57° Convegno Nazionale della Società Italiana di Gerontologia e Geriatria

Milano, *21-24 Novembre 2012*

Attualità del trattamento nel controllo glicemico nel paziente anziano

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Endocrinologia , Diabetologia e Metabolismo

Università e Azienda Ospedaliera Universitaria Integrata di Verona

ACCADEMIA NAZIONALE
VIRGILIANA DI SCIENZE,
LETTERE ED ARTI

ENDOCRINOLOGIA,
DIABETOLOGIA E METABOLISMO,
UNIVERSITÀ DI VERONA

5th Mantua

WORKSHOP on DIABETES MELLITUS

and Related Disorders

Head-to-Head in Controversial Issues

Mantova (Italy)

May 8-11, 2013

www.diabetesmantua2013.org

Enzo Bonora – Disclosure of Interest

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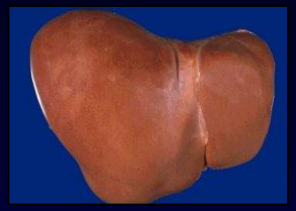
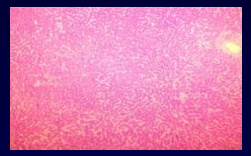
Anti-Diabetic Agents Available in Year 2012

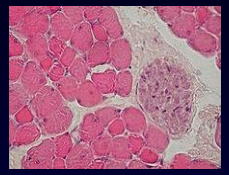
Classes	Molecules
α-Glycosidase Inhibitors	Acarbose
AMPK Activators	Metformin
SUR Agonists	Glibenclamide, Gliclazide, Glimepiride Repaglinide
DPP-4 Inhibitors	Saxagliptin, Sitagliptin, Vildagliptin, Linagliptin
GLP-1R Agonists	Exenatide, Liraglutide
SGLT-2 Inhibitors	Dapaglifozin (in 2013)
Insulin Receptors Agonists	Insulin and its analogs

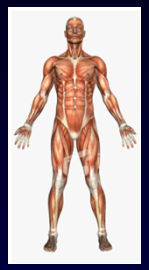
The Pathogenesis of Type 2 Diabetes Mellitus



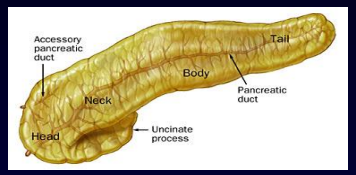


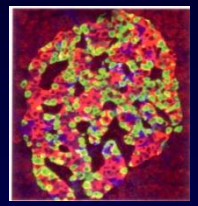
Liver
Increased endogenous glucose production





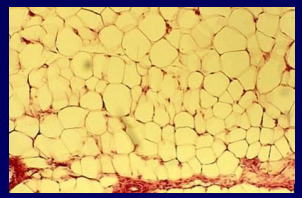
Skeletal muscle
Impaired glucose utilization (transport, storage, oxidation)





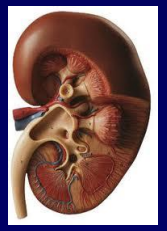
Endocrine pancreas
Impaired insulin secretion
Exaggerated glucagon secretion

Hyperglycemia



Adipose tissue
Release of diabetogenic molecules (FFA, adipocytokines)

Gut
Impaired incretin effect



Kidney
Increased glucose reabsorption

Brain
Abnormal metabolic control

Targeting Pathogenetic Defects in T2DM Year 2012

Defect	Agent
Insulin resistance	Biguanides, TZD
Impaired insulin secretion	SU, Glinides, Insulin Incretin mimetics & enhancers
Reduced beta-cell mass	Biguanides, TZD Incretin mimetics & enhancers
Increased glucagon levels	Incretin mimetics & enhancers
Reduced incretin levels	Incretin mimetics & enhancers
Increased glucose reabsorption	SGLT2 inhibitors
CNS dysfunction	Bromocriptine

Step 1	Step 2*	Step 3**	Step 4**
Metformin If contraindicated or not tolerated: Acarbose or Gliptin or Glitazone or Repaglinide or Sulphonylurea or GLP-1 Analog	Metformin + Acarbose	3 OHA	4 OHA
	Metformin + Gliptine	2 OHA + GLP-1 Analog	3 OHA + GLP-1 Analog
	Metformine + Glitazone	2 OHA + Basal insulin	3 OHA + Basal insulin
	Metformin + Repaglinide	Metformin + 2-4 insulin injections/day	Insulin 2-4 injections/day
	Metformin + Sulphonylurea	Insulin 2-4 injections/day	
	Metformin + GLP-1 Analog		
Insulin 1-4 injections/day (temporary or permanent)	Metformin + Basal Insulin		

*Other associations might be necessary in case of contraindication or intolerance to metformin (e.g., sulphonylurea or repaglinide or gliptin + glitazone; sulphonylurea o repaglinide + GLP-1 analog). **Some associations are off label

Criteria in the selection of an anti-diabetic drug

- Efficacy (glucose lowering effect)
- Additional benefits (BW, lipids, blood pressure, CVD, etc.)
- Hypoglycemia risk
- Safety and tolerability
- Interactions with other drugs
- Contraindications (temporary/permanent)
- Oral or injectable
- Number of pills/injections per day (adherence)
- Need to titrate the dose
- SMBG required (mainly to unveil hypoglycemia)
- Capability to modify the natural history of the disease (disease modifier)

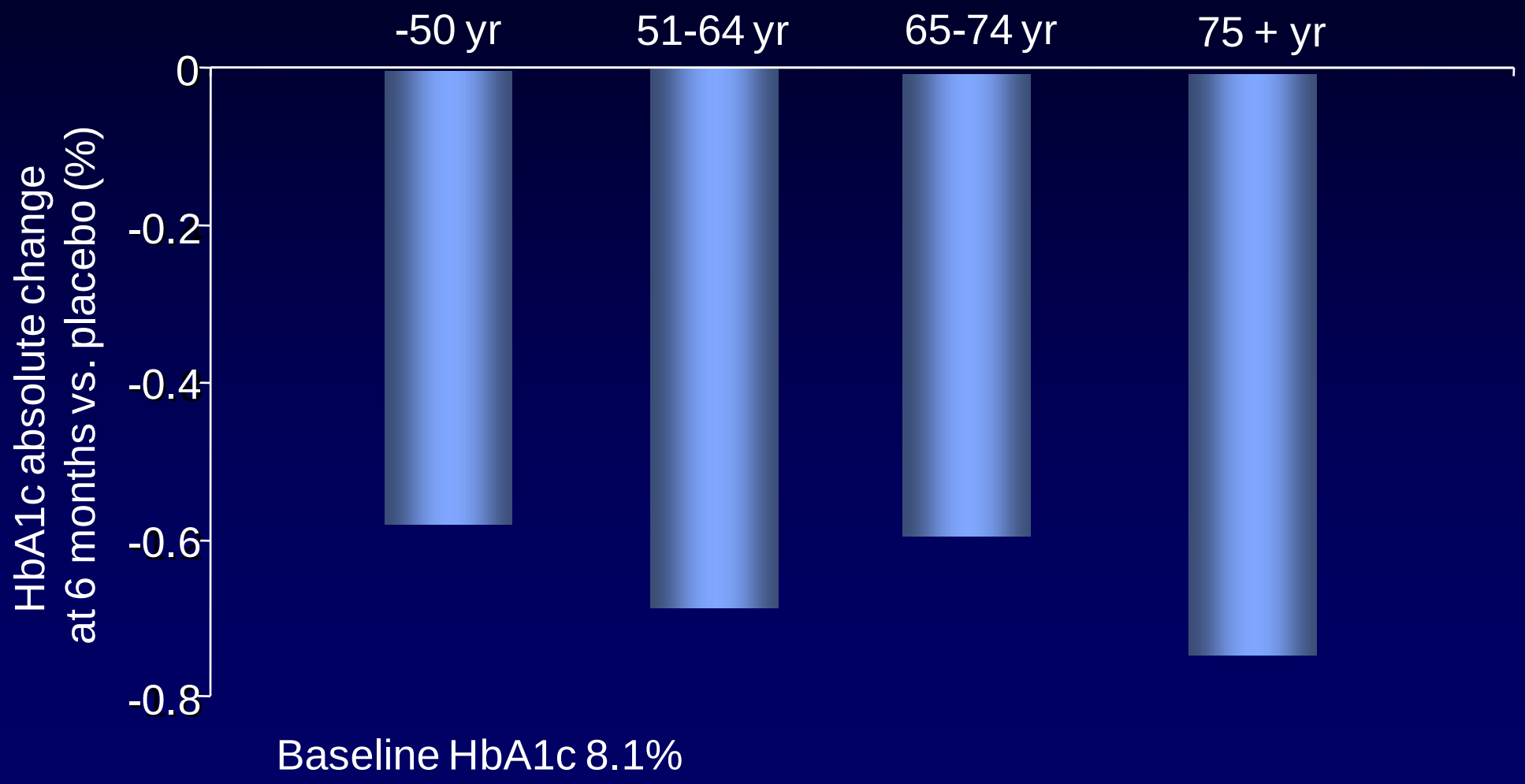
RCTs specificamente condotti nei soggetti anziani (>75 anni) vs. placebo o altro farmaco

- Metformina: NO
- Sulfoniluree: NO
- Glinidi: NO
- Acarbosio: NO

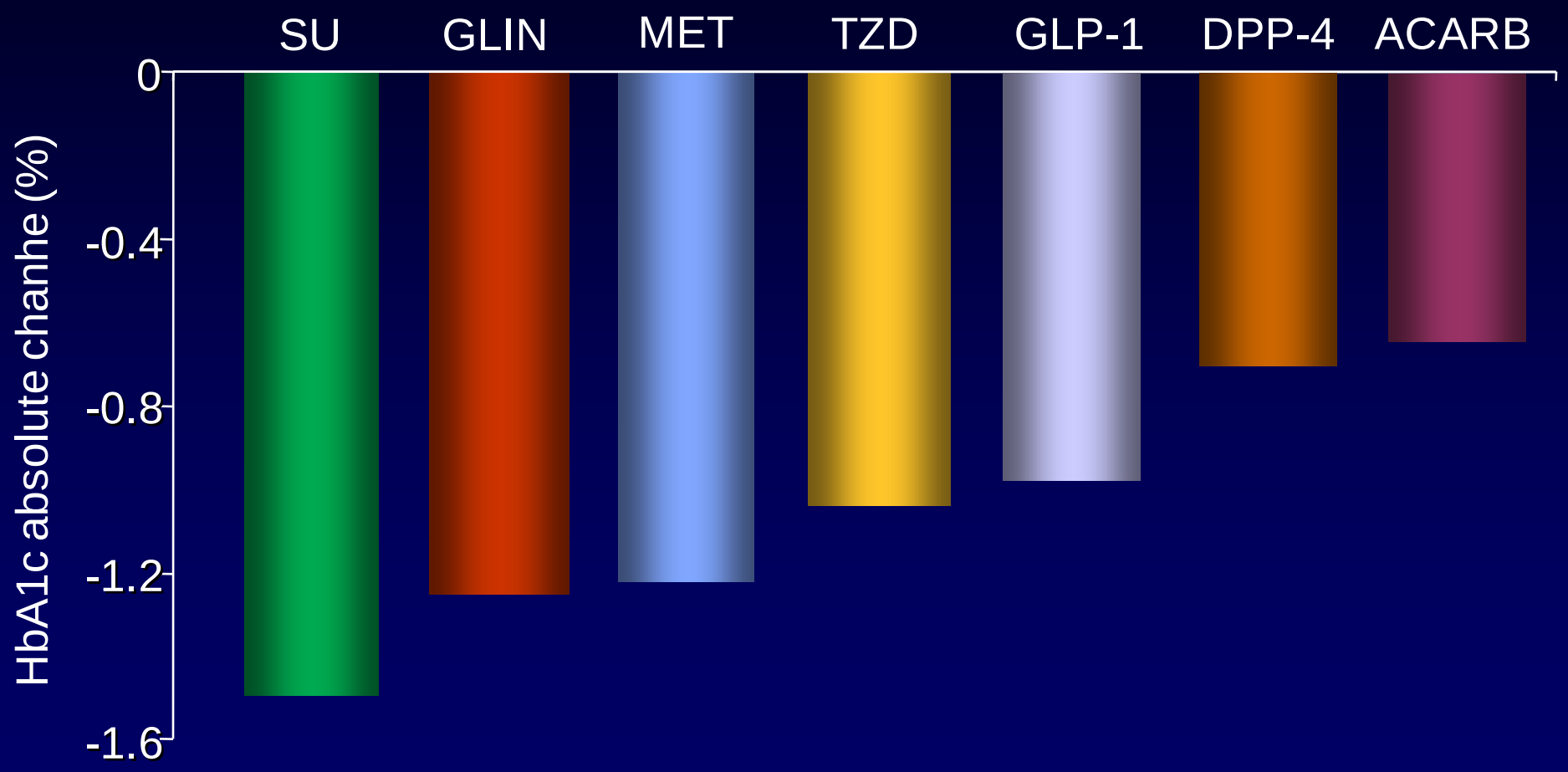
- Glitazoni: NO
- Inibitori DPP-4: NO
- Exenatide: NO
- Insulina: NO

Glucose lowering effect of linagliptin is comparable at all ages (pool of data from 4 phase 3 studies)

Patel EASD 2011 and Rendell ENDO 2011



Mean Reduction of HbA1c During 6-Month Therapy with Anti-Diabetic Agents vs. Placebo in RCTs

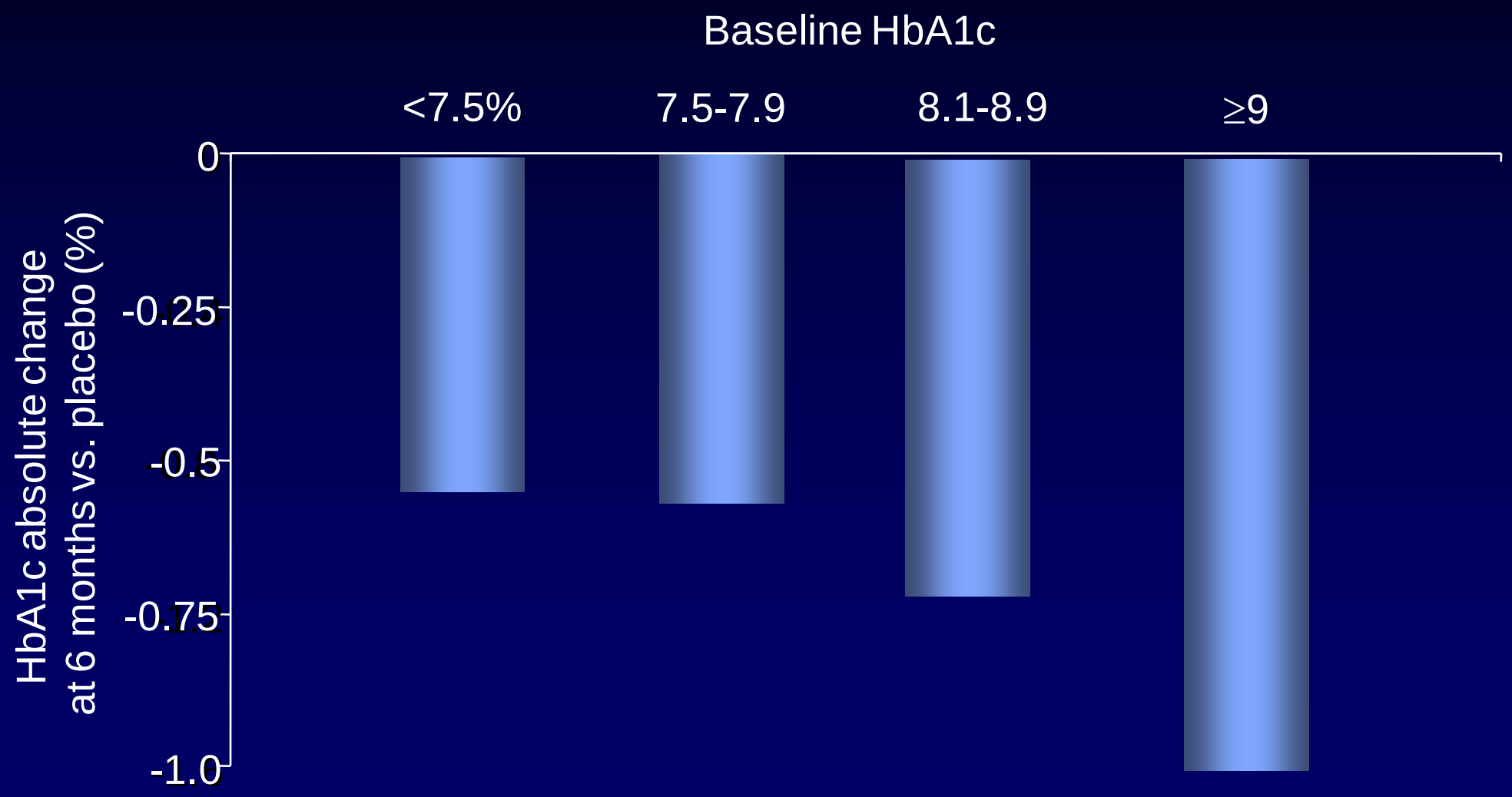


The Efficacy of a Given Hypoglycemic Agent is not the Same in All Subjects

Category of patients	Decrease in HbA1c
Very good responders	>1.8%
Good responders	1.2-1.8%
Average responders	0.6-1.1%
Poor responders	0.3-0.5%
No responders	<0.3%

Glucose lowering effect of linagliptin is greater in subjects with higher baseline HbA1c (pool of data from RCTs)

Del Prato et al - Diabetes Obes Metab 2011;13: 258–267



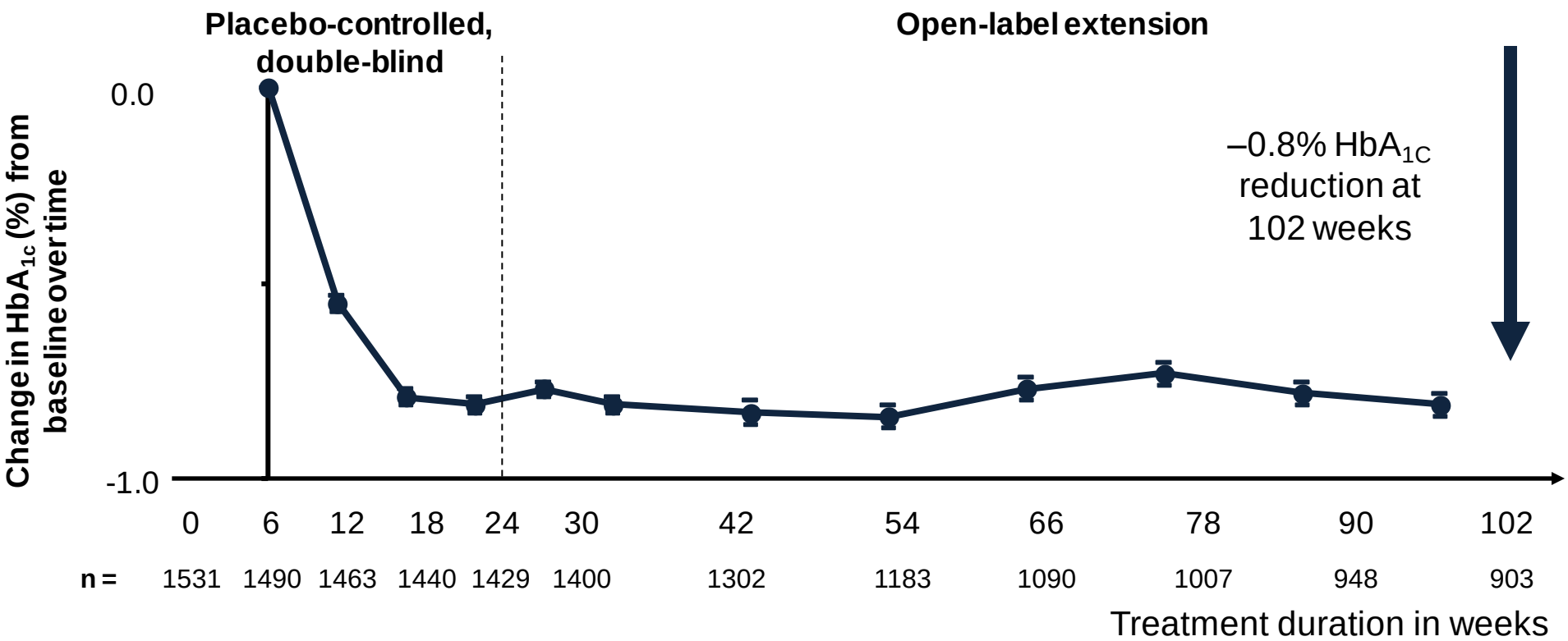
The Efficacy of Anti-Diabetic Agents Changes over Years According to Mechanism of Action

Durability is not the same

Class of OHA	Durability
Insulin receptor agonists	Unlimited
SUR agonists	Limited
AMPK activators	Fair
Alpha-glycosidase inhibitors	Poorly known
PPAR gamma agonists	Good
GLP-1 receptor agonists	Promisingly good
DPP-4 inhibitors	Promisingly good

Linagliptin provides sustained HbA_{1c} reductions over 102 weeks

Sustained efficacy as measured by coefficient of durability[2] of 0.14%, meaning no relevant change in HbA1c from week 24 to week 102 (p-value < 0.0001)

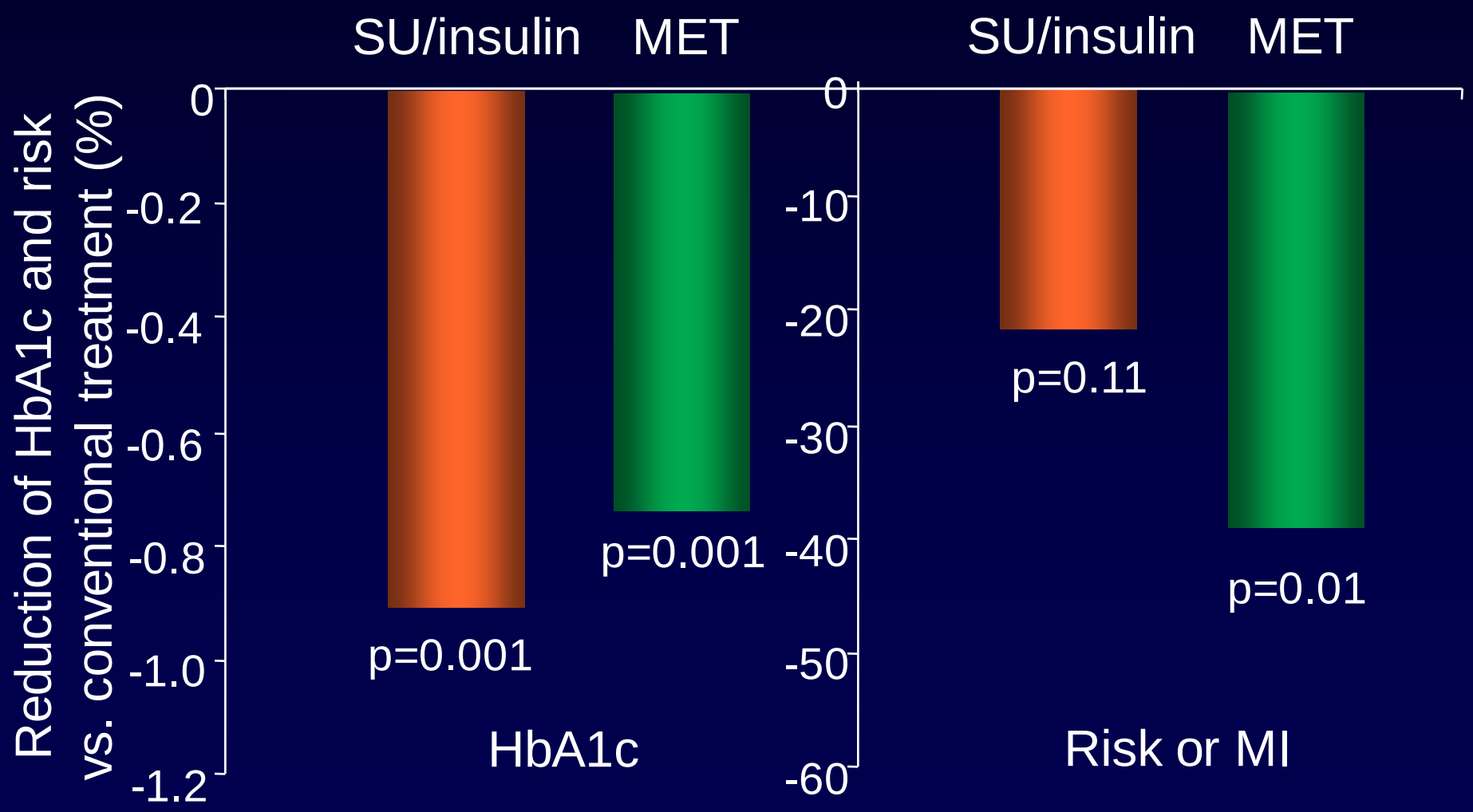


After 24 weeks double-blind, 78 week open-label extension of 4 randomized, controlled trials.
Patients were on 4 treatment regimens: linagliptin monotherapy (n=296); combination with metformin (n=457); combination with metformin & SU (n=544) and initial combination with pioglitazone (n=234).

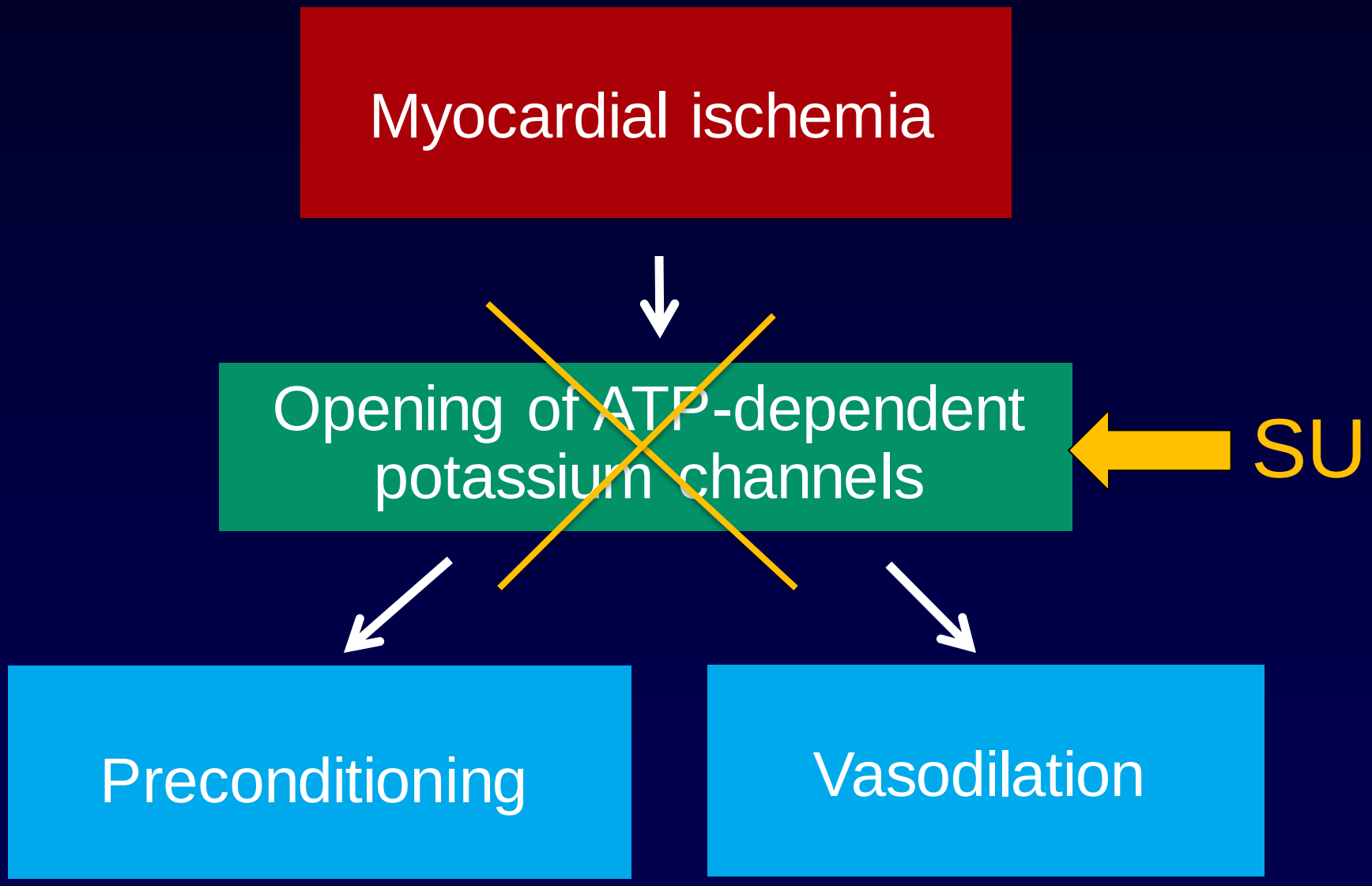
1. Pre-specified analysis of linagliptin treatment in oral mono-, dual and triple combination therapy (full analysis set, observed cases).
2. Coefficient of durability (COD) is defined as HbA1c at week 102 visit subtracted by HbA1c at week 24 visit

Source: Schlosser, Schlosser A et al. Diabetologia 2011;54(Suppl1):S108 EASD 2011

Effects of Intensive Treatment on HbA1c and the Risk of Myocardial Infarction in Overweight (mean BMI=31) Type 2 Diabetic Patients of the UKPDS

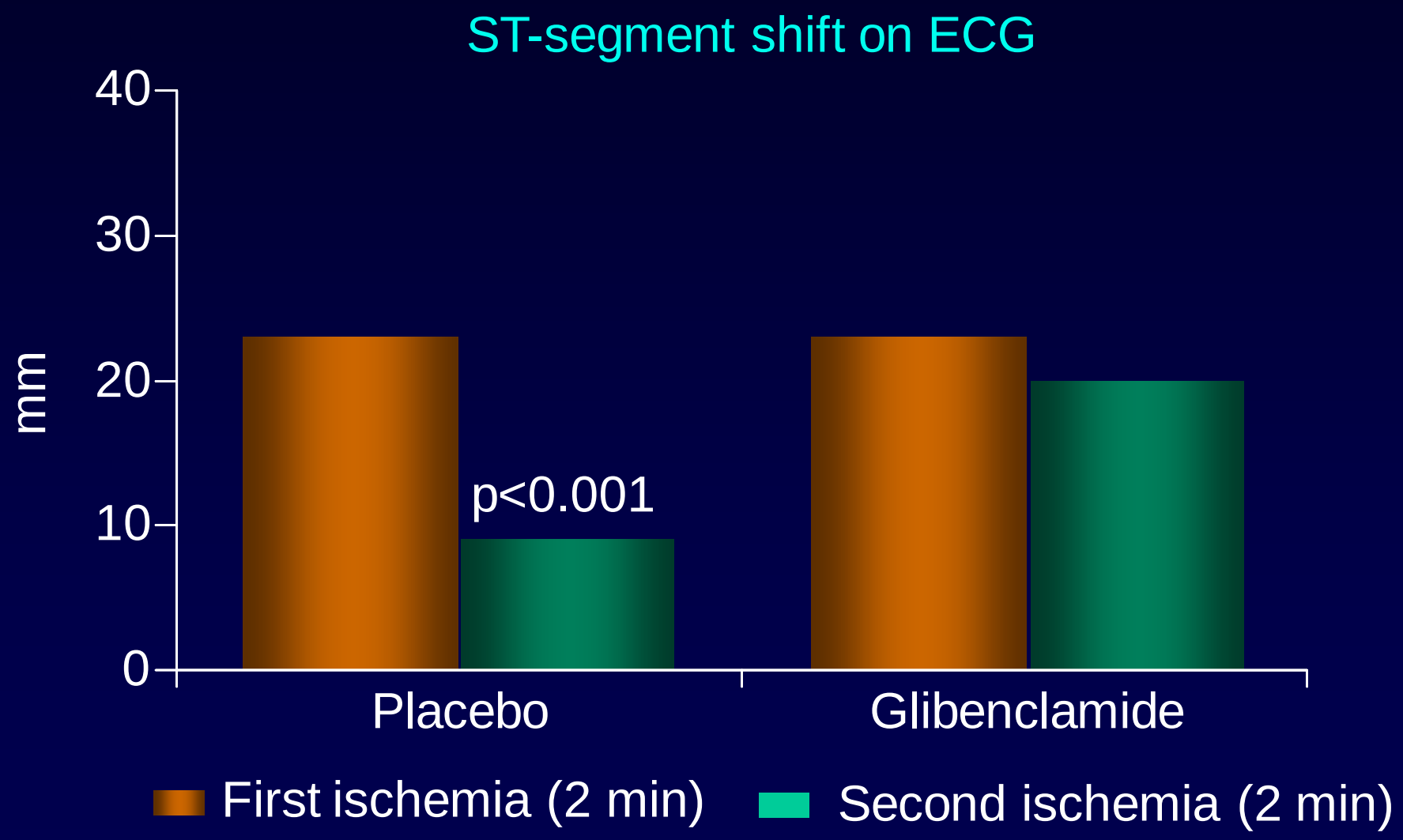


Ischemic preconditioning and sulphonylureas



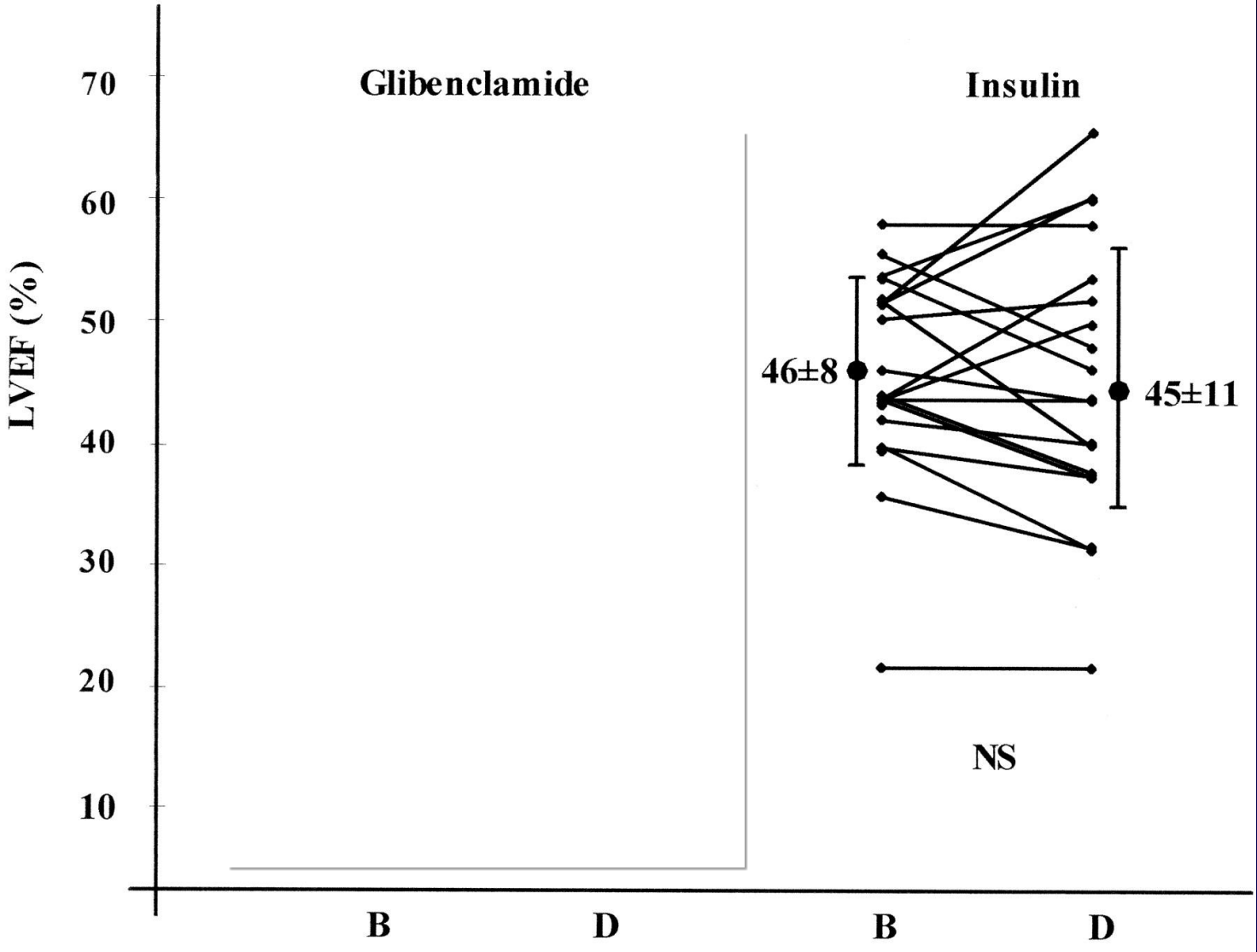
Ischemic preconditioning during PTCA
Effect of Glibenclamide

(Tomai et al; Circulation, 1994)



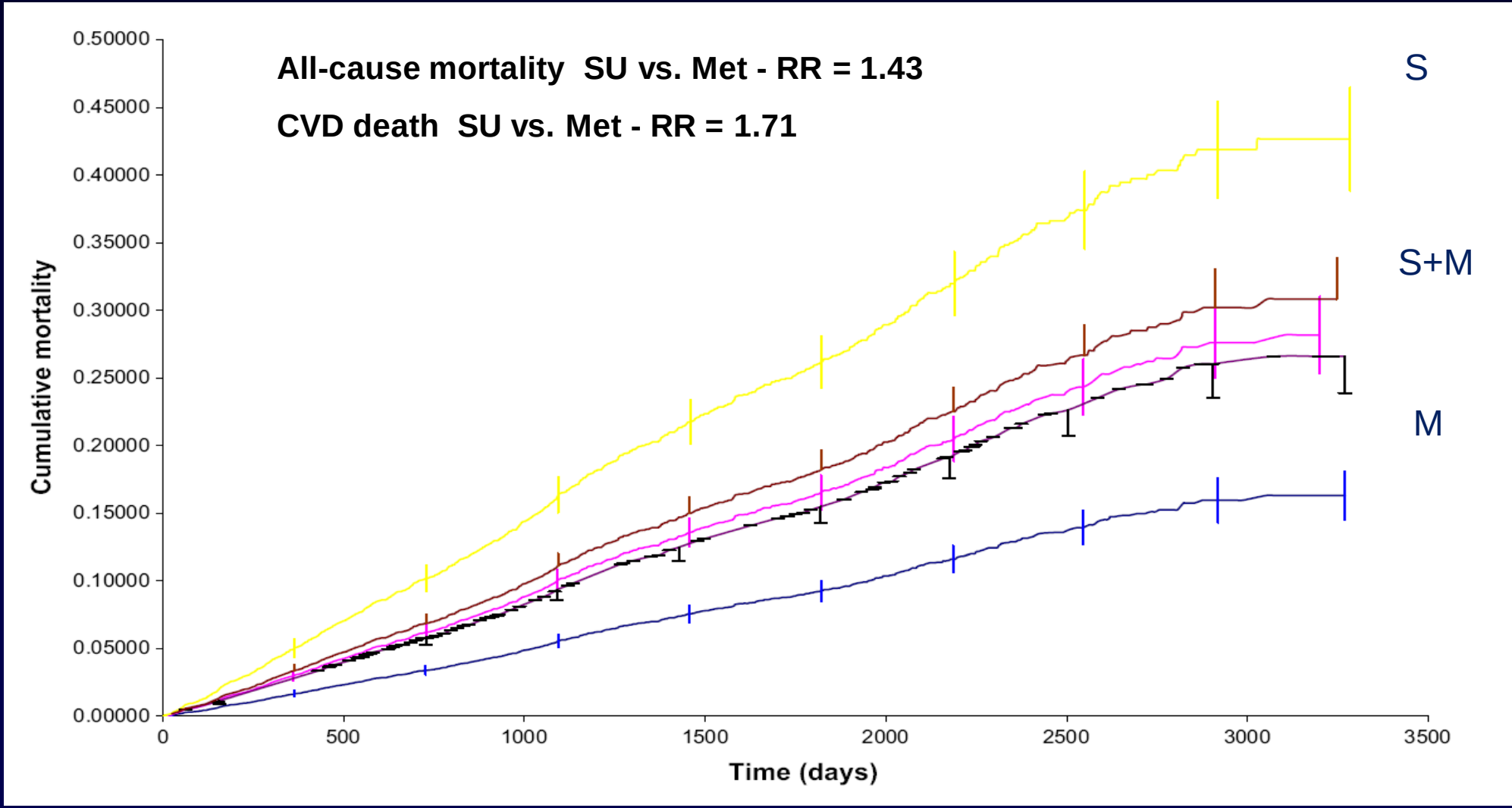
Effects of Treatment with Sulfonylurea vs. Insulin on Left Ventricular Function during Echostress with Dipiridamole in T2DM

(Scognamiglio et al – Diabetes 2002)



All-cause mortality in 5 Cohorts of T2DM Patients Treated with Sulphonylurea and/or Metformin

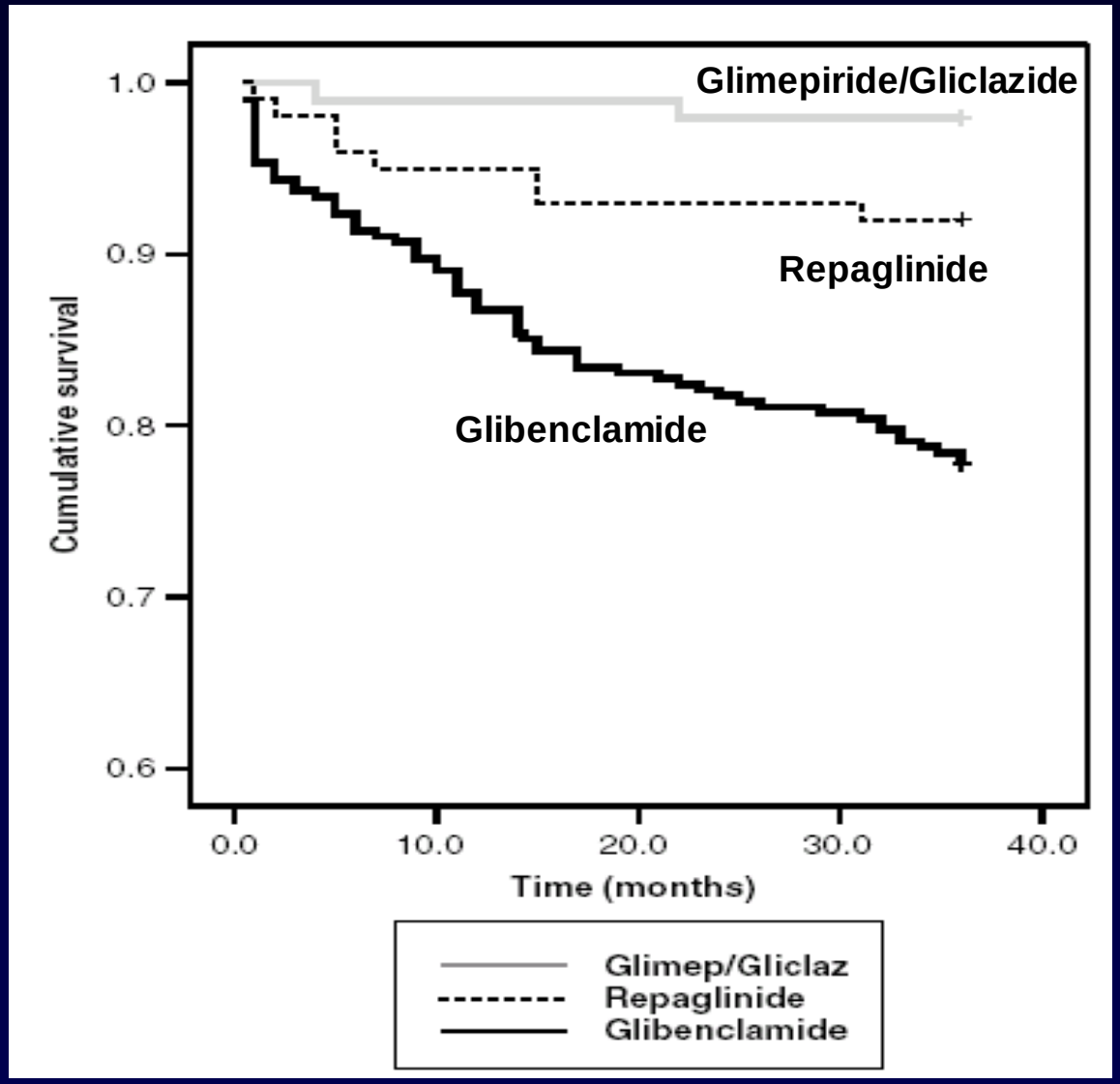
(Evans JMM - *Diabetologia* 2006)



Three-Year Mortality in T2DM Treated with Different Agonists to SUR

(Monami et al – Diab Metab Res Rev 22: 477-482, 2006)

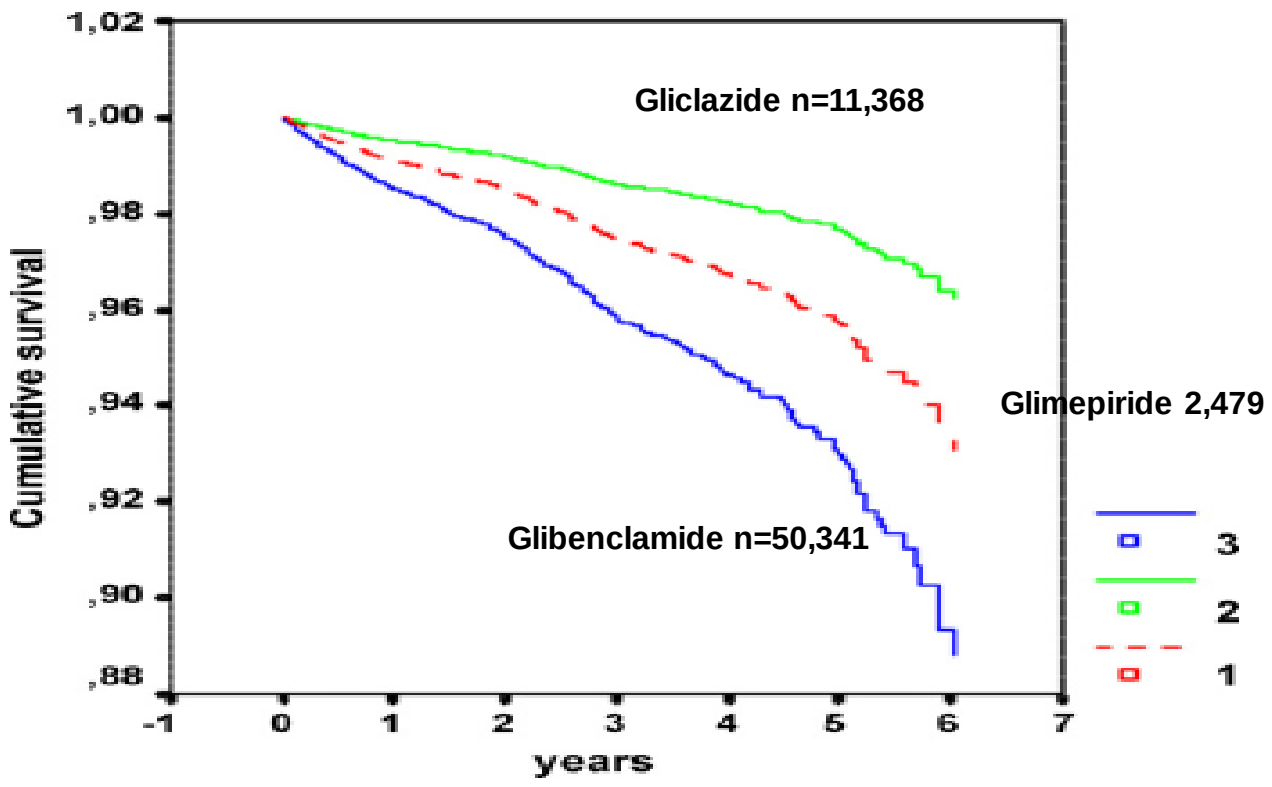
Selectivity
for B-cell SUR



N= 2002
Follow-up: 3 yrs

All-Cause Mortality According to Treatment with Different Sulphonylureas

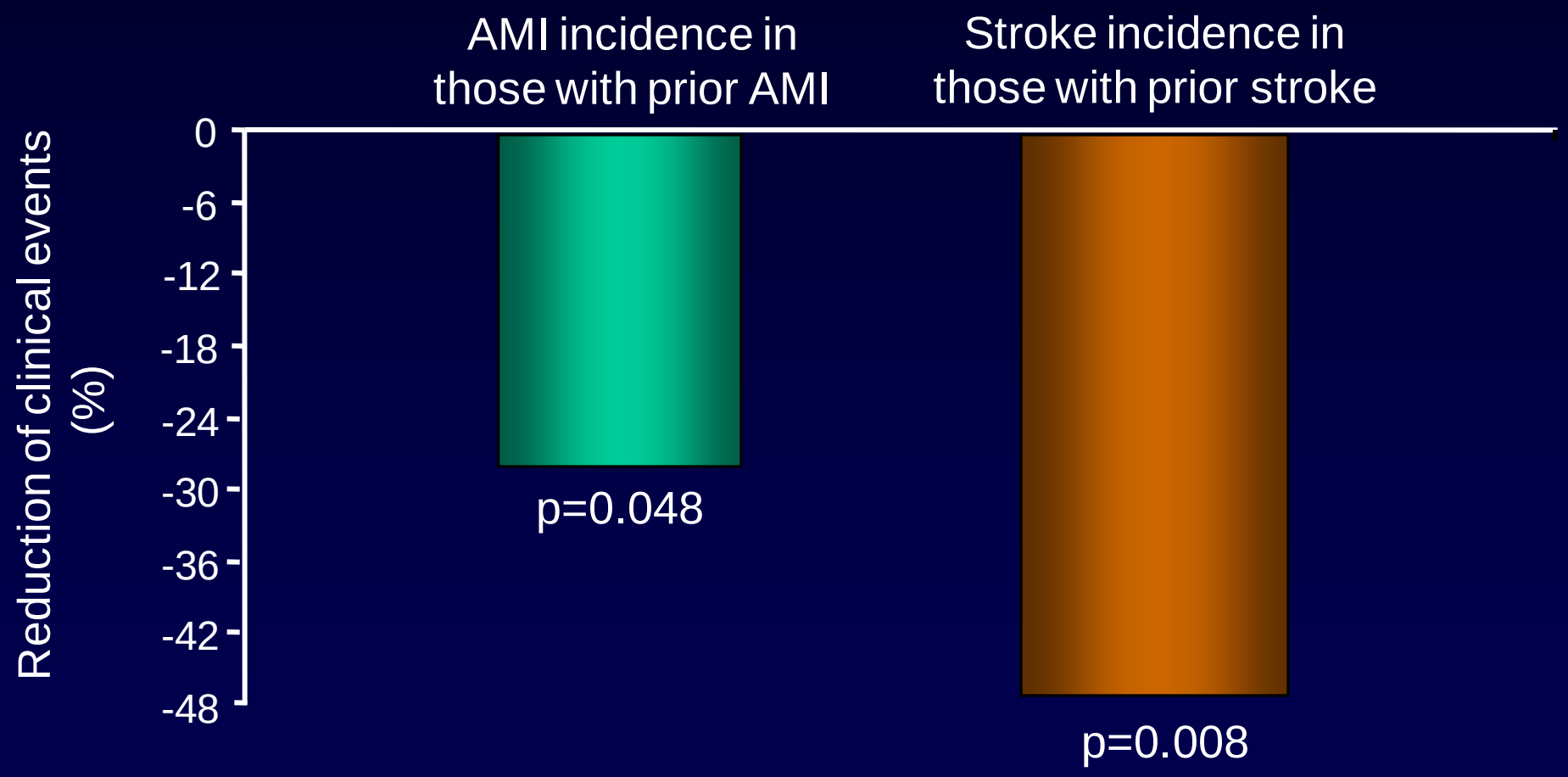
(Khalangot et al – Diab Res Clin Pract 86: 247-253, 2009)



CVD mortality Gliclazide vs. Glibenclamide
HR 0.29 [0.21-0.38], p<0.001

Secondary Prevention of CVD by Pioglitazone in T2DM: Secondary Analyses

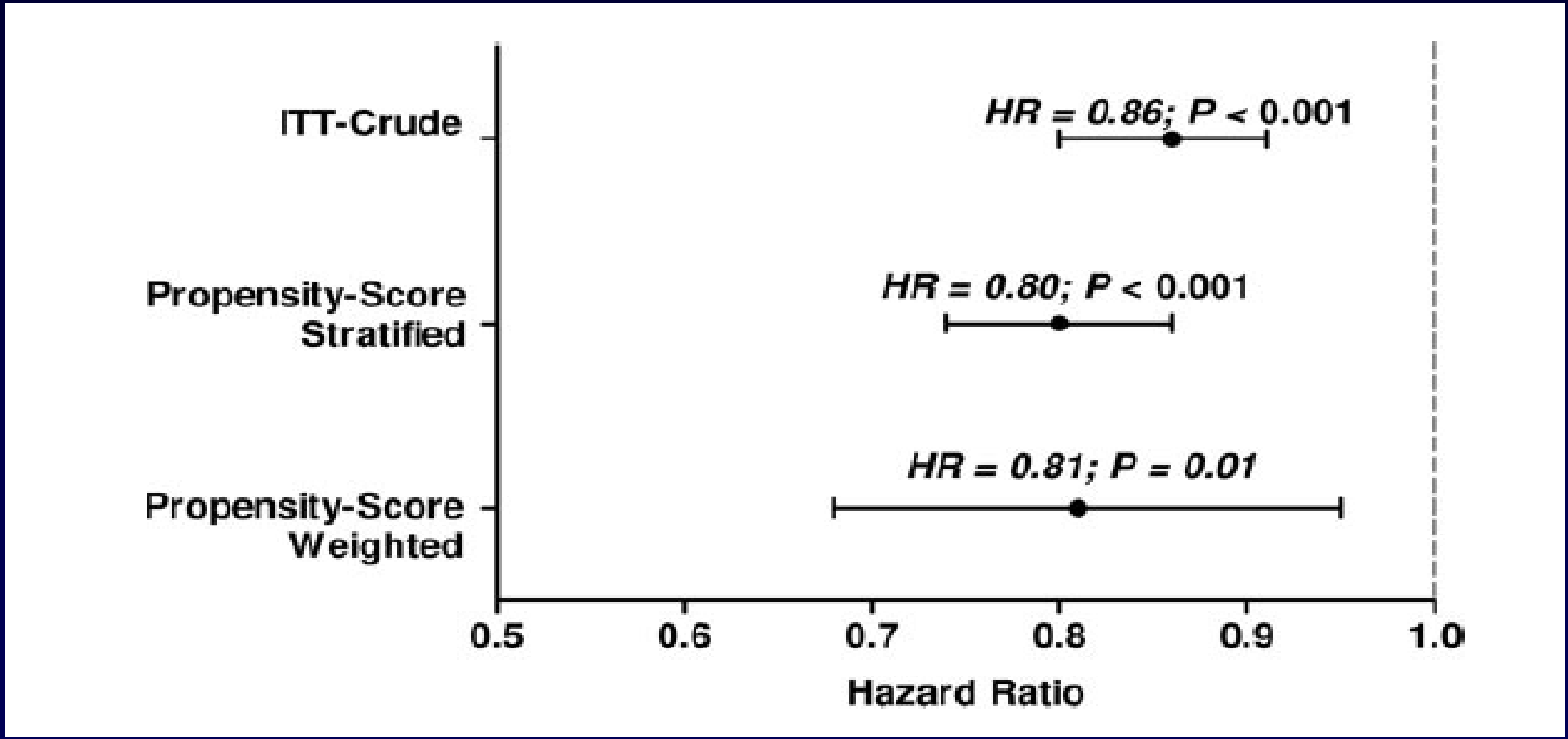
(PROactive Study; Erdmann, JACC 2007; Wilcox, Stroke 2007)



Risk of CVD in T2DM Treated with Exenatide vs. Other Anti-Diabetic Agents

A retrospective analysis of the LifeLink database

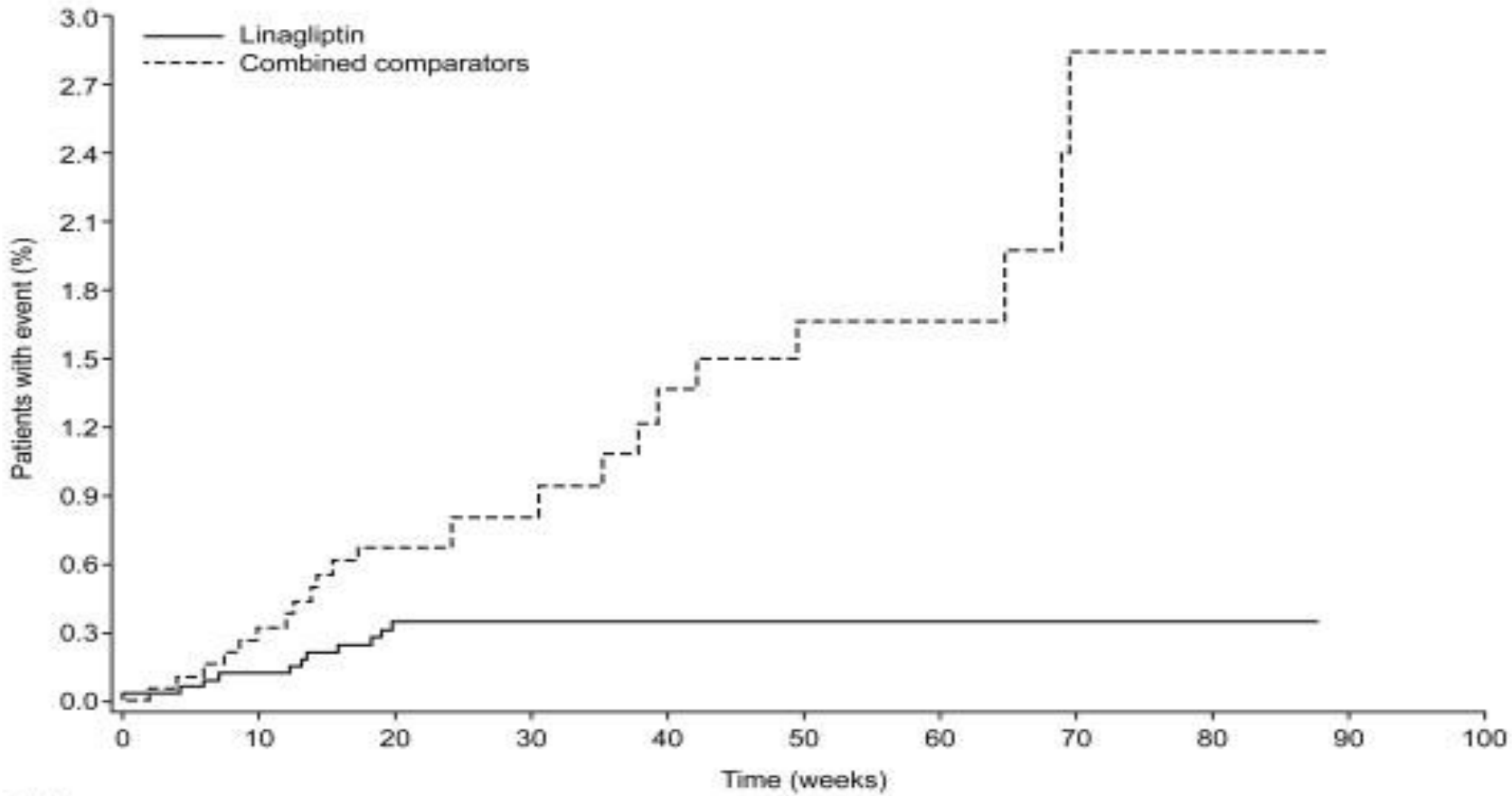
(Best et al – Diabetes Care 2011)



First new prescription: Exenatide (n=21,754) - Other agents (n=361,771)

Cardiovascular safety with linagliptin in patients with type 2 diabetes mellitus: a pre-specified, prospective, and adjudicated meta-analysis of a phase 3 programme

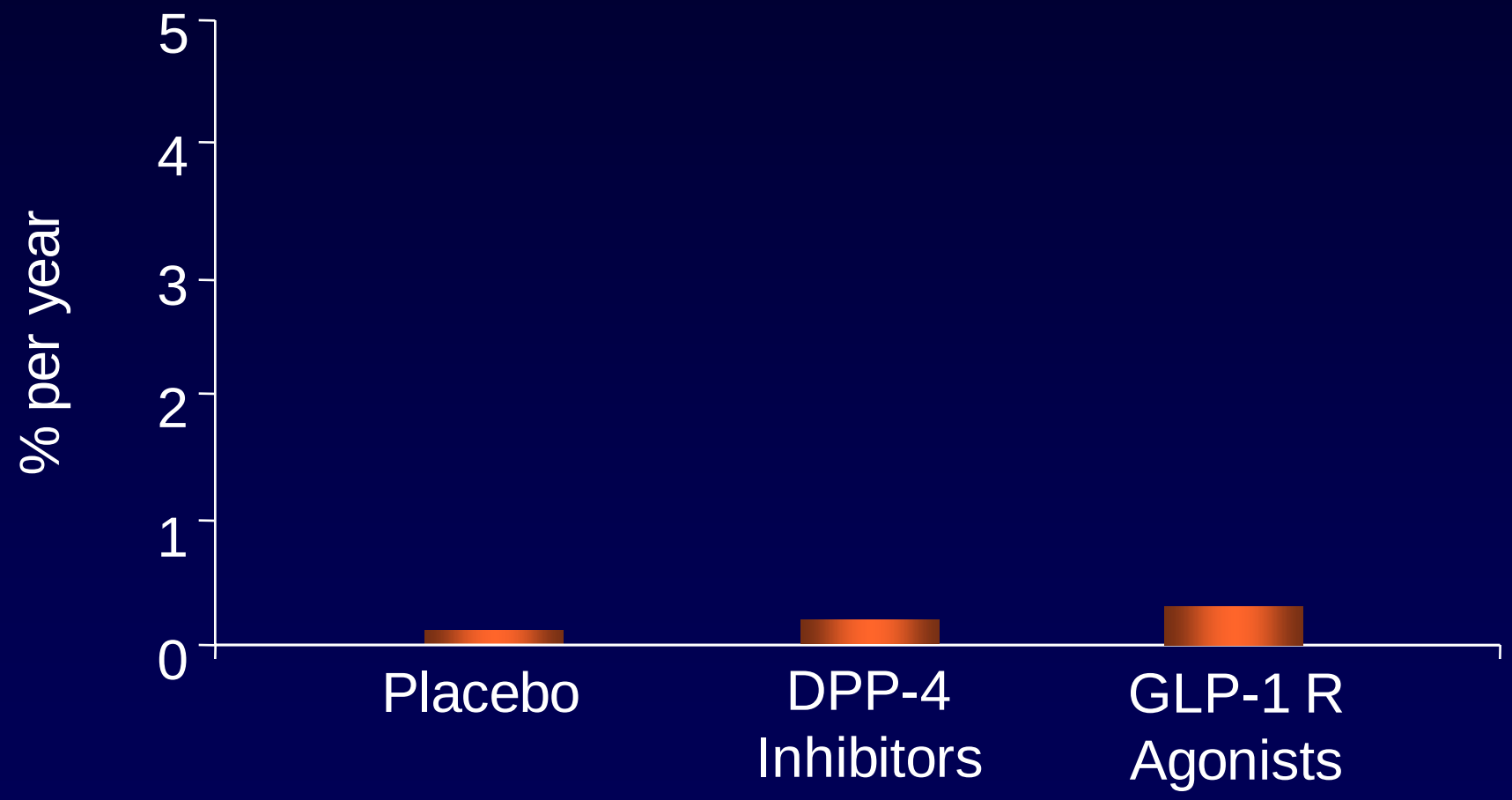
Johansen OE et al – Cardiovascular Diabetol 2012; 11: 3



Patients at risk:											
Linagliptin	3319	3220	2989	799	716	671	440	223	49	0	0
Total comparators	1920	1821	1602	730	689	648	419	211	46	0	0

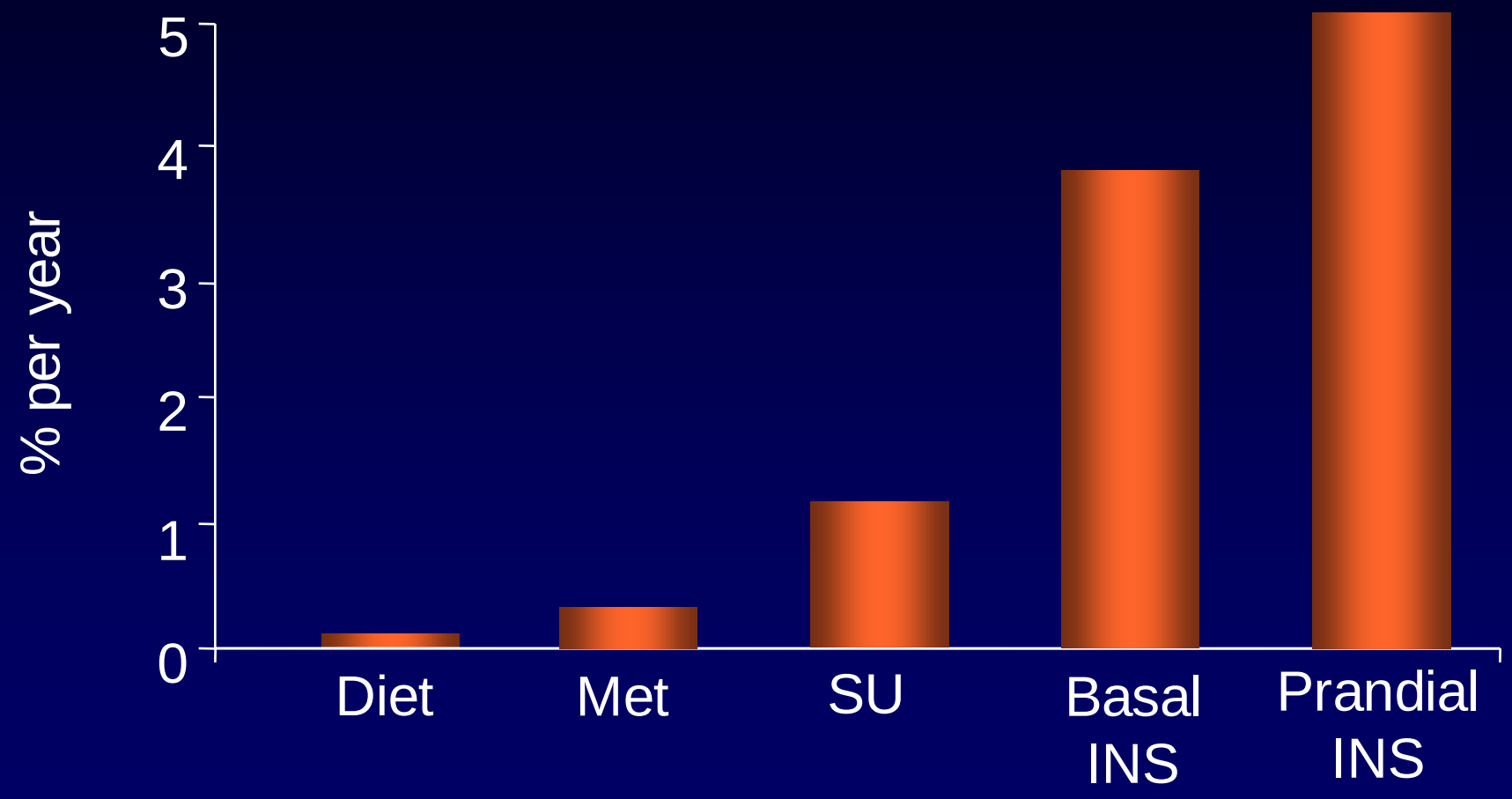
Hypoglycemia in T2DM Patients Treated in Monotherapy with the "Incretines"

(data from RCT)



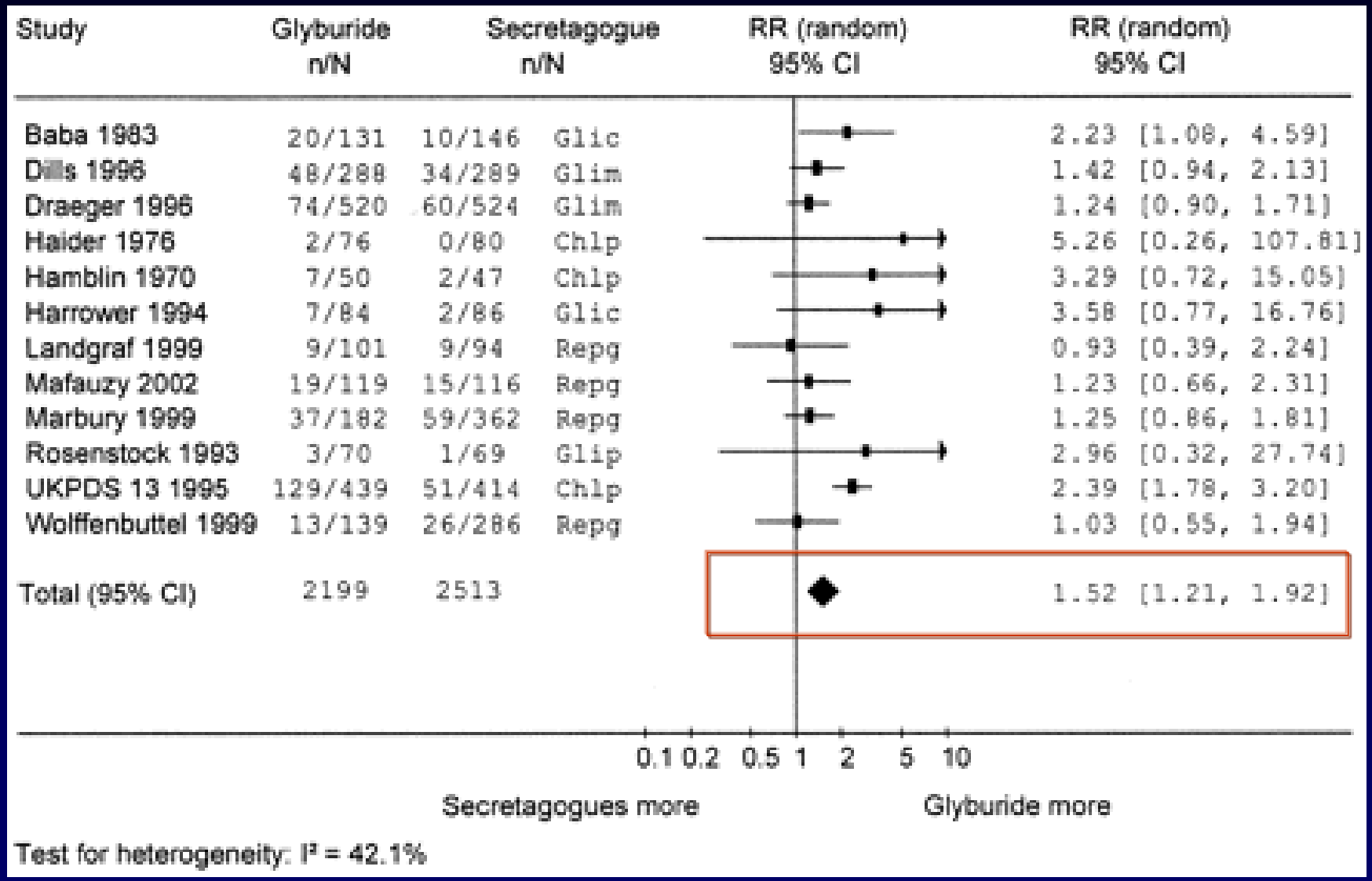
Hypoglycemia in T2DM patients randomized and maintained on monotherapy in the UKPDS

(J Diabetic Compl 20: 395, 2006)



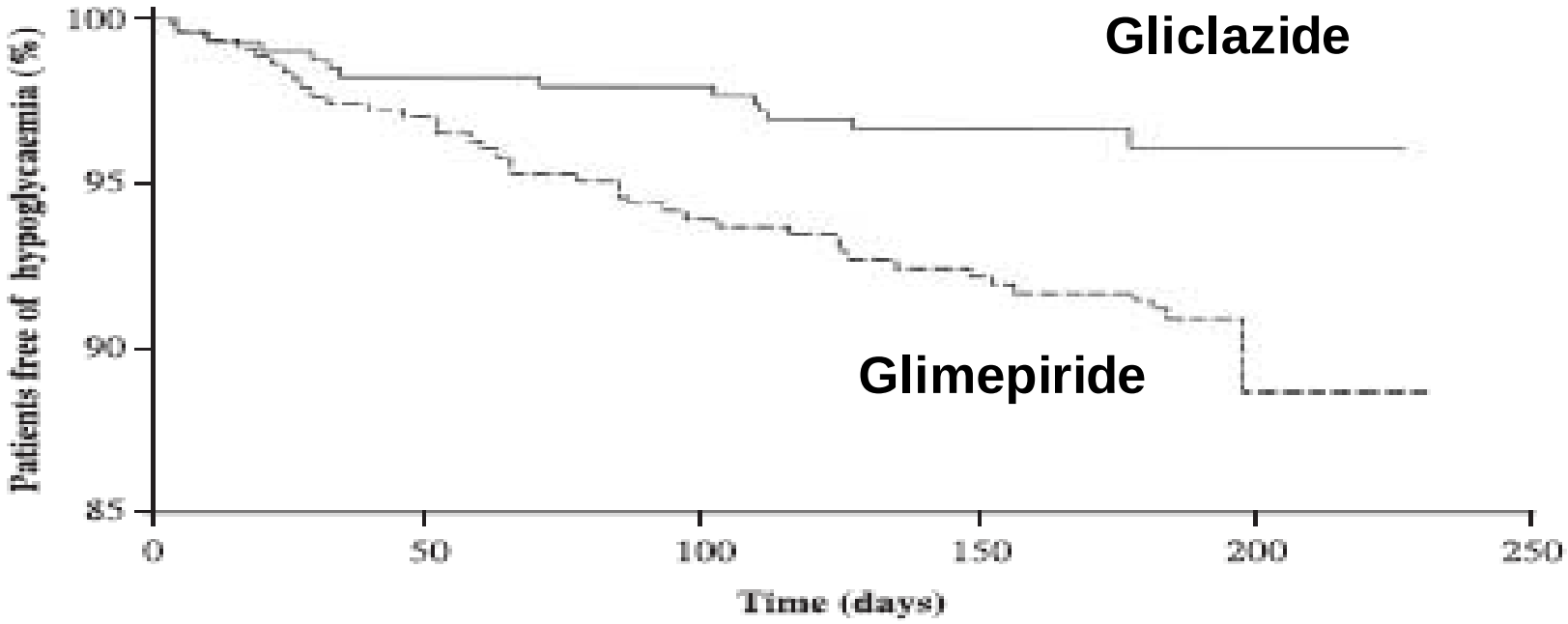
Glibenclamide is Associated to a Greater Hypoglycemia Risk than Other SUR Agonists

(Gangji et al – Diabetes Care 30: 389, 2007)



Hypoglycemia is Less Frequent with Gliclazide than Glimepiride in T2DM

(Scherthaner G et al - Europ J Clin Invest 34: 535–542, 2004)



Time to appearence of first hypoglycemia (blood glucose <3 mmol/l)

Association of Hypoglycemia and Rapid Hyperglycemia with Cardiac Ischemia in T2DM. A Study based upon Continuous Glucose and ECG Monitoring

(Desouza et al; Diabetes Care 26: 1485, 2003)

	Total episodes	Episodes with cardiac pain	Episodes with ECG abnormalities
Hypoglycemia	54	10	6
Asymptomatic	28	-	2
Symptomatic	26	10	4
Normoglycemia	-	0	0
Hyperglycemia	59	1	0
Glucose increase >100 mg in 1 h	50	9	2

VADT - Predictors of CVD Death

Variable	Hazard Ratio	P Value
Prior CVD event	3.116	0.0001
Age (per 10 yr)	2.090	<.0001
HDL (per 10 mg)	0.699	0.0079
Baseline HbA1c (per 1%)	1.213	0.0150
Severe Hypoglycemia	4.042	0.0076

The killing glycemic triad in type 2 diabetes

Fasting Hyperglycemia

Post-prandial hyperglycemia

Hypoglycemia

Factors predisposing to hypoglycemia

- Poor nutrition or irregular meals
- Cognitive impairment/dementia/depression
- Inability to face hypoglycemia/hypoglycemia unawareness
- Vision problems (difficulties with pills, glucometer, syringes)
- Organ failure (kidney, liver, etc.), comorbidities
- Polypharmacy

Interazioni farmacologiche della glibenclamide (da scheda tecnica)

Potenziamento dell'effetto ipoglicemizzante con:

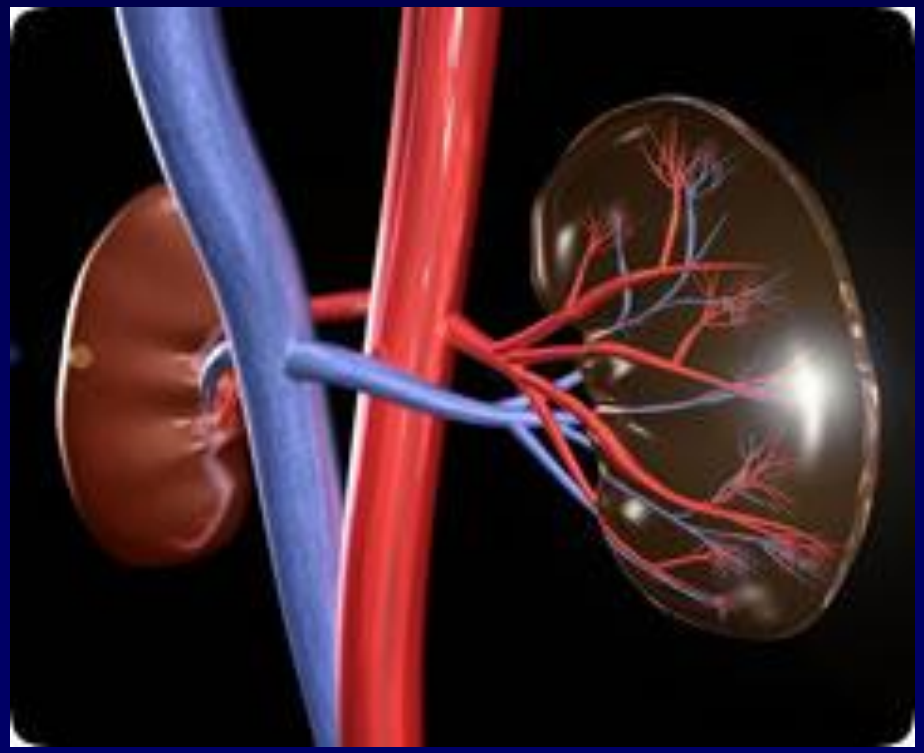
acido para-aminosalicilico, anabolizzanti, azapropazone, ciclofosfamide, chinolonici, cloramfenicolo, derivati cumarinici, disopiramide, fenfluramina, fenilbutazone, feniramidolo, fibrati, fluoxetina, H2-antagonisti, ifosfamide, inibitori delle MAO, miconazolo, pentossifillina (per via parenterale ad alte dosi), ossifenbutazone, probenecid, salicilati, simpaticolitici quali beta-bloccanti e guanetidina, sulfamidici, sulfinpirazone, tetracicline, tritoqualina, trofosfamide

Avvertenze per repaglinide (da scheda tecnica)

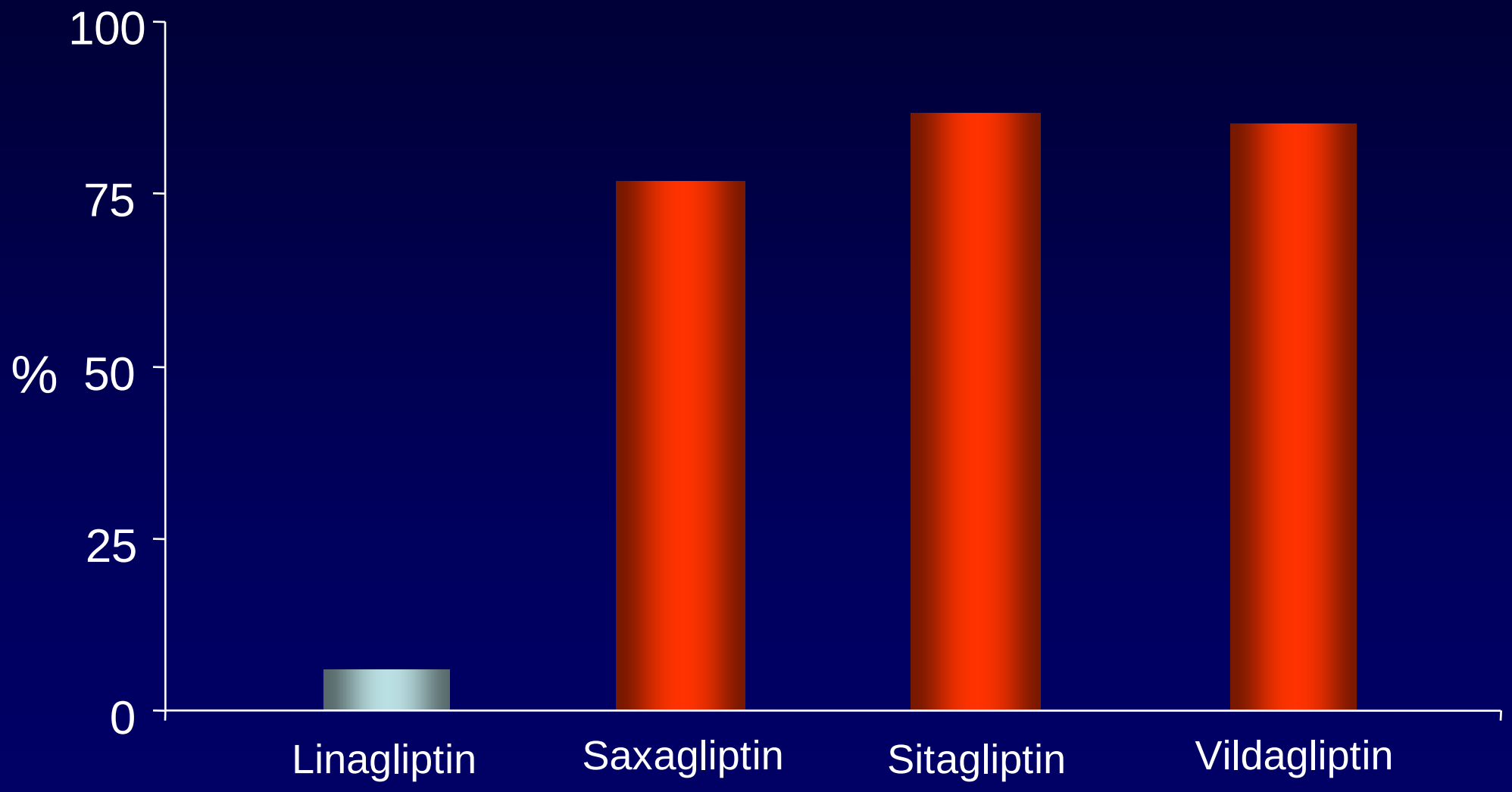
- Non sono stati effettuati studi di associazione con insulina, glitazoni, acarbosio, sulfoniluree
- Non sono stati effettuati studi in pazienti con insufficienza epatica
- Non sono stati effettuati studi nei pazienti di età <18 anni e >75 anni, pertanto in questi gruppi di pazienti il farmaco non è raccomandato
- **L'uso di repaglinide potrebbe essere associato ad aumentata incidenza di sindrome coronarica acuta**

GFR Thresholds Contraindicating Anti-Diabetic Agents

- Metformin: <60 ml/min (<30 ml/min)
- Sulphonylureas: <30 ml/min (not all)
- Repaglinide: none
- Acarbose: <25 ml/min
- Pioglitazone: <5 ml/min
- DPP-4 inhibitors: variable
- Exenatide: <30 ml/min
- Liraglutide: <60 ml/min (?)



Renal excretion of DPP-4 inhibitors (or their metabolites)



Conclusioni

- Esiste un ricco armamentario di farmaci ipoglicemizzanti che è possibile utilizzare nel diabetico anziano
- E' ragionevole ritenere che i farmaci ipoglicemizzanti siano efficaci nell'anziano come nel soggetto più giovane ma non ci sono molti trials specifici al riguardo
- I farmaci ipoglicemizzanti hanno raccomandazioni e avvertenze d'uso, controindicazioni e interazioni ben definite di cui va tenuto conto nell'anziano ancora più che nel soggetto giovane o di età matura
- La maneggevolezza (no interazioni con altri farmaci, nessuna necessità di aggiustamento della dose per insufficienza renale o epatica, ecc.) è di massima importanza e va valorizzata nella scelta del farmaco

Obiettivo principale della terapia ipoglicemizzante nel diabetico anziano

Non è TTT= Treat-to-Target

Ma è TTB= Treat-to-Benefit





Grazie