I° Congresso Congiunto AMD - SID

Piemonte e Valle d'Aosta

SINERGIE PER L'INNOVAZIONE

"se ci mettiamo insieme
ci sarà un perché"

Il diabetico tipo 2:

requiem per gli ipoglicemizzanti orali?

Marco Gallo

SCDU Endocrinologia Oncologica

AOU Città della Salute e della Scienza di Torino

Molinette - COES

Il relatore dichiara che negli ultimi due anni ha ricevuto compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- AstraZeneca
- Janssen
- Sanofi

Diabete nel mondo

Type 2 Diabetes: Why We Are Winning the Battle but Losing the War? 2015 Kelly West Award Lecture

K.M. Venkat Narayan

Diabetes Care 2016;39:653–663 | DOI: 10.2337/dc16-0205

past two decades (2) (Fig. 1). Mortality rates among both men and women with diabetes in the U.S. have declined substantially between 1997 and 2006 (3). Furthermore, rates of several diabetes complications have also declined between 1990 and 2010, including the incidence of acute myocardial infarction by 67.8%, death from hyperglycemic crisis by 64.4%, stroke by 52.7%, amputation by 51.4%, and end-stage renal disease by 28.3% (2). Such improvements are not limited to the U.S., as improvements in outcomes among people with diabetes have also been observed in other high-income countries (4,5).

Namely, large clinical trials such as the Diabetes Control and Complications Trial (DCCT), the UK Prospective Diabetes Study (UKPDS), the Steno-2 study, and their successor mega-trials have helped to shape our understanding of diabetes management, treatment intensity and targets, and clinical practice.

Evidence that we are winning the battle

- Improvements in risk factors among people with diabetes
- Declines in rates of complications

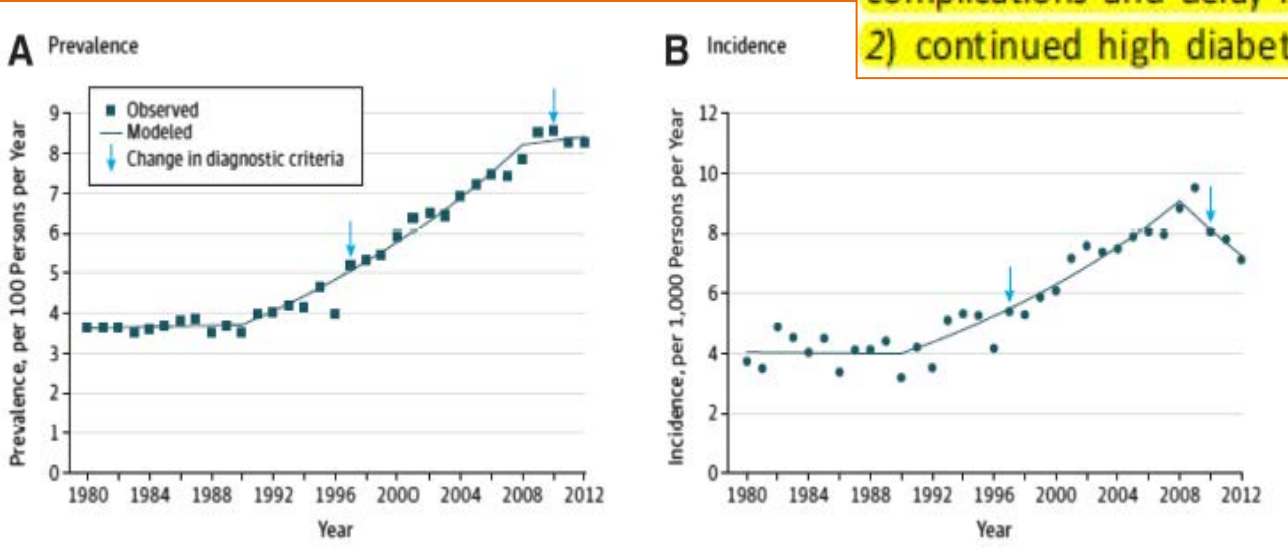
Diabete nel mondo

Type 2 Diabetes: Why We Are Winning the Battle but Losing the War? 2015 Kelly West Award Lecture

K.M. Venkat Narayan

Diabetes Care 2016;39:653–663 | DOI: 10.2337/dc16-0205

past 30 years. These increases in lifetime risk of diabetes are driven by two factors: *1*) improved survival among those with diabetes, thanks to better implementation of proven interventions to prevent complications and delay mortality, and *2*) continued high diabetes incidence.



Evidence that we are losing the war

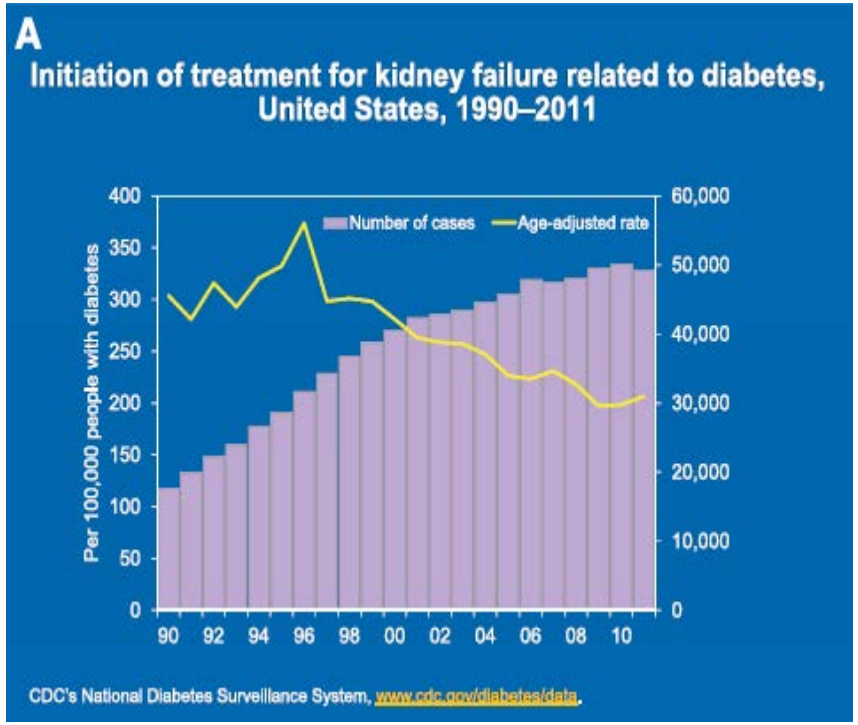
- High incidence of diabetes and increasing burden
- Explosion of diabetes globally

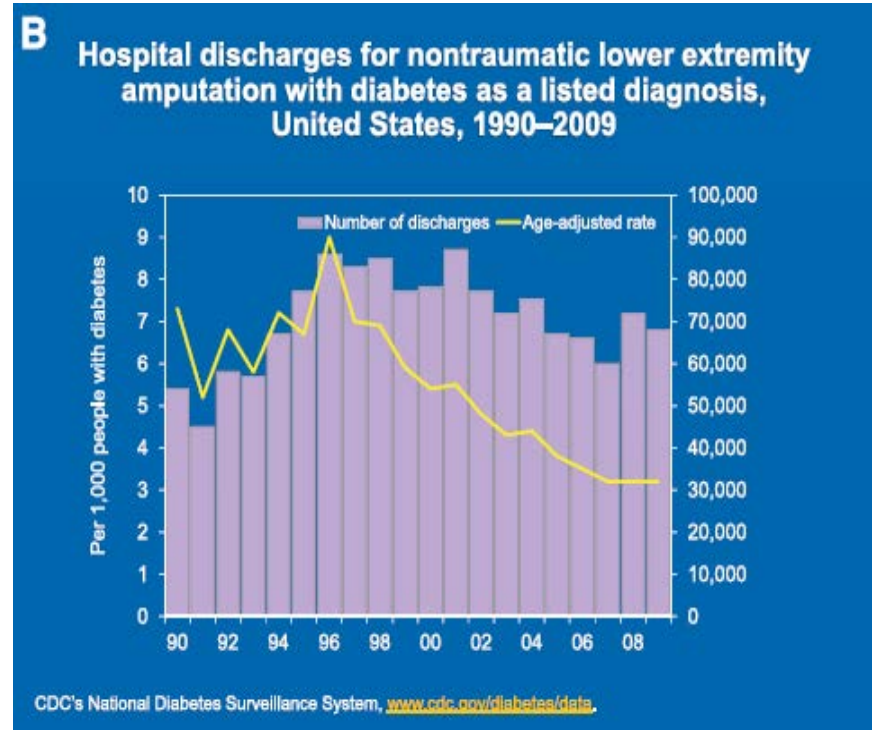
Diabete nel mondo

Type 2 Diabetes: Why We Are Winning the Battle but Losing the War? 2015 Kelly West Award Lecture

K.M. Venkat Narayan

Diabetes Care 2016;39:653–663 | DOI: 10.2337/dc16-0205





Diabete nel mondo

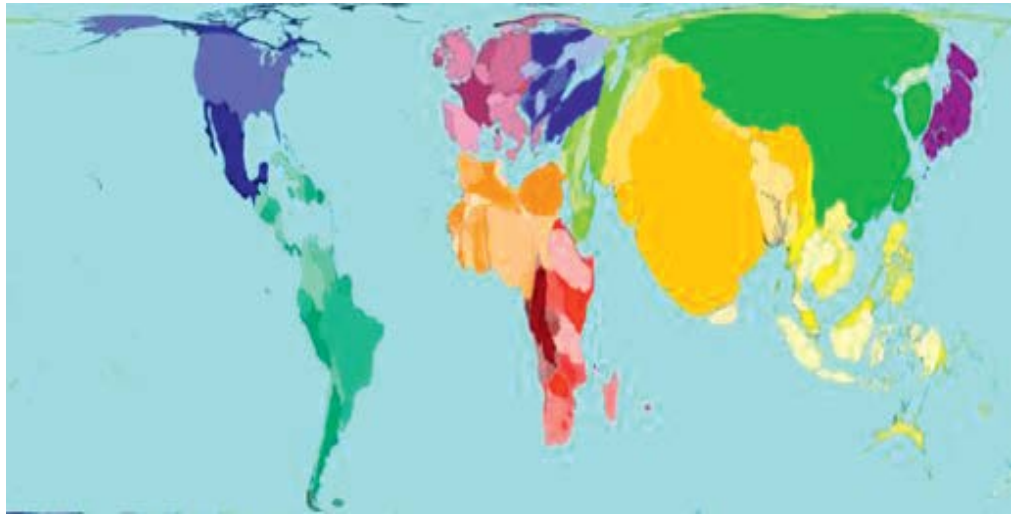
Type 2 Diabetes: Why We Are Winning the Battle but Losing the War? 2015 Kelly West Award Lecture

K.M. Venkat Narayan

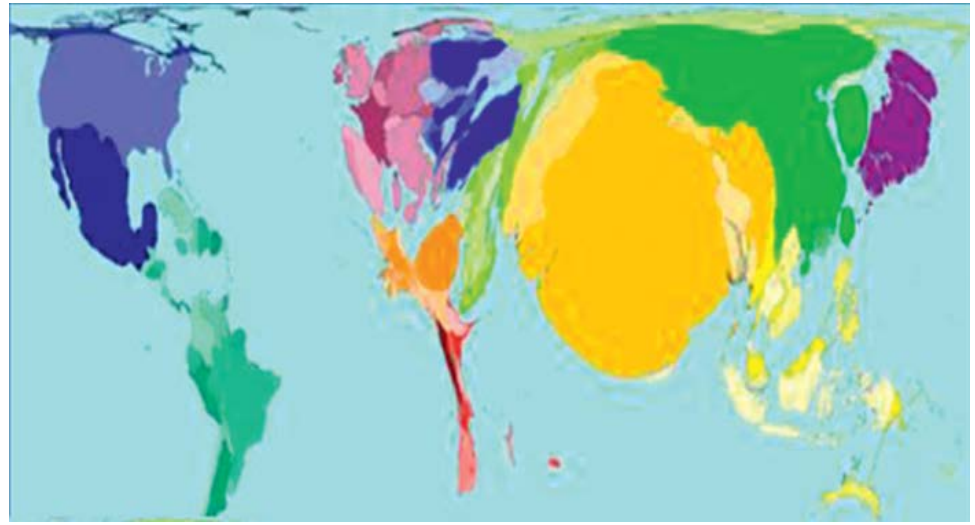
Diabetes Care 2016;39:653–663 | DOI: 10.2337/dc16-0205

International Diabetes Federation

75% delle persone con DM vive in Paesi a basso/medio reddito



popolazione



popolazione con DM

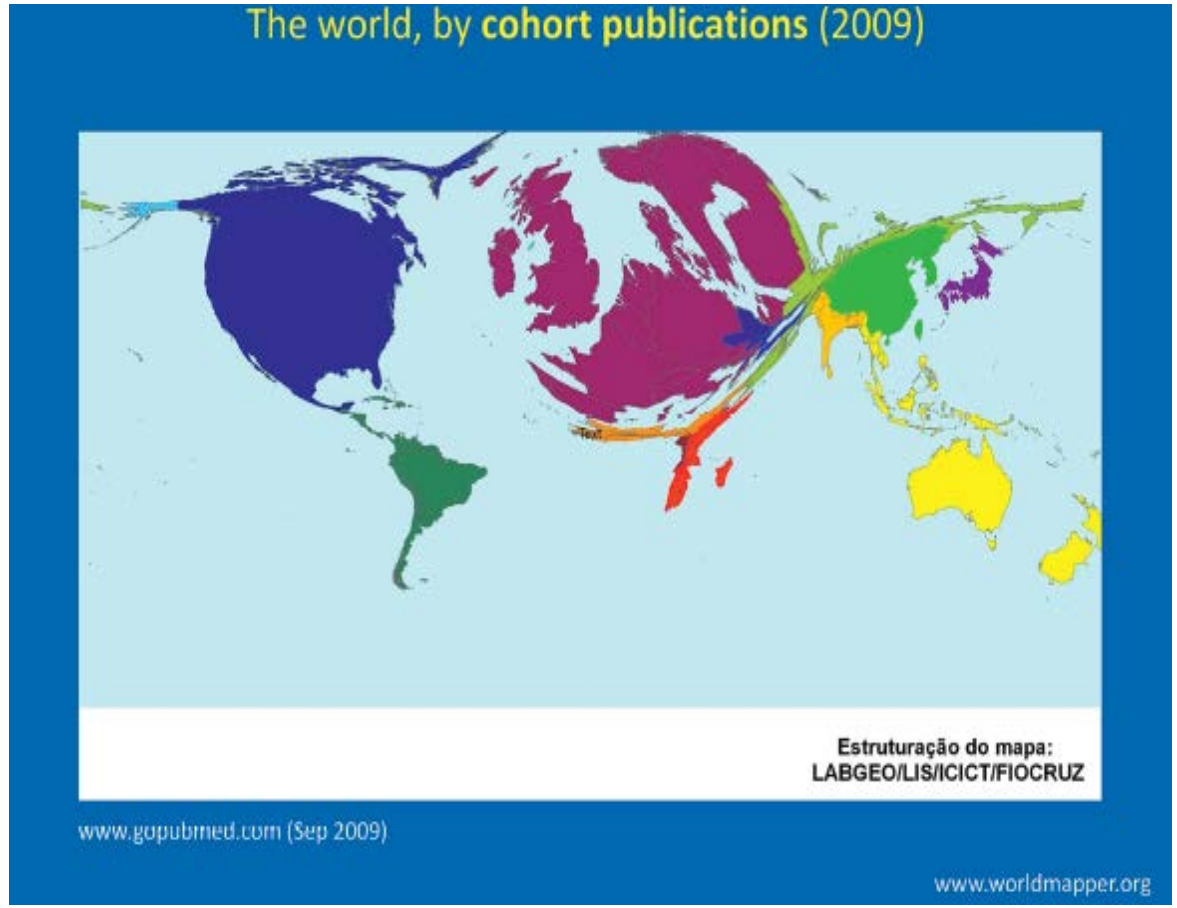
Diabete nel mondo

Type 2 Diabetes: Why We Are Winning the Battle but Losing the War? 2015 Kelly West Award Lecture

K.M. Venkat Narayan

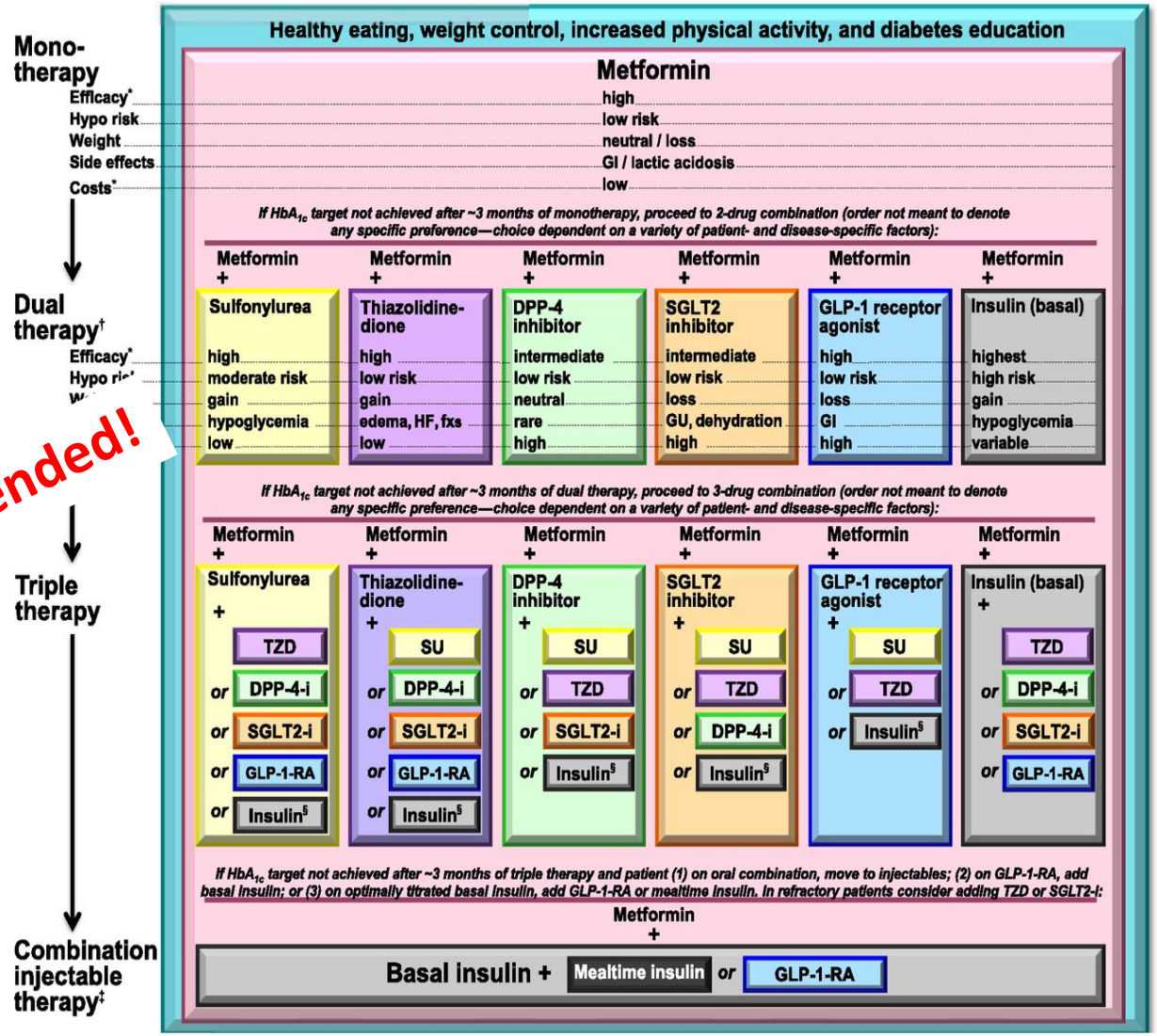
Diabetes Care 2016;39:653–663 | DOI: 10.2337/dc16-0205

The war will not be won without viewing type 2 diabetes in its global context as the world becomes rapidly more interconnected in the midst of major demographic, economic, and environmental transitions

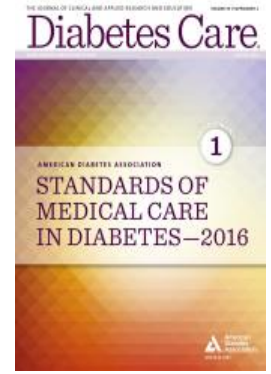


Studi sul DM

Standards ADA 2016

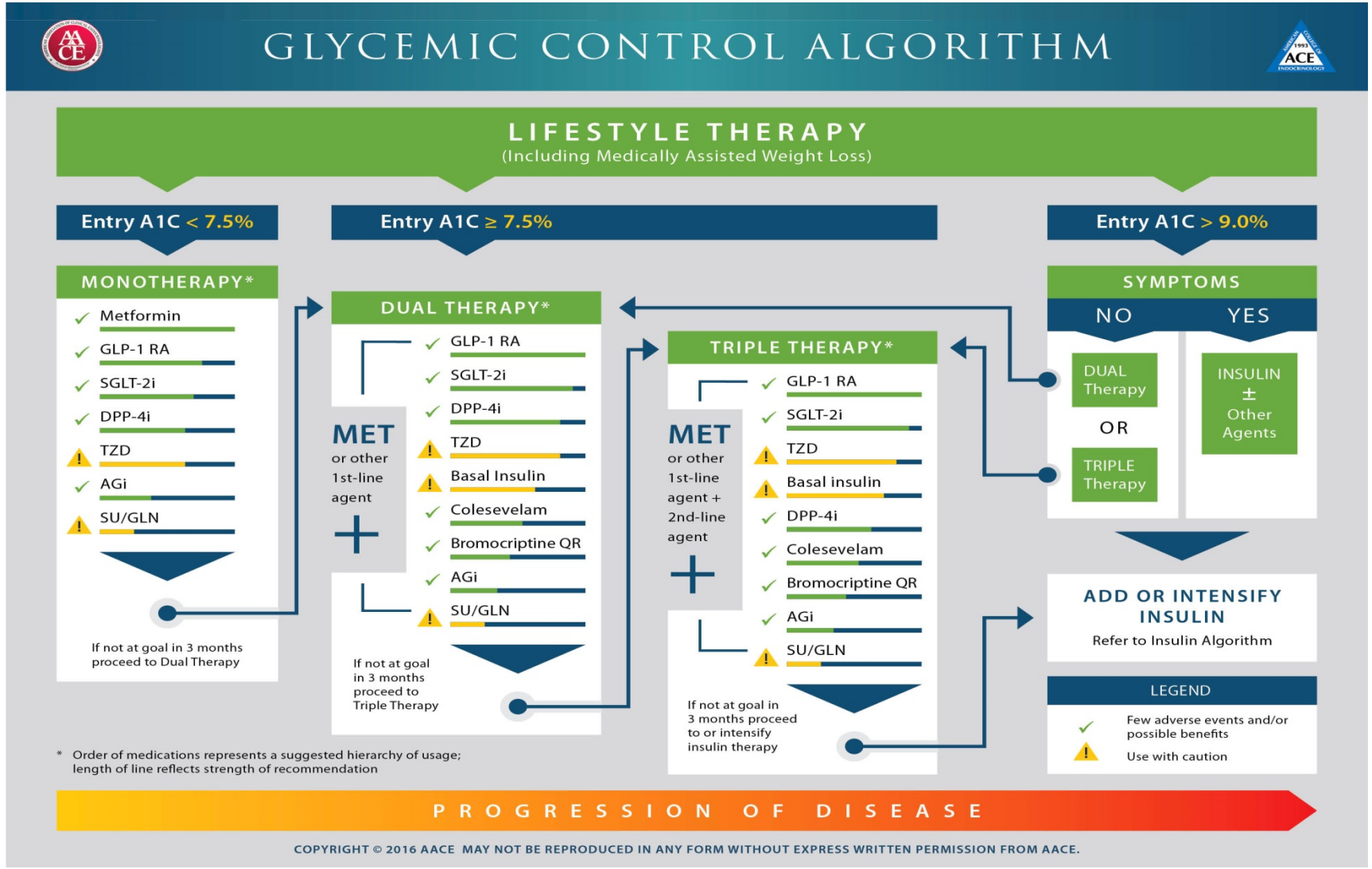


no priority is intended!



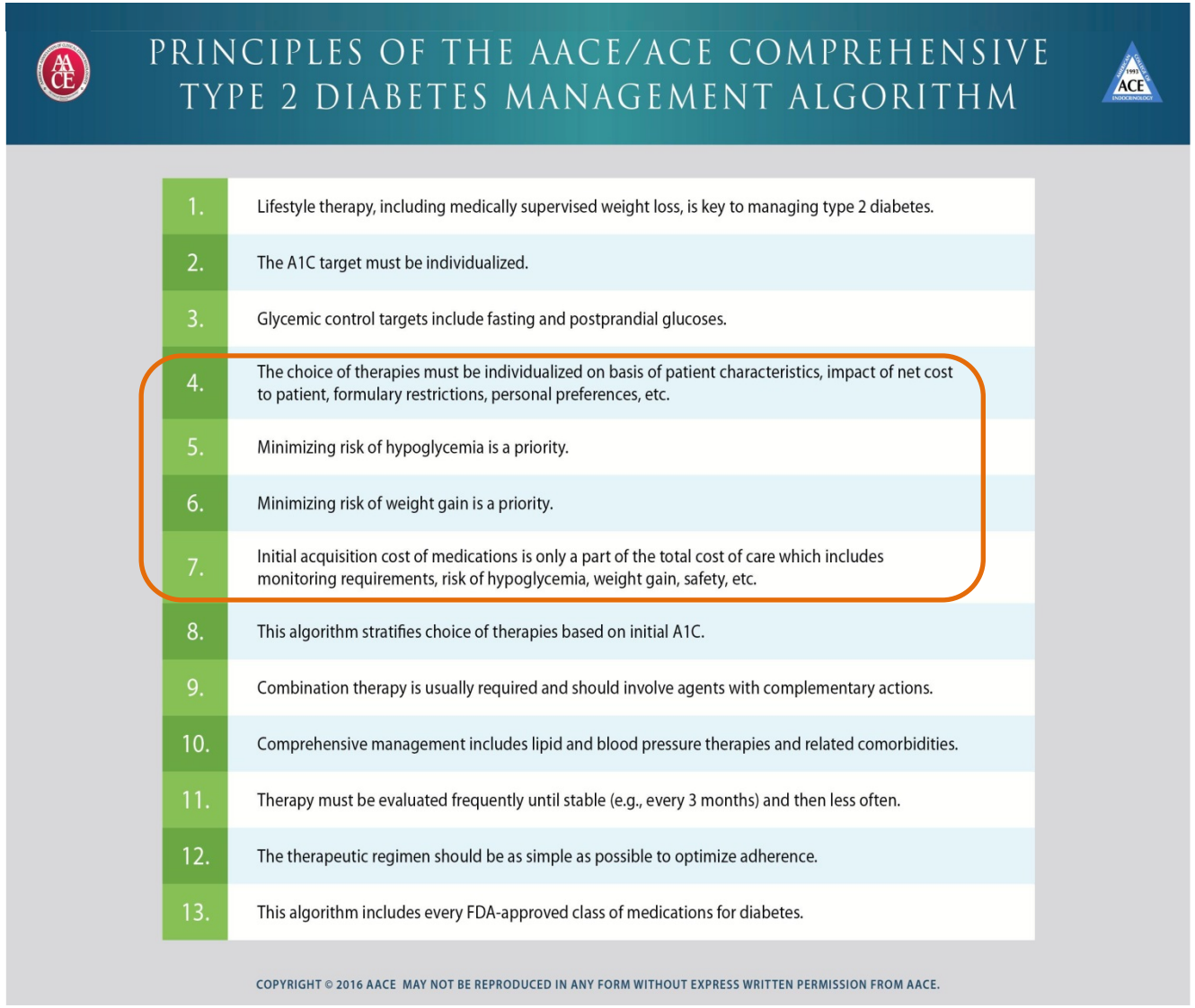
AACE/ACE Comprehensive Type 2 Diabetes Management Algorithm 2016

I° Congresso Congiunto AMD-SID
Piemonte e Valle d'Aosta
SINERGIE PER L'INNOVAZIONE
"se ci mettiamo insieme ci sarà un perché"



AACE/ACE Comprehensive Type 2 Diabetes Management Algorithm 2016

I° Congresso Congiunto AMD-SID
Piemonte e Valle d'Aosta
SINERGIE PER L'INNOVAZIONE
"se ci mettiamo insieme ci sarà un perché"



PRINCIPLES OF THE AACE/ACE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM

1.	Lifestyle therapy, including medically supervised weight loss, is key to managing type 2 diabetes.
2.	The A1C target must be individualized.
3.	Glycemic control targets include fasting and postprandial glucoses.
4.	The choice of therapies must be individualized on basis of patient characteristics, impact of net cost to patient, formulary restrictions, personal preferences, etc.
5.	Minimizing risk of hypoglycemia is a priority.
6.	Minimizing risk of weight gain is a priority.
7.	Initial acquisition cost of medications is only a part of the total cost of care which includes monitoring requirements, risk of hypoglycemia, weight gain, safety, etc.
8.	This algorithm stratifies choice of therapies based on initial A1C.
9.	Combination therapy is usually required and should involve agents with complementary actions.
10.	Comprehensive management includes lipid and blood pressure therapies and related comorbidities.
11.	Therapy must be evaluated frequently until stable (e.g., every 3 months) and then less often.
12.	The therapeutic regimen should be as simple as possible to optimize adherence.
13.	This algorithm includes every FDA-approved class of medications for diabetes.

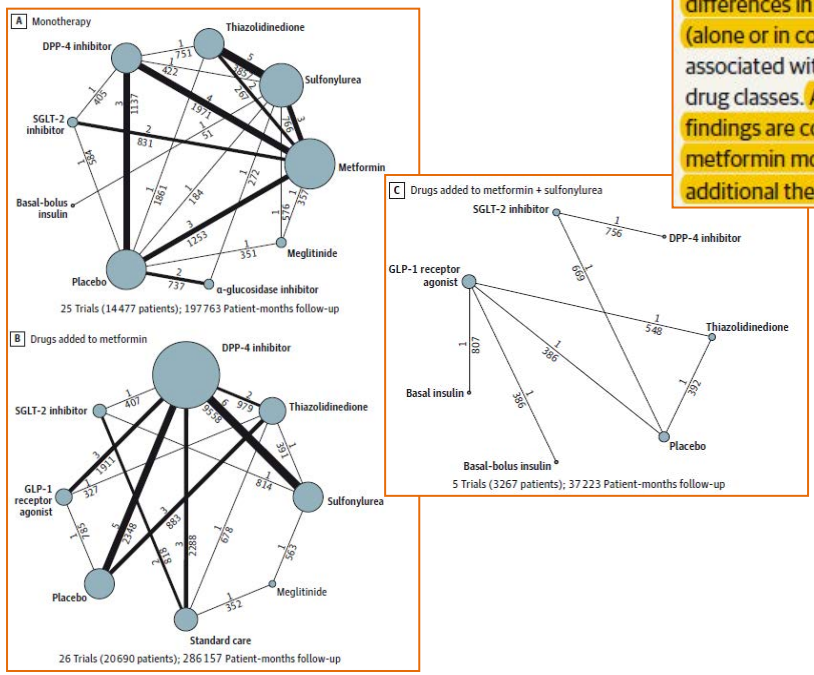
I° Congresso Congiunto AMD - SID
Piemonte e Valle d'Aosta
SINERGIE PER L'INNOVAZIONE
"se ci mettiamo insieme
ci sarà un perché"

Comparison of Clinical Outcomes and Adverse Events Associated With Glucose-Lowering Drugs in Patients With Type 2 Diabetes

A Meta-analysis

JAMA. 2016;316(3):313-324.

Suetonia C. Palmer, PhD; Dimitris Mavridis, PhD; Antonio Nicolucci, MD; David W. Johnson, PhD; Marcello Tonelli, MD; Jonathan C. Craig, PhD; Jasjot Maggo, MMed; Vanessa Gray, MSc; Giorgia De Berardis, MSc; Marinella Ruospo, MSc; Patrizia Natale, MSc; Valeria Saglimbene, MSc; Sunil V. Badve, MD; Yeoungjee Cho, PhD; Annie-Claire Nadeau-Fredette, MD; Michael Burke, MD; Labib Faruque, MSc; Anita Lloyd, MSc; Nasreen Ahmad, BSc; Yuanchen Liu; Sophanny Tiv, BSc; Natasha Wiebe, MMath; Giovanni F. M. Strippoli, PhD



CONCLUSIONS AND RELEVANCE Among adults with type 2 diabetes, there were no significant differences in the associations between any of 9 available classes of glucose-lowering drugs (alone or in combination) and the risk of cardiovascular or all-cause mortality. Metformin was associated with lower or no significant difference in HbA_{1C} levels compared with any other drug classes. All drugs were estimated to be effective when added to metformin. These findings are consistent with American Diabetes Association recommendations for using metformin monotherapy as initial treatment for patients with type 2 diabetes and selection of additional therapies based on patient-specific considerations.

OBJECTIVE To estimate the relative efficacy and safety associated with glucose-lowering drugs including insulin.

...olled Trials, MEDLINE, and EMBASE

...r longer duration.

...k meta-analysis.

Key Points

Question What are the most effective medical treatments for type 2 diabetes?

Findings In this systematic review with network meta-analysis, risks of cardiovascular and all-cause mortality were not different between any glucose-lowering drugs alone or in combination. Metformin was associated with lower or similar HbA_{1C} levels compared with all other drugs given as monotherapy. All drugs were estimated to be effective when added to metformin.

Meaning Metformin monotherapy is an appropriate initial treatment for patients with type 2 diabetes. Selection of additional therapies can be based on patient-specific considerations.

NICE National Institute for Health and Care Excellence

Managing blood glucose in adults with type 2 diabetes

http://pathways.nice.org.uk/pathways/type-2-diabetes-in-adults

Pathway last updated: 24 May 2016

Recommendations

This updated guideline includes new recommendations on:

- individualised care
- managing blood glucose levels:
  - HbA1c measurement and targets
  - self-monitoring of blood glucose
  - drug treatment
- antiplatelet therapy
- managing complications

NICE Pathways

For adults with type 2 diabetes, discuss the benefits and risks of drug treatment, and the options available. Base the choice of drug treatment(s) on:

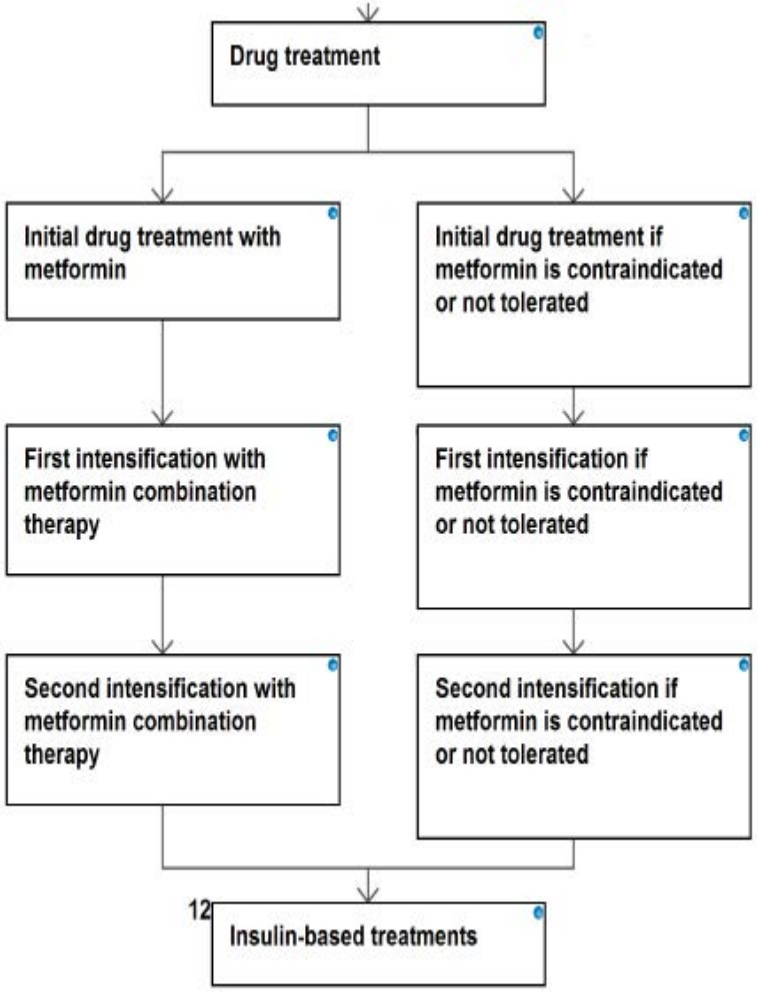
- the effectiveness of the drug treatment(s) in terms of metabolic response
- safety (see Medicines and Healthcare products Regulatory Agency [MHRA] guidance) and tolerability of the drug treatment(s)
- the person's individual clinical circumstances, for example, comorbidities, risks from polypharmacy
- the person's individual preferences and needs
- the licensed indications or combinations available
- cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).

NICE National Institute for Health and Care Excellence

Managing blood glucose in adults with type 2 diabetes

http://pathways.nice.org.uk/pathways/type-2-diabetes-in-adults

Pathway last updated: 24 May 2016



7 First intensification with metformin combination therapy

In this pathway, first intensification of drug treatment means treatment with 2 non-insulin blood glucose lowering therapies in combination (dual therapy).

In adults with type 2 diabetes, if initial drug treatment with metformin has not continued to control HbA1c to below the person's individually agreed threshold for intensification, consider dual therapy with:

- metformin and a DPP-4 inhibitor or
- metformin and pioglitazone[1] or
- metformin and a sulfonylurea.

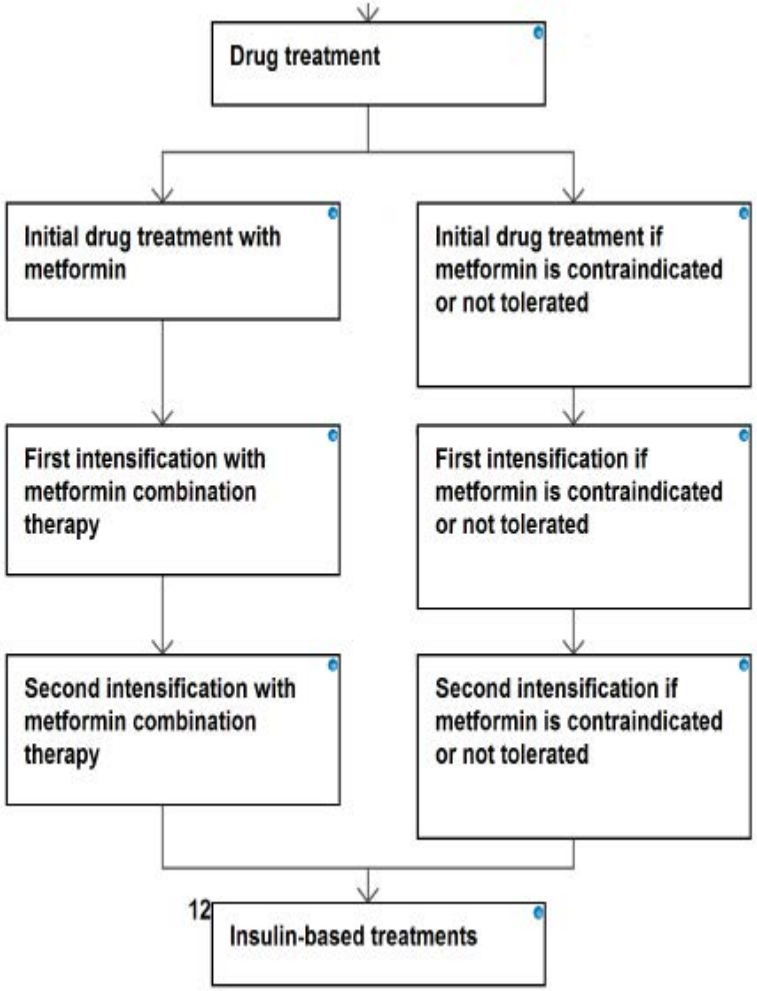
Treatment with combinations of medicines including SGLT-2 inhibitors may be appropriate for some people with type 2 diabetes; see below.

NICE National Institute for Health and Care Excellence

Managing blood glucose in adults with type 2 diabetes

http://pathways.nice.org.uk/pathways/type-2-diabetes-in-adults

Pathway last updated: 24 May 2016



9 Initial drug treatment if metformin is contraindicated or not tolerated

In this pathway, initial drug treatment means treatment with a single non-insulin blood glucose lowering therapy (monotherapy).

In adults with type 2 diabetes, if metformin is contraindicated or not tolerated, consider initial drug treatment[1] with:

- a DPP-4 inhibitor or
- pioglitazone[2] or
- a sulfonylurea.

Treatment with combinations of medicines including SGLT-2 inhibitors may be appropriate for some people with type 2 diabetes; see below.

Standard AMD-SID

I° Congresso Congiunto AMD-SID
Piemonte e Valle d'Aosta
SINERGIE PER L'INNOVAZIONE
"se ci mettiamo insieme
ci sarà un perché"

Tabella 13. Terapia farmacologica

1. Iniziare una terapia farmacologica orale quando gli interventi sullo stile di vita non sono più in grado di mantenere il controllo della glicemia ai valori desiderati (in genere HbA_{1c} 53 mmol/mol o <7%). Mantenere e rinforzare sempre l'orientamento del paziente verso un corretto stile di vita. Valutare l'eventuale inizio o aumento della dose del farmaco orale ogni 2-6 mesi, con il fine di raggiungere e mantenere nel tempo valori di HbA_{1c} 53 mmol/mol o <7%.

2. Iniziare con la metformina (prima scelta) partendo con basse dosi da incrementare nel tempo al fine di evitare intolleranza gastrointestinale. Ove tollerata e non controindicata, raggiungere sempre la dose di almeno 2 g/die, indipendentemente dagli obiettivi glicemici raggiunti. Controllare periodicamente la funzione renale (eGFR con CKD-EPI). Utilizzare particolare cautela per filtrato glomerulare <60 ml/min/1,73m^2 e sospendere per filtrato glomerulare <30 ml/min/1,73m^2 o in pazienti a rischio di insufficienza renale acuta; in caso di controindicazioni o di intolleranza, passare direttamente al paragrafo successivo.

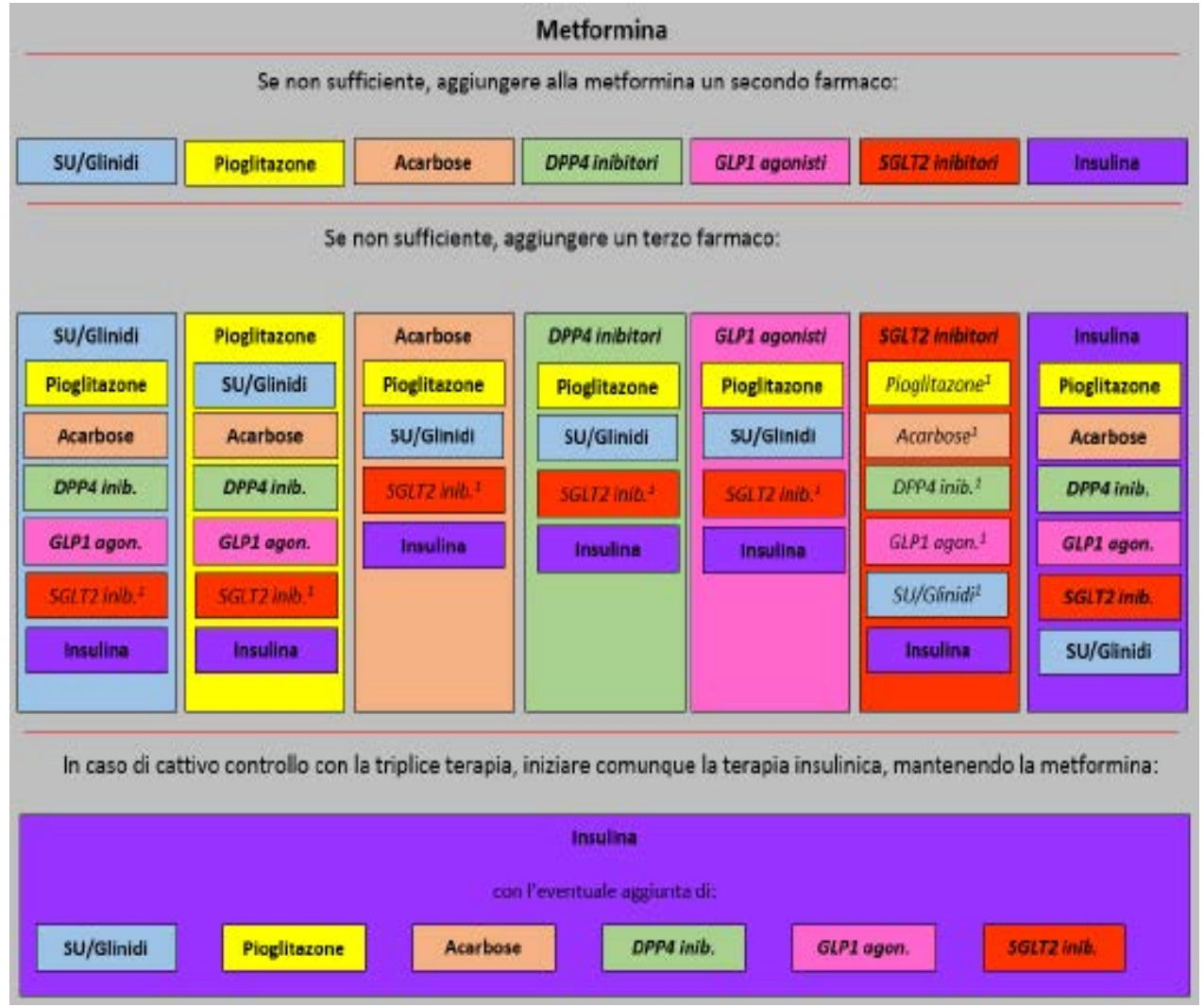
3. Aggiungere (o, in caso di intolleranza/controindicazione alla metformina, sostituire con) un secondo farmaco (acarbosio/sulfonilurea/repaglinide/glitazone/gliptina/agonista recettore GLP1/gliflozina/insulina) quando: a) la metformina da sola non riesce a mantenere il buon controllo della glicemia; b) non è tollerata o è controindicata; c) si ritiene che il valore di emoglobina glicata prima di iniziare il farmaco sia troppo elevato per raggiungere, con la sola metformina, il target terapeutico. Scegliere fra le diverse opzioni terapeutiche sulla base del profilo di rischio e beneficio, anche in funzione delle eventuali comorbilità, riportate in figura. Se la terapia può indurre ipoglicemia, prescrivere l'uso di presìdi per l'automonitoraggio. Quando la compliance può essere un problema, prediligere farmaci in monosomministrazione.

4. Usare la triplice terapia quando le associazioni precedentemente prescritte non sono in grado di mantenere il controllo dell'emoglobina glicata prescelta; non esistono studi di confronto che mostrino la superiorità di uno schema rispetto a un altro.

5. In ogni passaggio valutare la possibilità di un inizio precoce della terapia insulinica.

	Metfor-mina	Acarbosio	Agon-sta GLP-1	Gliflo-zina	Glip-tina	Pioglita-zone	SU/ glinide	Insulina basale	Insulina basal-bolus
Interazioni con altri farmaci	-	-	-	-	-	+	+++	+++	++++
Ipoglicemie	-	-	-	-	-	-	++	+++	++++
Aumento di peso	-	-	-	-	-	++	+	+++	++++
Pancreatiti	-	-	+/-	-	+/-	-	-	-	-
Fratture	-	-	-	-/+[a]	-	+++	-	-	-
Scompenso cardiaco	-	-	-	-	-/+[b]	++	+	-	-
Disturbi gastrointe-stinali	++	+++	++	-/+	-	-	-	-	-
Infezioni genitali	-	-	-	+	-	-	-	-	-

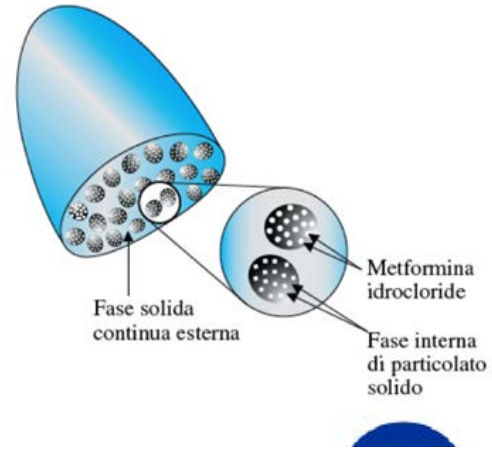
Standard italiani per la cura del diabete mellito 2016



Quindi:

- Come abbiamo curato il DM fino a ora va bene
- 1° obiettivo globale: stili di vita/prevenzione
- Efficacia e sicurezza: NON evidenti differenze
- Per il 75% delle persone con DM, i costi sono un problema

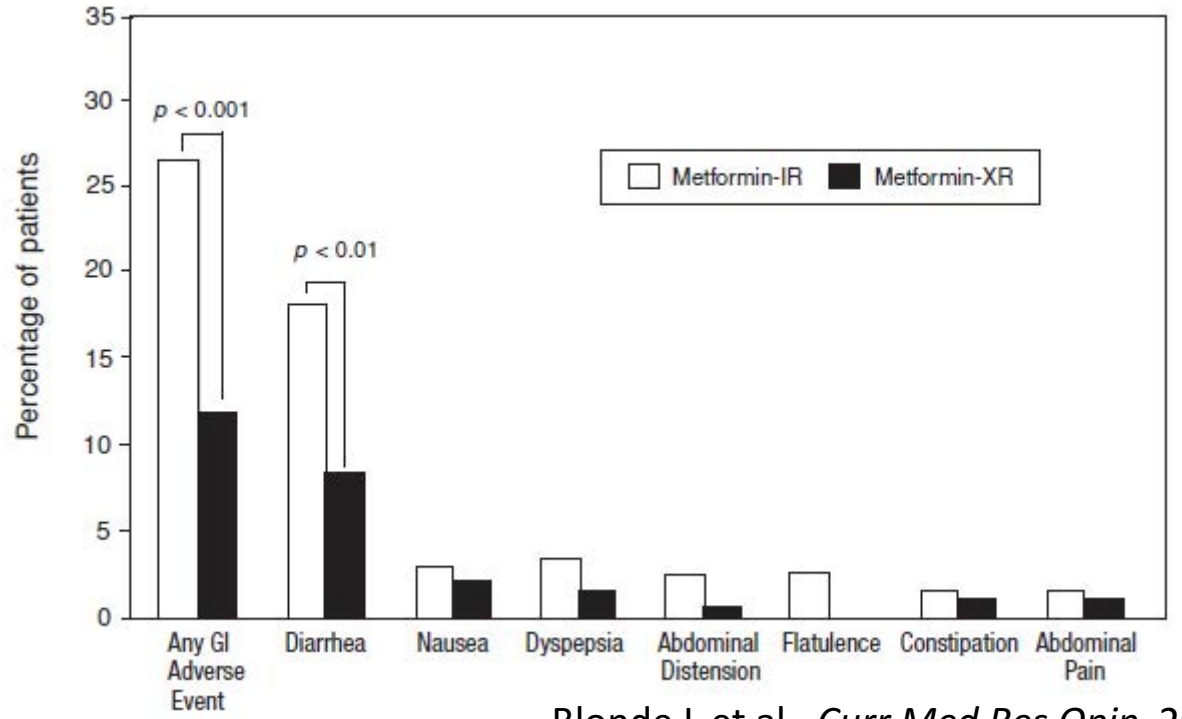
IL DIABETICO TIPO 2:
REQUIEM PER GLI IPOGLICEMIZZANTI ORALI?



14 Otto
EMA/60

Uso
este
ridot

Aggio
pazie



Blonde L et al., *Curr Med Res Opin* 2004

sulfoniluree

- costo/efficacia
- esperienza
- prescrivibilità

- ipoglicemie
- aumento ponderale
- safety CV
- durability

IL DIABETICO TIPO 2:
REQUIEM PER SULFONILUREE E GLINIDI?

sulfoniluree

Should Sulfonylureas Remain an Acceptable First-Line Add-on to Metformin Therapy in Patients With Type 2 Diabetes? Yes, They Continue to Serve Us Well!

Martin J. Abrahamson

Diabetes Care 2015;38:166–169 | DOI: 10.2337/dc14-1945

Should Sulfonylureas Remain an Acceptable First-Line Add-on to Metformin Therapy in Patients With Type 2 Diabetes? No, It's Time to Move On!

Saul Genuth

Diabetes Care 2015;38:170–175 | DOI: 10.2337/dc14-0565

sulfoniluree

1. Abbiamo realmente bisogno di loro, o i nuovi antidiabetici sono altrettanto efficaci?
2. Gli altri antidiabetici hanno una maggiore tollerabilità?
3. Gli altri antidiabetici garantiscono maggiori benefici sugli outcome cardiovascolari?

4. *Gli altri antidiabetici garantiscono maggiori benefici sulle complicanze microvascolari?*
5. *Gli altri antidiabetici garantiscono maggiore durability?*

sulfoniluree

1. Abbiamo realmente bisogno di loro, o i nuovi antidiabetici sono altrettanto efficaci?
2. Gli altri antidiabetici hanno una maggiore tollerabilità?
3. Gli altri antidiabetici garantiscono maggiori benefici sugli outcome cardiovascolari?
4. *Gli altri antidiabetici garantiscono maggiori benefici sulle complicanze microvascolari?*
5. *Gli altri antidiabetici garantiscono maggiore durability?*

sulfoniluree

1. Abbiamo realmente bisogno di loro, o i nuovi antidiabetici sono altrettanto efficaci?

Table 1—Effect of various oral drug additions to metformin on HbA_{1c}

	HbA_{1c} % (IQR)			
	Baseline	1 year	Difference, %	*P*
SU	8.3 (7.7–9.3)	7.3 (6.7–8.2)	1.0	<0.001
Pioglitazone	8.2 (7.7–9.1)	7.2 (6.7–7.9)	1.0	<0.001
Rosiglitazone	8.2 (7.7–9.1)	7.2 (6.7–7.9)	1.0	<0.001
DPP-4 inhibitor	8.0 (7.5–8.9)	7.3 (6.7–7.9)	0.7	<0.001

Data are from ref. 6, a retrospective study. IQR, interquartile range.

SGLT2-i?

"There is now abundant evidence that SUs are not essential as first-line additives to metformin as the alternative drugs are basically equal in glucose-lowering effectiveness"

sulfoniluree

1. Abbiamo realmente bisogno di loro, o i nuovi antidiabetici sono altrettanto efficaci?
2. Gli altri antidiabetici hanno una maggiore tollerabilità?
3. Gli altri antidiabetici garantiscono maggiori benefici sugli outcome cardiovascolari?
4. *Gli altri antidiabetici garantiscono maggiori benefici sulle complicanze microvascolari?*
5. *Gli altri antidiabetici garantiscono maggiore durability?*

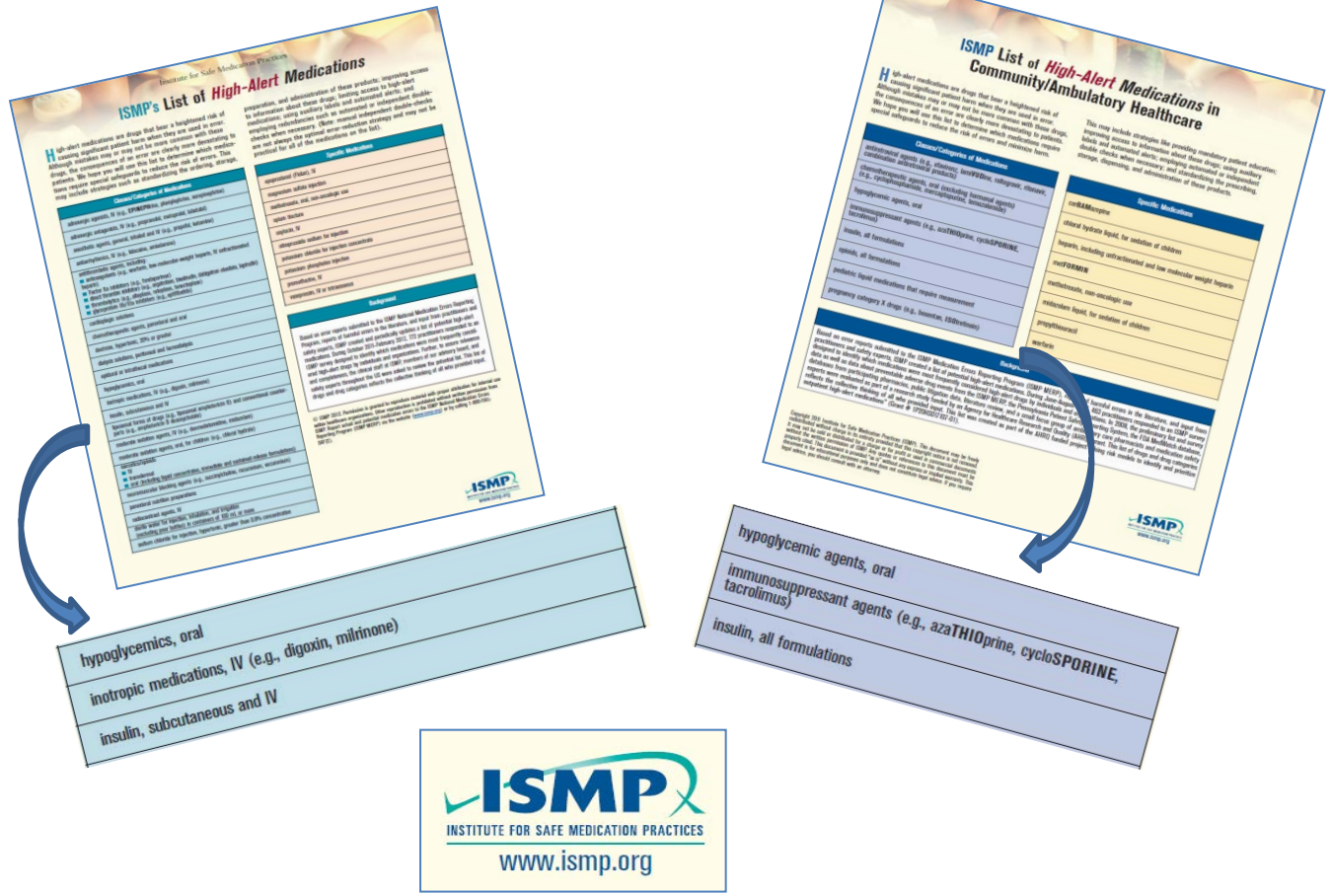
sulfoniluree

2. Gli altri antidiabetici hanno una maggiore tollerabilità?

Table 2—Risk of hypoglycemia of drugs added to metformin in treatment of T2DM

	Odds ratio (95% CI)
SU	2.1 (1.4–3.0)
TZD	0.5 (0.3–0.9)
DPP-4 inhibitor	0.3 (0.2–0.7)

Data are from ref. 31.



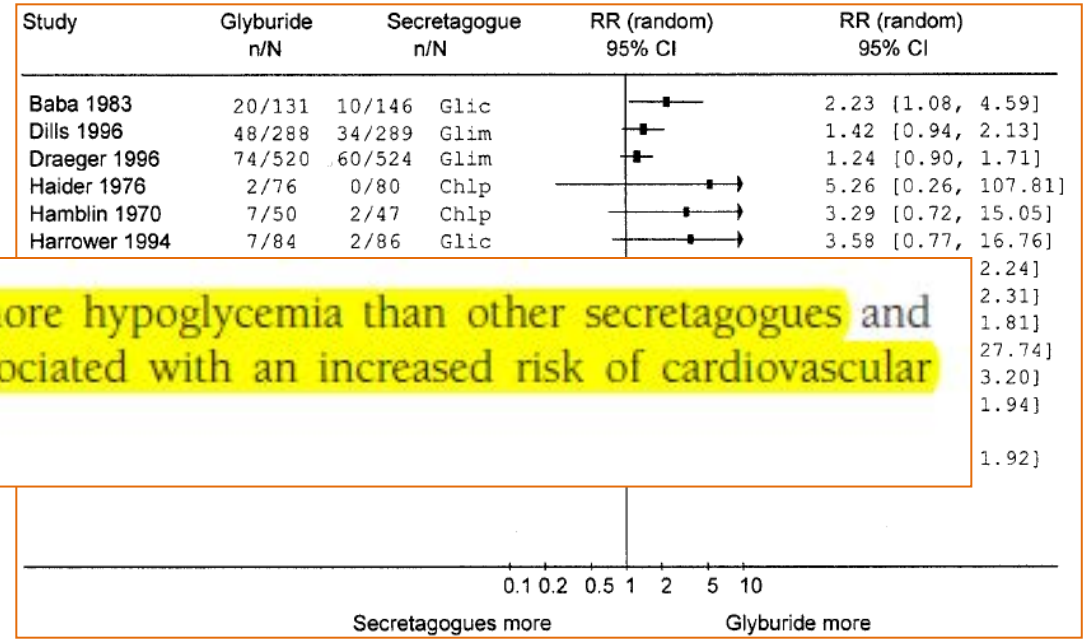
Glyburide was associated with almost twice as many episodes of hypoglycemia as other SUs

sulfoniluree

2. Gli altri antidiabetici hanno una maggiore tollerabilità?

A Systematic Review and Meta-Analysis of Hypoglycemia and Cardiovascular Events

A comparison of glyburide with other secretagogues and with insulin



CONCLUSIONS — Glyburide caused more hypoglycemia than other secretagogues and other sulfonylureas. Glyburide was not associated with an increased risk of cardiovascular events, death, or weight gain.

Ganji AS et al, *Diab Care* 2007

sulfoniluree

2. Gli altri antidiabetici hanno una maggiore tollerabilità?

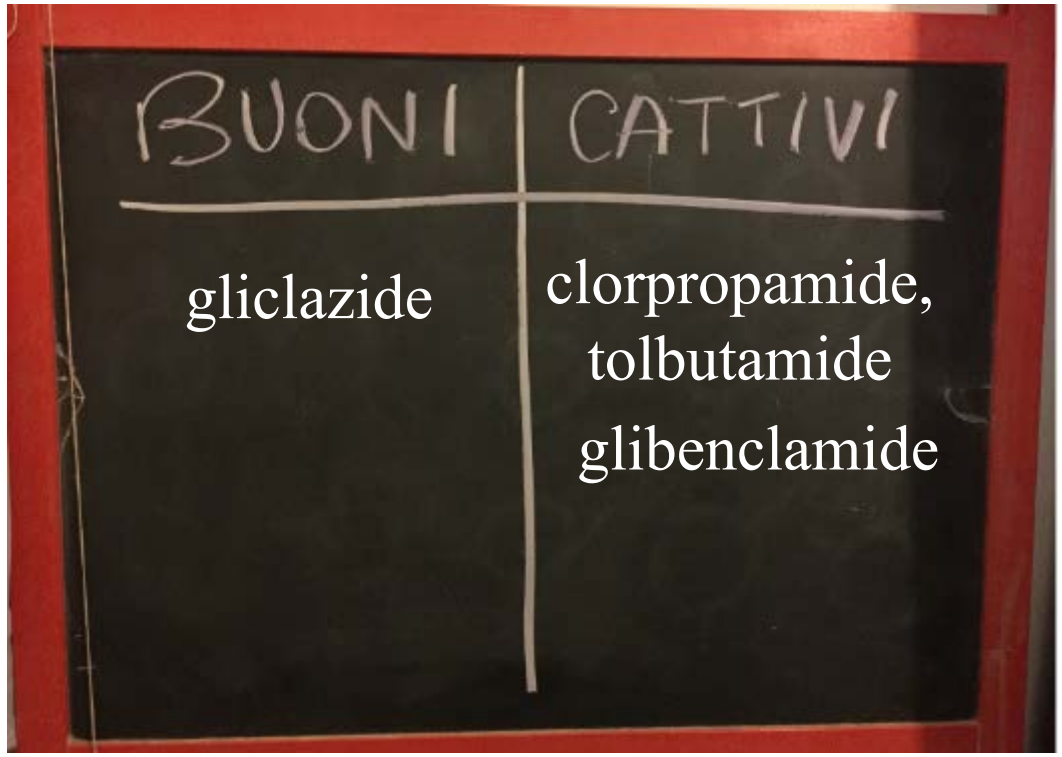
IPOGLICEMIE: LE SUs SONO TUTTE UGUALI?

Gliclazide vs glibenclamide:

- metabolismo interamente epatico
- alta affinità/specificità per K_{ATP} pancreatici
- somministrazione m.i.d.

Cordera R et al, *Diab Care* 2015 & Nutr Metab Cardiovasc Dis 2016


i buoni e i cattivi
edoardo bennato


BUONI
CATTIVI
gliclazide
clorpropamide,
tolbutamide
glibenclamide

Diabetes, Obesity and Metabolism 16: 977–983, 2014.

I° Congresso Congiunto AMD-SID
Piemonte e Valle d'Aosta
SINERGIE PER L'INNOVAZIONE
"se ci mettiamo insieme
ci sarà un perché"

Combination therapy with metformin plus sulphonylureas versus metformin plus DPP-4 inhibitors: association with major adverse cardiovascular events and all-cause mortality†

C. Ll. Morgan[1], J. Mukherjee[2], S. Jenkins-Jones[1], S. E. Holden[1,3] & C. J. Currie[1,3]

Table 2. Sulphonylurea (SU) and dipeptidyl peptidase-4 inhibitor (DPP-4i) types at cohort entry and exit.

SU	SU generation	First prescription, n (%)		Last prescription, n (%)		DPP-4i	First prescription, n (%)		Last prescription, n (%)	
Gliclazide	2	30 301	(89.2)	30 297	(89.2)	Sitagliptin	5864	(74.6)	5857	(74.5)
Glimepiride	2	2337	(6.9)	2397	(7.1)	Saxagliptin	996	(12.7)	1012	(12.9)
Glipizide	2	896	(2.6)	883	(2.6)	Vildagliptin	730	(9.3)	678	(8.6)
Glibenclamide	2	330	(1.0)	279	(0.8)	Linagliptin	274	(3.5)	317	(4.0)
Tolbutamide	1	119	(0.4)	127	(0.4)					
		33 983	(100.0)	33 983	(100.0)		7864	(100.0)	7864	(100.0)

Table 4. Events, crude rates, risk ratios and adjusted hazard ratios (aHRs) for first major adverse cardiovascular events (MACE) in patients treated with metformin plus sulphonylurea (SU) versus metformin plus dipeptidyl peptidase-4 inhibitor (DPP-4i) dual therapy.

Study design	Cohort (in combination with metformin)	n*	Events	Crude rates (per 1000 person-years)	Crude risk ratio (95% CI)	aHR (95% CI)	p
All subjects	SU	29 865	661	11.3	2.145 (1.629–2.824)	1.710 (1.280–2.285)	<0.001
	DPP-4i	7091	55	5.3			
Directly matched	SU	4423	58	7.7	1.469 (0.965–2.234)	1.323 (0.832–2.105)	0.237
	DPP-4i	4423	35	5.2			
Propensity-matched	SU	6175	88	8.8	1.688 (1.191–2.414)	1.547 (1.076–2.225)	0.019
	DPP-4i	6229	48	5.2			

*With no prior MACE.

Morgan CL et al Diabetes Obesi Metab, 2014

Risk of hypoglycaemia in users of sulphonylureas compared with metformin in relation to renal function and sulphonylurea metabolite group: population based cohort study

BMJ 2016;354:i3625

Judith van Dalem,[1,2,3] Martijn C G J Brouwers,[4] Coen D A Stehouwer,[5] André Krings,[2] Hubert G M Leufkens,[6] Johanna H M Driessen,[1,3,6] Frank de Vries,[1,6] Andrea M Burden[1,3,6]

WHAT THIS STUDY ADDS

The risk of a hypoglycaemic event is significantly increased in sulphonylurea only users with severe renal impairment receiving general care

The risk of hypoglycaemia did not differ between users of sulphonylureas with active metabolites and users of sulphonylureas with inactive metabolites

Our study does not confirm current guidelines that suggest the superiority of gliclazide to other sulphonylureas in reducing the risk of hypoglycaemia

	Risk of hypoglycaemia		
NIAA use	No of events	Adjusted hazard ratio (95% CI)*	Fully adjusted hazard ratio (95% CI)†
Current metformin only use	836	Reference	Reference
Current sulphonylurea only use	457	3.30 (2.94 to 3.69)	2.50 (2.23 to 2.82)
Sulphonylureas with active metabolites:	50	3.60 (2.70 to 4.78)	2.91 (2.18 to 3.87)
Glimepiride	28	2.46 (1.69 to 3.59)	1.97 (1.35 to 2.87)
Glibenclamide	22	8.76 (5.73 to 13.39)	7.48 (4.89 to 11.44)
Sulphonylurea with inactive metabolites:	406	3.26 (2.90 to 3.67)	2.46 (2.18 to 2.78)
Glipizide	14	2.61 (1.54 to 4.43)	2.11 (1.24 to 3.58)
Tolbutamide	<6	1.75 (0.56 to 5.42)	1.24 (0.40 to 3.87)
Gliclazide	389	3.32 (2.94 to 3.74)	2.50 (2.21 to 2.83)
Combination of metabolites	<6	3.75 (0.53 to 26.68)	2.65 (0.37 to 18.86)

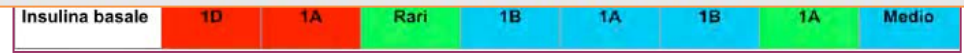
sulfoniluree

2. Gli altri antidiabetici hanno una maggiore tollerabilità?

Table 1—Comparison of medications that could be added to metformin

	SU	TZD	DPP-4	GLP-1	SGLT2	AGI	Colesevelam	Cycloset	Insulin
Efficacy	High	High	Moderate	High	High	Moderate	Moderate	Moderate	High
Major side effects	Well tolerated	Edema, CHF, fractures	Pancreatitis (rare)	Nausea, vomiting, pancreatitis (rare)	UTI, vaginal yeast infection, polyuria, orthostasis	Flatulence, diarrhea	Well tolerated	Nausea, vomiting	Well tolerated
Hypoglycemia risk	Moderate	Low	Low	Low	Low	Low	Low	Low	High
Weight	Gain	Gain	Neutral	Loss	Loss	Neutral	Neutral	Neutral	Gain
Cardiovascular safety	Neutral	Neutral	Neutral	Neutral	Unknown	May lower MACE	Neutral	May lower MACE	Neutral
Cost	Low	Low	High	High	High	Moderate	Moderate	Moderate	Variable

AGI, α-glucosidase inhibitors; MACE, major adverse cardiovascular events; UTI, urinary tract infection.



sulfoniluree

1. Abbiamo realmente bisogno di loro, o i nuovi antidiabetici sono altrettanto efficaci?
2. Gli altri antidiabetici hanno una maggiore tollerabilità
3. Gli altri antidiabetici garantiscono maggiori benefici sugli outcome cardiovascolari?
4. *Gli altri antidiabetici garantiscono maggiori benefici sulle complicanze microvascolari?*
5. *Gli altri antidiabetici garantiscono maggiore durability?*

sulfoniluree *e outcome CV*

3. Gli altri antidiabetici garantiscono maggiori benefici sugli outcome cardiovascolari?

Precondizionamento ischemico?

- Tolbutamide (UGDP study): legame recettori SUR1 e chiusura canali K_{ATP}
- In vitro/in vivo?
- Tutte le SUs?

Aumento eventi CV?

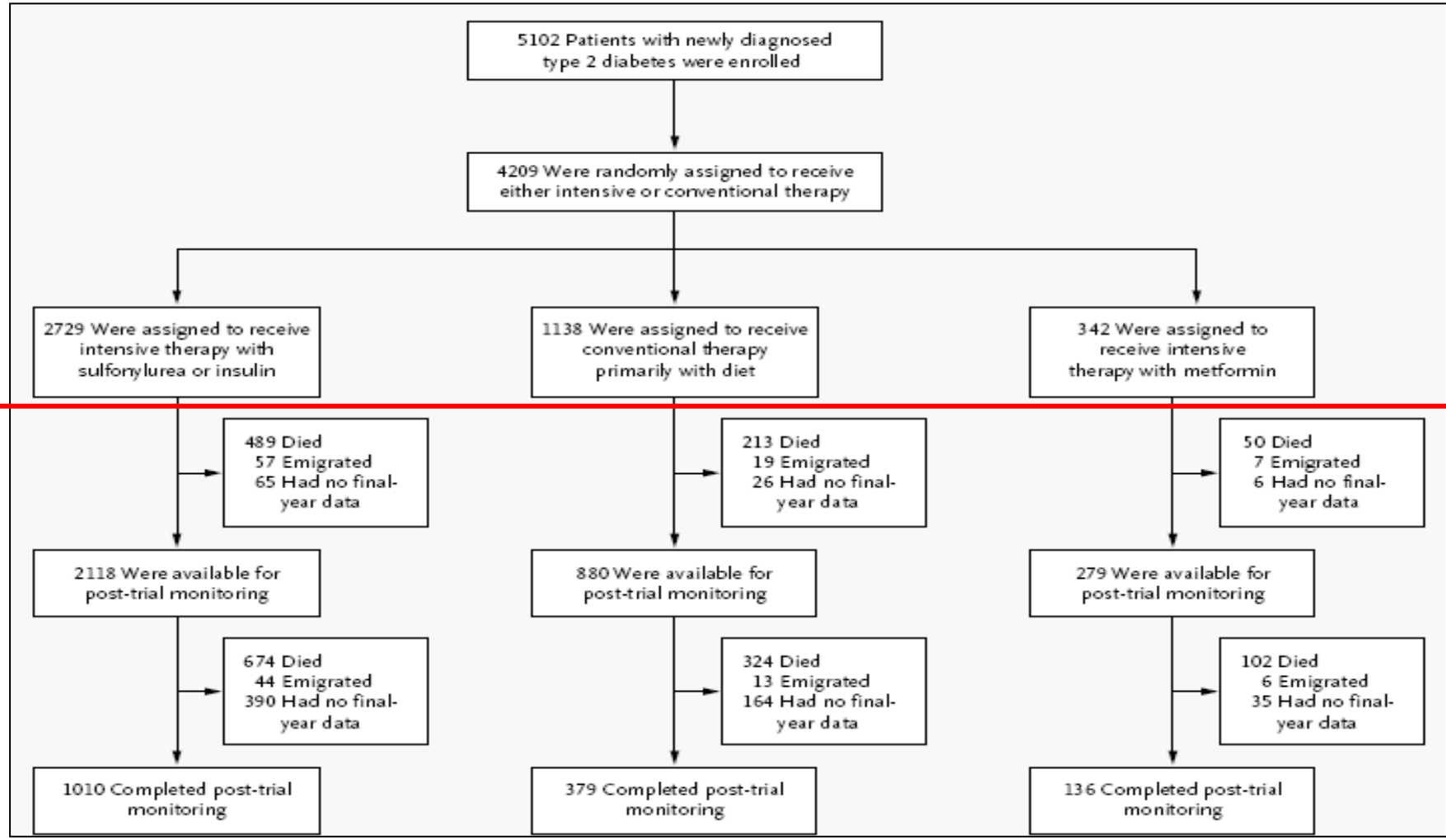
Aumento scompenso cardiaco?

Aumento mortalità CV?

ORIGINAL ARTICLE

N Engl J Med 2008;359.

10-Year Follow-up of Intensive Glucose Control in Type 2 Diabetes

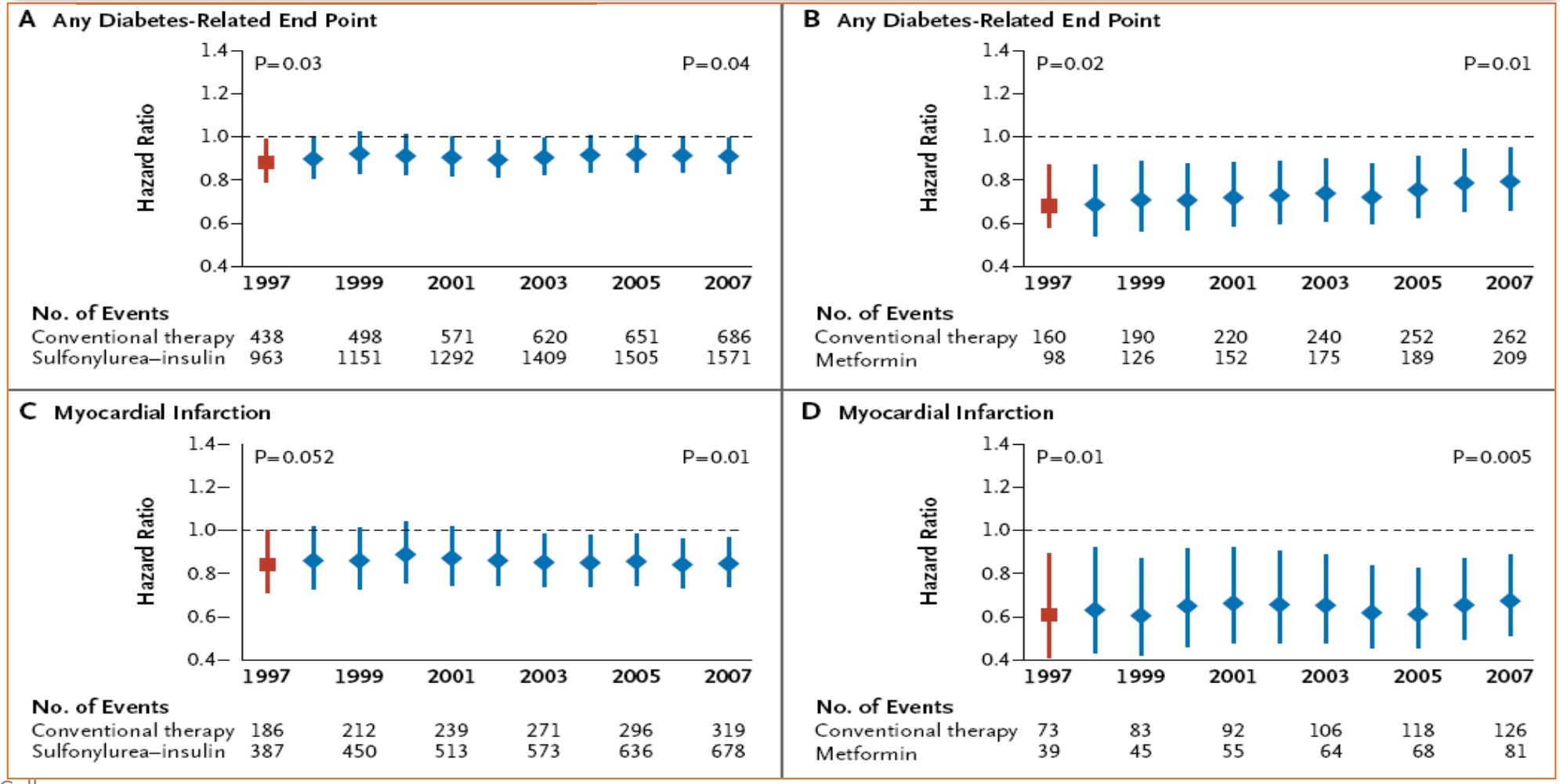


1997

78%

2007

UKPDS 80: Intervention in newly diagnosed DM

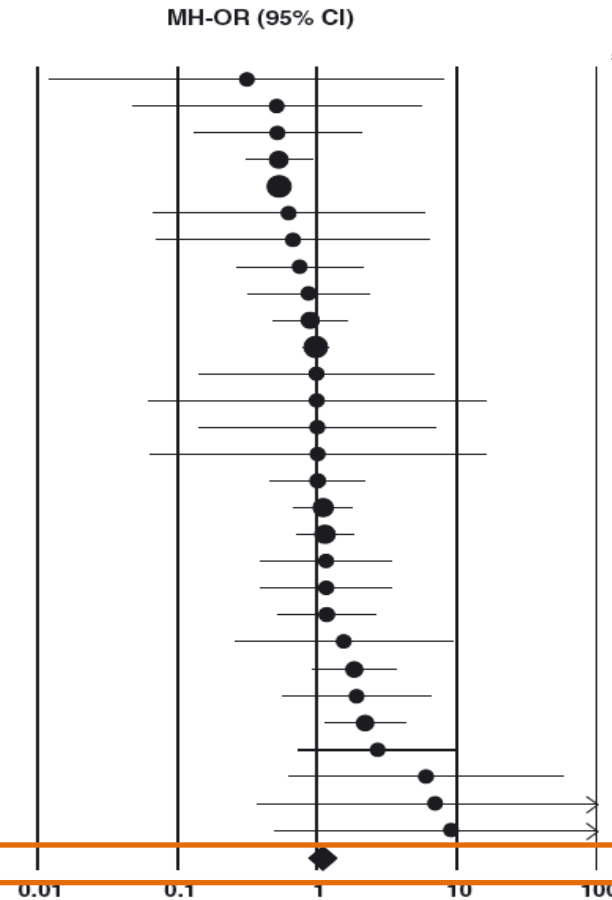


UKPDS 80. Holman R et al. *N Eng J Med* 2008

Cardiovascular safety of sulfonylureas: a meta-analysis of randomized clinical trials

I° Congresso Congiunto AMD-SID
Piemonte e Valle d'Aosta
SINERGIE PER L'INNOVAZIONE
"se ci mettiamo insieme ci sarà un perché"

major cardiovascular events for each individual trial with at least one event



First author (Year)	MH-OR	LL (95%. CI)	UL (95% CI)	p	Sulfonylureas # Events	Sulfonylureas # Patients	Comparator # Events	Comparator # Patients	Variance (%)
Birkeland 1996 [33]	0.315	0.012	8.269	0.489	0	18	1	18	0.07
Chou 2008 [41]	0.516	0.046	5.729	0.590	1	222	2	230	0.21
Perriello 2006 [99]	0.522	0.128	2.131	0.365	3	137	6	146	0.64
Gerstein 2010 [67]	0.534	0.301	0.945	0.031	20	339	35	333	3.42
UKPDS 33 1998 [130]	0.537	0.443	0.650	0.000	178	1234	432	1807	41.45
Hanefeld 2007 [76]	0.629	0.065	6.083	0.689	1	203	3	384	0.28
Seino 2010 [114]	0.674	0.069	6.545	0.734	1	132	3	268	0.28
Charbonnel 2005 [40]	0.755	0.259	2.201	0.607	6	313	8	317	1.00
Matthews 2005 [39]	0.871	0.314	2.416	0.790	7	626	8	624	1.07
Rubin 2008 [109]	0.896	0.475	1.693	0.736	14	591	32	1214	3.28
Home 2009 [80]	0.983	0.774	1.249	0.888	154	1105	158	1117	20.22
Arechavaleta 2011 [29]	0.994	0.140	7.085	0.995	2	519	2	516	0.28
va der Laar 2004 [132]	1.000	0.061	16.463	1.000	1	48	1	48	0.14
Mazzone 2006 [90]	1.009	0.141	7.224	0.993	2	228	2	230	0.28
Riddle 1998 [106]	1.014	0.062	16.529	0.992	1	72	1	73	0.14
Giles 2010 [70]	1.015	0.454	2.268	0.972	13	149	13	151	1.85
Tolman 2009 [126]	1.112	0.668	1.852	0.683	32	1046	29	1051	3.34
Kahn 2006 [85]	1.144	0.704	1.858	0.587	26	1441	46	2910	4.13
Goke 2010 [71]	1.164	0.388	3.492	0.787	7	430	6	428	0.93
Garber 2009 [65]	1.167	0.386	3.522	0.785	7	248	6	247	0.93
Nissen 2008 [5]	1.177	0.518	2.676	0.697	13	273	11	270	1.71
Ristic 2007 [118]	1.560	0.256	9.490	0.630	3	129	2	133	0.36
Ferrannini 2009 [56]	1.851	0.912	3.754	0.088	22	1393	12	1396	2.42
Bakris 2006 [30]	1.922	0.553	6.679	0.304	7	180	4	194	0.78
Gallwitz 2012 [62]	2.210	1.107	4.412	0.025	26	775	12	776	2.21
Jain 2006 [83]	2.722	0.714	10.380	0.143	8	251	3	251	0.78
Johnston 1998 [84]	6.034	0.619	58.837	0.122	3	92	1	180	0.28
Nauck 2011 [96]	7.035	0.362	136.640	0.197	3	401	0	400	0.21
Seck 2010 [112]	9.124	0.490	169.848	0.138	4	584	0	588	0.28
Overall	**1.041**	**0.825**	**1.312**	**0.736**	**617**	**13.327**	**878**	**16.456**	**100**

M Gallo

Monami M. et al., Diabetes Obes Metab. 2013

Cardiovascular safety of sulfonylureas: a meta-analysis of randomized clinical trials

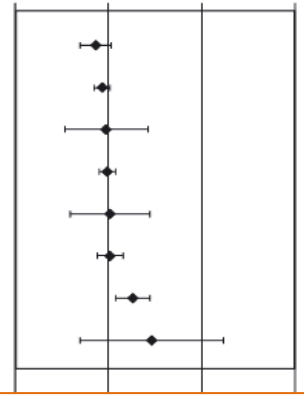
M. Monami[1], S. Genovese[2] & E. Mannucci[3]

Diabetes, Obesity and Metabolism 15: 938–953, 2013.

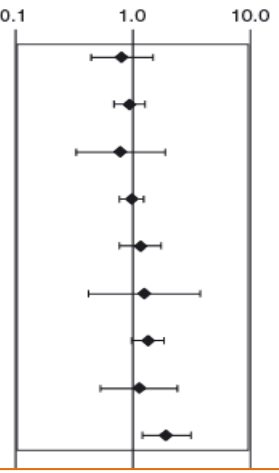
I° Congresso Congiunto AMD-SID
Piemonte e Valle d'Aosta
SINERGIE PER L'INNOVAZIONE
"se ci mettiamo insieme ci sarà un perché"

major cardiovascular events

Comparators	# Trials	MH-OR	LL	UL	p	Sulfonylureas # Events	Sulfonylureas # Patients	Comparator # Events	Comparator # Patients
Rosiglitazone	6	0.74	0.50	1.10	0.140	209	3.490	251	3.714
Placebo/No therapy	2	0.87	0.71	1.07	0.190	279	1.306	225	969
Metformin	2	0.95	0.34	2.70	0.93	78	1.589	85	1.610
Insulin	2	0.98	0.80	1.20	0.830	278	1.252	209	929
GLP-1RA	2	1.05	0.39	2.84	0.920	8	380	9	515
Pioglitazone	8	1.05	0.77	1.44	0.740	86	3.173	80	3.195
DPP-4i	5	1.85	1.20	2.87	0.005	61	3.701	32	3.704
AGi	2	2.95	0.50	17.27	0.230	4	140	2	228

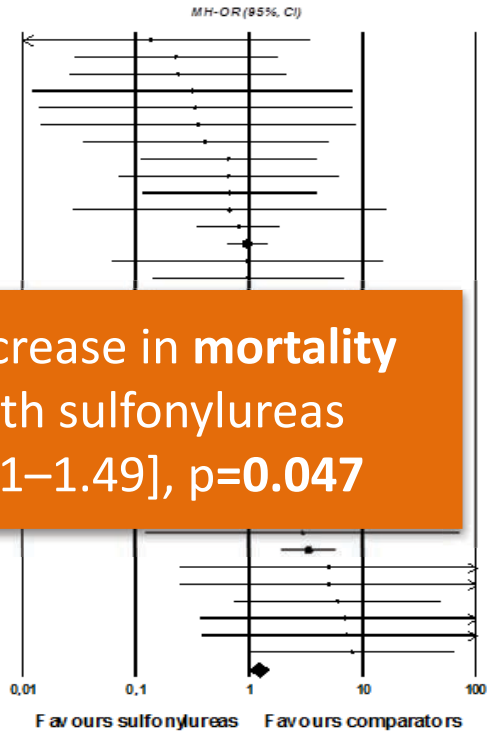


Sulfonylurea	# Trials	MH-OR	LL	UL	p	Sulfonylureas # Events	Sulfonylureas # Patients	Comparator # Events	Comparator # Patients
Gliclazide	4	0.81	0.44	1.49	0.49	19	1.205	24	1.220
Glibenclamide	10	0.95	0.70	1.29	0.75	231	4.127	584	7.214
Rosiglitazone	3	0.79	0.33	1.90	0.59	8	383	7	578
Insulin	2	0.99	0.78	1.26	0.93	140	882	209	1.184
Pioglitazone	3	1.18	0.78	1.78	0.43	53	1.446	45	1.453
Glipizide	5	1.28	0.58	2.83	0.54	86	1.902	80	1.905
Glimepiride	9	1.37	0.99	1.86	0.06	88	4.321	80	4.592
Pioglitazone	2	1.15	0.54	2.45	0.72	15	501	13	500
DPP-4i	3	1.94	1.23	3.14	0.007	50	2.687	26	2.688



all-cause and CV mortality

First autor (Year)	MH-OR	LL (95%. CI)	UL (95%. CI)	p
Yki-Jarvinen 1999	0,14	0,01	3,48	0,23
Rubin 2008	0,23	0,03	1,80	0,16
Tan 1977	0,24	0,03	2,19	0,20
Birkeland 1996	0,32	0,01	8,27	0,49
Mazzone 2006	0,33	0,01	8,26	0,50
Bakris 2006	0,36	0,01	8,83	0,53
Alvarsson 2010	0,41	0,03	5,03	0,49
Nissen 2008	0,66	0,11	3,96	0,65
Marbury 1999	0,66	0,07	6,40	0,72
Ferrannini 2009	0,67	0,11	4,00	0,66
Seino 2010	0,67	0,03	16,63	0,81
Gerstein 2010	0,81	0,35	1,91	0,63
Kahn 2006	0,96	0,62	1,48	0,86
Filozof 2012	0,96	0,06	15,44	0,98
Hamann 2008	0,98	0,14	6,98	0,98
UGDP Group 1974	3,37	1,90	5,98	0,00
Jain 2006	5,04	0,24	105,51	0,30
Matthews 2005	5,10	0,24	106,58	0,29
Tolman 2009	6,06	0,73	50,40	0,10
Nauck 2011	7,04	0,36	136,64	0,20
Barnett 2006	7,34	0,38	142,83	0,19
Seck 2010	8,15	1,02	65,39	0,05
Overall	**1.22**	**1.01**	**1.49**	**0.047**



But a significant increase in **mortality** was observed with sulfonylureas (MHOR: 1.22 [1.01–1.49], p=**0.047**

Il pieghevole dell'Appropriatezza Terapeutica

Classe	Molecola	Epatopatia			Nefropatia con GFR mL/min:				Cardiopatia		
		Child A	Child B	Child C	> 60	60-30	< 30	Dialisi	Assente	CHD	NYHA
Insulino-sensibilizzanti	Metformina	OK	No	No	Si	Ridurre dose	No	No	OK	OK	II-IV
	Pioglitazione	OK	Attenzione	No	Si	Si	Si	No	OK	OK	No
Inibitori α-glicosidasi	Acarbose	OK	Attenzione	No	Si	Si	No	No	OK	OK	OK
Secretagoghi	Glibenclamide	OK	Attenzione	No	OK	Attenzione	No	No	OK	Attenzione	Attenzione
	Glicazide	OK	Attenzione	No	OK	Attenzione	No	No	OK	Attenzione	OK
	Glimepiride	OK	Attenzione	No	OK	Attenzione	No	No	OK	Attenzione	OK
	Glipizide	OK	Attenzione	No	OK	Ridurre dose, monitorare	No	No	OK	Attenzione	OK
	Gliquidone	OK	Attenzione	No	OK	Ridurre dose	No	No	OK	Attenzione	OK
	Repaglinide	OK	Ridurre dose	No	OK	Attenzione	Attenzione	No	OK	Attenzione	OK
GLP1-RA	Exenatide BID	OK	OK	OK	OK	5 mg	No	No	OK	OK	OK
	Exenatide LAR	OK	OK	OK	OK	No	No	No	OK	OK	OK
	Liraglutide	OK	No	No	OK	OK	No	No	OK	OK	III e IV lim
	Lixisenatide	OK	OK	OK	OK	Attenzione	No	No	OK	OK	OK
Inibitori DPP-4	Sitagliptin	OK	OK	No	100 mg	50 mg	25 mg	25 mg	OK	OK	OK*
	Vildagliptin	OK	No	No	100 mg	50 mg	50 mg	50 mg c lim	OK	OK	IV No*
	Saxagliptin	OK	OK	No	5 mg	2.5 mg	2,5 mg c lim	No	OK	OK	III e IV c*
	Linagliptin	OK	OK	OK	5 mg	5 mg	5 mg	5 mg	OK	OK	OK*
	Alogliptin	OK	OK	No	25 mg	12,5 mg	6,25 mg	6,25 mg	OK	OK	OK*
SGLT2 inibitori	Canagliflozin	OK	OK	No	OK	GFR 60-45 dose max 100 mg	GFR < 45 No	No	OK	OK	OK
	Dapagliflozin	OK	OK	Ridurre dose	OK	No	No	No	OK	OK	OK
	Empagliflozin	OK	OK	No	OK	GFR 60-45 dose max 10 mg	GFR < 45 No	No	OK	OK	OK

Pioglitazone

PROACTIVE

- RCT di prevenzione secondaria in 5238 pz con T2DM ad alto rischio CV
- PIO vs. placebo (follow-up 34 mesi)

- riduzione eventi endpoint composito secondario

  mortalità totale, IMA non fatale, ictus

  (HR 0.84; IC95% 0.72-0.98; p = 0.027)

NNT per IMA (3 anni) = 48

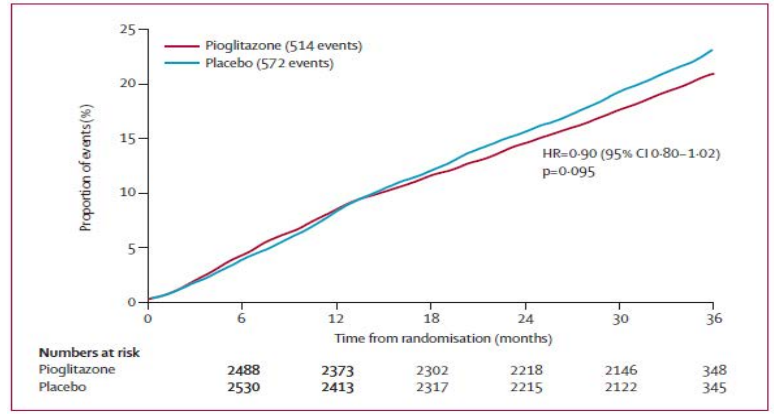


Figure 2: **Kaplan-Meier curve of time to primary endpoint***
*Death from any cause, non-fatal myocardial infarction (including silent myocardial infarction), stroke, acute coronary syndrome, leg amputation, coronary revascularisation, or revascularisation of the leg.

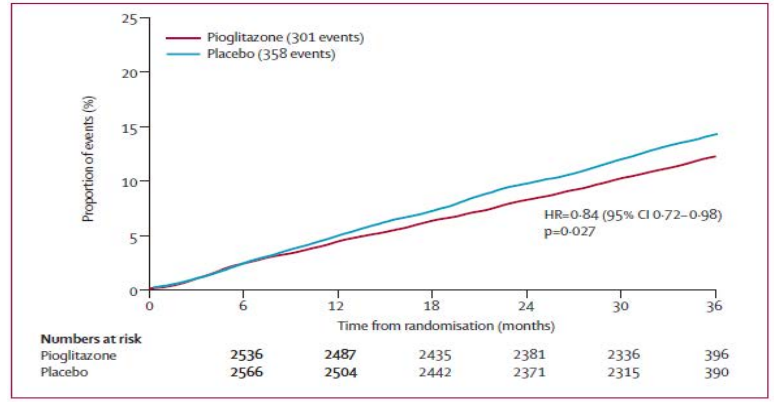
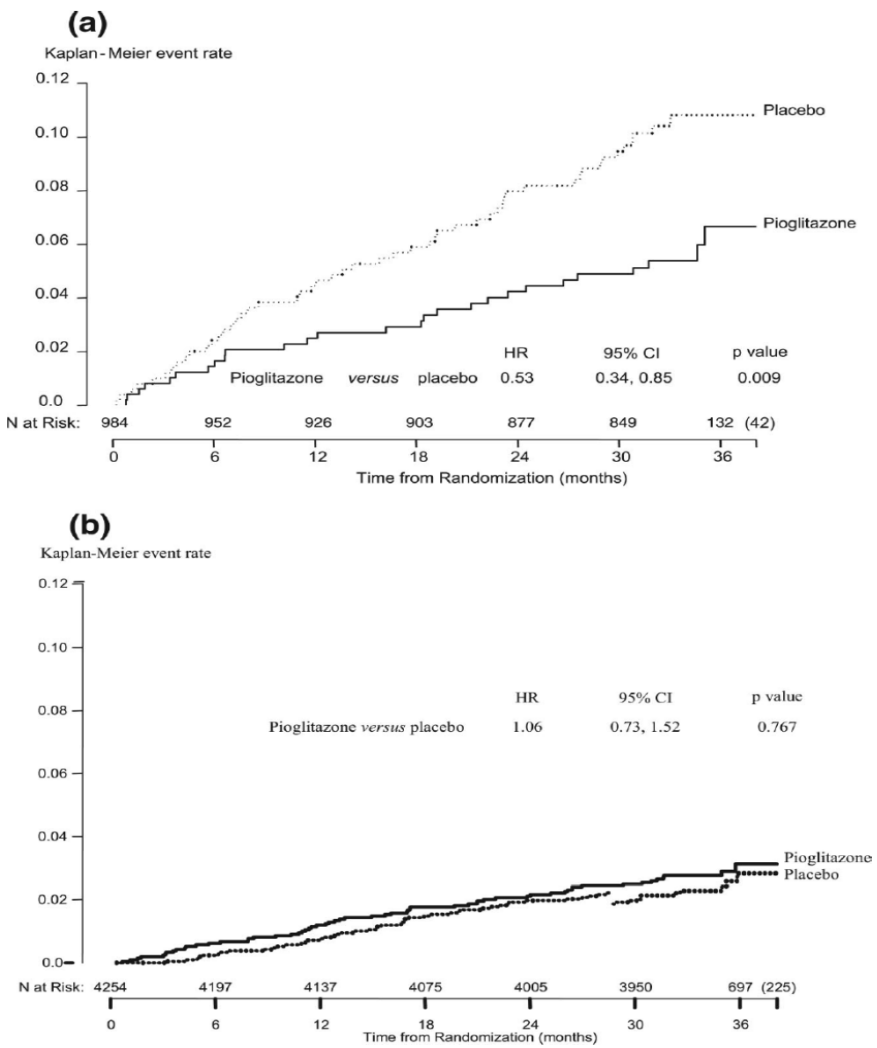


Figure 3: **Kaplan-Meier curve of time to main secondary endpoint***
*Death from any cause, non-fatal myocardial infarction (excluding silent myocardial infarction), or stroke.

Effects of Pioglitazone in Patients With Type 2 Diabetes With or Without Previous Stroke

Results From PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events 04)



Wilcox R. et al. *Stroke* 2007;38:865-73

The Effect of Pioglitazone on Recurrent Myocardial Infarction in 2,445 Patients With Type 2 Diabetes and Previous Myocardial Infarction

Results From the PROactive (PROactive 05) Study

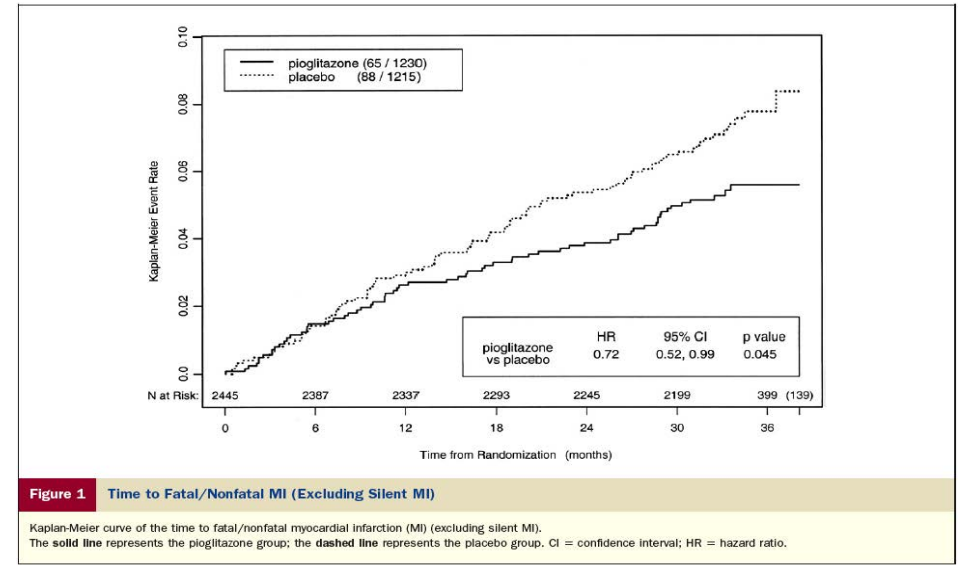


Figure 1 Time to Fatal/Nonfatal MI (Excluding Silent MI)

Kaplan-Meier curve of the time to fatal/nonfatal myocardial infarction (MI) (excluding silent MI).
The **solid line** represents the pioglitazone group; the **dashed line** represents the placebo group. CI = confidence interval; HR = hazard ratio.

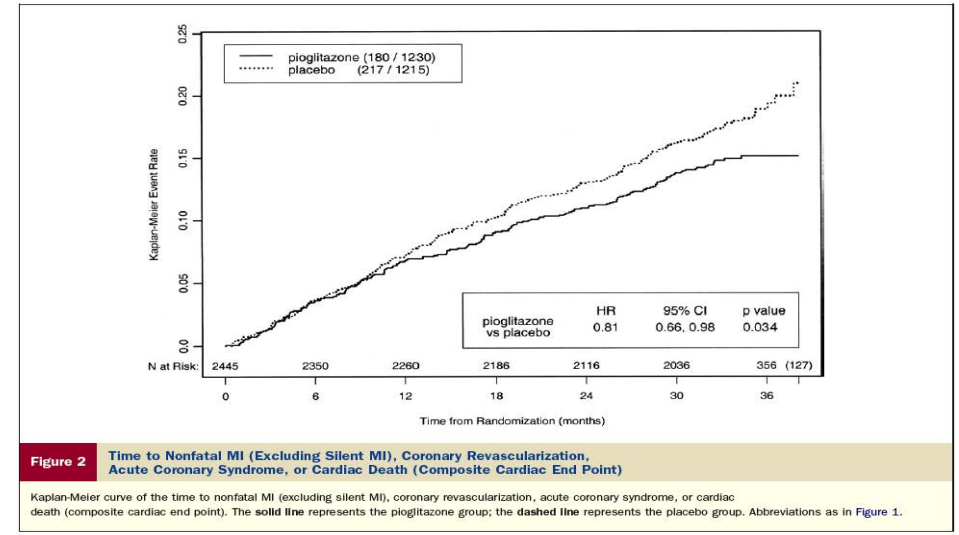


Figure 2 Time to Nonfatal MI (Excluding Silent MI), Coronary Revascularization, Acute Coronary Syndrome, or Cardiac Death (Composite Cardiac End Point)

Kaplan-Meier curve of the time to nonfatal MI (excluding silent MI), coronary revascularization, acute coronary syndrome, or cardiac death (composite cardiac end point). The **solid line** represents the pioglitazone group; the **dashed line** represents the placebo group. Abbreviations as in Figure 1.

Erdmann E. et al. *JACC* 2007;49:1772-80

SGLT2-i

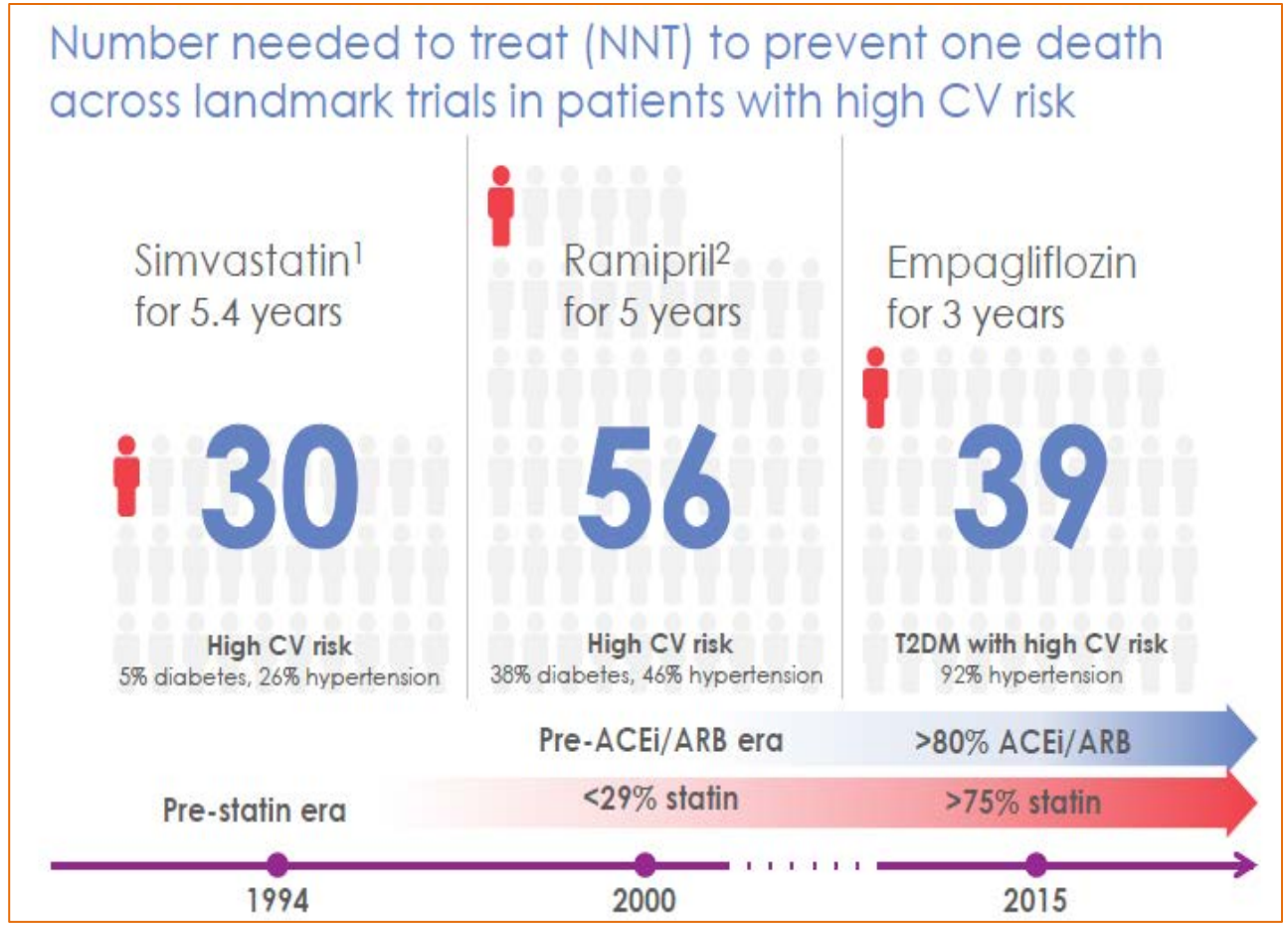
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

EMPA-REG OUTCOME®



Lessons learned from cardiovascular outcome clinical trials with dipeptidyl peptidase 4 (DPP-4) inhibitors

Table 1 Overview of cardiovascular outcome trials evaluating the effects of DPP-4 inhibitors on cardiovascular events

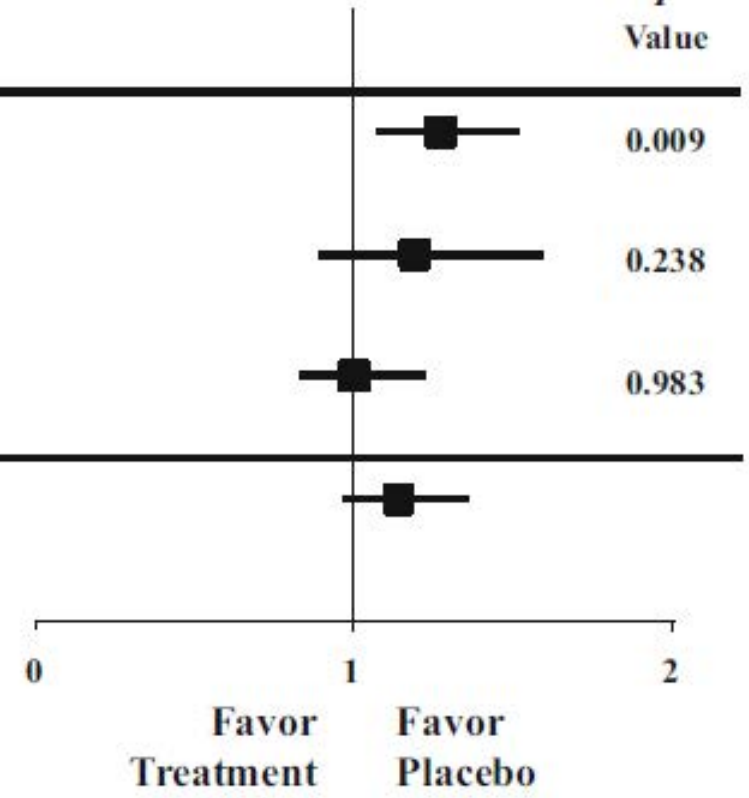
	SAVOR-TIMI [32] $N = 16.492$ Saxagliptin versus Placebo	EXAMINE [33] $N = 5.380$ Alogliptin versus Placebo	TECOS [34] $N = 14.671$ Sitagliptin versus Placebo
Primary endpoint definition	Cardiovascular death, non-fatal myocardial infarction or non-fatal stroke	Cardiovascular death, non-fatal myocardial infarction or non-fatal stroke	Cardiovascular death, non-fatal myocardial infarction or non-fatal stroke or unstable angina requiring hospitalization
Hazard ratio (HR) for primary outcome	1.00 (95 % CI 0.89, 1.12)	0.96 (upper boundary of 1-sided repeated CI 1.16)	0.98 (95 % CI 0.88, 1.09)
Hazard ratio (HR) for death from any cause	1.11 (95 % CI 0.96, 1.27) $P = 0.15$	0.88 (95 % CI 0.70, 1.09) $P = 0.23$	1.01 (95 % CI 0.90, 1.14) $P = 0.88$

Hospitalization for heart failure, no (%)	290 (3.5)	230 (2.8)	106 (3.9)	89 (3.3)	228 (3.1)	229 (3.1)
Hazard ratio (95 % CI)	1.27 (1.07–1.51); $P = 0.007$		1.19 (0.90–1.58); $P = 0.22$		1.00 (0.83–1.20); $P = 0.98$	

Fiorentino TV & Sesti G, *Endocrine* 2016

Lessons learned from cardiovascular outcome clinical trials with dipeptidyl peptidase 4 (DPP-4) inhibitors

	Study Drug n/N (%)	Placebo n/N (%)	Hazard Ratio	95% CI	*P* Value
SAVOR-TIMI 53 (Saxagliptin vs. placebo)	289/8280 (3.5%)	228/8212 (2.8%)	1.27	1.07, 1.51	0.009
EXAMINE (Alogliptin vs. placebo)	106/2701 (3.9%)	89/2679 (3.3%)	1.19	0.89, 1.58	0.238
TECOS (Sitagliptin vs. placebo)	228/7332 (3.1%)	229/7339 (3.1%)	1.00	0.83, 1.20	0.983
SAVOR + EXAMINE + TECOS	623/18313 (3.4%)	546/18230 (3.0%)	1.14	0.97, 1.34	



Test for Heterogeneity for 3 trials:
P=0.178, I^2=42%

Fiorentino TV & Sesti G, *Endocrine* 2016

DIABETES CARE, VOLUME 35, JUNE 2012

Diabetes Care Volume 38, January 2015

Comorbidities

Coronary artery disease Given the frequency with which type 2 diabetic patients develop atherosclerosis, optimal management strategies for those with or at high risk for coronary artery disease (CAD) are important. Since hypoglycaemia may exacerbate myocardial ischaemia and may cause dysrhythmias [111], it follows that medications that predispose patients to this adverse effect should be avoided, if possible. If they are required, however, to achieve glycaemic targets, patients should be educated to minimise risk. Because of possible effects on potassium channels in the heart, certain sulfonylureas have been proposed to aggravate myocardial ischaemia through effects on ischaemic preconditioning [112], but the actual clinical relevance of this remains unproven. Metformin may have some cardiovascular benefits and would appear to be a useful drug in the setting of CAD, barring prevalent contraindications [32]. In a single study, pioglitazone was shown to reduce modestly major adverse cardiovascular events in patients with established macrovascular disease. It may therefore also be considered, unless heart failure is present [60]. In very preliminary reports, therapy with GLP-1 receptor agonists and DPP-4 inhibitors has been associated with improvement in either cardiovascular risk or risk factors, but there are no long-term data regarding clinical outcomes [113]. There are very limited data suggesting that AGIs [114] and bromocriptine [115] may reduce cardiovascular events.

Dipeptidyl Peptidase 4 Inhibitors

One large trial involving the dipeptidyl peptidase 4 (DPP-4) inhibitor saxagliptin found no overall cardiovascular risk or benefit (although the follow-up was only slightly more than 2 years) compared with placebo (28). However, more heart failure hospitalizations occurred in the active therapy group (3.5% vs. 2.8%, $P = 0.007$) (28,29). Alogliptin, another DPP-4 inhibitor, also did not have any demonstrable cardiovascular excess risk over an even shorter period (18 months) in high-risk patients (30). A wider database interrogation indicated no signal for cardiovascular disease or heart failure (30,31). Several other trials are underway, and until the results of these are reported, this class should probably be used cautiously, if at all, in patients with preexisting heart failure.

DPP4-i

Risk of hospitalization for heart failure in patients with type 2 diabetes newly treated with DPP-4 inhibitors or other oral glucose-lowering medications: a retrospective registry study on 127,555 patients from the Nationwide OsMed Health-DB Database

Gian Paolo Fadini[1], Angelo Avogaro[1*], Luca Degli Esposti[2], Pierluigi Russo[3], Stefania Saragoni[2], Stefano Buda[2], Giuseppe Rosano[3,4,5], Sergio Pecorelli[3,6], and Luca Pani[3], on behalf of the OsMed Health-DB Network[†]

I° Congresso Congiunto AMD-SID
Piemonte e Valle d'Aosta
SINERGIE PER L'INNOVAZIONE
"se ci mettiamo insieme ci sarà un perché"

Table 1 Clinical characteristics of the entire study cohort

Characteristics	All	DPP-4i	Sulphonylureas	TZD	*P*-value
Number (%)	127 555 (100.0)	18 294 (14.3)	92 463 (72.5)	16 798 (13.2)	
Age, mean ± SD	67.0 ± 13.4	62.3 ± 11.6*	68.5 ± 13.5	63.5 ± 13.2***	<0.001
Sex, % male	51.9	56.3*	50.5**	54.6***	<0.001
Charlson index					
1	72.6	58.4*	76.8**	64.7***	<0.001
2–3	24.1	37.7*	20.1**	31.6***	
≥4	3.3	3.9*	3.1**	3.7***	

Table 4 Results of the Cox proportional hazard multiple regression analysis in the whole study population including hospitalization episodes with a primary or secondary HF diagnosis

Variable	Before propensity matching		After propensity matching	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Glucose-lowering medications				
Sulphonylureas (reference)	1.000		1.000	
Glitazones	0.926 (0.807–1.063)	0.277	0.777 (0.635–0.950)	0.014
DPP-4 inhibitors	0.751 (0.630–0.895)	0.001	0.642 (0.510–0.808)	<0.001

Fadini GP et al, *Eur Heart J* 2015

sulfoniluree

1. Abbiamo realmente bisogno di loro, o i nuovi antidiabetici sono altrettanto efficaci?
2. Gli altri antidiabetici hanno una maggiore tollerabilità?
3. Gli altri antidiabetici garantiscono maggiori benefici sugli outcome cardiovascolari?
4. *Gli altri antidiabetici garantiscono maggiori benefici sulle complicanze microvascolari?*
5. *Gli altri antidiabetici garantiscono maggiore durability?*

ORIGINAL ARTICLE

Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes

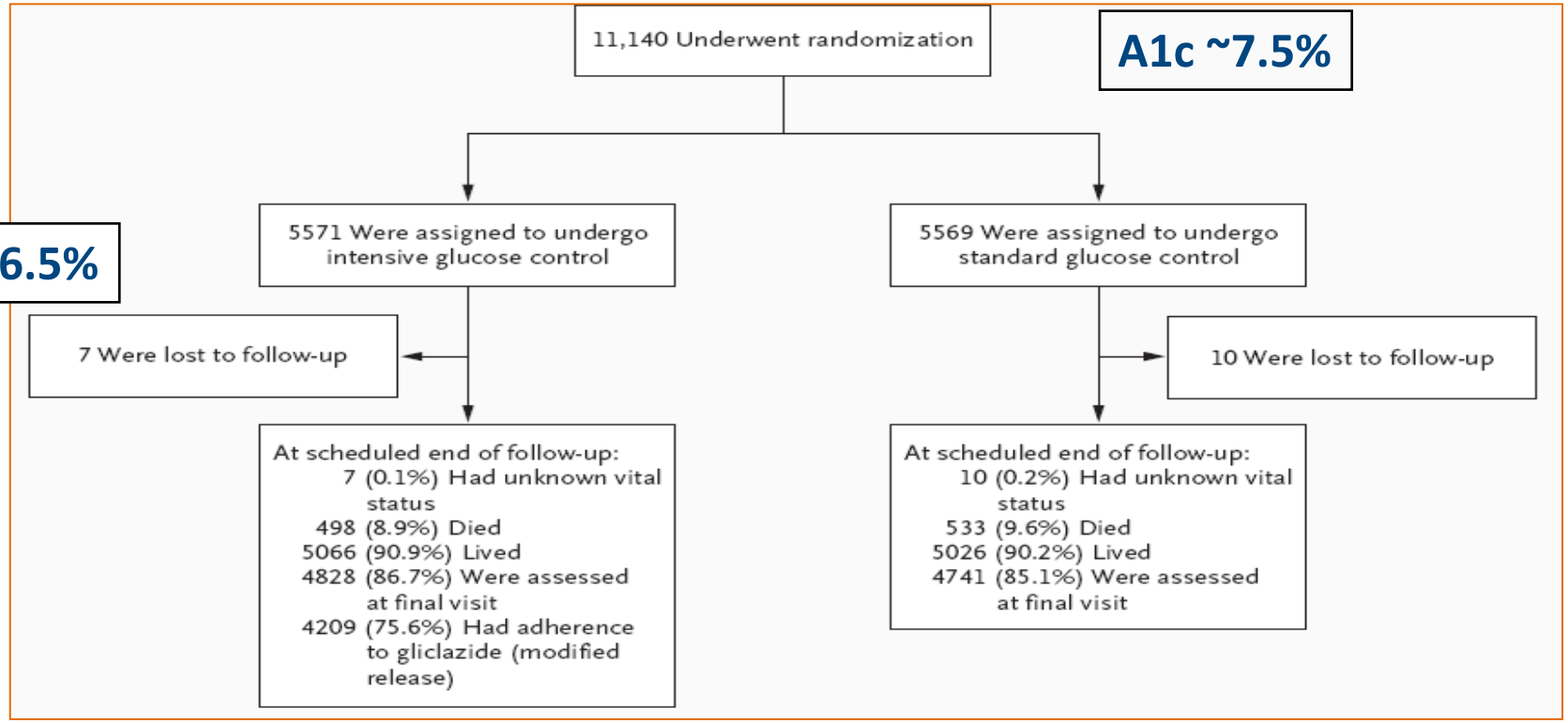
The ADVANCE Collaborative Group*

N Engl J Med 2008;358:2560-72.

ADVANCE

A1c ~7.5%

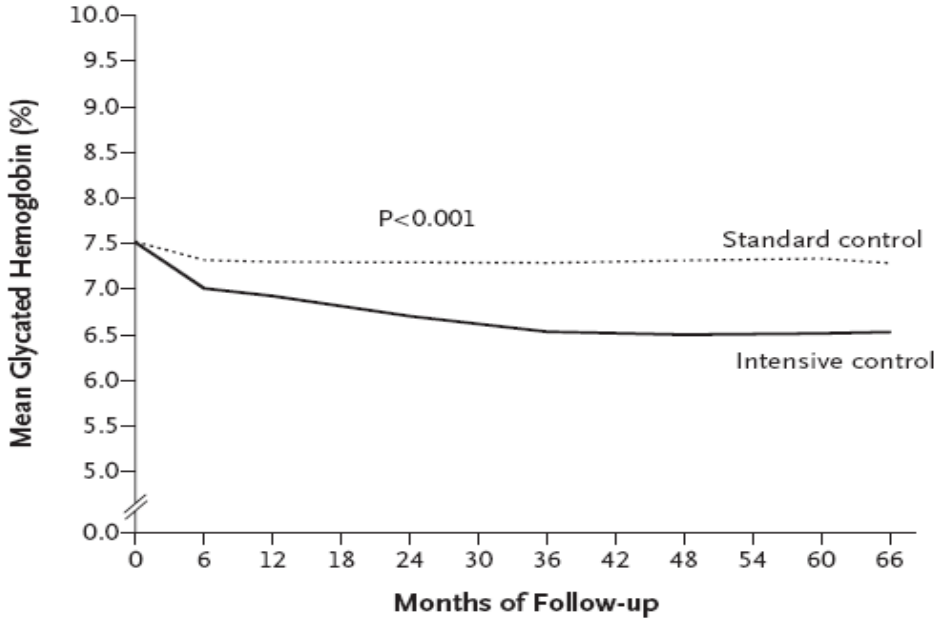
A1c </=6.5%



ADVANCE

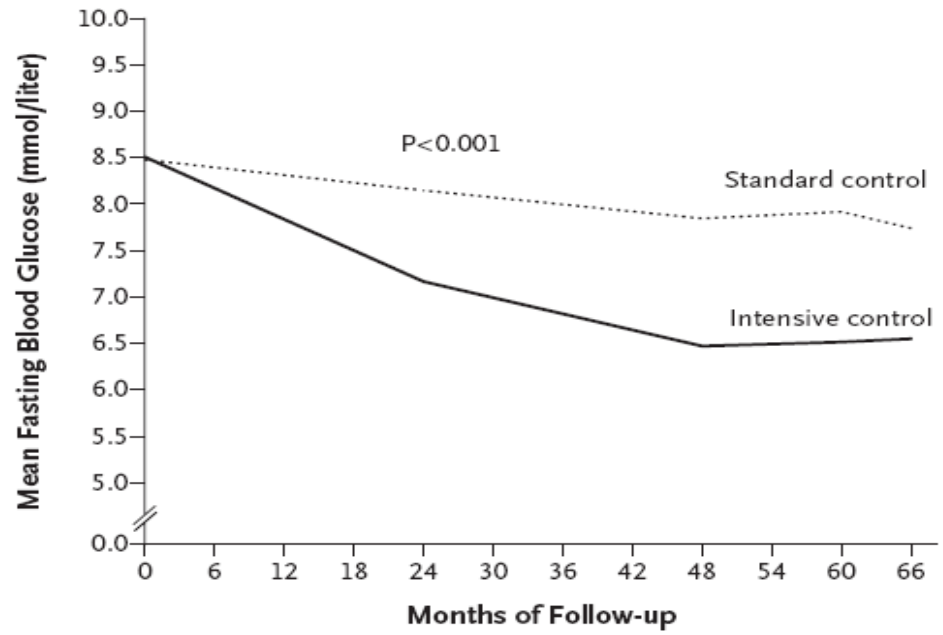
Basal and follow-up blood glucose control

A



Value							
Standard	7.32	7.30	7.29	7.29	7.31	7.33	7.29
Intensive	7.01	6.93	6.70	6.53	6.50	6.52	6.53

B



Level				
Standard	8.15	7.84	7.92	7.74
Intensive	7.17	6.47	6.51	6.55

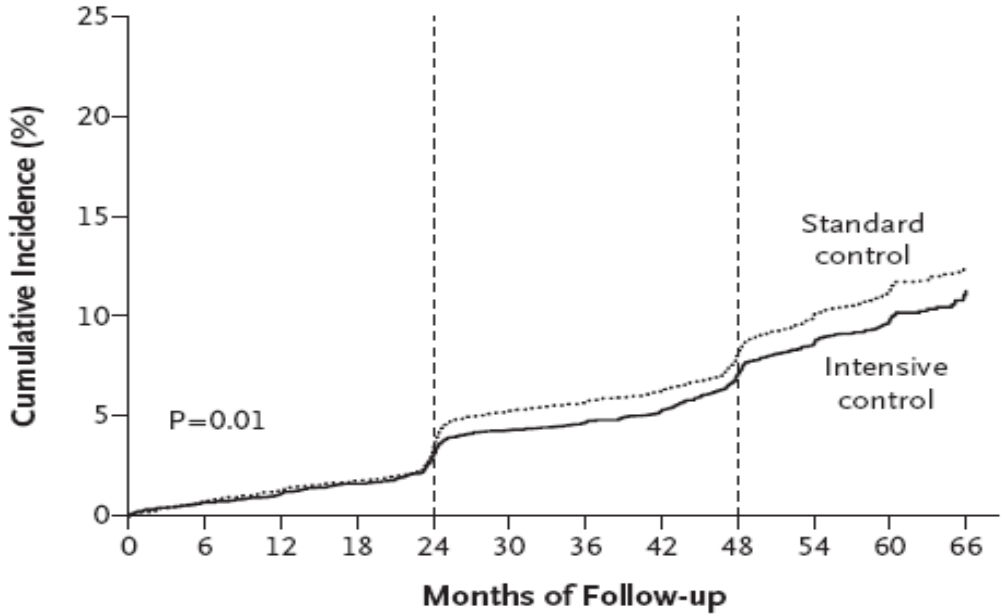
mean body weight during follow-up: 0.7 kg greater in the intensive-control group (P<0.001)

The ADVANCE Collaborative Group. *N Engl J Med 2008*

ADVANCE

Microvascular events

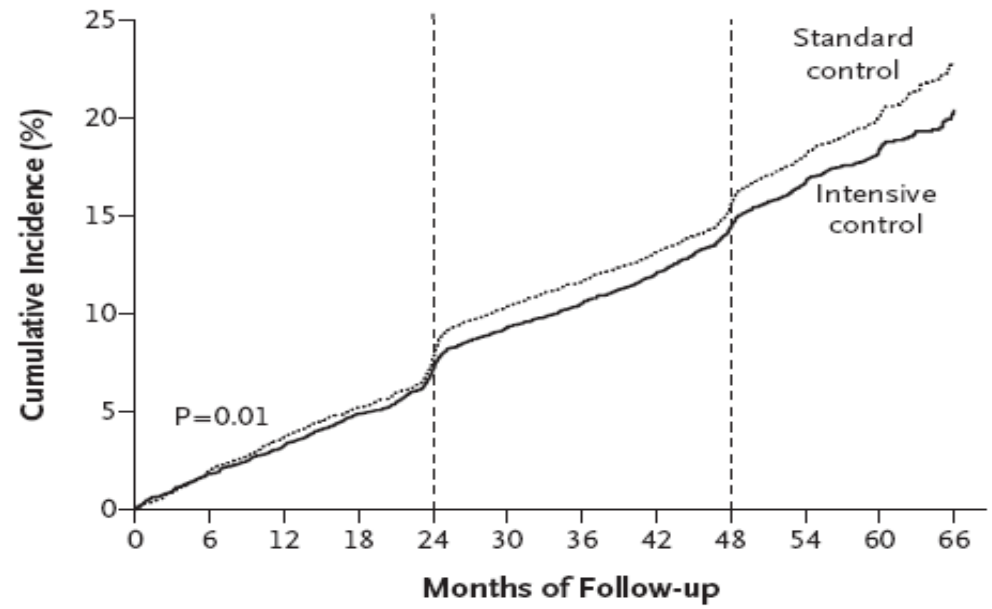
C Major Microvascular Events



No. at Risk

Intensive	5571	5495	5430	5358	5233	5120	5055	4968	4824	4258	1992	473
Standard	5569	5498	5431	5353	5207	5069	4995	4911	4764	4204	2024	494

A Combined Major Macrovascular and Microvascular Events



No. at Risk

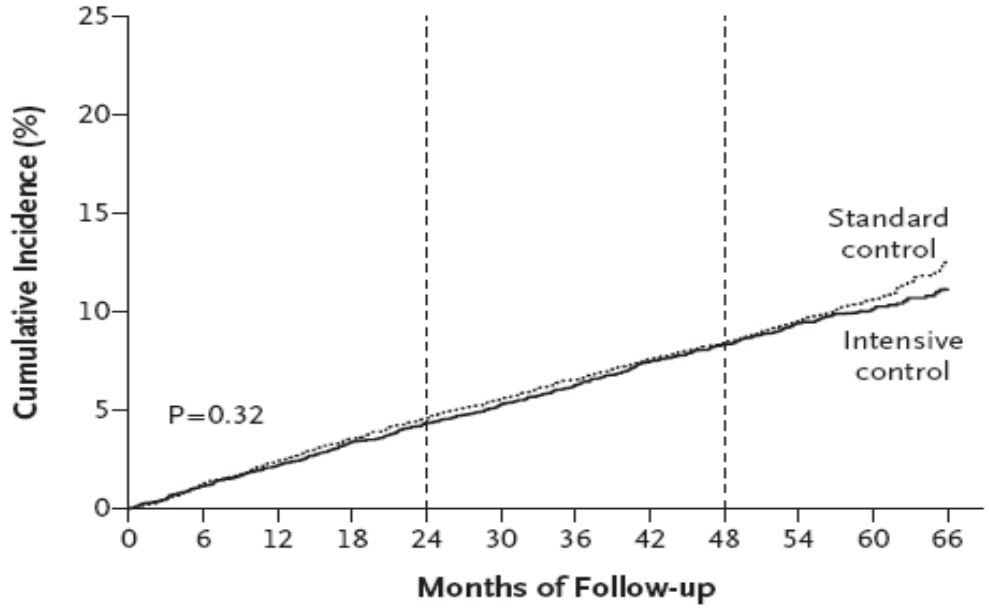
Intensive	5570	5457	5369	5256	5100	4957	4867	4756	4599	4044	1883	447
Standard	5569	5448	5342	5240	5065	4903	4808	4703	4545	3992	1921	470

The ADVANCE Collaborative Group. *N Engl J Med 2008*

ADVANCE

Macrovascular events

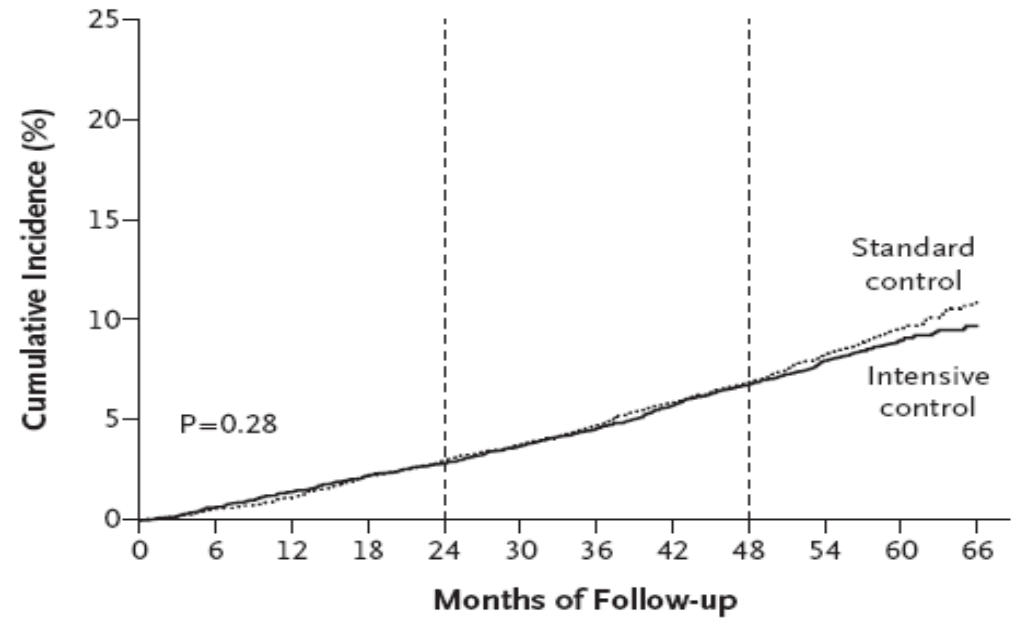
B Major Macrovascular Events



No. at Risk

Intensive	5570	5494	5428	5338	5256	5176	5097	5005	4927	4396	2071	486
Standard	5569	5486	5413	5330	5237	5163	5084	4995	4922	4385	2108	509

D Death from Any Cause



No. at Risk

Intensive	5571	5533	5490	5444	5411	5361	5312	5246	5189	4653	2211	523
Standard	5569	5537	5503	5445	5399	5354	5301	5237	5178	4643	2240	544

The ADVANCE Collaborative Group. *N Engl J Med 2008*

ADVANCE-ON

I° Congresso Congiunto AMD-SID
Piemonte e Valle d'Aosta
SINERGIE PER L'INNOVAZIONE
"se ci mettiamo insieme
ci sarà un perché"

Long-term Benefits of Intensive Glucose Control for Preventing End-Stage Kidney Disease: ADVANCE-ON

Diabetes Care 2016;39:694–700 | DOI: 10.2337/dc15-2322

OBJECTIVE

The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial reported that intensive glucose control prevents end-stage kidney disease (ESKD) in patients with type 2 diabetes, but uncertainty about the balance between risks and benefits exists. Here, we examine the long-term effects of intensive glucose control on risk of ESKD and other outcomes.

RESEARCH DESIGN AND METHODS

Survivors, previously randomized to intensive or standard glucose control, were invited to participate in post-trial follow-up. ESKD, defined as the need for dialysis or kidney transplantation, or death due to kidney disease, was documented overall and by baseline CKD stage, along with hypoglycemic episodes, major cardiovascular events, and death from other causes.

RESULTS

A total of 8,494 ADVANCE participants were followed for a median of 5.4 additional years. In-trial HbA_{1c} differences disappeared by the first post-trial visit. The in-trial reductions in the risk of ESKD (7 vs. 20 events, hazard ratio [HR] 0.35, $P = 0.02$) persisted after 9.9 years of overall follow-up (29 vs. 53 events, HR 0.54, $P < 0.01$). These effects were greater in earlier-stage CKD ($P = 0.04$) and at lower baseline systolic blood pressure levels ($P = 0.01$). The effects of glucose lowering on the risks of death, cardiovascular death, or major cardiovascular events did not differ by levels of kidney function ($P > 0.26$).

CONCLUSIONS

Intensive glucose control was associated with a long-term reduction in ESKD, without evidence of any increased risk of cardiovascular events or death. These benefits were greater with preserved kidney function and with well-controlled blood pressure.

…e gli altri antidiabetici orali?

Diabetes Care Volume 39, May 2016

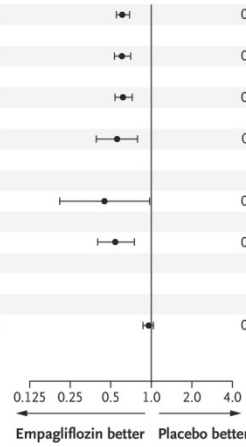
I° Congresso Congiunto AMD-SID
Piemonte e Valle d'Aosta
SINERGIE PER L'INNOVAZIONE
"se ci mettiamo insieme
ci sarà un perché"

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

Christoph Wanner, M.D., Silvio E. Inzucchi, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Maximilian von Eynatten, M.D., Michaela Mattheus, Dipl. Biomath., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Bernard Zinman, M.D., for the EMPA-REG OUTCOME Investigators*

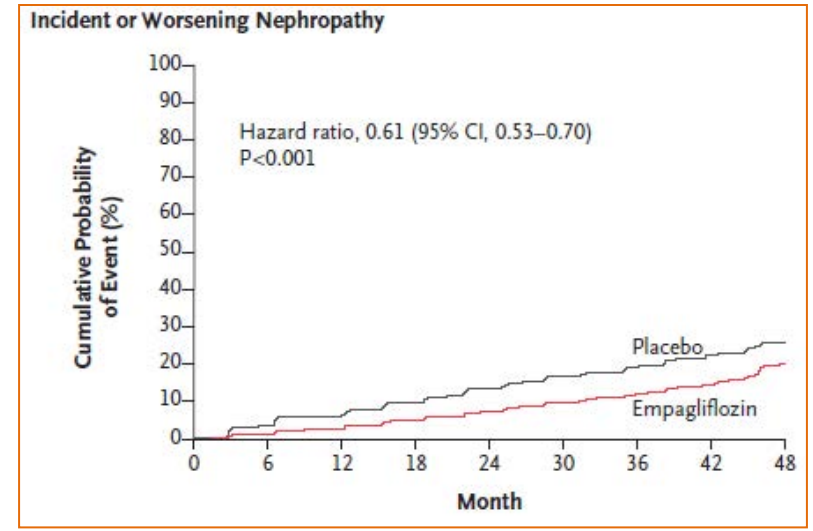
N ENGL J MED 375;4 NEJM.ORG JULY 28, 2016

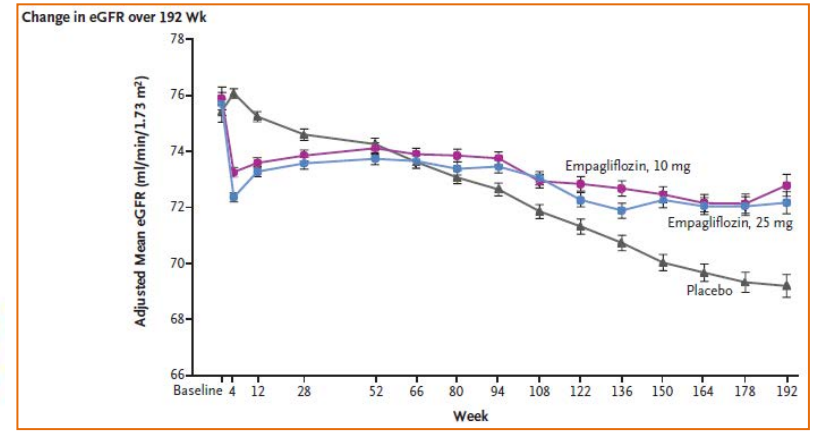
Renal Outcome Measure	Empagliflozin no. with event/ no. analyzed (%)	Empagliflozin rate/1000 patient-yr	Placebo no. with event/ no. analyzed (%)	Placebo rate/1000 patient-yr	Hazard Ratio (95% CI)	P Value
Incident or worsening nephropathy or cardiovascular death	675/4170 (16.2)	60.7	497/2102 (23.6)	95.9	0.61 (0.55–0.69)	<0.001
Incident or worsening nephropathy	525/4124 (12.7)	47.8	388/2061 (18.8)	76.0	0.61 (0.53–0.70)	<0.001
Progression to macroalbuminuria	459/4091 (11.2)	41.8	330/2033 (16.2)	64.9	0.62 (0.54–0.72)	<0.001
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m²	70/4645 (1.5)	5.5	60/2323 (2.6)	9.7	0.56 (0.39–0.79)	<0.001
Initiation of renal-replacement therapy	13/4687 (0.3)	1.0	14/2333 (0.6)	2.1	0.45 (0.21–0.97)	0.04
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m², initiation of renal-replacement therapy, or death from renal disease	81/4645 (1.7)	6.3	71/2323 (3.1)	11.5	0.54 (0.40–0.75)	<0.001
Incident albuminuria in patients with a normal albumin level at baseline	1430/2779 (51.5)	252.5	703/1374 (51.2)	266.0	0.95 (0.87–1.04)	0.25



CONCLUSIONS

In patients with type 2 diabetes at high cardiovascular risk, empagliflozin was associated with slower progression of kidney disease and lower rates of clinically relevant renal events than was placebo when added to standard care.





sulfoniluree

1. Abbiamo realmente bisogno di loro, o i nuovi antidiabetici sono altrettanto efficaci?
2. Gli altri antidiabetici hanno una maggiore tollerabilità?
3. Gli altri antidiabetici garantiscono maggiori benefici sugli outcome cardiovascolari?
4. *Gli altri antidiabetici garantiscono maggiori benefici sulle complicanze microvascolari?*
5. *Gli altri antidiabetici garantiscono maggiore durability?*

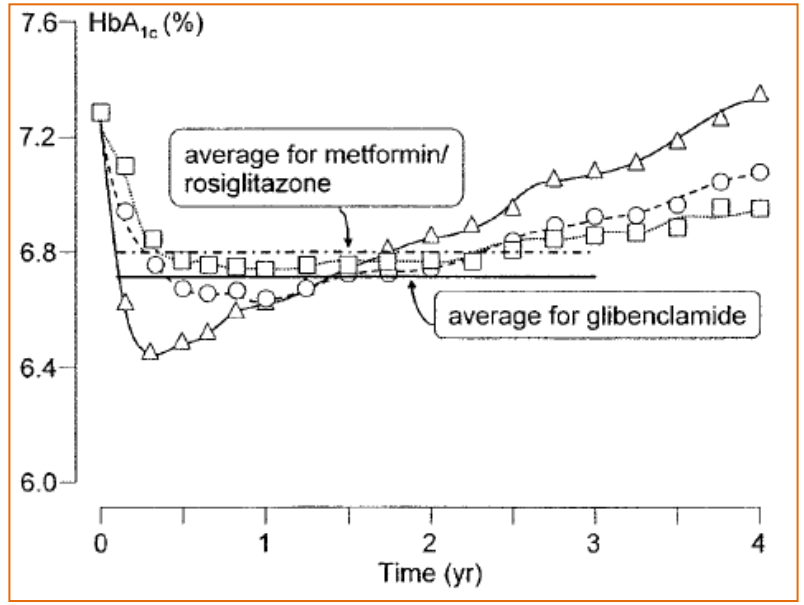
sulfoniluree *e durability*

ADOPT (glib, met, rosi)

- Alla conclusione dello studio, più 2nd failure con glib
- Per i primi 6-12 mesi, maggior efficacia di glib
- Dal 1° al 3° anno, efficacia sulla glicemia simile

Più eventi CV con rosi

oppure meno eventi con glib e met?!?



As glyburide use led to a more rapid decrease in glucose initially and as there is compelling evidence to treat patients with newly diagnosed type 2 diabetes more aggressively during the first years after diagnosis ***(because of the so-called legacy effect), use of SUs may well be appropriate, indeed preferred, to other drugs at this stage of the disease****.*

sulfoniluree *e durability*

Incidence and correlated factors of beta cell failure in a 4-year follow-up of patients with type 2 diabetes: a longitudinal analysis of the BETADECLINE study

Carlo B. Giorda[1] · Giuseppina T. Russo[2] · Stefania Cercone[3] · Salvatore De Cosmo[4] · Antonio Nicolucci[5] · Domenico Cucinotta[2]

Acta Diabetol Published online: 18 May 2016

Abstract

Aims Type 2 diabetes is associated with progressive deterioration of beta cell function and loss of glycemic control, with increased morbidity and mortality from microvascular and macrovascular complications. Factors predictive of beta cell decline are needed.

Methods We have conducted a prospective evaluation of baseline predictors of beta cell dysfunction and insulin initiation in a cohort of outpatients with type 2 receiving stable treatment with oral hypoglycem or dietary intervention, over a 4-year follow-up

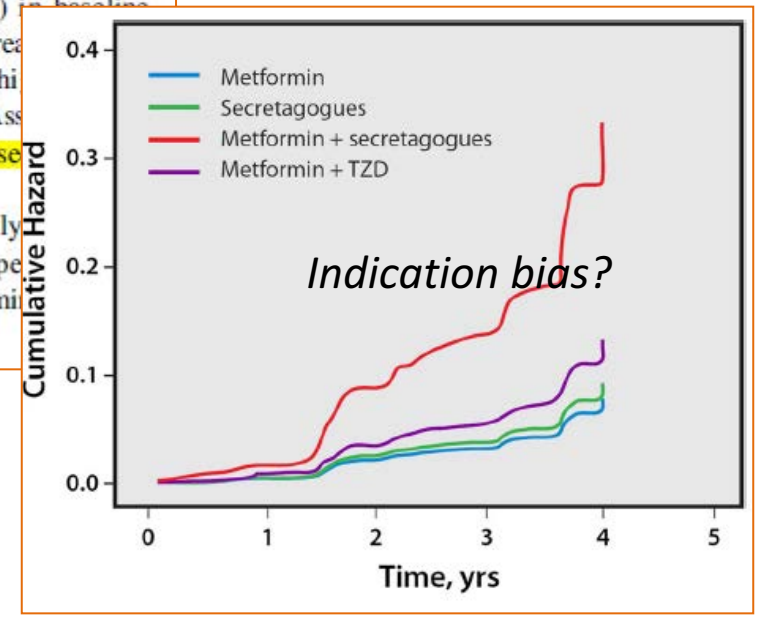
Results Of 507 patients enrolled, 56 (10.8 %) ex the study endpoint of initiation of insulin ther variate and multivariate Cox proportional

regression analyses revealed that the likelihood of initiating insulin therapy during follow-up increased with longer diabetes duration and with higher baseline values for hemoglobin A1c, fasting plasma glucose, triglycerides, proinsulin, interleukin-6, Homeostatic Model Assessment-IR and lower values for Homeostatic Model Assessment-B. The likelihood of initiating insulin therapy increased by

Table 3 Multivariate Cox regression analysis of risk of initiating insulin therapy

Characteristics	HR	95 % CI	*p*
Hemoglobin A1c	1.46	1.24–1.71	<0.0001
Interleukin-6	1.06	1.03–1.10	<0.0001
HOMA-B (quartiles)			
IV	1.0	–	–
III	2.32	0.74–7.30	0.15
II	2.23	0.72–6.97	0.17
I	3.67	1.25–10.79	0.02
Therapy			
Metformin	1.0	–	–
Secretagogues	1.19	0.25–5.77	0.83
Metformin + secretagogues	4.32	1.88–9.95	0.001
Metformin + thiazolidinediones	1.73	0.35–8.42	0.50

Variables tested and not significant: age, diabetes duration, fasting plasma glucose, triglycerides, proinsulin, homeostatic model assessment-IR



…qual è la durability dei nuovi antidiabetici orali?

durability

- **SGLT2-i e AGI:** non valutabili
- **Pioglitazone:** effetto di classe?
- **DPP4-i:** possibile

BMJ Open **Glycaemic durability with dipeptidyl peptidase-4 inhibitors in type 2 diabetes: a systematic review and meta-analysis of long-term randomised controlled trials**

Katherine Esposito,[1] Paolo Chiodini,[2] Maria Ida Maiorino,[3] Giuseppe Bellastella,[3] Annalisa Capuano,[4] Dario Giugliano[3]

In conclusion, the analysis of 12 randomised trials with duration up to 108 weeks suggests that the effect of DPP-4 inhibitors on HbA1c decreases during the second year of treatment.

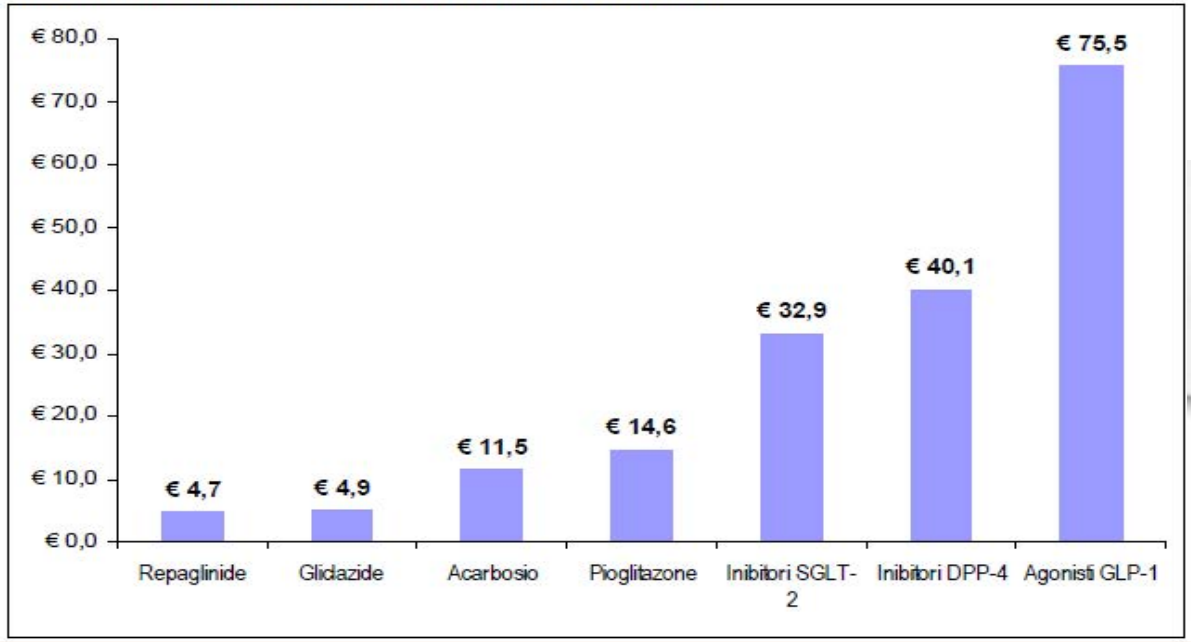
with long glycaemic durability. To the best of our knowledge, no other analysis assessed the glucose-lowering effect of DPP-4 inhibitors as a function of time in studies with long follow-up. We found that HbA1c decrease at the end of treatment with DPP-4 inhibitors was significantly lower than that recorded at intermediate points, suggesting that the glucose-lowering effect of DPP-4 inhibitors declines with time. Although extended trials are

REGIONE DEL VENETO

I° Congresso Congiunto AMD-SID
Piemonte e Valle d'Aosta
SINERGIE PER L'INNOVAZIONE
"se ci mettiamo insieme
ci sarà un perché"

Commissione Tecnica Regionale Farmaci (CTRF)

Grafico 1: Confronto del costo di 28 giorni di terapia ad una dose pari alla DDD delle alternative terapeutiche utilizzabili in aggiunta a metformina*



Commissione Tecnica Regionale Farmaci (CTRF)

Tabella 2: Le interazioni più importanti degli antidiabetici non insulinici

	MET	SU	REP	ACARB	PIO	DPP-4	GLP-1	SGLT-2
Dicumarolici		+						
FANS		+						
Antibiotici/antimicotici		+	+					
Fibrati		+			+			
Digossina				+				
Diuretici								+

REGIONE DEL VENETO

I° Congresso Congiunto AMD-SID
Piemonte e Valle d'Aosta
SINERGIE PER L'INNOVAZIONE
"se ci mettiamo insieme
ci sarà un perché"

Commissione Tecnica Regionale Farmaci (CTRF)

Tabella 3: Linee di indirizzo in funzione delle principali caratteristiche cliniche della terapia non insulinica nel diabete tipo 2, dopo fallimento della monoterapia con metformina (che è la prima scelta all'avvio della terapia del diabete) o in caso di soggetto non trattabile con metformina per insufficienza renale o per intolleranza al farmaco°

Caratteristica clinica	Farmaco di prima scelta	Scelte alternative	Attenzione/ controindicazione
Nessun problema particolare	Gliclazide (per il più basso costo)	Acarbosio Analogo GLP-1 Inibitore DPP-4 Inibitore SGLT2 Pioglitazone	Nessuna
Insufficienza cardiaca	Analogo GLP-1	Acarbosio Inibitore DPP-4 Inibitore SGLT2 Sulfonilurea/Glinide	Pioglitazone
Insufficienza epatica severa (Child-Pugh >9)	Linagliptin	Nessuna	Altri inibitori DPP-4 Acarbosio Analoghi GLP-1 Inibitori SGLT2 Pioglitazone Sulfonilurea/Glinide
Insufficienza renale severa (GFR <30 ml/min)	Inibitore DPP-4 (con eventuale titolazione se richiesta)	Pioglitazone	Acarbosio Analogo GLP-1 Inibitore SGLT2 Sulfonilurea/Glinide
Ipoglicemia da evitare per elevato rischio di conseguente morbilità oppure ipoglicemie ricorrenti	Inibitore DPP-4	Acarbosio Analogo GLP-1 Inibitore SGLT2 Pioglitazone	Sulfonilurea/Glinide
Malattia coronarica o cerebrovascolare	Pioglitazone	Acarbosio Analogo GLP-1 Inibitore DPP-4 Inibitore SGLT2	Sulfonilurea/Glinide
Osteoporosi	Gliclazide (per il più basso costo)	Acarbosio Analogo GLP-1 Inibitore DPP-4 Inibitore SGLT-2	Pioglitazone
Politerapia con potenziali interazioni fra farmaci	Inibitore DPP-4	Acarbosio Analogo GLP-1	Pioglitazone Inibitore SGLT2°° Sulfonilurea/Glinide
Sovrappeso/obesità	Analogo GLP-1 oppure Inibitore SGLT2	Acarbosio Inibitore DPP-4	Pioglitazone Sulfonilurea/Glinide
Steatosi epatica	Pioglitazone	Acarbosio Analogo GLP-1 Inibitore DPP-4 Inibitore SGLT2 Sulfonilurea/Glinide	

REGIONE DEL VENETO

I° Congresso Congiunto AMD-SID
Piemonte e Valle d'Aosta
SINERGIE PER L'INNOVAZIONE
"se ci mettiamo insieme
ci sarà un perché"

Commissione Tecnica Regionale Farmaci (CTRF)

Quesito 3: Quali sono i principali limiti legati all'impiego delle sulfoniluree ed esiste un criterio di scelta tra le molecole disponibili?

Raccomandazioni

Il trattamento con sulfoniluree si associa a maggior rischio di ipoglicemie, incremento ponderale e limitata persistenza dell'efficacia.

Livello della prova: I

Forza della raccomandazione: A

Un aumento del rischio cardiovascolare con l'uso di sulfoniluree è stato sostenuto da molti studi sperimentali e osservazionali, incluse alcune metanalisi. Questo aumentato rischio è plausibile dal punto di vista molecolare e fisiopatologico ma resta da dimostrare in maniera inequivocabile con specifici studi di intervento.

Livello della prova: III

Forza della raccomandazione: B

Tra le sulfoniluree, gliclazide sembra essere la molecola con il più favorevole rapporto rischio/beneficio e glibenclamide quella con il peggiore. L'uso di quest'ultima, associata a più frequenti ipoglicem aumentato rischio cardiovascolare non è raccomandabile.

Livello della prova: II

Forza della raccomandazione: B

Indicatori

1. Percentuale di pazienti in trattamento con metformina sul totale di pazienti che utilizzano farmaci antidiabetici: ≥70%
2. Percentuali di pazienti in trattamento con insulina sul totale dei pazienti che utilizzano farmaci antidiabetici: ≤30%
3. Percentuale di pazienti in trattamento con sulfoniluree oppure repaglinide sul totale di pazienti che utilizzano farmaci antidiabetici: ≤30% (di cui gliclazide ≥70%)
4. Percentuale di pazienti in trattamento con inibitori DPP-4 sul totale di pazienti che utilizzano farmaci antidiabetici: ≤20%
5. Percentuale di pazienti in trattamento con agonisti GLP-1 sul totale di pazienti che utilizzano farmaci antidiabetici: ≤5%
6. Percentuale di pazienti in trattamento con inibitori SGLT-2 sul totale dei pazienti che utilizzano farmaci antidiabetici: ≤5%

I° Congresso Congiunto AMD-SID
Piemonte e Valle d'Aosta

SINERGIE PER L'INNOVAZIONE

"se ci mettiamo insieme
ci sarà un perché"

Regione Emilia-Romagna

Linee guida terapeutiche /5

Nuovi farmaci per la cura del diabete, con particolare riferimento a incretino-mimetici (DPP-4 i e GLP-1 a.) e gliflozine (SGLT-2 i)

aggiornamento di Maggio 2016

A cura del Gruppo multidisciplinare sui farmaci per il diabete
Regione Emilia-Romagna

Raccomandazione 1 - Sulfaniluree *(compresa la repaglinide)*

Positiva debole

Nelle persone adulte con diabete mellito tipo 2 in terapia con metformina che necessitano di un secondo ipoglicemizzante, le sulfaniluree dovrebbero essere utilizzate nella maggior parte dei casi.

Raccomandazione formulata sulla base di:

★★☆☆ *evidenze considerate di qualità bassa*

☺ *bilancio benefici/rischi favorevole*

Indicatore di uso atteso

Sulla base della raccomandazione formulata il tasso di utilizzo atteso per le sulfaniluree è **almeno il 50%** delle persone con DM2 che a un trattamento in monoterapia con metformina aggiungono un secondo farmaco orale (in quanto la monoterapia con metformina non è più sufficiente a controllare adeguatamente la malattia).

Raccomandazione 2 - Incretino-mimetici

Positiva debole

Quando la terapia con metformina necessita di un secondo ipoglicemizzante, sia gli inibitori delle dipeptidil-peptidasi-4 (DPP-4i) sia gli analoghi del glucagon-like peptide-1 (GLP-1 a) possono essere utilizzati in alcuni sottogruppi di persone adulte con diabete mellito tipo 2.
Nella scelta del principio attivo, a parità di efficacia e sicurezza, dovrà essere privilegiata la molecola con il miglior rapporto costo/beneficio.

Raccomandazione formulata sulla base di:

★★☆☆ *evidenze considerate di qualità bassa*

☺ *bilancio benefici/rischi favorevole*

Indicatore di uso atteso

Sulla base della raccomandazione formulata il tasso di utilizzo atteso per gli incretino-mimetici è **fino al 30%** delle persone con DM2 che a un trattamento in monoterapia con metformina aggiungono un secondo farmaco orale (in quanto la monoterapia con metformina non è più sufficiente a controllare adeguatamente la malattia).

Raccomandazione 4 - SGLT2i (gliflozine)

Positiva debole

Quando la terapia con metformina necessita di un secondo ipoglicemizzante gli inibitori del co-trasportatore sodio-glucosio (SGLT-2) possono essere utilizzati in alcuni sottogruppi di persone adulte con diabete mellito tipo 2.
Nella scelta del principio attivo va considerato che attualmente solo empagliflozin ha mostrato una efficacia significativamente maggiore del placebo nel ridurre il rischio di eventi cardiovascolari in pazienti diabetici in prevenzione secondaria.

Raccomandazione formulata sulla base di:

★★★★ *evidenze considerate di qualità alta*

☺ *bilancio benefici/rischi favorevole*

Indicatori di uso atteso

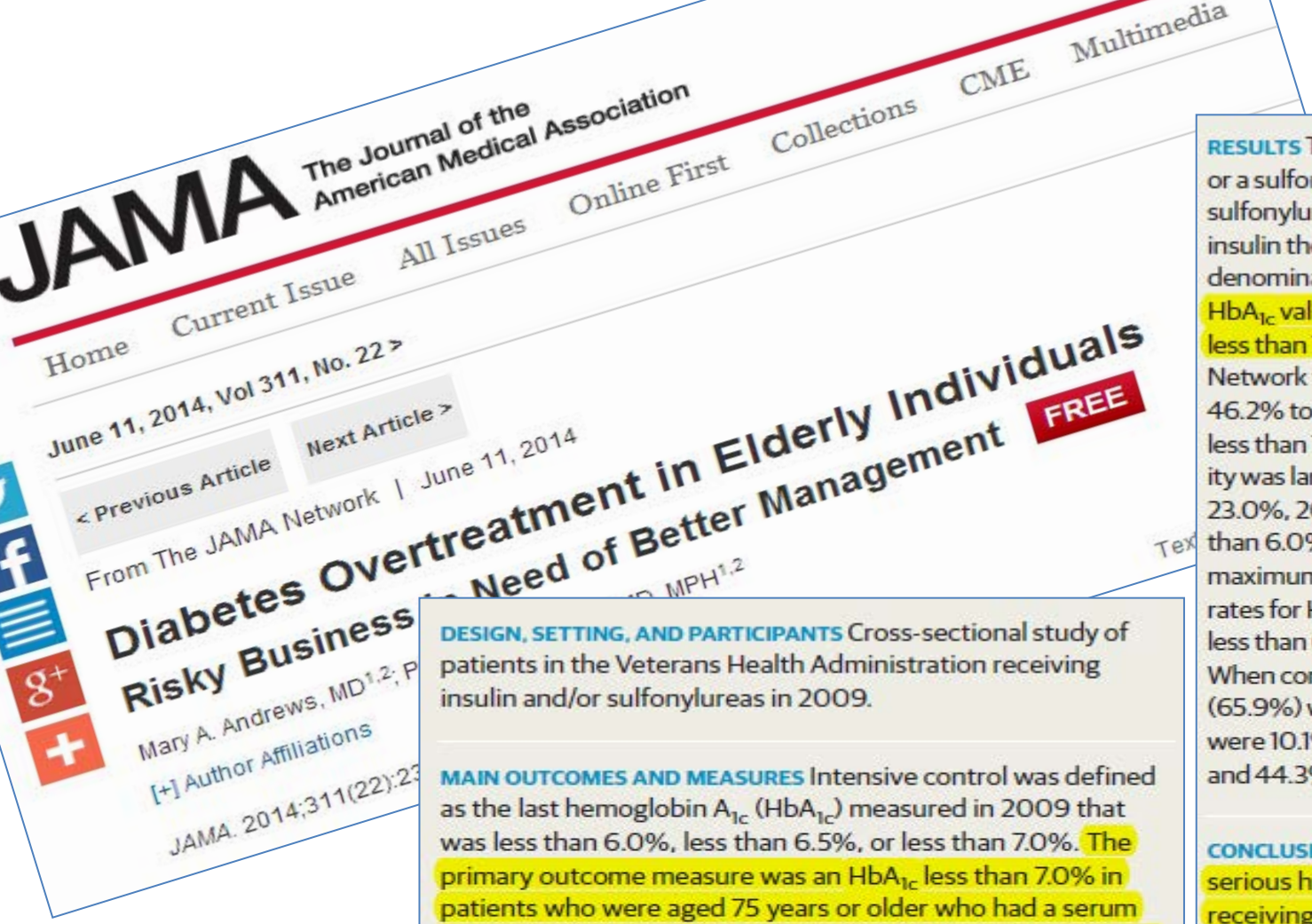
Sulla base della raccomandazione formulata il tasso di utilizzo atteso per gli SGLT-2i **per l'anno 2016** è **fino al 15%** delle persone con DM2 che a un trattamento in monoterapia con metformina aggiungono un secondo farmaco orale (in quanto la monoterapia con metformina non è più sufficiente a controllare adeguatamente la malattia).
Sulla base della raccomandazione formulata il tasso di utilizzo atteso di empagliflozin è **di almeno 33 %** delle persone con DM2 che a un trattamento in monoterapia con metformina aggiungono un farmaco SGLT-2i.

sulfoniluree

Da non prescrivere a:

- Anziani/pz fragili che vivono da soli
- Soggetti con alimentazione erratica, senza sostegno
- Soggetti con insufficienza epatica o renale
- Soggetti con insufficienza surrenalica
- Donne in gravidanza/allattamento
- *Soggetti con cardiopatia ischemica*

Occhio alle interazioni!



DESIGN, SETTING, AND PARTICIPANTS Cross-sectional study of patients in the Veterans Health Administration receiving insulin and/or sulfonylureas in 2009.

MAIN OUTCOMES AND MEASURES Intensive control was defined as the last hemoglobin A_{1c} (HbA_{1c}) measured in 2009 that was less than 6.0%, less than 6.5%, or less than 7.0%. The primary outcome measure was an HbA_{1c} less than 7.0% in patients who were aged 75 years or older who had a serum creatinine value greater than 2.0 mg/dL or had a diagnosis of cognitive impairment or dementia. We also assessed the rates in patients with other significant medical, neurologic, or mental comorbid illness. Variation in rates of possible glycemic overtreatment was evaluated among 139 Veterans Health Administration facilities grouped within 21 Veteran Integrated Service Networks.

RESULTS There were 652 378 patients who received insulin and/or a sulfonylurea with an HbA_{1c} test result. Fifty percent received sulfonylurea therapy without insulin; the remainder received insulin therapy. We identified 205 857 patients (31.5%) as the denominator for the primary outcome measure; 11.3% had a last HbA_{1c} value less than 6.0%, 28.6% less than 6.5%, and 50.0% less than 7.0%. Variation in rates by Veterans Integrated Service Network facility ranged 8.5% to 14.3%, 24.7% to 32.7%, and 46.2% to 53.4% for HbA_{1c} less than 6.0%, less than 6.5%, and less than 7.0%, respectively. The magnitude of variation by facility was larger, with overtreatment rates ranging from 6.1% to 23.0%, 20.4% to 45.9%, and 39.7% to 65.0% for HbA_{1c} less than 6.0%, less than 6.5%, and less than 7.0%, respectively. The maximum rate was nearly 4-fold compared with the minimum rates for HbA_{1c} less than 6.0%, followed by 2.25-fold for HbA_{1c} less than 6.5% and less than 2-fold for HbA_{1c} less than 7.0%. When comorbid conditions were included, 430 178 patients (65.9%) were identified as high risk. Rates of overtreatment were 10.1% for HbA_{1c} less than 6.0%, 25.2% for less than 6.5%, and 44.3% for less than 7.0%.

CONCLUSIONS AND RELEVANCE Patients with risk factors for serious hypoglycemia represent a large subset of individuals receiving hypoglycemic agents; approximately one-half had evidence of intensive treatment. A patient safety indicator derived from administrative data can identify high-risk patients for whom reevaluation of glycemic management may be appropriate, consistent with meaningful use criteria for electronic medical records.

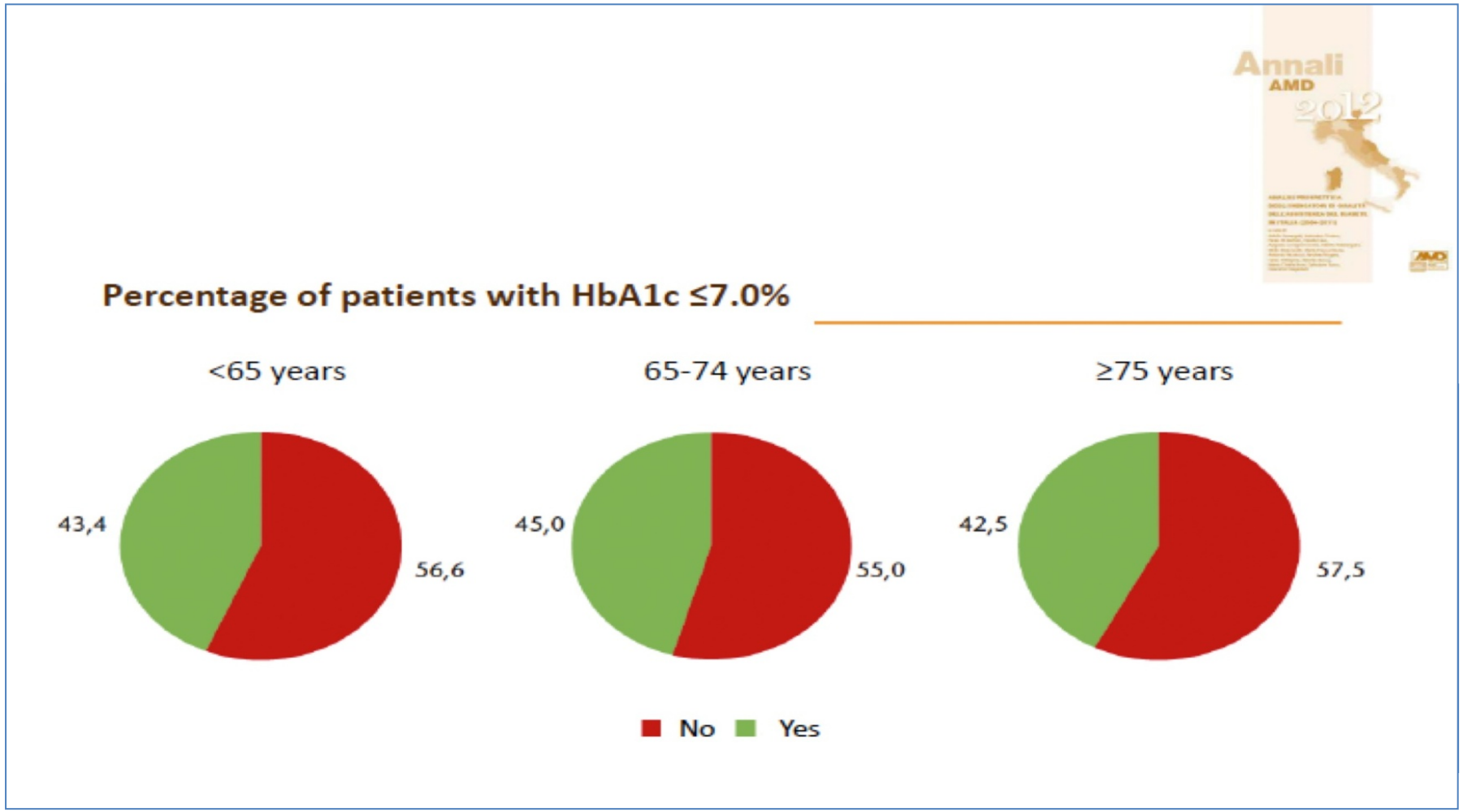
JAMA Intern Med. 2014;174(2):259-268.

Original Investigation | LESS IS MORE

Potential Overtreatment of Diabetes Mellitus in Older Adults With Tight Glycemic Control

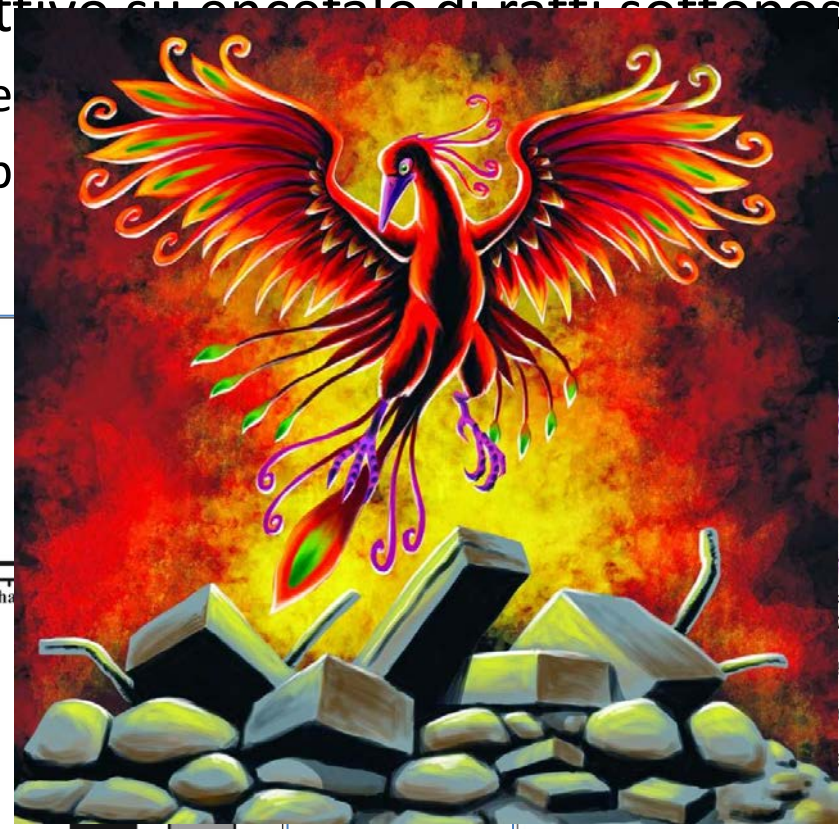
Kasia J. Lipska, MD, MHS; Joseph S. Ross, MD; Yinghui Miao, MPH; Nilay D. Shah, PhD; Sei J. Lee, MD, MAS; Michael A. Steinman, MD

JAMA Internal Medicine Published online January 12, 2015



Glibenclamide Improves Survival and Neurologic Outcome After Cardiac Arrest in Rats*

- Effetto neuroprotettivo su encefalo di ratti sottoposti ad arresto cardiaco
  - Riduzione necrosi e
  - Riduzione flogosi ip
  - Ruolo NF-κB



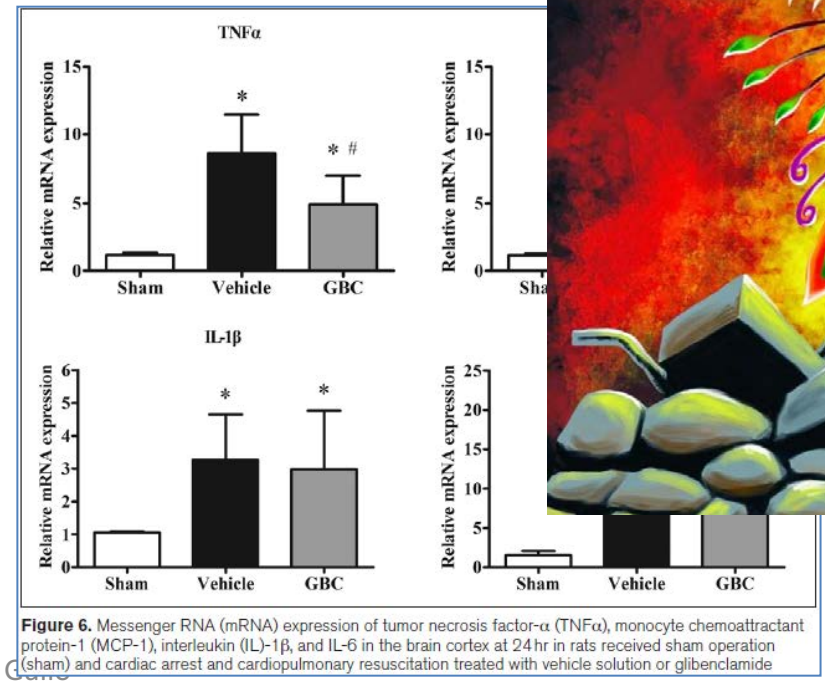


Figure 6. Messenger RNA (mRNA) expression of tumor necrosis factor-α (TNFα), monocyte chemoattractant protein-1 (MCP-1), interleukin (IL)-1β, and IL-6 in the brain cortex at 24 hr in rats received sham operation (sham) and cardiac arrest and cardiopulmonary resuscitation treated with vehicle solution or glibenclamide

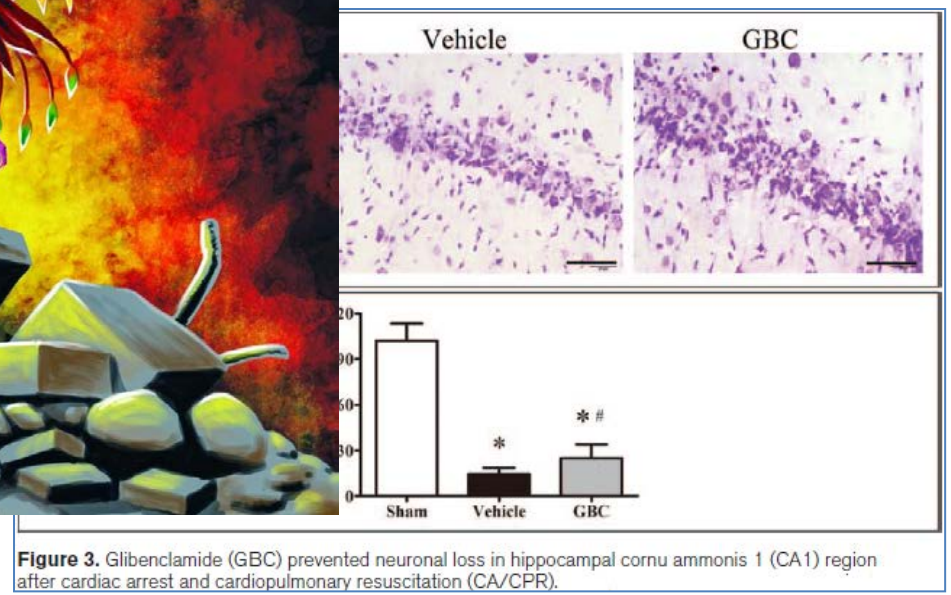
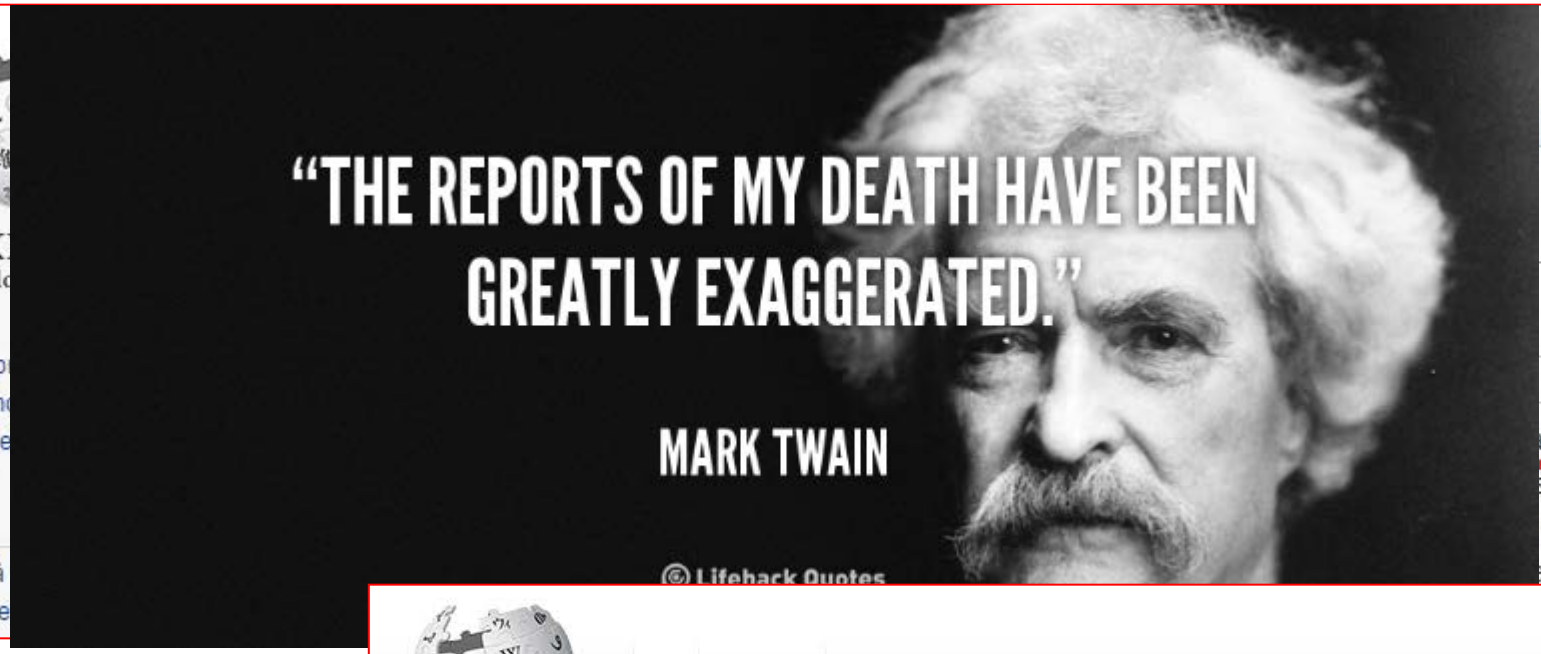


Figure 3. Glibenclamide (GBC) prevented neuronal loss in hippocampal cornu ammonis 1 (CA1) region after cardiac arrest and cardiopulmonary resuscitation (CA/CPR).

Huang K et al.; Simard JM & Shetth KN, Crit Care Med 2015

requiem per gli ipoglicemizzanti orali?

I° Congresso Congiunto AMD-SID
Piemonte e Valle d'Aosta
SINERGIE PER L'INNOVAZIONE
"se ci mettiamo insieme
un perché"



Modifica | Modifica wikit

del defunto. Può
so di eseguirla
religione cattolica le
enza di espiazione.

Voce | Discussione | Leggi | Modifica | Modifica wikitesto | Cronologia

Regione	Metformina	Sulfaniluree	Glinidi	Glitazonici	Acarbose
Liguria	24,7	18,8	2,0	1,1	1,0
	57,8	34,3	6,9	3,3	1,1
	+33,1	+15,5	+4,9	+2,2	+0,1
Piemonte/Val d'Aosta	29,0	27,2	3,1	0,4	1,0
	51,0	30,7	7,5	1,4	2,8
	+22,0	+3,5	+4,4	+1,0	+1,8

Bar
Il Wikipediano

La Messa di Requiem in Re minore K 626 è l'ultima composizione di Wolfgang Amadeus Mozart.
avvenuta il 5 dicembre 1791, fu completata successivamente da Franz Süssmayr.

I° Congresso Congiunto AMD - SID

Piemonte e Valle d'Aosta

SINERGIE PER L'INNOVAZIONE

"se ci mettiamo insieme
ci sarà un perché"

Il diabetico tipo 2:
requiem per gli ipoglicemizzanti orali?

Grazie!

Marco Gallo

SCDU Endocrinologia Oncologica
AOU Città della Salute e della Scienza di Torino
Molinette - COES