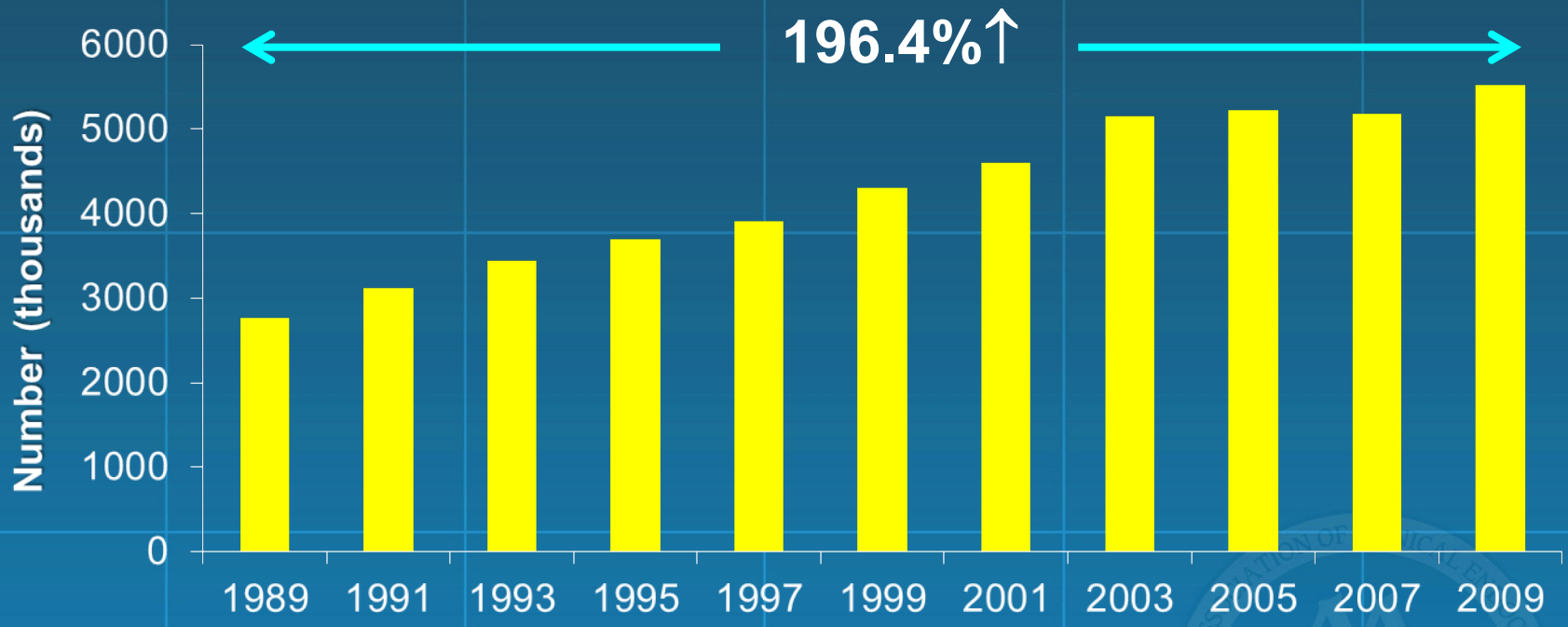
Management of Hyperglycemia in the Noncritical Care Setting

RECOGNITION AND DIAGNOSIS OF HYPERGLYCEMIA IN NONCRITICALLY ILL PATIENTS

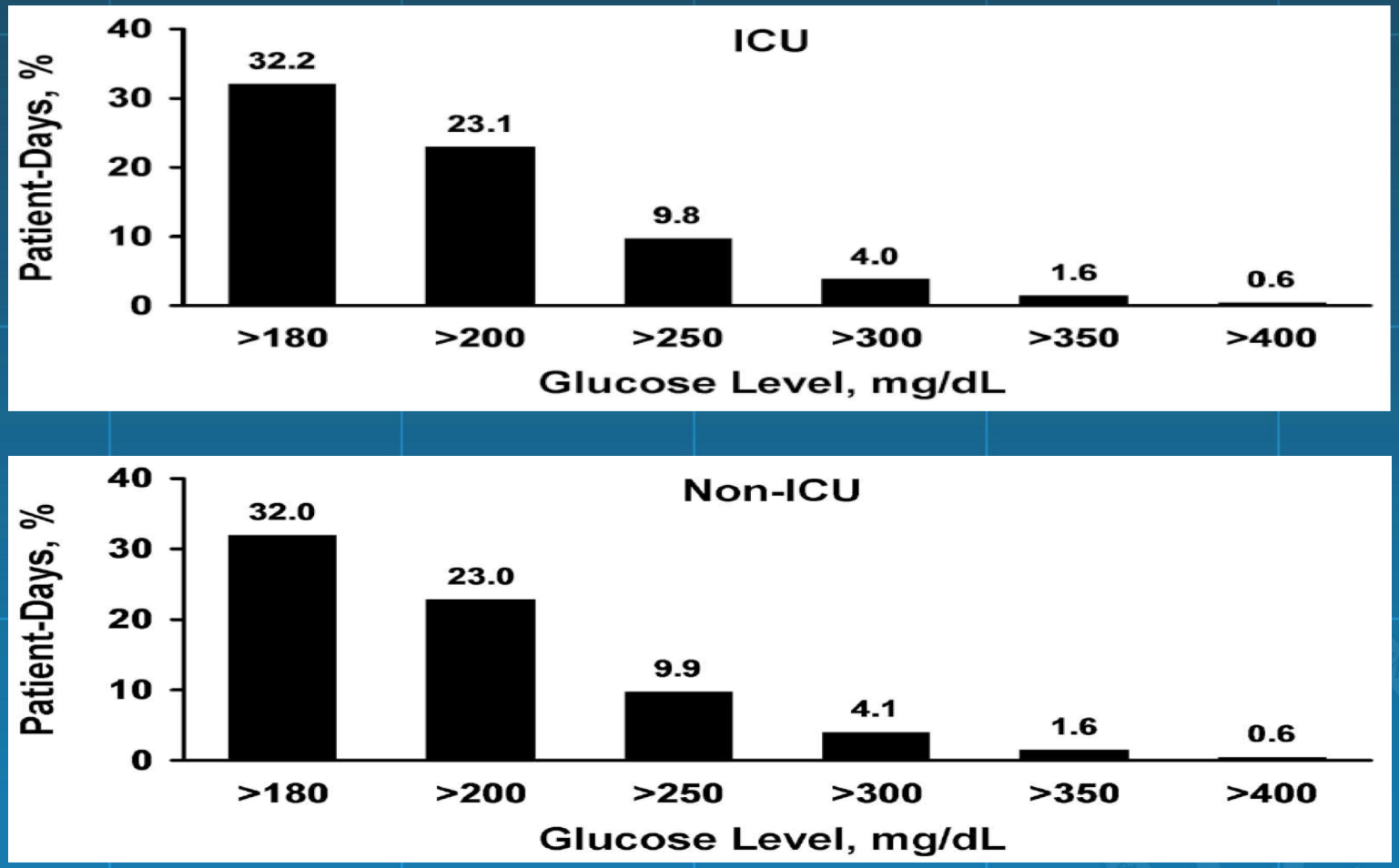
Number of US Hospital Discharges With Diabetes as Any-Listed Diagnosis



From 1988 to 2009, the number of hospital discharges with diabetes as any-listed diagnosis increased from 2.8 million to nearly 5.5 million.

CDCP. Diabetes Data and Trends. Available at: http://www.cdc.gov/diabetes/statistics/dmany/fig1.htm.

Distribution of Patient-Day-Weighted Mean POC-BG Values for ICU



~12 million BG readings from 653,359 ICU patients; mean POC-BG: 167 mg/dL.

Swanson CM, et al. *Endocr Pract*. 2011;17:853-861.

Recognition and Diagnosis of Hyperglycemia and Diabetes in the Hospital Setting

- All patients
  - Assess for history of diabetes
  - Test BG (using laboratory method) on admission independent of prior diagnosis of diabetes
- Patients without a history of diabetes
  - BG >140 mg/dL: Monitor with POC testing for 24-48 h
  - BG >140 mg/dL: Ongoing POC testing
  - Patients receiving therapies associated with hyperglycemia (eg, corticosteroids): monitor with POC testing for 24-48 h
    - BG >140 mg/dL: continue POC testing for duration of hospital stay
- Patients with known diabetes or with hyperglycemia
  - Test A1C if no A1C value is available from past 2-3 months

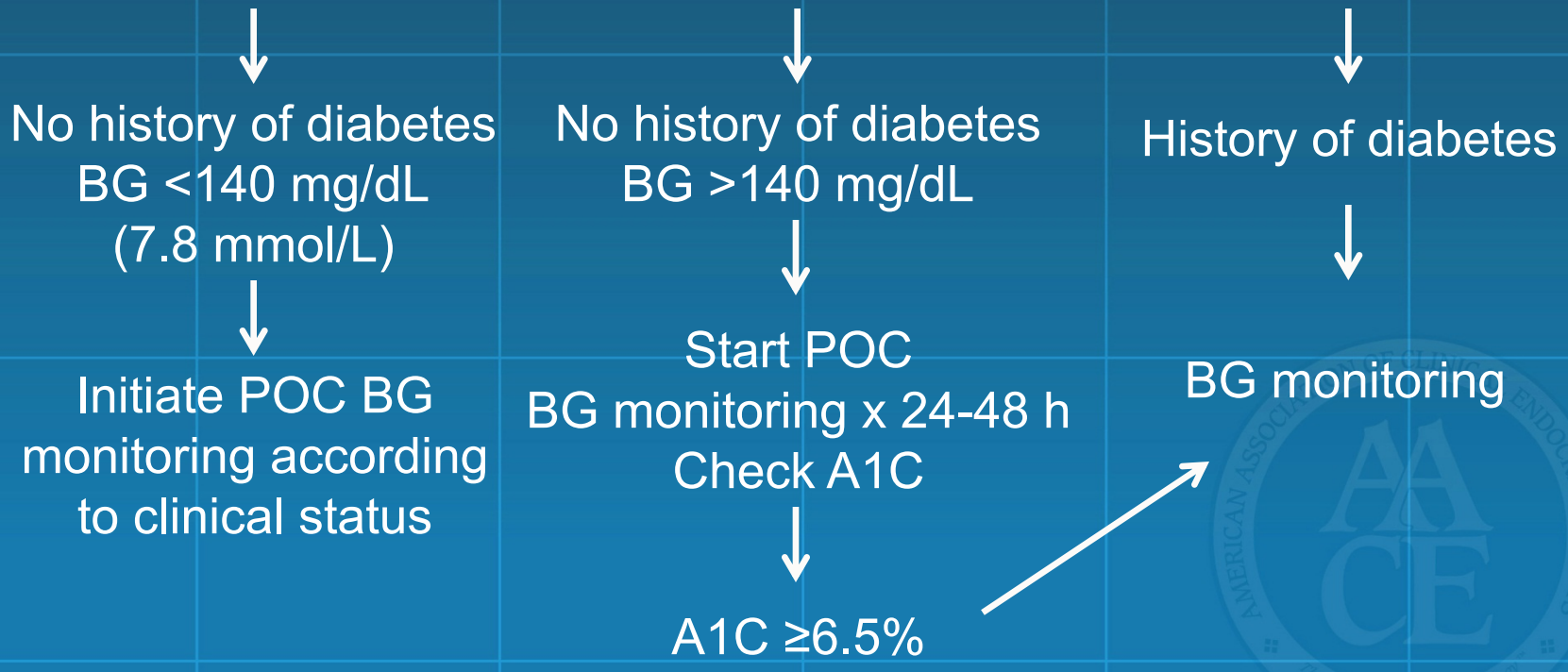
BG, blood glucose; POC, point of care.

Moghissi ES, et al. *Endocrine Pract.* 2009;15:353-369.
Umpierrez GE, et al. *J Clin Endocrinol Metab*. 2012;97:16-38.

Recognition and Diagnosis of Hyperglycemia and Diabetes in the Hospital Setting

Upon admission

- Assess all patients for a history of diabetes
- Obtain laboratory blood glucose testing



BG, blood glucose; POC, point of care.

Umpierrez GE, et al. *J Clin Endocrinol Metab*. 2012;97:16-38.

A1C for Diagnosis of Diabetes in the Hospital

- Implementation of A1C testing can be useful
  - Assist with differentiation of newly diagnosed diabetes from stress hyperglycemia
  - Assess glycemic control prior to admission
  - Facilitate design of an optimal regimen at the time of discharge
- A1C >6.5% indicates diabetes

Moghissi ES, et al. *Endocrine Pract.* 2009;15:353-369.
Umpierrez GE, et al. *J Clin Endocrinol Metab*. 2012;97:16-38.

Caveats to Using A1C for Diagnosis of Diabetes

- Values altered with several conditions
  - Hemoglobinopathies (eg, sickle cell disease)
  - High dose salicylates
  - Hemodialysis
  - Transfusions, iron deficiency anemia
- Analysis should be performed using a method certified by the National Glycohemoglobin Standardization program

Saudek CD, et al. *JAMA.* 2006;295:1688-1697.
ADA. *Diabetes Care*. 2013;36(suppl 1):S11-S66.

GLYCEMIC GOALS FOR NONCRITICALLY ILL PATIENTS

Inpatient Glycemic Management: Definition of Terms

Hospital hyperglycemia	Any BG >140 mg/dL
Stress hyperglycemia	Elevations in blood glucose levels that occur in patients with no prior history of diabetes and A1C levels that are not significantly elevated (<6.5%)
A1C value >6.5%	Suggestive of prior history of diabetes
Hypoglycemia	Any BG <70 mg/dL
Severe hypoglycemia	Any BG <40 mg/dL

Glycemic Targets in Noncritical Care Setting

- Maintain fasting and preprandial BG <140 mg/dL
- Modify therapy when BG <100 mg/dL to avoid risk of hypoglycemia
- Maintain random BG <180 mg/dL
- More stringent targets may be appropriate in stable patients with previous tight glycemic control
- Less stringent targets may be appropriate in terminally ill patients or in patients with severe comorbidities

Moghissi ES, et al. *Endocrine Pract.* 2009;15:353-369.
Umpierrez GE, et al. *J Clin Endocrinol Metab*. 2012;97:16-38.

Glucose Monitoring

ACHIEVING GLYCEMIC GOALS IN THE NONCRITICALLY ILL WHILE MINIMIZING HYPOGLYCEMIA RISK

Monitoring Glycemia in the Noncritical Care Setting

- POC testing
  - Preferred method for guiding ongoing glycemic management of individual patients
  - Use BG monitoring devices with demonstrated accuracy in acutely ill patients
  - Timing of glucose measures should match patient's nutritional intake and medication regimen
- Recommended schedules for POC testing
  - Before meals and at bedtime in patients who are eating
  - Every 4-6 h in patients who are NPO or receiving continuous enteral feeding

BG, blood glucose; POC, point of care.

Moghissi ES, et al. *Endocrine Pract.* 2009;15:353-369.
Umpierrez GE, et al. *J Clin Endocrinol Metab*. 2012;97:16-38.

Hospital Diet

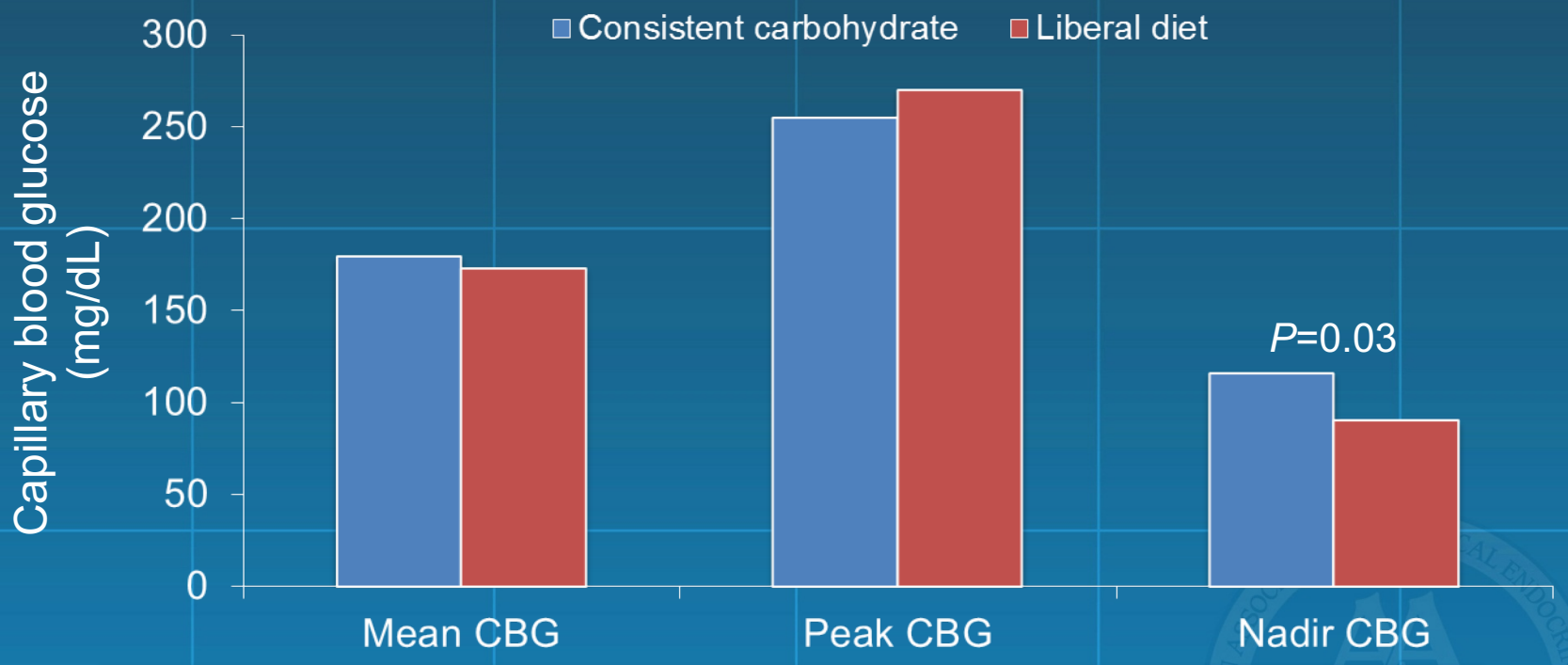
ACHIEVING GLYCEMIC GOALS IN THE NONCRITICALLY ILL WHILE MINIMIZING HYPOGLYCEMIA RISK

Medical Nutrition Therapy (MNT)

- MNT is an essential component of the glycemic management program for all hospitalized patients with diabetes and hyperglycemia
- Providing meals with a consistent amount of carbohydrate can be useful in coordinating doses of rapid-acting insulin to carbohydrate ingestion

Umpierrez GE, et al. *J Clin Endocrinol Metab*. 2012;97:16-38.

Glycemic Measures in Patients Assigned to Consistent Carbohydrate or Liberal Diets in the Hospital



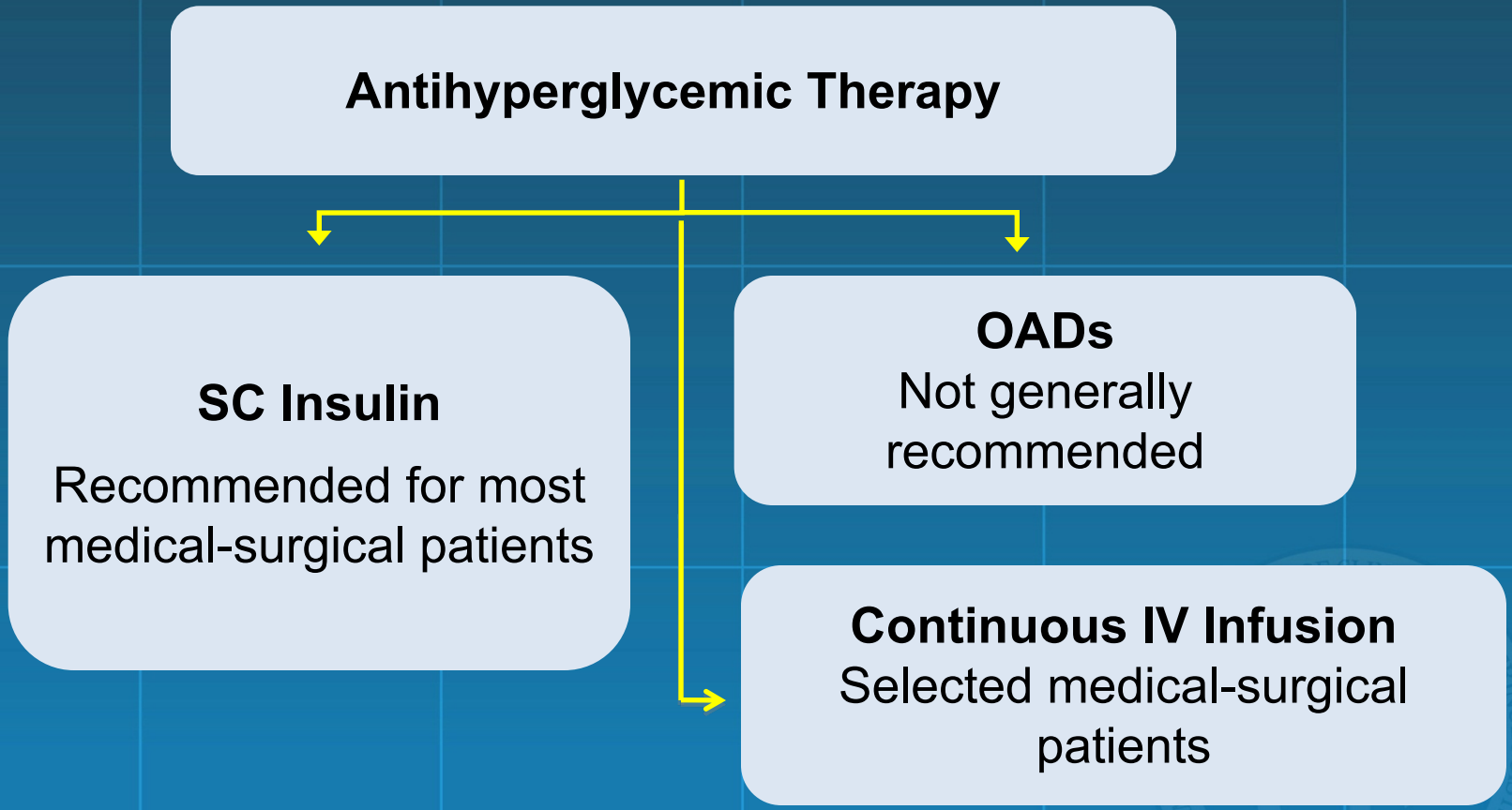
CBG values <70 mg/dL were less frequent in patients receiving the consistent carbohydrate diet (0.4 vs 3.2%, *P*=0.04)

Curll M, et al. *Qual Safety Health Care.* 2010;19:355-359.

Pharmacologic Therapy

ACHIEVING GLYCEMIC GOALS IN THE NONCRITICALLY ILL WHILE MINIMIZING HYPOGLYCEMIA RISK

Pharmacological Treatment of Hyperglycemia in Non-ICU Setting



Moghissi ES, et al. *Endocrine Pract.* 2009;15:353-369.
Umpierrez GE, et al. *J Clin Endocrinol Metab*. 2012;97:16-38.
Smiley D, et al. *J Hosp Med*. 2010;5:212-217.

Glycemic Management Strategies in Noncritically Ill Patients

- Insulin therapy preferred regardless of type of diabetes
  - Discontinue noninsulin agents at hospital admission of most patients with type 2 diabetes with acute illness
- Use scheduled SC insulin with basal, nutritional, and correction components
  - Modify insulin dose in patients treated with insulin before admission to reduce risk for hypoglycemia and hyperglycemia
- Avoid prolonged therapy with “sliding scale” insulin alone

Umpierrez GE, et al. *J Clin Endocrinol Metab*. 2012;97:16-38.

Noninsulin Therapies in the Hospital

- Time-action profiles of oral agents can result in delayed achievement of target glucose ranges in hospitalized patients
- Sulfonylureas are a major cause of prolonged hypoglycemia
- Metformin is contraindicated in patients with decreased renal function, use of iodinated contrast dye, and any state associated with poor tissue perfusion (CHF, sepsis)
- Thiazolidinediones are associated with edema and CHF
- α-Glucosidase inhibitors are weak glucose-lowering agents
- Pramlintide and GLP-1 receptor agonists can cause nausea and exert a greater effect on postprandial glucose
- DPP4 inhibitors may provide safe and effective blood glucose control when used alone or in combination with basal insulin

Insulin therapy is the preferred approach

Subcutaneous Insulin Options

Basal insulin	Controls blood glucose in the fasting state • Detemir (Levemir), glargine (Lantus), NPH
Nutritional (prandial) insulin	Blunts the rise in blood glucose following nutritional intake (meals, IV dextrose, enteral/parenteral nutrition) • Rapid-acting: aspart (NovoLog), glulisine (Apidra), lispro (Humalog) • Short-acting: regular (Humulin, Novolin)
Correction insulin	Corrects hyperglycemia due to mismatch of nutritional intake and/or illness-related factors and scheduled insulin administration

Initiating Insulin Therapy in the Hospital

Obtain patient weight in kg

↓

Calculate total daily dose (TDD)
as 0.2-0.4 units per kg/day

↓

Choose the dosing schedule

Give 50%-60% of TDD as basal insulin

Give 40%-50% of TDD as nutritional insulin

Use correction insulin for BG above goal range

↓

Adjust according to results of bedside glucose monitoring

Adjust dose for NPO status or changes in clinical status

Insulin Therapy in Patients With Type 2 Diabetes

- Discontinue noninsulin agents on admission
- Insulin naïve: starting total daily dose (TDD):
  - 0.3 U/kg to 0.5 U/kg
  - Lower doses in the elderly and patients with renal insufficiency
- Previous insulin therapy: reduce outpatient insulin dose by 20%-25%
- Half of TDD as basal insulin given at the same time of day and half as rapid-acting insulin in 3 equally divided doses (AC)

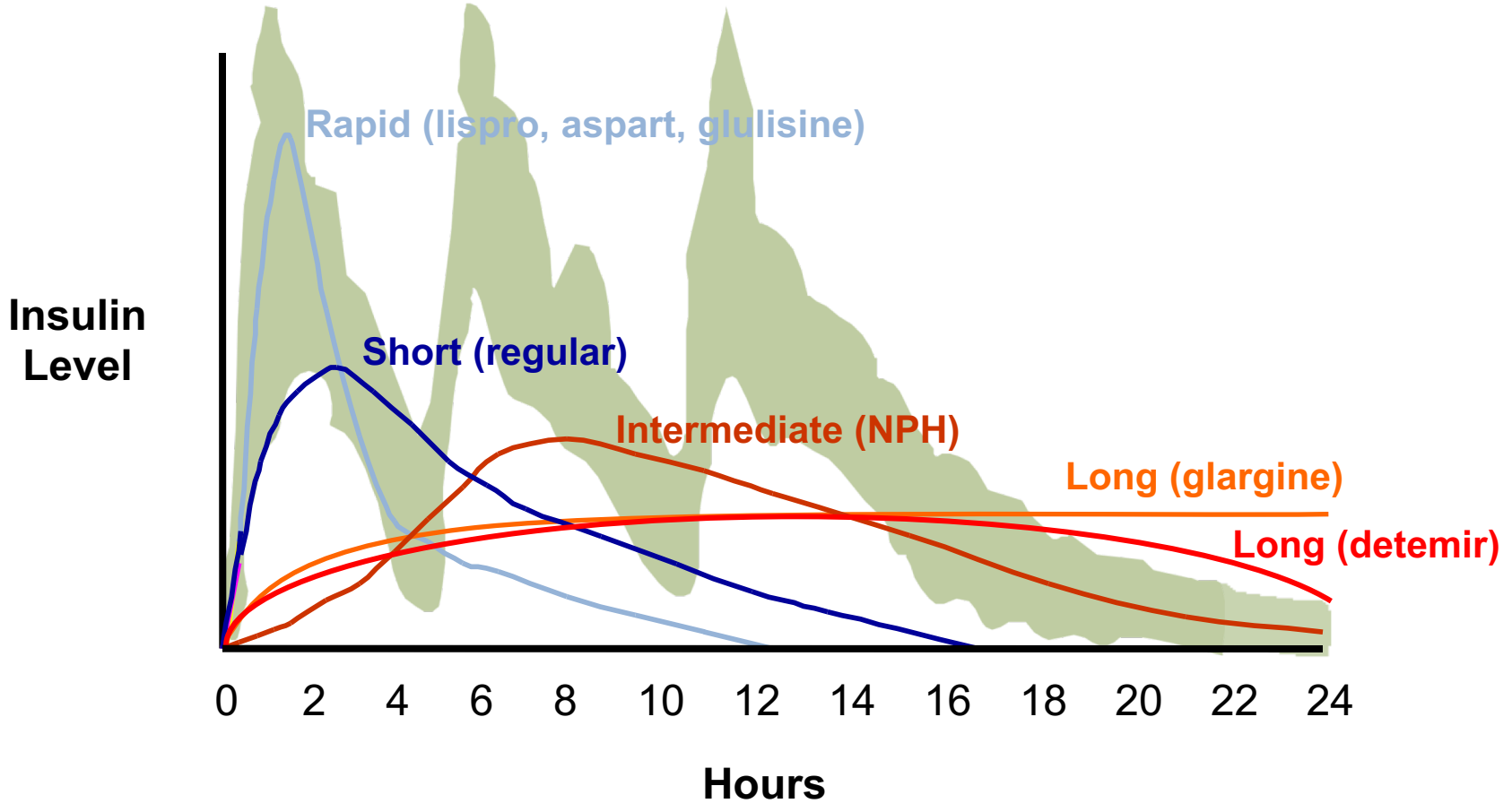
Umpierrez GE, et al. *Diabetes Care*. 2007;30:2181-2186.

Pharmacokinetics of Insulin Preparations

Insulin	Onset	Peak	Duration
Nutritional			
Rapid-acting analog (aspart, glulisine, lispro)	5-15 min	1-2 hours	4-6 hours
Regular	30-60 min	2-3 hours	6-10 hours
Basal			
Degludec	1 hour	Relatively peakless	>42 hours
Detemir U100	2 hours	Relatively peakless	16-24 hours
Detemir U200	2 hours	Relatively peakless	16-24 hours
Glargine U100	2-4 hours	Relatively peakless	20-24 hours
Glargine U300	6 hours	Relatively peakless	~32 hours
NPH	2-4 hours	4-10 hours	12-18 hours

Heise T. *Diabetes Obes Metab*. 2017;19:3-12. Hirsch I. *N Engl J Med*. 2005;352:174-183. Porcellati F, et al. *Diabetes Care*. 2007;30:2447-2552.

Pharmacokinetics of Insulin Products



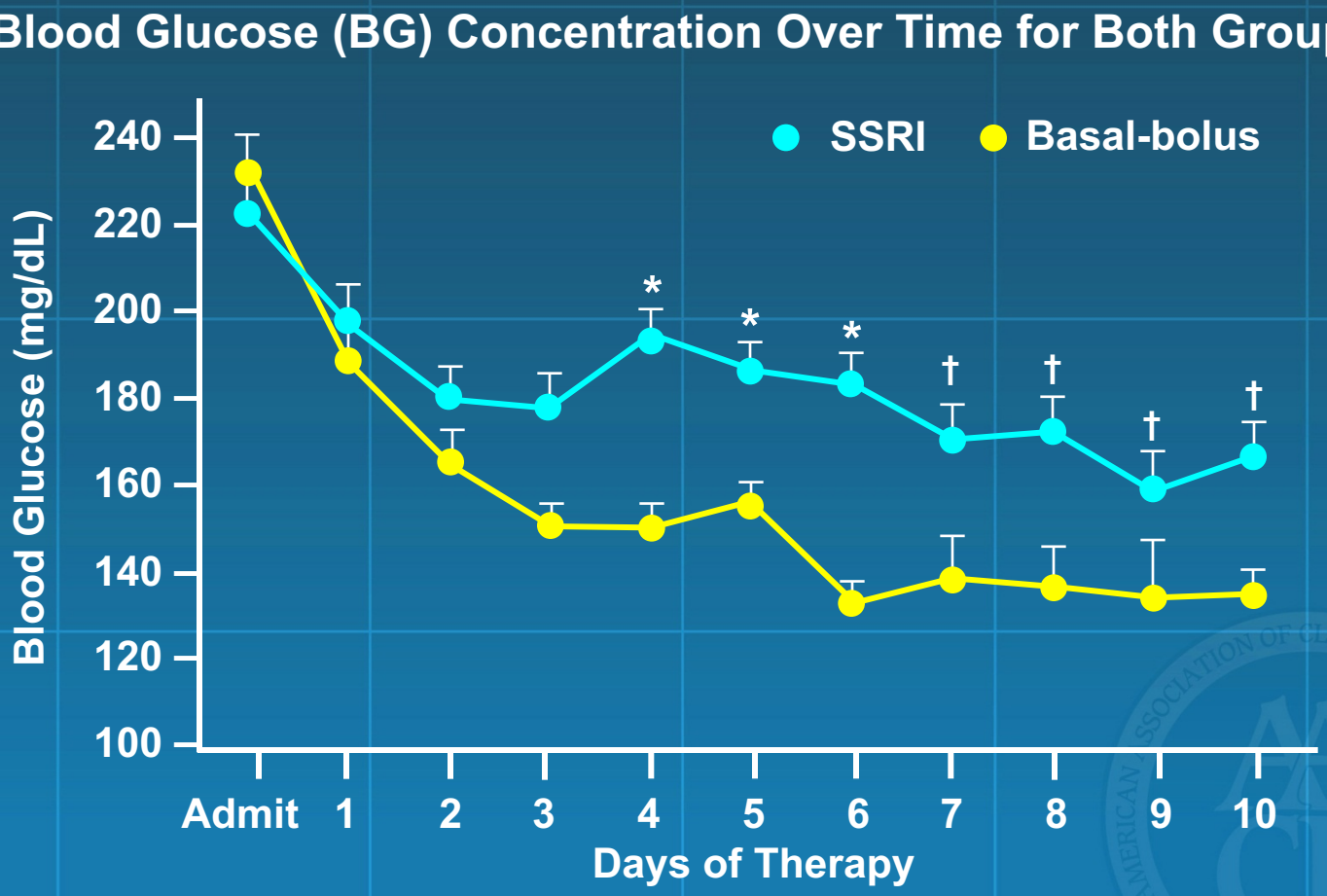
Adapted from Hirsch I. *N Engl J Med*. 2005;352:174–183.

Basal-Bolus Insulin Therapy in Inpatients With Type 2 Diabetes (RABBIT 2 Trial)

- 130 nonsurgical insulin-naïve patients age 18-80 with known type 2 diabetes admitted to noncritical care unit
- Randomly assigned to sliding scale insulin (SSI) or a basal-bolus regimen with glargine and glulisine
  - 0.4 units per kg/day for BG 140-200
  - 0.5 units per kg /day for BG >200
  - 50% given as glargine and 50% as glulisine
- Oral antidiabetic drugs discontinued
- 2 hypoglycemic events (BG <60 mg/dL) in each group

Umpierrez GE, et al. *Diabetes Care*. 2007;30:2181-2186.

Basal-Bolus Insulin Therapy in Inpatients With Type 2 Diabetes (RABBIT 2 Trial)



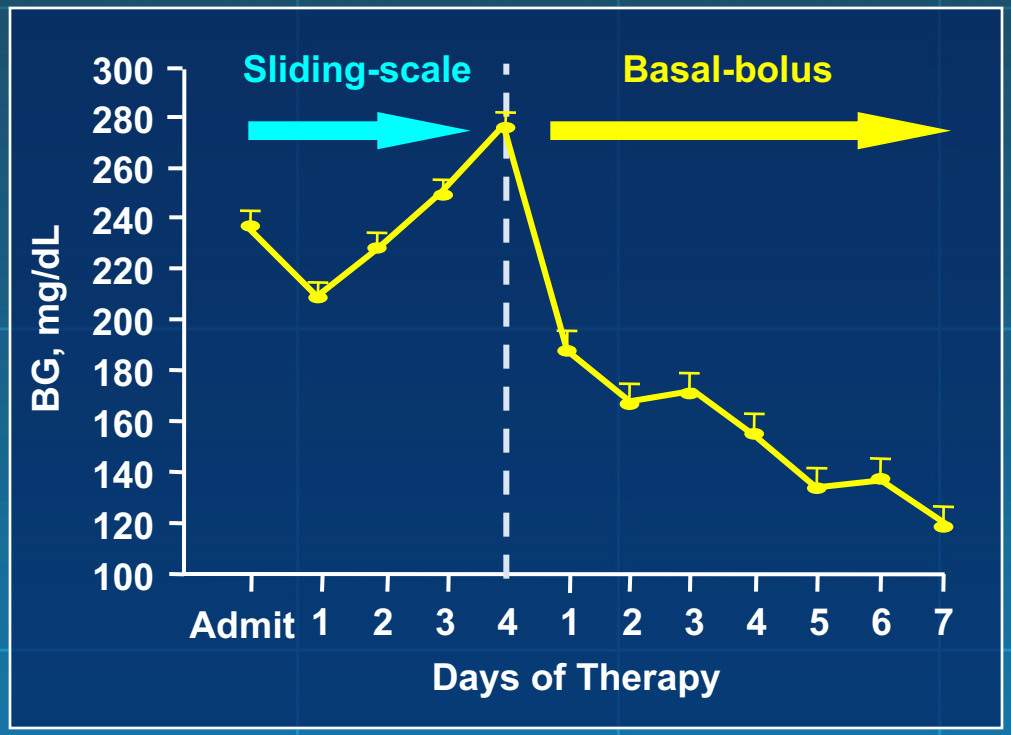
* *P*<0.01; † *P*<0.05.
SSRI, sliding scale regular insulin.
Umpierrez, et al. *Diabetes Care.* 2007;30:2181-2186.

Basal-Bolus Insulin Therapy in Inpatients With Type 2 Diabetes (RABBIT 2 Trial)

- Adjusting scheduled insulin regimen
  - If fasting and premeal BG >140 mg/dL, dose of glargine increased by 20%
  - For BG <70 mg/dL, glargine reduced by 20%

Umpierrez GE, et al. *Diabetes Care*. 2007;30:2181-2186.

Rabbit 2 Trial: SSI Resulted in Uncontrolled Hyperglycemia in Some Patients



Hypoglycemia Rate

Basal Bolus Group:

- BG <60 mg/dL: 3%
- BG <40 mg/dL: none

SSRI:

- BG <60 mg/dL: 3%
- BG <40 mg/dL: none

Persistent hyperglycemia (BG >240 mg/dL) is common (15%) with SSI therapy

Umpierrez GE, et al. *Diabetes Care*. 2007;30:2181-2186.

Glycemic Variability in Noncritical Care Patients with Type 2 Diabetes

Basal Plus Trial
Post-hoc Analysis

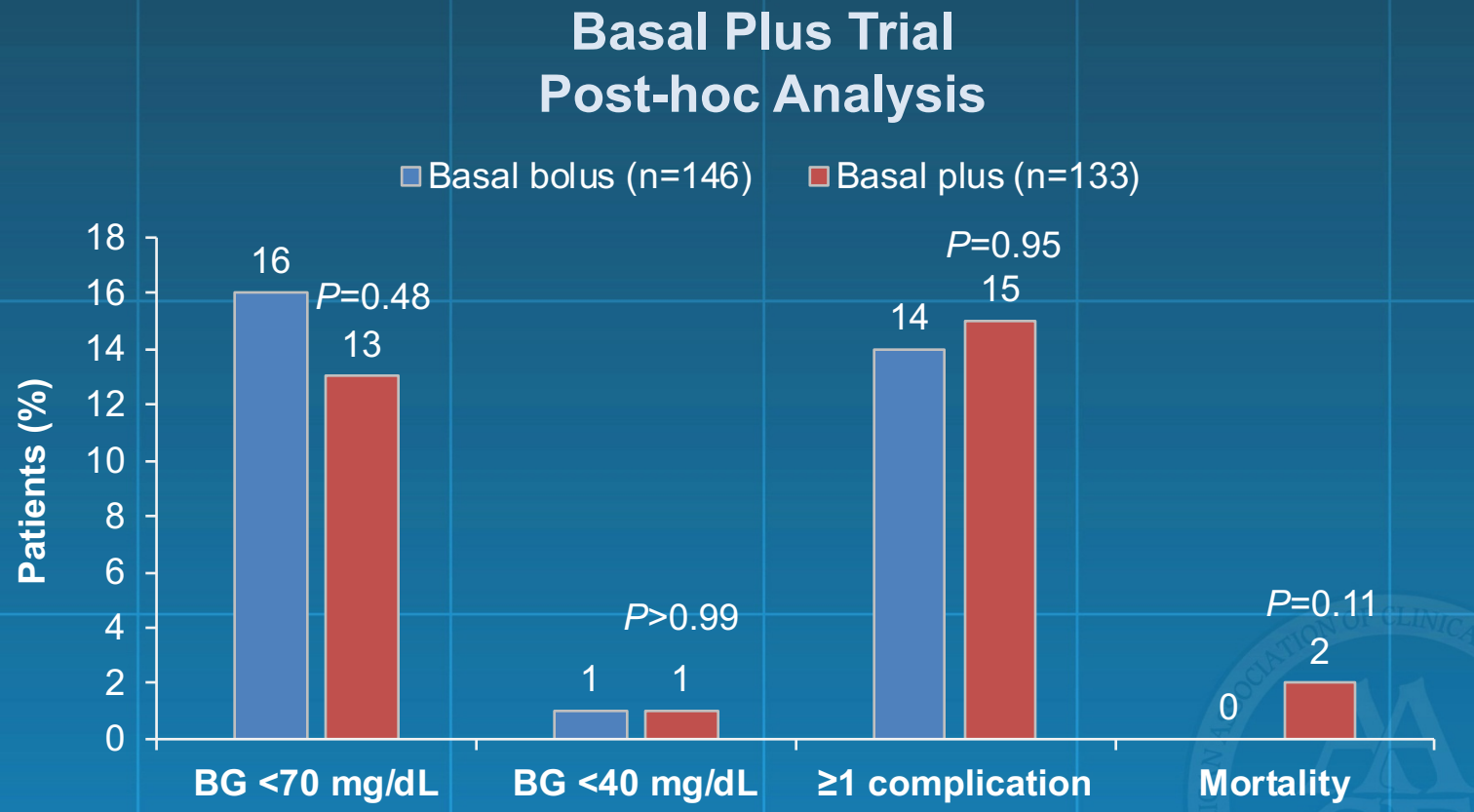
	Basal bolus	Basal plus	*P* value
General medicine	(n=82)	(n=76)	
Δ Daily blood glucose, mg/dL	70.7 ± 32	76.0 ± 34	0.42
Standard deviation, mg/dL	38.7 ± 17	41.4 ± 16	0.31
MAGE, mg/dL	65.7 ± 33	77.0 ± 41	0.15
Surgery	(n=64)	(n=57)	
Δ Daily blood glucose, mg/dL	74.9 ± 40	60.3 ± 32	0.02
Standard deviation, mg/dL	38.2 ± 18	31.2 ± 18	0.02
MAGE, mg/dL	69.9 ± 35	69.9 ± 35	0.009

Basal bolus = half once daily glargine, half glulisine before meals, plus correction doses before meals and at bedtime.
Basal plus = once daily glargine plus correction doses before meals and at bedtime

MAGE, mean amplitude of glycemic excursions.

Haw JS, et al. *Endocr Pract*. 2015;21:1333-1343.

Hypoglycemia and Complications in Noncritical Care Patients with Type 2 Diabetes Treated With Different Insulin Strategies



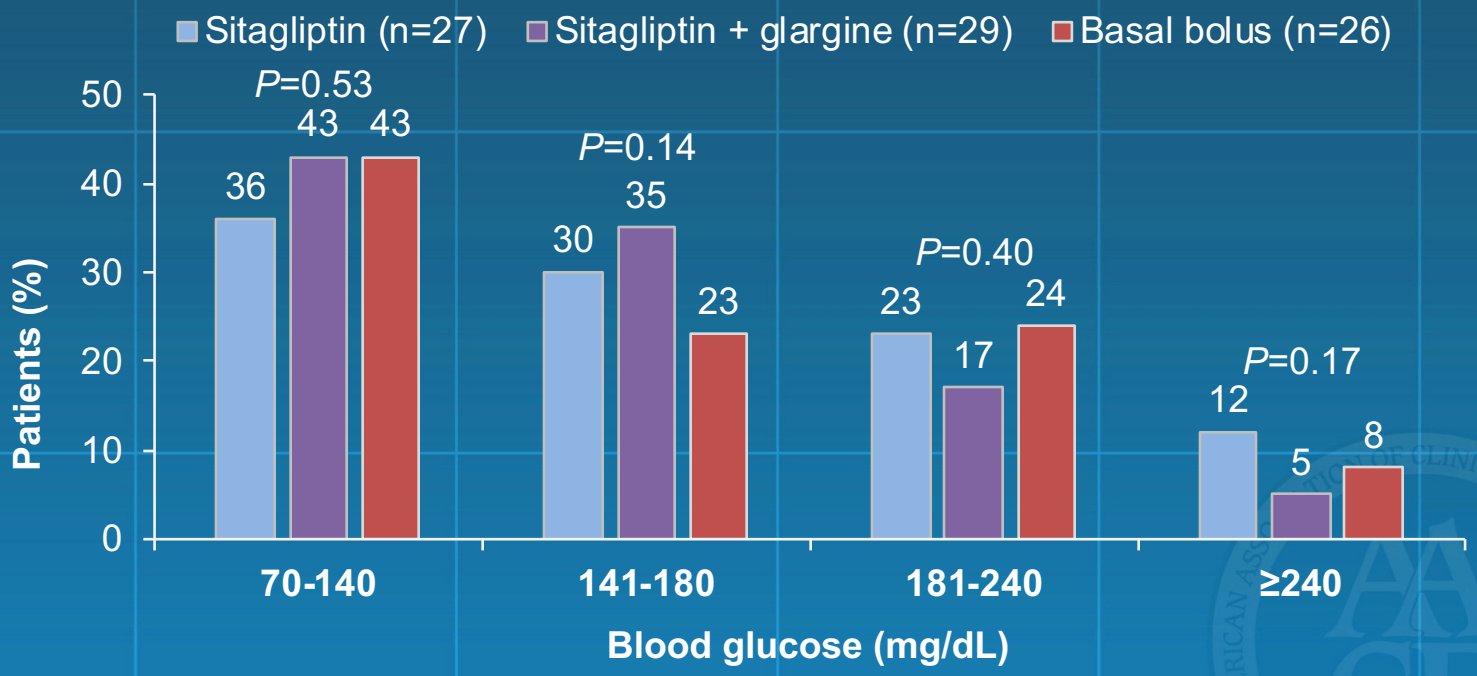
Basal bolus = half once daily glargine, half glulisine before meals, plus correction doses before meals and at bedtime.
Basal plus = once daily glargine plus correction doses before meals and at bedtime

BG, blood glucose.

Haw JS, et al. *Endocr Pract*. 2015;21:1333-1343.

Blood Glucose Levels in Noncritical Care Patients with Type 2 Diabetes Treated with Sitagliptin

Open-Label, Randomized Pilot Study



P values represent treatment comparisons across all 3 groups.

BG, blood glucose.

Umpierrez GE, et al. *Diabetes Care*. 2013;36:3430-3435.

Risk Factors for Hypoglycemia

Variable	*P* value	
	Univariate Analysis	Multivariate Analysis*
Age	<0.001	<0.001
GFR <60 mL/s	0.005	0.11
TDD ≥0.5 U/kg	0.006	0.31
Previous insulin use	<0.001	0.02
Insulin regimen (basal-bolus vs SSI)	<0.001	0.001

* Adjusted for age, total daily insulin dose (TDD) >0.5 U/kg, glomerular filtration rate (GFR) <60 mL/second, insulin regimen (basal-bolus vs sliding scale insulin [SSI]), and previous insulin therapy.

Farrokhi F, et al. ADA Scientific Sessions. 2011. Abstr. 2060-PO.

Strategies for Reducing Risk for Hypoglycemia in Noncritical Care Settings

- Avoidance of sliding-scale insulin alone
- Use caution in prescribing oral antihyperglycemic agents
- Modify outpatient insulin doses in patients treated with insulin prior to admission

Braithwaite SS, et al. *Endocr Pract.* 2004;10(suppl 2):89-99.

Insulin Pump Therapy

- Electronic devices that deliver insulin through a SC catheter
  - Basal rate (variable) + bolus delivery for meals
- Used predominately in type 1 diabetes
- “Pumpers” tend to be fastidious about their glycemic control
  - Often reluctant to yield control of their diabetes to the inpatient medical team
- Hospital personnel typically unfamiliar with insulin pumps
  - Hospitals do not stock infusion sets, batteries, etc, for insulin pumps (multiple models available from different manufacturers

AACE Position on CSII in the Hospital

- Patients who use CSII outside the hospital may use it inside if:
  - Patient has the mental and physical capacity to use CSII for self-management
  - Hospital personnel with CSII expertise are available
  - Nurses document basal and bolus doses at least daily
- Specialist responsible for ambulatory CSII management should be contacted to make decisions about infusion rate adjustments

A formal inpatient insulin pump protocol reduces confusion and treatment variability

CSII, continuous subcutatneous insulin infusion.

Grunberger G, et al. *Endocr Pract*. 2014;20:463-489.

Inpatient CSII Protocol

- An insulin pump should NEVER be discontinued without initiation of either subcutaneous or intravenous insulin
- If the pump is discontinued for any reason, additional insulin (either IV or subcutaneous) MUST be given 30 minutes prior to discontinuation
- Patient is to self-manage insulin pump and nurse is to verify and document all basal rates and bolus doses administered
- Insulin pumps must be discontinued for an MRI. If the pump is interrupted for more than 1 hour, another insulin source needs to be ordered

Noschese ML, et al. *Endocr Pract.* 2009;15:415-424.

Inpatient CSII Protocol

Patient Attestation

I confirm that I have been fully trained on the use of my insulin pump prior to this hospitalization.

I am capable and willing to manage my insulin pump independently during my hospital stay.

If at any time I feel that I am unable to manage the pump, I will alert my medical team.

Requires patient and witness signature

Bailon RM, et al. *Endocr Pract.* 2009;15:24-29.
Noschese ML, et al. *Endocr Pract.* 2009;15:415-424.

Inpatient Insulin Pump Therapy: A Single Hospital Experience

- N=65 patients (125 hospitalizations)
- Mean age: 57 ± 17 y
- Diabetes duration: 27 ± 14 y
- Pump use: 6 ± 5 y
- A1C: 7.3% ± 1.3%
- Length of stay: 4.7 ± 6.3 days

- Pump therapy continued 66%
- Endocrine consults in 89%
- Consent agreements in 83%
- Pump order sets completed in 89%
- RN assessment of infusion site in 89%
- Bedside insulin pump flow sheets in only 55%
- Mean BG 175 mg/dL (same as off pump)
- No AEs (1 catheter kinking)

Nassar AA, et al. *J Diabetes Sci Technol*. 2010;4:863-872.

A Validated Inpatient Insulin Pump Protocol

Hospitalizations After Implementation of an Inpatient Insulin Pump Protocol (IIPP)

	Mean BG (mg/dL)	*P* value
Group 1 - IIPP+DM consult (n=34)	173 ±43	NS
Group 2 - IIPP alone (n=12)	187 ±62	
Group 3 - Usual care (n=4)	218 ±46	

- More inpatient days with BG >300 mg/dL in Group 3 ($P<0.02$.)
- No differences in inpatient days with BG <70 mg/dL
- 1 pump malfunction; 1 infusion site problem; no SAEs
- 86% of pumpers expressed satisfaction with ability to manage DM in the hospital

Noschese ML, et al. *Endocr Pract*. 2009;15:415-424.

Clinical Outcomes with Inpatient CSII

Systematic Review
(N=11 Studies*; 624 Patients)

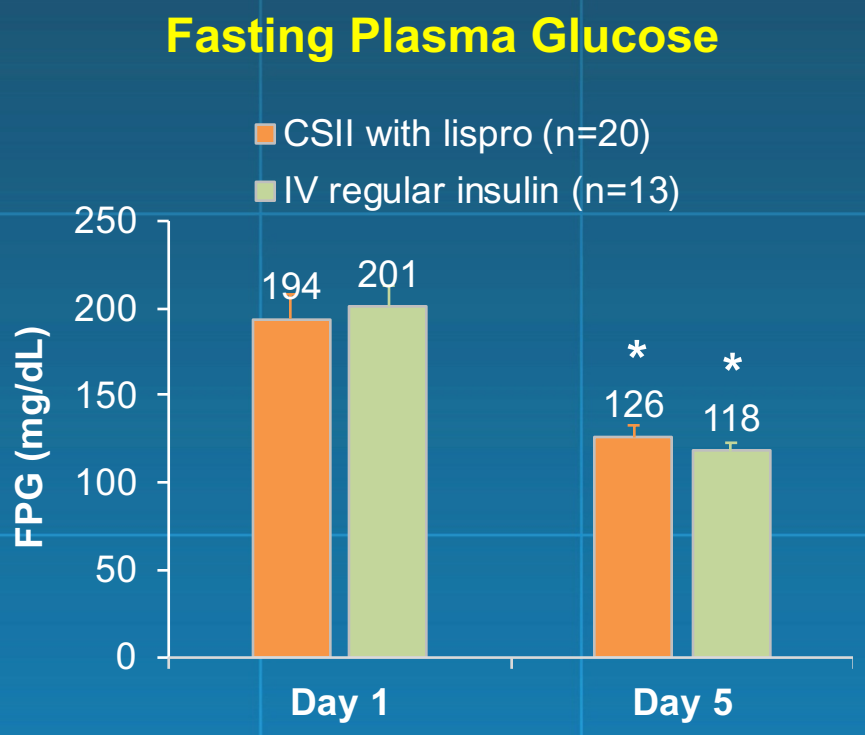
Inpatient mortality	None reported (only 1 study assessed mortality in 253 patients over 1000 patient-days)
Hyperglycemia	Trend toward less hyperglycemia with CSII
Hypoglycemia	Trend toward more hypoglycemia with CSII
Length of stay	Shorter stay with continued CSII (4.5 days) vs suspended CSII or IV infusion (7 days)
Average blood glucose	CSII continued: 175 mg/dL; suspended CSII or IV infusion: 178 mg/dL

*9 retrospective; 2 prospective, including 1 randomized, controlled study.

CSII, continuous subcutaneous insulin infusion; IV, intravenous.

Anstey J, et al. *Diabet Med*. 2015;32:1278-1288.

Efficacy of CSII in Hospitalized Patients with Type 2 Diabetes



*P<0.05 vs day 1.

BG, blood glucose; CBG, capillary blood glucose; CSII, continuous subcutaneous insulin infusion; IV, intravenous.

Boullu-Sanchis S, et al. *Diabetes Metab*. 2006;32:350-357.

- No significant differences between treatment groups in
  - Mean daily CBG levels
  - Percent of preprandial CBG values in the target range
  - Daily standard deviation of BG on day 5
- Insulin dose lower in CSII group (P<0.05)
- Hypoglycemia
  - CSII: 0.06 events/patient per day
  - IV insulin: 0.015 events/patient per day
  - Between group difference not statistically significant
  - No severe hypoglycemia reported in either group

Results of an Inpatient CSII Protocol

	IDS + IPP	IPP	No IDS/IPP
N (% female)	34 (32)	12 (50)	4 (75)
Age	48±15	51±16	36±12
LOS (days)	9.8±15.4	5.2±6.2	3±1.5
CSII use (days)	5.4±7.1	3.2±2.9	3±1.5
Mean CBG (mg/dL)	173±43	187±62	218±46
Patient days with			
≥1 CBG <70	21	10	20
All CBG 70-180	25	24	24
≥1 CBG 181-300	56	55	73
≥1 CBG >300	22	7	60

IDS, inpatient diabetes service; IPP, inpatient pump protocol.

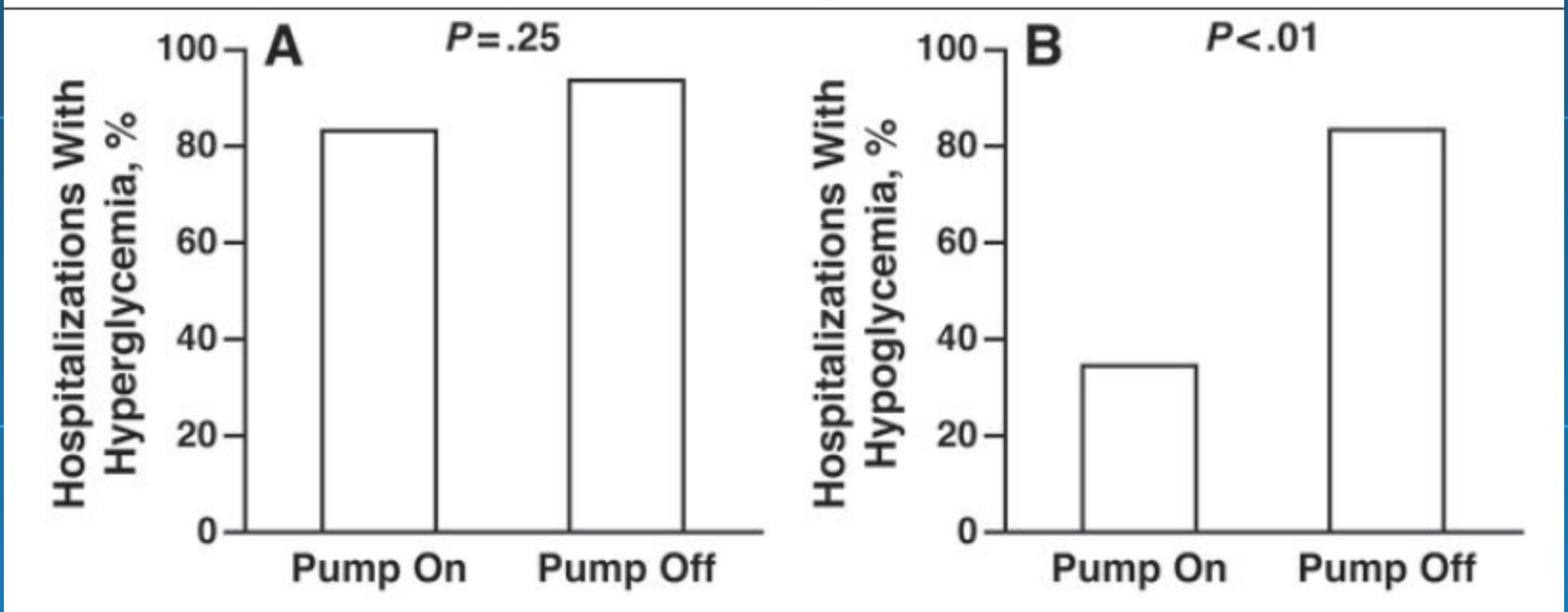
Noschese ML, et al. *Endocr Pract.* 2009;15:415-424.

Inpatient CSII Therapy in Patients Treated With Insulin as Outpatients

- Patients completing questionnaire (n=17) reported a high degree of satisfaction with their ability to continue CSII therapy in the hospital
- There were 2 CSII related adverse events
  - 1 infusion site problem
  - 1 pump malfunction

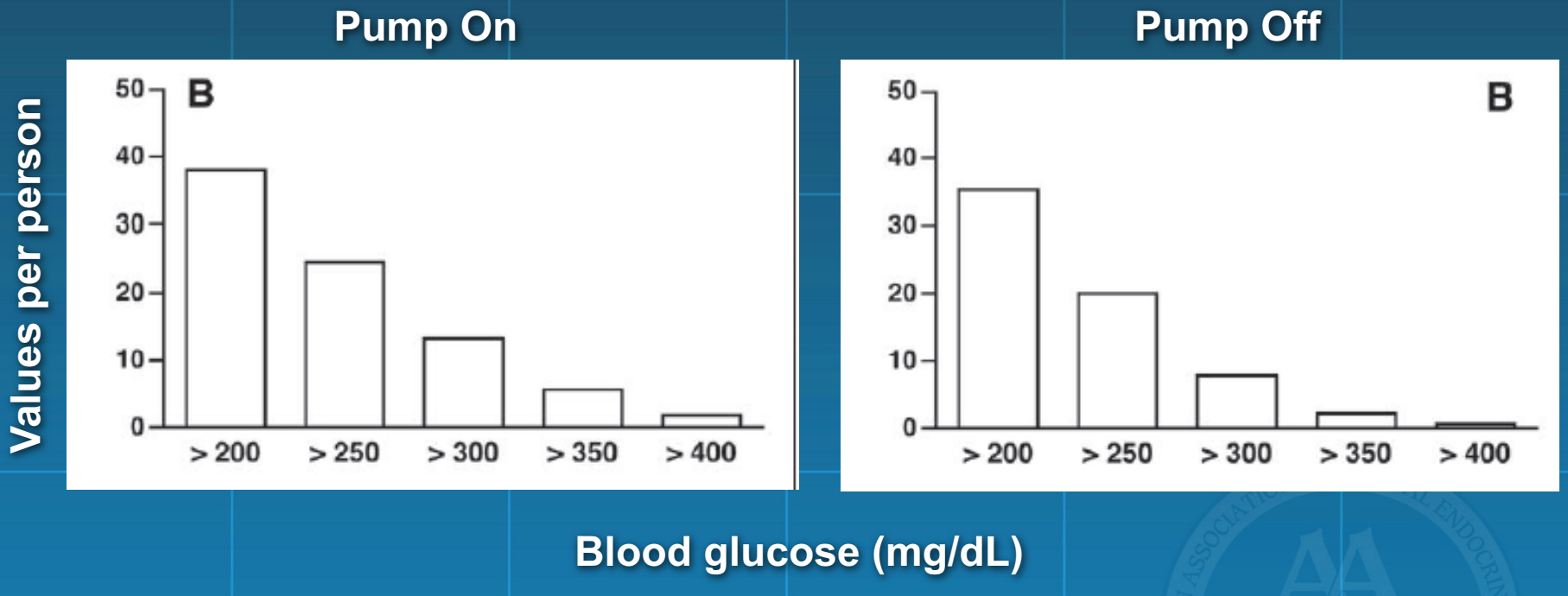
Inpatient CSII Therapy

Prevalence of hyperglycemia and hypoglycemia in inpatients who continued (pump on) or discontinued (pump off) CSII during their hospital stay



Bailon RM, et al. *Endocr Pract.* 2009;15:24-29.

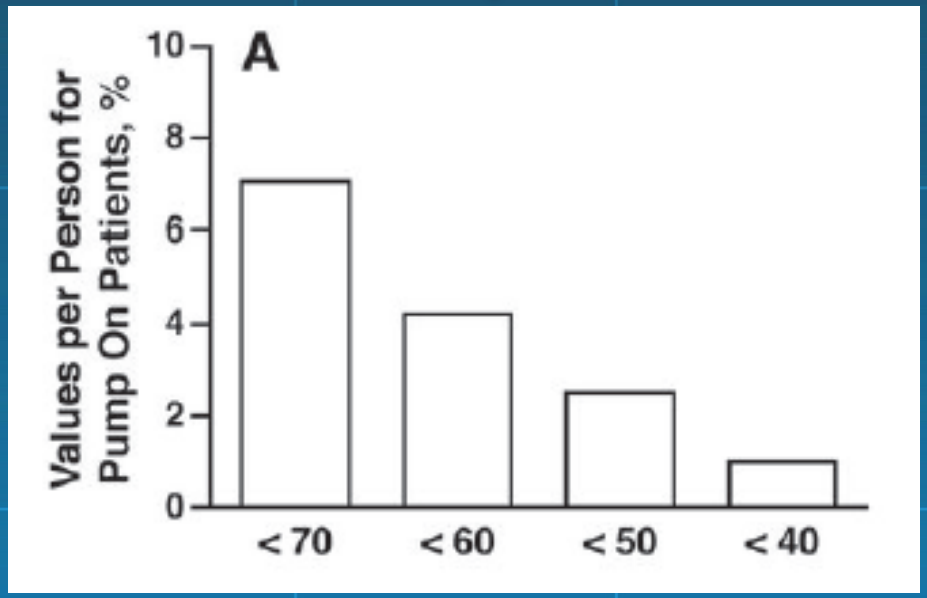
Hyperglycemic Events in Patients Continuing or Stopping CSII Therapy During Their Hospital Stays



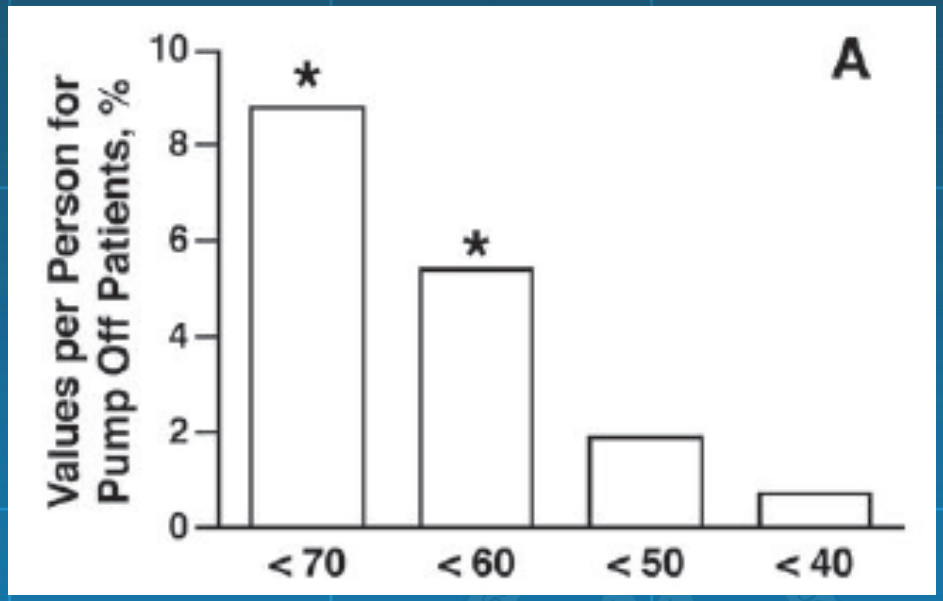
Bailon RM, et al. *Endocr Pract.* 2009;15:24-29.

Hypoglycemic Events in Patients Continuing or Stopping CSII Therapy During Their Hospital Stays

Pump On



Pump Off

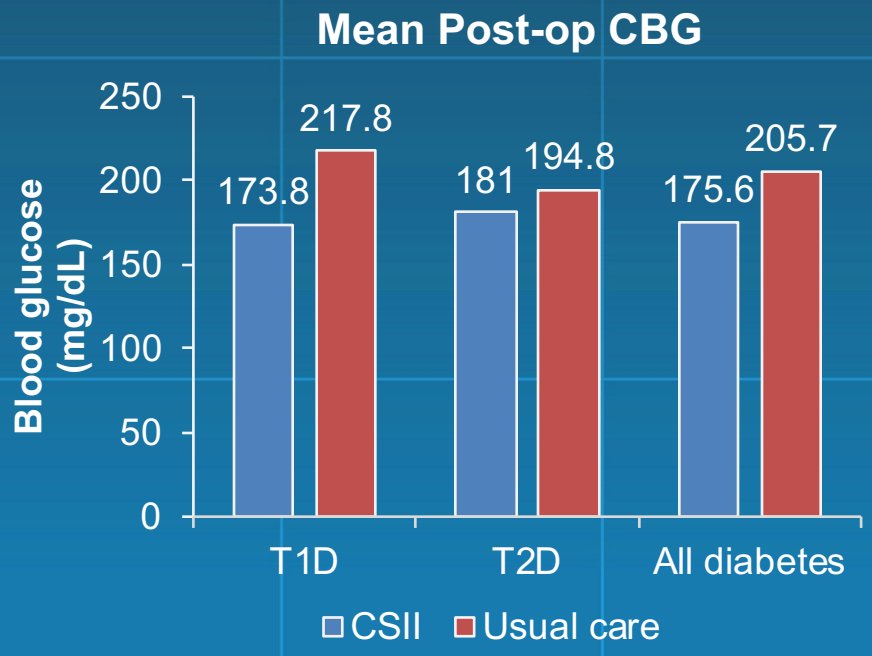


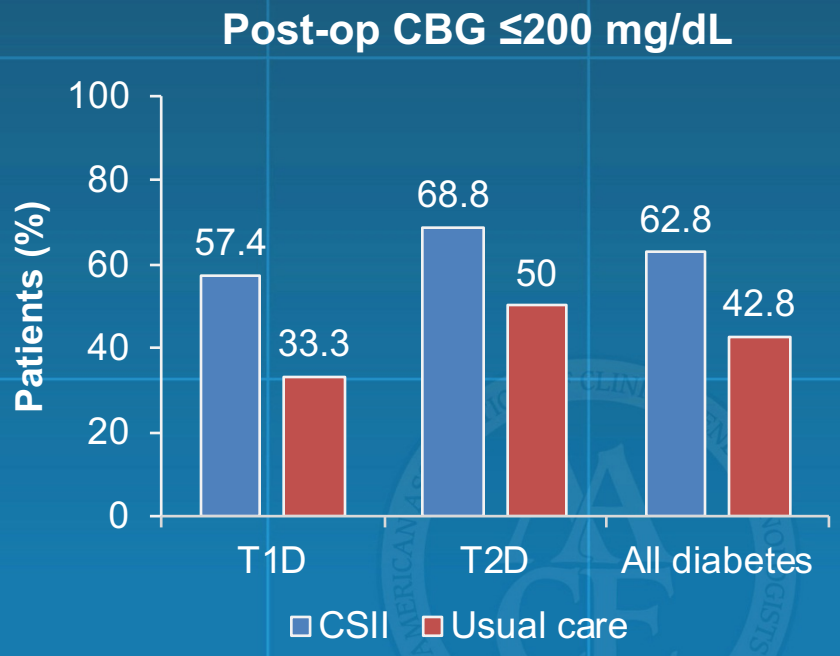
Blood glucose (mg/dL)

Bailon RM, et al. *Endocr Pract.* 2009;15:24-29.

Blood Glucose Levels with Peri-operative CSII

Patients with Diabetes Undergoing Same-Day Surgery (N=49)





CBG, capillary blood glucose; CSII, continuous subcutatneous insulin infusion.

Sobel SI, et al. *Endocr Pract*. 2015;21:1269-1276.

Inpatient Management of Hyperglycemia: Managing Safety Concerns

- Both undertreatment and overtreatment of hyperglycemia create safety concerns
- Areas of risk
  - Changes in carbohydrate or food intake
  - Changes in clinical status or medications
  - Failure to adjust therapy based on BG patterns
  - Prolonged use of SSI as monotherapy
  - Poor coordination of BG testing with insulin administration and meal delivery
  - Poor communication during patient transfers
  - Errors in order writing and transcription

Summary

- Target BG: 140-180 mg/dL for most noncritically ill patients
- Insulin therapy preferred method of glycemic control in the hospital
  - Scheduled SC basal-bolus insulin therapy is effective and safe for treatment of hyperglycemia in noncritically ill patients
  - Sliding scale regular insulin alone is inappropriate once an insulin requirement is established