



57° Congresso Nazionale della Società Italiana di Gerontologia e Geriatria

NUOVE OPPORTUNITA' TERAPEUTICHE PER IL GRANDE ANZIANO DIABETICO

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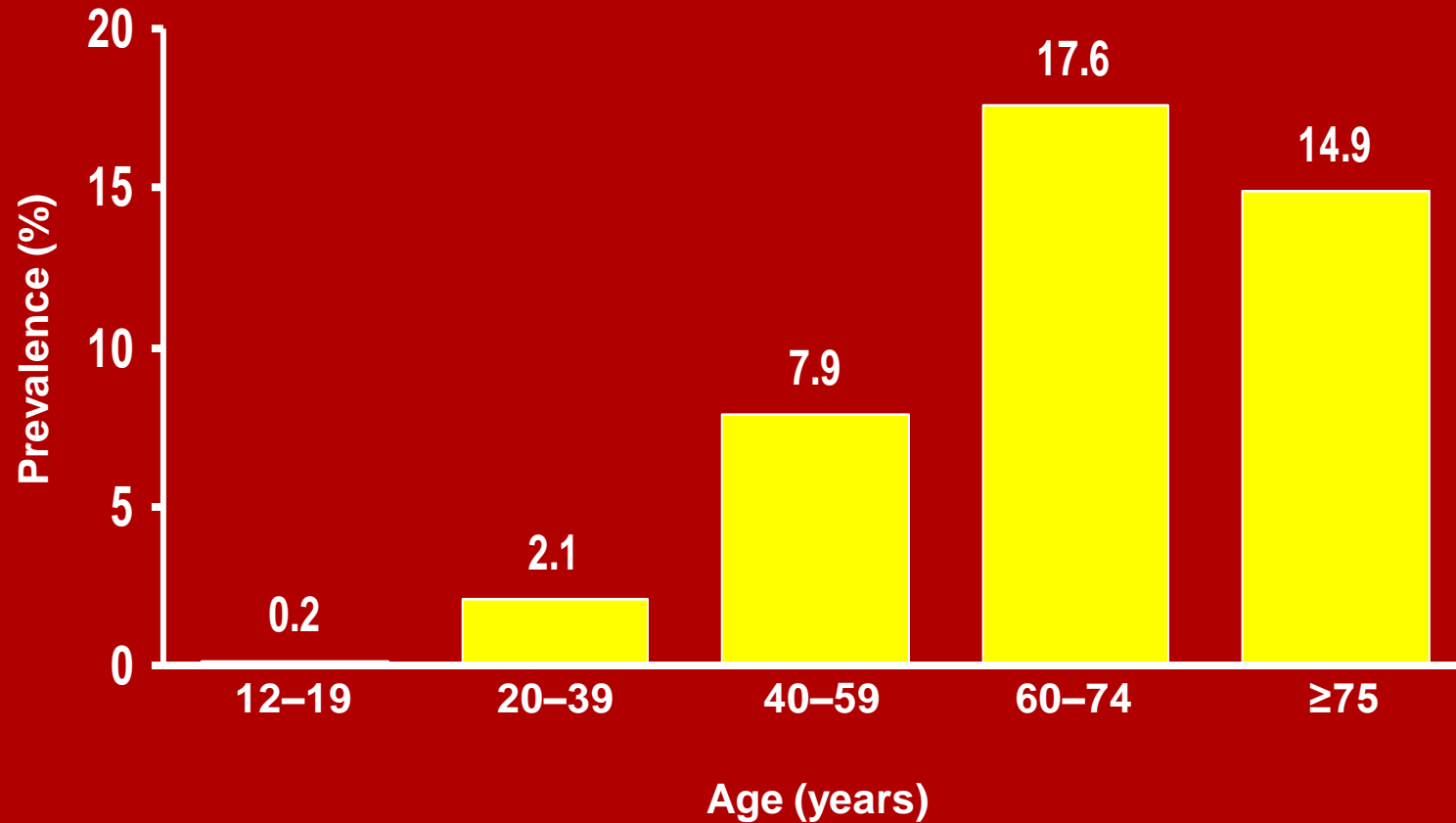


Prevalence of diabetes and IGT in Northern Italy (The Cremona Study): age as a risk factor

Age	Total diabetes (% patients)		IGT (% patients)	
	Males	Females	Males	Females
45–54 years	6.0	4.4	5.1	3.7
55–64 years	13.1	9.5	5.6	7.2
65–74 years	14.7	15.4	9.5	11.1
≥75 years	12.6	20.8	20.0	18.9
≥45 years	11.0	11.3	7.7	8.9

IGT=impaired glucose tolerance; T2DM=type 2 diabetes mellitus.

High prevalence of T2DM in the elderly population in the US (NHANES)



NHANES=National Health and Nutrition Examination Survey; T2DM=type 2 diabetes mellitus.

Cowie CC, et al. *Diabetes Care*. 2009;32:287-294.

Insulin sensitivity and ageing

	NGT	IGT
Insulin sensitivity (HOMA)	0.76 ± 0.04	0.53 ± 0.03
Correlation with age	NO (P=0.08)	NO (P=0.69)
Insulin sensitivity (clamp, mL.mg.kg⁻¹.min⁻¹.μU⁻¹)	16.9 ± 0.8	14.0 ± 0.8
Correlation with age	NO (P=0.83)	NO (P=0.20)^a

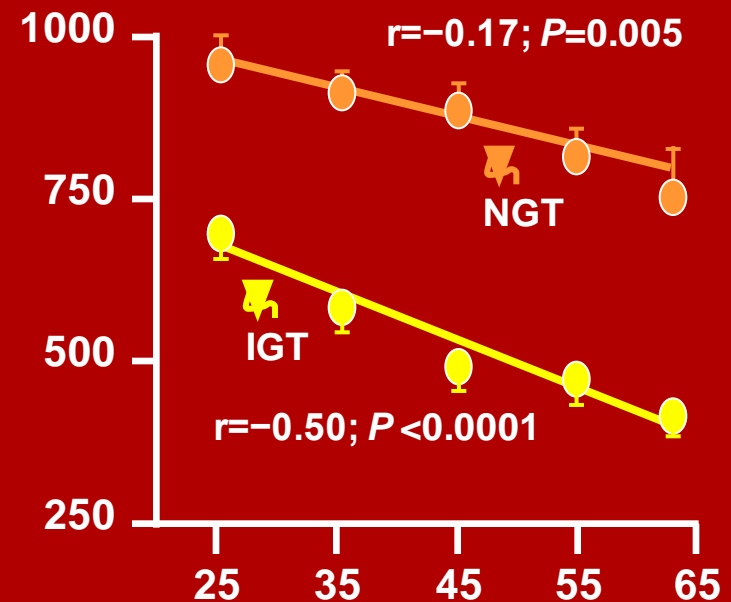
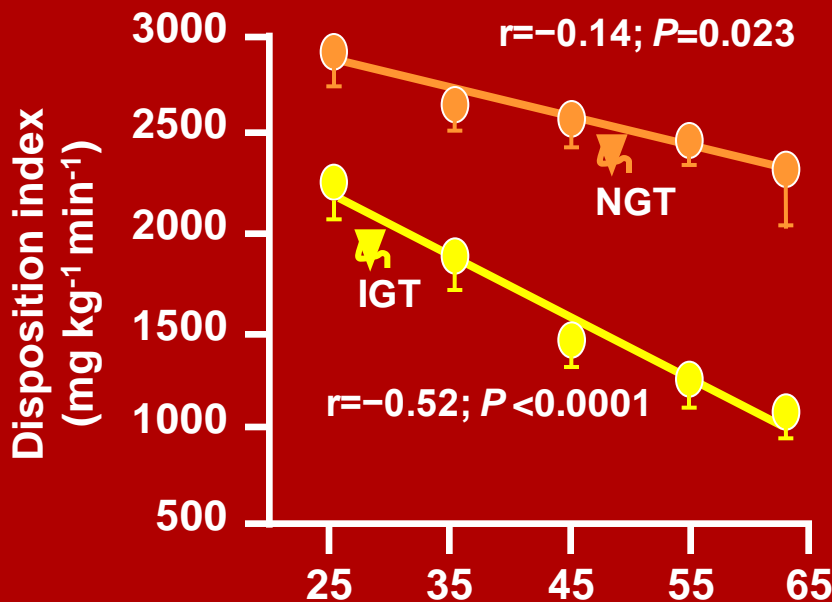
^aAdjusted for body mass index.

HOMA=Homeostatic Model Assessment; IGT=impaired glucose tolerance; NGT=normal glucose tolerance.
Szoke E, et al. *Diabetes Care*. 2008;31:539–543.

β -cell function and ageing

First-phase
insulin release

Second-phase
insulin release



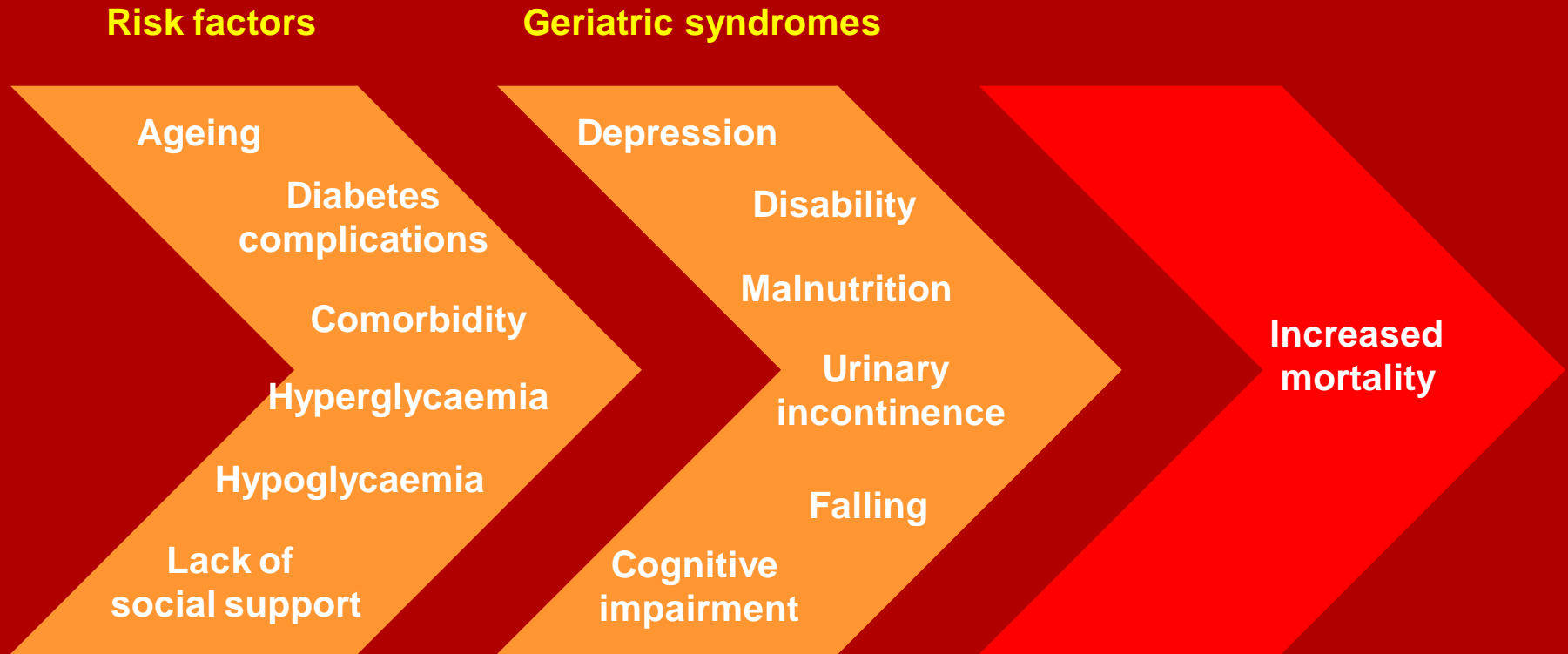
People with IGT had greater decreases as a function of age of both first and second-phase insulin release than people with NGT and that first phase decreased to a greater extent than second phase

Pathophysiology of glucose metabolism and diabetes with ageing

- **T2DM prevalence** increases with age, being a highly prevalent disease in elderly individuals
- **Insulin secretion** (both first and second phase) normally decreases with ageing
- In contrast, ageing per se has no effect on **insulin sensitivity**

T2DM=type 2 diabetes mellitus.

The management of T2DM in the elderly is challenging due to increased incidence of geriatric syndromes

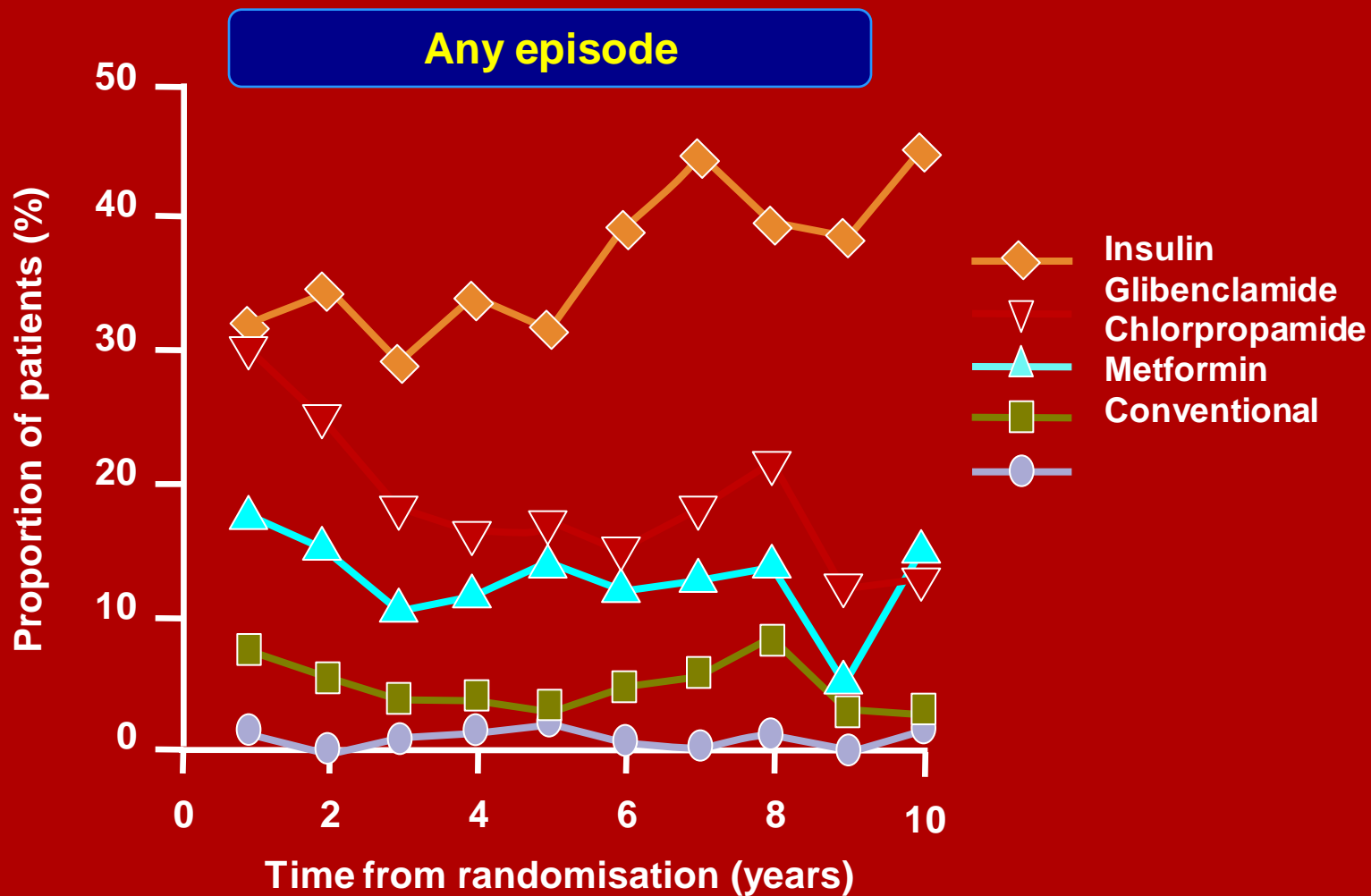


Focus on hypoglycaemia

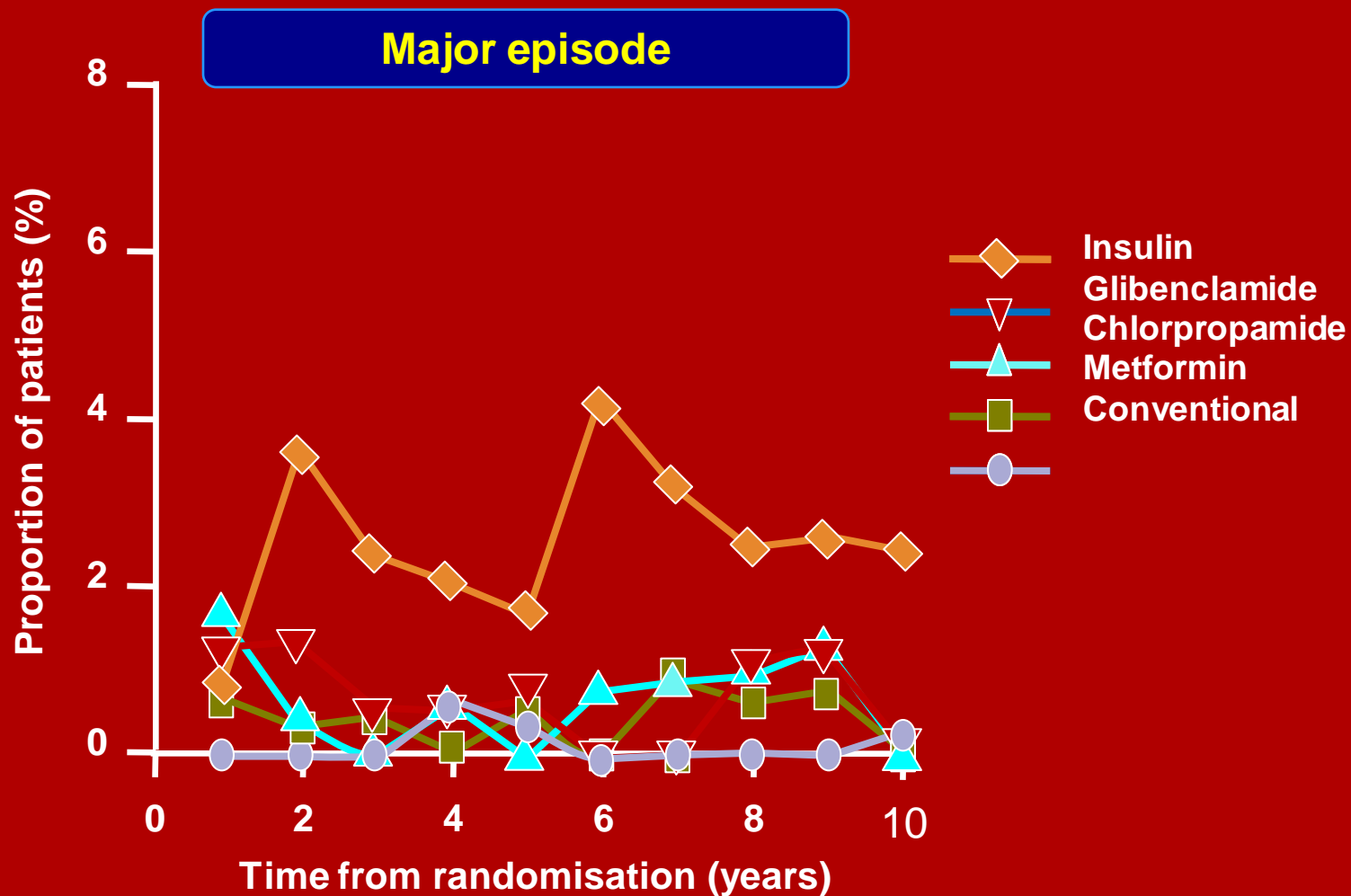
T2DM=type 2 diabetes mellitus.

Araki A, Ito H. *Geriatr Gerontol Int.* 2009;9:105–114.

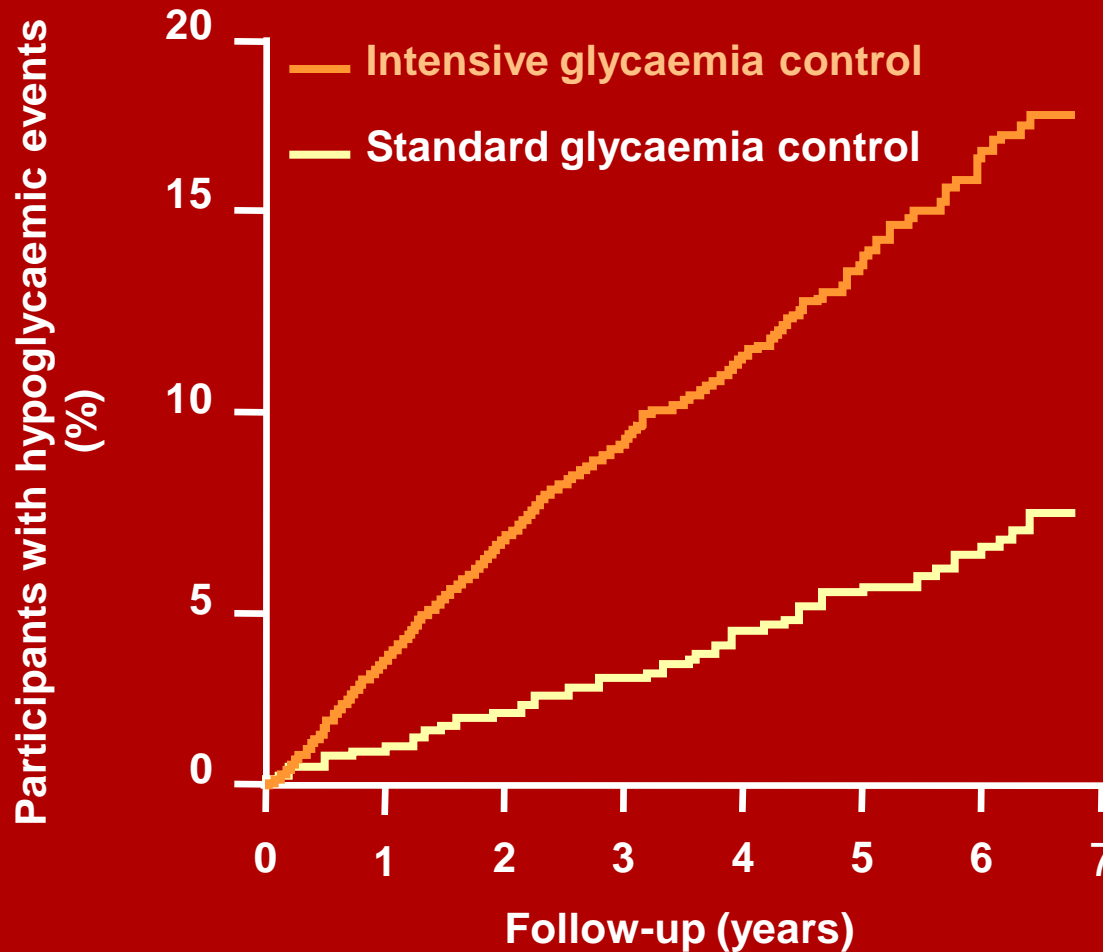
Hypoglycaemic episodes per annum



Hypoglycaemic episodes per annum



Hypoglycaemia in the ACCORD study



The annual incidence of hypoglycaemia was 3.14% in the intensive treatment group and 1.03% in the standard glycaemia group¹

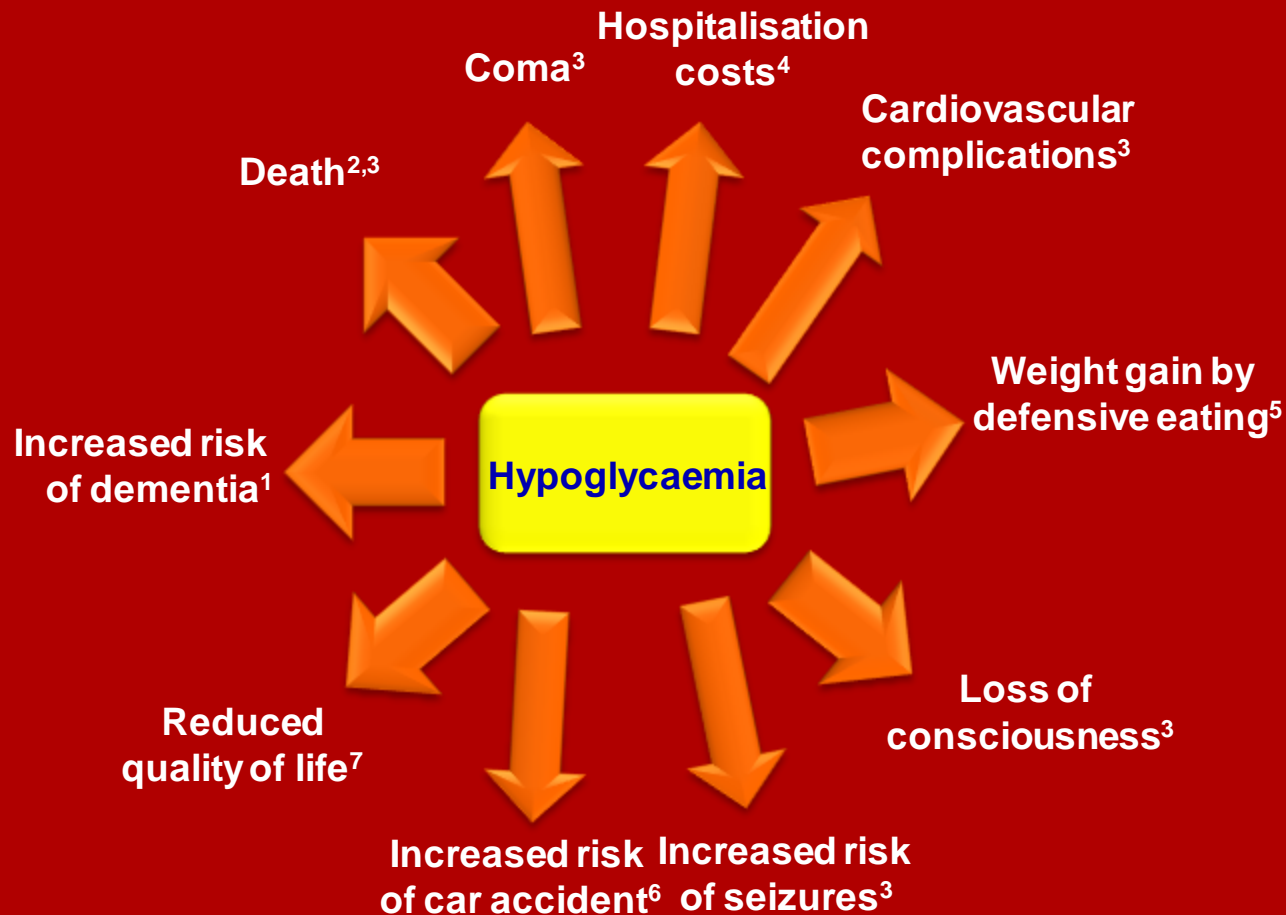
Symptomatic, severe hypoglycaemia was associated with an increased risk of death within each study arm²

Older participants were at increased risk for severe hypoglycaemia¹

ACCORD=Action to Control Cardiovascular Risk in Diabetes.

¹Miller ME, et al. *BMJ*. 2010;340:b5444; ²Bonds DE, et al. *BMJ*. 2010;340;b4909.

The possible consequences of hypoglycaemia



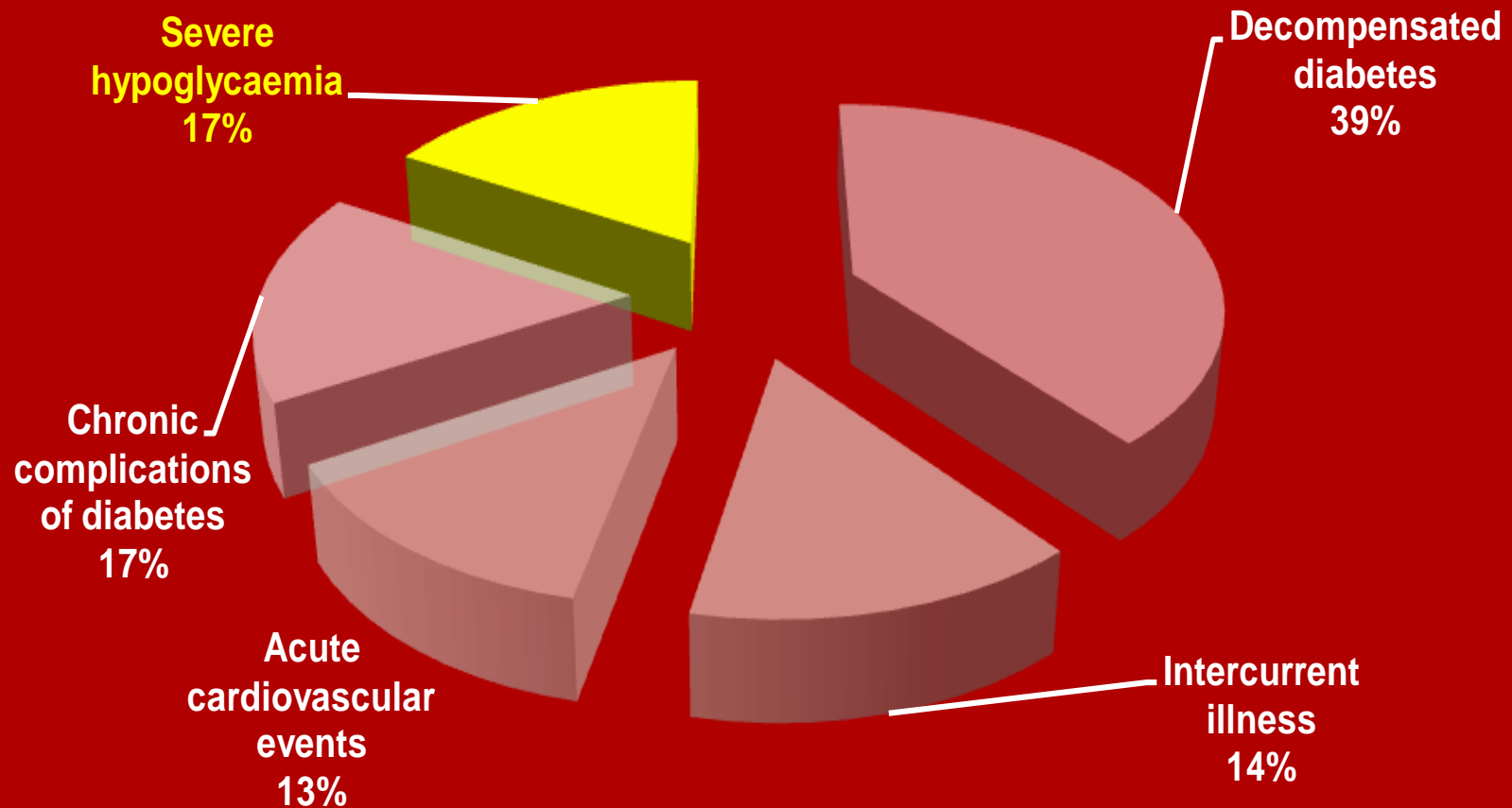
¹Whitmer RA, et al. *JAMA*. 2009;301:1565–1572; ²Bonds DE, et al. *BMJ*. 2010;340:b4909;

³Barnett AH. *Curr Med Res Opin*. 2010;26:1333–1342; ⁴Jönsson L, et al. *Value Health*. 2006;9:193–198;

⁵Foley JE, Jordan J. *Vasc Health Risk Manag*. 2010;6:541–548; ⁶Begg IS, et al. *Can J Diabetes*. 2003;27:128–140;

⁷McEwan P, et al. *Diabetes Obes Metab*. 2010;12:431–436.

Severe hypoglycaemia accounts for almost 20% of all hospitalisations for T2DM in the elderly



T2DM=type 2 diabetes mellitus.

Greco D, et al. *Exp Clin Endocrinol Diabetes*. 2010;118:215–219;

Greco D, Angileri G. *Diabetes Nutr Metab*. 2004;17:23–26.

Hypoglycaemia is a major challenge in the treatment of diabetes

Patient risk factors¹

- Advanced age
- Recent hospitalisation
- Intercurrent illness
- Chronic liver, renal or cardiovascular disease
- Endocrine deficiency (thyroid, adrenal, pituitary)
- Loss of normal counter-regulation
- Hypoglycaemic unawareness

Lifestyle risk factors¹

- Poor nutrition or fasting
- Prolonged physical exercise
- Alcohol (ethanol)

Drug risk factors²

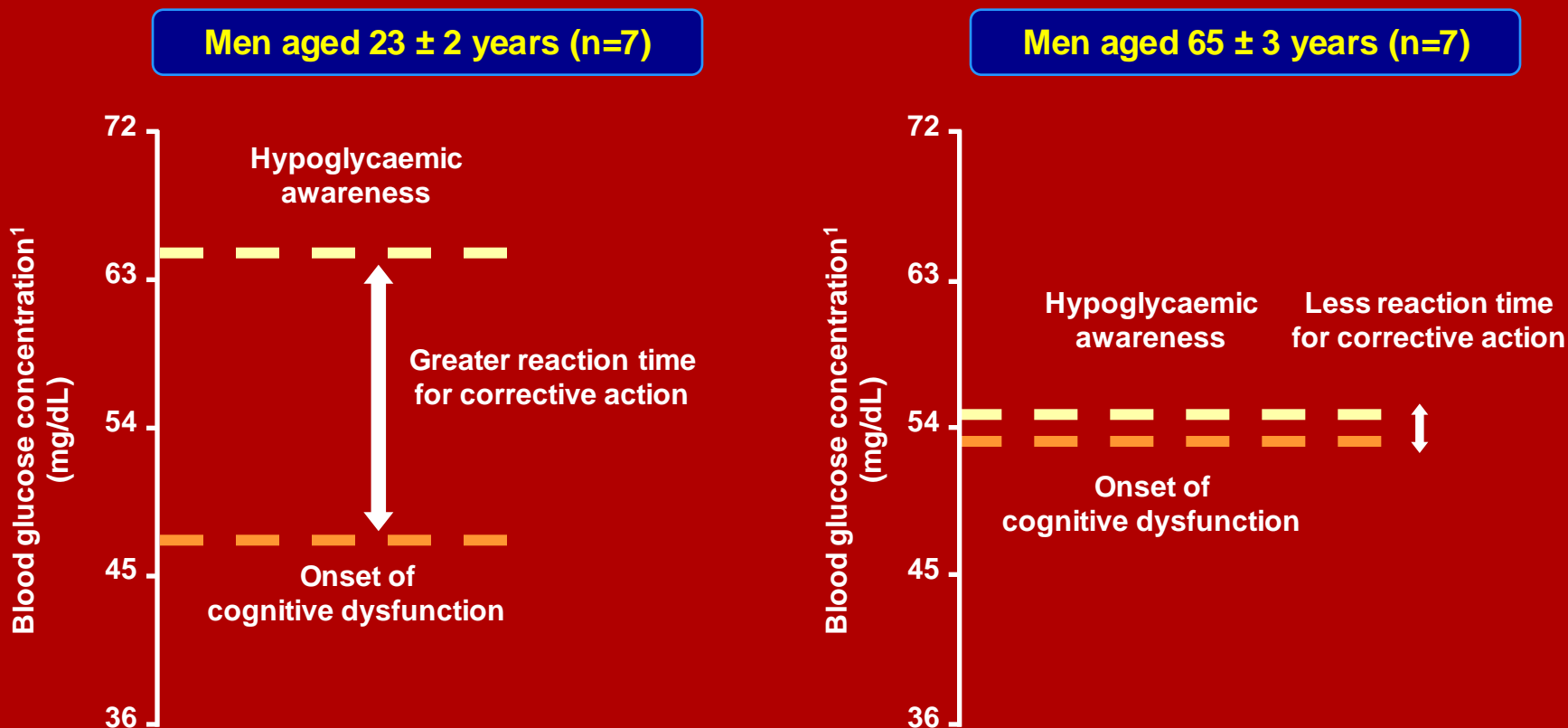
- Use of SU and / or insulin
- Drug interactions with SUs

The primary cause of hypoglycaemia in T2DM is diabetes medication, in particular SUs and insulin²

SU=sulfonylurea.

¹Chelliah A, Burge MR. *Drugs Aging*. 2004;21:511–530; ²Amiel SA, et al. *Diabet Med*. 2008;25:245–254;

Thresholds for hypoglycaemia symptoms vary with age^{a,1,2}



With increasing age, potential reaction time between awareness and onset of symptoms is decreased, contributing to an increased risk of asymptomatic hypoglycaemia and greater susceptibility to cognitive impairment^{a,1,2}

^aBased on data in non-diabetic patients with no family history of diabetes.

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

²Matyka K, et al. *Diabetes Care*. 1997;20:135–141.

**New therapeutic opportunities
in older adults with diabetes:**

focus on DPP4 inhibitors

Concern about hypoglycaemia is a major factor limiting intensive control of blood sugar: New therapeutic opportunities

Incretin-based therapies (eg DPP-4) act in a glucose-sensitive manner¹ and have a lower risk of hypoglycaemia compared with SUs²

DPP4-i efficacy and safety established in elderly patients aged ≥ 75 years³

Low risk of hypoglycaemic events associated with DPP4-i therapy in patients aged ≥ 75 years³

DPP-4=dipeptidyl peptidase-4; SU=sulfonylurea.

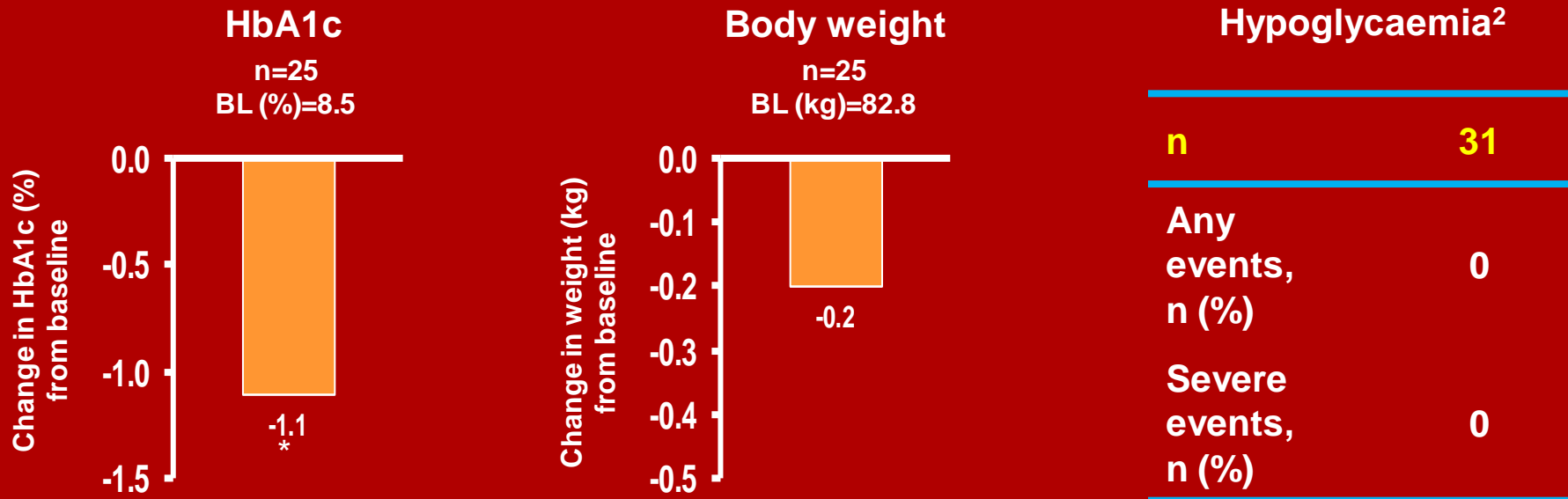
¹Stonehouse A, et al. *Curr Diabetes Rev.* 2008;4:101–109;

²Matthews DR, et al. *Diabetes Obes Metab.* 2010;12:780–789;

³Schweizer A, et al. *Diabetes Obes Metab.* 2011;13:55–64.

Vildagliptin plus metformin: a 1.1% reduction in HbA1c in the very elderly with a low risk of hypoglycaemia and with weight neutrality

Pooled analysis (24 weeks) of three add-on therapy studies in patients aged ≥ 75 years¹

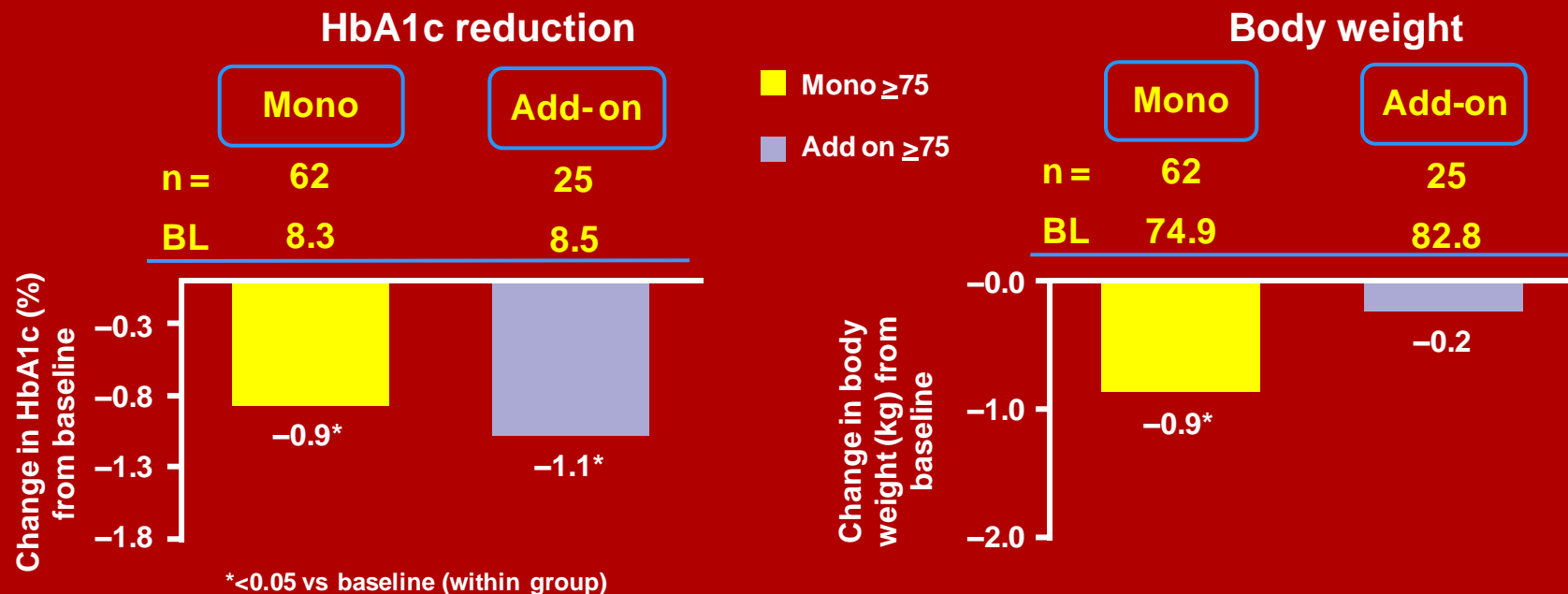


¹Efficacy analyses included studies with vildagliptin 50 mg bid that were randomised, double-blind, controlled, parallel groups, ≥ 24 weeks long and with patients aged ≥ 75 years. Seven monotherapy studies (pooled monotherapy efficacy population) and three add-on therapy to metformin studies (pooled add-on therapy to metformin efficacy population) were pooled; data shown are from the pooled add-on therapy to metformin efficacy population; ²Up to 24-week add-on therapy to metformin (excluding open-label) safety population (n=31 for patients aged ≥ 75 years;). Overall AEs, drug-related AEs and SAEs were all reported with a lower frequency in elderly patients receiving vildagliptin (133.9, 14.5 and 8.8 events per 100 SYE, respectively) than in elderly patients receiving comparators (200.6, 21.8 and 16.5 events per 100 SYE, respectively), and the incidence of discontinuations due to AEs was similar in the two treatment groups (7.2 vs 7.5 events per 100 SYE, respectively).

* $P < 0.05$ vs baseline (within group); AE=adverse event; bid=twice daily; BL=baseline; HbA1c=haemoglobin A1c; SAE=serious adverse events; SYE=subject-year exposure.

Very elderly patients (≥ 75 yrs old) pooled analysis: change in HbA1c and body weight, and hypoglycemic events after 24 weeks treatment

Pooled analysis at 24 weeks; 50 mg twice daily



Hypoglycemic events

Any events

Mono

Add-on

0.0

0.0

Severe events

0.0

0.0

Vildagliptin in the very elderly: lower frequency of AEs, SAEs and drug-related AEs than comparators (pooled analysis)

	Age <75 years		Age ≥75 years	
	Vilda 50 mg bid n=5984	Comparator s ^a n=6041	Vilda 50 mg bid n=132	Comparator s ^a n=169
Any AEs SYE-adj n (%)	147.9 4139 (69.2)	177.3 4174 (69.1)	133.9 86 (65.2)	200.6 114 (67.5)
Drug-related AEs SYE-adj n (%)	14.9 943 (15.8)	26.0 1325 (21.9)	14.5 18 (13.6)	21.8 24 (14.2)
SAEs SYE-adj n (%)	7.8 533 (8.9)	8.9 538 (8.9)	8.8 12 (9.1)	16.5 19 (11.2)
Discontinuation due to AEs SYE-adj n (%)	4.7 337 (5.6)	6.1 391 (6.5)	7.2 10 (7.6)	7.5 9 (5.3)
Deaths SYE-adj n (%)	0.3 24 (0.4)	0.3 21 (0.3)	0 0	1.7 2 (1.2)

AE=adverse event; bid=twice daily; SAE=serious adverse event; SYE=subject-year exposure; vilda=vildagliptin.
Pooled data from 35 Phase II and III studies (open-label studies were excluded).

^aComparator group includes active comparator or placebo.

DPP4-inhibitors vs conventional oral antidiabetics as add-on therapy to metformin in elderly T2D patients: The HYPOCRAS study

A large real-life population trial in elderly population

AIM:

A prospective observational study to compare DPP4-inhibitors (DPP4-i) with conventional oral antidiabetic drugs (COAD) in the real-life treatment of elderly patients with T2DM uncontrolled on metformin alone.

METHODS:

Two treatment cohorts (DPP4-i and COAD, constituted on the basis of the GP decision of add-on therapy at the 1st visit) were compared after 6 months. The primary objective was to assess the incidence of hypoglycaemic episodes in relationship with glycaemic control assessed by HbA(1c) level.

The HYPOCRAS study

Safety and efficacy of second OAD added on to metformin at 6 months

	DPP-4 inhibitor N=931	OOAD N=257	SU/ Glinide N=163	p-value DPP-4 inhibitor vs OOAD
At least 1 episode of hypoglycaemia	6.4%	20.1%	25.9%	<0.001 P
At least 1 episode of severe hypoglycaemia	0.1%	2.4%	3.2%	0.001 F
HbA1c, %	6.9 (0.8)	7.0 (0.7)		0.033 WMW
FPG, mg/dL	126 (28)	129 (26)		0.034 WMW
Success of bitherapy HbA1c ≤7% without hypoglycaemia	59.7%	45.5%	41.4%	<0.001 P
HbA1c categories				
6.5%-7%	58.1%	48.9%		
7%-7.5%	22.6%	26.1%		
7.5%-8%	9.0%	17.0%		
≥8%	10.3%	8.0%		
Treatment discontinued	1.6%	6.6%	6.7%	<0.001 P

Values are mean (SD) unless otherwise specified.
P, Pearson Chi² test; F, Fisher; WMW, Wilcoxon-Mann-Whitney; DPP-4, dipeptidyl peptidase-4;
FPG, fasting plasma glucose; OOAD, other oral anti-diabetic drug; SU, sulphonylurea

CONCLUSION:

This large cohort study of elderly T2DM patients in France shows that the incidence of hypoglycaemia was three times higher in patients prescribed a COAD versus a DPP4-i after 6 months while both treatments induced satisfactory glycaemic control.

Safety of vildagliptin vs placebo in patients with T2DM and moderate or severe RENAL impairment

The overall safety and tolerability of vildagliptin 50 mg qd in patients with moderate or severe RI was generally similar to placebo.

There was a trend towards a lower incidence of any AE with vildagliptin than with placebo in both moderate (67.5 vs. 72.9%) and severe (72.6 vs. 74.2%) RI.

Event category	Moderate RI [n (%)]		Severe RI [n (%)]	
	Vildagliptin 50 mg qd (n = 163)	Placebo (n = 129)	Vildagliptin 50 mg qd (n = 124)	Placebo (n = 97)

Vildagliptin added to ongoing antidiabetic therapy had a safety profile similar to placebo.

Further, relative to placebo, vildagliptin elicited a statistically and clinically significant decrease in A1C in patients with moderate or severe RI.

Elderly patients are likely to be taking several medications: vildagliptin has a low potential for drug–drug interactions

Vildagliptin has a low potential for drug–drug interactions¹

**Vildagliptin is not metabolised by the cytochrome P450 pathway¹;
this is important for patients on concomitant medications**

Studies in healthy volunteers showed vildagliptin had no clinically relevant pharmacokinetic interactions with digoxin (Pgp substrate), warfarin (CYP2C9 substrate), amlodipine, ramipril, valsartan or simvastatin¹

Summary

- High prevalence of T2DM in the elderly and very elderly¹
- Management of T2DM in the elderly is particularly challenging because of comorbidities, SU drug interactions and heterogeneity (healthy and fragile individuals)²
- Hypoglycaemic episodes in the elderly can precipitate serious events such as falls and hip fractures and severely reduce quality of life²
- Severe hypoglycaemic episodes are common in the elderly³
- Need to have appropriate therapeutic options for the treatment of T2DM in elderly patients

SU=sulfonylurea; T2DM=type 2 diabetes mellitus.

¹Cowie CC, et al. *Diabetes Care*. 2009;32:287–294;

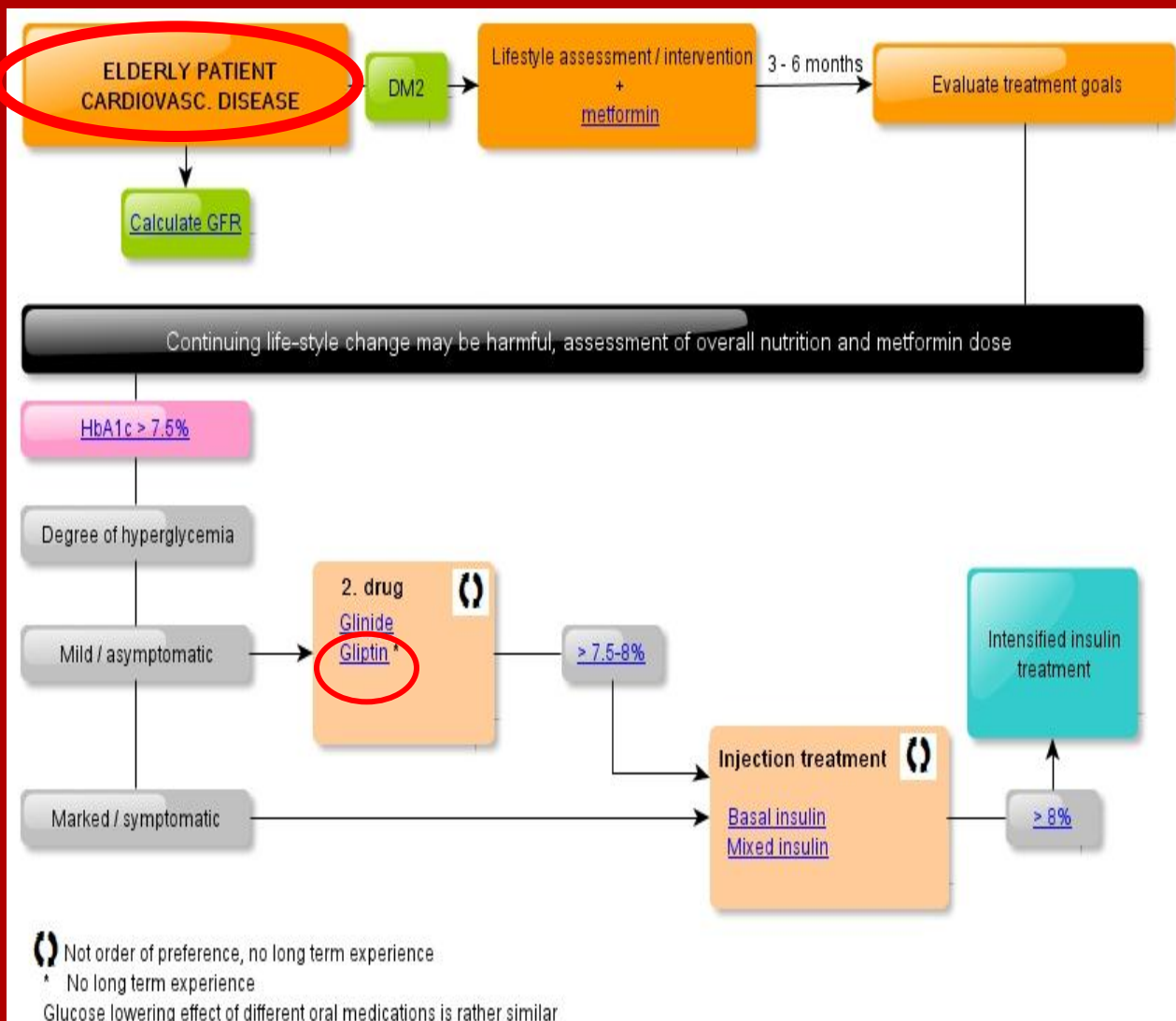
²*Geriatr Gerontol Int*. 2009;9:105–114;

³Chelliah A, et al. *Drugs Aging*. 2004;21:511–530.

Grazie!

Diabetes treatment algorithm in Elderly Patient

Diabetes Current Care Guideline in Finland



Safety of long-term treatment with saxagliptin in patients with T2DM and RENAL impairment

	Patients, <i>n</i> (%)	
	Saxagliptin 2.5 mg (<i>n</i> = 85)	Placebo (<i>n</i> = 85)
AEs*		
Patients reporting ≥ 1 AE	64 (75.3)	60 (70.6)
Patients reporting ≥ 1 serious AE	23 (27.1)	24 (28.2)
Discontinuation of study medication owing to AE	10 (11.8)	7 (8.2)
Discontinuation of study medication owing to serious AE	6 (7.1)	6 (7.1)
Death	3 (3.5)	4 (4.7)
Most common AEs ($\geq 5\%$ in either treatment group)†		
Urinary tract infection	6 (7.1)	3 (3.5)
Anaemia	5 (5.9)	7 (8.2)

Saxagliptin 2.5 mg providing sustained reductions in HbA1c, especially in patients with moderate or severe renal impairment, may be a useful option in long-term treatment of patients with T2DM and renal impairment

Meta-analysis of large, incretin-based clinical trials: *safety*

Relevant AEs	Number of studies	Risk ratio (95% CI)
Exenatide		
Hypoglycemia: vs placebo	5	2.30 (1.08–4.88)
vs insulin	2	1.02 (0.46–2.26)
Nausea	7	3.17 (2.16–4.64)
Vomiting	6	3.52 (2.64–4.70)
Diarrhea	6	2.27 (1.75–2.94)
Liraglutide		
Nausea	2	0.89 (0.27–3.01)
Vomiting	2	0.62 (0.13–2.91)
DPP4 inhibitors		
Hypoglycemia	20	0.97* (0.50–1.86)
Nasopharyngitis	12	1.17 (0.96–1.40)
Urinary tract infection	5	1.52 (1.04–2.21)
Headache	13	1.38 (1.10–1.72)

*hypoglycemia rates vs placebo
AEs=adverse events; CI=confidence intervals

Glucose-lowering effects, advantages, and disadvantages of various glucose-lowering agents in older adults with type 2 diabetes

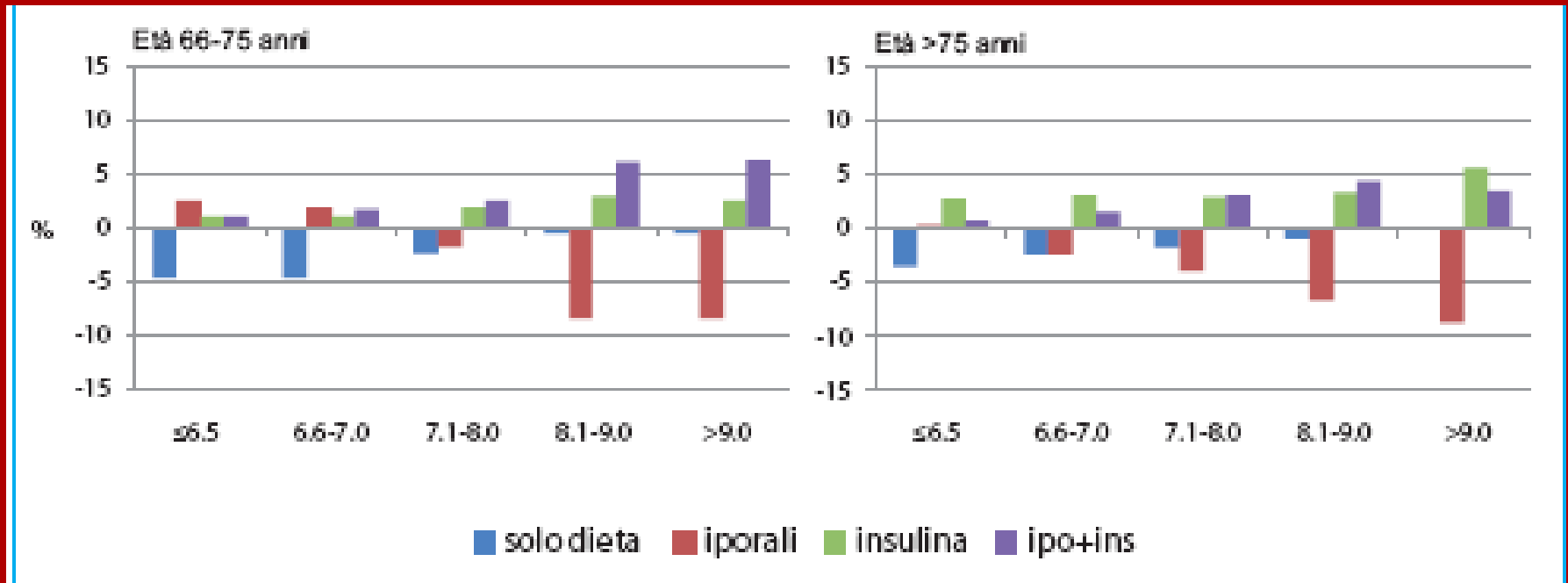
	A1c lowering effect, % ^a	Advantages	Disadvantages
Metformin	1.0-2.0	Proven effectiveness as the first-line therapy Low risk of hypoglycemia Neutral effect on weight Long-term clinical experience Low cost	Contraindicated when serum creatinine ≥ 1.5 mg/dL in men or ≥ 1.4 mg/dL in women, liver failure, and advanced heart failure GI side effects may cause poor appetite and malnutrition Concerns of vitamin B12 and folate deficiency
Sulfonylureas	1.0-2.0	Proven glucose-lowering efficacy Long-term clinical experience Relatively low cost	Frequent hypoglycemia Weight gain
Meglitinides	0.5-1.5	Rapid onset of action time Flexible dosing for those with irregular eating habits	Hypoglycemia Weight gain Frequent dosing Relatively high cost
DPP-4 inhibitors	0.5-0.8	Low risk of hypoglycemia Weight neutrality	Limited efficacy; only mild to moderate lowering of A1c by 0.5-0.8% Relatively high cost Limited long-term data
Alpha glucosidase inhibitors	0.5-0.8	Effectively reduce postprandial glucose No hypoglycemia	Frequent GI side effects Frequent dosing Relatively high cost
Thiazolidinediones	0.5-1.4	Reduce insulin resistance Durable effects on glycaemic control Low risk of hypoglycemia	Weight gain Fluid retention, which may exacerbate underlying heart failure Increased risk of bone fractures Concerns of bladder cancer
GLP-1 receptor agonists	0.5-1.0	Low risk of hypoglycemia Weight reduction (beneficial in obese patients)	Relatively high cost Need a parenteral injection GI side effects may not be tolerated in some older patients High cost Limited long-term experience
Insulin	1.5-3.5	Proven effectiveness No dose limitation	Need a parenteral injection Frequent hypoglycemia Weight gain Need glucose monitoring and adjusting the dose accordingly Require patient's executive functioning

GI, gastrointestinal; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1.

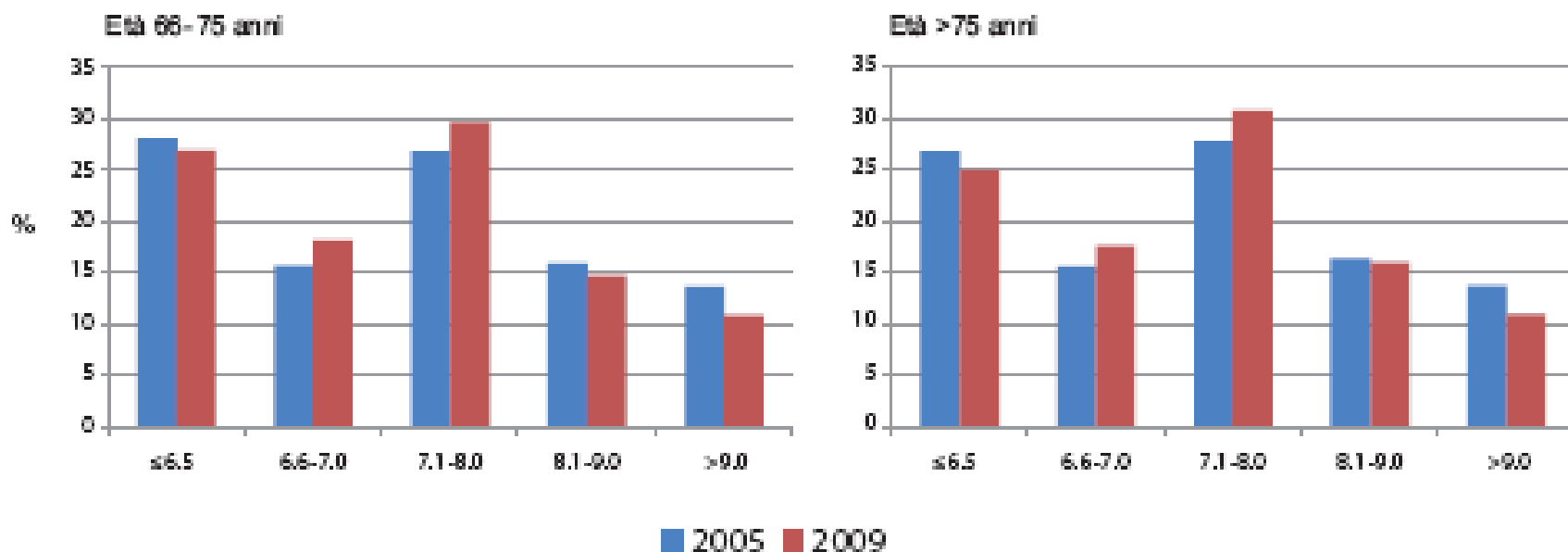
^aExpected reduction in HbA1c when used as a monotherapy.

Anti-diabetes treatment in Italian Elderly Population

Variazione assoluta 2009-2005 nella distribuzione delle classi di trattamento antidiabetico per le 2 fasce di età anziana



Distribuzione della popolazione anziana Con diabete per 5 classi di HbA1c



Guidelines Recommendations

Specifically designed for Older adults

Although there are several guidelines for the management of diabetes in general, only a few are specifically designed for older adults with diabetes :

- Brown AF, et al. California Healthcare Foundation/American Geriatrics Society Panel on Improving Care for Elders with Diabetes. **Guidelines for improving the care of the older person with diabetes mellitus**. J Am Geriatr Soc 2003;51(5 Suppl Guidelines):S265-80.
- Sinclair A, et al. **Diabetes mellitus in older people: position statement on behalf of the International Association of Gerontology and Geriatrics (IAGG), the European Diabetes Working Party for Older People (EDWPOP), and the International Task Force of Experts in Diabetes**. J Am Med Dir Assoc 2012;13:497-502

Guidelines Recommendations for Older adults

Main message

- Older adults who are functional, cognitively intact, and have significant life expectancy **should receive diabetes care using goals developed for younger adults.**
- Glycemic goals for older adults not meeting the above criteria may be relaxed using individual criteria, **BUT**



hyperglycemia leading to symptoms or risk of acute hyperglycemic complications, should be avoided in all patients

DPP-4 inhibitors in older adults with diabetes

Summary of main studies

- **Vildagliptin 100 mg** daily resulted in better glycemic control, tolerability, and fewer adverse events compared with metformin 1,500 mg daily in drug-naive elderly patients with type 2 diabetes (mean age of 71 years with 3 years of diabetes duration) . Schweizer A, Diabetes Obes Metab 2009;11:804-12.
- **Vildagliptin** is effective and well-tolerated in type 2 diabetic patients aged 75 years or older (mean age, 77 years) Schweizer A, Diabetes Obes Metab 2011;13:55-64
- **Sitagliptin** provides similar glycemic improvement with less hypoglycemia in the elderly with type 2 diabetes compared to sulfonylurea Shankar R, Diabetes 2012;61(Suppl 1):A278.

In older adults with type 2 diabetes, reductions in HbA1c after treatment with a DPP-4 inhibitor were not different from those in younger patients.

Treatment with DPP-4 inhibitors in older diabetic adults was associated with a low risk of hypoglycemia, and these agents were weight neutral

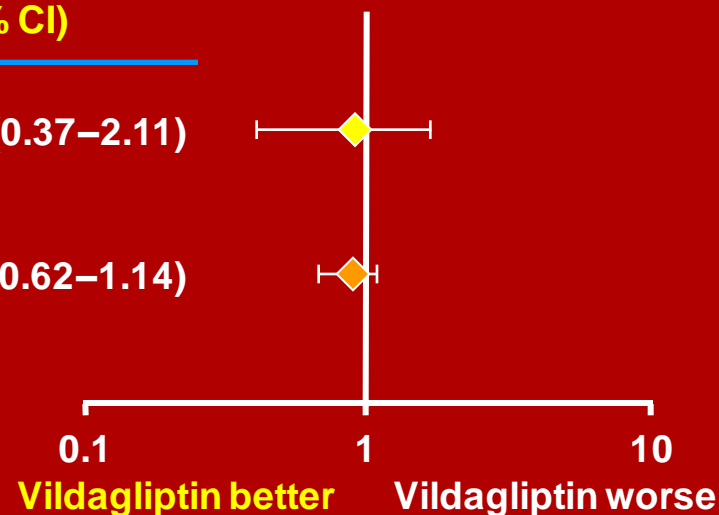
Schwartz SL. Am J Geriatr Pharmacother 2010;8:405-18.

No Increased Risk of Adjudicated CARDIOVASCULAR Events, relative to all comparators^a

Incidences and Odds Ratios for Adjudicated CV Events by Treatment

Risk Ratio

	Vildagliptin n / N (%)	Reference n / N (%)	M-H RR (95% CI)
Vilda 50 mg qd ^b	10 / 1393 (0.72)	14 / 1555 (0.90)	0.88 (0.37–2.11)
Vilda 50 mg bid ^b	81 / 6116 (1.32)	80 / 4872 (1.64)	0.84 (0.62–1.14)



bid=twice daily; CI=confidence interval; CV=cardiovascular; M-H RR=Mantel-Haenszel risk ratio; qd=once daily; vilda=vildagliptin.

^avs comparators (all non-vildagliptin treatment groups). All-study safety population.

^bMeta-analysis of vildagliptin 50 mg bid data vs all comparators according to the methodology set by the US Food and Drug Administration^c [50 mg bid odds ratio = 0.84 (95% CI 0.62–1.14)].

^cGuidance for Industry: Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes, U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER), December 2008.

Schweizer A, et al. *Diabetes Obes Metab.* 2010; 12: 485–494.

Comparison of β -cell function in elderly NGT or IGT patients

	NGT	IGT	P
HOMA			
% β -cell	150 \pm 9	114 \pm 7	0.008
Correlation with age	$r = -0.18$ $P = 0.003$ $Y = -2.1x + 238.6$	$r = -0.05$ $P = 0.53$ $Y = -0.37x + 131.8$	
Decrease/year	1.1%	—	
Hyperglycemic clamp			
First phase (μ U/ml)	186 \pm 7	139 \pm 8	<0.001
Correlation with age	$r = -0.14$ $P = 0.02$ $Y = -1.36x + 241.9$	$r = -0.19$ $P = 0.03$ $Y = -1.48x + 209.3$	
Second phase (μ U/ml)	68 \pm 3	51 \pm 3	0.001
Correlation with age	$r = -0.11$ $P = 0.064$ $Y = -0.54x + 89.8$	$r = -0.054$ $P = 0.54$ $Y = -0.14 + 57.6$	