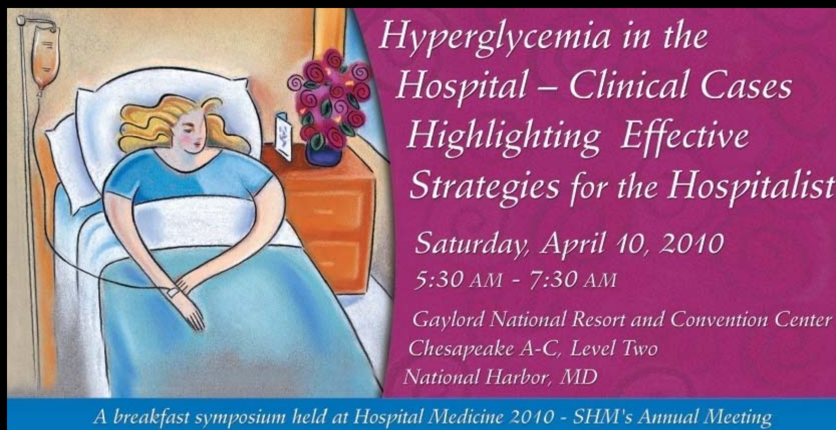

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Faculty Disclosures

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CEC

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Learning Objectives

1. Articulate the association between inpatient hyperglycemia and adverse clinical outcomes.
2. Differentiate factors that may alter the development of inpatient hyperglycemia and develop rational treatment strategies to address these factors to effectively control glucose in the hospital setting.
3. Translate and apply evidence-based practice recommendations from the ADA/AACE in different clinical scenarios.
4. Develop a framework for the successful transition of hospitalized patients to outpatient care.

Management of Stress Hyperglycemia in a Patient Admitted to the Surgical ICU

Michelle F. Magee, MD
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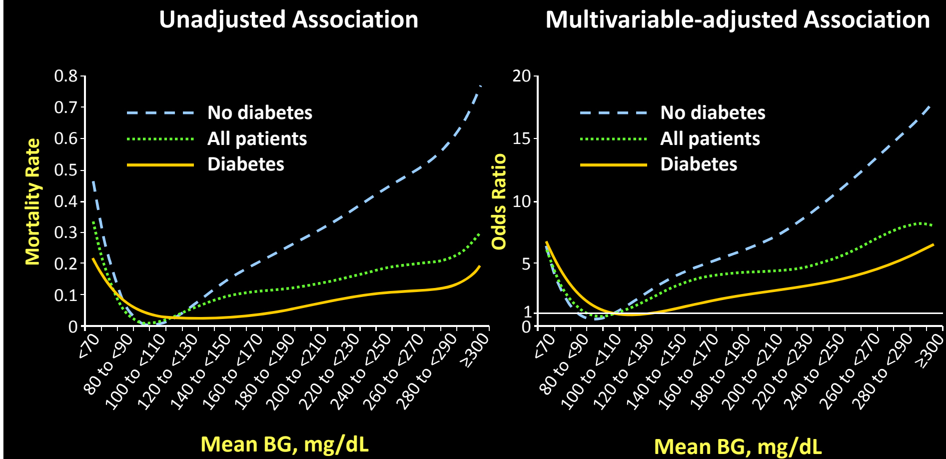
Etiology of Hospital Hyperglycemia

- Diabetes:
  - previously recognized
  - previously unrecognized
- Pre-diabetes
- Stress/illness-related hyperglycemia

Association Between Mean Glucose Level and In-hospital Mortality in AMI



Kosiborod M, et al. *Circulation.* 2008.

Implications of Hospital Hyperglycemia: Pathophysiology

Impaired perfusion
- ↓Endothelial function
- No reflow phenomenon

Deranged metabolism
- Serum FFA
- Insulin secretion
- Glycolysis
- Glucose oxidation
- Fluid and electrolyte imbalance

Pro-thrombotic
- Platelet aggregation
- Fibrinolysis
- Clotting factors

Impaired white blood cell function

Impaired LV function
- Ischemic preconditioning
- LV remodeling

Pro-inflammatory
- Cytokine
- Chemokines
- Biomarkers

Impaired wound healing

Insulin has the potential to reverse each of these effects

FFA = free fatty acids, LV = left ventricular

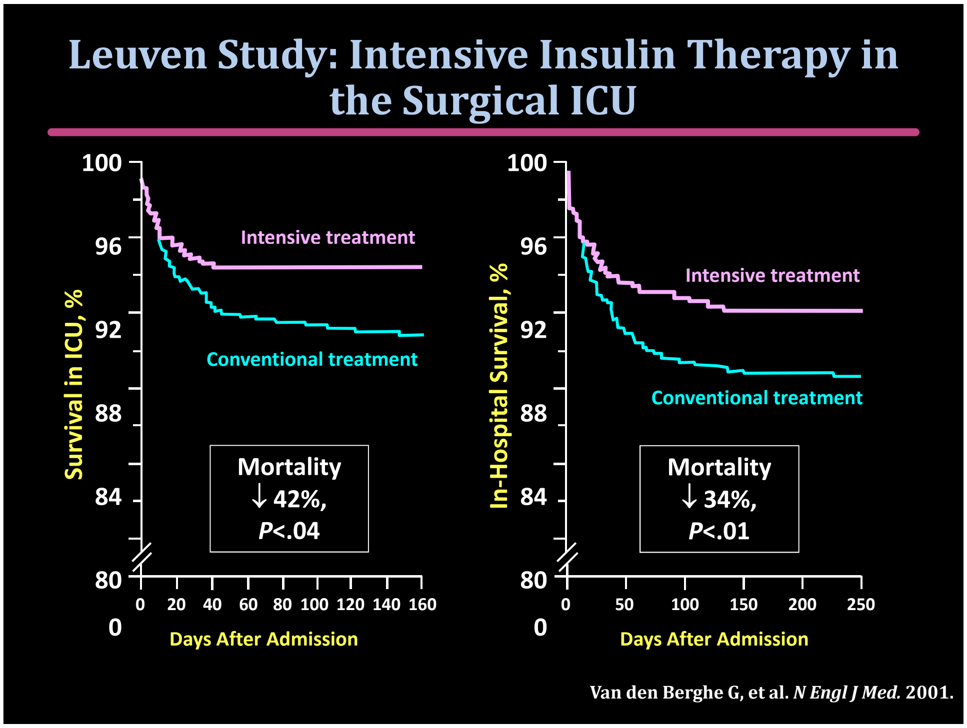
Adapted from Zarich SW. *Rev Cardiovasc Med*. 2006; Bauters C, et al. *Eur Heart J*. 2007; Kitabchi AE, et al. *Diabetes Care*. 2006; Zarich SW, et al. *Circulation*. 2007.

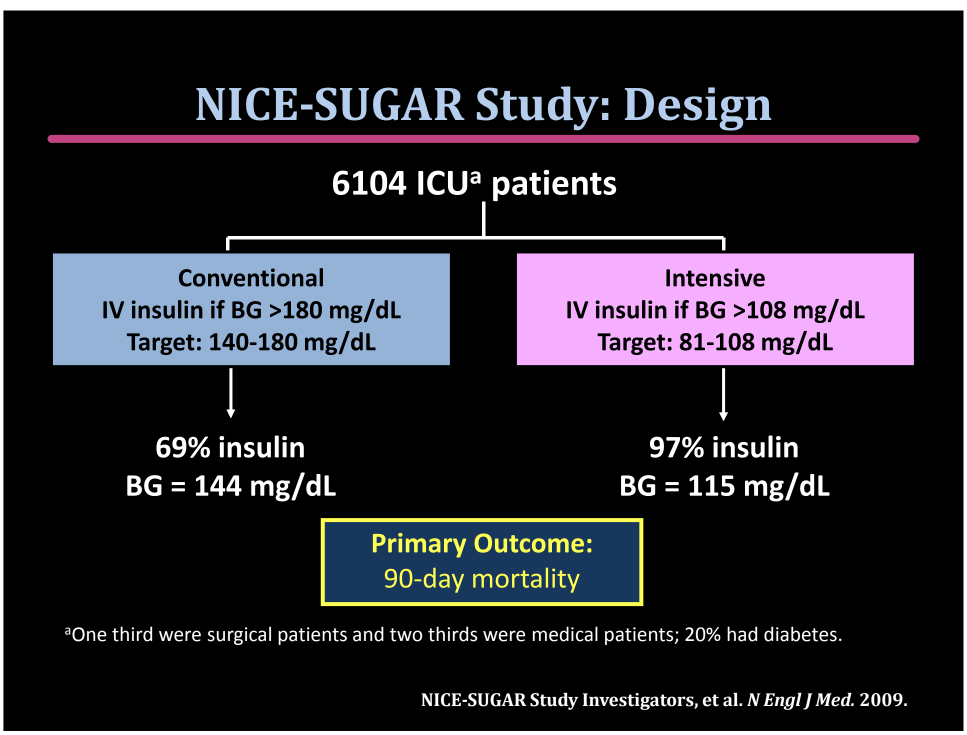
ICU Glycemic Control: Select Randomized Trials

Trial	N	Setting	BG Target (mg/dL)		BG Achieved[a] (mg/dL)		Primary Outcome	End Point Rate		ARR[b]	RRR[b]	Odds Ratio[b] (95% CI)
			Intensive	Conventional	Intensive	Conventional		Intensive	Conventional			
DIGAMI 1995	620	CCU (AMI)	126-196	Usual care	173	211	1-year mortality	18.6%	26.1%	7.5%	29%[c]	NR
Van den Berghe 2001	1548	SICU	80-110	180-200	103	153	ICU mortality	4.6%	8.0%	3.4%	42%	0.58[c] (0.38-0.78)
Van den Berghe 2006	1200	MICU	80-110	180-200	111	153	Hospital mortality	37.3%	40.0%	2.7%	7.0%	0.94[d] (0.84-1.06)
Glucontrol 2007	1101	ICU	80-110	140-180	118	144	ICU mortality	16.7%	15.2%	-1.5%	-10%	1.10[d] (0.84-1.44)
VISEP 2008	537[e]	ICU	80-110	180-200	112	151	28-day mortality	24.7%	26.0%	1.3%	5.0%	0.89[d] (0.58-1.38)
De La Rosa 2008	504	SICU MICU	80-110	180-200	117	148	28-day mortality	36.6%	32.4%	-4.2%[d]	-13%[d]	NR
NICE-SUGAR 2009	6104	ICU	81-108	≤180	115	145 mg/dL	90-day mortality	27.5%	24.9%	-2.6%	-10.6	1.14[c] (1.02-1.28)

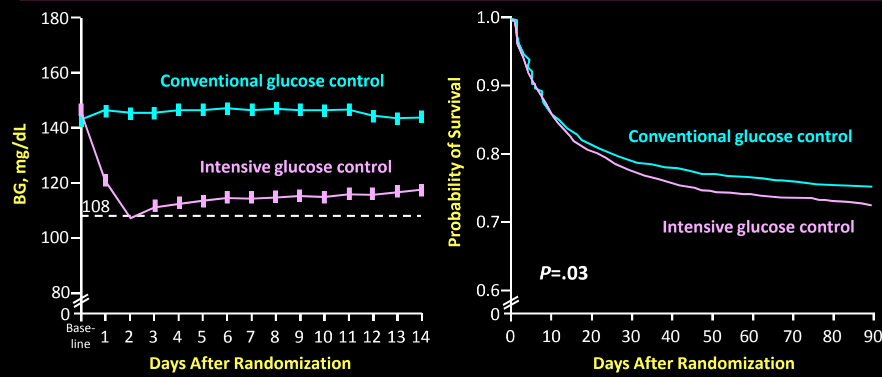
[a]Mean morning BG concentrations, except for the Glucontrol study, which reported mean overall BG concentrations; [b]intensive group vs. conventional group; [c]*P*<0.05; [d] not significant (p>0.05); [e]Composite of death, sternal infection, prolonged ventilation, cardiac arrhythmias, stroke, and renal failure at 30 days

ARR, absolute risk reduction; RRR, relative risk reduction; NR, not reported, ICU, intensive care unit (mixed); SICU, surgical intensive care unit; MICU, medical intensive care unit; GIK, glucose/insulin/potassium infusion.


Leuven Study: Intensive Insulin Therapy in the Surgical ICU
Survival in ICU, %
100
96
92
88
84
80
0
Intensive treatment
Conventional treatment
Mortality
↓ 42%,
P<.04
0 20 40 60 80 100 120 140 160
Days After Admission
In-Hospital Survival, %
Intensive treatment
Conventional treatment
Mortality
↓ 34%,
P<.01
0 50 100 150 200 250
Days After Admission
Van den Berghe G, et al. *N Engl J Med.* 2001.


NICE-SUGAR Study: Design
6104 ICU[a] patients
Conventional
IV insulin if BG >180 mg/dL
Target: 140-180 mg/dL
Intensive
IV insulin if BG >108 mg/dL
Target: 81-108 mg/dL
69% insulin
BG = 144 mg/dL
97% insulin
BG = 115 mg/dL
Primary Outcome:
90-day mortality
[a]One third were surgical patients and two thirds were medical patients; 20% had diabetes.
NICE-SUGAR Study Investigators, et al. *N Engl J Med.* 2009.

NICE-SUGAR Study: Results



- 3054 received IIT goal: 81-108 mg/dL (time weighted BG = 118 mg/dL)
- 3050 received CIT goal: <180 mg/dL (time-weighted BG = 145 mg/dL)
- 90-day mortality: IIT, 829 patients (27.5%); CIT, 751 (24.9%)
- Absolute mortality difference: 2.6% (95% CI, 0.4-4.8)
- Odds ratio for death with IIT: 1.14 (95% CI, 1.02-1.28; *P*=.02)

Reproduced with permission from NICE-SUGAR Study Investigators, et al. *N Engl J Med.* 2009.

Glycemic Control in the NICE-SUGAR & Leuven 1 Studies

	Glycemic Target	Results Mean (SD)	% Values in Target
NICE-SUGAR	81-108	118 (25)	***25***
LEUVEN I	80-110	103 (19)	***53***

	Control Target	Control Results Mean (SD)	% Overlap Within 2 SD of interventional mean
NICE-SUGAR	140-180	145 (26)	***80***
LEUVEN I	180-210	153 (33)	***30***

Responses to NICE-SUGAR in Literature

- Strengths – large multicenter study across range of ICUs; uniform insulin drip protocol; definitive primary outcome.
- Attempts to normalize glycemia do not provide a simple answer.
- Raise additional questions – contradict results of prior studies.
- Differences in nutritional support, % patients receiving insulin.
- What are implications of NICE-SUGAR for majority ICU patients with hyperglycemia? Would 'tight' control without hypoglycemia have had different results?

Cefalu WT. *Diabetes.* 2009; Sharma S, et al. *Int Anesthesiol Clin*. 2009.

Responses to NICE-SUGAR in Literature, continued

- Accept that glycemic goals in ICU should be more moderate, i.e. ‘’tight” control may not be better than “good” control
- Does NOT imply that we should accept hyperglycemia and revert back to days of ignoring glycemic levels and SSI

Cefalu WT. *Diabetes.* 2009; Sharma S, et al. *Int Anesthesiol Clin*. 2009.

Intensive Insulin Therapy & Mortality in ICU Patients: Meta-analysis of 26 Articles

ICU	no. deaths/total n IIT	no. deaths/total n Control	Risk ratio (95% CI)
Mixed	1351/5051	1301/5089	0.99 (0.87-1.12)
Medical	253/724	270/736	1.00 (0.78-1.28)
Surgical	77/1037	110/935	0.63 (0.44-0.91)
All	1681/6812	1681/6760	0.93 (0.83-1.04)

Griesdale DE, et al. *CMAJ.* 2009.

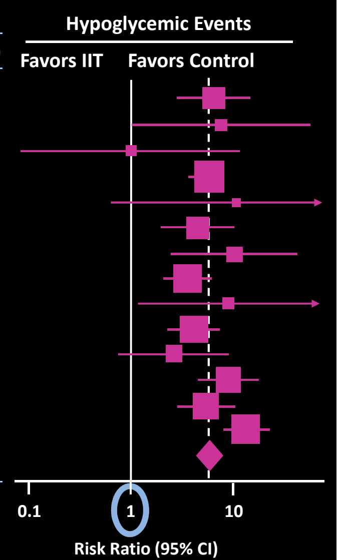
Intensive Insulin Therapy & Mortality in ICU Patients: Meta-analysis of 26 Articles

- IIT had no effect on overall risk of death
- IIT may benefit patients in SICU
- 6-fold increased risk of severe hypoglycemia among IIT patients compared with controls
- Risk for hypoglycemic events did not differ by type of ICU or by intensity of insulin therapy

Griesdale DE, et al. *CMAJ.* 2009.

Intensive Insulin Therapy and Mortality in Critically Ill Patients: A Meta-analysis

	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.

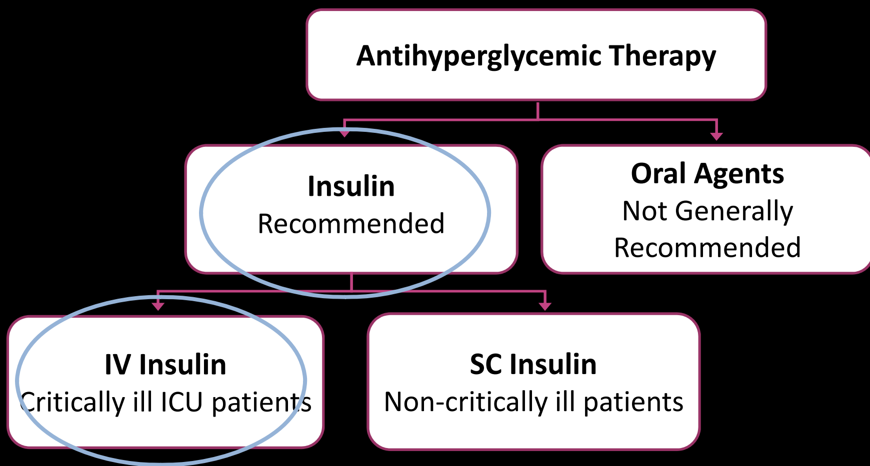
AACE/ADA Target Glucose Level in ICU Patients

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

Moghissi ES, et al. *Endocr Pract.* 2009.

Recommendations for Managing Inpatient Hyperglycemia



Clement S, et al. *Diabetes Care.* 2004; Moghissi ES, et al. *Endocr Pract.* 2009.

Safe, Effective Glycemic Control

- Choose a glycemic target that can be reached safely:
  - e.g., 140 mg/dL
- Avoid excessive severe hypoglycemia
- Use appropriate data monitoring tools
  - Glycemic values
  - Clinical and financial outcomes
- Minimize glycemic variability

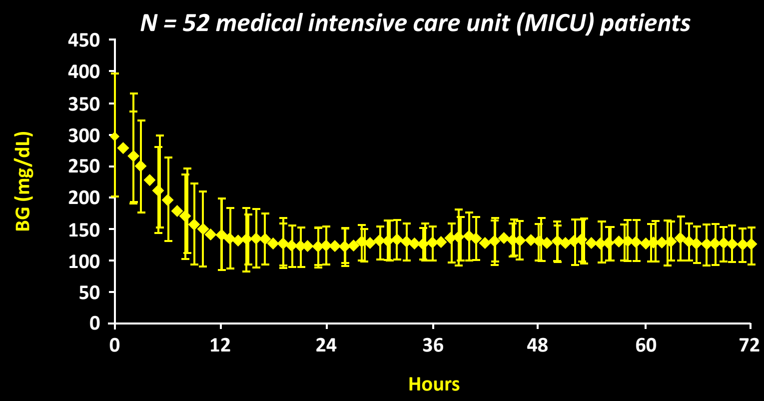
Krinsley JS, et al. *Crit Care.* 2008.

Strategies to Support Implementing Glycemic Control in the ICU

Successful IV Insulin Protocol

- Reaches and maintains BG successfully within a prespecified target range
- Includes a clear algorithm for making temporary corrective changes in the IV insulin rate as patient requirements change
- Incorporates the "rate of change" in BG, not just the absolute values
- Incorporates the current IV insulin rate
- Minimizes hypoglycemia; provides specific directions for its treatment when it occurs
- Provides specific guidelines for timing and selection of doses for the transition to SC insulin

Implementation of a Safe & Effective Insulin Infusion Protocol in the MICU



Goldberg PA, et al. *Diabetes Care*. 2004.

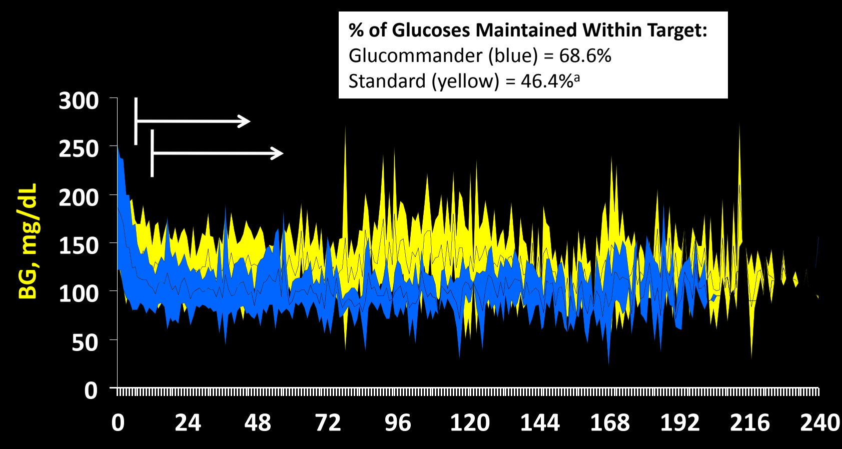
Software-based Insulin Infusion Protocols

Gluco-Tec Glucommander™

EndoTool™
Glucose Management System
FDA CLEARS MD SCIENTIFIC'S TIGHT GLUCOSE CONTROL SOFTWARE
EndoTool™ Glucose Management System Calculates Intravenous Insulin Dosing

85763
CH-20021 (MAR/17/05)
Page 1 of 1
Clarian Health Partners
Methodist | IU | Riley
Clarian GlucoStabilizer Insulin Infusion Program

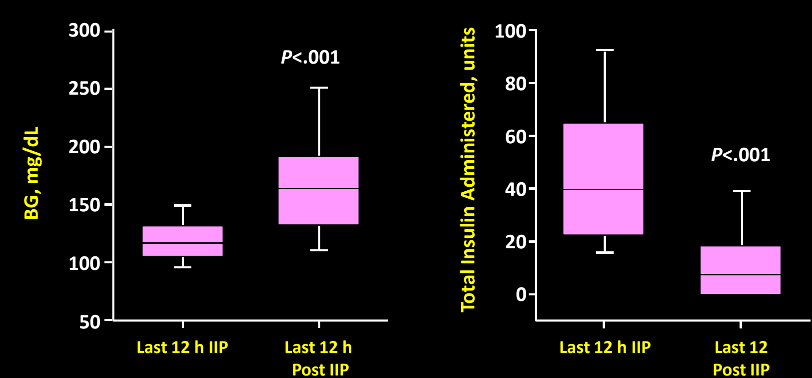
Glucommander vs. Standard Protocol: % of Glucose Values Maintained



[a]*P* <.0001

Newton CA, et al. *Diabetes.* 2008.

Transition From IV to SC Insulin: Mixed ICU Setting



IIP, intensive insulin protocol

Reproduced with permission from Czosnowski QA, et al. *J Hosp Med.* 2009.

Transitioning from IV to Subcutaneous Insulin: Do's & Don'ts

- Do overlap SC and IV insulin to minimize "hyperglycemia escape" because of short ½ life of IV insulin.
- Do use rapid analogs post-meal when uncertain of ability to consume food.
- Don't use basal insulin alone if the patient is eating.
- Do ensure adequate nutritional intake when switching patients with ketotic diabetes to SC insulin.
- Do arrange for follow-up of patients placed on temporary insulin.

Carlson R, et al. *Chest.* 2006.

Transition from IIT to SC Regimen in ICU

- Respiratory ICU with BG 80-110mg/dL range
- Prospective data collection
  - – Stable on drip – *and* –
  - – Leaving unit in 1-3 days – *or* –
  - – To begin po intake

Carlson R, et al. *Chest.* 2006.

Transition Algorithm

- Based on total daily insulin dose (TDD) at time of transition
- Basal insulin = 50% of TDD
- Carbohydrate ratio
- Correction doses based on "rule of 1700"
- Orders written by ICU PharmD

Transition from IIT to SC Regimen in ICU: RESULTS

- 84 patients with 2267 BG values analyzed
- Average infusion rate at transition was 3.9 units/hr
- Post-transition average BG was 125 mg/dL
- 85.7% of patients with average BG ≤ 140 mg/dL
- Hypoglycemia occurred in 1.2% of patients and 0.044% of all BG measures

Carlson R, et al. *Chest.* 2006.

Variables Impacting Total Daily Insulin Dose During Transition from IV to SC Insulin

- Phase of illness/stress level (insulin counter-regulatory hormones)
- Nutritional status
- Co-morbid conditions
- Pharmacotherapy (high dose steroids; vasopressors)

- Tailor the transition based upon TDI at time of transition and knowledge of anticipated clinical course

Management of Inpatient Hyperglycemia in a Patient with a Pre-existing Diagnosis of Diabetes

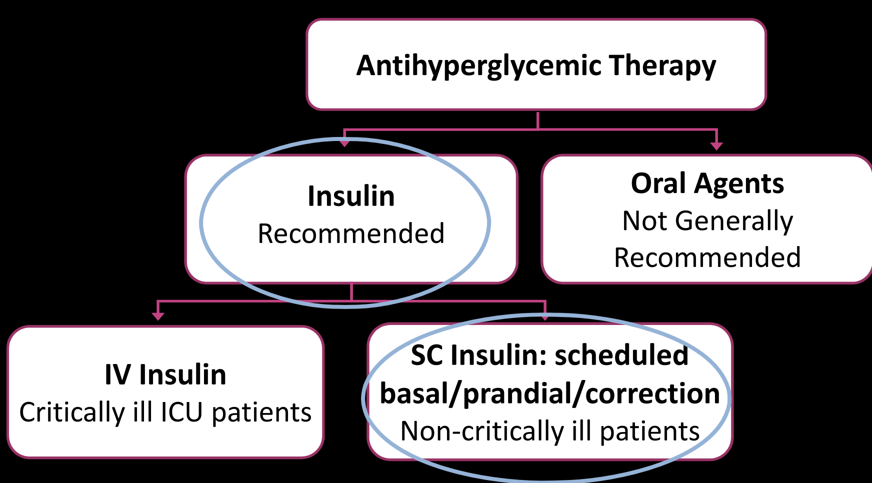
Cheryl O'Malley, MD, FAAP, FACP
University of Arizona College of Medicine
Phoenix, AZ

AACE/ADA Target Glucose Level in Non-ICU Patients

- **Non-Critically ill patients:**
  - "Premeal BG target should generally be <140 mg/dL in conjunction with random BG <180 mg/dL."

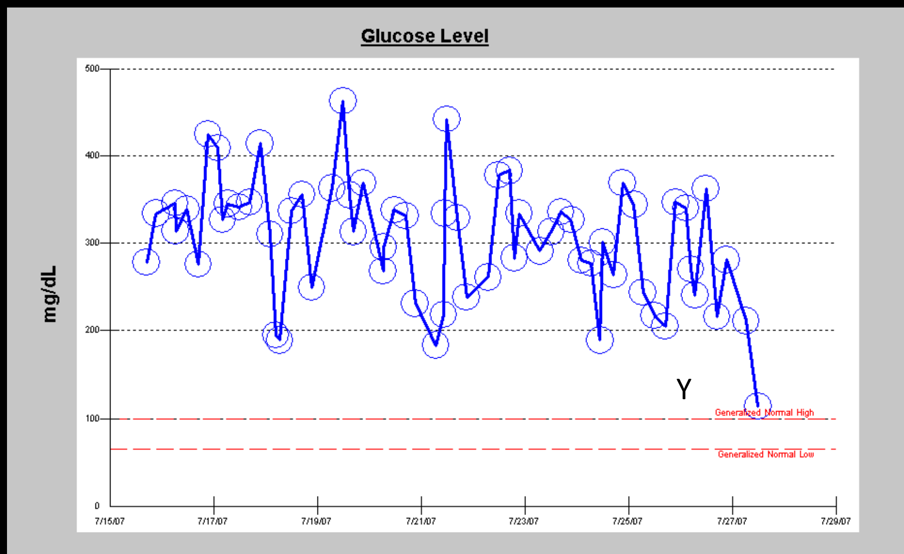
Moghissi ES, et al. *Endocr Pract.* 2009.

Recommendations for Managing Inpatient Hyperglycemia



Clement S, et al. *Diabetes Care.* 2004; Moghissi ES, et al. *Endocr Pract.* 2009.

Does this look familiar?

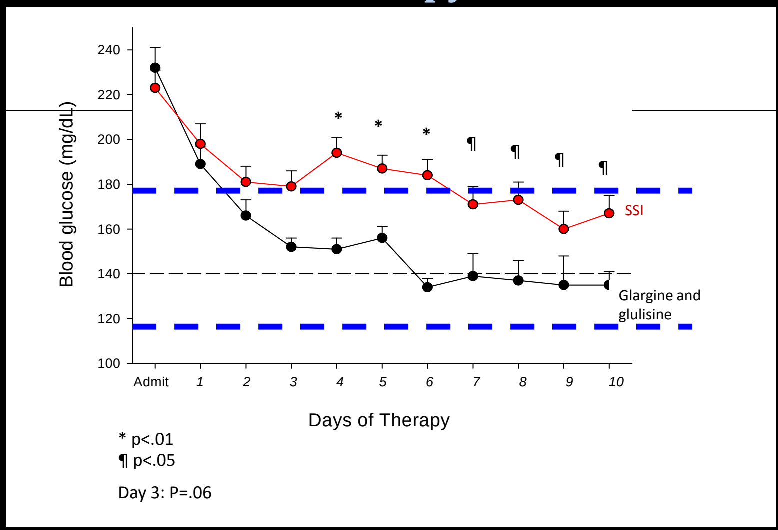


RABBIT-2 Trial: Basal/Bolus Arm

- D/C oral antidiabetic drugs on admission
- Starting total daily dose (TDD):
  - 0.4 U/kg/d x BG between 140-200 mg/dL
  - 0.5 U/kg/d x BG between 201-400 mg/dL
- Half of TDD as insulin glargine and half as rapid-acting insulin (glulisine)
  - Insulin glargine – once daily, at the same time/day
  - Rapid-acting insulin – three equally divided doses (AC)

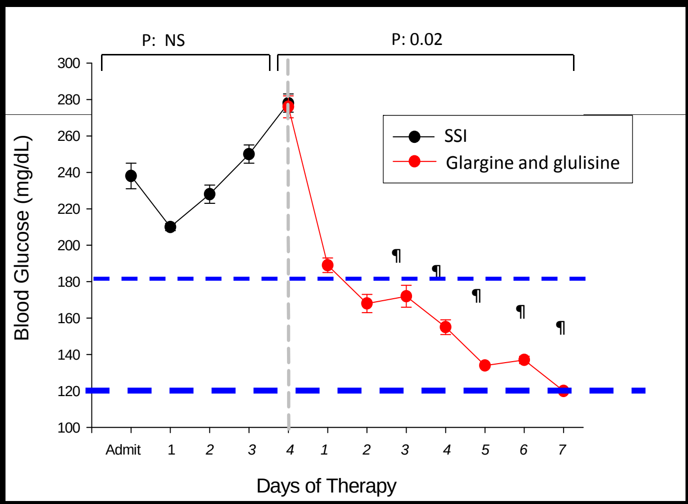
Smiley DD, et al. *South Med J*. 2006.

Mean Blood Glucose Levels During Insulin Therapy



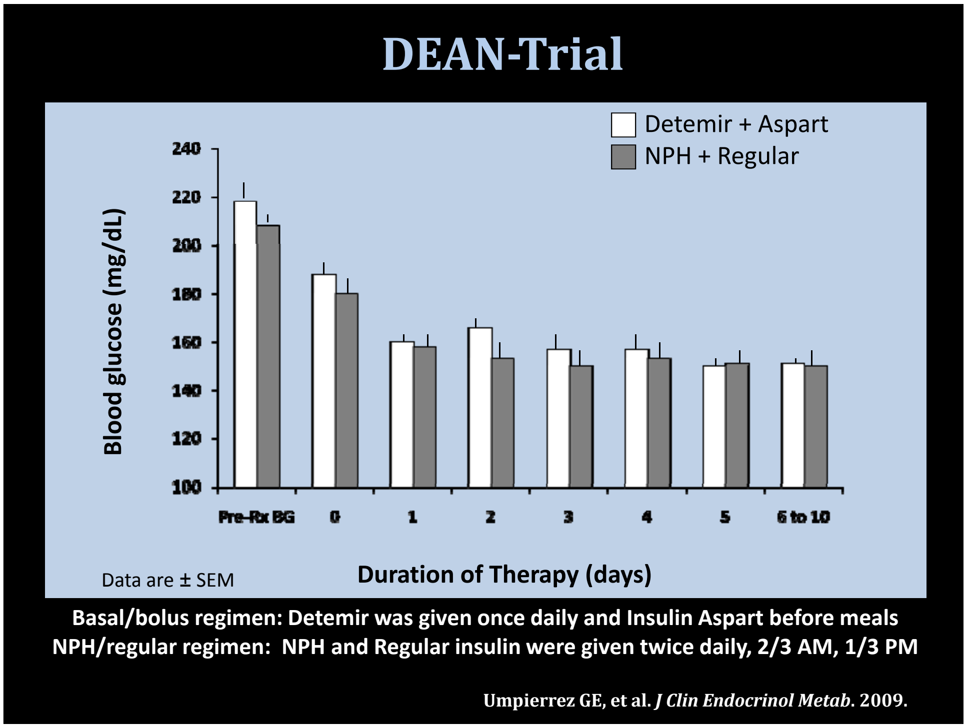
Umpierrez GE, et al. *Diabetes Care.* 2007.

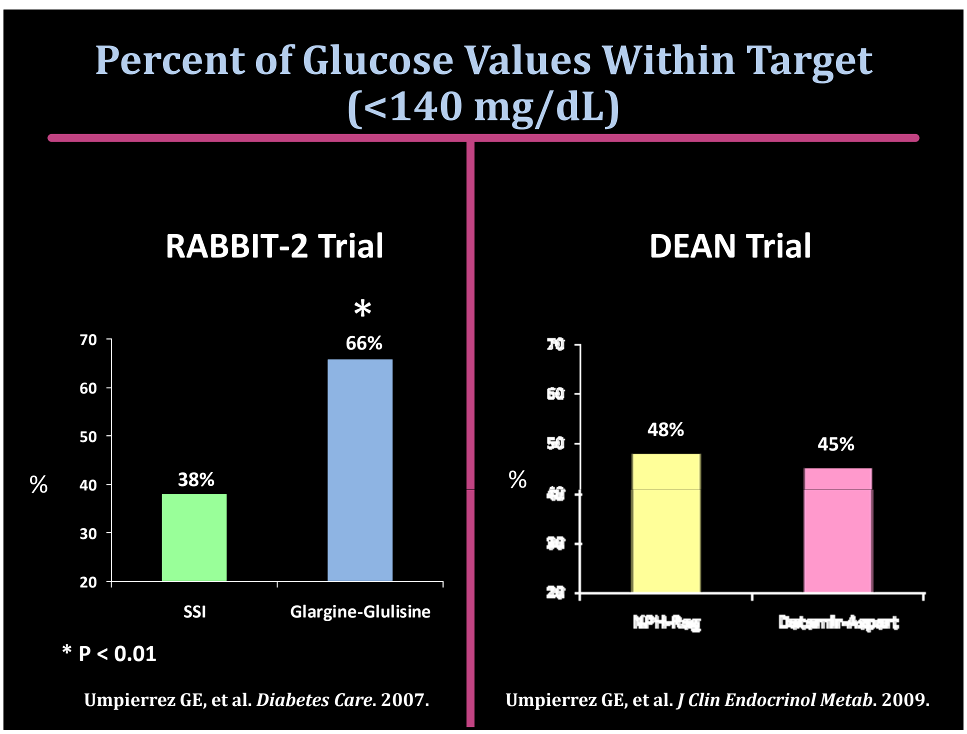
Blood Glucose Levels in Patients Who Failed SSI: Transition to Basal Bolus Insulin

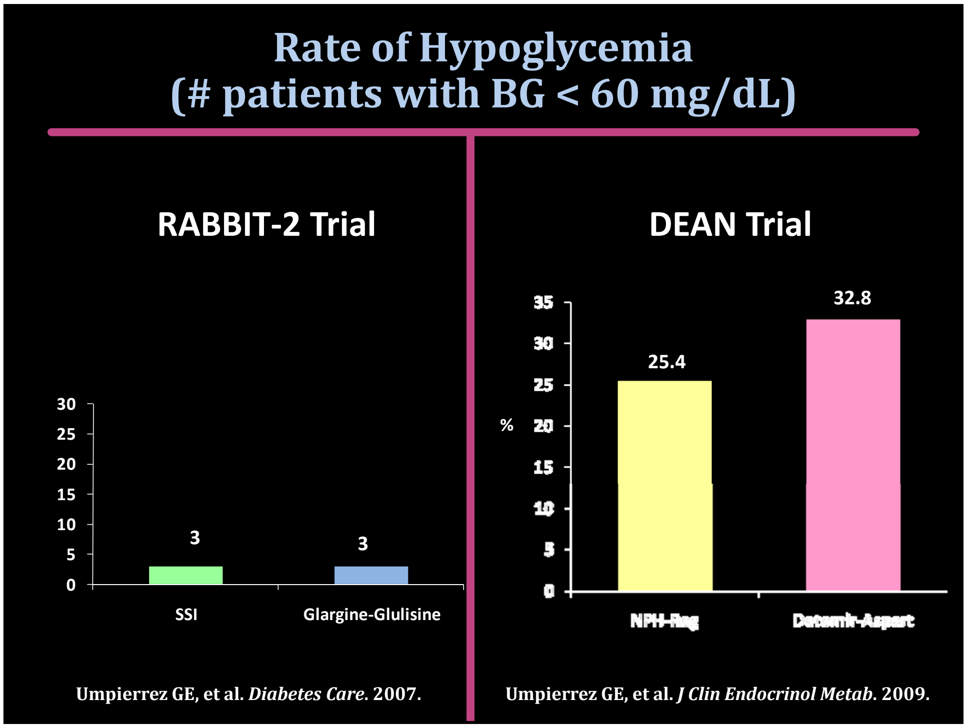


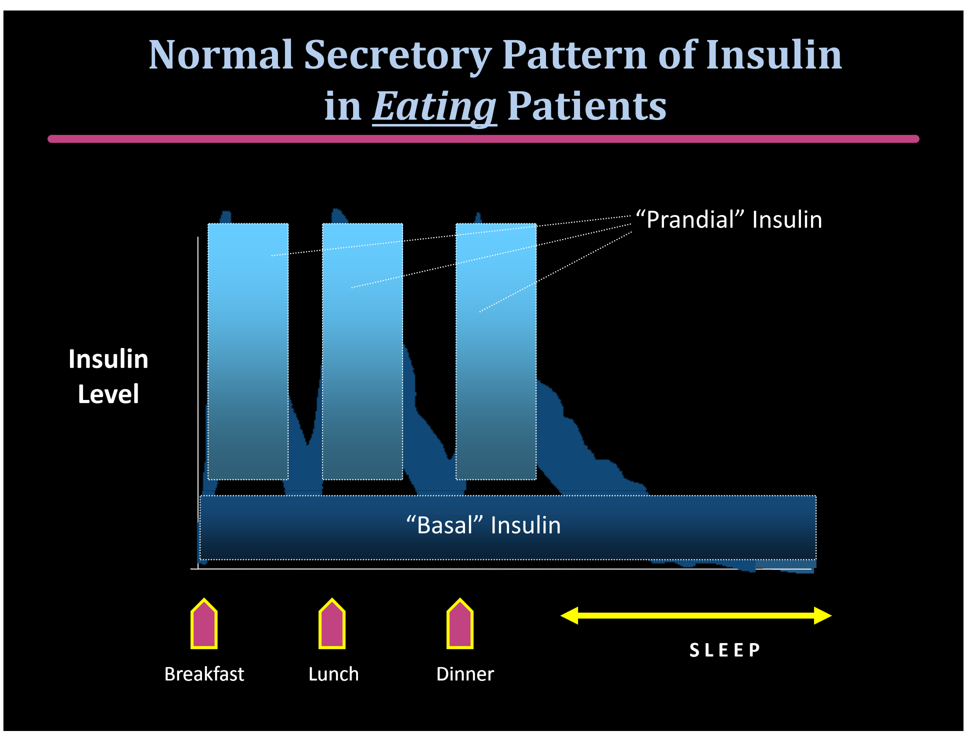
Failure was defined as 3 consecutive BG values > 240 mg/dL during SSI

Umpierrez GE, et al. *Diabetes Care.* 2007.


DEAN-Trial
Detemir + Aspart
NPH + Regular
Blood glucose (mg/dL)
240
220
200
180
160
140
120
100
Pre-Rx BG
0
1
2
3
4
5
6 to 10
Data are ± SEM
Duration of Therapy (days)
Basal/bolus regimen: Detemir was given once daily and Insulin Aspart before meals
NPH/regular regimen: NPH and Regular insulin were given twice daily, 2/3 AM, 1/3 PM
Umpierrez GE, et al. J Clin Endocrinol Metab. 2009.


Percent of Glucose Values Within Target (<140 mg/dL)
RABBIT-2 Trial
*
66%
38%
%
70
60
50
40
30
20
SSI
Glargine-Glulisine
* P < 0.01
Umpierrez GE, et al. Diabetes Care. 2007.
DEAN Trial
48%
45%
%
NPH-Reg
Detemir-Aspart
Umpierrez GE, et al. J Clin Endocrinol Metab. 2009.


Rate of Hypoglycemia
(# patients with BG < 60 mg/dL)
RABBIT-2 Trial
30
25
20
15
10
5
0
3
3
SSI
Glargine-Glulisine
Umpierrez GE, et al. *Diabetes Care*. 2007.
DEAN Trial
35
30
25
20
15
10
5
0
%
25.4
32.8
NPH-Reg
Detemir-Aspart
Umpierrez GE, et al. *J Clin Endocrinol Metab*. 2009.

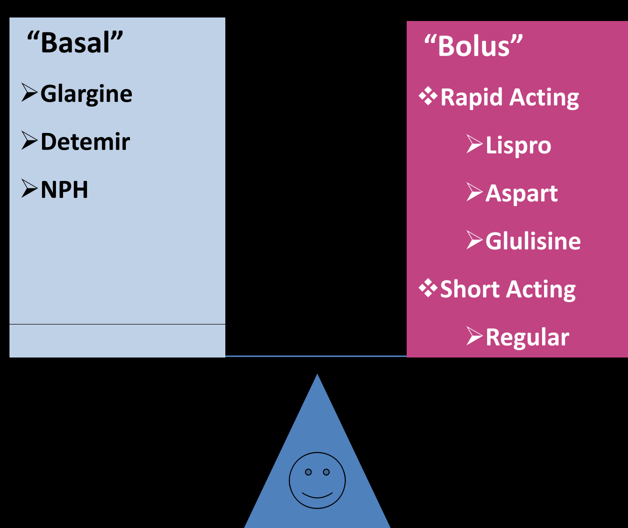

Normal Secretory Pattern of Insulin
in *Eating* Patients
"Prandial" Insulin
Insulin
Level
"Basal" Insulin
Breakfast
Lunch
Dinner
SLEEP

Comparison of Human Insulins and Insulin Analogues

Insulin Preparation	Onset	Peak	Duration
Lispro/Aspart Gluslisine	5-15 min	1-2 hrs	4-6 hrs
Human Regular	30-60 min	2-4 hrs	6-10 hrs
Human NPH	1-2 hrs	4-8 hrs	10-18 hrs
Glargine, Detemir	1-2 hrs	Flat	24 hrs

The time course of action of any insulin may vary in different individuals, or at different times or different injection locations in the same individual. Due to such variation, the time periods described above should be used as general guidelines only.

Total Daily Dose of Insulin Divided to Match Needs



3(+1) Steps to Using Basal/Bolus Insulin in the Hospital

1. Determine total daily insulin dose
2. Divide up to 50% basal insulin, 50% bolus
3. Reassess daily
4. USE YOUR HOSPITAL ORDER SETS

Wesorick D, et al. *J Hosp Med*. 2008.

Step 1: Calculate Starting Total Daily Dose (TDD)

1. IV requirements
2. Home total daily dose
3. Weight based
   A. BMI[1]
   - 0.3 ESRD
   - 0.4 units/kg/day lean (BMI <25)
   - 0.5 units/kg/day overweight (BMI 25-30)
   - 0.6 units/kg/day obese (BMI >30)

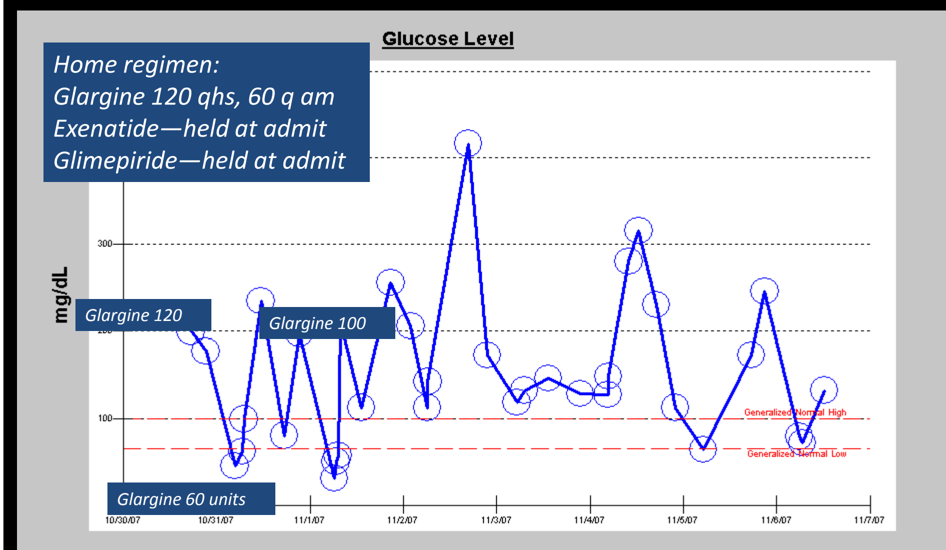
   B. Initial BG (used in RABBIT2[2])
   - 0.4 U/kg/d x BG between 140-200 mg/dL
   - 0.5 U/kg/d x BG between 201-400 mg/dL

[1]Wesorick D, et al. *J Hosp Med*. 2008; [2]Umpierrez GE, et al. *Diabetes Care*. 2007.

Step 2: Divide into Scheduled Basal vs. Nutritional Insulin

- 40-50% should generally be basal (glargine, detemir, or NPH)
- Remaining 50-60% divided evenly and given to cover nutritional intake
  - Rapid acting (lispro, aspart, glulisine) easier to match with meals in hospital
  - Regular insulin also an option

Case: Hypoglycemia Why?

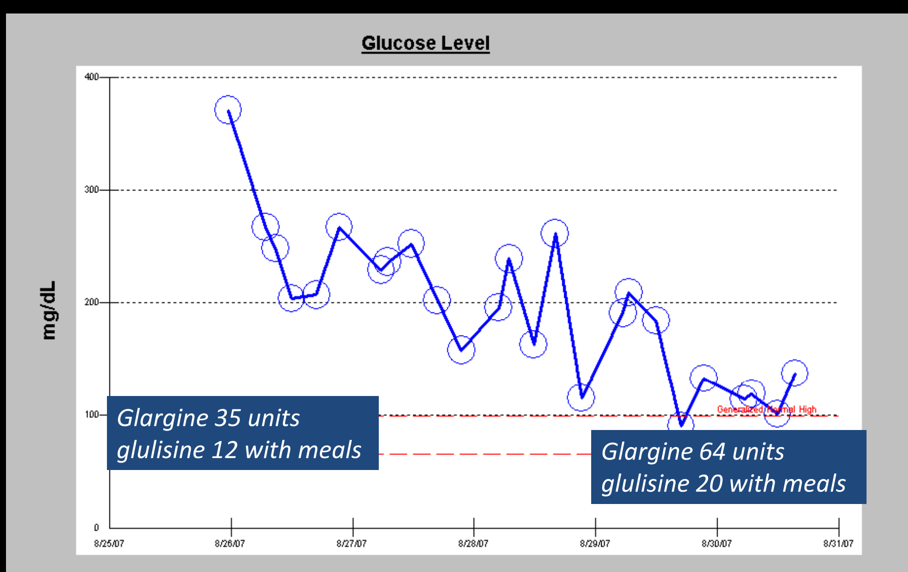


Step 3: Assess Doses Daily

- Hypoglycemia prevention
  - If some BG were <100 mg/d →Reassess dose
  - If any BG <70 mg/dL→ Decrease dose
- Hyperglycemia: If fasting >140, or random over 180 mg/dL and none less than 100 then
  - Add 10-20% to the TDDI from the prior day
  - Re-divide the new TDDI to preserve the desired ratio

Moghissi ES, et al. *Endocr Pract.* 2009; Umpierrez GE, et al. *Diabetes Care*. 2007; Umpierrez GE, et al. *J Clin Endocrinol Metab*. 2009.

Daily Adjustments



Clinical Inertia is Common

- Retrospective Analysis 2,916 discharges
- Teaching hospital (200 bed; metro. Phoenix)
- LOS 3 or more days; non-ICU
- Mean 1st 24 hours 170 → stay 167 mg/dL→ last 24 h 165 mg/dL
- Highest tertile (mean 218 mg/dL)
  - 46% still only on SSI
  - only 60% increased insulin doses

Cook CB, et al. *J Hosp Med*. 2007.

3 (+1) Steps to Using Basal/Bolus Insulin in the Hospital

1. Determine total daily insulin dose
2. Divide up to 50% basal insulin, 50% bolus
3. Reassess daily
4. USE YOUR HOSPITAL ORDER SETS

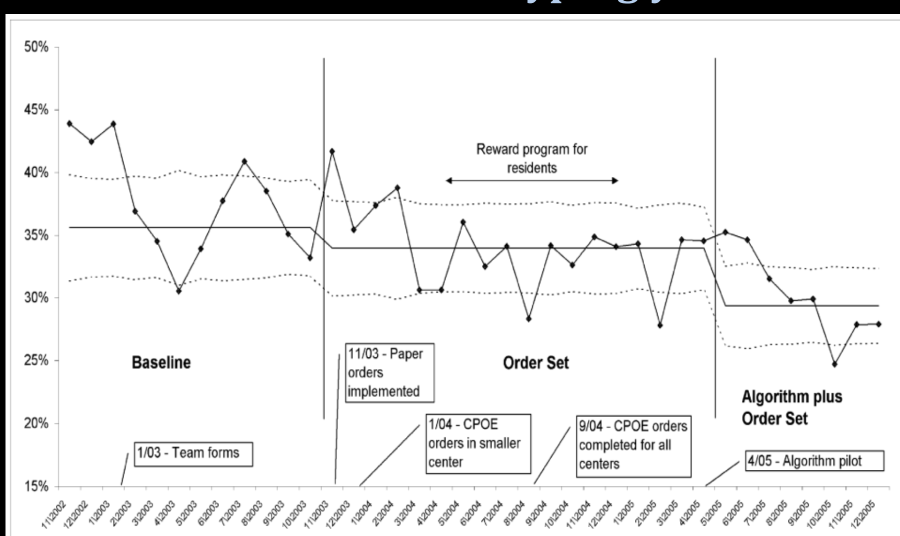
Effect of Structured Insulin Orders and an Insulin Management Algorithm – UCSD

5,530 patients with DM or Hyperglycemia and > 7 POC Glucose readings TP3:TP1

- RR Uncontrolled Patient-Day
  - 0.77 (0.74 - 0.80)
- RR Uncontrolled Patient-Stay (70% controlled vs. 60%)
  - 0.73 (0.66 - 0.81)
- RR Hypoglycemic Patient-Day (prevents 208 / year)
  - 0.68 (0.59 - 0.80)
- RR Hypoglycemic Patient-Stay
  - 0.77 (0.64 - 0.92)

Maynard G, et al. *J Hosp Med*. 2009.

UCSD Experience % of 9,314 Patient-Stays with Uncontrolled Hyperglycemia



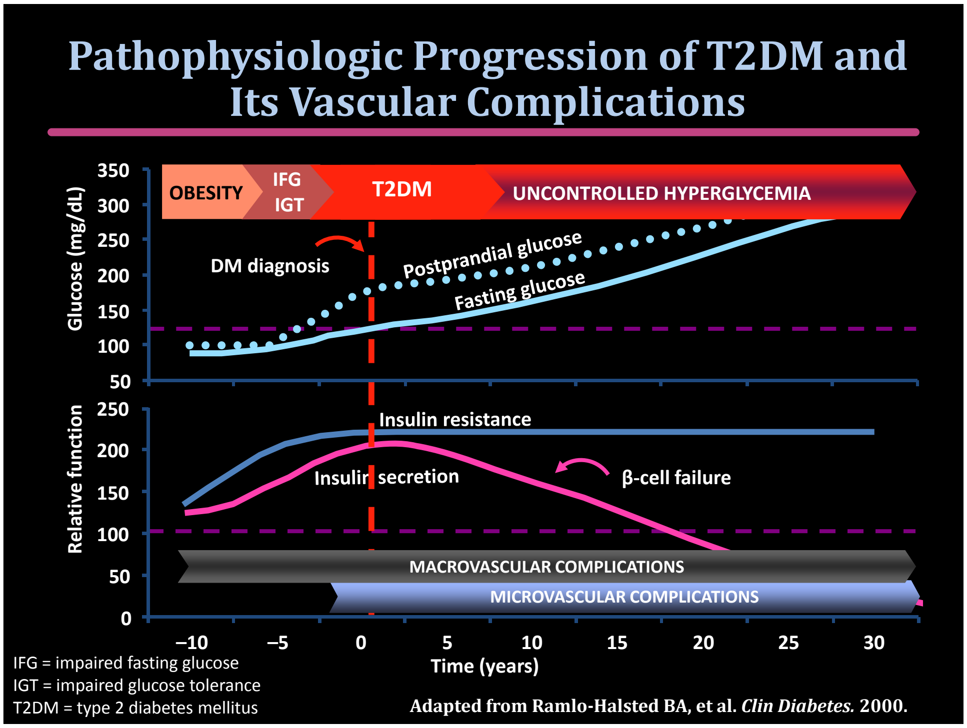
Maynard G, et al. *J Hosp Med*. 2009.

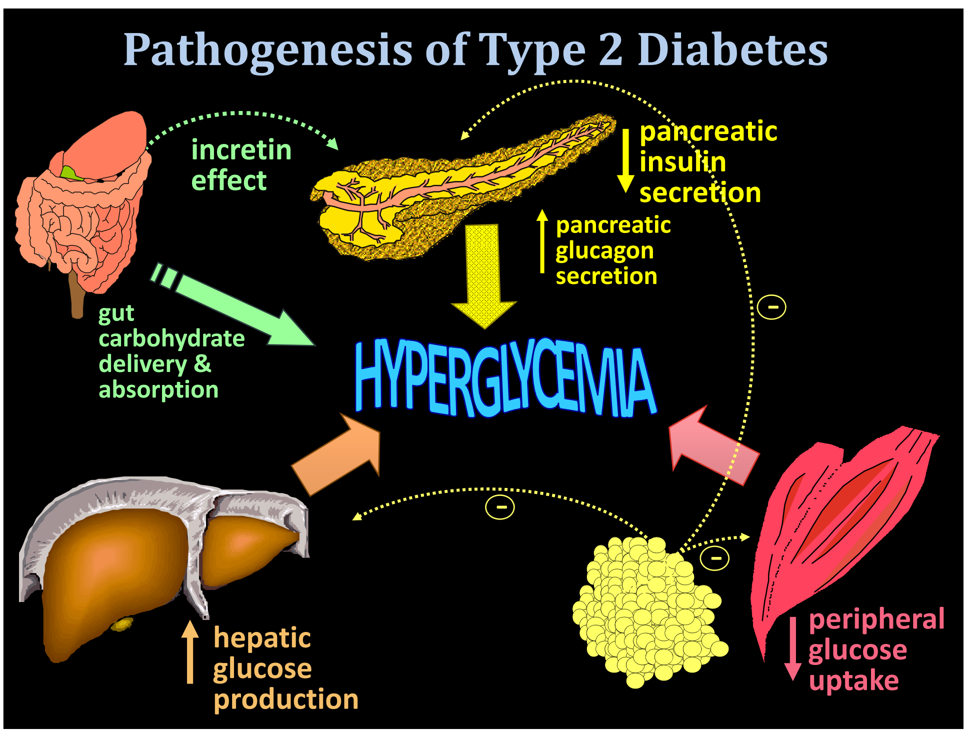
Summary

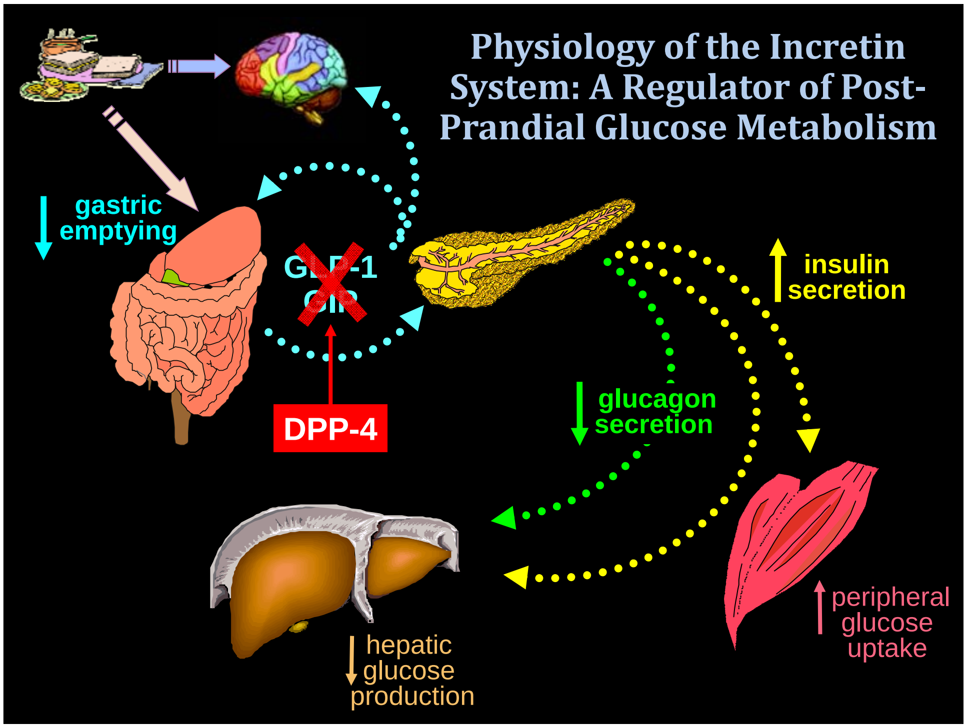
- Sliding scale insulin doesn't work in achieving moderate control for most patients on the general med-surg ward
- Basal-Bolus regimens have demonstrated improved efficacy with no increase in hypoglycemia
- We are still waiting on studies to define optimal targets and demonstrate clinical benefits
- Use the 3+1 steps (calculate TDD, divide about 50/50 basal/bolus, adjust daily, and use your hospital protocols)

Transition from Inpatient to Outpatient Care: Practical Strategies for the Hospitalist

Silvio Inzucchi, MD
Yale University School of Medicine
New Haven, CT


Pathophysiologic Progression of T2DM and Its Vascular Complications
OBESITY
IFG
IGT
T2DM
UNCONTROLLED HYPERGLYCEMIA
Glucose (mg/dL)
350
300
250
200
150
100
50
DM diagnosis
Postprandial glucose
Fasting glucose
Relative function
250
200
150
100
50
0
Insulin resistance
Insulin secretion
β-cell failure
MACROVASCULAR COMPLICATIONS
MICROVASCULAR COMPLICATIONS
−10
−5
0
5
10
15
20
25
30
Time (years)
IFG = impaired fasting glucose
IGT = impaired glucose tolerance
T2DM = type 2 diabetes mellitus
Adapted from Ramlo-Halsted BA, et al. Clin Diabetes. 2000.


Pathogenesis of Type 2 Diabetes
incretin effect
pancreatic insulin secretion
pancreatic glucagon secretion
gut carbohydrate delivery & absorption
HYPERGLYCEMIA
hepatic glucose production
peripheral glucose uptake

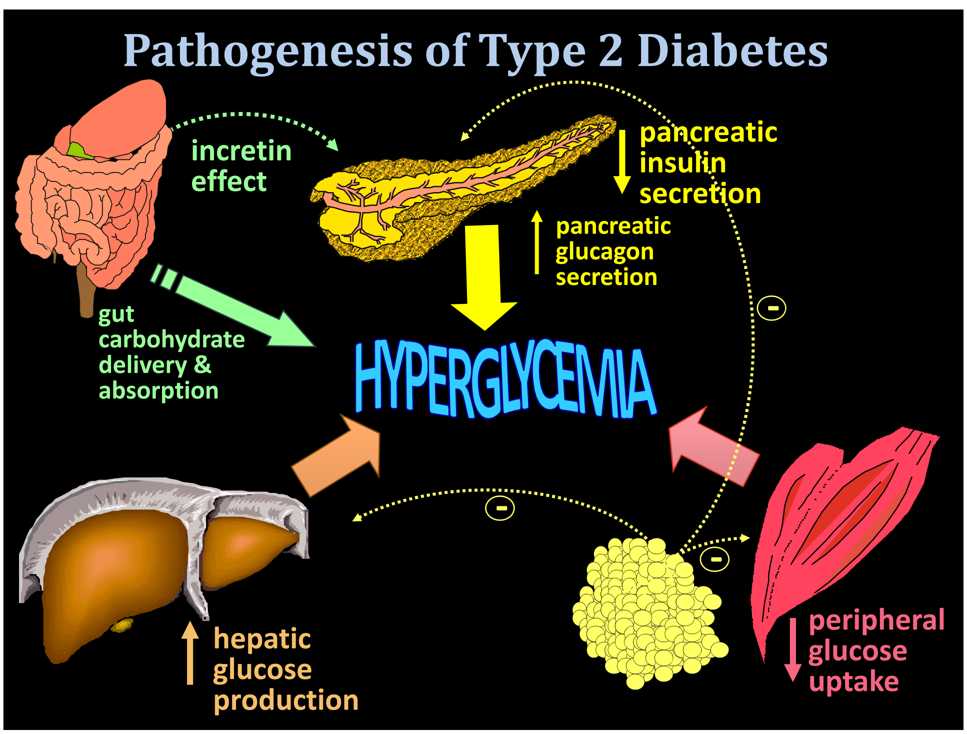


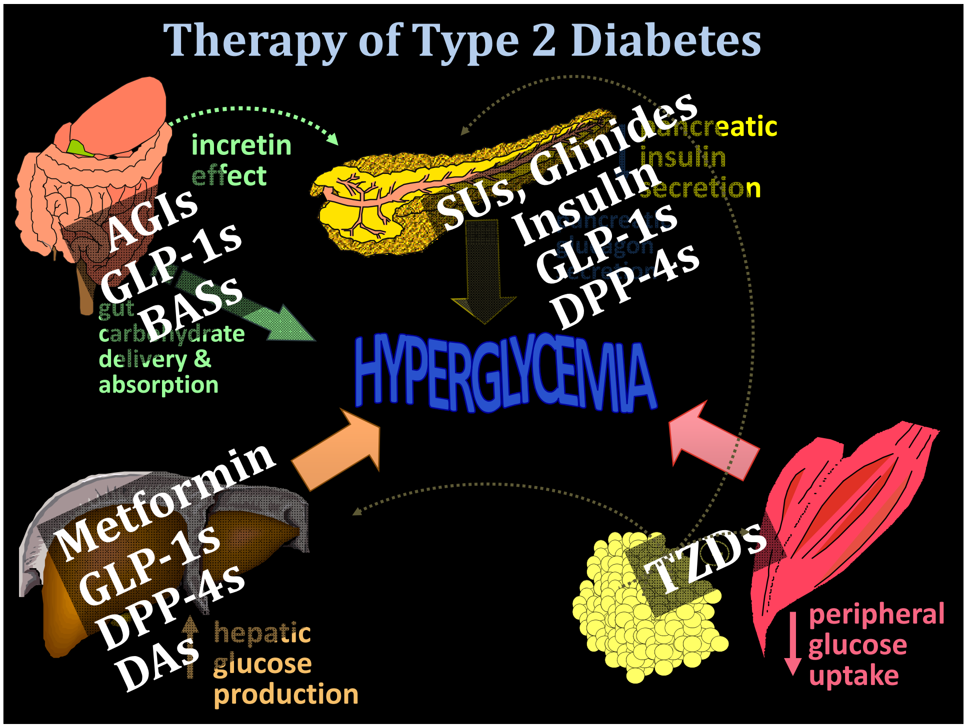
2010 Therapeutic Landscape for T2DM

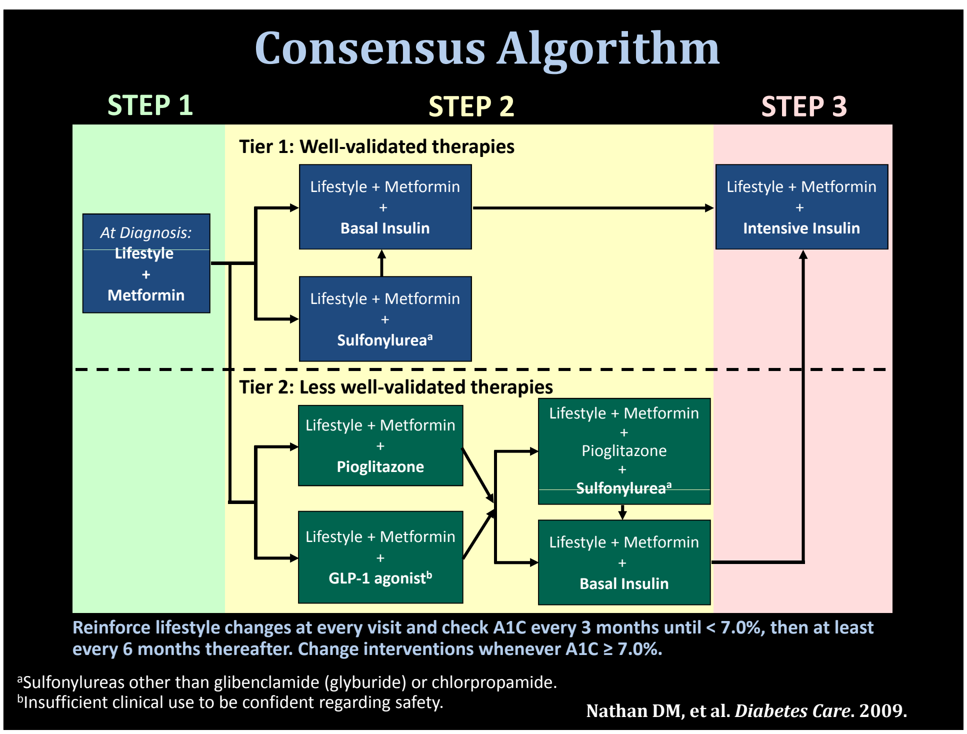
Agent	Examples	Mechanism	Action
SUs	Glyburide, Glipizide, Glimepiride	Closes K_{ATP} channels	↑ Pancreatic insulin secretion
'Glinides	Repaglinide, Nateglinide	Closes K_{ATP} channels	↑ Pancreatic insulin secretion
Biguanides	Metformin	Activates AMP-kinase	↓ Hepatic glucose production
TZDs	Rosiglitazone, Pioglitazone	Activates PPAR-γ	↑ Peripheral insulin sensitivity
α-GIs	Acarbose, Miglitol	Blocks SB alpha-glucosidase	↓ Intestinal carbohydrate absorption
GLP-1 agonists	Exenatide, Liraglutide	Activates GLP-1 receptors	↑ Pancreatic insulin secretion; ↓ glucagon secretion; delays gastric emptying; ↑ satiety
Amylin mimetics	Pramlintide	Activates amylin receptors	↓ Pancreatic glucagon secretion; delays gastric emptying; ↑ satiety
DPP-4 inhibitors	Sitagliptin,Saxagliptin	Inhibits DPP-4, ↑ endogenous incretins	↑ Pancreatic insulin secretion; ↓ pancreatic glucagon secretion
Bile acid sequestrants	Colesevelam	Binds bile acid cholesterol	?
D2 agonists	Bromocriptine	Activates dopaminergic receptors	'Resets hypothalamic circadian organization';↑insulin sensitivity

Distinguishing Therapies for T2DM

Agent	↓A1c	Advantages	Diadvantages	Cost
GLP-1 agonists	1%	Wt loss,? β-cell preservation ? CV benefits	Nausea / vomiting; ? pancreatitis; injectable ? C-cell hyperplasia/tumors	$ $ $
Amylin mimetics	0.5%	Wt loss, ↓PPG	Nausea / vomiting; dosing frequency; injectable	$ $ $
DPP-4 inhibitors	0.6-0.8%	No hypo	Urticaria / ? angioedema; ? Pancreatitis	$ $ $
Bile acid sequest.	0.5%	No hypo; ↓LDL-C	Constipation; ↑TGs; dosing	$ $ $
D2 agonists	0.5%	No hypo	Dizziness/syncope; Nausea; fatigue; rhinitis	?
Insulin	No limit	↓Microvasc risk Always effective	Hypo, wt gain, injectable	$ $




Therapy of Type 2 Diabetes
incretin effect
AGIs
GLP-1s
BASS
carbohydrate delivery & absorption
SUs, Glinides
Insulin
GLP-1s
DPP-4s
secretion
HYPERGLYCEMIA
Metformin
GLP-1s
DPP-4s
DAs
hepatic glucose production
TZDs
peripheral glucose uptake

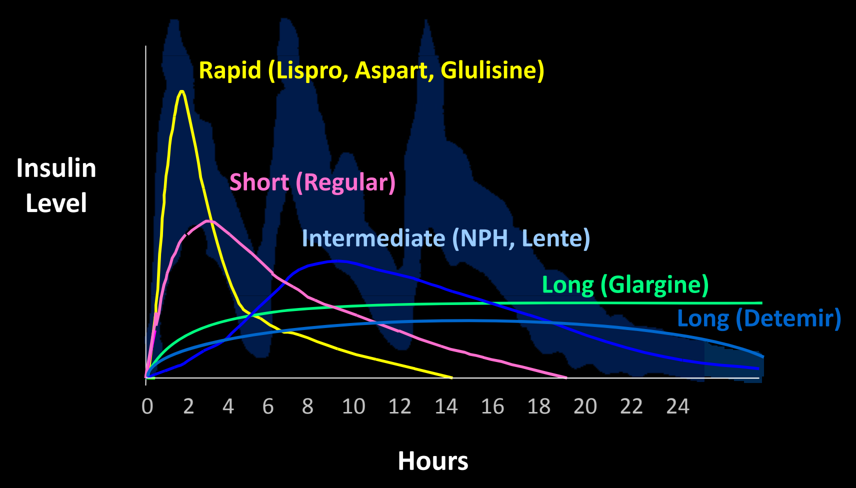

Consensus Algorithm
STEP 1
STEP 2
STEP 3
Tier 1: Well-validated therapies
At Diagnosis: Lifestyle + Metformin
Lifestyle + Metformin + Basal Insulin
Lifestyle + Metformin + Sulfonylurea[a]
Lifestyle + Metformin + Intensive Insulin
Tier 2: Less well-validated therapies
Lifestyle + Metformin + Pioglitazone
Lifestyle + Metformin + GLP-1 agonist[b]
Lifestyle + Metformin + Pioglitazone + Sulfonylurea[a]
Lifestyle + Metformin + Basal Insulin
Reinforce lifestyle changes at every visit and check A1C every 3 months until < 7.0%, then at least every 6 months thereafter. Change interventions whenever A1C ≥ 7.0%.
[a]Sulfonylureas other than glibenclamide (glyburide) or chlorpropamide.
[b]Insufficient clinical use to be confident regarding safety.
Nathan DM, et al. Diabetes Care. 2009.

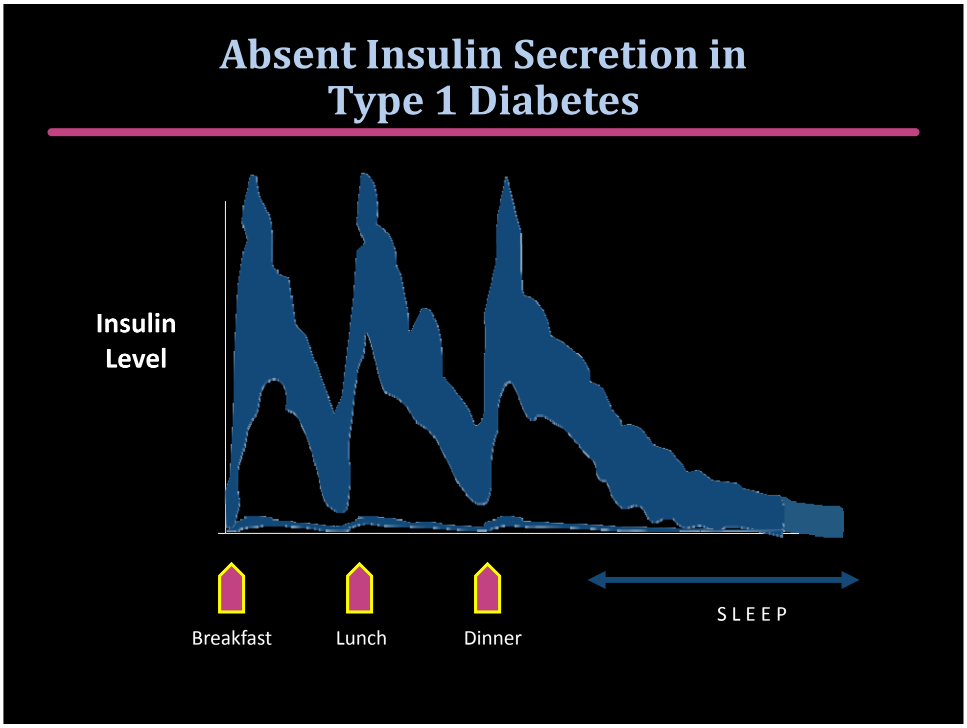
Comparison of Human Insulins and Insulin Analogues

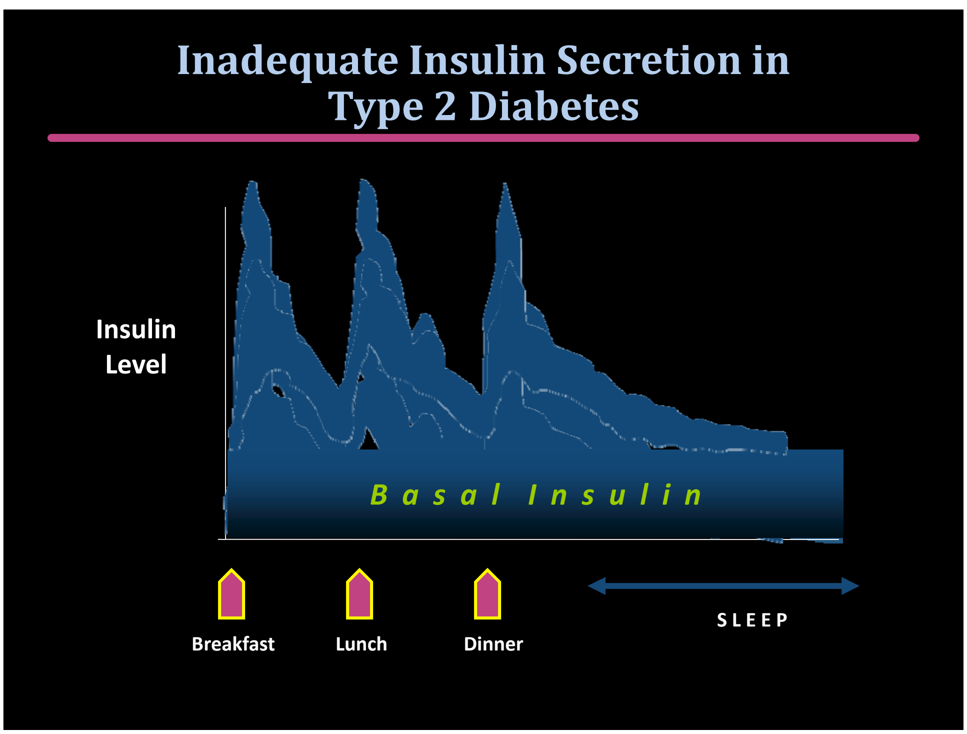
Insulin Preparation	Onset	Peak	Duration
Lispro / Aspart Gluslisine	5-15 min	1-2 hrs	4-6 hrs
Human Regular	30-60 min	2-4 hrs	6-10 hrs
Human NPH	1-2 hrs	4-8 hrs	10-18 hrs
Glargine, Detemir	1-2 hrs	Flat	24 hrs

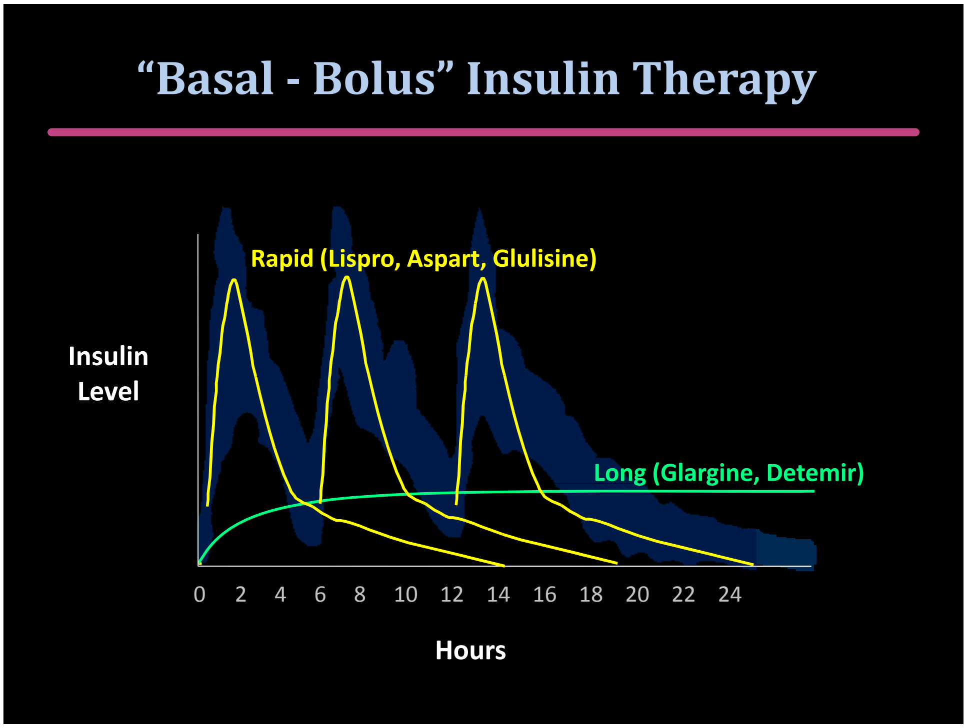
The time course of action of any insulin may vary in different individuals, or at different times or different injection locations in the same individual. Due to such variation, the time periods described above should be used as general guidelines only.

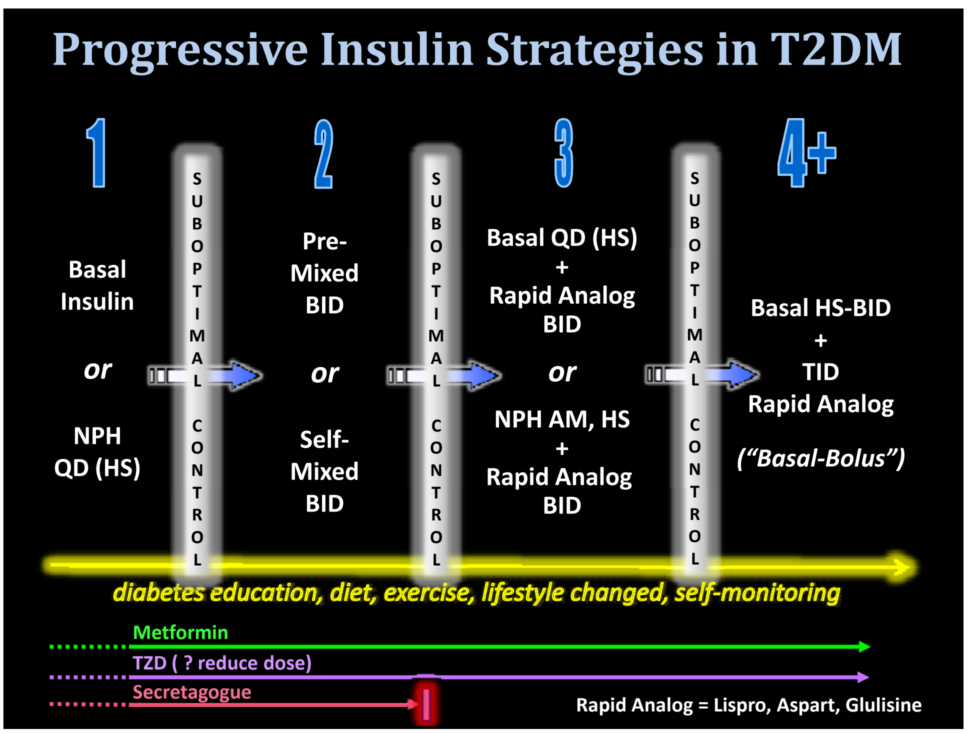
Pharmacokinetic Profiles of Available Insulin Formulations




Absent Insulin Secretion in Type 1 Diabetes
Insulin Level
Breakfast
Lunch
Dinner
SLEEP


Inadequate Insulin Secretion in Type 2 Diabetes
Insulin Level
Basal Insulin
Breakfast
Lunch
Dinner
SLEEP


"Basal - Bolus" Insulin Therapy
Rapid (Lispro, Aspart, Glulisine)
Insulin Level
Long (Glargine, Detemir)
0 2 4 6 8 10 12 14 16 18 20 22 24
Hours

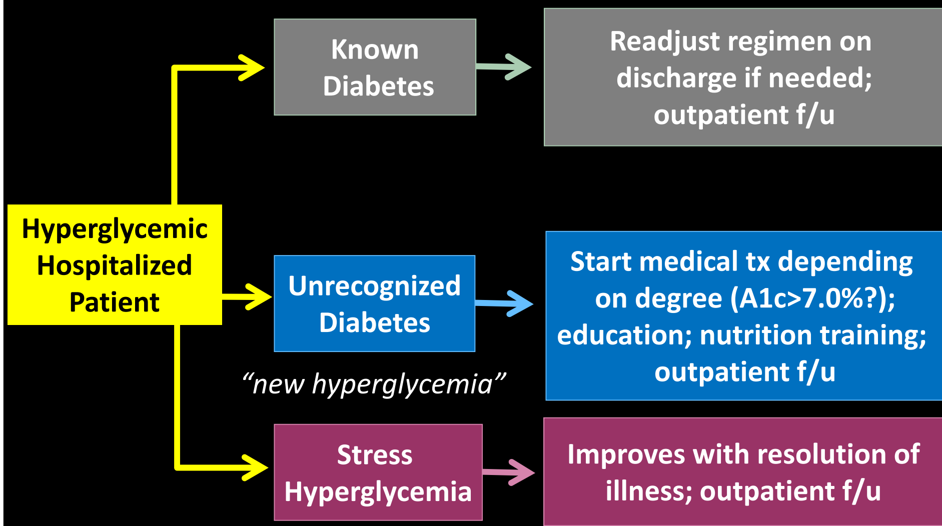

Progressive Insulin Strategies in T2DM
1
Basal Insulin
or
NPH QD (HS)
SUBOPTIMAL CONTROL
2
Pre-Mixed BID
or
Self-Mixed BID
SUBOPTIMAL CONTROL
3
Basal QD (HS) + Rapid Analog BID
or
NPH AM, HS + Rapid Analog BID
SUBOPTIMAL CONTROL
4+
Basal HS-BID + TID Rapid Analog
("Basal-Bolus")
diabetes education, diet, exercise, lifestyle changed, self-monitoring
Metformin
TZD (? reduce dose)
Secretagogue
Rapid Analog = Lispro, Aspart, Glulisine

Insulin Therapy: Balancing Convenience and Control

Discharge Planning

- Be proactive! Start early (2-3 days before.)
- What can this patient handle at home?
- Consider side effects, drug intolerances, comorbidities, costs.
- Education!
- Outpatient follow-up is key.

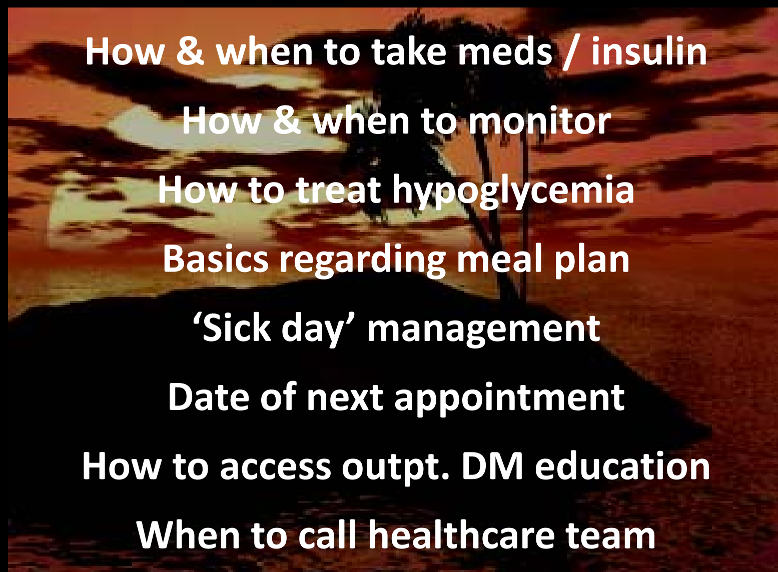
Discharge Planning



Pre-discharge Checklist

1. Diet information
2. Monitor / strips (& Rx)
3. Rx for / supplies of meds, insulin, needles
4. Treatment goals
5. Contact phone numbers
6. Medi-Alert bracelet
7. *"Survival Skills"* training

"Survival Skills"



Diagnosis of Diabetes

	ADA 1997-2009	Int'l Expert Committee	ADA 2010
FPG	≥ 126 mg/dL (7.0 mmol/l)	≥ 126 mg/dL (7.0 mmol/l)	**≥ 126 mg/dL* (7.0 mmol/l)**
2hPG (OGTT)	≥ 200 mg/dL (11.1 mmol/l)	≥ 200 mg/dL (11.1 mmol/l)	**≥ 200 mg/dL (11.1 mmol/l)**
A1C	---	≥ 6.5%	**≥ 6.5%***

Frank hyperglycemia (≥ 200 mg/dl [11.1 mmol/l]) also diagnostic if accompanied by classic symptoms.

** If FPG & A1c results discordant, default to most abnormal test.*