

II DIABETE OGGI:

UNA MALATTIA SEMPRE PIÙ COMPLESSA

L'importanza del trattamento insulinico: l'uso delle insuline basali

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La Dr.ssa Ilaria Barchetta dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Astra Zeneca
- Novo Nordisk

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

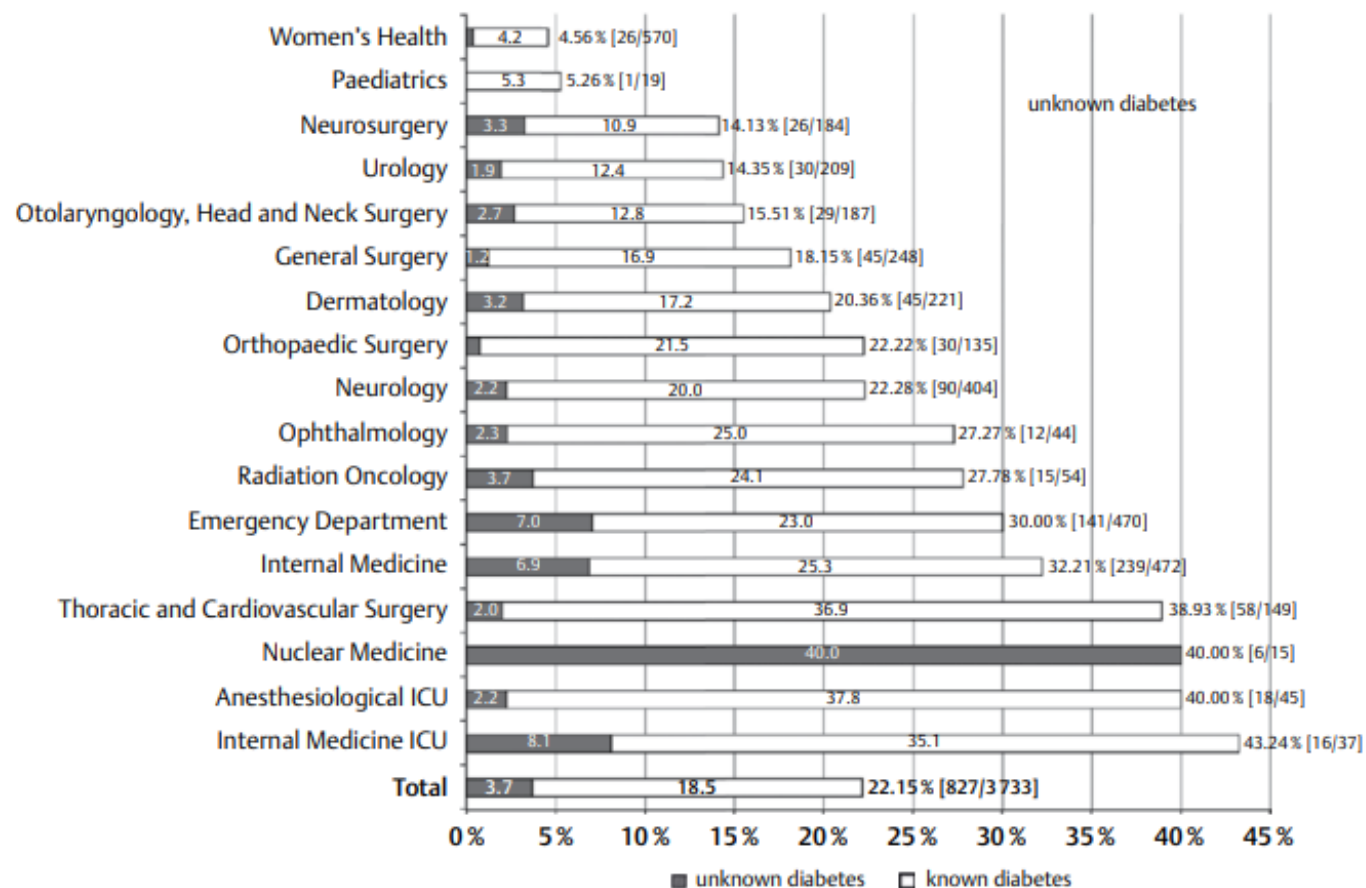
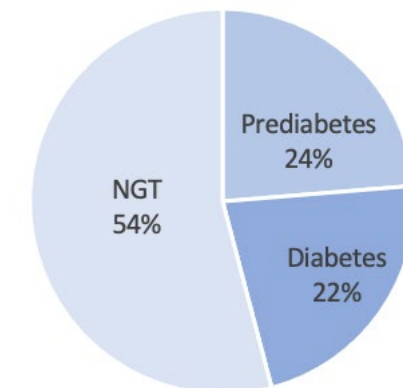


Agenda

- Diabete nei pazienti ospedalizzati: l'importanza del controllo metabolico
- A quali obiettivi glicemici puntare
- Come raggiungere il controllo glicemico adeguato:
 - la terapia insulinica nel paziente ospedalizzato
 - il ruolo delle insuline basali

Prevalence and Distribution of Diabetes Mellitus in a Maximum Care Hospital: Urgent Need for HbA_{1c}-Screening

Prevalence of diabetes mellitus in a maximum care hospital ($n=3733$)



23.68% of the patients had prediabetes and 22.15% had diabetes with a high variation between the specialized departments (range 5–43%)

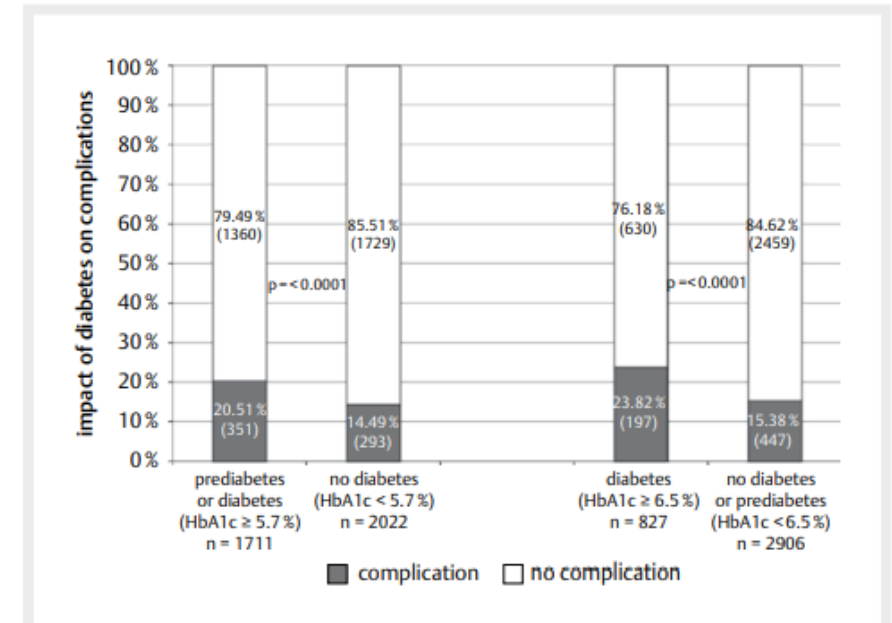


Prevalence and Distribution of Diabetes Mellitus in a Maximum Care Hospital: Urgent Need for HbA_{1c}-Screening

↑ Length of stay

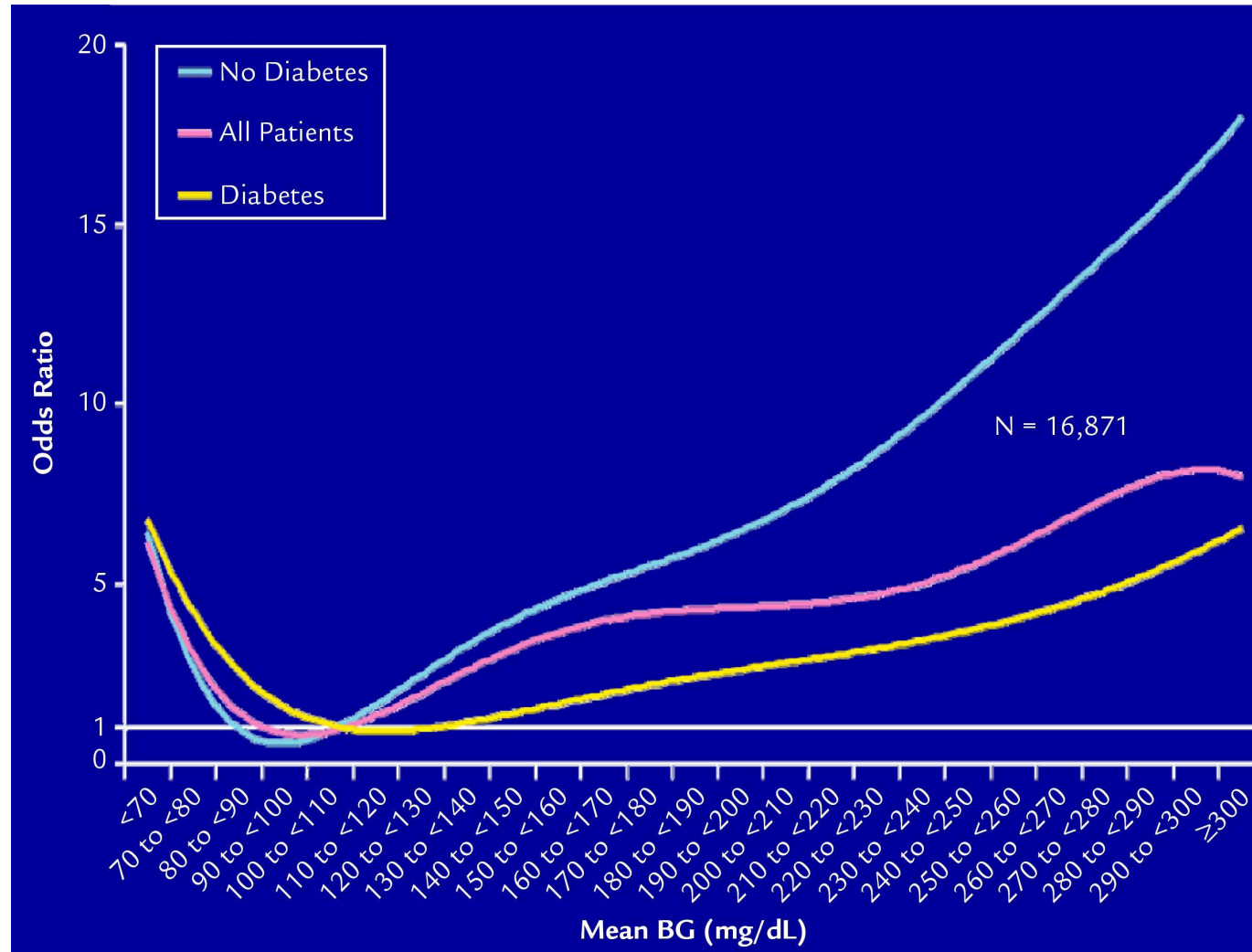
predictor	parameter estimate	SE	95% CI	p-value
intercept	-1.572	0.456	[-2.466; -0.678]	0.0006
diabetes status* (ref.: no diabetes)	1.101	0.335	[0.444; 1.757]	0.0010
complication (ref.: no complication)	5.141	0.356	[4.444; 5.840]	<.0001
age	0.009	0.008	[-0.006; 0.024]	0.2382
gender (ref.: female)	0.211	0.211	[-0.322; 0.744]	0.4376
death (ref.: normal discharge or relocation to other healthcare facility)	-0.754	0.944	[-2.605; 1.097]	0.4246
* diabetes: HbA _{1c} ≥ 6.5% and/or diabetes documentation				
no diabetes: HbA _{1c} < 6.5% and no diabetes documentation				
R ² = 0.0609; adjusted R ² = 0.0597; sum of squares SS = 263 483; p < 0.0001; N = 3 733;				
CI confidence interval; SE standard error				

↑ Complications



► **Fig. 4** Impact of diabetes on complications; grey bars: percentage of patients with acquired complications, white bars: percentage of patients with no acquired complications.

Relationship between mean glucose levels and mortality during hospitalization for nearly 17,000 acute myocardial infarction patients. Hyperglycemia is associated with more adverse outcomes, especially in non-diabetic individuals.



(Reference: Mean BG 100–110 mg/dl)

Kosiborod M et al. *Circulation* 2008
Bogun M, Inzucchi SE. *Clin Ther* 2013;35:724–33



- **Hyperglycemia**
 - **Hypoglycemia**
 - **Glucose variability**
- **Adverse outcomes and death**

Clement S, et al. Diabetes Care 2004;27:553–91
Moghissi ES, et al. Diabetes Care 2009;32:1119–31
Bogun M, Inzucchi SE. Clin Ther 2013;35:724–33

*Hospital management of diabetes is facilitated by **preadmission treatment** of hyperglycemia in patients having elective procedures, a **dedicated inpatient diabetes service** applying well-developed standards, and **careful transition out** of the hospital to prearranged outpatient management.*

These steps can shorten hospital stays and reduce the need for readmission, as well as improve patient outcomes.

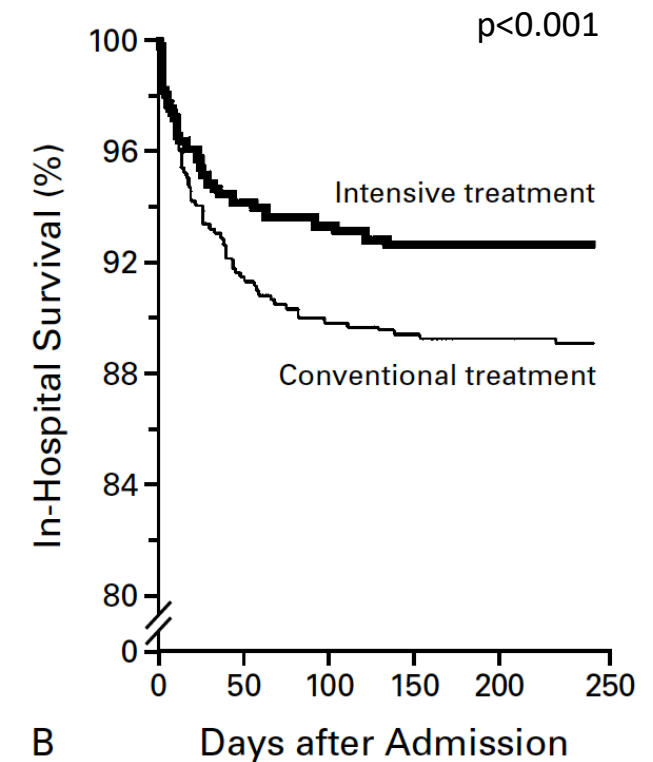
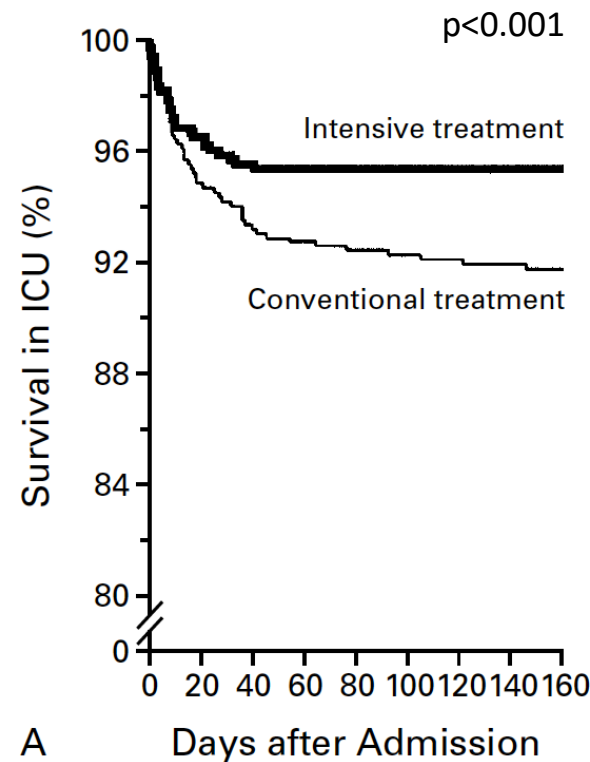


INTENSIVE INSULIN THERAPY IN CRITICALLY ILL PATIENTS

RCT prospective, 12 month FU, n= 1548

Intensive insulin therapy (BG: 80-110 mg/dl)
vs
conventional treatment (infusion of insulin only
if the blood glucose level exceeded 215 mg/dl,
maintenance of glucose at a level between 180
and 200 mg/dl)

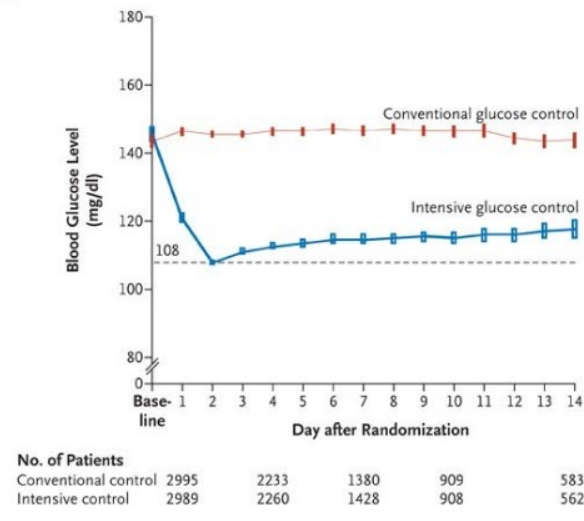
Conclusions Intensive insulin therapy to maintain blood glucose at or below 110 mg per deciliter reduces morbidity and mortality among critically ill patients in the surgical intensive care unit. (N Engl J Med 2001;345:1359-67.)



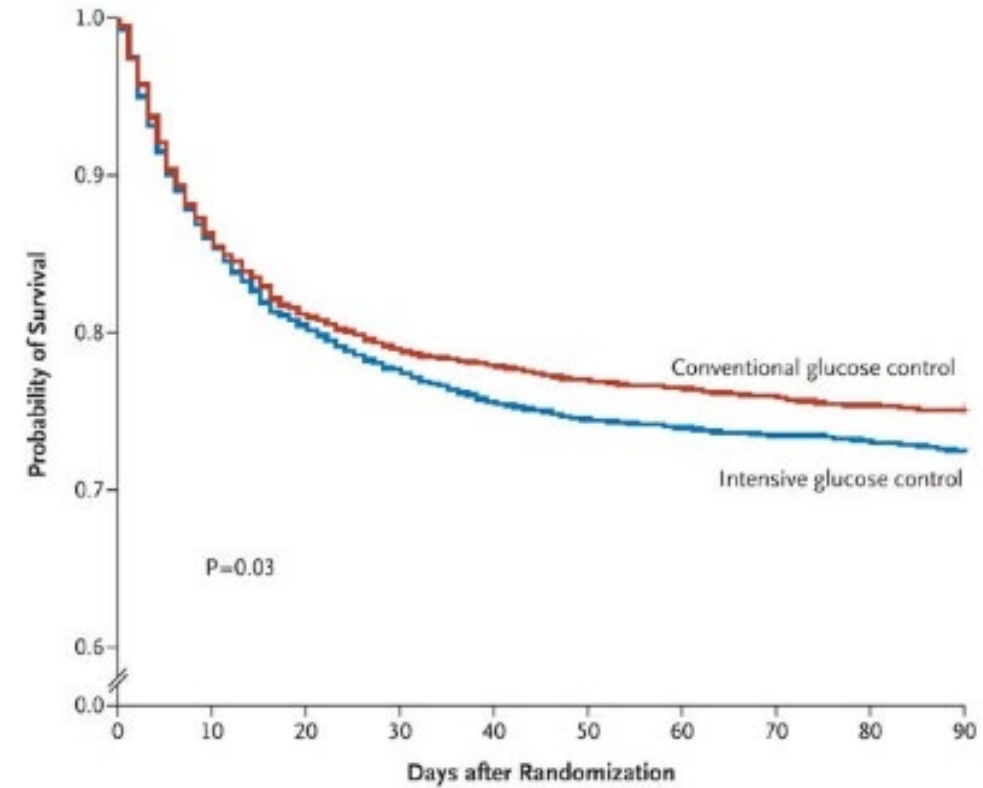
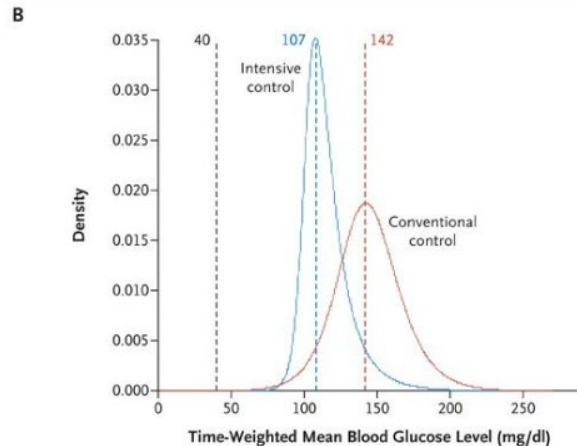
Intensive versus Conventional Glucose Control in Critically Ill Patients

The NICE-SUGAR Study Investigators*

n= 6104



BG target:
80-110 mg/dl
vs
140-180 mg/dl



No. at Risk				
Conventional control	3014	2379	2304	2261
Intensive control	3016	2337	2227	2182

Severe hypoglycemia (≤ 40 mg per deciliter) was recorded in 6.8% pts undergoing intensive glucose control vs 0.5% undergoing conventional control (OR: 14.7; 95% CI, 9.0 to 25.9; $P < 0.001$).

The recorded number of episodes of severe hypoglycemia was 272 in the intensive-control group, as compared with 16 in the conventional-control group

Diabetes Care in the Hospital: *Standards of Medical Care in Diabetes—2022*



GLYCEMIC TARGETS IN HOSPITALIZED PATIENTS

Recommendations

- 16.4** Insulin therapy should be initiated for treatment of persistent hyperglycemia starting at a threshold ≥ 180 mg/dL (10.0 mmol/L) (checked on two occasions). Once insulin therapy is started, a target glucose range of 140–180 mg/dL (7.8–10.0 mmol/L) is recommended for the majority of critically ill and noncritically ill patients. **A**
- 16.5** More stringent goals, such as 110–140 mg/dL (6.1–7.8 mmol/L), may be appropriate for selected patients if they can be achieved without significant hypoglycemia. **C**

HOSPITAL CARE DELIVERY STANDARDS

Recommendations

- 16.1** Perform an A1C test on all patients with diabetes or hyperglycemia (blood glucose >140 mg/dL [7.8 mmol/L]) admitted to the hospital if not performed in the prior 3 months. **B**
- 16.2** Insulin should be administered using validated written or computerized protocols that allow for predefined adjustments in the insulin dosage based on glycemic fluctuations. **B**

Glucose levels between 180 mg/dL and 250 mg/dL may be acceptable in patients with severe comorbidities and in inpatient care settings where frequent glucose monitoring or close nursing supervision is not feasible

Terapia durante il ricovero

Diabetes Care in the Hospital:
Standards of Medical Care in
Diabetes—2022

Diabetes Care 2022;45(Suppl. 1):S244–S253 | <https://doi.org/10.2337/dc22-S016>



La terapia insulinica è il trattamento di scelta nel paziente ospedalizzato

- **Critical Care Setting:** *In the critical care setting, continuous intravenous insulin infusion is the most effective method for achieving glycemic targets* → validated written or computerized protocols
- **Basal insulin,** *or a basal plus bolus correction regimen, is the preferred treatment for noncritically ill hospitalized patients* with poor oral intake or those who are restricted from oral intake. An insulin regimen with basal, prandial, and correction components is the preferred treatment for noncritically ill hospitalized patients with good nutritional intake. A



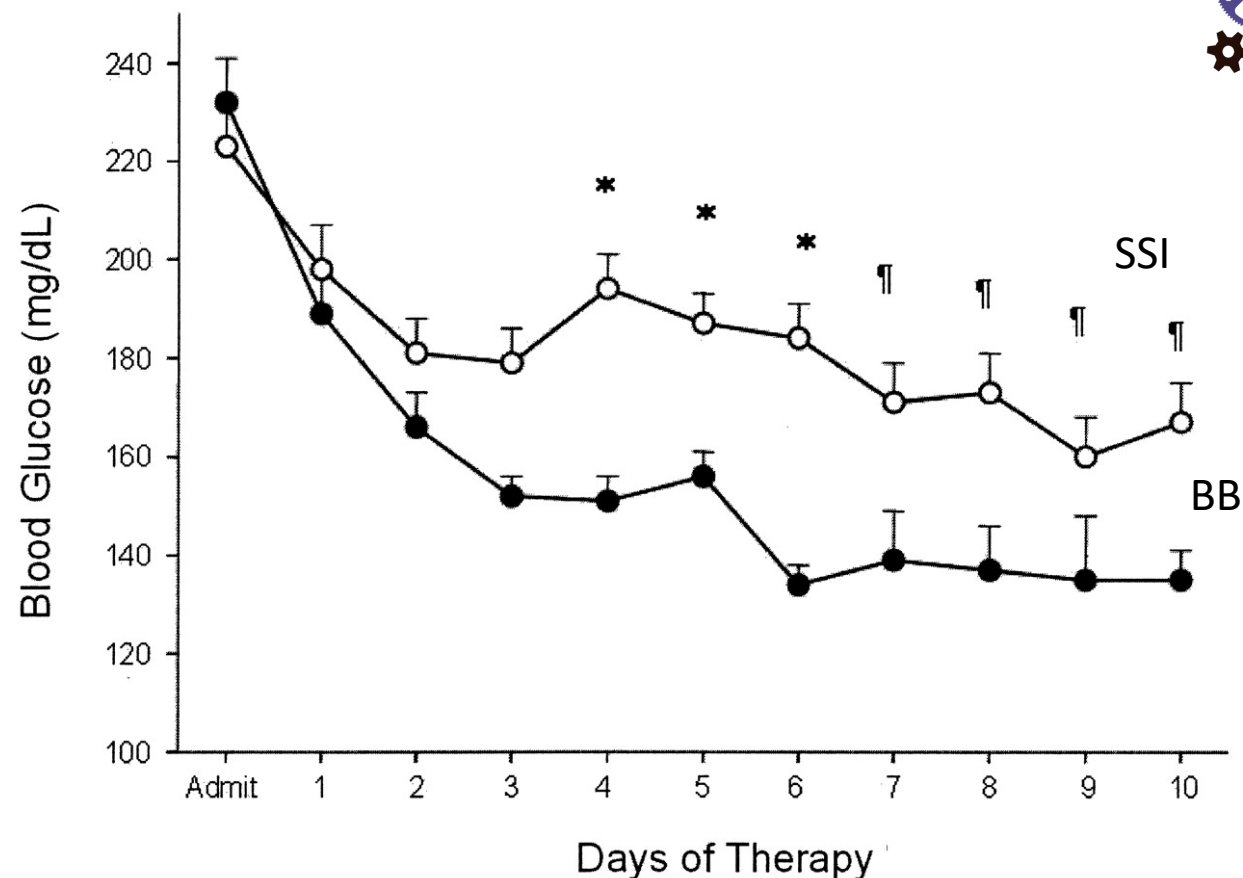
Randomized Study of Basal-Bolus Insulin Therapy in the Inpatient Management of Patients With Type 2 Diabetes (RABBIT 2 Trial)

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DAWN SMILEY, MD¹
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Prospective, multicenter, randomized trial to compare the efficacy and safety of a basal-bolus insulin regimen with that of sliding-scale regular insulin (SSI) in patients with type 2 diabetes (n= 130)

- 50% basal + 50% bolus vs
- SSI: pre-meal or regular insulin four times daily for glucose levels >140mg/dl



Treatment with insulin glargine and glulisine resulted in significant improvement in glycemic control compared with that achieved with the use of SSI alone, without increased hypos.

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Nine (14%) patients treated with SSI remained with blood glucose 240 mg/dl despite increasing the SSI dose to the maximal scale.

Glycemic control rapidly improved in all of the SSI failure subjects after they were switched to the basal-bolus insulin regimen.

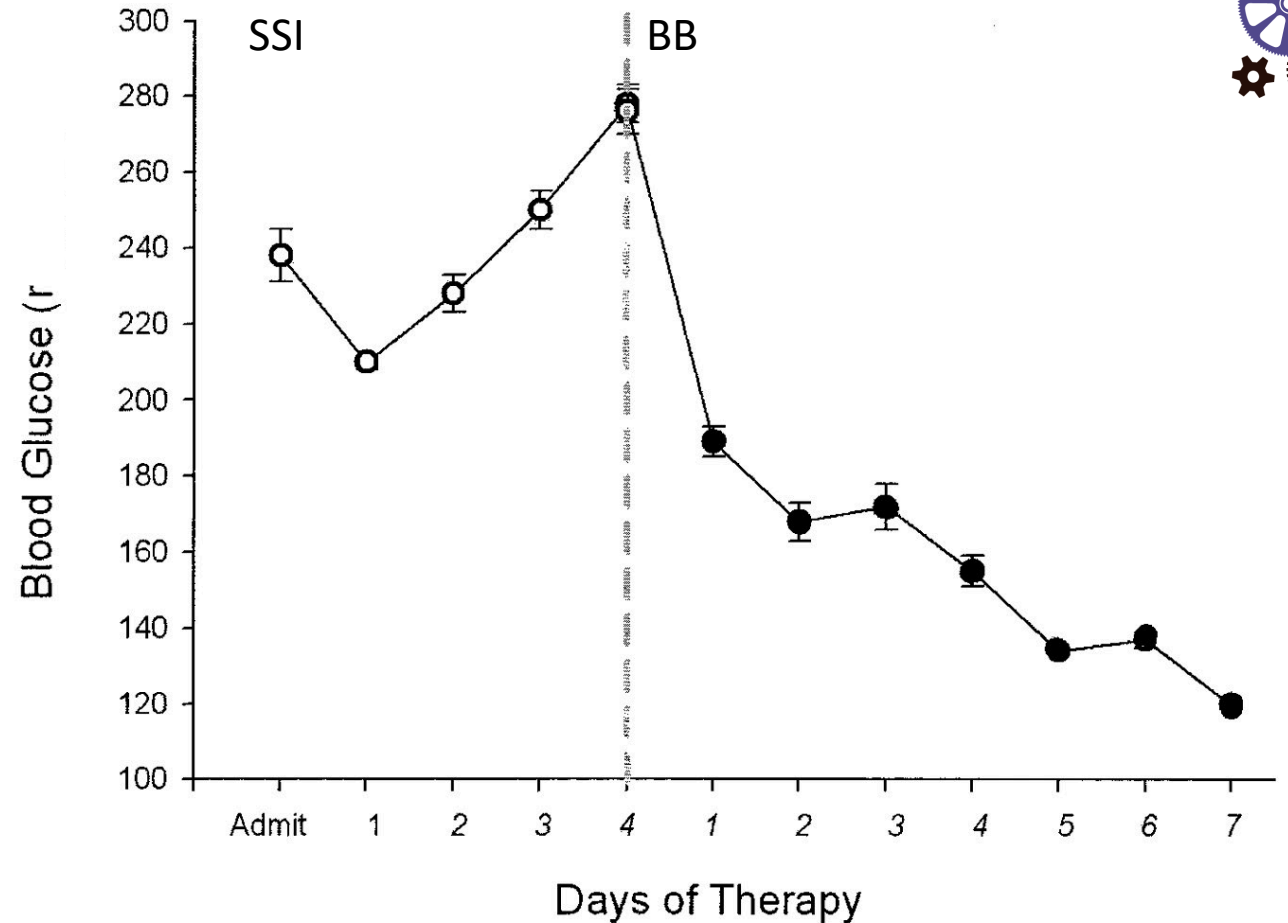


Figure 2—Mean blood glucose concentration in subjects who remained with severe hyperglycemia despite increasing doses of regular insulin per the sliding-scale protocol (○). Glycemic control rapidly improved after switching to the basal-bolus insulin regimen (●). $P < 0.05$.

Basal-bolus insulin regimen is preferred over SSI in the management of non-critically ill, hospitalized patients with type 2 diabetes

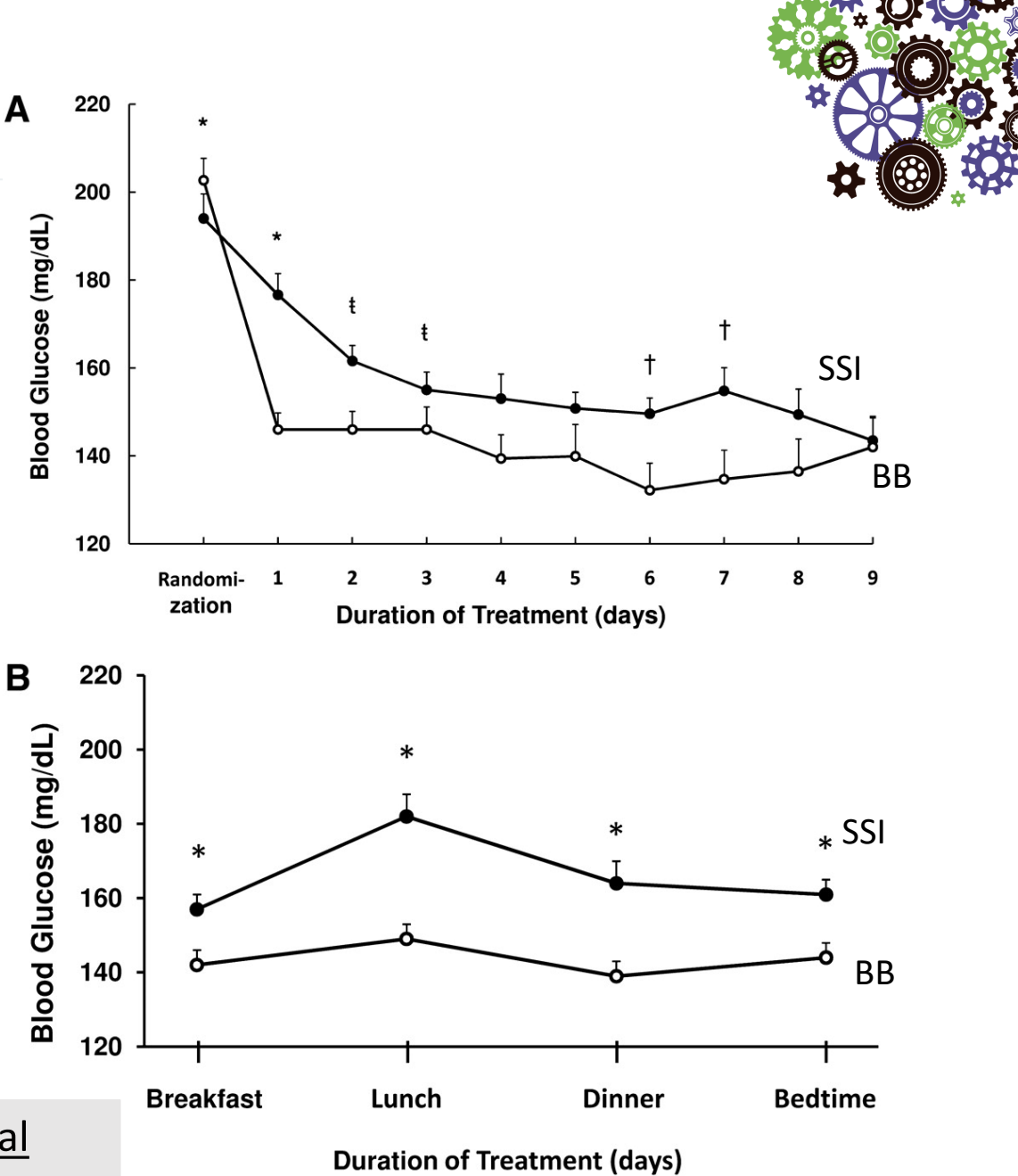
Randomized Study of Basal-Bolus Insulin Therapy in the Inpatient Management of Patients With Type 2 Diabetes Undergoing General Surgery (RABBIT 2 Surgery)

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MONICA RIZZO, MD⁶

Basal-bolus treatment with glargine once daily plus glulisine before meals improved glycemic control and reduced hospital complications compared with sliding scale (reactive) insulin therapy in general surgery patients.

Basal-bolus insulin regimen is preferred over SSI in the hospital management of general surgery patients with type 2 diabetes



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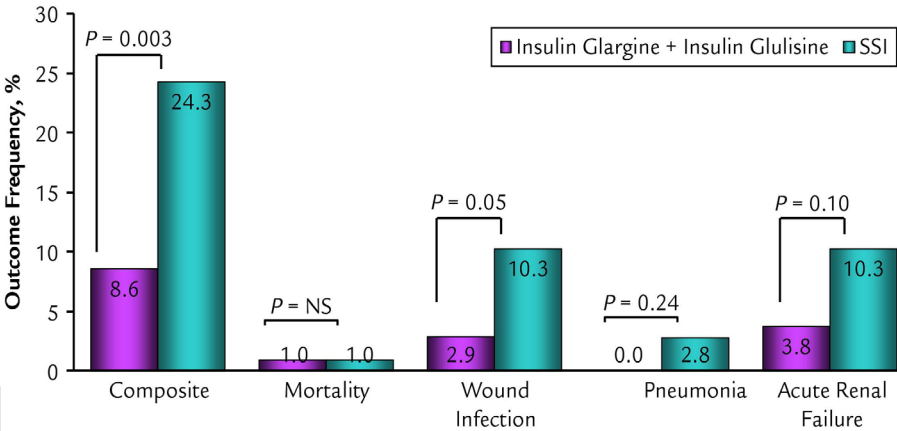
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Table 2—Composite hospital complications and outcomes composite hospital complications

	All	SSI	Basal-bolus insulin	P value
Wound infections	14	11	3	0.050
Pneumonia	3	3	0	0.247
Acute respiratory failure	6	5	1	0.213
Acute renal failure	15	11	4	0.106
Bacteremia	3	2	1	0.999
Number of patients with complications	35	26	9	0.003
Mortality	2	1	1	NS
Postsurgery ICU admission (%)	16	19.6	12.5	NS
Length of stay (days)				
ICU	2.51 ± 1.90	3.19 ± 2.14	1.23 ± 0.60	0.003
Hospital	6.8 ± 8.9	6.3 ± 5.6	7.23 ± 11.39	NS



Insulin Therapy and Glycemic Control in Hospitalized Patients With Diabetes During Enteral Nutrition Therapy

A randomized controlled clinical trial

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ESRA KARSLIOGLU, MD¹

ALMOATAZBELLAH M. IDRIS, MD¹
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FREDERICO G.S. TOLEDO, MD¹

To compare SSRI (n=25) and BB (n=25) for glycemic management of hyperglycemia in non-critically ill hospitalized patients with diabetes during enteral nutrition therapy (ENT)

The majority of non-critically ill inpatients will require basal insulin during ENT to achieve and maintain a reasonable degree of glucose control.

Although SSRI may be an acceptable initial therapy in the setting of mild hyperglycemia or in patients without prior diabetes, scheduled insulin is required once a consistent insulin requirement is demonstrated.



	Glargine	SSRI	P
n	25	25	
Age (years)	67 ± 10	63 ± 10	0.20
Sex (female)	36	44	0.56
BMI (kg/m ²)	29.1 ± 5.8	26.9 ± 1.7	0.22
Previous diabetes	11 (44)	14 (56)	0.40
LOS (days)	24.2 ± 18.2	23.8 ± 18.8	0.85
Severity-of-illness score	110 ± 25	105 ± 24	0.27
Charlson score	4.9 ± 3.3	3.6 ± 3.4	0.17
Primary diagnosis			
GI cancer/mass	13	13	
Esophageal tear/rupture	3	1	
Pancreatitis	1	3	
Head and neck cancer	2	1	
Other	6	7	
Glycemic data			
Entry glucose (mmol/l)	9.8 ± 2.7	9.9 ± 2.7	
Study day 1	9.6 ± 2.3	9.6 ± 2.5	0.59
Study day 2	9.7 ± 2.6	9.2 ± 2.3	0.52
Study day 3	9.6 ± 2.3	9.2 ± 2.4	0.57
Study day 4	9.4 ± 2.1	9.3 ± 2.4	0.98
Study day 5	8.8 ± 1.8	9.1 ± 1.9	0.66
Study day 6	8.6 ± 1.4	8.4 ± 1.6	0.62
Study day 7	8.8 ± 1.8	7.8 ± 1.3	0.27
Study day 8	7.8 ± 1.8	8.0 ± 1.4	0.48
Mean study glucose (mmol/l)	9.1 ± 1.6	8.9 ± 1.6	0.71
Mean peak glucose (mmol/l)	11.4 ± 2.7	11.5 ± 2.9	0.95
Mean nadir glucose (mmol/l)	6.9 ± 1.6	6.7 ± 1.2	0.51
Hypoglycemia			
Patient days	2.7	4.8	0.34
Blood glucose measures	1.3	1.1	0.35
Insulin			
Total daily dose (units)	27.2 ± 20.5	27.0 ± 28.5	0.33
SSRI (units/day)	11.3 ± 9.3	15.7 ± 12.4	0.22
Total daily dose (units · kg ⁻¹ · day ⁻¹)	0.33 ± 0.26	0.33 ± 0.33	
Basal insulin (%)	66.9 ± 13.8	24.0 ± 28.7	0.001
NPH and SSRI (%)*	NA	55.1 ± 7.0	0.45†
Triglycerides (mmol/l)			
Baseline	1.6 ± 0.5	1.6 ± 0.8	0.52
End of study	1.6 ± 0.5	1.6 ± 0.5	0.95
Adverse events (n)			
Body temperature >100.4°F (days)	0	8	0.003
Antibiotic use (days)	64	74	0.13
Arrhythmias	1	2	1.0
Pulmonary emboli	2	1	0.49
Deep venous thrombosis	2	0	1.0
Wound infection	1	0	
Respiratory symptoms	2	2	1.0
Cardiac arrest	0	1	1.0
Liver abscess	1	0	1.0

Data are percent, n (%), or means ± SD unless otherwise indicated. *n = 12. †Compared with the glargine group. GI, gastrointestinal; NA, not available.



[Intervention Review]

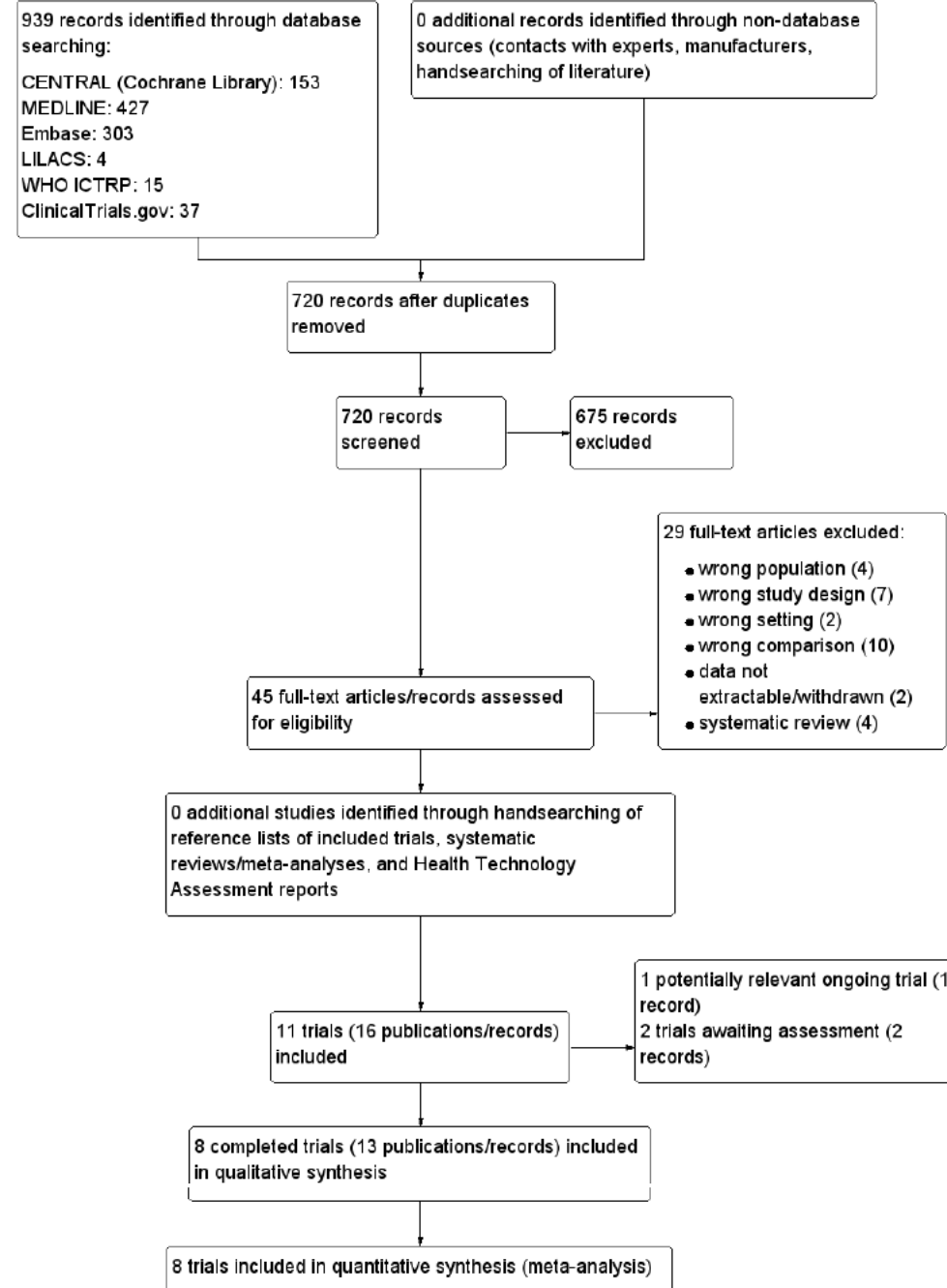
Sliding scale insulin for non-critically ill hospitalised adults with diabetes mellitus

Luis Enrique Colunga-Lozano¹, Francisco Javier Gonzalez Torres², Netzahualpilli Delgado-Figueroa³, Daniel A Gonzalez-Padilla⁴, Adrian V Hernandez⁵, Yuani Roman⁶, Carlos A Cuello-García⁷

2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd

Of 720 records screened, we included eight trials that randomised 1048 participants with type 2 diabetes (387 SSI participants and 615 participants in comparator groups were available for final analysis). We included non-critically ill medical and surgical adults with the diagnosis of diabetes mellitus. The mean follow-up time was measured by the mean length of hospital stay and ranged between five and 24 days. The mean age of participants was 44.5 years to 71 years.

Overall, we judged the risk of bias on the trial level as unclear for selection bias, high for outcome-related performance and detection bias with regard to hypoglycaemic episodes, other adverse events, and mean glucose levels, and low for all-cause mortality and length of hospital stay. Attrition bias was low for all outcome measures.

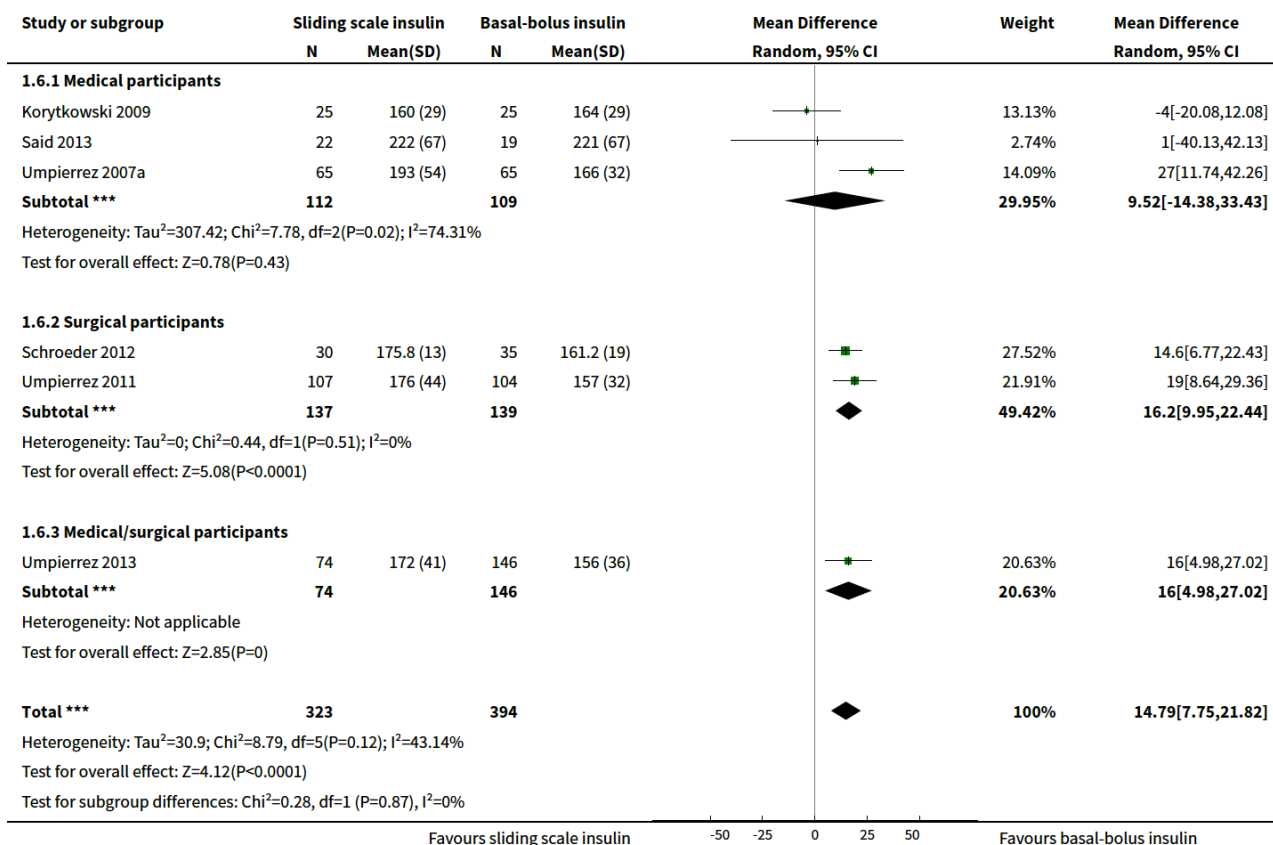




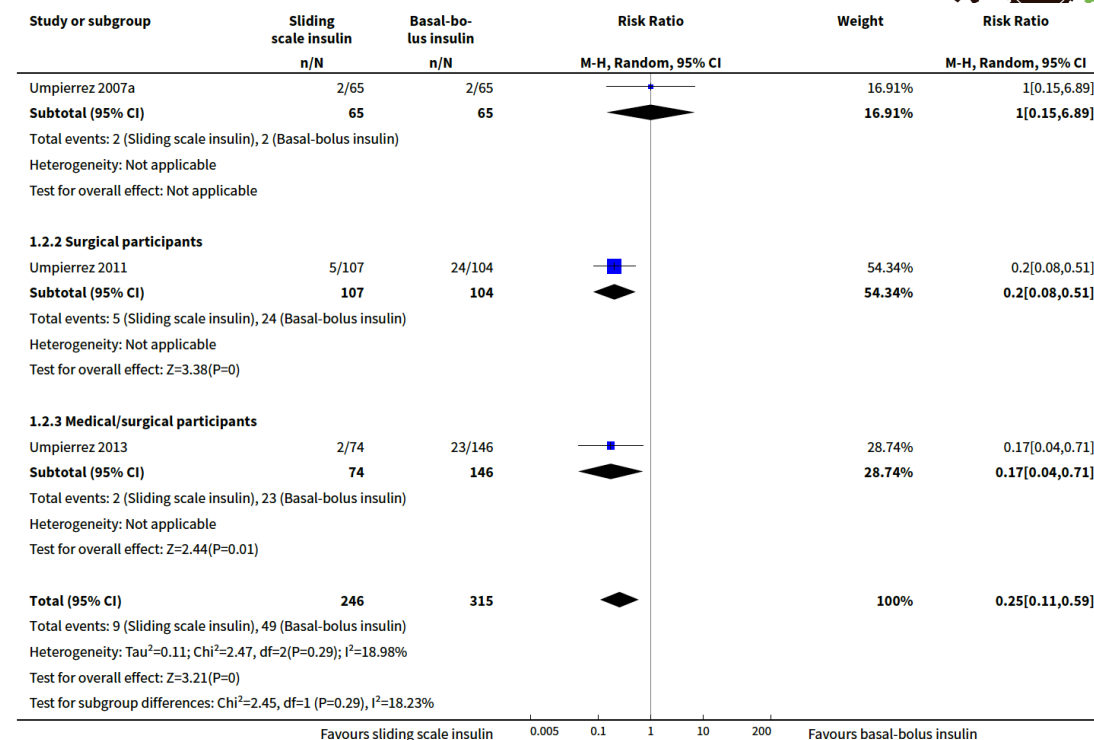
[Intervention Review]

Sliding scale insulin for non-critically ill hospitalised adults with diabetes mellitus

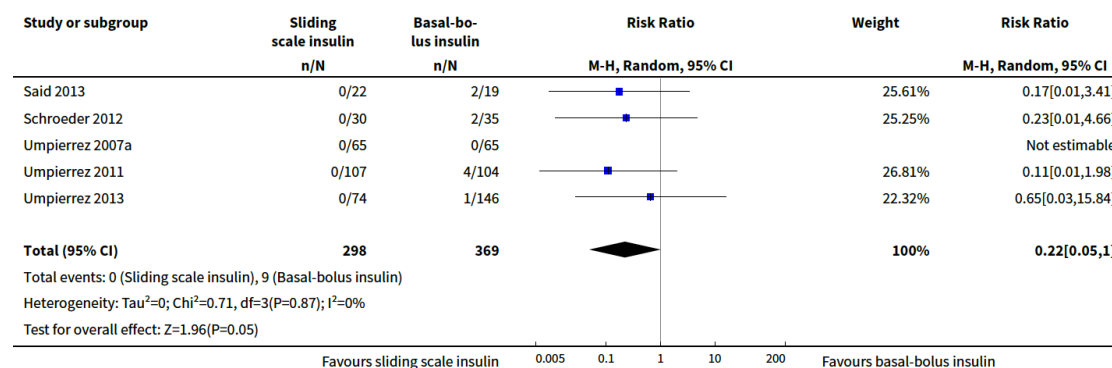
Analysis 1.6. Comparison 1 Sliding scale insulin versus basal-bolus insulin regimen, Outcome 6 Mean glucose levels.



Non-severe hypos



Severe hypos

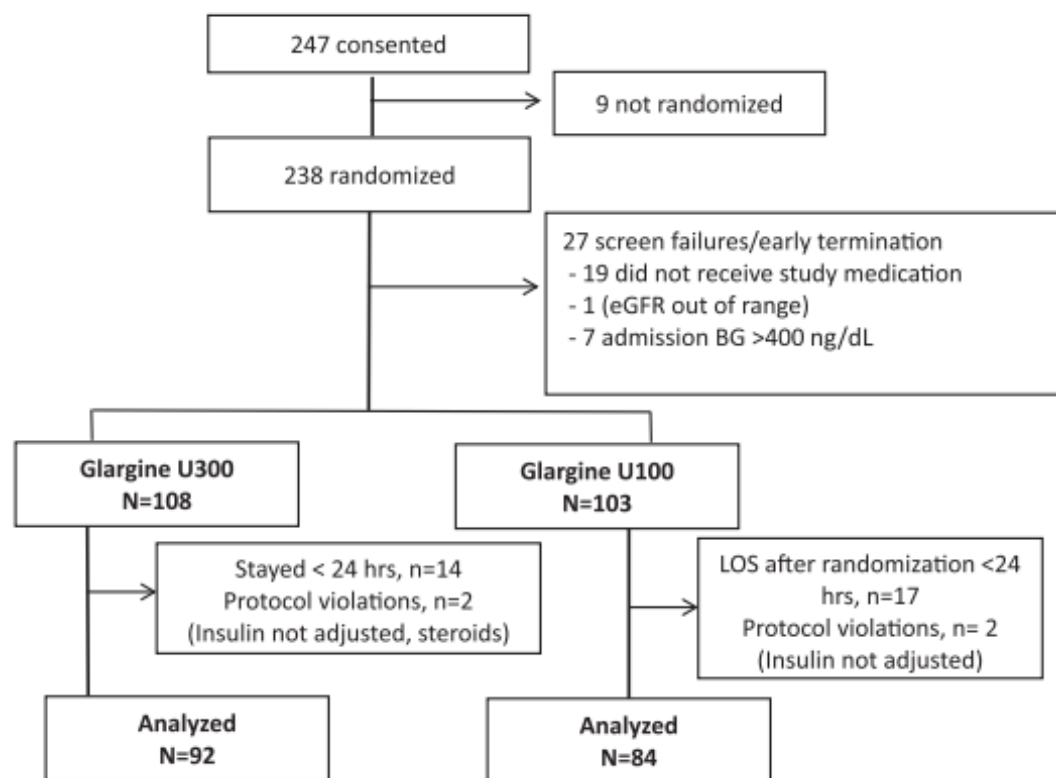




A Randomized Controlled Trial Comparing Glargine U300 and Glargine U100 for the Inpatient Management of Medicine and Surgery Patients With Type 2 Diabetes: Glargine U300 Hospital Trial

Diabetes Care 2020;43:1242–1248 | <https://doi.org/10.2337/dc19-1940>

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Saumeth Cardona,¹ Bonnie Albury,¹
Rodolfo J. Galindo,¹ Maya Fayfman,¹
Georgia Davis,¹ Alexandra Migdal,¹
Priyathama Vellanki,¹ Limin Peng,⁴ and
Guillermo E. Umpierrez¹



Multicenter, prospective, noninferiority randomized study at five academic hospitals in the U.S. (n= 238)

Target fasting and predinner BG between 100 mg/dL and 180 mg/dL (same titration scheme)

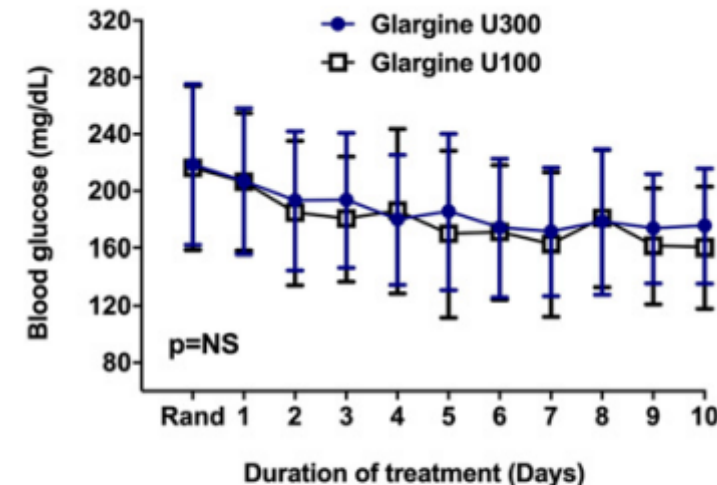


Figure 2—Mean daily BG concentrations measured in patients treated with glargine U300 or glargine U100. Data are mean $\pm$ SD.



A Randomized Controlled Trial Comparing Glargine U300 and Glargine U100 for the Inpatient Management of Medicine and Surgery Patients With Type 2 Diabetes: Glargine U300 Hospital Trial

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Table 2—Glycemic data, length of stay, and hospital complications

	Glargine U300 (n = 92)	Glargine U100 (n = 84)	P value
Daily BG by POC, mg/dL	186 ± 40	184 ± 46	0.62
BG 70–180 mg/dL by POC, %	50.3 ± 27.5	54.9 ± 29.3	0.30
Insulin TDD, units/kg/day	0.43 ± 0.2	0.42 ± 0.2	0.70
Insulin TDD, units/day	43.9 ± 25.4	42.8 ± 22.4	0.99
Basal insulin, units/day	29.0 ± 17.1	28.3 ± 14.4	0.87
Prandial insulin, units/day	14.4 ± 9.3	13.3 ± 8.7	0.57
Supplemental insulin, units/day	7.6 ± 3.6	7.5 ± 4.1	0.43
Any BG <70 mg/dL by POC	8 (8.7)	8 (9.5)	0.99
Any BG <54 mg/dL by POC	0 (0)	5 (6.0)	0.02
Treatment failure	18 (19.6)	9 (10.7)	0.14
Length of stay, days	6.0 (4.0, 8.0)	4.0 (3.0, 7.0)	0.07
Composite of complications	6 (6.5)	9 (11)	0.42

Continuous data are presented as the mean ± SD or median (IQR) and discrete data as n (%). Treatment failures were considered if there was persistent hyperglycemia (two or more glucose readings ≥400 mg/dL, three or more consecutive glucose readings >280 mg/dL, or mean daily BG concentration ≥280 mg/dL).

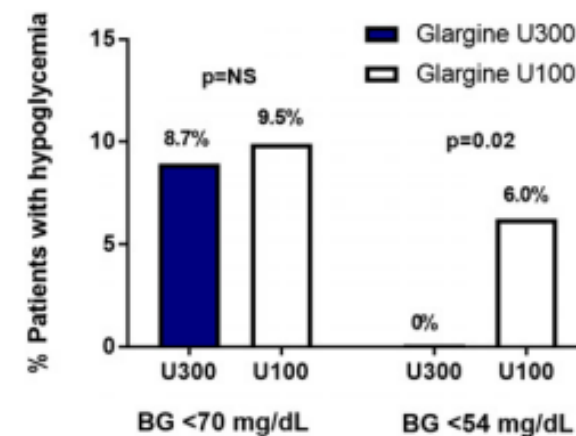


Figure 3—Proportion of patients with hypoglycemic episodes by POC testing.

Glargine U300 in the hospital setting is as effective as glargine U100 for the management of medical and surgical patients with T2D. In addition, the use of glargine U300 may decrease the incidence of hypoglycemia in this population.

Raccomandazioni specifiche

Diabetes Care in the Hospital:
*Standards of Medical Care in
Diabetes—2022*

Diabetes Care 2022;45(Suppl. 1):S244–S253 | <https://doi.org/10.2337/dc22-S016>

Transizione terapia insulinica in infusione e.v. → insulina basale (o basal/bolus)

A patient with type 1 or type 2 diabetes being transitioned to a subcutaneous regimen should receive a dose of subcutaneous basal insulin 2 h before the intravenous infusion is discontinued.

- The*
- *Insulin pens have been the subject of an FDA warning because of potential blood-borne infections; the warning “For single patient use only” should be rigorously followed.*
 - *For patients [...] in regimens with **concentrated insulin** in the inpatient setting, it is important to ensure correct dosing by utilizing an individual pen and cartridge for each patient and by meticulous supervision of the dose administered.*



Messaggi finali

- Il trattamento insulinico basale è il più regime insulinico più sicuro ed appropriato nei pazienti con diabete in regime di ricovero in area non critica.
- La terapia con insulina basale o un regime con insulina basale + boli correttivi rappresenta il trattamento di scelta per i pazienti ospedalizzati non critici con scarsa/nulla assunzione di cibo *per os*.
- Un regime insulinico con insulina basale, boli prandiale ed eventuali correzioni è il trattamento preferibile per i pazienti ospedalizzati non critici con un buon apporto nutrizionale.
- L'uso di un regime insulinico *sliding scale* in regime di ricovero ospedaliero è sconsigliato.

CONGRESSO REGIONALE
AMD-SID LAZIO

II DIABETE OGGI:

UNA MALATTIA SEMPRE PIÙ COMPLESSA

Grazie per l'attenzione!

Ilaria Barchetta

Dipartimento di Medicina Sperimentale

Università Sapienza, Roma

