



GRG-Journal Club
25 maggio 2007

Il diabete mellito nell'anziano: la complessità della terapia

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**La glicemia è un
fantasma della mente!!!**



Credo ut intelligam et intelligo ut credam

S. Tommaso D'Aquino

Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year

K Malmberg, L Ryden, S Efendic, et al

Department of Cardiology, Karolinska Hospital, Stockholm, Sweden.

J Am Coll Cardiol, 1995; 26:57-65

Intense metabolic control by means of insulin in patients with diabetes mellitus and myocardial infarction (DIGAMI 2): effects on mortality and morbidity.

K Malmberg, L Ryden, H Wedel, et al

Department of Cardiology, Karolinska Hospital, Stockholm, Sweden.

Eur Heart J 2005; 26: 650-61

Hyperglycemia: An Independent Marker of In-Hospital Mortality in Patients with Undiagnosed Diabetes

Guillermo E. Umpierrez, Scott D. Isaacs, Niloofar Bazargan, Xiangdong You, Leonard M. Thaler, and Abbas E. Kitabchi
J Clin Endocrinol Metab 2002 87: 978-982

Admission Glucose and Mortality in Elderly Patients Hospitalized With Acute Myocardial Infarction: Implications for Patients With and Without Recognized Diabetes

Mikhail Kosiborod, Saif S. Rathore, Silvio E. Inzucchi, Frederick A. Masoudi, Yongfei Wang, Edward P. Havranek and Harlan M. Krumholz
Circulation 2005;111;3078-3086; originally published online Jun 6, 2005;

Characteristics in 1156 Patients with Diabetes, without History of Diabetes Mellitus and Normo -Glycemic Patients Admitted to Sub Intensive Care Unit.

	n=1155	With Diabetes n=333	Without Diabetes n=307	Normoglycemia n=515
<u>Characteristics</u>		M (±SD)	M (±SD)	M (±SD)
Age	79.2 (±8.4)	78.3 (±8.2)	79.6 (±8.4)	79.5±8.7
Gender (male), n (%)		164 (49.2 %)	162 (52.8%)	246(47.7%)
MMSE score (0-30) at discharge	20.5 (±9.8)	20.4 (±9.4)	3.4 (±3.1)	21.2 (±9.4)
GDS	3.4 (±3.0)	3.7 (±3.1)	3.3 (±3.2)	3.3 (±3.1)
Barthel Index (0-100) before admission	69.7(±31.3)	67.1 (±32.4)	70.1 (±30.8)	72.4 (±30.7)
Charlson Index (0-33)	6.3 (±1.9)	6.7 (±1.8)	6.1 (±1.9)	5.9 (±1.9)
APACHE II score (0-71)	15.2 (±6.1)	15.2(±5.6)	15.2 (±6.1)	14 (±5.7)
APS (0-33)	9.8 (±18.7)	9.3 (±5.6)	9.3 (±5.6)	8.3 (±5.3)
S-Albumin (g/dl)	3.3 (±1.3)	3.4 (±2.3)	3.3 (±0.6)	3.3 (±0.6)
S-Cholesterol (mg/dl)	166 (±50)	163.8 (±53.6)	164.8 (±53.7)	167.5 (±49.6)
Number of drugs (n)	7.6 (±3.1)	8.3 (±3.0)	7.3 (±3.0)	7.1±3
Length of stay in SICU (hours)	72 (±60.7)	71.3(±59)	72.3(±61.3)	74.3 (±64.9)
Length of stay in hospital (days)	6.5 (±5.1)	6.3(±3.8)	6.7(±5.5)	7.1 (± 6.1)
In-hospital mortality, n (%)	129 (15.7)	38 (11.4)	129 (15.7)	58 (11.3 %)

Rates of Mortality According to Glycemic Value in 1156 Patients with Diabetes and without History of Diabetes Mellitus

	Blood glucose 60-126	Blood glucose 126-180	Blood glucose >180
With Diabetes n (%)	11 (8,8 %)	10 (12.7 %)	17 (13.2 %)
No History of Diabetes n (%)	58 (11.3 %)	35 (17.3 %)	36 (34.4 %)

Association between glycemia values and in-hospital mortality in non-diabetic elderly patients

	RR	sign.
Age (80+)	1.7	.00
Females	0.8	.51
APS (6+)	6.1	.00
Albumin (<3.5g/dl)	1.4	.14
Charlson Index (2+)	1.1	.89
Drugs (4+)	2.4	.00
IADL (2+)	4.4	.00
Stroke	2.0	.02
COPD	1.2	.48
Cancer	2.7	.00
Glycemia		
61-126 mg/dl	1.0 (ref.)	
127-180 mg/dl	1.1	.97
>180 mg/dl	2.8	.00

**Glucose is a modifiable mediator of adverse event or
simply a marker of critical illness?**

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INTENSIVE INSULIN THERAPY IN CRITICALLY ILL PATIENTS

GREET VAN DEN BERGHE, M.D., PH.D., PIETER WOUTERS, M.Sc., FRANK WEEKERS, M.D., CHARLES VERWAEST, M.D.,
FRANS BRUYNINCKX, M.D., MIET SCHEZ, M.D., PH.D., DIRK VLASSELAERS, M.D., PATRICK FERDINANDE, M.D., PH.D.,
PETER LAUWERS, M.D., AND ROGER BOUILLON, M.D., PH.D.

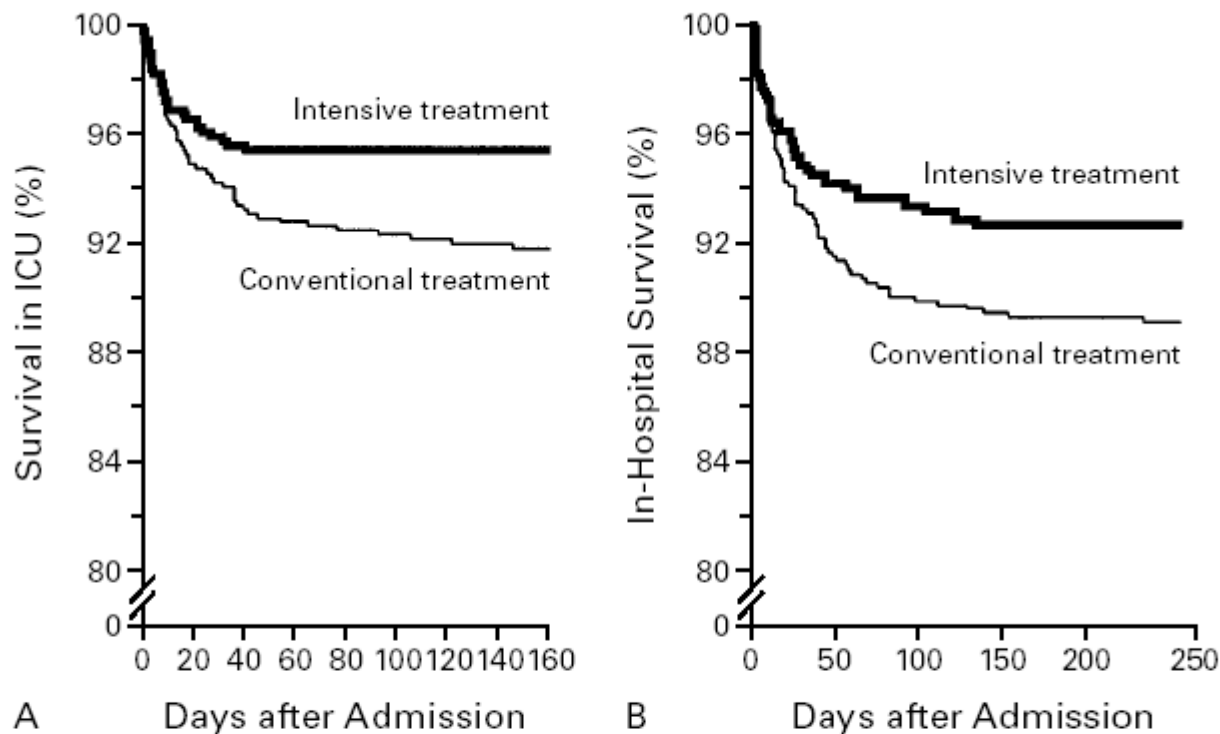


Figure 1. Kaplan–Meier Curves Showing Cumulative Survival of Patients Who Received Intensive Insulin Treatment or Conventional Treatment in the Intensive Care Unit (ICU).

Patients discharged alive from the ICU (Panel A) and from the hospital (Panel B) were considered to have survived. In both cases, the differences between the treatment groups were significant (survival in ICU, nominal $P=0.005$ and adjusted $P<0.04$; in-hospital survival, nominal $P=0.01$). P values were determined with the use of the Mantel–Cox log-rank test.

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Intensive Insulin Therapy in the Medical ICU

Greet Van den Berghe, M.D., Ph.D., Alexander Wilmer, M.D., Ph.D., Greet Hermans, M.D.,
Wouter Meersseman, M.D., Pieter J. Wouters, M.Sc., Ilse Milants, R.N., Eric Van Wijngaerden, M.D., Ph.D.,
Herman Bobbaers, M.D., Ph.D., and Roger Bouillon, M.D., Ph.D.

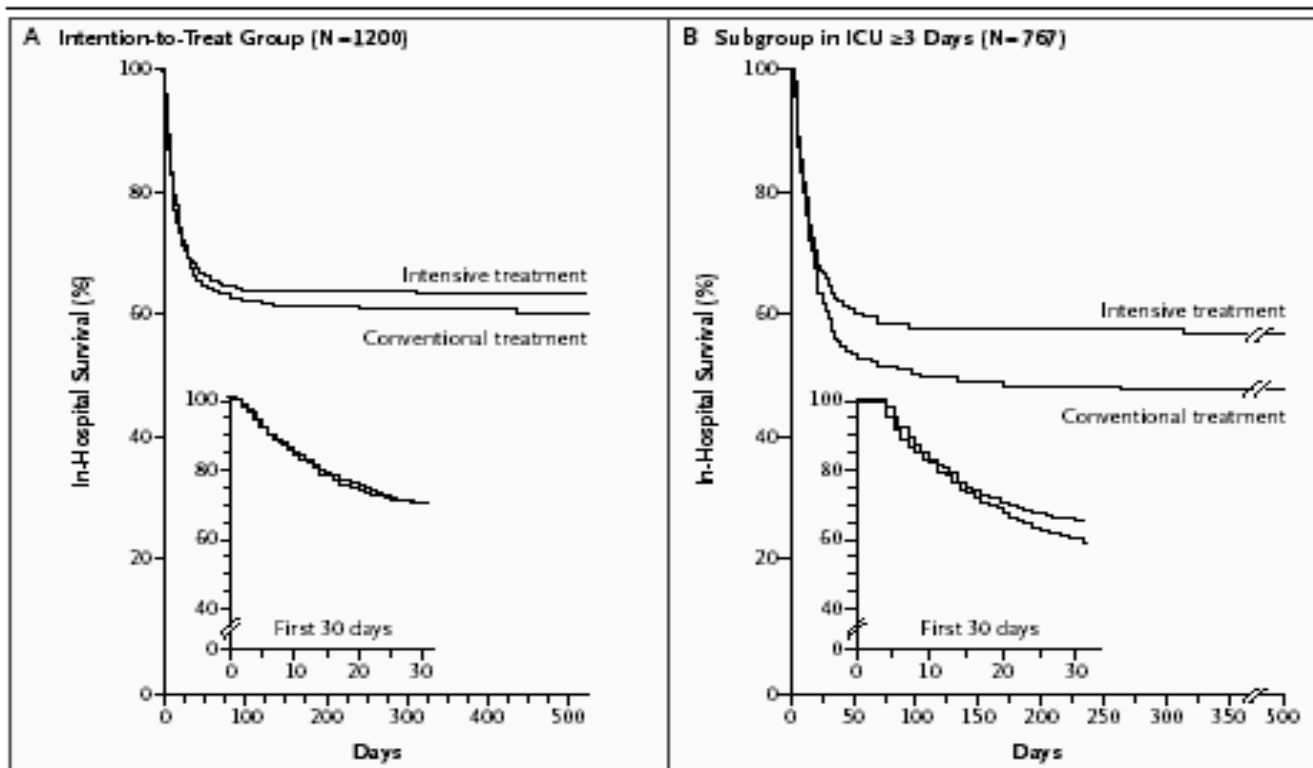


Figure 4. Kaplan-Meier Curves for In-Hospital Survival.

The effect of intensive insulin treatment on the time from admission to the intensive care unit (ICU) until death is shown for the intention-to-treat group (Panel A) and the subgroup of patients staying in the ICU for three or more days (Panel B). Patients discharged alive from the hospital were considered survivors. P values calculated by the log-rank test were 0.40 for the intention-to-treat group and 0.02 for the subgroup staying in the ICU for three or more days. P values calculated by proportional-hazards regression analysis were 0.30 and 0.02, respectively.

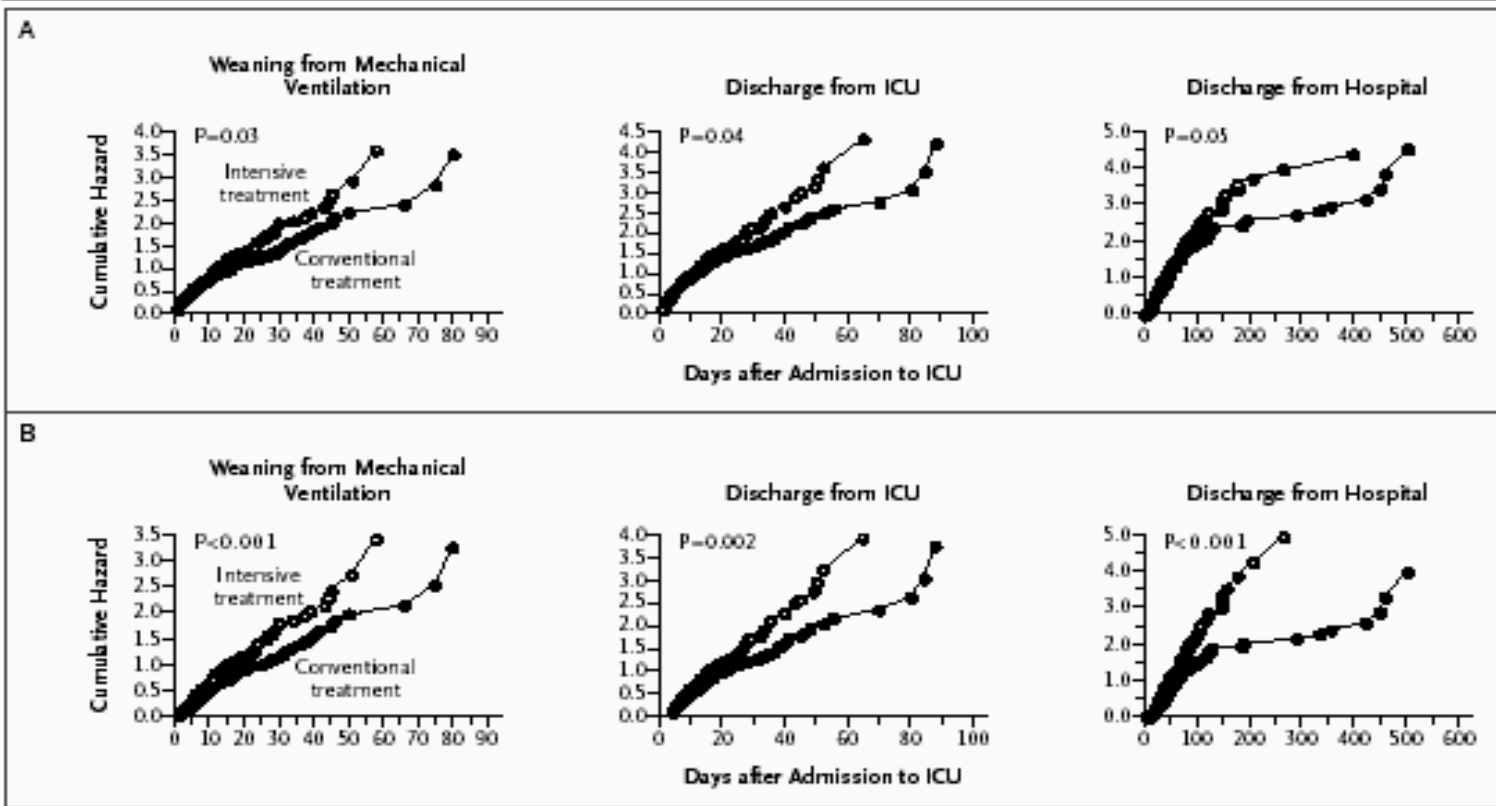


Figure 3. Effect of Intensive Insulin Therapy on Morbidity.

The effect of intensive insulin therapy on time to weaning from mechanical ventilation, time to discharge from the intensive care unit (ICU), and time to discharge from the hospital is shown for all patients (intention-to-treat analysis, Panel A) and for the subgroup of 767 patients staying in the ICU for three or more days (Panel B). P values for the comparison between the two groups were calculated by proportional-hazards regression analysis with censoring for early deaths. Circles represent patients.

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CLINICAL PRACTICE

Management of Hyperglycemia in the Hospital Setting

Silvio E. Inzucchi, M.D.

N Engl J Med 2006;355:1903-11.

Table 1. Recommended Target Blood Glucose Levels for Hospitalized Patients.*

Location	American Diabetes Association³⁶	American College of Endocrinology²
ICU	As close to 110 mg/dl as possible; generally <180 mg/dl	<110 mg/dl
General ward	As close to 90–130 mg/dl as possible; <180 mg/dl postprandial	<110 mg/dl before a meal; maximal <180 mg/dl

* The author believes these targets may be too stringent, on the basis of the available evidence. To convert values for glucose to millimoles per liter, multiply by 0.05551.

.....Although the precise glucose target for hospitalized patients remain controversial, having a precise target may be less important than recognizing that diabetes should not be ignored during hospitalization; that insulin therapy, when possible, should be proactive, with frequent adjustment to optimize control; that insulin infusion should be used when necessary.....

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EDITORIALS



Intensive Insulin in Intensive Care

Atul Malhotra, M.D.

.....In my opinion, a reasonable approach would be to provide adequate exogenous insulin to achieve target glucose values of less than 150 mg per deciliter at least during the first three days in the ICU. If critical illness persists beyond three days....., a goal of normoglycemia (80-110 mg per deciliter) could then be considered.....although this approach requires further study, it would seem to be a reasonable strategy that incorporates the best available evidence until more definitive data emerge.

IL Diabete Mellito: la terapia

- **Terapia farmacologica:**
 - Ipoglicemizzanti orali
 - Insulina
 - Aspirina
 - Statine
 - ACE inibitore
- **Terapia non farmacologica**
 - Dieta
 - Attività fisica

Ipoglicemizzanti orali

Aumentano la secrezione di insulina:
sulfaniluree o meglitinide

Aumentano la risposta all'insulina endogena:
biguanide e thiazolidinedione

**Modificano l'assorbimento intestinale dei
carboidrati:** inibitori dell'alfa-glucosidasi

Biguanidi

- **Metformina:**
 - Farmaco di 1° scelta
 - Riduzione o stabilizzazione del peso

Preferibilmente da non utilizzare nei pz con:

Età > 80 anni

Insufficienza renale

Malattie epatiche

Malattie cardiache

Etilisti

Sulfaniluree

- **Educare il paziente agli episodi di ipoglicemia: **severe e prolungate****

I fattori di rischio che favoriscono l'ipoglicemia:

Età avanzata

Abuso di alcool

Malnutrizione

Insufficienza renale

Meglitinidi

- Simili alle sulfaniluree ma più costose
 - Nei pz con allergia o intolleranza alle sulfaniluree
 - **Nateglinide**: metabolizzato al livello epatico, escrezione renale di metaboliti attivi. Ipoglicemie nell'insufficienza renale
 - **Repaglinide**: metabolizzato a livello epatico, meno del 10 % escreto per via renale. Non richiede aggiustamenti della posologia nell'insufficienza renale

Thiazolidinedioni

- **Riduce l'insulino-resistenza, associato ad un lieve incremento di peso. Ritenzione idrica, da usare con cautela nello scompenso cardiaco**
 - Troglitazone
 - Rosglitazone
 - Pioglitazone

Gli inibitori dell'alfa glucosidasi

- **Da usare in associazione agli altri ipoglicemizzanti**
- **Poco tollerati: molti effetti collaterali al livello intestinale**

NON SONO MUTUABILI

Insulina

- **Ultra rapida:** emivita 4-5 ore, da praticare 0-15 min prima del pasto. Simile all'insulina endogena
- **Rapida:** emivita 6-8 ore, da praticare 20-30 min prima del pasto
- **Intermedia:** emivita 12-16 ore, il picco a 6-10 ore
- **Ultralenta:** emivita 18-20 ore.
- **Long-acting:** glargina e levimir. Emivita 24 e 20 ore rispettivamente

Rapid-acting: Lispro, Aspart, and Glulisine: duration 4–5 hours, given 0–15 min before meals, mimic natural mealtime insulin release

Short-acting: Regular: duration 6–8 hours, given 20–30 min before meals, may cause late postprandial hypoglycemia

Intermediate-acting: NPH: duration 12–16 hours, usually given twice daily, peak effect 6–10 hours

Intermediate/long-acting: Ultralente: duration 18–20 hours, given once or twice daily, unpredictable absorption and peaks

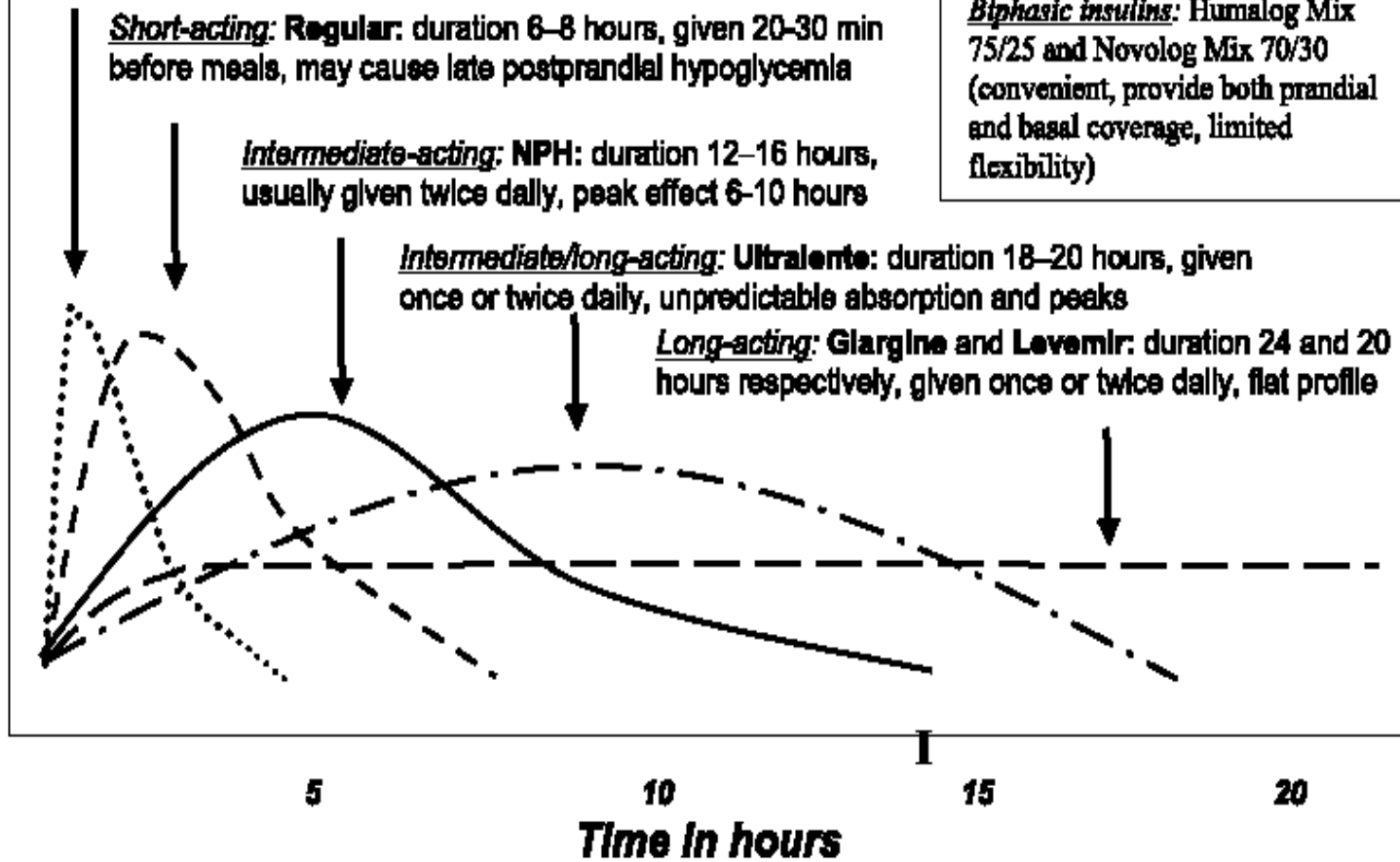
Long-acting: Glargine and Levemir: duration 24 and 20 hours respectively, given once or twice daily, flat profile

Not shown:

Premixed insulins: Humulin 70/30 and Novolin 70/30

Biphasic insulins: Humalog Mix 75/25 and Novolog Mix 70/30 (convenient, provide both prandial and basal coverage, limited flexibility)

Action



La dieta

Clinical characteristics of the three groups of patients

Patient characteristics	Nursing home		Ambulatory Diabetics
	Nondiabetics	Diabetics	
	(n= 61)	(n=47)	(n=64)
Age (years)	80.2 ± 1.2	81 ± 1.6	66.2 ± 0.6
Underweight	15 (24 .5 %)	10 (21 %)	2 (3 %)
Overweight	0 (0%)	4 (8.5 %)	15 (23 %)

Multiply adjusted hazard ratios for all-cause mortality associated with weight loss of 10 or more pounds, by diabetes mellitus status and gender

Weight loss \geq 10 pounds	Hazard Ratio	Adjusted Hazard ratio	95% CI
Men			
Nondiabetic (n=628)	1.38	1.41	1.06-1.80
Diabetic (n=140)	3.66	3.85	2.15-6.24
Women			
Nondiabetic (n=933)	1.76	1.73	1.33-2.34
Diabetic (n=90)	1.65	1.58	0.70-3.87

Adjusted for age, current or recent smoking, and exercising less than 10 year earlier

- **Negli anziani il rischio di malnutrizione è simile al rischio di obesità**
- **Una dieta leggermente ristretta migliora la qualità della vita, in assenza o con minimo di beneficio sul controllo della malattia diabetica**
- **Il calo di peso aumenta il rischio di morbidità e mortalità negli anziani**

Exercise Training and Nutritional Supplementation for Physical Frailty in Very Elderly People

Maria A. Fiatarone, Evelyn F. O'Neill, Nancy Doyle Ryan, Karen M. Clements, Guido R. Solares, Miriam E. Nelson, Susan B. Roberts, Joseph J. Kehayias, Lewis A. Lipsitz, and William J. Evans

N Engl J Med. 1994 Jun 23;330(25):1769-75.

Exercise adherence and 10- year mortality in chronically ill older adults

Miriam Morey, Carl Pieper, Gail Crowley, Robert Sullivan, Carmel Puglisi

J Am Geriatr Soc. 2002; 50: 1929-1933

Exercise in the healthy older adult

Reena Karani, Mary McLaughlin, Christine K. Cassel

AJGC. 2001; 10: 269-273

Esercizio fisico

- **E' importante per i pazienti anziani:**
 - **Mantenere la funzionalità**
 - **Riduce il rischio cardiovascolare**
 - **Riduce l'insulino resistenza**
 - **Riduce il dolore artrosico**
 - **Riduce le cadute**
 - **Riduce la depressione**
 - **Migliora la qualità di vita e la sopravvivenza**

IL Diabete Mellito: la terapia

- **In ospedale**
- **A domicilio**

IL Diabete Mellito: la terapia

- **In ospedale**
- A domicilio

Ipoglicemizzanti orali

- **La terapia può essere continuata nei pazienti non critici**
- **Metformina da sospendere: Insufficienza renale, scompenso cardiaco e esami radiologici con mezzo di contrasto**
- **Thiazolidinedioni: sospendere nello scompenso cardiaco e alterazioni della funzionalità epatica. L'effetto ipoglicemizzante dura per settimane dopo la sospensione**
- **Le sulfaniluree: da sospendere nei pazienti che non si alimentano regolarmente o apporto calorico ridotto e nell'insufficienza renale**

Considerare il passaggio all'insulina quando:

I valori di glicemia sono elevati all'ingresso

Durante il ricovero scarso controllo della glicemia

Sliding – scale insulin

- Insulina rapida ogni 4-6 ore, a seconda dei valori glicemici
- Va utilizzata come supplemento ad un appropriato regime basale

Regime basale: 1-2 lente o 1 long acting e 3 rapide o ultrarapide

0.6 U/kg/die; circa 40 % per l'insulina basale

Correzioni: 1 U /50 mg di glucosio nel diabete tipo 1

2 U /50 mg nel diabete tipo 2

Infusione insulina e.v

- Preparazione di insulina 1 U in 1 ml di salina.
- Dose iniziale ($300 \text{ MG /dl} : 70 = 4,2$; $150 : 70 = 2,1$)
- Monitoraggio ogni ora fino al target terapeutico (se 3 determinazioni di seguito nel range terapeutico)
- Monitoraggio ogni 2 ore (se per 12-24 ore stabile)
- Monitoraggio ogni 4-6 ore

N.B: da non dimenticare i boli preprandiali

IL Diabete Mellito: la terapia

- In ospedale
- **A domicilio**

Glycemic targets in older patients who have diabetes

	Healthy	Frail
Fasting blood glucose	<126 mg/dl	<180 mg/dl
2-h postmeal glucose	<180 mg/dl	<252 mg/dl
HbA1C	< 7 %	<8.5 %

Blood pressure and lipid targets in older people who have diabetes

	Healthy	Frail
Blood pressure	< 140/80 mmHg	<150/90 mmHg
LDL Chol	< 116 mg/dl	
TG	< 202 mg/dl	

- **Elimination of symptoms of uncontrolled hyperglycemia (polyuria, nocturia, vision disturbances, and weakness) and avoiding treatment-related hypoglycemia.**
- **Individualization of care, taking into account the patient's longevity, personalized glucose goals, and life situation.**
- **Attention to nonglycemic risk factors that contribute to cardiovascular mortality (blood pressure, dyslipidemia, smoking, and physical inactivity).**

Start low and go slow

Individualizing management

- **Gli anziani sono una popolazione eterogenea**
 - **Persone indipendenti che vivono in comunità**
 - **Persone che vivono nelle residenze**
 - **Persone che vivono assistiti a domicilio**

Anziani robusti sani e anziani fragili con numerose comorbilità e funzionalmente disabili

Terapia iniziale

- **Metformina**
- **Sulfaniluree**
- **Thiazolidinedione**
- **Inibitori dell'alfa glicosidasi**

Terapia combinata orale

- **Metformina più sulfaniluree**
- **Metformina più thiazolidinedione**
- **Sulfaniluree più thiazolidinedione**
- **Inibitori dell'alfa glicosidasi**

Terapia mista: ipoglicemizzante orale e insulina

- **Non vi sono evidenze sulla triplice terapia con ipoglicemizzanti orali**
- **Molti effetti collaterali, non migliora il controllo glicemico, profilo aterogenico e costi elevati**
- **L'insulina sopprime il rilascio di glucosio epatico, causa principale dell'iperglicemia a digiuno**
- **Migliore controllo della glicemia, riduzione dei valori di emoglobina glicata, meglio tollerata e meno episodi di ipoglicemia**

L'obiettivo nella cura del diabete negli anziani robusti è simile a quella degli adulti giovani e include il controllo della glicemia e i rischi ad esso correlati.