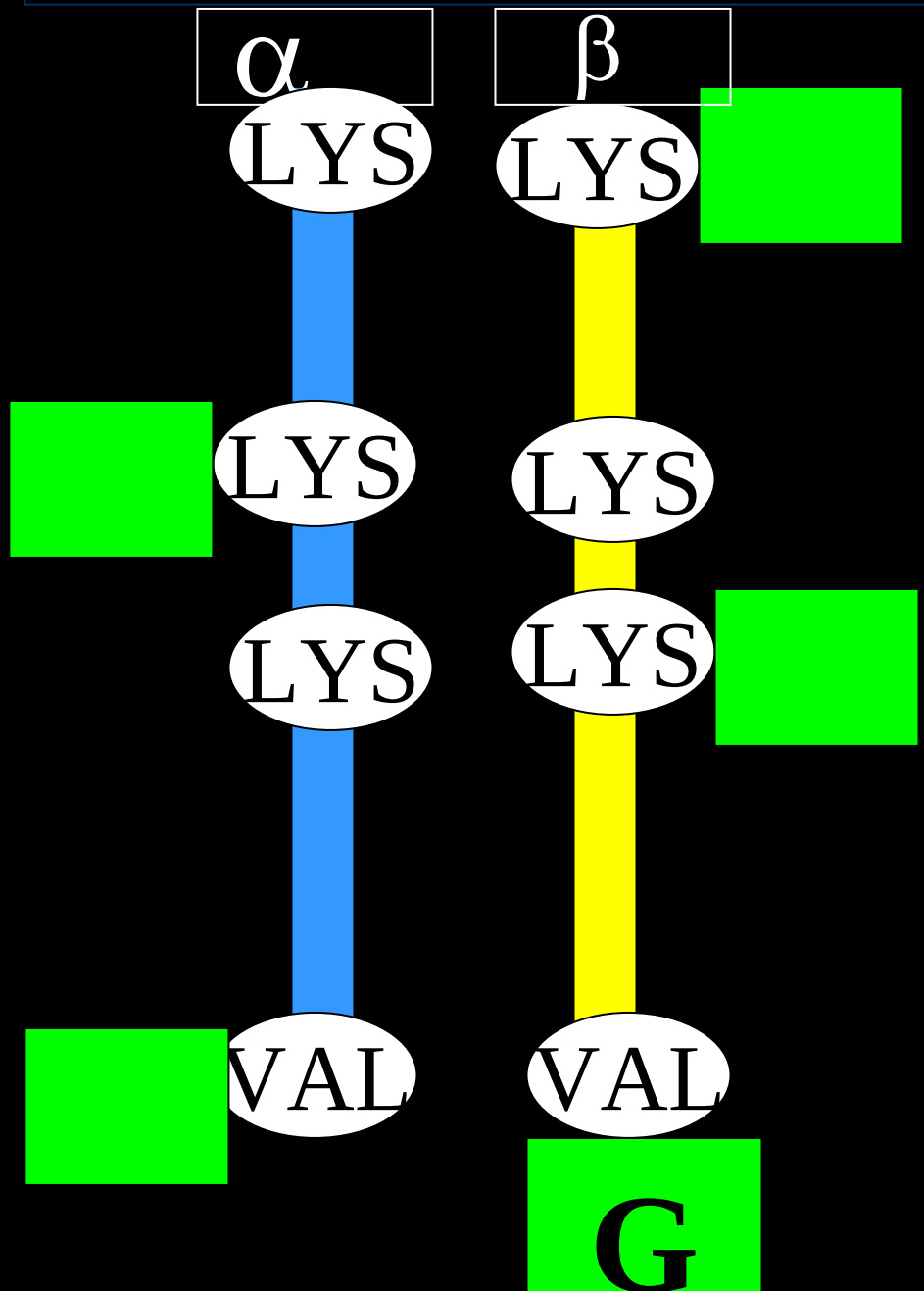
Ruolo dell’emoglobina glicata nel monitoraggio del paziente diabetico

Mariarosa Carta

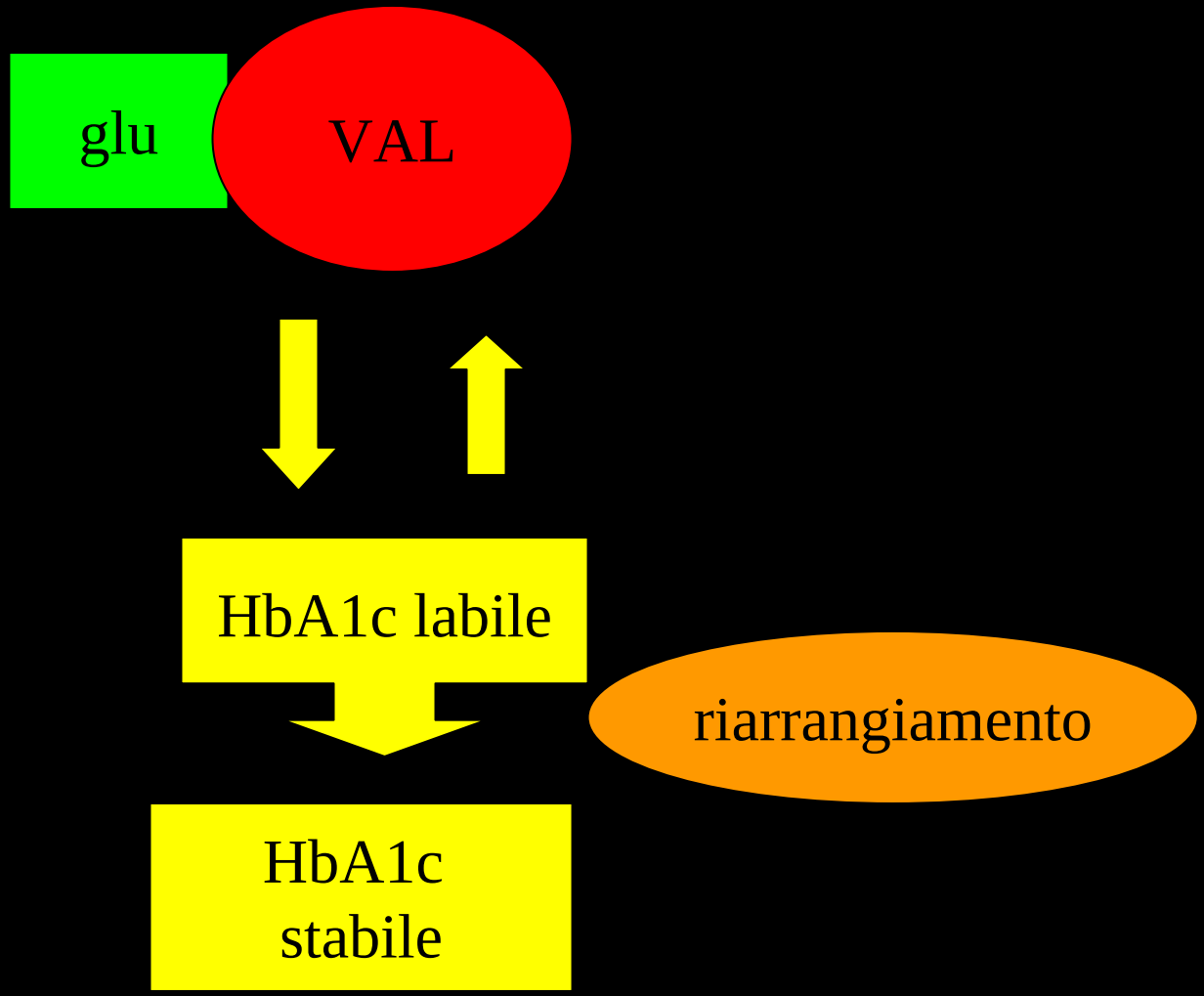
Laboratorio di chimica clinica ed ematologia

Ospedale S. Bortolo, Vicenza

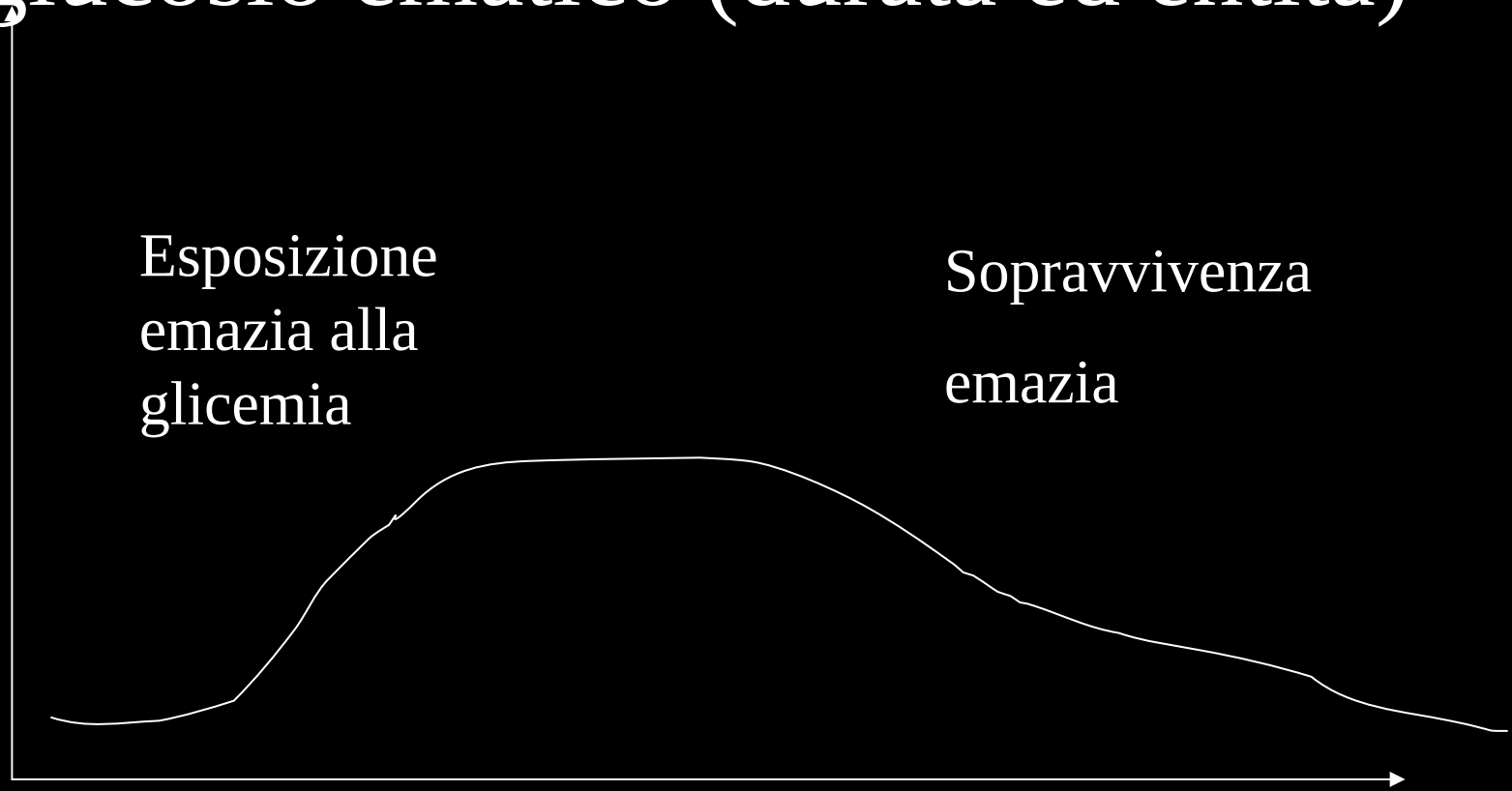
Emoglobina glicata:cos'è



Emoglobina glicata:la reazione



La concentrazione HbA1c dipende dall'esposizione dell'emoglobina al glucosio ematico (durata ed entità)



.. E quindi dall'emivita emazie

eritroblasto

Emazia vecchia

Glicazione 0

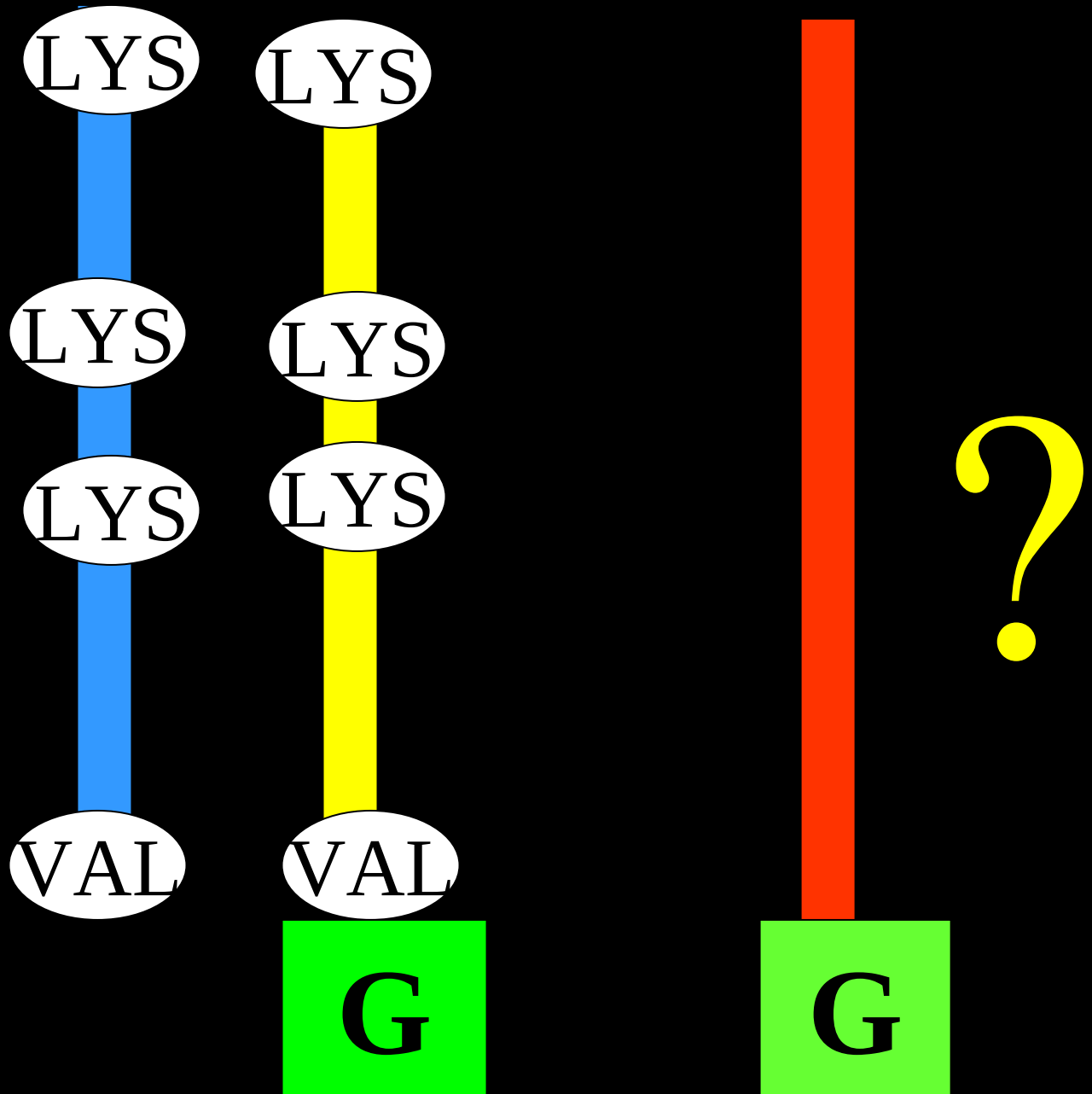
Glicazione max

Goldsterin, 1995

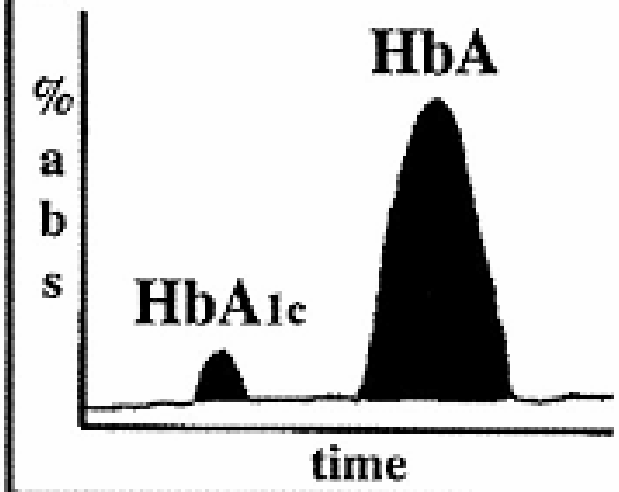
Tutte le cause che comportano una riduzione dell’emivita delle emazie possono determinare una sottostima del valore di HbA1c

Interferenze con il dosaggio dell'emoglobina glicata

- Riduzione emivita emazie
- Varianti emoglobiniche
- Vitamina E e vitamina C
- Ipertrigliceridemia, iperbilirubinemia
- Uricemia
- Alcoolismo cronico
- Dipendenza da oppiacei


LYS
LYS
LYS
LYS
LYS
LYS
VAL
VAL
G
G
?

A

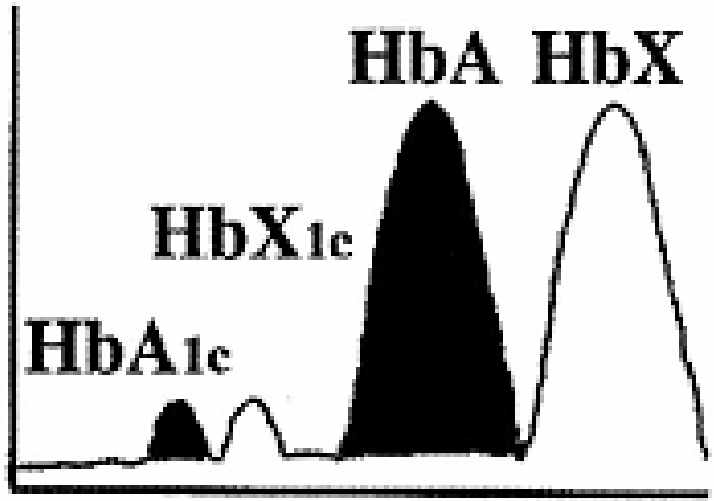


Separation of HbA from HbA1c

$$100 \times \frac{HbA_{1c}}{HbA + HbA_{1c}}$$

Normal estimation of %HbA1c

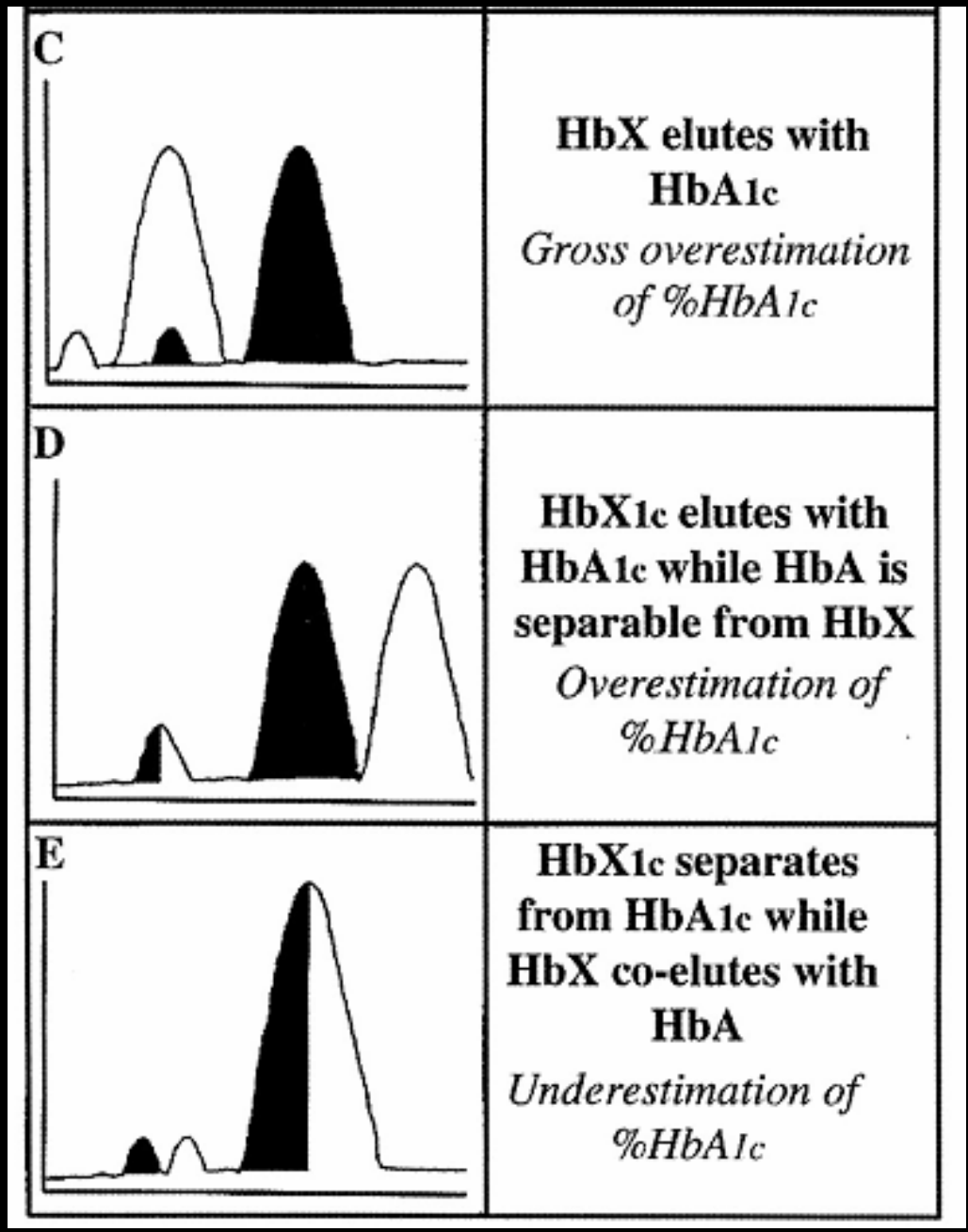
B



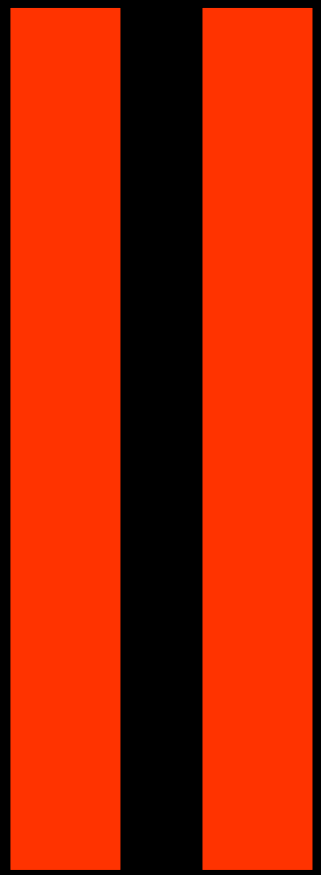
Separation of HbA from HbX and HbA1c from HbX1c

Normal estimation of %HbA1c

Bry, L. et al. Clin Chem 2001;47:153-163



Bry, L., et al. Clin Chem 2001;47:153-163



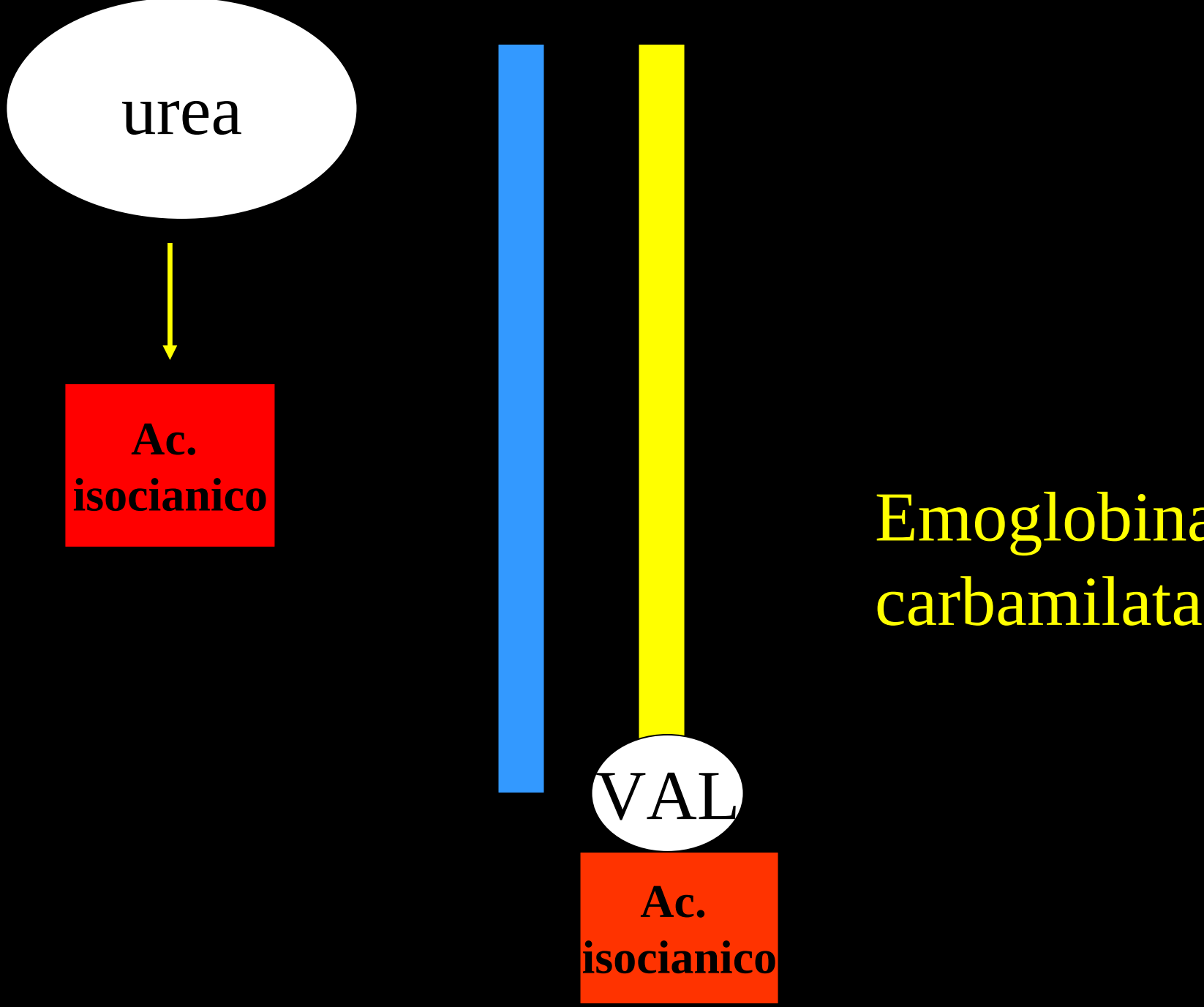
X X

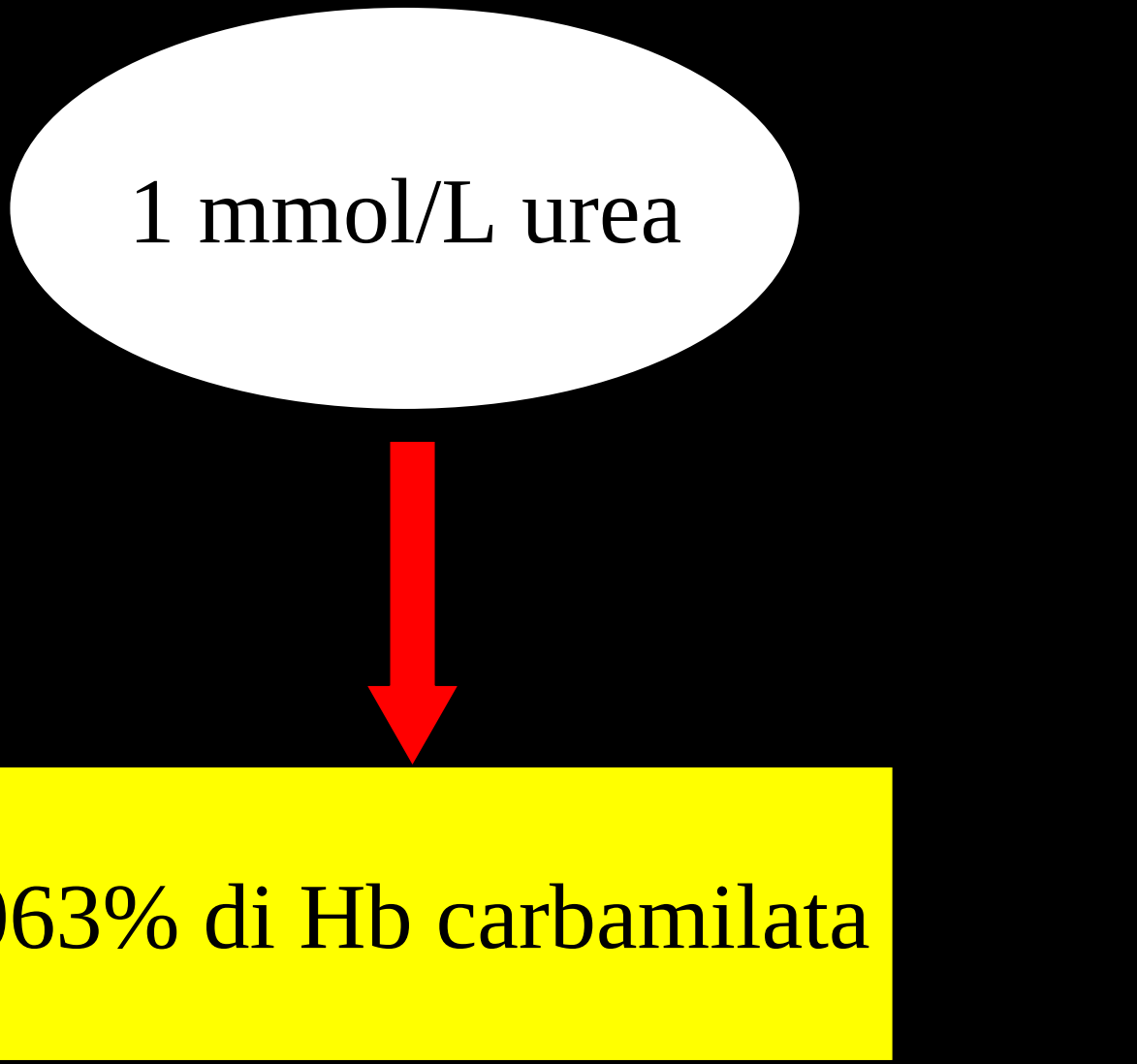
HbCC

HbSC

HbSS

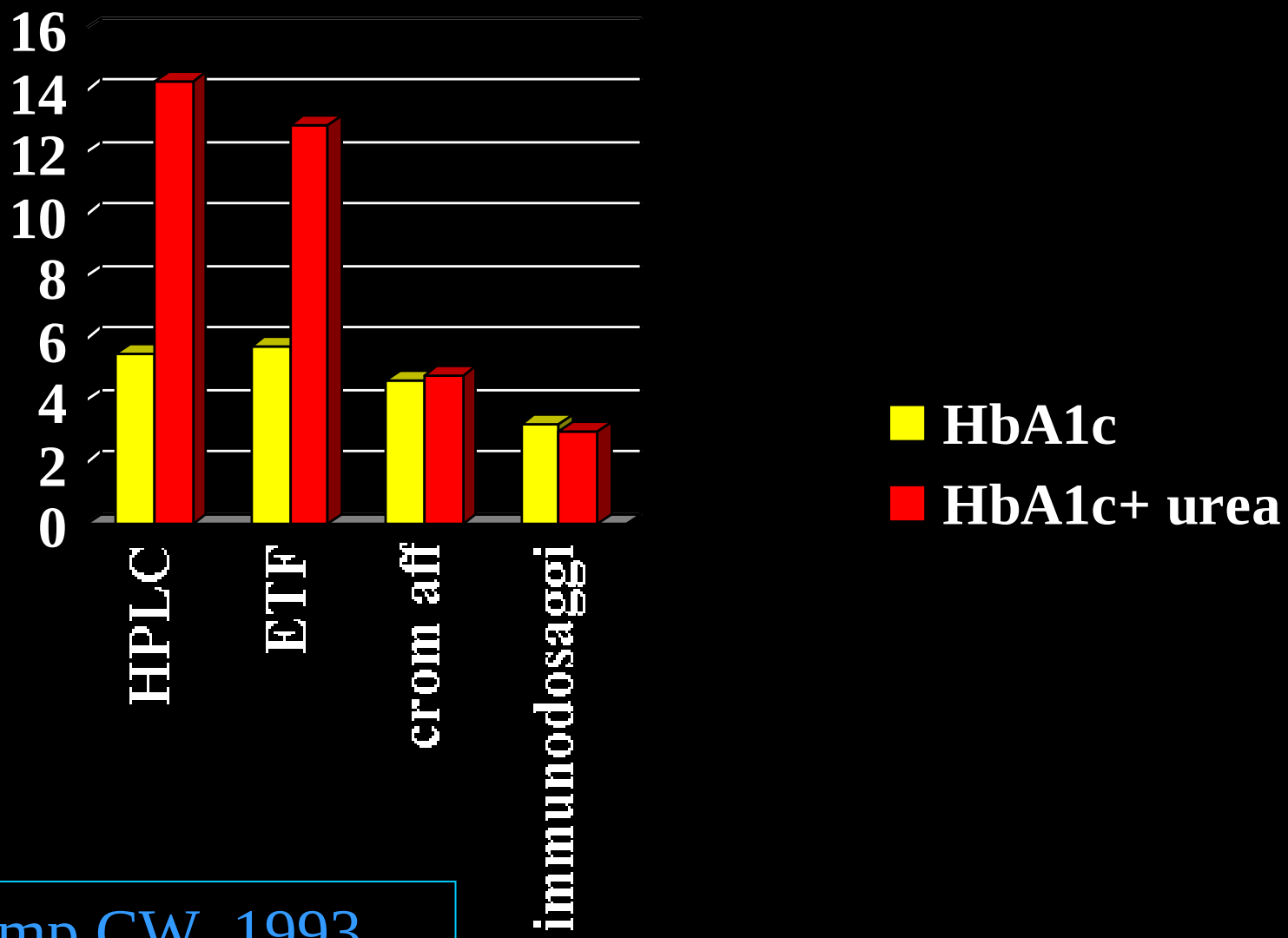
HbA1c


urea
Ac. isocianico
VAL
Ac. isocianico
Emoglobina carbamilata



Weykamp CW, 1993

Effetto della presenza di emoglobina carbamilata sul dosaggio di HbA1c in metodi diversi



Weykamp CW, 1993

Terapia con ASA

Ac. acetilsaliciclico

Ac. acetico

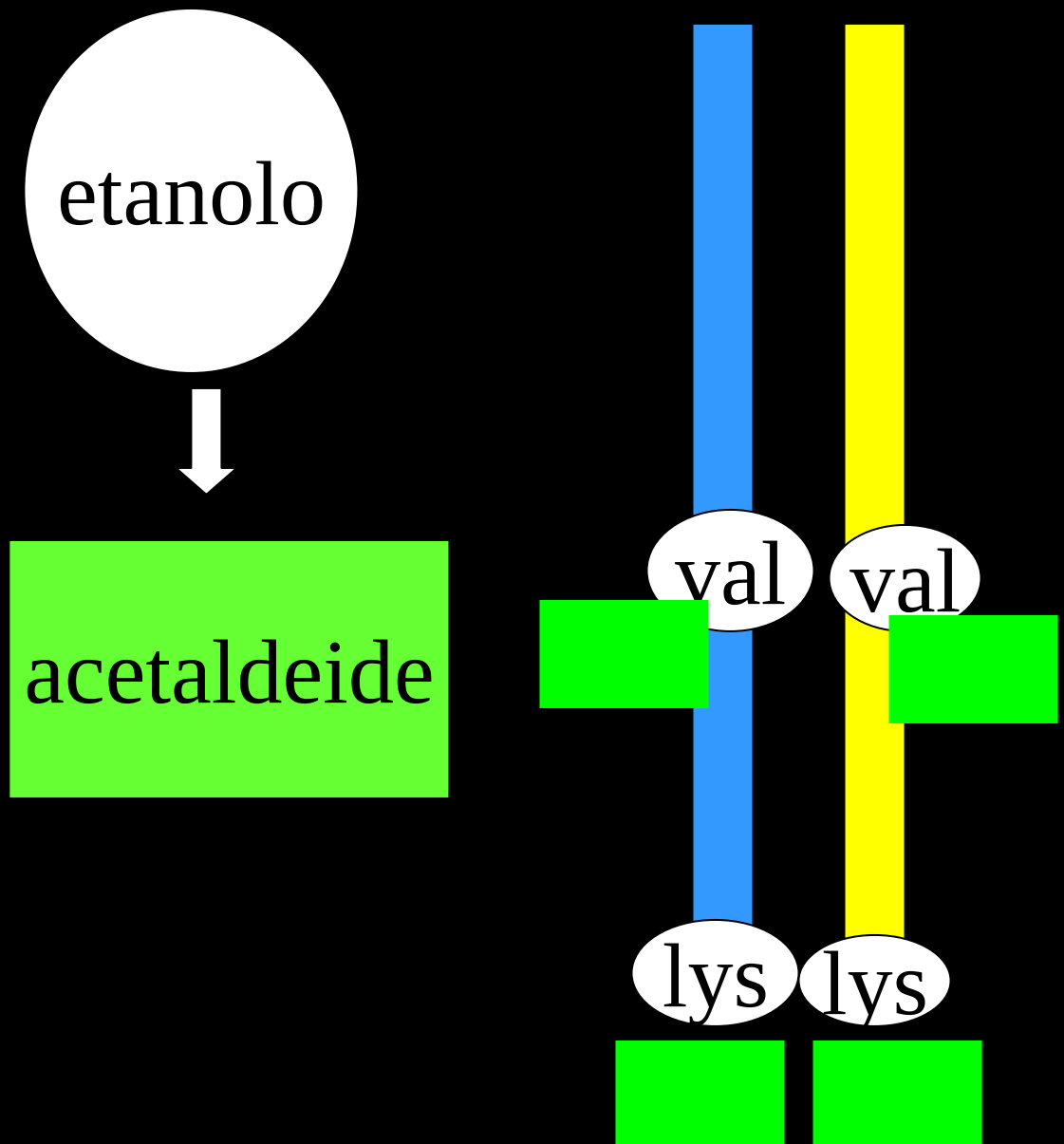
LYS LYS

Emoglobina acetilata

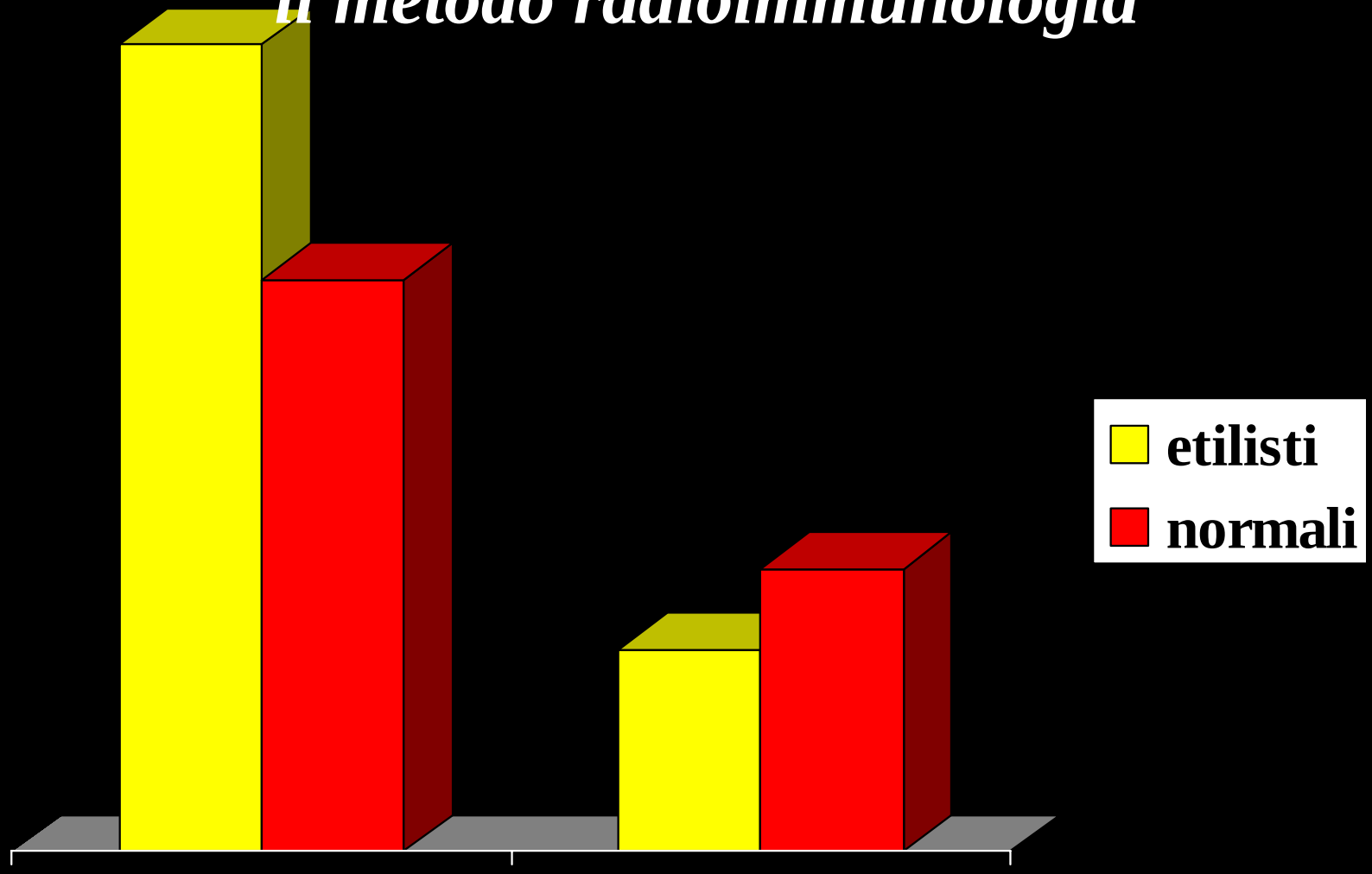
L’uso cronico di piccole dosi (200-300 mg/d) di ASA non causa incrementi significativi dell’HbA1c, così come l’utilizzo di dosi elevate (2g/d) per un breve periodo.

Weykamp CW, 1993

Etilismo cronico



Livelli di glicoemoglobina in etilisti cronici e normali determinata con la cromatografia e con il metodo radioimmunologia



Stevens, 1981

Vitamina C ed E

La vitamina C ed E possono inibire con meccanismo di tipo competitivo la glicosilazione dell'emoglobina

Davies, 1992

Ceriello, 1991

Alternative al dosaggio HbA1c

- Albumina glicata: risente delle 2 settimane precedenti
  - 17% corrisponde a 6% di Hba1c
  - 19.8% 7% di Hba1c

Utilizzo clinico dell’emoglobina glicata

L’HbA1c ci indica la glicemia media delle ultime 8-10 settimane

preceding days	contribution %	
30	50	
60	25	
90	15	
120	10	*(NCCLS, C44-P, 10/99*

Esiste una stretta correlazione tra l’HbA1c e la glicemia media degli ultimi 3 mesi

Diabetes Care -- American Diabetes Association 31 (1): S12 Table 9 - Microsoft Internet Explorer fornito da ULSS 6 Vicenza

Table 9— Correlation between A1C level and mean plasma glucose levels on multiple testing over 2–3 months

A1C (%)	Mean plasma glucose	
	mg/dl	mmol/l
6	135	7.5
7	170	9.5
8	205	11.5
9	240	13.5
10	275	15.5
11	310	17.5
12	345	19.5

These estimates are based on DCCT data (34). An updated version of this table, based on final results of the ADAG Trial, will be available at www.diabetes.org after publication of the study's findings in 2008.

Start 15.57

Diabetologia
Clinical and Experimental Diabetes and Metabolism
© Springer-Verlag 2007
10.1007/s00125-007-0803-0

Article

Relationship between glycated haemoglobin levels and mean glucose levels over time

D. M. Nathan[1, 2] ✉, **H. Turgeon**[1, 2] **and S. Regan**[1, 2]

(1) Diabetes Center, Department of Biostatistics, Massachusetts General Hospital, 50 Staniford Street, Suite 340, Boston, MA 02114, USA

(2) Department of Medicine, Harvard Medical School, Boston, MA, USA

CONCLUSIONS AND INTERPRETATION: HbA(1c) correlates closely with a complete measure of average glycaemia over the preceding 8-12 weeks. The translation of HbA(1c) to an average glucose level for reporting and management purposes is feasible.

European Association for the Study of Diabetes 43rd Annual Meeting

Hba1c Out, Average Glucose In? ADAG Results Support New Reference Method for Chronic Glycemia

from Heart*wire* — a professional news service of WebMD

Shelley Wood

Information from Industry

CAMPTOSAR®(irinotecan HCl injection)

Review emerging approaches to managing metastatic colorectal cancer and the role of combination therapies in helping extend overall survival.

- Important Safety Information
- Prescribing Information

September 19, 2007 **(Amsterdam, the Netherlands)** - Results of the **$HbA1_c$-derived Average Glucose** (ADAG) trial show that an estimated average glucose (eAG), calculated using $HbA1_c$ measurements, correlates very closely with glucose measurements obtained by repeated measurements over three months. The findings support the use of a new method for reporting chronic glycemia values that experts say will make more sense to patients and will help standardize reporting methods globally.

Reviews/Commentaries/ADA Statements
Consensus Statement

Consensus Statement on the Worldwide Standardization of the Hemoglobin A1C Measurement

The American Diabetes Association, European Association for the Study of Diabetes, International Federation of Clinical Chemistry and Laboratory Medicine, and the International Diabetes Federation

Consensus Committee*

1: N Engl J Med. 1976 Aug 19;295(8):417-20.

Correlation of glucose regulation and hemoglobin Alc in diabetes mellitus.

Koenig RJ, Peterson CM, Jones RL, Saudek C, Lehrman M, Cerami A.

We studied the increased levels of hemoglobins AIa+Ib and AIc in five hospitalized diabetic patients to determine whether changes in diabetic control would cause parallel changes in the levels of these hemoglobins. Before control of diabetes the mean fasting blood sugar for all patients was 343 mg per deciliter (range, 280 to 450), and hemoglobin AIc concentration 9.8 per cent (range, 6.8 to 12.1). During optimal diabetic control the blood sugar concentration was 84 mg per deciliter (range, 70 to 100), and hemoglobin AIc concentration 5.8 per cent (range, 4.2 to 7.6). Hemoglobin AIc concentration appears to reflect the mean blood sugar concentration best over previous weeks to months. The periodic monitoring of hemoglobin AIc levels provides a useful way of documenting the degree of control of glucose metabolism in diabetic patients and provides a means whereby the relation of carbohydrate control to the development of sequelae can be assessed.

DCCT Research Group. N Engl J Med 1993;329:977-86

The NEW ENGLAND JOURNAL of MEDICINE

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Abstract | Full Text

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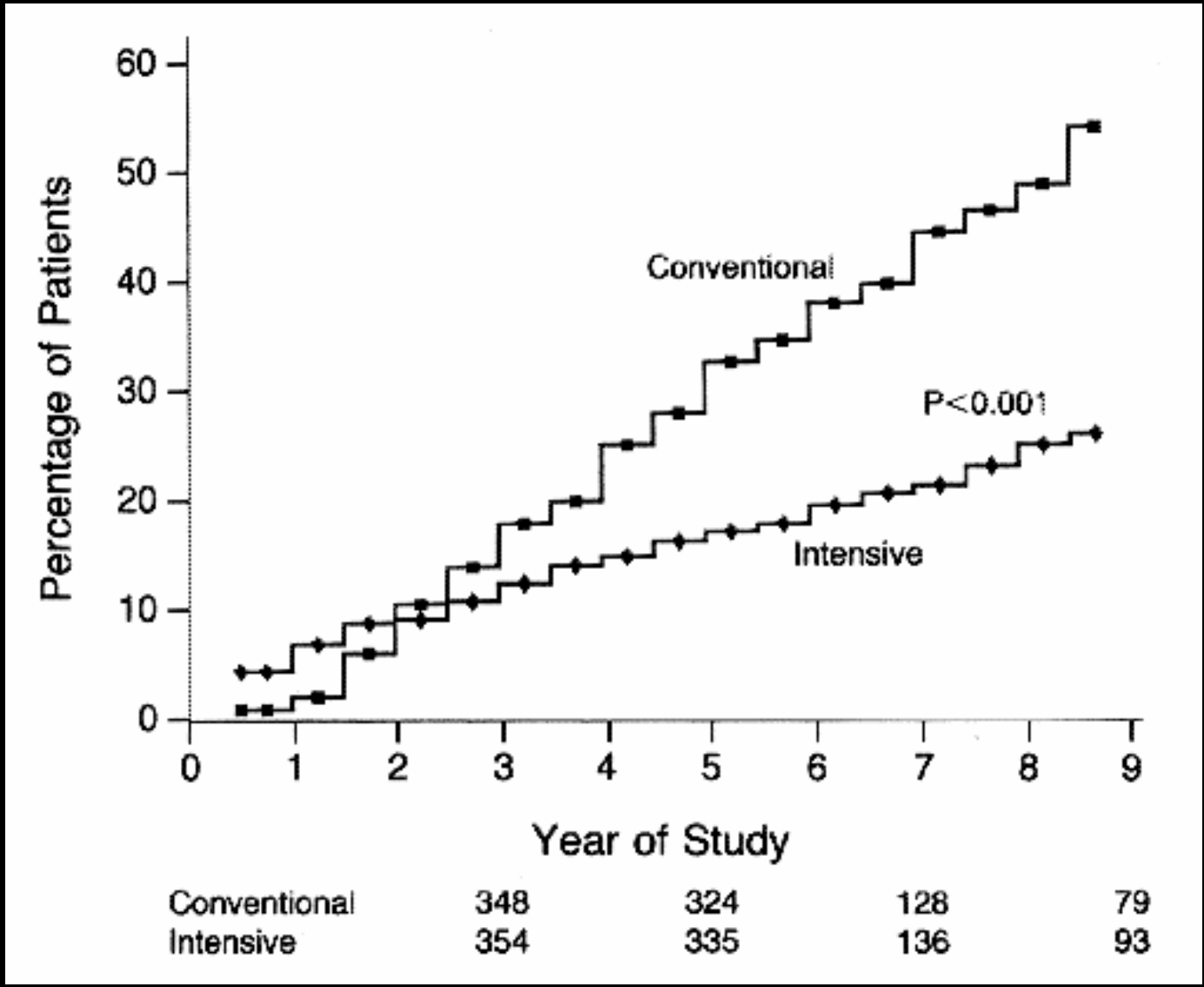
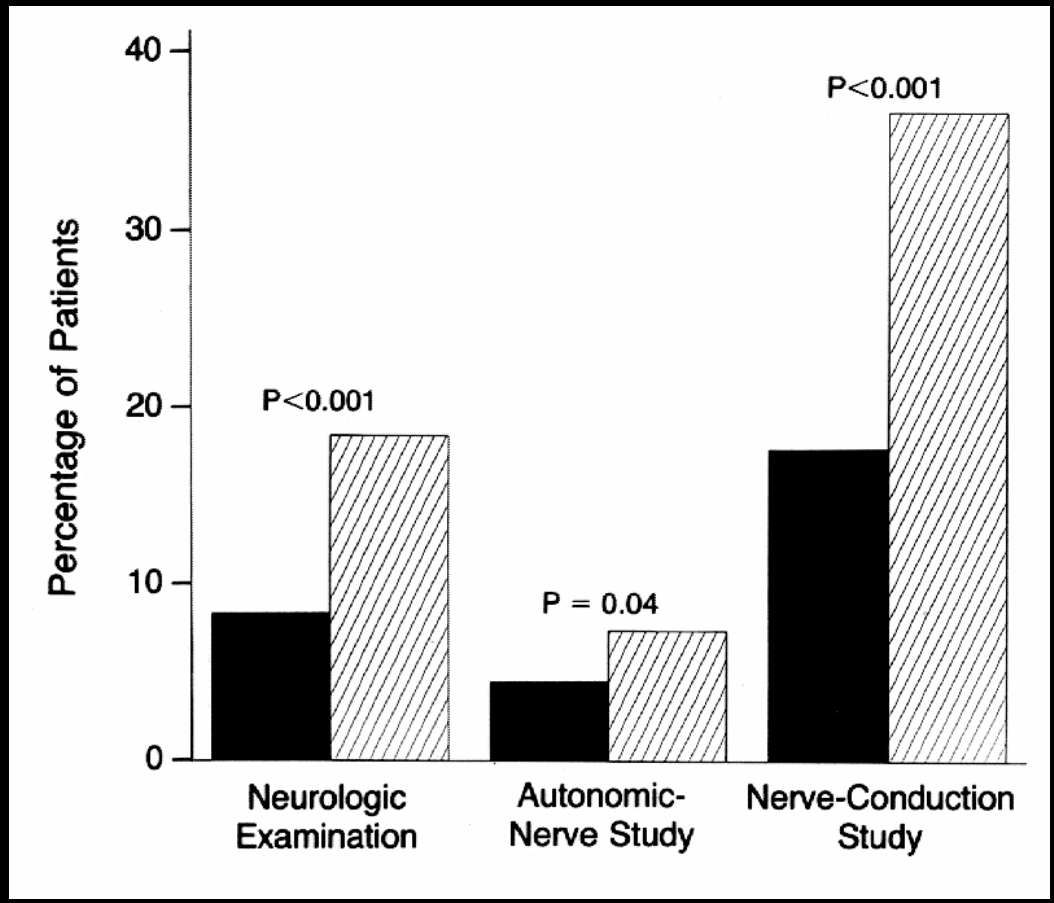


Riduzione delle anomalie neurologiche nei pazienti trattati con terapia intensiva

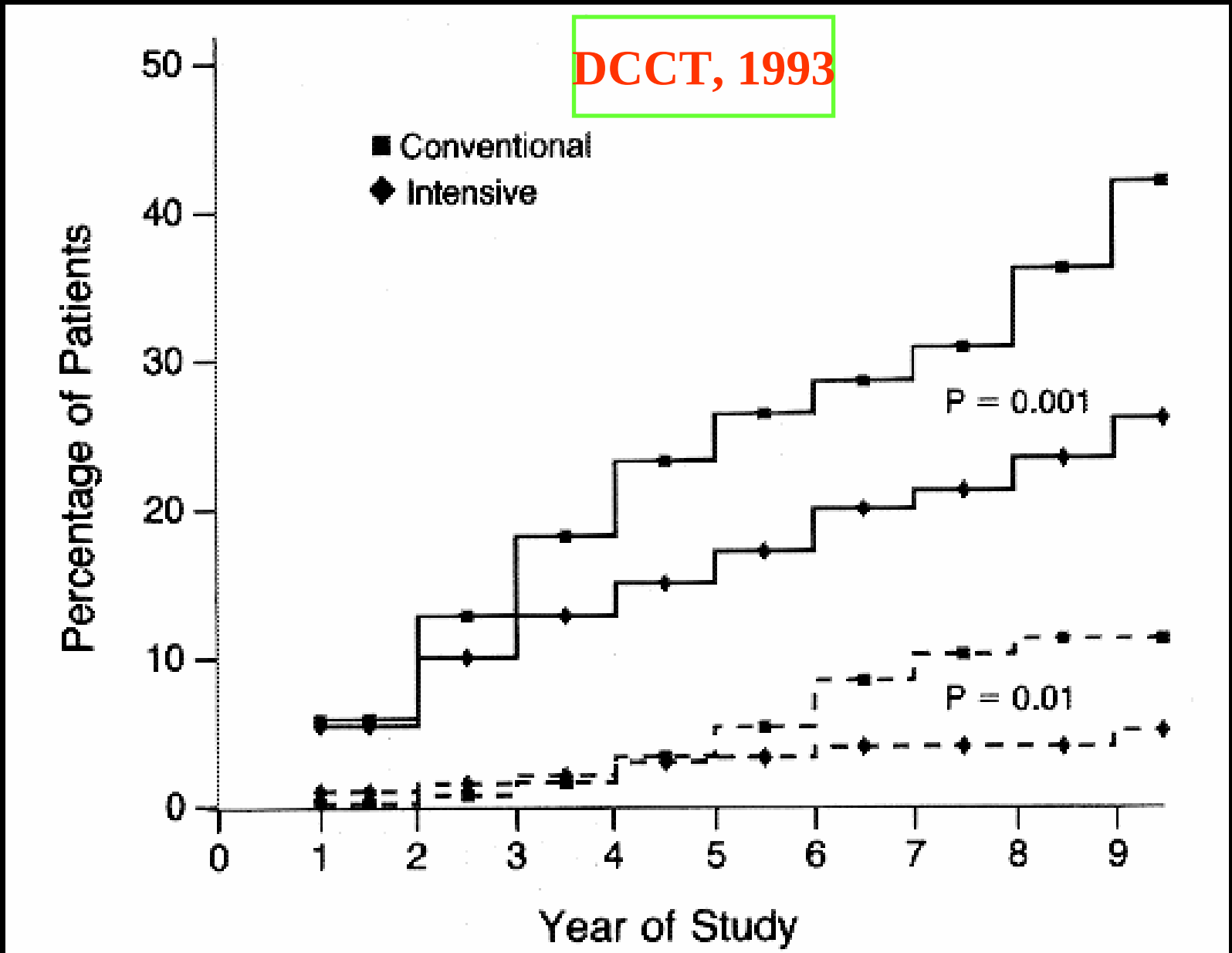


Pz in terapia convenzionale

Pz in terapia intensiva

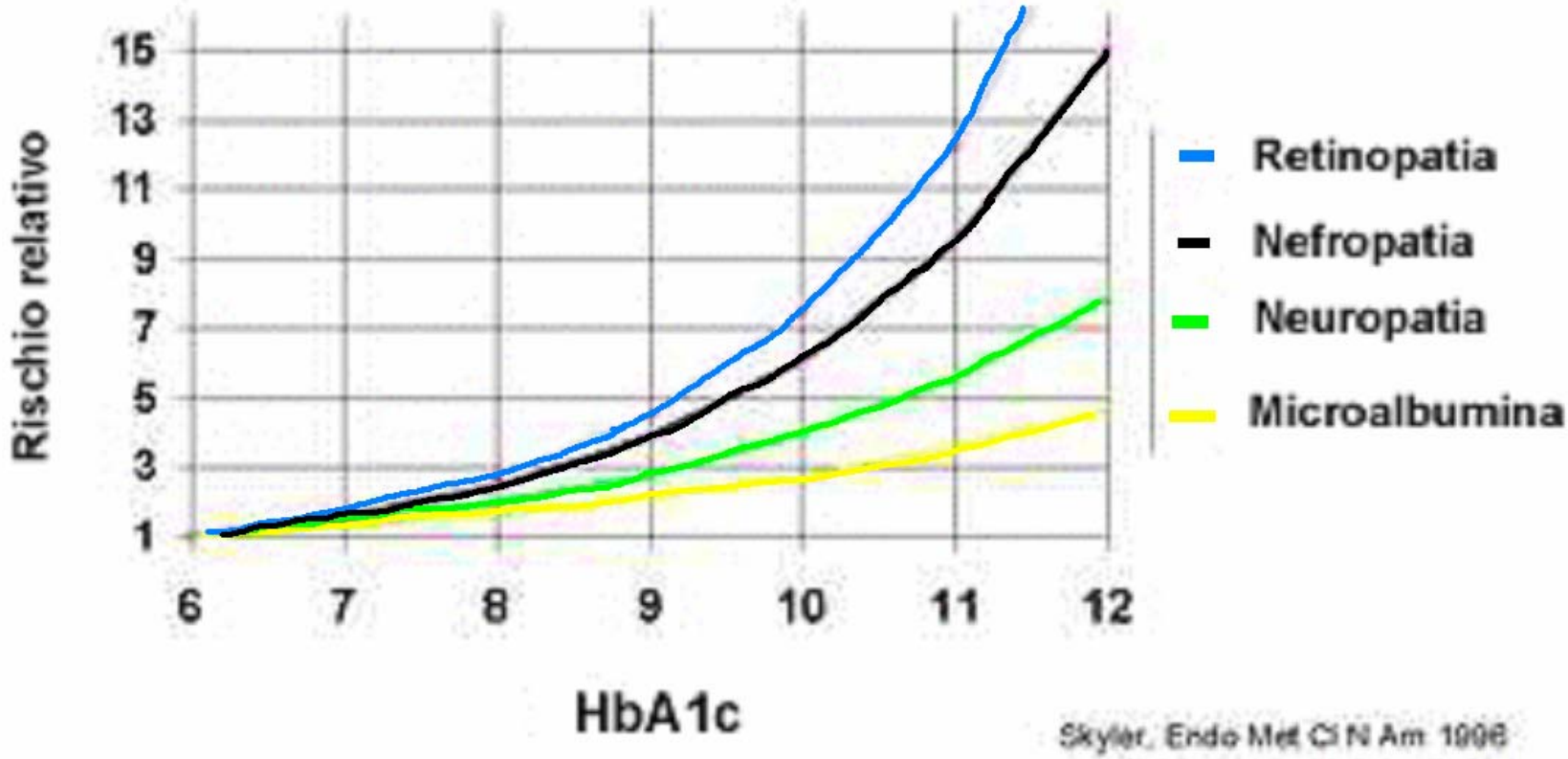
DCCT, 1993

Riduzione del rischio di albuminuria (54%) e microalbuminuria (39%) nei pazienti trattati in maniera intensiva



RISCHIO RELATIVO DI PROGRESSIONE PER LE COMPLICANZE DEL DIABETE IN FUNZIONE DEI LIVELI DI HbA1c

Sulla base dei dati DCCT



Skyler, Endo Met Cl N Am 1996

ScienceDirect - The Lancet : Intensive blood-glucose control with sulphonylureas or insulin com - Microsoft Internet Explorer
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The Lancet
Volume 352, Issue 9131 , 12 September 1998, Pages 837-853

doi:10.1016/S0140-6736(98)07019-6 Cite or link using doi
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Article

Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33)

UK Prospective Diabetes Study (UKPDS) Group[1, *]

Available online 20 October 1998.

Abstract

Background Improved blood-glucose control decreases the progression of diabetic microvascular disease, but the effect on macrovascular complications is unknown. There is concern that sulphonylureas may increase cardiovascular mortality in patients with type 2 diabetes and that high

Help is Available
Internet

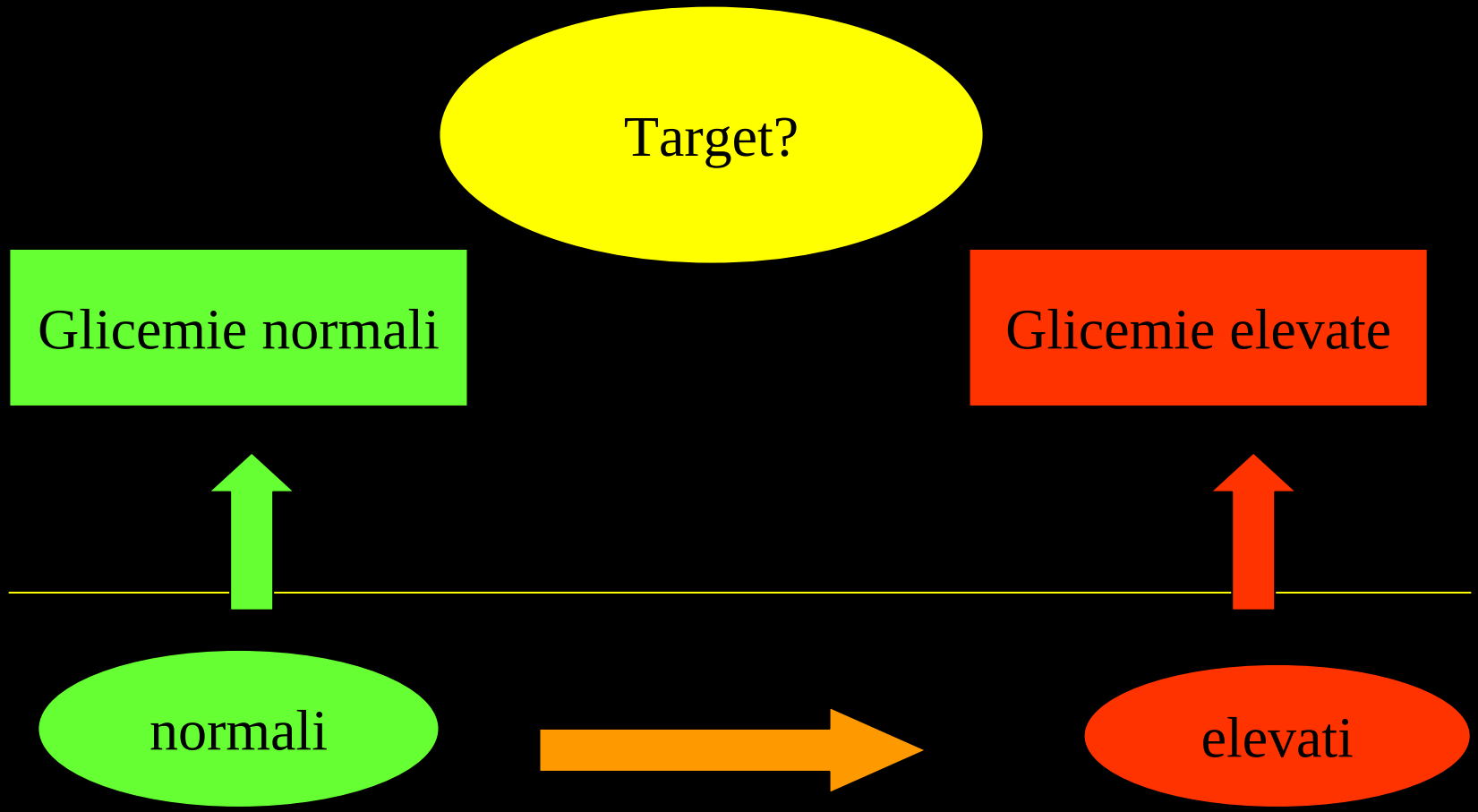
Good Glycaemic Control Reduces Incidence of Complications

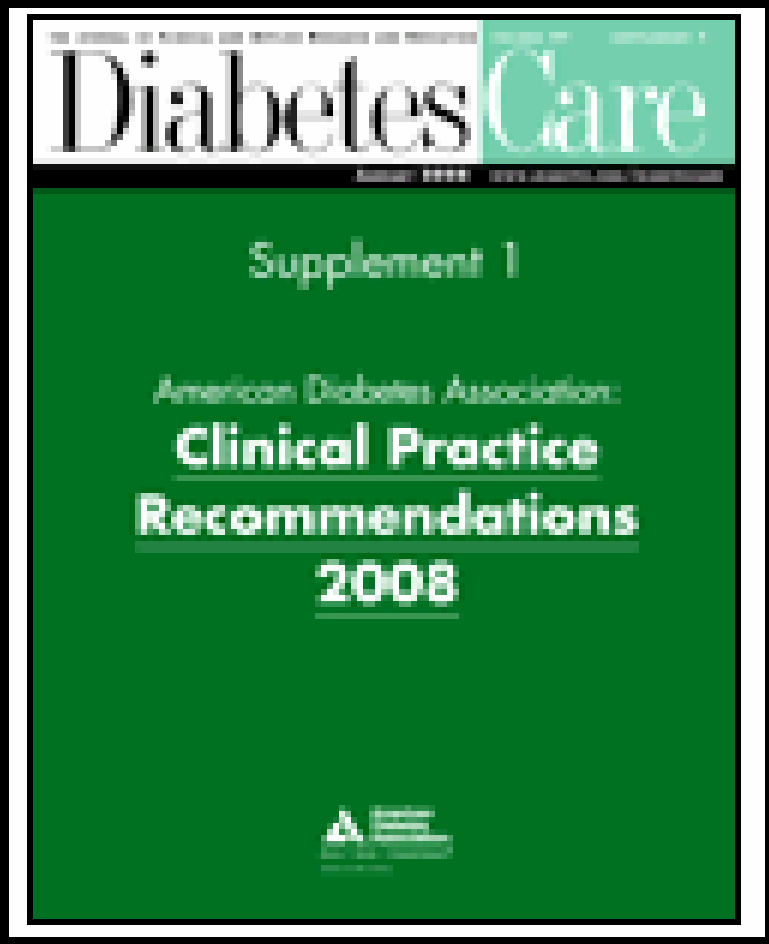
Complications of diabetes mellitus	Risk reduction by decrease in A1C (%) DCCT[1,2] (9% → 7%)	Ohkubo[3] (9% → 7%)	UKPDS[4] (8% → 7%)
Retinopathy	-63%	-69%	-21%
Nephropathy	-54%	-70%	-34%
Neuropathy	-60%	–	–
Macrovascular disease	-41%*	–	-16%*

*Not statistically significant.
DCCT, Diabetes Control and Complications Trial; UKPDS, United Kingdom Prospective Diabetes Study.

1. DCCT Research Group. *N Engl J Med.* 1993;329:977-986.
2. DCCT Research Group. *Diabetes.* 1995;44:968-983.
3. Ohkubo Y et al. *Diabetes Res Clin Pract.* 1995;28:103-117.

Valori di HbA1c nei pz diabetici




Diabetes Care
Supplement 1
American Diabetes Association:
Clinical Practice Recommendations 2008

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

Annals of Internal Medicine | CLINICAL GUIDELINES

Glycemic Control and Type 2 Diabetes Mellitus: The Optimal Hemoglobin A_{1c} Targets. A Guidance Statement from the American College of Physicians

Amir Qaseem, MD, PhD, MHA; Sandeep Vijan, MD, MS; Vincenza Snow, MD; J. Thomas Cross, MD, MPH; Kevin B. Weiss, MD, MPH; and Douglas K. Owens, MD, MS, for the Clinical Efficacy Assessment Subcommittee of the American College of Physicians*

This guidance statement is derived from other organizations' guidelines and is based on an evaluation of the strengths and weaknesses of the available guidelines. We used the Appraisal of Guidelines, Research and Evaluation in Europe (AGREE) appraisal instrument to evaluate the guidelines from various organizations. On the basis of the review of the available guidelines, we recommend:

Statement 1: To prevent microvascular complications of diabetes, the goal for glycemic control should be as low as is feasible without undue risk for adverse events or an unacceptable burden on patients. Treatment goals should be based on a discussion of the benefits and harms of specific levels of glycemic control with the patient. A hemoglobin A_{1c} level less than 7% based on individualized assessment is a reasonable goal for many but not all patients.

Statement 2: The goal for hemoglobin A_{1c} level should be based on individualized assessment of risk for complications from diabetes, comorbidity, life expectancy, and patient preferences.

Statement 3: We recommend further research to assess the optimal level of glycemic control, particularly in the presence of comorbid conditions.

Ann Intern Med. 2007;147:417-422. www.annals.org

For author affiliations, see end of text.

Con che frequenza fare l’HbA1c ?

•Perform the A1C test at least two times a year in patients who are meeting treatment goals (and who have stable glycemic control). (E)

•Perform the A1C test quarterly in patients whose therapy has changed or who are not meeting glycemic goals. (E)

For any individual patient, the frequency of A1C testing should be dependent on the clinical situation, the treatment regimen used, and the judgment of the clinician.

HbA1c come indicatore di rischio di patologie cardiovascolari ?

ARTICLE

Meta-Analysis: Glycosylated Hemoglobin and Cardiovascular Disease in Diabetes Mellitus

Elizabeth Selvin, MPH; Spyridon Marinopoulos, MD, MBA; Gail Berkenblit, MD, PhD; Tejal Rami, MPH; Frederick L. Brancati, MD, MHS; Neil R. Powe, MD, MPH, MBA; and Sherita Hill Golden, MD, MHS

Il rischio cardiovascolare aumenta nei pazienti diabetici con l'aumentare dell'HbA1c

- Associazione simile nei pazienti con diabete 1 e 2
- Indipendente dagli altri fattori di rischio per malattie cardiovascolari
- Ipotesi: il glucosio potrebbe reagire con diverse proteine causando alterazioni strutturali.
- Possibile ruolo dei prodotti finali di glicazione avanzata (AGE's)nel determinare alterazioni endoteliali, fomazione di placche e aterosclerosi
- Il processo sarebbe graduale e avverrebbe dopo decadi di esposizione a elevate concentrazioni di glucosio

L’associazione tra Hba1c e rischio cardiovascolare potrebbe estendersi anche al di sotto della soglia diagnostica per il diabete

Association of Hemoglobin A1c with Cardiovascular Disease and Mortality in Adults: The European - Microsoft Internet Explorer f
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ARTICLE

Association of Hemoglobin A_{1c} with Cardiovascular Disease and Mortality in Adults: The European Prospective Investigation into Cancer in Norfolk

Kay-Tee Khaw, MBBChir FRCP; Nicholas Wareham, MBBS, FRCP; Sheila Bingham, PhD; Robert Luben, BSc; Ailsa Welch, BSc; and Nicholas Day, PhD

21 September 2004 | Volume 141 Issue 6 | Pages 413-420

Background: Increasing evidence suggests a continuous relationship between blood glucose concentrations and cardiovascular risk, even below diagnostic threshold levels for diabetes.

Objective: To examine the relationship between hemoglobin A_{1c}, cardiovascular disease, and total mortality.

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Nei soggetti non diabetici con glicemia normale, un incremento dell'1% nei livelli di HbA1c sarebbe associato ad un aumento del 28% del rischio di morte per cause cardiovascolari, indipendentemente dall'età, dalla pressione, dai livelli di colesterolo, dal fumo

Everyone should watch glycosated hemoglobin and blood sugar levels, not just diabetics, research says.

Levenson D.

PMID: 15505932 [PubMed - indexed for MEDLINE]

L’HbA1c nello screening e nella diagnosi di diabete?

B. Diagnosis of diabetes

Recommendations

- The fasting plasma glucose (FPG) test is the preferred test to diagnose diabetes in children and nonpregnant adults. (E)
- Use of the A1C for the diagnosis of diabetes is not recommended at this time. (E)

HbA_{1c} or glucose for diabetes diagnosis?

Author: Kilpatrick, Eric S.[1]
Source: Annals of Clinical Biochemistry, Volume 42, Number 3, May 2005 , pp. 165-166(2)
Publisher: Royal Society of Medicine Press

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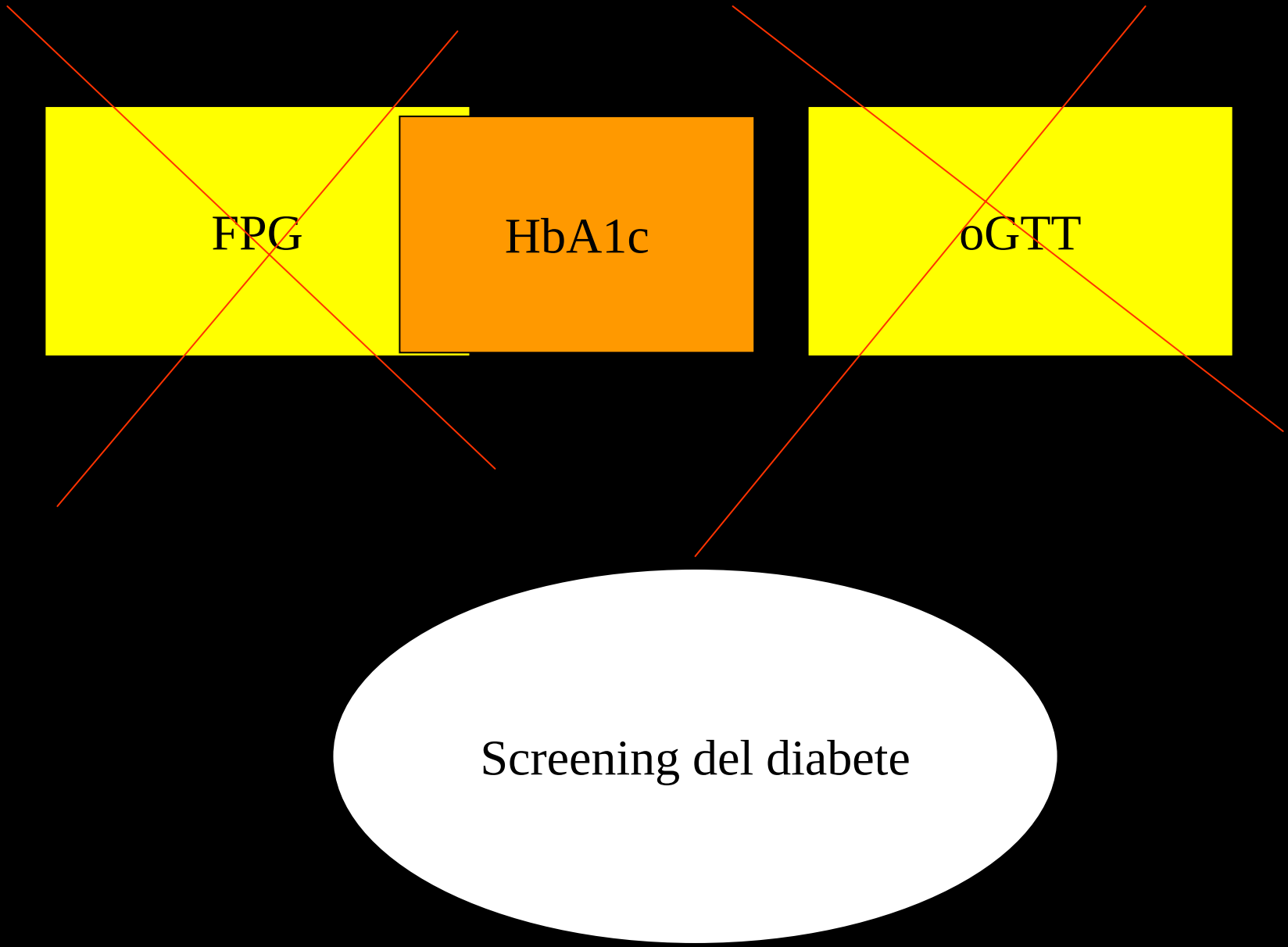
The Lancet 1997; **349**:223-224

DOI:10.1016/S0140-6736(05)64858-1

Commentary

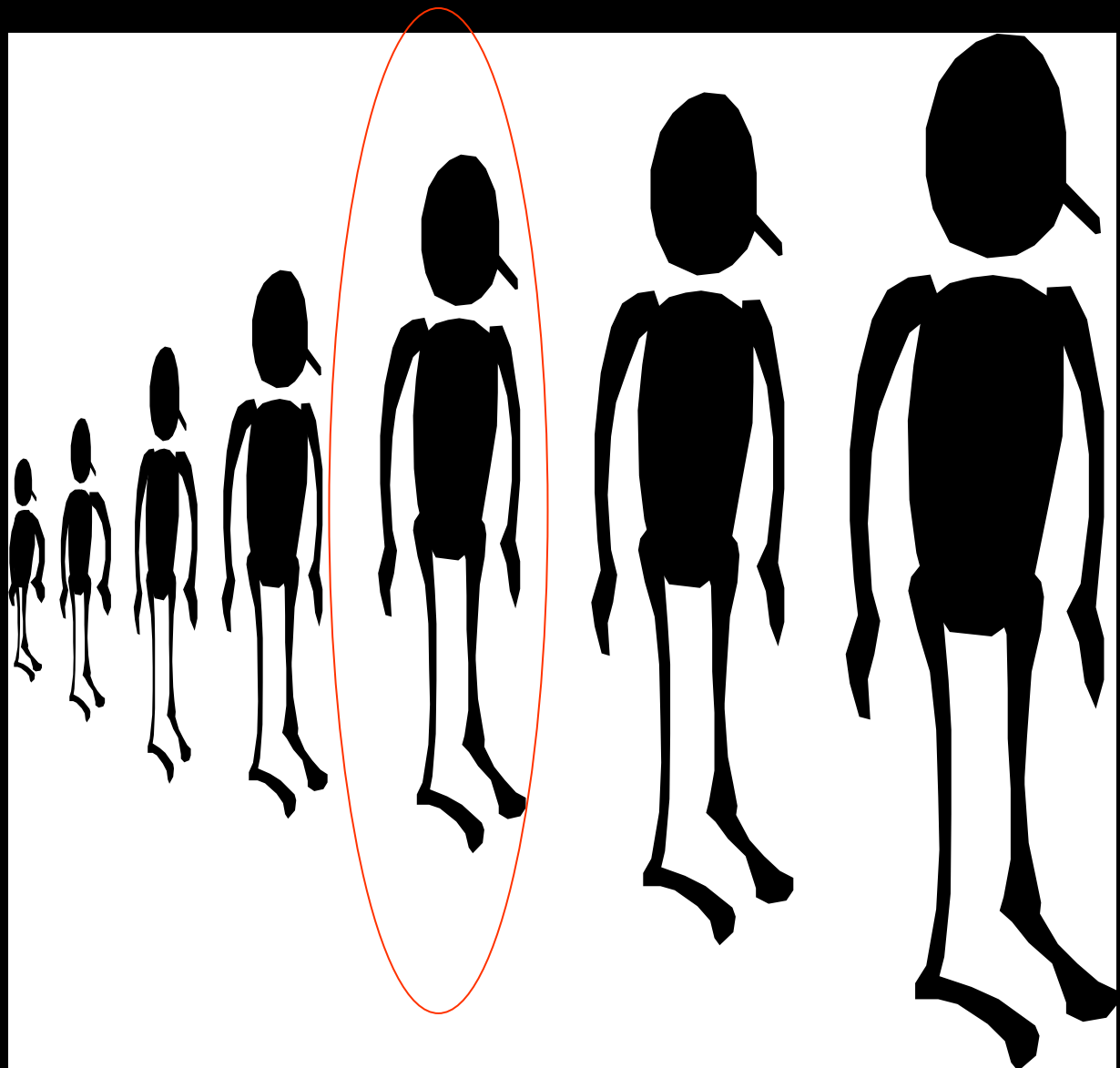
Will glycosylated haemoglobin replace the oral glucose-tolerance test?

Murray Stewart [a]


FPG
HbA1c
oGTT
Screening del diabete

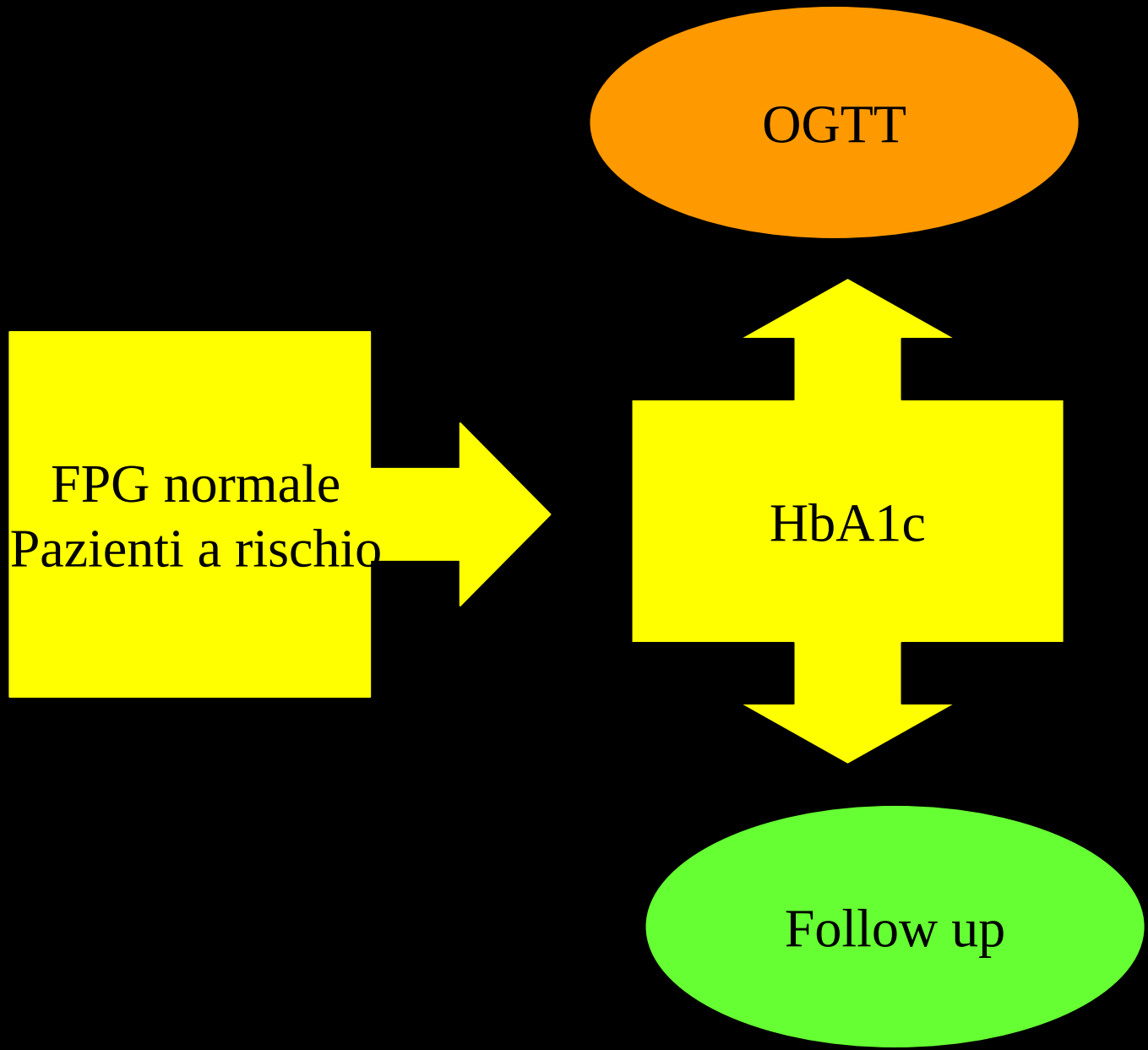
Diabete?

Prediabete?



FPG

OGTT


OGTT
FPG normale
Pazienti a rischio
HbA1c
Follow up

Abstract

A combination of HbA1c, fasting glucose and BMI is effective in screening for individuals at risk of future type 2 diabetes: OGTT is not needed

M. NORBERG[1], J. W. ERIKSSON[2], B. LINDAHL[3], C. ANDERSSON[4], O. ROLANDSSON[4,5], H. STENLUND[1] & L. WEINEHALL[1,6]

From the Sections of [1]Epidemiology and Public Health Sciences, [2]Medicine, [3]Behavioral Medicine, [4]Family Medicine and [5]Nutritional Research, Department of Public Health and Clinical Medicine, Umeå University, Umeå; and [6]Research Department, National Institute of Public Health, Stockholm, Sweden

Journal of internal medicine, 2006

- L’HbA1c correla con la glicemia alla 2 ora in OGTT ma non con la FPG
- Nella determinazione dell’HbA1c a valori bassi gioca un ruolo importante la glicemia postprandiale, più che la glicemia a digiuno
- Analoga situazione per la glicemia del pomeriggio e della sera

Negli stadi prediabetici FPG e HbA1c insieme potrebbero riflettere meglio, integrandosi, i valori della glicemia sia basale che postprandiale

Original Article

HbA_{1c} predicts the likelihood of having impaired glucose tolerance in high-risk patients with normal fasting plasma glucose

Tarekegn Geberhiwot, Angela Haddon and Mourad Labib

Ann Clin Biochem 2005; 42: 155–158

Introduction

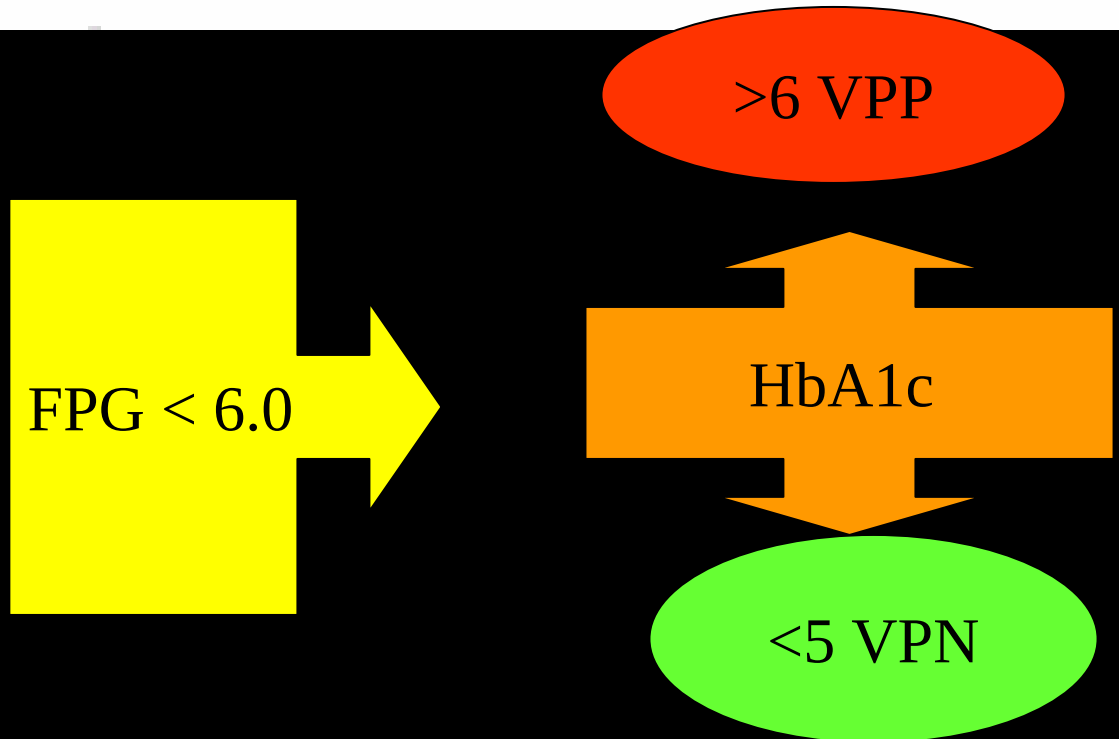
Pre-diabetes, classified as impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), is a risk category for diabetes and cardiovascular disease (CVD). There is evidence that pre-diabetes shares many of the metabolic abnormalities seen in type 2 diabetes and that diagnosing IGT at an early stage may have the potential to modify the clinical course of diabetes and its complications.[1]

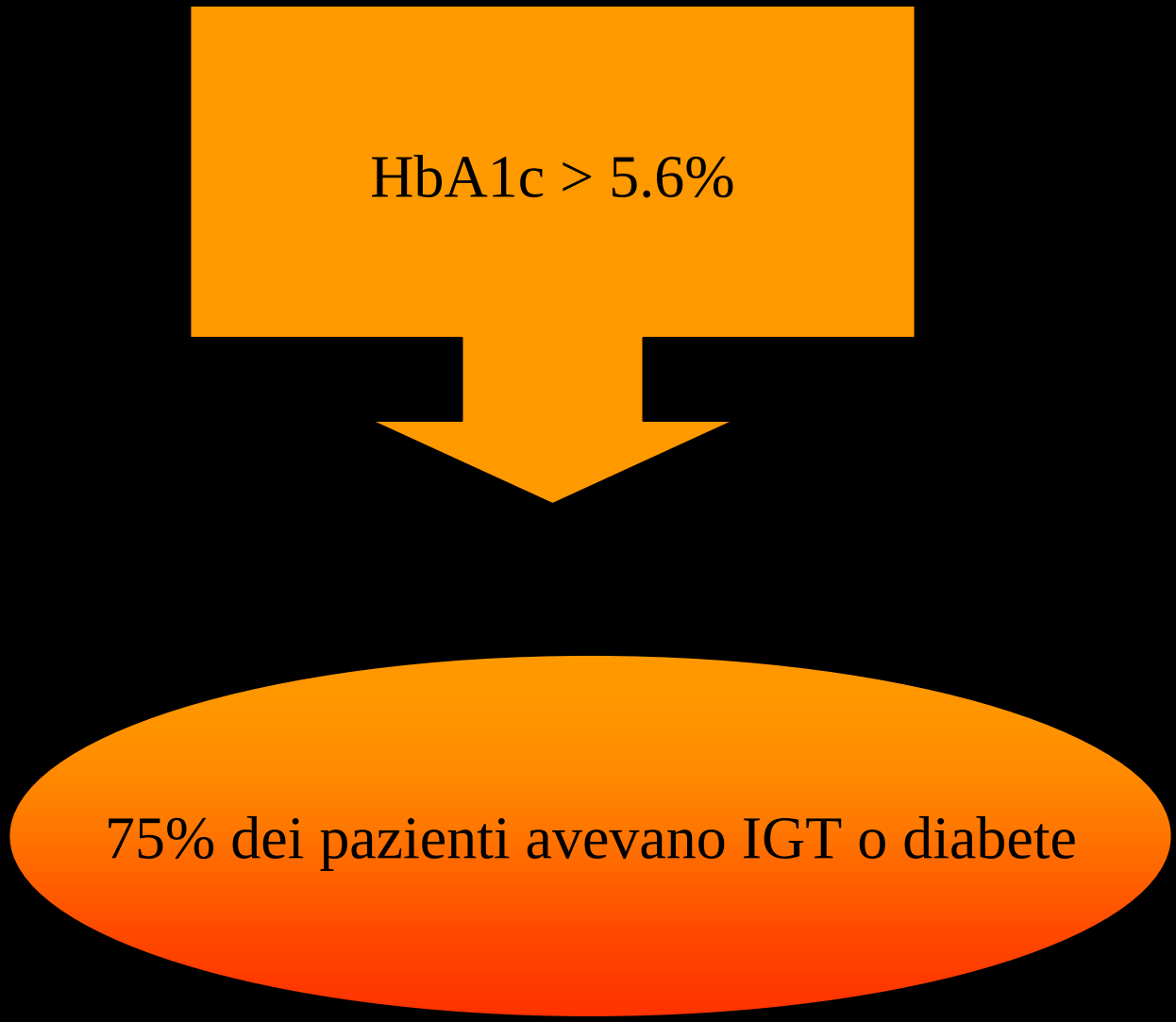
The 75 g oral glucose tolerance test (OGTT) using the World Health Organization (WHO) criteria is considered to be the gold standard in the diagnosis of glucose intolerance and diabetes.[2] However, this test is

glucose ≤ 6.0 mmol/L should have yearly assessments.[3,4] In our clinical practice, we have observed that a significant proportion of patients with FPG concentrations ≤ 6.0 mmol/L have IGT. We have therefore sought an alternative screening method for selecting patients with FPG ≤ 6.0 mmol/L who may benefit from having their pre-diabetes state identified using the OGTT. Although the use of glycated haemoglobin (HbA_{1c}) as a screening test for diabetes has been debated,[5] we hypothesized that in patients with FPG ≤ 6.0 mmol/L but who have risk factors for diabetes, the measurement of HbA_{1c} may be useful in selecting patients for an OGTT.

Ann Clin Biochem, 2005

HbA_{1c} analysis is a relatively simple test which gives a more comprehensive measure of total glycaemic exposure than FPG and, hence, it may be a better predictor of abnormal glucose tolerance. Although the use of HbA_{1c} as a diagnostic test in the general population remains controversial,[6] in populations who are at high risk, it has been shown to correlate well with the diagnosis of diabetes. Our results confirm that the use of




HbA1c > 5.6%
75% dei pazienti avevano IGT o diabete

Uso clinico dell'HbA1c

- Nel monitoraggio del paziente diabetico
- Come fattore di rischio per CVD ?
- Nello screening del diabete e prediabete ?

Sono però necessari

- ulteriori studi
- prestazioni analitiche adeguate