Gruppo di ricerca geriatrica

GRG-Journal Club
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Il punto sulla terapia del Diabete Mellito tipo 2

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- **Classificazione**
- **Diagnosi**
- **Terapia**

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- Diagnosi
- Terapia
- Obiettivi

Diabete mellito tipo 1: (distruzione delle cellule beta pancreatiche, deficit assoluto d'insulina)

a) Immunomediato

b) Idiopatico

Diabete mellito tipo 2: varia da una predominante insulino resistenza con relativa carenza di insulina ad un predominante difetto secretorio associato ad insulino-resistenza

Altri tipi specifici:

a) difetti genetici della cellule beta pancreatiche (MODY 1-6, difetti cromosomici)

b) difetti genetici nell'azione dell'insulina (es. diabete lipoatrofico)

c) patologie del pancreas esocrino (es pancreatiti)

d) malattie endocrine (es ipertiroidismo,S. di Cushing)

e) da farmaci (es. glucocorticoidi)

f) infezioni (es. citomegalovirus)

g) rare forme immunomediate (es. Ab anti recettore insulinico)

h) altre sindromi genetiche che a volte si associano al diabete (es. S. Down, S. Turner)

i) diabete gestazionale

ADA, Diabetes care 2007

Patients with any form of diabetes may require insulin treatment at some stage of their disease. Such use of insulin does not, of itself, classify the patient.

ADA, Diabetes care 2007

- Classificazione
- **Diagnosi**
- Terapia

Normal fasting plasma glucose (FPG): < 100 mg/dl

Impaired fasting glucose (IFG): FPG ≥ 100 to 125 mg/dl

Impaired glucose tollerance (IGT): two-hour value in an OGTT (2-h PG) ≥ 140 to 199 mg/dl

Diabetes Mellitus: Any one of these criteria must be repeated on subsequent testing

FPG ≥ 126 mg/dl

2-h PG ≥ 200 mg/dl

random PG > 200 mg/dl in the presence of symptoms (thirst, polyuria, weight loss, visual blurring)

HbA1c is not yet recommended for diagnosis.

ADA, Diabetes care 2007

IL Diabete Mellito: la terapia

- **Terapia farmacologica:**
  - **Ipoglicemizzanti orali**
  - **Insulina**
  - **Aspirina**
  - **Statine**
  - **ACE inibitore**

IL Diabete Mellito: la terapia

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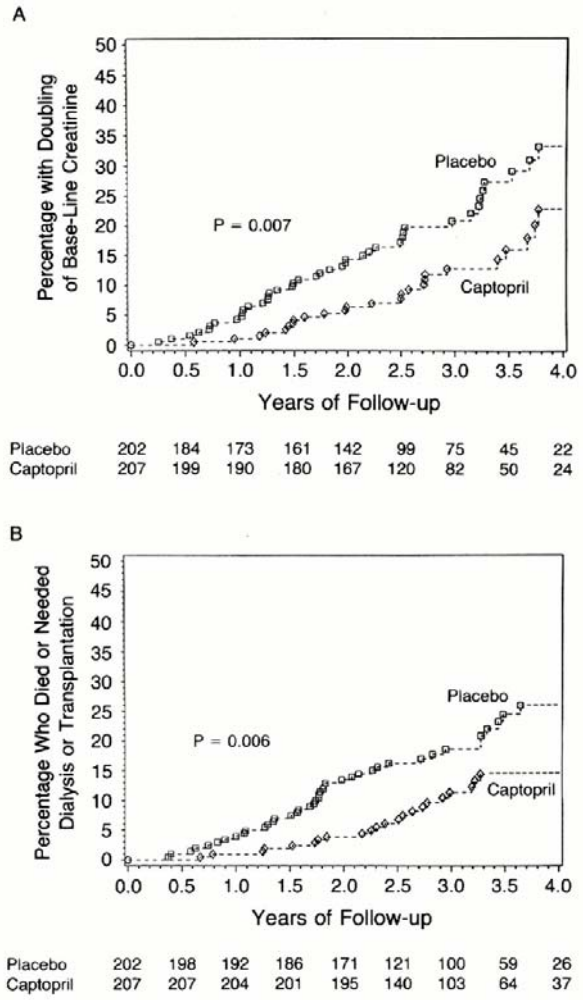
Cumulative Incidence of Events in Patients with Diabetic Nephropathy in the Captopril and Placebo Groups



Lewis E et al. N Engl J Med 1993;329:1456-1462

AHA/ADA Scientific Statement

Primary Prevention of Cardiovascular Diseases in People With Diabetes Mellitus

A Scientific Statement From the American Heart Association and the American Diabetes Association

John B. Buse, MD, PhD, Co-chair; Henry N. Ginsberg, MD, FAHA, Co-chair; George L. Bakris, MD, FAHA; Nathaniel G. Clark, MD, MS, RD; Fernando Costa, MD, FAHA; Robert Eckel, MD, FAHA; Vivian Fonseca, MD; Hertzel C. Gerstein, MD, MSc, FRCPC; Scott Grundy, MD, FAHA; Richard W. Nesto, MD, FAHA; Michael P. Pignone, MD, MPH; Jorge Plutzky, MD; Daniel Porte, MD; Rita Redberg, MD, FAHA; Kimberly F. Stitzel, MS, RD; Neil J. Stone, MD, FAHA

Circulation 2007; 115:114-126

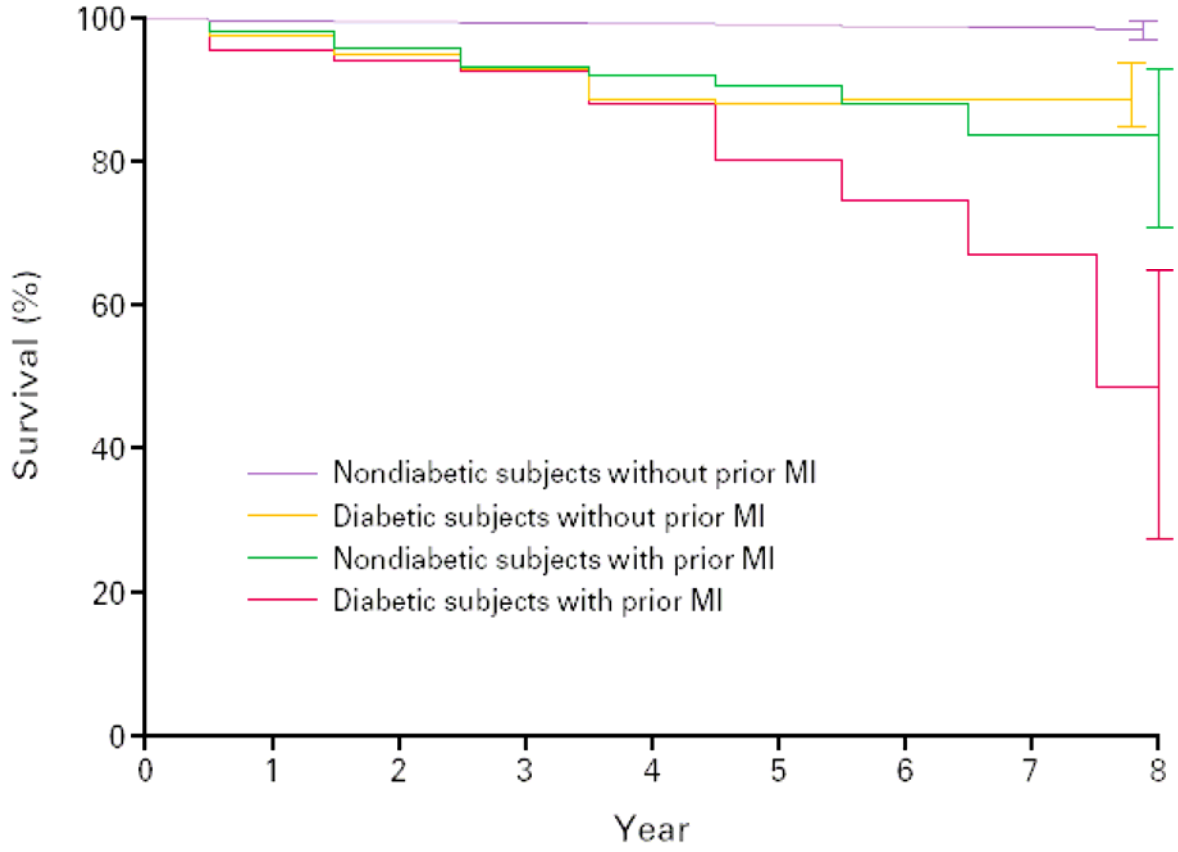
Recommendations for Antiplatelet Therapy

- **Aspirin therapy (75 to 162 mg/d) should be recommended as a primary prevention strategy in those with diabetes at increased cardiovascular risk, including those who are 40 years of age or who have additional risk factors (family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria).**

- **People with aspirin allergy, bleeding tendency, existing anticoagulant therapy, recent gastrointestinal bleeding, and clinically active hepatic disease are not candidates for aspirin therapy. Other antiplatelet agents may be a reasonable alternative for patients at high risk.**

- **Aspirin therapy should not be recommended for patients under the age of 21 years because of the increased risk of Reye's syndrome associated with aspirin use in this population. People under the age of 30 years have not been studied.**

Circulation 2007; 115:114-126



Haffner et al. N Engl J Med 1998; 339:229

CHD EQUIVALENTS

- **Diabetes mellitus**
- Symtomatic carotid artery disease
- Peripheral arterial disease
- Abdominal aortic aneurysm
- Multiple risk factors that confer a 10-year risk of CHD > 20 percent

Grundy et al. Circulation 2004; 110:227

TABLE 2. ATP III LDL-C Goals and Cutpoints for TLC and Drug Therapy in Different Risk Categories and Proposed Modifications Based on Recent Clinical Trial Evidence

Risk Category	LDL-C Goal	Initiate TLC	Consider Drug Therapy**
High risk: CHD* or CHD risk equivalents† (10-year risk >20%)	<100 mg/dL (optional goal: <70 mg/dL)‖	≥100 mg/dL#	≥100 mg/dL†† (<100 mg/dL: consider drug options)**
Moderately high risk: 2+ risk factors‡ (10-year risk 10% to 20%)§§	<130 mg/dL¶	≥130 mg/dL#	≥130 mg/dL (100–129 mg/dL; consider drug options)‡‡
Moderate risk: 2+ risk factors‡ (10-year risk <10%)§§	<130 mg/dL	≥130 mg/dL	≥160 mg/dL
Lower risk: 0–1 risk factor§	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160–189 mg/dL: LDL-lowering drug optional)

*CHD includes history of myocardial infarction, unstable angina, stable angina, coronary artery procedures (angioplasty or bypass surgery), or evidence of clinically significant myocardial ischemia.

†CHD risk equivalents include clinical manifestations of noncoronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease [transient ischemic attacks or stroke of carotid origin or >50% obstruction of a carotid artery]), diabetes, and 2+ risk factors with 10-year risk for hard CHD >20%.

‡Risk factors include cigarette smoking, hypertension (BP ≥140/90 mm Hg or on antihypertensive medication), low HDL cholesterol (<40 mg/dL), family history of premature CHD (CHD in male first-degree relative <55 years of age; CHD in female first-degree relative <65 years of age), and age (men ≥45 years; women ≥55 years).

§§Electronic 10-year risk calculators are available at www.nhlbi.nih.gov/guidelines/cholesterol.

§Almost all people with zero or 1 risk factor have a 10-year risk <10%, and 10-year risk assessment in people with zero or 1 risk factor is thus not necessary.

‖Very high risk favors the optional LDL-C goal of <70 mg/dL, and in patients with high triglycerides, non-HDL-C <100 mg/dL.

¶Optional LDL-C goal <100 mg/dL.

#Any person at high risk or moderately high risk who has lifestyle-related risk factors (eg, obesity, physical inactivity, elevated triglyceride, low HDL-C, or metabolic syndrome) is a candidate for therapeutic lifestyle changes to modify these risk factors regardless of LDL-C level.

**When LDL-lowering drug therapy is employed, it is advised that intensity of therapy be sufficient to achieve at least a 30% to 40% reduction in LDL-C levels.

††If baseline LDL-C is <100 mg/dL, institution of an LDL-lowering drug is a therapeutic option on the basis of available clinical trial results. If a high-risk person has high triglycerides or low HDL-C, combining a fibrate or nicotinic acid with an LDL-lowering drug can be considered.

‡‡For moderately high-risk persons, when LDL-C level is 100 to 129 mg/dL, at baseline or on lifestyle therapy, initiation of an LDL-lowering drug to achieve an LDL-C level <100 mg/dL is a therapeutic option on the basis of available clinical trial results.

Grundy et al. Circulation 2004; 110:227

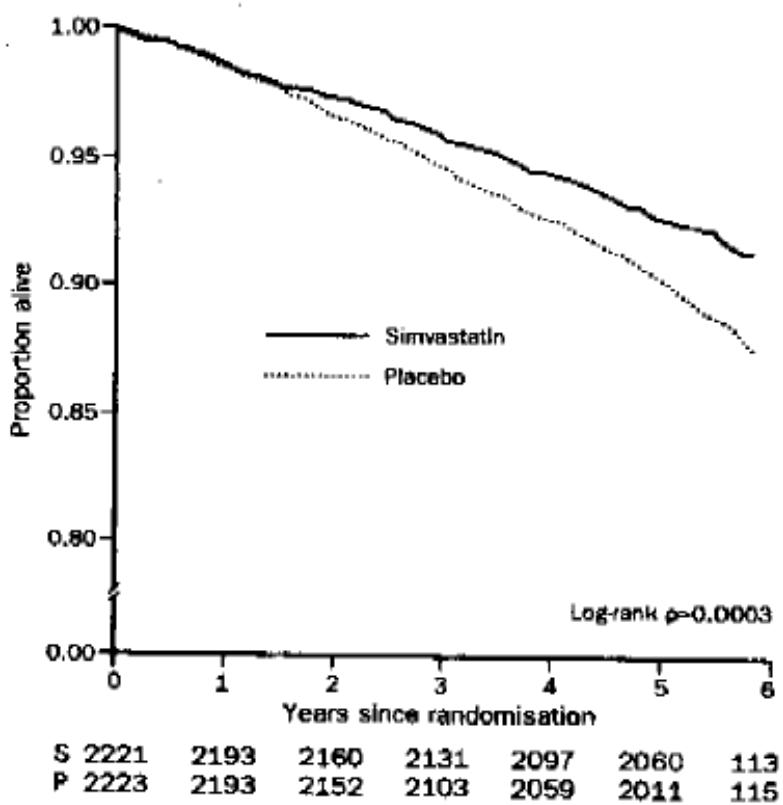


Figure 1: **Kaplan-Meier curves for all-cause mortality**
Number of patients at risk at the beginning of each year is shown below the horizontal axis

4S, Lancet 1994; 344:1383

IL Diabete Mellito: la terapia

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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

INCRETINE

Ormoni prodotti a livello gastrointestinale e sono principalmente:

- Glucagon-like peptide 1 (GLP-1), prodotto dalle cellule L dell''ileo/colon
- Glucose-dependent insulinotropic peptide(GIP), prodotto dalle cellule K del duodeno

Sono secreti dopo i pasti e agiscono:

- aumentando la secrezione di insulina
- diminuendo la secrezione di glucagone
- rallentando la motilità e dunque lo svuotamento gastrico e diminuendo l'appetito.

Il GLP-1 è rapidamente degradato dall'enzima dipeptidil-peptidasi IV (DPP-IV)

Analoghi del GLP-1:

Exenatide e exenatide LAR: Byetta sc, 2 iniezioni al giorno, il dosaggio va aggiustato in base alla funzione renale. In associazione con gli ipoglicemizzanti orali

Liraglutide: **non ancora in commercio**.

Inibitori del DPP-IV:

Sitagliptin: Januvia 100 mg cp. Non richiede aggiustamenti nell'insufficienza epatica. Aggiustamento del dosaggio nell'insufficienza renale. Non ipoglicemie

Vildagliptin: Galvus

AMILINA o *Human Islet Amyloid Precursor Polypeptide (hIAPP)*,

Ormone secreta nelle beta cellule con l'insulina

Presenta numerose funzioni:

rallenta il transito gastrico

inibisce la secrezione del glucagone

stimola la sazietà

Pramlintide: symlin fl sc, 3 volte al giorno nel diabete sia di tipo 1 che tipo 2

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**

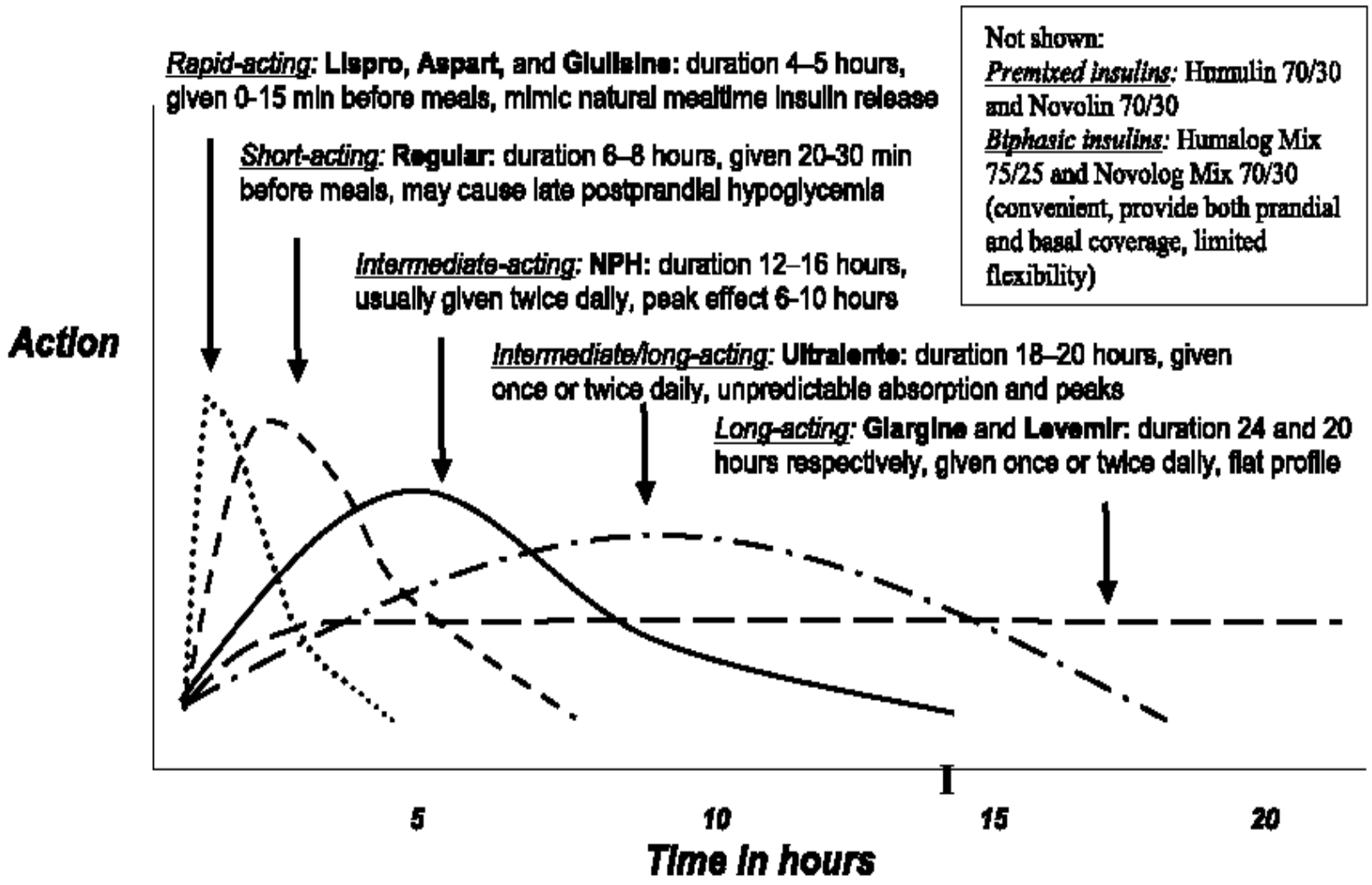
Gli inibitori dell'alfa glucosidasi

- **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
5
10
15
20
Time in hours

IL Diabete Mellito: la terapia

GRAND ROUNDS
AT THE JOHNS HOPKINS HOSPITAL

CLINICIAN'S CORNER

Using Clinical Guidelines Designed for Older Adults With Diabetes Mellitus and Complex Health Status

JAMA 2006; 295: 1935-1940

Estimate the patient's approximate life expectancy compared with the median for individuals of that age-sex cohort by considering the presence or absence of unusually good or poor health and function

Establish the patient's health care goals and preferences for treatment

Evaluate and manage geriatric syndromes consistent with the patient's goals and the impact that these may have on the management of other medical conditions

Help the patient to prioritize treatment options for diabetes mellitus and other medical conditions consistent with the patient's goals and treatment preferences and the magnitude and time to benefit in the context of the patient's overall health

Remember that for older adults with diabetes and an absence of significant medical illness or disability, intensive management of blood pressure and lipid levels and use of aspirin therapy have the greatest chance of benefit within 2 to 3 years

Consider intensive glycemic targets for older adults with a life expectancy of longer than 8 years and a low risk of hypoglycemia, and for those who have existing microvascular complications, who may benefit from intensive glycemic management in a shorter time frame

Frail older adults, those with a high burden of illness, difficulty adhering to therapy, significant risks from intensive management of macrovascular and microvascular risks, or a short life expectancy are more likely to benefit from symptom management and strategies to improve quality of life

JAMA 2006; 295: 1935-1940