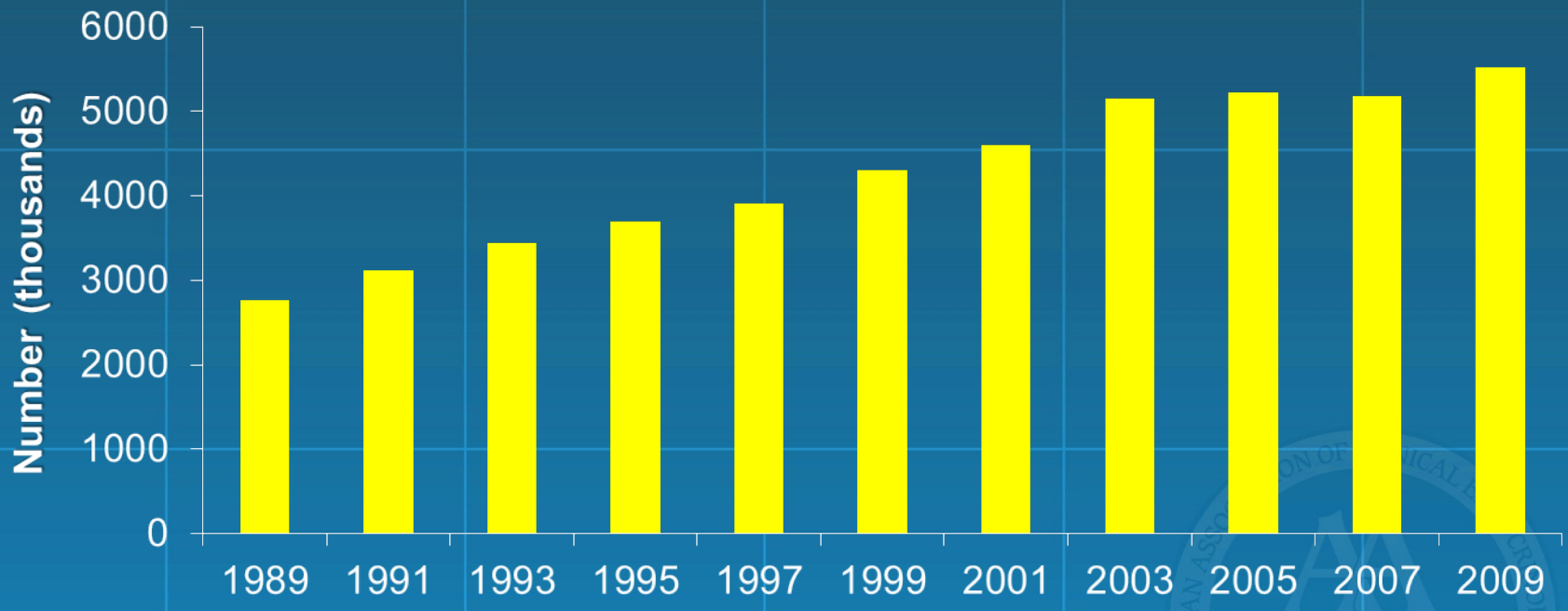
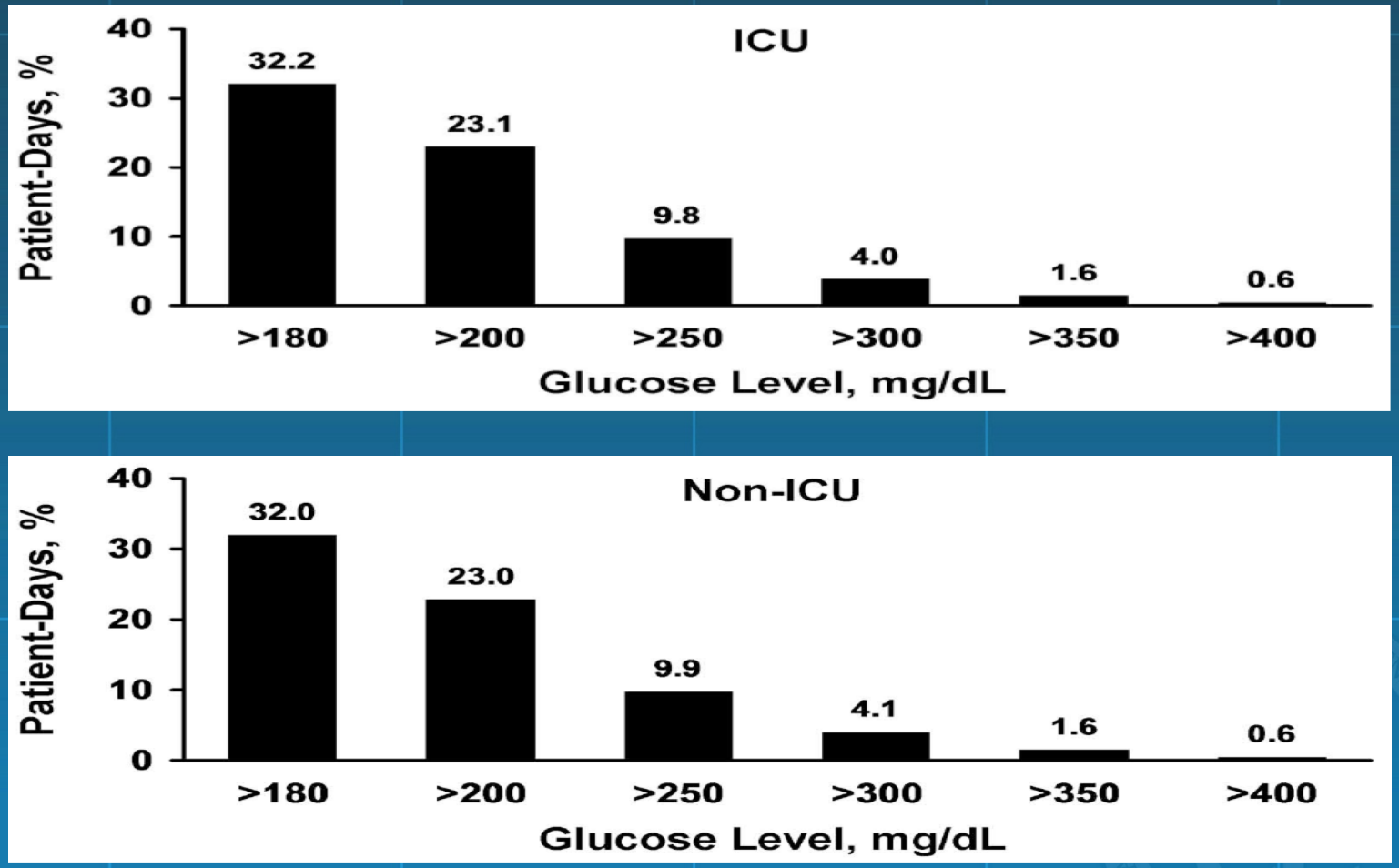
Clinical Evidence for Glucose Control in the Inpatient Setting

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



Centers for Disease Control and Prevention. Diabetes Data and Trends. Available at: http://www.cdc.gov/diabetes/statistics/dmany/fig1.htm.

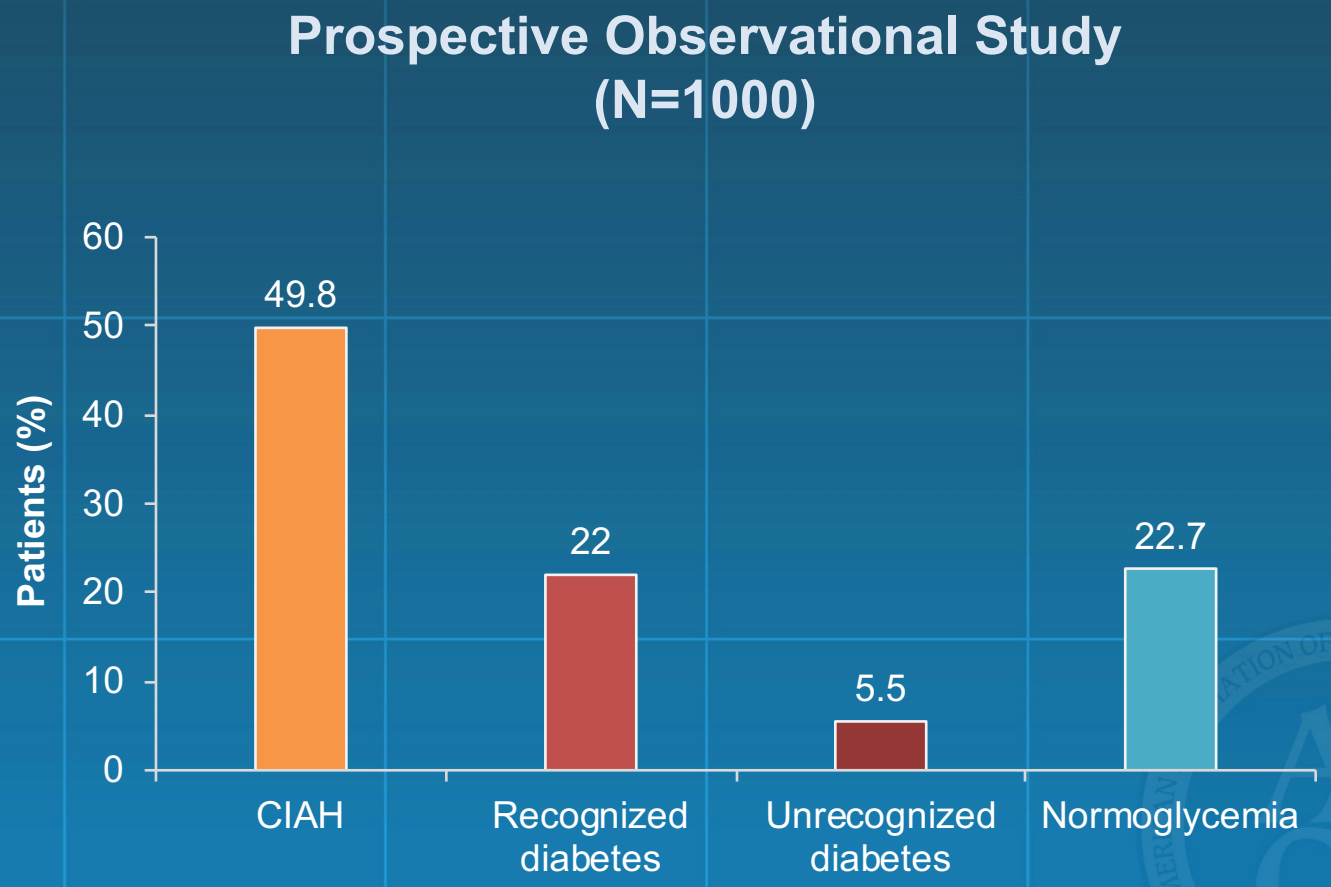
Distribution of Patient-Day-Weighted Mean POC-BG Values for ICU



~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.

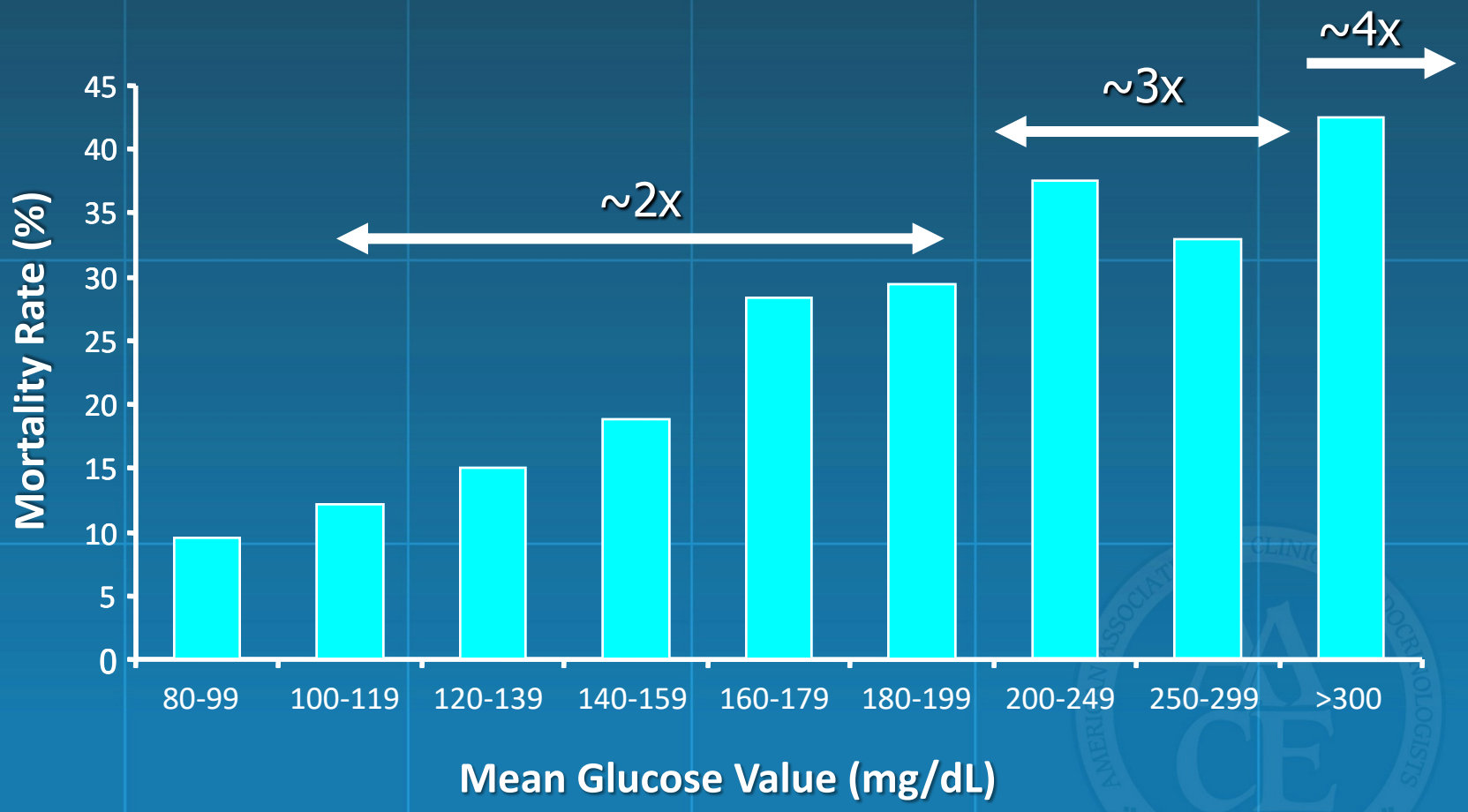
Prevalence of Hyperglycemia in Critically Ill Patients



CIAH, critical illness associated hyperglycemia.

Plummer MP, et al. *Intensive Care Med*. 2014;40:973-980.

Hyperglycemia and Mortality in the Medical Intensive Care Unit

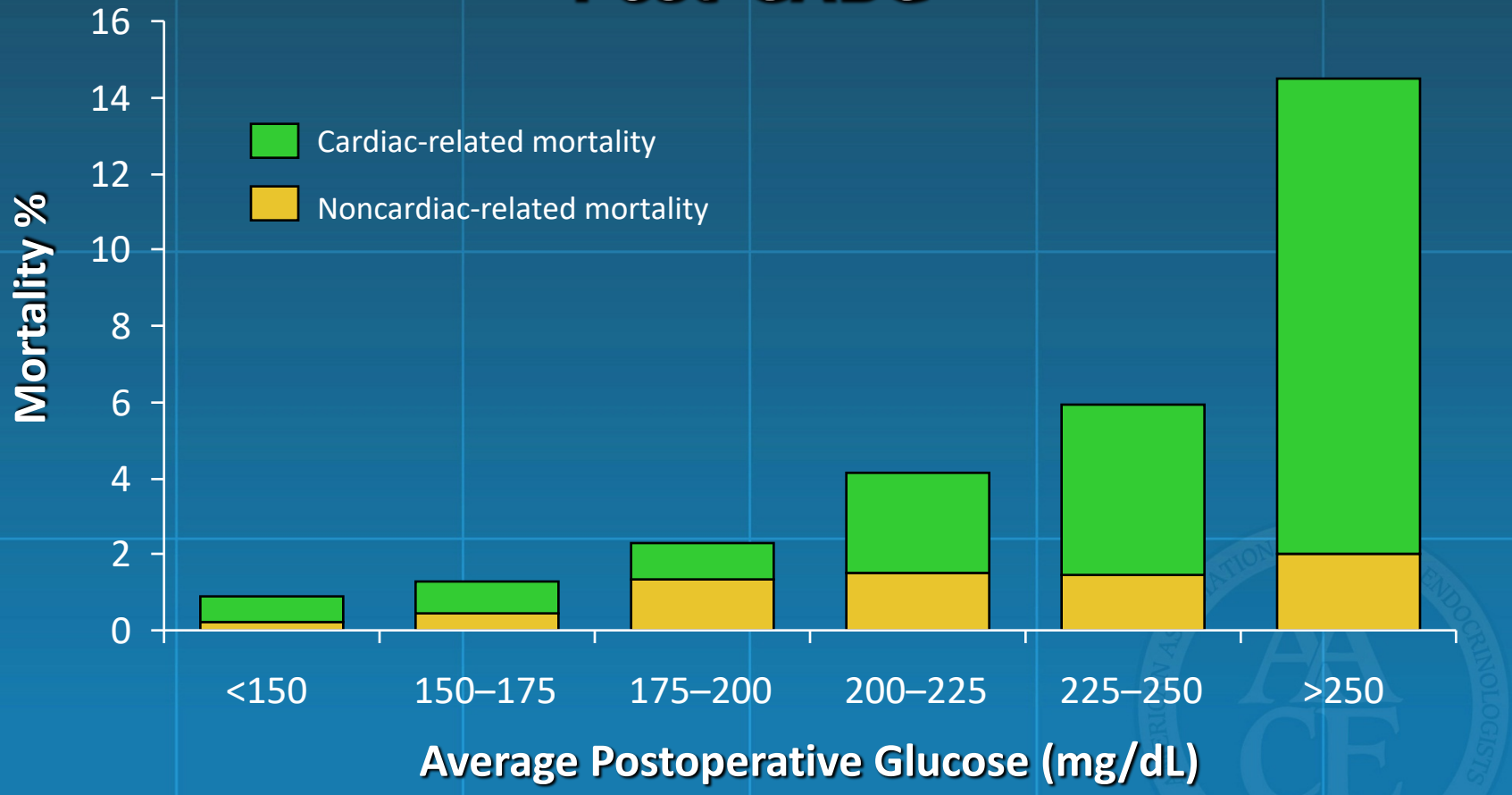


N=1826 ICU patients.

Krinsley JS. *Mayo Clin Proc*. 2003;78:1471-1478.

Mortality Increases With Increases in Average BG Levels

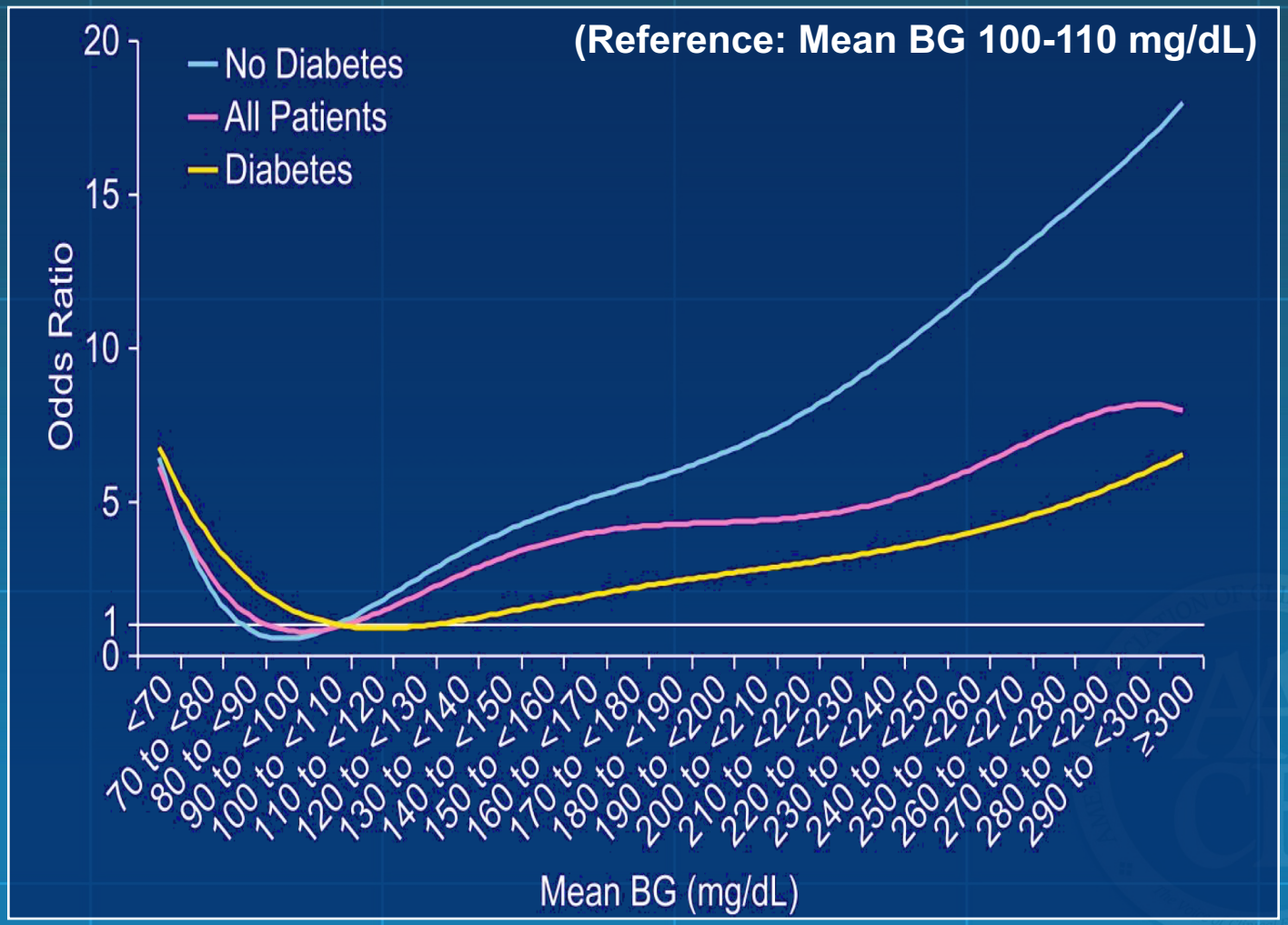
Post-CABG



CABG, coronary artery bypass graft.

Furnary AP et al. *J Thorac Cardiovasc Surg.* 2003;125:1007-1021.

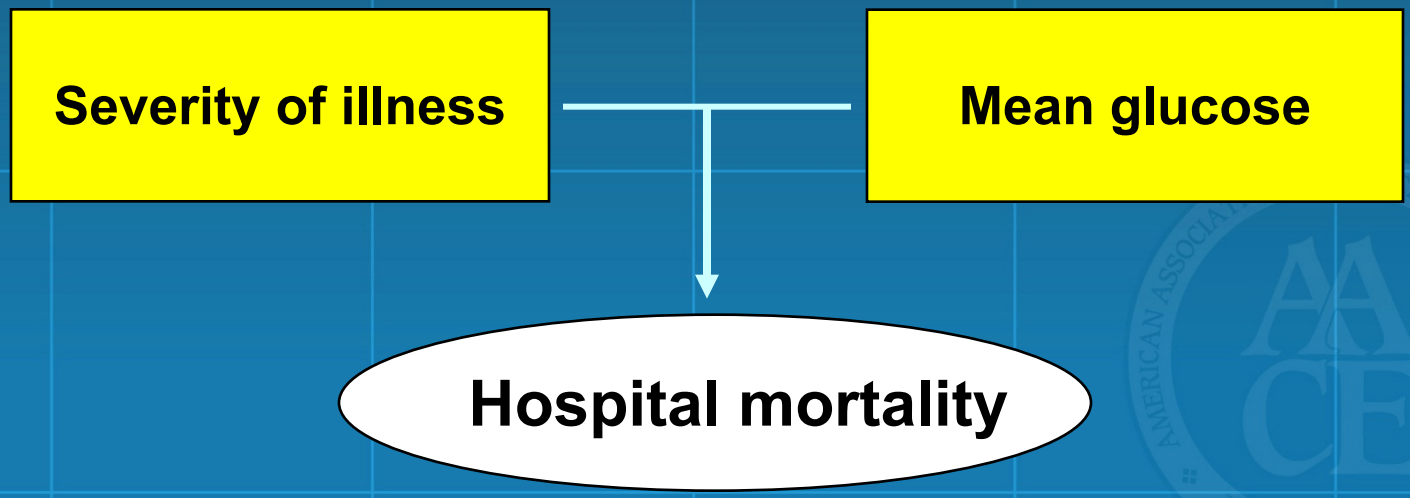
Mean Glucose and In-Hospital Mortality in 16,871 Patients With Acute MI



Kosiborod M, et al. *Circulation.* 2008:117:1018-1027.

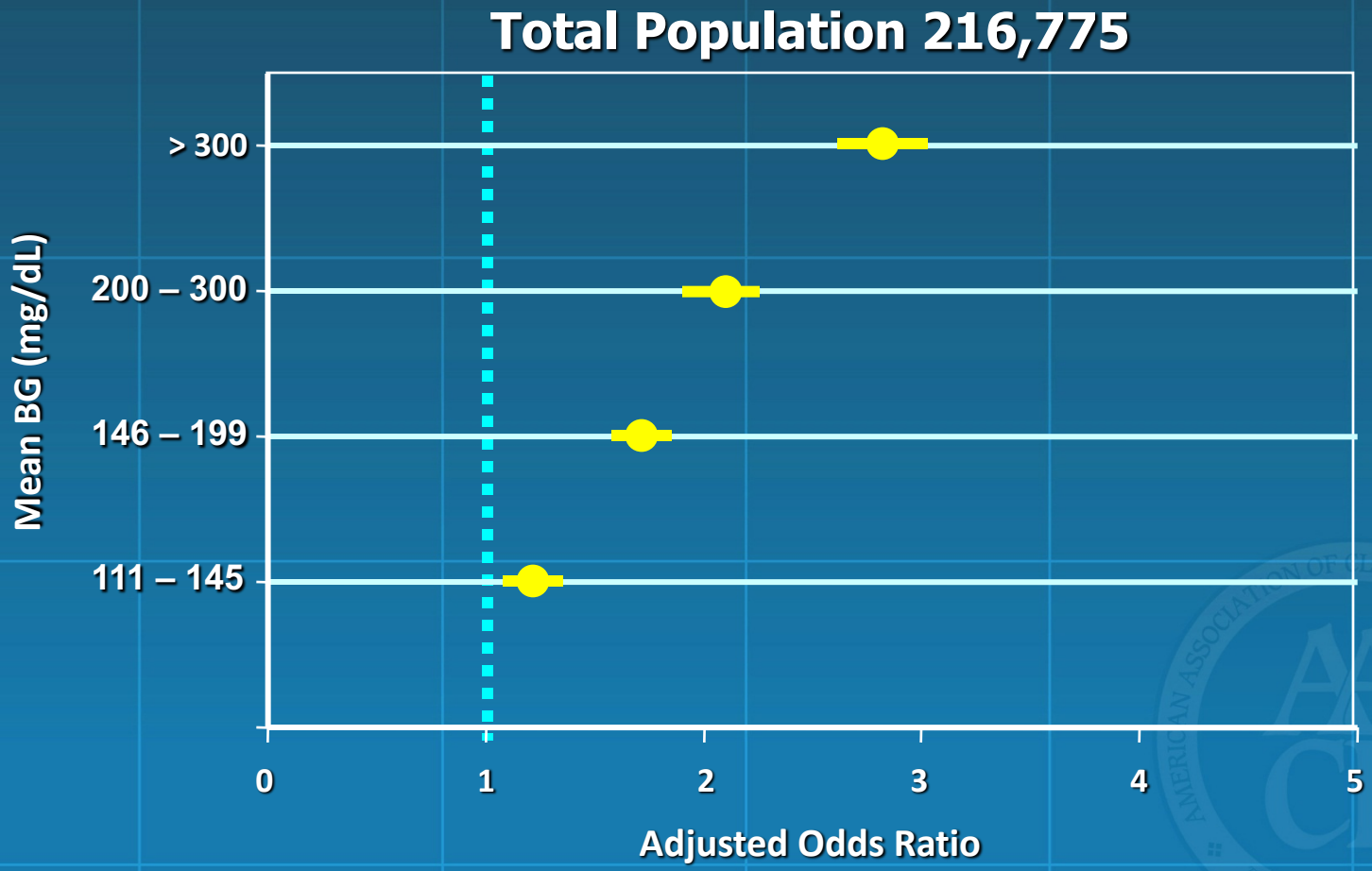
Hyperglycemia and Mortality in 259,040 Critically Ill Patients

216,775 consecutive first admissions
173 surgical, medical, cardiac ICUs
73 geographically diverse VAMC 9/02–3/05



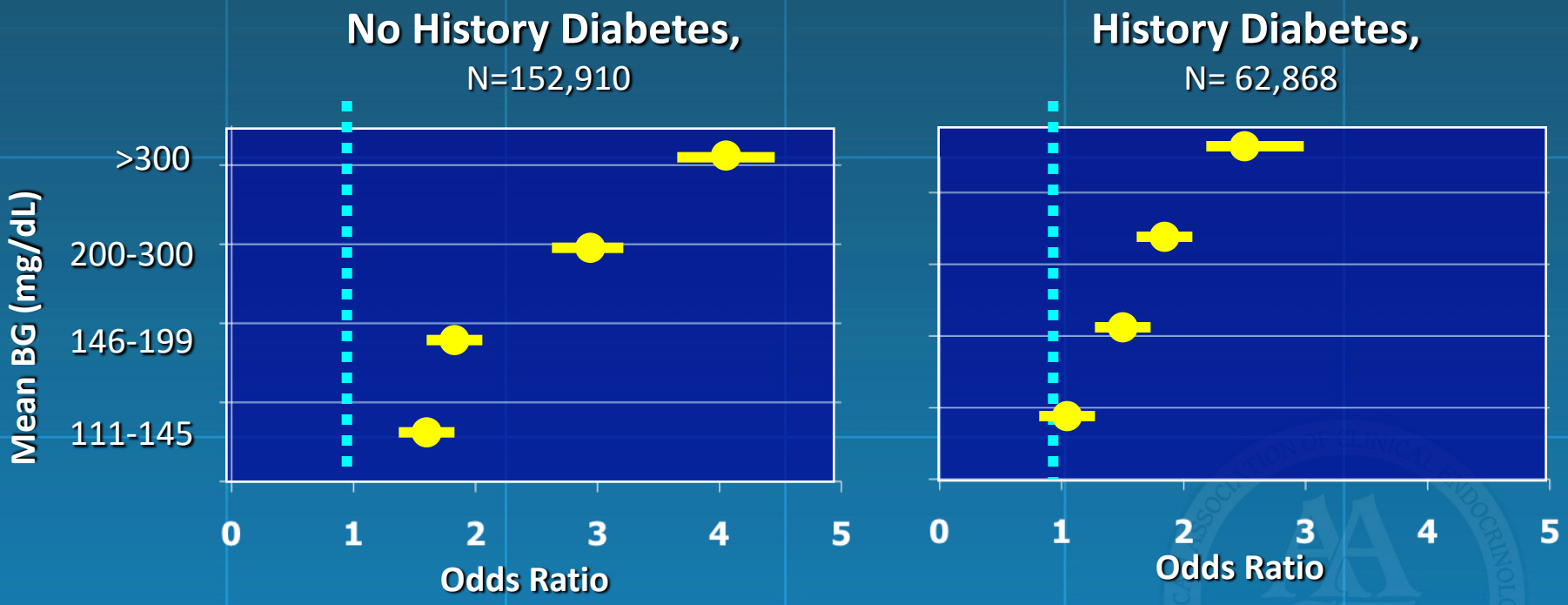
Falciglia M, et al. *Crit Care Med*. 2009;37:3001-3009.

Hyperglycemia Is Associated With Increased Risk-Adjusted Mortality



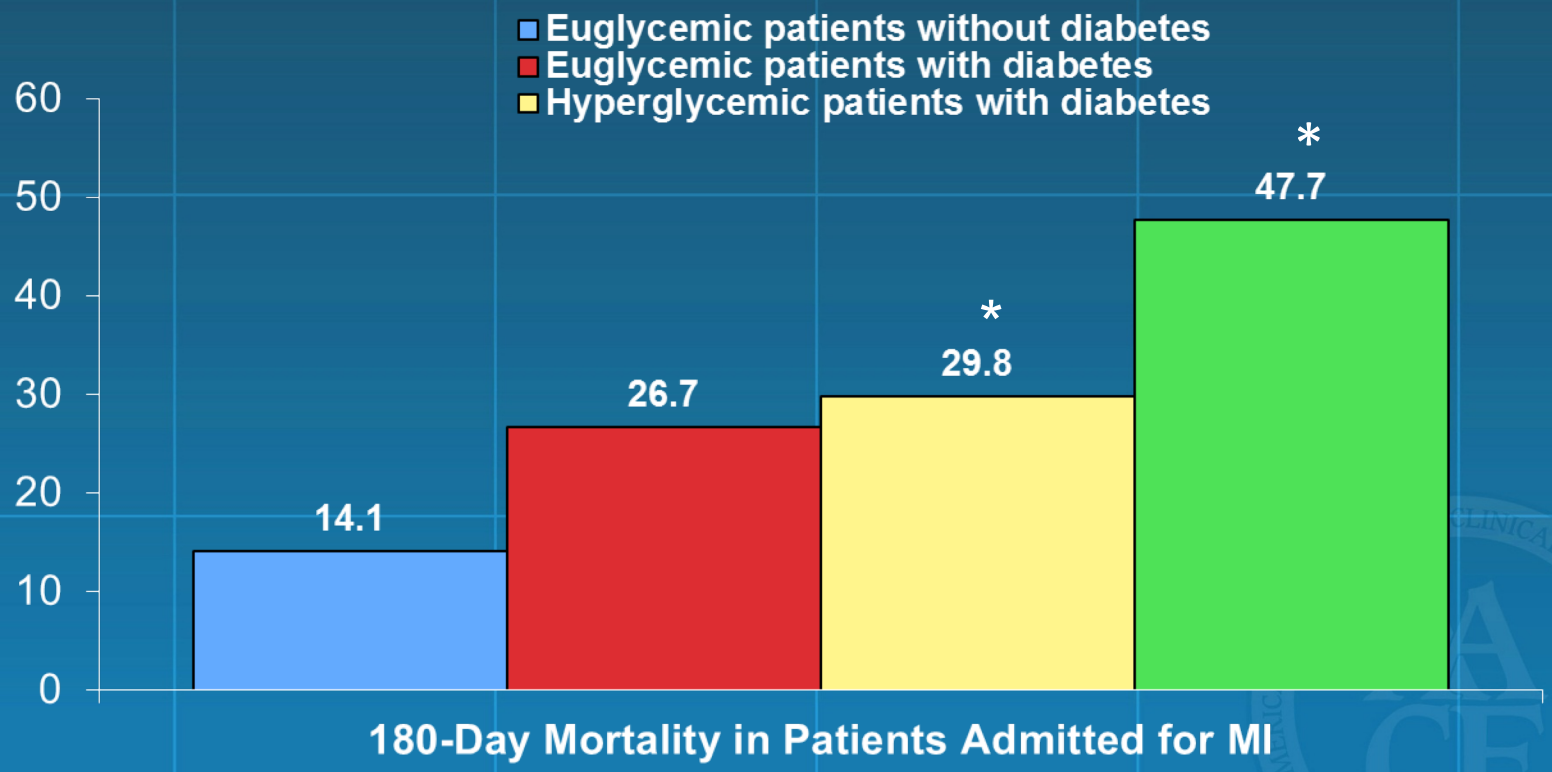
Falciglia M, et al. *Crit Care Med*. 2009;37:3001-3009.

Mortality Risk Is Greater in Hyperglycemic Patients Without History of Diabetes



Falciglia M, et al. *Crit Care Med*. 2009;37:3001-3009.

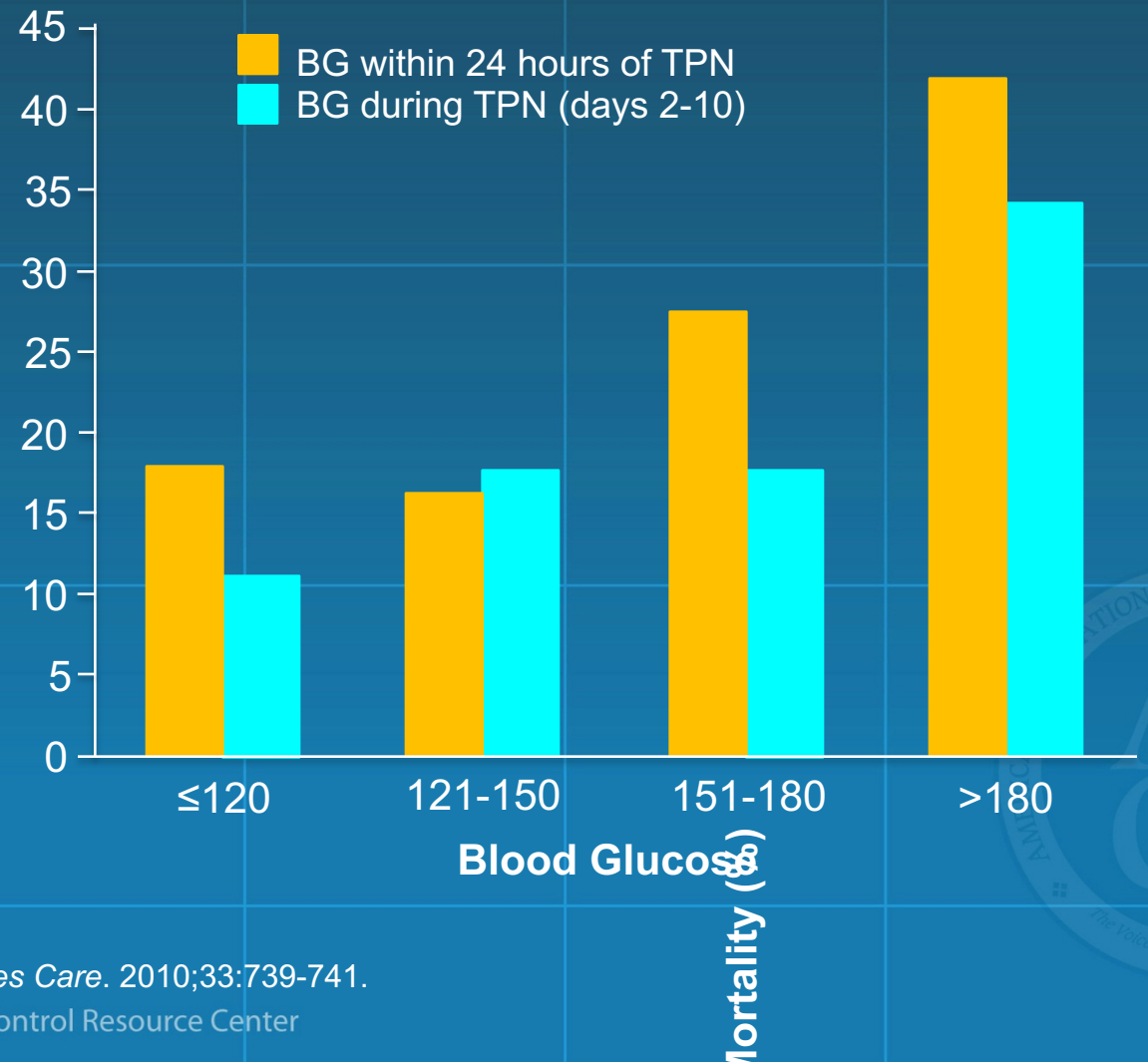
Hyperglycemia Is Linked to Mortality Regardless of Diabetes Status



* ≥200 mg/dL.

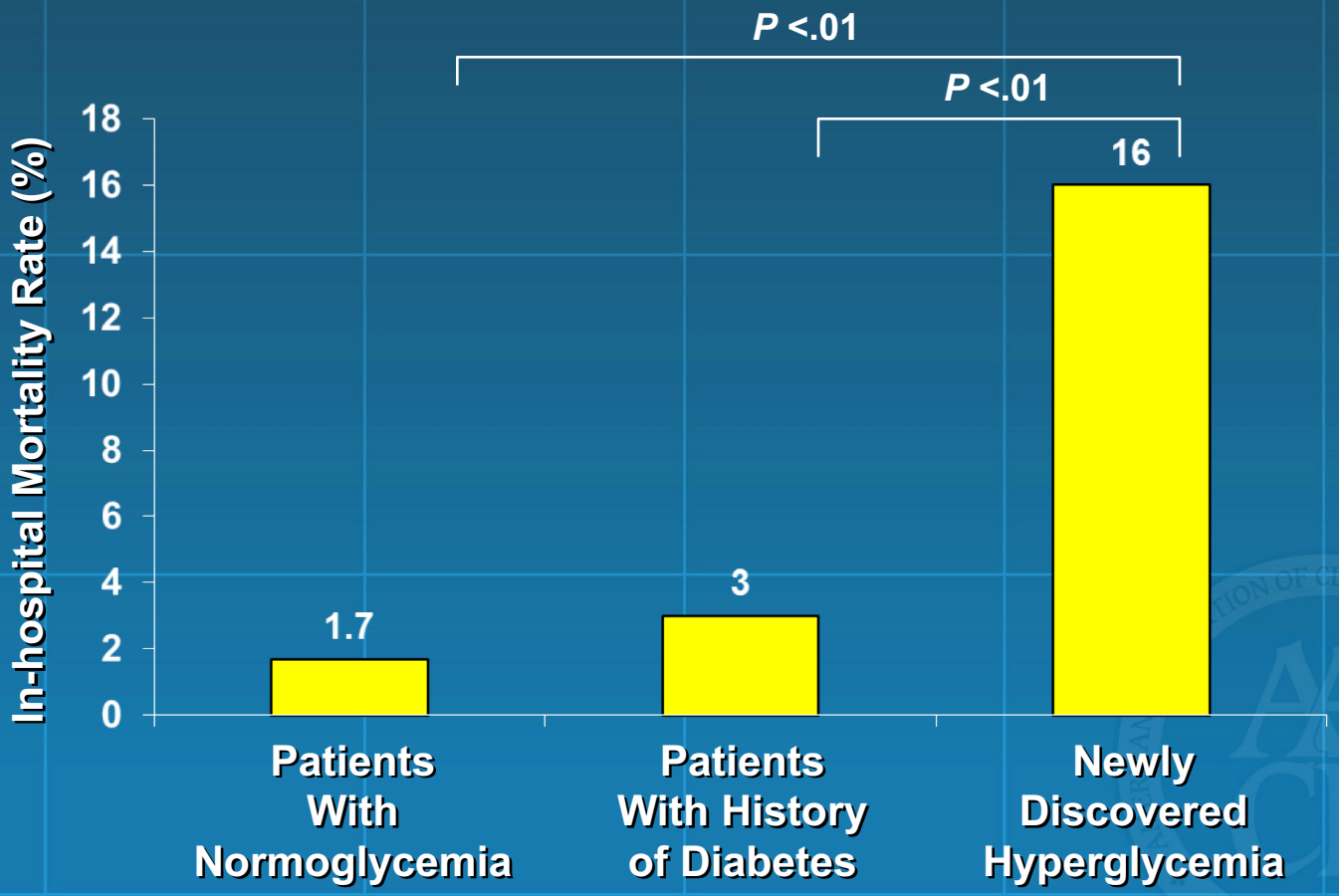
Rady MY, et al. *Mayo Clin Proc*. 2005;80:1558-1567.
Ainla MIT, et al. *Diabet Med*. 2005;22:1321-1325.

Hyperglycemia During TPN Is Associated With Greater Risk of Hospital Mortality



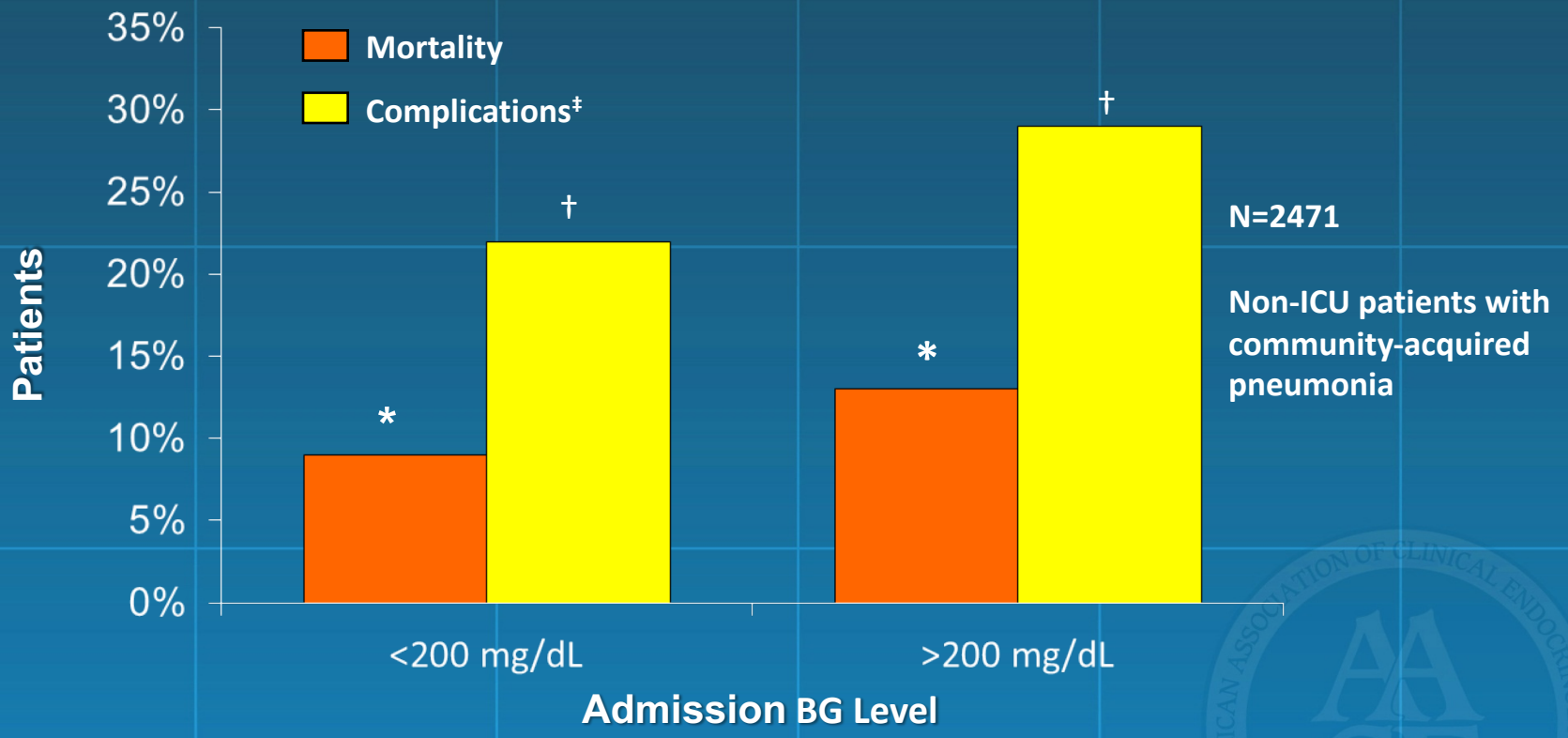
Pasquel FJ, et al. *Diabetes Care*. 2010;33:739-741.

Mortality in Inpatients With "New Hyperglycemia"



Umpierrez GE, et al. *J Clin Endocrinol Metab*. 2002;87:978-982.

Admission Hyperglycemia Is Also Associated With Adverse Outcomes in Non-ICU Settings



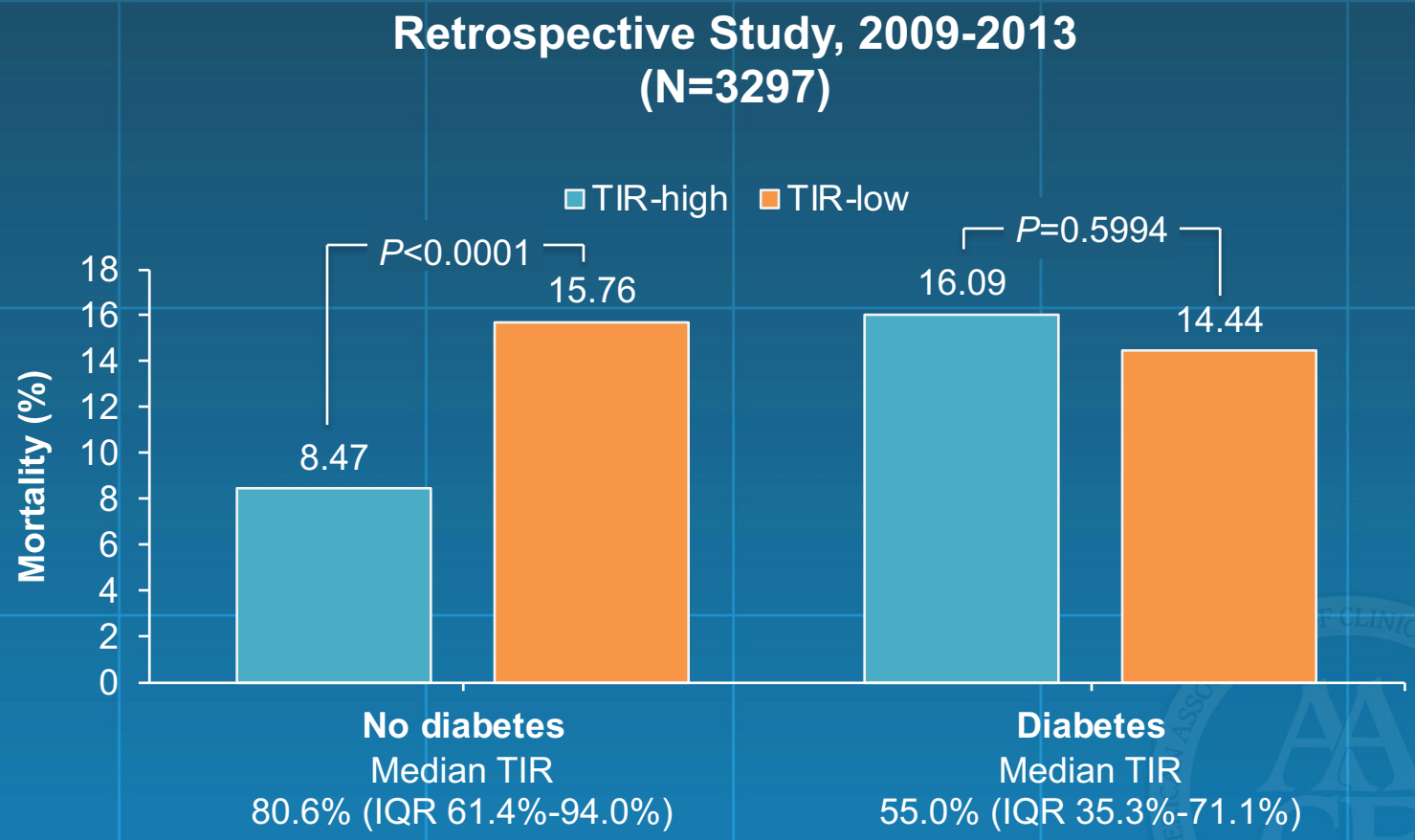
* *P*=0.03; †*P*=0.01.

‡ Complications include all in-hospital complications except for abnormalities of glucose.

McAlister FA, et al. *Diabetes Care*. 2005;28:810-815.

OUTCOMES ASSOCIATED WITH GLYCEMIC CONTROL IN THE HOSPITAL

Association Between Mortality and Time in Target Blood Glucose Range



IQR, interquartile range; TIR, time in range; TIR-high, time in targeted blood glucose range above median value for cohort; TIR-low, time in targeted blood glucose range below median value for cohort.

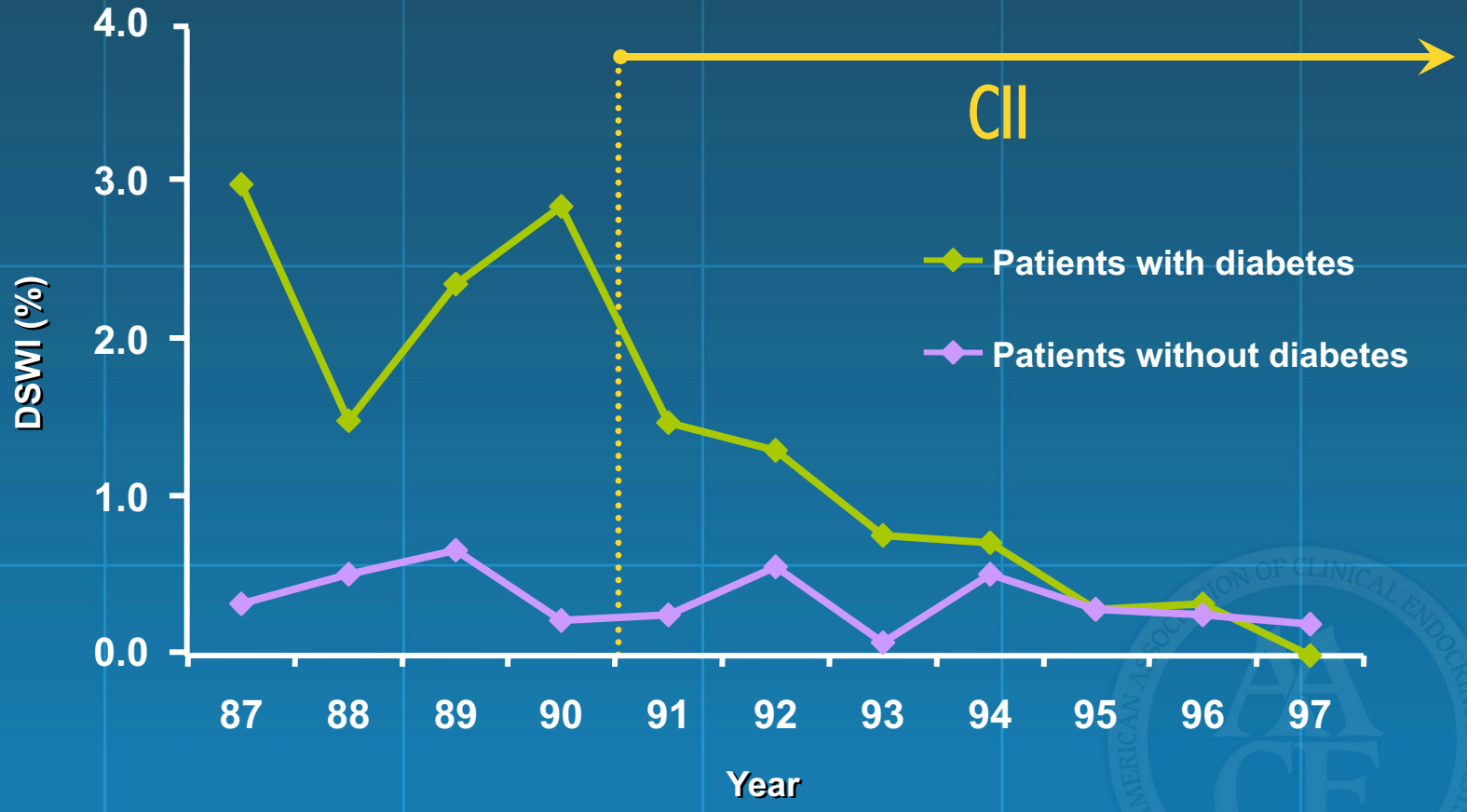
Krinsley JS, Preiser J-C. *Crit Care*. 2015;19:179.

Benefits of Tight Glycemic Control: Observational Studies and Early Intervention Trials

Study	Setting	Population	Clinical Outcome
Furnary, 1999	ICU	DM undergoing open heart surgery	65% ↓ infection
Furnary, 2003	ICU	DM undergoing CABG	57% ↓ mortality
Krinsley, 2004	Medical/surgical ICU	Mixed, no Cardiac	29% ↓ mortality
Malmberg, 1995	CCU	Mixed	28% ↓ mortality After 1 year
Van den Berghe, 2001*	Surgical ICU	Mixed, with CABG	42% ↓ mortality
Lazar, 2004	OR and ICU	CABG and DM	60% ↓ A Fib post op survival 2 year

Kitabchi AE, et al. *Metabolism*. 2008;57:116-120.

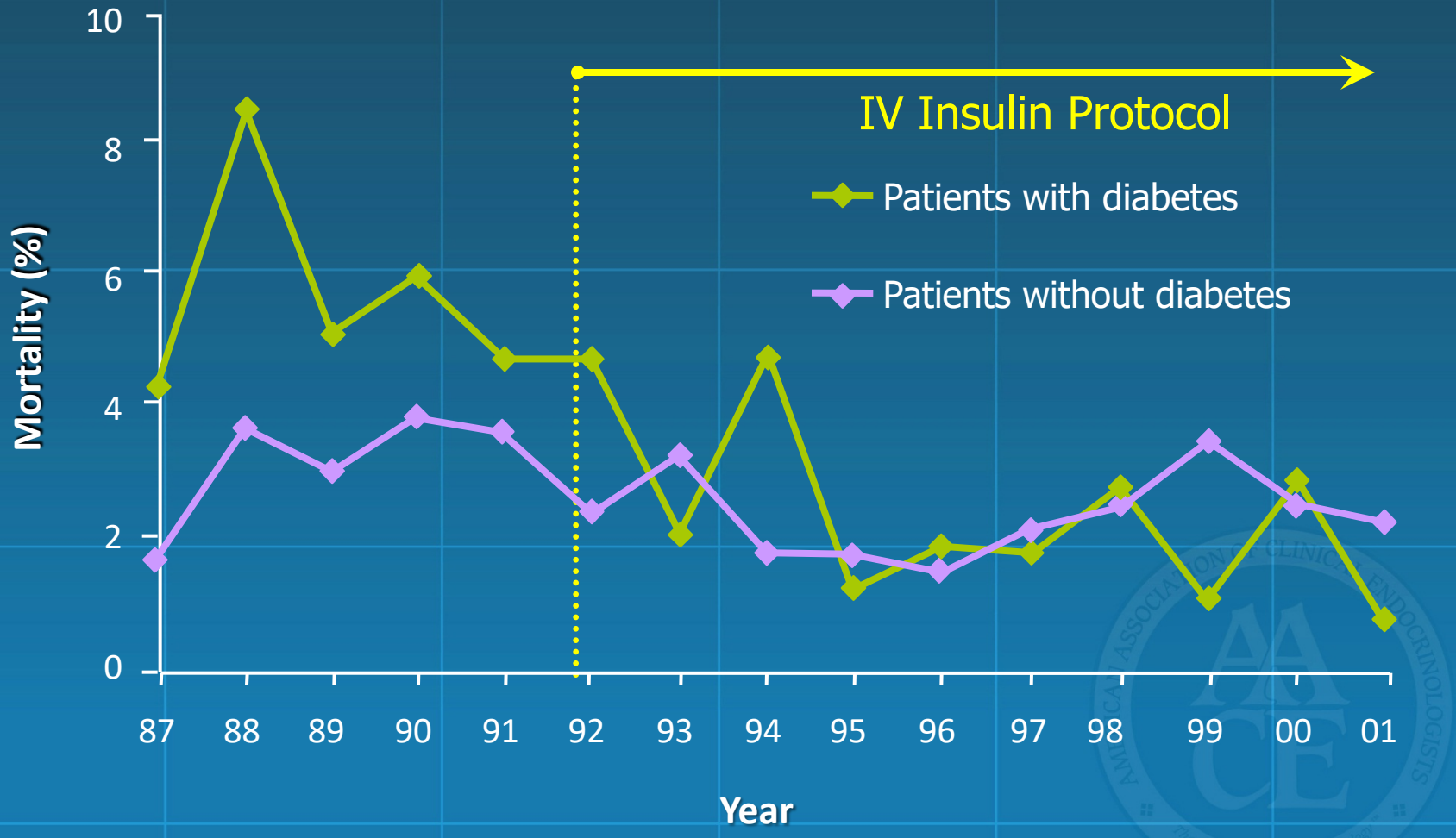
Portland Diabetic Project
Incidence of DSWI and Impact of Implementation of Insulin Infusion Protocols; 1987-1997



DSWI, deep sternal wound infection; CII, continuous insulin infusion.

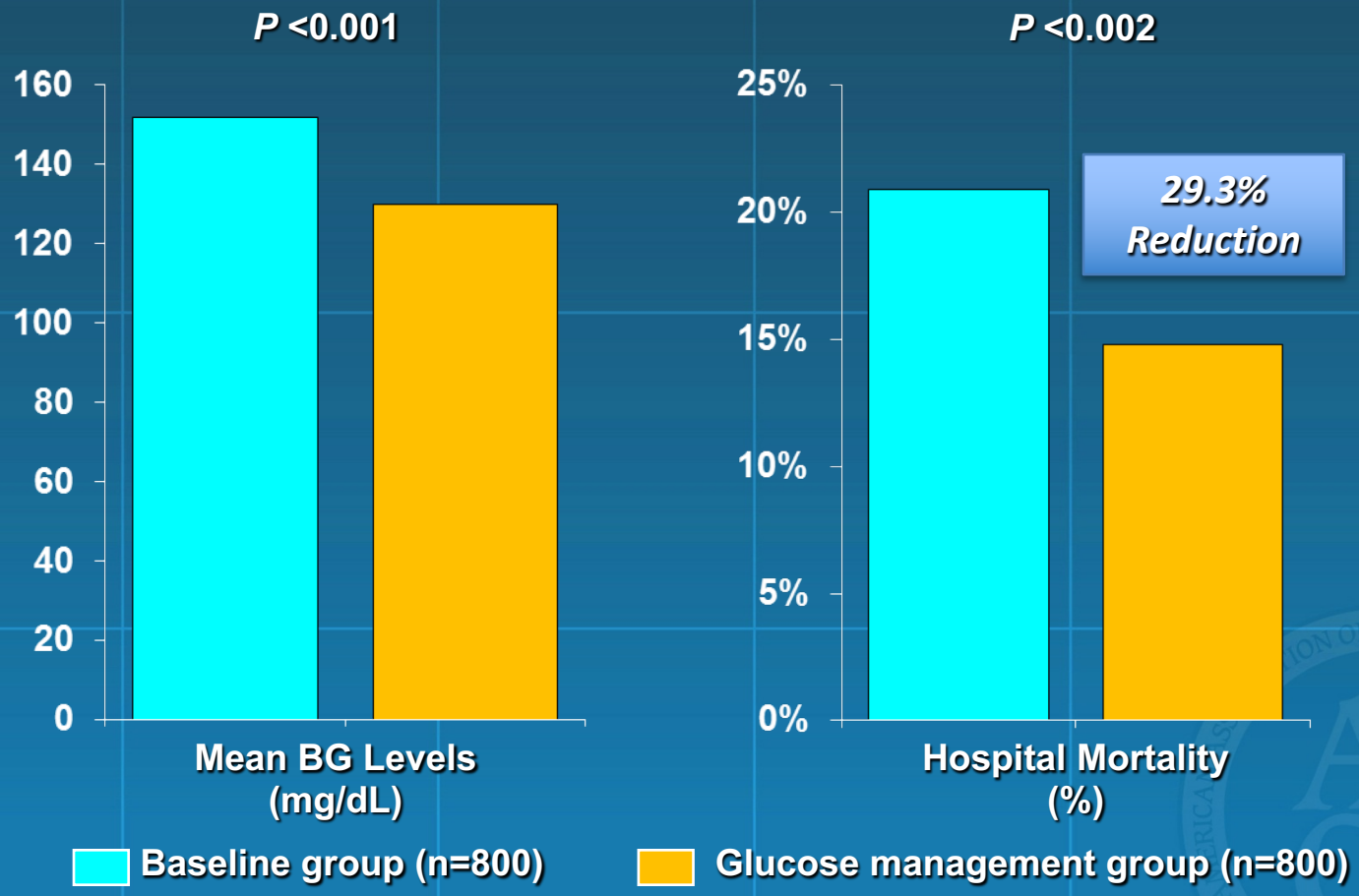
Furnary AP, et al. *Ann Thorac Surg*. 1999;67:352-362.

Glucose Control With IV Insulin Lowers Mortality Risk After Cardiac Surgery



Furnary AP, et al. *J Thorac Cardiovasc Surg.* 2003;125:1007-1021.

Intensive Insulin Management in Medical-Surgical ICU



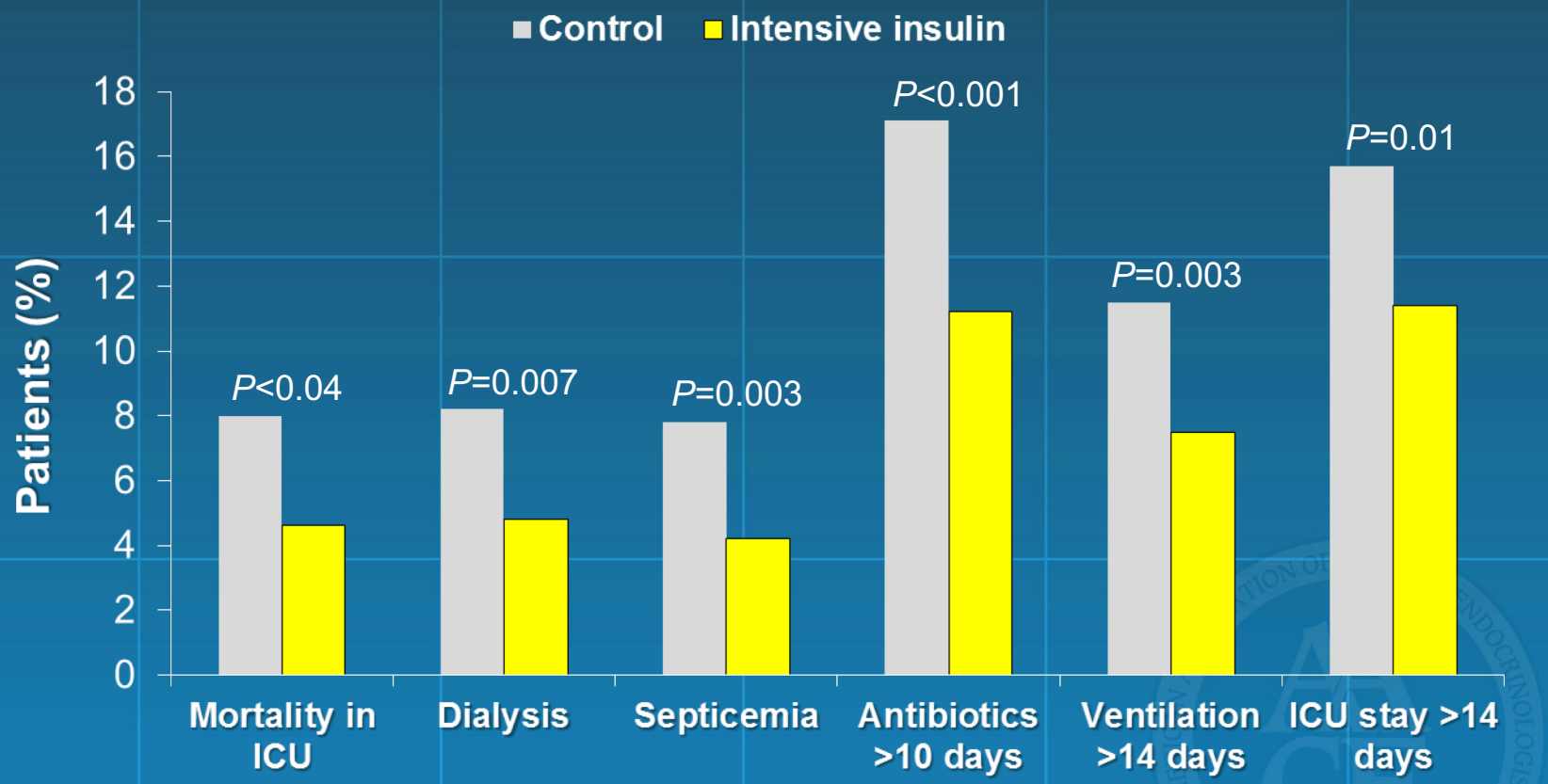
Krinsley JS. *Mayo Clin Proc*. 2004;79:992-1000.

Intensive Insulin Therapy in Critically Ill Patients: The Leuven SICU Study

- Randomized controlled trial
  - 1548 patients admitted to a surgical ICU, receiving mechanical ventilation
- Patients assigned to receive either:
  - Conventional therapy: IV insulin only if BG >215 mg/dL
    - Target BG levels: 180-200 mg/dL
    - Mean daily BG: 153 mg/dL
  - Intensive therapy: IV insulin if BG >110 mg/dL
    - Target BG levels: 80-110 mg/dL
    - Mean daily BG: 103 mg/dL

Van den Berghe G, et al. *N Engl J Med*. 2001;345:1359-1367.

Intensive Insulin Therapy in Critically Ill Patients: SICU



Van den Berghe G, et al. *N Engl J Med*. 2001;345:1359-1367.

RCTs of Inpatient Glucose Management

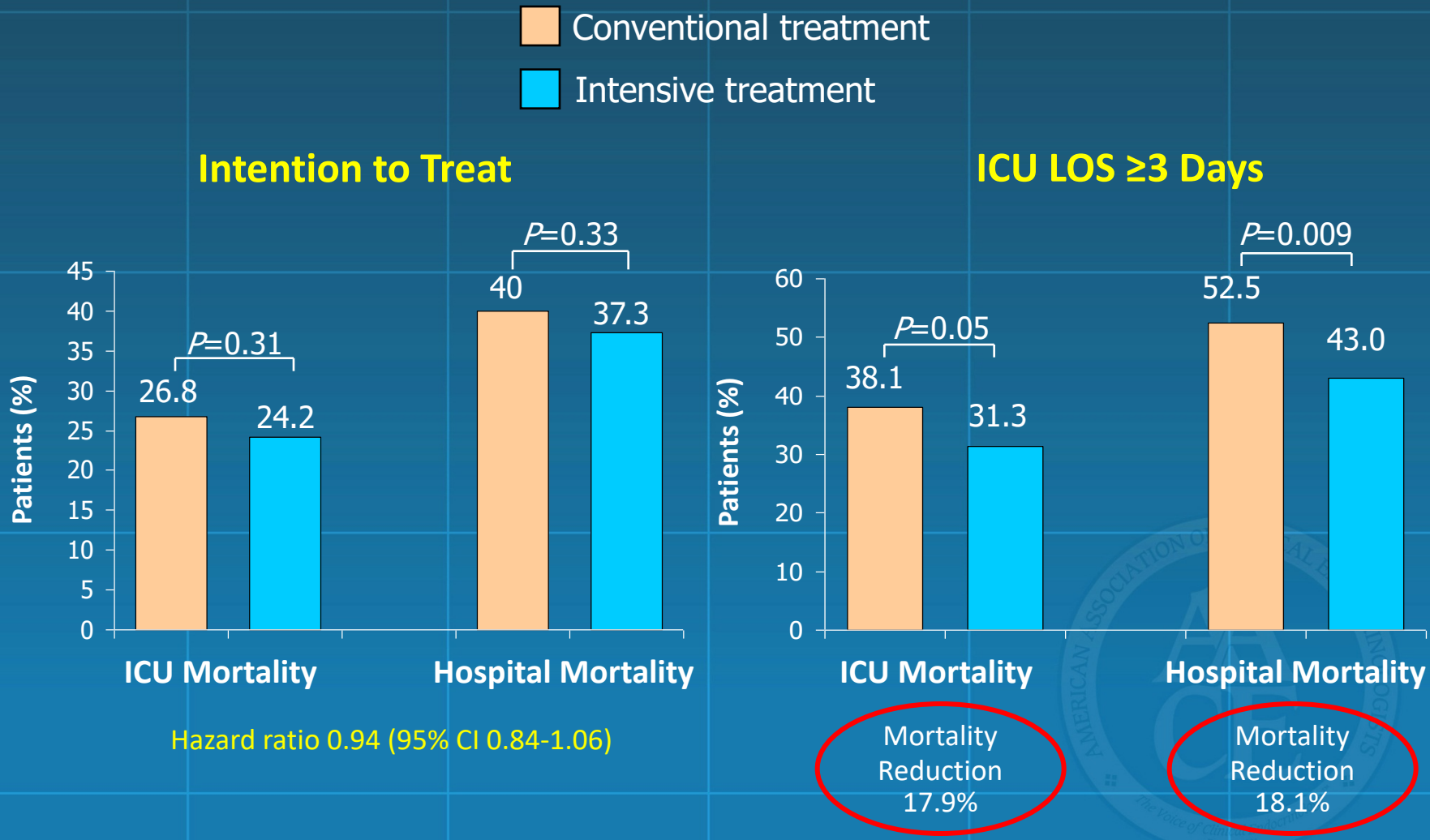
Trial	N	Setting	Primary Outcome	Odds Ratio (95% CI)	P value
Van den Berghe 2006	1200	MICU	Hospital mortality	0.94 (0.84-1.06)	N.S.
HI-5 2006	240	CCU AMI	6-mo mortality	NR	N.S.
Glucontrol 2007	1101	ICU	ICU mortality	1.10 (0.84-1.44)	N.S.
VISEP 2008	537	ICU	28-d mortality	0.89 (0.58-1.38)	N.S.
De La Rosa 2008	504	SICU MICU	28-d mortality	NR	N.S.
NICE-SUGAR 2009	6104	ICU	3-mo mortality	1.14 (1.02-1.28)	<0.05
Rabbit 2 Surgery 2011	211	SICU	Composite of postop outcomes	3.39 (1.50-7.65)	0.003

Intensive Insulin Therapy in the Medical Intensive Care Unit: The Leuven Study

- Randomized controlled trial
  - 1200 patients admitted to a medical ICU
- Patients assigned to receive either:
  - Conventional therapy: IV insulin if BG >215 mg/dL
    - Target BG levels: 180-200 mg/dL
    - Mean daily BG: 153 mg/dL
  - Intensive therapy: IV insulin if BG >110 mg/dL
    - Target BG levels: 80-110 mg/dL
    - Mean daily BG: 111 mg/dL

Van Den Berghe G, et al. *N Engl J Med.* 2006;354:449-461.

Intensive Insulin Therapy in MICU: Hospital Mortality



Van Den Berghe G, et al. *N Engl J Med.* 2006;354:449-461.

Intensive Insulin Therapy in MICU: Hypoglycemia

	Conventional (605)	Intensive (595)
Hypoglycemia events # (%)	19 (3.1)	111 (18.7)
Two or more episodes	5 (0.8)	23 (3.9)
Glucose level (mg/dL)	31 ± 8	32 ± 5

Identified hypoglycemia as an "independent risk factor for death"

Van Den Berghe G, et al. *N Engl J Med.* 2006;354:449-461.

Glucontrol Trial

- Compare the effects of 2 regimens of insulin therapy on clinical outcome:
  - Intensive therapy group:
    - Target BG: 80-110 mg/dL
      Achieved mean BG: 118 mg/dL (109-131 mg/dL)
  - Conventional therapy group:
    - Target BG: 140-180 mg/dL
      Achieved mean BG: 147 mg/dL (127-163 mg/dL)
  - Nondiabetic patients: 872
  - Diabetic patients: 210

Preiser JC, et al. *Intensive Care Med*. 2009;35:1738-1748.

Glucontrol Trial

	Intensive Insulin Therapy (n=536)	Conventional Insulin Therapy (n=546)	P
Nondiabetic patients			
872 patients	446	426	0.738
Deaths	17.0%	16.2%	
Diabetic patients			
210 patients	90	120	0.298
Deaths	16.7%	11.7%	

Preiser JC, et al. *Intensive Care Med*. 2009;35:1738-1748.

Glucontrol Trial

	Intensive Insulin Therapy (n=536)	Conventional Insulin Therapy (n=546)	P
Mortality rate, %	16.97	15.20	0.465
Patients with hypoglycemia,* %	8.6	2.4	<0.0001
Death among patients with hypoglycemia,* %	32.6	53.8	0.1621

* Blood glucose <40 mg/dL.

Preiser JC, et al. *Intensive Care Med*. 2009;35:1738-1748.

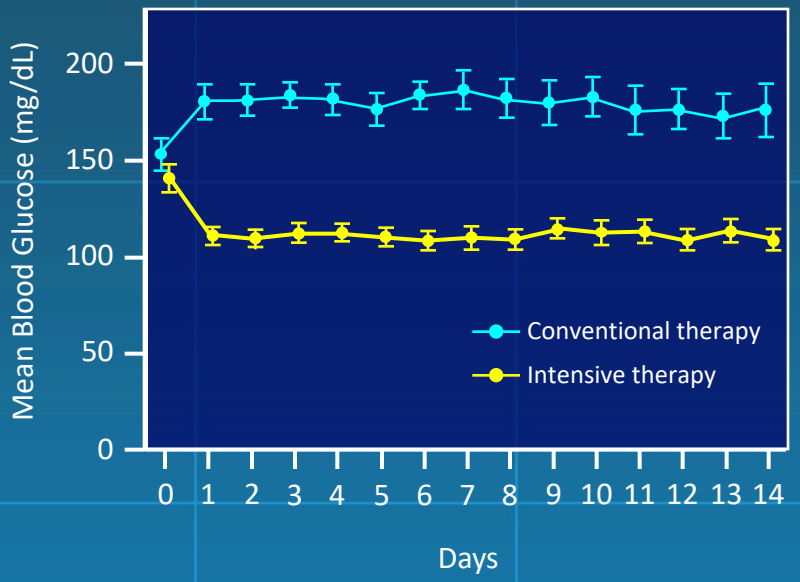
VISEP Trial

- Study aim: evaluate clinical outcome in 600 subjects with sepsis randomized to conventional or intensive insulin therapy in 18 academic hospitals in Germany
  - Conventional therapy: Continuous insulin infusion (CII) started at BG >200 mg/dL and adjusted to maintain a BG 180-200 mg/dL (mean BG 151 mg/dL)
  - Intensive therapy: CII started at BG >110 mg/dL and adjusted to maintain BG 80-110 mg/dL (mean BG 112 mg/dL)
- Primary outcomes
  - Mortality (28 days) and morbidity (sequential organ failure dysfunction, SOFA)
  - Safety end-point: hypoglycemia (BG <40 mg/dL)

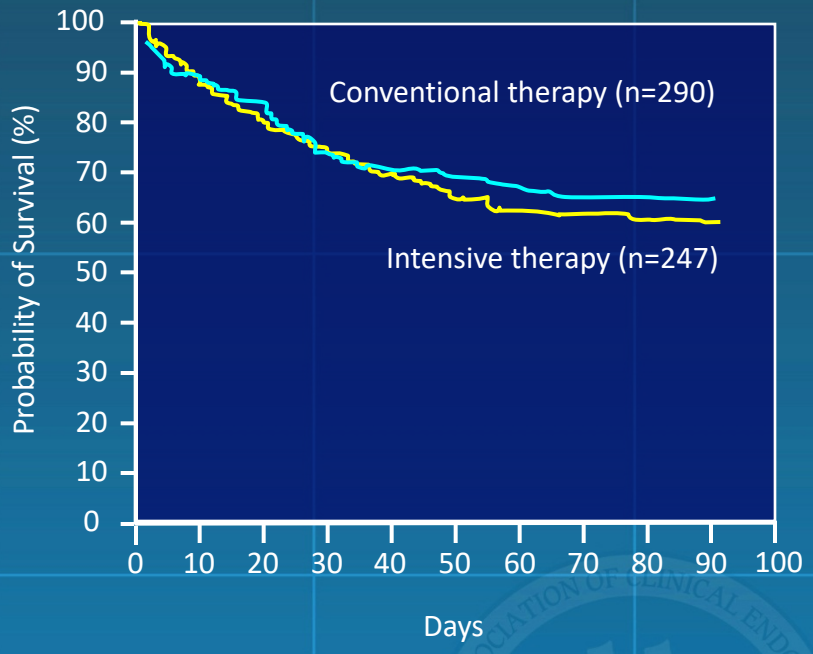
Brunkhorst FM, et al. *N Engl J Med.* 2008:358:125-139.

VISEP Trial

Blood Glucose



Overall Survival
No difference in mortality



Data from 537 patients:
247 received IIT goal: 80-110 mg/dL: mean BG 112 mg/dL
290 received CIT goal: 180-200 mg/dL: mean BG 151 mg/dL

IIT, intensive insulin therapy; CIT, conventional insulin therapy.
Brunkhorst FM, et al. *N Engl J Med.* 2008:358:125-139.

VISEP Trial

	Intensive Insulin Therapy (n=247)	Conventional Insulin Therapy (n=290)	P
Mortality rate, % 28 days 90 days	24.7 39.7	26.0 35.4	0.74 0.31
Patients with hypoglycemia,* %	17.0%	4.1%	<0.001
SOFA score (mean) 95% CI	7.8 7.3-8.3	7.7 7.3-8.2	0.16

* Blood glucose ≤40 mg/dL.

Brunkhorst FM, et al. *N Engl J Med.* 2008:358:125-139.

Intensive Insulin Therapy in Severe Sepsis and Severe Hypoglycemia (VISEP Study)

	Conventional Insulin Therapy (n=290)	Intensive Insulin Therapy (n=247)
	(Glucose ≤40 mg/dL)	
# of patients with hypo events	12	42
% of patients with hypo events	4.1	17.0
% of patients with life-threatening hypo events	2.1	5.3

Hypoglycemia identified as an independent risk factor for mortality*

* Personal communication, Dr. Frank Brunkhorst

Brunkhorst FM, et al. *N Engl J Med.* 2008:358:125-139.

Intensive Glycemic Control in a Mixed ICU

	Intensive (n=254)	Standard (n=250)
Mean AM glucose, mg/dL	117	148
28-day mortality, n (%)	93 (36.6)	81 (32.4)
In-hospital mortality, n (%)	102 (40)	96 (38.4)
Severe hypoglycemia (≤40 mg/dL), n (%)	21 (8.3)	2 (0.8)

504 patients; ~1/2 medical; single-center study from Colombia

De La Rosa Gdel C, et al. *Crit Care.* 2008;12:R120.

NICE-SUGAR Study

- Multicenter-multinational randomized, controlled trial (Australia, New Zealand, and Canada; N=6104 ICU patients)
  - Intensive BG target: 4.5-6.0 mmol/L (81-108 mg/dL)
  - Conventional BG target: <10.0 mmol/L (180 mg/dL)
- Primary outcome: Death from any cause within 90 days after randomization
- Patient population
  - Mean APACHE II score: ~21; APACHE >25: 31%
  - Reason for ICU admission: surgery: ~37%, medical: 63%
  - History of DM: 20% (T1DM: 8%, T2DM: 92%)
  - At randomization: sepsis: 22%, trauma: 15%

Finfer S, et al. *N Engl J Med*. 2009;360:1283-1297.

NICE-SUGAR: Baseline Characteristics

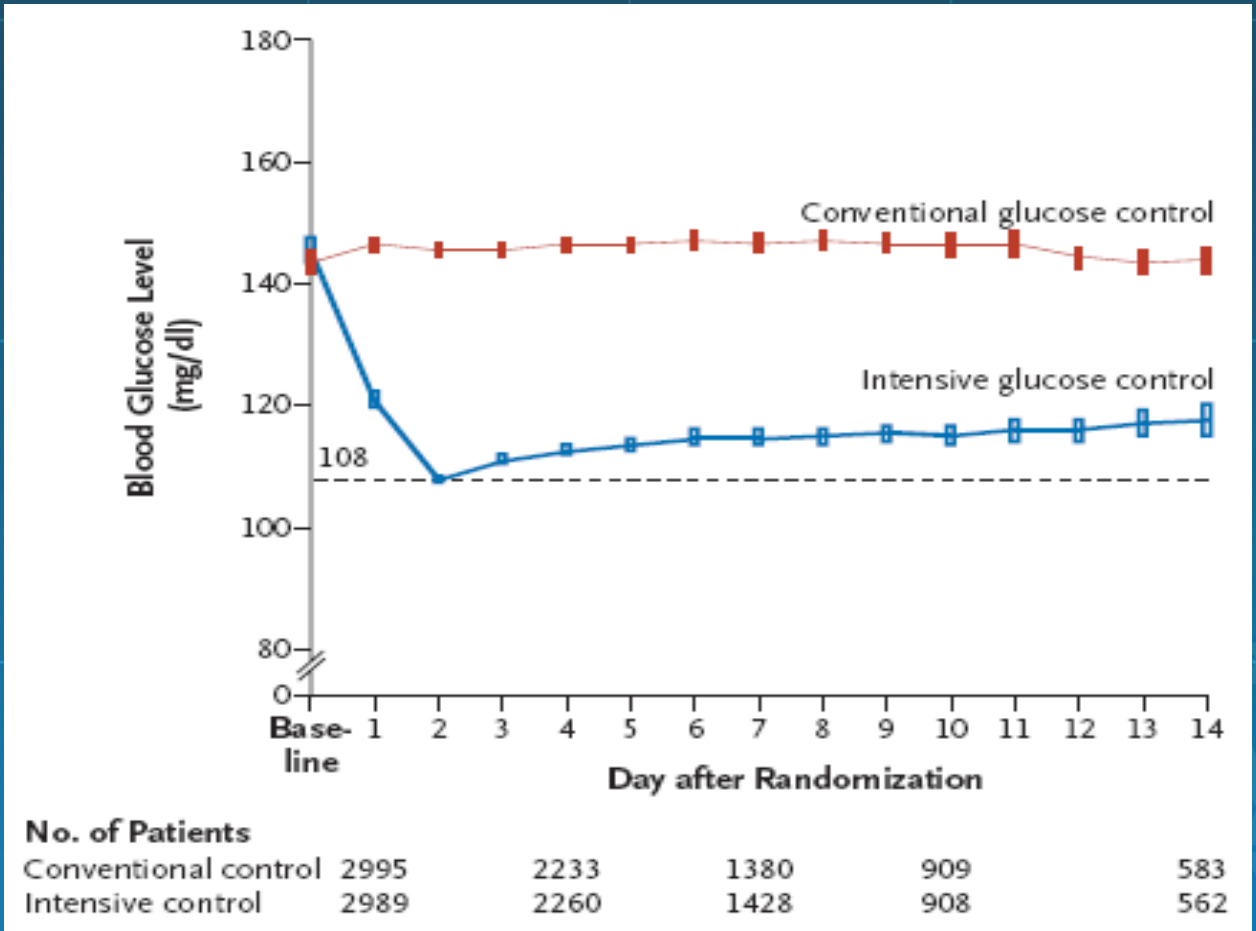
- Age: ~60 years
- Gender: ~36% female
- Diabetes: ~20% (BMI ~28 kg/m^2)
- Interval, ICU admission to randomization: 13.4 h
- Reason for ICU admission:
  - Operative* ~37%
  - Non-operative† ~63%
- Sepsis: ~22%
- Trauma: ~15%

* No significant numbers of CT surgery patients.

† No significant numbers of CCU patients.

Finfer S, et al. *N Engl J Med*. 2009;360:1283-1297.

NICE-SUGAR: Intensive vs Conventional Glucose Control in Critically Ill Patients

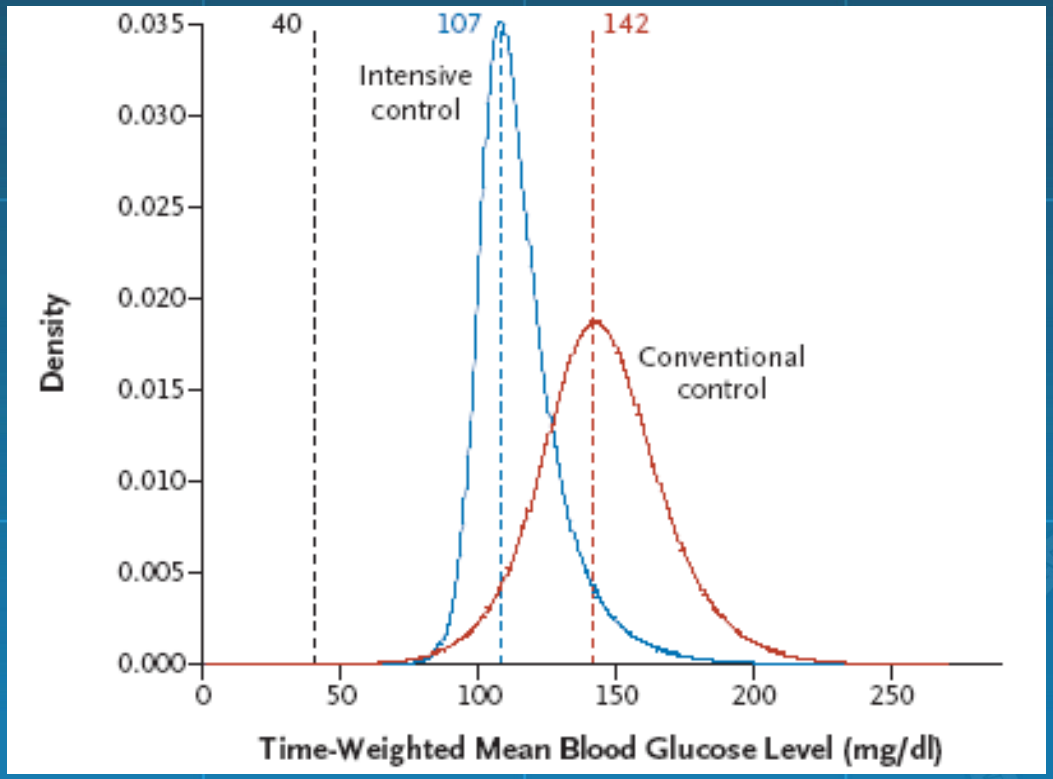


Bars are 95% confidence intervals. Dashed line =108 mg/dL (upper limit of intensive glucose control target range).

Finfer S, et al. *N Engl J Med*. 2009;360:1283-1297.

NICE-SUGAR: Intensive vs Conventional Glucose Control in Critically Ill Patients

Density Plot for Mean Time-Weighted Blood Glucose Levels for Individual Patients



The dashed lines indicate the modes (most frequent values) in the intensive control group (blue) and the conventional-control group (red), as well as the upper threshold for severe hypoglycemia (black).

Finfer S, et al. *N Engl J Med*. 2009;360:1283-1297.

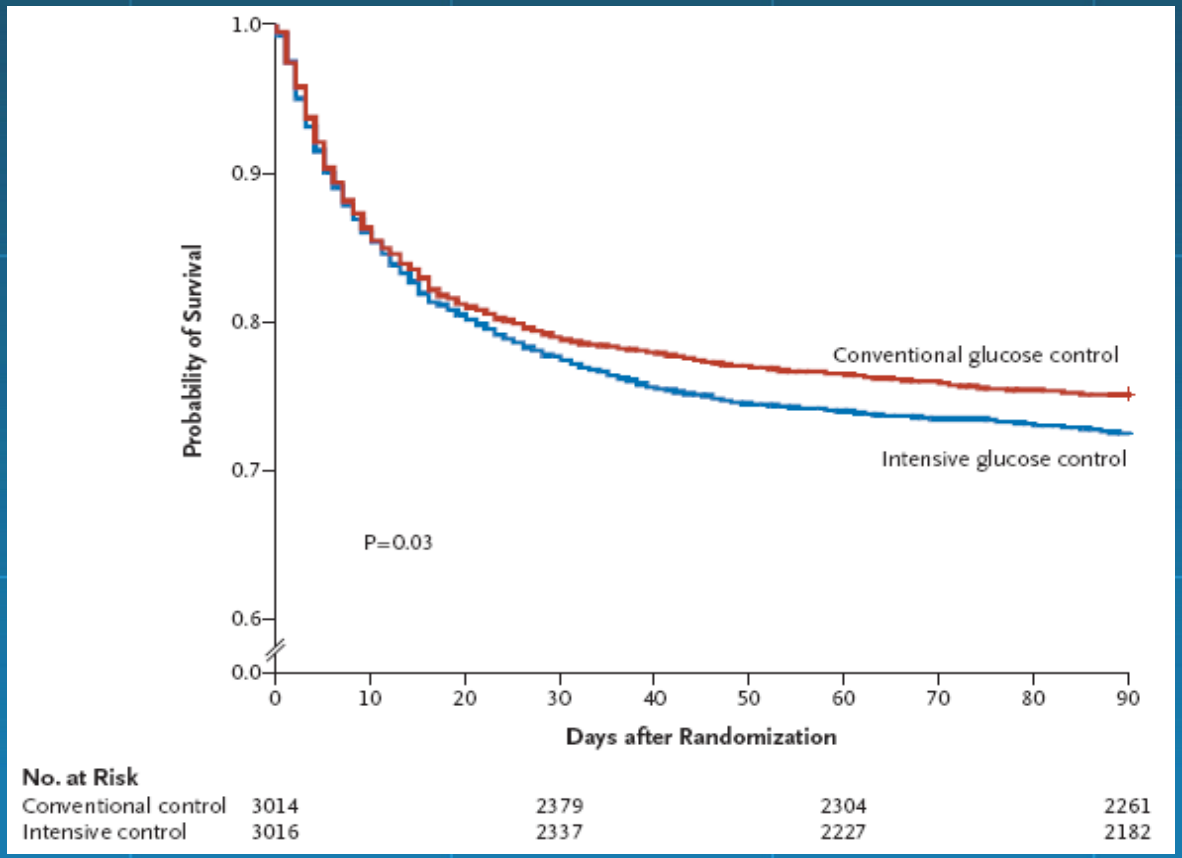
NICE-SUGAR Study Outcomes

Outcome Measure	Intensive Group	Conventional Group
Morning BG (mg/dL)	118 ± 25	145 ± 26
Hypoglycemia (≤40mg/dL)	206/3016 (6.8%)	15/3014 (0.5%)
28-Day Mortality (*P*=0.17)	22.3%	20.8%
90-Day Mortality (*P*=0.02)	27.5%	24.9%

Finfer S, et al. *N Engl J Med*. 2009;360:1283-1297.

NICE-SUGAR: Intensive vs Conventional Glucose Control in Critically Ill Patients

Kaplan–Meier Estimates for the Probability of Survival

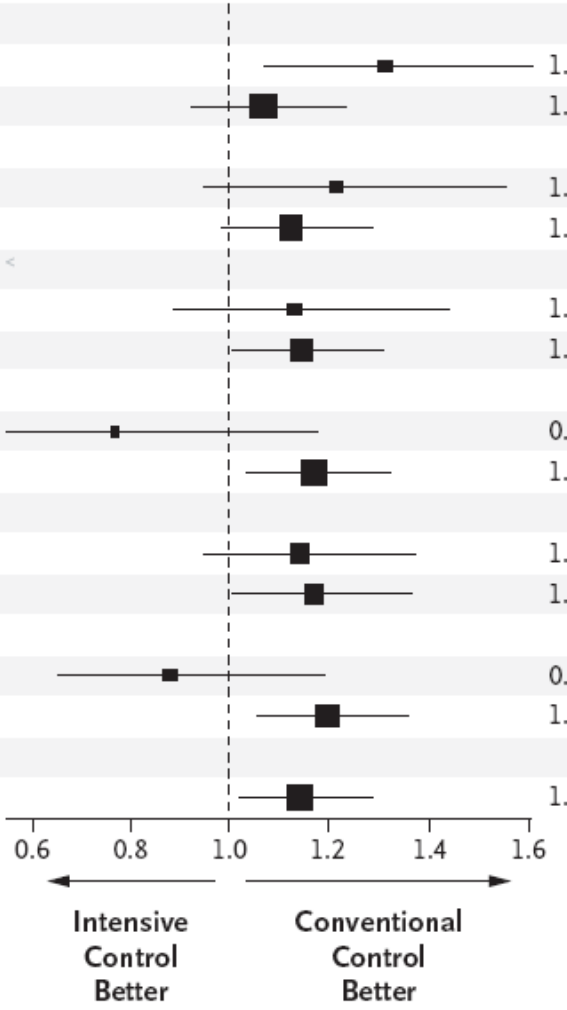


% HR = 1.11
95 confidence interval: (1.01-1.23)

Finfer S, et al. *N Engl J Med*. 2009;360:1283-1297.

NICE-SUGAR: Probability of Survival and Odds Ratios for Death, According to Treatment Group

Subgroup	Intensive Control (N=3010)	Conventional Control (N=3012)	Odds Ratio for Death (95% CI)	P Value for Heterogeneity
	no. of deaths/no. with data available			
Operative admission				0.10
Yes	272/1111	222/1121	1.31 (1.07–1.61)	
No	557/1898	529/1891	1.07 (0.93–1.23)	
Diabetes				0.60
Yes	195/615	165/596	1.21 (0.95–1.55)	
No	634/2394	586/2416	1.12 (0.99–1.28)	
Severe sepsis				0.93
Yes	202/673	172/626	1.13 (0.89–1.44)	
No	627/2335	579/2386	1.15 (1.01–1.31)	
Trauma				0.07
Yes	41/421	57/465	0.77 (0.50–1.18)	
No	788/2587	694/2547	1.17 (1.04–1.32)	
APACHE II score				0.84
≥25	386/927	363/944	1.14 (0.95–1.37)	
<25	442/2080	387/2066	1.17 (1.01–1.36)	
Corticosteroids				0.06
Yes	134/392	140/378	0.88 (0.66–1.19)	
No	695/2616	611/2634	1.20 (1.06–1.36)	
All deaths at day 90	829/3010	751/3012	1.14 (1.02–1.28)	0.02



Finfer S, et al. *N Engl J Med*. 2009;360:1283-1297.

NICE-SUGAR: Conclusions

- This large, international, randomized trial found that intensive glucose control did not offer any benefit in critically ill patients
- Blood glucose target of <180 mg/dL with the achieved target of 144 mg/dL resulted in lower (90-day) mortality than did a target of 81-108 mg/dL
- There was increased hypoglycemia with lower glucose targets

Finfer S, et al. *N Engl J Med*. 2009;360:1283-1297.

NICE-SUGAR: Strengths

- Large (N=6104)
- Multicenter
- Patients characteristic of a general ICU population
- Uniformly applied, web-based IV insulin protocol
- Hard primary endpoint (90-day mortality)
- Robust analytical plan

Finfer S, et al. *N Engl J Med*. 2009;360:1283-1297.

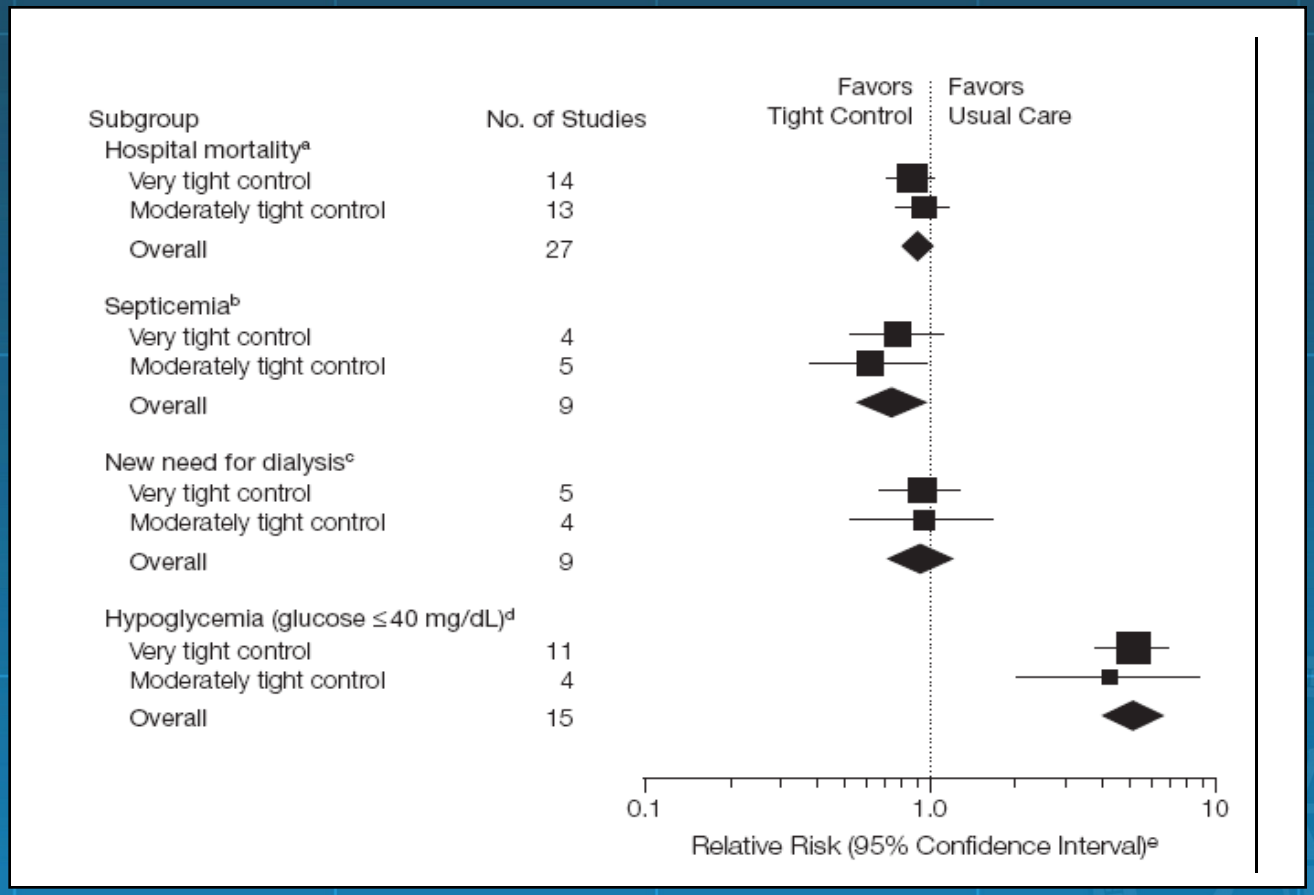
NICE-SUGAR: Limitations

- Specified BG targets and ultimate BG separation (-27 mg/dL) not as distinct as prior trials
- Treatment target not achieved in the intensive arm
- Variable methods/sources for BG measurement
- More steroid therapy in intensive arm
- More hypoglycemia in intensive arm (15-fold)
- No explanation of increased mortality in intensive arm (? hypoglycemia)
- ~10% early withdrawals in intensive arm; "per-protocol" ("completers") analysis not provided

Finfer S, et al. *N Engl J Med*. 2009;360:1283-1297.

Tight Glycemic Control in Critically Ill Adults

A Meta-analysis of 29 Randomized Controlled Trials



Very tight, moderately tight glycemia control and severe hypoglycemia

Wiener RS, et al. *JAMA.* 2008:300:933-944.

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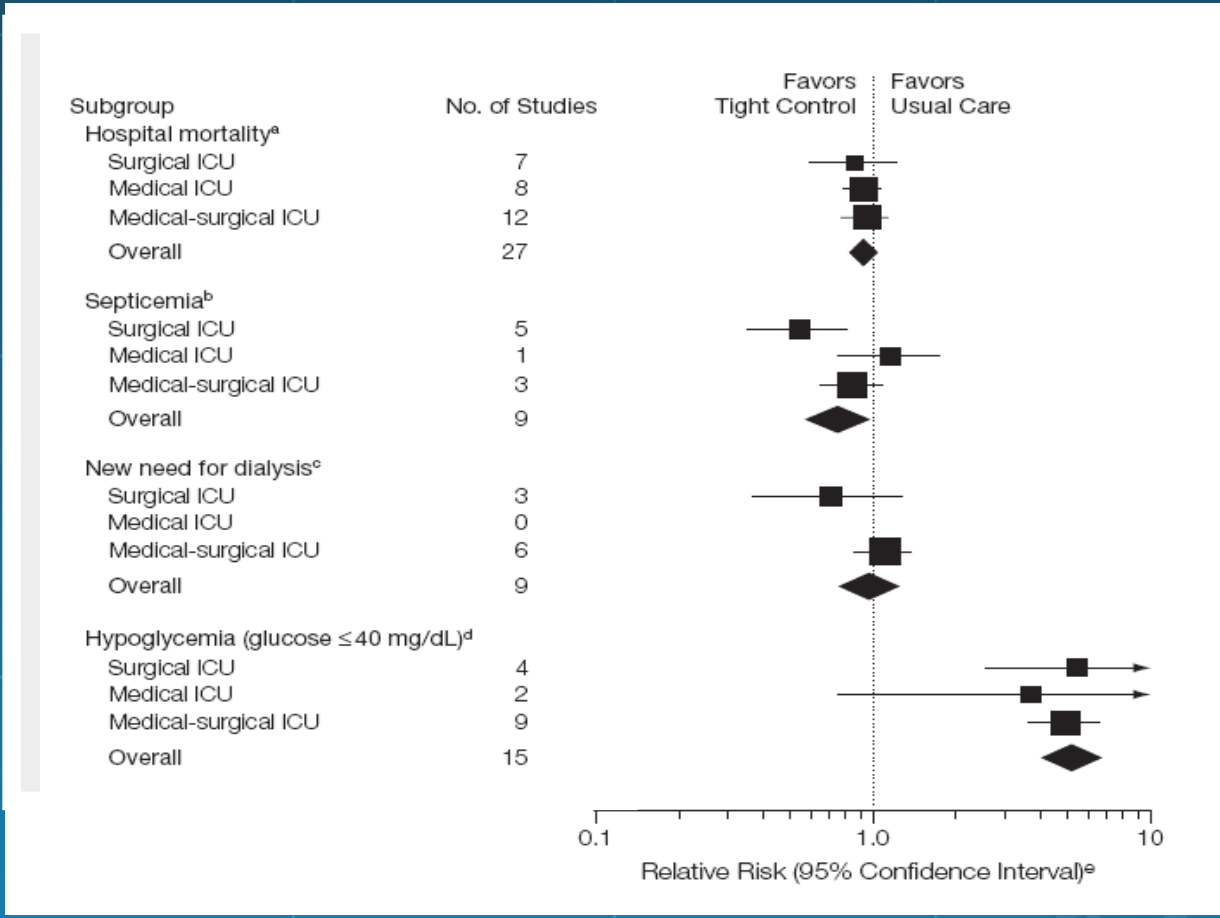
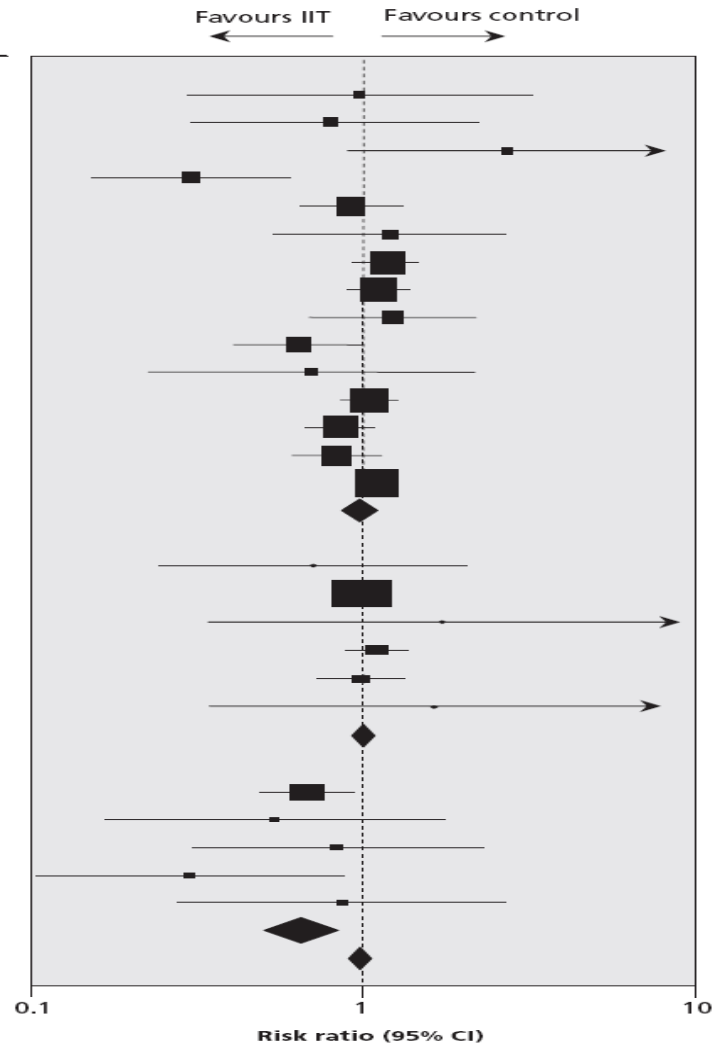


SICU, MICU, mixed ICU, and severe hypoglycemia

Wiener RS, et al. *JAMA.* 2008:300:933-944.

Meta-analysis: Intensive Insulin Therapy and Mortality

Study	No. deaths / total no. patients: IIT	Control	Risk ratio (95% CI)
Mixed ICU			
Yu et al.[39]	4/28	4/27	0.96 (0.27–3.47)
Henderson et al.[31]	5/32	7/35	0.78 (0.28–2.22)
Mitchell et al.[35]	9/35	3/35	3.00 (0.89–10.16)
Wang et al.[38]	7/58	26/58	0.27 (0.13–0.57)
Azevedo et al.[22]	38/168	42/169	0.91 (0.62–1.34)
McMullin et al.[34]	6/11	4/9	1.23 (0.49–3.04)
Devos et al.[13]	107/550	89/551	1.20 (0.93–1.55)
Brunkhorst et al.[11]	98/247	102/288	1.12 (0.90–1.39)
Iapichino et al.[32]	15/45	12/45	1.25 (0.66–2.36)
He et al.[30]	16/58	29/64	0.61 (0.37–1.00)
Zhang et al.[40]	4/168	6/170	0.67 (0.19–2.35)
De La Rosa Gdel et al.[12]	102/254	96/250	1.05 (0.84–1.30)
Arabi et al.[10]	72/266	83/257	0.84 (0.64–1.09)
Mackenzie et al.[33]	39/121	47/119	0.82 (0.58–1.15)
NICE-SUGAR[18]	829/3010	751/3012	1.10 (1.01–1.20)
All mixed ICU patients	1351/5051	1301/5089	0.99 (0.87–1.12)
Medical ICU			
Bland et al.[25]	1/5	2/5	0.50 (0.06–3.91)
Van den Berghe et al.[9]	214/595	228/605	0.95 (0.82–1.11)
Walters et al.[37]	1/13	0/12	2.79 (0.12–62.48)
Farah et al.[27]	22/41	22/48	1.17 (0.77–1.78)
Oksanen et al.[36]	13/39	18/51	0.94 (0.53–1.68)
Bruno et al.[26]	2/31	0/15	2.50 (0.13–49.05)
All medical ICU patients	253/724	270/736	1.00 (0.78–1.28)
Surgical ICU			
Van den Berghe et al.[8]	55/765	85/783	0.66 (0.48–0.92)
Grey et al.[28]	4/34	6/27	0.53 (0.17–1.69)
Bilotta et al.[24]	6/40	7/38	0.81 (0.30–2.20)
He et al.[29]	7/150	6/38	0.30 (0.11–0.83)
Bilotta et al.[23]	5/48	6/49	0.85 (0.28–2.60)
All surgical ICU patients	77/1037	110/935	0.63 (0.44–0.91)
All ICU patients	1681/6812	1681/6760	0.93 (0.83–1.04)



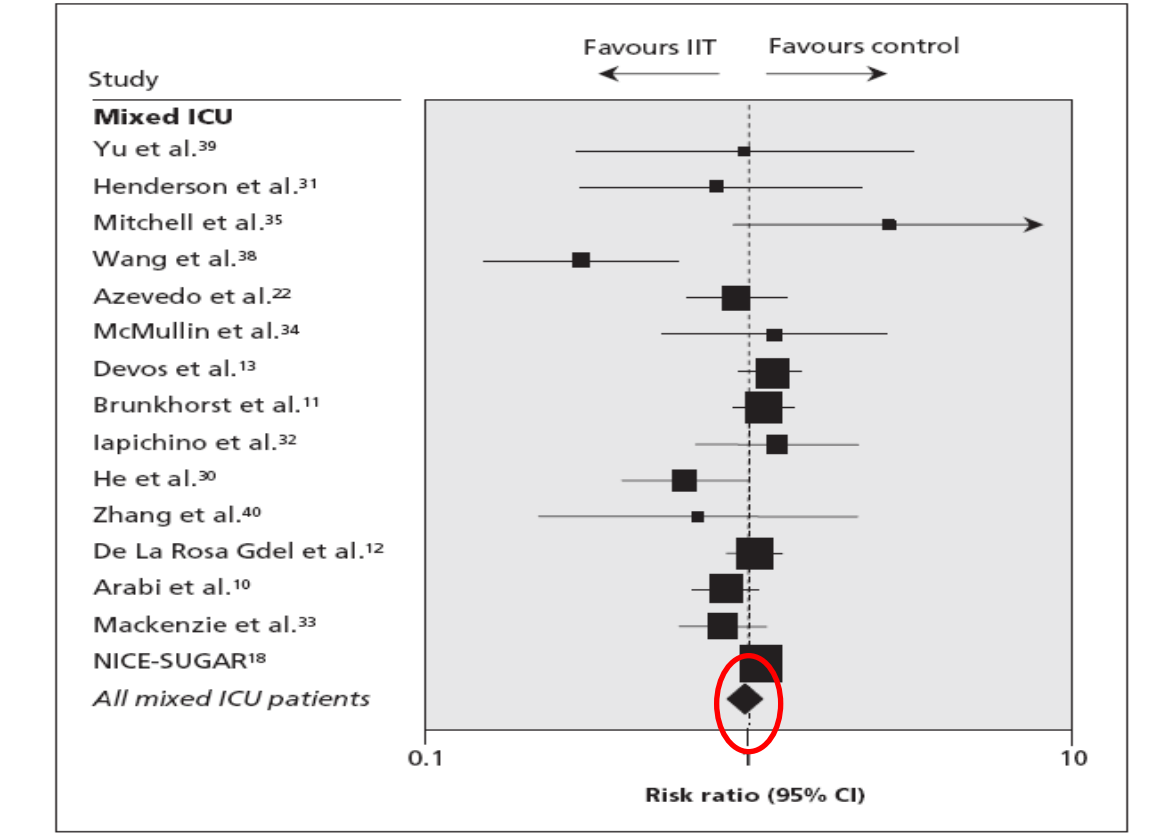
Griesdale DE, et al. *CMAJ*. 2009;180:821-827.

Tight Glycemic Control in Critically Ill Adults

A Meta-analysis of 26 Randomized Controlled Trials (13,567 patients)

All-Cause Mortality

Mixed ICU



Griesdale DE, et al. *CMAJ*. 2009;180:821-827.

Tight Glycemic Control in Critically Ill Adults

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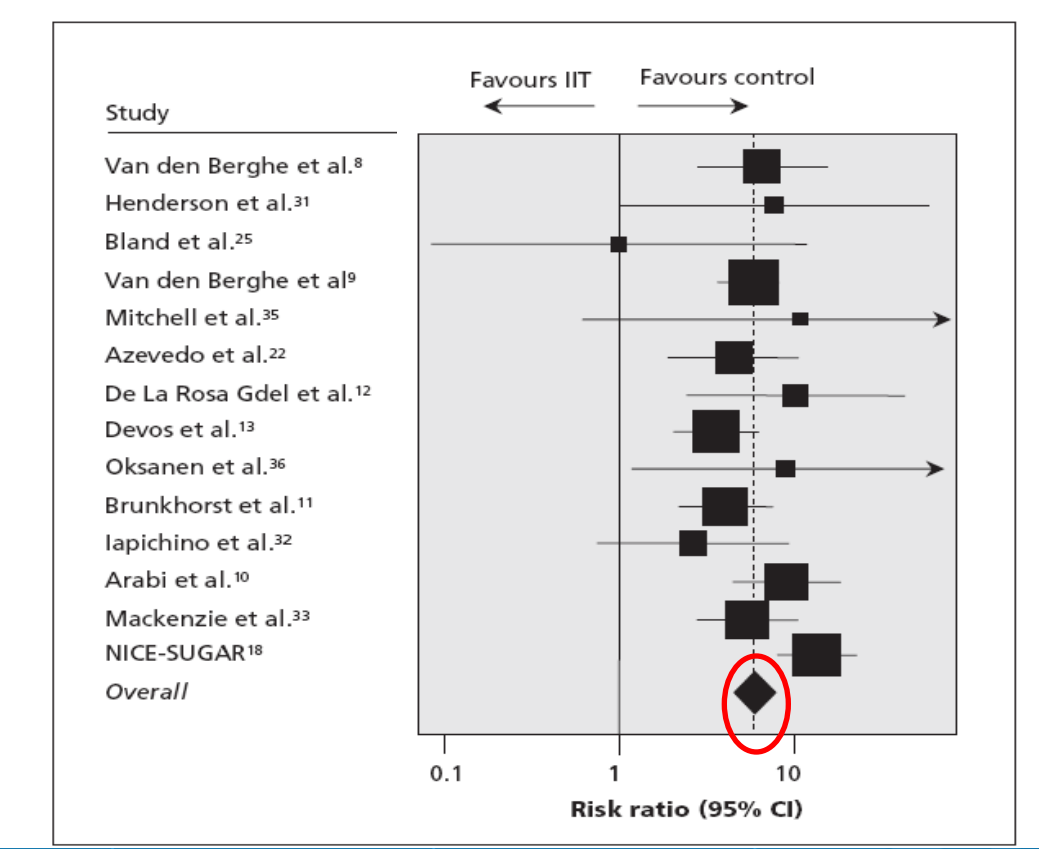
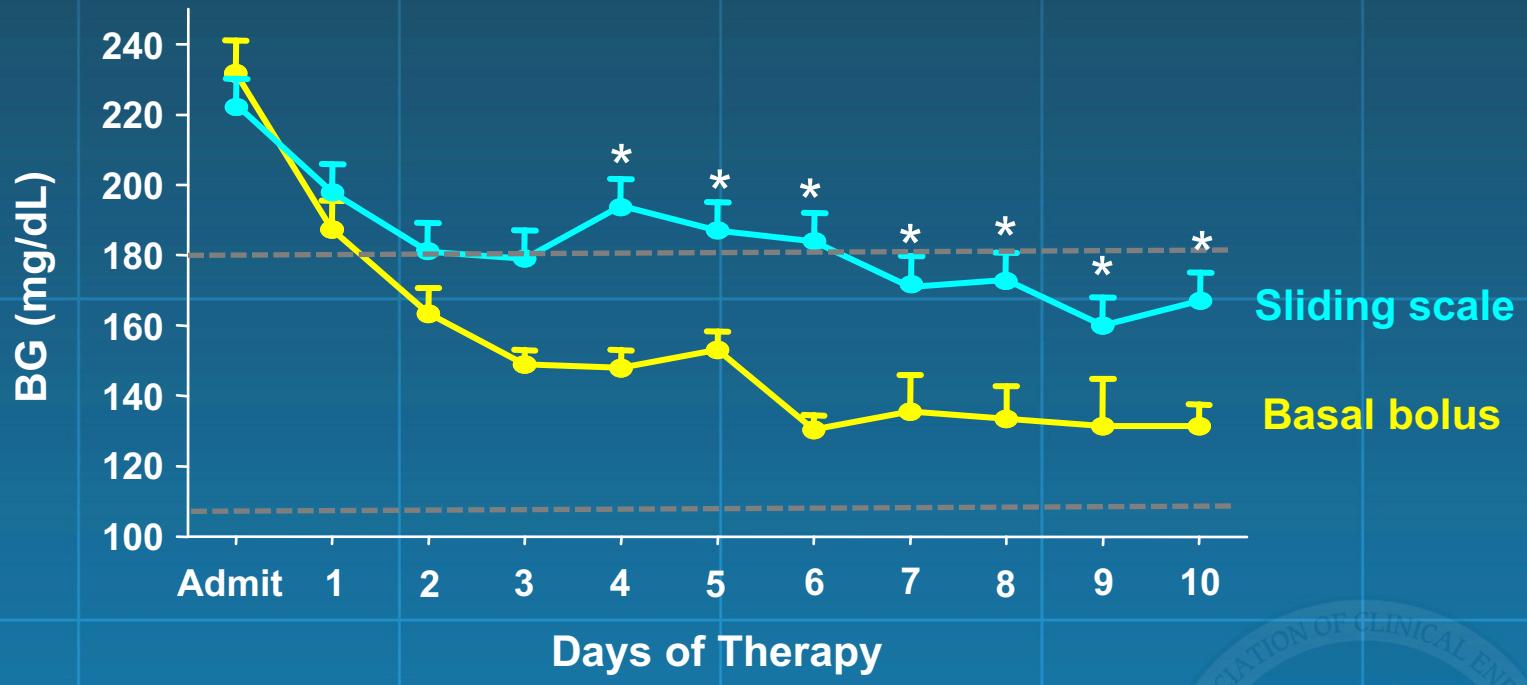
Severe Hypoglycemia (≤40 mg/dL)



Griesdale DE, et al. *CMAJ*. 2009;180:821-827.

Rabbit 2 Trial: Changes in Glucose Levels With Basal-Bolus vs Sliding Scale Insulin

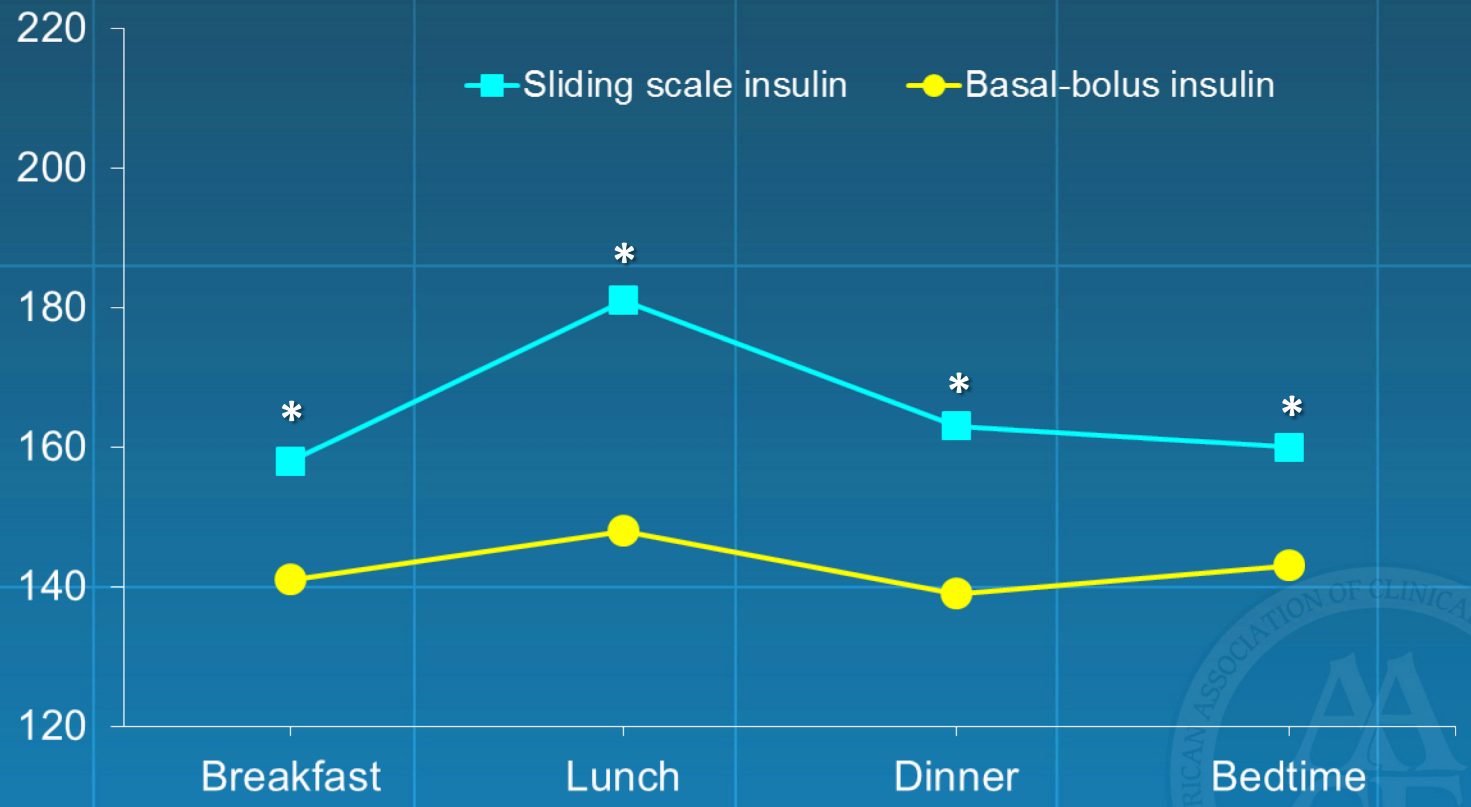


* *P*<0.05.

Sliding scale regular insulin (SSRI): given 4 times daily.
Basal-bolus regimen: glargine once daily; glulisine before meals.
0.4 U/kg/d x BG between 140-200 mg/dL
0.5 U/kg/d x BG between 201-400 mg/dL

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

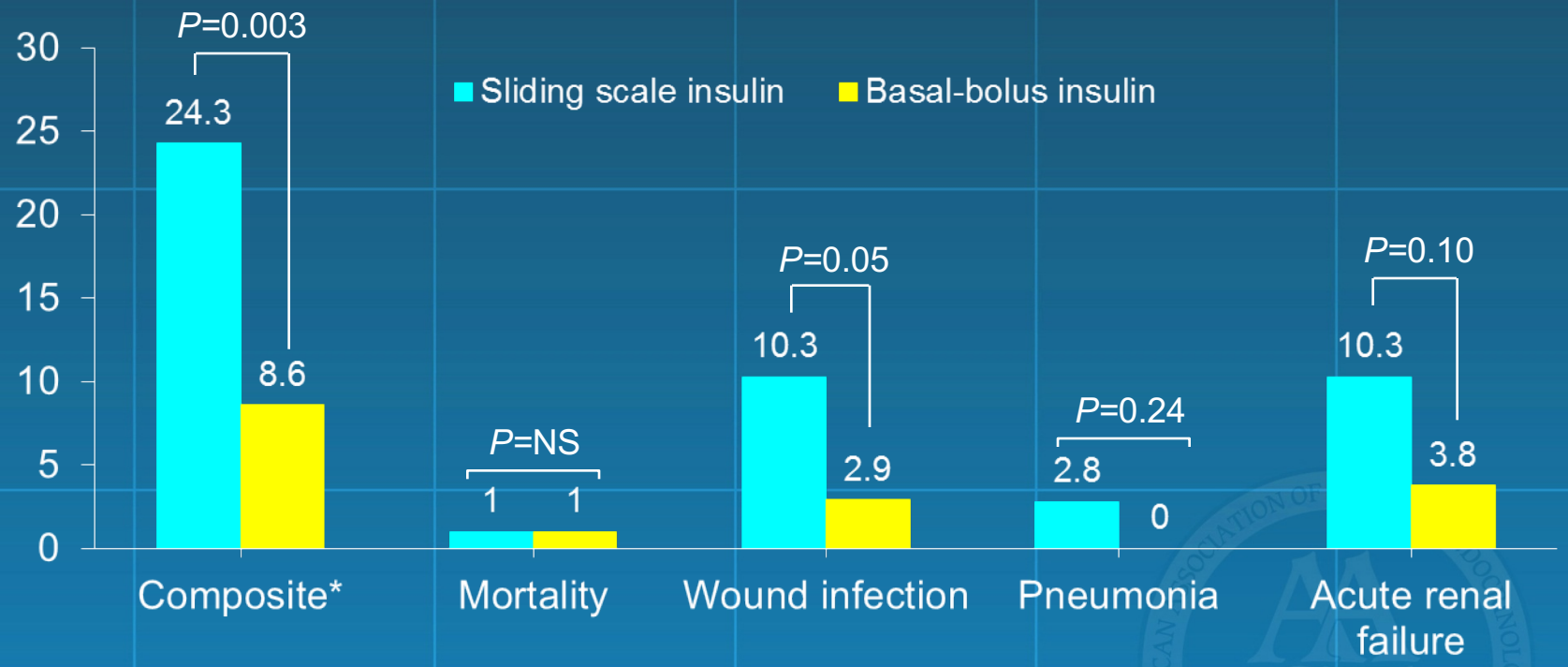
Mean BG Before Meals and at Bedtime During Basal-Bolus and SSI Therapy in General Surgery Patients



* *P*<0.001.

Umpierrez GE, et al. *Diabetes Care.* 2011;34: 256-261.

Postoperative Complications During Basal-Bolus and SSI Therapy in General Surgery Patients



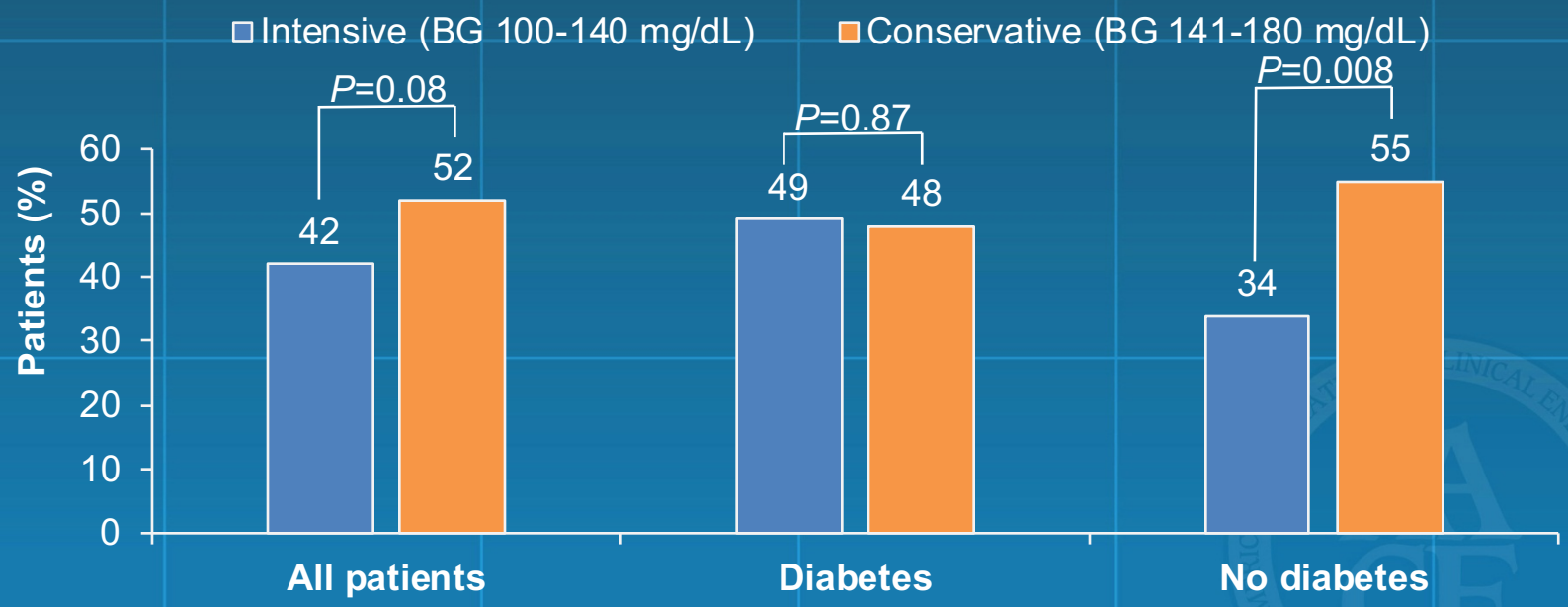
* Wound infection, pneumonia, respiratory failure, acute renal failure, and bacteremia.

Umpierrez GE, et al. *Diabetes Care.* 2011;34: 256-261.

Effect of Intensive Glucose Control on Complications in CABG

Randomized, Controlled Trial (N=302)

Prevalence of Complications

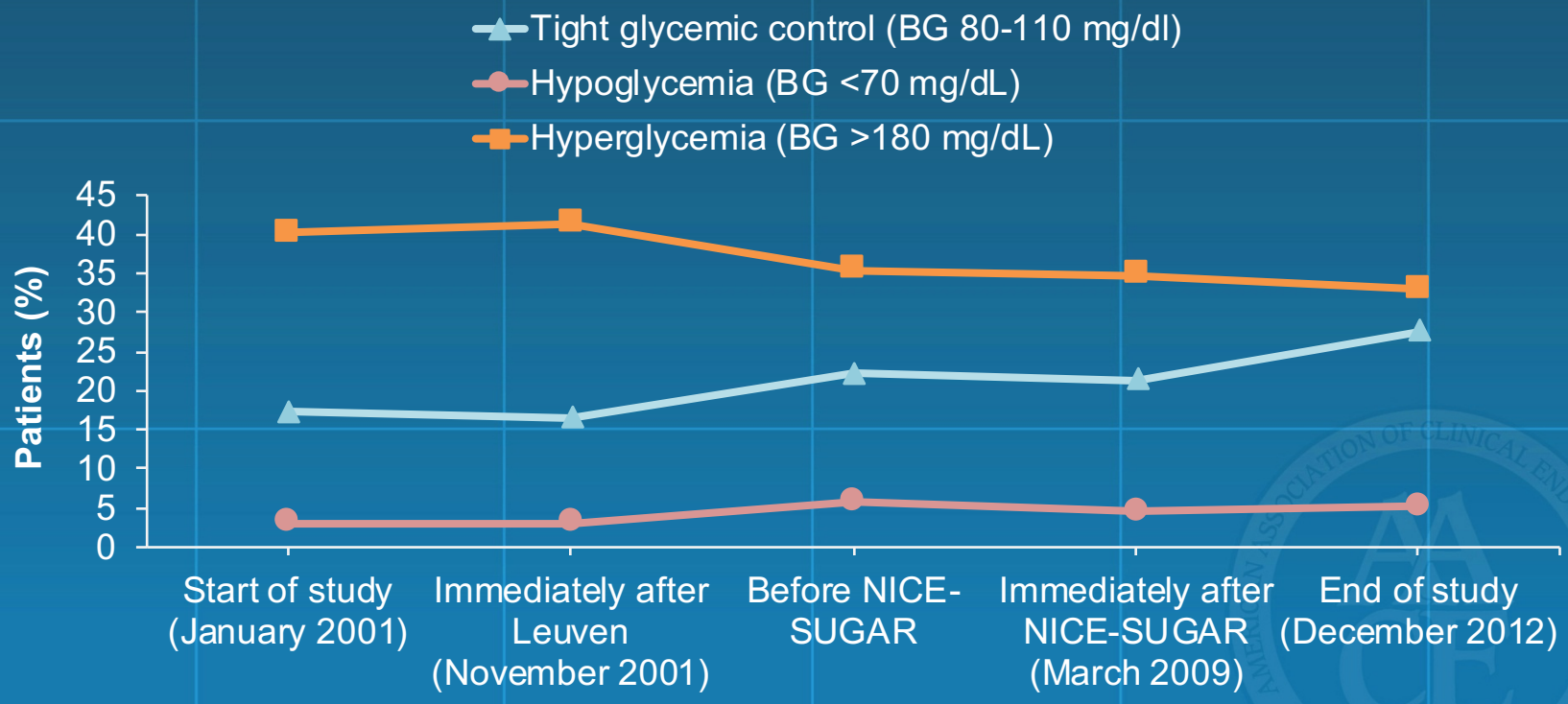


BG, blood glucose; CABG, coronary artery bypass surgery.

Umpierrez G, et al. *Diabetes Care*. 2015;38:1665-1672.

Practice Changes in ICUs in Response to Clinical Trial Evidence

Time Series Analysis, 2001-2012
(N=113 ICUs, 353,464 patients)



NICE-SUGAR, Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation.

Niven DJ, et al. *JAMA Intern Med*. 2015;175:801-809.

Clinical Trials Summary

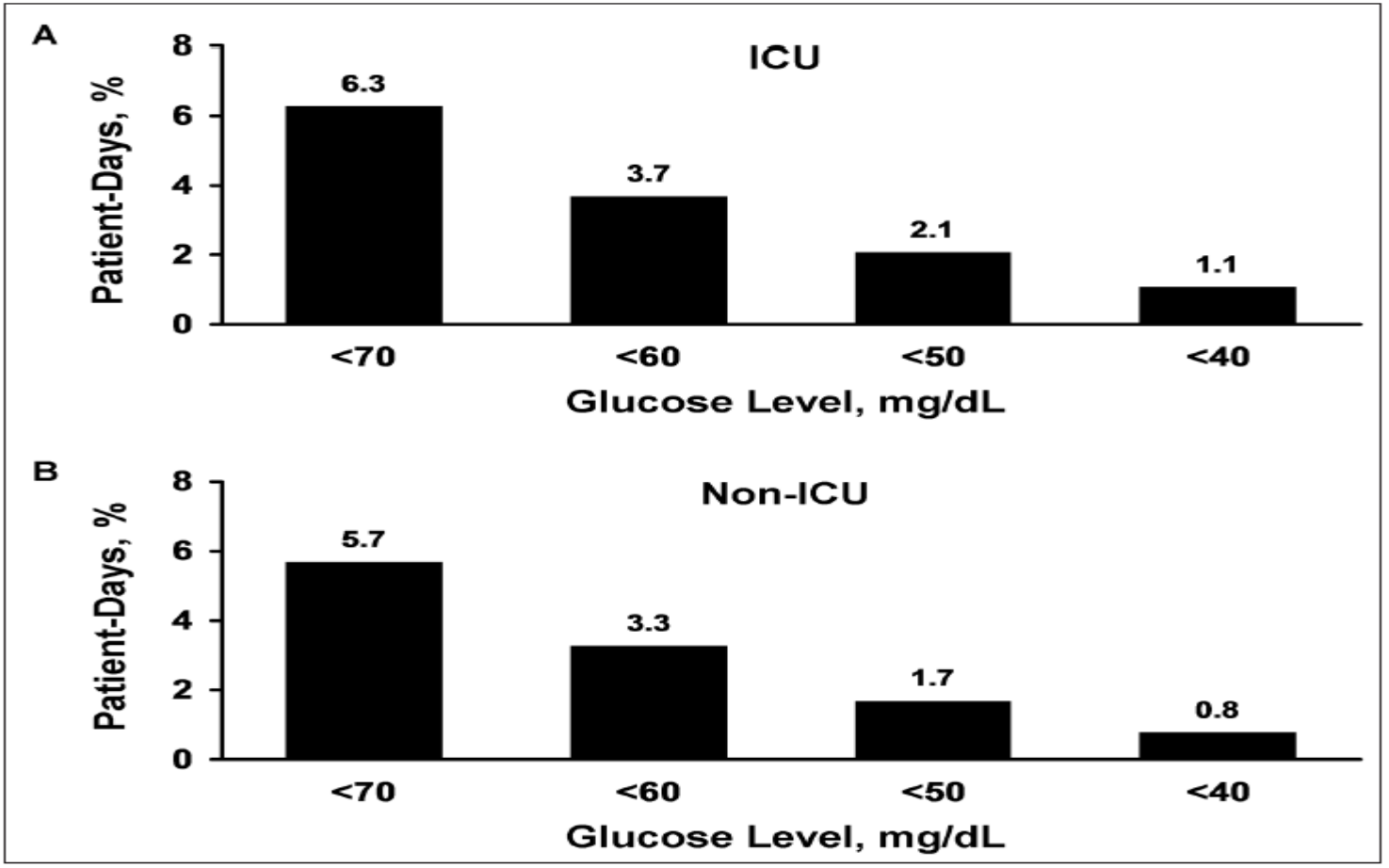
- Hyperglycemia is associated with poor clinical outcomes across many disease states in the hospital setting
- Despite the inconsistencies in clinical trial results, good glucose management remains important in hospitalized patients
- More conservative glucose targets should result in lower rates of hypoglycemia while maintaining outcome benefits

What Should We Take Away From These Trials?

- Good glucose control, as opposed to near-normal control, is likely sufficient to improve clinical outcomes in the ICU setting
- Hyperglycemia and hypoglycemia are markers of poor outcome in critically and noncritically ill patients
- Importantly, the recent studies do not endorse a laissez-faire attitude toward inpatient hyperglycemia that was prevalent a decade ago

IS HYPOGLYCEMIA LIFE THREATENING?

Prevalence of Hypoglycemia in Patients Receiving POC Glucose Testing



No. patients: 3,484,795

No. POC-BG: 49,191,313

ICU: 12,176,299

Non-ICU: 37,015,014

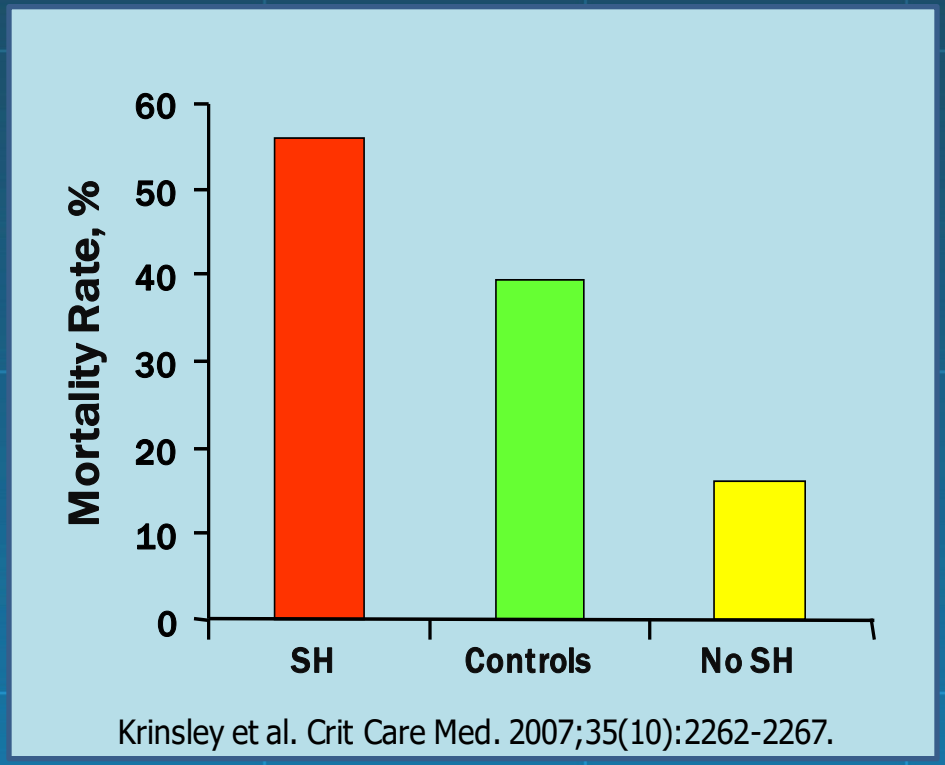
Swanson CM, et al. *Endocr Pract*. 2011;17:853-861.

Severe Hypoglycemia as an Independent Risk Factor for Mortality in the ICU

Condition	Severe Hypoglycemia	Mortality
Diabetes	3.07*	0.97
Septic shock	2.03*	1.33
Creatinine >3 mg/dL	1.10	1.30*
Mechanical ventilation	2.11*	2.43*
Tight glycemia control	1.59*	0.67*
APACHE II score	1.07*	1.14*
Age	1.01	1.03*
Severe hypoglycemia (≤40 mg/dL)	—	2.28*

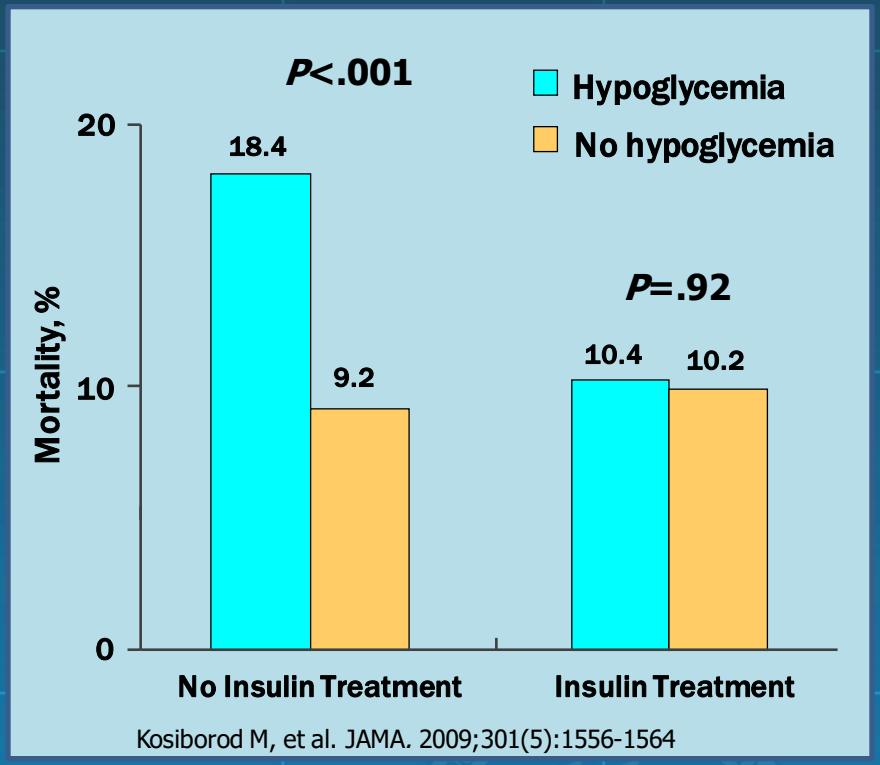
Krinsley JS, Grover A. *Crit Care Med*. 2007;35:2262-2267.

Hypoglycemia and Hospital Mortality



Krinsley et al. Crit Care Med. 2007;35(10):2262-2267.

Severe hypoglycemia (<40 mg/dL) is associated with an increased risk of mortality (OR, 2.28; 95% CI, 1.41-3.70; *P*=.0008)

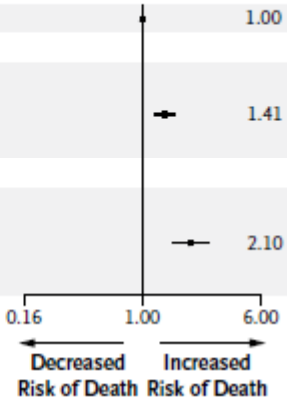


Kosiborod M, et al. JAMA. 2009;301(5):1556-1564

Hypoglycemia was a predictor of higher mortality in patients not treated with insulin, but not in patients treated with insulin

Hypoglycemia Mortality in Patients Receiving and Not Receiving Insulin

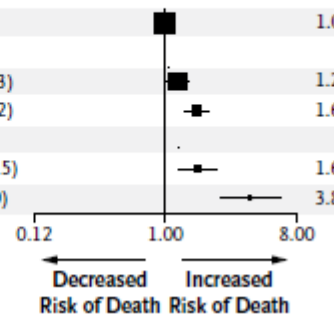
Subgroup	Deaths	Population	Median Time from Randomization to Hypoglycemia (IQR)	Median Time from Hypoglycemia to Death (IQR)	Hazard Ratio (95% CI)	P Value
	no.		*days*			
No hypoglycemia	726	3089			1.00	
Moderate hypoglycemia	774	2714	1 (0–2)	7 (2–21)		
Stratified by treatment and adjusted for baseline and postrandomization characteristics					1.41 (1.21–1.62)	<0.001
Severe hypoglycemia	79	223	4 (2–9)	8 (3–15)		
Stratified by treatment and adjusted for baseline and postrandomization characteristics					2.10 (1.59–2.77)	<0.001



Risk of death with severe hypoglycemia vs no hypoglycemia

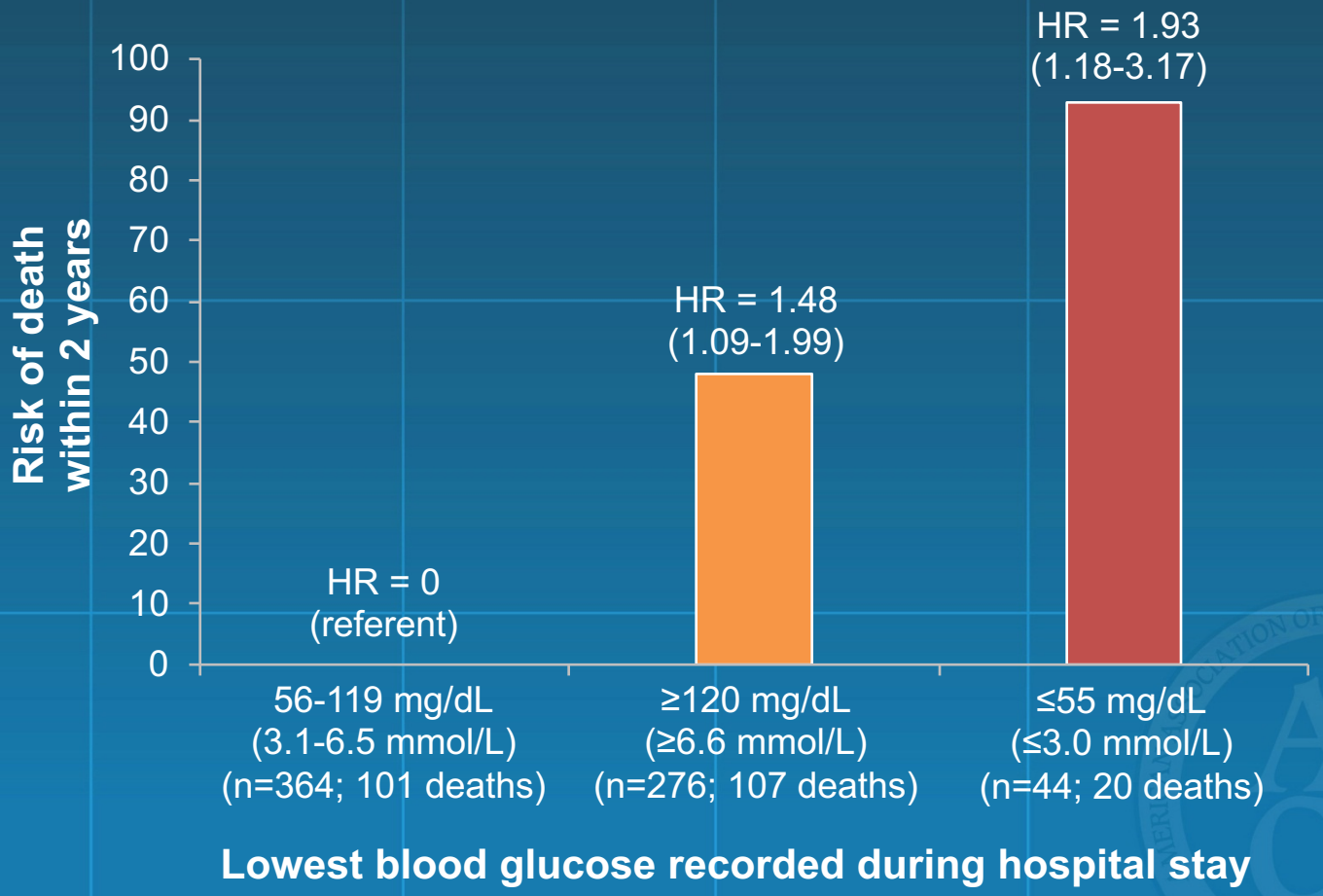
- ↑ 1.7-fold in patients receiving insulin
- ↑ 3.8-fold in patients <u>not</u> receiving insulin

Subgroup	Deaths	Population	Median Time from Hypoglycemia to Death (IQR)	Hazard Ratio (95% CI)	P Value
	no.		*days*		
No hypoglycemia	726	3089		1.00	
Moderate hypoglycemia					0.007
Insulin	545	2066	9 (3–23)	1.22 (1.03–1.44)	
No insulin	136	378	5 (1–22)	1.64 (1.34–2.01)	
Severe hypoglycemia					0.003
Insulin	57	186	10 (4–15)	1.68 (1.23–2.29)	
No insulin	22	37	1 (0–9)	3.84 (2.37–6.23)	



NICE-SUGAR Study Investigators. *N Engl J Med.* 2012;367:1108-1118.

Blood Glucose During Hospitalization and Incidence of Death Within 2 Years



HR, hazard ratio.

Svensson AM, et al. *Eur Heart J*. 2005 26:1255-1261.

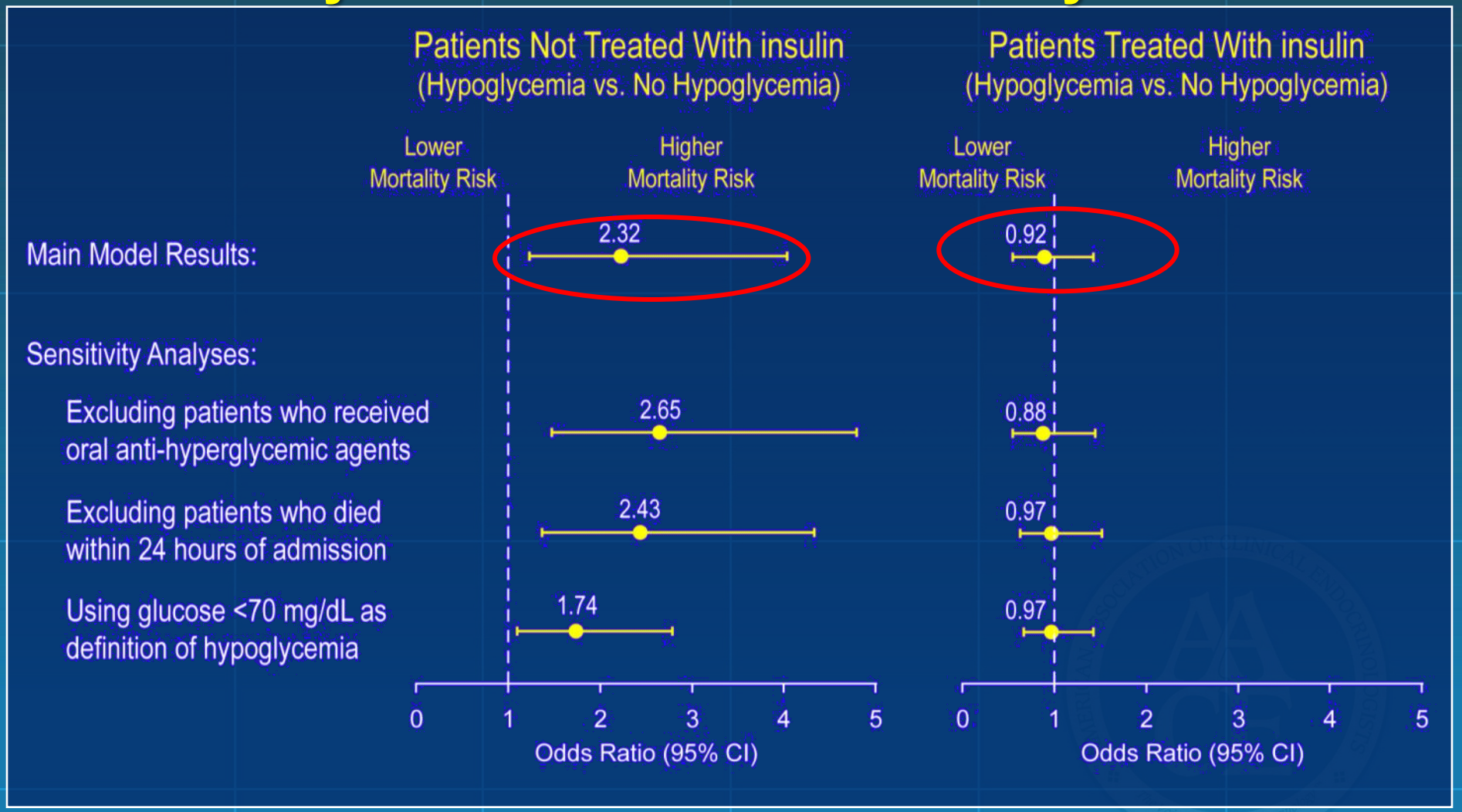
Hypoglycemia in Patients With Acute Coronary Syndrome

Unadjusted Results

	Hypoglycemia	No hypoglycemia	*P* value
All patients	n=482	n=7338	
In-hospital mortality	61 (12.7%)	701 (9.6%)	0.026
No insulin treatment	n=136	n=4639	
In-hospital mortality	25 (18.4%)	425 (9.2%)	0.0003
Insulin-treated patients	n=346	n=2699	
In-hospital mortality	36 (10.4%)	276 (10.2%)	0.92

Kosiborod M, et al. *JAMA*. 2009;301:1556-1564.

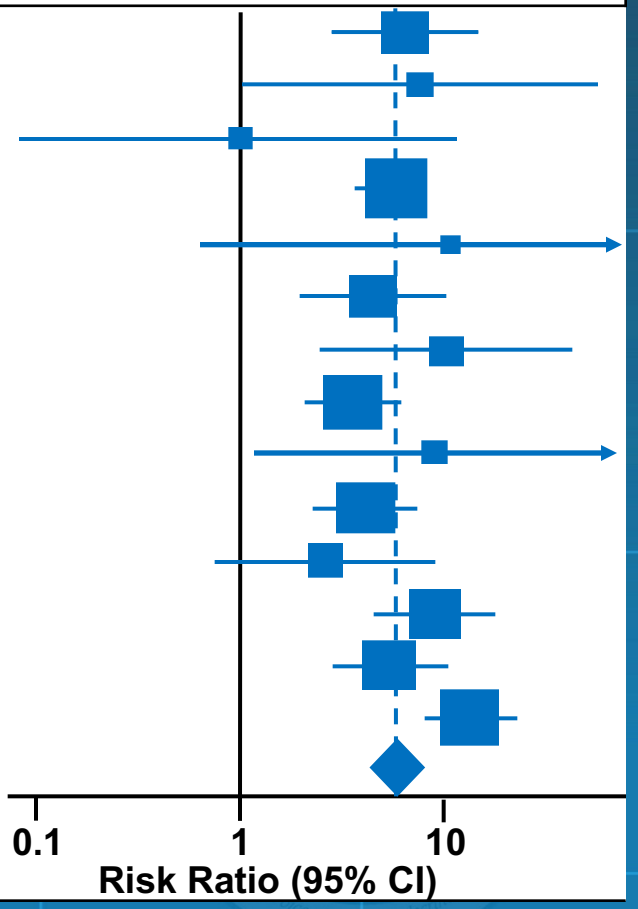
Hypoglycemia in Patients With Acute Coronary Syndrome: Multivariate Analysis



Kosiborod M, et al. *JAMA*. 2009;301:1556-1564.

Intensive Insulin Therapy and Hypoglycemic Events in Critically Ill Patients

	No. Events/Total No. Patients		
Study	**IIT**	**Control**	**Risk ratio (95% CI)**
Van den Berghe et al	39/765	6/783	6.65 (2.83-15.62)
Henderson et al	7/32	1/35	7.66 (1.00-58.86)
Bland et al	1/5	1/5	1.00 (0.08-11.93)
Van den Berghe et al	111/595	19/605	5.94 (3.70-9.54)
Mitchell et al	5/35	0/35	11.00 (0.63-191.69)
Azevedo et al	27/168	6/169	4.53 (1.92-10.68)
De La Rosa et al	21/254	2/250	10.33 (2.45-43.61)
Devos et al	54/550	15/551	3.61(2.06-6.31)
Oksanen et al	7/39	1/51	9.15 (1.17-71.35)
Brunkhorst et al	42/247	12/290	4.11(2.2-7.63)
Iapichino et al	8/45	3/45	2.67 (0.76-9.41)
Arabi et al	76/266	8/257	9.18 (4.52-18.63)
Mackenzie et al	50/121	9/119	5.46 (2.82-10.60)
NICE-SUGAR	206/3016	15/3014	13.72 (8.15-23.12)
Overall	654/6138	98/6209	5.99 (4.47-8.03)



Griesdale DE, et al. *CMAJ*. 2009;180:821-827.

Hypoglycemia Is Associated With Cardiovascular Complications

- Tachycardia and high blood pressure
- Myocardial ischemia
  - Silent ischemia, angina, infarction
- Cardiac arrhythmias
  - Transiently prolonged corrected QT interval
  - Increased QT dispersion
- Sudden death

Wright RJ, Frier BM. *Diabetes Metab Res Rev.* 2008;24:353-363.

CURRENT RECOMMENDATIONS

Guidelines From Professional Organizations on the Management of Glucose Levels in the ICU

Year	Organization	Patient Population	Treatment Threshold	Target Glucose Level	Definition of Hypoglycemia	Updated since NICE-SUGAR Trial, 2009
2009	American Association of Clinical Endocrinologists and American Diabetes Association	ICU patients	180	140-180	<70	Yes
2009	Surviving Sepsis Campaign	ICU patients	180	150	Not stated	Yes
2009	Institute for Healthcare Improvement	ICU patients	180	<180	<40	Yes
2008	American Heart Association	ICU patients with acute coronary syndromes	180	90-140	Not stated	No
2007	European Society of Cardiology and European Association for the Study of Diabetes	ICU patients with cardiac disorders	Not stated	"Strict"	Not stated	No

Kavanagh BP, McCowen KC. *N Engl J Med.* 2010;363:2540-2546.

Guidelines From Professional Organizations on the Management of Glucose Levels in Noncritically Ill Patients

Year	Organization	Patient Population	Treatment Threshold	Target	Definition of Hypoglycemia	Updated since NICE-SUGAR Trial, 2009
2009	AACE and ADA Consensus Statement	Non-critically ill patients	180 mg/dL	Premeal <140 mg/dL	<70 mg/dL (reassess treatment if <100 mg/dL)	Yes
2012	Endocrine Society Clinical Practice Guideline	Non-critically ill patients	180 mg/dL	Premeal <140 mg/dL	(reassess treatment if <100 mg/dL)	Yes

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

AACE/ADA Recommended Target Glucose Levels in ICU Patients

- ICU setting:
  - Starting threshold no higher than 180 mg/dL
  - Once IV insulin is started, the glucose level should be maintained between 140 and 180 mg/dL
  - Lower glucose targets (110-140 mg/dL) may be appropriate in selected patients
  - Targets <110 mg/dL or >180 mg/dL are not recommended

Moghissi ES, et al. *Endocr Pract*. 2009;15:353-369.

AACE/ADA Recommended Target Glucose Levels in Non-ICU Patients

- Non–ICU setting:
  - Premeal glucose targets <140 mg/dL
  - Random BG <180 mg/dL
  - To avoid hypoglycemia, reassess insulin regimen if BG levels fall below 100 mg/dL
  - Occasional patients may be maintained with a glucose range below and/or above these cut-points

Hypoglycemia = BG <70 mg/dL
Severe hypoglycemia = BG <40 mg/dL

Moghissi ES, et al. *Endocr Pract*. 2009;15:353-369.

Endocrine Society Recommended Target Glucose Levels in Non-ICU Patients

- Blood glucose targets for the majority of patients
  - Premeal: <140 mg/dL
  - Random: <180 mg/dL
- Glycemic targets should be modified according to clinical status
  - For patients who achieve and maintain glycemic control without hypoglycemia, a lower target range may be reasonable
  - For patients with terminal illness and/or with limited life expectancy or at high risk for hypoglycemia, a higher target range (BG <200 mg/dl) may be reasonable
- To avoid hypoglycemia, reassess and modify diabetes therapy when BG is ≤100 mg/dL
- Modification of glucose-lowering treatment is usually necessary when BG values are <70 mg/dL

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