I target della HbA_{1c}

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

POSITION STATEMENT

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


POSITION STATEMENT
Standards of Medical Care for Patients With Diabetes Mellitus

Special Article

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

JEAN PIRART

DIABETES CARE, VOL. 1 NO. 3, MAY-JUNE 1978

Goals

…us effort to achieve levels of blood
…se **as close to those in the**
…iabetic person as feasible.

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

…concept is particularly applicable to
…diabetic p…
developin…
complicat…
middle-a…

Also, in c…
shorter li… expectancy may preclude the need for achieving lower glucose levels, providing they are asymptomatic.

and prese…
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**

DCCT 1993

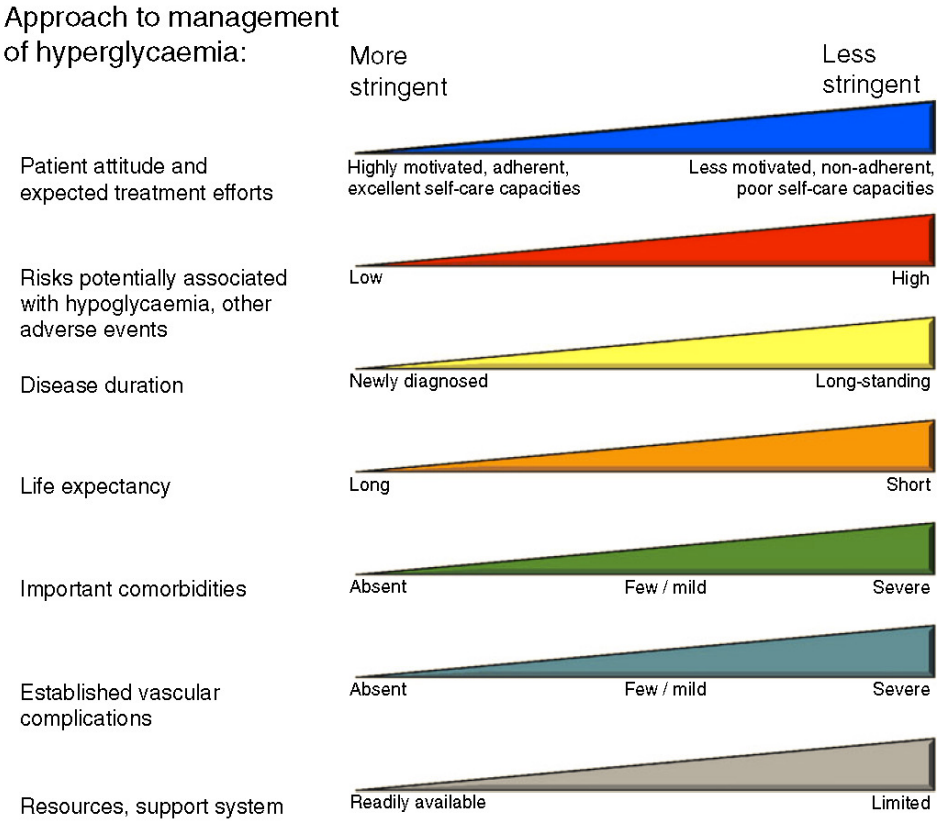
UKPDS 1998

Standards of Medical Care for Patients With Diabetes Mellitus Diabetes Care 13:10-13; January 1990

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



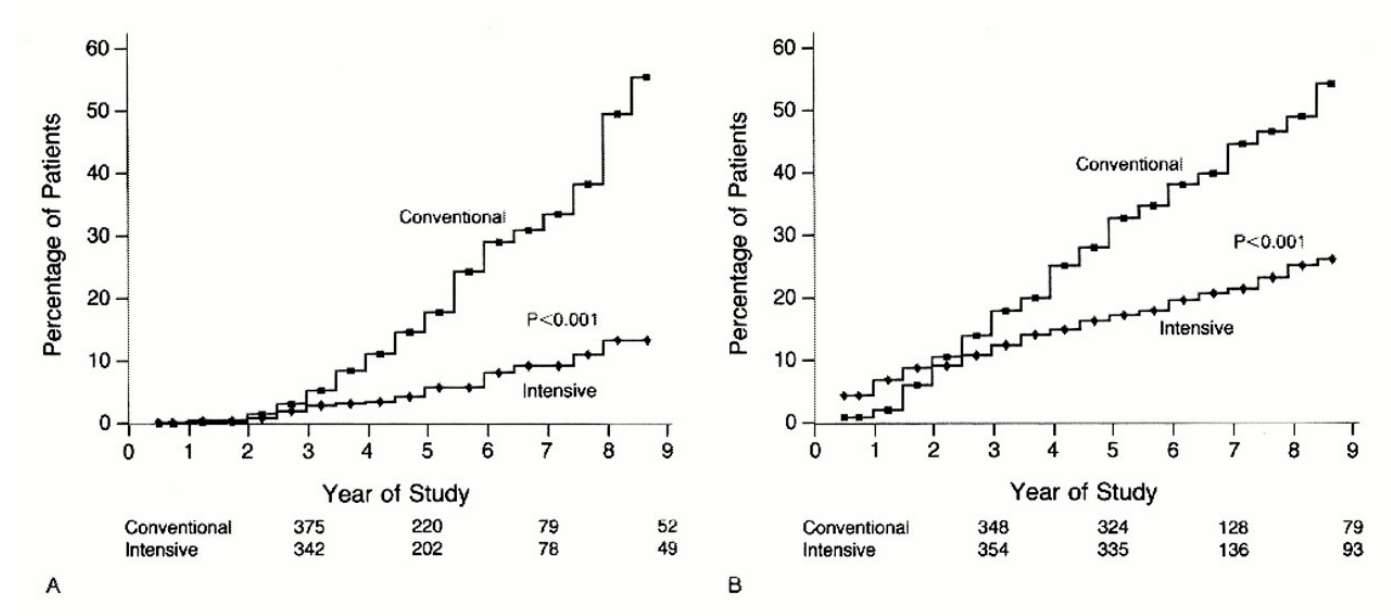
Diabetes Care, Diabetologia. 19 April 2012 [Epub ahead of print]

(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

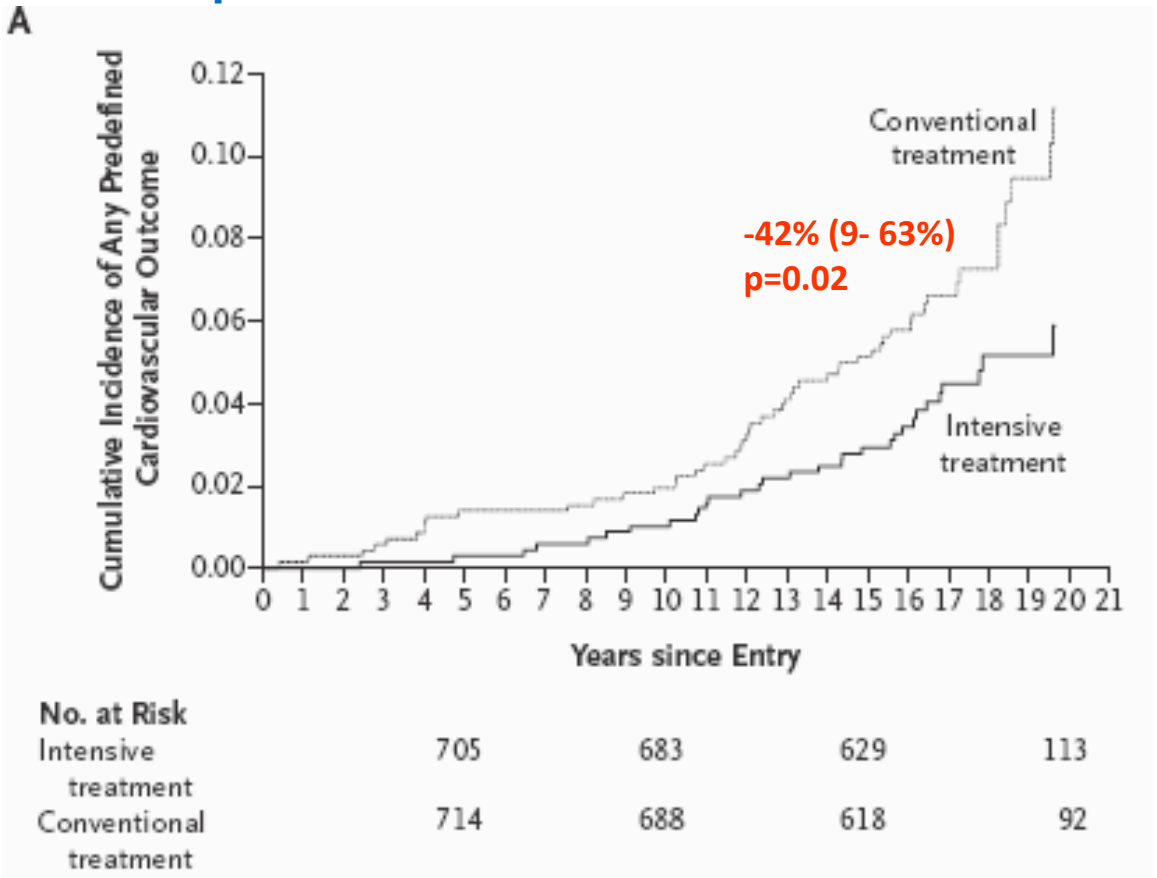
Cumulative Incidence of a Sustained Change in Retinopathy in Patients with IDDM Receiving Intensive or Conventional Therapy



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

Diabete tipo 1: compenso glicemico e complicanze macroangiopatiche

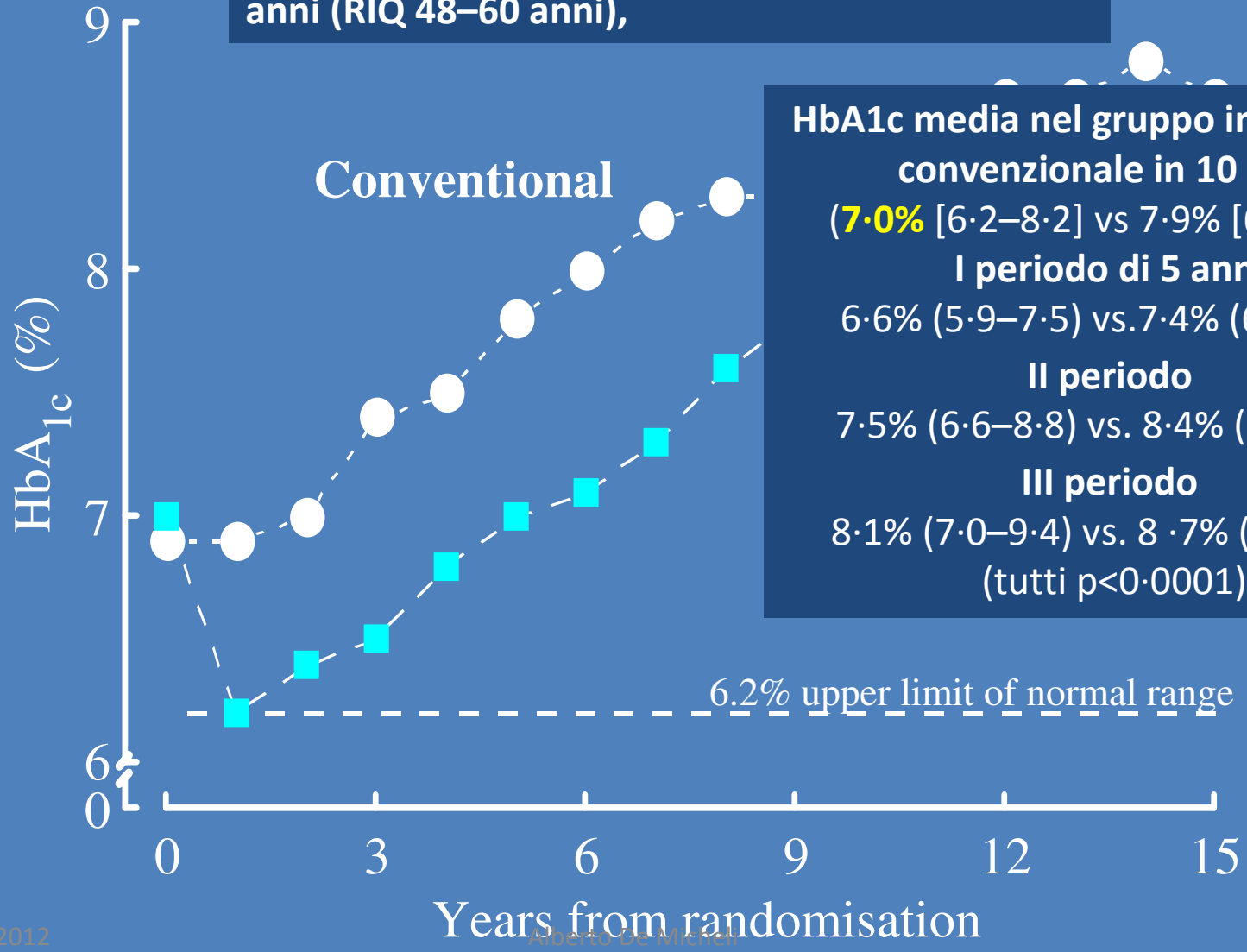
Incidenza cumulativa di eventi cardiovascolari in pazienti con diabete tipo 1 in terapia insulinica convenzionale o intensiva



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

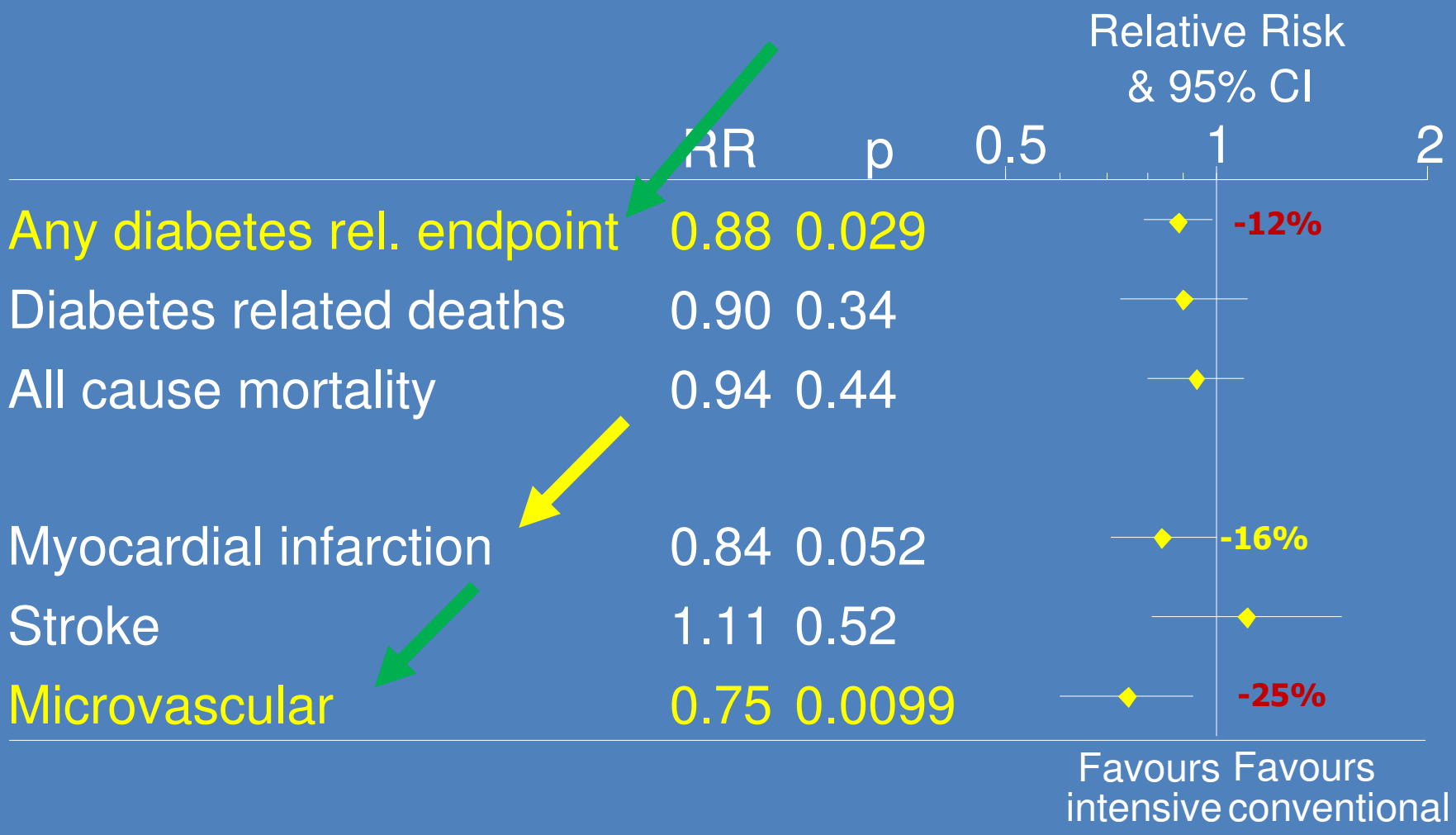
3867 diabetici t2 neo-diagnosticati, età media 54 anni (RIQ 48–60 anni),



HbA1c 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)

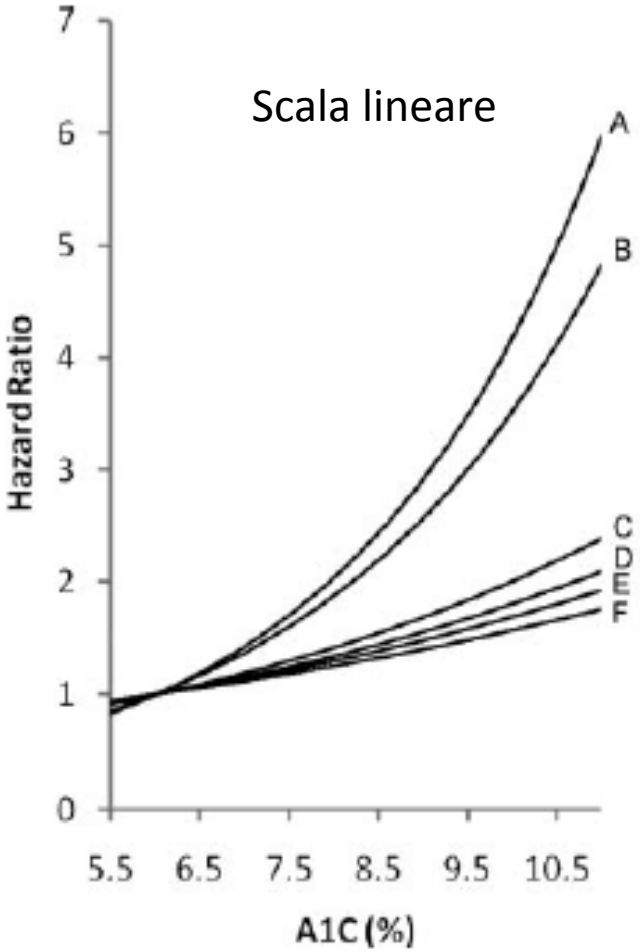
UKPDS 33, Lancet 1998; 352: 837-53

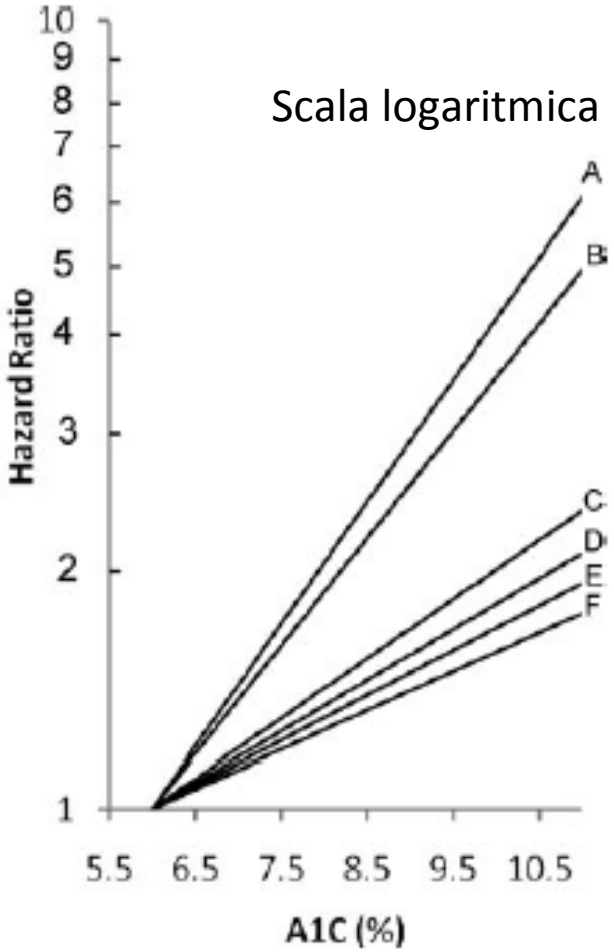
UKPDS: Compenso glicemico e complicanze del diabete



UKPDS 33, Lancet 1998; 352: 837-53

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





Incremento per 1% Hb A1c

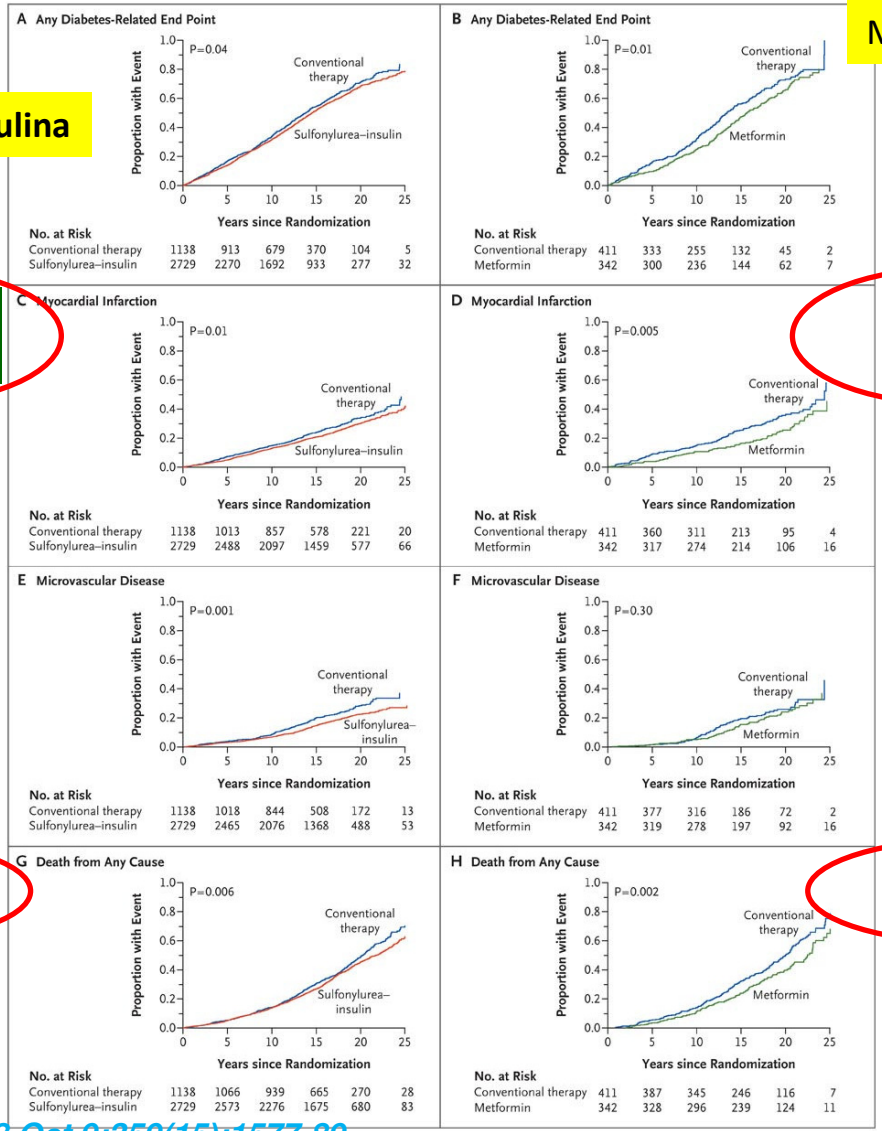
A Amput. morte per VP 43%
B. Retino- o nefropatia 37%
C. Cataratta 19%
D. Scompenso cardiaco 16%
E. Mortalità per IMA e tot 14%
F. Ictus 12%

UKPDS 35, Stratton IM, BMJ 2000; 321:405-12
Gerstein HC Circulation 2009, 119:773-775

Intervento all'esordio: UKPDS follow up 10 anni

Metformina

Sulfonilurea- Insulina



IMA p<0.01

IMA p<0.005

Mortalità tot p<0.01

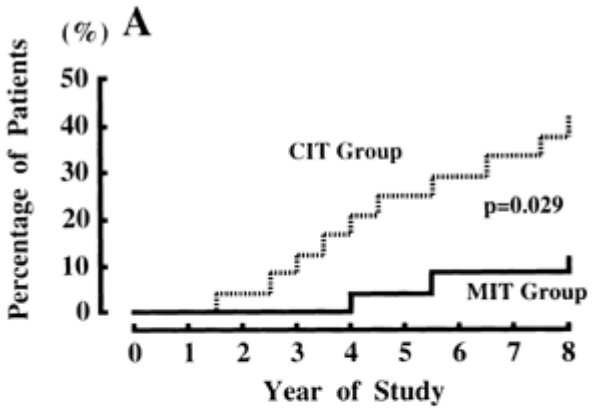
Mortalità tot p<0.002

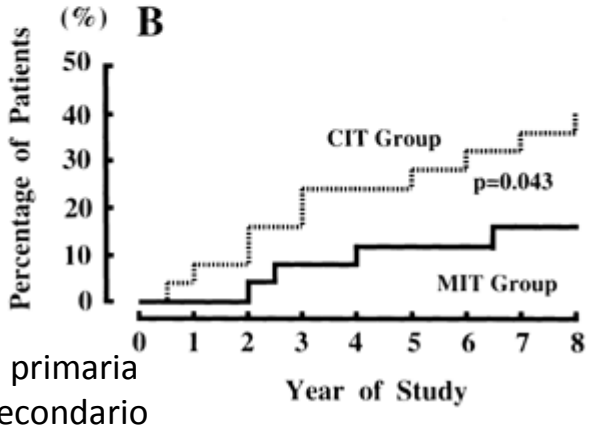
Holman R et al. N Engl J Med. 2008 Oct 9;359(15):1577-89

The NEW ENGLAND JOURNAL of MEDICINE

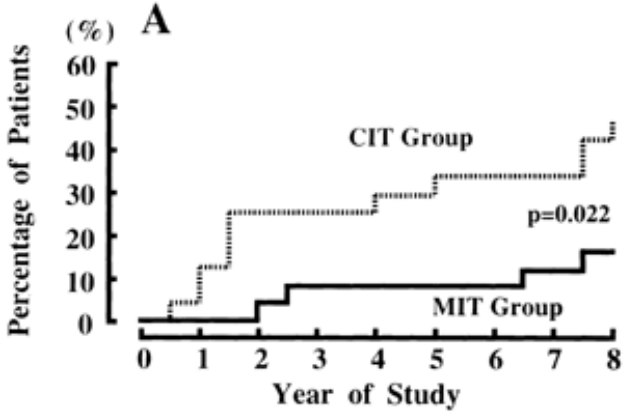
Kumamoto study: complicanze microangiopatiche

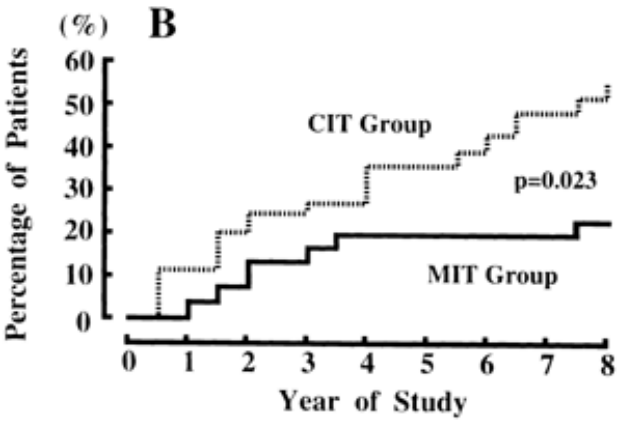
Nefropatia





Retinopatia





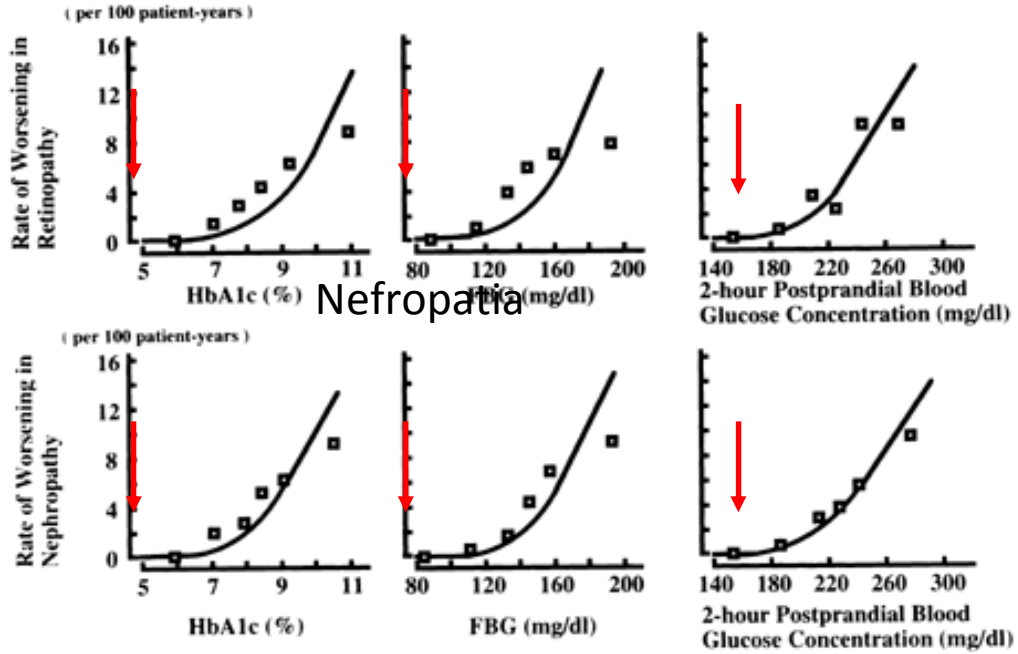
A prevenzione primaria
B intervento secondario

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

Kumamoto study: Relazione fra compenso glicemico e complicanze

Retinopatia

Nefropatia



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

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_{1c} (%)	<6	<7	>8

These values are for nonpregnant individuals. "Action suggested" depends on individual patient circumstances. Hemoglobin A_{1c} is referenced to a nondiabetic range of 4.0–6.0% (mean 5.0%, standard deviation 0.5%).

IDDM

- ❑DCCT an average hemoglobin A1c of 7.2%
- ❑in intensively treated .The reduction in risk correlated continuously with the reduction in hemoglobin Alc .
- ❑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 oexisting diseases that will materially shorten life expectancy).

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

Standards of Medical Care for Patients With Diabetes Mellitus

AMERICAN DIABETES ASSOCIATION

DIABETES CARE, VOLUME 25, NUMBER 1, JANUARY 2002


Reviews/Commentaries/Position Statements
POSITION STATEMENT

Standards of Medical Care for Patients With Diabetes Mellitus

AMERICAN DIABETES ASSOCIATION

Table 6 —*Glycemic control for nonpregnant individuals with diabetes*

	Normal	Goal	Additional action suggested *
Plasma values†			
Average preprandial glucose (mg/dl)	<110	90–130	<90/>150
Average bedtime glucose (mg/dl)	<120	110–150	<110/>180
Whole blood values†			
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

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:

- A1C is the primary target for glycemic control
- Goals should be individualized based on:
  - duration of diabetes
  - pregnancy status
  - age
  - comorbid conditions
  - hypoglycemia unawareness
  - individual patient considerations
- More stringent glycemic goals (i.e., a normal A1C, <6%) may further reduce complications at the cost of increased risk of hypoglycemia
- Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals

- **Lowering A1C to an average of < 7% has clearly been shown to reduce microvascular and neuropathic complications of diabetes and, possibly, acrovascular 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)**

Standards of Medical Care for Patients With Diabetes Mellitus Diabetes Care 31(S1): S12- S64; 2008

STANDARD ITALIANI PER LA CURA DEL DIABETE MELLITO

Obiettivi glicemici in diabetici adulti di tipo 1 e 2

HbA_{1c} <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

I quesiti

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*

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*

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

Obiettivi e metodi

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 rosiglitazone, 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)	**0.9 (0.82- 0.98)** Macro 0.94 (0.84- 1.06) **Micro 0.86 (0.77- 0.97)**
HR per mortalità totale	**1.22 (1.01- 1.46)**	1.07 (0.81- 1.42)	0.93 (0.83- 1.06)
HR per mortalità CV	**1.35 (1.04- 1.76)**	1.32 (0.81- 2.14)	0.88 (0.74- 1.04)
Hb A_{1c} mediana raggiunta	**Intensivo 6.4%** **Standard 7.5%**	**Intensivo 6.9%** **Standard 8.5%**	**Intensivo 6.3%** **Standard 7.0%**
Variazione ponderale	**Intensivo +3.5 kg** **Standard +0.4 kg**	**Intensivo +7.8 Kg** **Standard +3.4 kg**	**Intensivo - 0.1 kg** **Standard -1.0 kg**
Ipoglicemie severe	**Intensivo 16.2%** **Standard 5.1%**	**Intensivo 21.2%** **Standard 9.9%**	**Intensivo 2.7%** **Standard 1.5%**

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_{1c} (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**.

Dluhy RG and McMahon GT, NEJM 2008; 358: 2630- 33

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.

Cefalu WT, NEJM 2008, 358; 2633- 35

JAMA®

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

COMMENTARY

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

Annals of Internal Medicine | PERSPECTIVE

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 HbA1c targets for clinical use cannot be the same when used to measure quality of care. Policymakers who want to use HbA_{1c} as a performance measure should use an upper limit, such as an HbA_{1c} 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, HbA1c level 7%).

Montori, VM, Fernandez-Balsells M, *Ann Intern Med. 2009; 150: 803- 808*

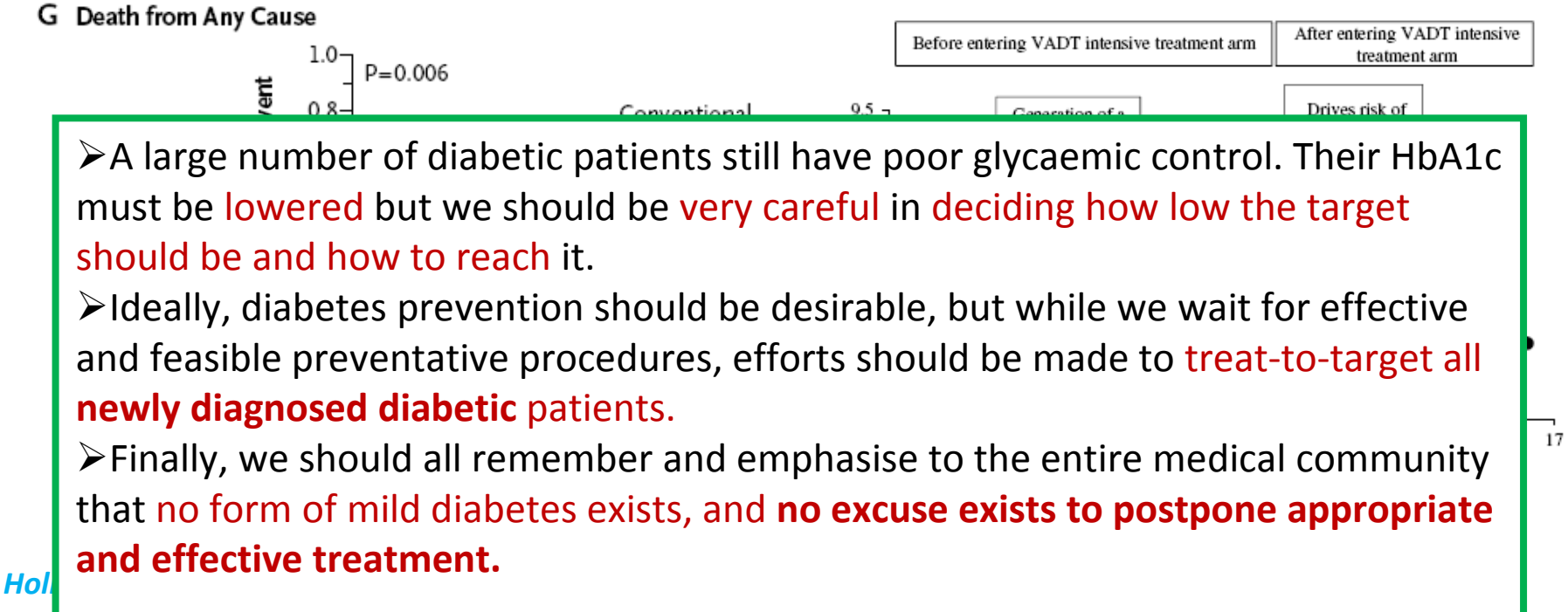
COMMENTARY

Megatrials in type 2 diabetes. From excitement to frustration?

S. Del Prato

Storia dell'UKPDS

Storia del VADT



- 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.**

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 glucosel owering agents including insulin.

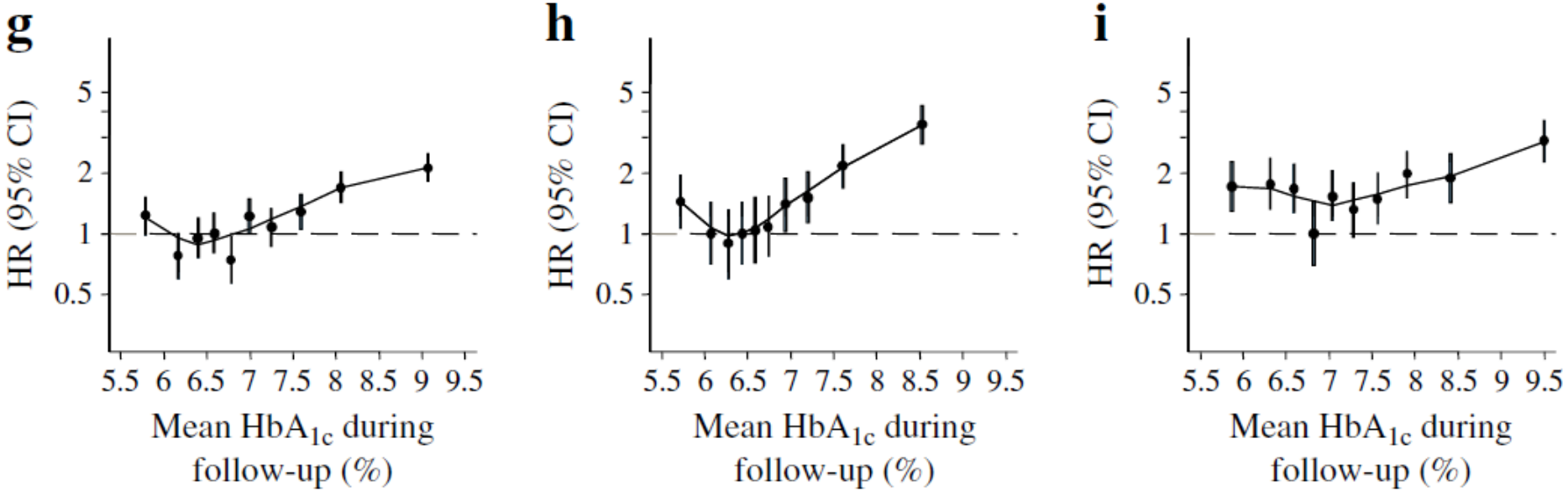
ADA, C-level recommendation; ACC/ AHA, class IIa recommendation (level of evidence C).

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

I target e gli algoritmi

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

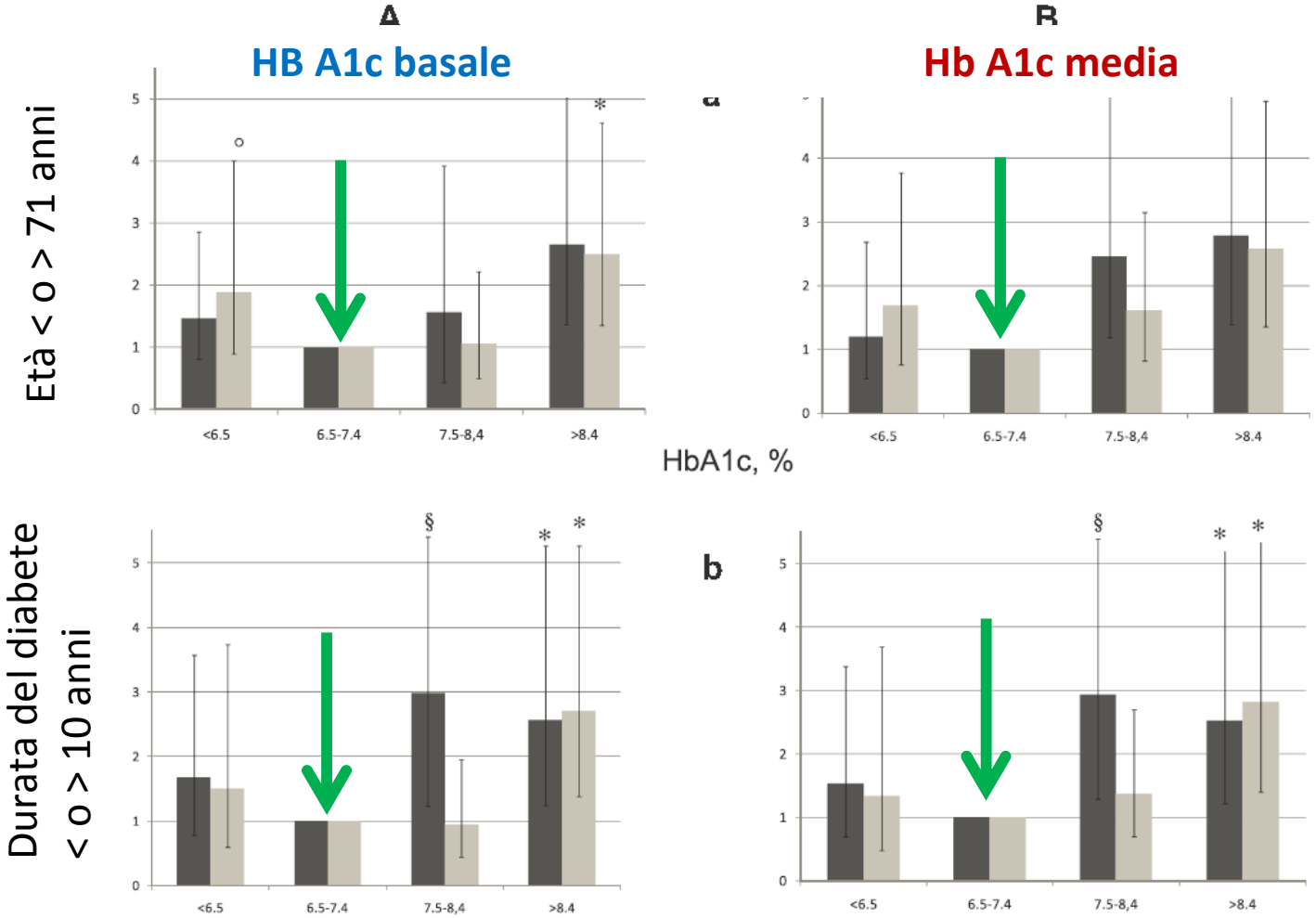
Morte per ogni causa



Tutti **Intensiva** **Standard**

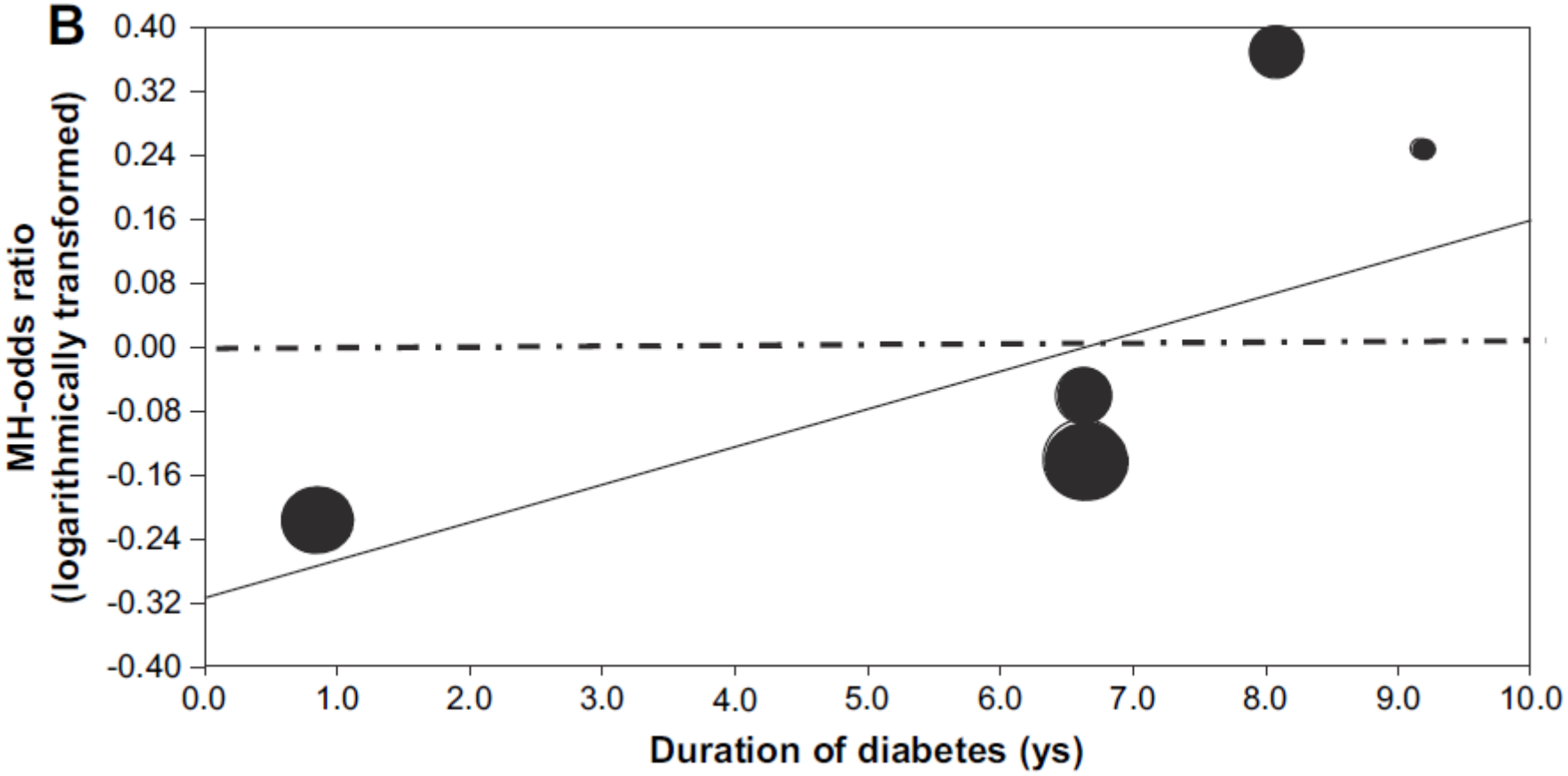
Zoungas S Diabetologia 2012, DOI 10.1007/s00125-011-2404-1

Mortalità per ogni causa e Hb A1c



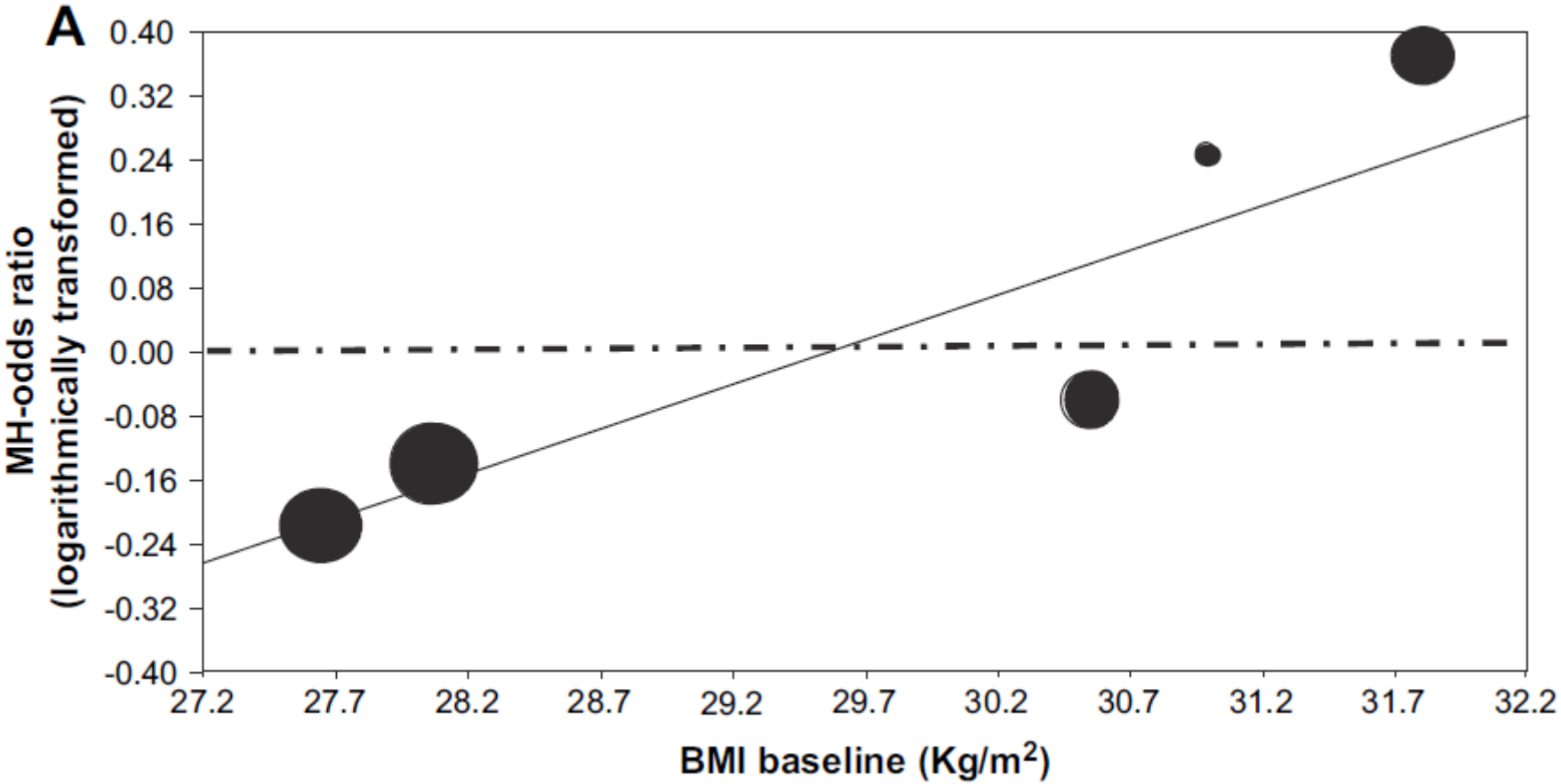
Monami M Nutrition, Metabolism & Cardiovascular Diseases 2013: 23, 300 -306

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



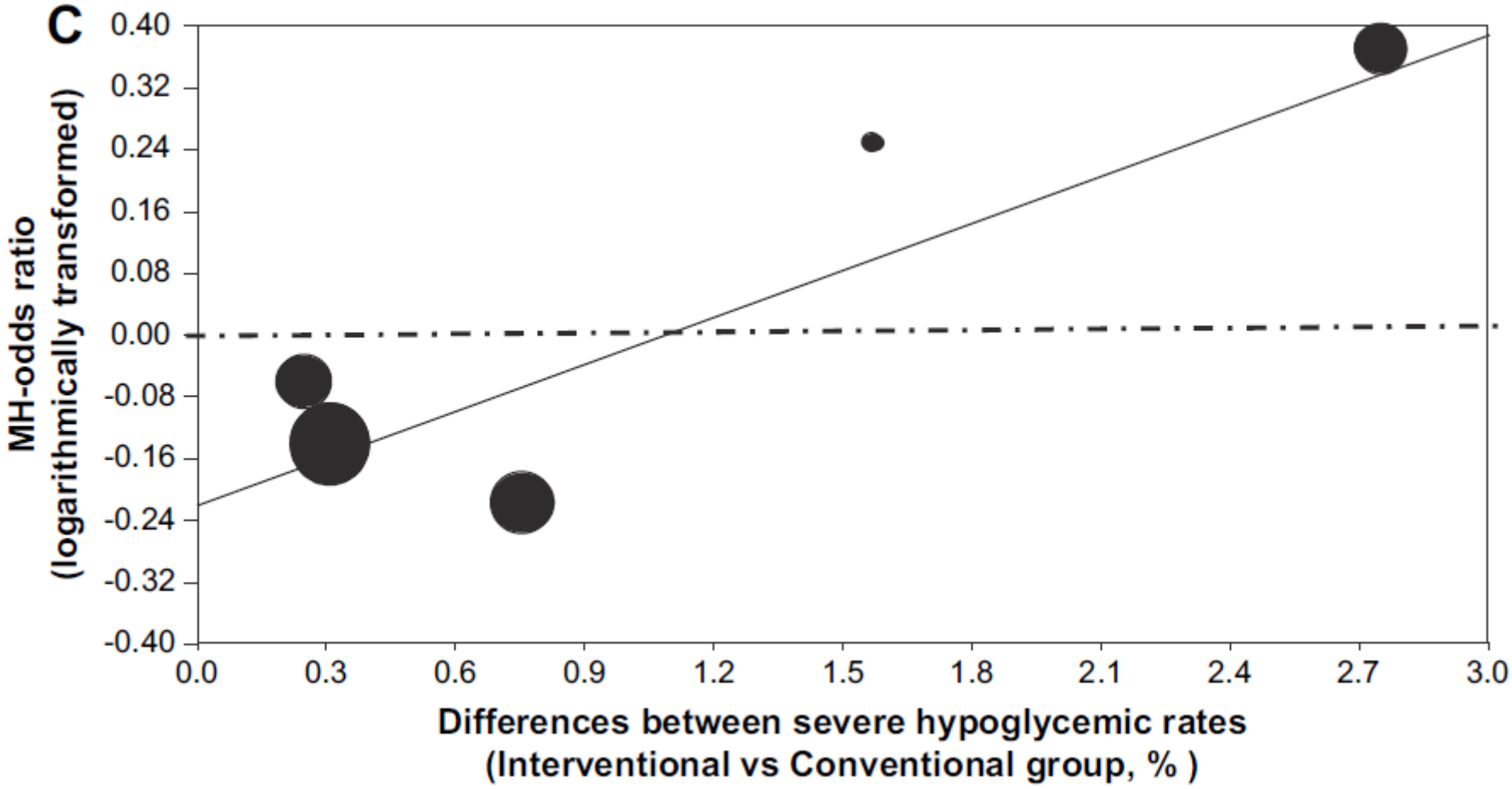
Mannucci E Nutrition, Metabolism & Cardiovascular Diseases 2009; 19, 604- 612

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

Il NNH per l'ipoglicemia: la metanalisi di Kelly

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

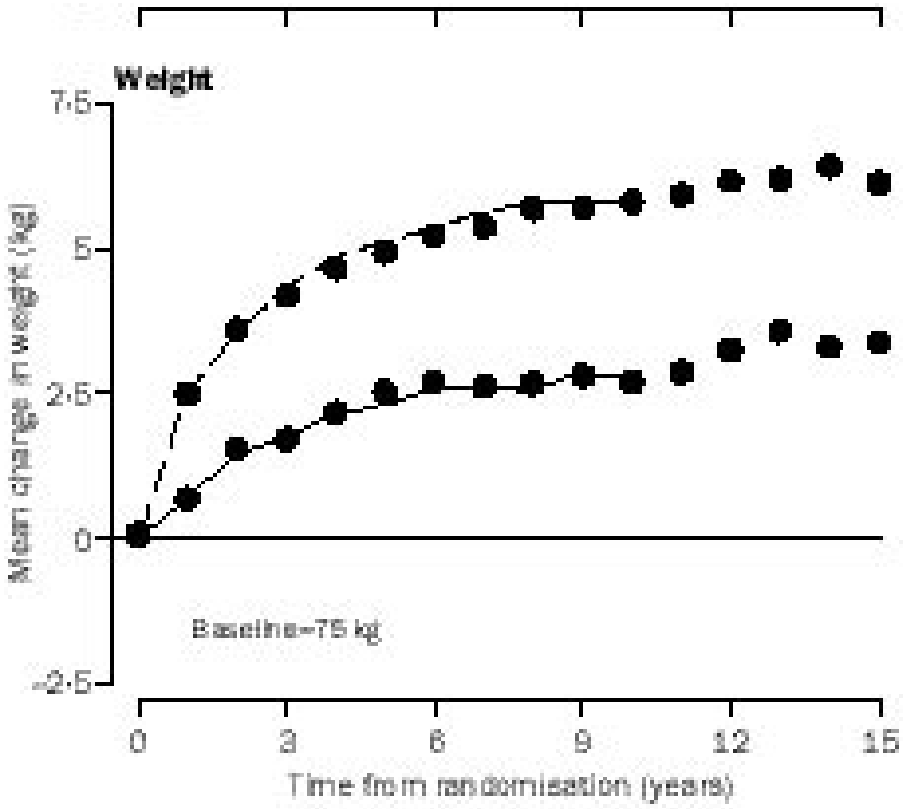
Kelly, T. N. et. al. Ann Intern Med 2009;151:394-403

Possibili relazioni fra ipoglicemia ed eventi cv

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

Betsy B, Diabetes Spectrum 2008; 21: 150- 152

Variazioni ponderali nell'UKPDS

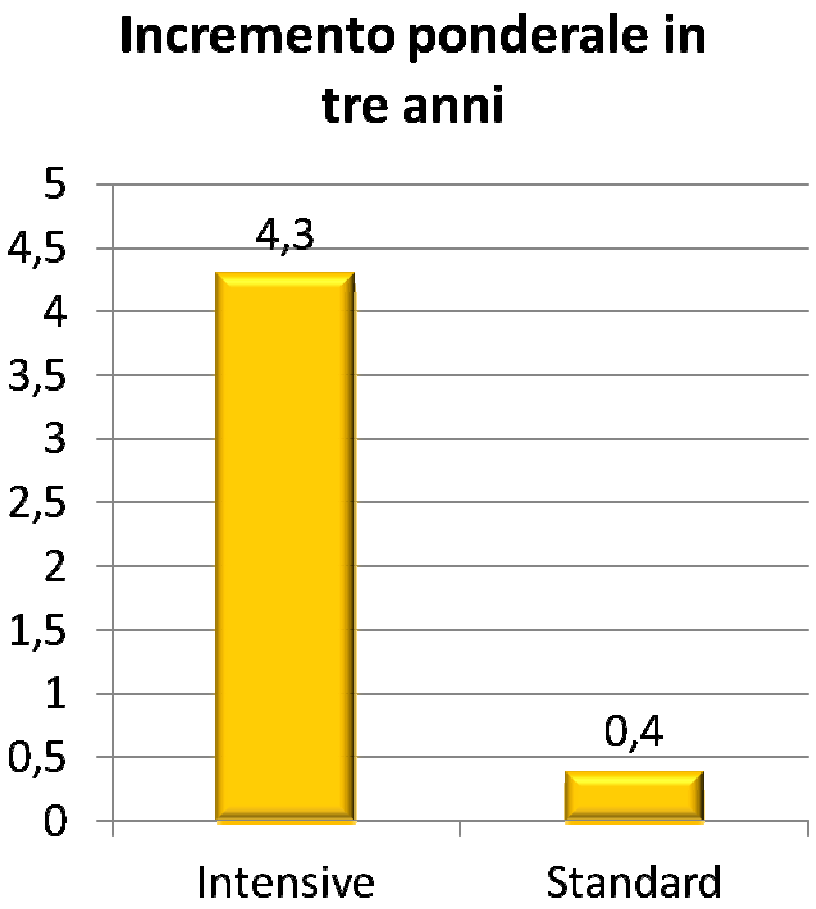


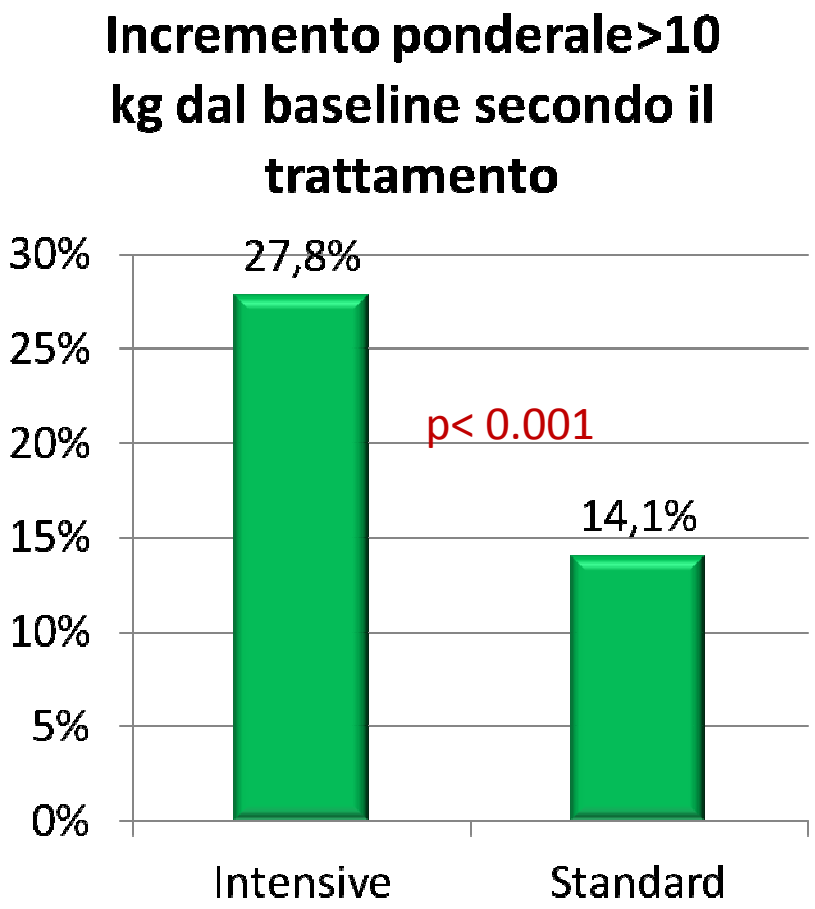
intensive

conventional

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

ACCORD: incremento ponderale

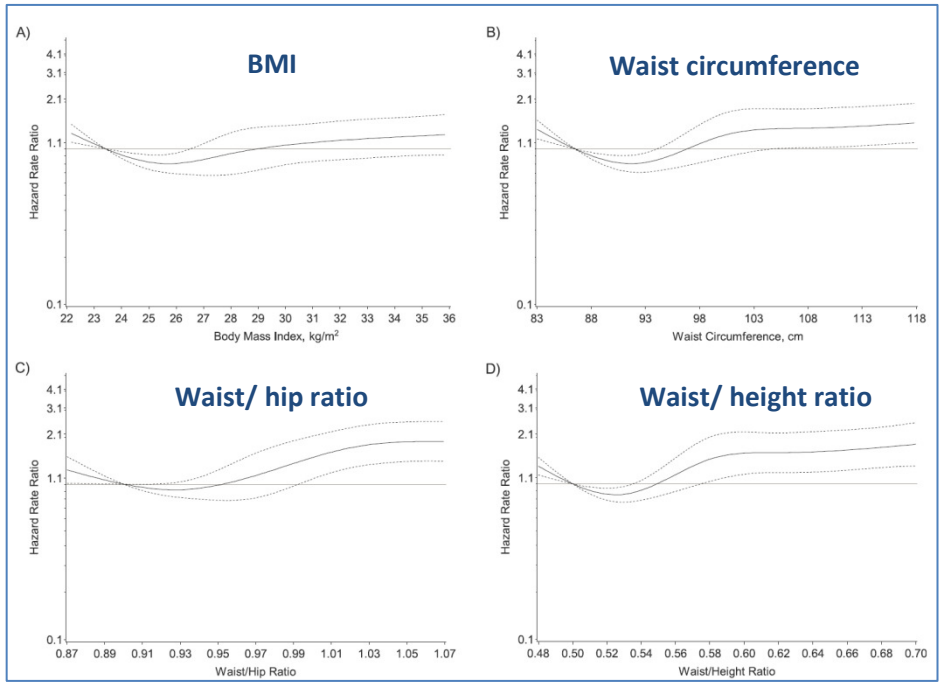




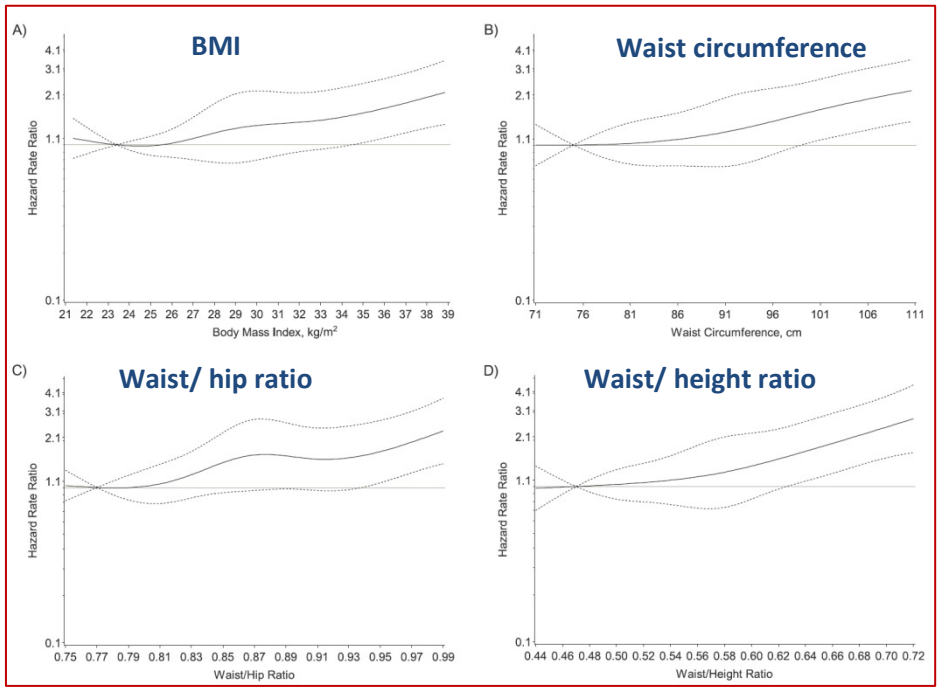
The Action to Control Cardiovascular Risk in Diabetes Study Group. N Engl J Med 2008;358:2545-59

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 glycemic control vs. conventional RCT

Intensive glycaemic control compared to conventional glycaemic control for type 2 diabetes mellitus

Patient or population: patients with type 2 diabetes mellitus
Settings:
Intervention: Intensive glycaemic control
Comparison: 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				
All-cause mortality 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** [1]	
Cardiovascular mortality 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** [2]	
Non-fatal myocardial infarction 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** [3]	
Non-fatal stroke 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** [4]	

Hemmingsen B, Cochrane Database of Systematic Reviews 2011, Issue 6. Art.No.: CD008143. DOI: 10.1002/14651858.CD008143.pub2

Cochrane: intensive glycemic control vs. conventional RCT

	Conventional	Intensive			
Amputation of lower extremity 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** [5]
End-stage renal disease 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** [6]
Severe hypoglycaemia 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** [7]

*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;

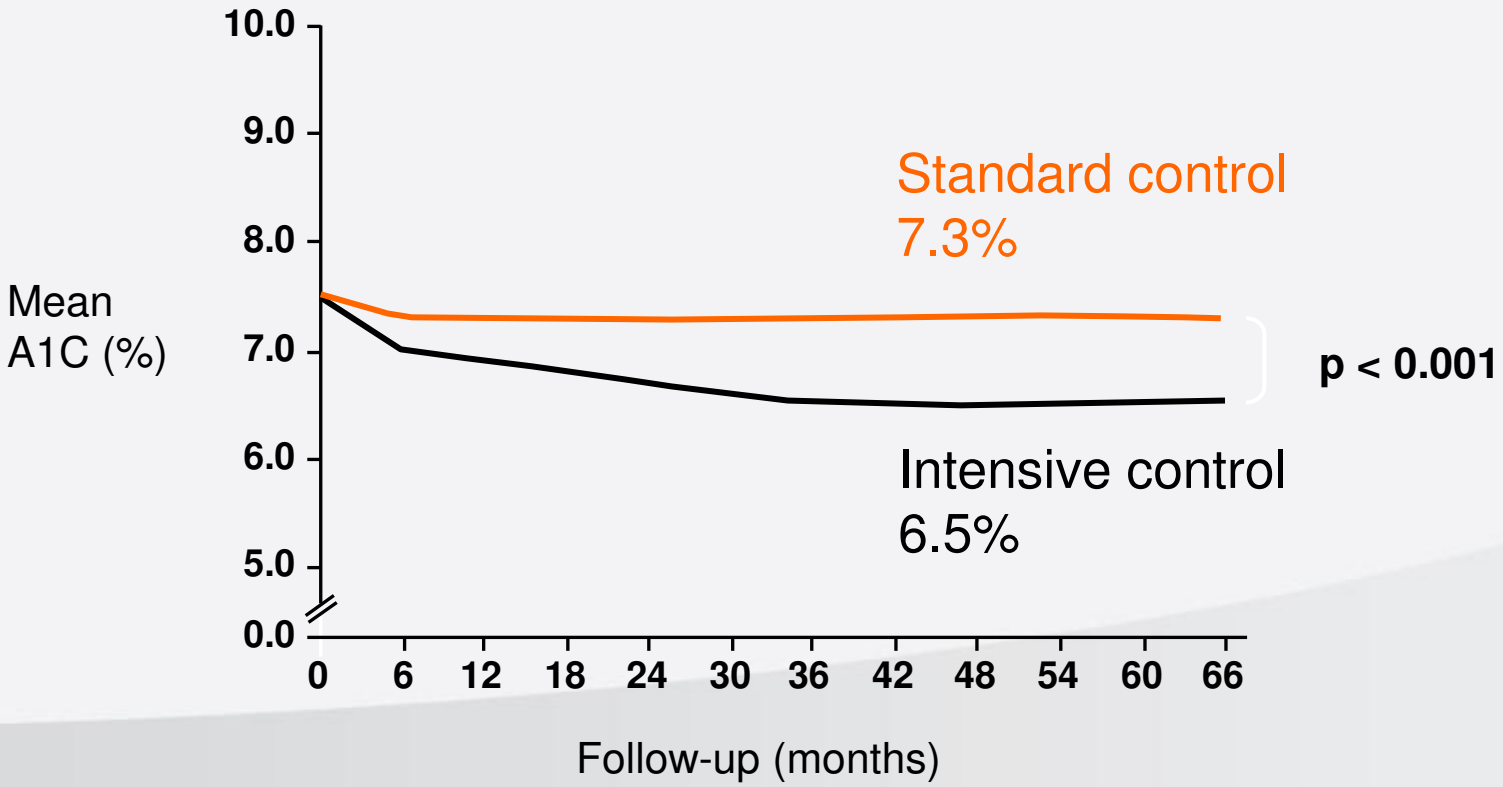
- Composite microvascular disease (RR 0.89, 95% CI 0.83 to 0.95; P = 0.0006; 25,760 participants, 4 trials),
- Retinopathy RR **0.79, 95% CI 0.68 to 0.92**; P = 0.002; 10,986 participants, 8 trials),
- Retinal photocoagulation (**RR 0.77, 95% CI 0.61 to 0.97;** P = 0.03; 11,142 participants, 7 trials),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

Hemmingsen B, Cochrane Database of Systematic Reviews 2011, Issue 6. Art.No.: CD008143. DOI: 10.1002/14651858.CD008143.pub2

La scelta del target ogni giorno

Why ≤ 6.5% ?

ADVANCE: Glucose Control

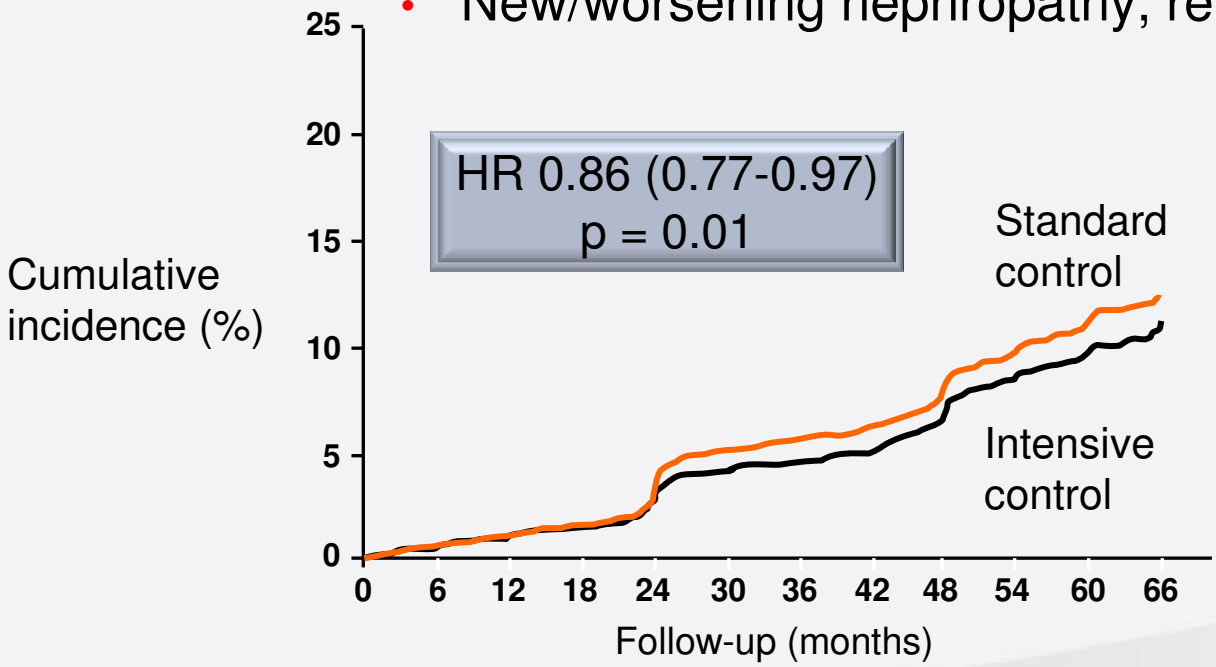


ADVANCE Collaborative Group. N Engl J Med 2008;358:24.

Canadian Diabetes Association

ADVANCE: Treatment Effect on the Primary Microvascular Outcomes

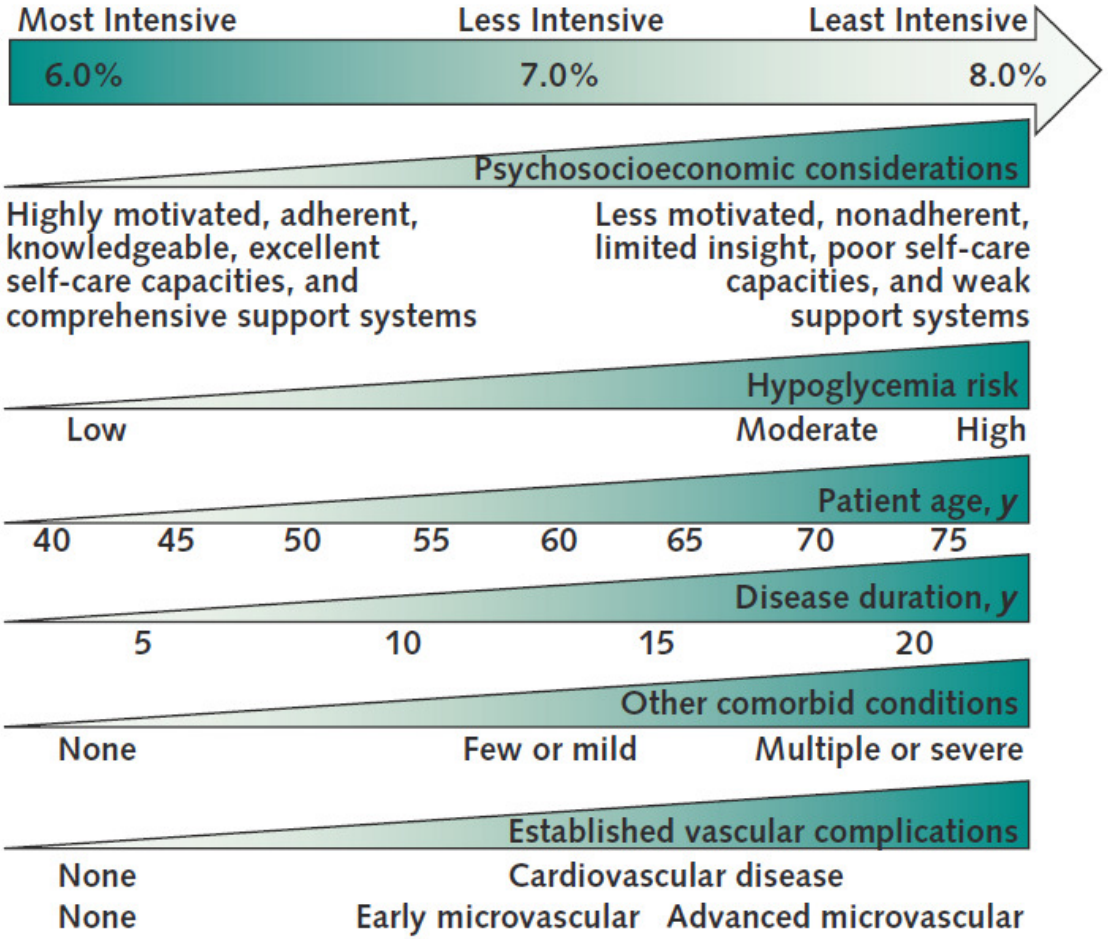
- New/worsening nephropathy, retinopathy



	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

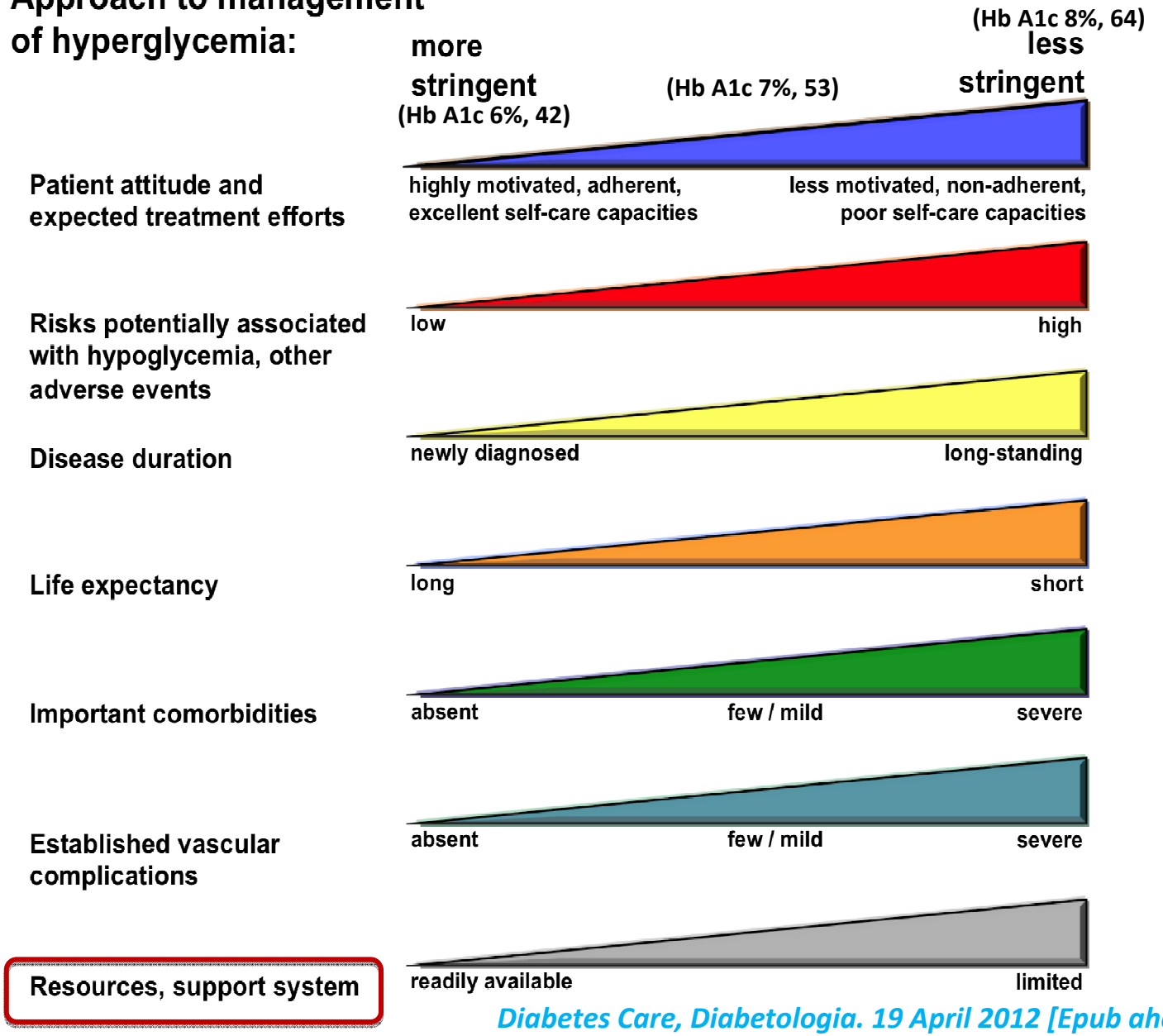
ADVANCE Collaborative Group. N Engl J Med 2008;358:24.

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:



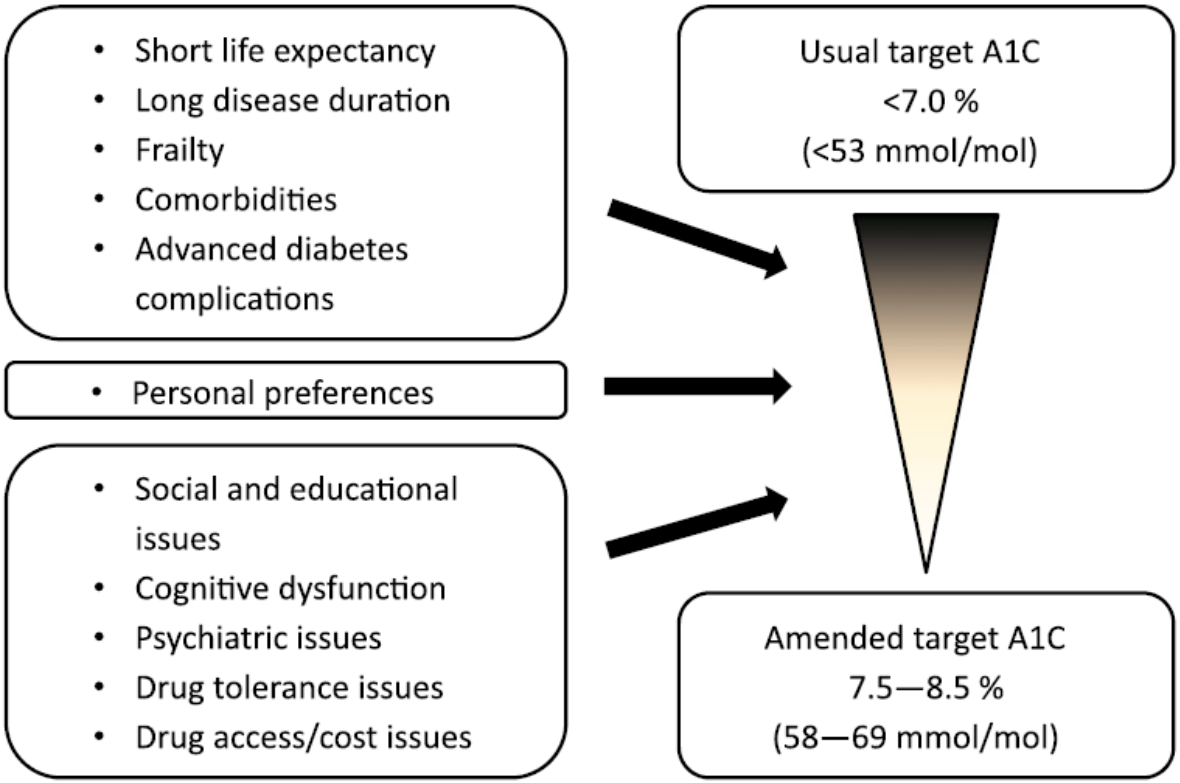
Diabetes Care, Diabetologia. 19 April 2012 [Epub ahead of print]

(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[1]
Matthew C. Riddle, MD[2]
Julio Rosenstock, MD[3]
John B. Buse, MD, PHD[4]
Silvio E. Inzucchi, MD[5]
Philip D. Home, DM, DPHIL[6]
Stefano Del Prato, MD[7]
Ele Ferrannini, MD[8]
Juliana C.N. Chan, MD[9]
Lawrence A. Leiter, MD[10]
Derek LeRoith, MD, PHD[11]
Ralph DeFronzo, MD[12]
William T. Cefalu, MD[13]



Raz I Diabetes Care 2013; 36:1779–1788

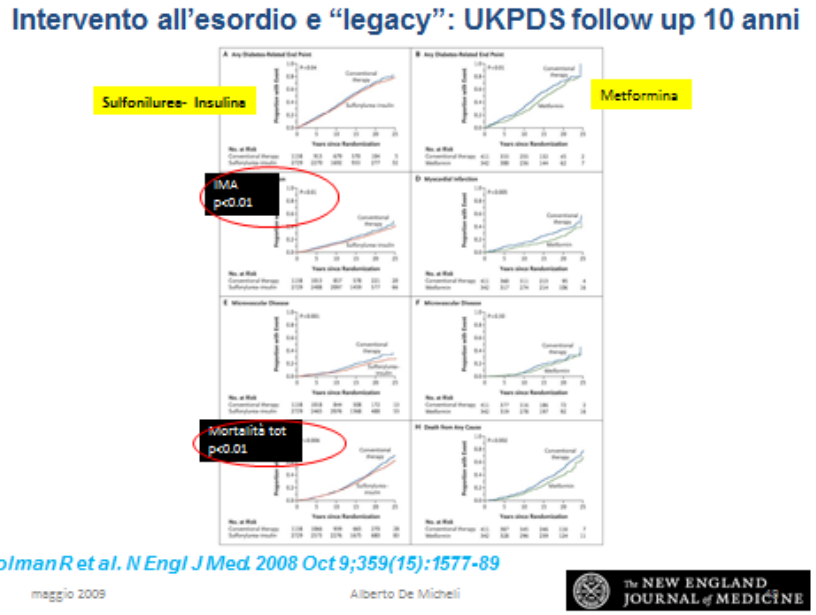
Ridotta attesa di vita e comorbilità

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

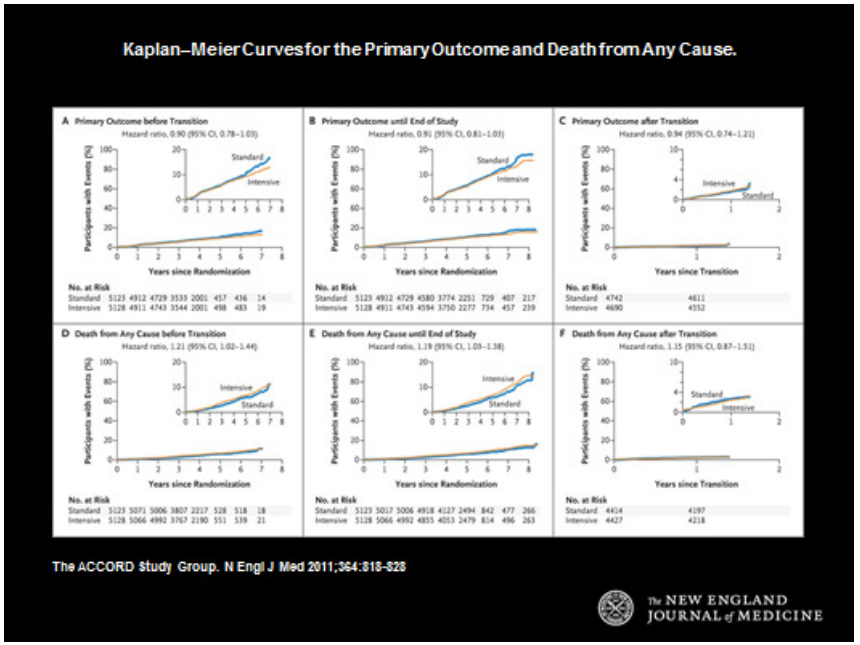
Ismail-Beigi F, Ann Intern Med. 2011; 154 :554 -559.

Lunga durata di malattia

Legacy



ACCORD



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

The ACCORD Study GroupN 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.***

Età

Età bassa

- lunga esposizione all'iperglicemia

Età elevata

- Comorbilità
- Ridotta attesa di vita

Characteristic	Mean Glycated Hemoglobin Reduction during Follow-up (95% CI)	Intensive Control (N=5571)	Standard Control (N=5569)	Hazard Ratio (95% CI)	Relative Risk Reduction (95% CI)
	percent	*number of patients (percent)*			*percent*
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

Diabetes and aging study: una curva ad U

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)

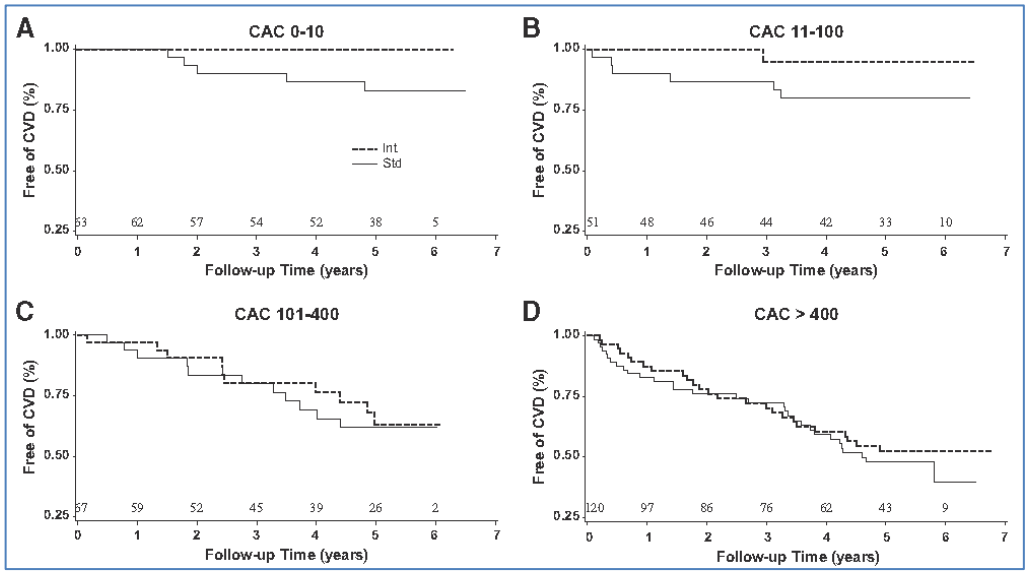
Huang ES, Diabetes Care 2011; 34:1329- 1336

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

Fragilità

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 vista 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, Churcill Livingstone 2000

Evidence-Based Persuasion

An Ethical Imperative

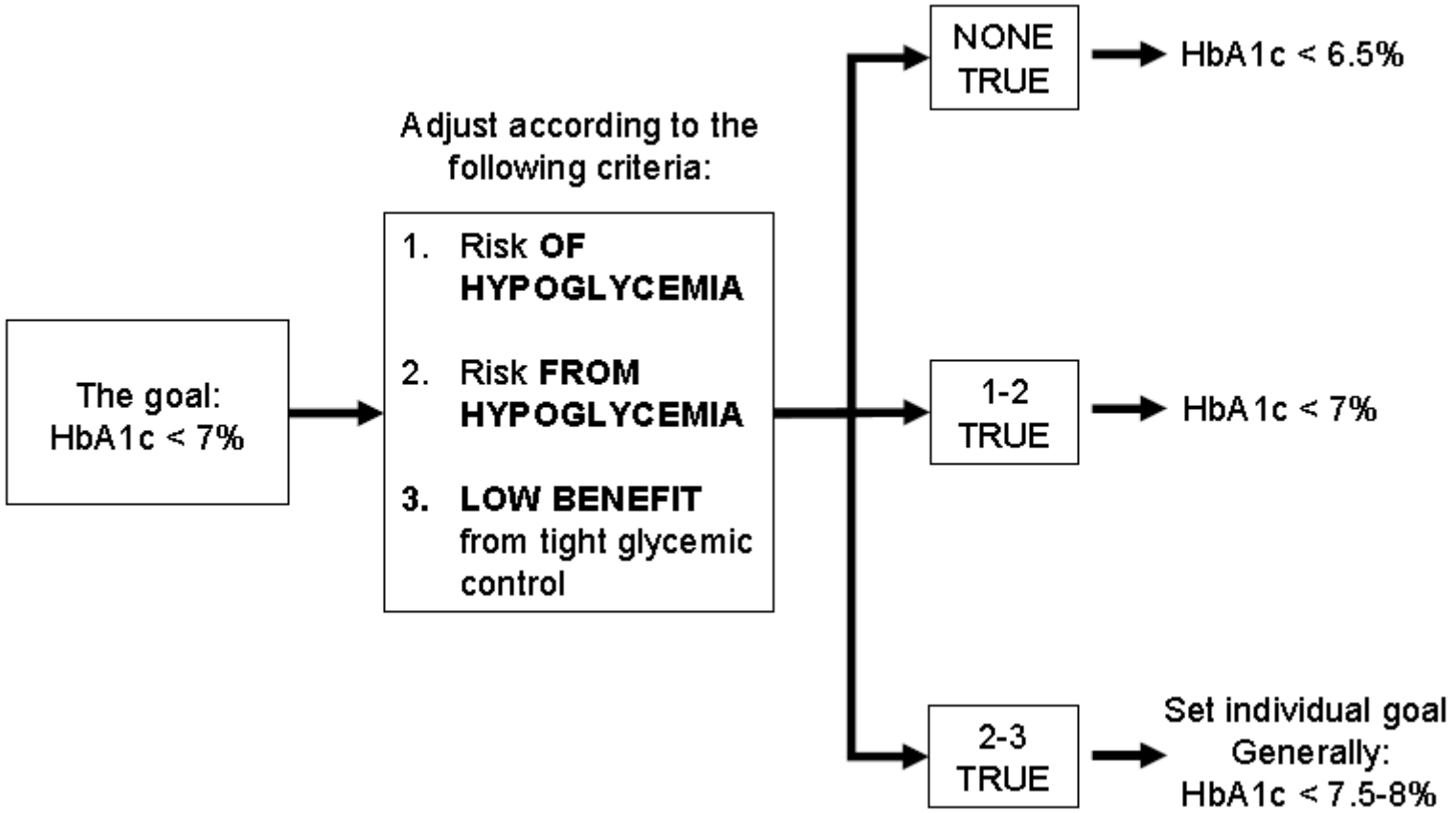
E' impossibile rispettare l'autonomia del paziente senza la persuasione:

- 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

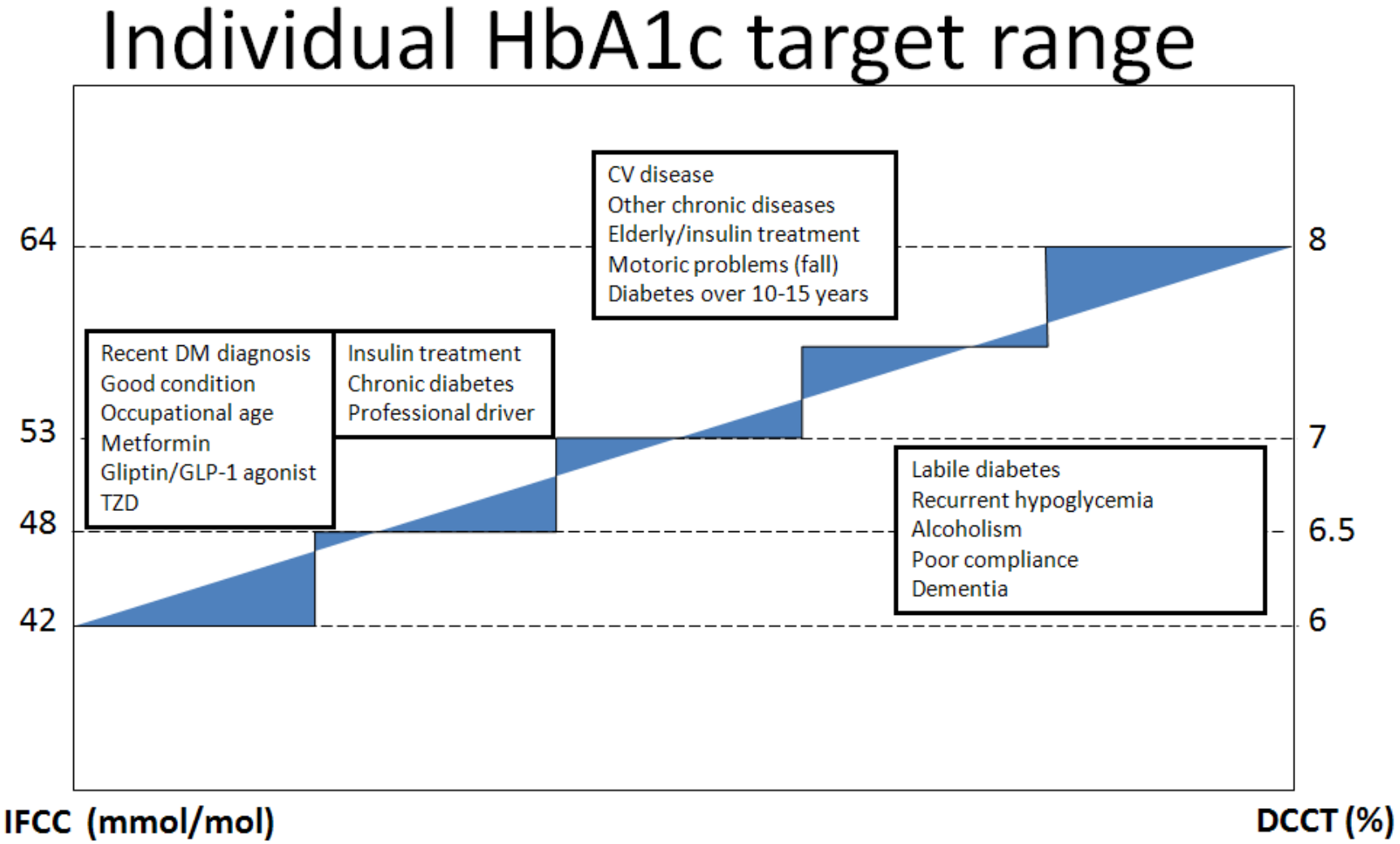
Indicazioni di linee guida, consensus algoritmi

Target glicemico: rapporto rischio/ beneficio



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

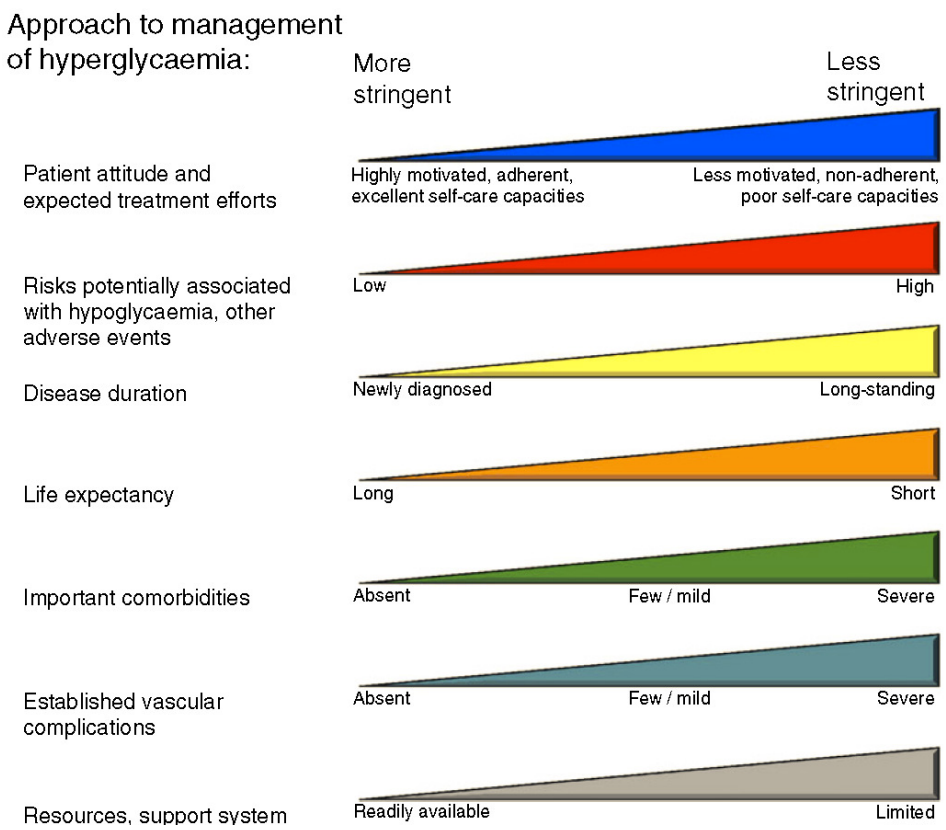
Finnish Current Care Guideline for Diabetes



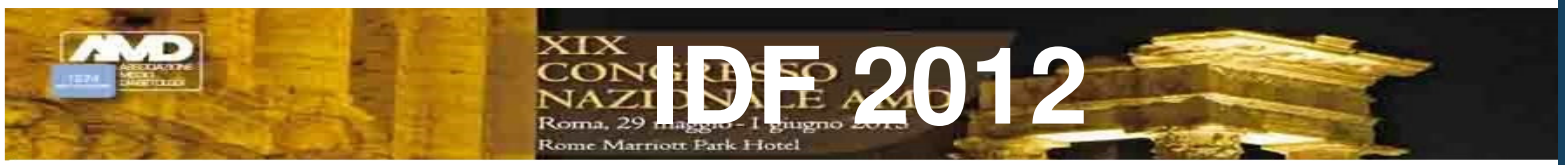
http://www.terveysportti.fi/xmedia/ccs/varhainen_diabetes_en.html

ADA EASD position statement 2012

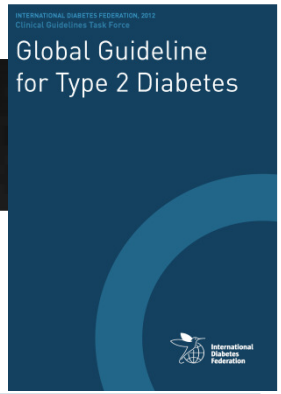
- **HbA1c to <7.0% (<53 mmol/mol) in most patients**
  - **Mean plasma glucose of ~8.3– 8.9 mmol/l (~150–160 mg/dl);**
  - **Fasting and pre-meal glucose at <7.2mmol/l (<130mg/dl)**
  - **postprandial glucose at <10 mmol/l (<180 mg/dl).**
- **More stringent HbA1c targets (e.g. 6.0–6.5% [42–48 mmol/mol]) 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**



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)



IDF 2012



	Normal	Target
HbA_{1c}	< 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 HbA1c target may be considered if it is easily and safely achieved.
- A higher HbA1c 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 HbA1c target should be regularly reviewed taking into account benefits, safety and tolerability.
- Advise those in whom target HbA1c levels cannot be reached that any improvement is beneficial

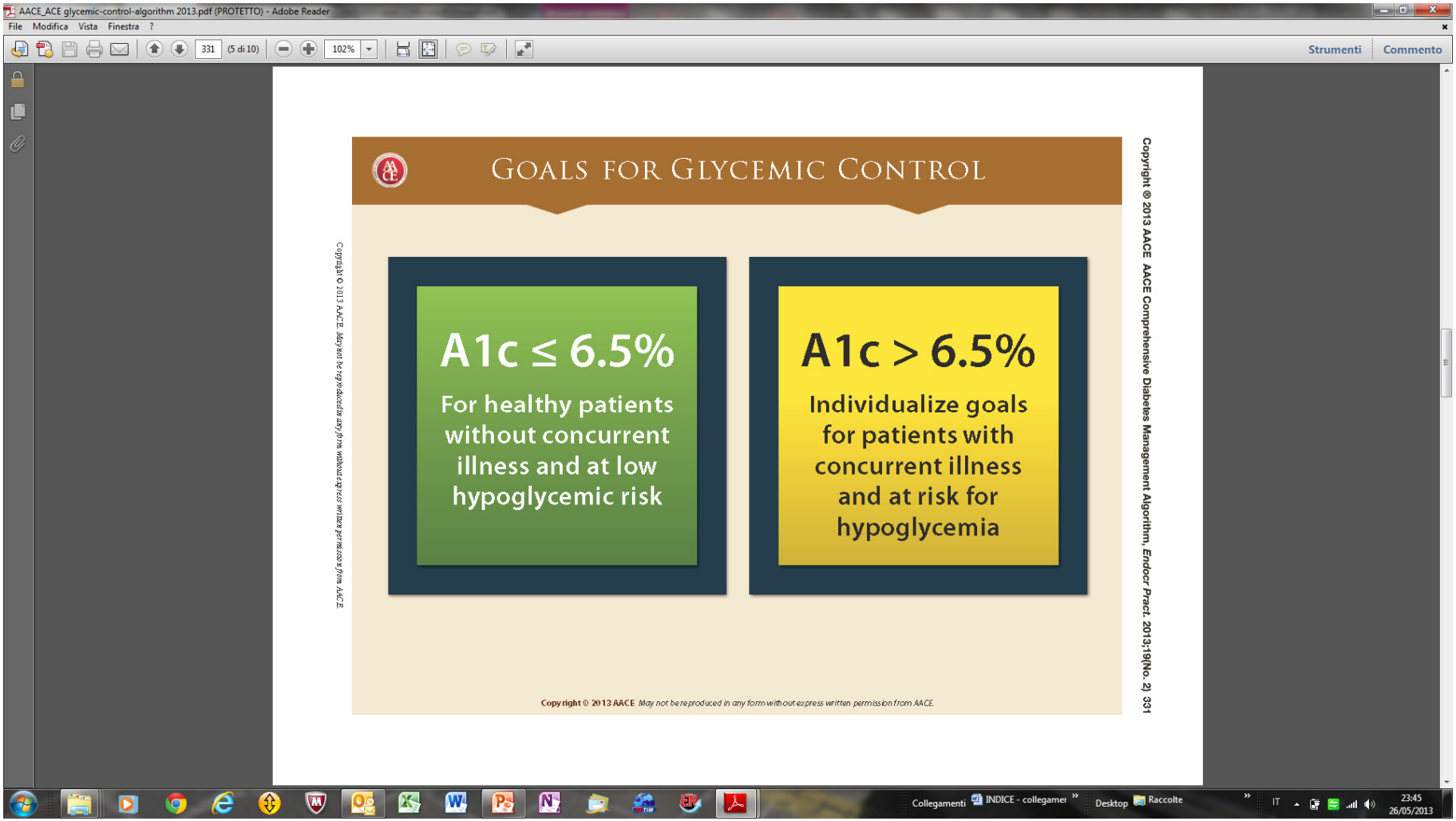
INTERNATIONAL DIABETES FEDERATION, 2012 Clinical Guidelines Task Force, Global Guideline for Type 2 Diabetes
http://www.idf.org/global-guideline-type-2-diabetes-2012

ADA Standard 2013

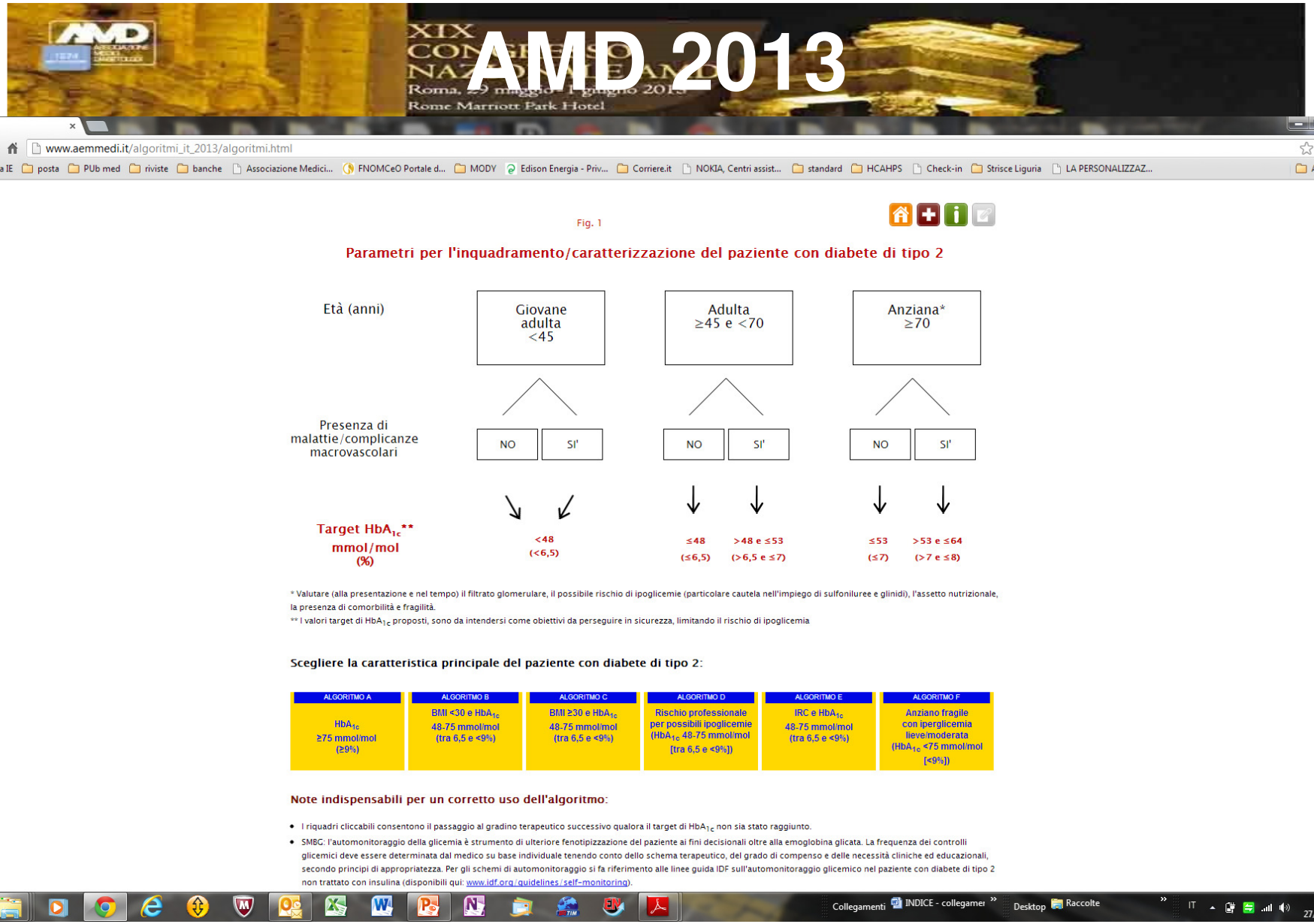
- A reasonable A1C goal for many non pregnant adults is **<7%.** (B)
- **<6.5%**: for selected individual patients, if
- this can be achieved without significant hypoglycemia or other adverse effects of treatment.
- Appropriate patients might include those with
  - short duration of diabetes,
  - long 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



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



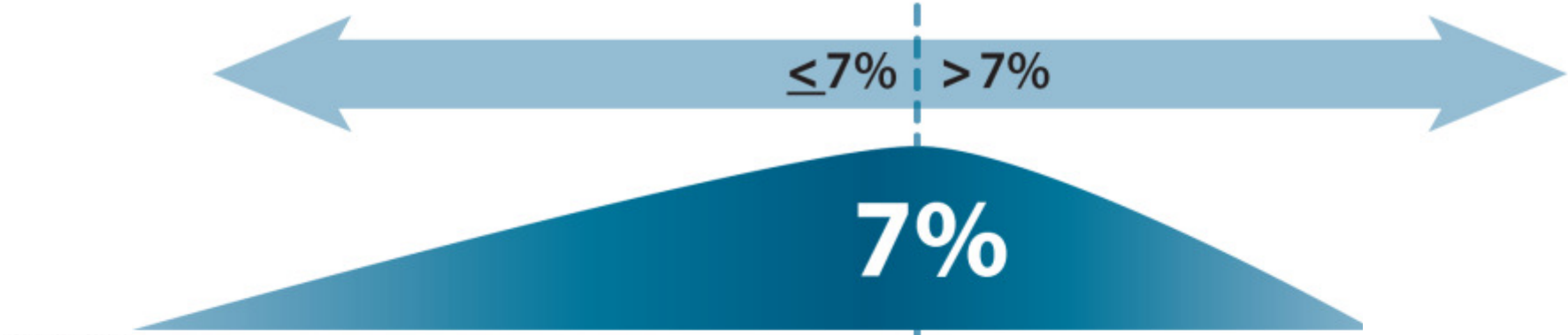
http://www.aemmedi.it/algoritmi_it_2013/algoritmi.html

Canadian Diabetes Association 2013

Targets Checklist

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

Individualizing A1C Targets 2013



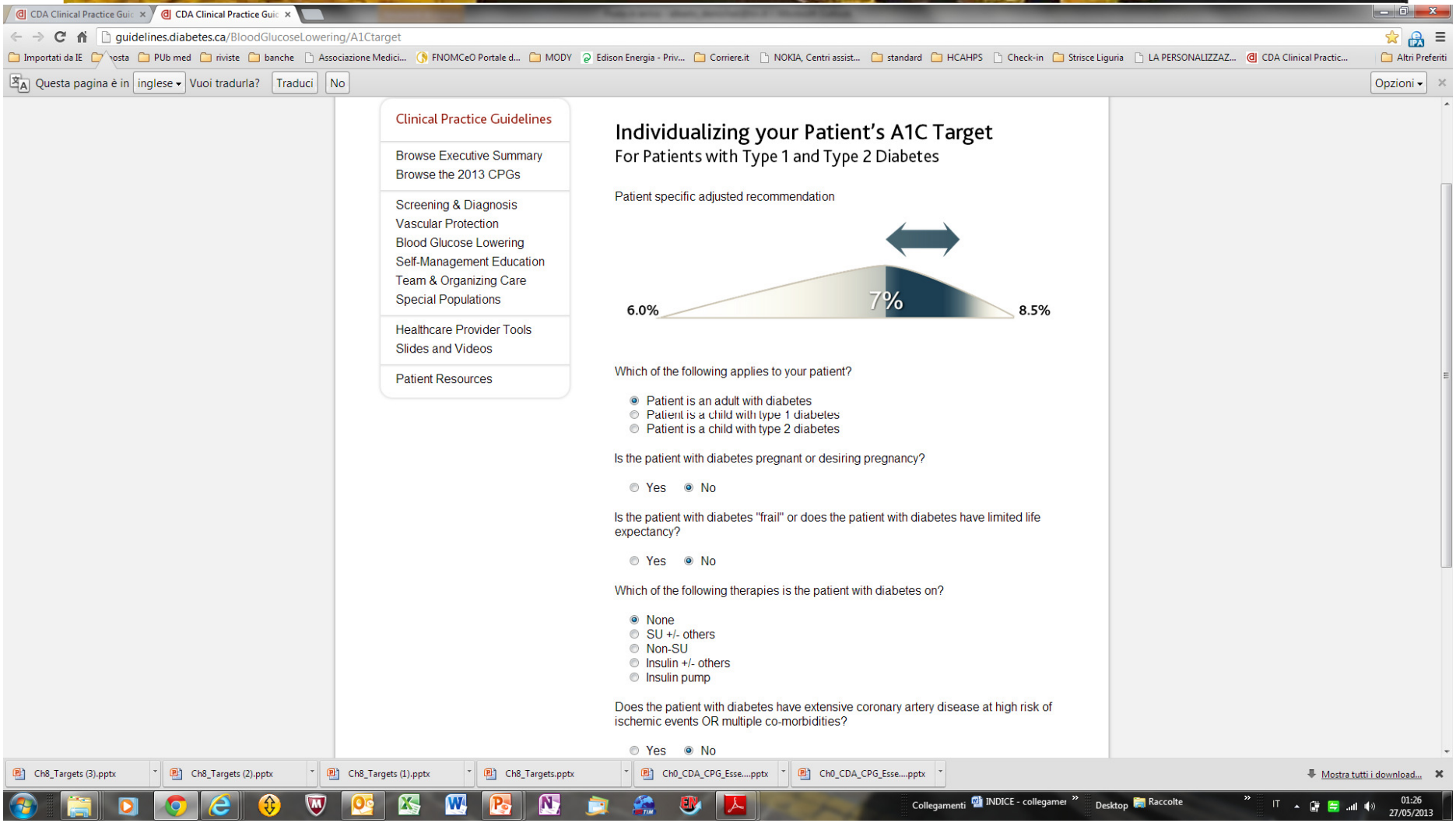
A target A1C ≤6.5% may be considered in some patients with type 2 diabetes to further lower the risk of nephropathy and retinopathy which must be balanced against the risk of hypoglycemia

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 ≤7%, despite effective doses of multiple antihyperglycemic agents, including intensified basal-bolus insulin therapy

CDA motore di calcolo

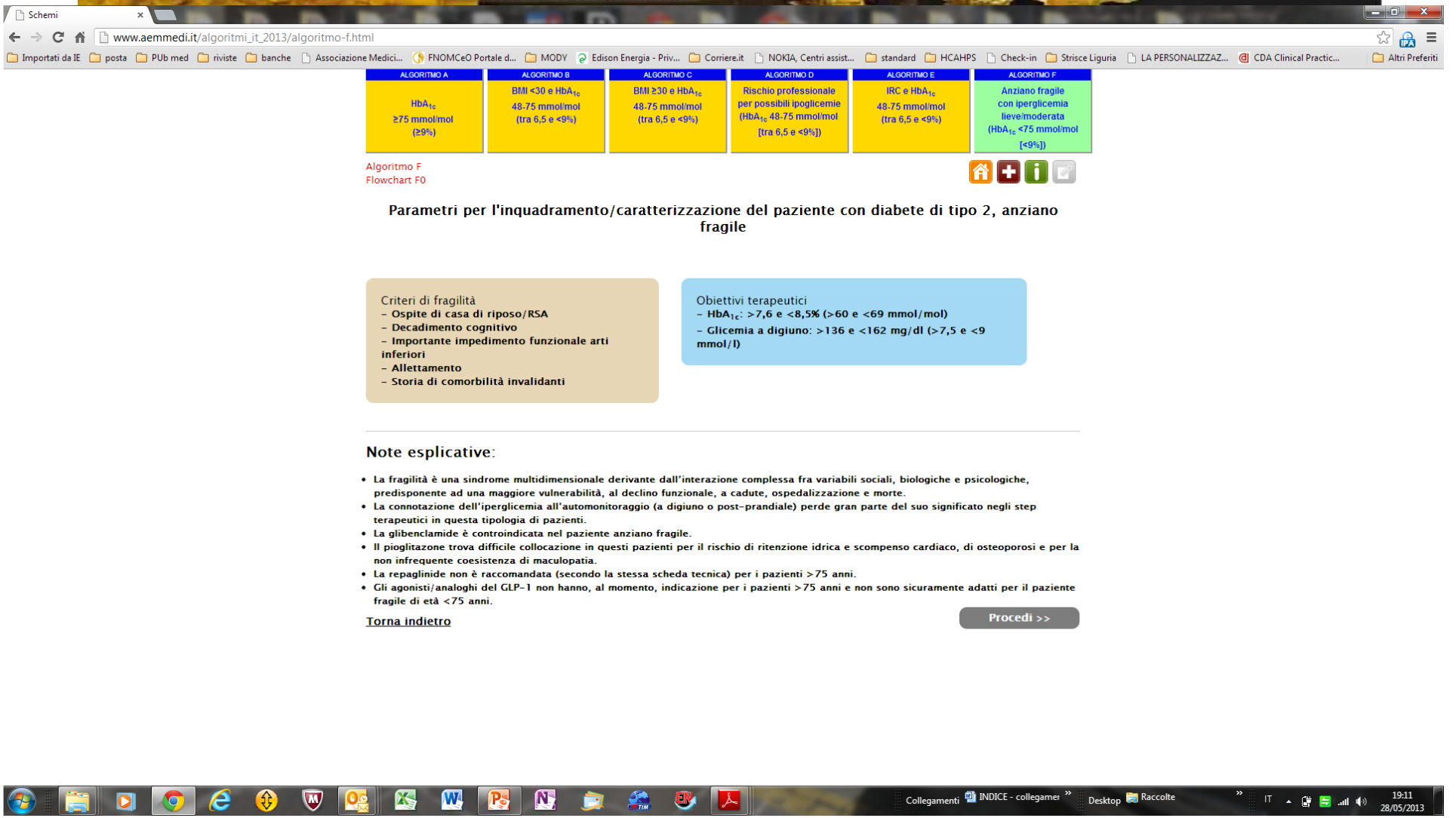


European Diabetes Working Party for Older People 2011 Clinical Guidelines for Type 2 Diabetes Mellitus (EDWPOP)

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

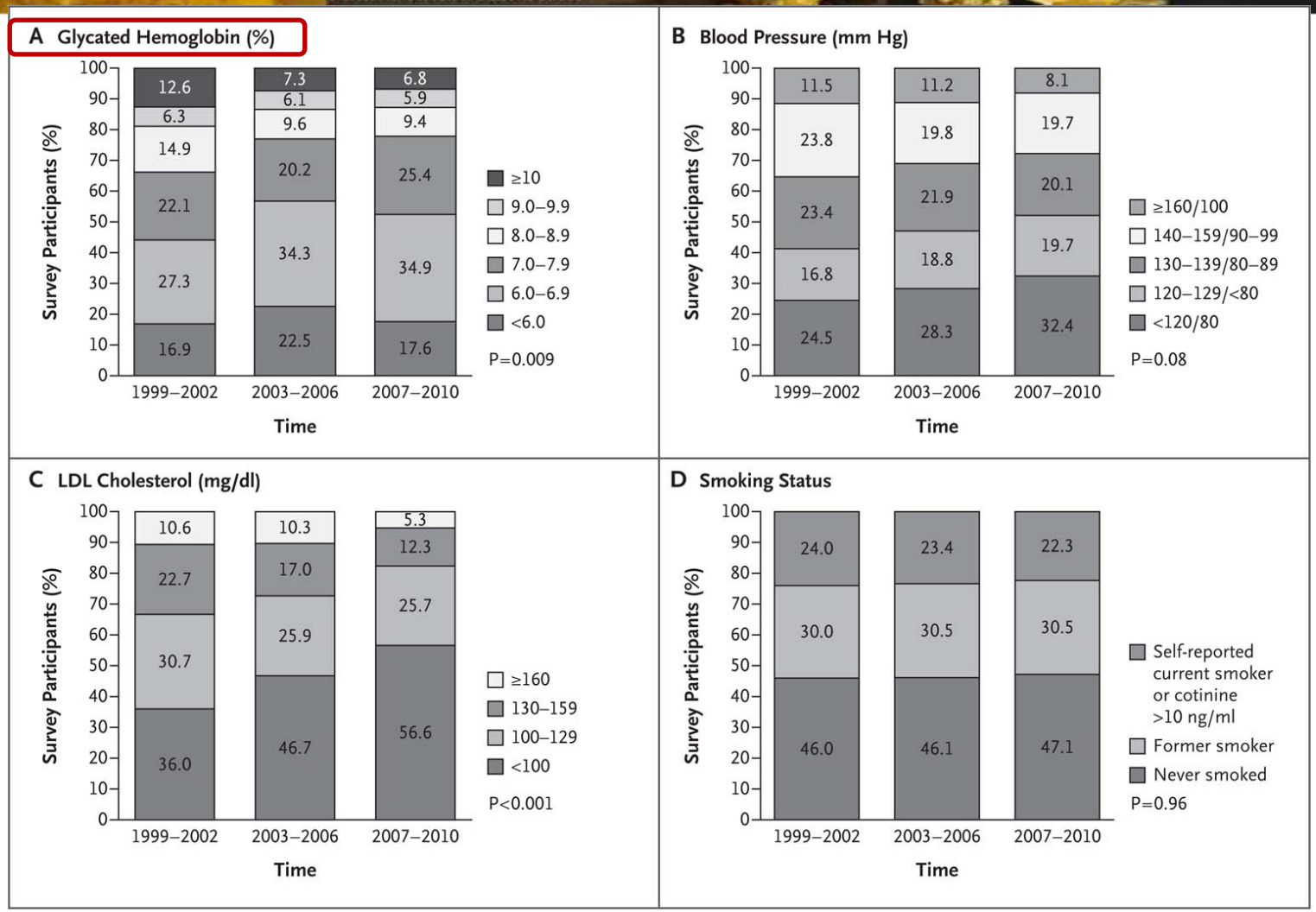
Sinclair AJ Diabetes & Metabolism 2011; 37: S27- S38

AMD 2013: anziano fragile



Dal target alla terapia personalizzata

Obiettivi raggiunti in periodi diversi



Ali MK et al. N Engl J Med 2013;368:1613-1624

The NEW ENGLAND JOURNAL of MEDICINE

Soggetti con HbA1c ≤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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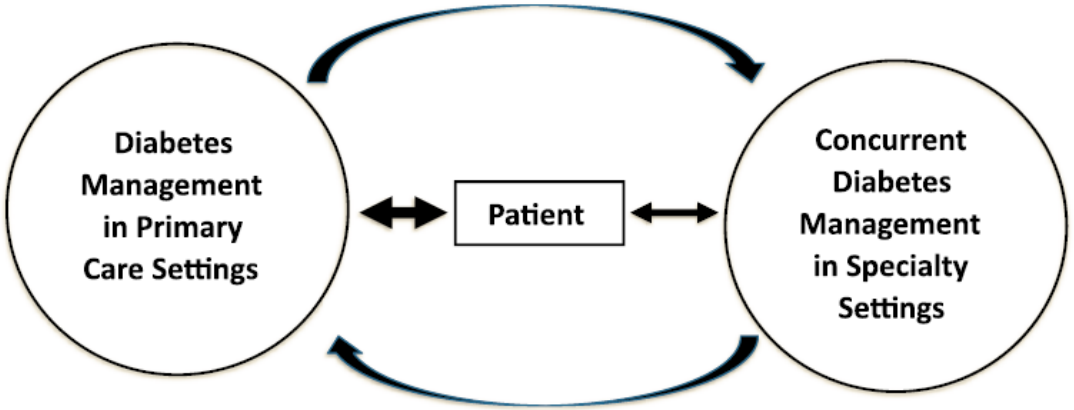
Lawrence A. Leiter, MD[10]
Derek LeRoith, MD, PHD[11]
Ralph DeFronzo, MD[12]
William T. Cefalu, MD[13]



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

Raz I Diabetes Care 2013; 36:1779–1788

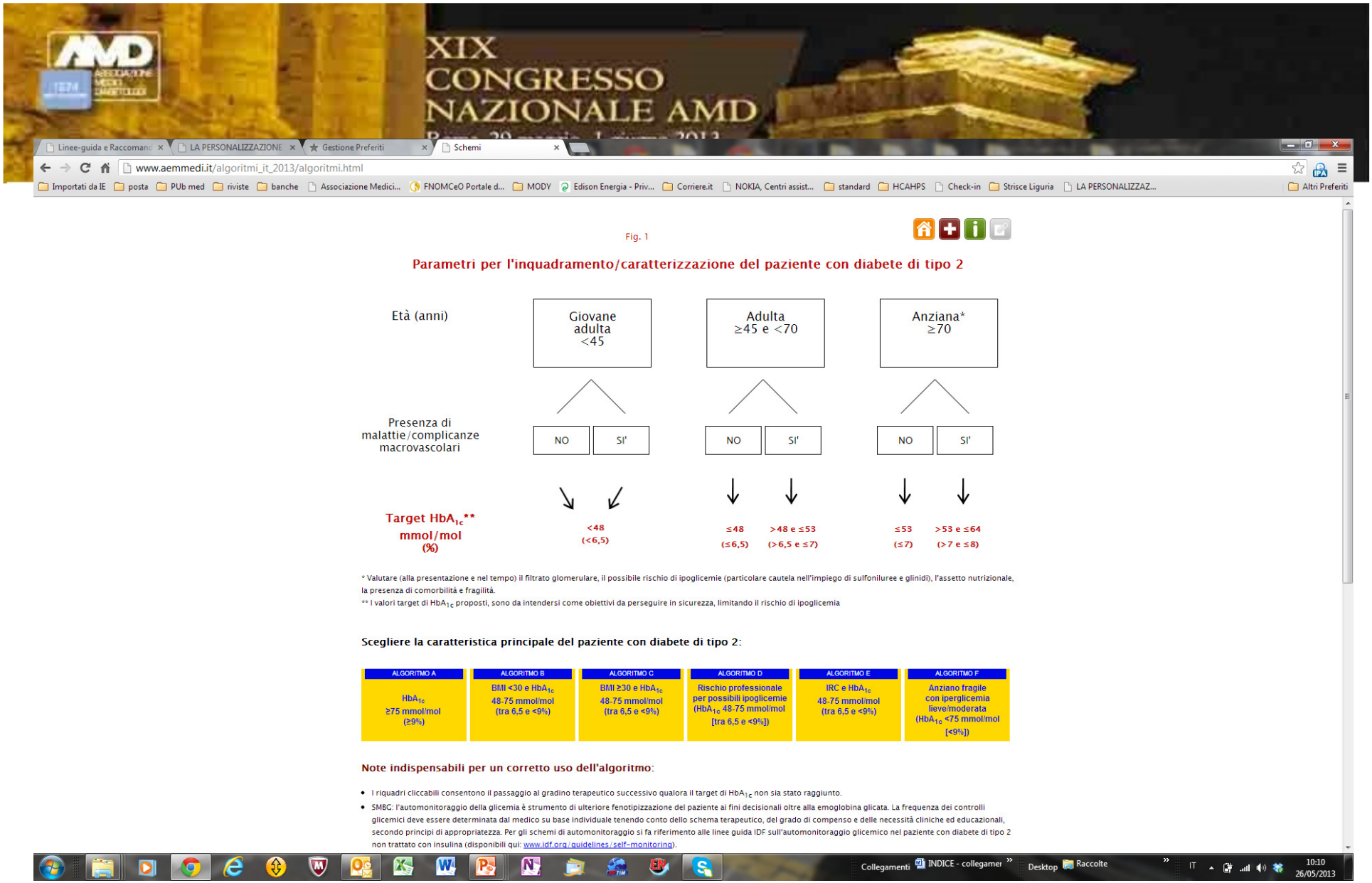
Classi

- 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/algoritmi_it_2013/algoritmi.html

Grazie per l'attenzione