Inpatient Diabetes Management: The Slippery Slope of Sliding Scale Insulin

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Big Sky Conference 2017

Dr. David Newman,
Personal/Professional Financial Relationships with Industry

External Industry Relationships *	Company Name(s)	Role
Equity, stock, or options in biomedical industry companies or publishers	None	
Board of Directors or officer	None	
Royalties from from external entity	None	
Industry funds	None	

Learning Objectives

➢ Upon Completion of this conference, participants should be able to:
- Define various **forms of insulin** and their durations of action
- Describe the **blood sugar targets** in hospitalized patients
- Recognize the **outcomes** associated hyperglycemia and hypoglycemia in the hospital
- Evaluate **strategies to maintain euglycemia** in the inpatient setting

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The Inpatient Movement
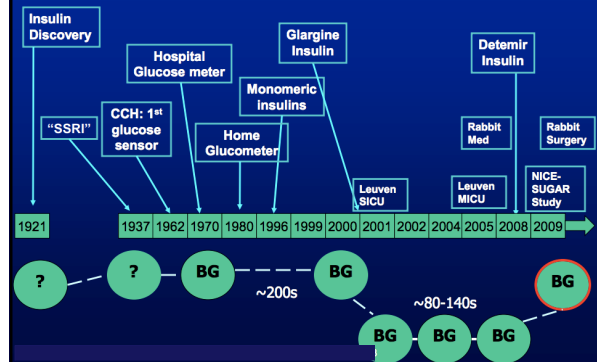

Early Cohort Studies & Randomized Trials

Study	Setting	Population	Clinical Outcome
Malmberg, 1995	CCU	Mixed	28% ↓ mortality After 1 year
Furnary, 1999	ICU	DM undergoing open heart surgery	65% ↓ infection
Furnary, 2003	ICU	DM undergoing CABG	57% ↓ mortality
Lazar, 2004	OR and ICU	DM undergoing CABG	60% ↓ A Fib post op survival 2 yr
Krinsley, 2004	Med/Surg ICU	Mixed, no Cardiac	29% ↓ mortality
Van den Berghe, 2001*	Surgical ICU	Mixed, with CABG	34% ↓ mortality
Van den Berghe, 2006*	Medical ICU	Mixed	18% ↓ mortality

*RCT, randomized clinical trial.
Kitabchi & Umpierrez. *Metabolism*. 2008;57:116-120.
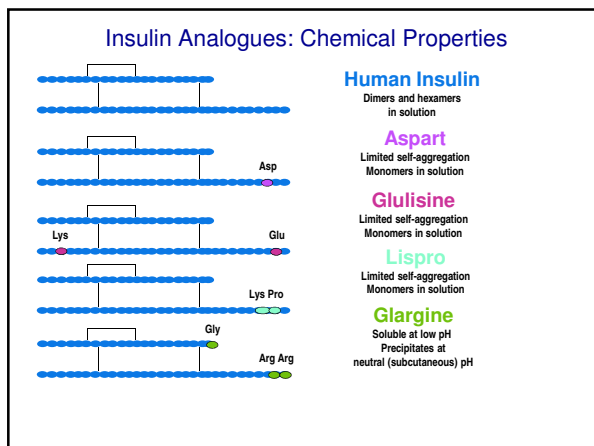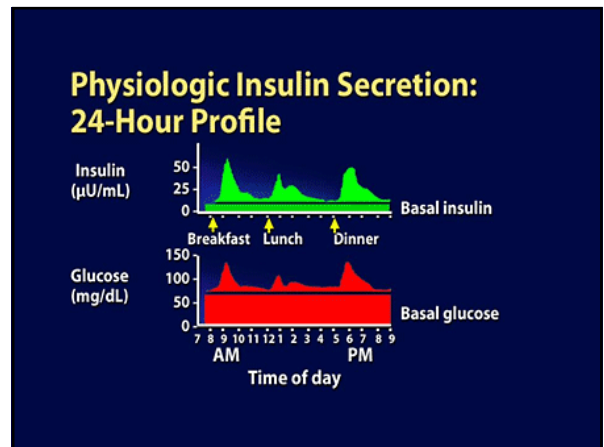

General Inpatient medicine

➢ Intern: "Yeah, he also has diabetes, I think, he was insulin as an outpatient."
➢ Dr. Wiisanen: "So what should we do about his blood sugars?"
➢ Intern: "Maybe start some insulin?"

Confused?
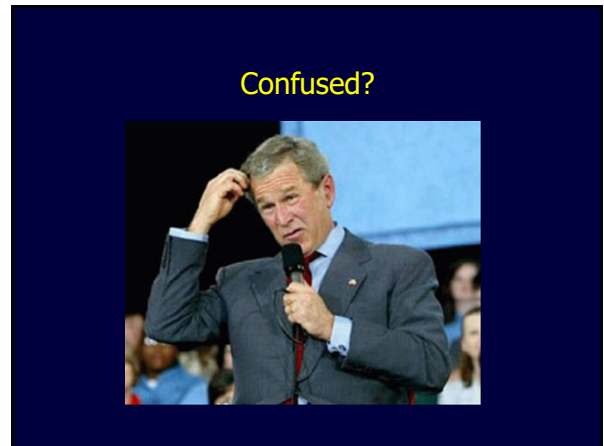
Insulin Basics

➢ Basal: Long Duration
➢ Bolus: Rapid Acting, Short Duration
- Sliding Scale – check whenever, give rapid acting insulin
- Prandial – rapid acting given before meals based on meal size
- Corrective (Supplemental) – rapid acting given before meals based on blood sugars

Physiologic Insulin Secretion: 24-Hour Profile

Insulin Analogues: Chemical Properties

Human Insulin
Dimers and hexamers in solution

Aspart
Limited self-aggregation
Monomers in solution

Glulisine
Limited self-aggregation
Monomers in solution

Lispro
Limited self-aggregation
Monomers in solution

Glargine
Soluble at low pH
Precipitates at
neutral (subcutaneous) pH

Detemir: Way different

➢ Fatty acid tail (myristic acid) added to human insulin
➢ Complexes with albumin→>20 hour action

http://www.nature.com/nrd/journal/v1/n7/images/nrd836-i2.gif

Neutral Protamine Hagedorn Insulin

Available Insulin Formulations

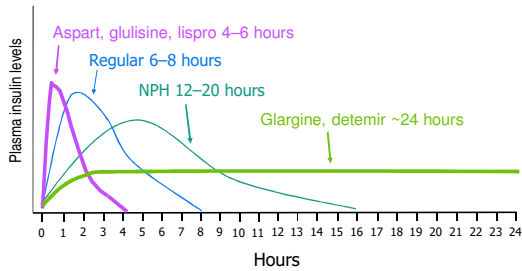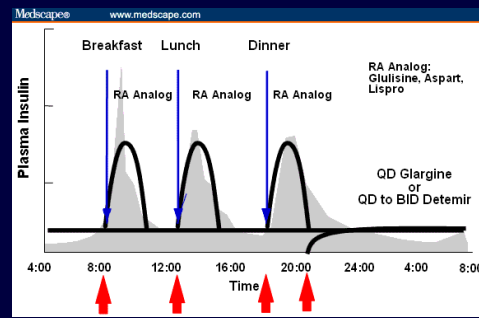**Human Insulin**
- Regular
- NPH
- Mixed (70/30)

"Analog" Insulin

Rapid acting
- aspart (Novolog)
- glulisine (Apidra)
- lispro (Humalog)

Mixed
- Humalog 50/50, Humalog 75/25
- Novolog 70/30

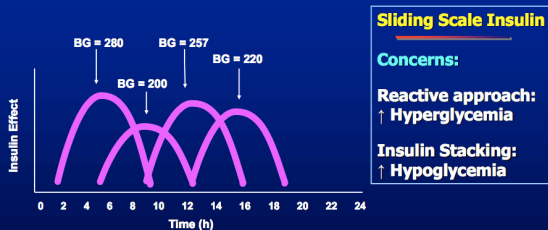**Long acting**
- glargine (Lantus, Basaglar)
- detemir (Levemir)

Action Profiles of Injected Modified Human Insulins and Insulin Analogues

Aspart, glulisine, lispro 4–6 hours

Regular 6–8 hours

NPH 12–20 hours

Glargine, detemir ~24 hours

Plasma insulin levels

Hours
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24

Ideal Situation

Sliding-Scale Regular Insulin

BG = 280   BG = 257
BG = 200   BG = 220

Insulin Effect

Time (h)
0 2 4 6 8 10 12 14 16 18 20 22 24

Sliding Scale Insulin

Concerns:

Reactive approach:
↑ **Hyperglycemia**

Insulin Stacking:
↑ **Hypoglycemia**

Adapted from the following sources:
- DeWitt DE and Dugdale DC. *JAMA*. 2003;289:2265-2269.
- Skyler JS. In: DeFronzo RA, ed. *Current Therapy of Diabetes Mellitus*. St Louis, MO: Mosby–Year Book, Inc. 1998:36-49.

Cardiology: Post Call with Dr. Jessen

- Intern: "He was well controlled on metformin and sitagliptan as an outpatient."
- Dr. Jessen: "We need to off load the RV to increase his EF to maximize his PMI!"
- Intern: "I think we will start insulin and get an A1c"
- Dr. Jessen: "What should his blood sugar be?"

Slide 1

Clinical Guidelines for the Management of Hyperglycemia in Hospitalized Patients in a Non-Critical Care Setting

The Endocrine Society,
European Endo Society,
American Heart Association,
American Diabetes Association,
Society of Hospitalist Medicine,
American Association of Diabetes Educators
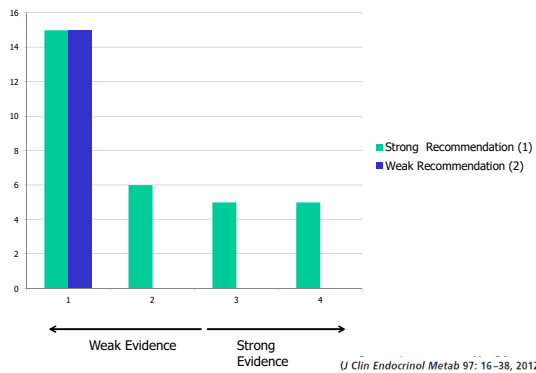
Slide 2

Management of Hyperglycemia in Hospitalized Patients in Non-Critical Care Setting: An Endocrine Society Clinical Practice Guideline

Guillermo E. Umpierrez, Richard Hellman, Mary T. Korytkowski, Mikhail Kosiborod, Gregory A. Maynard, Victor M. Montori, Jane J. Seley, and Greet Van den Berghe
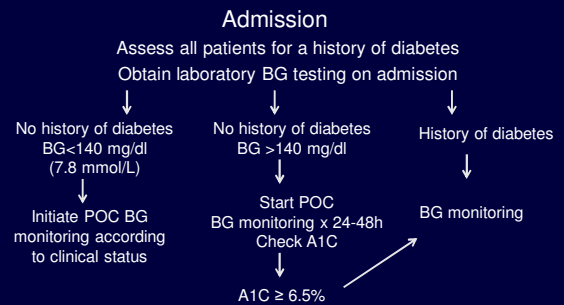
Slide 3
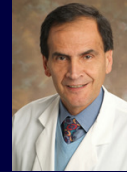
Strength of Recommendations and Level of Evidence Supporting Hospital Glucose Suggestions.

Legend: Strong Recommendation (1), Weak Recommendation (2)

Weak Evidence   Strong Evidence

Slide 4

Diagnosis & recognition of hyperglycemia and diabetes in the hospital setting

Admission

Assess all patients for a history of diabetes
Obtain laboratory BG testing on admission

- No history of diabetes
BG<140 mg/dl
(7.8 mmol/L)
  → Initiate POC BG monitoring according to clinical status

- No history of diabetes
BG >140 mg/dl
  → Start POC BG monitoring x 24-48h
Check A1C
  → A1C ≥ 6.5%

- History of diabetes
  → BG monitoring

Slide 5

A1C for Diagnosis of Diabetes in the Hospital

➤ HbA1c should be measured in non-diabetic subjects with hyperglycemia (BG>140 mg/dl) and in subjects with diabetes if not done within 2-3 months prior to admission.

➤ In the presence of hyperglycemia, a patient with HbA1c > 6.5% can be identified as having diabetes.

➤ Implementation of A1C testing can be useful:
  ➤ assess glycemic control prior to admission
  ➤ assist with differentiation of newly diagnosed diabetes from stress hyperglycemia
  ➤ designing an optimal regimen at the time of discharge

Slide 6

Glycemic Targets in Non-Critical Care Setting

1. Premeal BG target of <140 mg/dl and random BG <180 mg/dl for the majority of patients.

2. Glycemic targets be modified according to clinical status.
   - For patients who achieve and maintain glycemic control without hypoglycemia, a lower target range may be reasonable.
   - Patients with terminal illness, a higher target range (BG <200 mg/dl) may be reasonable.

3. For avoidance of hypoglycemia, we suggest that diabetic therapy be reassessed when BG<100 mg/dl).

Recommendations for Managing Patients With Diabetes in the Hospital Setting

Antihyperglycemic Therapy

Insulin Recommended

OADs Not Generally Recommended
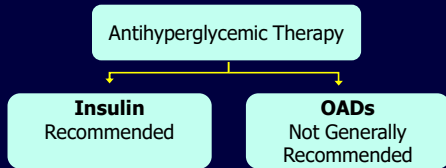
1. ACE/ADA Task Force on Inpatient Diabetes. *Diabetes Care*. 2006 & 2009
2. *Diabetes Care*. 2009;31(suppl 1):S1-S110..

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Insulin Therapy in patients with T2D

- D/C oral antidiabetic drugs on admission
- **Insulin naïve:** starting total daily dose (TDD):
  - 0.3 U/kg to 0.5 U/kg
  - Lower doses in the elderly and renal insufficiency
- **Previous insulin therapy:** reduce outpatient insulin dose by 20-25%
- Scheduled SQ insulin consists of basal or intermediate acting insulin in combination with prandial rapid-acting insulin
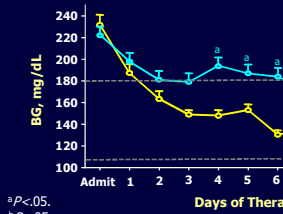
So no sliding scale!?!

Umpierrez et al, Diabetes Care 30:2181–2186, 2007; Baldwin et al, Diabetes Care 10:1970-4, 2011; Rubin et al, Diabetes Care 34:1723-8, 2011

Show me the evidence!
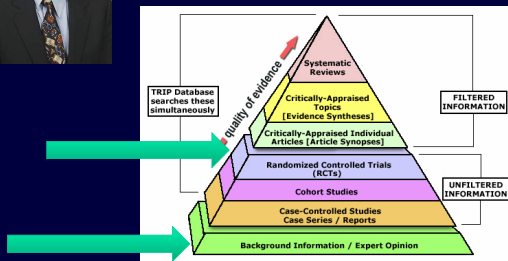
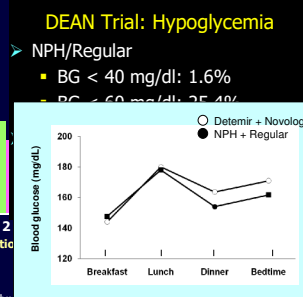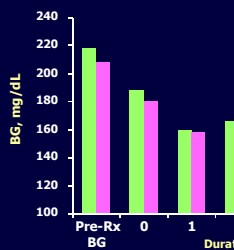## Rabbit 2 Trial: Changes in Glucose Levels With Basal-Bolus vs. Sliding Scale Insulin

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

[a] $P<.05$.
[b] $P<.05$.

- Sliding scale regular insulin (SSRI) was given 4 times daily
- Basal-bolus regimen: glargine was given once daily; glulisine was given 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(9):2181-2186.

DEAN Trial: Changes in Mean Daily Blood Glucose Concentration

DEAN Trial: Hypoglycemia
- NPH/Regular
  - BG < 40 mg/dl: 1.6%
  - BG < 60 mg/dl: 25.4%

Detemir + Novolog
NPH + Regular

Data are means ±SEM.

Basal-bolus regimen: detemir was given once daily;
NPH/regular regimen: NPH and regular insulin were given twice daily, two thirds in AM, one third in PM.

Umpierrez GE, et al. *J Clin Endocrinol Metab*. 2009;94(2):564-569.

Insulin Treatment in in Non-ICU Setting

T2DM with BG > 140 mg/dl (7.7 mmol/l)

NPO
Uncertain oral intake

Adequate
Oral intake

Basal insulin
- Start at 0.2-0.25 U/Kg/day*
- Correction doses with rapid acting insulin AC
- Adjust basal as needed

Basal Bolus
TDD: 0.4-0.5 U/Kg/day
-½ basal, ½ bolus
-- adjust as needed
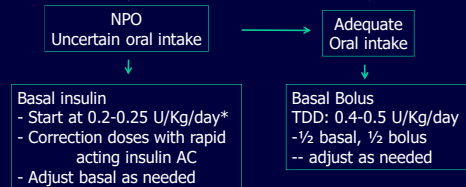
Do you need basal bolus in ALL patients?

Basal Plus Correction vs. Basal Bolus

Basal plus supplements
- Starting glargine*: 0.25 units/kg
- Correction with glulisine for BG >140 mg/dl per sliding scale

* Reduce TDD to 0.15 U/kg in patients ≥70 yrs and/or serum creatinine ≥ 2.0 mg/dL

Basal Bolus Regimen
- Starting TDD*: 0.5 U/kg
  - Glargine: 0.25 U/kg
  - Glulisine: 0.25 U/kg in three equally divided doses (AC)
  - Correction with glulisine for BG >140 mg/dl per sliding scale

* Reduce TDD to 0.3 U/kg in patients ≥70 yrs and/or serum creatinine ≥ 2.0 mg/dL

Umpierrez et al. Diabetes Care. July, 2013
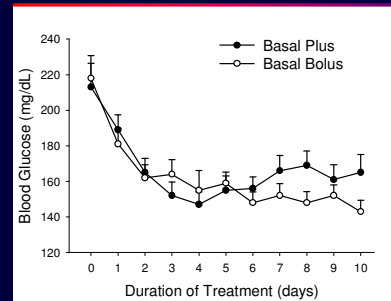

Basal-PLUS vs Basal Bolus: 300 medical & surgical non-ICU patients

Basal Plus: glargine once daily 0.25 U/kg plus glulisine supplements

Basal Bolus: TDD: 0.5 U/kg/d Glargine 50% glulisine 50%

Preliminary results: Basal bolus 51 patients, basal-plus: 49 patients

Umpierrez et al. Diabetes Care. July, 2013

Glycemic control and frequency of treatment failures in patients treated with basal bolus and basal plus regimens
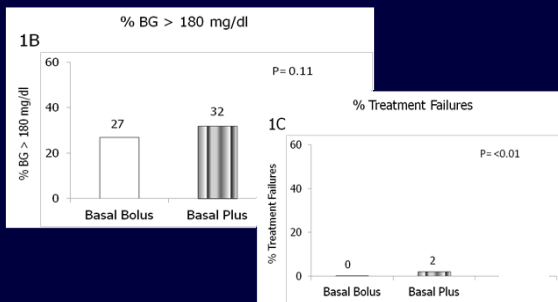
Umpierrez et al. Diabetes Care. July, 2013

Basal-PLUS vs Basal Bolus: Medicine and Surgery Patients
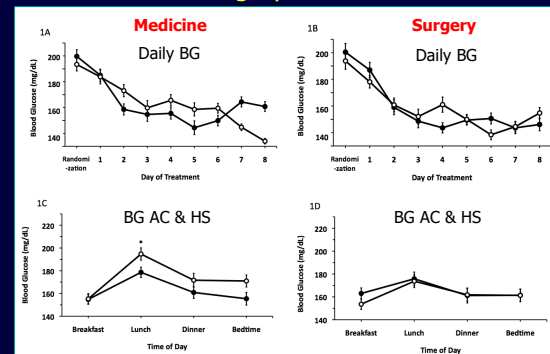
Smiley et al, J Diabetes & Complications, August 2013

Oncology rounds with Dr. Glatt

- Intern: "So he is having his tumor surgically removed on Thursday."
- Dr. Glatt: "Did you read last week's Blood, JAMA, and NEJM?"
- Intern: "No. Nobody does that."

Thirty Day Mortality and Inhospital Complications in diabetic and non-diabetic subjects Undergoing Non-Cardiac Surgery
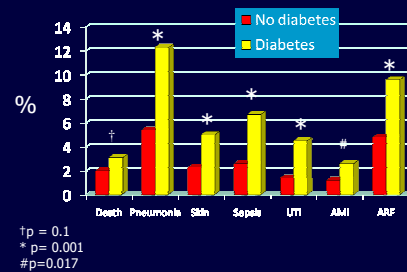
†p = 0.1
* p= 0.001
#p=0.017

A Frisch et al. Diabetes Care, May 2010

Adverse Events Stratified by Perioperative Hyperglycemia

Diabetes   No Diabetes

Categories: Hospital Deaths, Re-operations, Composite Infections

- BG > 180 mg/dl (red)
- BG < 180 mg/dl (yellow)

* P <0.01
§ p <0.05

Proportion of Patients (%)

BG at any point on the day of surgery, post-op day 1 and 2
N= 11,633, colorectal and bariatric surgery;
29.1% with hyperglycemia

Known et al. Ann Surg 2013

Randomized study of basal bolus insulin therapy in the management of general surgery patients with T2DM (Rabbit Surgery)

Research Question:

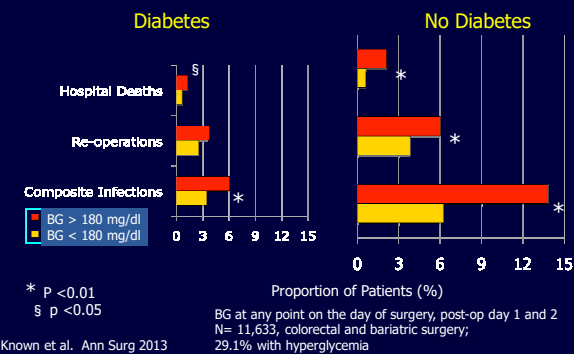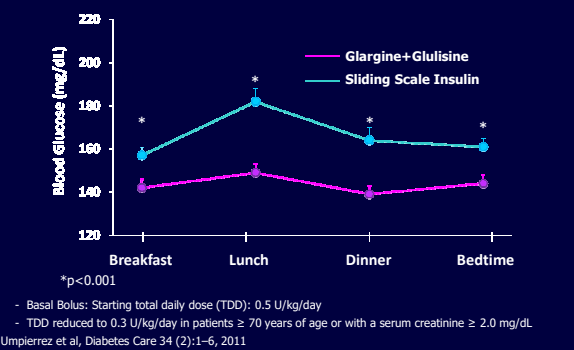In patients with T2DM on diet, oral agents or insulin treatment, does treatment with basal bolus regimen with glargine and glulisine is superior to SSRI?
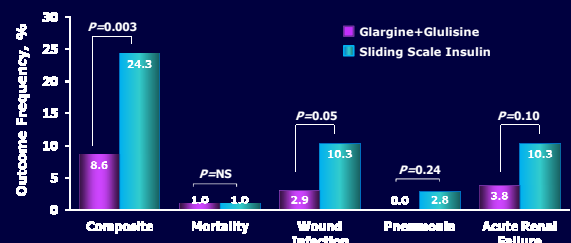
Primary Outcomes:
- Differences between groups in mean daily BG
- Composite of hospital complications: wound infection, pneumonia, respiratory failure, acute renal failure, and bacteremia

Umpierrez et al, Diabetes Care 34 (2):1–6, 2011

Mean BG before meals and at bedtime during basal bolus and SSI therapy

- Glargine+Glulisine
- Sliding Scale Insulin

Y-axis: Blood Glucose (mg/dL)
X-axis: Breakfast, Lunch, Dinner, Bedtime

*p<0.001

- Basal Bolus: Starting total daily dose (TDD): 0.5 U/kg/day
- TDD reduced to 0.3 U/kg/day in patients ≥ 70 years of age or with a serum creatinine ≥ 2.0 mg/dL

Umpierrez et al, Diabetes Care 34 (2):1–6, 2011

Postoperative Complications

Y-axis: Outcome Frequency, %

- Glargine+Glulisine
- Sliding Scale Insulin

	Composite	Mortality	Wound Infection	Pneumonia	Acute Renal Failure
Glargine+Glulisine	8.6	1.0	2.9	0.0	3.8
Sliding Scale Insulin	24.3	1.0	10.3	2.8	10.3
p-value	P=0.003	P=NS	P=0.05	P=0.24	P=0.10

* Composite of hospital complications: wound infection, pneumonia, respiratory failure, acute renal failure, and bacteremia.

Umpierrez et al, Diabetes Care 34 (2):1–6, 2011

Rabbit Surgery: Cost Analysis

	Basal-bolus insulin	SSI	p-value
Number of patients	88	92	
Number of patients with complications*	6	22	0.002
Length of Stay (days)			
ICU	0.9 ± 0.5	2.7 ± 3.5	0.005
Hospital	7.3 ± 5.1	8.5 ± 5.9	0.15
Total Charges (US $, K)	46.3 ± 25.3	53.9 ± 32.2	0.10
Total Cost (US $, K ± SD)†	22.9 ± 12.0	26.8 ± 15.9	0.09
- Pharmacy	14.7 ± 10.2	17.9 ± 15.1	0.21
- Radiology	4.5 ± 6.1	14.5 ± 8.4	0.25
- Laboratory	72.3 ± 55.3	86.3 ± 9.2	0.65
- Consult service	10.4 ± 12.6	18.5 ± 29.0	0.21
- ICU	1.1 ± 0.3	2.7 ± 3.5	0.17

Cost difference (log transformation) between SSI and Basal: $2105, 95% CI -$3303, $7000

Non-adjusted without adjustment, the mean cost difference is $3843 with 95% CI -36090, 43776.

Endocrinology with Dr. Newman

- Dr. Newman: "What about their sugars?"
- Intern: "I did everything you said, and my patient's blood sugars still suck"
- Dr. Newman: "Work Harder"

PROACTIVE
~~REACTIVE~~

Tailoring Insulin Regimens

- Control any raised random reading by adjusting the dose of *previously* administered regular insulin.
- For example: a high post lunch reading will *NOT* be controlled by increasing the dose of next insulin (as in sliding scale), rather adjustment of the pre-lunch regular insulin on the next day will bring down raised reading to the required levels.

Dose Adjustments – Rabbit 2

Fasting BG	Adjustment
100-140 mg/dl	No change
140-180 mg/dl	Increase TDD by 10% daily
>180 mg/dl	Increase TDD by 20% daily
70-99 mg/dl	Decrease TDD by 10%
<70 mg/dl	Decrease TDD by 20%

➤ Only increase insulin if not getting values less than 100 during the day
➤ Adjust for other factors (NPO, steroids, dialysis)

Non-ICU hypoglycemia –LOS
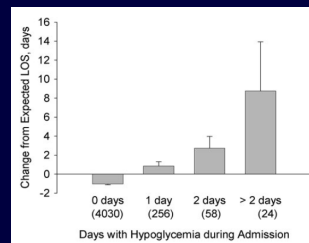
Retrospective cohort 4363 admissions 2,582 pts with DM. Hypoglycemia BG≤50 mg/dl was seen in 7.7% admissions.

Multivariate analysis; LOS increased by 2.5 days compared with the average for the disease for each additional day with a hypoglycemic episode ($P<0.001$).

Turchin. Diabetes Care.32(7). 85(3):1153-7.2009.

Non-ICU hypoglycemia –Inhospital Mortality
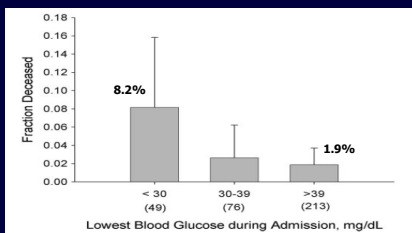
Retrospective cohort study of 2,582 DM pts on general ward. Hypoglycemia BG≤50 mg/dl (7.7%). Mean hospital BG 168±48

Turchin. Diabetes Care.32(7). 85(3):1153-7.2009.

Inpatient (Non ICU) Summary

➤ Stop oral drugs
➤ Use basal bolus therapy
➤ If previously on insulin, decrease outpatient regimen by 20%
➤ Starting insulin
  - 0.4 units per kg in most patients
    - Less if old or with kidney problems
    - More if sugars are over 200
  - Half basal and half bolus
➤ ***Targets 140 to 180***

Intensive Care Unit

- ➢Intern: "And her blood sugars are high. I think we should start insulin.
- ➢Dr. Myrmoe: "Sounds good."
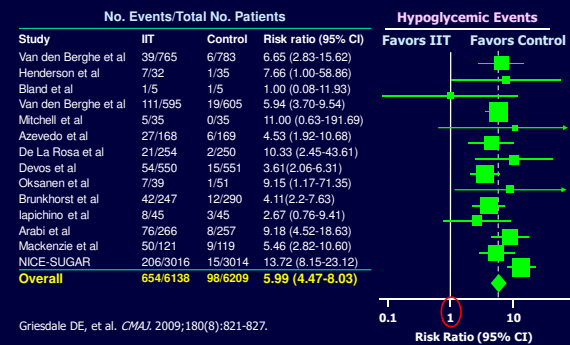- ➢Intern: "Do they need tight control?"
- ➢Dr. Myrmoe: "Define tight"

Intensive Glucose Management in RCT

Trial	N	Setting	Primary Outcome	ARR	RRR	Odds Ratio (95% CI)	P-value
Van den Berghe 2006	1200	MICU	Hospital mortality	2.7%	7.0%	0.94* (0.84-1.06)	N.S.
Glucontrol 2007	1101	ICU	ICU mortality	-1.5%	-10%	1.10* (0.84-1.44)	N.S.
Ghandi 2007	399	OR	Composite	2%	4.3%	1.0* (0.8-1.2)	N.S.
VISEP 2008	537	ICU	28-d mortality	1.3%	5.0%	0.89* (0.58-1.38)	N.S.
De La Rosa 2008	504	SICU MICU	28-d mortality	-4.2% *	-13%*	NR	N.S.
NICE-SUGAR 2009	**6104**	**ICU**	**3-mo mortality**	**-2.6%**	**-10.6**	**1.14 (1.02-1.28)**	**< 0.05**

*not significant

Griesdale DE, et al. *CMAJ*. 2009;180(8):821-827.

Intensive Insulin Therapy and Hypoglycemic Events in Critically Ill 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(8):821-827.

NICE-SUGAR Trial: Hypoglycemia and Mortality
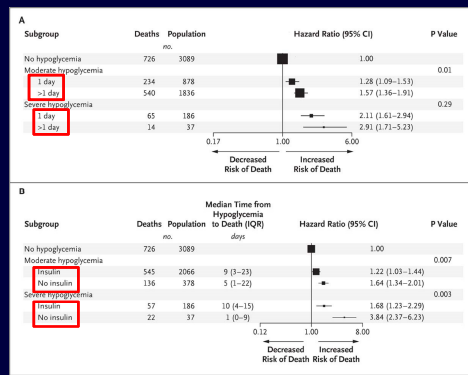
The NICE-SUGAR Study Investigators. N Engl J Med 2012;367:1108-1118

Hazard Ratio for Death from Specific Causes According to the Occurrence of Moderate or Severe Hypoglycemia.

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

The NEW ENGLAND JOURNAL of MEDICINE
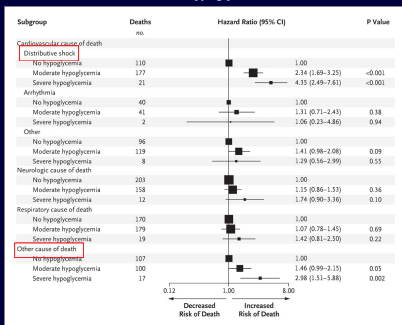
AACE/ADA Recommended Target Glucose Levels in ICU Patients

➢ **ICU setting:**
- Starting threshold of 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

Not recommended <110	Acceptable 110-140	Recommended 140-180	Not recommended >180

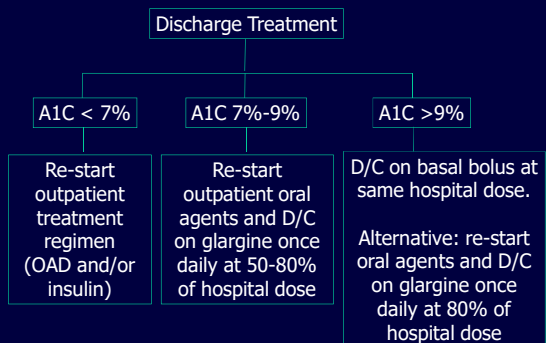Moghissi ES, et al; AACE/ADA Inpatient Glycemic Control Consensus Panel. *Endocr Pract*. 2009;15(4).
http://www.aace.com/pub/pdf/guidelines/InpatientGlycemicControlConsensusStatement.pdf.

General Medicine with Dr. Lien

- Intern: "Yeah, we found him a ride, so he can go home."
- Dr. Lien: "What about his diabetes"
- Intern: "He probably needs a meter."

Discharge Insulin Algorithm

Discharge Treatment

A1C < 7%	A1C 7%-9%	A1C >9%
Re-start outpatient treatment regimen (OAD and/or insulin)	Re-start outpatient oral agents and D/C on glargine once daily at 50-80% of hospital dose	D/C on basal bolus at same hospital dose. Alternative: re-start oral agents and D/C on glargine once daily at 80% of hospital dose

Umpierrez et al, ADA Scientific Sessions, 2012

Hospital Discharge Algorithm Based on Admission HbA1C for the Management of Patients with T2DM

Primary outcome:
- change in A1C at 4 wks and 12 wks after discharge

	All Patients	OAD	OAD + Glargine	Glargine+ Glulisine	Glargine
# patients, n (%)	224	81 (36)	61 (27)	54 (24)	20 (9)
A1C Admission, %	8.7±2.5	6.9±1.5	9.2±1.9	11.1±2.3	8.2±2.2
A1C 4 Wks F/U, %	7.9±1.7*	7.0±1.4	8.0±1.4ψ	8.8±1.8ψ	7.7±1.7
A1C 12 Wks F/U, %	7.3±1.5*	6.6±1.1	7.5±1.6*	8.0±1.6*	6.7±0.8*
BG<70 mg/dl, n (%)	62 (29)	17 (22)	17 (30)	23 (44)	5 (25)
BG<40 mg/dl, n (%)	7 (3)	3 (4)	0 (0)	3 (6)	0 (0)

* $p < 0.001$ vs. Admission A1C; ψp=0.08

Umpierrez et al, ADA Scientific Sessions, 2012

Special Situations

- Steroids
  - Need more insulin, especially mealtime
- Type 1 Diabetes
  - Don't stop basal insulin!
- Insulin drips
  - Give basal insulin before stopping
- Insulin pumps
  - Call endocrine

Summary

- Targets almost always **_140 to 180_**
- Use **_basal bolus therapy_** instead of sliding scale – bolus **_before_** eating!
- Be **_proactive_** instead of reactive
- Use **_discharge_** as an opportunity to tailor diabetes medications
- **_Treat the patient, not the disease_**

Thank you

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