LABORATORY RESULTS:

- A1C, 6.8%
- Plasma glucose, 98 mg/dL
- Creatinine, 1.5mg/dL
- eGFR (CDK-EPI), 36 mL/minute per 1.73m²

- Total cholesterol, 194 mg/dL
- LDL-C, 105 mg/dL (calc)
- HDL-C, 43 mg/dL
- Triglycerides, 210 mg/dL

Case Study #1 (cont'd)

- **MEDICATIONS:**
  - Metformin 1000/glyburide 10 mg twice daily
  - Warfarin 2.5 mg once daily in the morning(remains within therapeutic range 80% of the time)
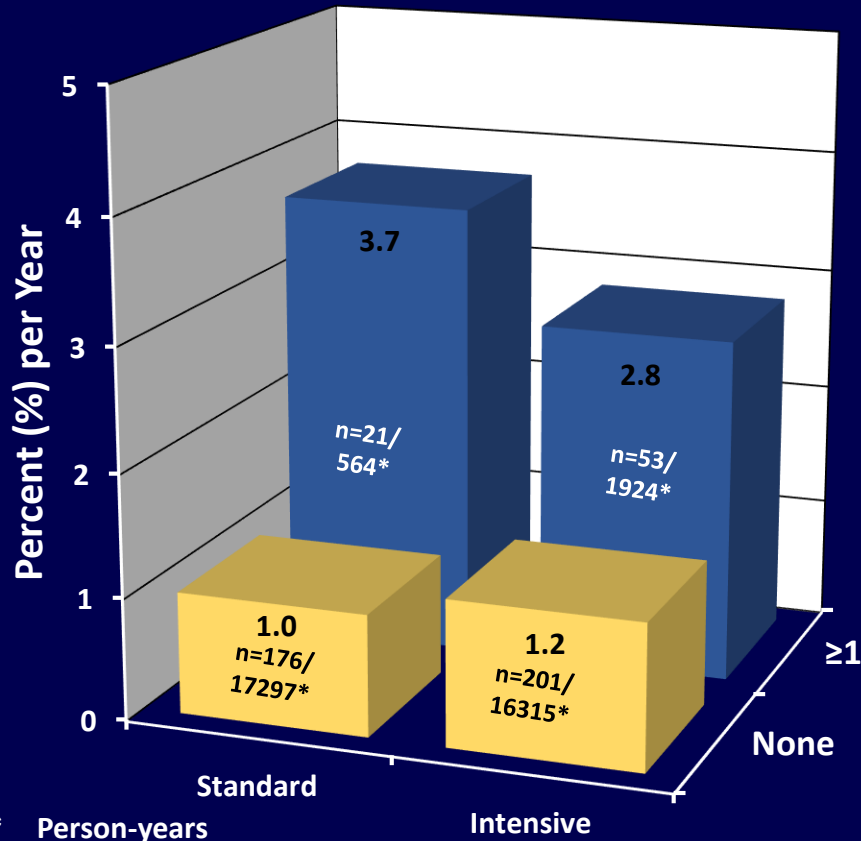 - Simvastatin 20 mg once daily with dinner

What are the risks of hypoglycemia for this patient?

ADA/Endocrine Society Classification of Hypoglycemia in Diabetes

- **Severe Hypoglycemia:** event requiring assistance of another to take corrective action, such as actively administering carbohydrates, glucagon, or take other corrective actions

- **Documented Symptomatic Hypoglycemia:** event during which typical symptoms of hypoglycemia are accompanied by a measured blood glucose (BG) $\leq$70 mg/dL (3.9 mmol/L)

- **Asymptomatic Hypoglycemia:** event not accompanied by typical symptoms but with a measured BG $\leq$70 mg/dL (3.9 mmol/L)

- **Probable Symptomatic Hypoglycemia:** event during which symptoms typical of hypoglycemia are not accompanied by a BG but that was presumably caused by a value $\leq$70 mg/dL (3.9 mmol/L)

- **Pseudo-hypoglycemia:** event during which the person with diabetes reports any of the typical symptoms of hypoglycemia with a measured BG concentration >70 mg/dL (3.9 mmol/L) but is approaching that level
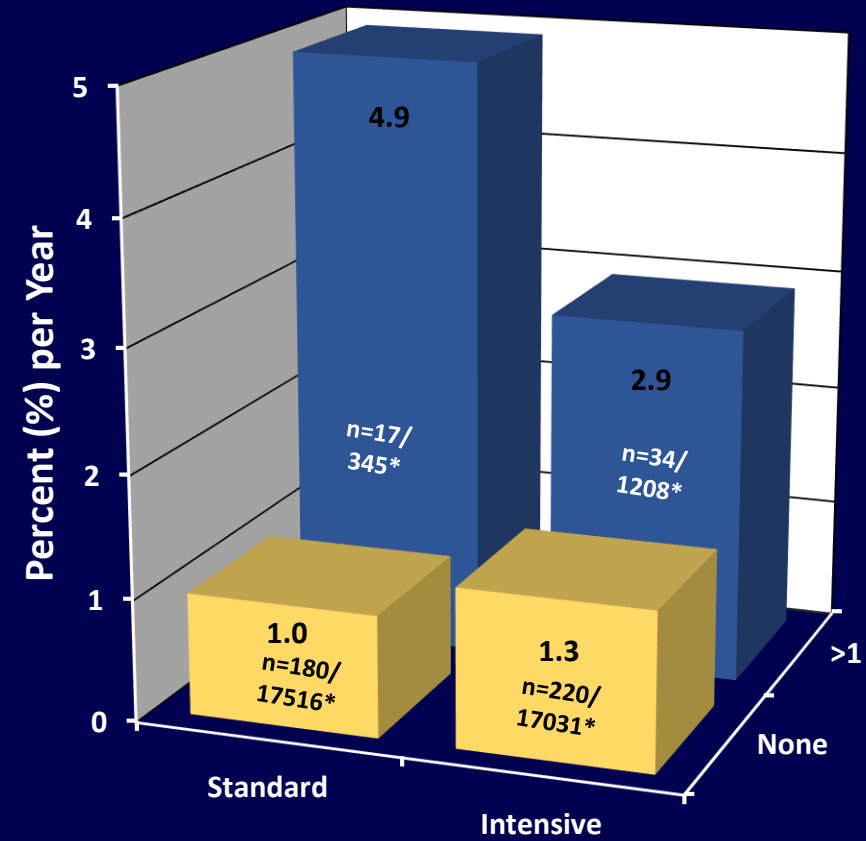
Seaquist ER, et al. *Diabetes Care*. 2013;36:1384-1395.

Hypoglycemia and Annualized Mortality Rates Within Treatment Groups: ACCORD

Requiring Any Assistance, Medical or Non-medical (HA)†

Requiring Medical Assistance (HMA)‡

Mortality Rate (n=451 deaths)

Left chart (Percent (%) per Year):
- ≥1: Standard 3.7 (n=21/564*), Intensive 2.8 (n=53/1924*)
- None: Standard 1.0 (n=176/17297*), Intensive 1.2 (n=201/16315*)

Right chart (Percent (%) per Year):
- >1: Standard 4.9 (n=17/345*), Intensive 2.9 (n=34/1208*)
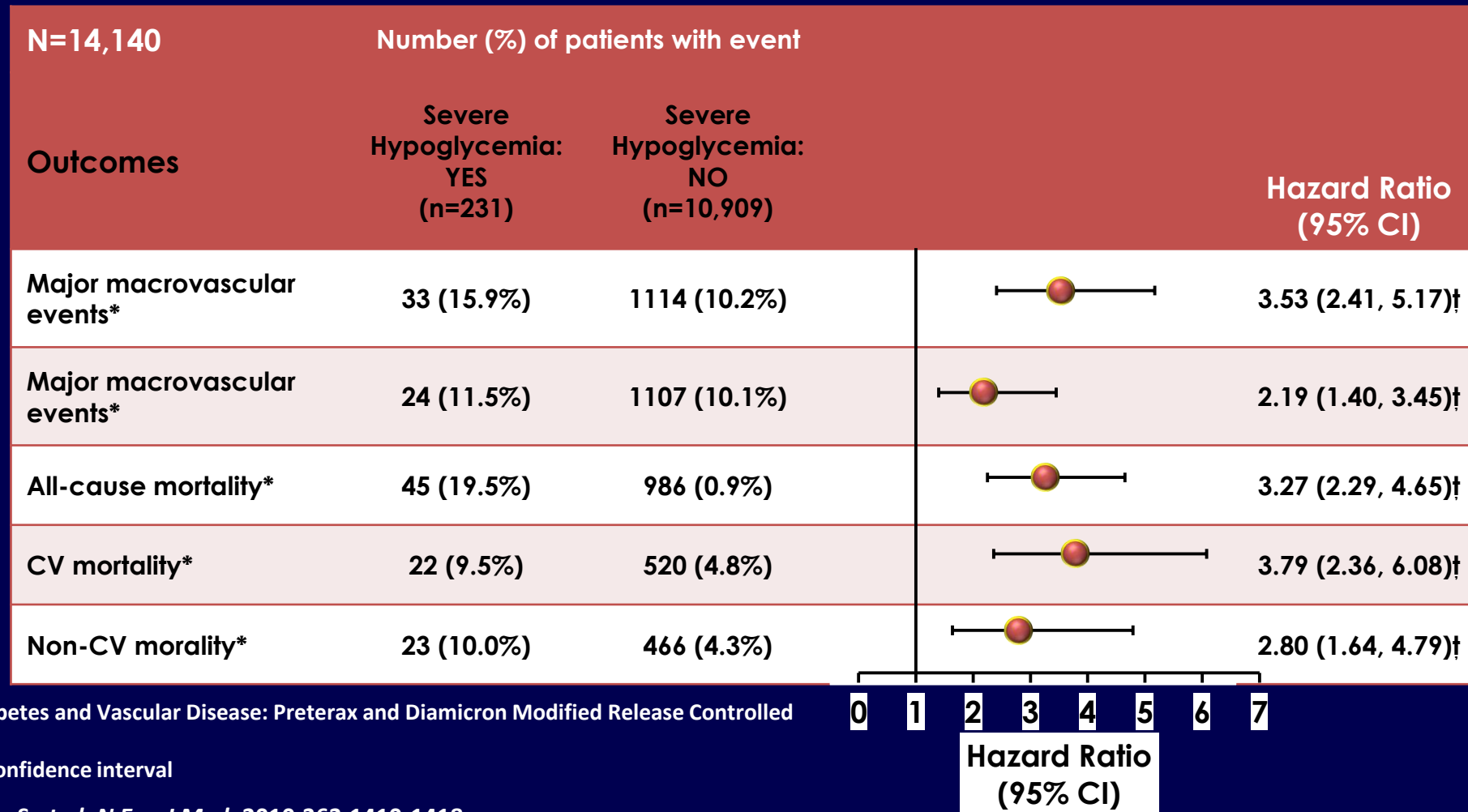- None: Standard 1.0 (n=180/17516*), Intensive 1.3 (n=220/17031*)

* Person-years
† $p = .076$ for interaction between history of hypoglycemia requiring any assistance and glycemia intervention
‡ $p = .009$ for interaction between history of hypoglycemia requiring medical assistance and glycemia intervention

Adapted from: Bonds DE, et al. *BMJ*. 2010;340:b4909.

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Influence of Severe Hypoglycemia on Cardiovascular Events: ADVANCE Study

N=14,140	Number (%) of patients with event		Hazard Ratio (95% CI)
Outcomes	Severe Hypoglycemia: YES (n=231)	Severe Hypoglycemia: NO (n=10,909)	
Major macrovascular events*	33 (15.9%)	1114 (10.2%)	3.53 (2.41, 5.17)ʈ
Major macrovascular events*	24 (11.5%)	1107 (10.1%)	2.19 (1.40, 3.45)ʈ
All-cause mortality*	45 (19.5%)	986 (0.9%)	3.27 (2.29, 4.65)ʈ
CV mortality*	22 (9.5%)	520 (4.8%)	3.79 (2.36, 6.08)ʈ
Non-CV morality*	23 (10.0%)	466 (4.3%)	2.80 (1.64, 4.79)ʈ

Hazard Ratio (95% CI) — axis: 0 1 2 3 4 5 6 7

* **Adjusted model**

ADVANCE=Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE);
CV=cardiovascular; CI=confidence interval

ʈ $p < .001$

Adapted from: Zoungas S *et al. N Eng J Med*. 2010;363:1410-1418.

How Might Acute Hypoglycemia Cause Death?

- Increases in the QTc interval[1]
  - Associated with episodes of nocturnal hypoglycemia in patients with type 1 diabetes[2]

- Activates proinflammatory molecules
  - ICAM-1, VCAM-1, E-selectin, VEGF, IL-6[3,4]

- Increases platelet activation[3]

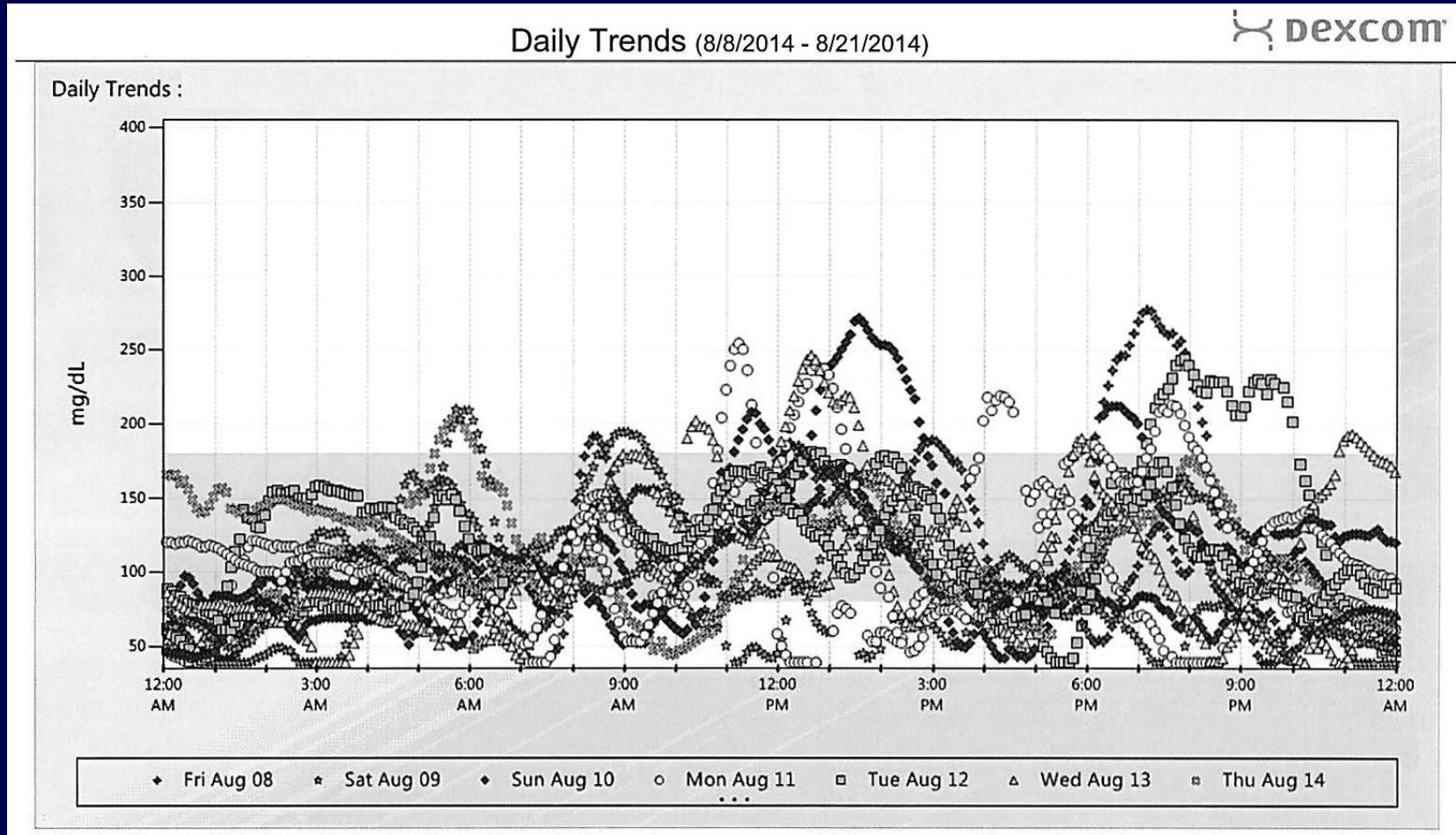- Decreases systemic fibrinolytic balance by increasing in PAI-1[4]

Adapted from:
1. Marques JBL, *et al*. *Diabetic Med.* 1997;14:648–654.
2. Murphy NP, et al. *Diabetologia.* 2004;47:1940–1947.
3. Giménez M, et al. *Diabetes Care*. 2011;34:198-203.
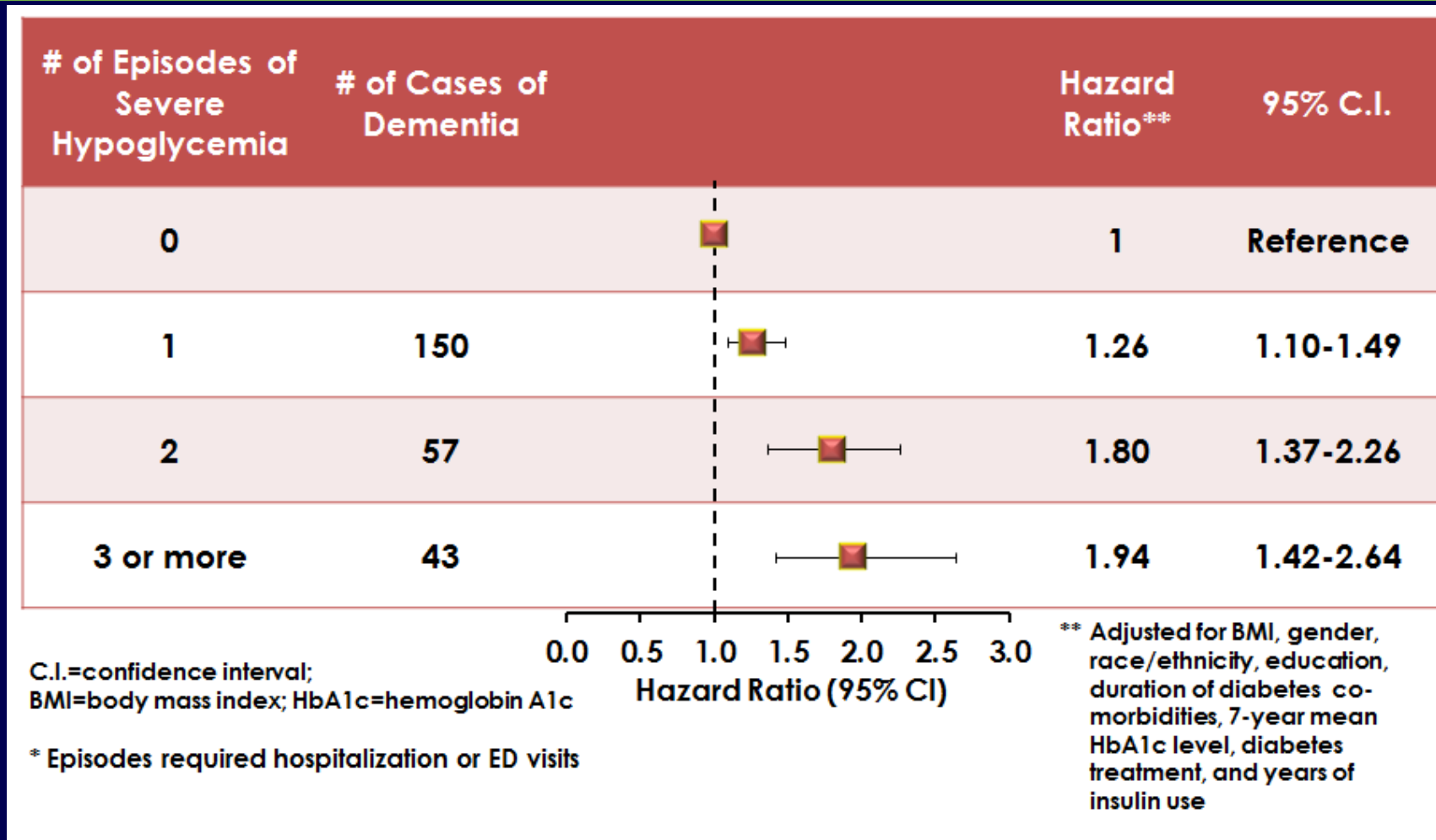4. Gogitidze-Joy N , et al. *Diabetes Care*. 2010;33:1529-1535.

Hypoglycemia Associated Autonomic Failure (HAAF)

- Defined as attenuation of the sympathoadrenal response to hypoglycemia that leads to impaired awareness of hypoglycemia which increases the risk for severe hypoglycemia.

- It is often induced by antecedent hypoglycemia.

- The diagnosis is made generally made clinically, based on the patient's subjective sense of a reduction in symptoms of hypoglycemia.

- This impaired awareness is reversible by 2 – 3 weeks of hypoglycemia avoidance.

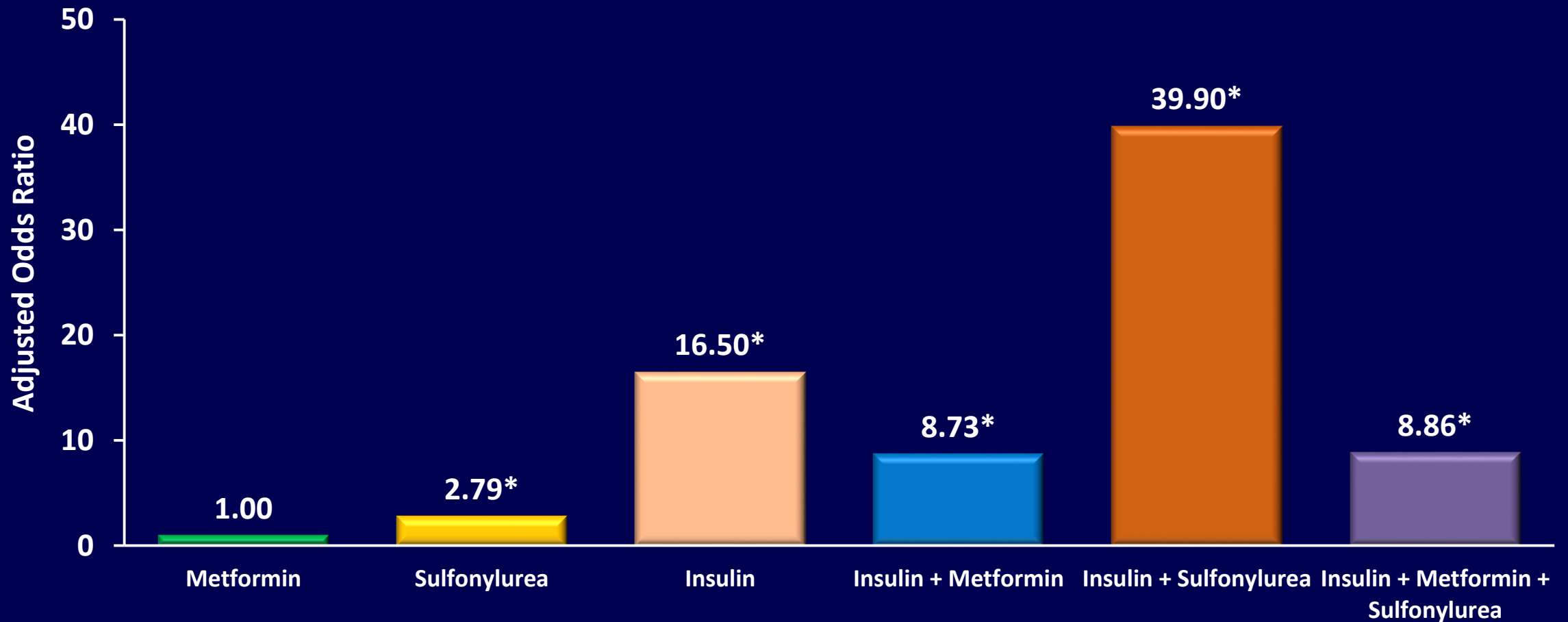- Educational programs exist to help patients restore their sense of lows.

Case: Hypoglycemia

Severe Hypoglycemia* Increases Risk of Dementia

# of Episodes of Severe Hypoglycemia	# of Cases of Dementia	Hazard Ratio**	95% C.I.
0		1	Reference
1	150	1.26	1.10-1.49
2	57	1.80	1.37-2.26
3 or more	43	1.94	1.42-2.64

Hazard Ratio (95% CI)
0.0 0.5 1.0 1.5 2.0 2.5 3.0

C.I.=confidence interval;
BMI=body mass index; HbA1c=hemoglobin A1c

* Episodes required hospitalization or ED visits

** Adjusted for BMI, gender, race/ethnicity, education, duration of diabetes co-morbidities, 7-year mean HbA1c level, diabetes treatment, and years of insulin use

Pharmacologic Intervention and Hypoglycemia in Patients with Type 2 Diabetes

Adapted from: Marques JBs, et al. Diabetic Med. 2017;14:648–654.

* $p < .0001$ compared to metformin (reference 1.00)

Pharmacologic Intervention and Hypoglycemia in Patients with Type 2 Diabetes (cont'd)

Class	Relative HbA1c Lowering	Hypoglycemia	Other Therapeutic Considerations
Alpha-glucosidase inhibitor (acarbose)	↓	Rare	Improved post-prandial control; GI side effects
Incretin agents: DPP-4 inhibitor GLP-1 receptor agonists	↓↓ ↓↓ to ↓↓↓	Rare Rare	GI side effects
SGLT2 inhibitors	↓↓	Rare	Genitourinary infections; polyuria; volume depletion; increase in LDL-C; increase in creatinine
Insulin	↓↓↓	Yes	No dose ceiling; flexible regimens
Insulin secretagogue: Meglitinide Sulfonylurea	↓↓ ↓↓	Yes Yes	Less hypoglycemia in context of missed meals but requires 3-4X/day dosing
Thiazolidinedione	↓	Rare	CHF, edema, fractures, rare bladder cancer, CV implications; 6-12 weeks required for maximal effect

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Case Study #1

- **CURRENT ASSESSMENT:**
    - 68-year-old woman with a 9-year history of T2DM
    - HbA1c levels are <7.0%
    - Mild episodes of hypoglycemia and one recent severe episode
    - History of AF (controlled with warfarin 2.5 mg once daily)
- **GOALS OF TREATMENT:**
    - Maintain HbA1c levels <7.0%
    - Reduce hypoglycemic events
- **WHAT IS THE RISK OF ANOTHER HYPOGLYCEMIC EPISODE FOR THIS PATIENT?**
- **WHAT IS THE NEXT STEP IN THIS PATIENT'S TREATMENT PLAN?**

Case Study #2:

Intensification of Treatment Beyond Basal Insulin: Which Therapy for Whom?

Case Study #2

- **INTRODUCTION:** EJ is a 76-year old Caucasian male with h/o of T2DM and HTN. He comes in for a 6-month follow-up exam

- **PAST MEDICAL HISTORY:**
  - Diagnosed w/ T2DM 13-years ago (A1C, 10.4%; FPG, 218 mg/dL); prescribed metformin and increase in physical activity
  - Reduced weight by 18 lbs
  - HbA1c declined to 9.4% after adding glipizide (target of 8.0%)
  - Started basal insulin (NPH 10 units once daily at bedtime, titrating to 22 units once daily at bedtime)
  - Complains of difficulty reading the newspaper due to poor vision

Case Study #2 (cont'd)

- **SOCIAL HISTORY:** Retired; widower; quit smoking 6 years ago; 1-2 glasses of wine w/ dinner 3X/week; no illicit drug use; on Medicare and lives off his Social Security check every month; stopped walking after wife died

- **PHYSICAL EXAM**: SBP/DBP, 132/87 mmHg; pulse, 69 bpm; height 5'8" (180 cm); weight, 194 lb (88.2 kg); BMI, 28.6 kg/m^2

- **LABORATORY RESULTS:**
  - SMA-6, WNL
  - A1C, 8.3%
  - FPG, 167 mg/dL

Case Study #2 (cont'd)

- **MEDICATIONS:**
  - Metformin 1000 mg/glipizide 10 mg once daily
  - Aspirin 81 mg once daily
  - Ramipril 10 mg once daily
  - Insulin detemir 22 units once daily at bedtime
  - Agreed to start on liraglutide 0.6 mg once daily, but could not tolerate the drug due to excessive nausea

What considerations should you to take into account for the management of this patient?

Insufficiency of Oral + Basal Insulin Treatment

- 50% of patients using basal insulin do not reach an A1C target at initiation and with titration of dose(s)[1,2]

- Natural history of pancreatic disease in type 2 diabetes, with expected further degradation of glycemic control requiring additional pharmacologic intervention(s) [3]

- Very high dose of basal insulin without significant effect on FBG[3]

  - Weight gain

  - Hypoglycemic risk during titration of basal insulin, making difficult to reach FBG target

1. Riddle M, *et al. Treat To Target. Diabetes Care* 2003;28:2080-2086.
2. Giugliano D, et al. *Diab Res Clin Prac*. 2011;92:1–10.
3. Monnier et al. Diab Metab. 2006;32:7-13.

Severe Hypoglycemia Associated With Increased Risk of Mortality and CV Events

Event	O.R.	95% CI	ADVANCE[1]		p-value
Macrovascular	3.45	2.34, 5.08			< .001
All-cause mortality	3.30	2.31, 4.72			<.001
CV mortality	3.78	2.34, 4.11			<.001
Non-CV mortality	2.86	1.67, 4.90			<.001
			VADT[2]		
Macrovascular	3.30	2.31, 4.72			<.001
All-cause mortality	3.78	2.34, 4.11			<.001
CV mortality	2.86	1.67, 4.90			<.001

Odds Ratio (O.R.) (95% C.I.)

CV=cardiovascular; C.I.=confidence interval

Adapted from: 1. Zoungas S, *et al. N Eng J Med*. 2010; 363:1410-1418. 2. Duckworth W, et al. *N Engl J Med*. 2009;360:129-139.

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Treatment Regimens with Basal Insulin Analogues and A1C Target of <7% in Type 2 Diabetes:
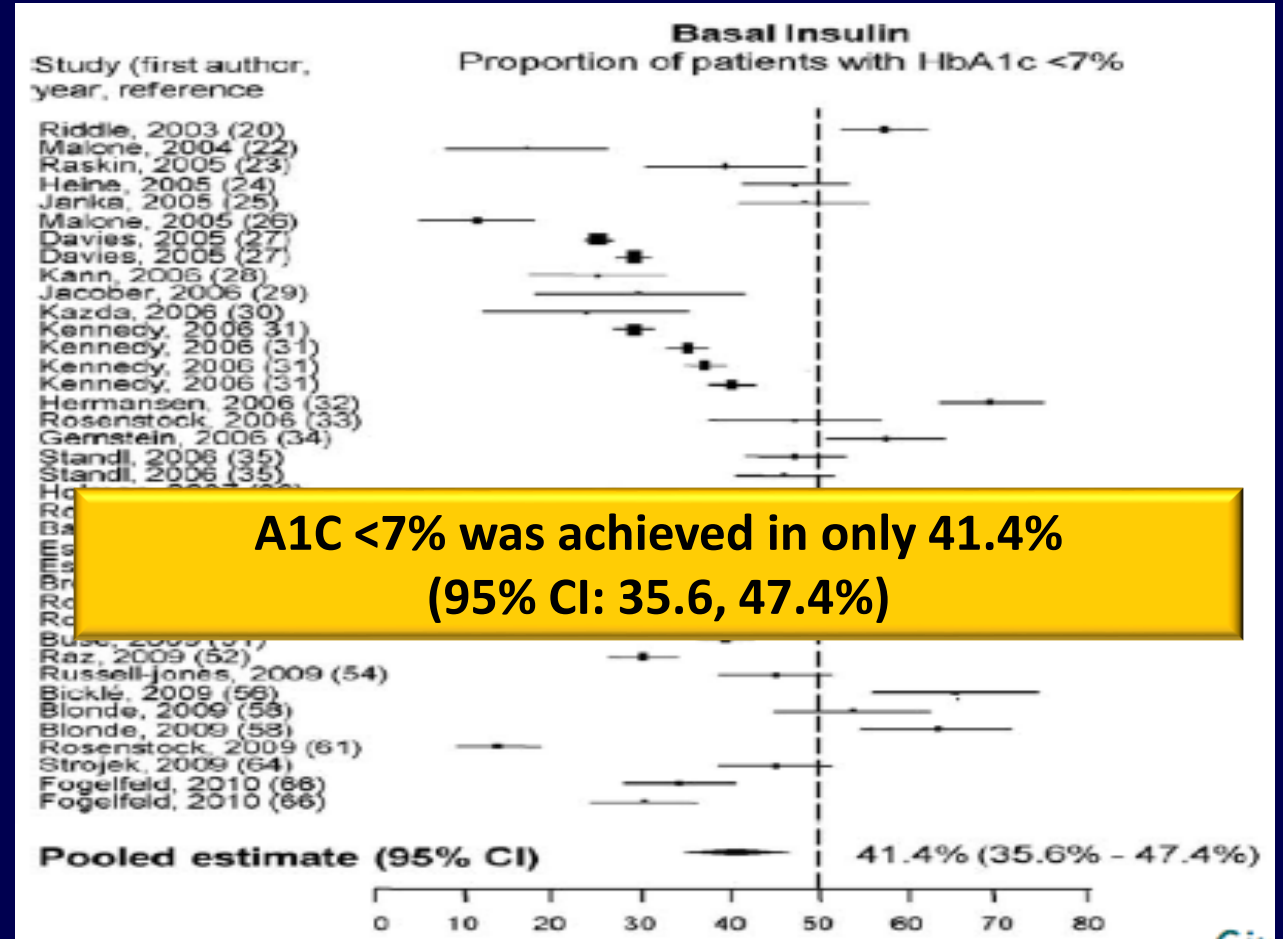## *A Systematic Review*

29 trials, with 17,588 patients

Predictor of Response:
- First insulin treatment
- Lower insulin dose
- Use of 2 oral drugs

Adverse Events
- Hypoglycemia: ranged from 0 to 4.71 events/patient per 30 days
- Weight gain: ~1.75 kg

Basal Insulin
Proportion of patients with HbA1c <7%

Study (first author, year, reference

Riddle, 2003 (20)
Malone, 2004 (22)
Raskin, 2005 (23)
Heine, 2005 (24)
Janka, 2005 (25)
Malone, 2005 (26)
Davies, 2005 (27)
Davies, 2005 (27)
Kann, 2006 (28)
Jacober, 2006 (29)
Kazda, 2006 (30)
Kennedy, 2006 (31)
Kennedy, 2006 (31)
Kennedy, 2006 (31)
Kennedy, 2006 (31)
Hermansen, 2006 (32)
Rosenstock, 2006 (33)
Gerstein, 2006 (34)
Standl, 2006 (35)
Standl, 2006 (35)
Busc, 2009 (51)
Raz, 2009 (52)
Russell-Jones, 2009 (54)
Bickle, 2009 (58)
Blonde, 2009 (58)
Blonde, 2009 (58)
Rosenstock, 2009 (61)
Strojek, 2009 (64)
Fogelfeld, 2010 (66)
Fogelfeld, 2010 (66)

A1C <7% was achieved in only 41.4% (95% CI: 35.6, 47.4%)

Pooled estimate (95% CI)   41.4% (35.6% – 47.4%)

0   10   20   30   40   50   60   70   80

Giugliano D, et al. *Diab Res Clin Prac*. 2011;92:1–10.

When Basal is Not Enough: Strategies to Optimize Insulin Therapy to Achieve and Maintain Glycemic Control

Recommended Treatment Goals[2]

A1C	<7.0%
Preprandial PG	70–130 mg/dL
2-Hour postprandial PG	<180 mg/dL

Basal plus

- GLP-1 RA
- DPP4 inhibitors
- SGLT-2 Inhibitors

Basal-Bolus
Add prandial insulin before 3 meals

Basal Plus Two (or Premix)
Rapid-acting analog at 2 main meals

Basal Plus One (or Premix)
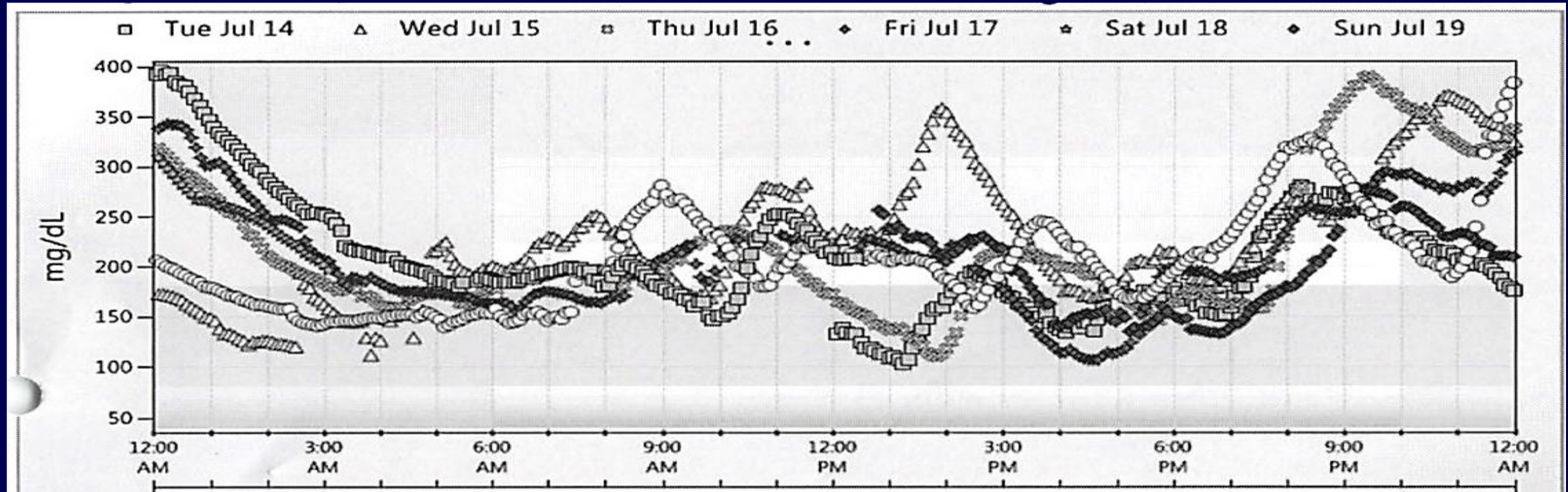Rapid-acting analog at main meal

If not controlled after FBG target is reached (or if basal insulin dose >0.5 U/kg/day)
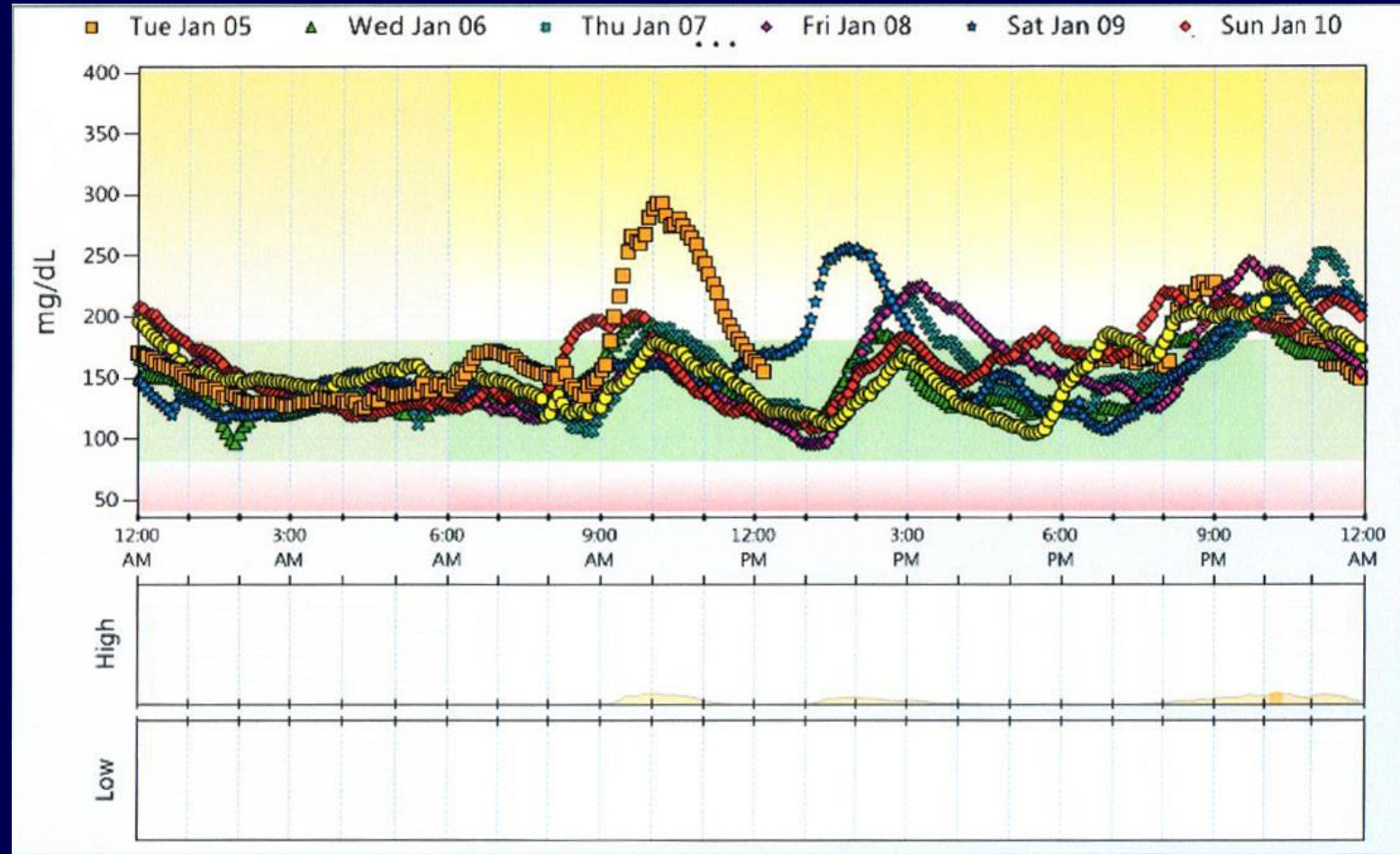
Add basal insulin and titrate

Lifestyle changes plus oral antidiabetic medications:
Metformin ± agents

Adapted from: 1. Raccah D, et al. *Diabetes Metab Res Rev.* 2007;23:257–264. 2.Inzucchi SE, et al. Diabetes Care 2015;38:140–149.

Patient Before

Patient After

Combining GLP-1 RAs and Basal Insulin

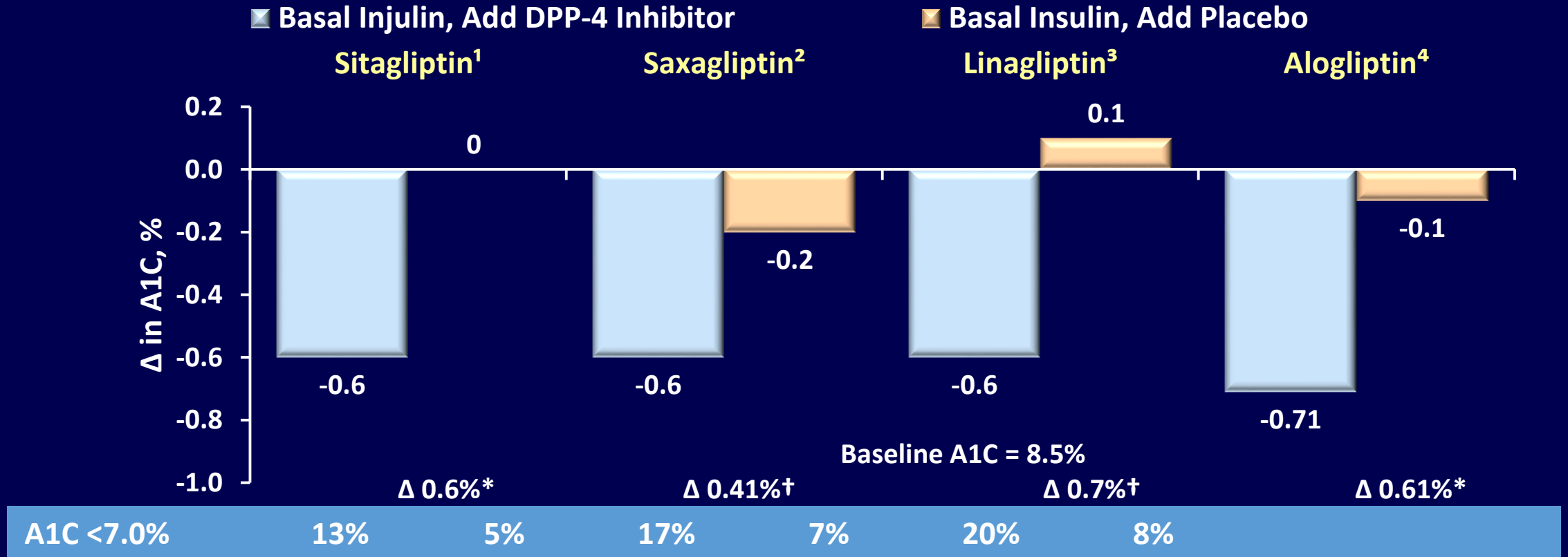| Outcome	GLP-1 RA Added to Basal Insulin[1]		Basal Insulin Added to GLP-1 RA[2]	
Outcome	Exenatide BID	Placebo	Detemir + Liraglutide	Liraglutide
A1C, %	-1.70*	-1.00	-0.50*	0.02
Weigh, %	-1.78*	0.96	-0.16*	-0.95
Minor hypoglycemia, %	25	29	9.2	1.3

- GLP-1 RAs and basal insulin in combination improved glycemic control versus monotherapy components, regardless of the order of addition[1-3]
- Body weight, body mass index, and blood pressure reductions only when exenatide was added to basal insulin[3]
- Consider lowering the dose of basal insulin when GLP-1 RAs are added to decrease the risk of hypoglycemia[4]

* $p = .05$

GLP-1 RA=glucagon-like peptide receptor agonist

1. Buse JB, et al. *Ann Intern Med*. 2011;154:103-112. 2. DeVries J, et al. *Diabetes Care*. 2012;3:1446-145. 3. Pawaskar M, et al. *Endocr Pract*. 2012;18:796-711. 4. Inzucchi SE, et al. *Diabetes Care*. 2015;38:140–149.
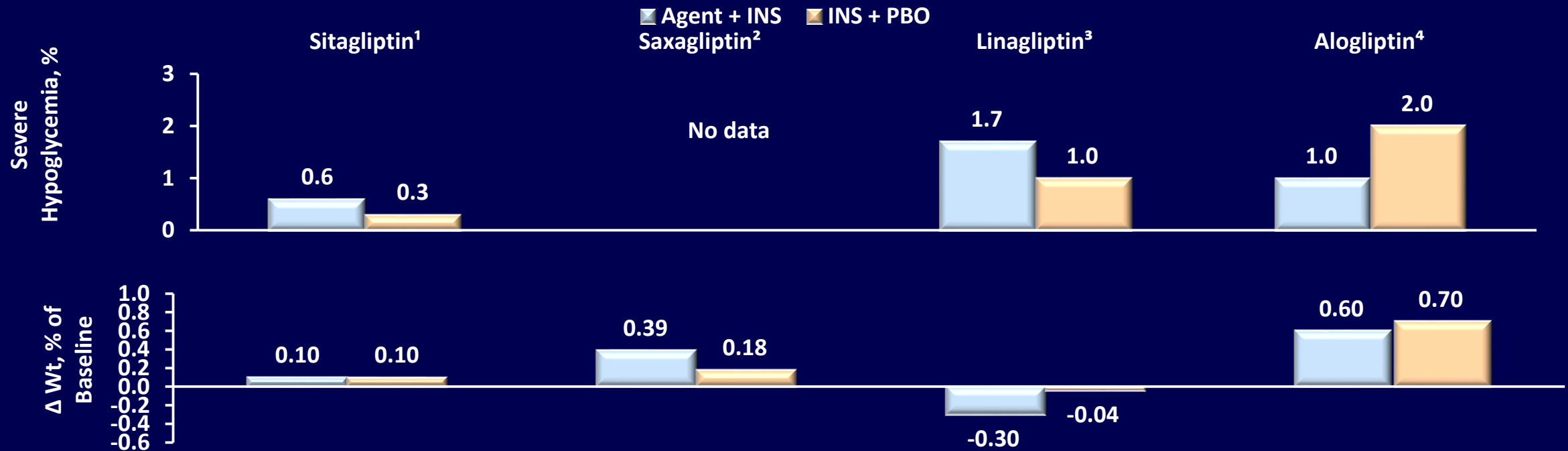
DPP-4 Inhibitors as Add-on Therapy to Basal Insulin (With or Without Oral Agents)

Basal Injulin, Add DPP-4 Inhibitor
Basal Insulin, Add Placebo

	Sitagliptin[1]		Saxagliptin[2]		Linagliptin[3]		Alogliptin[4]	

Δ in A1C, %

0.2 — 0.0 — -0.2 — -0.4 — -0.6 — -0.8 — -1.0

Sitagliptin: -0.6, 0
Saxagliptin: -0.6, -0.2
Linagliptin: -0.6, 0.1
Alogliptin: -0.71, -0.1

Baseline A1C = 8.5%

Δ 0.6%*   Δ 0.41%†   Δ 0.7%†   Δ 0.61%*

A1C <7.0%	13%	5%	17%	7%	20%	8%

*p < 0.001; †p < 0.0001

1. Vilsbøll T, et al. *Diabetes Obes Metab*. 2010;12:167-177. 2. Barnett AH, et al. *Curr Med Res Opin*. 2012;28:513-523. 3. Yki-Järvinen H, et al. *Diabetes Care*. 2013;36:3875-3881. 4. Rosenstock J, et al. *Diabetes Obes Metab*. 2009;11:1145-1152.

DPP-4 Inhibitors and Basal Insulin: Low Risk of Severe Hypoglycemia or Weight Gain
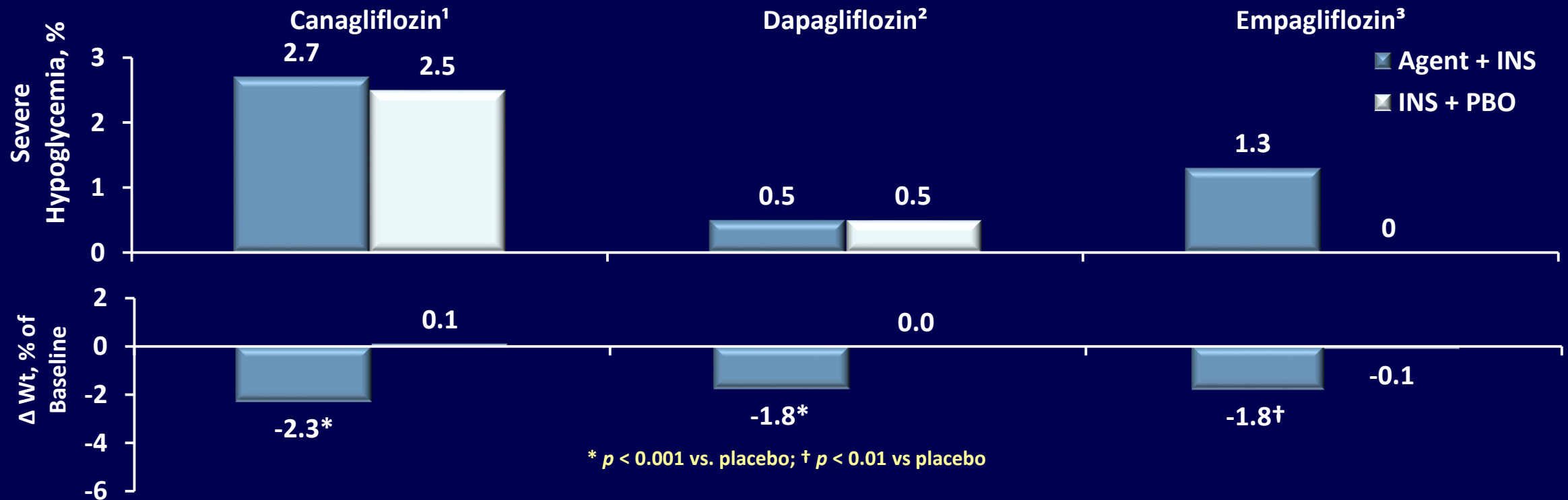

Legend: ■ Agent + INS ■ INS + PBO

Severe Hypoglycemia, % chart:
- Sitagliptin[1]: Agent + INS = 0.6, INS + PBO = 0.3
- Saxagliptin[2]: No data
- Linagliptin[3]: Agent + INS = 1.7, INS + PBO = 1.0
- Alogliptin[4]: Agent + INS = 1.0, INS + PBO = 2.0

Δ Wt, % of Baseline chart:
- Sitagliptin: Agent + INS = 0.10, INS + PBO = 0.10
- Saxagliptin: Agent + INS = 0.39, INS + PBO = 0.18
- Linagliptin: Agent + INS = -0.30, INS + PBO = -0.04
- Alogliptin: Agent + INS = 0.60, INS + PBO = 0.70

The proportion of patients attaining A1C <7% with sitagliptin, alogliptin, or linagliptin in combination with basal insulin ranged from 8% to 20%;[1] no data for saxagliptin

1. Vilsbøll T, et al. *Diabetes Obes Metab*. 2010;12:167-177. 2. Barnett AH, et al. *Curr Med Res Opin*. 2012;28:513-523. 3. Yki-Järvinen H, et al. *Diabetes Care*. 2013;36:3875-3881.
4. Rosenstock J, et al. *Diabetes Obes Metab*. 2009;11:1145-1152.

# SGLT2 Inhibitors and Basal Insulin (INS): Impact on Hypoglycemia and Body Weight

Proportion of patients attaining A1C <7% with SGLT-2 inhibitors, in combination with basal insulin, ranged from 11% to 25%[1-3]
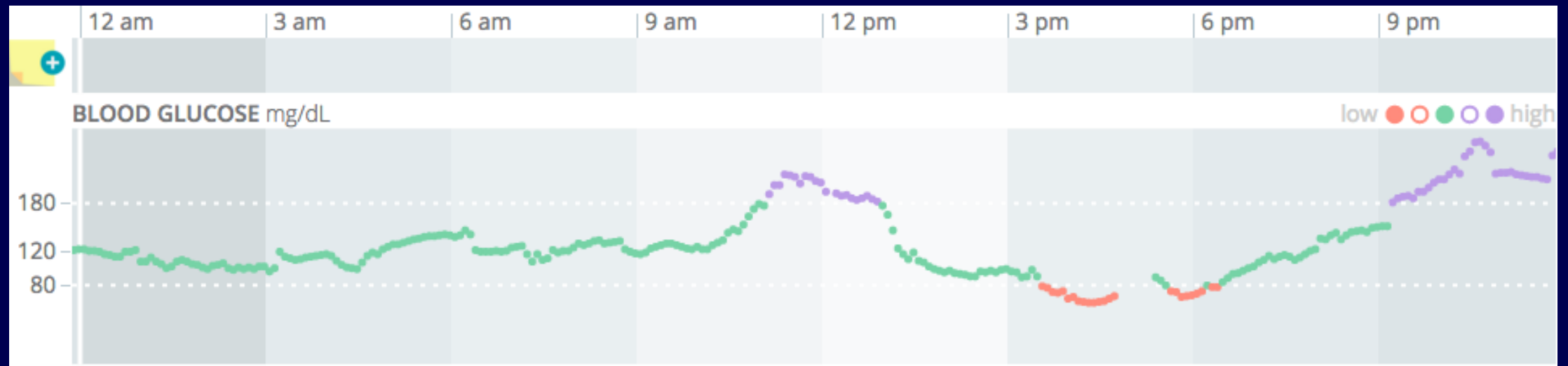

Canagliflozin[1] Dapagliflozin[2] Empagliflozin[3]

Severe Hypoglycemia, %

2.7   2.5   0.5   0.5   1.3   0

■ Agent + INS
■ INS + PBO

Δ Wt, % of Baseline

0.1   0.0   -0.1

-2.3*   -1.8*   -1.8†

*p < 0.001 vs. placebo; † p < 0.01 vs placebo

1. Neal B, et al. *Diabetes Care*. 2015;38:403-411. 2. Cefalu WT, et al. *Diabetes Care*. 2015;38:1218-1227. 3.Rosenstock J, et al. *Diabetes Obes Metab*. 2015;17:936-948.
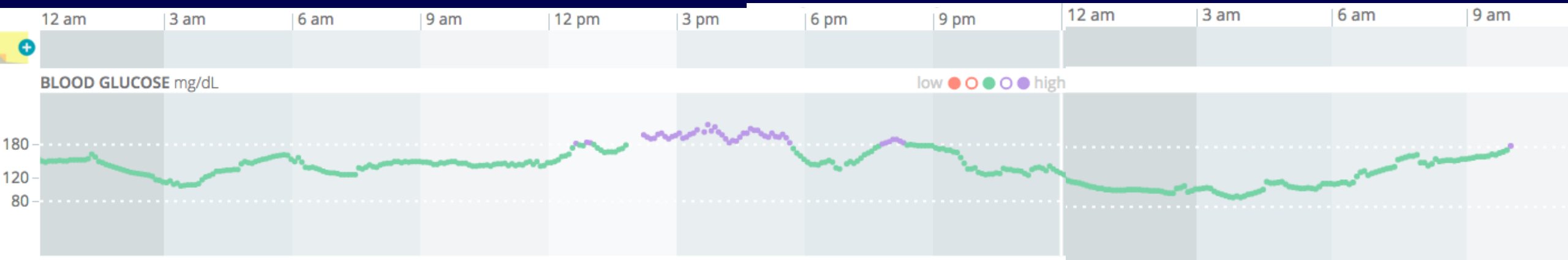
Blip Saga—Baseline
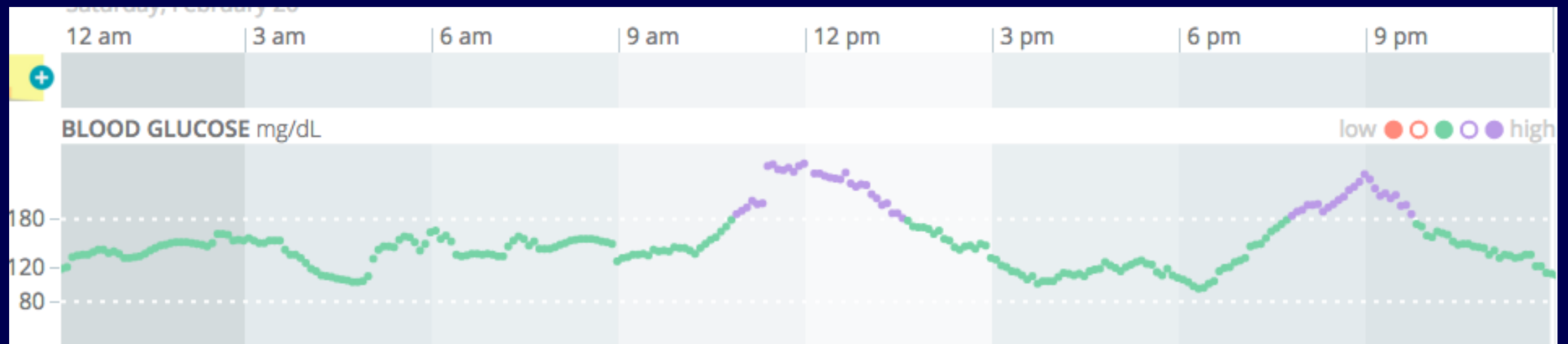
Blip Saga—Basal Insulin

Blip Saga—DPP-IV Restarted

Case Study #2

- **CURRENT ASSESSMENT:**
  - 76-year old male w/ T2DM and HTN
  - T2DM uncontrolled despite the addition of insulin
  - HTN controlled with medication

- **GOALS OF TREATMENT:**
  - Achieve a target A1C of 8.0%
  - Maintain a FPG of ≤140 mg/dL
  - Reduce body weight by 10%

- **WHAT IS THE TREATMENT PLAN??**

Panel Discussion
Anne L. Peters, MD and Thomas A. Buchanan, MD

Audience Q&A

Concluding Remarks
Jay S. Skyler, MD, MACP