Ipoglicemia: trattamento e strategie di prevenzione

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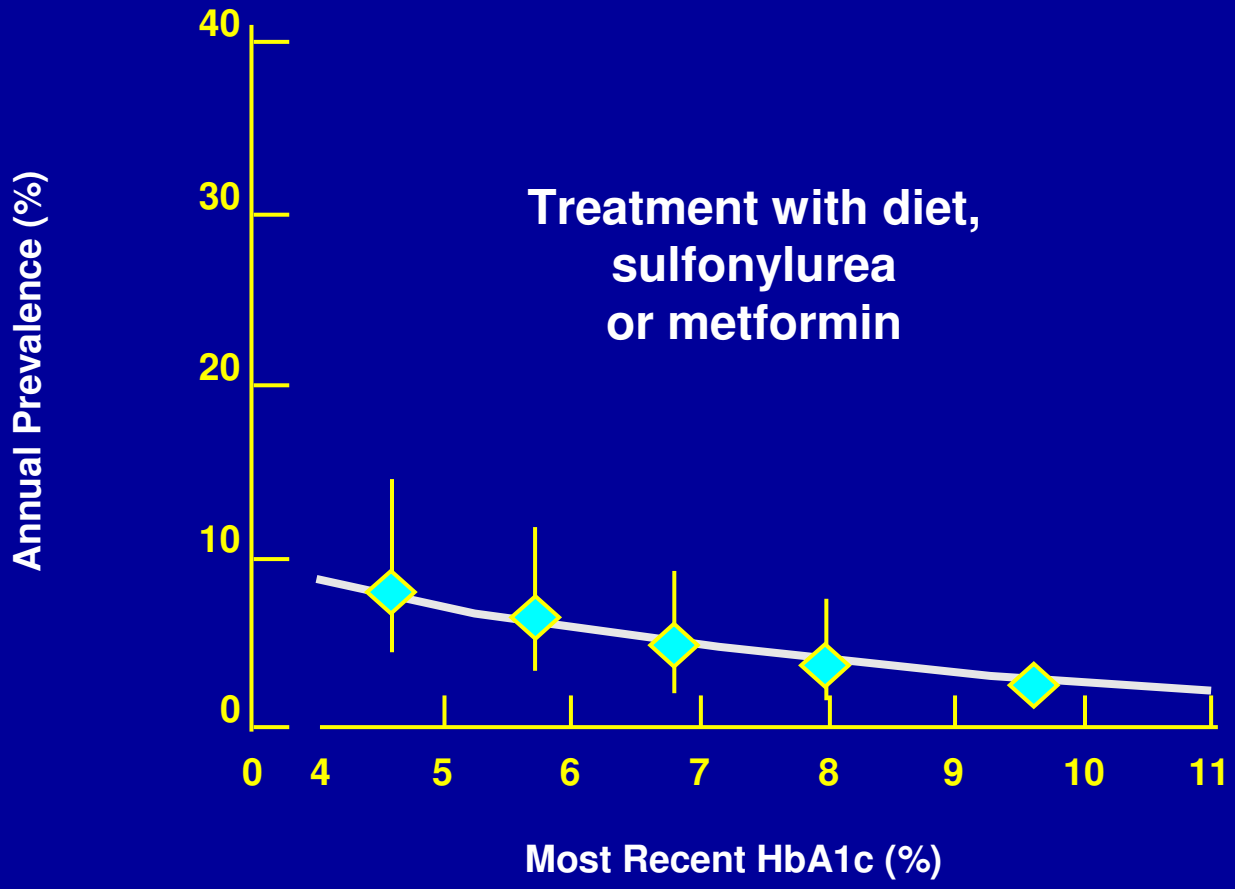
Frequency of Hypoglycemia Increases as HbA1c Declines in Patients with Type 2 Diabetes



Wright et al (2006) J Diabetes Complications 20:395

Classification of Hypoglycemia (Clinical definition)

Defined by individual's ability to self-treat or not

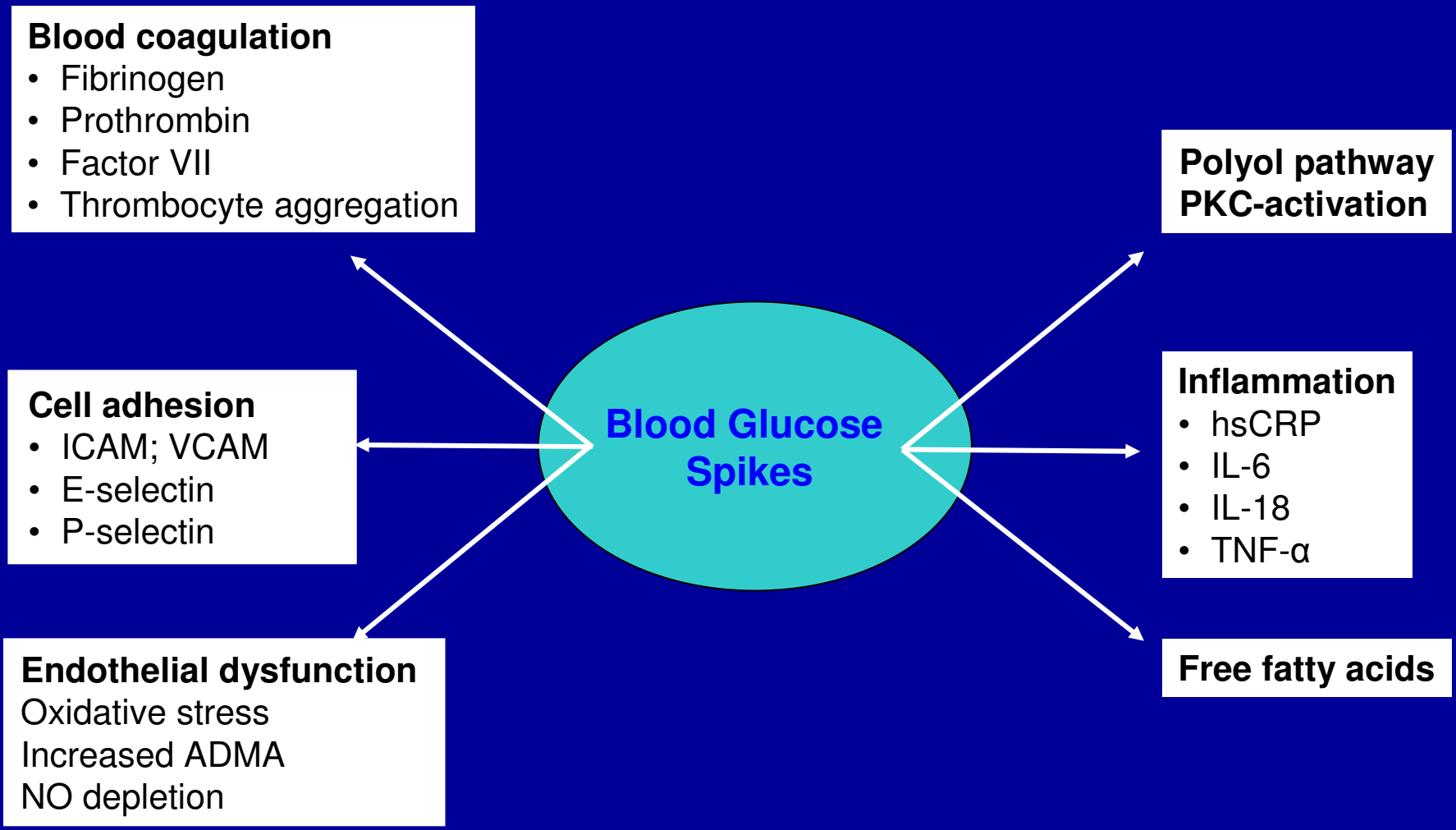
MILD = self-treated

SEVERE = external help required for recovery

Severity is not determined by:

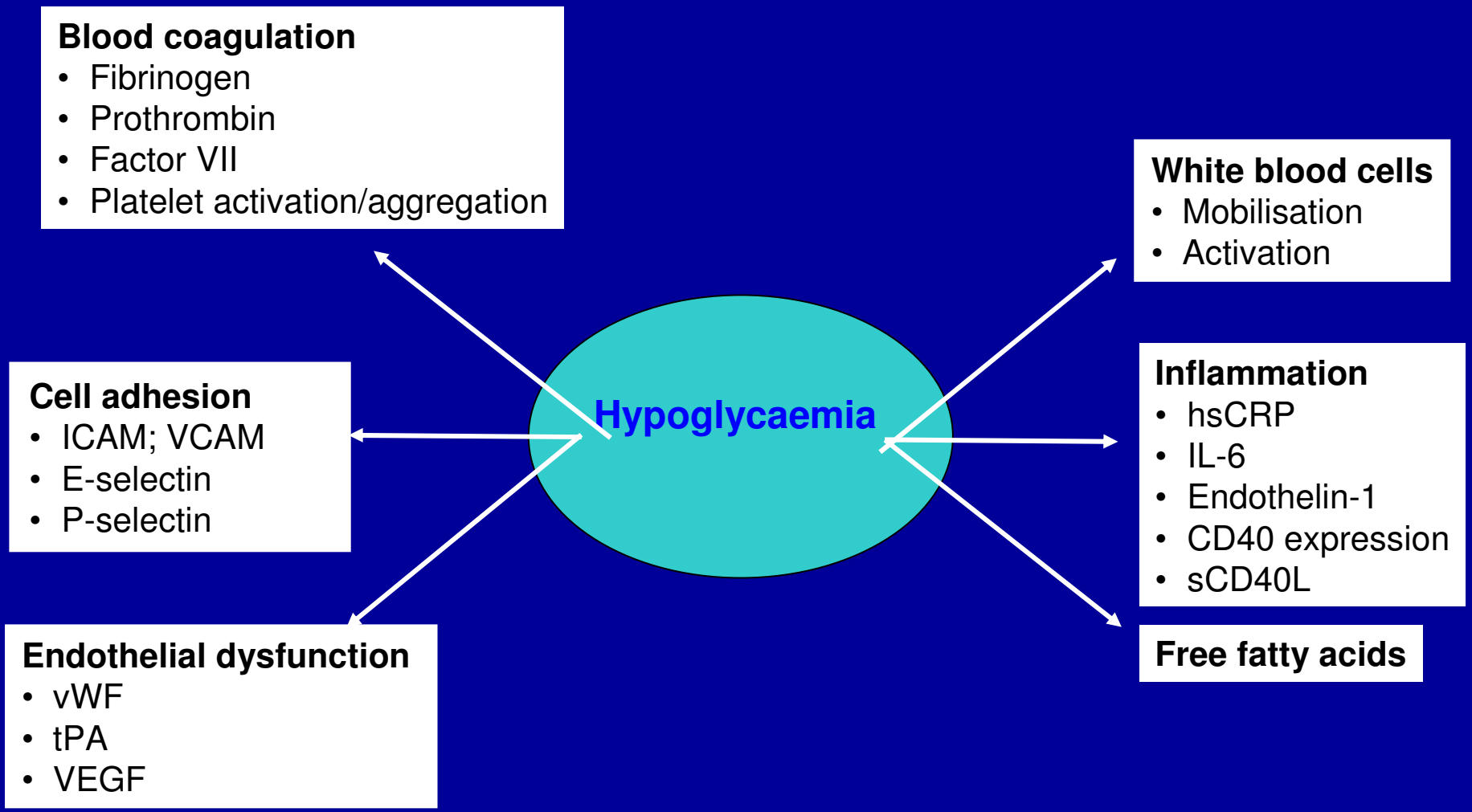
- symptom response
- conscious level
- nature of treatment

Pathophysiology of High Blood Glucose Excursions



ADMA: Asymmetrical dimethyl arginine; hsCRP: high sensitive C-reactive protein; ICAM: Intercellular adhesion molecule; IL: Interleukin; NO: Nitric oxide; PKC: Protein kinase C; TNF: Tumour necrosis factor; VCAM: Vascular cell adhesion molecule.

Pathophysiology of Low Blood Glucose Excursions



hsCRP: high sensitive C-reactive protein; ICAM: Intercellular adhesion molecule; IL: Interleukin; tPA: tissue plasminogen activator; sCD40L: soluble CD40 Ligand; vWF: von Willebrand Factor; VCAM: Vascular cell adhesion molecule; VEGF: Vascular Endothelial Growth Factor.

Hypoglycemia as Pro-atherosclerotic factor

EDITORIAL (SEE P. 1529 AND P. 1591)

Proinflammatory and Prothrombotic Effects of Hypoglycemia

Hypoglycemia is known to be intrinsic to the treatment of diabetes because insulin is a powerful glucose-lowering agent and sulfonylureas exert their effect through insulin release by the pancreatic β-cells. Hypoglycemia occurs in association with these two common modes of therapy and was previously accepted as a part of the treatment of this condition. With the arrival of other modes of diabetes treatment, such as metformin, thiazolidenediones, α2-glucosidase inhibitors, and incretins, which do not induce hypoglycemia except when administered in combination with insulin and sulfonylureas, the issue of hypoglycemia has to be assessed in the context of both the immediate risk related to neuroglycopenia and the possible long-term risk of diabetic vascular complications.

Vascular complications of hypogiycemia have to be tackled with greater urgency now because two recent trials of intensified diabetes treatment with insulin, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial and Veteran's Affairs Diabetes Trial (VADT), did not demonstrate a reduction in cardiovascular events (1,2). In fact, the intensified insulin treatment arm of the ACCORD trial had to be halted because of an increase in overall mortality, despite a reduction in acute myocardial infarction. The rate of hypoglycemia in both trials was significantly increased with intensified insulin treatment. Although the analysis of the ACCORD data did not support the hypothesis that the increased mortality in the study was a result of hypoglycemia, the fact that hypoglycemia may often be asymptomatic leaves us with the possibility that it may be responsible.

The fact that hypogiycemia results in platelet hyperaggregability (3) and an increase in several factors involved in the coagulation cascade has been known for over 2 decades. Activated partial thromboplastin time is shortened, fibrinogen and factor VIII increase, and platelet counts fall in association with hypoglycemia (4). More recently, two studies have shown that hypoglycemia induces proinflammatory changes including an increase in the plasma concentration of interleukin (IL)-6 (5) and increases in other proinflammatory mediators, including leucocytosis, reactive oxygen species (ROS) generation, lipid peroxidation, and levels of tumor necrosis factor-α (TNFα), IL-1β, and IL-8 (5). Two studies published in this issue of *Diabetes Care* confirm that hypoglycemia does, indeed, induce an increase in proinflammatory mediators and platelet activation, and has an inhibitory effect on fibrinolytic mechanisms. Wright et al. (6) and Gogitidze Joy et al. (7) both used an insulin infusion to gradually induce hypoglycemia and then clamped glucose at hypoglycemic levels of 2.5 and 2.9 mmol/l, respectively. The former maintained hypoglycemia for 60 min while the latter maintained it for 120 min. As is evident from the data, the effects of the longer duration of hypoglycemia in the study by Gogitidze Joy et al. are more impressive as reflected in the increase in proinflammatory mediators, in spite of the fact that glucose concentrations were not as low as those in the study by Wright et al. The increases in the indexes of inflammation and oxidative stress in the study by Razavi Nematollahi et al. (5) were even more impressive, probably because the mode of induction of hypoglycemia was by a bolus intravenous injection, which led to a rapid fall in blood glucose concentrations leading to a rapid release of catecholamines and the stimulation of the inflammatory response. In the study by Wright et al., hypoglycemia induced an increase in CD40 expression on mononuclear cells and plasma concentration of CD40L, as well as an increase in platelet-monocyte aggregates and P-selectin concentrations with a trend toward an increase in von Willebrand factor concentrations. In the study by Gogitidze Joy et al., hypoglycemia led to an increase in intercellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM), P-selectin, and E-selectin, as well as plasminogen activator inhibitor-1 (PAI-1). TNFα, IL-6, and vascular endothelial growth factor (VEGF).

Both of these studies included control arms in which the effect of insulin infusions administered at the same rates as above were investigated while maintaining glucose concentrations in the normal range through the appropriate titration of glucose infusion rates. Both studies confirmed the presence of an anti-inflammatory effect of insulin during infusions when euglycemia was maintained (8). Again, the anti-inflammatory effects of insulin were more impressive in the study by Gogitidze Joy et al. because they maintained the infusion of insulin for 120 min, whereas the study by Wright et al. infused insulin for only 60 min. Previous work has consistently shown impressive anti-inflammatory effects of insulin infused for 120 min or more (8). Thus, in situations where insulin infusions are used for the anti-inflammatory and cardioprotective actions of insulin, extreme care has to be exercised because hypoglycemia reverses the effects of euglycemic hyperinsulinemia. It is of interest that hypoglycemia exerts proinflammatory effects similar to those of hyperglycemia and glucose intake (9,10).

Clearly, hypoglycemia results in the induction of rapid inflammatory, platelet proaggregatory, antifibrinolytic, and prothrombotic responses. This effect of hypoglycemia overrides the anti-inflammatory, antiplatelet, and profibrinolytic effects of insulin observed under euglycemic conditions. In addition, there is also an increase in ROS generation and lipid peroxidation, reflecting oxidative stress. Although the hypoglycemic episodes are transient, repeated occurrences of such episodes may have cumulative effects that are detrimental to inflammation-based processes such as atherogenesis and its thrombotic complications. These detrimental effects would add to the previously demonstrated relationship between both silent and symptomatic hypoglycemia on cardiac angina. In one study involving diabetic patients with coronary heart disease who were continuously monitored for blood glucose concentrations and electrocardiographic changes, it was demonstrated that there was chest pain associated with hypoglycemia in 20% of the patients, of whom 40% had concomitant electrocardiogram (ECG) changes consistent with ischemia (11).

DIABETES/METABOLISM RESEARCH AND REVIEWS
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REVIEW ARTICLE

Vascular disease and diabetes: is hypoglycaemia an aggravating factor?

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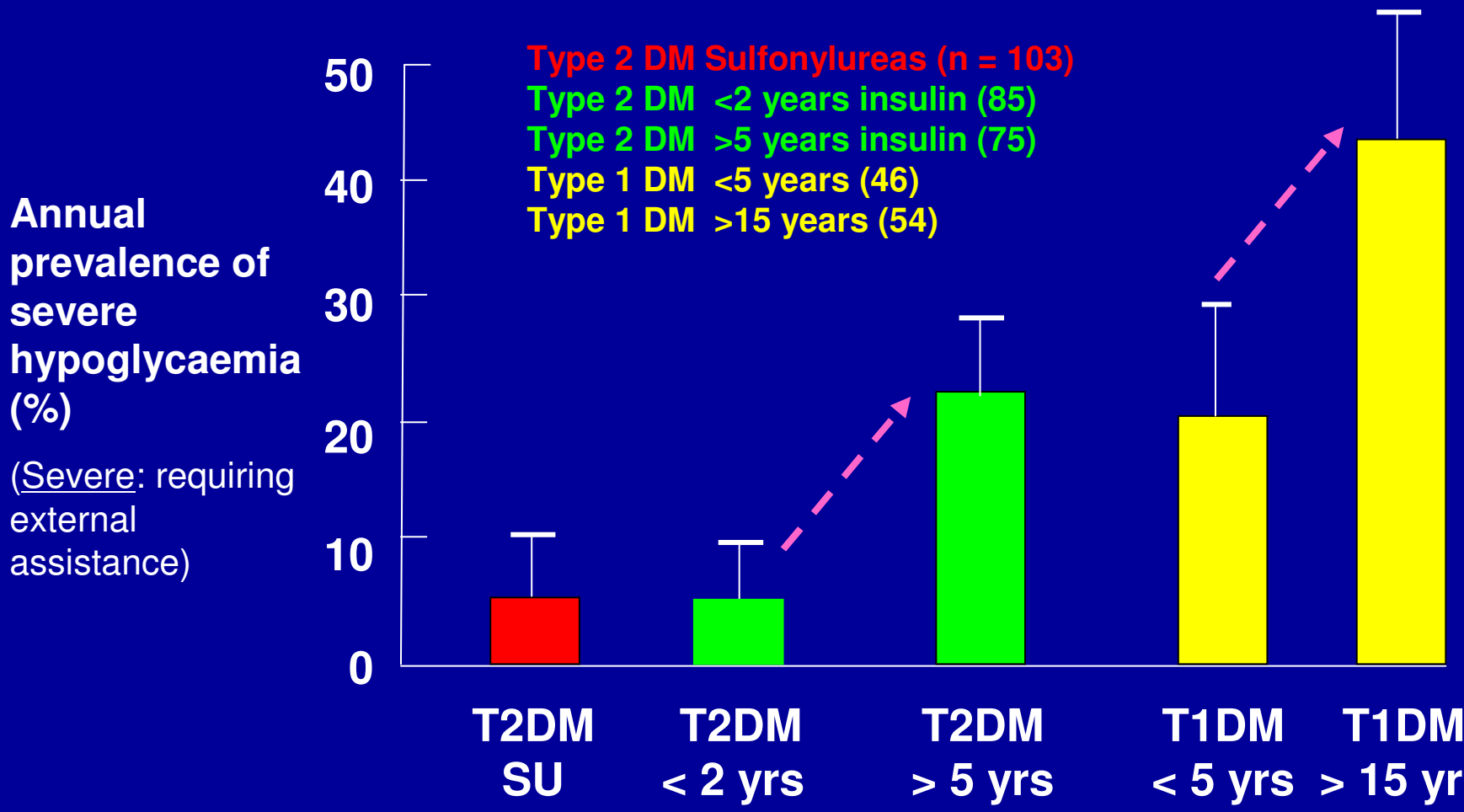
Summary

Acute hypoglycaemia provokes profound physiological changes affecting the cardiovascular system and several haematological parameters, principally as a consequence of sympatho-adrenal activation and counter-regulatory hormonal secretion. Many of these responses have an important role in protecting the brain from neuroglycopenia, through altering regional blood flow and promoting metabolic changes that will restore blood glucose to normal. In healthy young adults the cardiovascular effects are transient and have no obvious detrimental consequences. However, some of the effected changes are potentially pathophysiological and in people with diabetes who have developed endothelial dysfunction, they may have an adverse impact on a vasculature that is already damaged. The acute haemodynamic and haematological changes may increase the risk of localized tissue ischaemia, and major vascular events can certainly be precipitated by acute hypoglycaemia. These include myocardial and cerebral ischaemia and occasionally infarction. Established diabetic retinopathy often deteriorates after strict glycaemic control is instituted, the latter being associated with a threefold increase in frequency of severe hypoglycaemia, and enhanced exposure to mild hypoglycaemia. The possible mechanisms underlying these hypoglycaemia-induced effects include haemorrheological changes, white cell activation, vasoconstriction, and the release of inflammatory mediators and cytokines. The concept that acute hypoglycaemia could aggravate vascular complications associated with diabetes is discussed in relation to evolving comprehension of the pathogenesis of atherosclerosis and blood vessel disease. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords diabetes; hypoglycaemia; coagulation; inflammation; vascular complications

Hypoglycaemia is a common and much feared side effect of insulin treatment for diabetes, and is the major barrier to achieving and maintaining optimal glycaemic control. Strict glycaemic control using intensive insulin therapy increases the risk of severe hypoglycaemia threefold [1]. Despite the frequency of this metabolic problem, the short-term consequences of exposure to hypoglycaemia are not fully elucidated. Although the immediate effects on the brain affecting cognition, mood, and conscious level are widely recognized, it is often overlooked that hypoglycaemia also exerts profound effects on various constituents of the blood and on the vasculature. Although the effects are transient and unlikely to exert any long-term consequences on a healthy circulation, the potentially deleterious effects on a damaged vasculature should be considered. People with diabetes have an increased risk of developing vascular disease, and many have established micro- and macrovascular complications of varying severity. Figure 1 depicts the

Frequency of Severe Hypoglycaemia in Types 1 and 2 Diabetes

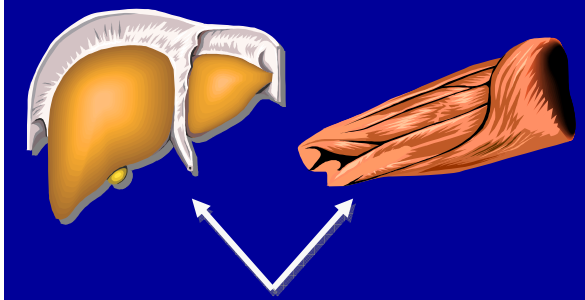


Error bars = 95% confidence intervals

Adapted from: *UK Hypoglycaemia Study Group (2007) Diabetologia 50:1140.*

Options for Antidiabetic Treatment

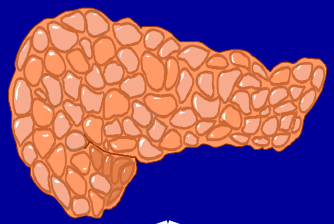
Insulin Resistance



Metformin

Pioglitazone

Insulin Secretion



Glucose independent

Sulfonylurea

Glinides

Exogenous Insulin

Glucose dependent

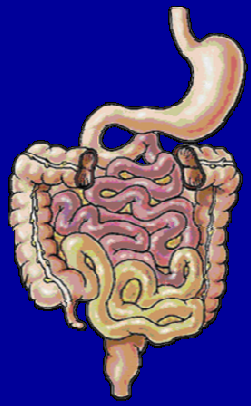
DPP-4 Inhibitors (Alogliptin, Linagliptin, Saxagliptin, Sitagliptin, Vildagliptin)

GLP-1 RA (Exenatide, Liraglutide, Lixisenatide)

Canaglifozin

Dapagliflozin

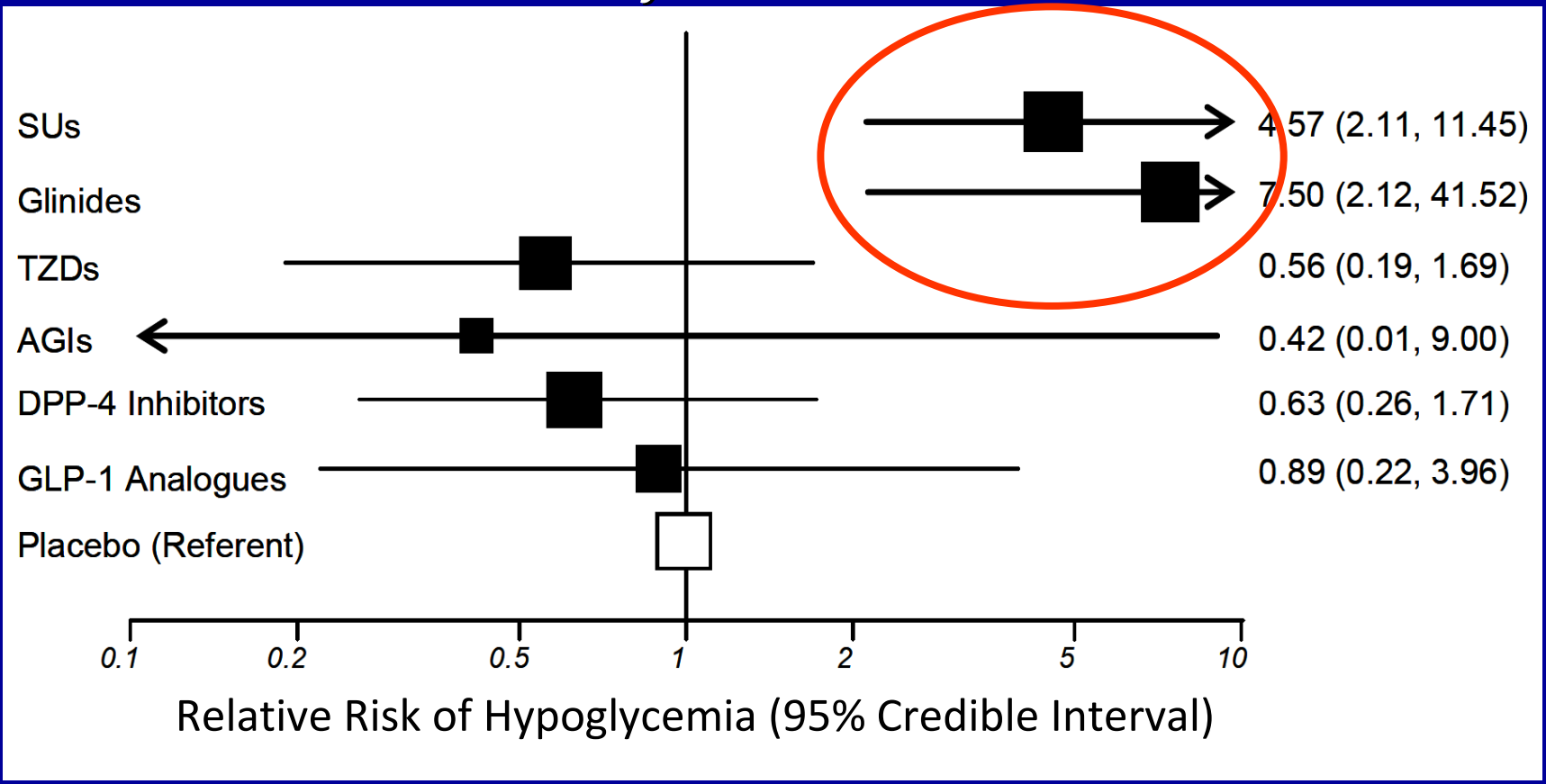
Inhibition of Glucose Absorption



α-Glucosidase Inhibitors (Acarbose,)

Combination Therapy with Non-insulin Antidiabetes Drugs: Hypoglycaemia Risk

Meta-analysis of Mixed Treatment Analysis of 24 trials

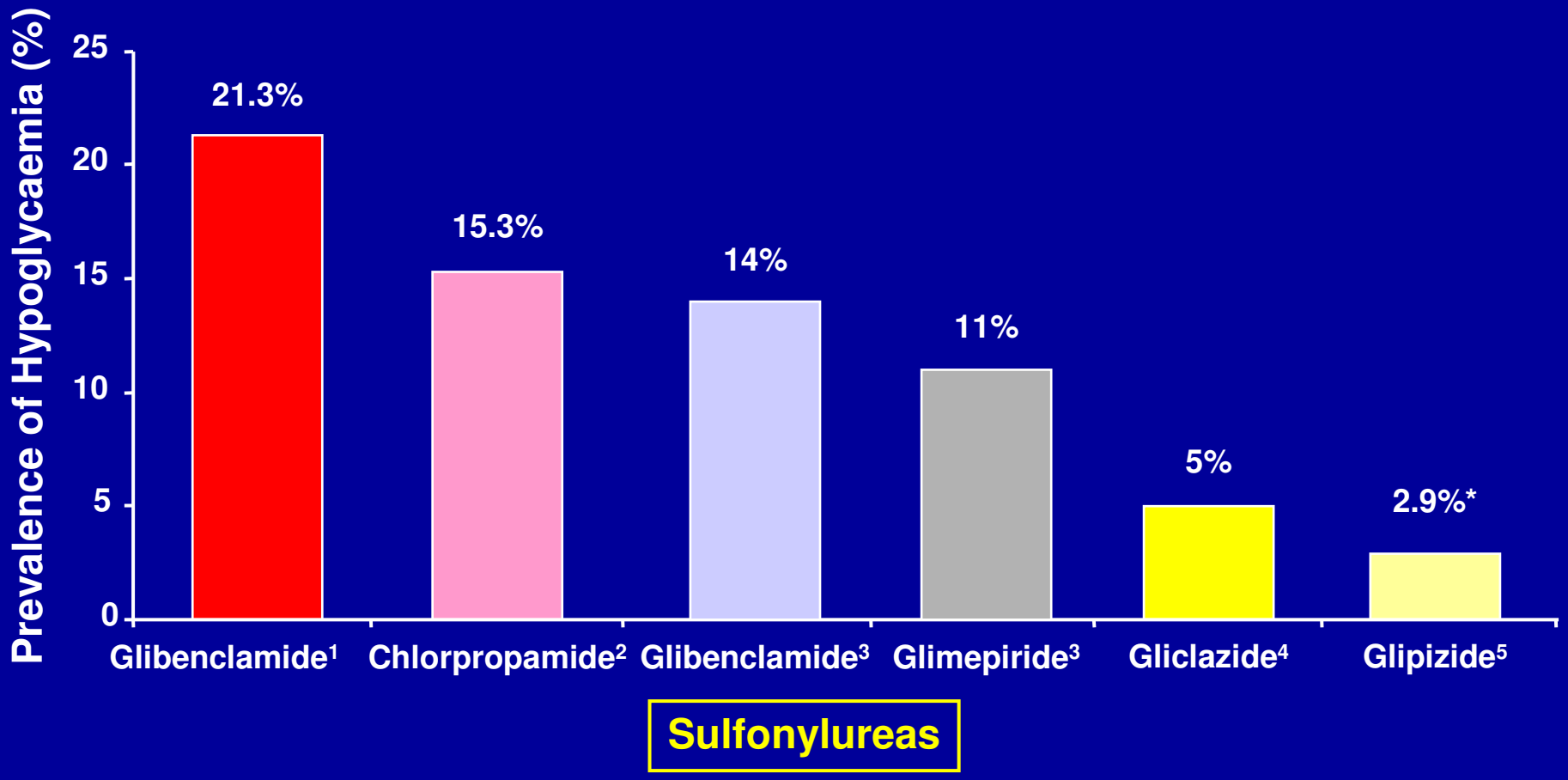


Phung et al, 2010 JAMA 303: 1410

Hypoglycaemia and Sulfonylureas

- Severe hypoglycaemia is more likely to occur within the first month of treatment *(Asplund K et al. (1983) Diabetologia **24:**412. Bodmer M et al. (2008) Diabetes Care **31:**2086)*
- Hypoglycaemia occurs more commonly when patients are treated with low doses (more sensitive to effect of drug)
- Hypoglycaemia is more common with long-acting preparations like glibenclamide
- Coma and serious morbidity occur secondary to sulfonylurea-induced hypoglycaemia *(Asplund K et al. (1983) Diabetologia **24:**412. Asplund K et al. (1991) Diabet Med **8:**726. Malouf & Brust, (1985) Ann Neurol **17**: 421)*

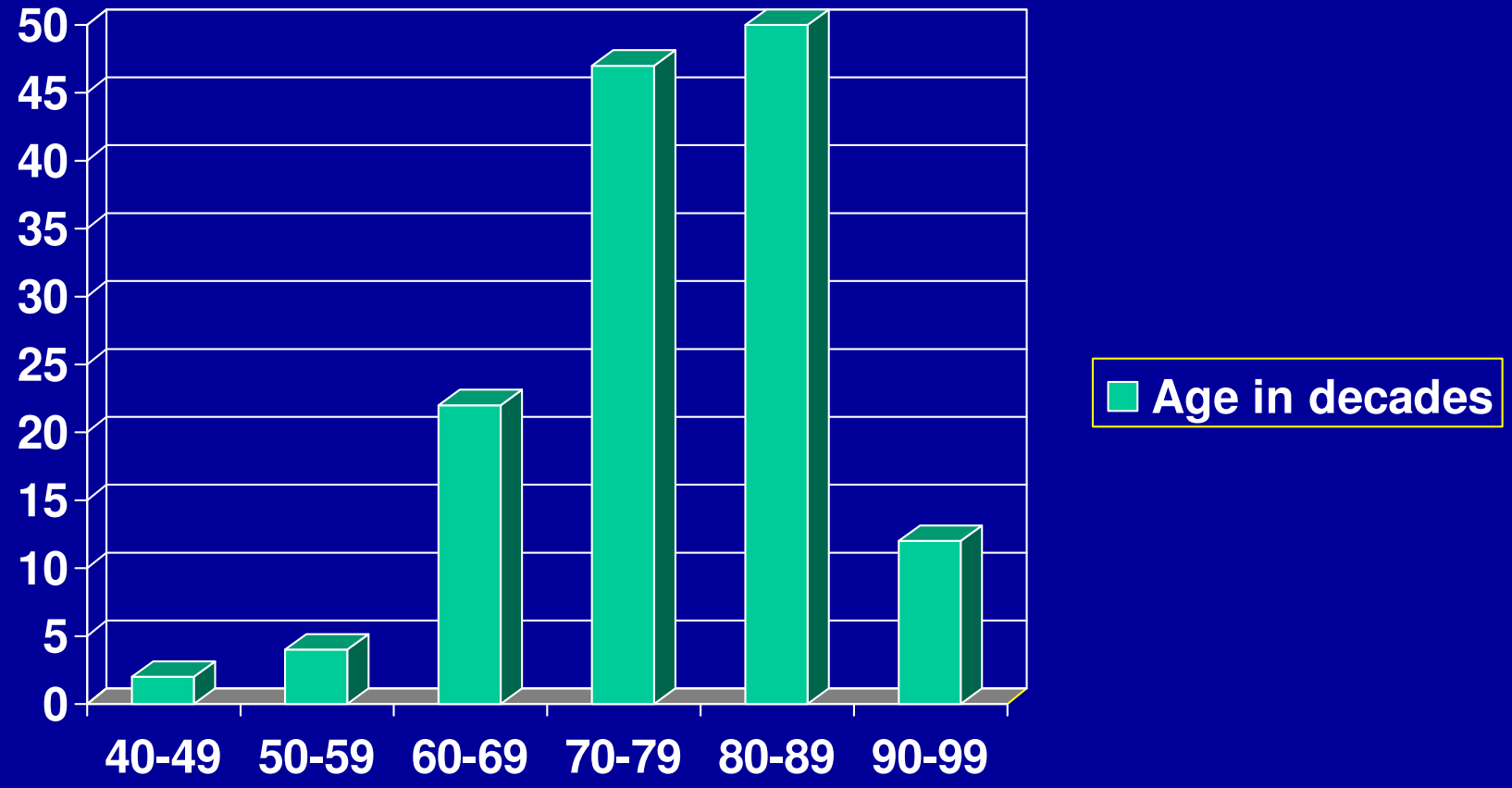
Hypoglycaemia Associated With Sulfonylureas



***Hypoglycaemia: capillary blood glucose <2.75 mmol/L (≤50 mg/dL)**

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

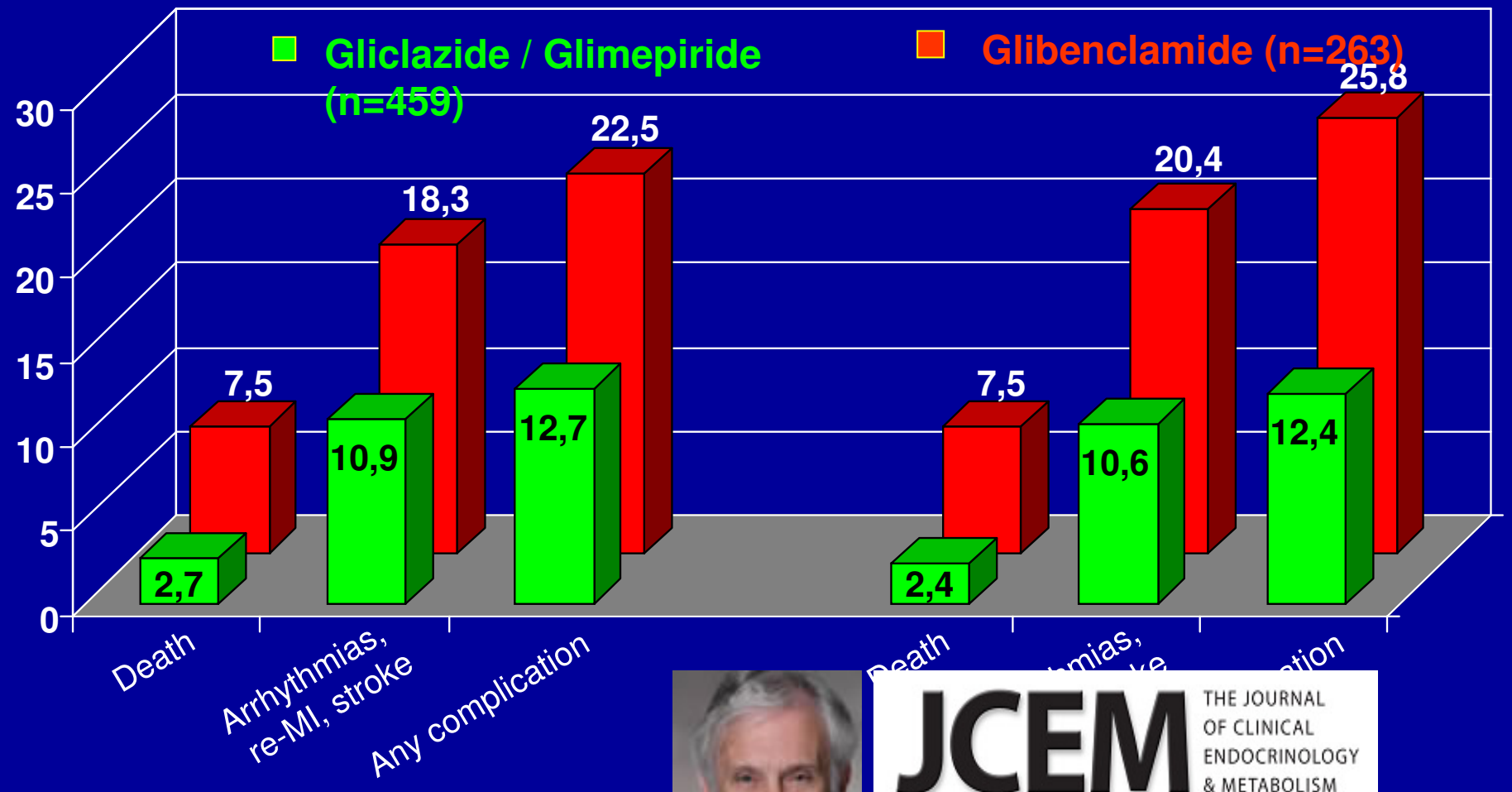
Age Distribution of Patients with Type 2 Diabetes with SU-induced Hypoglycaemia (n=139)



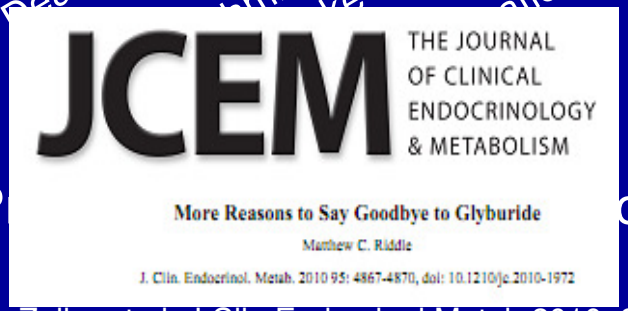
One third of cases were patients in nursing homes or being cared for by a home nursing service

Holstein et al (2010) Expert Opinion Drug Safety 9: 675

Impact of Type of previous Sulfonylurea Therapy on Mortality and CV Outcomes in Diabetic Patients with Acute Myocardial Infarction



Patients on previous sulfonylurea therapy



ohorts

Zeller et al. J Clin Endocrinol Metab 2010; 95:4993-5002

Effects of oral antidiabetic Drugs on HbA1c, Hypoglycemic Events & Weight Gain in 4 randomisied double blind large Studies (Quartet)

	Number of Patients	HbA1c (%)	Hypoglycemia (%)	Weight Change (kg)	Weight Difference (kg)
[1] Metformin	597	-1,5	1,3	-2,5	4,4
[1] Pioglitazone	597	-1,4	1.5	+1,9	
[2] SU	626	-1,35	10.1	+1.9	0,9
[2] Pioglitazone	624	-1,43	3.5	+2.8	
[3] Metformin + Pioglitazone	317	-1,5	1.3	+1,5	0,1
[3] Metformin + SU	317	-1,4	11.2	+1,4	
[4] SU + Pioglitazone	319	-1,35	10.7	+2,8	3,8
[4] SU + Metformin	320	-1,43	14.1	-1,0	

SU = Sulfonylureas

[1] Schernthaner et al; JCEM 2004; 89:6068

[2] Charbonell et al; Diabet Med. 2005; 22:399

[3] Matthews et al; Diab.Metab Res.Rev.2005; 21:167

[4] Hanefeld et al; Diab.Care 2004;27:141

IDF Statement on Personalized Targets and Care in the Glycaemic Management of People with Type 2 Diabetes

Properties of currently available blood glucose lowering agents

	AGIs	Metformin	SUs	Glinides	TZDs	DPP-Inhibitors	GLP 1-agonists	Insulin
Effect on fasting glucose*	0	+++	+++	+	+++	+	+++	++++
Effect on post prandial glucose*	+++	+	++	+++	+	+++	+++	++++
Weight**	0	0	++	+	+++	0	-	++++
Hypoglycemia risk§	0	0	+++	++	+	0	+	++++
Side effects§	++	+	0	0	++++	+	++	0
Cost***	++	+	+	+++	++	+++	++++	variable
Global availability#	++	++++	++++	+	++	+	+	++++
Experience with the medication#	++	++++	++++	++	++	+	+	++++

***Effect:** 0 = neutral; + = mild; ++ = moderate; +++ = moderate to marked; ++++ = marked

****Effect:** - = favourable; 0 = neutral; + = mild gain; ++ = moderate gain; +++ = moderate to marked gain; ++++ = marked gain

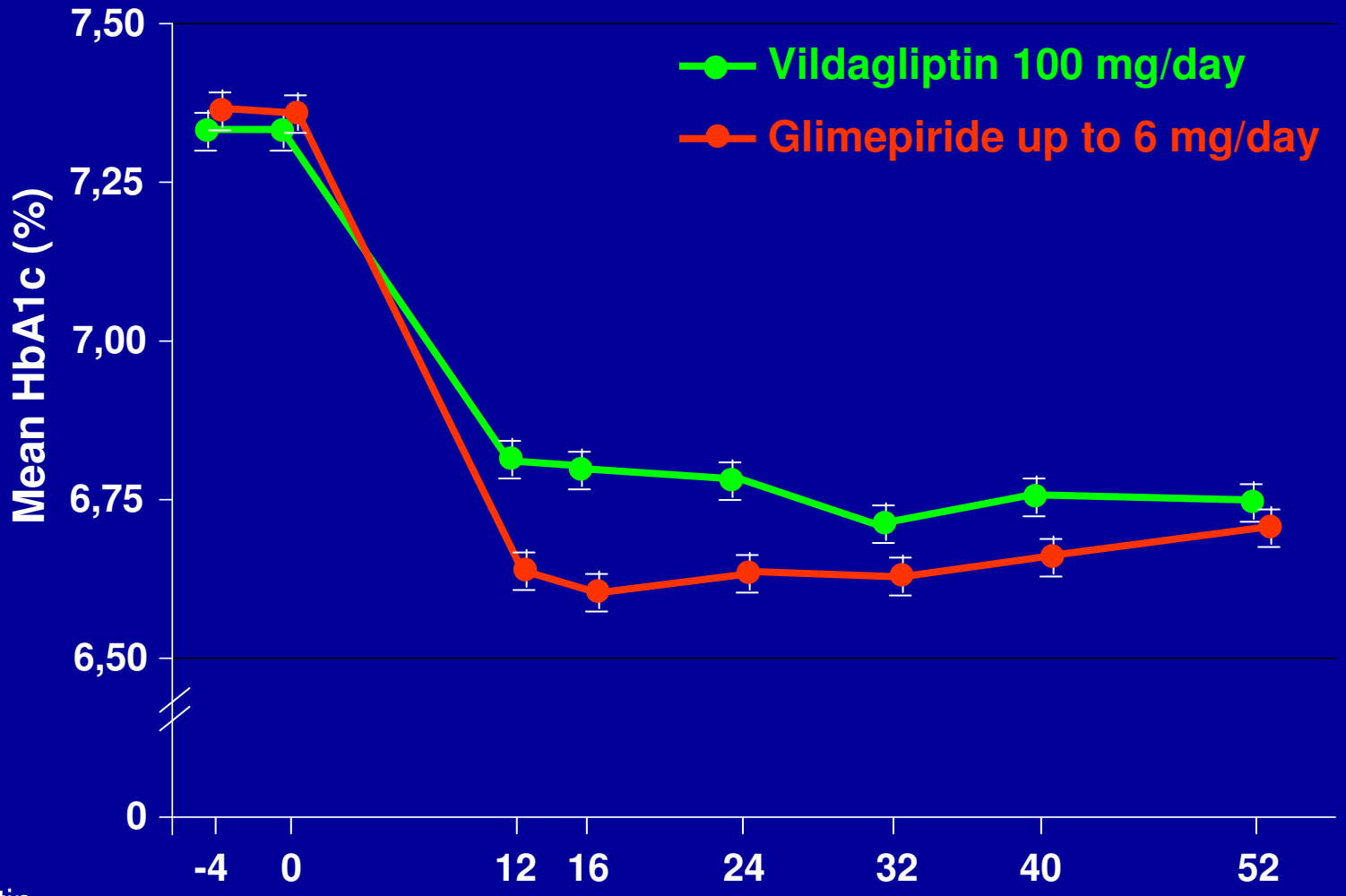
§Risk: 0 = neutral; + = mild; ++ = moderate; +++ = moderate to marked; ++++ = marked

*****Cost:** + = cheap; ++ = quite cheap; +++ = expensive; ++++ = very expensive

#Availability and experience: + = very small; ++ = small; +++ = high; ++++ = very high

There needs to be unequivocal cost-effectiveness advantages to justify the use of more expensive therapies, especially in poor countries

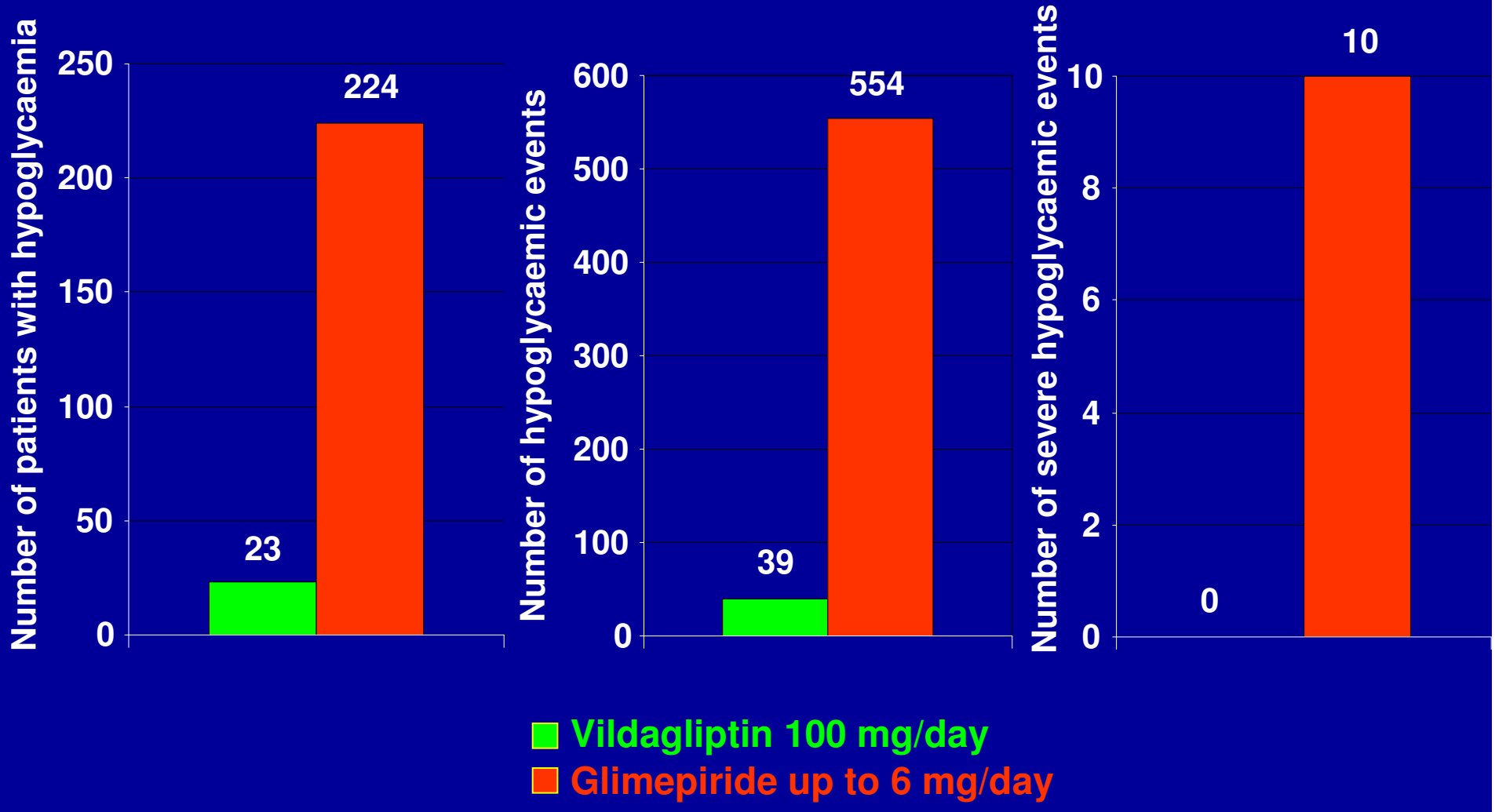
Changes of mean HbA1c by treatment and visit: Vildagliptin or Glimepiride add-on to Metformin



Vildagliptin 100 mg/day n =	1118	1081	1062	1081	1037	1023	992
Glimepiride up to 6 mg/day n =	1072	1042	1011	1039	1001	989	976

Ferrannini et al. Diabetes, Obesity and Metabolism 2009; 11:157-166

Incidence and Severity of Hypoglycaemic Events with Vildagliptin or Glimepiride during the 52 week treatment period

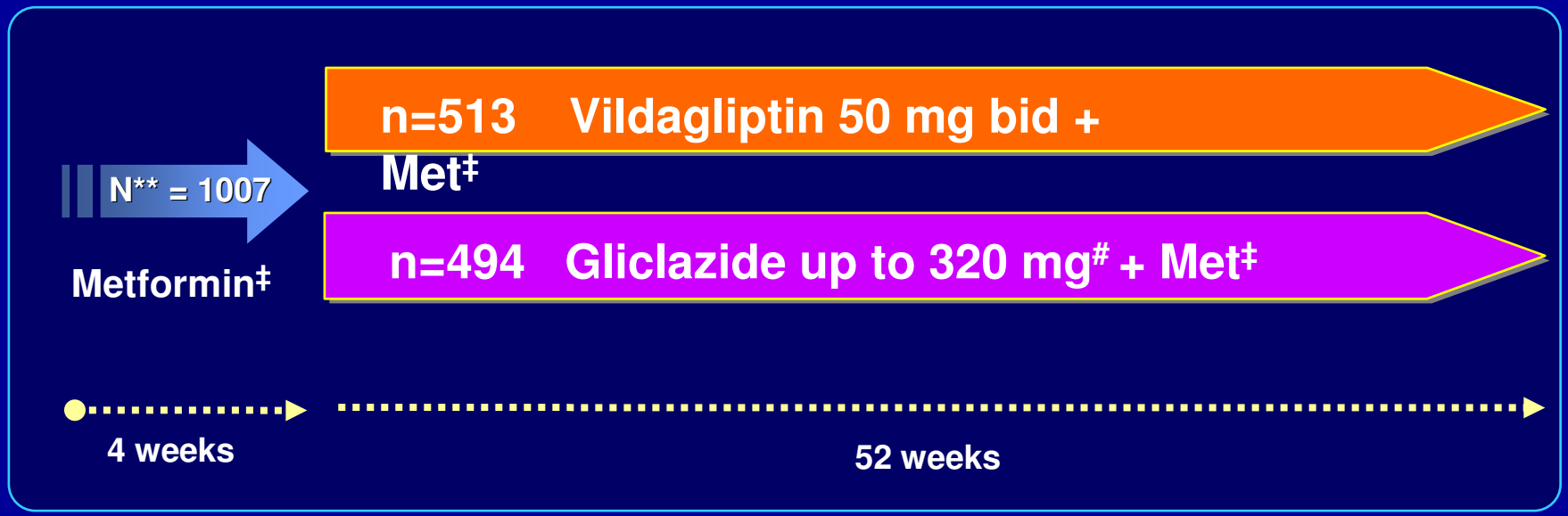


Ferrannini et al. Diabetes, Obesity and Metabolism 2009; 11:157-166

Vildagliptin vs. gliclazide as add on to metformin

Study purpose: to compare the effect of 52 weeks treatment with Vidagliptin 50 mg bid to gliclazide up to 320 mg daily as add-on therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy

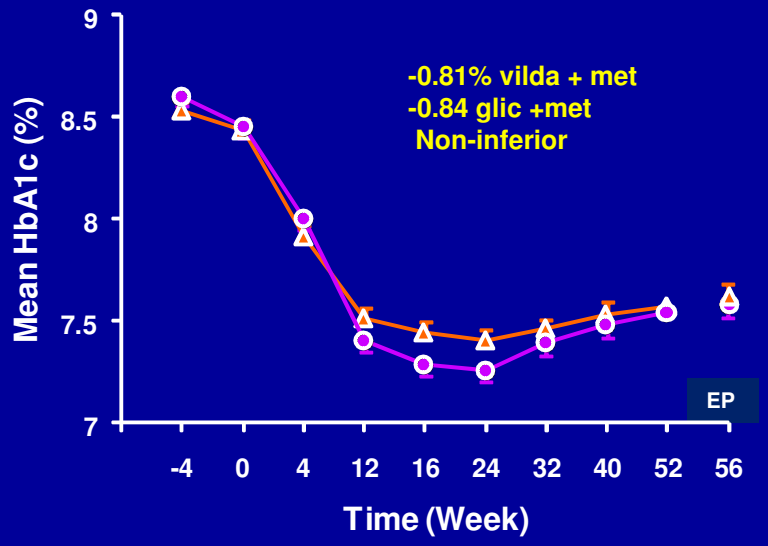
Target population: T2DM patients inadequately controlled on a stable metformin monotherapy (baseline HbA1c 7.5-11%)



Filozof and Gautier. *Diabetes Medicine.* 2010; 27: 318-326.

Vildagliptin provides similar HbA1c reduction as gliclazide but with a better tolerability profile

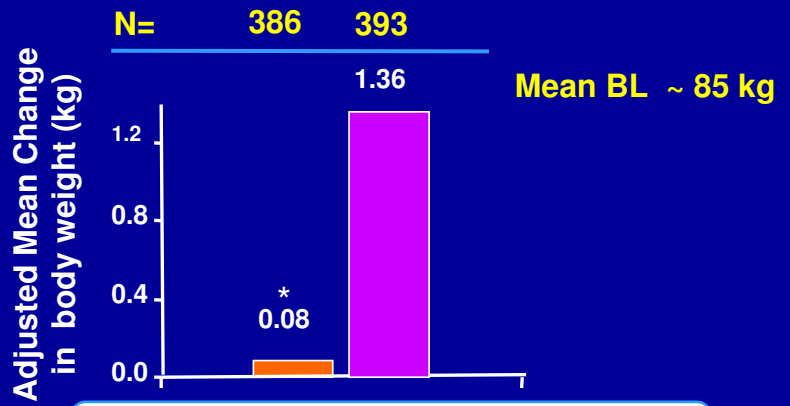
Mean HbA1c



Mean difference of adjusted values:
0.04% 95%CI: -0.11, 0.20

Vilda 50 mg bid + Met
Glic up to 320 mg + Met

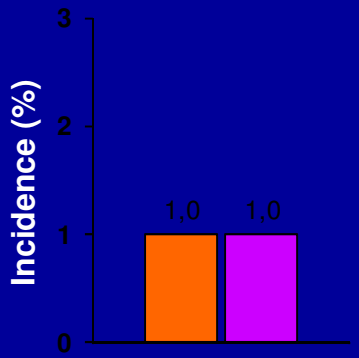
Change Body weight[b] from BL to week 52



Hypoglycemic events[c]

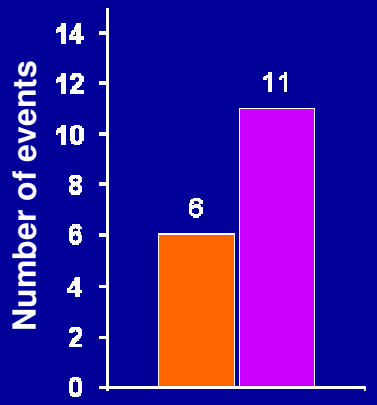
Patients with one or more hypos (%)

n/N= 5 / 510 5 / 493



Number of hypoglycemic events#

N= 510 493



Glic= gliclazide; Met= metformin; Vilda= vildagliptin; BL= baseline; EP= end point; * p<0.001 Vilda vs Glic, 95% CI (-1.77, -0.79), adjusted mean change from BL to EP; b) per protocol population; c) safety population;
# All hypoglycemic events: grade 1

Filozof and Gautier. *Diabetes Medicine.* 2010; 27: 318-326.

Addition of Sitagliptin to Rosiglitazone and Metformin Study: Incidence of Hypoglycemia at 54 Weeks

All-Patients-as-Treated Population[a]

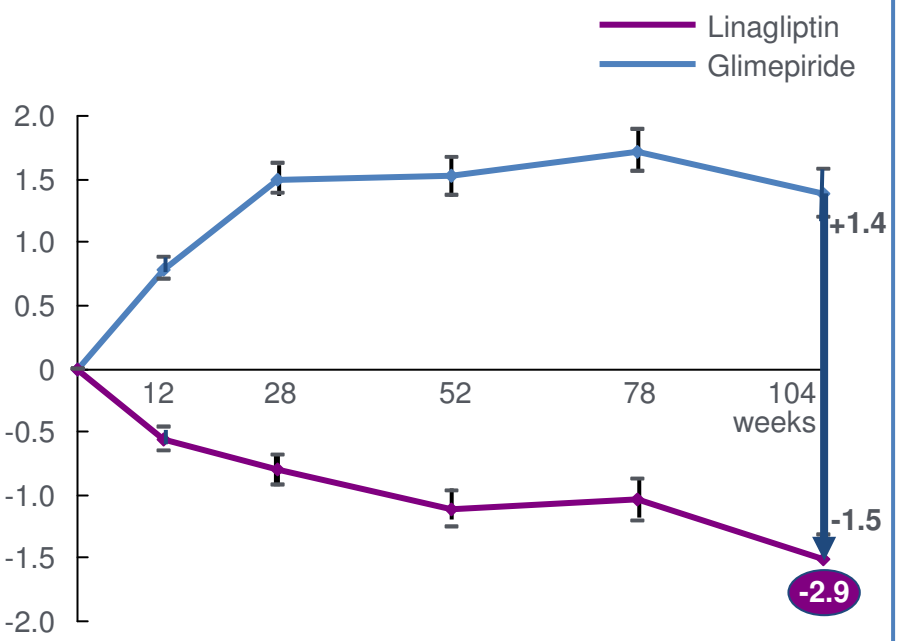
Treatment Group	N	Patients With ≥1 Episode, n (%)	Total Number of Episodes, n
Sitagliptin 100 mg	170	7 (4.1)	10
Placebo	92	1 (1.1)	1

[a]Excluding data after initiation of glycemic rescue therapy.

Data on file, MSD.

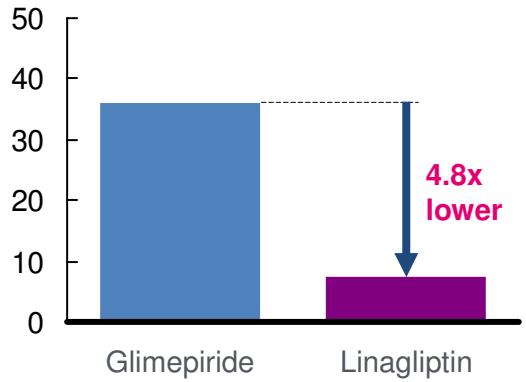
Significant relative weight loss and lower incidence of hypoglycemia with linagliptin compared to glimepiride

Adjusted[1] means for body weight change from baseline ± SE
Kg - FAS (OC)



Significant relative weight loss with linagliptin as compared to glimepiride (p-value < 0.0001)

Incidence of hypoglycemia[2]
Percent of patients - Treated set



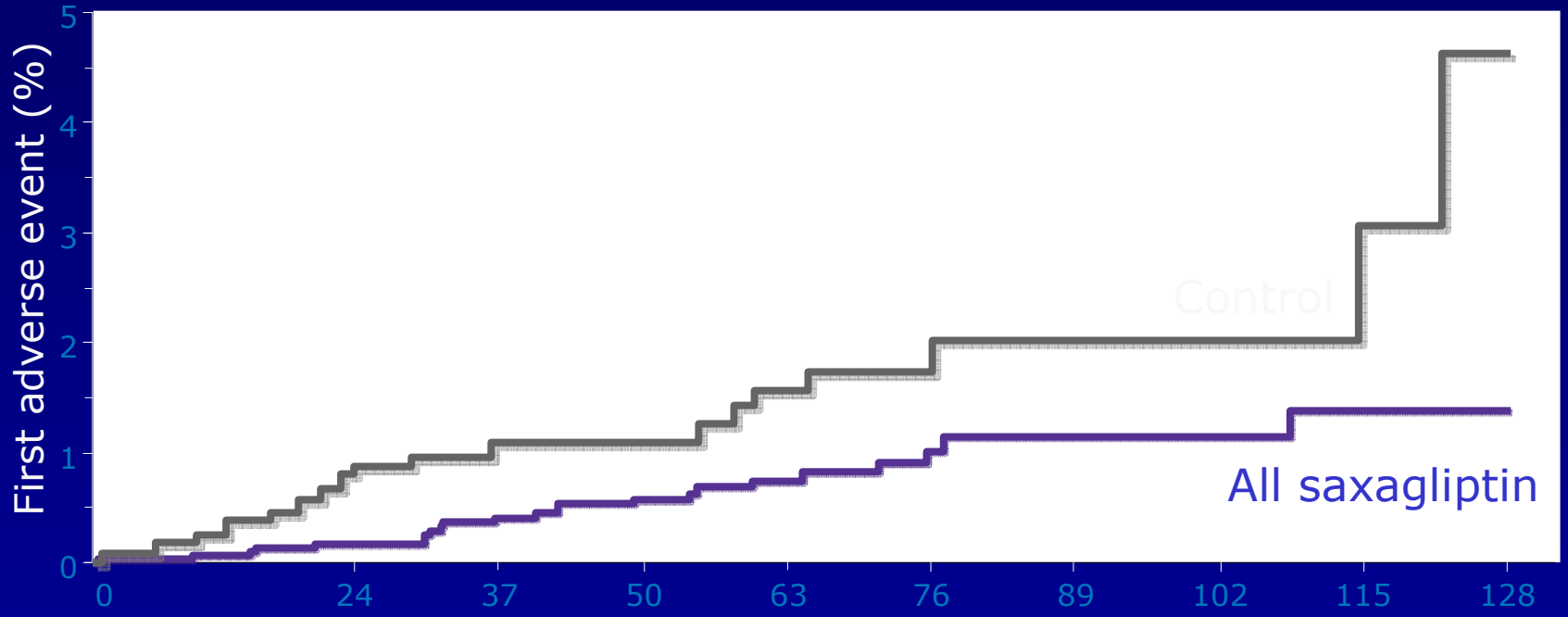
	Glimepiride	Linagliptin
Number of patients	775	776
Number of patients with hypoglycemia (% of total)	280 (36.1)	58 (7.5)
Patients with severe hypoglycemic episode[3] (% of patients with hypoglycemia)	12 (4.3)	1 (1.7)

Significantly lower incidence of hypoglycemia with linagliptin as compared to glimepiride (p-value < 0.0001)

1 Model includes baseline HbA1c, baseline weight, number of prior OADs, treatment, week repeated within patients and week by treatment interaction
2 Hypoglycemic episode defined by a blood glucose ≤70 mg/dl
3 Event requiring assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions
Source: Gallwitz et al. American Diabetes Association, 71th Scientific Sessions, San Diego, CA, June 24-28, 2011; 39-LB

Cardiovascular events: Saxagliptin controlled Phase 2b/3 pooled population

Time to onset of first primary Major Adverse Cardiovascular Event (MACE)



Patients at risk

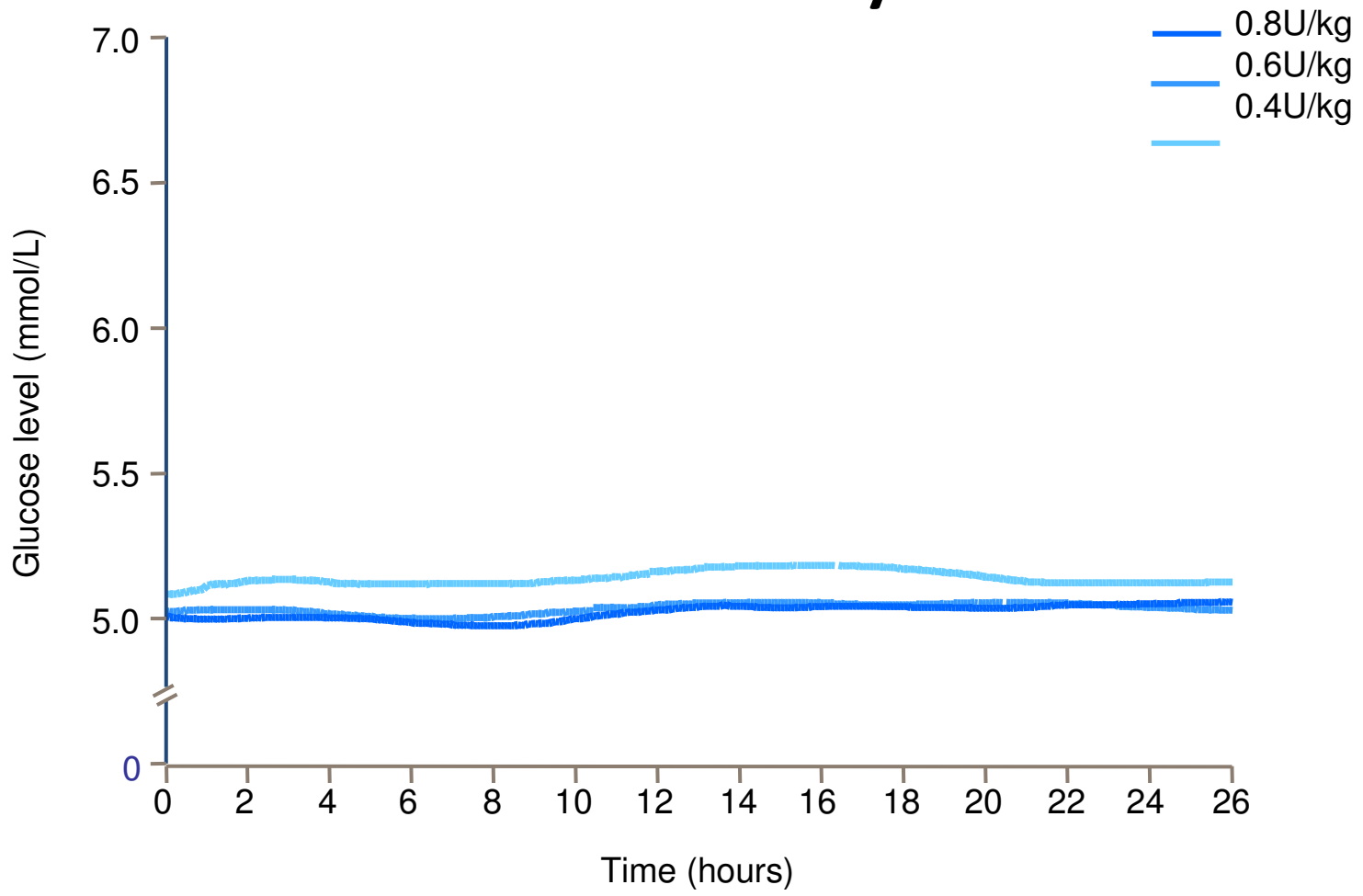
Control	1,251	935	860	774	545	288	144	123	102	57
All saxagliptin	3,356	2,615	2,419	2,209	1,638	994	498	436	373	197

Saxagliptin, FDA's Endocrinologic and Metabolic Drugs Advisory Committee Briefing Document for April 2009 Meeting: NDA 22-350. Available at http://www.fda.gov/OHRMS/DOCKETS/ac/09/briefing/2009-4422b1-02-Bristol.pdf. Accessed: 7 May, 09.

Objectives of developing IDeg

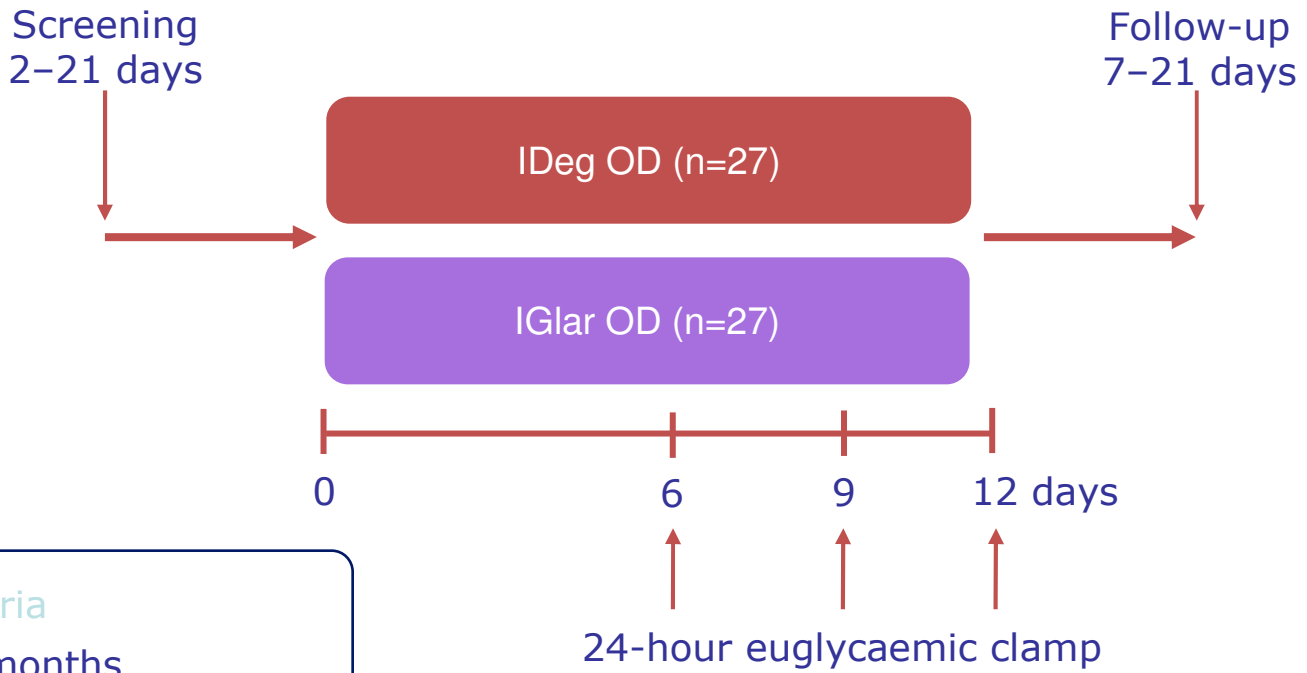
- Duration of action:
  - Control fasting blood glucose with one injection in all individuals
- Flat time–action profile:
  - Lower risk of hypoglycaemia
- Day-to-day variability:
  - Less hypoglycaemia and hyperglycaemia

Mean 26-hour Blood Glucose Level Profiles at Steady-state



Nosek L et al. *Diabetologia* 2011;54(suppl. 1):S429 (1055-P); ADA 2011;49-LB (NN1250-1987)

Within-subject variability of IDeg and IGlar in T1DM



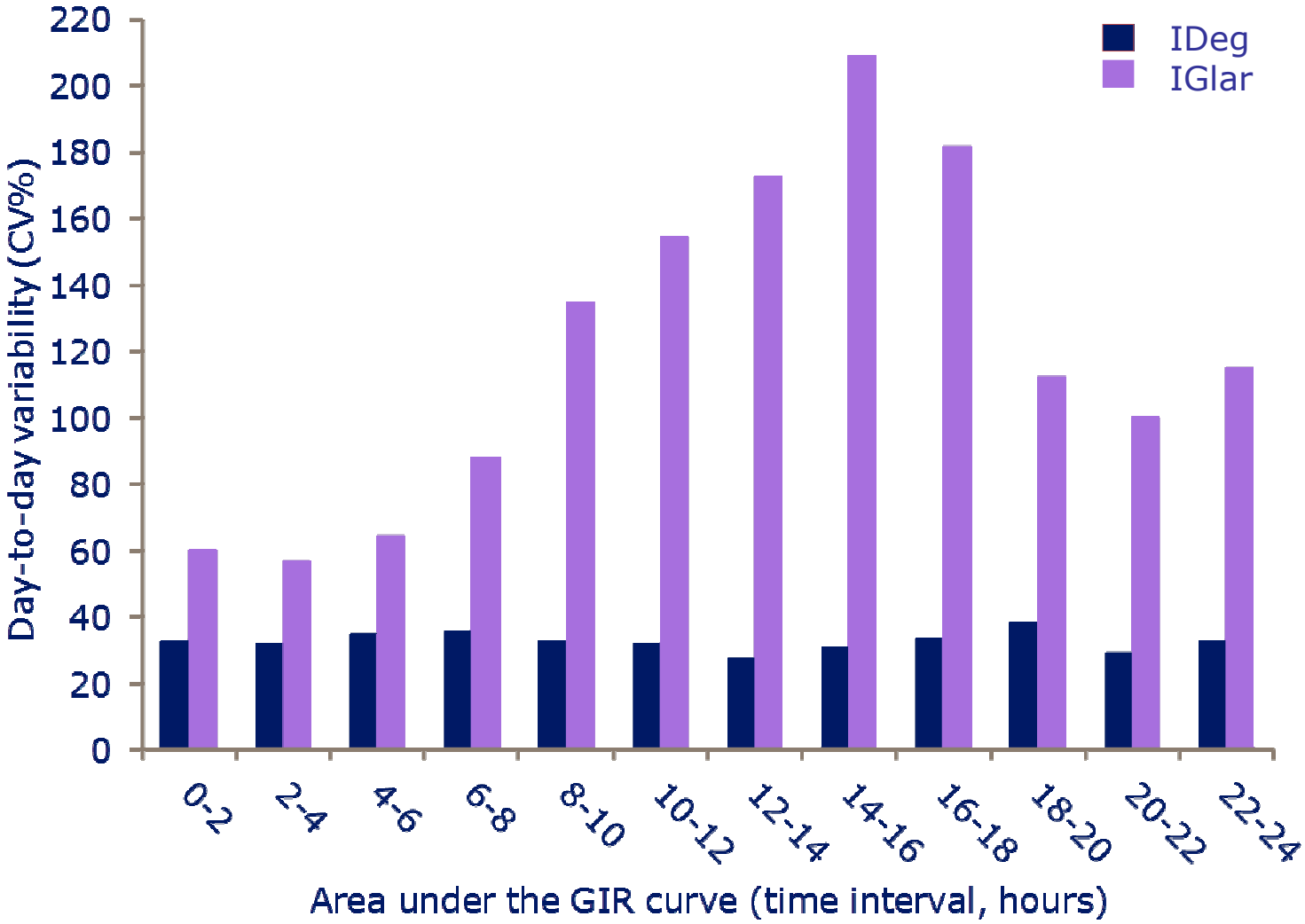
Inclusion criteria

- T1DM ≥12 months
- HbA_{1c}≤10.0%
- BMI 18–28 kg/m^2
- Age 18–65 years

Clinical trial.gov identifier: NCT00961324

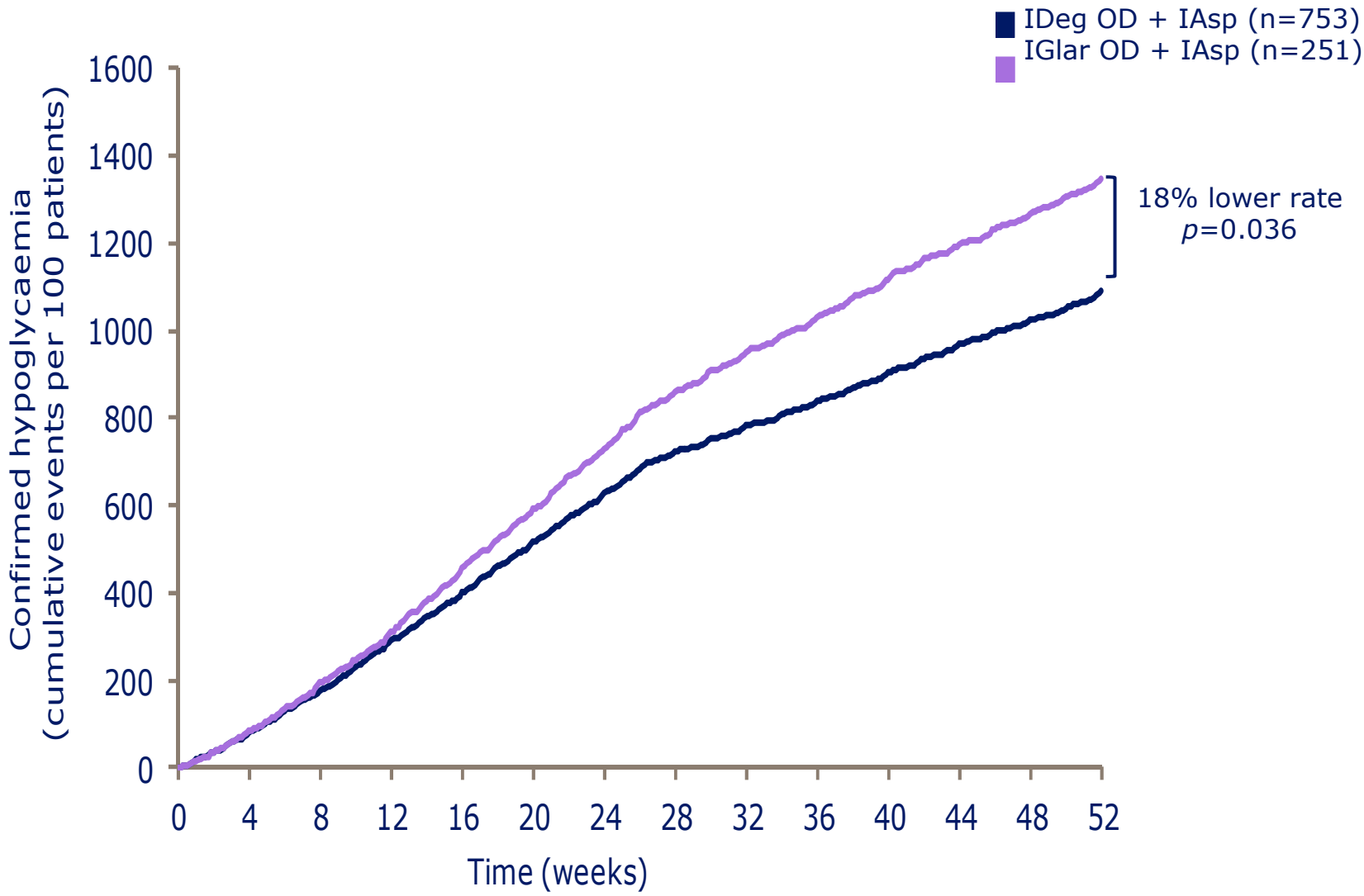
Heise *et al. Diabetes* 2011;60(Suppl. 1):A263 (Abstract 960-P)

Within-subject variability over time



Heise *et al. Diabetes* 2011;60(Suppl. 1):A263

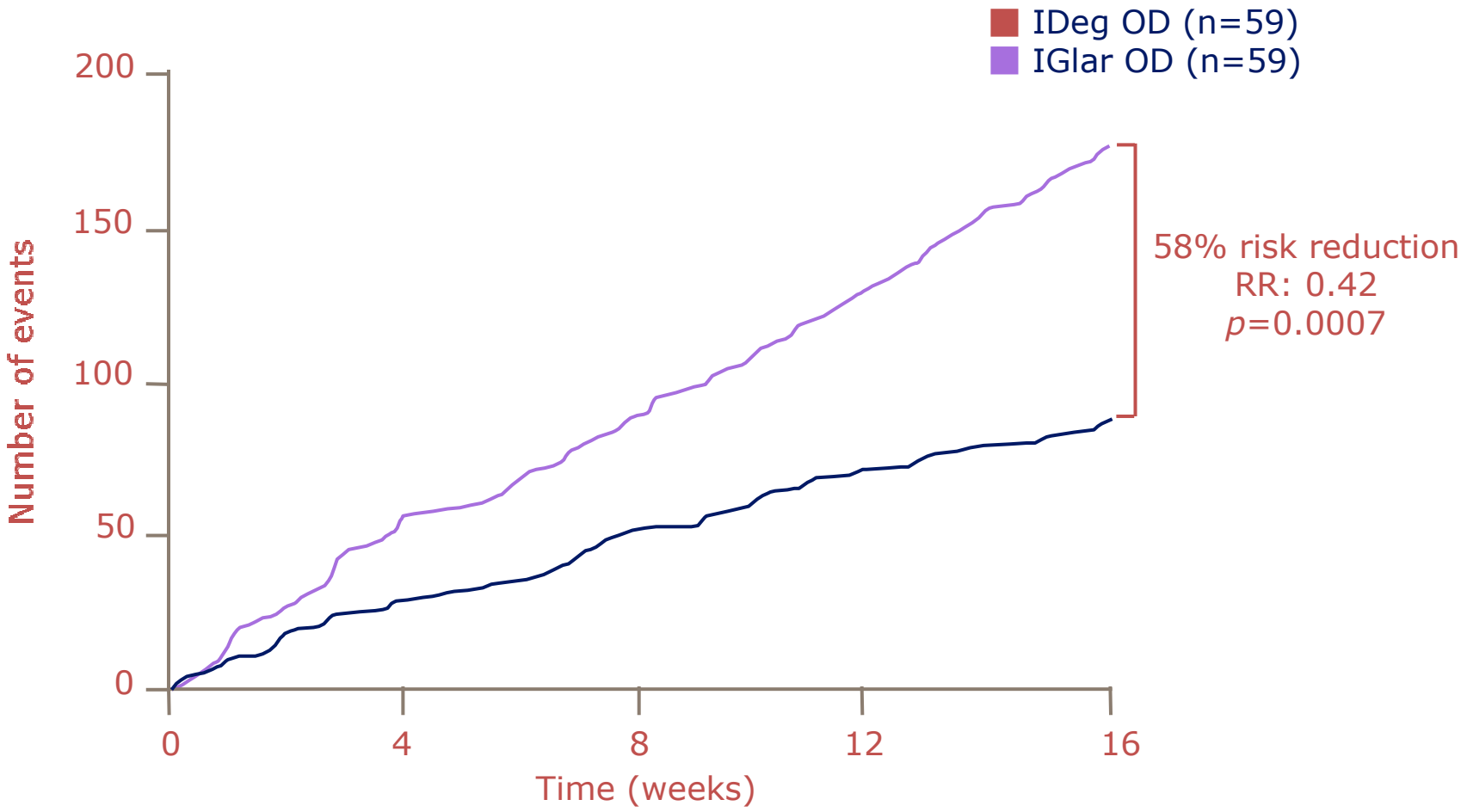
Confirmed Hypoglycaemia



SAS
Comparisons: Estimates adjusted for multiple covariates

Hollander *et al.* IDF 2011:P-1442; *Diabetologia* 2011;54(suppl. 1):S421; Garber *et al. Diabetes* 2011;60(suppl. 1):A203 (NN1250-3582)

Hypoglycaemia: nocturnal episodes



Mean cumulative function

Birkeland *et al. Diabetes Care* 2011;34:661–5

There is increasing Evidence that Hypoglycemia has to be avoided in Risk Situations of Patients with Type 2 Diabetes

- Long duration of Diabetes/Macrovascular Complications
- Acute Myocardial Infraction/Stroke
- Impaired Renal Function (Chronic Kidney Disease)
- Coronary Revascularisation
- Intensive Care Unit (CCU)
- Unawareness to Hypoglycemia
- High Age with Hypovigilance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