Inpatient Management of Diabetes

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Disclosures

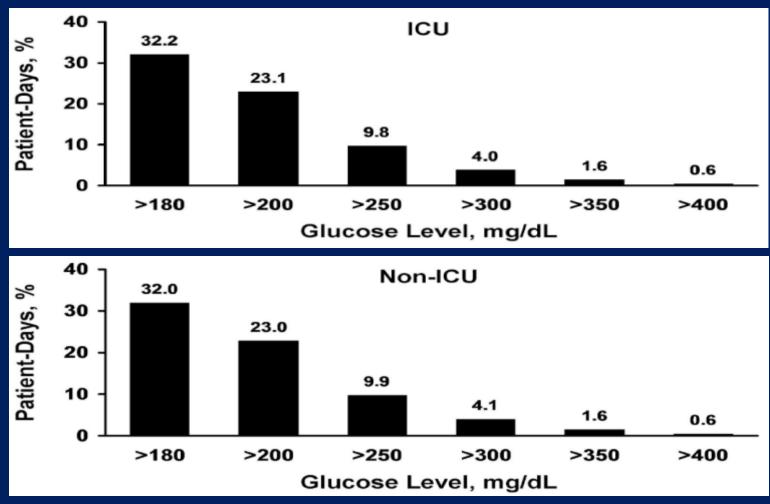
External Industry Relationships *	Company Name(s) / Institution	Role
Equity, stock, or options in biomedical industry companies or publishers	BMJ-Diabetes Research and Care	Social Media Editor
Industry Advisory/Consultant activities	Merck Boehringer Ingelhein Sanofi Lilly Astra Zeneca	Consultant activities
Industry Research	Merck, Novo, Sanofi Dexcom	PI or co-I
Federal	NIH / NIGMS	PI

Objectives

 1) To discuss the relevance of inpatient diabetes care and current treatment recommendations

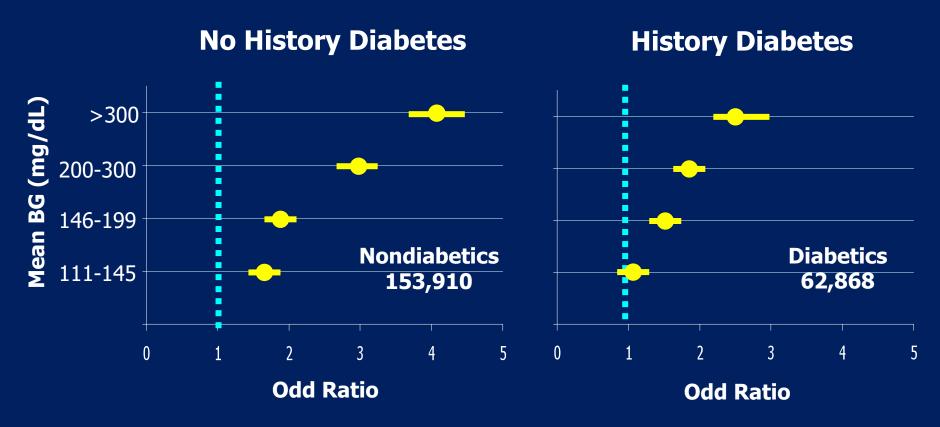
 2) To discuss novel inpatient management approaches (non-insulin agents) and the use of diabetes technology in the hospital

Distribution of patient-day-weighted mean POC-BG values for ICU



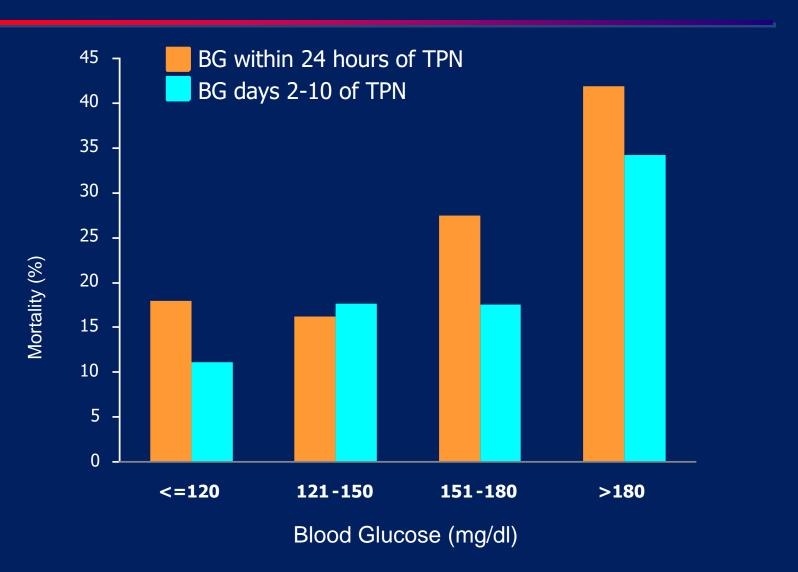
Data from ~12 million BG readings from 653,359 ICU patients - mean POC-BG: 167 mg/dL

Mortality Risk Greater in Hyperglycemic Patients without History of Diabetes

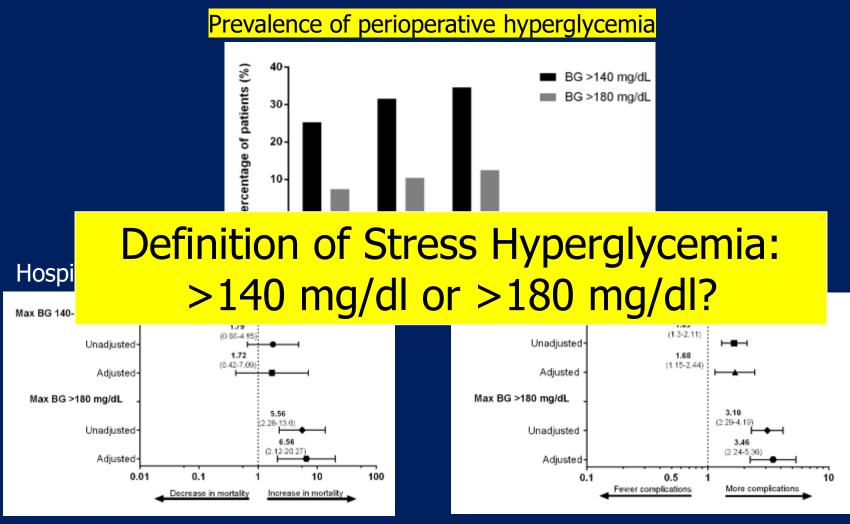


216,775 consecutive first admission 177 surgical, medical, cardiac ICUs 73 geographically diverse VAMC

Hyperglycemia during TPN and Hospital Mortality

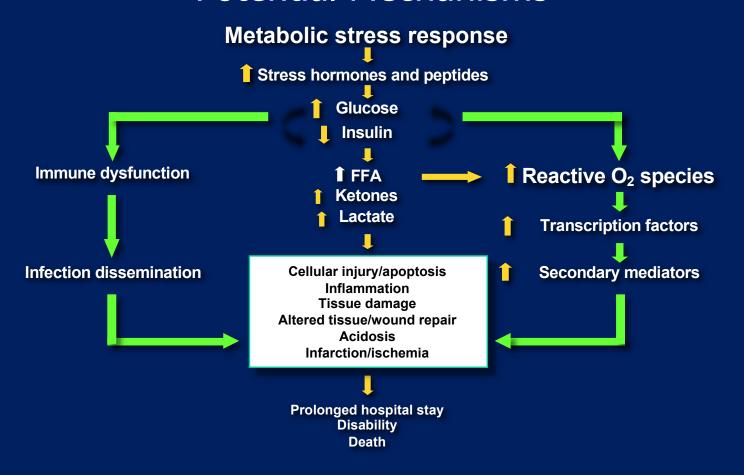


Pasquel et al, Diabetes Care. 33(4):739-41, 2010



Davis et al. J Diabetes & Its Complications, 2018

Link Between High Blood Glucose and Poor Outcomes: Potential Mechanisms



Diagnóstico de la hiperglucemia y la diabetes en el hospital

Admisión

Evaluar a todos los pacientes con historia de diabetes

Obtener glucosa a la admisión

Sin historia de diabetes BG<140 mg/dl (7.8 mmol/L)

Iniciar monitoreo de acuerdo al estado clínico

Sin historia de diabetes
BG >140 mg/dl
LEMPEZAR POC
Monitorizar x 24-48h
Medir A1C
A1C ≥ 6.5%

Historia de diabetes
Monitorizar la glucosa

POC BG: glicemia capilar

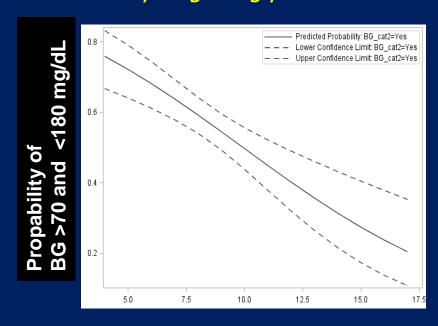
A1C en el Hospital

- ➤ Medición de A1C puede ser útil:
 - Diferenciación de nuevos casos de diabetes de la hiperglucemia de estrés
 - > Control glucémico antes de la admisión
 - Predecir control glucémico e hipoglucemia
 - Diseñar el régimen óptimo al momento del alta hospitalaria

Probabilidad de buen control glucémico y de hipoglucemia de acuerdo a Hemoglobina A1c

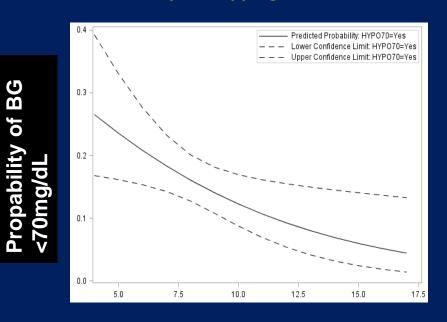
BG

Probability of good glycemic control



Hemoglobin A1C (%)

Probability of hypoglucemia



Hemoglobin A1C (%)

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. 2018 American Diabetes Association glucose target 140-180 mg/dl for most patients with T2D
- 3. Glycemic targets be modified according to clinical status.

2020 Recommendation:

For average Recommendation:

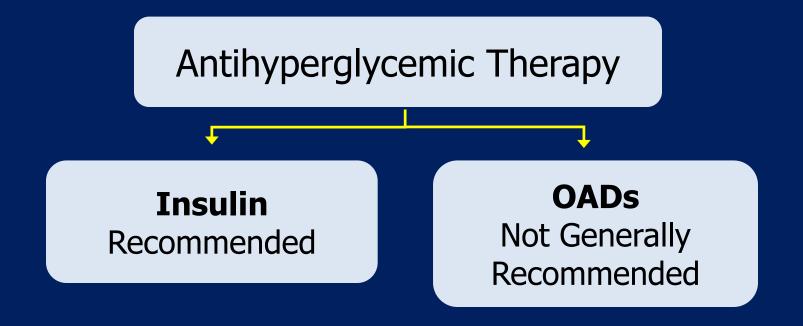
Keep BG < 180 mg/dl!

ADA/AACE Guidelines, Diabetes Care 2009; Endocrine Society. J Clin Endocrinol Metabol, 2012; Under Revision 2018 2018 Standard of Diabetes Care, # 14, Hospital Management of Diabetes, Diabetes Care 2018

How should we treat noncritically ill patients?

Is there a rol for non-insulin agents?

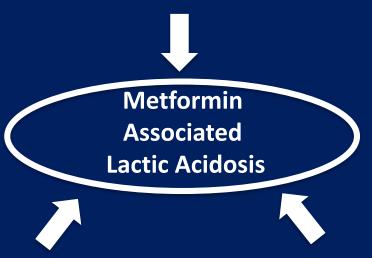
Recommendations for Managing Patients With Diabetes in the Hospital Setting



Metformina y Acidosis Láctica

Impaired Metformin Clearance

Acute and chronic kidney failure



Impaired Tissue Oxygenation

Severe sepsis and septic shock

Hypovolemia, shock (e.g. surgery)

Decompensated heart failure

Impaired Lactate Metabolism

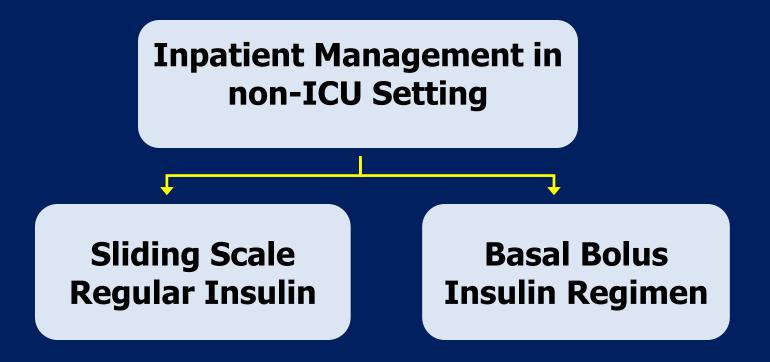
Alcohol abuse

Liver failure

Nucleoside reverse transcriptase inhibitors

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%
- ➤ Basal bolus regimen: Half of TDD as basal and half as rapid-acting insulin before meals

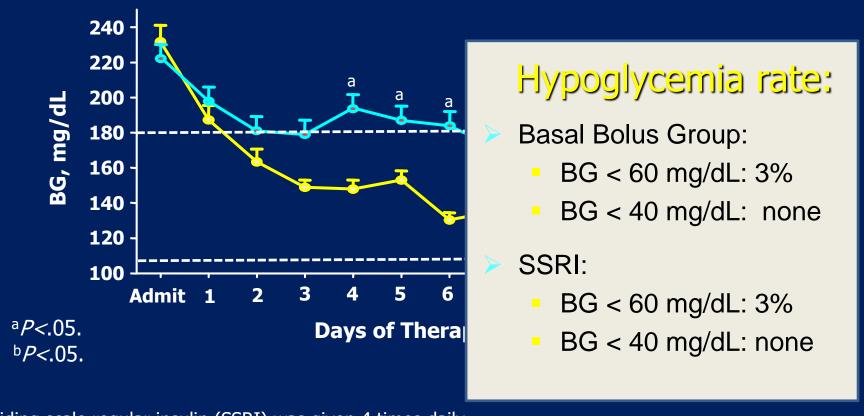


RABBIT-2D TRIAL:

- Research Question:

In insulin naïve patients with T2DM, does treatment with basal bolus regimen with glargine once daily and glulisine before meals is superior to sliding scale regular insulin?

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



- 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



RABBIT-2 Surgery Trial:

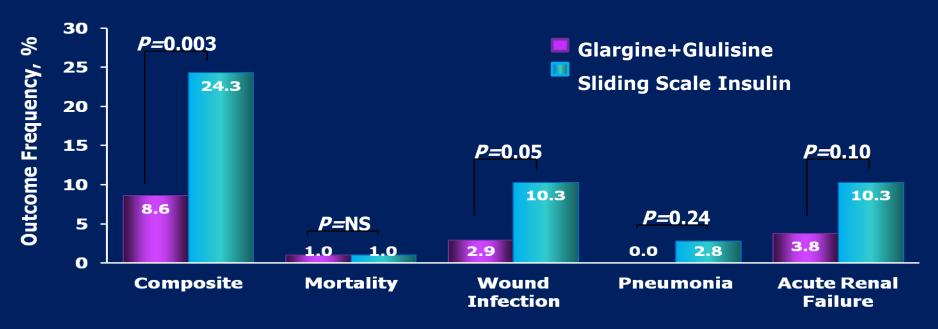
- Research Question:

T2DM on diet, oral agents or insulin treatment, does treatment with basal bolus regimen with glargine and glulisine is superior to SSRI?

Composite of hospital complications: wound infection, pneumonia, respiratory failure, acute kidney injury, and bacteremia

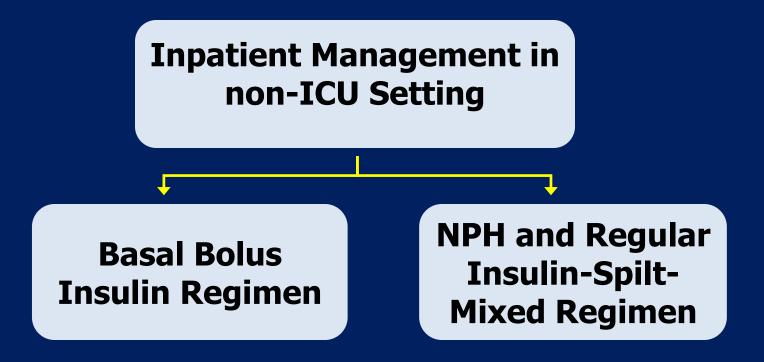
Umpierrez et al, Diabetes Care 34 (2):1–6, 2011

Postoperative Complications



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

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

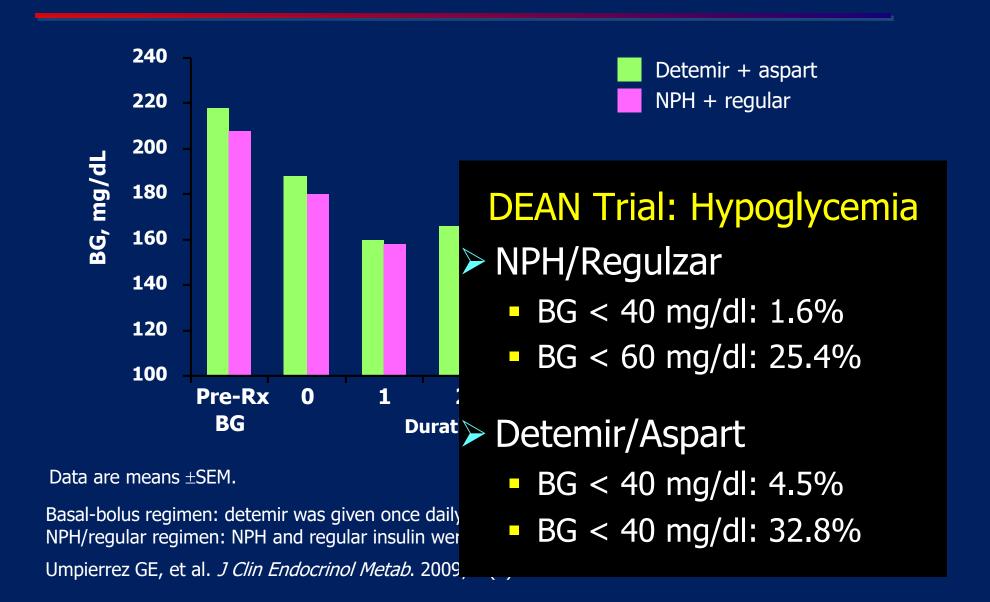


DEAN TRIAL:

- Research Question:

In patients with T2DM on diet, oral agents or insulin treatment, does treatment with basal bolus regimen with detemir once daily and aspart before meals is superior to NPH and Regular split-mixed insulin regimen?

DEAN Trial: Changes in Mean Daily Blood Glucose Concentration



Basal Plus Trial: Basal + Correction vs. Basal Bolus

Basal plus supplements

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

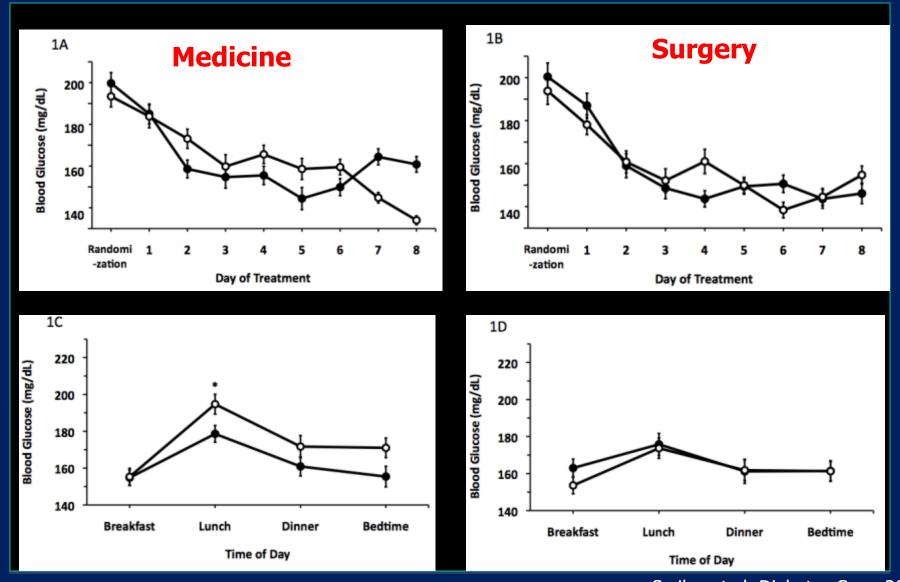
* Reduce TDD to 0.15 U/kg in patients ≥70 yrs and/or serum creatinine ≥ 2.0 mg/dL

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

Basal-PLUS vs Basal Bolus: Medicine and Surgery Patients



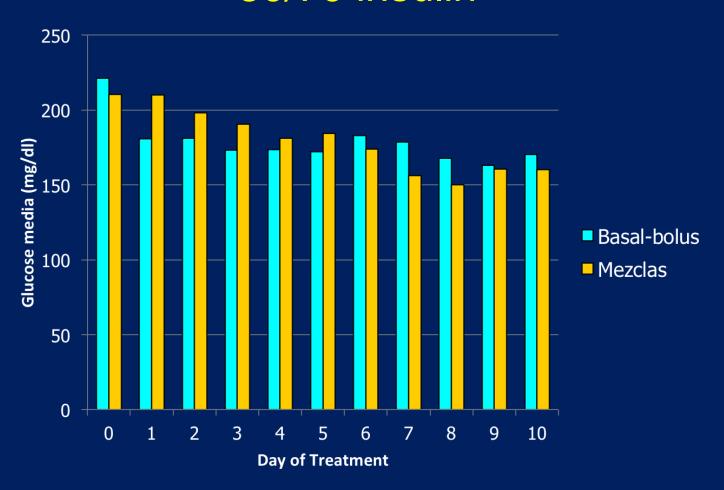
Basal Bolus is the Preferred Insulin Regimen for the Management of Non-ICU Patients With Type 2 Diabetes

Inpatient
Management in
non-ICU

Regimens50% Basal
50% Prandial

What about Premixed 70/30 insulin?

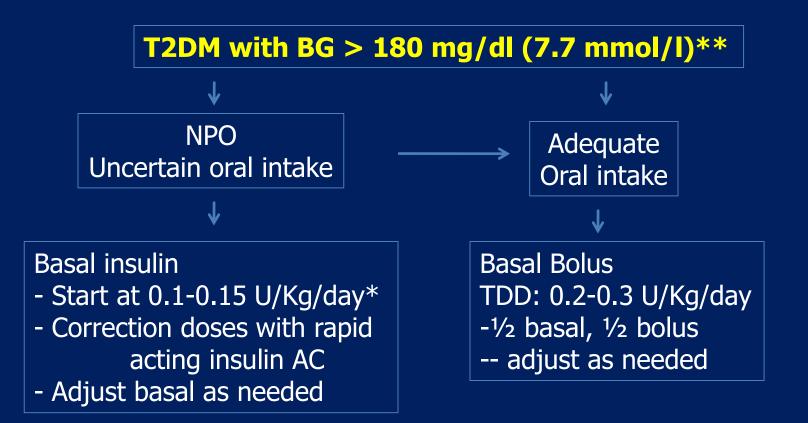
Mean Daily Blood Glucose during Treatment with Basal Bolus and Premixed 30/70 insulin



Hypoglycemia during Treatment with Basal Bolus and Premixed 30/70 insulin

	Basal-bolus regimen	Premixed reimen	P value
Hypoglycemic events (BG concentration <70 mg/dL)			
BG tests per patient/day	5.7 ± 0.8	5.6 ± 0.8	0.716
Overall, patients with hypoglycemia	8 (24.2)	25 (64.1)	0.001
Events, n	20	65	
BG readings, %	1.4	3.2	
Fasting or prebreakfast hypoglycemia	1 (3.0)	5 (12.8)	0.134
Events, n	•	-	
Morning or prelunch	Hypoglycemia and	Trial Suspens	sion
Events, n		•	
Afternoon or predinner	Following a planned	interim safety	anal-
Events, n		-	
Evening, after dinner to midnight	ysis after the enrollment of half of the		
Events, n	potionts the trial w	as tarminated	aarlu
Night, midnight to 6:00 A.M.	patients, the trial w	as terminated	earry
Events, n	owing to an incre	ased frequen	cv of
	owing to an incide	asca megacii	· · · · ·

Management of diabetes in hospitalized older adults



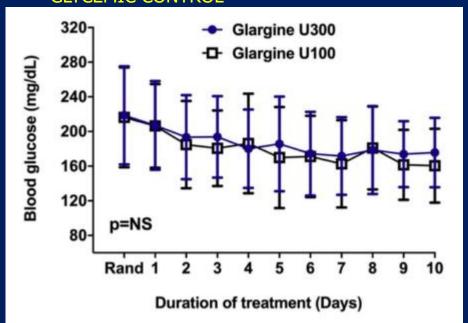
**The use of DPP-4 inhibitors alone or in combination with basal insulin may represent an alternative to basal-bolus regimens in elderly patients

New long acting insulin in the hospital?

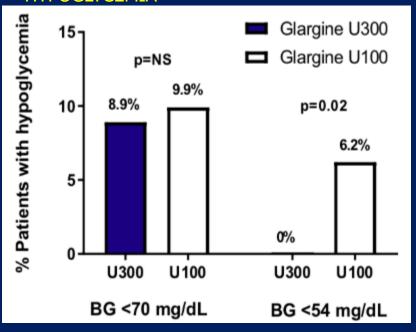
Glargine U300 vs U100 in non-ICU Setting

This prospective, open-label, randomized clinical trial included 176 poorly controlled patients with T2D (HbA1c: $9.5\pm2.2\%$), treated with oral agents or insulin prior to admission. Patients were treated with a basal bolus regimen with glargine U300 (n=92) or glargine U100 (n=84) and glulisine before meals.

GLYCEMIC CONTROL

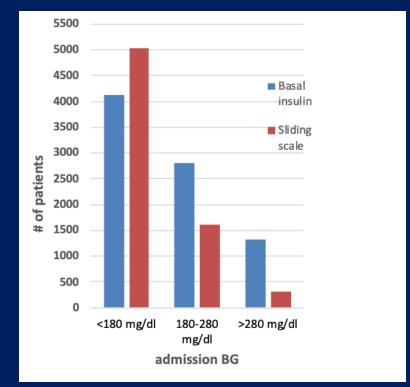


HYPOGLYCEMIA



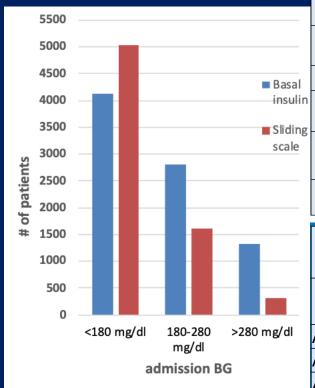
Sliding Scale Insulin Use in Non-Critical Care Settings: Who Can Slide?

- Retrospective cohort
- Population: 15,348
 hospitalized patients with
 T2DM at Emory University
 Hospitals between 6/1/20106/30/2018
- Treated with SSI: 7052 (45%)
- Admission BG 155 mg/dl (vs. 192 mg/dl on basal insulin)



Migdal et al. ADA Meeting, 2019

Sliding Scale Insulin Use in Non-Critical Care Settings: Who Can Slide?



Inpatient outcomes by Treatment Group						
	Basal insulin	Sliding scale	p-value			
Charlson score	4.2 ± 2.4	4.0 ± 2.5	<0.001			
Mean hospital BG, mg/dl	176 ± 54	150 ± 42	<0.001			
BG <70mg/dl, n (%)	1115 (14)	477 (6.9)	<0.001			
BG <54 mg/dl, n (%)	98 (1.2)	39 (0.56)	<0.001			

Percentage (%) of patient achieving good glycemic control on SSI by admission BG

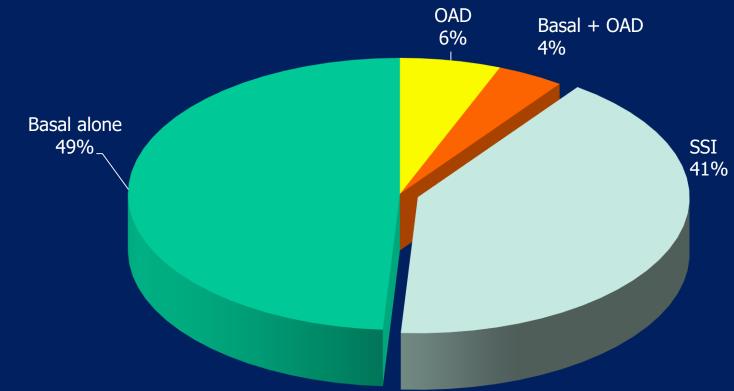
	Adequate	Inadequate
	control	control
Admit BG <180 mg/dl, n (%)	4684 (93%)	353 (7%)
Admit BG 180-280 mg/dl, n (%)	825 (51%)	788 (49%)
Admit BG >280 mg/dl, n (%)	47 (15%)	266 (85%)

Migdal et al. ADA Meeting, 2019

Can you treat patients with oral agents in the hospital?

Inpatient Management in non-ICU **Basal Bolus What about Oral** or **Basal Plus Agents?** Regimens

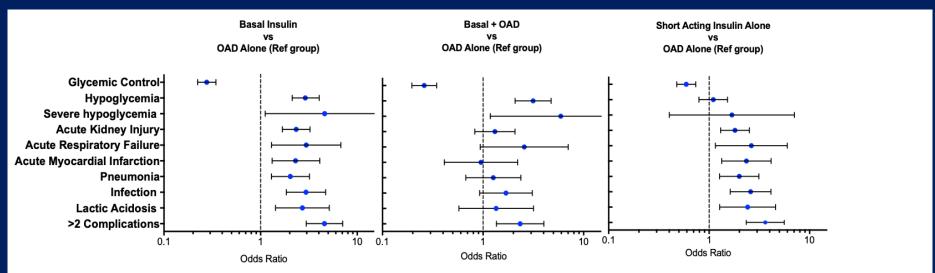
Distribution of OAD use in hospitalized patients



^{*}Data includes patients exposed to OAD or basal insulin for ≥ 48hrs, or complete hospital stay (if <48hrs)

OADs in the Hospital

Adjusted Odds Ratios^a for the Association of Complications with insulin or Oral Antidiabetes Drugs in the Hospital



OAD: Oral antiadiabetes drugs; Glycemic control:average BG <180mg/dl and no hypoglycemia. Models adjusted for age, gender, BMI, admission BG, hospital setting (medical vs surgical), admission creatinine, and Charlson score.

Safety and Efficacy of Sitagliptin Therapy for the Inpatient Management of General Medicine and Surgery Patients With Type 2 Diabetes

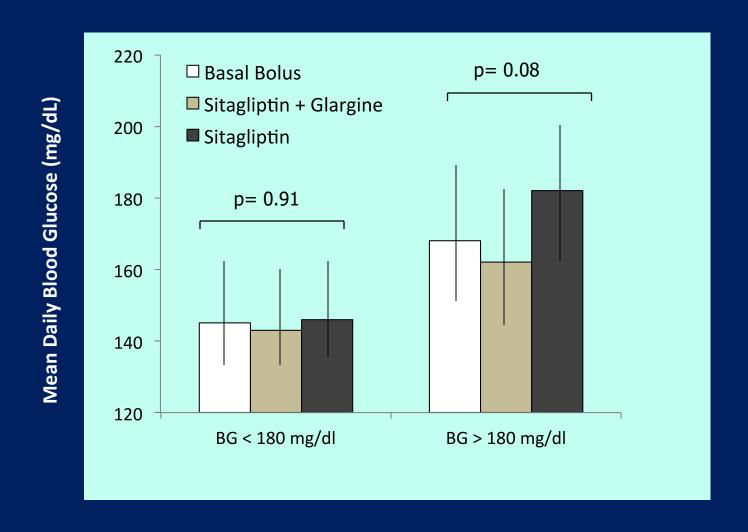
A pilot, randomized, controlled study

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SOL JACOBS, MD¹
DAVID H. WESORICK, MD
CHRISTOPHER NEWTON, MD¹

FARNOOSH FARROKHI, MD¹
LIMIN PENG, PHD³
DAVID REYES, MD¹
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FRANCISCO PASQUEL, MD¹

acting insulin preparations in combination with short- (regular) or rapid-acting insulin analogs has been proven to be safe and effective for glycemic management in patients with diabetes or hyperglycemia (10–12). Recent studies in general medi-

Randomization Blood Glucose (<180 mg/dl and >180 mg/dl) and Mean Daily Glucose concentration

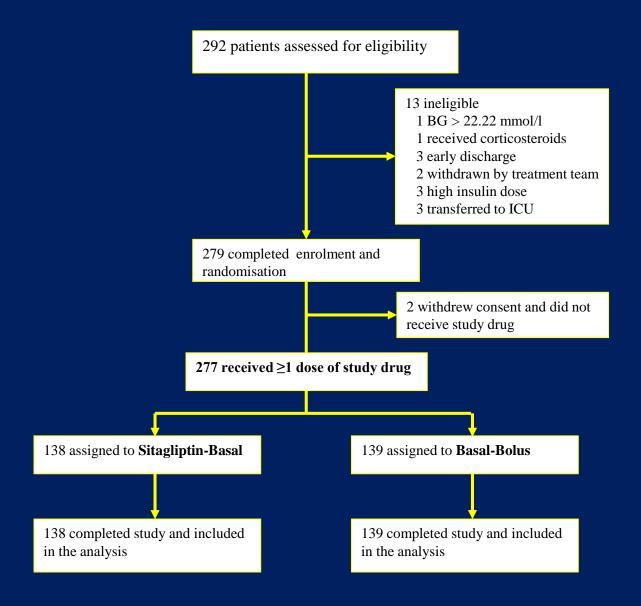


Efficacy of sitagliptin for the hospital management of general medicine and surgery patients with type 2 diabetes (Sita-Hospital): a multicentre, prospective, open-label, non-inferiority randomised trial

Francisco J Pasquel, Roma Gianchandani, Daniel J Rubin, Kathleen M Dungan, Isabel Anzola, Patricia C Gomez, Limin Peng, Israel Hodish, Tim Bodnar, David Wesorick, Vijay Balakrishnan, Kwame Osei, Guillermo E Umpierrez

- Desenlace primario: no-inferioridad en las diferencias de promedio de glucosa entre los grupos
- Desenlaces secundarios: hipoglucemia, hiperglucemia no-controlada que condujo al fracaso del tratamiento, complicaciones

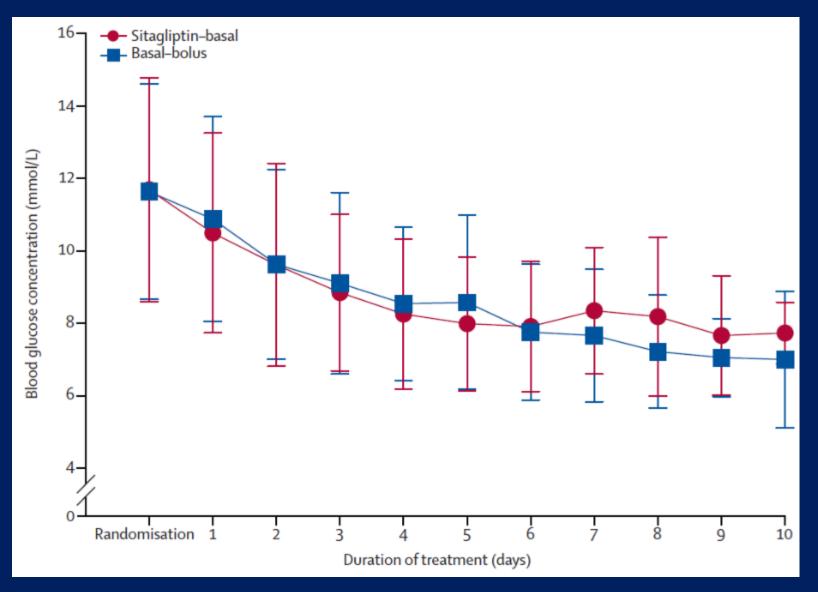
Study profile



Características Basales de la Población de Estudio

	All (n=277)	Sitagliptin–basal	Basal-bolus
Admission diabetes therapy (n=275)		J .	
Diet alone	33 (12%)	15 (11%)	18 (13%)
Oral drugs	116 (42%)	57 (41%)	59 (42%)
Insulin alone	66 (24%)	34 (25%)	32 (23%)
Insulin plus oral drugs	60 (22%)	31 (22%)	29 (21%)
Glycaemic control at baseline			
*HbA _{1C} (% [SD])	8.7% (2.3)	8.7% (2.4)	8.6% (2.1)
*HbA _{1C} <7%	72 (26%)	42 (30%)	30 (22%)
*HbA _{1c} 7%–≤9%	110 (40%)	52 (38%)	58 (42%)
*HbA _{1C} >9%	92 (33%)	44 (32%)	48 (35%)
Admission random blood glucose concentration (mmol/L)	12.0 (6.0)	11.9 (6.1)	12.1 (5.9)
Randomisation blood glucose concentration (mmol/L)	11.7 (3.0)	11.8 (3.1)	11.6 (2.9)
Randomisation blood glucose concentration ≤10 mmol/L	105 (38%)	54 (39%)	51 (37%)
Randomisation blood glucose concentration >10 mmol/L	172 (62%)	84 (61%)	88 (63%)

Concentraciones Promedio de Glucosa en el Hospital



Hipoglucemia

	Sitagliptin + Basal	Basal bolus	P-value
# patients BG <70 mg/dl, n (%)	13 (9%)	17 (12%)	0.45
# patients BG <40 mg/dl, n (%)	0 (0%)	0 (0%)	> 0.99

Dosis de insulina & # Inyeciones/día

	Sitagliptin + Basal	Basal Bolus	P-value
Total daily dose, U/kg/day	0.2 ± 0.1	0.3 ± 0.2	< 0.001
Total daily dose, U/day	24.1 ± 16.2	34.0 ± 20.1	< 0.001
Basal- Glargine, U/day	17.9 ± 12.5	16.8 ± 10.4	0.94
Prandial- aspart/lispro, U/day		11.7 ± 7.9	< 0.001
Supplements- U/day*	5.8 ± 5.7	5.5 ± 4.7	0.91
Number of Injections			
# injections/day (Hospital stay)	2.2 ± 1.0	2.9 ± 0.9	< 0.001

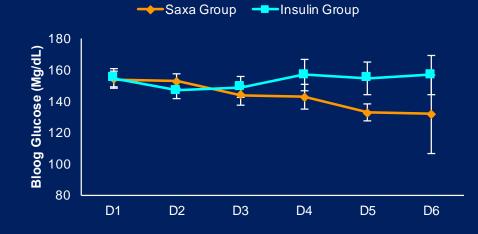
Complicaciones Hospitalarias

Complications	Sitagliptin + Basal	Basal Bolus	P Value
Total # of patients with complications, n (%) Total # of complications, n	13 (9)	10 (7)	0.52
AKI, n (%)	7 (5)	6 (4)	0.79
Infections, n (%)	2 (1)	2 (1)	>0.99
Stroke, n (%)	1 (1)	1 (1)	>0.99
AMI, n (%)	0 (0)	1 (1)	>0.99
Respiratory failure, n (%)	2 (1)	1 (1)	0.62
Surgical re-intervention, n (%)	1 (1)	1 (1)	>0.99
Pneumonia, n (%)	0 (0)	0 (0)	>0.99

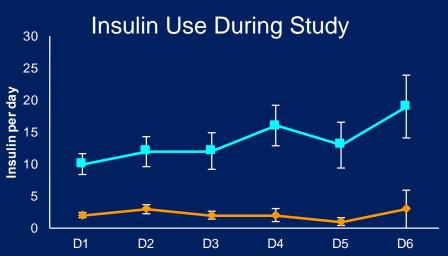
AKI: acute kidney injury; AMI: acute myocardial infarction

Saxagliptin in Non-Critically ill Hospitalized Patients with T2D and Mild Hyperglycemia

Mean Blood Glucose During Study



N= 62 Mean A1c: 6.6% Random BG: 158 mg/dl







Linagliptin Surgery Trial

A Randomized Controlled Trial on the Safety and Efficacy of Linagliptin Therapy for the Inpatient Management of General Surgery Patients with Type 2 Diabetes

General Surgery Patients

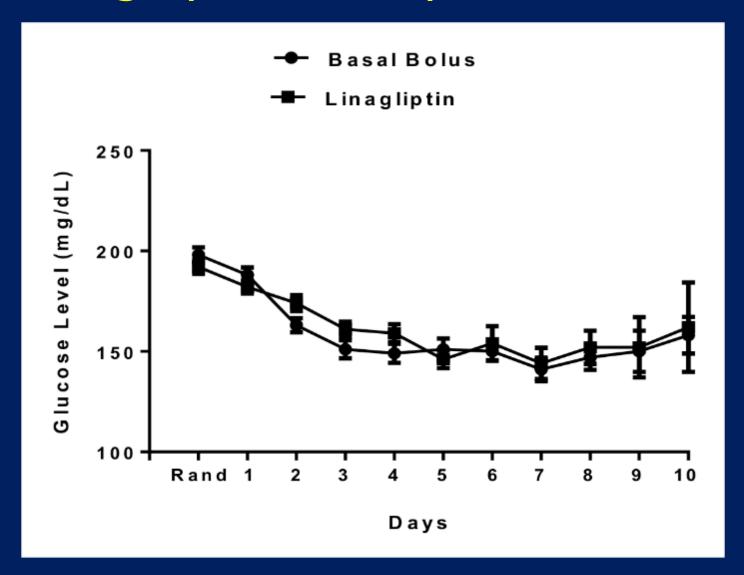
Basal Bolus
0.4-0.5 U/Kg/D

Linagliptin
5 mg/day

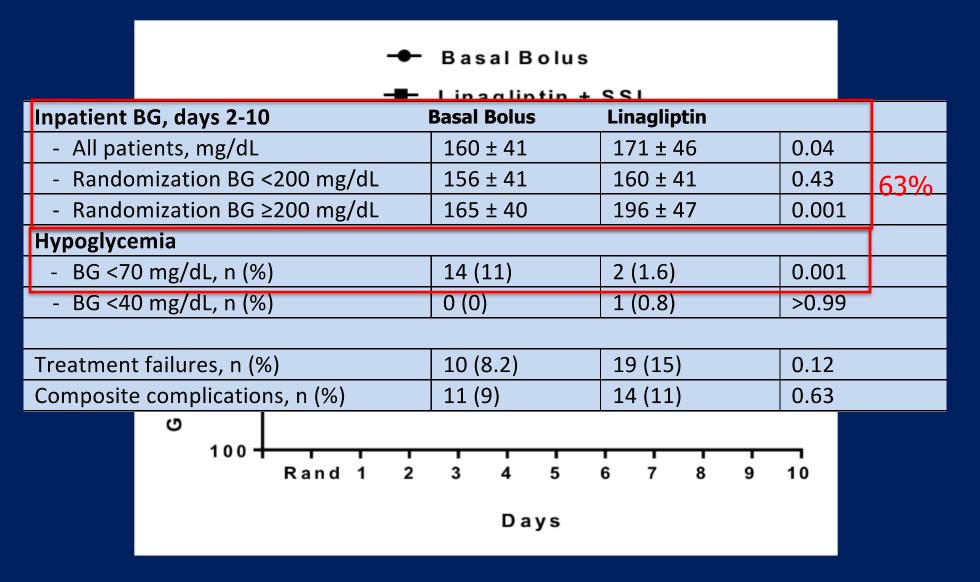
General surgery (non-cardiac) patients with T2DM admitted with BG between 140-400 mg/dl, treated with diet, OADs and insulin at TDD < 0.5 Unit/kg

* Supplemental (correction) doses of rapid-acting insulin analog per sliding scale given as needed before meals for BG > 140 mg/dl or bedtime > 200 mg/dl

Lina Surgery Trial: Daily Glucose Levels



Lina Surgery Trial: Daily Glucose Levels



SGLT-2i en el hospital



Dyspnea [baseline to Day 4]Change in Dyspnea on VAS analogue scale (AUC)

Diuretic Response [Total weight change from baseline to Day 4] Weight change from baseline per 40 mg of Furosemide equivalent

Length of Stay [within 60 days]Hospital stay of Index admission

Plasma NTproBNP [From baseline to Day 4]Change in NTproBNP

GLP-1 RA in the Hospital

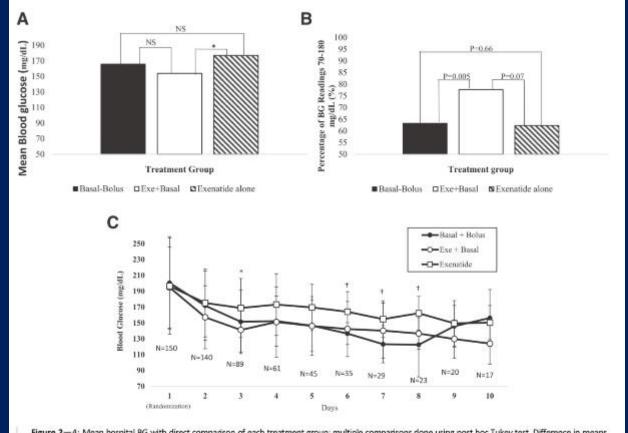
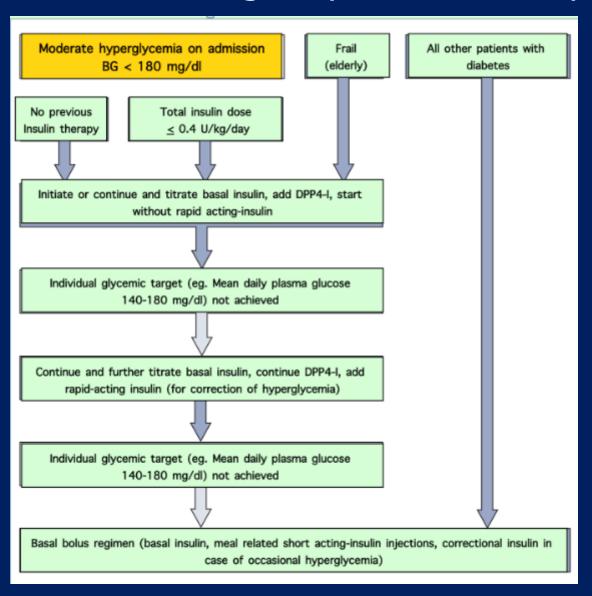


Figure 2—A: Mean hospital BG with direct comparison of each treatment group: multiple comparisons done using post hoc Tukey test. Difference in means between exenatide alone and exenatide plus basal: 11 mg/dL (P = 0.39). Difference in means between exenatide alone and exenatide plus basal: 23 mg/dL (P = 0.02). Difference in means between basal bolus and exenatide plus basal: 12 mg/dL (0.31). NS, not significant (P > 0.05). B: Hospital BG within target range 70–180 mg/dL. Differences in number of BGs within target of 70–180 mg/dL reported as percentage of all BG readings. Multiple comparisons of each pair were performed using Wilcoxon tests. C: Daily mean hospital BG. Significant differences in treatment groups: P = 0.01; P = 0.05. Exe, exenatide; N, number of patients.

Agentes no-insulinicos en el hospital y al alta

	MTF	SU	TZD	DPP4 -i	SGLT2 -i	GLP1- RA
Eficacia	++	++	++	+	++	+++
		?			Ambulatorio (uso prolongado)	

Approach to the glycaemic management of general medical and surgical patients in hospital



Management of Patients With Diabetes a After Hospital Discharge

Inpatient
Management in
non-ICU

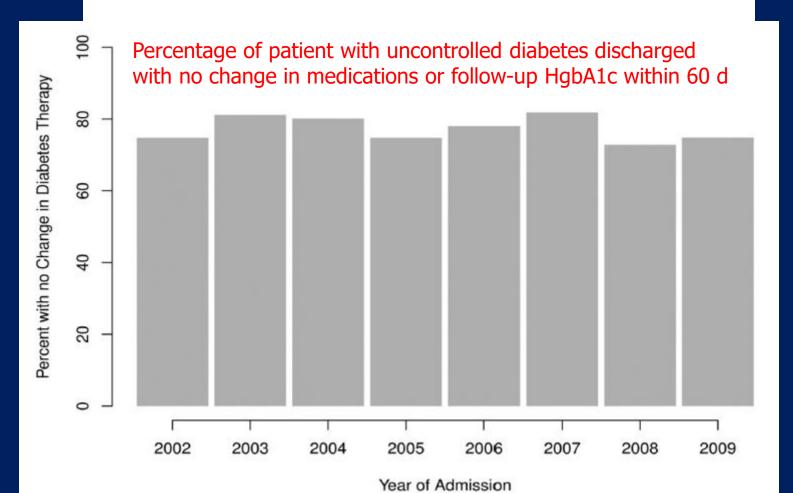
Basal Bolus or Basal Plus Regimens

What Regimen
Should We Use at
Hospital
Discharge?

Clinical Inertia on Discharge Planning

ORIGINAL ARTICLE
Endocrine Care

Clinical Inertia of Discharge Planning among Patients with Poorly Controlled Diabetes Mellitus





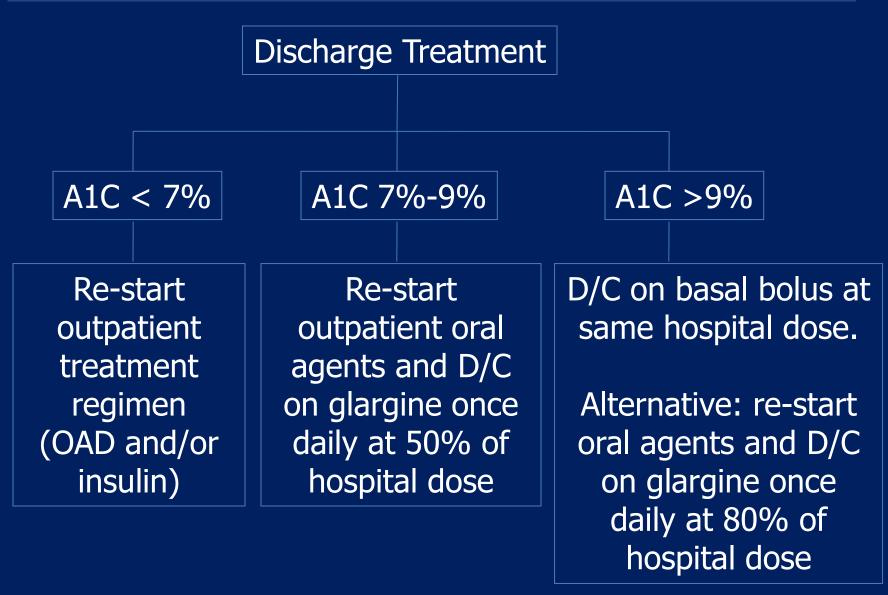


Hospital Discharge Algorithm Based on Admission HbA_{1c} for the Management of Patients With Type 2 Diabetes Guillermo E. Umpierrez,¹ David Reyes,¹
Dawn Smiley,¹ Kathie Hermayer,²
Amna Khan,³ Darin E. Olson,^{1,4}
Francisco Pasquel,¹ Sol Jacobs,¹
Christopher Newton,¹ Limin Peng,⁵
and Vivian Fonseca³

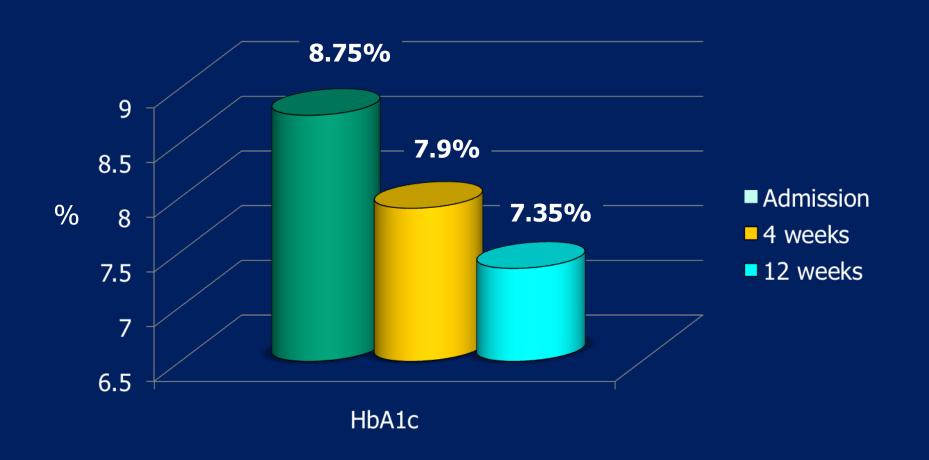
Methods:

Prospective, multicenter open-label study aimed to determine the safety and efficacy of a hospital discharge algorithm based on admission HbA1c.

Discharge Insulin Algorithm



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



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)

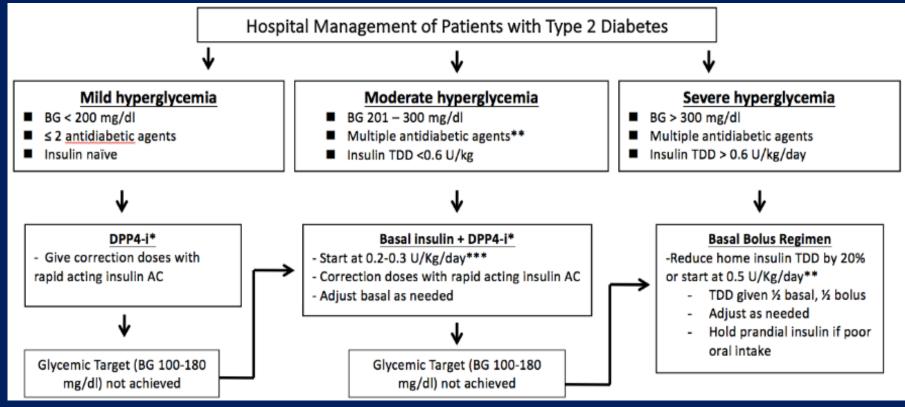
^{*} p< 0.001 vs. Admission A1C; ψ p=0.08

GLP-1 RA at Discharge



- Similar change in HbA1c compared to glargine.
- Liraglutide treatment resulted in less hypoglycemia,
- Greater weight reduction
- Expected increased gastrointestinal adverse events.

Change in the paradigm of diabetes management in the hospital



Suggested algorithm to start anti-hyperglycemic therapy in hospitalized patients with type 2 diabetes based on randomized controlled trials. AC: before meals, BG: blood glucose, TDD: total daily dose.

^{*} Adjust dose according to eGFR (sitagliptin or saxagliptin), no adjustment is needed with linagliptin.

^{**} Antidiabetic agents: oral agents and GLP1-RA

^{***} In patients with hypoglycemia risk (frail, elderly, acute kidney injury) reduce starting dose to 0.15 U/Kg/day (basal alone) or TDD 0.3 U/Kg/day (basal bolus). No prospective studies have determined the efficacy of other oral antidiabetic drugs in the hospital setting.

Nueva Tecnología en el Hospital?

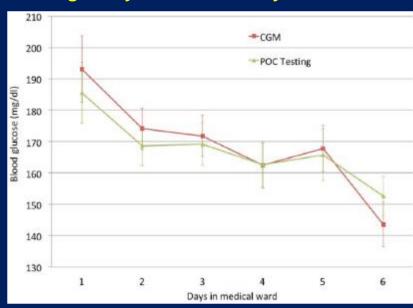
CGM





CGM in Non-ICU Insulin-Treated Patients with T2D

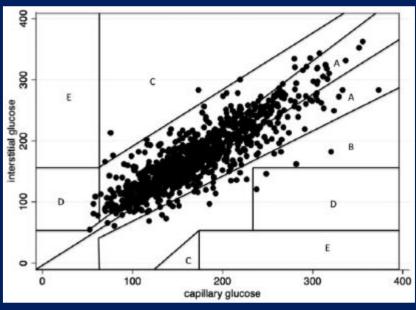
Average daily BG measured by CGM and POC



No differences in daily BG between CGM and POC. Higher # of hypoglycemia detected by CGM CGM than POC (55 vs 12, P < .01).

Gomez et al. J Diabetes Science & Technology 2016

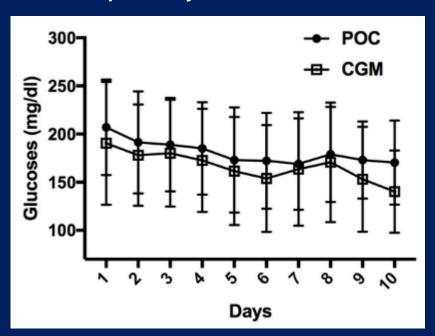
Clinical accuracy BG levels measured by CGM



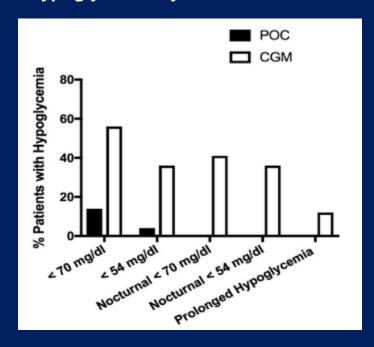
Glucose measurements were clinically valid, with 91.9% of patients falling within the Clarke error grid A and B zones.

Freestyle Libre Pro Flash CGMS vs. POC Capillary Glucose Testing in Hospitalized Patients with T2D

Mean Hospital Daily Glucose



Hypoglycemia by POC and CGM



The Effect of Continuous Glucose Monitoring in Preventing Inpatient Hypoglycemia in General Wards: The Glucose Telemetry System

Journal of Diabetes Science and Technology 1–6

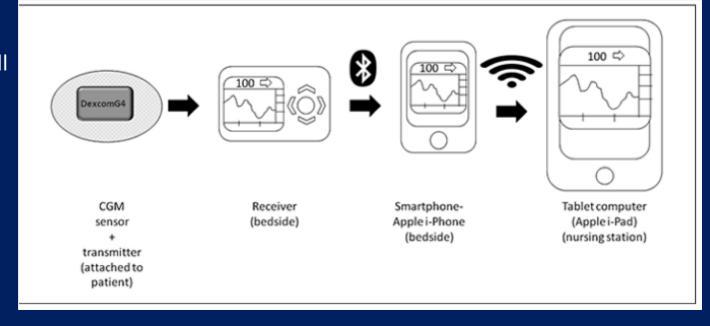
© 2017 Diabetes Technology Society

Spanakis et al.Baltimore VAMC, University of Maryland

Pilot study.

BG results < 85 mg/dl were transmitted to nursing station allowing early intervention to prevent hypoglycemia.

NCT02904512

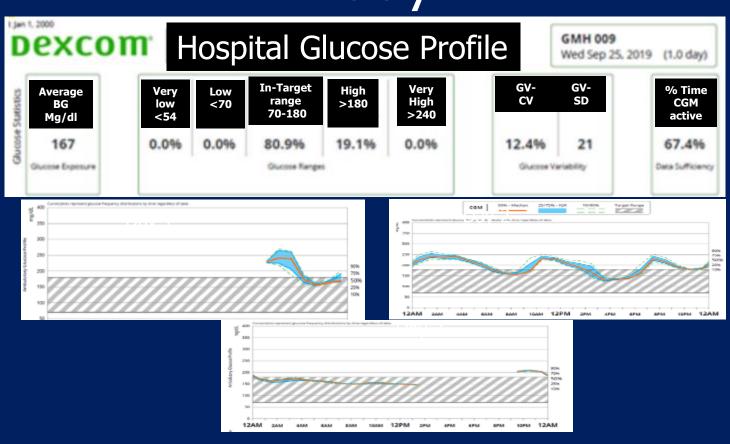


CGM Hospital Use

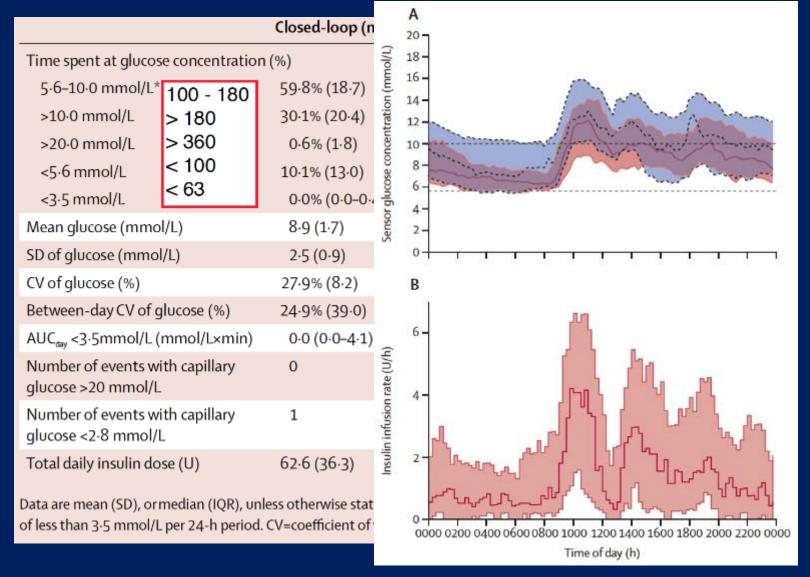




CGM Hospital Use: Intervention Study



Closed Loop in the Hospital: Overall glucose control based on sensor glucose measurements



Thabit et al. Lancet Diabetes Endocrinol 2017; 5: 117–24

In Summary

- Diabetes management in the hospital is evolving
 - Consideration of non-insulin agents (OAD use is common)
 - Discharge considerations
- New technology in the hospital
 - CGM to guide therapy
 - Closed loop



Pacientes con crisis hiperglucémicas (DKA/HHS combo)

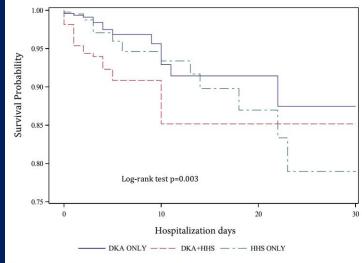


Figure 2—Adjusted survival analysis comparing the probability of 30-day inpatient mortality according to hyperglycemic crises category. Higher mortality risk was observed for those with combined DKA-HHS vs. isolated HHS (HR 2.7; 95% CI 1.4, 5.3), DKA-HHS vs. isolated DKA (HR 1.8; 95% CI 0.9, 3.6); log-rank test P = 0.003.

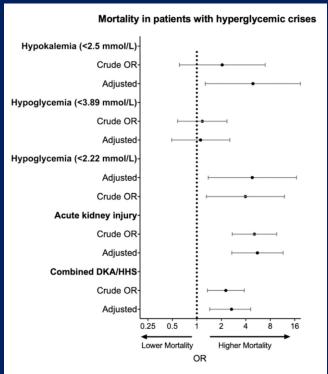


Figure 1—Odds of mortality according hospital complications and hyperglycemic crises. AKI: defined as an elevation of creatinine of 0.5 mg/dL from admission; hypoglycemia, <40 mg/dL; hypokalemia, <2.5 mEq/L; mortality occurring during admission. Model adjusted for age, sex, BMI, race, and Charlson Comorbidity Index.

Pasquel et al. Diabetes Care 2019, ahead of print