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UNIVERSITÀ DI BOLOGNA  
DIPARTIMENTO DI SCIENZE  
MEDICHE E CHIRURGICHE - DIMEC

**Em\*** società italiana medicina  
d'emergenza-urgenza

# CONVEGNO HYPOTHESES

HYPOglycemia Treatment  
in the Hospital Emergency System



**BOLOGNA**, 28 novembre 2013

Palazzo dell'Archiginnasio - Aula Stabat Mater

**IMPORTANZA DELL'IPOGLICEMIA NELLA GESTIONE  
DEL DM**

**Ivana Zavaroni - Parma**

# Sintomi dell'ipoglicemia

## Neurogenici<sup>1,2</sup>

- **Adrenergici**
  - Palpitazioni
  - Tremori
  - Ansia/eccitazione
- **Colinergici**
  - Sudorazione
  - Fame
  - Parestesia

## Neuroglicopenici<sup>1,2</sup>

- **Disturbi cognitivi**
- **Cambiamenti comportamentali**
- **Alterazioni psicomotorie**
- **Alterazione dello stato di coscienza**
- **Coma**

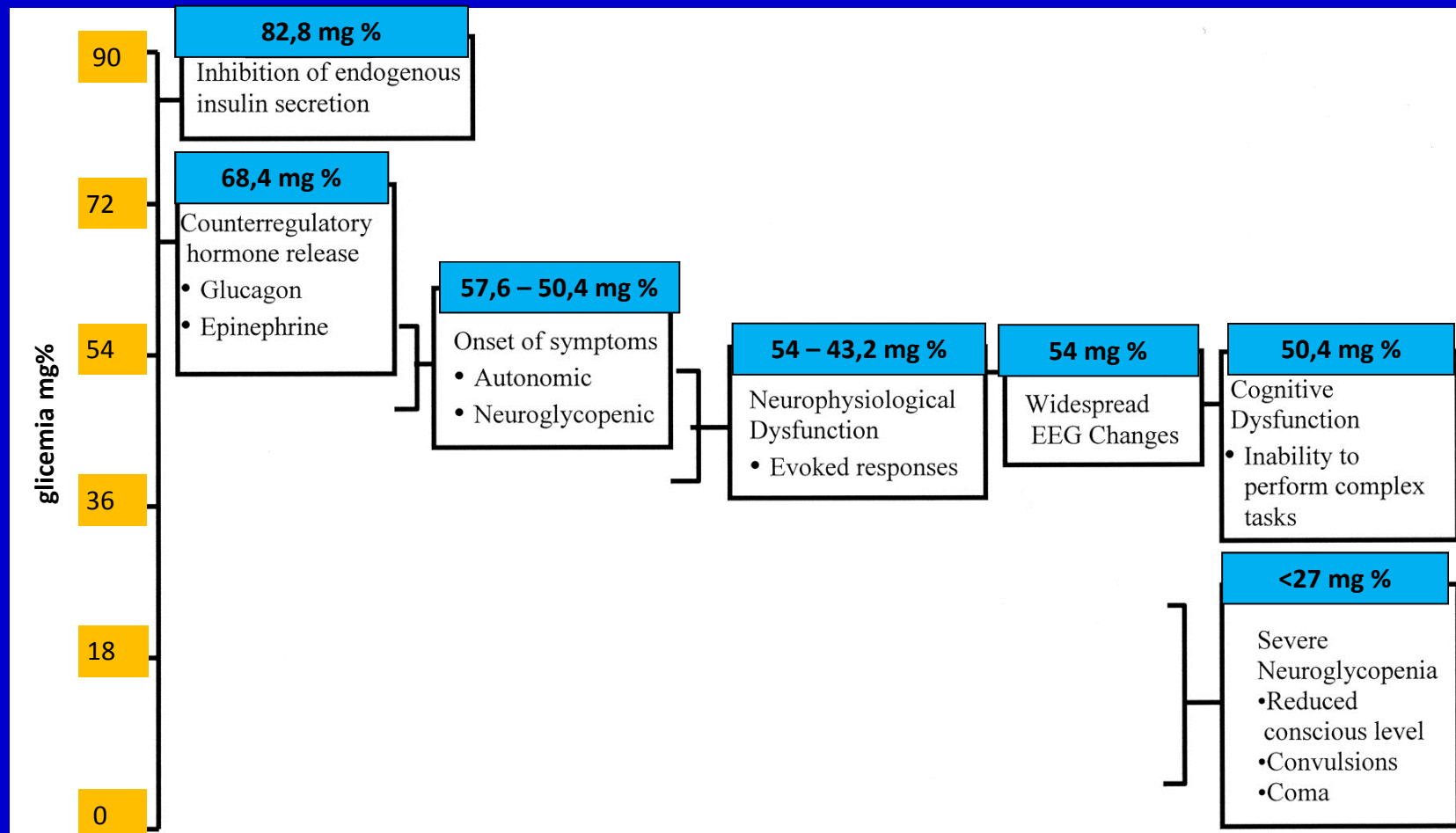
**Factors affecting glycemic thresholds for responses are poorly controlled type 1 and type 2 diabetes, tight glycemic control in type 1 diabetes, and older age.<sup>2,3</sup>**

1. Cryer PE. *J Clin Invest.* 2007;117:868–870.

2. Cryer PE. *Diabetes Care.* 2003;26:1902–1912.

3. Meneilly GS et al. *J Clin Endocrinol Metab.* 1994;78:1341–1348.

# Soglie glicemiche di attivazione degli ormoni controregolatori e di inizio di sintomi e alterazioni evocati dall' ipoglicemia nel soggetto non diabetico



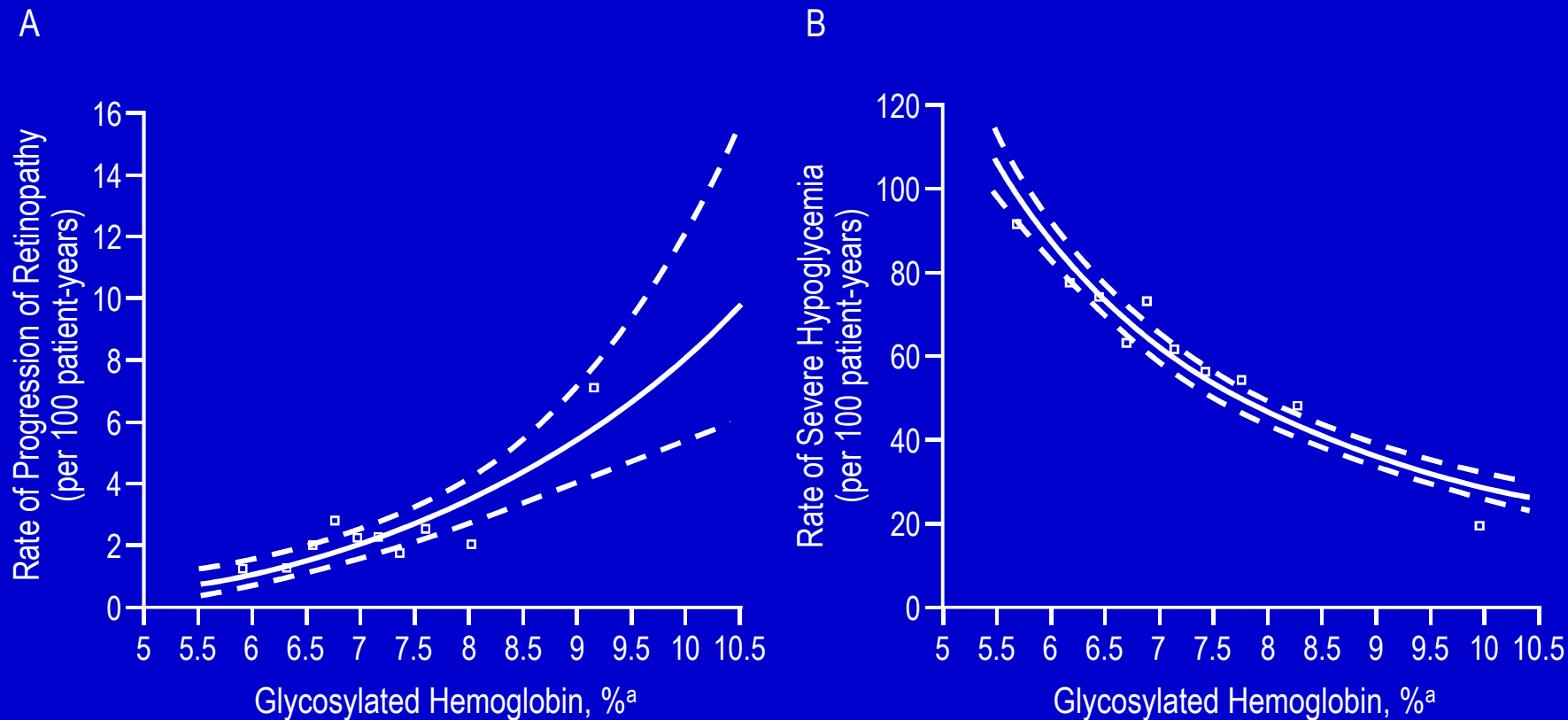


## ADA/Endocrine Society: Classification of Hypoglycemia in Diabetes

Alert value for hypoglycemia:  
PG  $\leq 70$  mg/dL ( $\leq 3.9$  mmol/L)

Severe hypoglycemia	<ul style="list-style-type: none"><li>• Requires assistance of another person to administer carbohydrates, glucagon, or take other actions</li><li>• PG concentrations may not be available during an event<ul style="list-style-type: none"><li>– Neurological recovery following euglycemia considered sufficient evidence that event was induced by low PG</li></ul></li></ul>
Documented symptomatic hypoglycemia	<ul style="list-style-type: none"><li>• Typical hypoglycemia symptoms are accompanied by measured PG <math>\leq 70</math> mg/dL (<math>\leq 3.9</math> mmol/L)</li></ul>
Asymptomatic hypoglycemia	<ul style="list-style-type: none"><li>• Not accompanied by typical hypoglycemia symptoms but with measured PG <math>\leq 70</math> mg/dL (<math>\leq 3.9</math> mmol/L)</li></ul>
Probable symptomatic hypoglycemia	<ul style="list-style-type: none"><li>• Typical hypoglycemia symptoms not accompanied by PG determination but likely caused by PG <math>\leq 70</math> mg/dL (<math>\leq 3.9</math> mmol/L)</li></ul>
Pseudo-hypoglycemia	<ul style="list-style-type: none"><li>• Reports of typical hypoglycemia symptoms with measured PG <math>&gt; 70</math> mg/dL (<math>&gt; 3.9</math> mmol/L) but approaching hypoglycemia threshold</li></ul>

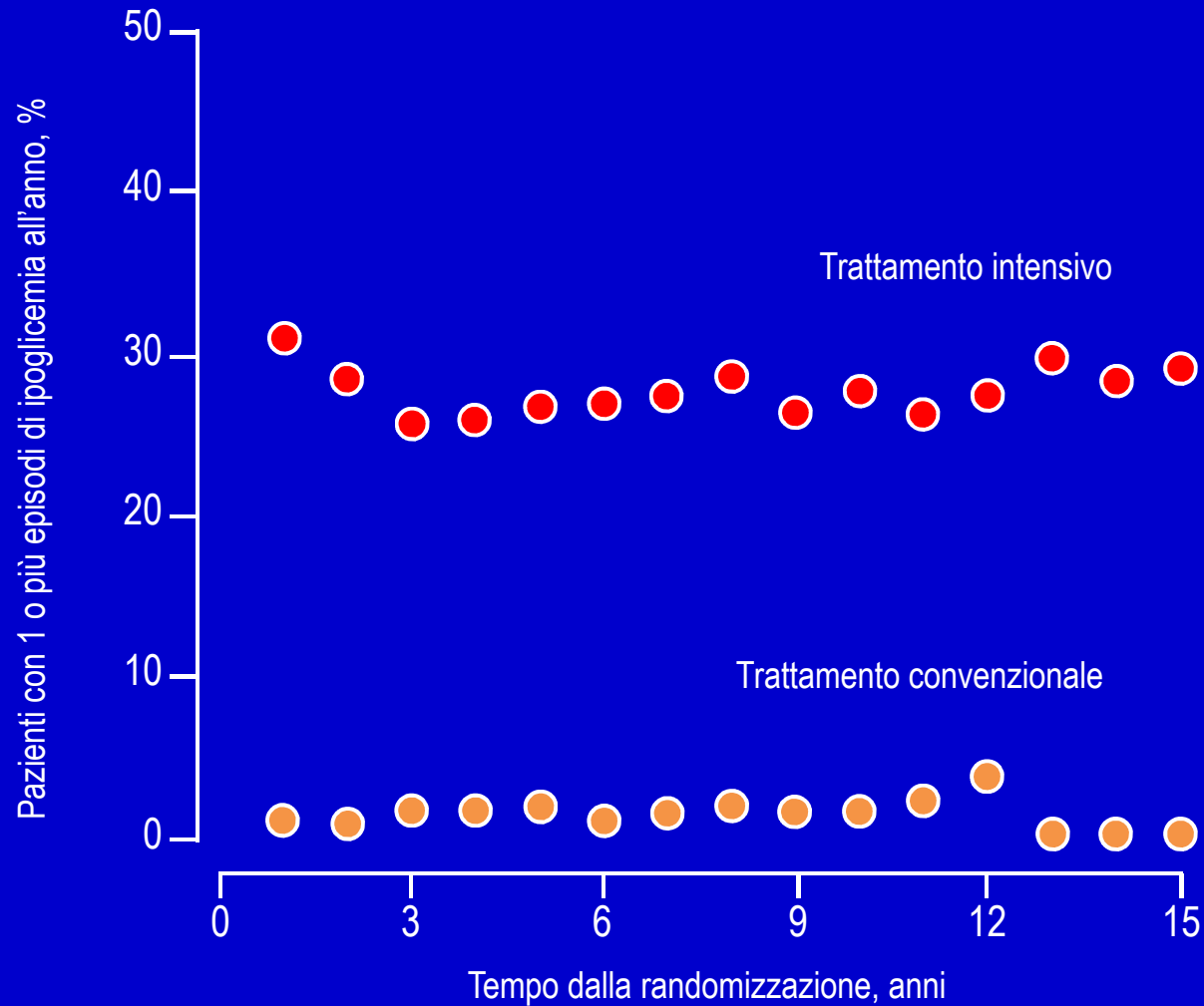
# DCCT: Prevenzione delle complicanze vs Ipoglicemia<sup>1</sup>



<sup>a</sup>Each square corresponds to more than 400 patients-years.

1. Copyright © 1993 Massachusetts Medical Society. All rights reserved. DCCT Research Group. *N Engl J Med.* 1993;329(14):977-986.

# UKPDS: il controllo intensivo della glicemia si associa a più frequenti ipoglicemie<sup>1</sup>



1. Reprinted from UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352(9131):837-853. Copyright 1998, with permission from Elsevier.

**L'ipoglicemia  
nei trials clinici:**

**Focus su ACCORD, ADVANCE, e VADT**

# ACCORD/VADT/ADVANCE

## Obiettivi glicemici

	ACCORD <sup>1</sup>	VADT <sup>2</sup>	ADVANCE <sup>3</sup>
<b>Pazienti, N</b>	10,251	1791	11,140
<b>Obiettivi glicemici: terapia intensiva</b>	HbA <sub>1c</sub> <6.0%	HbA <sub>1c</sub> <6% and 1.5% <standard therapy	HbA <sub>1c</sub> ≤6.5%
<b>Obiettivi glicemici: terapia standard</b>	HbA <sub>1c</sub> 7.0%– 7.9%	HbA <sub>1c</sub> <9% and 1.5% >intensive therapy	Local standards
<b>Media HbA<sub>1c</sub>, %</b>	8.3	9.4	7.5
<b>Media durata del diabete, anni</b>	10 <sup>a</sup>	11.5	7.9–8.0

<sup>a</sup>Median value.

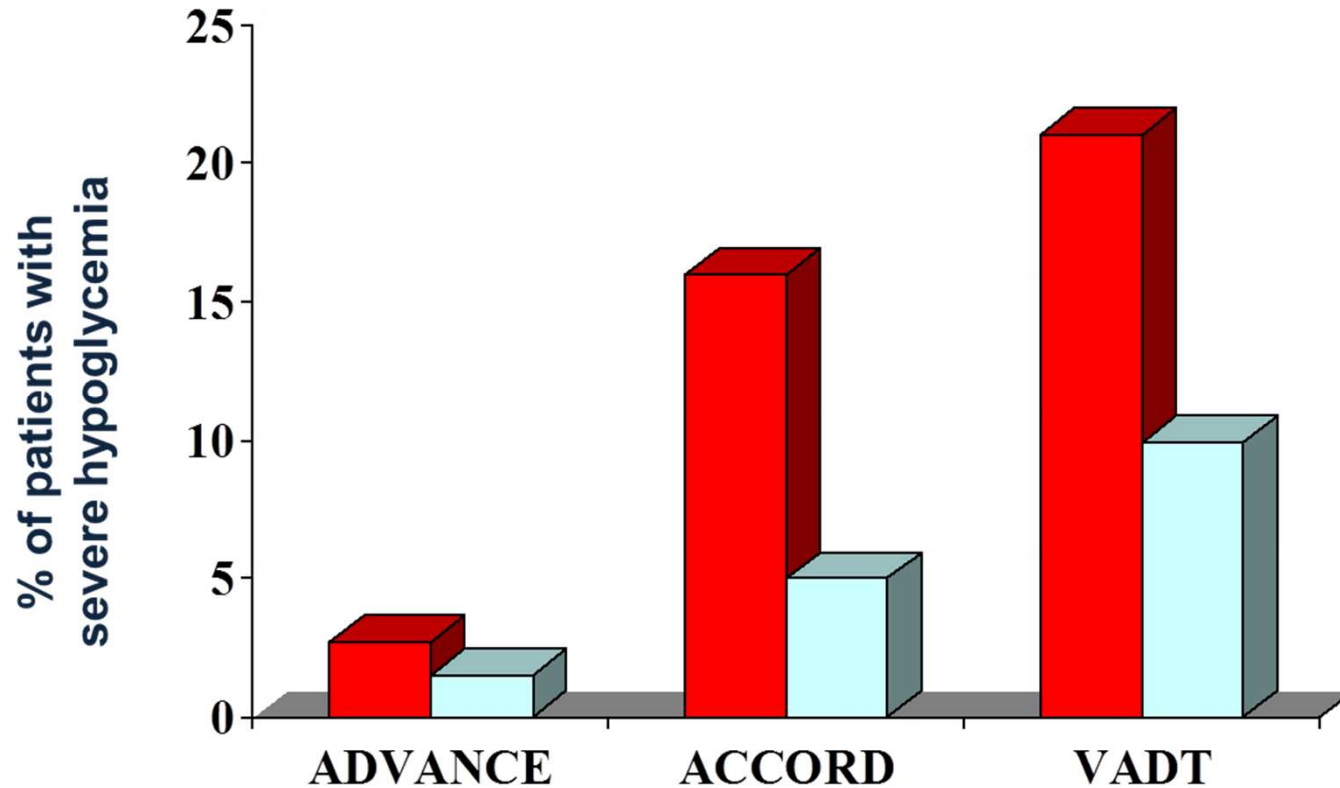
1. ACCORD Study Group et al. *N Engl J Med.* 2008;358:2545–2559.

2. Duckworth W et al. *N Engl J Med.* 2009;360:129–139.

3. ADVANCE Collaborative Group et al. *N Engl J Med.* 2008;358:2560–2572.



# Incidence of severe hypoglycemia in intensively vs standard treated type 2 patients



1. ADVANCE Collaborative Group. N Engl J Med. 358:2560-72, 2008
2. Action to Control Cardiovasc. Risk in Diabetes Study Group. N Engl J Med. 358:2560-72, 2008
3. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med. 360:129-39, 2009

# L'ipoglicemia nello studio ACCORD<sup>1</sup>

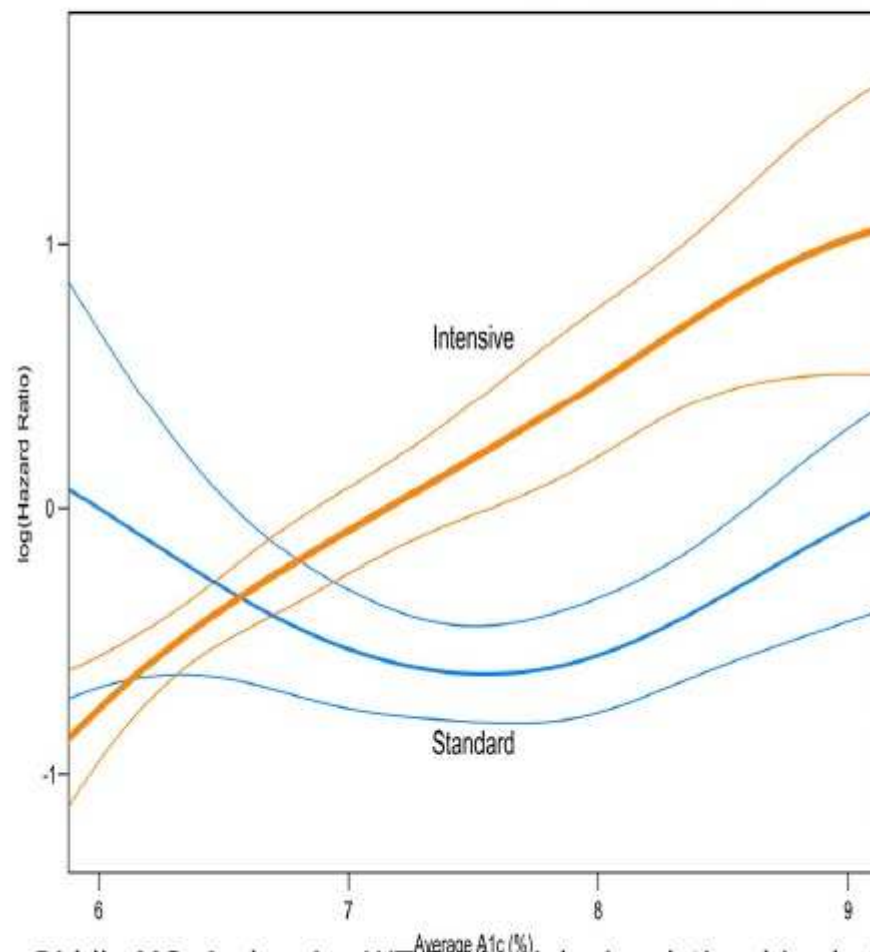
	Gruppo con terapia standard (n=5123)	Gruppo con terapia intensiva (n=5128)
Mediana HbA <sub>1c</sub> livelli a 1 anno, %	7.5	6.4
Ipoglicemie che richiedono assistenza medica, %	3.5	10.5
Ipoglicemie che necessitano assistenza, %	5.1	16.2
Decessi attribuiti a qualsiasi causa, n (%)	203 (4)	257 (5)

Grave ipoglicemia: ipoglicemia con glicemia documentata <50 mg/dL o sintomi che si risolvono con carboidrati orali, glucosio per via endovenosa, o glucagone che richiede assistenza di personale medico o paramedico.<sup>2</sup>

1. ACCORD Study Group et al. *N Engl J Med.* 2008;358:2545–2559.

2. Bonds DE et al. *Am J Card.* 2007;99(12A):80i–89i.

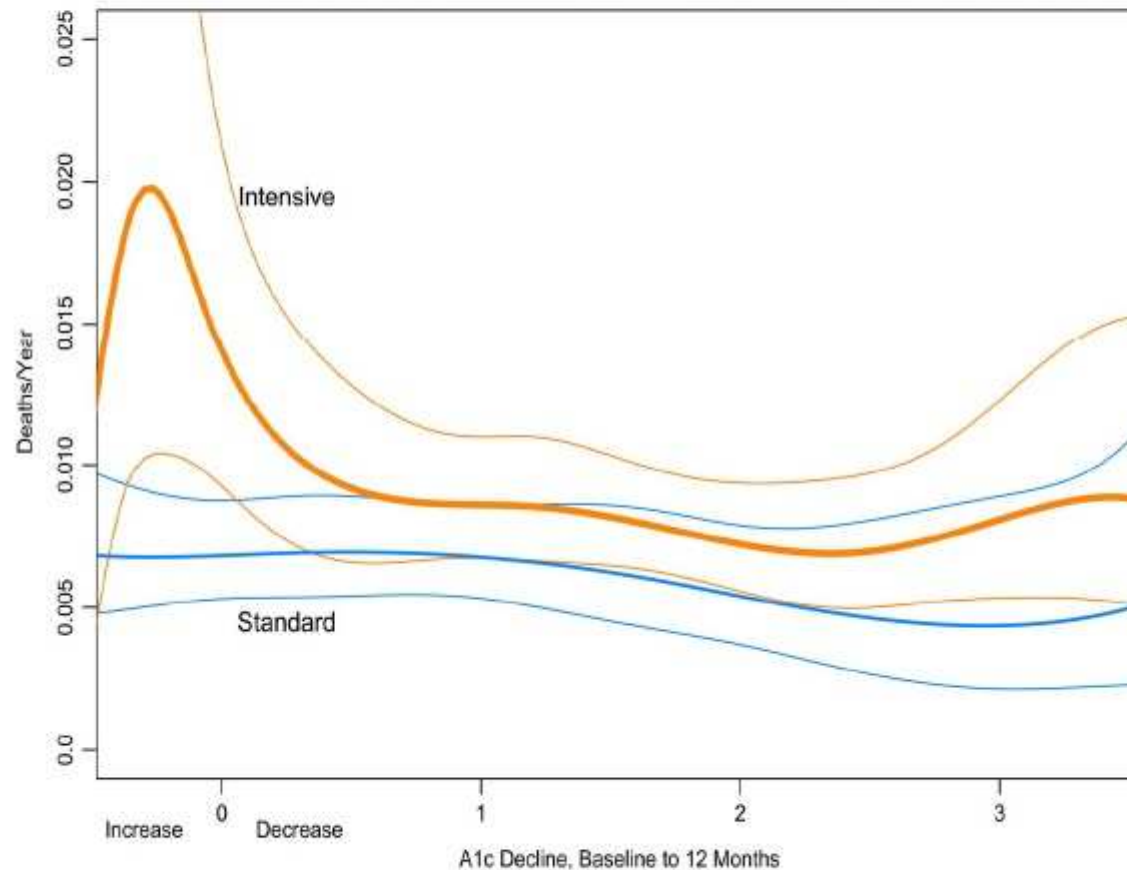
## ACCORD : Adjusted log HR by treatment strategy



The excess risk associated with intensive glycemic treatment occurred among those participants whose average A1C, contrary to the intent of the strategy, was >7%.

Riddle MC, Ambrosius WT. Epidemiologic relationships between A1C and all cause mortality during a median 3.4-year follow-up of glycemic treatment in the ACCORD trial. *Diabetes Care* 2010;33: 983–990

# ACCORD: Adjusted mortality rates by treatment strategy



Riddle MC, Ambrosius WT Epidemiologic relationships between A1C and all cause mortality during a median 3.4-year follow-up of glycemic treatment in the ACCORD trial. *Diabetes Care* 2010;33: 983–990

## Risultati dei trials ACCORD, ADVANCE, e VADT<sup>1-3</sup>

- L'intervento intensivo non è risultato efficace nella prevenzione della malattia cardiovascolare rispetto all'usual care
- Si sono verificati più episodi di ipoglicemia severa nel braccio trattato in maniera intensiva
- Non c'è chiara dimostrazione del ruolo dell'ipoglicemia sull'outcome di mortalità cardiovascolare

1. ACCORD Study Group. *N Engl J Med.* 2008;358:2545–2559.

2. Duckworth W et al. *N Engl J Med.* 2009;360:129–139.

3. ADVANCE Collaborative Group et al. *N Engl J Med.* 2008;358:2560–2572.

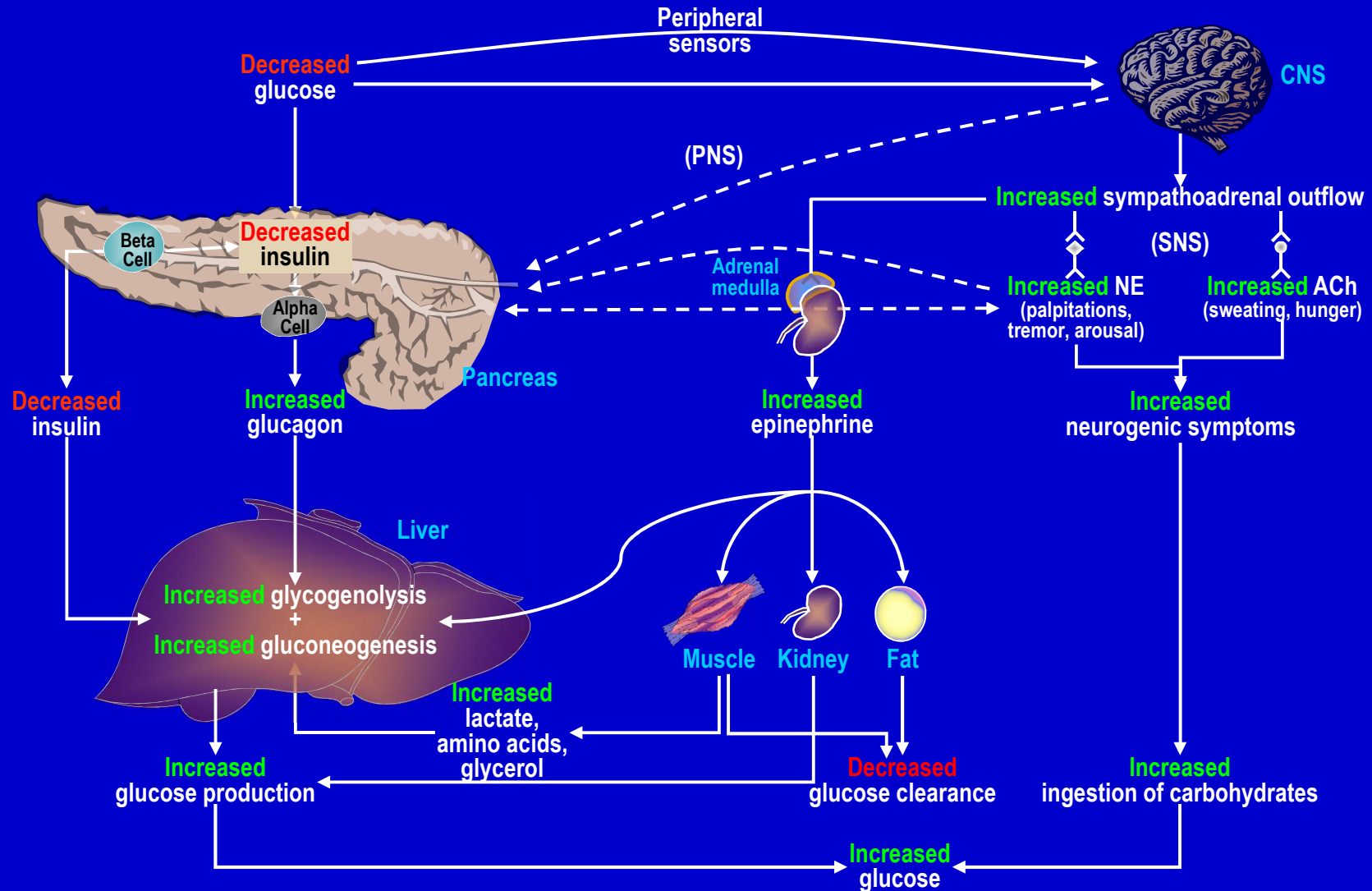
# Fattori di rischio per l'ipoglicemia nei diabetici di Tipo 2

- Terapia insulinica o con secretagoghi
- Età > 65
- Insufficienza renale
- insufficienza epatica
- Lunga durata del diabete
- Irregolarità nell'assunzione dei pasti
- Hypoglycemia unawareness
- Modificazioni nell'attività fisica
- Demenza

1. Amiel SA et al. *Diabet Med.* 2008;25:245–254.
2. ADA Workgroup on Hypoglycemia. *Diabetes Care.* 2005;28:1245–1249.
3. Miller CD et al. *Arch Intern Med.* 2001;161:1653–1659.
4. Landstedt-Hallin L et al. *J Intern Med.* 1999;246:299–307.
5. Cryer PE. *J Clin Invest.* 2007;117:868–870.

# **Fisiopatologia e hypoglycemia unawareness**

# Risposte fisiologiche all'ipoglicemia<sup>1</sup>

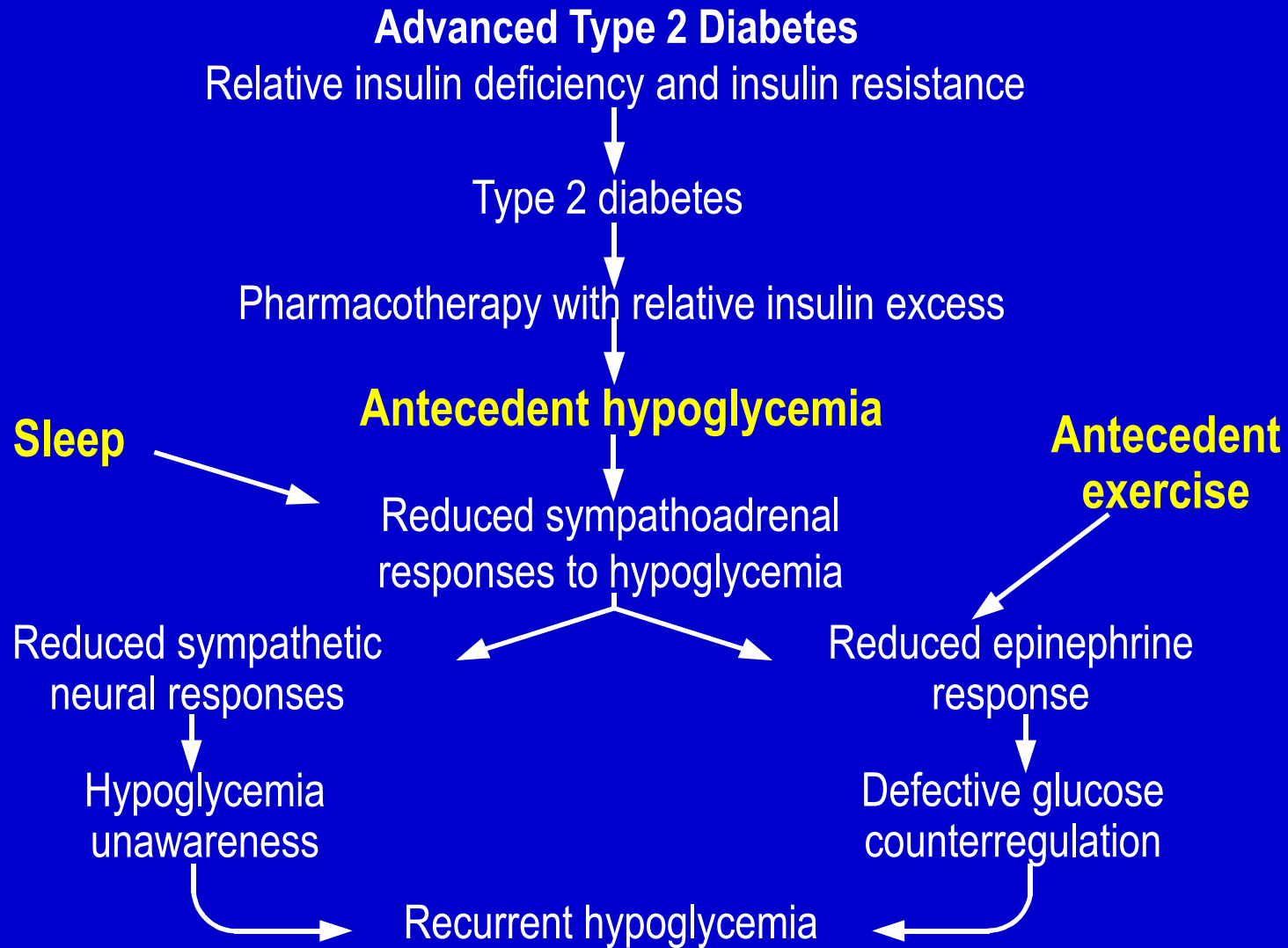


ACh=acetylcholine; CNS=central nervous system; NE=norepinephrine; PNS=parasympathetic nervous system; SNS=sympathetic nervous system.

1. Reproduced with permission of American Society for Clinical Investigation, from Cryer PE. *J Clin Invest.* 2006;116(6):1470-1473; permission conveyed through Copyright Clearance Center, Inc.

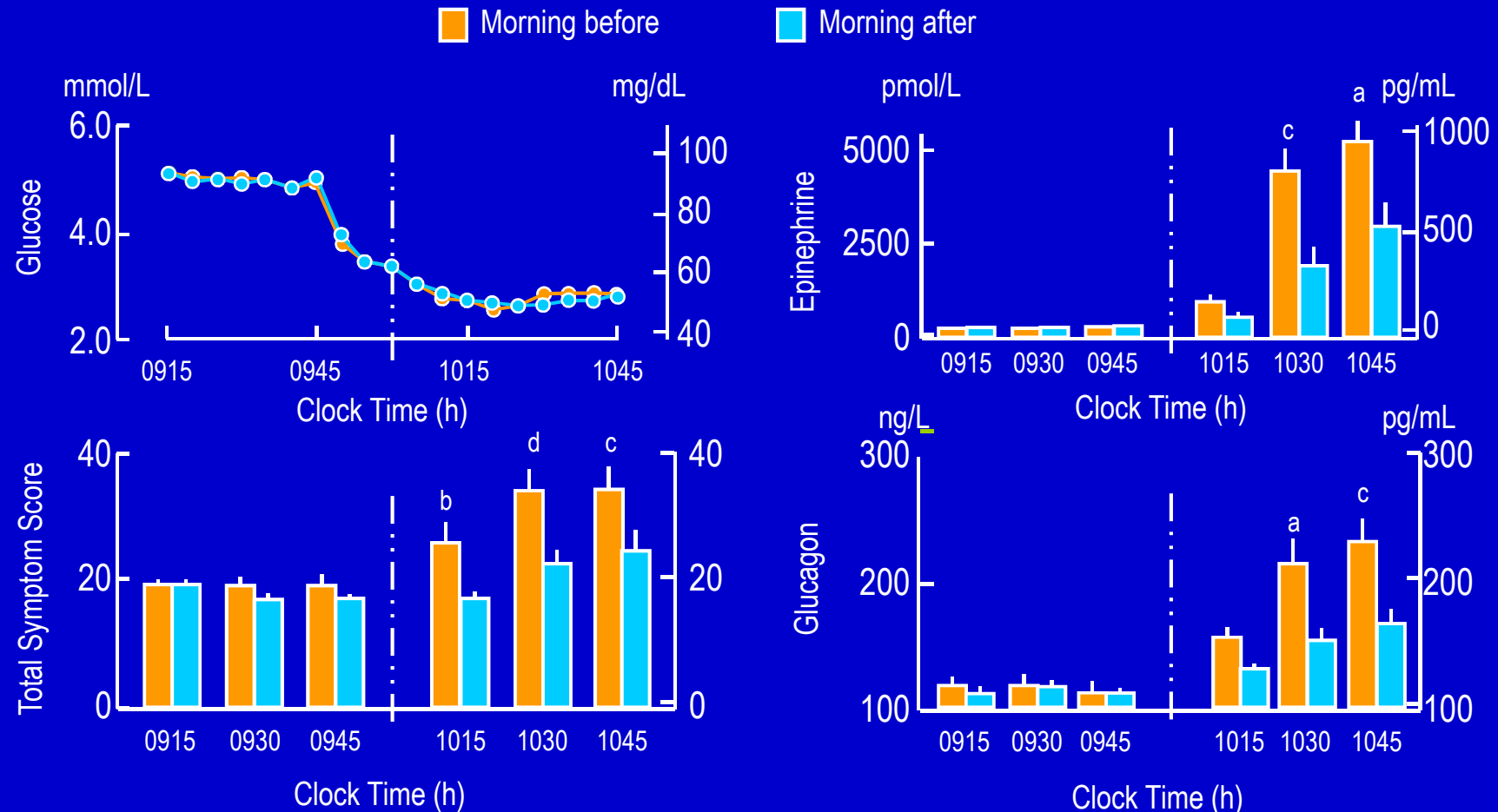


# Una ridotta risposta controregolatoria determina Hypoglycemia Unawareness e ricorrenti ipoglicemie



1. Cryer PE. *J Clin Invest.* 2006;116:1470–1473.  
2. Cryer PE. *N Engl J Med.* 2004;350(22):2272–2279.

# Un'ipoglicemia precedente attenua la risposta controregolatoria ad un'ipoglicemia successiva in soggetti non diabetici



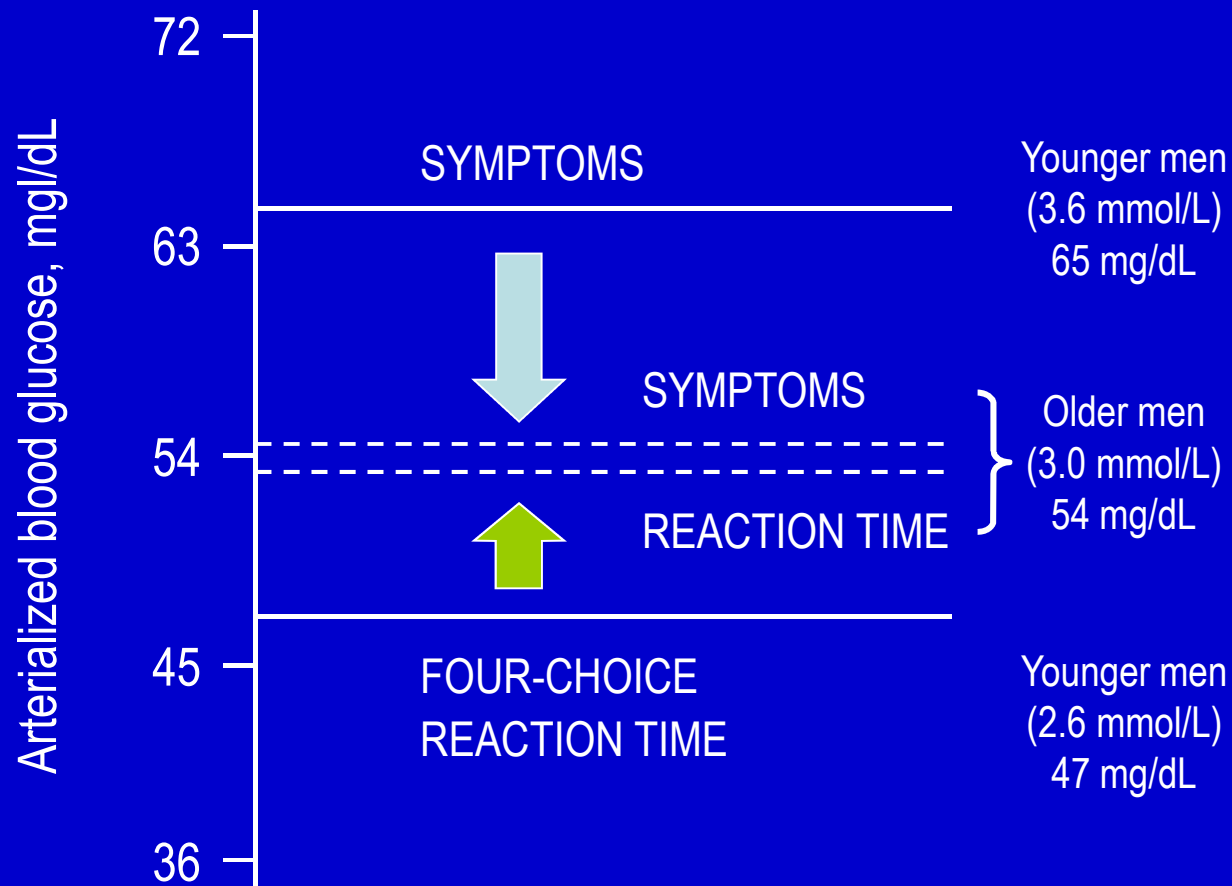
Hyperinsulinemic hypoglycemic clamps on 2 consecutive mornings, with interval afternoon clamped hypoglycemia in adults without diabetes.

<sup>a</sup>P<0.05; <sup>b</sup>P<0.02; <sup>c</sup>P<0.01; <sup>d</sup>P<0.0001.

1. Copyright © 1991 American Diabetes Association. Heller SR. *Diabetes*. 1991;40(2):223–226. Reprinted with permission from the American Diabetes Association.

# Soglia di Hypoglycemia Awareness ed insorgenza di alterazioni cognitive

Soglia glicemica per la consapevolezza dei sintomi di ipoglicemia ed insorgenza di alterazioni cognitive nei giovani e anziani sani



1. Zammitt NN et al. *Diabetes Care*. 2005;28:2948–2961.

2. McAulay V et al. In: *Diabetes in Old Age*. 2nd ed. John Wiley and Sons. 2001;133–152. Reproduced with permission of John Wiley and Sons. McAulay V et al. In: *Diabetes in Old Age*. 2nd ed. John Wiley and Sons. 2001;133–152. Permission conveyed through Copyright Clearance Center, Inc.

# La Hypoglycemia Awareness è associata ad un aumentato rischio di ipoglicemie severe in diabetici tipo 2 in terapia insulinica

Potenziali fattori di rischio	Rischio di ipoglicemie severe (Any Event)		
	OR	95% CI	P
Durata della terapia insulinica	1.07	1.01–1.13	0.018
Durata del diabete	1.02	0.98–1.06	0.400
Alterata percezione dell'ipoglicemia	2.66	1.55–4.56	<0.001
Insulina 2 volte al giorno	2.89	0.67–12.6	0.157
Insulina 4 volte al giorno	4.81	1.05–22.1	0.043

CI=confidence interval; OR=odds ratio.

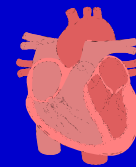
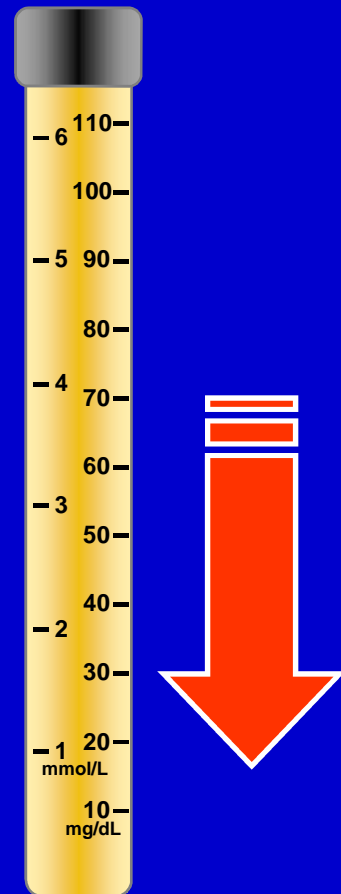
<sup>a</sup>Association between being married and increased risk of severe hypoglycemia may be due to increased reporting as a result of the spouse diagnosing a severe hypoglycemic event.

1. Akram K et al. *Diabetes Med.* 2006;23:750–756. Copyright © 2006 Reproduced with permission of Blackwell Publishing Ltd.

# **Potenziali Complicanze di ipoglicemie severe e prolungate**

# Potenziali complicanze ed effetti di una ipoglicemia severa

Livello glucosio nel sangue



## Aritmia<sup>1</sup>

- Anormale prolungamento ripolarizzazione cardiaca  
-  $\uparrow$  QTc e QT
- Morte cardiaca

## Neuroglicopenia<sup>2</sup>

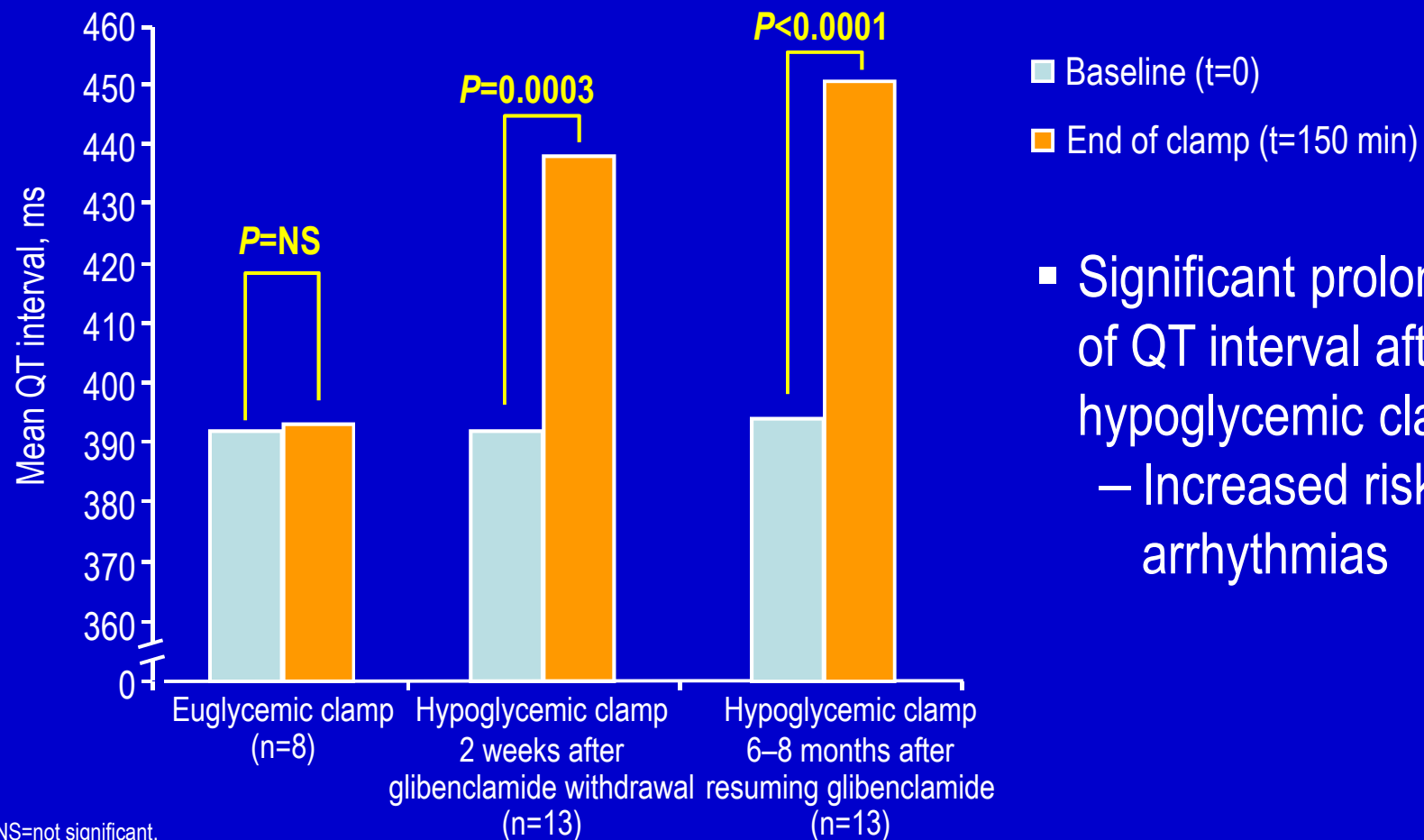
- Deterioramento cognitivo
- Comportamento insolito
- Alterazione dello stato di coscienza
- Coma
- Morte cerebrale

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

2. Cryer PE. *J Clin Invest.* 2007;117:868–870.

# Una ipoglicemia severa può indurre un allungamento del intervallo QT in pazienti diabetici

All patients participated in one hypoglycemic clamp while on treatment with insulin only, and another during combined glibenclamide and insulin therapy.



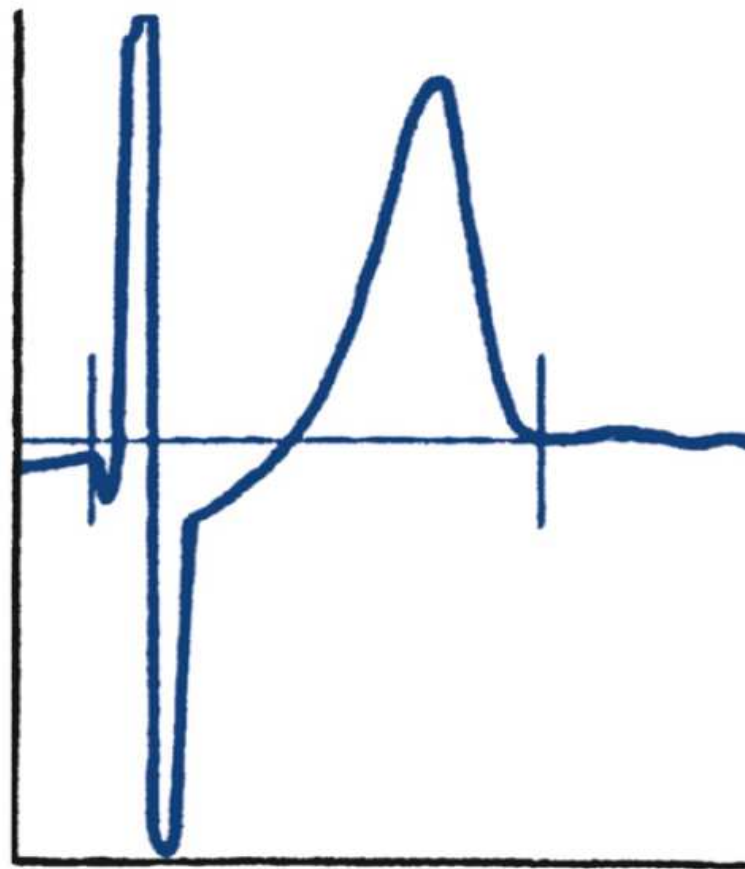
- Significant prolongation of QT interval after hypoglycemic clamps – Increased risk of arrhythmias

NS=not significant.

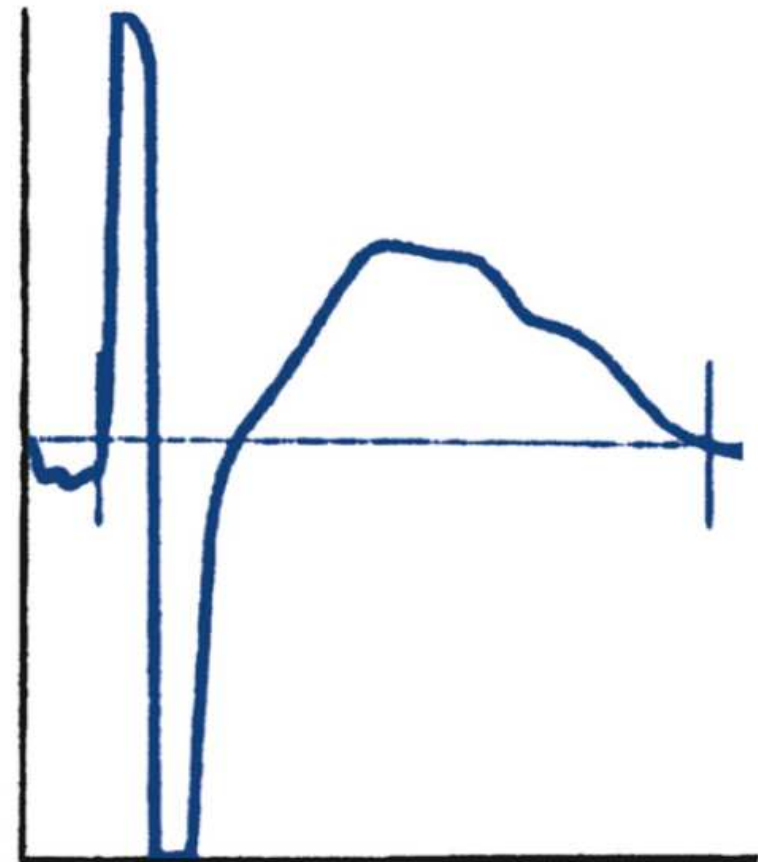
Thirteen patients with type 2 diabetes taking combined insulin and glibenclamide treatment were studied during hypoglycemia; 8 participated in the euglycemic experiment clamped between 5.0 and 6.0 mmol/L. The aim was to achieve stable hypoglycemia between 2.5 and 3.0 mmol/L (45 and 54 mg/dL) during the last 60 minutes of the experiment.

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

## Effect of experimental hypoglycemia on QT interval



5.0 mM



2.5 mM



# L'ipoglicemia può essere associata ad angina ed alterazioni ECG<sup>1</sup>

- Study included insulin-treated patients (n=19; mean age, 58 ± 16 years; mean HbA<sub>1c</sub>, 7.1%) with type 2 diabetes, history of frequent hypoglycemia, HbA<sub>1c</sub> < 8%, and coronary artery disease (defined as history of myocardial infarction, coronary bypass surgery, or angioplasty).

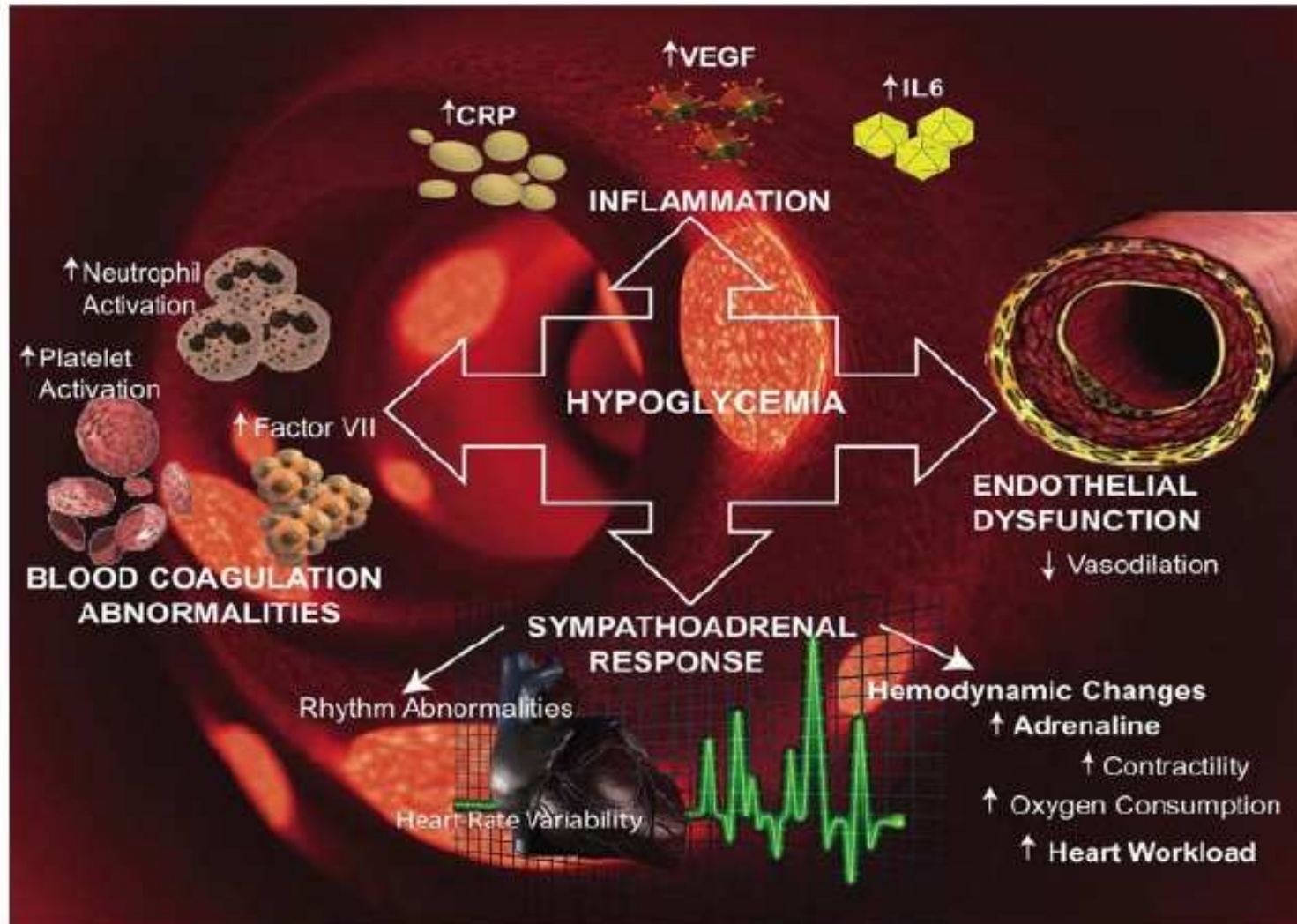
## CGMS and Holter monitoring abnormalities

	Total Episodes	Episodes With Chest Pain/Angina	Episodes With ECG Abnormalities
<b>Hypoglycemia (blood glucose &lt;70 mg/dL)</b>	54	10 <sup>a</sup>	6 <sup>a</sup>
Symptomatic	26	10 <sup>a</sup>	4 <sup>a</sup>
Asymptomatic	28	—	2
<b>Normoglycemia without rapid changes</b>	N/A	0	0
<b>Hyperglycemia</b>	59	1	0
<b>Rapid changes in glucose (&gt;100 mg/dL/h)</b>	50	9 <sup>a</sup>	2

ECG=electrocardiographic. <sup>a</sup>P<0.01 vs episodes during hyperglycemia and normoglycemia.

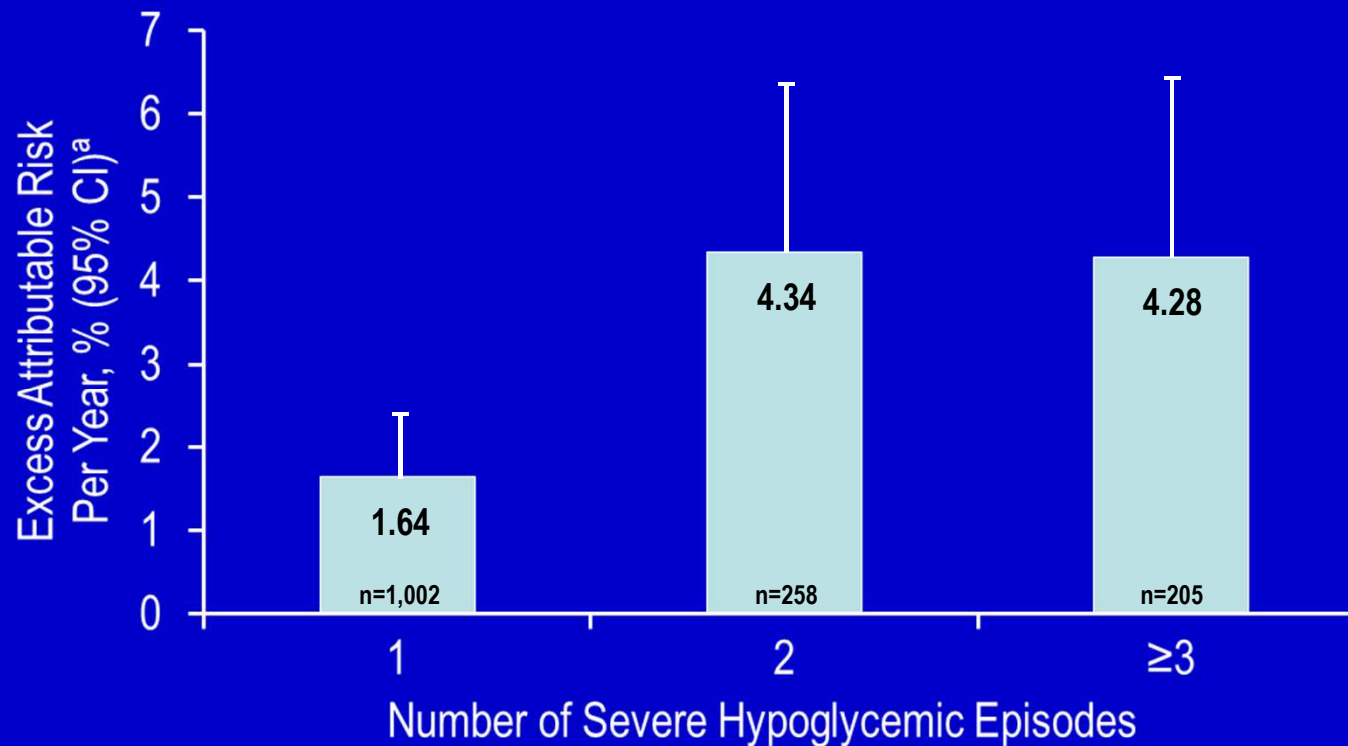
1. Copyright © 2003 American Diabetes Association. Desouza C et al. *Diabetes Care*. 2003;26:1485–1489. Reprinted with permission from the *American Diabetes Association*.

# Mechanisms by which hypoglycemia may affect cardiovascular events



# In uno studio longitudinale , una storia di severe ipoglicemie è risultato associato a maggiore rischio di demenza

Rischio di demenza attribuibile a qualsiasi ipoglicemia: 2.39% (1.72–3.01)<sup>a</sup>



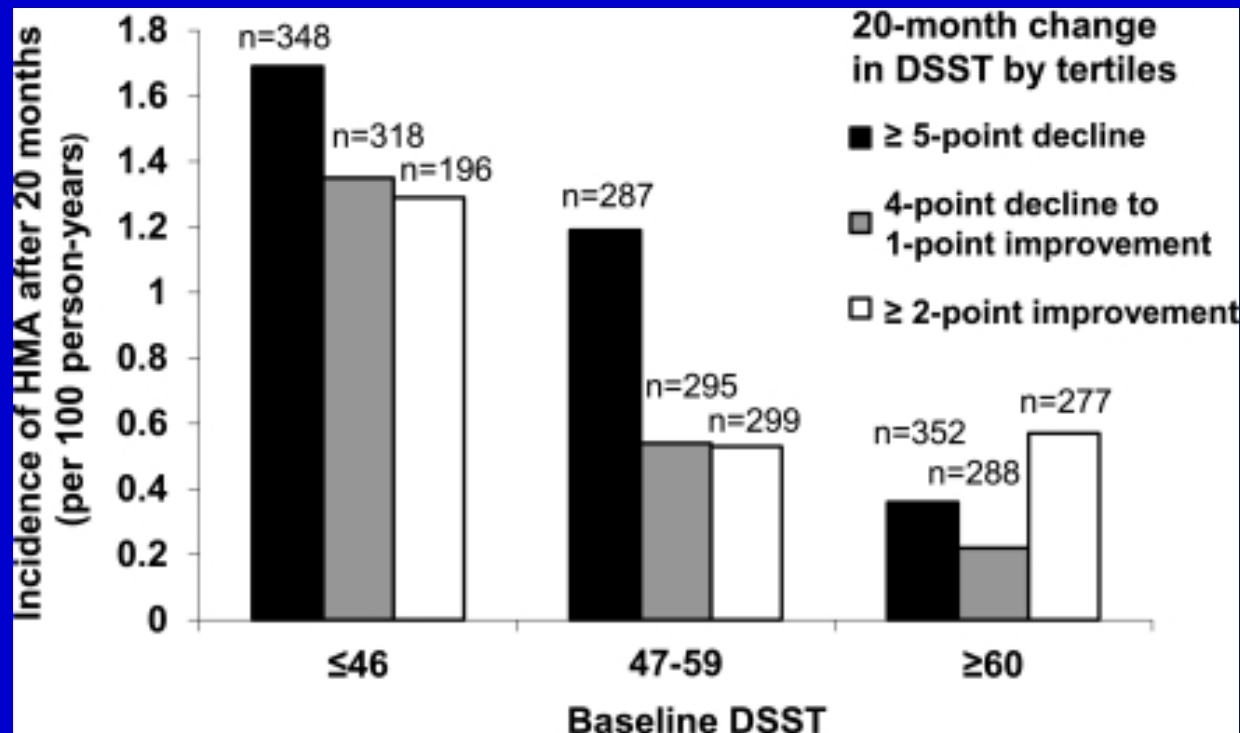
The clinical significance of minor glycemc episodes with dementia risk is unknown.

<sup>a</sup>Attributable risk calculated as difference between rate in group and rate in reference group (0 hypoglycemic events).

1. Whitmer RA et al. *JAMA*. 2009;301:1565–1572.

# Ipoglicemie severe e disturbi cognitivi in diabetici di tipo 2

Post hoc epidemiologic analysis of the ACCORD trial



Effect of 20-month change in DSST score on crude incidence of severe hypoglycemia requiring medical assistance after 20 months, according to baseline thirds of DSST score. Number of individuals in each category is presented above each bar

# Potenziali conseguenze di ipoglicemie severe

- Morte cerebrale<sup>1</sup>
- Alterazioni dell'ECG associate a:<sup>2</sup>
  - Aritmia ventricolare
  - Morte improvvisa
- Evento cardiaco non fatale – infarto del miocardio<sup>3</sup>
- Ictus
- Incidenti stradali<sup>3</sup>
- unrecognized hypoglycemia<sup>4</sup>
- Employment limitations<sup>3</sup>

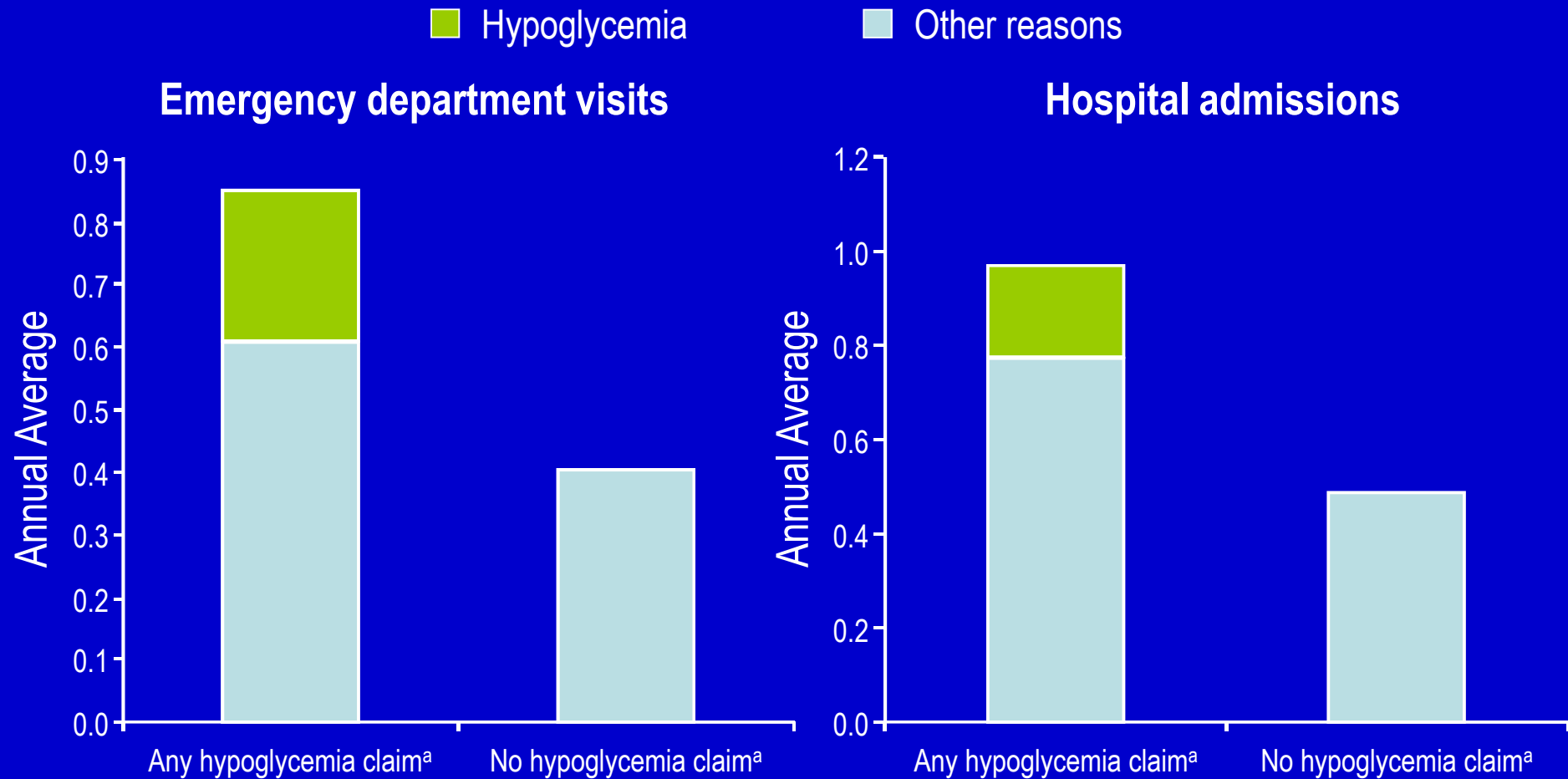
1. Cryer PE. *J Clin Invest.* 2007;117:868–870.

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

3. Frier BM. *Diabetes Metab Res Rev.* 2008;24:87–92.

4. Cryer PE et al. *J Clin Invest.* 2006;116:1470–1473.

# Gli accessi al pronto soccorso e il ricovero in reparti di emergenza sono più elevati in presenza di ipoglicemia



<sup>a</sup>Includes insulin-treated patients with type 1 and type 2 diabetes; US medical insurance claims.  
 Hypoglycemia occurrence= claims coded by (ICD-9-CM) 250.8, 251.1, or 251.2 at any time in the identified period.  
 1. Copyright © 2005. Rhoads GG et al. *J Occup Environ Med.* 2005;47(5):447–452. Reprinted with permission.

# L' ipoglicemia come ostacolo alla gestione ottimale della malattia diabetica

- Decreased adherence<sup>1</sup>
- Increased worry/fear of hypoglycemia<sup>2,3</sup>
- Lower quality of life<sup>4</sup>
- Lower health-related quality of life<sup>5</sup>
- Decreased work productivity<sup>6</sup>

1. Álvarez Guisasola FA et al. *Diab Obes Metab.* 2008;10 (suppl 1):25–32.

2. Mohamed M. *Curr Med Res Opin.* 2008;24:507–514.

3. Leiter LA et al. *Can J Diabetes.* 2005;29:186–192.

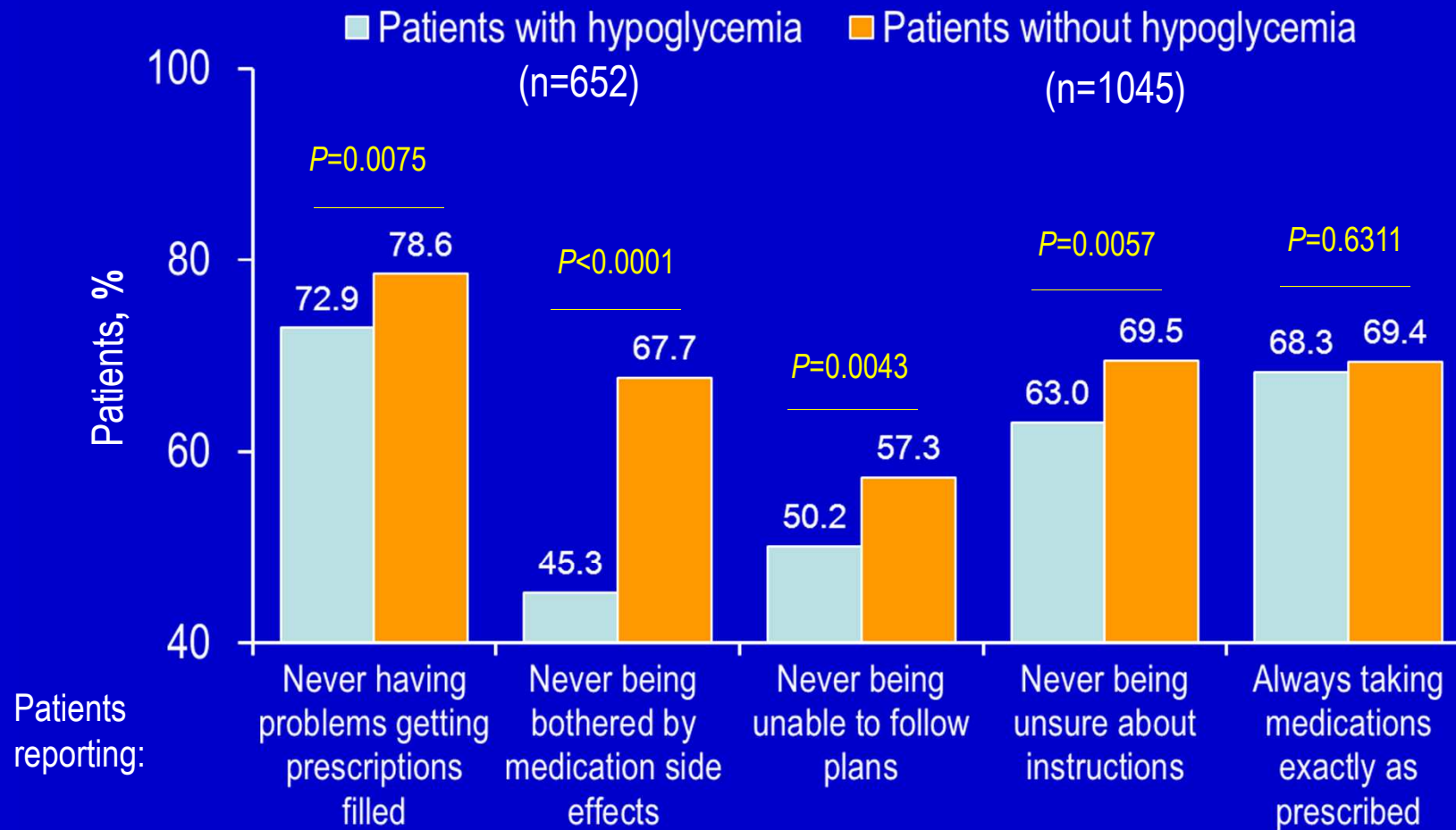
4. Pettersson B et al. *Diabetes Res Clin Pract.* 2011;92:19-25.

5. Álvarez Guisasola F et al. *Health Qual Life Outcomes* 2010;8:86–93.

6. Brod M et al. *Value Health.* 2011;14:665–671.

# RECAP-DM: l'ipoglicemia rappresenta un ostacolo alla aderenza terapeutica

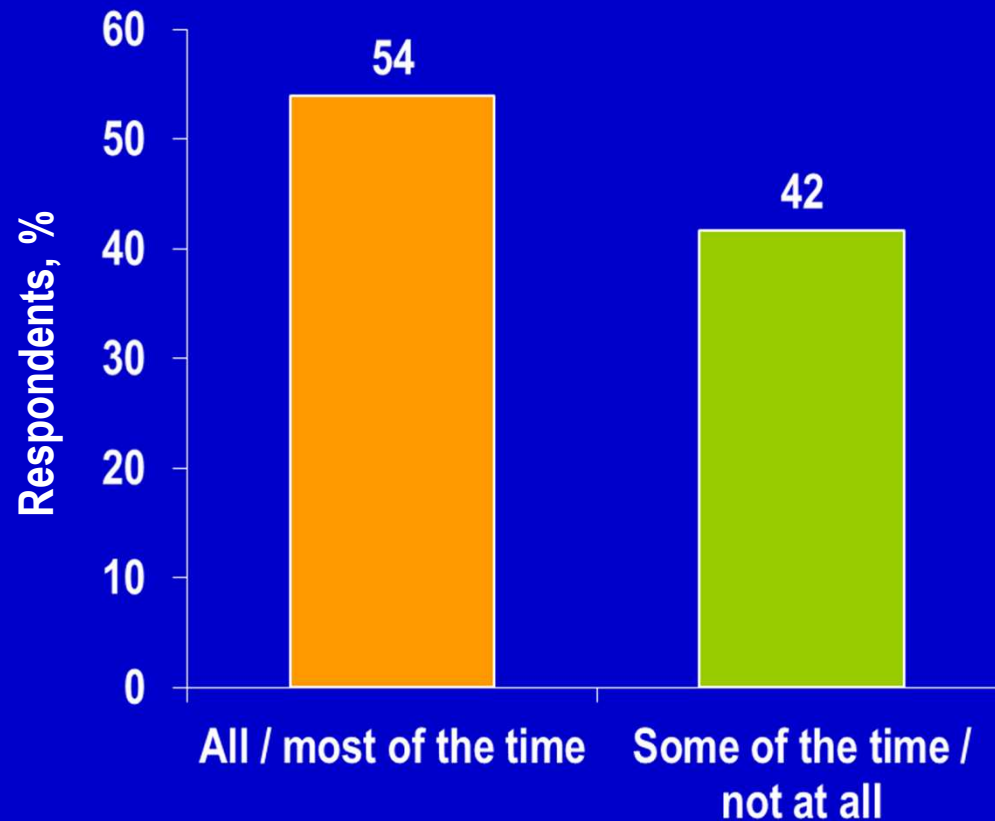
Cross-sectional study in 7 European countries





# Pazienti hanno paura del rischio di ipoglicemia

Diabcare-Asia 2003 cross-sectional survey of 15,549 Asian patients with diabetes (96% type 2, 4% type 1); answer to the question “I am worried about the risk of hypoglycemic events”



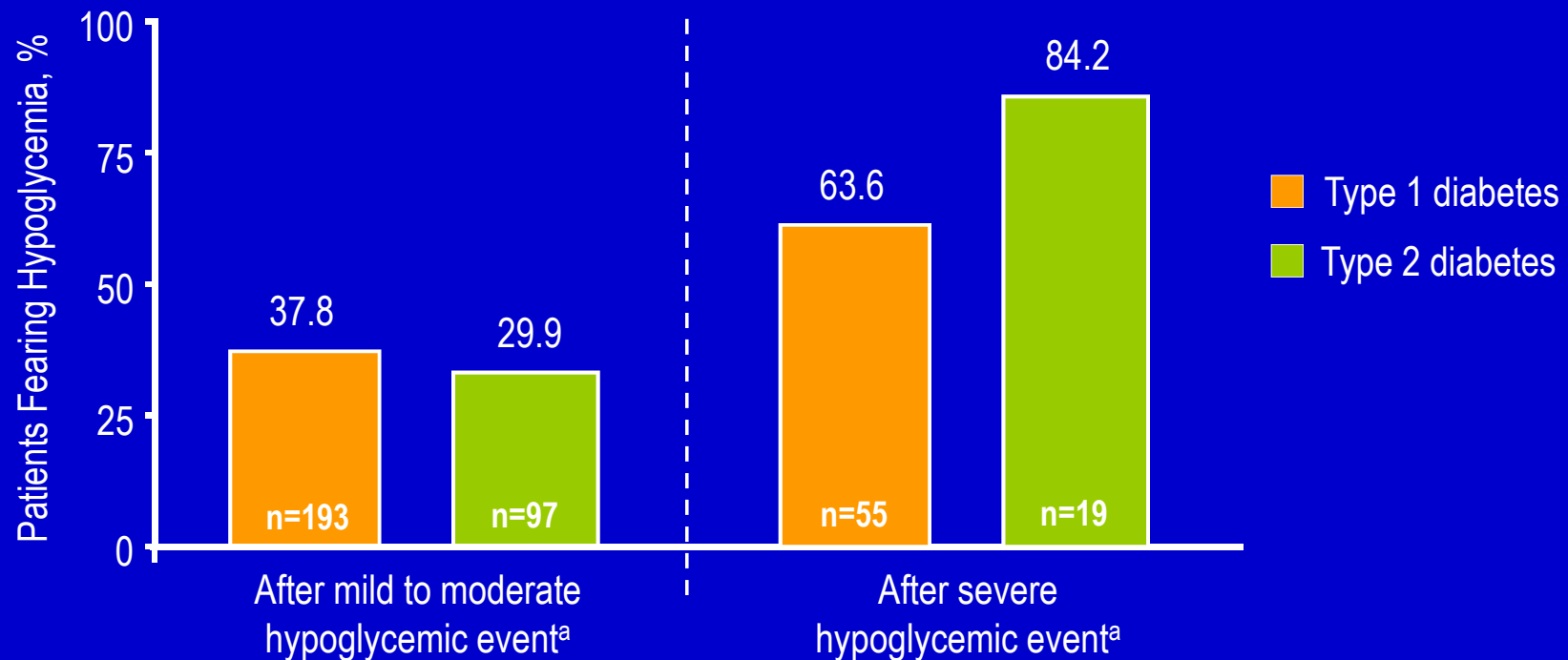
24% of patients in this study were on insulin therapy.

T2DM=type 2 diabetes.

1. Mohamed M. *Curr Med Res Opin.* 2008;24(2):507-514.

# La paura della ipoglicemia è maggiore dopo un episodio di ipoglicemia

Questionnaire-based survey of 335 insulin-treated patients with type 1 or type 2 diabetes; patients who responded “sometimes” or “always” to having a fear of recurrent hypoglycemic episodes<sup>1</sup>



Patients recorded the frequency of mild or moderate hypoglycemic episodes experienced during the preceding month and the frequency of severe hypoglycemia experienced during the preceding 12-month period and lifetime.

T2DM=type 2 diabetes.

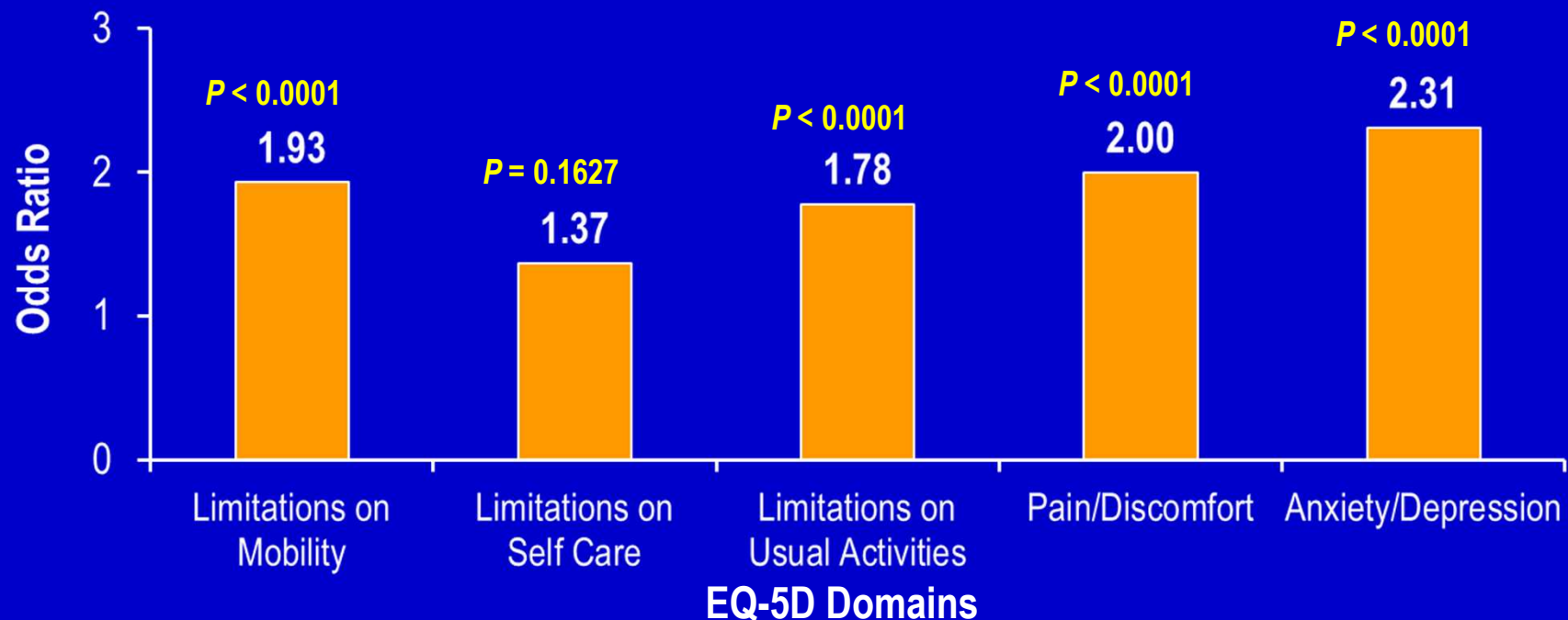
<sup>a</sup>Definitions of mild or moderate hypoglycemia as a glucose level  $\leq 4.0$  mmol/L and severe hypoglycemia requiring external assistance and plasma glucose  $< 2.8$  mmol/L were used.

1. Leiter LA et al. *Can J Diabetes*. 2005;29(3):186–192.

# L' ipoglicemia comporta nei pazienti diabetici la percezione di una qualità di vita, relativa allo stato di salute, peggiore

Cross-sectional, internet-based survey<sup>a</sup> of 2,074 patients with type 2 diabetes who were taking  $\geq 1$  oral antidiabetic agent (excluding insulin)

Adjusted effects of experiencing hypoglycemia symptoms on HRQL



CI=confidence interval; EQ-5D=EuroQoL-5D, a standardized measure of HRQL; HRQL=health-related quality of life; OR=odds ratio.

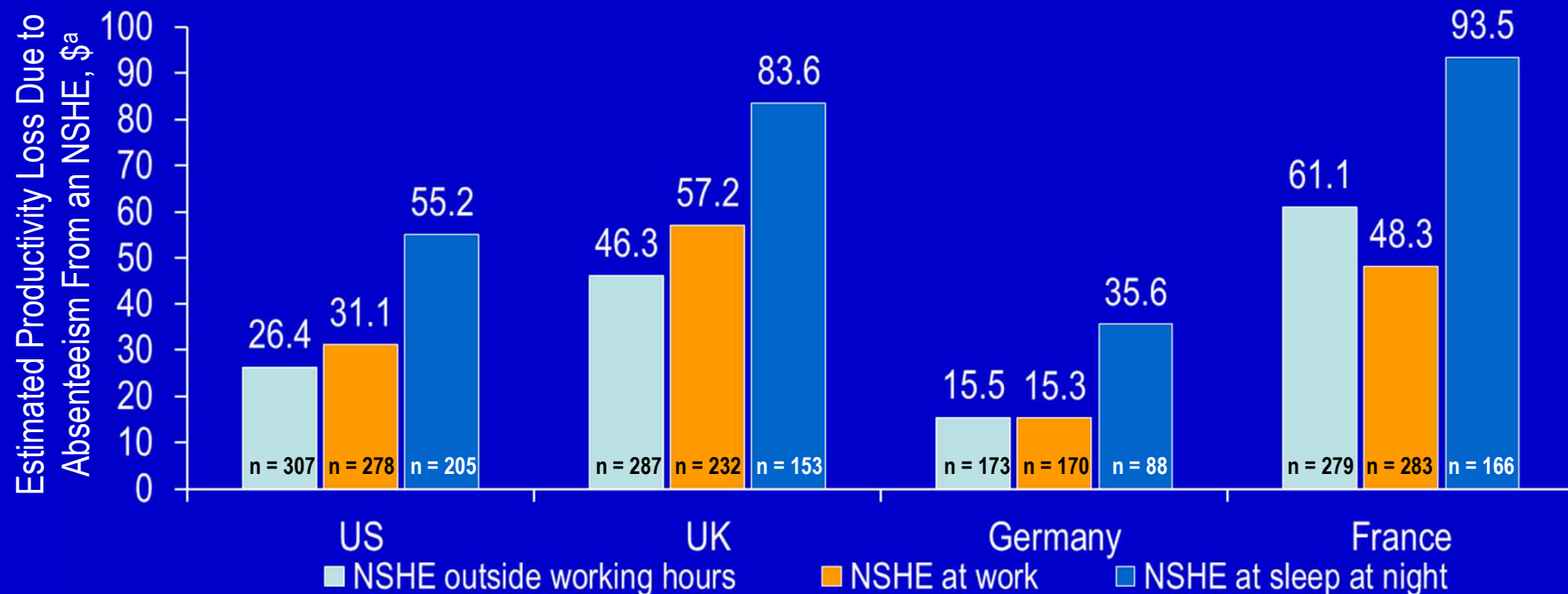
<sup>a</sup>Survey used a 30-item Diabetes Symptom Measure (DSM) to assess the frequency of cognitive and physiological symptoms in the 2 weeks prior to the survey. Data were not verified against clinician diagnoses or chart reviews, nor were reports of low blood sugar confirmed by blood glucose monitoring.

1. Williams SA et al. *Diab Res Clin Pract.* 2011;91:363–370.

# Eventi ipoglicemici si ripercuotono anche sulla attività lavorativa

1,404 adult patients with self-reported type 1 or type 2 diabetes participated in a 20-minute internet survey conducted in 4 countries to assess the effect of NSHEs occurring during work, outside of work hours, and overnight, on productivity.

Analysis sample consisted of all respondents who reported an NSHE in the past month.



The majority of patients were treated with insulin (72.9% with insulin vs 27.1% with oral antihyperglycemic agents). Significant cross-country differences were found for age, gender, and diabetes duration ( $P < 0.001$  for each).

NSHE=non-severe hypoglycemic event.

<sup>a</sup>These estimates were calculated based on the proportion of respondents reporting missed work, multiplied by hourly income and hours missed; the 2009 gross domestic product per capita was used to estimate annual income.

1. Brod M et al. *Value Health*. 2011;14:665–671.



## 380,000 visite al Pronto Soccorso all'anno negli USA sono attribuite a casi di ipoglicemia (1993–2005)<sup>1</sup>

- 5 million emergency department visits<sup>a</sup> between 1993 and 2005 for hypoglycemia
  - 25% resulted in hospital admission
  - 72% of patients had hypoglycemia as the primary (first-listed) diagnosis
  - ~44% of reported cases occurred in adults  $\geq 65$  years of age

<sup>a</sup>Patients with type 1 diabetes and type 2 diabetes.

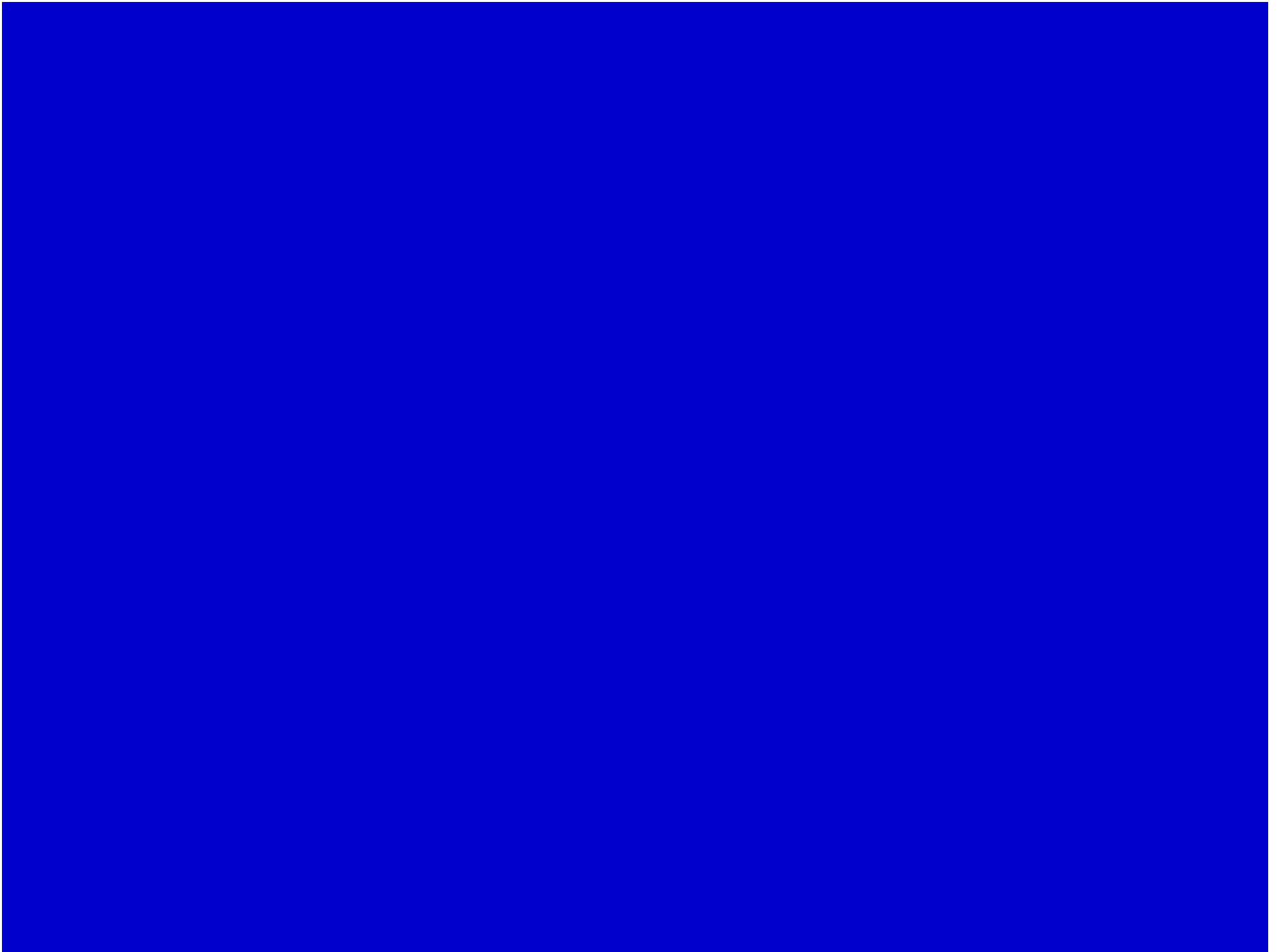
1. Ginde AA et al. *Diabetes Care*. 2008;31:511–513.

# I tassi di ospedalizzazione per complicanze diabetiche acute in Italia, 2001-2010.

	Acute diabetic complications			Acute hyperglycemic complications			Hypoglycemic coma		
	N	rate/100,000 residents*	rate/1,000 diabetic people (95% CI)	n	rate/100,000 residents*	rate/1,000 diabetic people (95% CI)	n	rate/100,000 residents*	rate/1,000 diabetic people (95% CI)
2001	32,096	56.3	14.4 (13.8-15.1)	30,302	53.2	13.6 (13.1-14.3)	1,794	3.1	0.81 (0.84-0.77)
2002	30,304	53.1	13.7 (13.1-14.3)	28,546	50.0	12.9 (12.4-13.5)	1,758	3.1	0.80 (0.76-0.83)
2003	30,072	51.7	13.5 (12.9-14.1)	28,457	49.0	12.7 (12.2-13.3)	1,615	2.8	0.72 (0.69-0.76)
2004	27,694	46.9	11.9 (11.3-12.4)	26,202	44.4	11.2 (10.7-11.7)	1,492	2.5	0.64 (0.61-0.67)
2005	26,861	44.7	11.0 (10.5-11.6)	25,395	42.3	10.4 (9.9-10.9)	1,466	2.4	0.60 (0.57-0.63)
2006	26,512	43.5	10.2 (9.7-10.7)	25,067	41.2	9.6 (9.2-10.1)	1,445	2.3	0.56 (0.53-0.58)
2007	25,177	40.7	9.3 (8.9-9.7)	23,714	38.4	8.7 (8.4-9.1)	1,463	2.3	0.54 (0.52-0.56)
2008	24,732	39.3	8.6 (8.3-9.0)	23,361	37.2	8.2 (7.8-8.5)	1,371	2.1	0.48 (0.46-0.50)
2009	22,052	34.5	7.7 (7.3-8.0)	20,777	32.6	7.2 (6.9-7.5)	1,275	1.9	0.44 (0.42-0.46)
2010	20,874	32.4	7.1 (6.8-7.4)	19,707	30.6	6.7 (6.4-7.0)	1,167	1.7	0.39 (0.38-0.41)
,%**		-42.5	-51.1		-42.4	-51.1		-45.1	-51.7

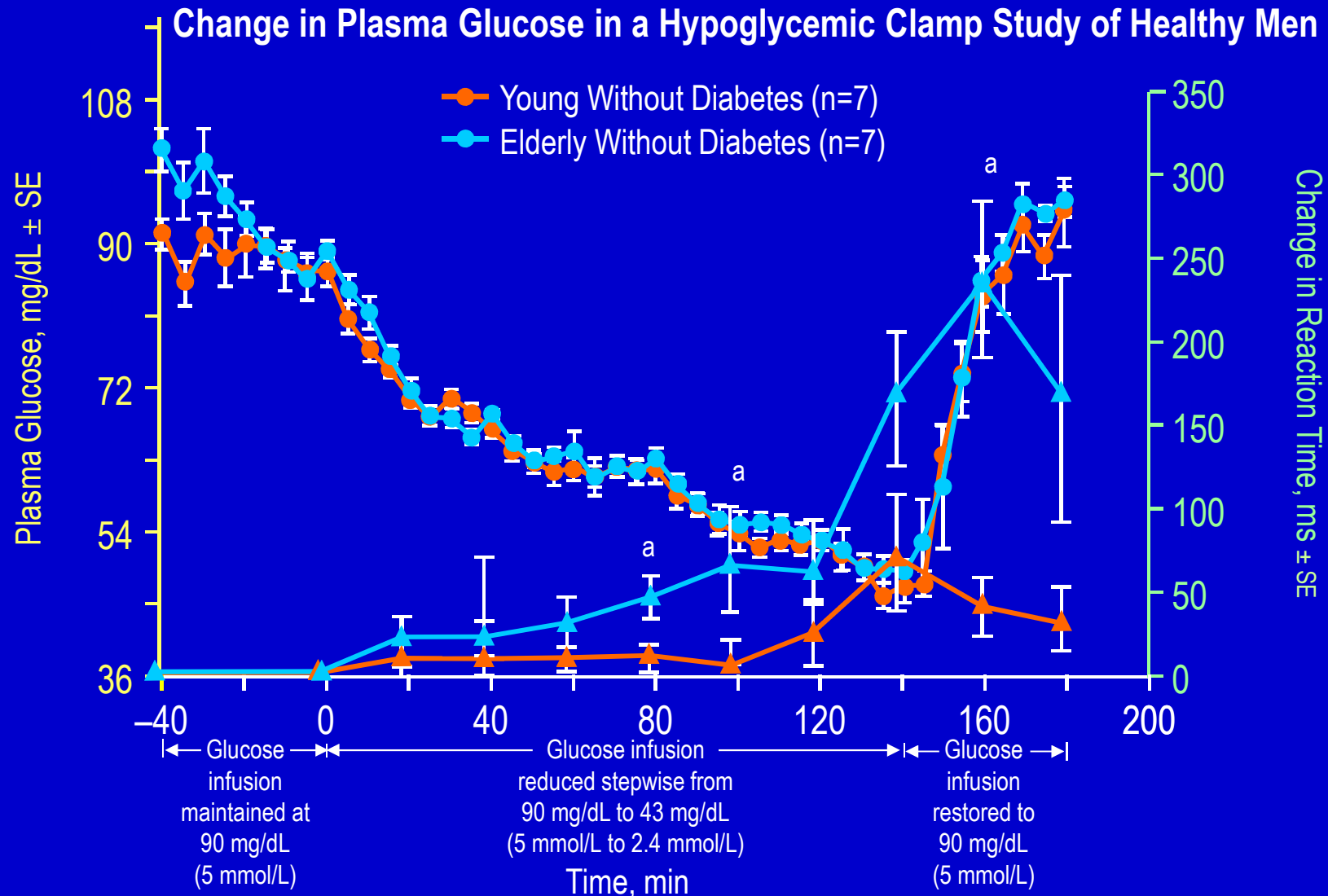
\*Standardized by age and gender on 2001 Italian population.  
 \*\*Relative percentage variation from 2001 to 2010.  
 doi:10.1371/journal.pone.0063675.t002

Lombardo F, Maggini M, Gruden G, Bruno G (2013) Temporal Trend in Hospitalizations for Acute Diabetic Complications: A Nationwide Study, Italy, 2001–2010. PLoS ONE 8(5): e63675. doi:10.1371/journal.pone.0063675





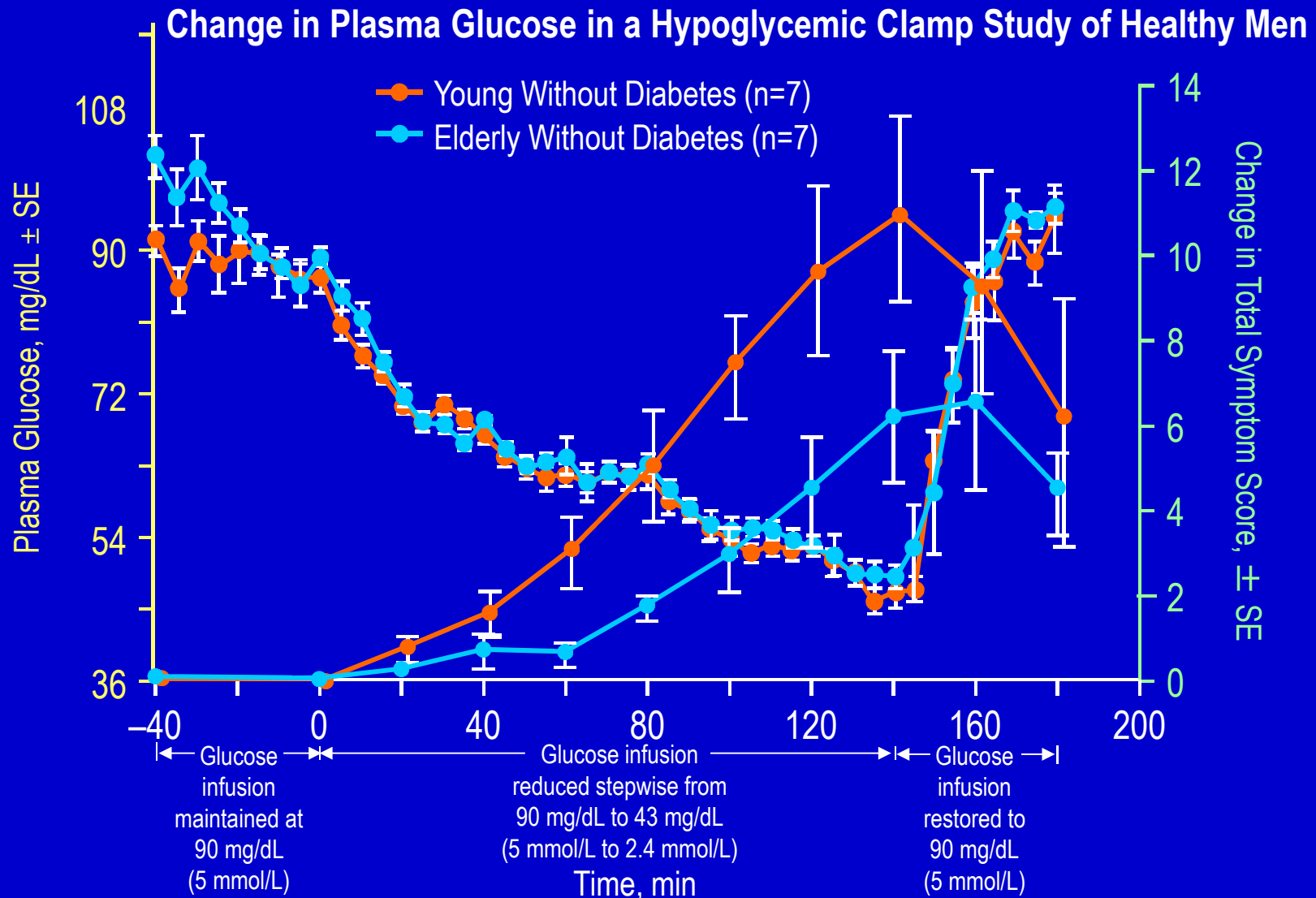
# Declino delle funzioni psicomotorie indotto dalla ipoglicemia negli anziani

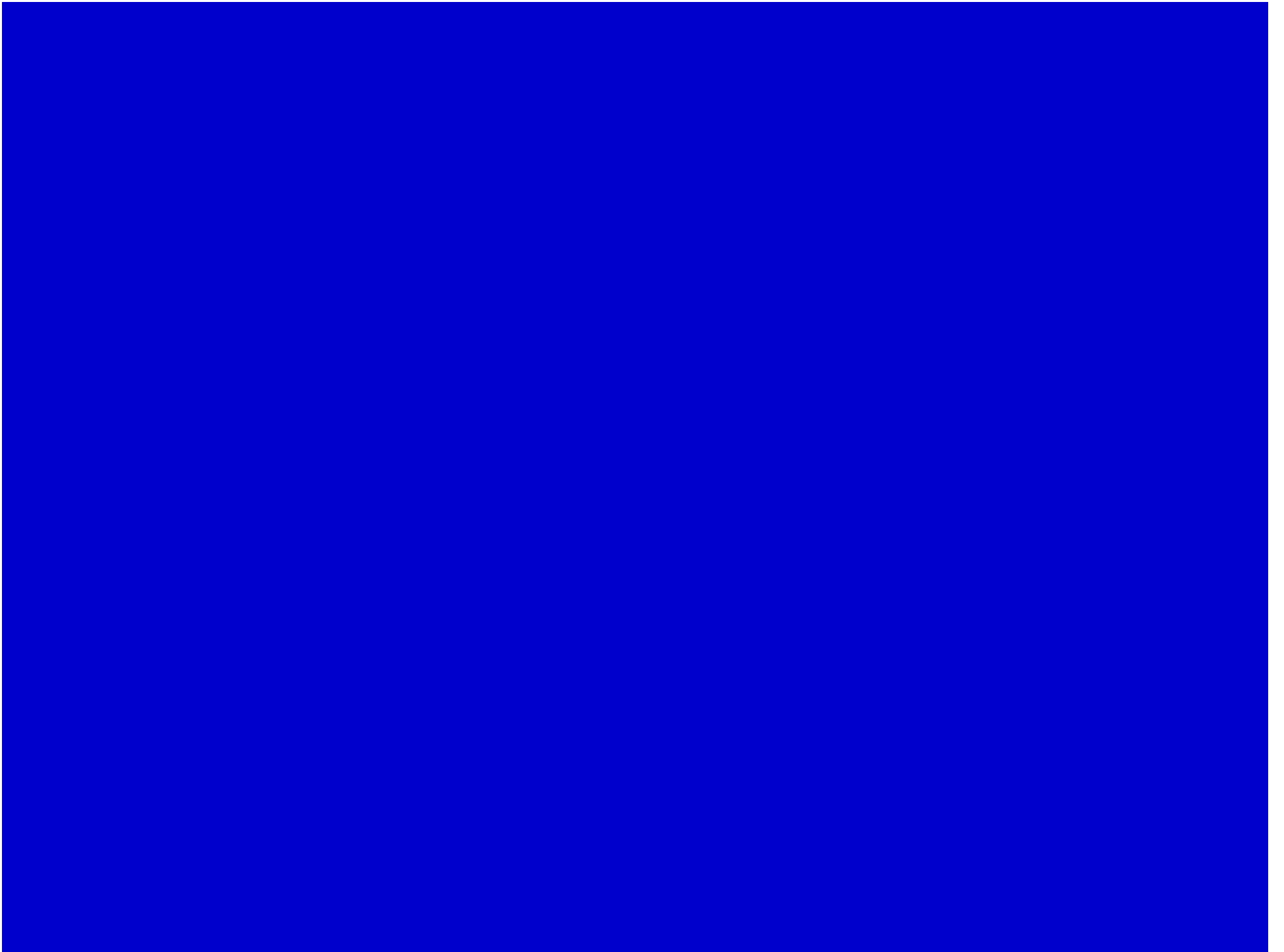


<sup>a</sup>P<0.05.

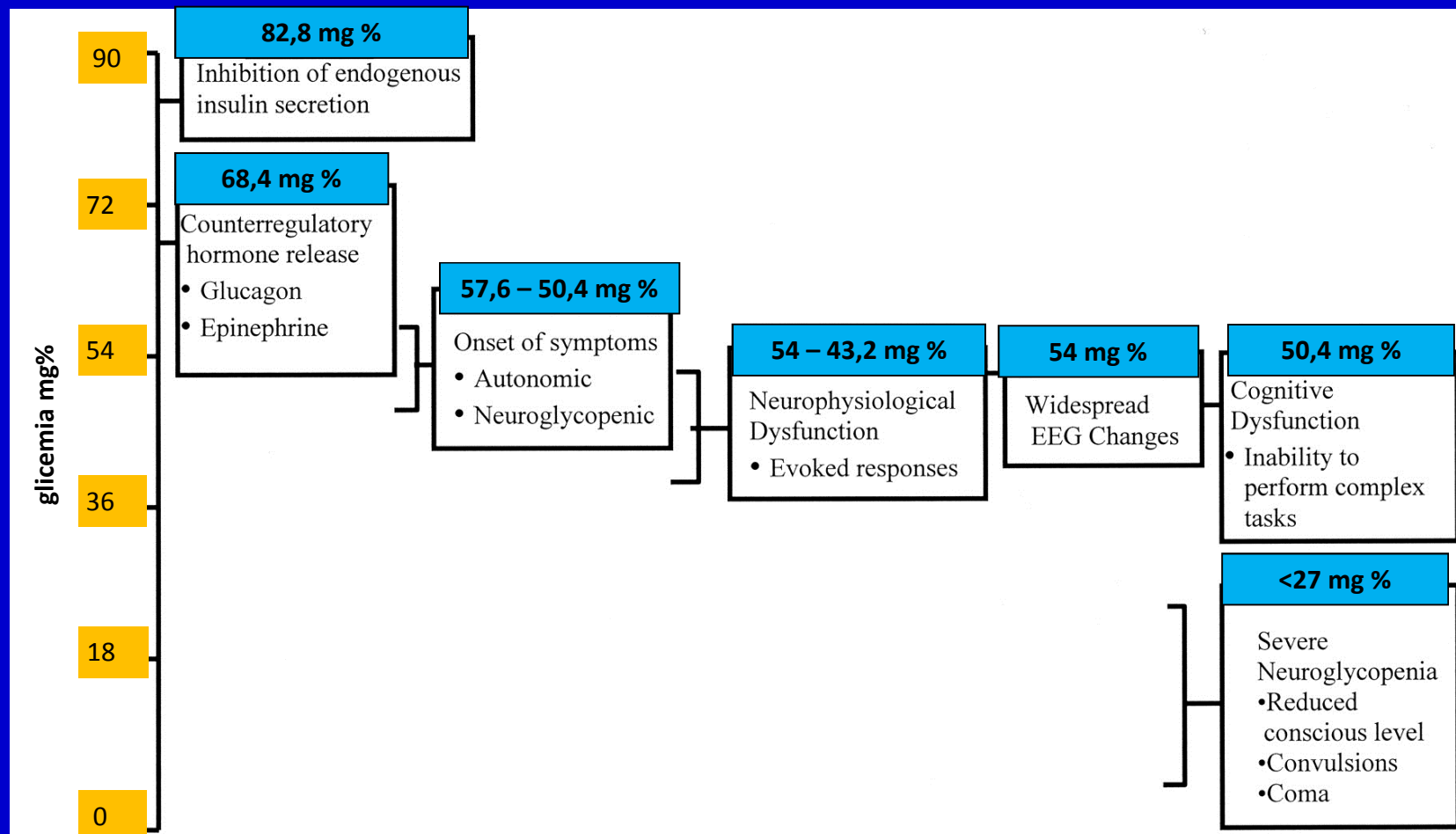
1. Copyright ©1997 American Diabetes Association. Matyka K et al. *Diabetes Care*. 1997;20(2):135-141. Adapted with permission from *The American Diabetes Association*.

# La percezione dei sintomi di ipoglicemia nei soggetti anziani



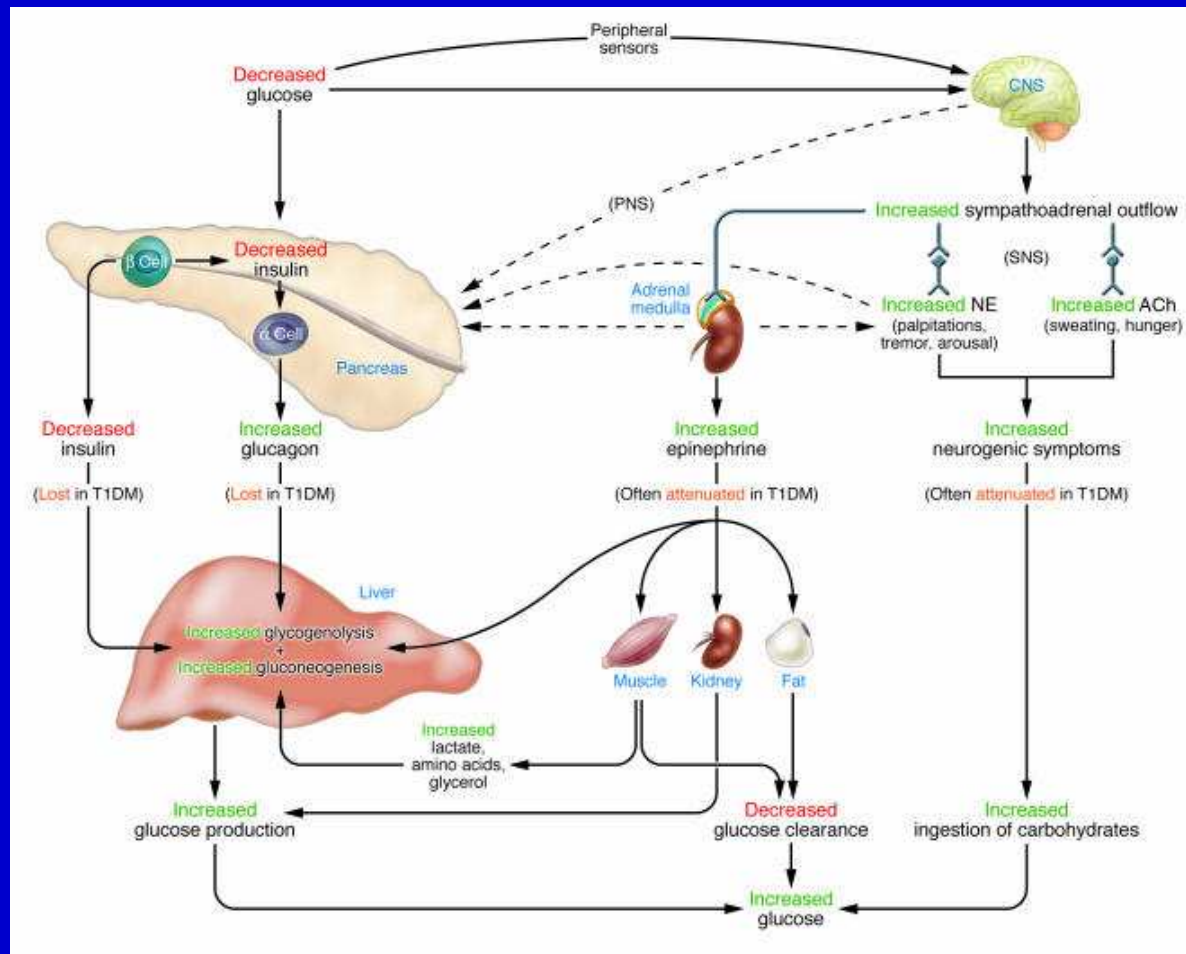


# Soglie glicemiche di attivazione degli ormoni controregolatori e di inizio di sintomi e alterazioni evocati dall' ipoglicemia nel soggetto non diabetico



Zammit N N , and Frier B M Dia Care 2005;28:2948-2961

## Physiological and behavioral defenses against hypoglycemia



# Hypoglycemia Treatment<sup>1</sup>

- Hypoglycemia is defined as plasma glucose level <70 mg/dL.
- For conscious patients, initial treatment is 15 to 20 g of glucose or glucose- or carbohydrate-containing foods.
  - Repeat every 15 minutes until glucose level is >70 mg/dL, then eat!
- Glucagon should be prescribed for those at high risk of severe hypoglycemia.
- Consider increasing HbA<sub>1c</sub> goals for appropriate patients, such as those with
  - A history of severe hypoglycemia
  - Hypoglycemia unawareness

# COMPLICANZE DELL'IPOGLICEMIA

■	90/5.0
■	82/4.5
■	72/4.0
■	64/3.5
■	54/3.0
■	45/2.5
■	36/2.0
■	28/1.6

Rilascio di  
epinefrina e  
norepinefrina

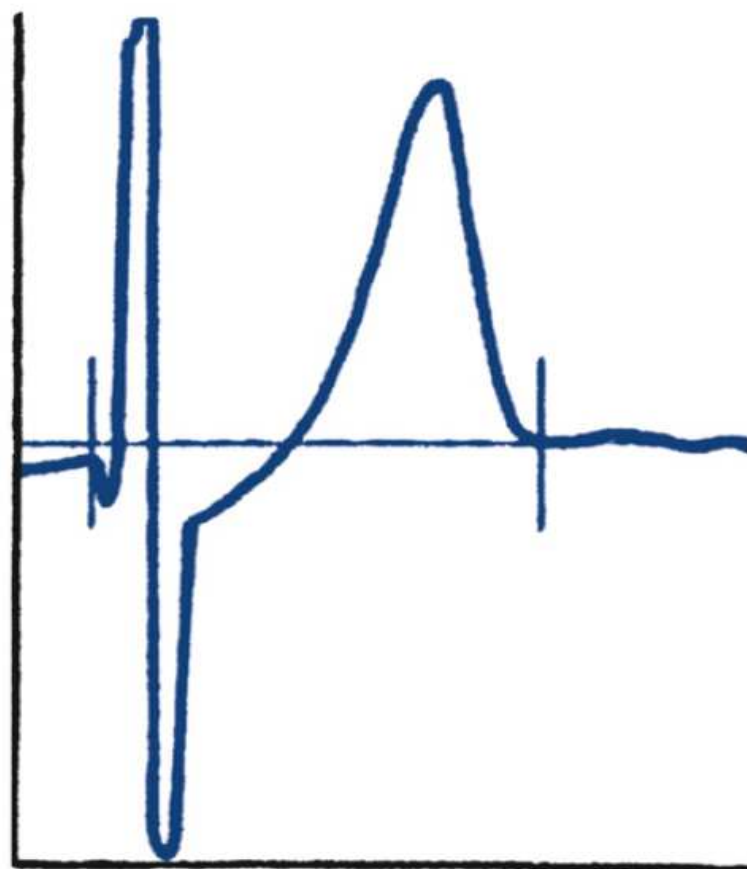
## Aumento del rischio di aritmie cardiache

- Anormale prolungamento ripolarizzazione cardiaca -  $\uparrow$  QTc e QTd - associato con incremento dei livelli di epinefrina e ipokalemia
- Morte cardiaca

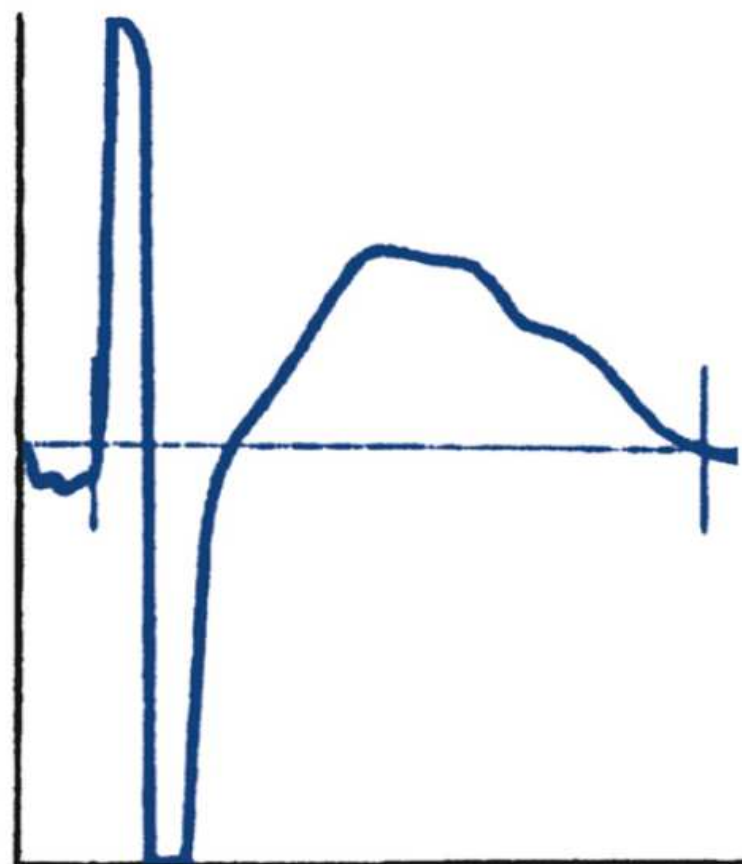
## Neuroglicopenia

- Ridotta capacità di attenzione
- Incapacità di concentrarsi
- Cambiamento di personalità
- Confusione
- Coma
- Morte cerebrale

## Effect of experimental hypoglycemia on QT interval



5.0 mM



2.5 mM



## *Hypoglycemia and cardiac ischemia*

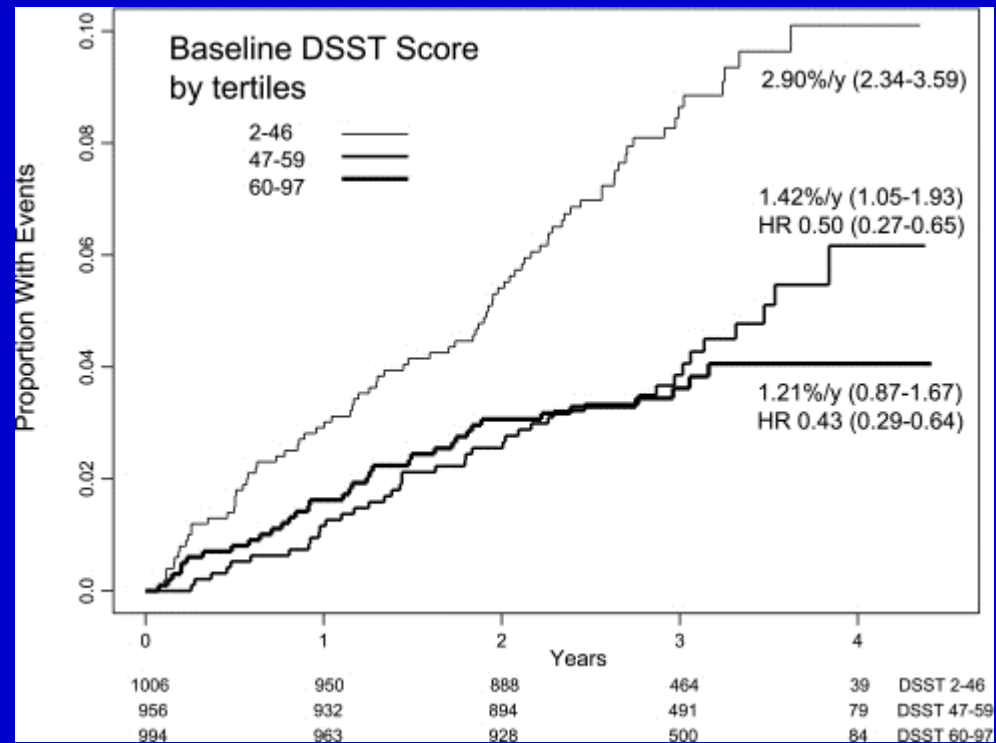
Parameter	Value
Mean duration of known diabetes (years)	12.9 ± 5.6
Mean age at diagnosis of diabetes (years)	50.4 ± 7.1
Number of patients taking $\beta$ -blockers	15
Number of patients with known neuropathy	10
Mean episodes of hypoglycemia per patient (mg/dl)	3.2 ± 1.6
Mean episodes of rapid glucose changes per patient (mg/dl)	3.8 ± 2.1
Mean duration of hypoglycemia per patient (h)	3.01 ± 0.5
Mean duration of hyperglycemia per patient (h)	6.44 ± 0.92
Mean duration of normoglycemia per patient (h)	61.72 ± 5.6
Mean depth of hypoglycemia per patient (mg/dl)	50.1 ± 7.6

Data are means  $\pm$  SD.

## *CGMS and Holter monitoring abnormalities*

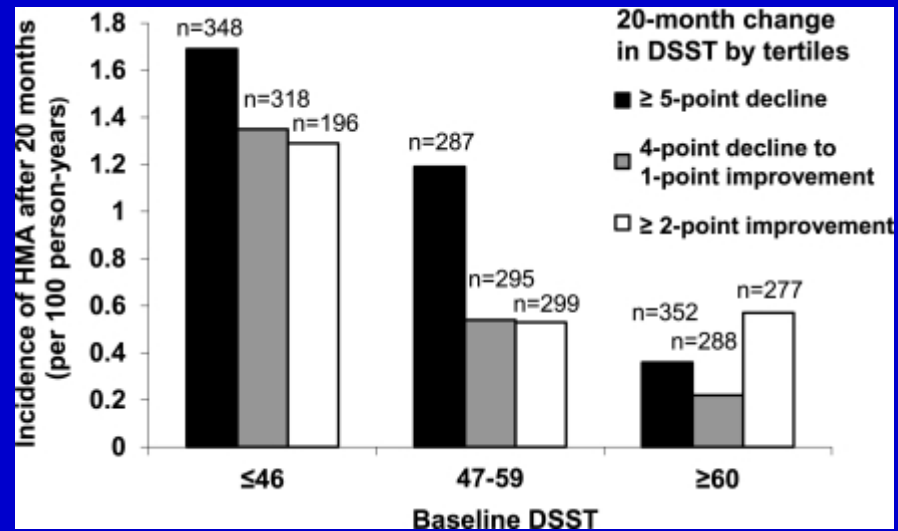
	Total episodes	Episodes with chest pain/angina	Episodes with ECG abnormalities
Hypoglycemia	54	10*	6*
Symptomatic	26	10*	4*
Asymptomatic	28	—	2
Normoglycemia without rapid changes	N/A	0	0
Hyperglycemia	59	1	0
Rapid changes in glucose ( $>100 \text{ mg} \cdot \text{dl}^{-1} \cdot \text{h}^{-1}$ )	50	9*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

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



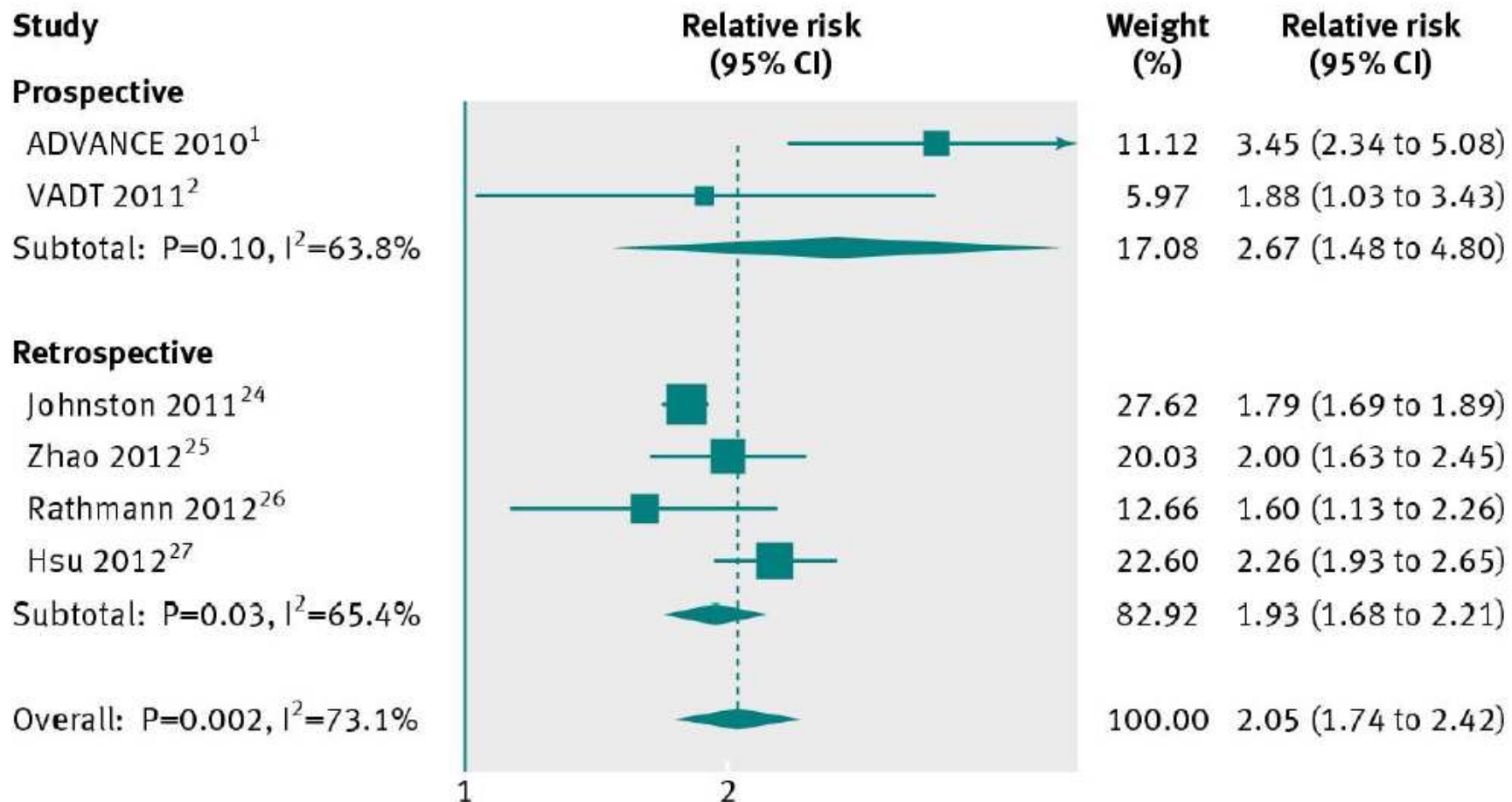
## Severe hypoglycemia and cognitive dysfunction in type 2 diabetes

Post hoc epidemiologic analysis of the ACCORD trial



Effect of 20-month change in DSST score on crude incidence of severe hypoglycemia requiring medical assistance after 20 months, according to baseline thirds of DSST score. Number of individuals in each category is presented above each bar

## Severe hypoglycaemia and cardiovascular disease: systematic review and meta-analysis with bias analysis

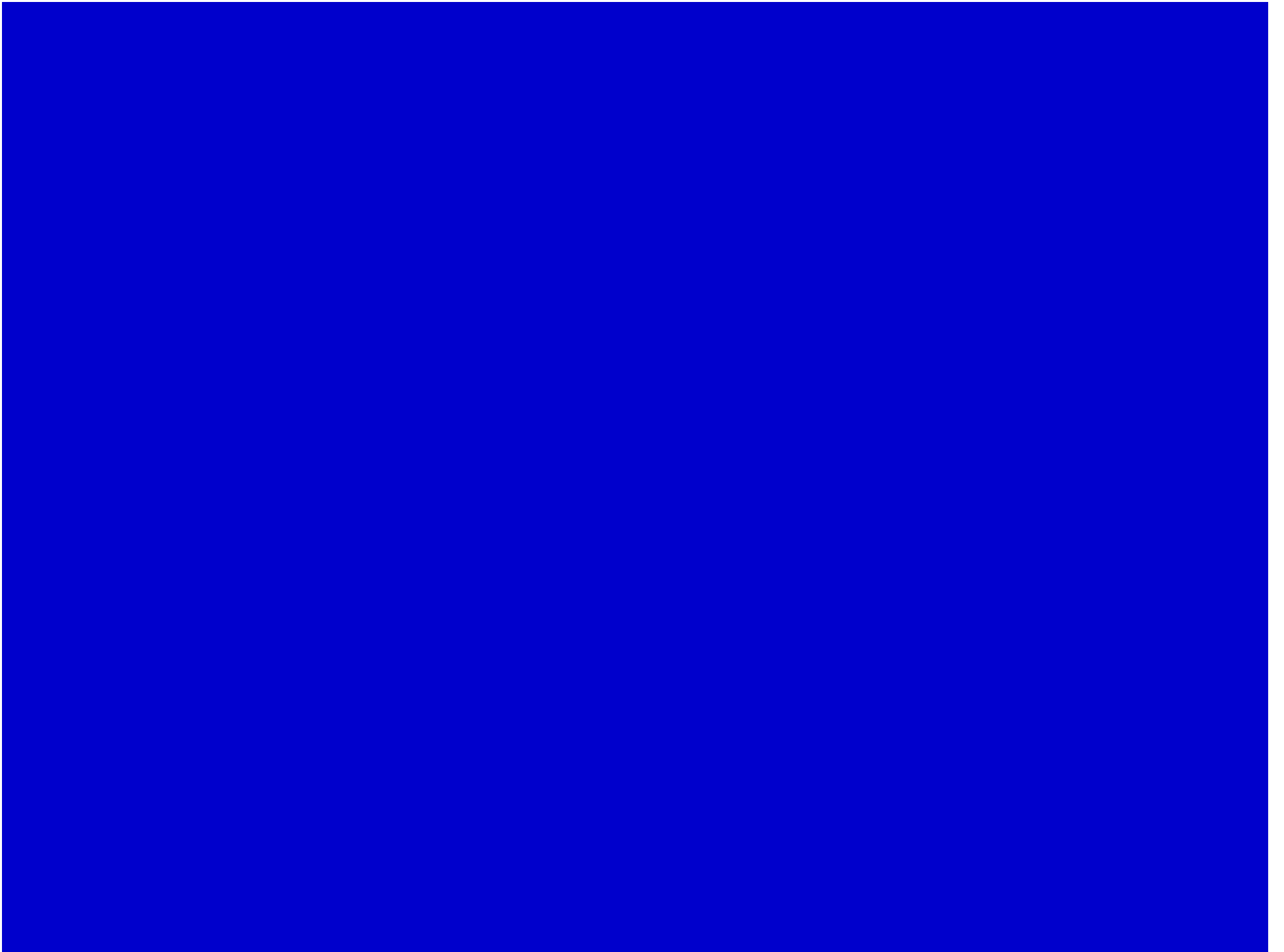


Conventional random effects meta-analysis according to study design. ADVANCE=Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation; VADT=Veterans Affairs Diabetes Trial. Dots indicate relative risks for severe hypoglycaemia and cardiovascular events in people with type 2 diabetes. Horizontal lines indicate 95% confidence intervals for relative risks. Diamonds represent pooled relative risk estimates with 95% confidence intervals

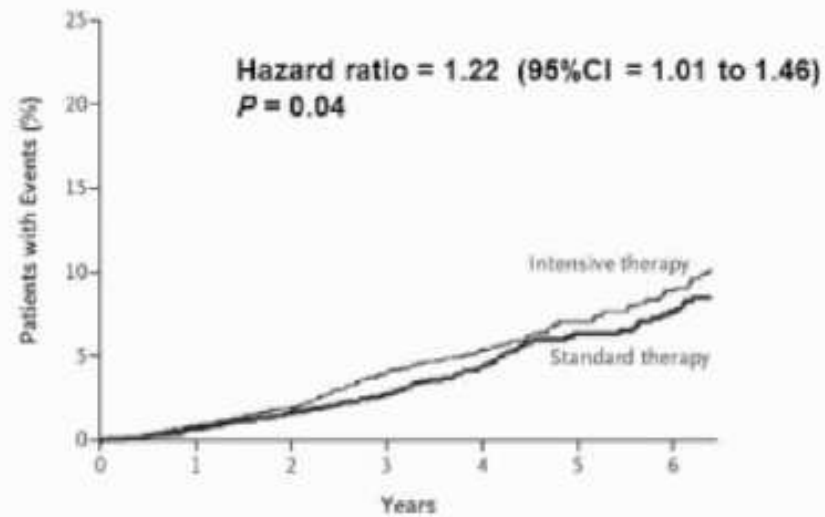
Severe Hypoglycemia and Cardiovascular Disease Incidence in Type 1 Diabetes  
The EURODIAB Prospective Complications Study

Episodes of severe hypoglycemia at baseline examination	Model 1	Model 2	Model 3
	OR (95% CI)	OR (95% CI)	OR (95% CI)
0	1.00	1.00	1.00
1–2	0.87 (0.55–1.37)	0.90 (0.55–1.48)	0.94 (0.57–1.55)
3+	1.09 (0.68–1.75)	1.23 (0.75–2.04)	1.33 (0.80–2.22)

Role of severe hypoglycemia in incidence of CVD in the prospective study;  
results of logistic regression analyses



## ACCORD: Total mortality



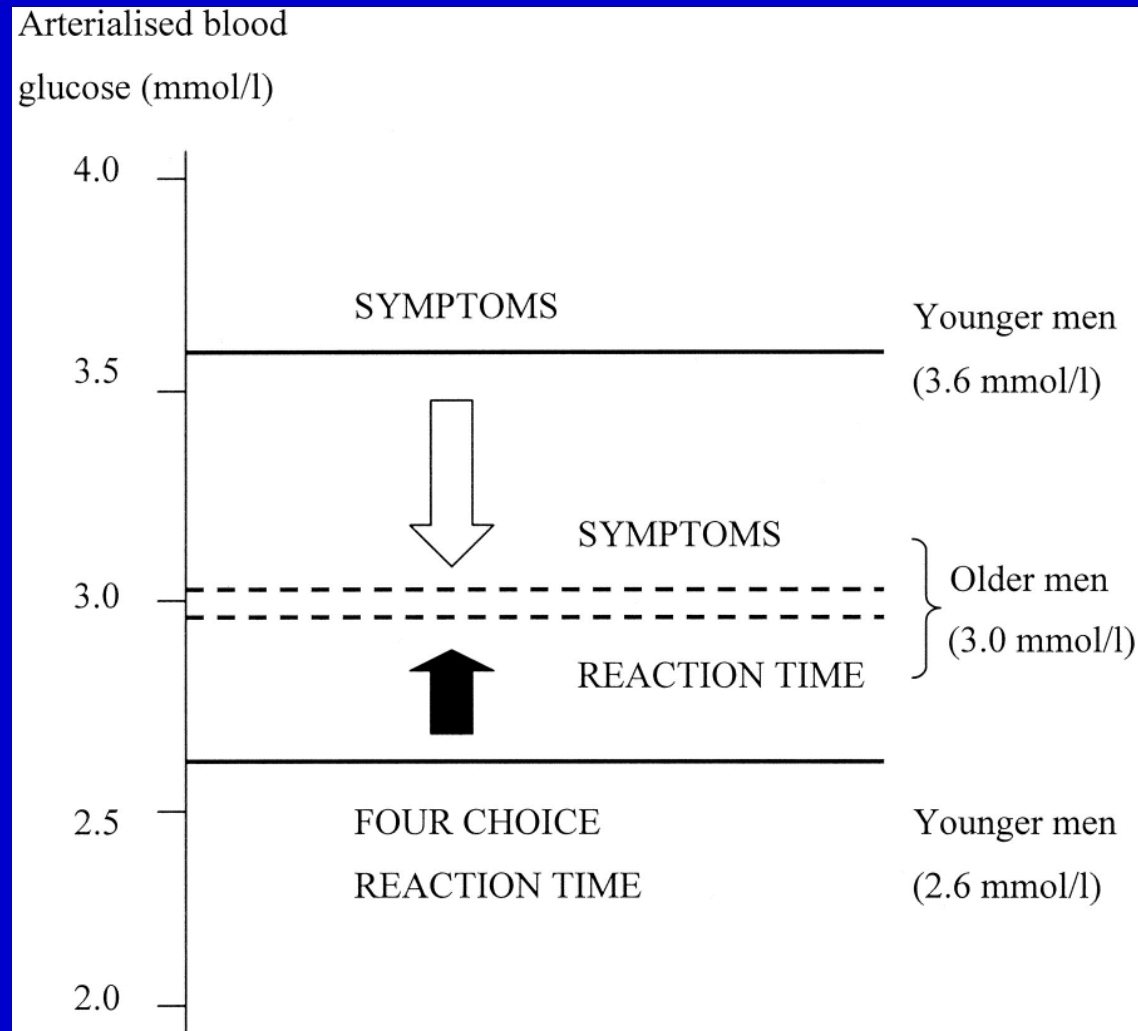
### No. at Risk

Intensive therapy	5128	4972	4803	3250	1748	523	506
Standard therapy	5123	4971	4700	3180	1642	499	480

ACCORD Study Group : *N.Engl.J.Med.*, 358, 2545, 2008.



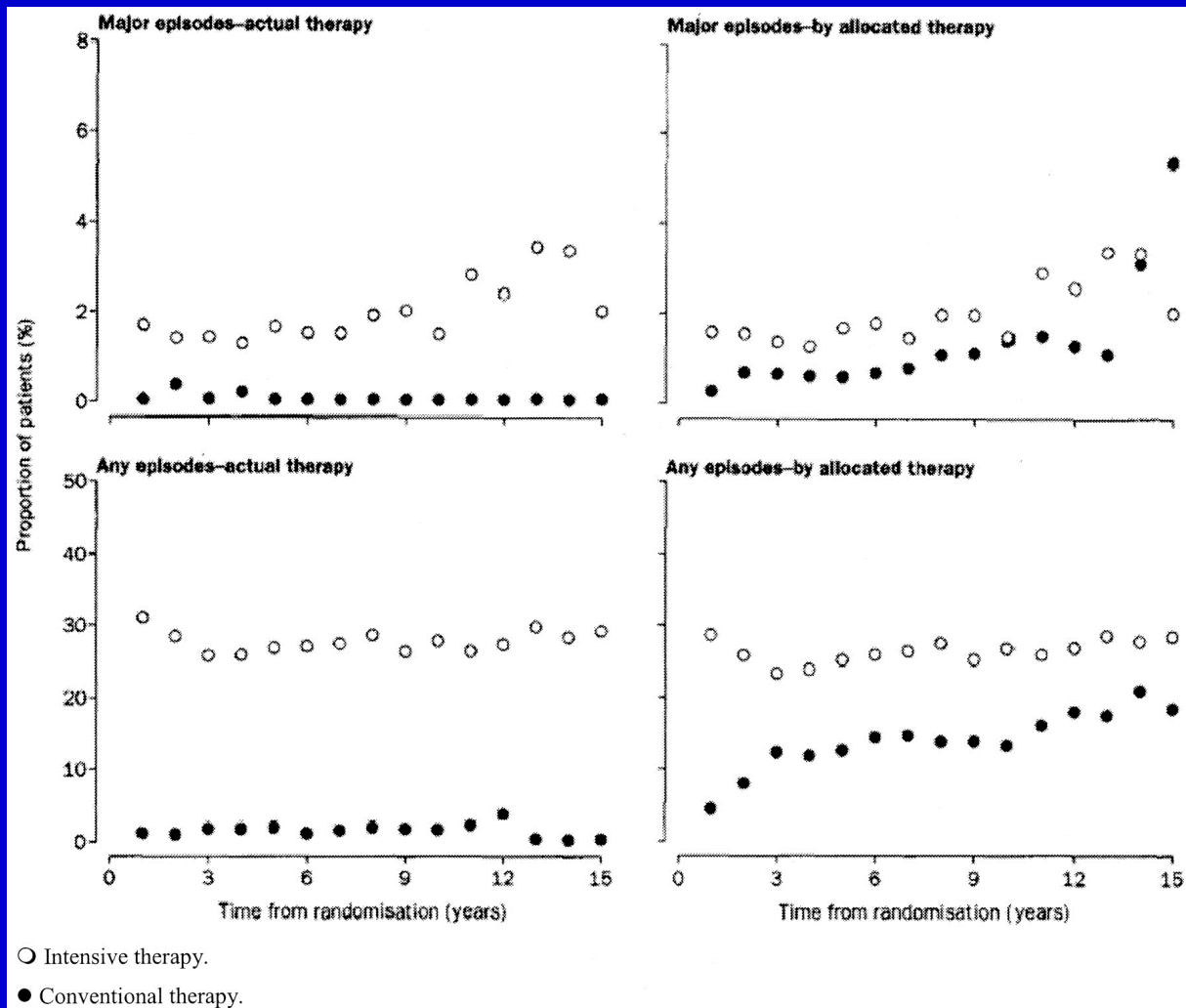
## Glycemic thresholds for subjective symptomatic awareness of hypoglycemia and for the onset of cognitive dysfunction in young and elderly nondiabetic males.



Zammit N N , and Frier B M Dia Care 2005;28:2948-2961



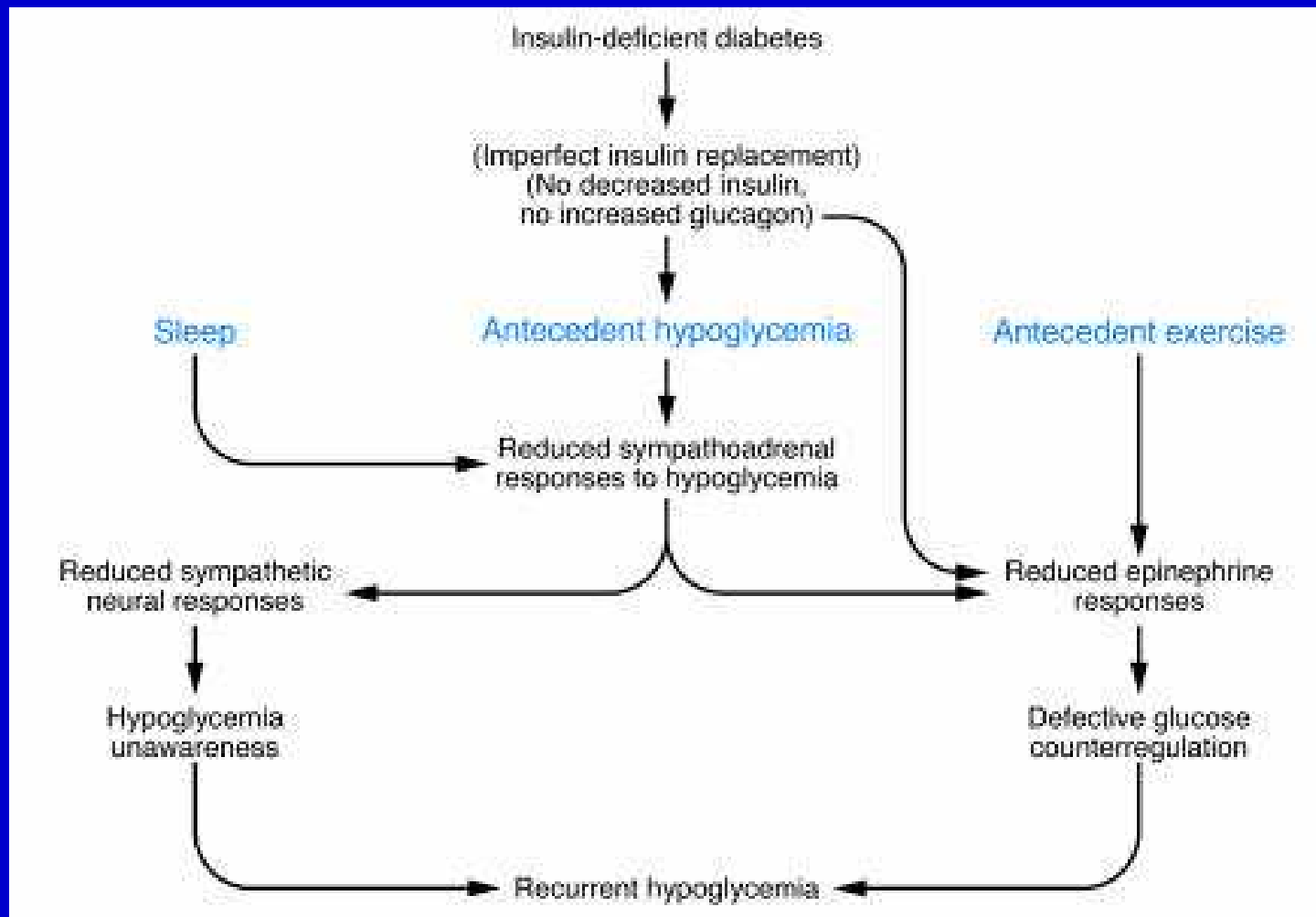
## Major and any hypoglycemic episodes per year by intention-to-treat analysis and actual therapy for intensive and conventional treatment.



Zammit N N , and Frier B M Dia Care 2005;28:2948-2961

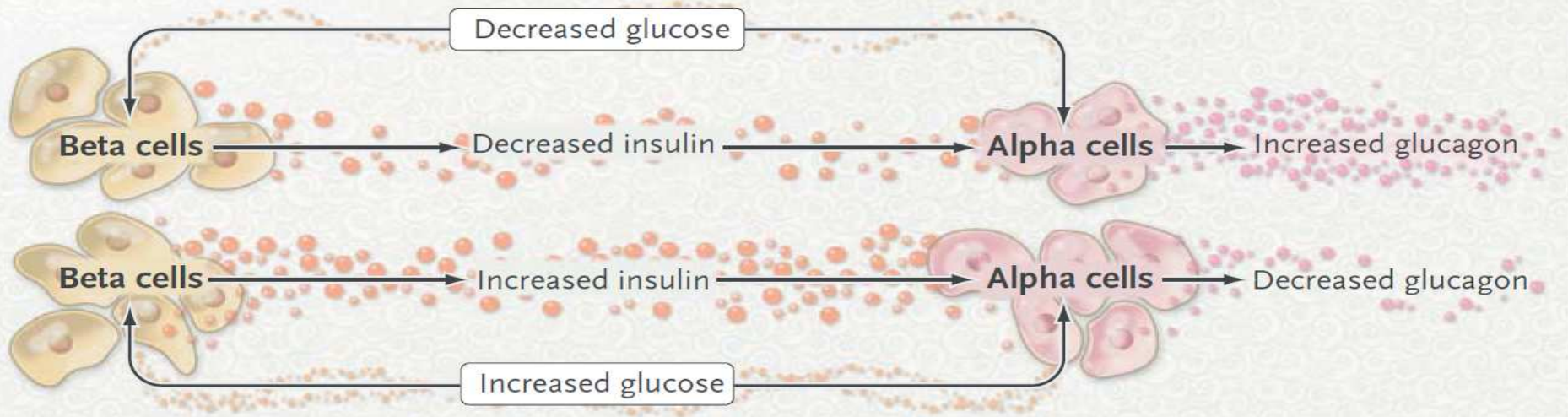


# Hypoglycemia-associated autonomic failure in T1DM and advanced T2DM

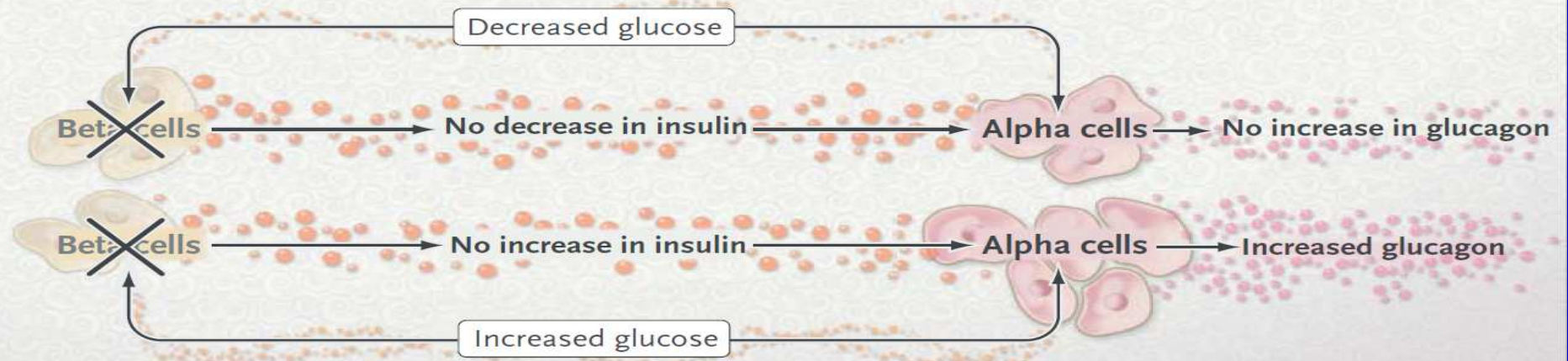


# Mechanisms of Loss of the Glucagon Response.

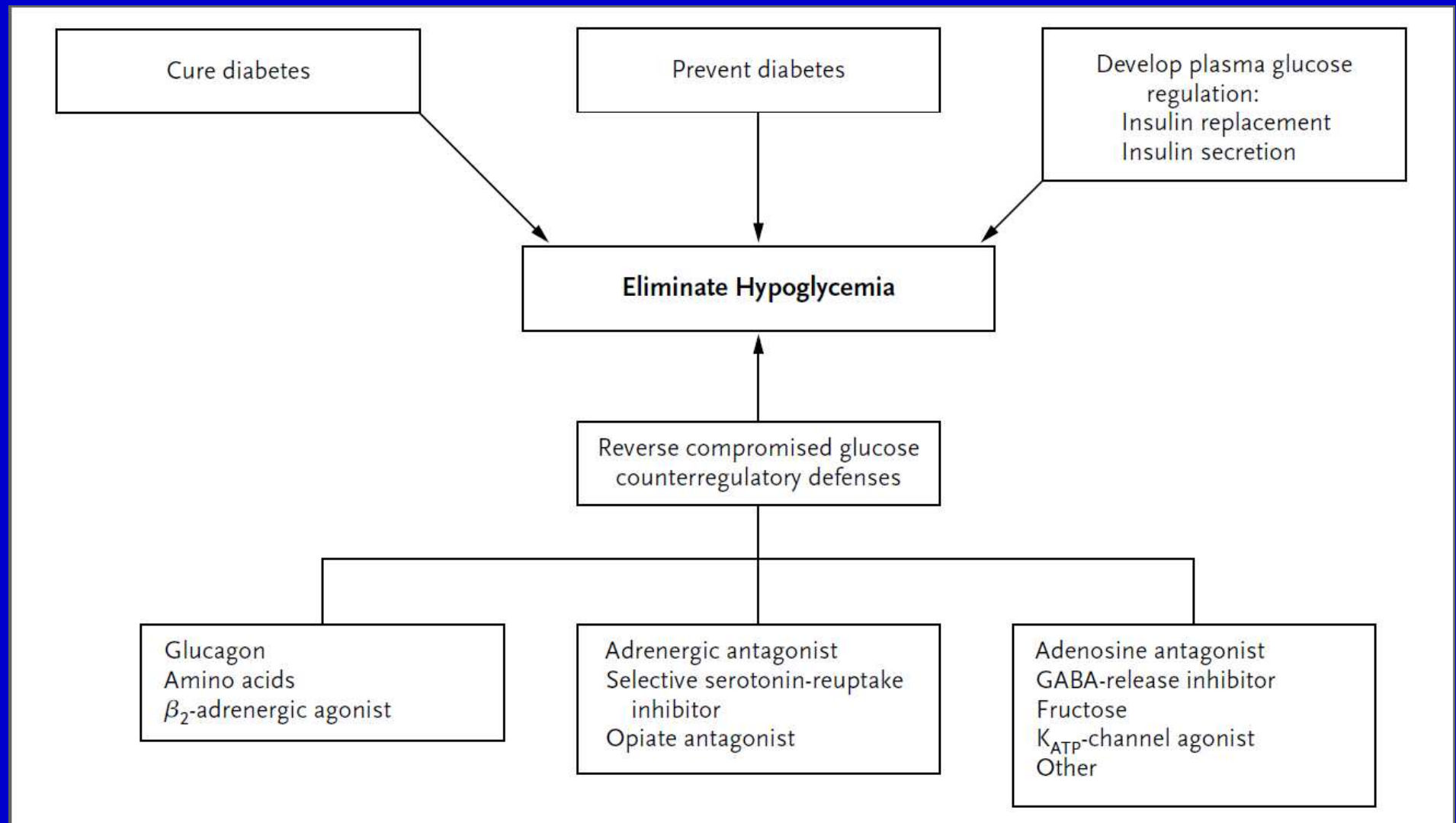
## A Normal physiology



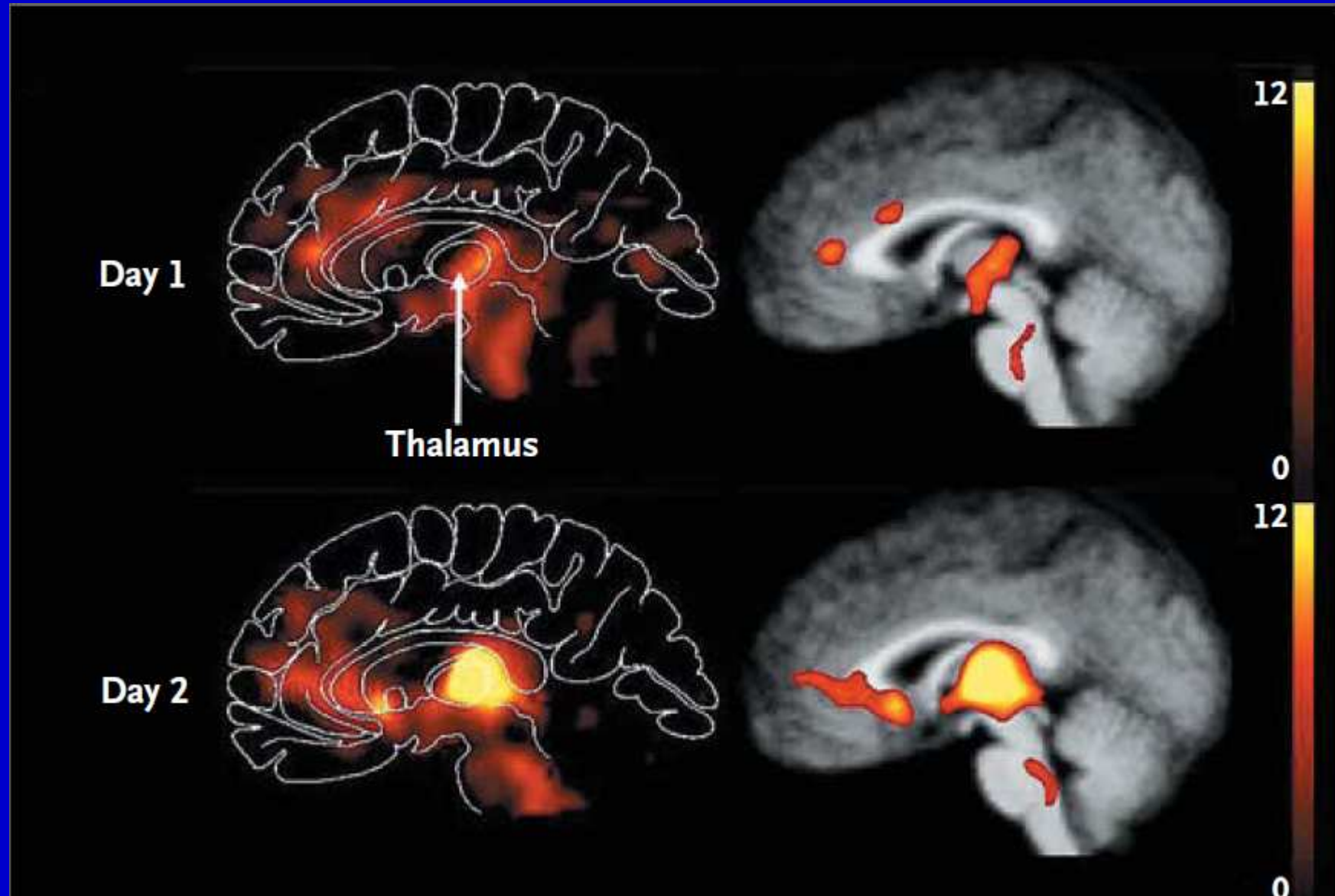
## B Pathophysiology in diabetes



# Elimination of Hypoglycemia from the Lives of People with Diabetes



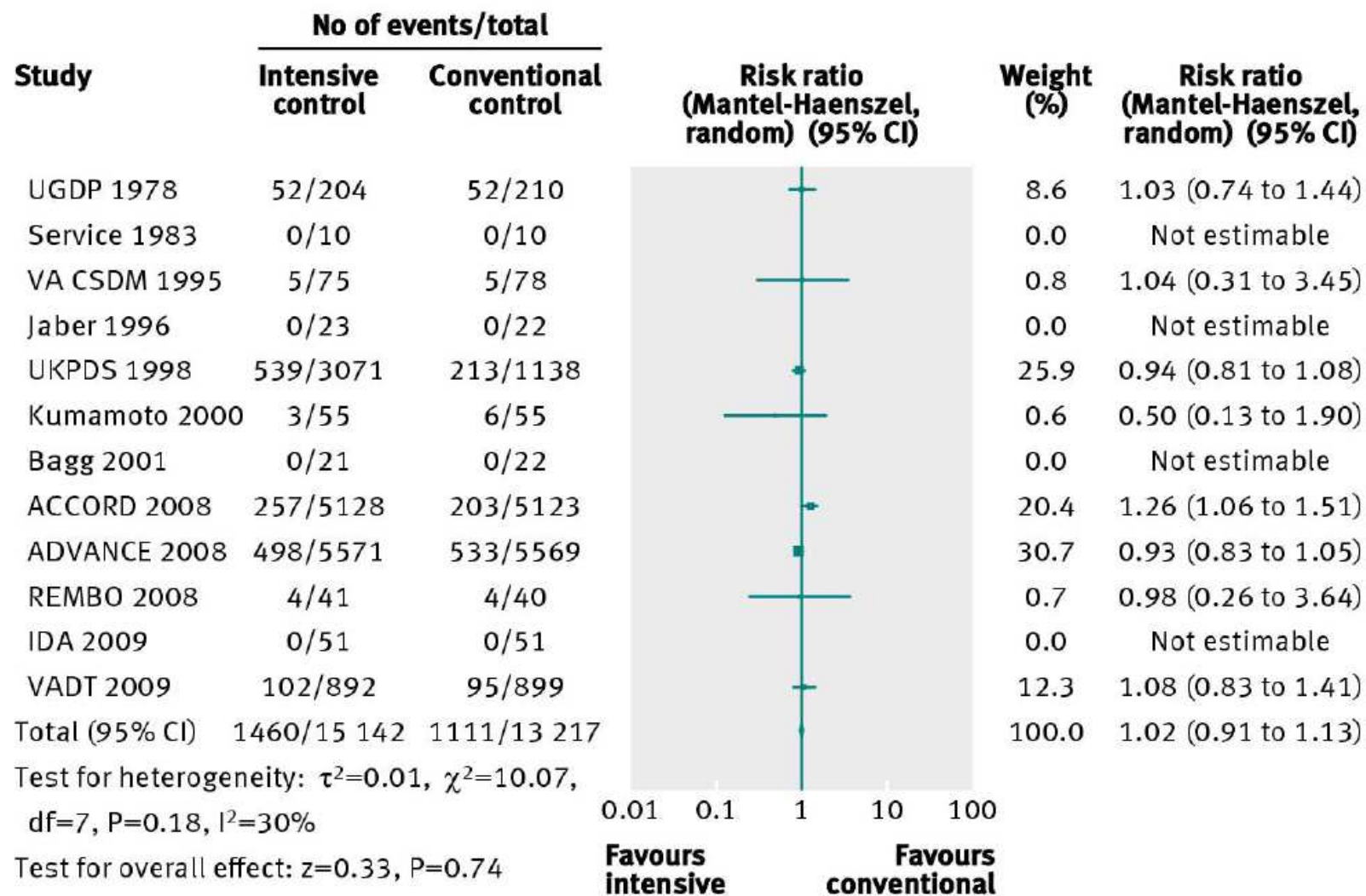
# Increased Thalamic Response to Hypoglycemia in a Model of HAAF



# Intensive glycaemic control for patients with type 2 diabetes: systematic review with meta-analysis and trial sequential analysis of randomised clinical trials

Bianca Hemmingsen *PhD student*<sup>1</sup>, Søren S Lund *physician*<sup>2</sup>, Christian Gluud *chief physician and head of department*<sup>1</sup>, Allan Vaag *professor*<sup>3</sup>, Thomas Almdal *chief physician and head of department*<sup>2</sup>, Christina Hemmingsen *research assistant*<sup>1</sup>, Jørn Wetterslev *chief physician*<sup>1</sup>

BMJ 2011;343:d6898 doi: 10.1136/bmj.d6898 (Published 24 November 2011)



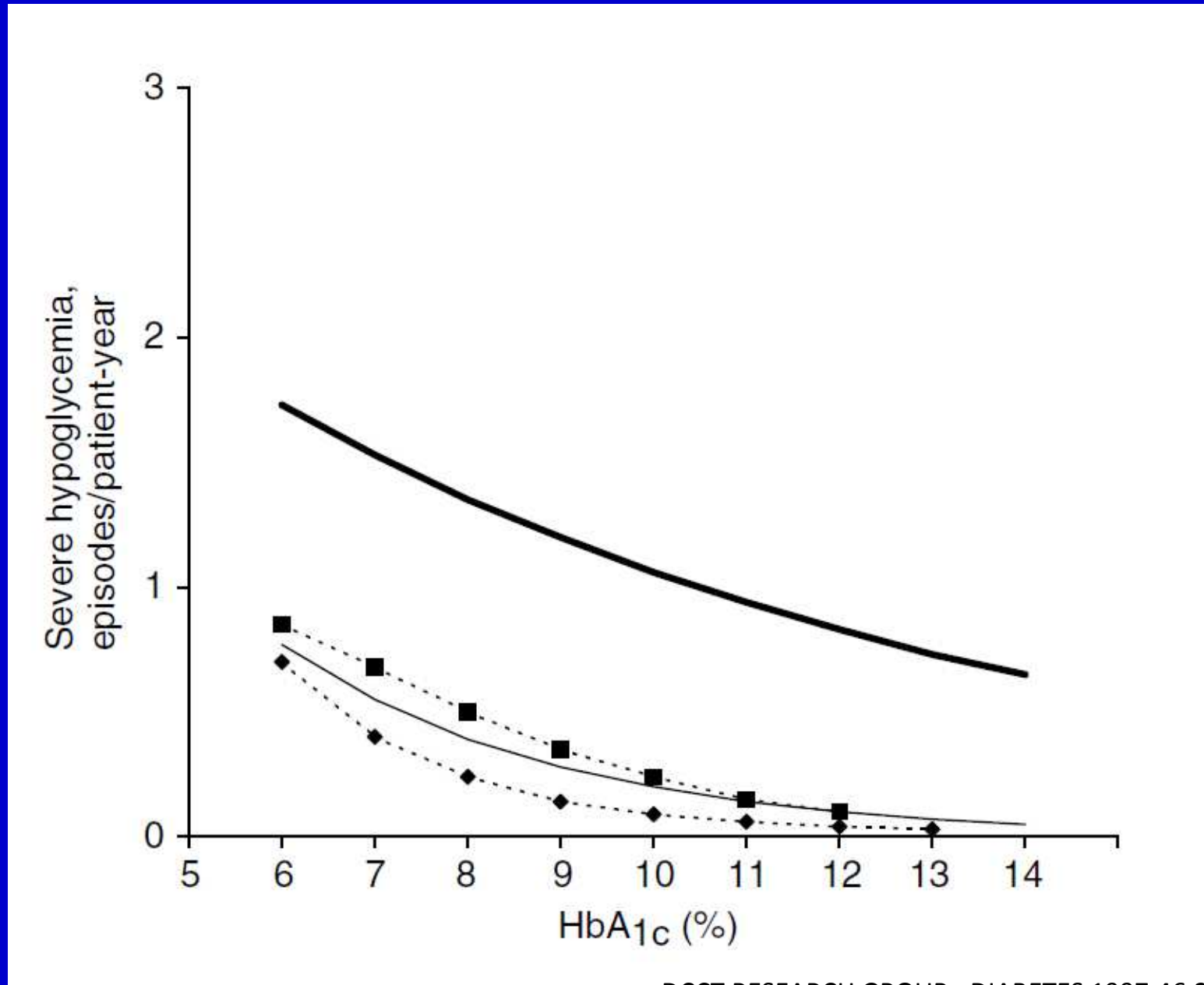
# DCCT

- **DCCT 1,441 patients with T1DM:**
  - 3,788 episodes of severe hypoglycemia
  - 1,027 of these episodes were associated with coma and/or seizure.
- **Severe hypoglycemia** (at least one episode):
  - 65% percent of patients in the intensive group
  - 35% of patients in the conventional group
- **Overall rates of severe hypoglycemia:**
  - Intensive group: 61.2 per 100 patient-years
  - Conventional group: 18.7 per 100 patient-years
  - RR: 3.28

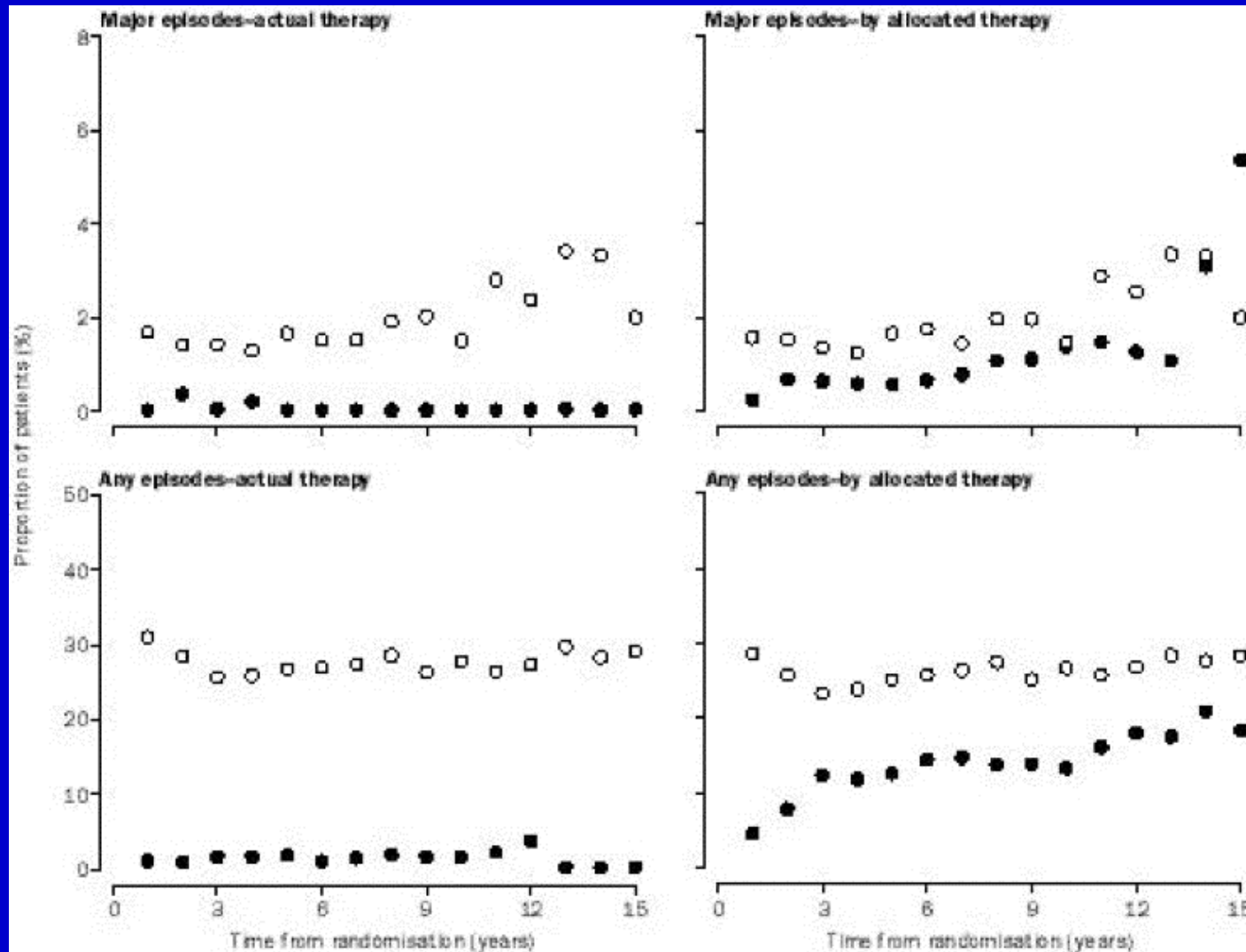


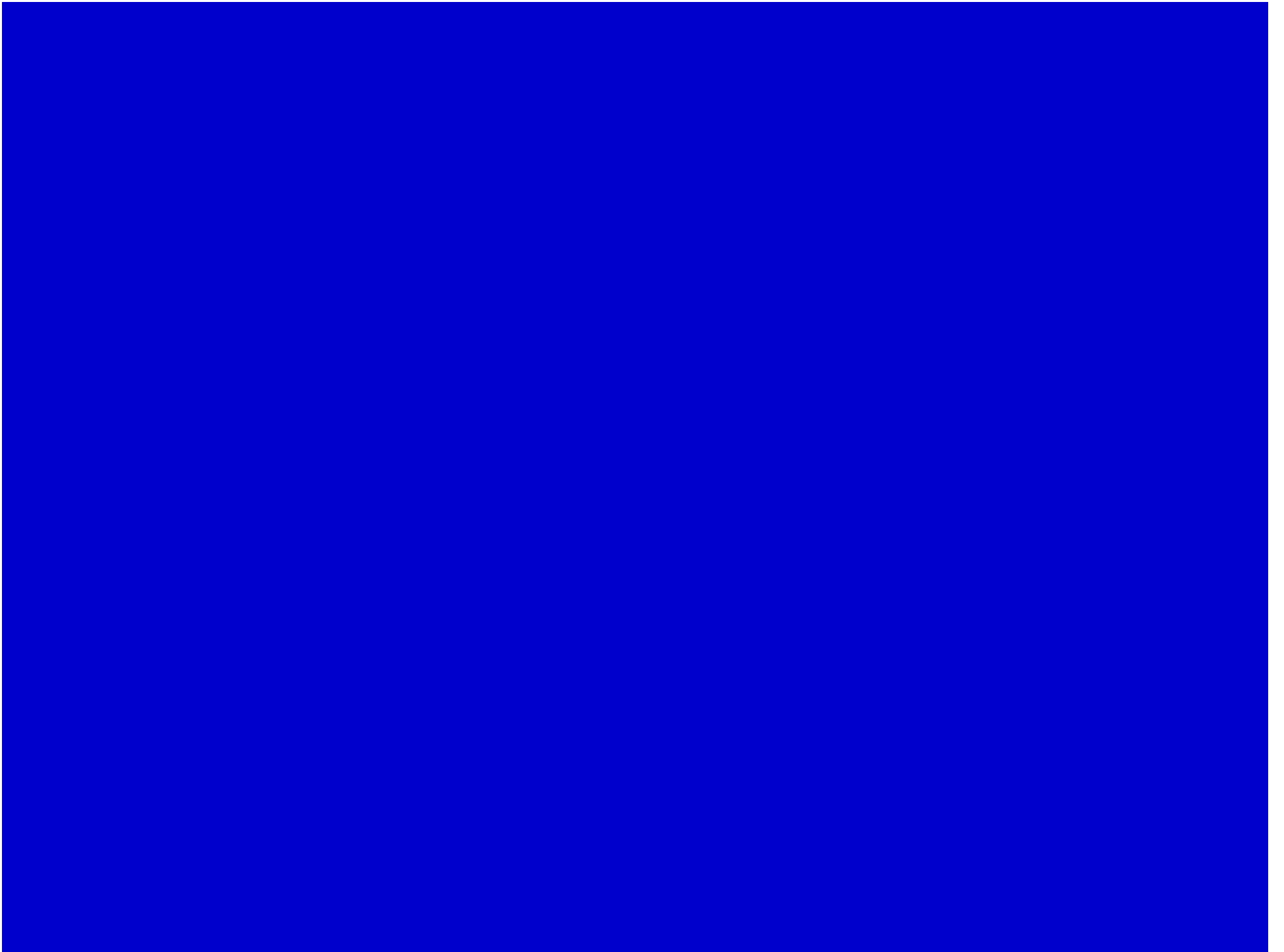


## Univariate relationship between risk of severe hypoglycaemia and HbA<sub>1c</sub>

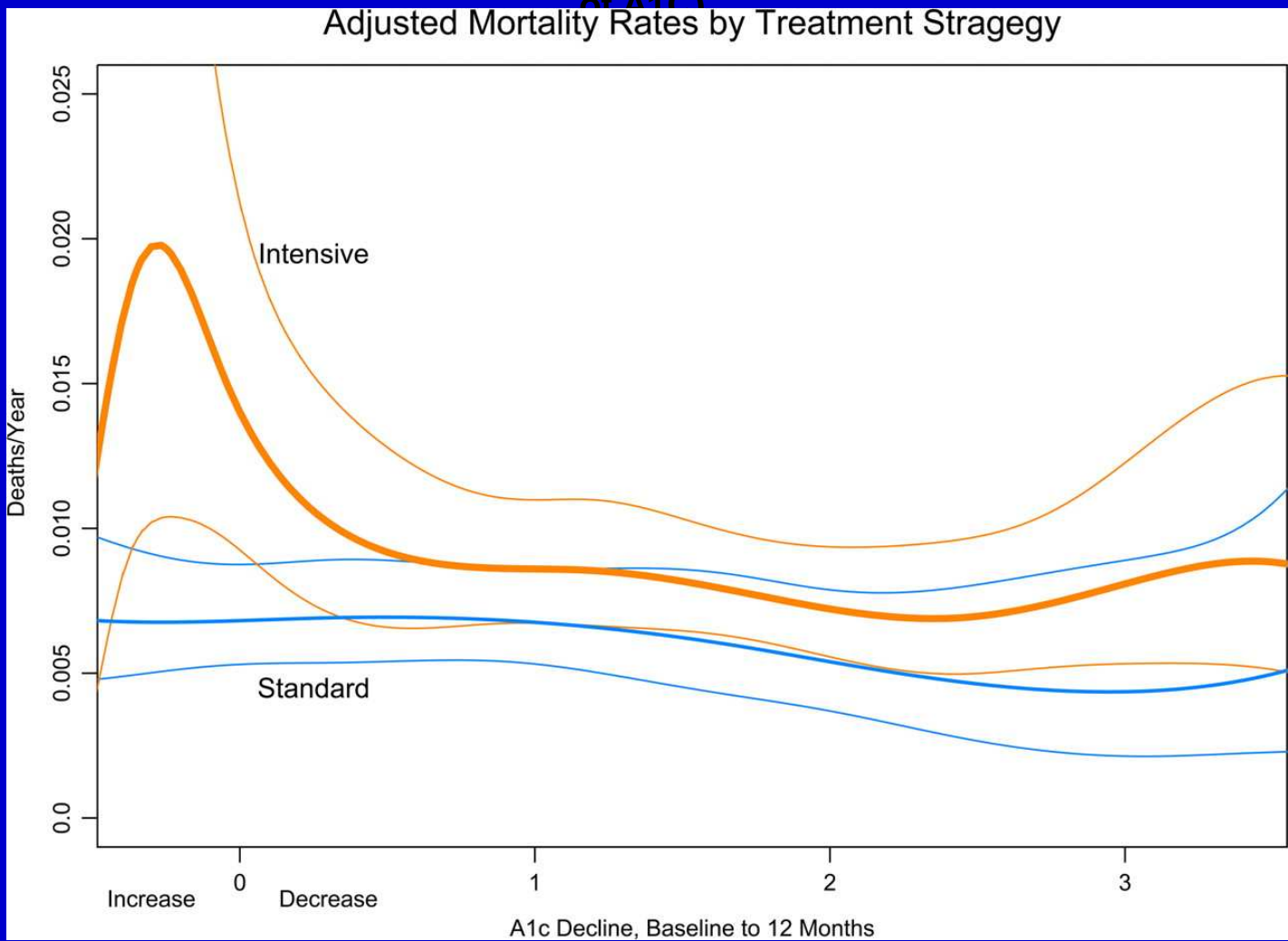


# Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33)





Curves displaying all-cause mortality rates by treatment for the whole period of follow-up, over a range of decreases in A1C from baseline in the 1st year of treatment (as a percentage of A1C)

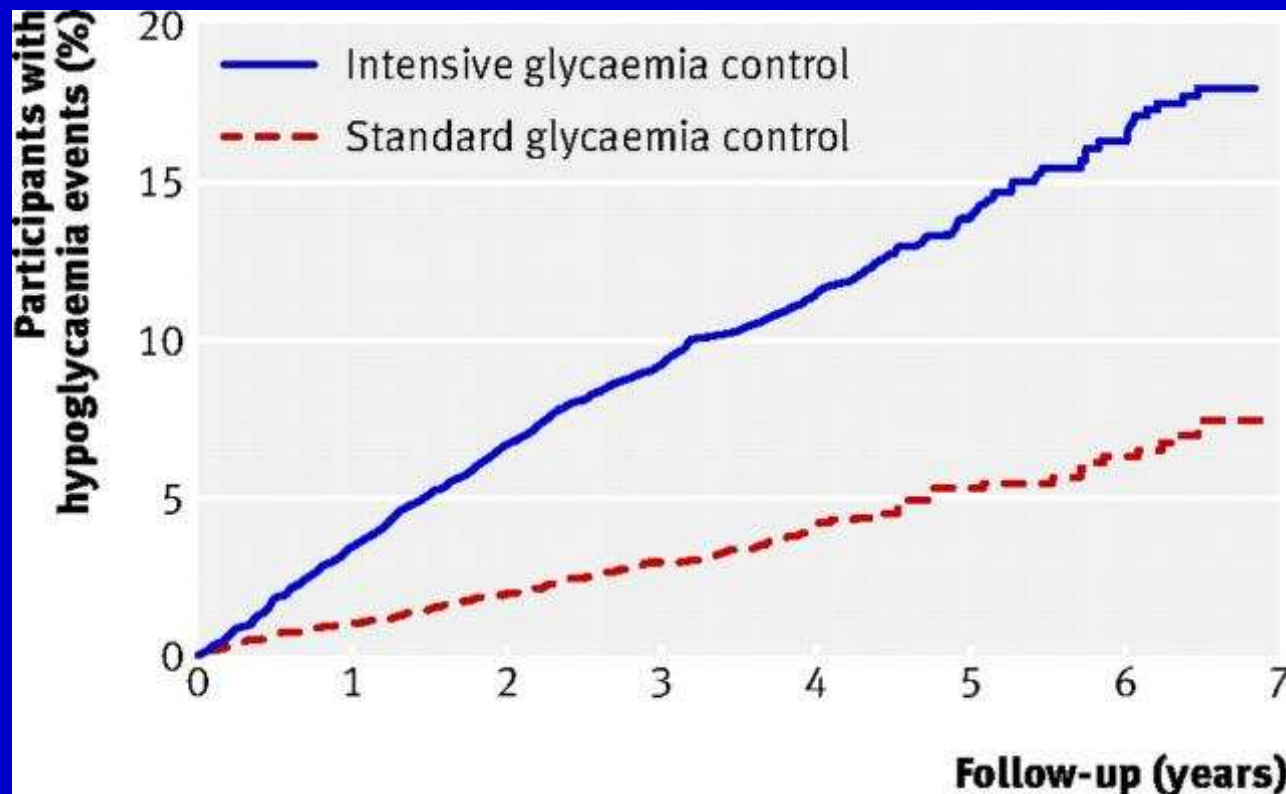


Riddle M C et al. Dia Care 2010;33:983-990



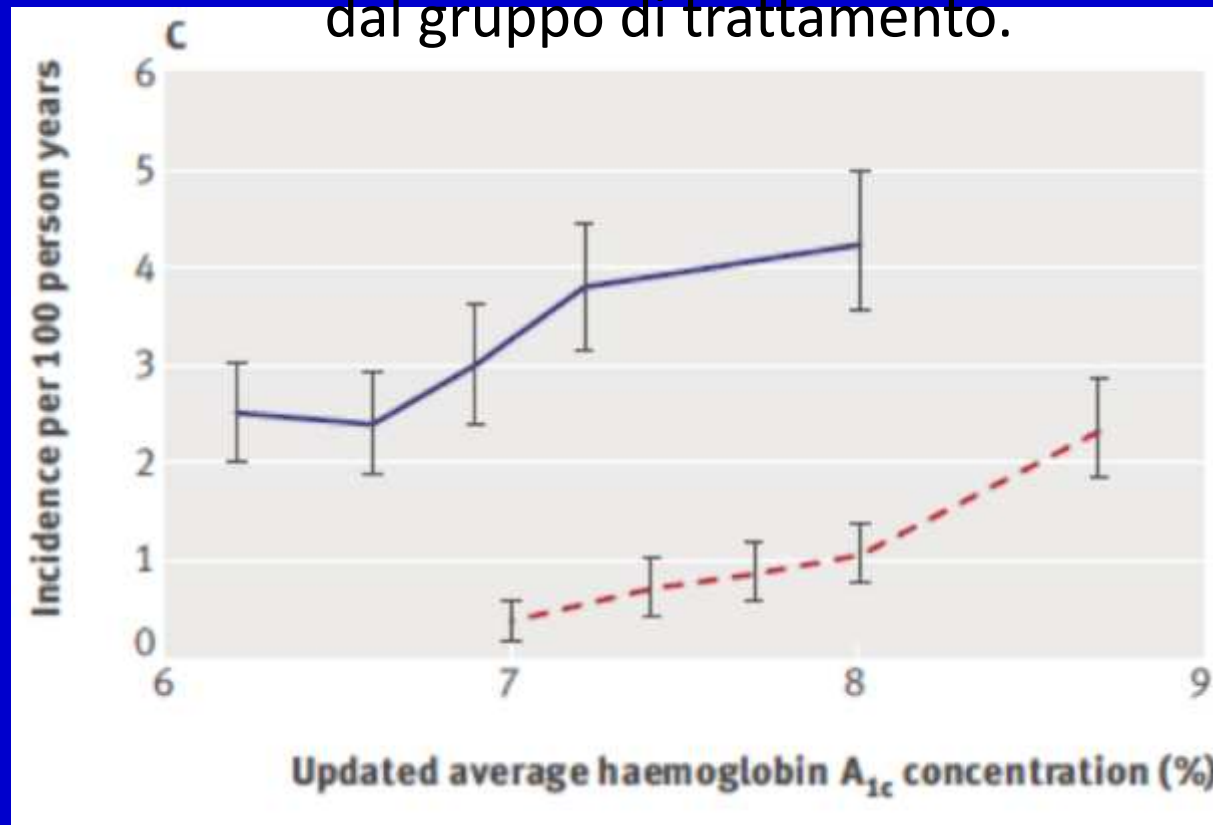
# Rischio di ipoglicemia grave: post hoc analisi epidemiologica dello studio ACCORD

L'incidenza di ipoglicemia grave è stato superiore nel gruppo in trattamento intensivo rispetto al gruppo in terapia standard



## Rischio di ipoglicemia grave: post hoc analisi epidemiologica dello studio ACCORD

I pazienti che avevano uno scarso controllo glicemico hanno presentato un rischio di ipoglicemia maggiore, a prescindere dal gruppo di trattamento.



# The Impact of Frequent and Unrecognized Hypoglycemia on Mortality in the ACCORD Study

ELIZABETH R. SEAQUIST, MD<sup>1</sup>

DAVID C. GOFF JR., MD, PHD<sup>5</sup>

Diabetes 2012



# ACCORD Substudy: Impact of Frequent and Unrecognized Hypoglycemia on Mortality—*Design*

*Subanalysis of subjects from ACCORD cohort (N=10,096) excluding those with frequent or severe hypoglycemic episodes*

At all visits, subjects

- Queried re: episodes of low blood glucose and symptomatic, severe hypoglycemia requiring medical assistance
- Assessed for incidence of hypoglycemic episodes not requiring medical assistance and hypoglycemia unawareness (at each 4-month visit)

Responses analyzed; hazard ratios obtained using Cox proportional hazards regression models.

Models examined:

- (1) annualized number of hypoglycemic episodes
- (2) previous hypoglycemia requiring medical attention
- (3) interaction term between previous hypoglycemia requiring medical attention and annualized number of hypoglycemic episodes
- (4) annualized number of intervals of hypoglycemia unawareness

Each model controlled for baseline covariates that predicted mortality in the ACCORD cohort

ACCORD=Action to Control Cardiovascular Risk in Diabetes.





## ACCORD Substudy: Impact of Frequent and Unrecognized Hypoglycemia on Mortality—Results

	Standard (n=5,051)	Intensive (n=5,045)
<b>≥1 hypoglycemic event requiring medical assistance</b>	n=215	n=565
<b>Mean number of hypoglycemic episodes in 7 days preceding 4-month visit (SMBG &lt;70 mg/dL)</b>	0.29 (SD, 0.49)	1.06 (SD, 0.98)
<b>Hypoglycemia unawareness reported</b>	2.6% of visits	5.8% of visits
<b>Hazard ratio for models including mortality and frequency of hypoglycemic episodes</b>	0.98 (95% CI, 0.91–1.06); <i>P</i> =0.615	0.93 (95% CI, 0.90–0.97); <i>P</i> <0.001

**ACCORD=Action to Control Cardiovascular Risk in Diabetes.**

**CI=confidence interval; SD=standard deviation; SMBG=self-monitoring of blood glucose.**