



VI CONVEGNO NAZIONALE
CENTRO STUDI E RICERCHE - FONDAZIONE AMD
NAPOLI, 18-20 OTTOBRE 2012



CENTRO CONGRESSI
STAZIONE MARITTIMA



“VI Convegno Nazionale Centro Studi e Ricerche Fondazione AMD”

"Ipoglicemie e rischio cardiovascolare"

Valeria Manicardi

**Direttore Unità Internistica Multidisciplinare
Ospedale di Montecchio E.
AUSL di Reggio Emilia**

**Consigliere Nazionale AMD
Napoli, 18-20 Ottobre 2012**





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Ipoglicemia e rischio CV



l'altra faccia della medaglia



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Ipoglicemia e rischio CV

- **Ipoglicemia e mortalità**
- **Ipoglicemia e Cuore**
- **Ipoglicemia e Cervello**
- **La lezione dei Trials**





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Survival as a function of HbA_{1c} in people with type 2 diabetes: a retrospective cohort study

Lancet 2010; 375: 481-89

Craig J Currie, John R Peters, Aodán Tynan, Marc Evans, Robert J Heine, Oswaldo L Bracco, Tony Zagar, Chris D Poole

Summary

Background Results of intervention studies in patients with type 2 diabetes have led to concerns about aiming for normal blood glucose concentrations. We assessed survival as a function of HbA_{1c} in type 2 diabetes.

Methods Two cohorts of patients aged 50 years and older with type 2 diabetes were generated from the Practice Research Database from November 1986 to November 2008. We identified 27 965 patients who had been intensified from oral monotherapy to combination therapy with oral blood-glucose lowering agents in 20005 who had changed to regimens that included insulin. Those with diabetes secondary to other causes were excluded. All-cause mortality was the primary outcome. Age, sex, smoking status, cholesterol, cardiovascular morbidity were identified as important confounding factors, and Cox survival models were fitted adjusting for these factors accordingly.

Findings For combined cohorts, compared with the glycated haemoglobin (HbA_{1c}) decile with the lowest HbA_{1c} (median HbA_{1c} 7.5%, IQR 7.5–7.6%), the adjusted hazard ratio (HR) of all-cause mortality in the lowest HbA_{1c} decile (median 6.4%, IQR 6.1–6.6) was 1.52 (95% CI 1.32–1.76), and in the highest HbA_{1c} decile (median 10.5%, IQR 10.1–10.9) was 1.79 (95% CI 1.56–2.06). Results showed a general U-shaped association, with the lowest HR at the lowest HbA_{1c} decile. HR for all-cause mortality in people given insulin-based regimens (2834 deaths) versus those given oral agents (2035) was 1.49 (95% CI 1.39–1.59).

Interpretation Low and high mean HbA_{1c} values were associated with increased all-cause mortality in type 2 diabetes. If confirmed, diabetes guidelines might need revision to include a minimum HbA_{1c} value.

STUDIO di COORTE:
2 coorti di DT2 > 50 a.
27965 In Ter IPO
20005 in Ins
Dal 1986 – 2008

La mortalità- corretta per i fattori confondenti - è più elevata nei decili più bassi
E più alti di HbA_{1c} :
HR di 1,52 x 6,4 %
HR di 1,79 x 10,5%
Mentre la mortalità più bassa si ha nei p. con HbA_{1c} di 7,5%

CURVA a U



Ipoglicemia e Mortalità

CURVA a U tra HbA1c e mortalità

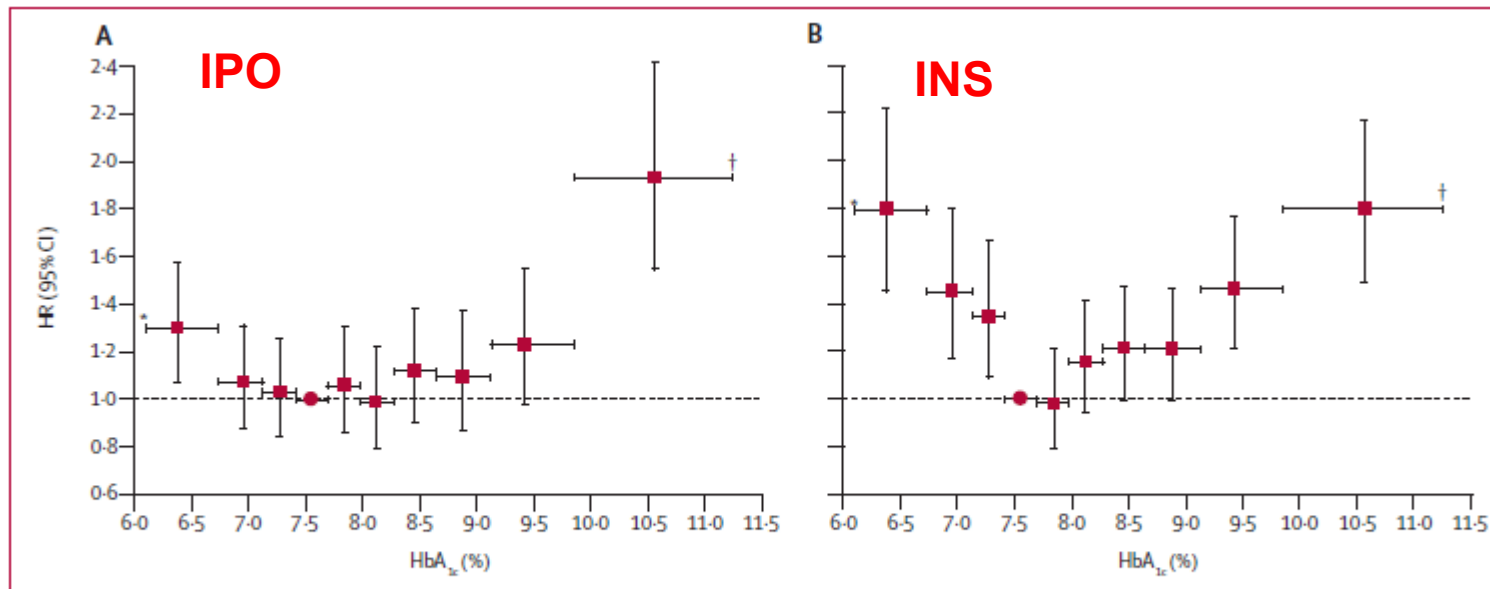


Figure 1: Adjusted hazard ratios for all-cause mortality by HbA_{1c} deciles in people given oral combination and insulin-based therapies
Cox proportional hazards models were used, with the HbA_{1c} base case scenario. Vertical error bars show 95% CIs, horizontal bars show HbA_{1c} range. Red circle=reference decile. *Truncated at lower quartile. †Truncated at upper quartile. Metformin plus sulphonylureas (A); and insulin-based regimens (B).

Lo stesso fenomeno si evidenzia per Diabetici con Insufficienza renale cronica.

Shurraw – Arch.Intern.Med.2011,171:1920

E nei pazienti Dializzati

Ricks – Diabetes 2012,61:708

**La Curva ad U esiste anche per altri parametri vitali,
quali PA , BMI, ma non per il fumo**



Ipoglicemia e rischio CV

**CURVA a U
tra HbA1c ed eventi
macrovascolari**

**Perché valori glicemici
normali possono essere
Dannosi nei Diabetici ?**

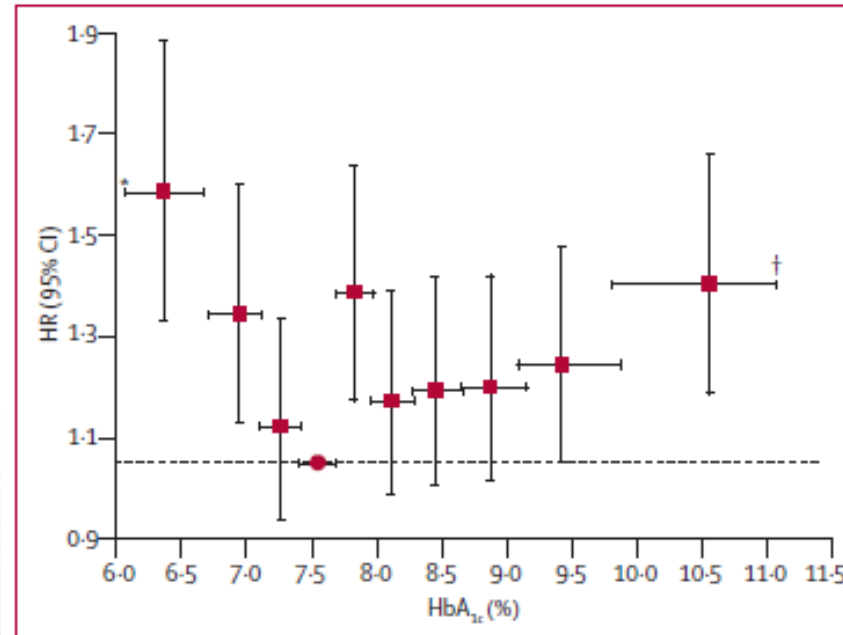
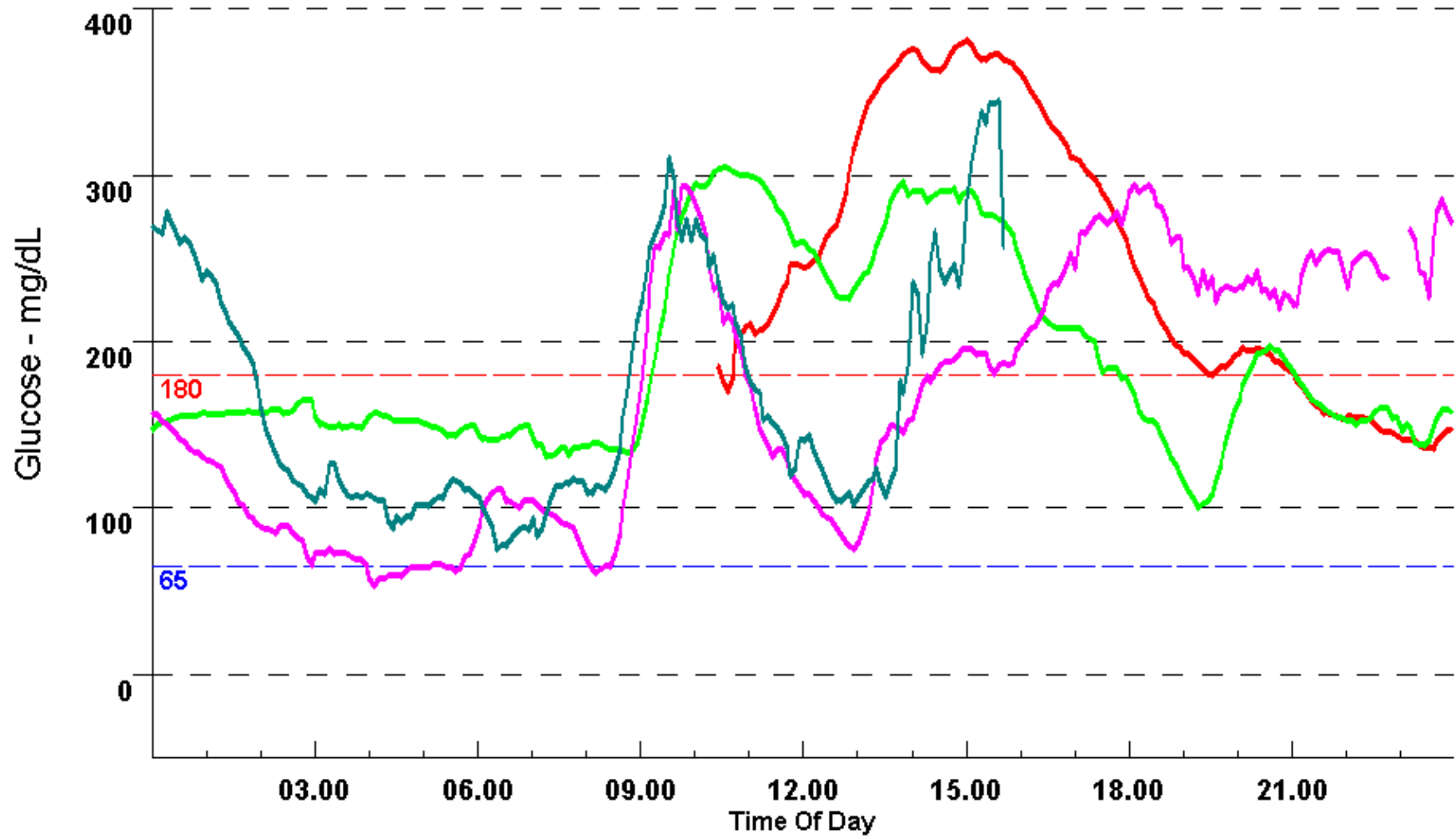


Figure 3: Hazard ratios for progression to first large-vessel disease event by HbA_{1c} decile, with Cox proportional hazards model
Vertical error bars show 95% CIs, horizontal bars show HbA_{1c} range. Red circle=reference decile. *Truncated at lower quartile. †Truncated at upper quartile. Model specification, for people with no previous cardiovascular disease only: age, sex, Charlson index (age unadjusted), total cholesterol, smoking status history, and cohort membership.

**Tuttavia gli studi di COORTE possono solo evidenziare
questa associazione , ma non possono definire se esiste un rapporto causale**

L'HbA1c esprime una media glicemica , ma non la variabilità glicemica



Ipoglicemia e Mortalità per Infarto Miocardico

- U-Shaped Relationship of Blood Glucose with adverse outcomes among patients with ST-segment elevation Myocardial Infarction.
Pinto, IACC 46:178, 2005

- *Metanalisi di 16 studi in paz con STEMI : 4224 paz.*

Mortalità per classi di Glicemia:

- *4,6% per Glic < 81*
- *1,0 per Normoglicemie*
- *4,7% per Glic > 199*

Recidive di IMA:

- *10,5% per Glic < 81*
- *4,2 per paz con euglicemia.*
- *7,2 per Glic > 199*



Ipo - Iper



Morte



Ipoglicemia e rischio CV

La cascata di eventi che l'ipoglicemia innesca: IPOGLICEMIA Acuta

- Inibizione della secrezione endogena di Insulina
- Ormoni della controregolazione: GLUCAGONE e ADRENALINA

Alterazioni ECG

CHD/IpArt/IMA ?



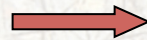
- Comparsa dei sintomi: Autonomici e Neuroglicopenici



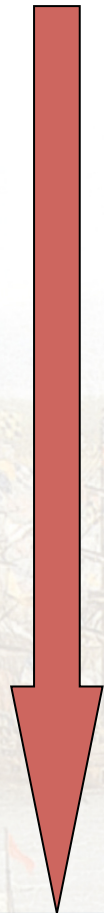
- Disfunzioni neurofisiologiche

- Alterazioni EEG

STROKE/TIA ?



- Turbe cognitive
- Riduzione dello stato di coscienza
- Convulsioni
- coma





Ipoglicemia e rischio CV

- Ipoglicemia e mortalità
- **Ipoglicemia e Cuore**
 - **Morte improvvisa**
- Ipoglicemia e Cervello
 - **Aritmie**
- La lezione dei Trials
 - **Ischemia**
 - **Scompenso**





ECG in corso di Ipoglicemia sperimentale :



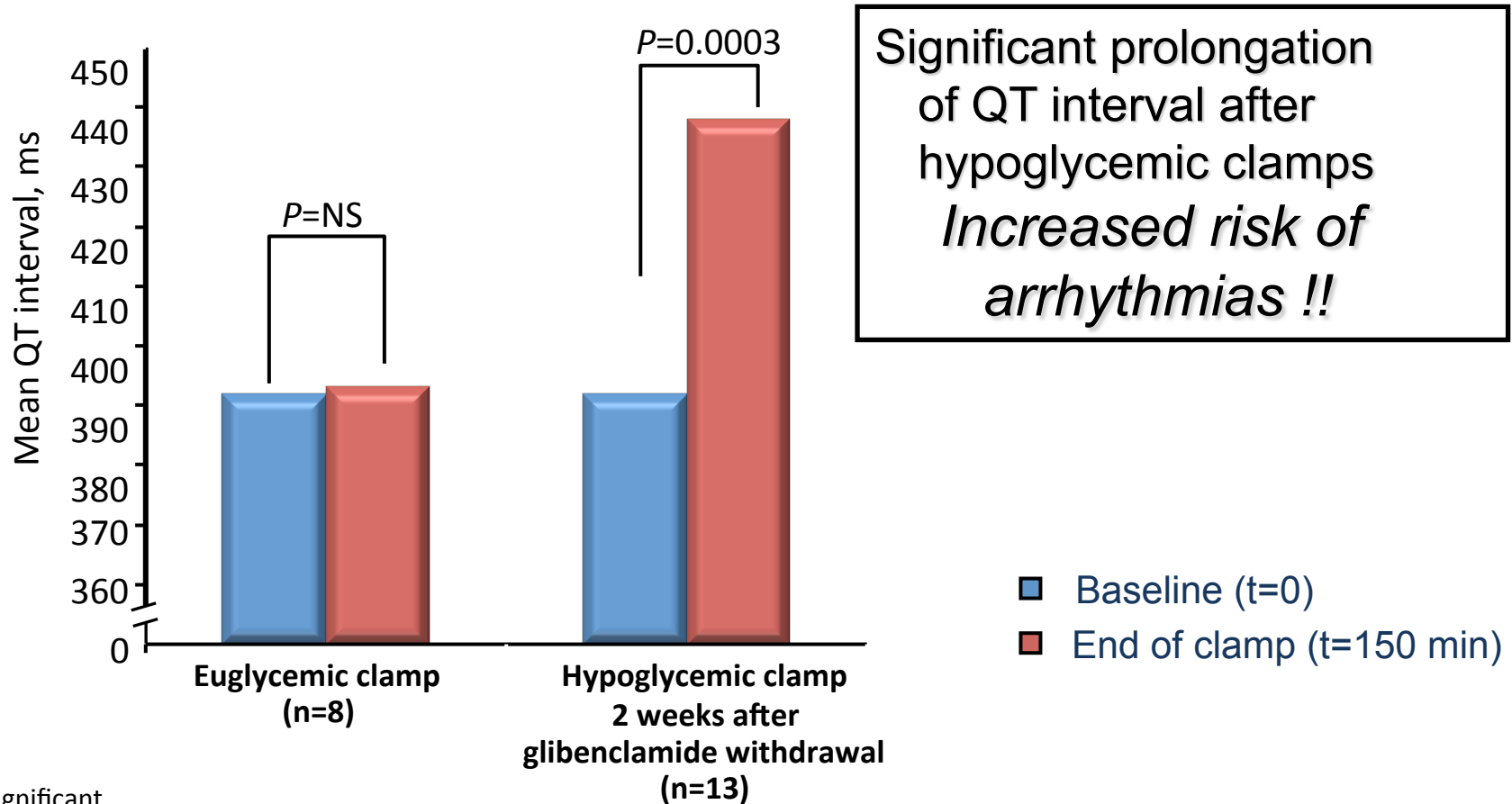
Allungamento dell'intervallo QT
E della ripolarizzazione cardiaca
(stato pro-aritmico)



Aritmie : - Tachicardia Ventricolare,
- Torsione di punta
- Fibrillazione Vn
ma anche
- Bradicardia,
- blocco seno-atriale
- Arresto cardiaco

Alterazione della contrattilità dei miociti → alterata
contrattilità

Severe Hypoglycemia May Cause a Prolongation of QT Interval in Patients With Type 2 Diabetes



NS=not significant.

Thirteen patients with type 2 diabetes taking combined insulin and glibenclamide treatment were studied during hypoglycemia; 8 participated in the euglycemic experiment. The aim was to achieve stable hypoglycemia between 2.5 and 3.0 mmol/L (45 and 54 mg/dL) during the last 60 minutes of the experiment.

Landstedt-Hallin L et al. *J Intern Med.* 1999;246:299–307.



50 sudden deaths in Type 1 Diabetes in Uk in 1990

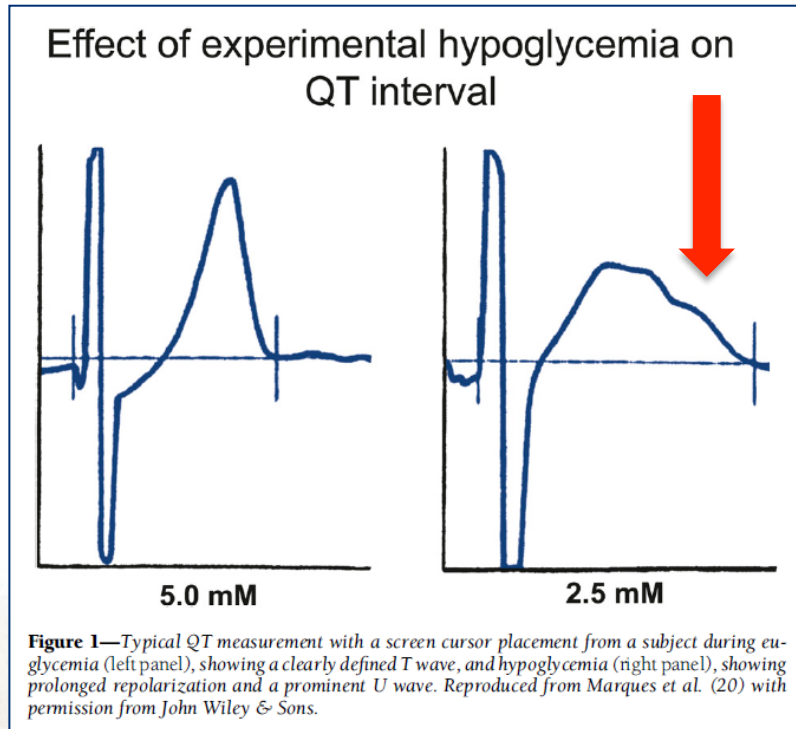
Tattersell, Diabet.Med.1991

- Dead in Bed Syndrome – **22 /50**
- Suicide
- Hypoglycaemic Brain Damage
- Definite Cause of Death
- DKA
- Unexplained

**La morte improvvisa è un evento raro e devastante ,
più frequente nei diabetici di Tipo 1 rispetto
ai non diabetici di pari età**



Ipoglicemia e Aritmie



**Ma le Ipoglicemie
sono frequenti
e le morti improvvise
sono rare**

**La Neuropatia autonoma
cardiaca è
una importante concausa
dell'evento fatale.**

DIABETES CARE, VOLUME 34, SUPPLEMENT 2, MAY 2011

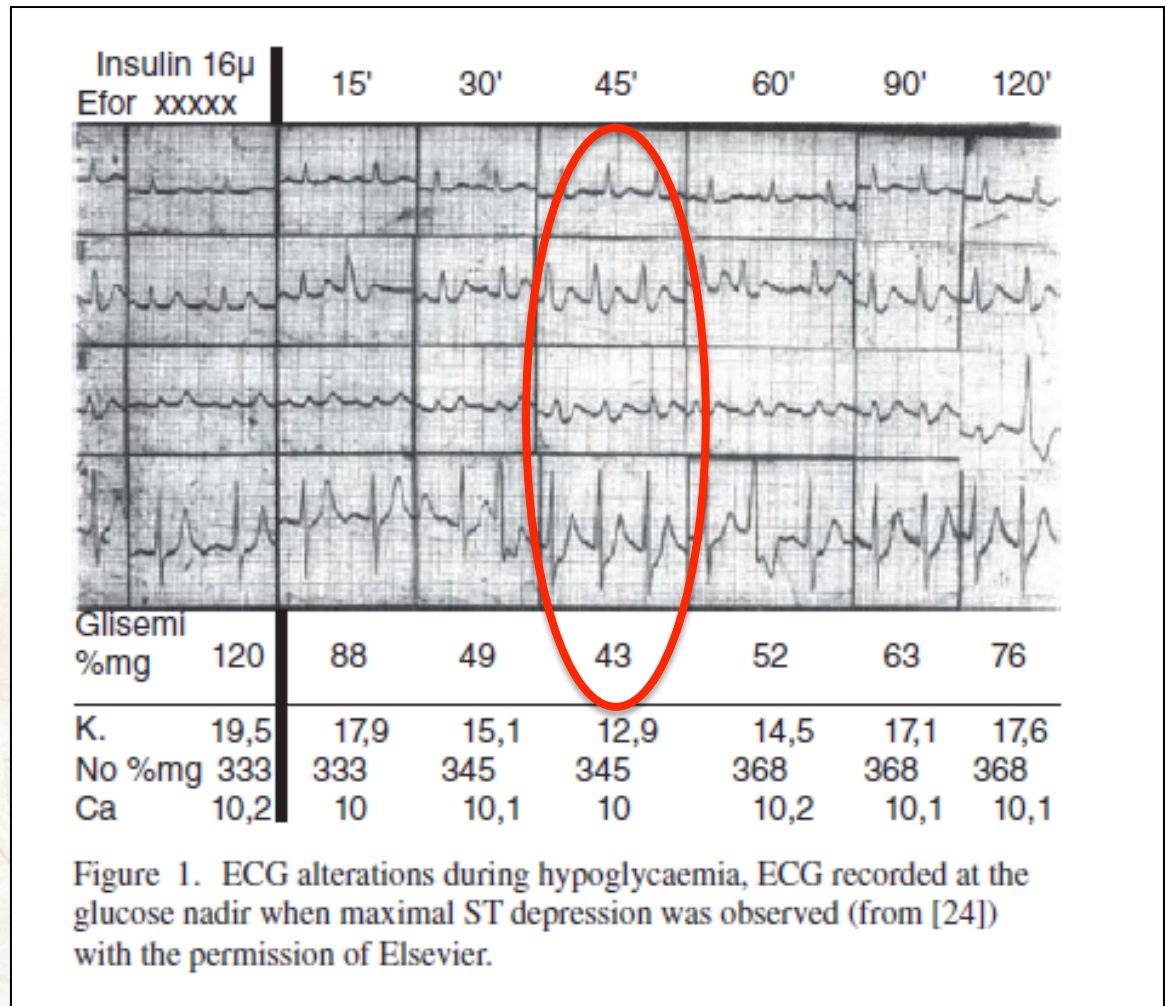
Autonomic neuropathy itself can be associated with QTc lengthening and possibly sudden death [31], and a recent study has found QTc prolongation to be common in adolescent patients with type 1 diabetes with early autonomic dysfunction et [32]



Ipoglicemia e Ischemia Cardiaca

Case report :

Ischemia cardiaca Indotta da ipoglicemia severa





L' **IPOGLICEMIA Acuta**, è il **secondo** più potente stimolo alla **secrezione di Adrenalina**, dopo l'**Infarto Miocardico Acuto**, che è in assoluto il **più potente**.

Inzucchi:

anche ipoglicemie modeste (50 mg/dl) aumentano **l'adrenalina di 100 volte**

→ Vasocostrizione → aumento della PA → K^+ intracell → aumento FFA (*cardiotossicità diretta*) → *aumentato consumo di ossigeno*

Effects of euglycaemic and hypoglycaemic hyperinsulinaemia on sympathetic and parasympathetic regulation of haemodynamics in healthy subjects.

Clin Sci (Lond). 2003 Sep;105(3):315-22.

- Euglycaemic hyperinsulinaemia did not change: plasma catecholamine concentrations, HR Variability, heart rate, blood pressure, stroke volume, cardiac output or peripheral resistance.
- Hyperinsulinaemic hypoglycaemia resulted in an 11.7-fold increase in the plasma adrenaline concentration, and a modest 1.3-fold increase in the plasma noradrenaline concentration compared with baseline. Significant decreases in diastolic blood pressure and peripheral resistance

Metabolismo Miocardico in condizioni di Ischemia

- In condizioni normali il Miocardio consuma soprattutto Ac Grassi Liberi , come fonte di energia - più efficiente (1 molecola di Palmitato produce 130 Mol di ATP) , ma più dispendiosa di O₂ (via mitocondriale- aerobica) ed il Glucosio viene immagazzinato a Glicogeno.
- In condizioni di Ischemia il Miocardio cambia substrato : usa soprattutto Glucosio, la cui ossidazione richiede meno O₂ :1 molecola di Gl consuma 12 atomi di O₂ , meno di 1/3 rispetto ad una molecola di Palmitato(FFA)
- Durante l'ischemia c'è perciò un'augmentata utilizzazione del Gl per produrre piruvato e - per via anaerobia - lattato e quindi ATP.
- Ma in assenza o in carenza di INSULINA il muscolo cardiaco non può utilizzare Gl, e quindi si riduce la produzione di ATP e l'efficienza contrattile, soprattutto del territorio non ischemico.
- Anche in corso di IPOGLICEMIA c'è un incremento degli FFA per l'effetto lipolitico dell'Adrenalina: manca il Glucosio e ci sono gli FFA come substrato energetico → **umentato consumo di O₂** → **maggiore estensione dell'Area di Necrosi** → **< FE%** → **< Flusso Coronarico**.

Ipoglicemia e S. Coronarica acuta

- *Svensson, Eur H J 26:1255, 2005*

"Association between hyper- and hypoglycaemia and 2 year all-cause mortality risk in diabetic patients with acute coronary events"

713 paz con Diabete con SCA: Angina Instabile o IMA-Non Q.

- *2,66* rischio di morte nel quartile di Glicemia più elevata all'ingresso in UTIC , vs il più basso,
- *ma 1,77* è il rischio di morte per chi ha avuto qualche Ipoglicemia durante il ricovero in UTIC.
- *L'iperglicemia all'ingresso in UTIC e le Ipoglicemie durante la degenza* sono entrambi indicatori indipendenti di peggiore prognosi, a 2 anni dall'evento.

Association of Hypoglycemia and Cardiac Ischemia

A study based on continuous monitoring

CYRUS DESOUZA, MD¹
HOLGER SALAZAR, MD²
BENJAMIN CHEONG, MD²

JOSEPH MURGO, MD²
VIVIAN FONSECA, MD¹

- Hypoglycemia is more like to be associated with cardiac ischemia
 - 19 patients CGMS +cardiac Holter
 - + recording of chest pain or symptoms of hypo

Table 2—CGMS and Holter monitoring abnormalities

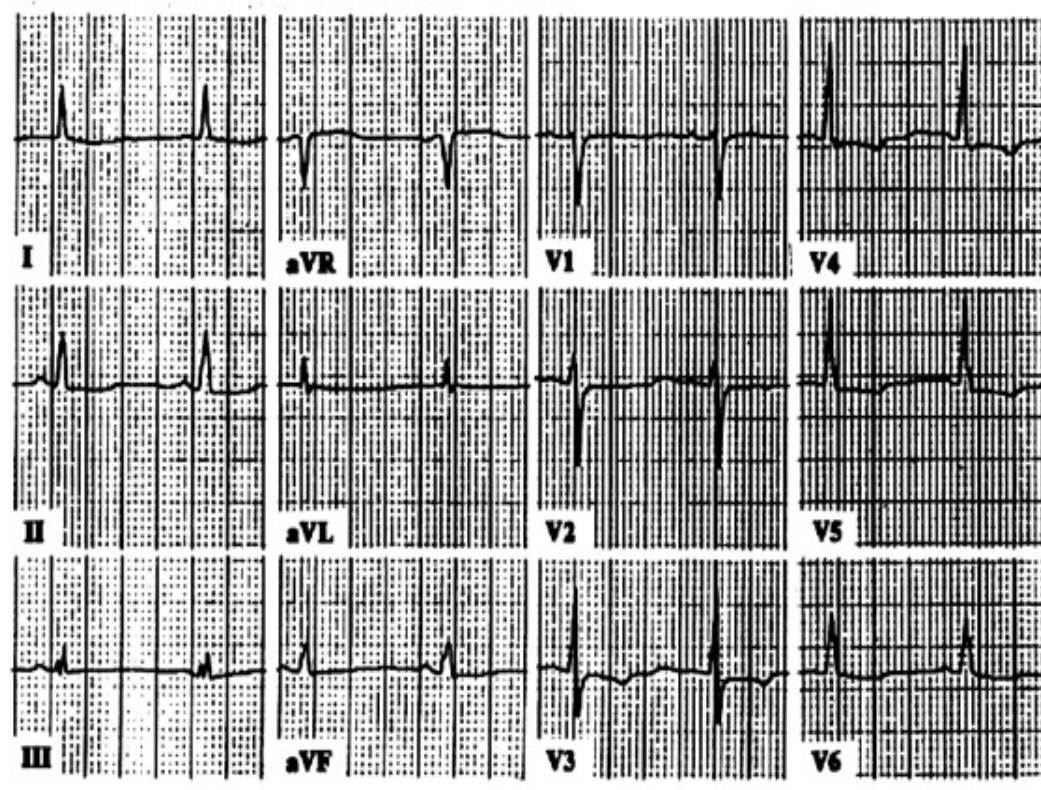
	Total episodes	Episodes with chest pain/angina	Episodes with ECG abnormalities
Hypoglycemia	54	10*	6*
Symptomatic	26	10*	4*
Asymptomatic	28	—	2
Normoglycemia without rapid changes	N/A	0	0
Hyperglycemia	59	1	0
Rapid changes in glucose (>100 mg · dl ⁻¹ · h ⁻¹)	50	9*	2

*P < 0.01 vs. episodes during hyperglycemia and normoglycemia.

Hypoglycemia induced angina pectoris in a T2DM patient, 61 yrs, in Insulin Therapy

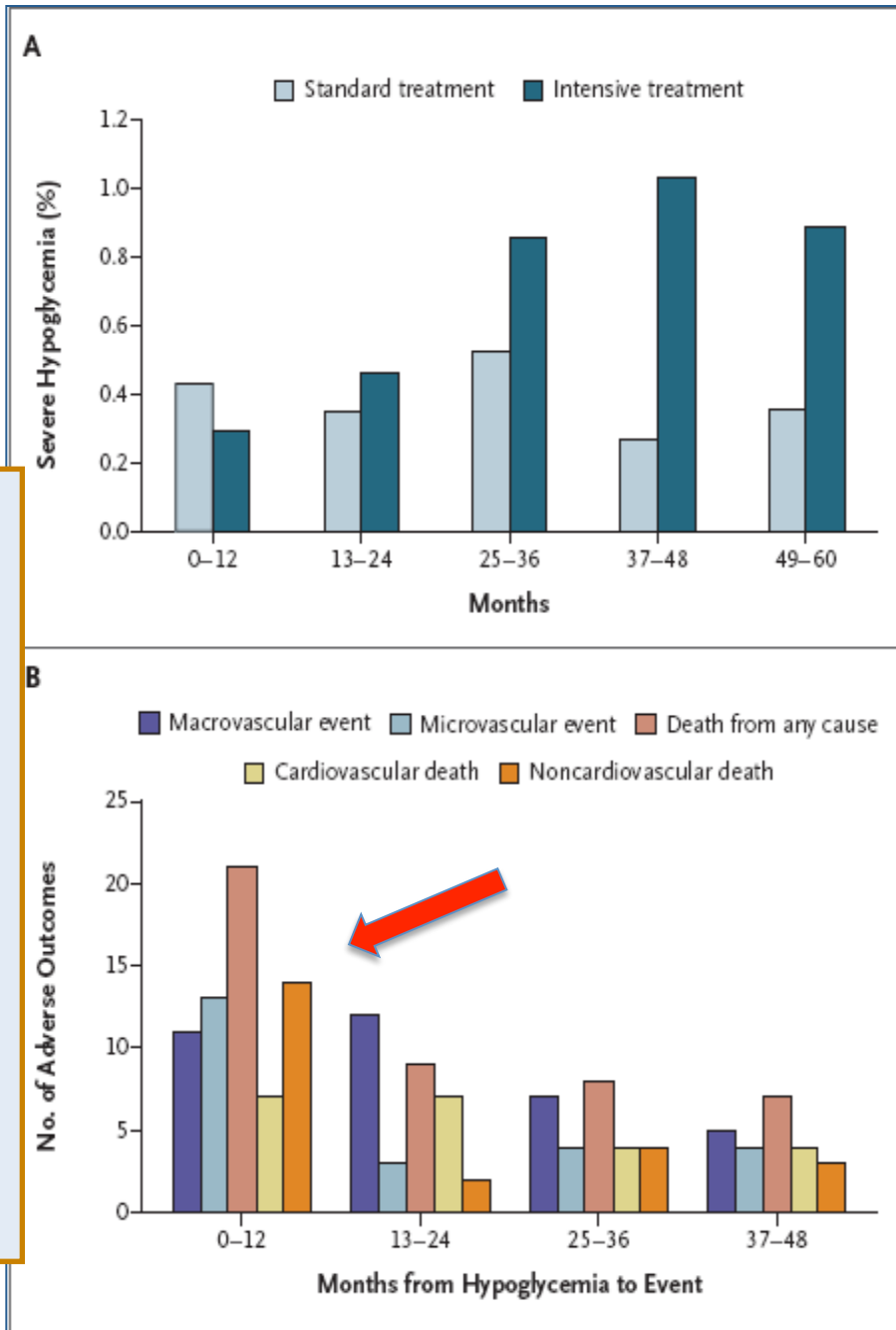
After Recovery

Case report :



Severe Hypoglycemia and Risks of Vascular Events and Death

Severe hypoglycemia is strongly associated with increased risks of various adverse clinical outcomes, ... **severe hypoglycemia may contribute to these outcomes, or it may alternatively be a marker of vulnerability to these events.**





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Ipoglicemia

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Severe Hypoglycemia and Risks of Vascular
Events and Death

The presence of coexisting conditions could increase a patient's vulnerability to both severe hypoglycemia and an adverse clinical outcome in the absence of a direct causal link between the two



Impact of Hypoglycemia Associated With Antihyperglycemic Medications on Vascular Risks in Veterans With Type 2 Diabetes

YINGNAN ZHAO, PHD^{1,2,3}
CLAUDIA R. CAMPBELL, PHD²

VIVIAN FONSECA, MD^{3,4}
LIZHENG SHI, PHD^{2,3,4}

OBJECTIVE—Hypoglycemia is associated with failure to show cardiovascular benefit & increased mortality of intensive glycemic control in randomized clinical trials. This retrospective cohort study aimed to examine the impact of hypoglycemia on vascular events in clinical practice.

RESEARCH DESIGN AND METHODS—Patients with type 2 diabetes were identified ICD-9-CM codes (250.xx except for 250.x1 and 250.x3) between 1 January 2004 and 1 September 2010 from the Veterans Integrated Service Network 16. Index date was defined as the first date of new antihyperglycemic medications (index treatment). Patients with 1-year preindex records of hypoglycemia, cardiovascular, and microvascular diseases were excluded. The hypoglycemia group was identified by ICD-9-CM codes (250.8, 251.0, 251.1, and 251.2) within the index treatment period. A propensity score–matched group was used as control subjects. Cardiovascular events, microvascular complications, and all-cause death were compared using Kaplan-Meier analysis and Cox proportional hazards regression model.

RESULTS—Among the unmatched sample ($N = 44,261$), the hypoglycemia incidence rate was 3.57/100 patient-years. The matched sample (hypoglycemia group: $n = 761$; control group: $n = 761$) had a median follow-up of 3.93 years, mean age of 62.6 ± 11.0 years, and preindex HbA_{1c} of $10.69 \pm 2.61\%$. The 1-year change in HbA_{1c} was similar (hypoglycemia group -0.51 vs. control group -0.32% , $P = 0.7244$). The hypoglycemia group had significantly higher risks of cardiovascular events (hazard ratio 2.00 [95% CI 1.63–2.44]) and microvascular complications (1.76 [1.46–2.11]) but no statistical mortality difference. Patients with at least two hypoglycemic episodes were at higher risks of vascular events than those with one episode (1.53 [1.10–1.66]).

CONCLUSIONS—Hypoglycemia is associated with higher risks of incident vascular events. Patients with hypoglycemia should be monitored closely for vascular events.

Diabetes Care 35:1126–1132, 2012

Patients without CVD and microvascular complications recorded during one year before the index date

N=43,500

Patients without CVD and microvascular complications recorded during one year before the index date

N=761

... control ... of major ... trials (9–13).

The development of hypoglycemia as a result of intensive treatment is one of the major barriers to intensifying treatment and to preventing patients from achieving the benefits of good glycemic control. A systematic review of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, the Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) trial, and the Veterans Affairs Diabetes Trial (VADT) found that hypoglycemic events were 2.5 times as common in the intensively treated group as in the control group (14). In the ACCORD trial, the increased risk of hypoglycemia with intensive therapy was threefold. Hypoglycemia related to the use of antihyperglycemic medications has been associated with the excess mortality

Studio retrospettivo
Dati ricavati dalle
codifiche ospedaliere
ICD-9-CM

Veterans Integrated
service Network 16

2004 – 2010
Index treatment:
Primo giorno di nuova
Ter. Ipoglicemizzante
per cattivo compenso

Follow up per 3 anni – eventi Cv in base all'Hypogl. Index

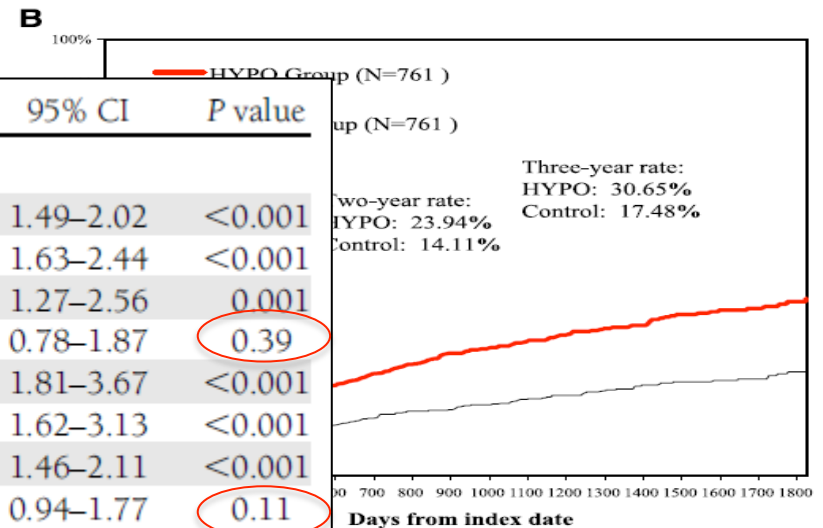
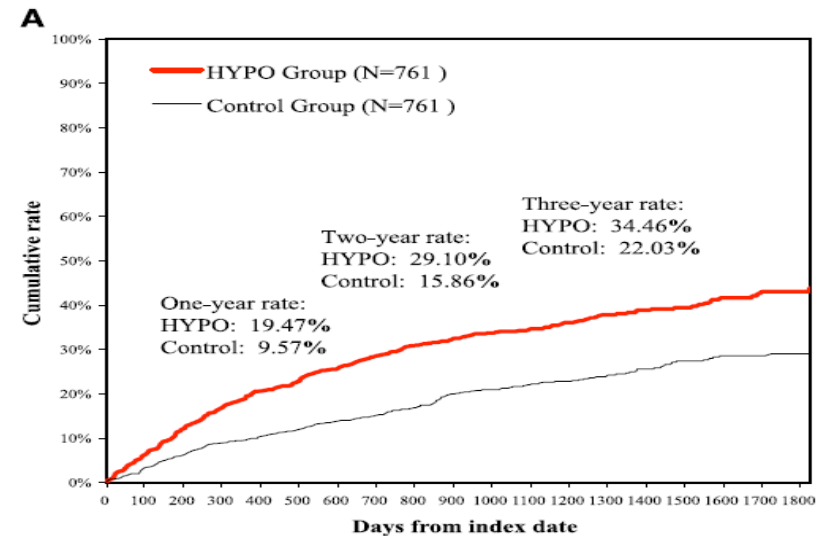


Ipoglicemia e rischio CV

Complicanze Macrovascolari - A

Complicanze Microvascolari - B

Hypoglycemia and vascular risks



Outcome	Coefficient	SE	HR	95% CI	P value
Vascular events					
All vascular event end points	0.5496	0.0770	1.73	1.49-2.02	<0.001
CVD	0.6910	0.1029	2.00	1.63-2.44	<0.001
Congestive heart failure	0.5911	0.1789	1.81	1.27-2.56	0.001
Myocardial infarction	0.1906	0.2231	1.21	0.78-1.87	0.39
Peripheral vascular disease	0.9468	0.1803	2.58	1.81-3.67	<0.001
Stroke	0.8118	0.1683	2.25	1.62-3.13	<0.001
Microvascular complications	0.5623	0.0949	1.76	1.46-2.11	<0.001
All-cause death	0.2563	0.1600	1.29	0.94-1.77	0.11

Cox proportional hazards regression models were used to control for confounding factors, including sociodemographics, illness characteristics, prior drug use, and index drug type. Best predicting model was selected for each outcome measure. Only the statistics of group membership are presented.

Figure 1. Cumulative incidence rate of CVD events by group. B: Cumulative incidence rate of microvascular complications by group. HYPO, hypoglycemia. Log-rank test showed significance for both groups. (A and B figures are available in the online issue.)



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Ipoglicemia e TIA

Il Cervello ha bisogno di zucchero !!!

- “Transient hypoglycemic hemiparesis”. *J Natl Med Assoc.* 2002 Nov;94(11):999-1001 - Case Report (18 yr old F- DT1)
- Transient hypoglycemic hemiparesis is a rare but important presentation of hypoglycemia that is frequently misdiagnosed as stroke, and - if misdiagnosed - could result in permanent neurological damage.

➔ Montgomery, "Transient hypoglycemic hemiplegia"
Arch Intern Med 1964 pp. 680-687

➔ Andrade, R.; "Hypoglycemic hemiplegic syndrome"
Ann Emerg Med 1984 pp. 529-531

➔ Pasevic, J.D.; "Hypoglycemic hemiplegia"
J Am Osteopath Assoc 1990 pp. 539-541

➔ Wattoo, M.A "Alternating transient dense hemiplegia due to episodes of hypoglycemia" *West J Med* 1999 pp. 170-171



Nuovo o vecchio fattore di rischio ?

ma ancora con meccanismi non tutti chiari



Ipoglicemia e Cervello

Update in the CNS Response to Hypoglycemia

Rory J. McCrimmon

University of Dundee, Biomedical Research Institute, Dundee DD1 9SY, Scotland, United Kingdom

J Clin Endocrinol Metab, January 2012, 97(1):1-8



Hypoglycemia-Induced Suppression of Neuroendocrine Counterregulation: Adaptive or Maladaptive?

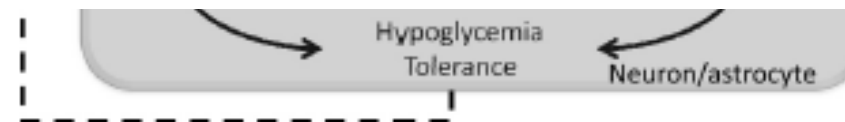


FIG. 1. Hypothetical model of hypoglycemia tolerance developing in response to recurrent hypoglycemia. Hypoglycemia develops initially in the context of a relative hyperinsulinemia and a hypoglycemia-specific glucagon defect. At a cellular level,



Ipoglicemia e Cervello

“Hypoglycemic encephalopathy with extensive lesions in the cerebral white matter.” Case report

- Paziente in Ipoglicemia (27 mg/dl) per 4 ore, e rimasto in coma per 22 mesi, nonostante il rapido ripristino della normoglicemia. Senza segni di ipotensione o ipossia.

“Hypoglycemia-induced brain damage:”

- Post-mortem examination revealed superficial laminar necrosis throughout the cerebral cortex and neuronal necrosis in the Hippocampus.
- The cerebral blood flow is decreased during severe hypoglycemia :
- white matter lesions and boundary-zone infarctions may develop primarily in uncomplicated hypoglycemia.

Il Cervello ha bisogno di zucchero !!!



Ipoglicemia Acuta:

- Stanchezza
- Confusione mentale
- Scosse tonico-cloniche simil-epilettiche
- Crisi ipertensive
- TIA → Stroke

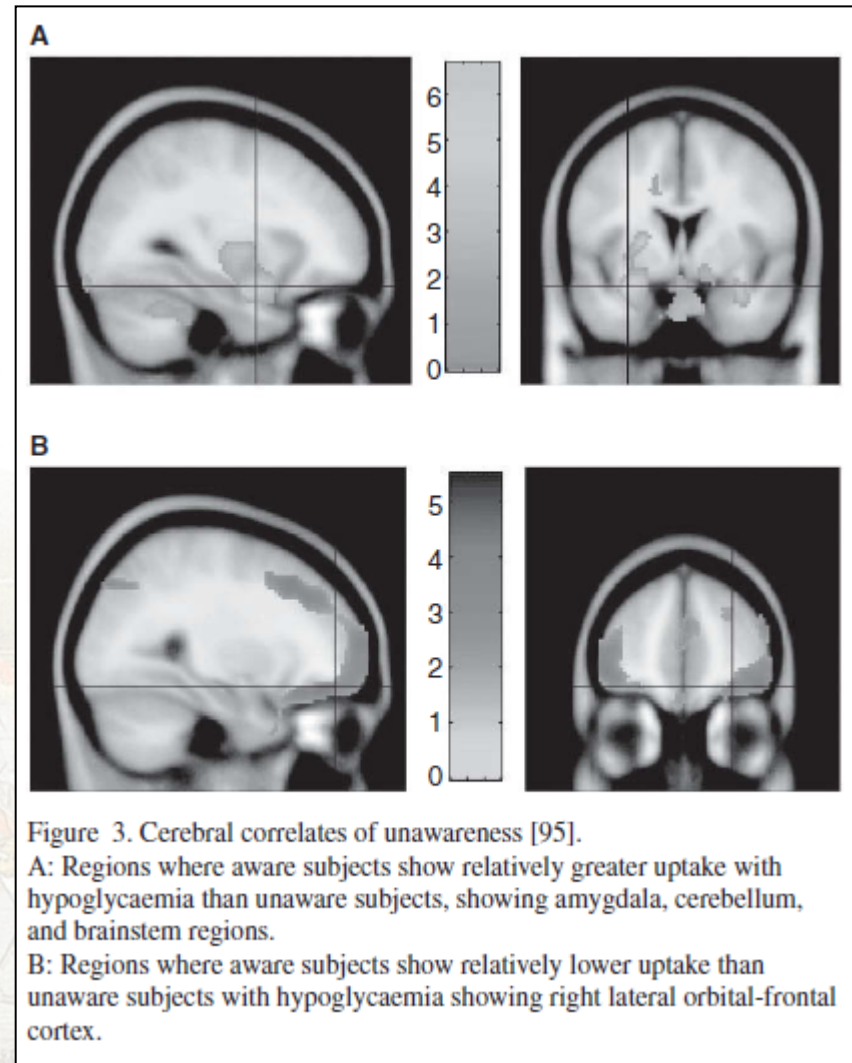
Ipoglicemia Cronica:

- Demenza
- Deficit Cognitivo

Ipoglicemia severa e protratta:

- Atrofia corticale e ippocampo
- Dopo 14 gg da ipoglicemia
- Di almeno 4 ore

Neuroimmagini in corso di Ipoglicemia



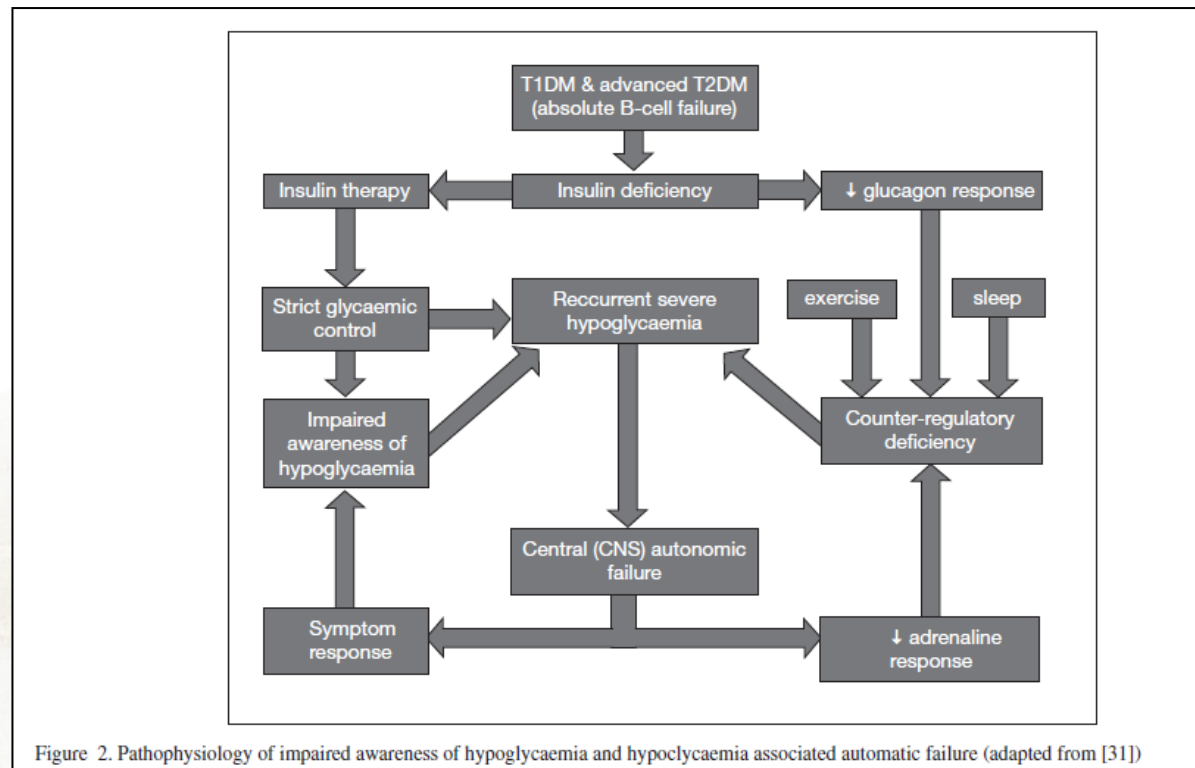


Ipoglicemia e SNC

Impaired awareness of hypoglycaemia: a review

A. J. Graveling, B. M. Frier*

Diabetes & Metabolism 36 (2010) S64–S74



Diabetici T1

3 Cause di ridotta risposta alle ipoglicemie:

- Sovrainsulinizzazione
- Ridotta risposta del Glucagone
- Ridotta risposta Simpato-adrenergica, che si riduce per ipoglicemie ripetute

Hypoglycaemia in the Elderly:

Diabetes is often diagnosed for the first time in patient with the heart infarct, brain stroke, diabetic foot or even hyperosmolar coma.

Hypoglycaemia in the elderly is a very serious problem.

- It can cause arrhythmia, a rise in the blood pressure, unconsciousness, falls and injuries.

More frequent reasons:

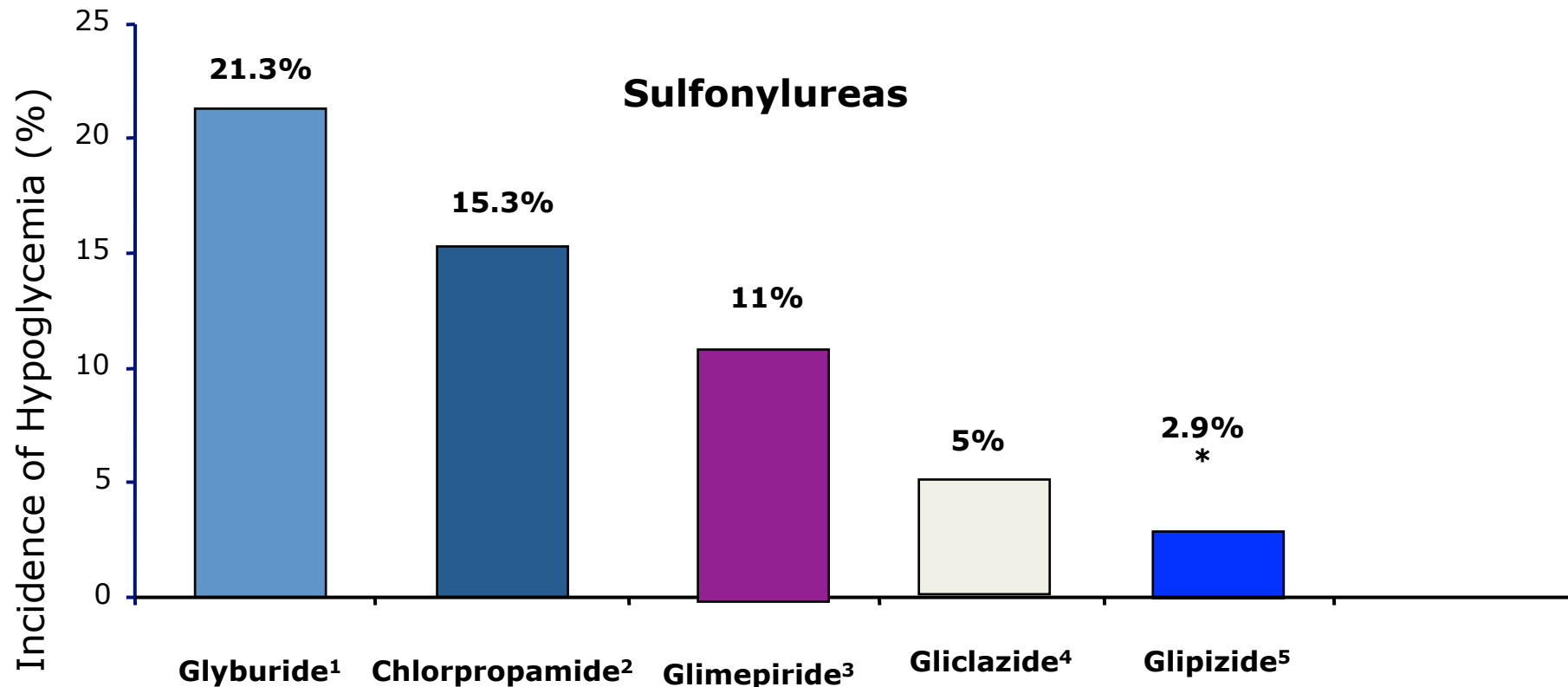
- long-acting derivatives of sulphonylurea,
- treatment with insulin and irregular meals.
- Impaired Kidney function

With age :

- **The symptoms of hypoglycaemia may become less intense**
- **There is an attenuation of autonomic activation**

The ageing process modify the counterregulatory - hormonal response to hypoglycaemia ?

L'ipoglicemia è frequente con le sulfoniluree: freq di ipoglicemie (< 50 mg/dl) sintomatiche con diverse molecole di SU



*Hypoglycemia: fingerstick blood glucose measurement ≤ 50 mg/dL (2.75 mmol/L)

•1. Glucovance [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2004. 2. UKPDS Group. *Lancet* 1998; 352: 837–853. 3. Draeger KE, et al. *Horm Metab Res.* 1996; 28: 419–425. 4. McGavin JK, et al. *Drugs* 2002; 62; 1357–1364. 5. Metaglip [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2002

"Hypoglycaemia in Type 2 Diabetes "

Zammit, Diab.Care, 28:2948-2961, 2005

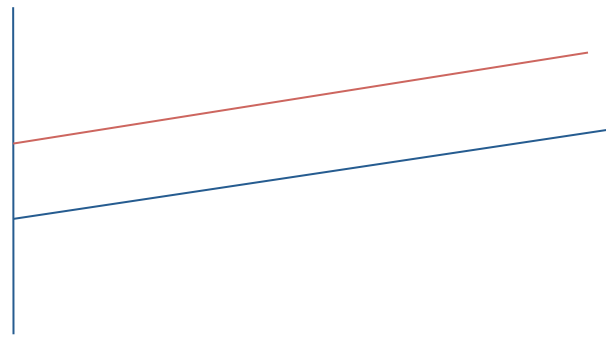
Effetto dell'ETA' "per sé :

- ❑ C'è una riduzione con l'età della soglia glicemica di comparsa dei sintomi:
La soglia glicemica di risposta del Glucagone e della Epinefrina è più elevata nei giovani (59 mg/dl) vs negli anziani (50 mg/dl), dove spesso coincide con il deficit cognitivo (*Diabetes Care 20:135, 1997*)

Relazione con i livelli glicemici e di HabA1c :

- ❑ La soglia glicemica in cui scatta la risposta della controregolazione è più elevata nel DT2 , vs il DT1 (fenomeno protettivo?) (Levy, 1998)
- ❑ E correla con il controllo metabolico : se i livelli glicemici scendono, con ter insulinica, anche la soglia della ipoglicemia si abbassa.

Glic mmol/L



■ Diab T2
■ Diab T1

Levy et al.1998



VI CONVEGNO NAZIONALE
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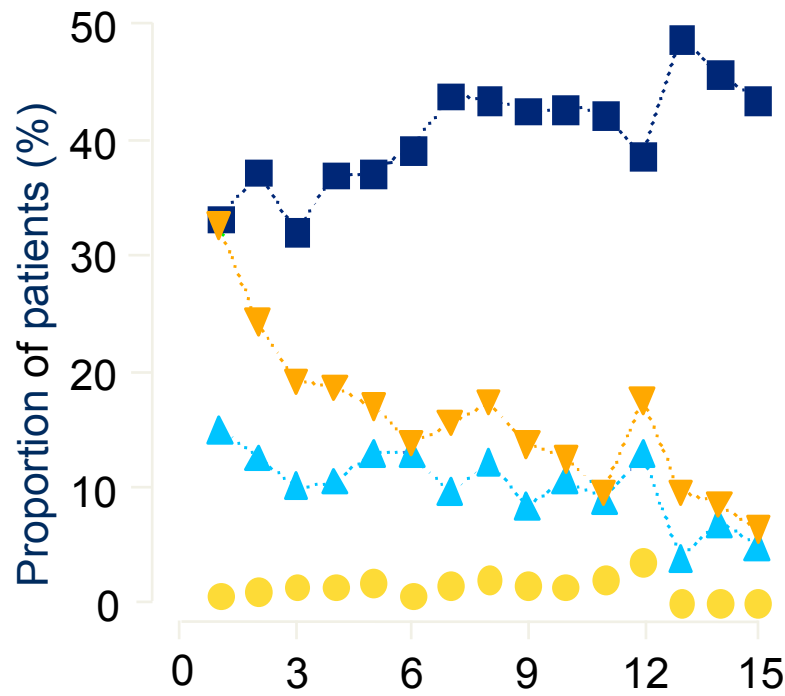
Ipoglicemia e rischio CV

- Ipoglicemia e mortalità
- Ipoglicemia e Cuore
- Ipoglicemia e Cervello
- **La lezione dei Trials**

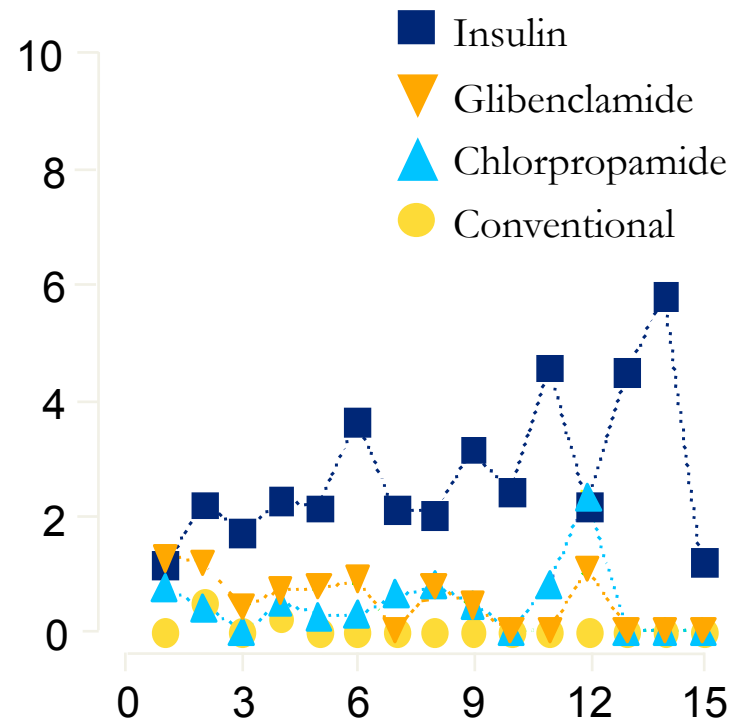


Treatment intensification is known to increase risk of hypoglycaemia

Any episode: actual therapy



Major episodes: actual therapy

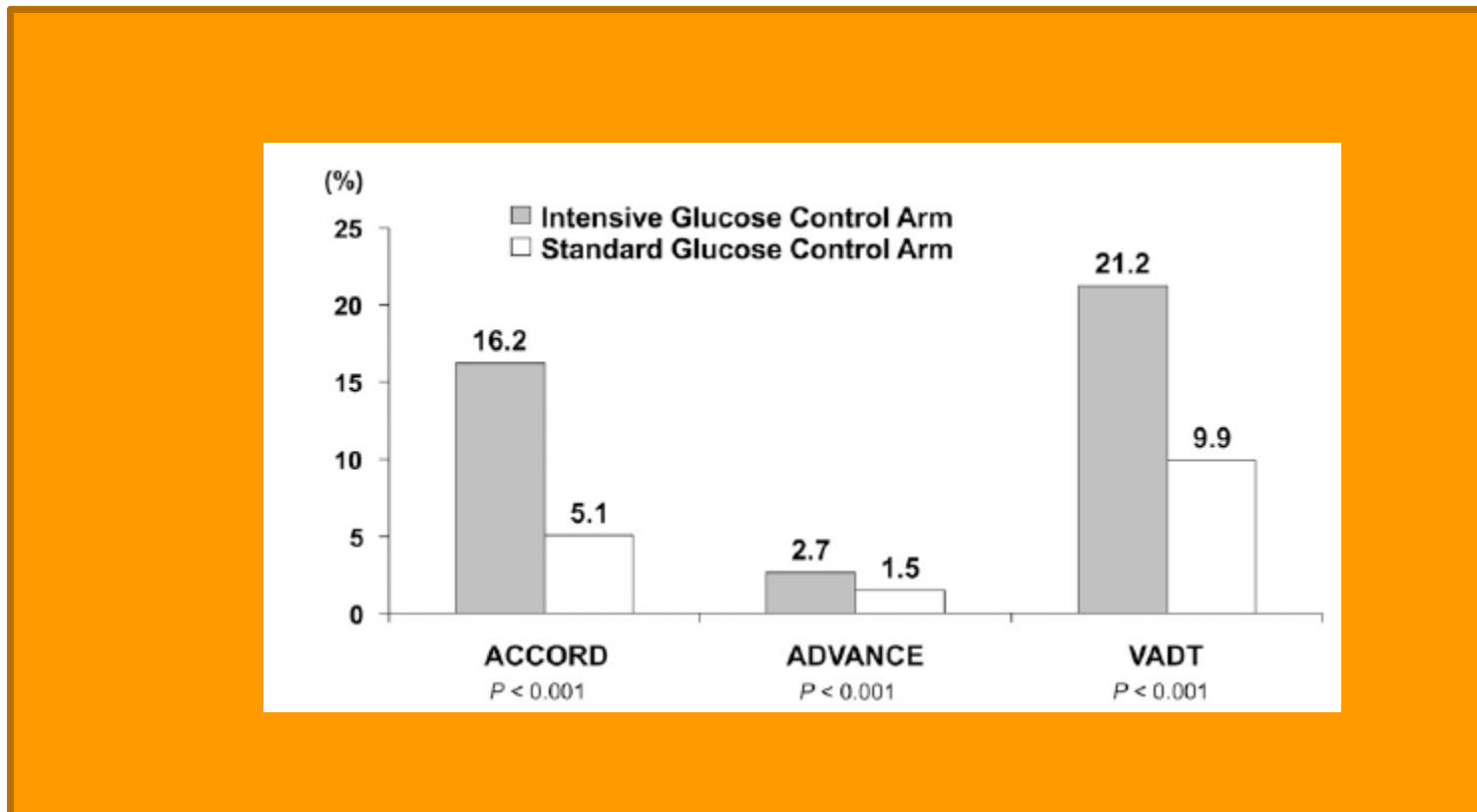


Years from randomisation

Hypoglycemia and Cardiovascular Risks

BRIAN M. FRIER, MD¹
 GUNTRAM SCHERNTHANER, MD²
 SIMON R. HELLER, MD³

DIABETES CARE, VOLUME 34, SUPPLEMENT 2, MAY 2011



Mortalità CV aumentata nei gr. a trattamento intensivo

Ipoglicemia nei Trials



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Mortalità in rapporto alla presenza di almeno 1 ipoglicemia severa, sia nel gr. a trattamento intensivo che in quello Standard la mortalità di questi è aumentata in entrambi, ed è addirittura > nel gr. Standard

CONCLUSIONI

la ipoglicemia è un fattore di rischio per severi outcomes, ma le terapie che la inducono no: questo suggerisce che la ipoglicemia Identifica soggetti più fragili.

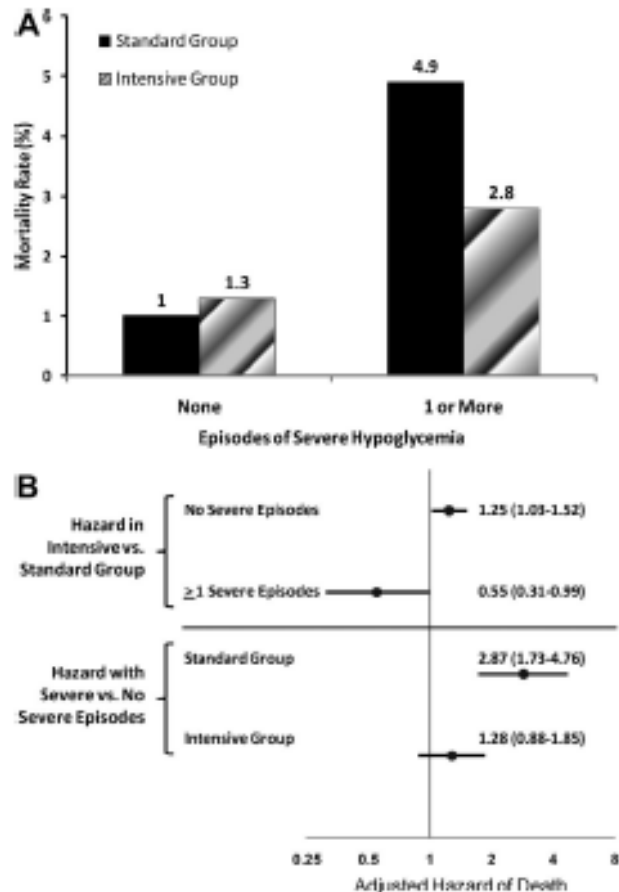


Figure. A, Annualized mortality rates (% per year) in patients with at least 1 episode of severe hypoglycemia requiring medical assistance and in those with no such episodes in the ACCORD trial.⁴⁵ Rates are given for both the standard- and the intensive-therapy groups. B, Adjusted HR (95% CI) for all-cause mortality in relation to severe hypoglycemic episodes requiring medical assistance in the ACCORD trial.⁴⁵ Top, Hazard of death in the intensive-therapy group versus the standard-therapy group among those with no severe hypoglycemic episodes and in those with at least 1 such episode. Bottom, Hazard of death associated with at least 1 such episode (vs none) in the intensive-therapy group and in the standard-therapy group.

Fattori che aumentano il rischio di ipoglicemia :

- Insuff epatica e renale
- Abitudini etiliche
- Declino funzioni cognitive
- Demenza
- Cancro e perdita di peso
- Farmaci



Ipoglicemia e rischio CV

Serious Cardiovascular Outcomes in Diabetes The Role of Hypoglycemia

Natalia Yakubovich, MSc, MD; Hertzell C. Gerstein, MD, MSc

(*Circulation*. 2011;123:342-348.)

These studies are reviewed and summarized below so as to address the following questions:

1. Does an intervention that increases the risk of hypoglycemic episodes increase the risk of serious cardiovascular outcomes?
2. Are hypoglycemic episodes a risk factor for serious cardiovascular outcomes?
3. Do hypoglycemic episodes precipitate serious cardiovascular events?

Recenti Metanalisi di tutti gli studi di intervento : trattamento Intensivo vs Standard

In cronico

DCCT – DCCT/EDIC: **HbA1c 7%**

UKPDS

ACCORD - **HbA1c 6,4 %**

ADVANCE

VADT

In Critically ill pat.

Meta-Analisi 26 studi
incluso il Nice-Sugar

ORIGINAL ARTICLE

Hypoglycemia and Risk of Death in Critically Ill Patients

The NICE-SUGAR Study Investigators*

ABSTRACT

BACKGROUND

Whether hypoglycemia leads to death in critically ill patients is unclear.

METHODS

We examined the associations between moderate and severe hypoglycemia (blood glucose, 41 to 70 mg per deciliter [2.3 to 3.9 mmol per liter] and ≤ 40 mg per deciliter [2.2 mmol per liter], respectively) and death among 6026 critically ill patients in intensive care units (ICUs). Patients were randomly assigned to intensive or conventional glucose control. We used Cox regression analysis with adjustment for treatment assignment and for baseline and postrandomization covariates.

RESULTS

Follow-up data were available for 6026 patients: 2714 (45.0%) had moderate hypoglycemia, 2237 of whom (82.4%) were in the intensive-control group (i.e., 74.2% of the 3013 patients in the group), and 223 patients (3.7%) had severe hypoglycemia, 208 of whom (93.3%) were in the intensive-control group (i.e., 6.9% of the patients in this group). Of the 3089 patients who did not have hypoglycemia, 726 (23.5%) died, as compared with 774 of the 2714 with moderate hypoglycemia (28.5%) and 79 of

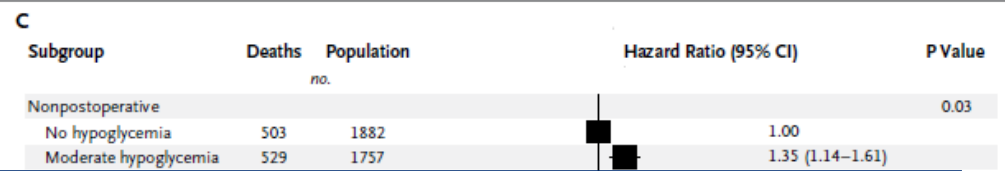
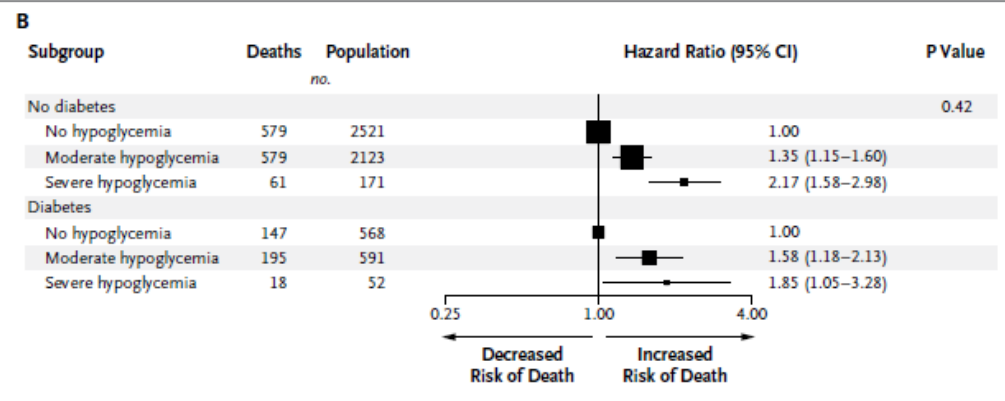
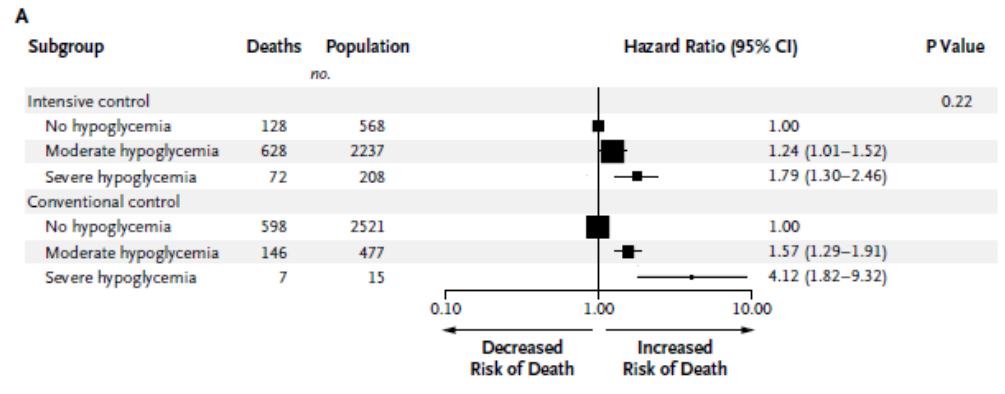
CONCLUSIONS

In critically ill patients, intensive glucose control leads to moderate and severe hypoglycemia, both of which are associated with an increased risk of death. The association exhibits a dose-response relationship and is strongest for death from distributive shock. However, these data cannot prove a causal relationship. (Funded by the Australian National Health and Medical Research Council and others; NICE-SUGAR ClinicalTrials.gov number, NCT00220987.)

CON

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SUGAR ClinicalTrials.gov number, NCT00220987.)



nonpostoperative patients (Panel C). The size of the squares is proportional to the number of deaths.

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Management of Hypoglycaemia

....if hypoglycemia is a problem, **the principles of intensive glycaemic therapy should be considered and applied.**

Ma

Indiscriminate application of intensive glucose-lowering therapy that could provoke dangerous hypoglycemia in frail elderly people with type 2 diabetes, or in patients with overt CVD, should be avoided.

DIABETES CARE, VOLUME 34, SUPPLEMENT 2, MAY 2011

**Evaluation and Management of Adult Hypoglycemic Disorders:
An Endocrine Society Clinical Practice Guideline.**

J Clin Endocrinol Metab, March 2009, 94(3):709–728



Management of Hypoglycaemia

Che fare ?

- **Educazione**
 - **TARGET** glicemici e di HbA1c
 - **Terapia personalizzata**
 - **Autocontrollo domiciliare**

