



XIX  
CONGRESSO  
NAZIONALE AMD  
Roma, 29 maggio - 1 giugno 2013  
Rome Marriott Park Hotel

# I target della HbA<sub>1c</sub>



Alberto De Micheli  
Agenzia Regionale Sanitaria Liguria  
Genova



**Ai sensi dell'art. 3.3 del Regolamento applicativo dell'Accordo Stato-Regioni 05.11.2009, dichiaro che negli ultimi due anni non ho avuto rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario**

In fede,

*Alberto De Micheli*

# Standards of Medical Care for Patients With Diabetes Mellitus

Roma, 29 maggio - 1 giugno 2013  
Rome Marriott Park Hotel

DIABETES CARE VOL 13 SUPPL 1 JANUARY 1990

## Special Article



### Diabetes Mellitus and Its Degenerative Complications: A Prospective Study of 4,400 Patients Observed Between 1947 and 1973

JEAN PIRART

and presented in **DIABETES CARE, VOL. 1 NO. 3, MAY-JUNE 1978**

diabetes or **other medical** conditions. Implementation of the management plan requires that **each aspect** be understood by the patient and the care provider and that the goals and means be considered **realistic**.

The management plan should include:

- **Statement of goals**

## Goals

...us effort to achieve levels of blood glucose as close to those in the **diabetic person as feasible**.

...usly, **patient needs and resources** also be carefully assessed and the **individualized** accordingly.

...concept is particularly applicable to diabetic patients at greatest risk of developing complications.

# DCCT 1993 UKPDS 1998

Also, in **shorter life expectancy**, may preclude the need for achieving lower glucose levels, providing they are asymptomatic.

**D**isease is a threat. From the impact on the individual and the community, it is a leading cause of death and disability in the United States. The burden of disease is increasing, and the impact on the individual and the community is growing. The burden of disease is increasing, and the impact on the individual and the community is growing. The burden of disease is increasing, and the impact on the individual and the community is growing.

**Standards of Medical Care for Patients With Diabetes Mellitus**

**Goals**

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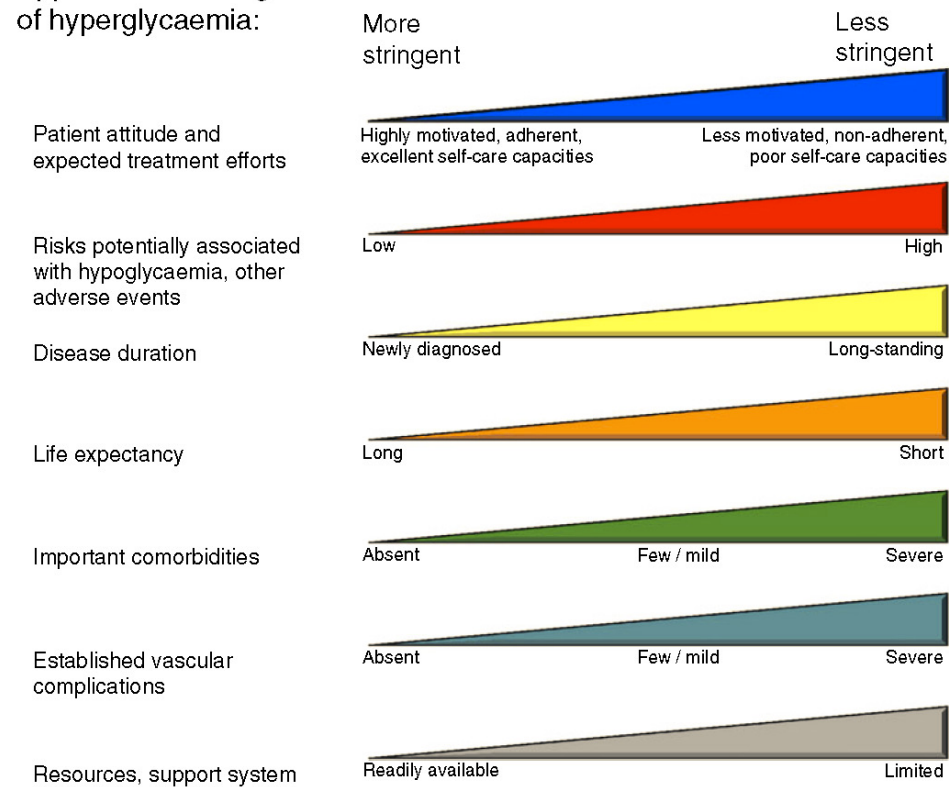


**Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)**

S. E. Inzucchi • R. M. Bergenstal • J. B. Buse • M. Diamant • E. Ferrannini • M. Nauck • A. L. Peters • A. Tsapas • R. Wender • D. R. Matthews

Received: 24 February 2012 / Accepted: 24 February 2012  
© Springer-Verlag 2012

Approach to management of hyperglycaemia:



*Diabetes Care, Diabetologia. 19 April 2012 [Epub ahead of print]*

*(Adapted with permission from: Ismail-Beigi F, et al. Ann Intern Med 2011;154:554)*

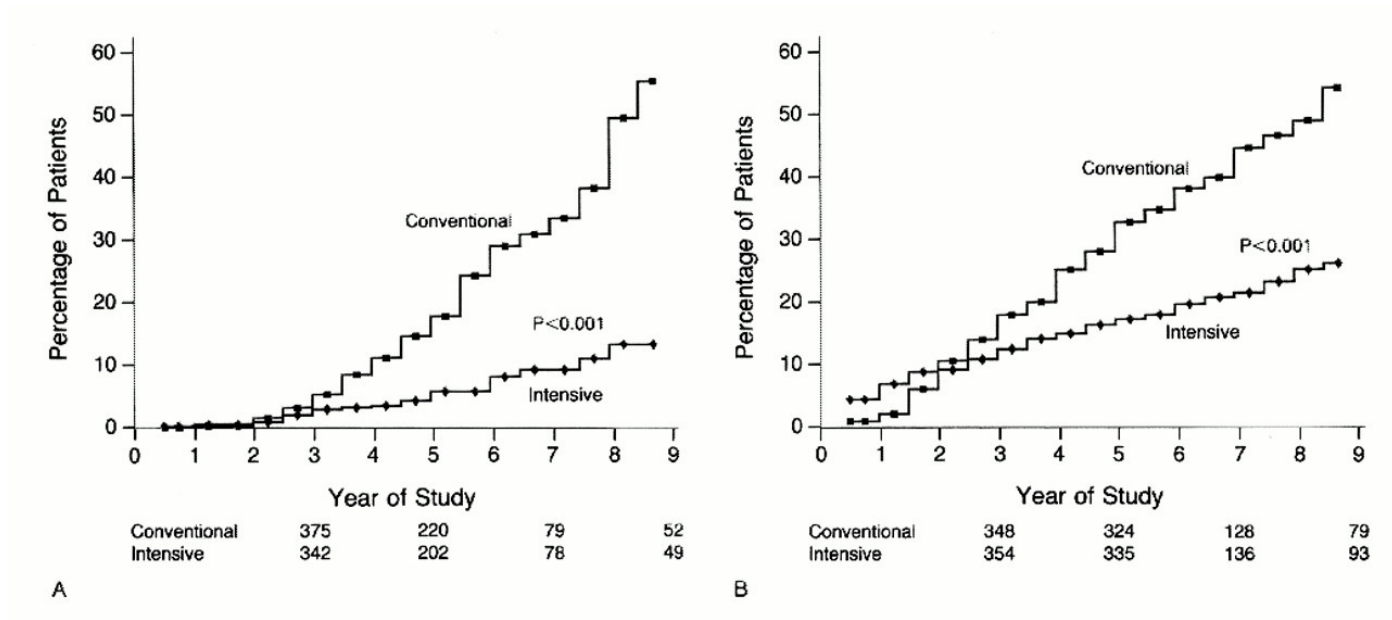


## Il razionale del target glicemico: gli anni '90 del secolo scorso

# Diabete tipo 1: compenso glicemico e complicanze microangiopatiche

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## Cumulative Incidence of a Sustained Change in Retinopathy in Patients with IDDM Receiving Intensive or Conventional Therapy

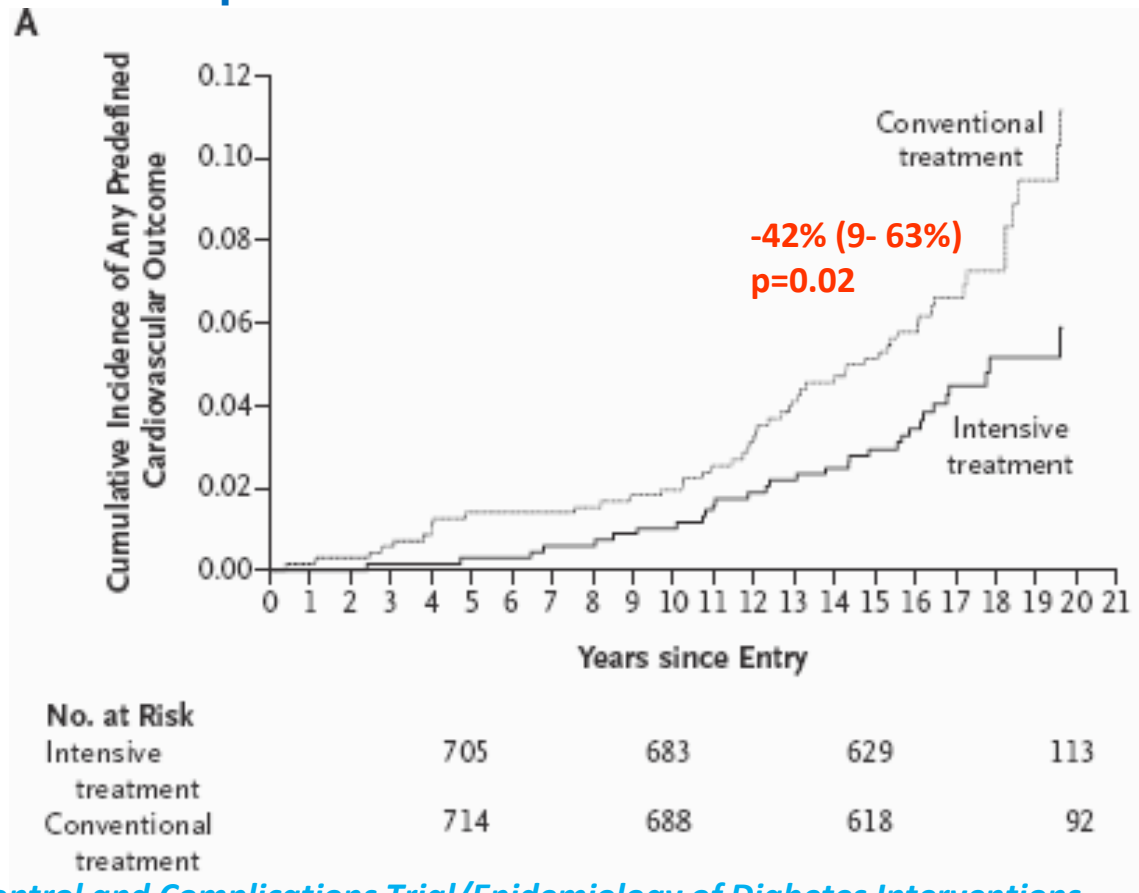


*The Diabetes Control and Complications Trial Research Group, N Engl J Med 1993;329:977-986*

# Diabete tipo 1: compenso glicemico e complicanze macroangiopatiche

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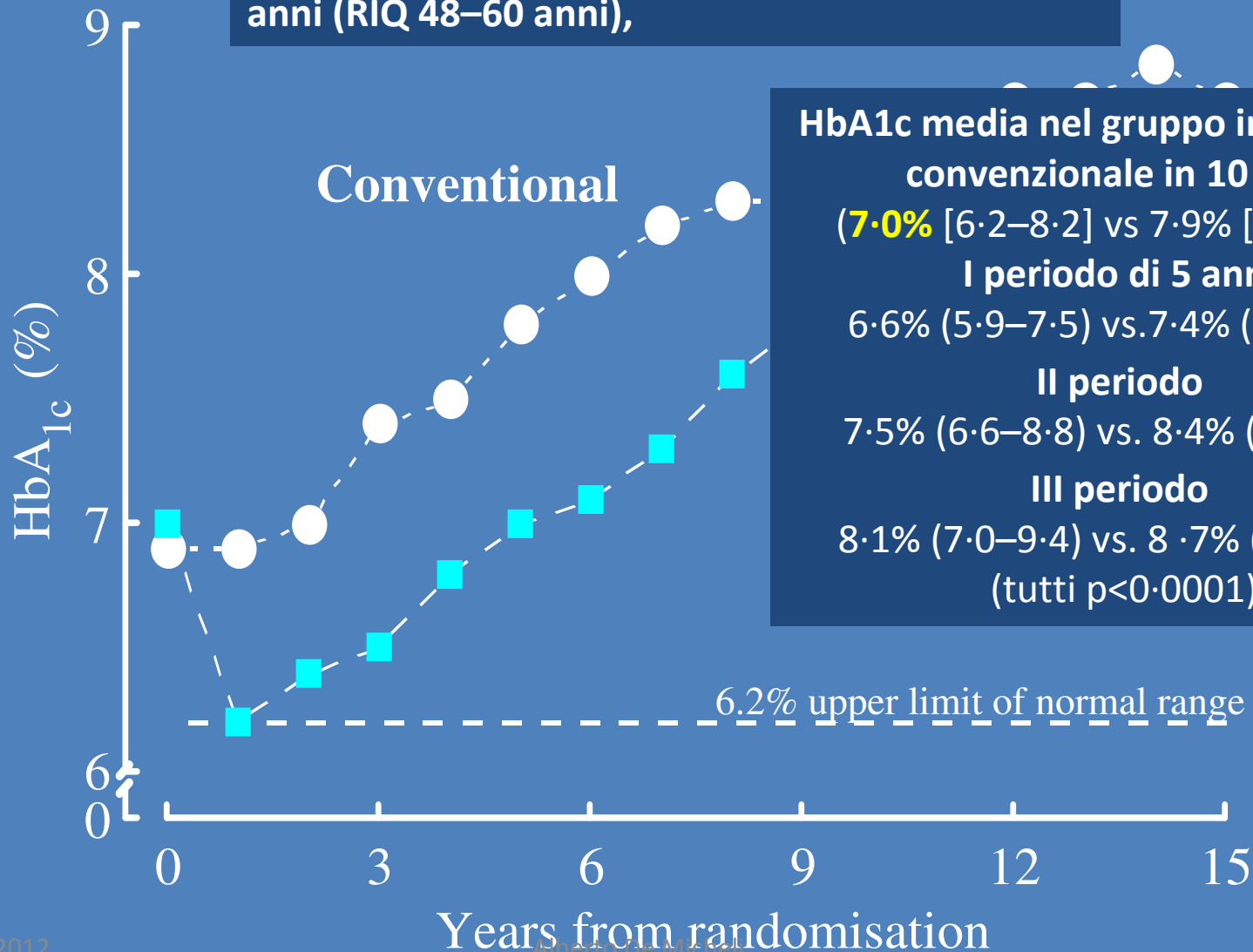
## Incidenza cumulativa di eventi cardiovascolari in pazienti con diabete tipo 1 in terapia insulinica convenzionale o intensiva



*The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study N Engl J Med 2005; 353: 2643- 53*

# UKPDS: Hb A1c nel corso di 10 anni

3867 diabetici t2 neo-diagnosticati, età media 54 anni (RIQ 48–60 anni),



**HbA<sub>1c</sub> media nel gruppo intensivo vs convenzionale in 10 anni**

**(7.0% [6.2–8.2] vs 7.9% [6.9–8.8],**

**I periodo di 5 anni**

**6.6% (5.9–7.5) vs. 7.4% (6.4–8.5)**

**II periodo**

**7.5% (6.6–8.8) vs. 8.4% (7.2–9.4)**

**III periodo**

**8.1% (7.0–9.4) vs. 8.7% (7.5–9.7)**

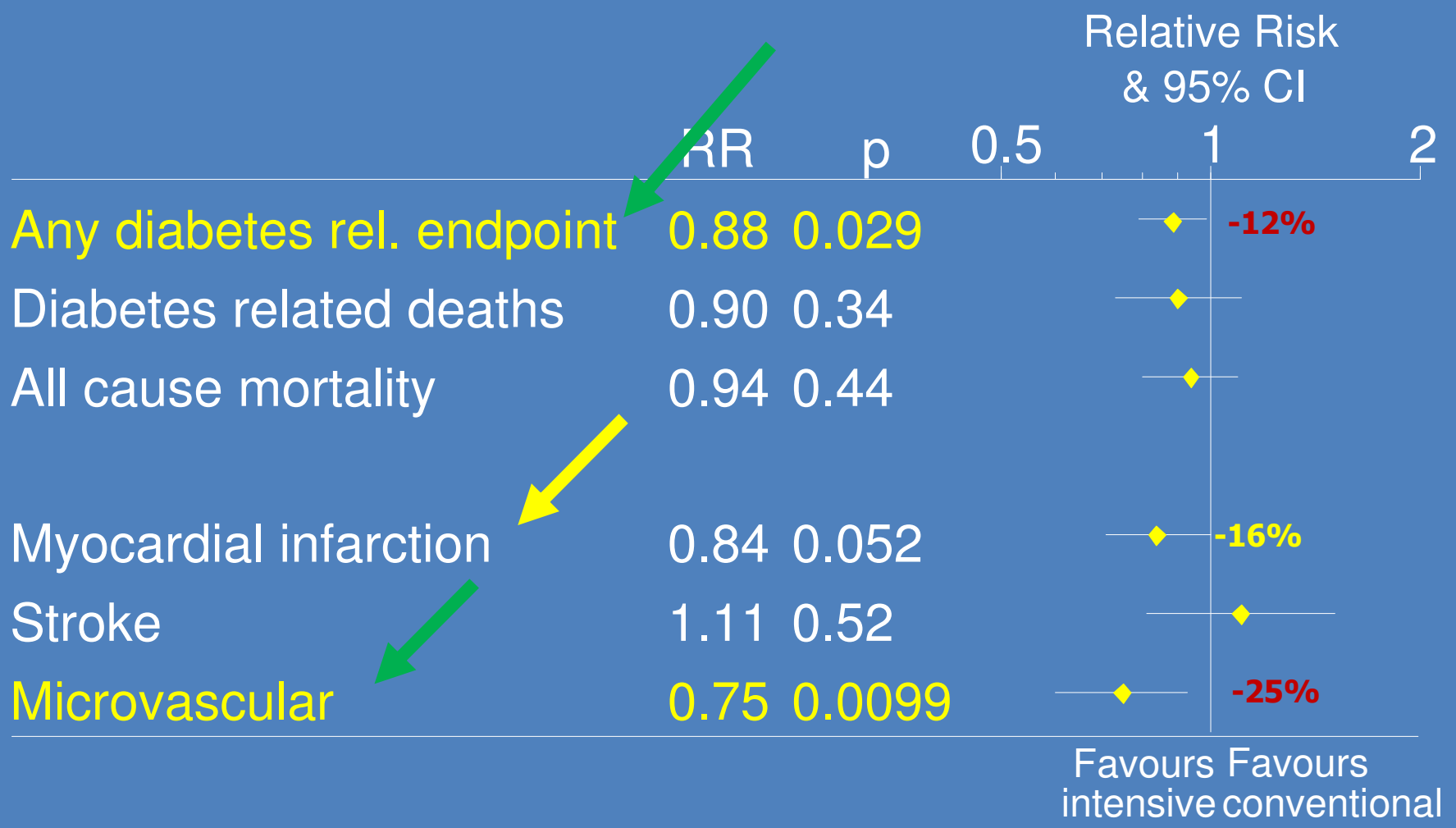
**(tutti p<0.0001)**





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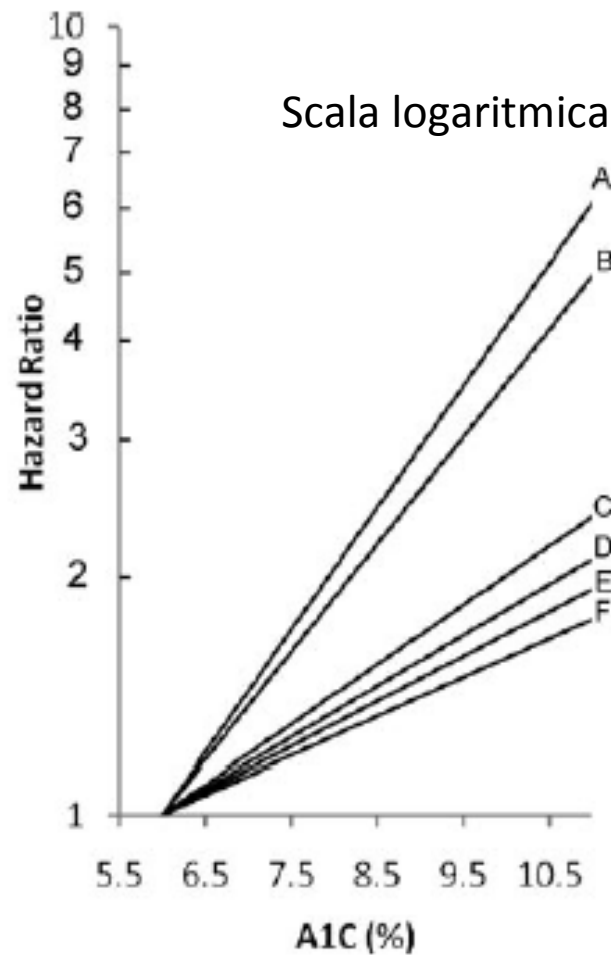
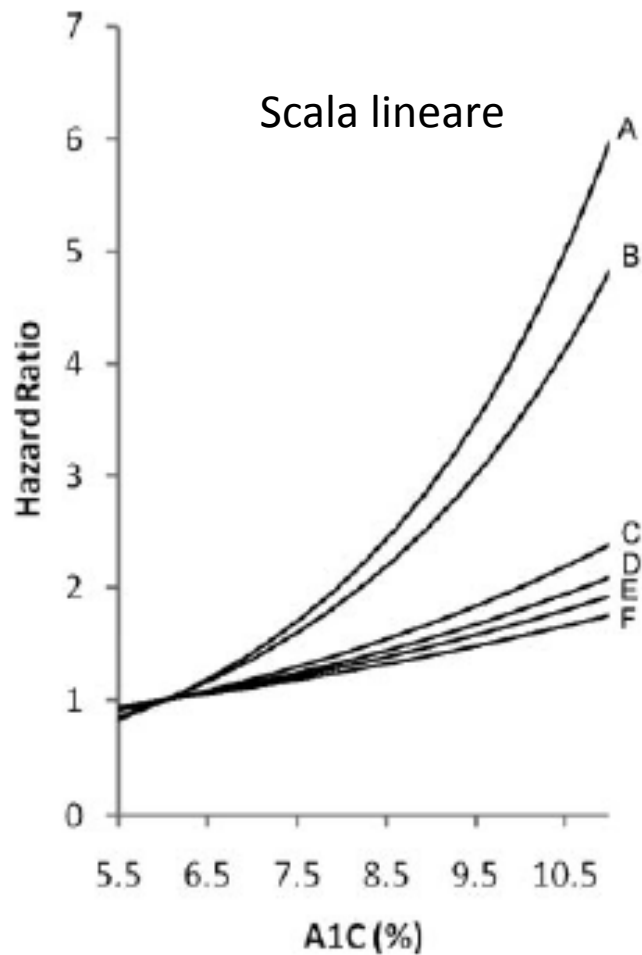
# UKPDS: Compenso glicemico e complicanze del diabete



UKPDS 33, Lancet 1998; 352: 837-53  
Maggio 2012

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# Correlazione fra Hb A1c e complicanze in soggetti diabetici T2 neo- diagnosticati



**Incremento per 1% Hb A1c**

- A Amput. morte per VP 43%**
- B. Retino- o nefropatia 37%**
- C. Cataratta 19%**
- D. Scoppio cardiaco 16%**
- E. Mortalità per IMA e tot 14%**
- F. Ictus 12%**

*UKPDS 35, Stratton IM, BMJ 2000; 321:405-12*

*Gerstein HC Circulation 2009, 119:773-775*

# Intervento all'esordio: UKPDS follow up 10 anni

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Sulfonilurea- Insulina

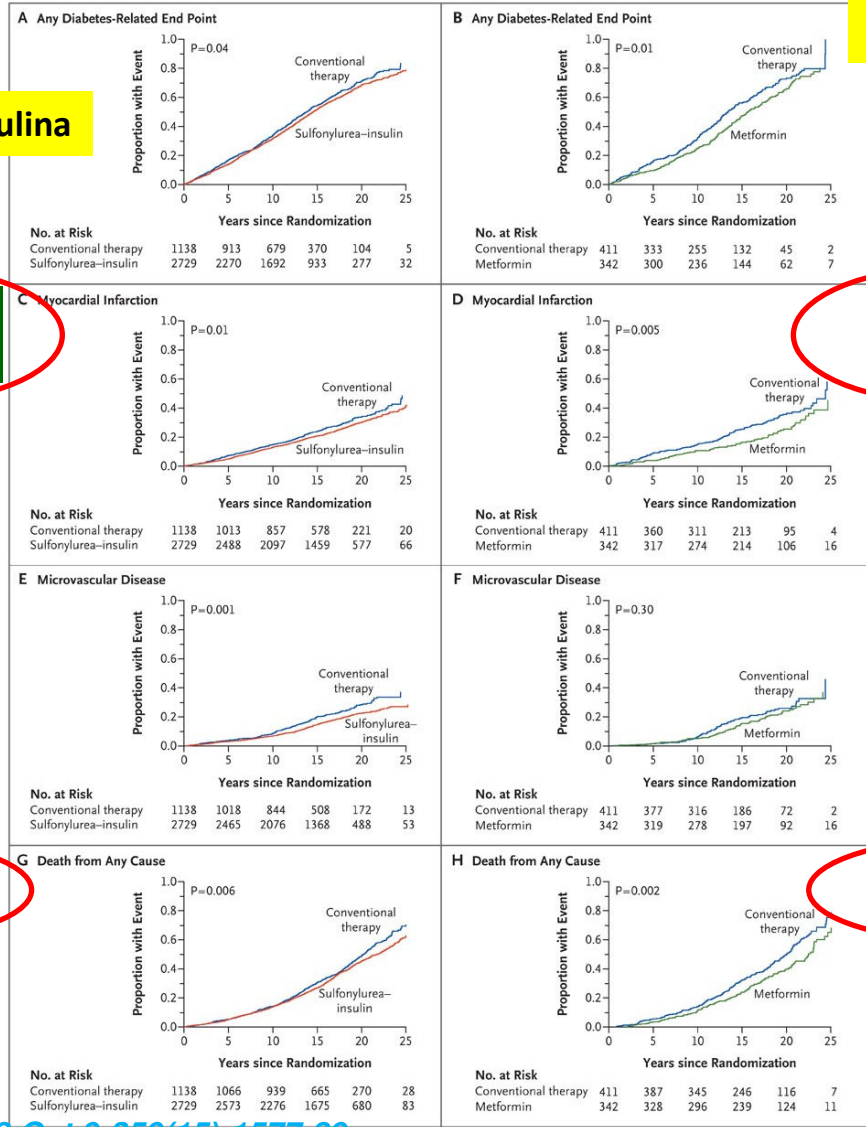
Metformina

IMA  
 $p < 0.01$

IMA  
 $p < 0.005$

Mortalità tot  
 $p < 0.01$

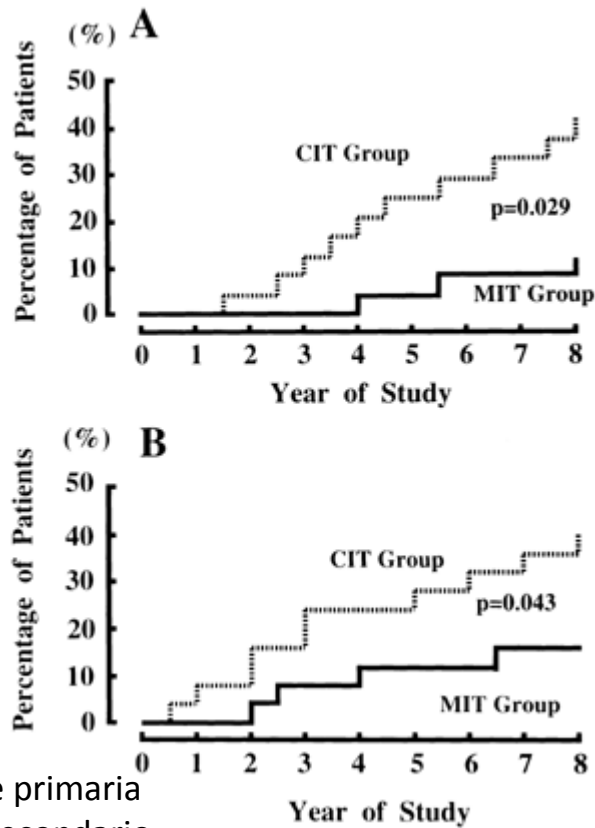
Mortalità tot  
 $p < 0.002$





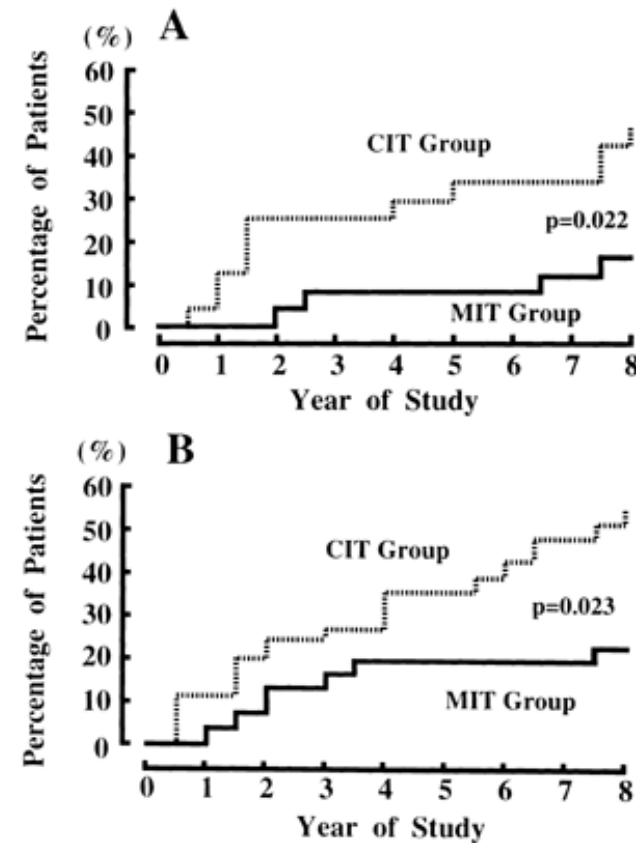
# Kumamoto study: complicanze microangiopatiche

## Nefropatia



A prevenzione primaria  
B intervento secondario

## Retinopatia



*Shichiri M Diabetes Care 2000; 23 (Suppl. 2): B21– B29*

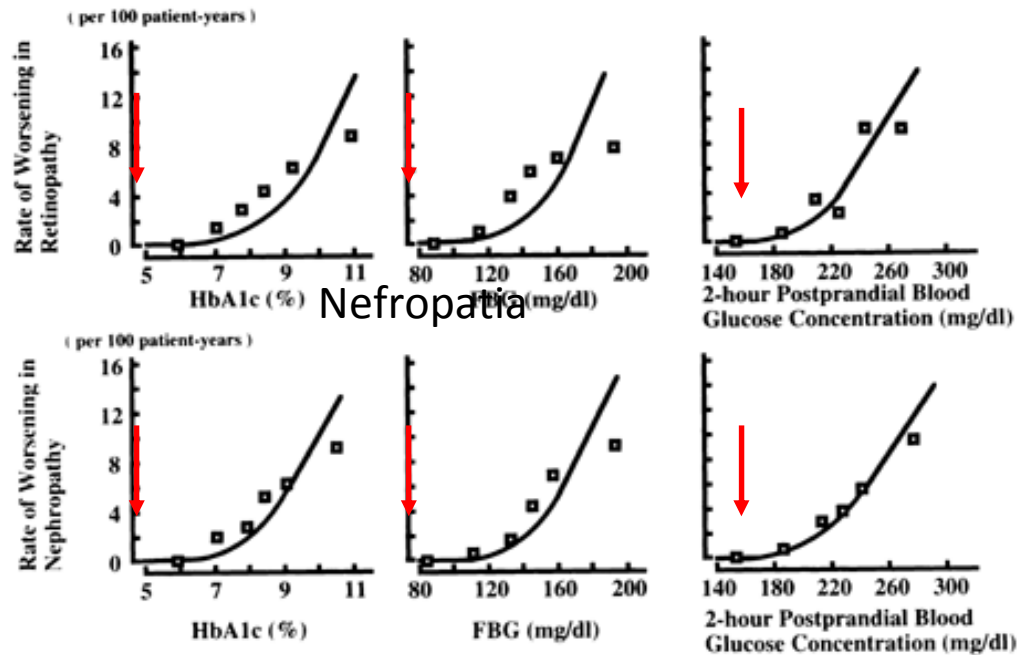
Alberto De Micheli





# Kumamoto study: Relazione fra compenso glicemico e complicanze

## Retinopatia



No worsening of retinopathy or nephropathy was observed in patients whose HbA1c, FBG, and 2-h postprandial blood glucose concentration were below

- 6.5%,
- 110 mg/dl
- 180 mg/dl, respectively.

*Shichiri M Diabetes Care 2000; 23 (Suppl. 2): B21– B29*



# Standards of Medical Care for Patients With Diabetes Mellitus

AMERICAN DIABETES ASSOCIATION

DIABETES CARE, VOLUME 18, SUPPLEMENT 1, JANUARY 1995

Table 1—Glycemic control for people with diabetes

Biochemical index	Nondiabetic	Goal	Action suggested
Preprandial glucose	<115	80–120	<80 >140
Bedtime glucose (mg/dl)	<120	100–140	<100 >160
Hemoglobin A <sub>1c</sub> (%)	<6	<7	>8

These values are for nonpregnant individuals. “Action suggested” depends on individual patient circumstances. Hemoglobin A<sub>1c</sub> is referenced to a nondiabetic range of 4.0–6.0% (mean 5.0%, standard deviation 0.5%).

## NIDDM

- Thus far, there are no randomized clinical trial results similar to those of the DCCT that prove the benefits of near normalization of blood glucose in NIDDM.
- However, in NIDDM considerable evidence exists for a relationship between microvascular disease and hyperglycemia similar to that proven for IDDM. Therefore, it is reasonable to employ the same glycohemoglobin and blood glucose goals detailed above for IDDM, pending the outcomes of clinical trials that are studying the benefits of achieving such goals in NIDDM. When setting treatment goals for NIDDM, the same individual patient characteristics should be considered as for IDDM

*Standards of Medical Care for Patients With Diabetes Mellitus Diabetes Care 18(S1):8-15; 1995*

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## Standards of Medical Care for Patients With Diabetes Mellitus

American Diabetes Association

Diabetes is a chronic illness that requires ongoing medical care and education to prevent acute complications and to reduce the risk of long-term complications. People with diabetes should receive their treatment and care from a physician-coordinated team. Such teams include, but are not limited to, physicians, nurses, dietitians, and mental health professionals with expertise and a special interest in diabetes.

The following standards define basic medical care for people with diabetes. These standards do not intend to preclude more extensive evaluation and management of the patient by other health care providers.

These standards of diabetes care will provide 1) Physicians and other health-care professionals who treat people with diabetes with a means to

- Set treatment goals
- Assess the quality of diabetes treatment provided
- Identify areas where more attention or self-management training is needed
- Define needs and necessary referral patterns to appropriate specialists

2) People with diabetes with a means to

- Assess the quality of medical care they receive

Originally approved October 1998. Revisions approved October 1999. For a related article on this subject see Diabetes Care 22:1518-1522, 1999.

Developing appropriate for their role in the medical treatment

Compare their treatment outcomes to standard goals

For more detailed information, refer to Medical Management of Insulin-Dependent Type 1 Diabetes, Individual Management of Non-Insulin-Dependent Type 2 Diabetes, and Therapy for Diabetes Mellitus and Related Disorders.

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2) People with diabetes with a means to

- Assess the quality of medical care they receive

Originally approved October 1998. Revisions approved October 1999. For a related article on this subject see Diabetes Care 22:1518-1522, 1999.

The danger of acute decompensation can rise in diabetes, particularly in hyperosmolar hyperglycemic nonketotic syndrome, with their accompanying morbidity and mortality, is markedly reduced.

The symptoms of polyuria, polydipsia, fatigue, weight loss, and polyphagia, blurred vision, and cognitive or behavior abnormalities.

The risk of development or progression of diabetes among people with impaired glucose tolerance is greatly decreased. It is possible that these complications may not be prevented by early institution of metabolic status.

Near normalization of blood glucose has not yet been demonstrated to reduce the risk for atherosclerotic vascular disease. However, in the Complications of Insulin-Dependent Diabetes Mellitus Study, the reduction in risk of these complications correlated continuously with the reduction in hemoglobin A<sub>1c</sub> produced by intensive treatment.

Adopting near-normal or normal blood glucose levels in patients with many types of diabetes requires comprehensive training in self-management and, for most individuals, intensive treatment programs. Such programs include the following components according to individual patient needs:

- Regular self-monitoring of blood glucose
- Medication assessment to avoid planning
- Physiologically based insulin regimens (i.e., individualized daily injections of short- and longer-acting insulins or continuous subcutaneous insulin infusion)
- IDDM and severe NIDDM patients
- Goal-oriented treatment regimens or self-management systems in some NIDDM patients
- Individualized assessment and treatment of hypoglycemia and other acute and chronic complications
- Comprehensive patient and provider education
- Periodic assessment of treatment goals

To be effective, treatment programs require ongoing support from the clinical care team.

Specific goals of treatment

IDDM

Setting individual patient glycemic targets should take into account the results of prospective randomized clinical trials, most notably the Diabetes Control and Complications Trial (DCCT). This trial conclusively demonstrated that in patients with IDDM the risk of development or progression of retinopathy, nephropathy, and neuropathy is reduced 50–75% by intensive treatment regimens when compared with conventional treatment regimens. These benefits were observed with an average hemoglobin A<sub>1c</sub> of 7.2% in intensively treated groups of patients compared with 9.0% in conventionally treated groups of patients. The reduction in risk of these complications correlated continuously with the reduction in hemoglobin A<sub>1c</sub> produced by intensive treatment.

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## IDDM

- DCCT an average hemoglobin A1c of 7.2%
- in intensively treated .The reduction in risk correlated continuously with the reduction in hemoglobin A1c .
- This relationship implies that complete normalization of glycemia levels may prevent complications.
- These targets should be further adjusted ....recurrent severe or unrecognized hypoglycemia, the patient's capacity to understand and carry out the treatment regimen, the patient's risk for severe hypoglycemia, and other patient factors that may increase risk or decrease benefit (e.g., very young or old age, end-stage renal disease, advanced cardiovascular or cerebral vascular disease, or other coexisting diseases that will materially shorten life expectancy).



# Standards of Medical Care for Patients With Diabetes Mellitus

AMERICAN DIABETES ASSOCIATION

DIABETES CARE, VOLUME 25, NUMBER 1, JANUARY 2002

Reviews/Commentaries/Position Statements

## Standards of Medical Care for Patients With Diabetes Mellitus

American Diabetes Association

**D**uring the chronic illness that is diabetes mellitus, medical care and lifestyle management interventions to prevent acute complications and to reduce the risk of long-term complications. Diabetes care is a complex endeavor that requires a team approach. A large body of evidence suggests that aggressive management can improve diabetes outcomes.

These standards of care are intended to provide clinicians, patients, researchers, payers, and other interested parties with the components of diabetes care, to assess goals, and to evaluate the quality of care. While individual preferences, comorbidities, and other patient factors may require modification of goals, these standards are intended to provide targets that are realistic for most patients with diabetes in practice. These standards are not intended to guide more extensive evaluation and management of the patient by other specialists as needed. For more detailed information, refer to *Diabetes Care* and *Diabetes Mellitus: Medical Management of Type 2 Diabetes*.

The recommendations included are diagnostic and therapeutic actions that are favored or believed to be strongly favored based on scientific evidence. A grading system (Table 1), developed by the Association, is included after each recommendation to indicate the level of evidence on which the recommendation is based. Hypoglycemia is not sufficient to meet the diagnostic criteria for diabetes in the absence of other required testing (fasting glucose [FG], 2-hour glucose tolerance test [2h-GTT], or random glucose [RG]). Depending on whether it is fasting or random, the test is designated as FG or 2h-GTT or RG. The classification of diabetes includes four clinical classes:

- Type 1 diabetes (T1D) is characterized by an absolute deficiency of insulin.
- Type 2 diabetes (T2D) results from a progressive insulin resistance and/or a relative deficiency of insulin secretion.
- Gestational diabetes mellitus (GDM) is diagnosed during pregnancy.
- Latent autoimmune diabetes in adults (LADA) and other forms of autoimmune diabetes are not included in this classification.

Copyright © 2002 American Diabetes Association. 0893-2753/02/2501-0001\$15.00/0. DOI: 10.2337/0125-0001

Diabetes Care, Volume 25, Number 1, January 2002

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Table 6 — Glycemic control for nonpregnant individuals with diabetes

	Normal	Goal	Additional action suggested*
<b>Plasma values†</b>			
Average preprandial glucose (mg/dl)	<110	90–130	<90/>150
Average bedtime glucose (mg/dl)	<120	110–150	<110/>180
<b>Whole blood values‡</b>			
Average preprandial glucose (mg/dl)	<100	80–120	<80/>140
Average bedtime glucose (mg/dl)	<110	100–140	<100/>160
A1C (%)	<6	<7	>8

- ❑ The values shown in this table are by necessity generalized to the entire population of individuals with diabetes.
- ❑ Patients with comorbid diseases, the very young and older adults, and others with unusual conditions or circumstances may warrant different treatment goals.

- ❑ However, epidemiological analysis of the UKPDS cohort showed a statistically significant effect of HbA1c lowering...
- ❑ There are no clinical trial data available for the effects of glycemic control in patients with advanced complications, the elderly (>65 years of age), or young children (<13 years of age).
- ❑ In summary, treatment regimens that reduced average A1C to <7% (1% above the upper limits of normal) were associated with fewer long-term, microvascular complications;
- ❑ However, intensive control has been found to increase risk of hypoglycemia and weight gain.
- ❑ Epidemiological analyses suggest that there is no threshold or lower limit of A1C above normal levels at which further lowering has no benefit

Standards of Medical Care for Patients With Diabetes Mellitus Diabetes Care 25:213- 229; 2002

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**Standards of Medical Care in Diabetes—2008**  
 AMERICAN DIABETES ASSOCIATION

**D**etailed information on the standards of medical care in diabetes is available in the full text of the Standards of Medical Care in Diabetes—2008, published by the American Diabetes Association. The full text is available at [www.diabetes.org/standards](http://www.diabetes.org/standards).

**1. Classification and Diagnosis**  
 1.1. Classification  
 1.2. Diagnosis

**2. Glycemic Targets**  
 2.1. A1C  
 2.2. Fasting Plasma Glucose  
 2.3. Postprandial Plasma Glucose

**3. Medical Nutrition Therapy**  
 3.1. General Principles  
 3.2. Carbohydrate  
 3.3. Protein  
 3.4. Fat  
 3.5. Fiber

**4. Physical Activity and Exercise**  
 4.1. General Principles  
 4.2. Aerobic Activity  
 4.3. Resistance Training

**5. Diabetes Self-Monitoring of Blood Glucose**  
 5.1. General Principles  
 5.2. Frequency of Testing  
 5.3. Interpretation of Results

**6. Diabetes Technology**  
 6.1. General Principles  
 6.2. Insulin Pumps  
 6.3. Continuous Glucose Monitoring

**7. Psychosocial Aspects of Diabetes**  
 7.1. General Principles  
 7.2. Depression  
 7.3. Anxiety  
 7.4. Diabetes Distress

**8. Complications of Diabetes**  
 8.1. Microvascular Complications  
 8.2. Macrovascular Complications  
 8.3. Diabetic Eye Disease  
 8.4. Diabetic Kidney Disease  
 8.5. Diabetic Neuropathy

**9. Pregnancy in Women With Diabetes**  
 9.1. General Principles  
 9.2. Preconception Care  
 9.3. Management of Diabetes in Pregnancy  
 9.4. Postpartum Management

**10. Diabetes in Children, Adolescents, and Young Adults**  
 10.1. General Principles  
 10.2. Classification and Diagnosis  
 10.3. Management of Diabetes

**11. Diabetes in Older Adults**  
 11.1. General Principles  
 11.2. Classification and Diagnosis  
 11.3. Management of Diabetes

**12. Diabetes in Special Populations**  
 12.1. General Principles  
 12.2. Diabetes in the Elderly  
 12.3. Diabetes in the Hospitalized Patient  
 12.4. Diabetes in the Long-Term Care Facility

**13. Diabetes in the Workplace**  
 13.1. General Principles  
 13.2. Diabetes in the Workplace

**14. Diabetes in the Community**  
 14.1. General Principles  
 14.2. Diabetes in the Community

**15. Diabetes in the Home**  
 15.1. General Principles  
 15.2. Diabetes in the Home

**16. Diabetes in the Hospital**  
 16.1. General Principles  
 16.2. Diabetes in the Hospital

**17. Diabetes in the Long-Term Care Facility**  
 17.1. General Principles  
 17.2. Diabetes in the Long-Term Care Facility

**18. Diabetes in the End-of-Life Care**  
 18.1. General Principles  
 18.2. Diabetes in the End-of-Life Care

**19. Diabetes in the Palliative Care**  
 19.1. General Principles  
 19.2. Diabetes in the Palliative Care

**20. Diabetes in the Hospice Care**  
 20.1. General Principles  
 20.2. Diabetes in the Hospice Care

**21. Diabetes in the Nursing Home**  
 21.1. General Principles  
 21.2. Diabetes in the Nursing Home

**22. Diabetes in the Assisted Living Facility**  
 22.1. General Principles  
 22.2. Diabetes in the Assisted Living Facility

**23. Diabetes in the Residential Care Facility**  
 23.1. General Principles  
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**24. Diabetes in the Residential Care Facility**  
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**62. Diabetes in the Residential Care Facility**  
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# Standards of Medical Care in Diabetes—2008

AMERICAN DIABETES ASSOCIATION

DIABETES CARE, VOLUME 31, SUPPLEMENT 1, JANUARY 2008

Table 8—Summary of glycemic recommendations for adults with diabetes

A1C	<7.0%*
Preprandial capillary plasma glucose	70–130 mg/dl (3.9–7.2 mmol/l)
Peak postprandial capillary plasma glucose†	<180 mg/dl (<10.0 mmol/l)
Key concepts in setting glycemic goals:	
<ul style="list-style-type: none"> <li>• A1C is the primary target for glycemic control</li> <li>• Goals should be individualized based on:               <ul style="list-style-type: none"> <li>• duration of diabetes</li> <li>• pregnancy status</li> <li>• age</li> <li>• comorbid conditions</li> <li>• hypoglycemia unawareness</li> <li>• individual patient considerations</li> </ul> </li> <li>• More stringent glycemic goals (i.e., a normal A1C, &lt;6%) may further reduce complications at the cost of increased risk of hypoglycemia</li> <li>• Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals</li> </ul>	

- ❑ Lowering A1C to an average of < 7% has clearly been shown to reduce microvascular and neuropathic complications of diabetes and, possibly, atherosclerotic disease. Therefore, the A1C goal for nonpregnant adults in general is <7%. (A)
- ❑ Epidemiologic studies have suggested an incremental (albeit, in absolute terms, a small) benefit to lowering A1C from 7% into the normal range. Therefore, the A1C goal for selected individual patients is as close to normal (<6%) as possible without significant hypoglycemia. (B)
- ❑ Less stringent A1C goals may be appropriate for patients with a history of severe hypoglycemia, patients with limited life expectancies, children, individuals with comorbid conditions, and those with longstanding diabetes and minimal or stable microvascular complications. (E)





## STANDARD ITALIANI PER LA CURA DEL DIABETE MELLITO

### Obiettivi glicemici in diabetici adulti di tipo 1 e 2

HbA<sub>1c</sub> <7,0%\* (<6,5% in singoli pazienti)

Glicemia a digiuno e pre-prandiale 90-130 mg/dl°

Glicemia post-prandiale† <180 mg/dl°

\* Facendo riferimento ai valori di 4,0-6,0% della popolazione non diabetica, con il metodo utilizzato dal DCCT.

† La misurazione della glicemia post-prandiale deve essere effettuata 2 ore dopo l'inizio del pasto

° Valori a digiuno <110mg/dl e valori post-prandiali <145 mg/dl sono perseguibili nel diabete di tipo 2 (IDF 2005)

***Standard italiani per la cura del diabete mellito, Diabete Italia, AMD, SID, 2007***



# I dubbi e le prospettive del XXI secolo



**The NEW ENGLAND  
JOURNAL of MEDICINE**

ESTABLISHED IN 1812      JUNE 12, 2008      VOL. 358 NO. 24

Effects of Intensive Glucose Lowering in Type 2 Diabetes  
The Action to Control Cardiovascular Risk in Diabetes Study Group<sup>†</sup>

**BACKGROUND**  
Epidemiologic studies have shown a relationship between glycated hemoglobin levels and cardiovascular events in patients with type 2 diabetes. We investigated whether intensive therapy to target normal glycated hemoglobin levels would reduce cardiovascular events in patients with type 2 diabetes who had either established cardiovascular disease or additional cardiovascular risk factors.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes  
The ADVANCE Collaborative Group<sup>†</sup>

**BACKGROUND**  
In patients with type 2 diabetes, the effects of intensive glucose control on vascular outcomes remain uncertain.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes

**BACKGROUND**  
The effects of intensive glucose control on cardiovascular events in patients with longstanding type 2 diabetes mellitus remain uncertain.

*The Action to Control Cardiovascular Risk in Diabetes Study Group. N Engl J Med 2008;358:2545-59; Duckworth W. N Engl J Med 2009; 360: 129- 39; The ADVANCE Collaborative Group N Engl J Med 2008;358:2560-72*



## ACCORD

### Obiettivo glicemico

**Intensivo:** Hb A1c < 6.0%

**Controllo:** Hb A1c 7.0- 7.9%

### Strategia terapeutica

Qualunque ADO o insulina aggiunta al corretto stile di vita (*in USA, Gliclazide RM non è in commercio*)

Nel gruppo intensivo sono stati utilizzati più farmaci ed a dosaggio superiore

*The Action to Control Cardiovascular Risk in Diabetes Study Group. N Engl J Med 2008;358:2545-59*

## VADT

### Obiettivo glicemico

**Intensivo:** Hb A1c <6.0% (*azione se >6.5%*)

**Controllo:** programmata differenza 1.5%

### Strategia terapeutica

2 gruppi (randomizzati a blocchi per eventi vascolari precedenti ed uso di insulina) trattati con dosaggi diversi di rosigitazione, glimepiride, metformina e insulina

Ai pazienti non è stato proibito l'uso di alcun farmaco. A tutti i pazienti sono state prescritte aspirina ed una statina.

*Duckworth W. N Engl J Med 2009; 360: 129- 39*

## ADVANCE

### Obiettivo glicemico

**Intensivo:** Hb A1c ≤ 6.5%

**Controllo:** secondo LG locali

### Strategia terapeutica

#### Terapia intensiva

Trattamento con Gliclazide MR\* (1-4 cpr. a colazione) per ottenere un target di HbA1c<6.5%. Utilizzo, se necessario, anche altri ADO, tranne sulfoniluree, ed insulina

#### Terapia standard

Terapia usuale basata sulle linee guida. I pazienti potevano essere trattati anche con sulfonilurea, ma diversa da gliclazide

*The ADVANCE Collaborative Group. N Engl J Med 2008;358:2560-72*



# Risultati principali degli studi ACCORD, ADVANCE, VADT

	ACCORD	VADT	ADVANCE
HR per endpoint primario	0.90 (0.78- 1.04)	0.88 (0.74- 1.05)	<b>0.9 (0.82- 0.98)</b> Macro 0.94 (0.84- 1.06) Micro <b>0.86 (0.77- 0.97)</b>
<b>HR per mortalità totale</b>	<b>1.22 (1.01- 1.46)</b>	1.07 (0.81- 1.42)	0.93 (0.83- 1.06)
<b>HR per mortalità CV</b>	<b>1.35 (1.04- 1.76)</b>	1.32 (0.81- 2.14)	0.88 (0.74- 1.04)
Hb A <sub>1c</sub> mediana raggiunta	Intensivo 6.4% Standard 7.5%	Intensivo 6.9% Standard 8.5%	Intensivo 6.3% Standard 7.0%
<b>Variazione ponderale</b>	<b>Intensivo +3.5 kg</b> <b>Standard +0.4 kg</b>	<b>Intensivo +7.8 Kg</b> <b>Standard +3.4 kg</b>	<b>Intensivo - 0.1 kg</b> <b>Standard -1.0 kg</b>
<b>Ipoglicemie severe</b>	<b>Intensivo 16.2%</b> <b>Standard 5.1%</b>	<b>Intensivo 21.2%</b> <b>Standard 9.9%</b>	<b>Intensivo 2.7%</b> <b>Standard 1.5%</b>

# Caratteristiche dei pazienti inclusi nei 3 studi

	ACCORD	VADT	ADVANCE
Pazienti inclusi (N)	10.251	1.791	11.400
Età media	62.1	60,4	66
BMI	32.3	31,3	28
HbA <sub>1c</sub> (mediana)	8.3	9,4	7.2
PAS	135.9	132	145
PAD	74.8	76	81
Durata del diabete	10	11,5	8
Terapia insulinica	35%	52%	1.5%
Pregressa pat. CV	35%	40%	32%

### UKPDS

Età 53.3 ± 8-6  
 BMI 27.5 ± 5.2  
 PAS 135 ± 20  
 PAD 82 ± 10  
 Hb A1c 7.08 ±  
 1.51

### UKPDS :Criteri di esclusione

- Creatininemia > 2 mg/dl
- IMA entro 1 anno
- Angina
- Scompenso di circolo
- >1 evento cv
- Ipertensione maligna
- Retinopatia da trattare con laser



## EDITORIALS



### Intensive Glycemic Control in the ACCORD and ADVANCE Trials

Robert G. Dluhy, M.D., and Graham T. McMahon, M.D., M.M.Sc.

- ❑ Neither the ADVANCE trial nor the ACCORD trial undermines the importance of meeting the current guidelines for care, and they **should not be interpreted as diminishing the importance of glycemic control.**
- ❑ The results also underscore the **difficulty of showing additional improvements in outcome**, since care is progressively optimized.
- ❑ Clinicians caring for patients with diabetes should continue to **focus on smoking cessation, dietary and exercise counseling, blood-pressure control, and providing aspirin and a statin** to a greater extent than achieved even in the ADVANCE and ACCORD studies.
- ❑ For now, **rather than changing our current glycemic target**, we may best serve our patients with type 2 diabetes by **implementing programs to help more of them reach the currently recommended goals.**

## EDITORIALS



# Glycemic Targets and Cardiovascular Disease

William T. Cefalu, M.D.

**Are the results of these studies broadly applicable to the treatment of the majority of patients with type 2 diabetes?**

- Unfortunately, these studies did not address strategies for lowering of glycated hemoglobin levels in **low-risk patients** who did not have cardiovascular disease or additional cardiovascular risk factors.
- In the ACCORD trial, patients in the intensive-therapy group who did **not have a history of a cardiovascular event or whose baseline glycated hemoglobin level was below 8%** had significantly fewer fatal and nonfatal cardiovascular events than did patients at higher risk. These findings suggest that intensive therapy was **beneficial at least in this subgroup**.
- **Whether achieving glycemic targets below 7% will be beneficial to the vast majority of patients with type 2 diabetes and a low risk of cardiovascular disease remains another unanswered question.**





# JAMA<sup>®</sup>

Online article and related content  
current as of November 5, 2008.

## Glucose Lowering to Control Macrovascular Disease in Type 2 Diabetes: Treating the Wrong Surrogate End Point?

Mark O. Goodarzi; Bruce M. Psaty

*JAMA*. 2008;300(17):2051-2053 (doi:10.1001/jama.2008.510)

- ❑ Elevated glucose levels in patients with type 2 diabetes, like the **high white blood cell counts in patients with bacterial pneumonia**, are a consequence of insulin resistance together with inadequate compensatory hyperinsulinemia
- ❑ Because several recent trials evaluating the strategy of lowering glucose levels have shown little or no benefit in terms of cardiovascular disease prevention in patients with type 2 diabetes, **it may be appropriate to focus also on the aggressive control of insulin levels or insulin resistance rather than only on the aggressive control of glucose levels.**
- ❑ Future trials of cardiovascular disease prevention in type 2 diabetes **should test specific insulin-lowering agents or strategies** rather than allowing multiple agents to be used with the goal of simply lowering HbA1c levels.
- ❑ For the prevention of cardiovascular disease in patients with type 2 diabetes, **intensive treatment of glucose levels may resemble aggressive efforts to reduce white blood cell counts in patients with bacterial pneumonia.**

***Goodarzi MO, Psaty BM JAMA 2008; 300: 2051- 53***

# The ACCORD Trial and Control of Blood Glucose Level in Type 2 Diabetes Mellitus

## *Time to Challenge Conventional Wisdom*

### Four lessons

- ❑ **Observational data** should not be used to justify using pharmaceutical agents.
- ❑ **Surrogate markers** should not serve as the basis for making assumptions.
- ❑ **Reading the medical literature** to assess evidence is critical to good patient care...critically read published trials **themselves** and not follow either summaries and interpretations by others or drug companies.
- ❑ Type 1 and type 2 DM are 2 **distinct diseases** with similar end points.
- ❑ Controlling high **BP and high blood cholesterol** levels significantly reduces .... Clinicians should therefore focus more on controlling these other risk factors
- ❑ **Weight control and regular physical activity** are safe, effective ways to prevent and control type 2 DM
- ❑ Physicians should use **drugs** to control blood glucose level only if demonstrated through **RCTs to be both safe and efficacious in reducing important clinical outcomes** (eg, metformin) or if needed for symptomatic relief.
- ❑ I would not recommend trying to achieve HBA1c levels **lower than 7% unless it can be done through nonpharmacologic means and/or metformin therapy.**
- ❑ Prudence would dictate **not using multiple oral agents at this time.**

*Havas S. Arch Intern Med. 2009 ;169: 150- 4*

## Glycemic Control in Type 2 Diabetes: Time for an Evidence-Based About-Face?

Victor M. Montori, MD, MSc, and Mercè Fernández-Balsells, MD

- ❑ Glycemic targets can be adjusted up or down according to the burden of treatment; side effects; and the patient's context, values, and preferences.
- ❑ Given the possibility that tighter control may be beneficial, some patients who are less concerned about downsides, and are ready to do whatever may possibly help, may choose tighter control.
- ❑ The need to set individual glycemic targets suggests that HbA<sub>1c</sub> targets for clinical use cannot be the same when used to measure quality of care. Policymakers who want to use HbA<sub>1c</sub> as a performance measure should use an upper limit, such as an HbA<sub>1c</sub> level greater than 9%, to indicate possibly inadequate care, rather than one that would invite clinicians to ignore patient burden, context, and goals (for example, HbA<sub>1c</sub> level 7%).



## Megatrials in type 2 diabetes. From excitement to frustration?

S. Del Prato

### Storia dell'UKPDS

### Storia del VADT

#### G Death from Any Cause

1.0  
0.8  
P=0.006

Before entering VADT intensive treatment arm

After entering VADT intensive treatment arm

Conventional

9.5

Generation of a

Drives risk of

- A large number of diabetic patients still have poor glycaemic control. Their HbA1c must be **lowered** but we should be **very careful** in **deciding how low the target should be and how to reach it**.
- Ideally, diabetes prevention should be desirable, but while we wait for effective and feasible preventative procedures, efforts should be made to **treat-to-target all newly diagnosed diabetic patients**.
- Finally, we should all remember and emphasise to the entire medical community that **no form of mild diabetes exists, and no excuse exists to postpone appropriate and effective treatment**.

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# ADA position statement (2009, january) 1

- ❑ **Microvascular disease:** Lowering A1C to below or around 7% has been shown to reduce microvascular and neuropathic complications of type 1 and type 2 diabetes. Therefore, the A1C goal for non pregnant adults in general is 7%.

**ADA, A-level recommendation; ACC/ AHA, class I recommendation (level of evidence A).**

- ❑ **Macrovascular disease:** In type 1 and type 2 diabetes, randomized controlled trials of intensive versus standard glycemic control have not shown a significant reduction in CVD outcomes during the randomized portion of the trials. However, long-term follow-up of the DCCT and UKPDS cohorts suggests that treatment to A1C targets below or around 7% in the years soon after the diagnosis of diabetes is associated with long-term reduction in risk of macrovascular disease. Until more evidence becomes available, the general goal of 7% appears reasonable.

**ADA, B-level recommendation; ACC/AHA, class IIb recommendation (level of evidence A).**

*Skyler JS, Diabetes Care 2009; 32: 187- 192*



## ADA position statement (2009, january) 2

- **For selected individual patients**, providers might reasonably suggest **even lower A1C goals than the general goal of 7%** if this can be achieved without significant hypoglycemia or other adverse effects of treatment. **Such patients might include those with short duration of diabetes, long life expectancy, and no significant cardiovascular disease.**

**ADA, B-level recommendation; ACC/ AHA, class IIa recommendation (level of evidence C).**

- **Less stringent A1C** goals than the general goal of 7% may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, or extensive comorbid conditions or those with long-standing diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose lowering agents including insulin.

**ADA, C-level recommendation; ACC/ AHA, class IIa recommendation (level of evidence C).**

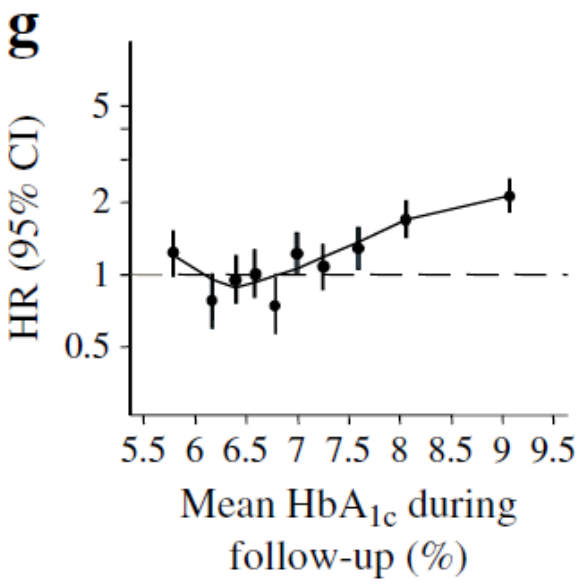
*Skyler JS, Diabetes Care 2009; 32: 187- 192*



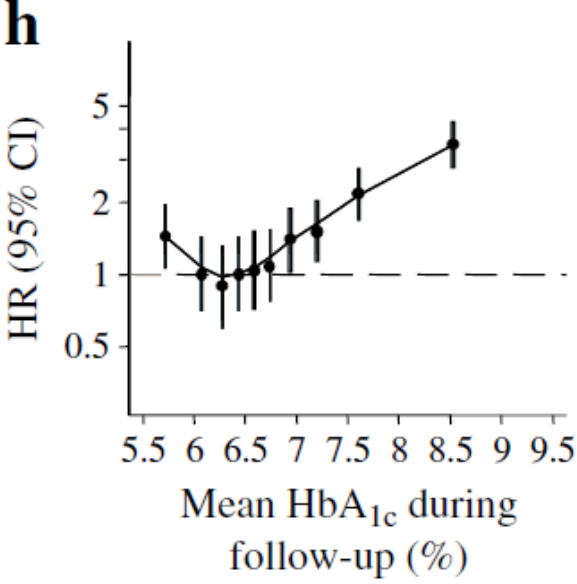
# I target e gli algoritmi

Analisi epidemiologica dello studio ADVANCE:  
evidenza di soglie glicemiche di rischio

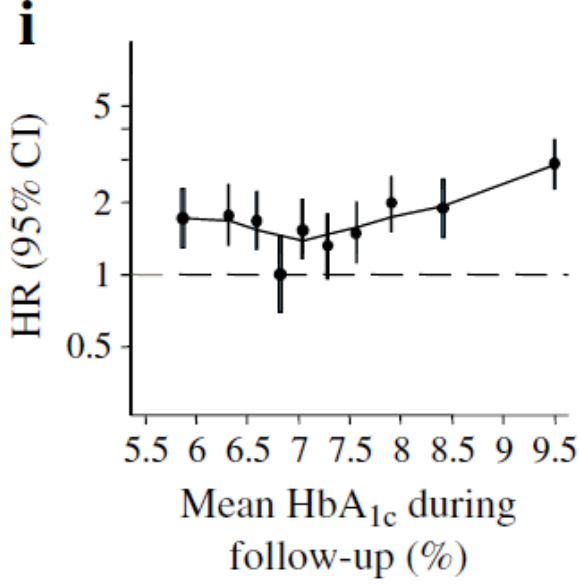
**Morte** per ogni causa



**Tutti**



**Intensiva**

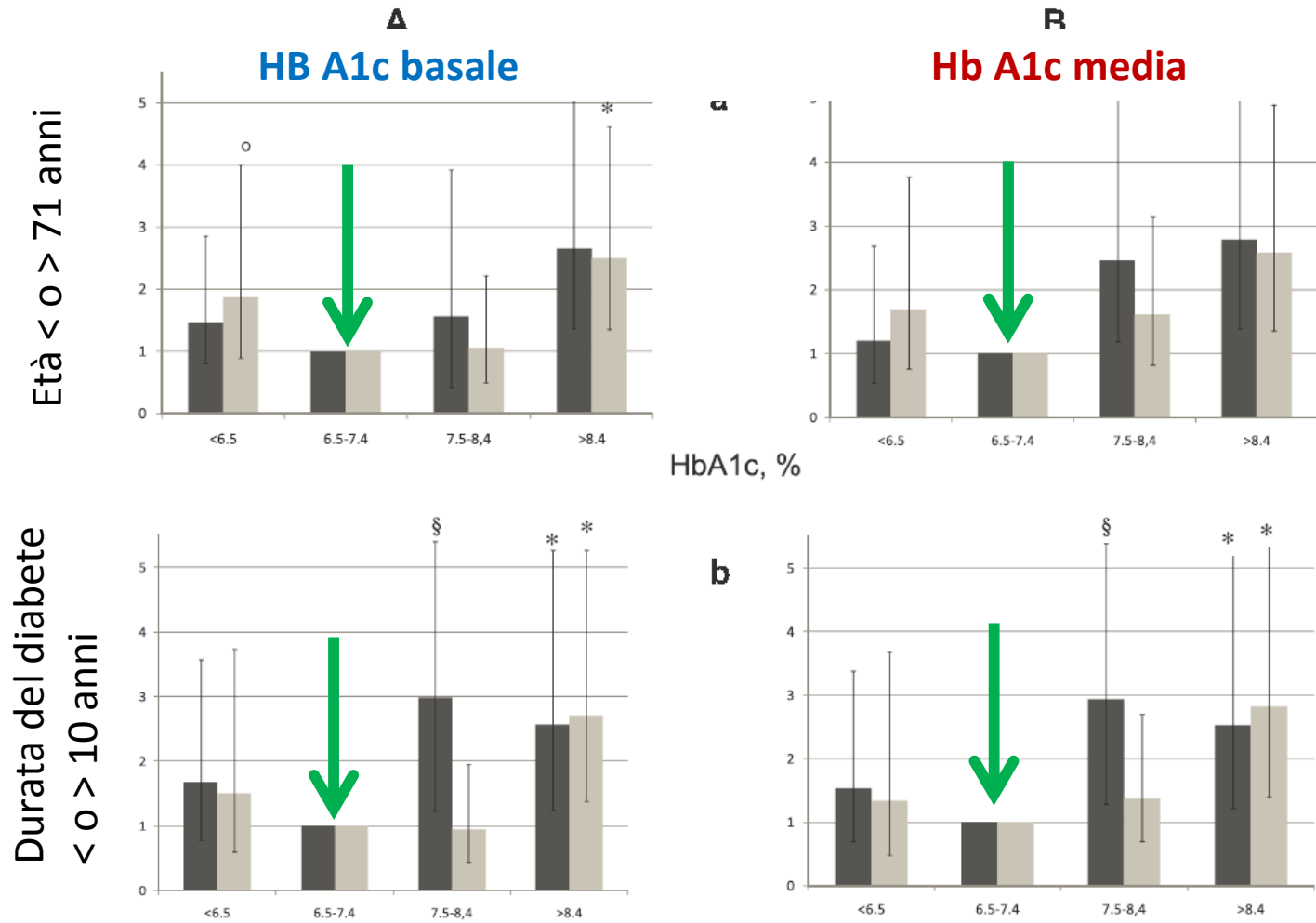


**Standard**

*Zoungas S Diabetologia 2012, DOI 10.1007/s00125-011-2404-1*

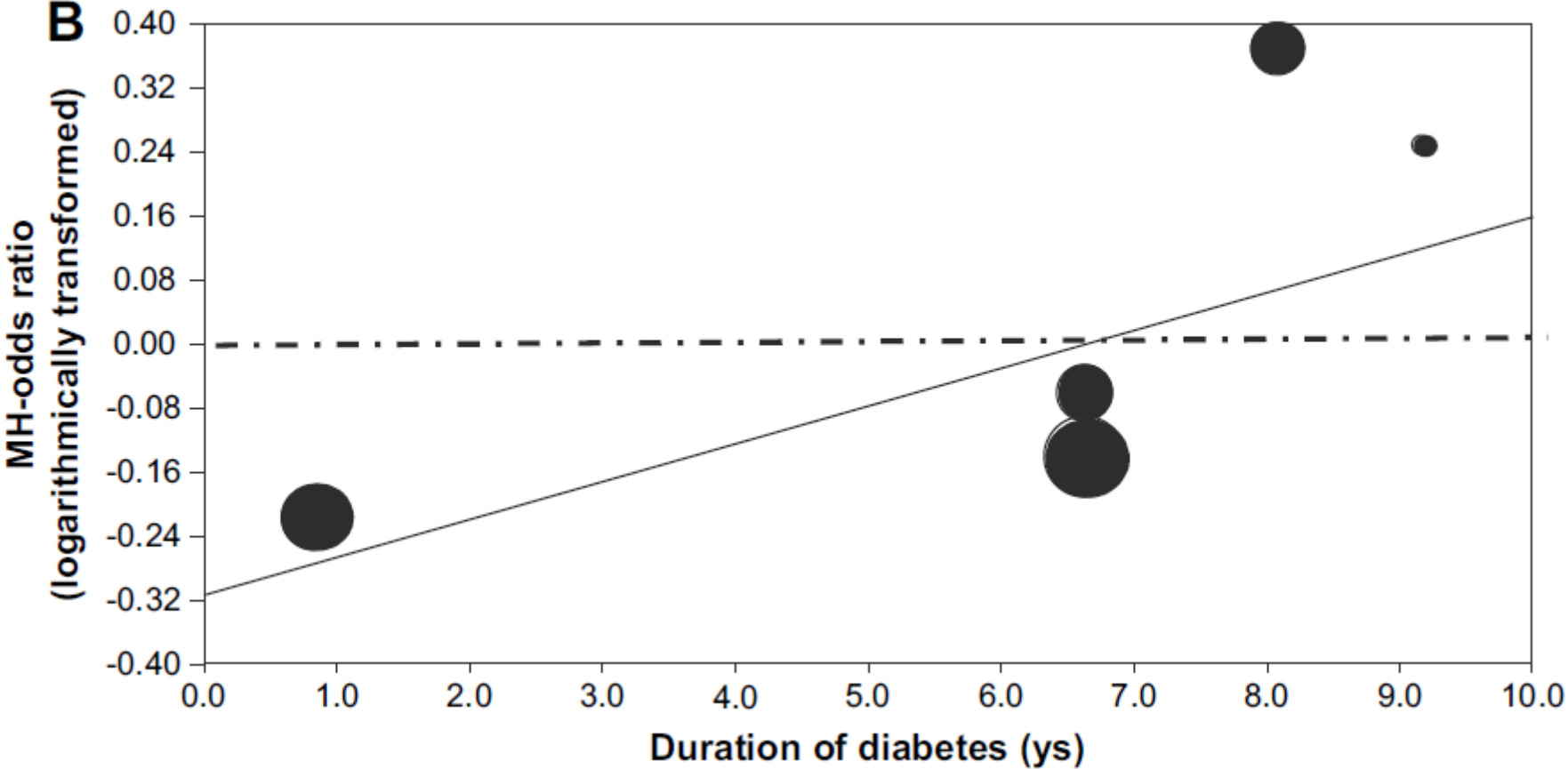


# Mortalità per ogni causa e Hb A1c



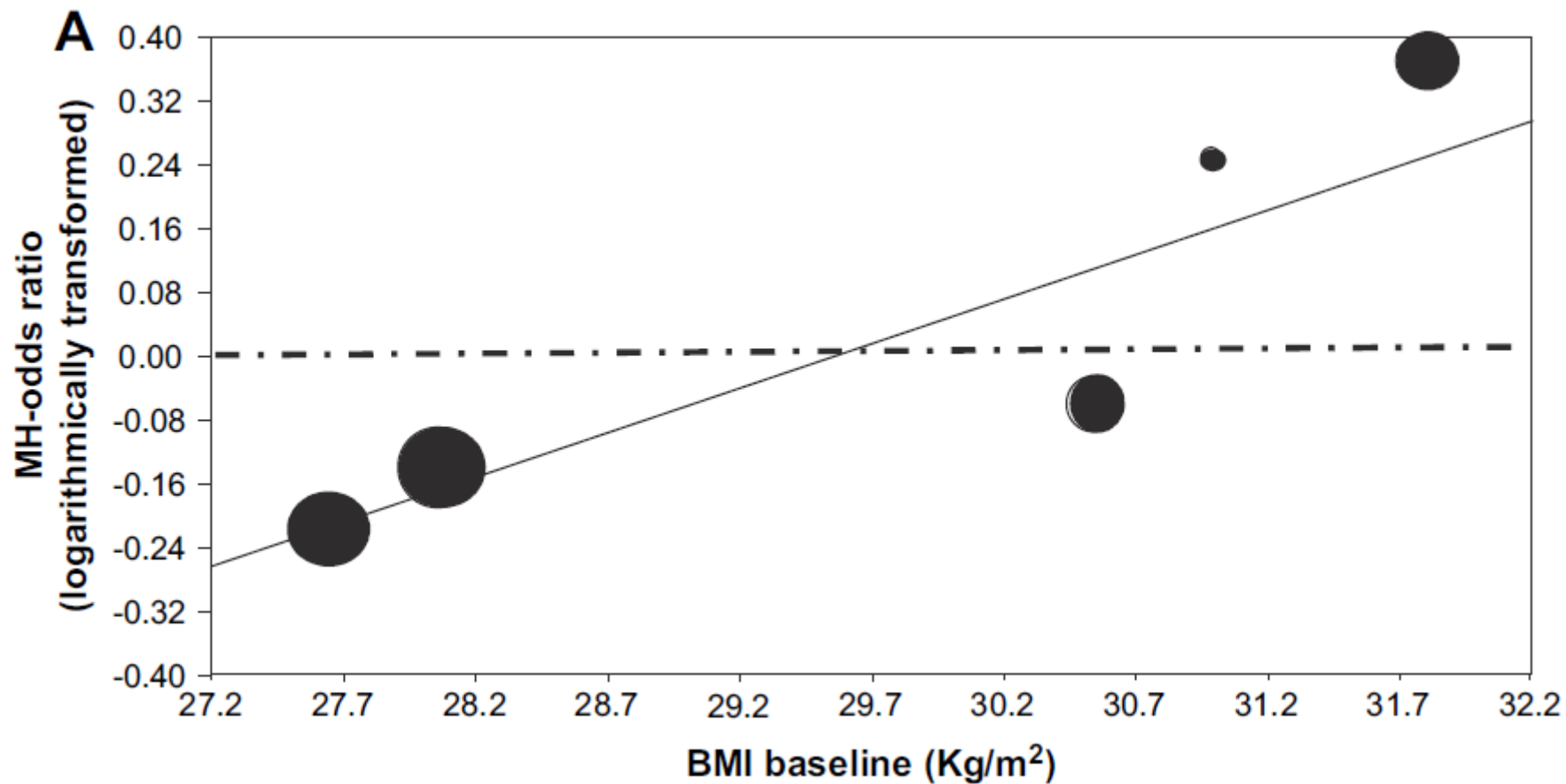
Monami M Nutrition, Metabolism & Cardiovascular Diseases 2013: 23, 300-306

Correlazione della durata del diabete con l'effetto del controllo glicemico intensivo sulla mortalità cv



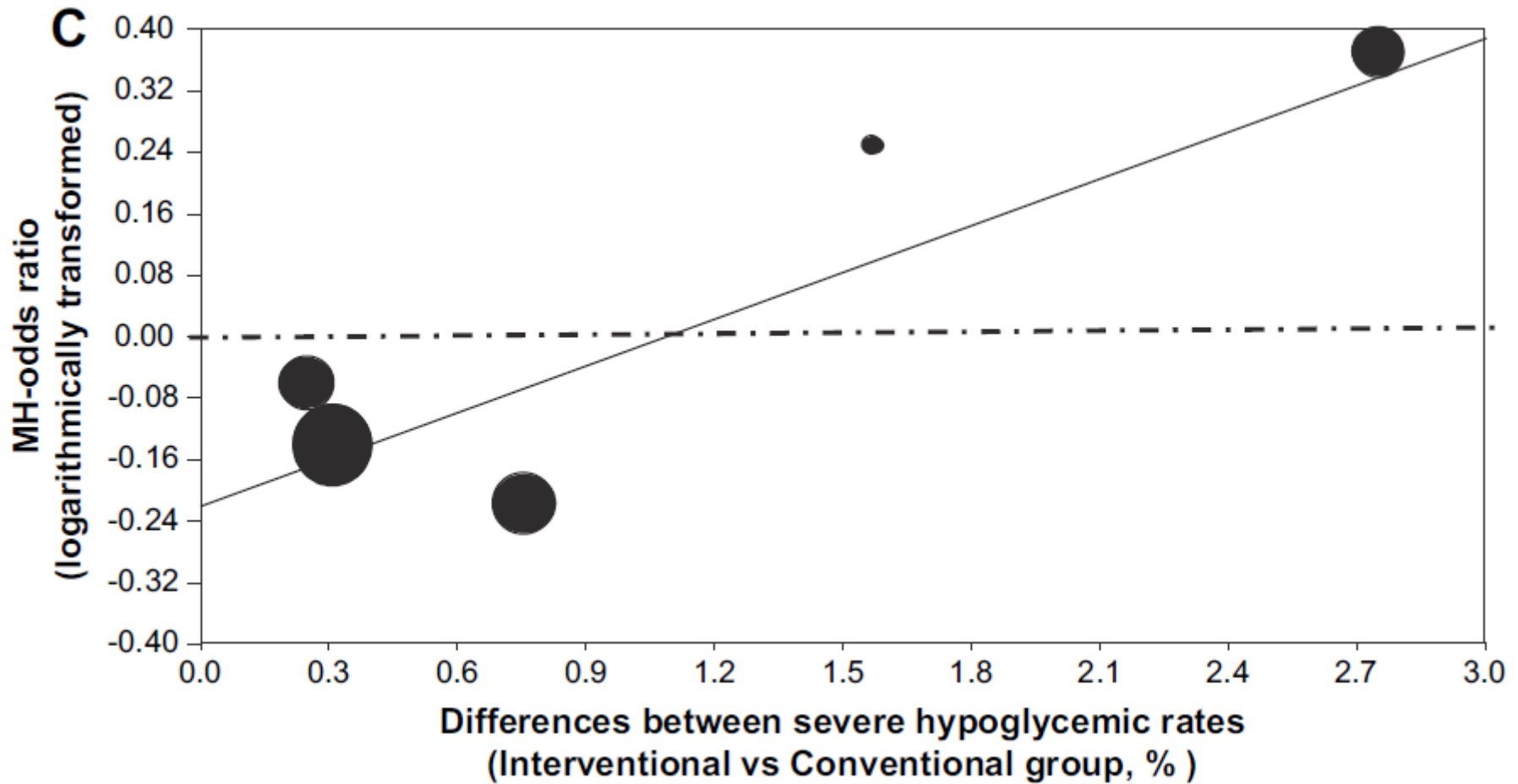
*Mannucci E Nutrition, Metabolism & Cardiovascular Diseases 2009; 19, 604- 612*

**Correlazione del BMI basale con l'effetto del controllo glicemico intensivo sulla mortalità cv**



*Mannucci E, Nutrition, Metabolism & Cardiovascular Diseases 2009; 19: 604- 612*

# Correlazione fra l'aumentata incidenza di ipoglicemia e la mortalità cardiovascolare



Mannucci E, Nutrition, Metabolism & Cardiovascular Diseases 2009; 19: 604- 612  
Maggio 2012





Event	RR (95% IC)	DR* (95% IC)	NNT/ NNH
CV disease	0.90 (0.83 a 0.98)	-15 (-24 to -5)	66.6
CHD	0.89 (0.81 a 0.96)	-20 (-38 a -1)	50
Non fatal MI	0.80 (0.65 a 0.98)	-9 (-13 a -5)	111.1
Death from CVD	0.97 (0.76 a 1.24)	-3 (-14 a 7]	
Death from Any Cause	0.98 (0.84 a 1.15)	-4 (-17 a 10)	
Severe hypoglycemia	2.03 (1.46 a 2.81)	39 (7 a 71)	25.6

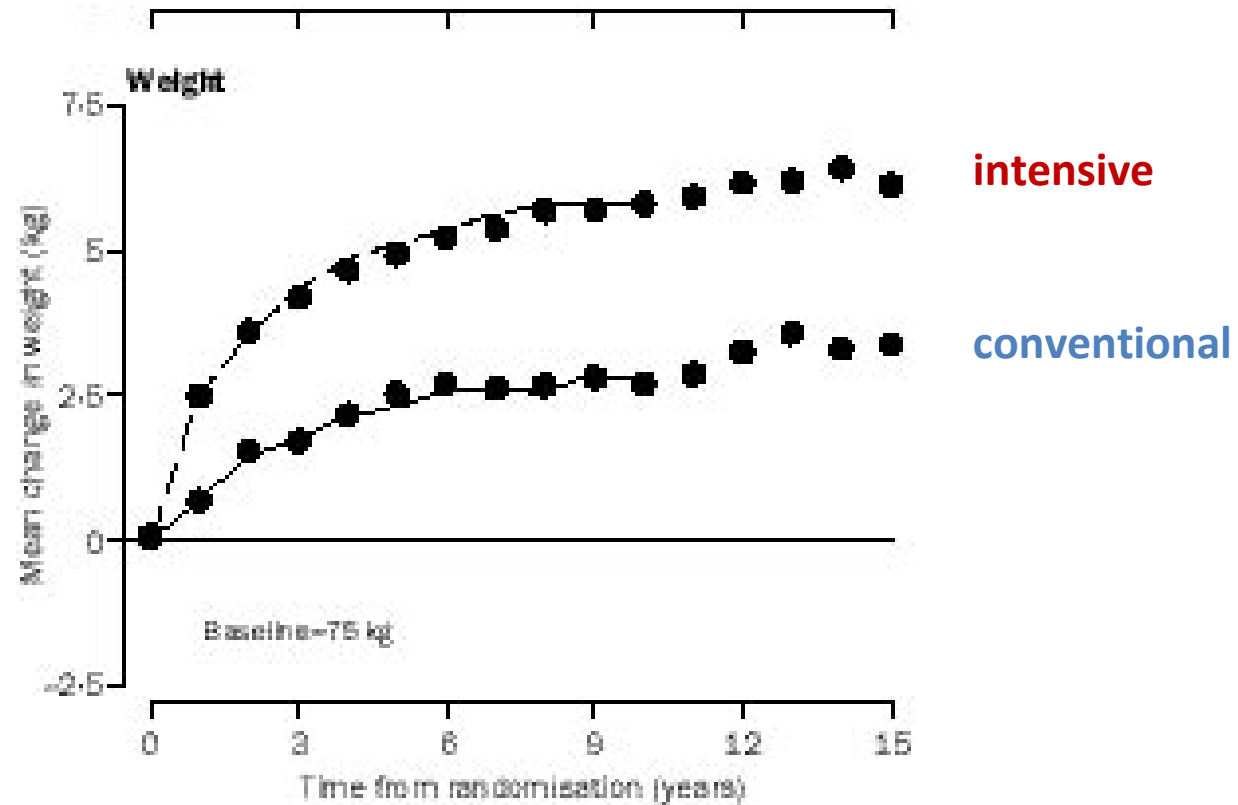
\*Absolute risk difference 1000 patients – 5 years



# Possibili relazioni fra ipoglicemia ed eventi cv

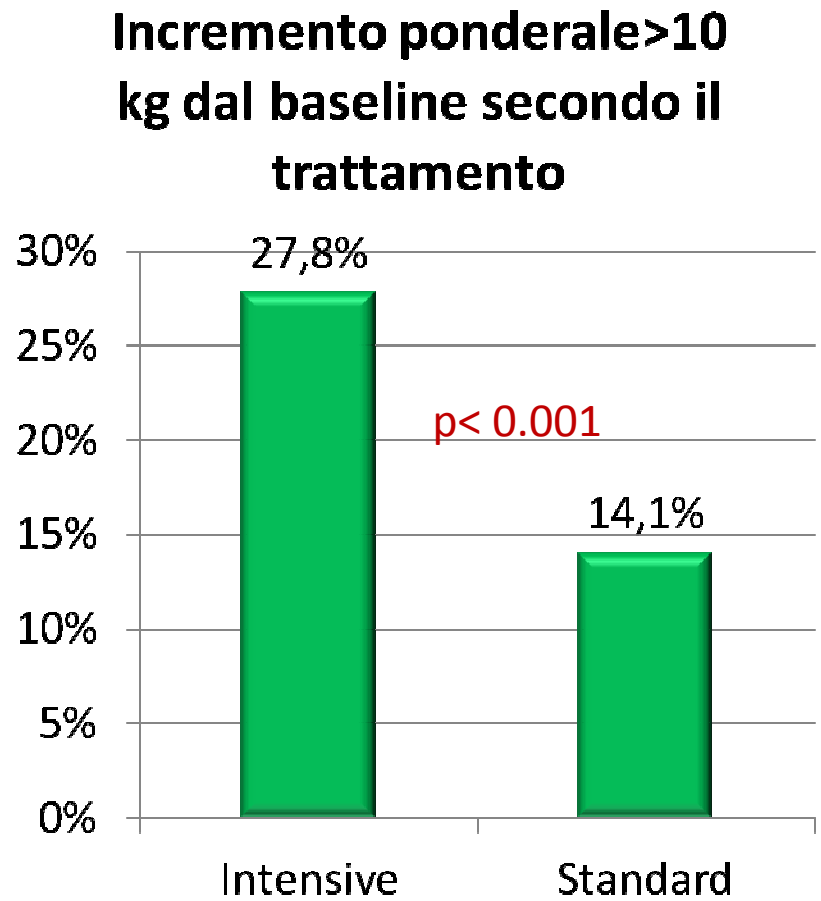
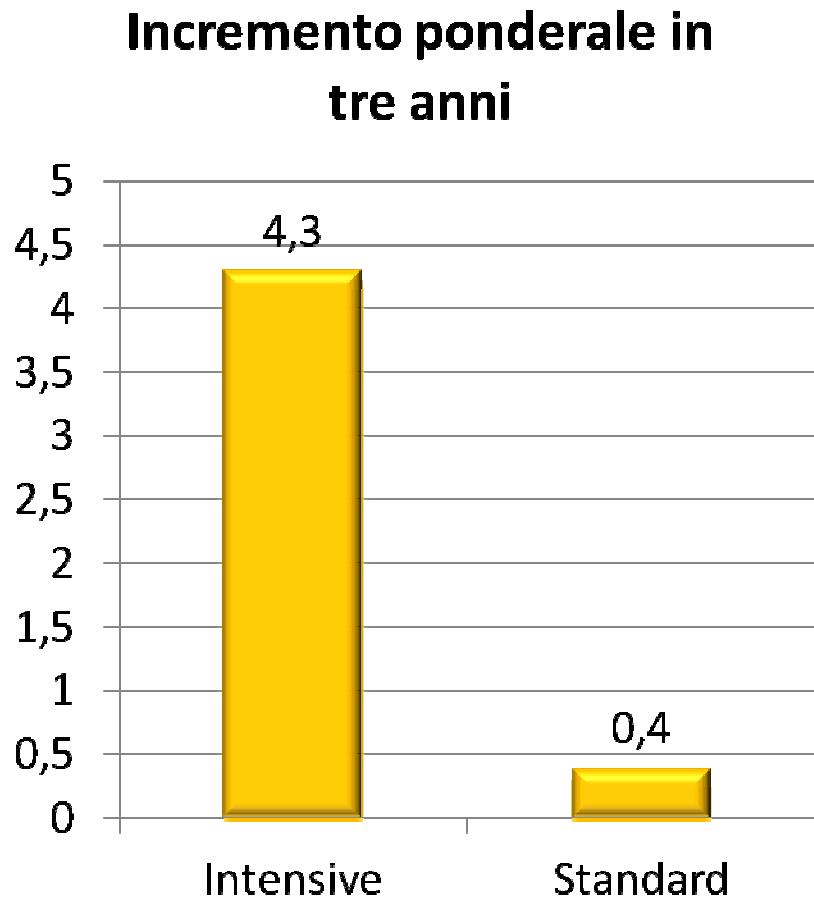
- Attivazione simpatica:
  - tachicardia
  - ipertensione
  - sovraccarico di lavoro cardiaco
  - destabilizzazione della placca
- Ipoglicemia inavvertita

# Variazioni ponderali nell'UKPDS



*UK Prospective Diabetes Study (UKPDS) Group Lancet 1998; 352: 837– 53*

# ACCORD: incremento ponderale

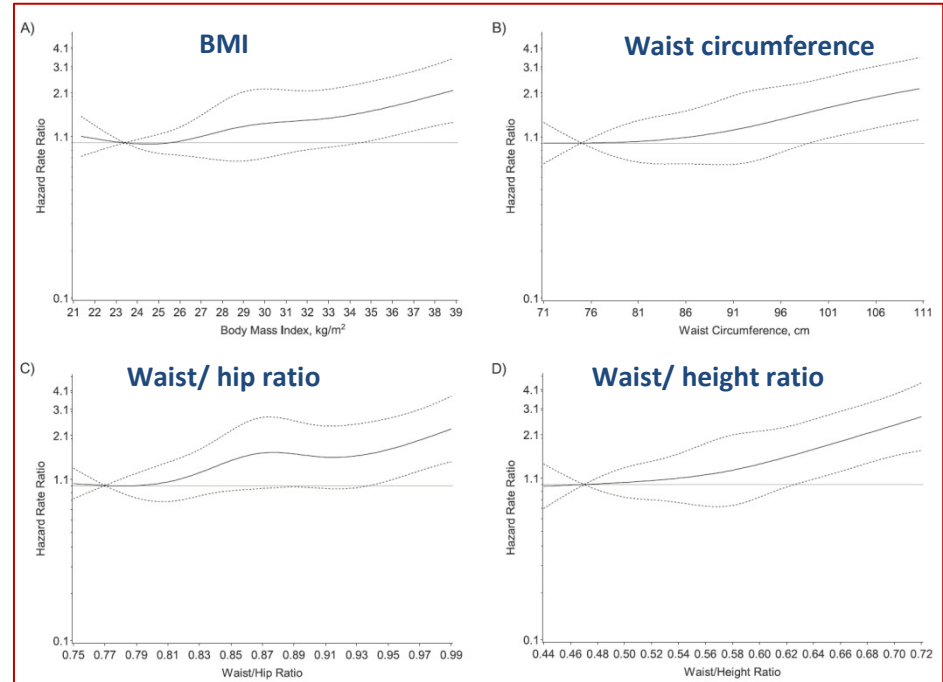
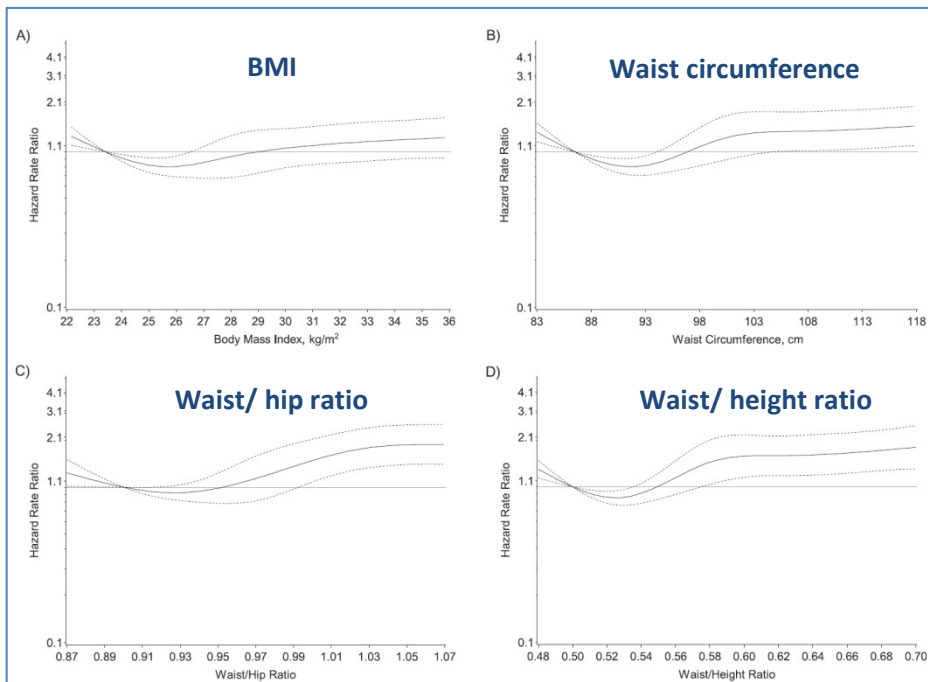


*The Action to Control Cardiovascular Risk in Diabetes Study Group. N Engl J Med 2008;358:2545-59*

# HR per mortalità in uomini e donne europei diabetici al baseline nel 1992–2000 in relazione ai parametri di obesità

## Maschi

## Femmine

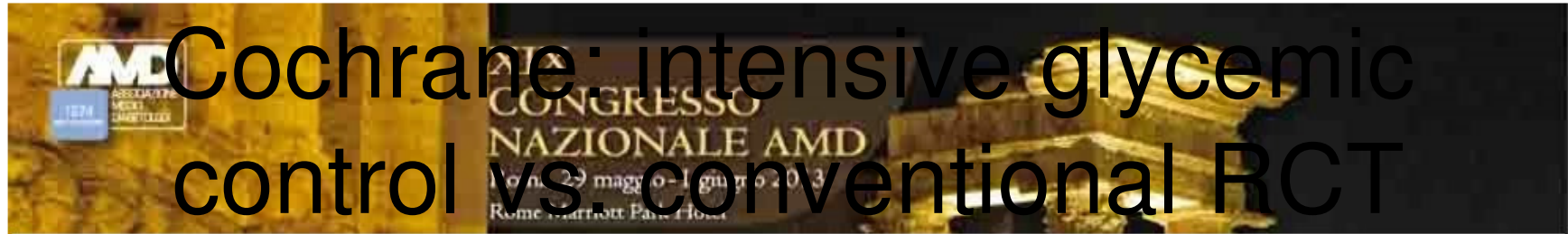


*Sluik D Am J Epidemiol. 2011; 174: 22– 34*



# Cochrane: intensive glycaemic control vs. conventional RCT

Intensive glycaemic control compared to conventional glycaemic control for type 2 diabetes mellitus							
<b>Patient or population:</b> patients with type 2 diabetes mellitus <b>Settings:</b> <b>Intervention:</b> Intensive glycaemic control <b>Comparison:</b> conventional glycaemic control							
Outcomes	Illustrative comparative risks* (95% CI)			Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk					
	conventional glycaemic control	Intensive glycaemic control	glycaemic control				
<b>All-cause mortality</b> Follow-up: median 23.1 months	88 per 1000	89 per 1000 (79 to 99)		RR 1.01 (0.9 to 1.13)	29731 (18 studies)	⊕⊕⊕○ moderate <sup>1</sup>	
<b>Cardiovascular mortality</b> Follow-up: median 23.1 months	45 per 1000	48 per 1000 (40 to 57)		RR 1.06 (0.9 to 1.26)	29731 (18 studies)	⊕⊕⊕○ moderate <sup>2</sup>	
<b>Non-fatal myocardial infarction</b> Follow-up: median 51 months	48 per 1000	42 per 1000 (36 to 48)		RR 0.87 (0.76 to 1.00)	29174 (12 studies)	⊕⊕⊕○ moderate <sup>3</sup>	
<b>Non-fatal stroke</b> Follow-up: median 3.5 years	29 per 1000	28 per 1000 (23 to 34)		RR 0.96 (0.8 to 1.16)	28760 (11 studies)	⊕⊕⊕○ moderate <sup>4</sup>	



# Cochrane: intensive glycemie control vs. conventional RCT

Conventional Intensive

	Conventional	Intensive	RR	Participants	Quality
<b>Amputation of lower extremity</b> Follow-up: median 7.8 years	20 per 1000	13 per 1000 (9 to 19)	RR 0.64 (0.43 to 0.95)	6960 (8 studies)	⊕⊕○○ low <sup>5</sup>
<b>End-stage renal disease</b> Follow-up: median 10.0 years	16 per 1000	14 per 1000 (11 to 17)	RR 0.87 (0.71 to 1.06)	28075 (7 studies)	⊕⊕⊕○ moderate <sup>6</sup>
<b>Severe hypoglycaemia</b> Follow-up: median 2.9 years	30 per 1000	61 per 1000 (42 to 91)	RR 2.05 (1.39 to 3.02)	28127 (12 studies)	⊕⊕⊕⊕ high <sup>7</sup>

\*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

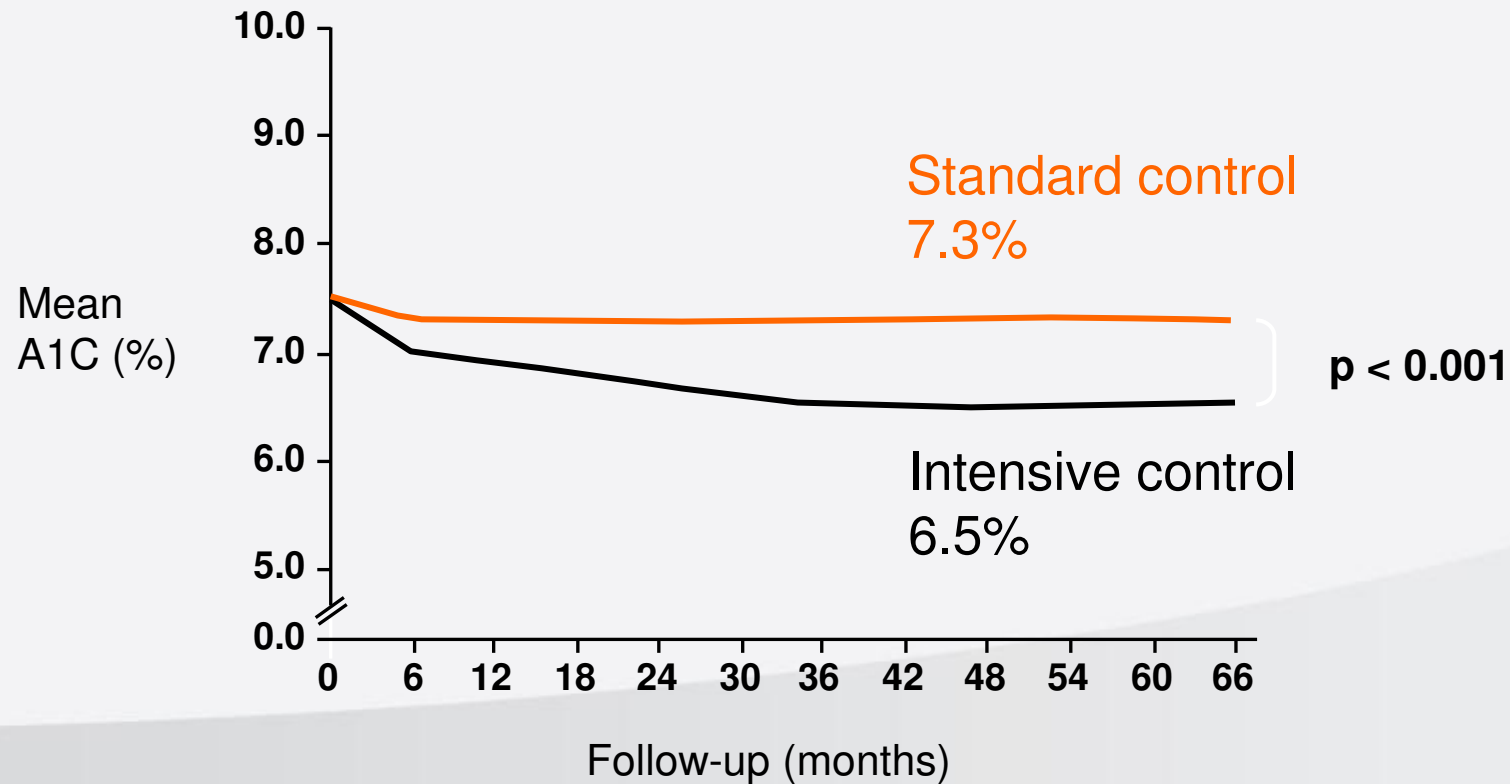
- ❑ Composite microvascular disease (RR 0.89, 95% CI 0.83 to 0.95; P = 0.0006; 25,760 participants, 4 trials),
- ❑ Retinopathy (RR 0.79, 95% CI 0.68 to 0.92; P = 0.002; 10,986 participants, 8 trials),
- ❑ Retinal photocoagulation (RR 0.77, 95% CI 0.61 to 0.97; P = 0.03; 11,142 participants, 7 trials), and
- ❑ Nephropathy (RR 0.78, 95% CI 0.61 to 0.99; P = 0.04; 27,929 participants, 9 trials).



La scelta del target ogni giorno

Why  $\leq 6.5\%$  ?

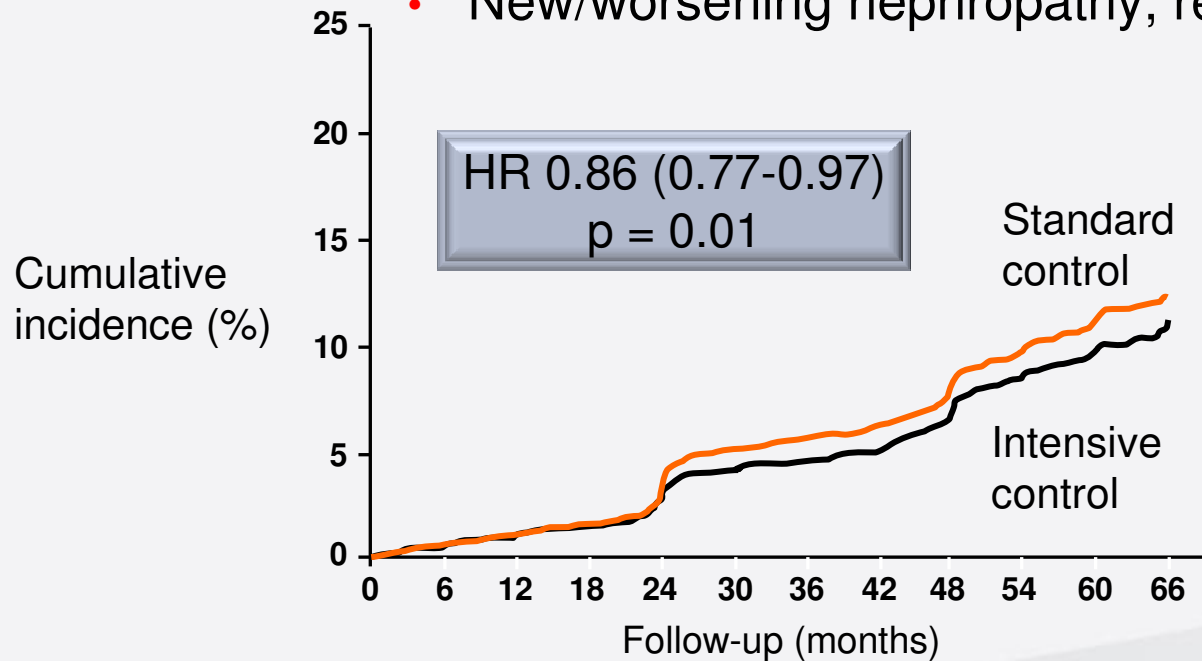
# ADVANCE: Glucose Control





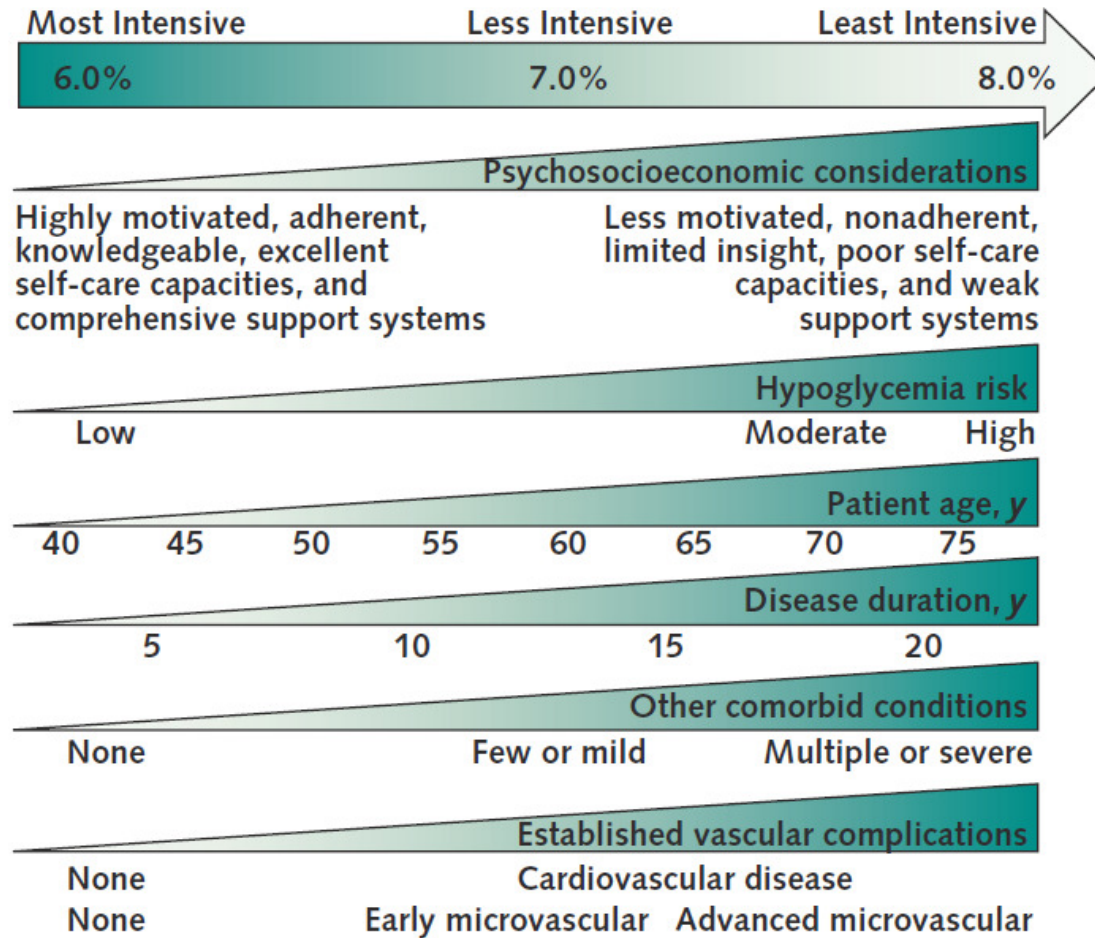
# ADVANCE: Treatment Effect on the Primary Microvascular Outcomes

- New/worsening nephropathy, retinopathy



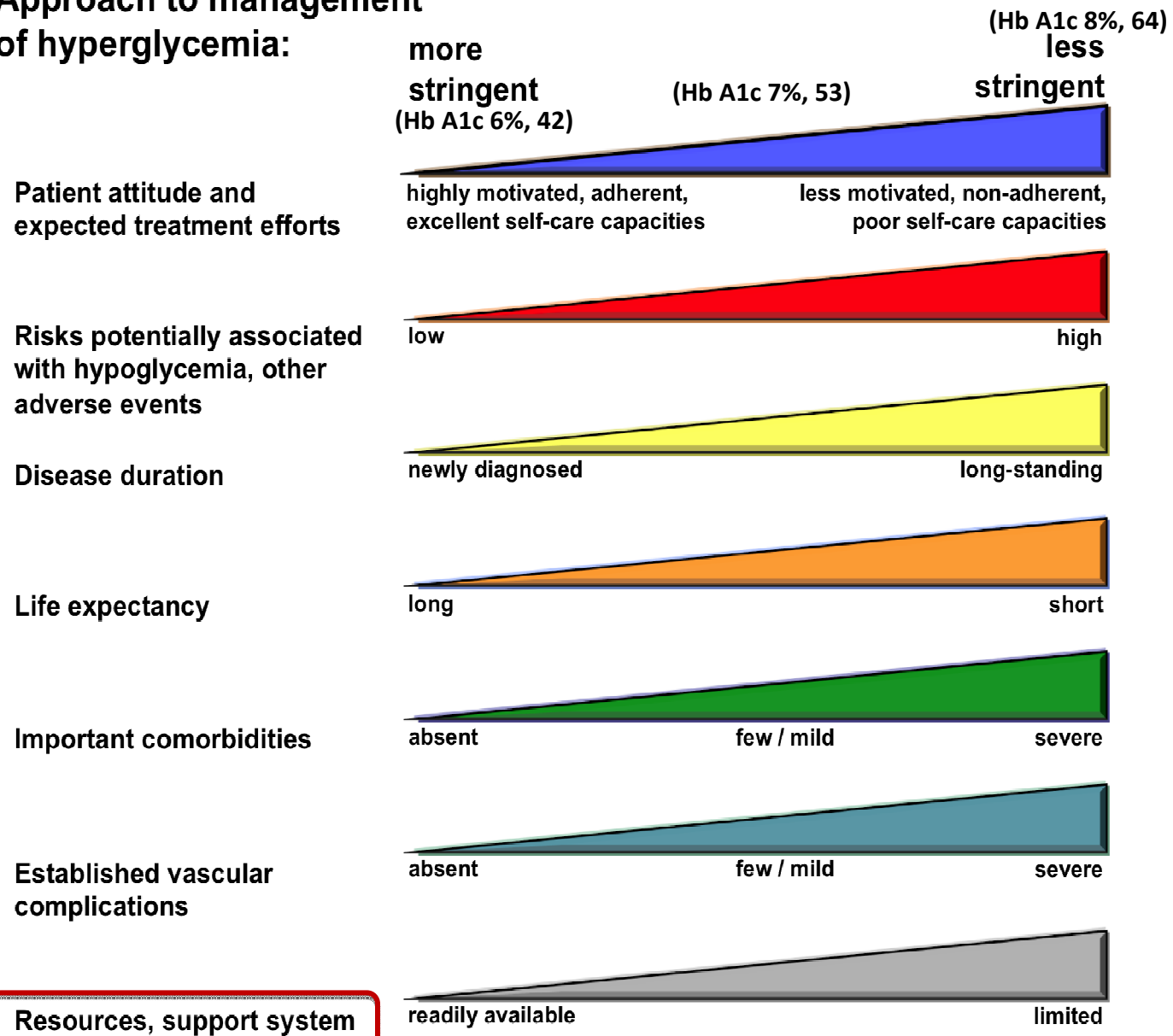
	Intensive	Standard	HR	p
Nephropathy/retinopathy (%)	9.4	10.9	0.86	0.01
Nephropathy (%)	4.1	5.2	0.79	0.006
Retinopathy (%)	6.0	6.3	0.95	NS

**Framework to assist in determining glycemic treatment targets in patients with type 2 diabetes.**



*Ismail-Beigi F, Ann Intern Med. 2011; 154 :554 -559.*

## Approach to management of hyperglycemia:



*Diabetes Care, Diabetologia. 19 April 2012 [Epub ahead of print]*

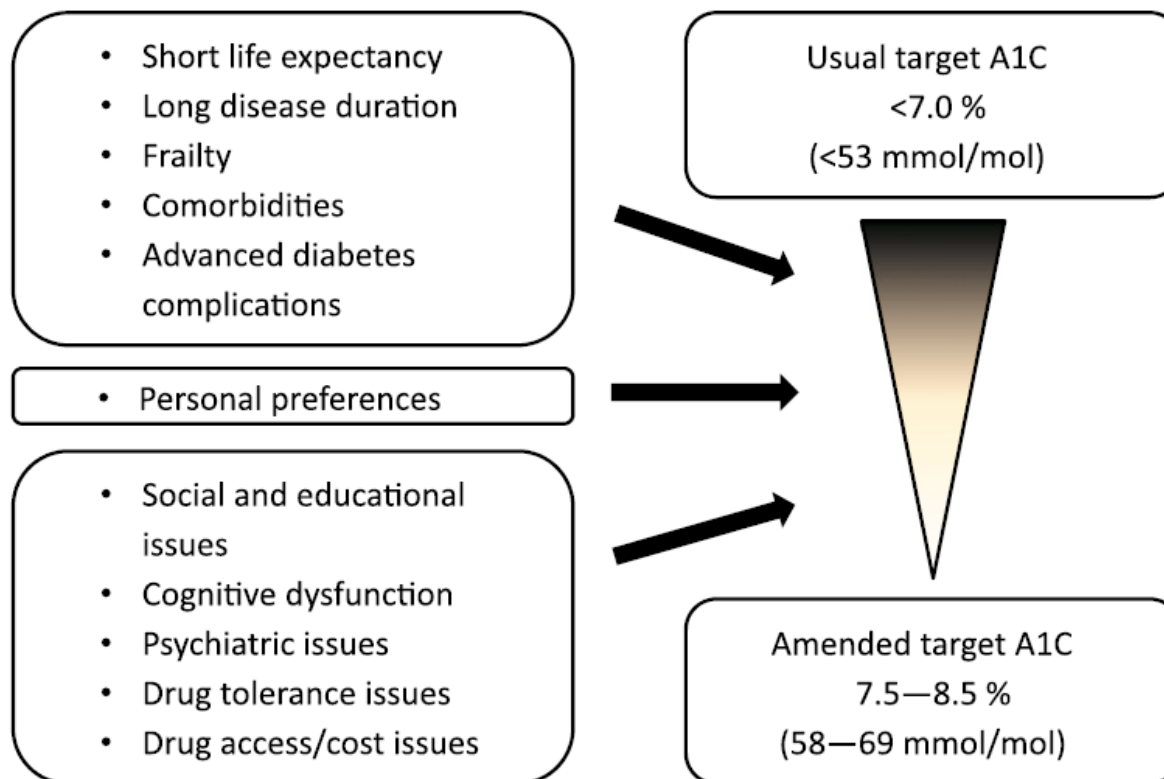
*(Adapted with permission from: Ismail-Beigi F, et al. Ann Intern Med 2011;154:554)*

# Personalized Management of Hyperglycemia in Type 2 Diabetes

Reflections from a *Diabetes Care* Editors' Expert Forum

ITAMAR RAZ, MD<sup>1</sup>  
MATTHEW C. RIDDLE, MD<sup>2</sup>  
JULIO ROSENSTOCK, MD<sup>3</sup>  
JOHN B. BUSE, MD, PHD<sup>4</sup>  
SILVIO E. INZUCCHI, MD<sup>5</sup>  
PHILIP D. HOME, DM, DPHIL<sup>6</sup>  
STEFANO DEL PRATO, MD<sup>7</sup>

ELE FERRANNINI, MD<sup>8</sup>  
JULIANA C.N. CHAN, MD<sup>9</sup>  
LAWRENCE A. LEITER, MD<sup>10</sup>  
DEREK LEROI TH, MD, PHD<sup>11</sup>  
RALPH DEFONZO, MD<sup>12</sup>  
WILLIAM T. CEFALU, MD<sup>13</sup>



*Raz | Diabetes Care 2013; 36:1779–1788*



# Ridotta attesa di vita e comorbidità

- ❑ Ridotto periodo per lo sviluppo delle complicanze del diabete
- ❑ Patologie debilitanti
- ❑ Polifarmacologia:
  - Confusione
  - Errori
  - Scarsa aderenza
  - Effetti collaterali
  - Interazioni fra farmaci
  - Costi
  - Frustrazione

*Ismail-Beigi F, Ann Intern Med. 2011; 154 :554 -559.*



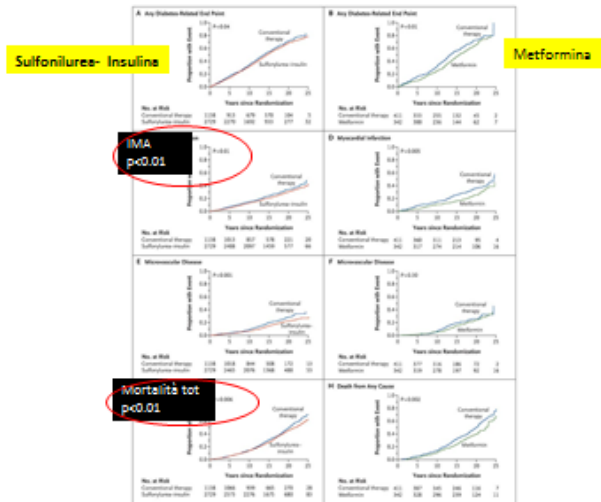


# Lunga durata di malattia

## Legacy

## ACCORD

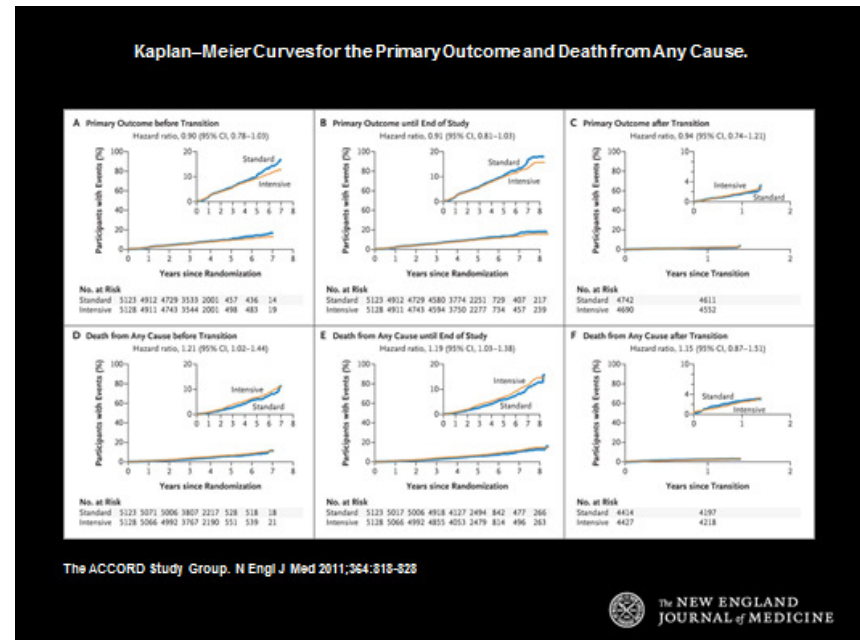
Intervento all'esordio e "legacy": UKPDS follow up 10 anni



Holman Ret al. N Engl J Med. 2008 Oct 9;359(15):1577-89

maggio 2009

Alberto De Micheli



The ACCORD Study Group. N Engl J Med 2011;364:818-28



Holman R et al. N Engl J Med 2008;359: 1577-89

The ACCORD Study Group N Engl J Med 2011;364:818-28

**These findings imply (but do not prove) that intensive treatment is more likely to have benefits the earlier it is begun** *Ismail-Beigi F, Ann Intern Med. 2011; 154 :554 -559.*

Maggio 2012

Alberto De Micheli

52



## Età bassa

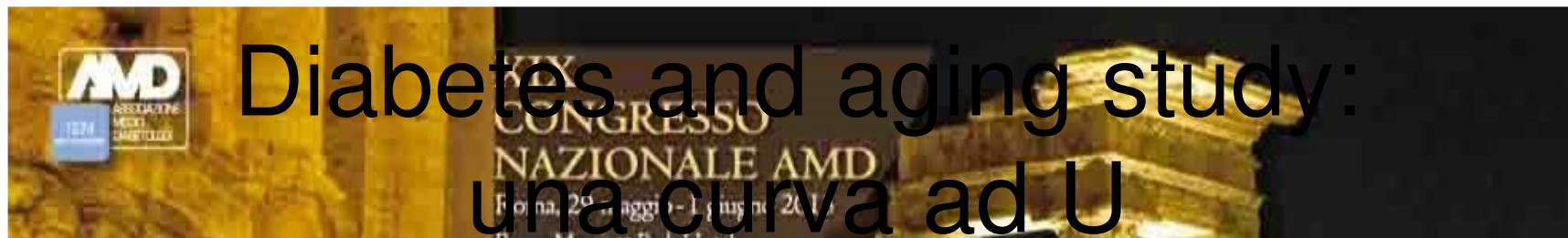
- lunga esposizione all'iperglicemia

## Età elevata

- Comorbidità
- Ridotta attesa di vita

Characteristic	Mean Glycated Hemoglobin Reduction during Follow-up (95% CI) <i>percent</i>	Intensive Control (N=5571) <i>number of patients (percent)</i>	Standard Control (N=5569)	Hazard Ratio (95% CI)	Relative Risk Reduction (95% CI) <i>percent</i>
Age					
<65 yr	0.70 (0.65 to 0.75)	367 (16.1)	421 (18.7)		14 (1 to 25)
≥65 yr	0.70 (0.65 to 0.75)	642 (19.5)	695 (21.0)		8 (-3 to 17)

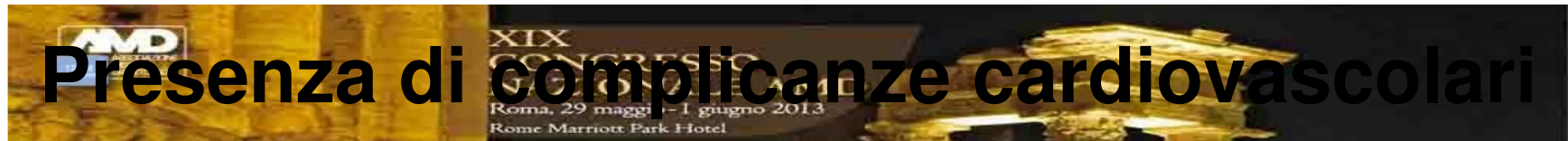
*The ADVANCE Collaborative Group. N Engl J Med 2008;358:2560-72*



Outcome	Baseline A1C				
	<6.0	6.0–6.9	7.0–7.9	8.0–8.9	≥9
Mortality					
Age-group					
60–69	1	0.92 (0.79–1.07)	0.83 (0.70–0.99)	0.91 (0.74–1.11)	1.17 (0.96–1.43)
70–79	1	0.83 (0.75–0.92)	0.85 (0.75–0.96)	0.86 (0.73–1.01)	1.11 (0.93–1.32)
≥80	1	0.83 (0.74–0.93)	0.83 (0.72–0.95)	1.05 (0.86–1.27)	1.20 (0.96–1.50)
Any complication					
Age-group					
60–69	1	1.12 (1.00–1.25)	1.20 (1.07–1.35)	1.44 (1.26–1.64)	1.58 (1.38–1.81)
70–79	1	1.08 (0.98–1.19)	1.21 (1.09–1.35)	1.35 (1.19–1.53)	1.50 (1.30–1.73)
≥80	1	1.11 (0.97–1.27)	1.18 (1.02–1.38)	1.28 (1.03–1.58)	1.43 (1.12–1.83)
Any complication or death					
Age-group					
60–69	1	1.04 (0.94–1.14)	1.08 (0.98–1.20)	1.28 (1.14–1.44)	1.43 (1.27–1.60)
70–79	1	0.98 (0.91–1.06)	1.07 (0.98–1.17)	1.18 (1.06–1.31)	1.36 (1.20–1.53)
≥80	1	0.94 (0.86–1.04)	0.96 (0.85–1.07)	1.13 (0.96–1.33)	1.25 (1.04–1.51)

*Huang ES, Diabetes Care 2011; 34:1329- 1336*

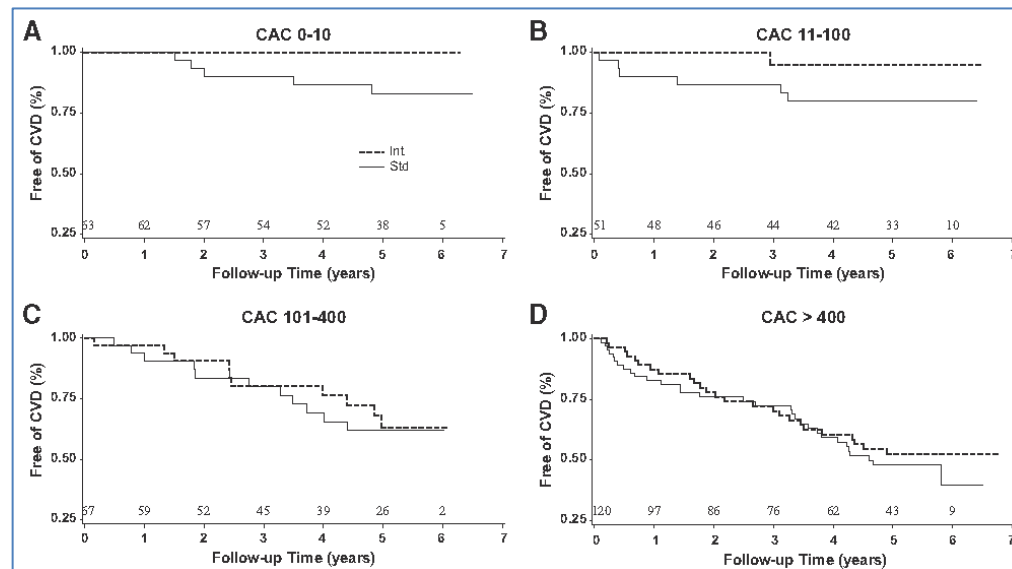
# Presenza di complicanze cardiovascolari



History of macrovascular disease						
No	0.67 (0.63 to 0.70)	591 (15.6)	678 (18.0)			14 (4 to 23)
Yes	0.67 (0.62 to 0.72)	418 (23.3)	438 (24.4)			4 (-10 to 16)
History of microvascular disease						
No	0.65 (0.62 to 0.68)	799 (16.0)	892 (17.9)			11 (2 to 19)
Yes	0.79 (0.69 to 0.90)	210 (36.8)	224 (38.4)			4 (-16 to 21)

*The ADVANCE Collaborative Group. N Engl J Med 2008;358:2560-72*

VADT



*Reaven PD Diabetes 2009; 58: 2642-2648, 2009*



The effective management of the older patient with diabetes requires an emphasis on:

- safety
- diabetes prevention
- early treatment for vascular disease
- functional assessment of disability because of
  - limb problems,
  - eye disease
  - stroke.
- other diabetes-related complications
- associated conditions, such as
  - cognitive dysfunction,
  - functional
  - dependence,
  - depression

*Sinclair A, JAMDA 2012; 13: 497- 502*





# Obiettivi nell'anziano fragile

- ❑ Obiettivo generale: HbA1c 53 – 59 mmol/mol (7.0% - 7.5 %)
- ❑ Mai glicemia a digiuno < 110 mg/ dl in terapia
- ❑ Mai iniziare terapia se glicemia a digiuno non stabilmente > 126 mg/ dl
- ❑ Evitare glicemie > 90 mg/ dl
- ❑ Evitare glicemie > 200 per controllare i sintomi

*Sinclair A, JAMDA 2012; 13: 497- 502*



# Rischio di ipoglicemia

## Elementi di rischio

- ❑ Bassa funzione cognitiva (ADVANCE)
- ❑ Ipoglicemie pregresse
- ❑ Rischio professionale

## Conseguenze

- ❑ Rischio demenza
- ❑ Rischio ischemia
- ❑ Rischio aritmie
- ❑ Aumento mortalità

*Ismail-Beigi F, Ann Intern Med. 2011; 154 :554 -559.*



# Contesto psicosocioeconomico

- ❑ Capacità di autogestione
- ❑ Contesto familiare (vivere soli)
- ❑ Depressione
- ❑ Ridotta funzione cognitiva (MMSE)

*Ismail-Beigi F, Ann Intern Med. 2011; 154 :554 -559.*



# Effetti collaterali dei farmaci

- ❑ Incremento ponderale
- ❑ Edema
- ❑ Scompenso di circolo
- ❑ Fratture
- ❑ Effetti avversi gastrointestinali
- ❑ Interferenze fra farmaci
- ❑ Valutazione rischio beneficio di ogni nuovo farmaco in polifarmacia

*Ismail-Beigi F, Ann Intern Med. 2011; 154 :554 -559.*



# Qualità di vita e preferenze personali

## Qualità di vita

Obiettivo finale del trattamento:

➤ Migliorare la qualità della vita nel breve e nel lungo termine

## Preferenze personali

EBM

- L'integrazione delle migliori prove di efficacia clinica con la esperienza e l'abilità del medico ed i **valori del Paziente**
- L'uso cosciente, esplicito e giudizioso delle migliori evidenze (cioè prove di efficacia) biomediche al momento disponibili, al fine di prendere le decisioni per **l'assistenza del singolo Paziente**

*Ismail-Beigi F, Ann Intern Med. 2011; 154 :554 -559.*

*Sackett D BMJ 1996; 312: 71*

*Sackett D. et al. Evidence- Based Medicine. How to Practice and Teach EBM, Churchill Livingstone 2000*



# Evidence-Based Persuasion

## An Ethical Imperative



### **E' impossibile rispettare l'autonomia del paziente senza la persuasione:**

- Rimuovi i pregiudizi e conosci i desideri del paziente
- Fornisci informazioni EBM oneste ed imparziali su danni e benefici
- Dai una interpretazione razionale di queste informazioni, compresa la tua opinione motivata
- Usa la ragione più che l'emozione
- Evita di creare nuovi pregiudizi
- Sii attento alle preferenze mutanti del paziente, perché la persuasione può cambiare l'atteggiamento e l'opinione del paziente

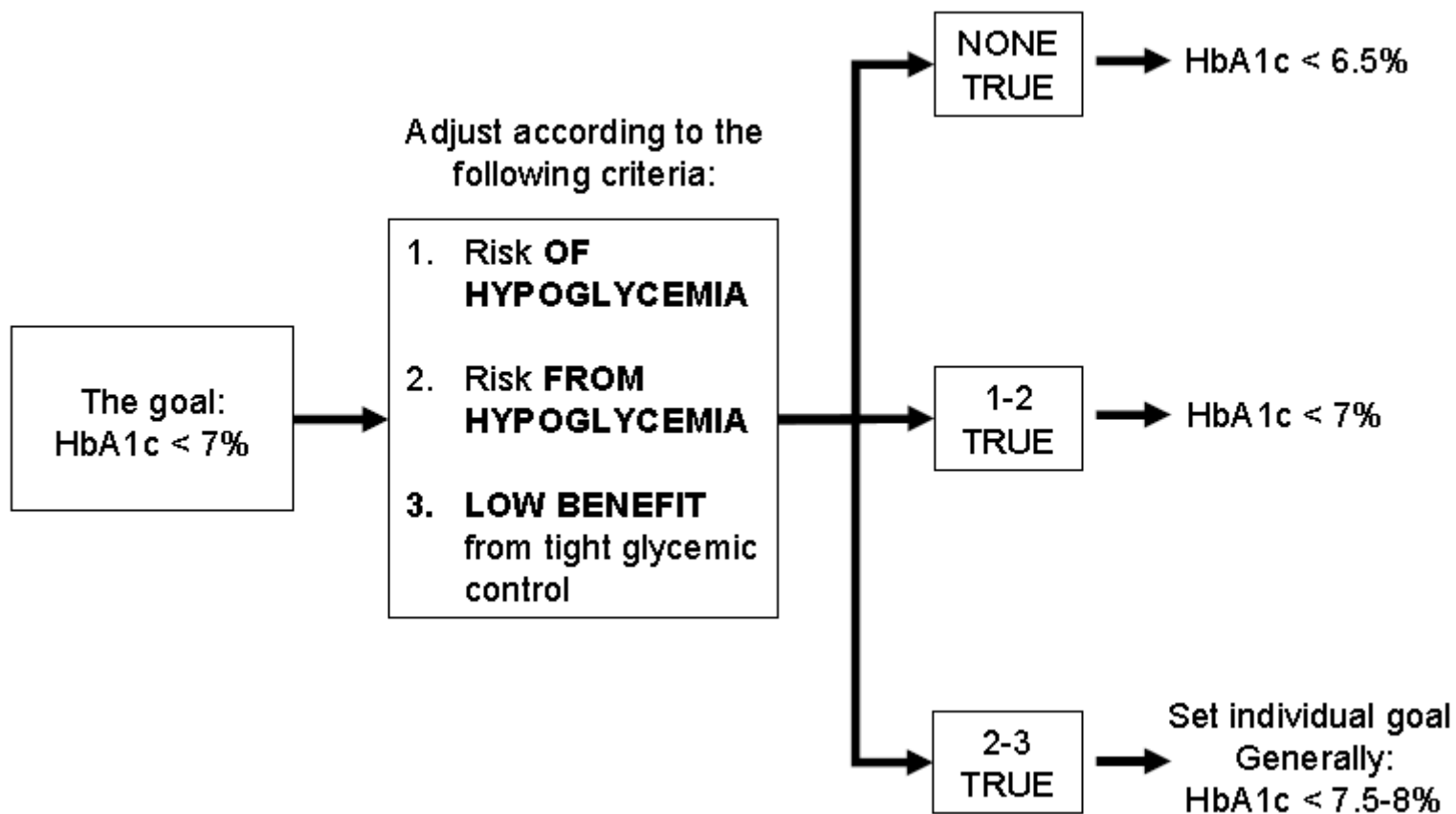
*Shaw D, Elger B . JAMA Published Online: April 8, 2013.doi:10.1001/jama.2013.2179*





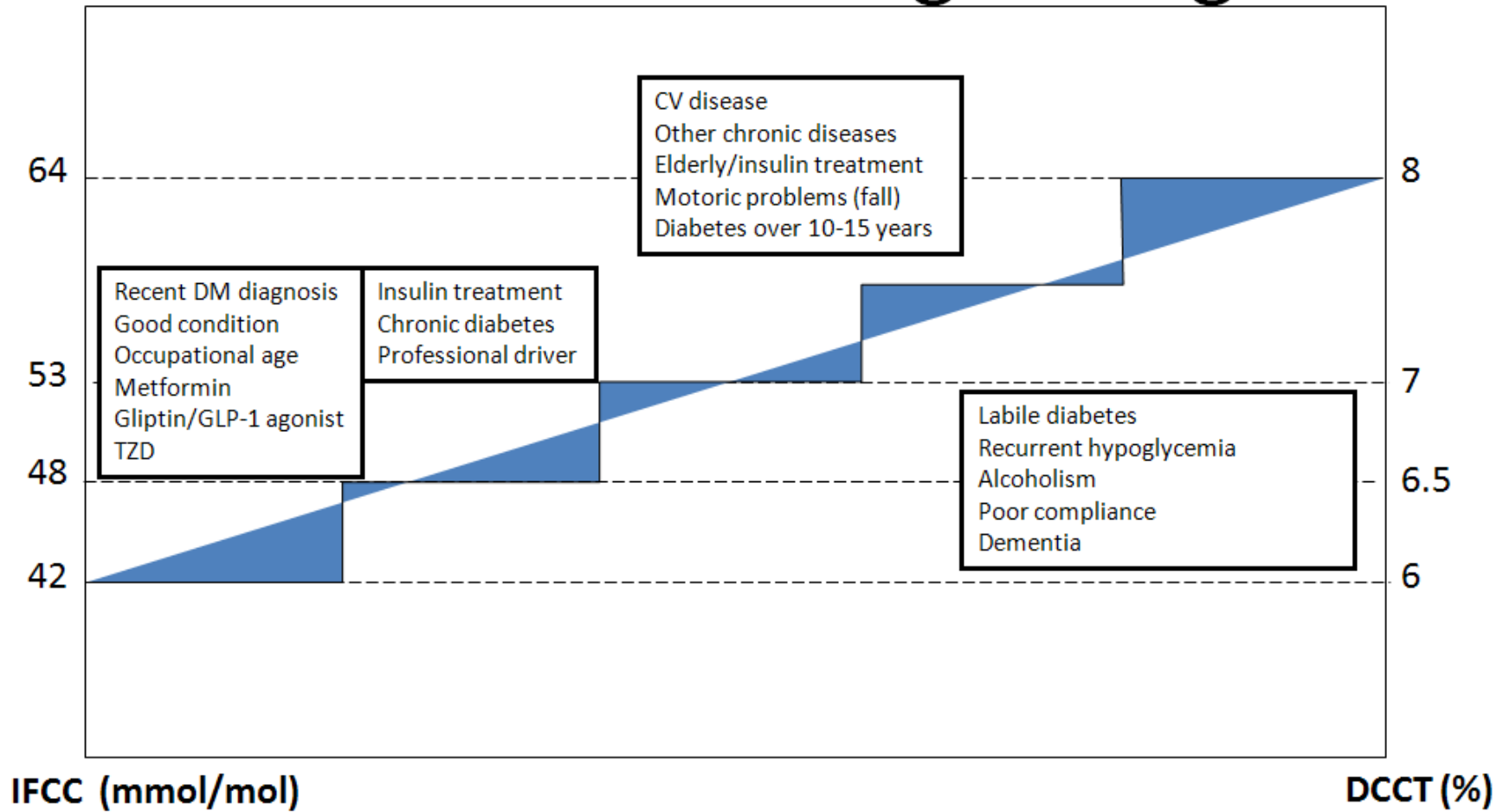
## Indicazioni di linee guida, consensus algoritmi

# Target glicemico: rapporto rischio/ beneficio



*Eldor R & Raz I, Rev Diabet Stud 2009; 6: 6-12*

# Individual HbA1c target range

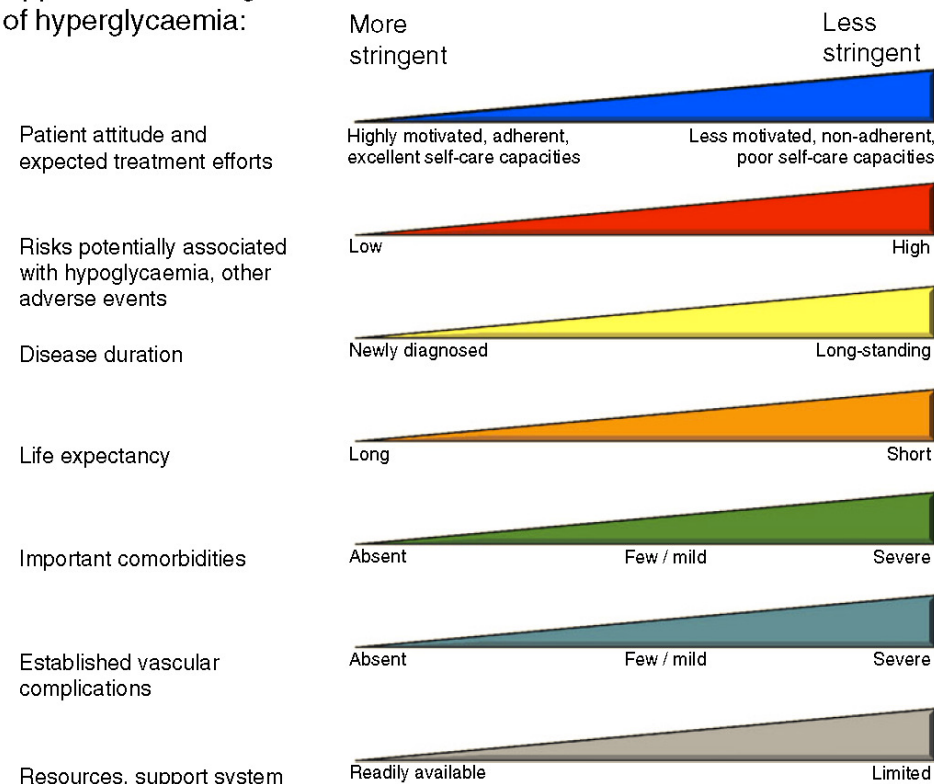


[http://www.terveysportti.fi/xmedia/ccs/varhainen\\_diabetes\\_en.html](http://www.terveysportti.fi/xmedia/ccs/varhainen_diabetes_en.html)

# ADA EASD position statement 2012

- **HbA1c to <7.0% (<53 mmol/mol) in most patients**
  - Mean plasma glucose of ~8.3– 8.9 mmol/l (~150–160 mg/dl);
  - Fasting and pre-meal glucose at <7.2mmol/l (<130mg/dl)
  - postprandial glucose at <10 mmol/l (<180 mg/dl).
- **More stringent HbA1c targets (e.g. 6.0–6.5% [42–48 mmol/mol]) might be considered in selected patients (with short disease duration, long life expectancy, no significant CVD) if this can be achieved without significant hypoglycaemia or other adverse effects of treatment [20, 43].**
- **7.5–8.0% (58–64 mmol/mol) or even slightly higher—are appropriate for patients with a history of severe hypoglycaemia, limited life expectancy, advanced complications, extensive comorbid conditions and those in whom the target is difficult to attain despite intensive ...**
- **Important to individualise treatment targets**

Approach to management of hyperglycaemia:



*Diabetes Care, Diabetologia. 19 April 2012 [Epub ahead of print]  
 (Adapted with permission from: Ismail-Beigi F, et al. Ann Intern Med 2011;154:554)*



	Normal	Target
HbA <sub>1c</sub>	< 6.0% / 42 mmol/mol	< 7.0% / 53 mmol/mol
Fasting/pre-meal capillary plasma glucose	5.5 mmol/l (100 mg/dl)	6.5 mmol/l (115 mg/dl)
Post meal capillary plasma glucose	7.8 mmol/l (140 mg/dl)	9.0 mmol/l (160 mg/dl)

- ❑ A **lower** HbA<sub>1c</sub> target may be considered if it is **easily and safely** achieved.
- ❑ A **higher** HbA<sub>1c</sub> target may be considered for people with **co-morbidities** or when **previous attempts** to optimise **control** have been associated with unacceptable hypoglycaemia.
- ❑ An **individual's HbA<sub>1c</sub> target should be regularly reviewed** taking into account benefits, safety and tolerability.
- ❑ Advise those in whom target HbA<sub>1c</sub> levels cannot be reached that **any improvement is beneficial**



# ADA Standard 2013

XIX CONGRESSO NAZIONALE  
Roma, 29 maggio - 4 giugno 2013  
Rome Marriott Park Hotel

- ❑ A reasonable A1C goal for many non pregnant adults is **<7%**. (B)
- ❑ **<6.5%**: for selected individual patients, if
- ❑ this can be achieved without significant hypoglycemia or other adverse effects of treatment.
- ❑ Appropriate patients might include those with
  - short duration of diabetes,
  - long life expectancy,
  - no significant CVD. (C)
- ❑ **<8%**: may be appropriate for patients with
  - a history of severe hypoglycemia,
  - limited life expectancy,
  - advanced microvascular or macrovascular complications,
  - extensive comorbid conditions,
  - those with long-standing diabetes in whom the general goal is difficult to attain despite diabetes self-management education (DSME), appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin(B)

*Executive Summary: Standards of Medical Care in Diabetes Diabetes Care 2013 36:S4-S10*



# AACE Comprehensive Diabetes Management Algorithm 2013

GOALS FOR GLYCEMIC CONTROL

**A1c ≤ 6.5%**  
For healthy patients without concurrent illness and at low hypoglycemic risk

**A1c > 6.5%**  
Individualize goals for patients with concurrent illness and at risk for hypoglycemia

Copyright © 2013 AACE. May not be reproduced in any form without express written permission from AACE.

Copyright © 2013 AACE AACE Comprehensive Diabetes Management Algorithm, Endocr Pract. 2013;19(No. 2): 331

*Garber AJ AACE Comprehensive Diabetes Management Algorithm, Endocr Pract. 2013; 19: 327- 36*

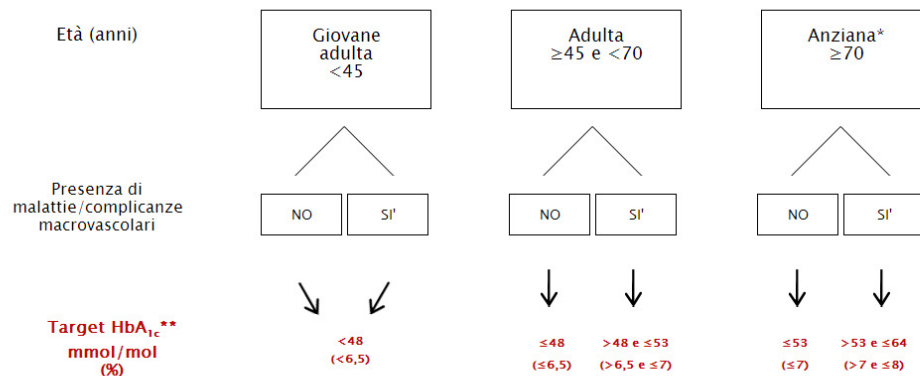


# AMD 2013



Fig. 1

## Parametri per l'inquadramento/caratterizzazione del paziente con diabete di tipo 2



\* Valutare (alla presentazione e nel tempo) il filtrato glomerulare, il possibile rischio di ipoglicemie (particolare cautela nell'impiego di sulfoniluree e glinidi), l'assetto nutrizionale, la presenza di comorbidità e fragilità.

\*\* I valori target di HbA<sub>1c</sub> proposti, sono da intendersi come obiettivi da perseguire in sicurezza, limitando il rischio di ipoglicemia

### Scegliere la caratteristica principale del paziente con diabete di tipo 2:

ALGORITMO A	ALGORITMO B	ALGORITMO C	ALGORITMO D	ALGORITMO E	ALGORITMO F
HbA <sub>1c</sub> ≥75 mmol/mol (≥9%)	BMI <30 e HbA <sub>1c</sub> 48-75 mmol/mol (tra 6,5 e <9%)	BMI ≥30 e HbA <sub>1c</sub> 48-75 mmol/mol (tra 6,5 e <9%)	Rischio professionale per possibili ipoglicemie (HbA <sub>1c</sub> 48-75 mmol/mol (tra 6,5 e <9%))	IRC e HbA <sub>1c</sub> 48-75 mmol/mol (tra 6,5 e <9%)	Anziano fragile con iperglicemia lieve/moderata (HbA <sub>1c</sub> <75 mmol/mol (<9%))

### Note indispensabili per un corretto uso dell'algoritmo:

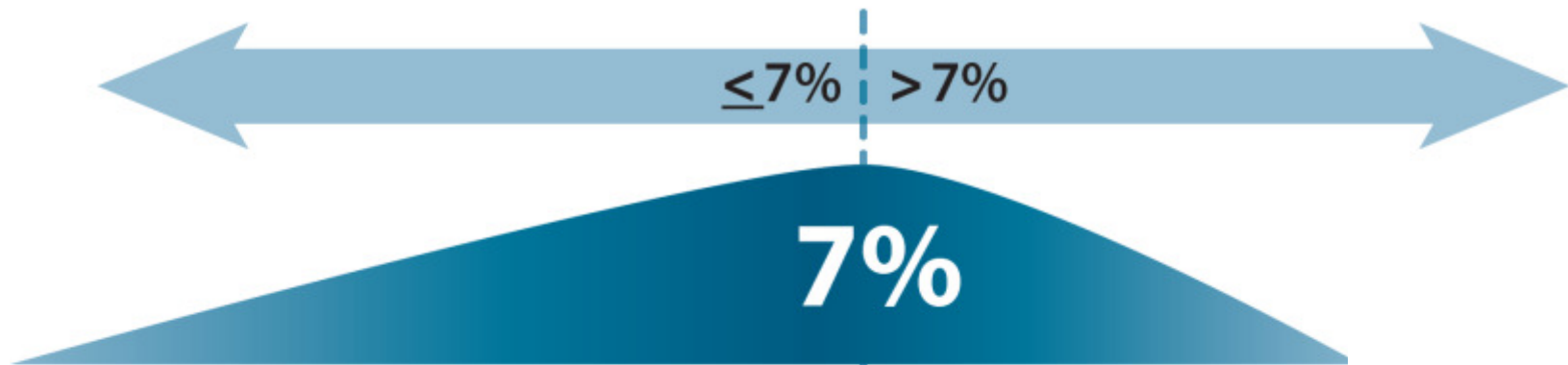
- I riquadri cliccabili consentono il passaggio al gradino terapeutico successivo qualora il target di HbA<sub>1c</sub> non sia stato raggiunto.
- SMBG: l'automonitoraggio della glicemia è strumento di ulteriore fenotipizzazione del paziente ai fini decisionali oltre alla emoglobina glicata. La frequenza dei controlli glicemici deve essere determinata dal medico su base individuale tenendo conto dello schema terapeutico, del grado di compenso e delle necessità cliniche ed educazionali, secondo principi di appropriatezza. Per gli schemi di automonitoraggio si fa riferimento alle linee guida IDF sull'automonitoraggio glicemico nel paziente con diabete di tipo 2 non trattato con insulina (disponibili qui: [www.idf.org/guidelines/self-monitoring](http://www.idf.org/guidelines/self-monitoring)).



## Targets Checklist

- ✓ **A1C  $\leq$  7.0%** for **MOST** people with diabetes
- ✓ **A1C  $\leq$  6.5%** for **SOME** people with T2DM
- ✓ **A1C 7.1-8.5%** in people with specific features

# Individualizing A1C Targets 2013



A target A1C  $\leq 6.5\%$  may be considered in some patients with type 2 diabetes to further lower the risk of nephropathy and retinopathy which must be balanced against the risk of hypoglycemia

**Most patients  
with type 1  
and type 2  
diabetes**

## **Consider 7.1-8.5% if:**

- Limited life expectancy
- High level of functional dependency
- Extensive coronary artery disease at high risk of ischemic events
- Multiple co-morbidities
- History of recurrent severe hypoglycemia
- Hypoglycemia unawareness
- Longstanding diabetes for whom it is difficult to achieve an A1C  $\leq 7\%$ , despite effective doses of multiple antihyperglycemic agents, including intensified basal-bolus insulin therapy

# CDA motore di calcolo

The screenshot displays a web browser window with the URL <http://guidelines.diabetes.ca/BloodGlucoseLowering/A1Ctarget>. The page title is "Individualizing your Patient's A1C Target For Patients with Type 1 and Type 2 Diabetes".

**Clinical Practice Guidelines**

- Browse Executive Summary
- Browse the 2013 CPGs
- Screening & Diagnosis
- Vascular Protection
- Blood Glucose Lowering
- Self-Management Education
- Team & Organizing Care
- Special Populations
- Healthcare Provider Tools
- Slides and Videos
- Patient Resources

**Individualizing your Patient's A1C Target For Patients with Type 1 and Type 2 Diabetes**

Patient specific adjusted recommendation

6.0% 7% 8.5%

Which of the following applies to your patient?

- Patient is an adult with diabetes
- Patient is a child with type 1 diabetes
- Patient is a child with type 2 diabetes

Is the patient with diabetes pregnant or desiring pregnancy?

- Yes
- No

Is the patient with diabetes "frail" or does the patient with diabetes have limited life expectancy?

- Yes
- No

Which of the following therapies is the patient with diabetes on?

- None
- SU +/- others
- Non-SU
- Insulin +/- others
- Insulin pump

Does the patient with diabetes have extensive coronary artery disease at high risk of ischemic events OR multiple co-morbidities?

- Yes
- No



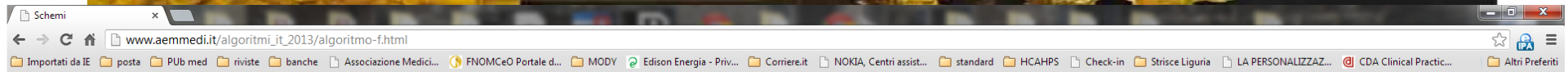
# European Diabetes Working Party for Older People 2011 Clinical Guidelines for Type 2 Diabetes Mellitus (EDWPOP)

Paziente	Obiettivo Hb A1c	Obiettivo glicemia a digiuno	Livello di prova/ Forza della raccomandazione
Anziano privo di altre co- morbilità maggiori	7- 7.5%	100- 135 mg/ dl	1+/ A 2++/ A
Anziano fragile (non autonomo, malattie multisistemiche; in casa di cura; demente)	7.6- 8.5%	135- 172 mg/ dl	1+/ A 2+/ C

*Sinclair AJ Diabetes & Metabolism 2011; 37: S27- S38*



# AMD 2013: anziano fragile



ALGORITMO A	ALGORITMO B	ALGORITMO C	ALGORITMO D	ALGORITMO E	ALGORITMO F
HbA <sub>1c</sub> ≥75 mmol/mol (≥9%)	BMI <30 e HbA <sub>1c</sub> 48-75 mmol/mol (tra 6,5 e <9%)	BMI ≥30 e HbA <sub>1c</sub> 48-75 mmol/mol (tra 6,5 e <9%)	Rischio professionale per possibili ipoglicemie (HbA <sub>1c</sub> 48-75 mmol/mol (tra 6,5 e <9%))	IRC e HbA <sub>1c</sub> 48-75 mmol/mol (tra 6,5 e <9%)	Anziano fragile con iperglicemia lieve/moderata (HbA <sub>1c</sub> <75 mmol/mol <9%)

Algoritmo F  
Flowchart F0



## Parametri per l'inquadramento/caratterizzazione del paziente con diabete di tipo 2, anziano fragile

**Criteri di fragilità**

- Ospite di casa di riposo/RSA
- Decadimento cognitivo
- Importante impedimento funzionale arti inferiori
- Allettamento
- Storia di comorbilità invalidanti

**Obiettivi terapeutici**

- HbA<sub>1c</sub>: >7,6 e <8,5% (>60 e <69 mmol/mol)
- Glicemia a digiuno: >136 e <162 mg/dl (>7,5 e <9 mmol/l)

### Note esplicative:

- La fragilità è una sindrome multidimensionale derivante dall'interazione complessa fra variabili sociali, biologiche e psicologiche, predisponente ad una maggiore vulnerabilità, al declino funzionale, a cadute, ospedalizzazione e morte.
- La connotazione dell'iperglicemia all'automonitoraggio (a digiuno o post-prandiale) perde gran parte del suo significato negli step terapeutici in questa tipologia di pazienti.
- La glibenclamide è controindicata nel paziente anziano fragile.
- Il pioglitazone trova difficile collocazione in questi pazienti per il rischio di ritenzione idrica e scompenso cardiaco, di osteoporosi e per la non infrequente coesistenza di maculopatia.
- La repaglinide non è raccomandata (secondo la stessa scheda tecnica) per i pazienti >75 anni.
- Gli agonisti/analoghi del GLP-1 non hanno, al momento, indicazione per i pazienti >75 anni e non sono sicuramente adatti per il paziente fragile di età <75 anni.

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[Procedi >>](#)

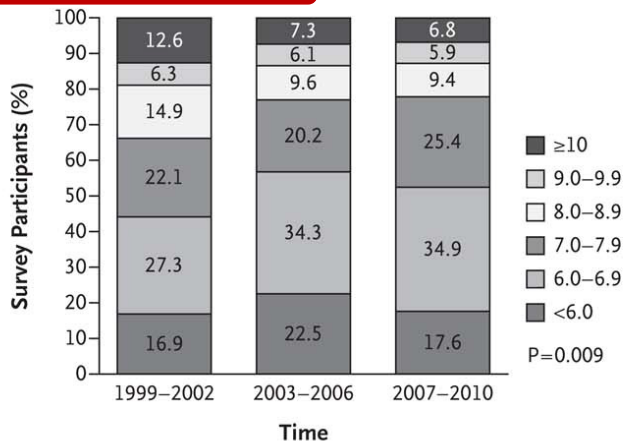




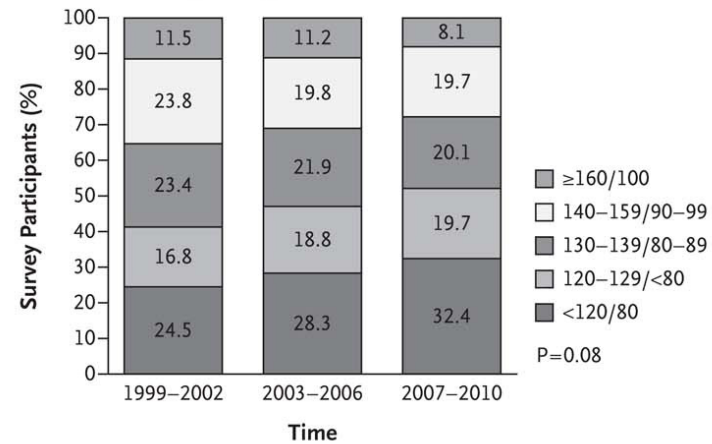
## Dal target alla terapia personalizzata

# Obiettivi raggiunti in periodi diversi

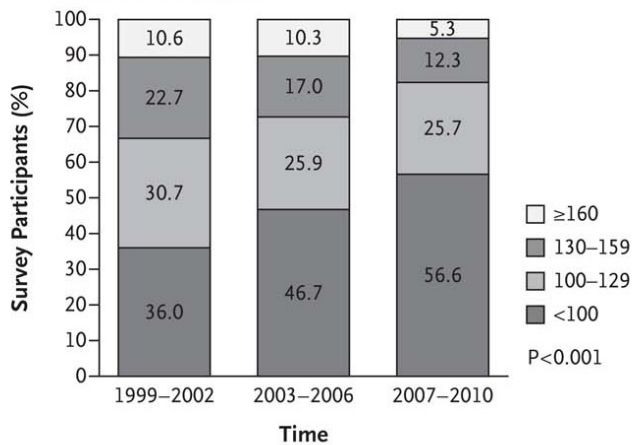
**A Glycated Hemoglobin (%)**



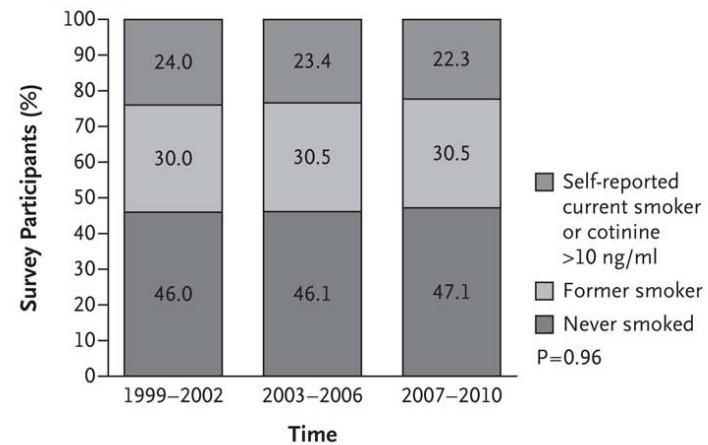
**B Blood Pressure (mm Hg)**



**C LDL Cholesterol (mg/dl)**



**D Smoking Status**





## Soggetti con HbA1c $\leq 7,0\%$



## Soggetti con HbA1c $>8,0\%$



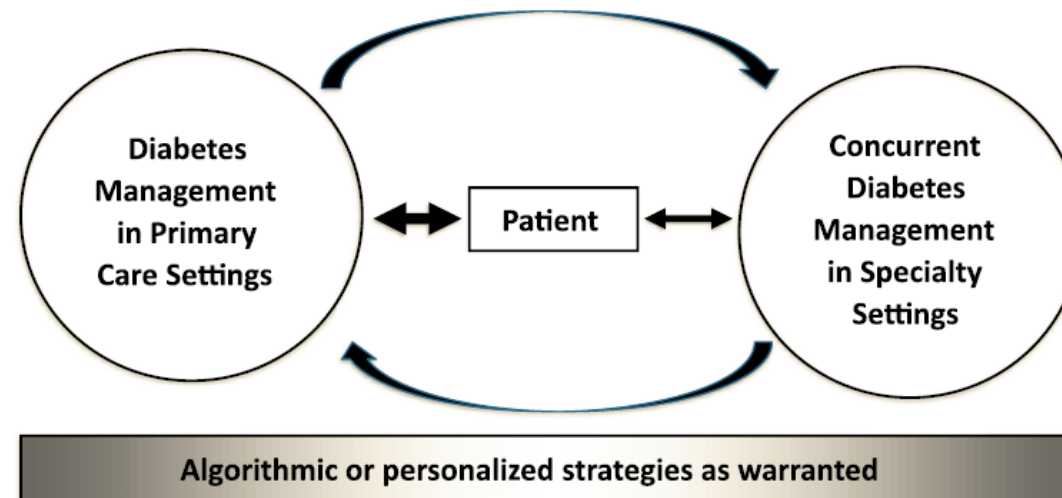
<http://www.infodiabetes.it/files/ANNALI-AMD/2012/Annali%202012.pdf>

# Personalized Management of Hyperglycemia in Type 2 Diabetes

Reflections from a *Diabetes Care* Editors' Expert Forum

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## Consider referral in cases involving:

- Failure to achieve glycemic targets
- Failure to respond to therapy
- Recurrent hypoglycemia
- Multiple drug intolerances/contraindications
- Development of complications
- Hyperglycemia during hospitalization
- Pregnancy
- Suspicion of unusual variants such as LADA, MODY, or secondary diabetes
- Heavy proteinuria with short disease duration in the absence of other microvascular complications
- Other complicating circumstances



## DOCUMENTO DI INDIRIZZO POLITICO E STRATEGICO PER LA BUONA ASSISTENZA ALLE PERSONE CON DIABETE

### Classi

- ❑ **Classe 1:** serio e grave pericolo per la vita o l'autosufficienza : **ricovero urgente**
- ❑ **Classe 2:** complicanza acuta intervento specialistico urgente, anche in ricovero, non sono in immediato pericolo: **ricovero con supporto diabetologico**
- ❑ **Classe 3:** intervento specialistico o multidisciplinare non urgente, ma comunque indifferibile: **percorso ambulatoriale predefinito prioritario**
- ❑ **Classe 4:** compenso instabile: **percorso ambulatoriale predefinito**
- ❑ **Classe 5:** buon compenso metabolico FR a target, non complicanze in atto: **gestione integrata**
- ❑ **Classe 6:** cronicità multiple e riduzione dell'autosufficienza, allettati: **cura domiciliare integrata con MMG**
- ❑ **Classe 7:** popolazione generale : **MMG**

### Esempi

1. Infarto acuto, coma, intervento di bypass, sepsi, amputazione
2. Gangrena, angioplastica, scompenso senza coma, grave ipoglicemia con perdita di coscienza e recupero, ricovero in reparto non di terapia intensiva
3. Neo diagnosi, GDM, ulcera senza infezione
4. Compenso instabile, fuori target, complicanze
5. HbA1c<7,0%, stabili, complicanze stabilizzate
6. Cronici in gestione domiciliare
7. Prevenzione generale o specifica

[http://www.aemmedi.it/files/Linee-guida\\_Raccomandazioni/2010/2010-documento\\_indirizzo.pdf](http://www.aemmedi.it/files/Linee-guida_Raccomandazioni/2010/2010-documento_indirizzo.pdf)



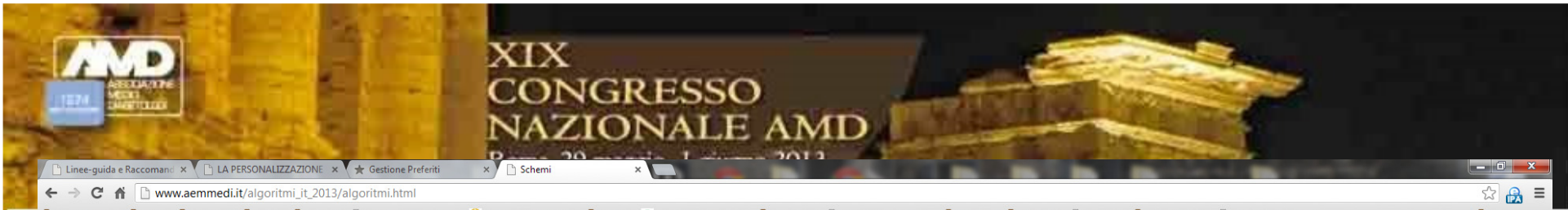
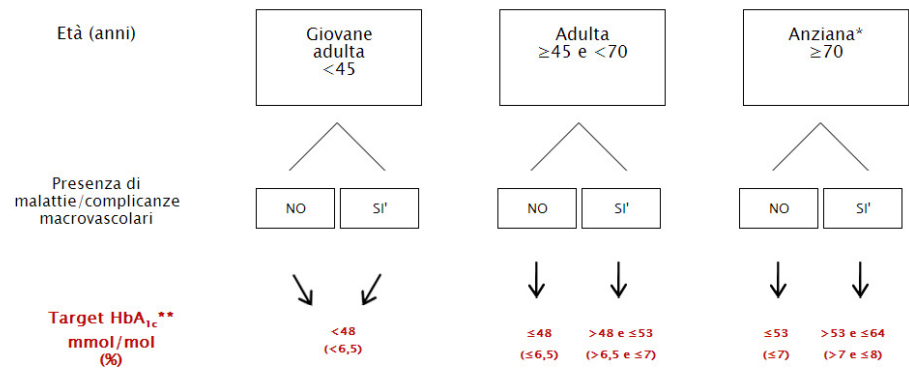


Fig. 1

**Parametri per l'inquadramento/caratterizzazione del paziente con diabete di tipo 2**



\* Valutare (alla presentazione e nel tempo) il filtrato glomerulare, il possibile rischio di ipoglicemie (particolare cautela nell'impiego di sulfoniluree e glinidi), l'assetto nutrizionale, la presenza di comorbidità e fragilità.  
 \*\* I valori target di HbA<sub>1c</sub> proposti, sono da intendersi come obiettivi da perseguire in sicurezza, limitando il rischio di ipoglicemia

**Scegliere la caratteristica principale del paziente con diabete di tipo 2:**

<b>ALGORITMO A</b> HbA <sub>1c</sub> ≥75 mmol/mol (≥9%)	<b>ALGORITMO B</b> BMI <30 e HbA <sub>1c</sub> 48-75 mmol/mol (tra 6,5 e <9%)	<b>ALGORITMO C</b> BMI ≥30 e HbA <sub>1c</sub> 48-75 mmol/mol (tra 6,5 e <9%)	<b>ALGORITMO D</b> Rischio professionale per possibili ipoglicemie (HbA <sub>1c</sub> 48-75 mmol/mol [tra 6,5 e <9%])	<b>ALGORITMO E</b> IRC e HbA <sub>1c</sub> 48-75 mmol/mol (tra 6,5 e <9%)	<b>ALGORITMO F</b> Anziano fragile con iperglicemia lieve/moderata (HbA <sub>1c</sub> <75 mmol/mol [ <9%])
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**Note indispensabili per un corretto uso dell'algoritmo:**

- I riquadri cliccabili consentono il passaggio al gradino terapeutico successivo qualora il target di HbA<sub>1c</sub> non sia stato raggiunto.
- SMBG: l'automonitoraggio della glicemia è strumento di ulteriore fenotipizzazione del paziente ai fini decisionali oltre alla emoglobina glicata. La frequenza dei controlli glicemici deve essere determinata dal medico su base individuale tenendo conto dello schema terapeutico, del grado di compenso e delle necessità cliniche ed educazionali, secondo principi di appropriatezza. Per gli schemi di automonitoraggio si fa riferimento alle linee guida IDF sull'automonitoraggio glicemico nel paziente con diabete di tipo 2 non trattato con insulina (disponibili qui: [www.idf.org/guidelines/self-monitoring](http://www.idf.org/guidelines/self-monitoring)).



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CONGRESSO  
NAZIONALE AMD  
Roma, 29 maggio - 1 giugno 2013  
Rome Marriott Park Hotel

# Grazie per l'attenzione