Corso di Aggiornamento
OMCeO BG via G. Manzù 25 - Bergamo

Introduzione: quali spazi terapeutici per i “vecchi farmaci” per il diabete mellito tipo 2?

Antonio C. Bossi
Humanitas Gavazzeni Bergamo
2 Febbraio 2022

HUMANITAS
GAVAZZENI

DISCLOSURES

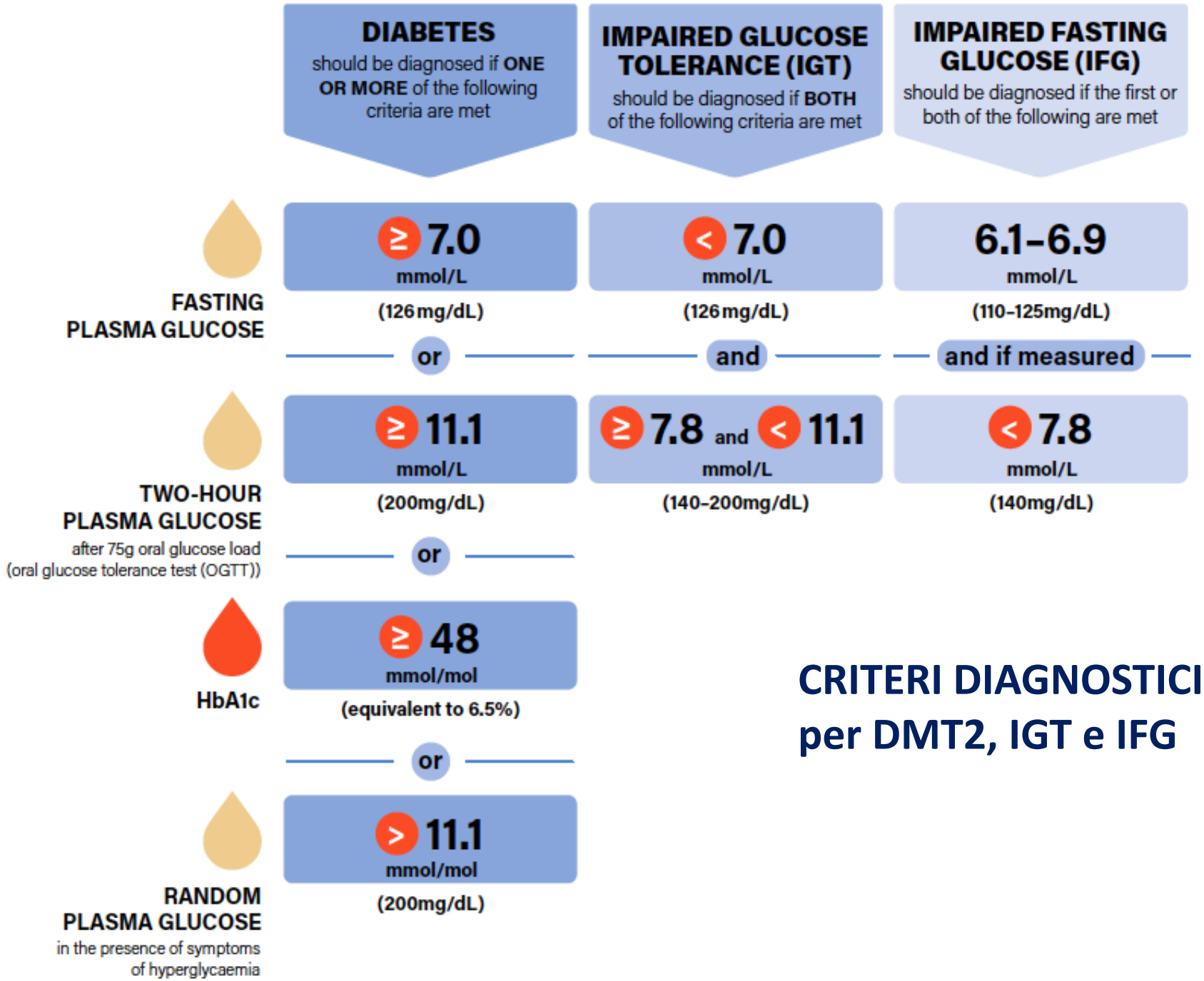
In the last ten years, ACB reports:

- Research grants from: Novo-Nordisk Dk
  Eli Lilly USA
  Bayer SA D
  Sanofi Italia SpA
  Pikdare Italia SpA
- Personal fees from: MSD Int. USA
  Alfasigma Italia SpA
  Johnson & Johnson Italia SpA
  Boehringer Ingelheim Italia SpA
  Astra Zeneca Italia SpA
  Takeda Italia SpA
  Mundipharma Italia SpA

I acknowledge the Italian Diabetes Society (SID) for its contribution to my scientific and clinical education.

www.siditalia.it

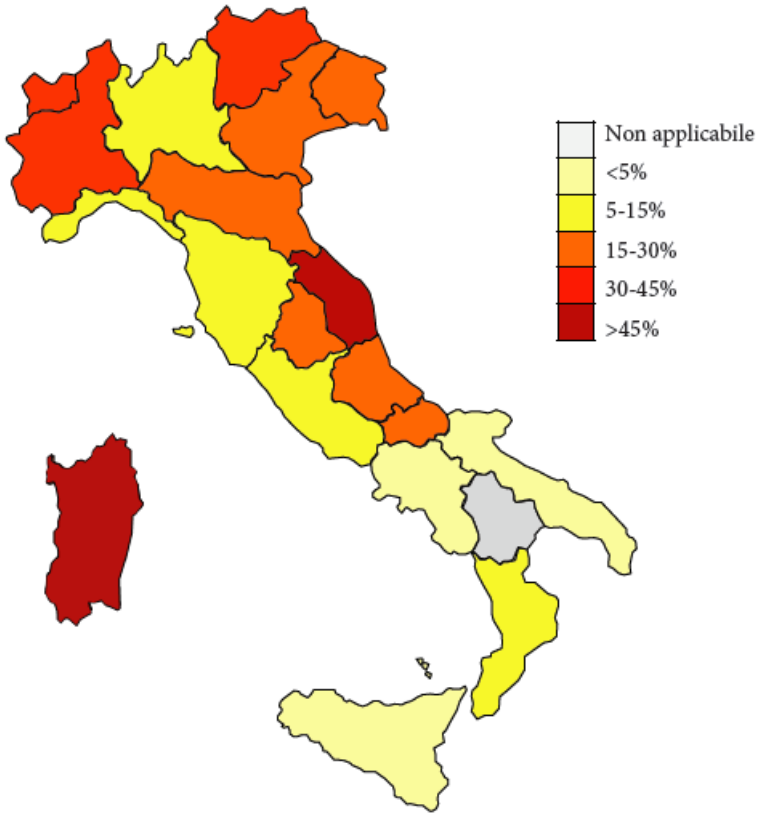
SID
Società Italiana di Diabetologia

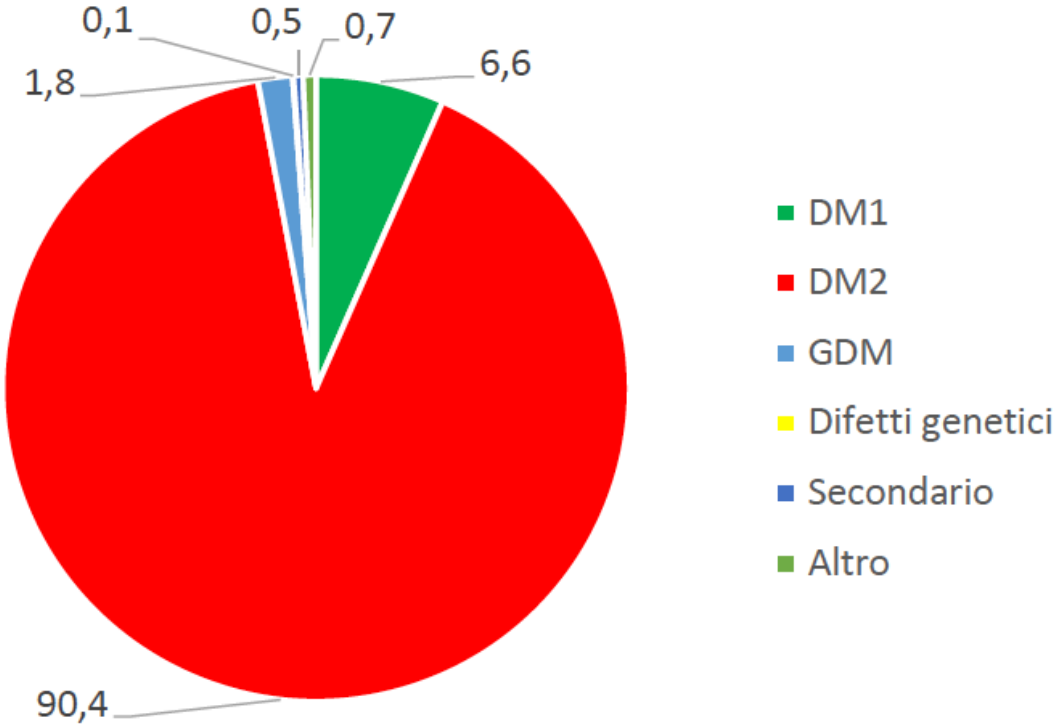


CRITERI DIAGNOSTICI per DMT2, IGT e IFG

Contesto epidemiologico

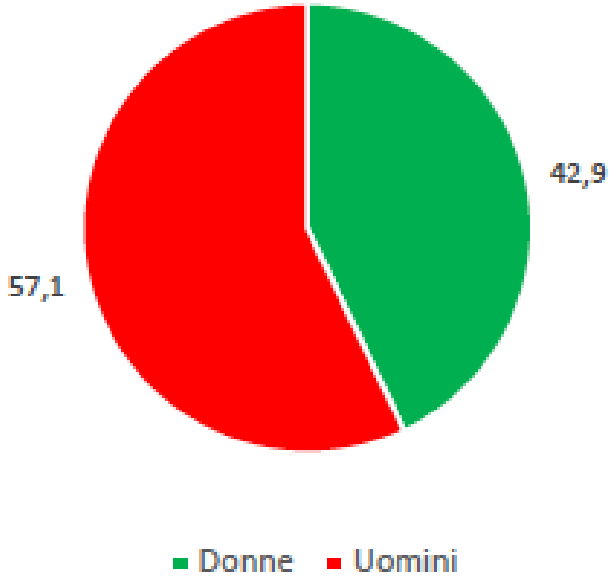
- In Italia, i casi noti di diabete erano circa 1,5 milioni nel 1985 e ora si avvicinano ai 4 milioni, quindi sono **più che raddoppiati in 30 anni**.
- I dati epidemiologici italiani suggeriscono circa **250.000 nuove diagnosi di DMT2/anno**
  (fonte Il diabete in Italia - SID 2016).
- **Annali AMD 2020**: 524.029 pazienti visti nel corso del 2018 in 258 Servizi di diabetologia italiani. Di questi, 508.445 (34.705 DM1 e 473.740 DM2) costituiscono la coorte degli Annali 2020.

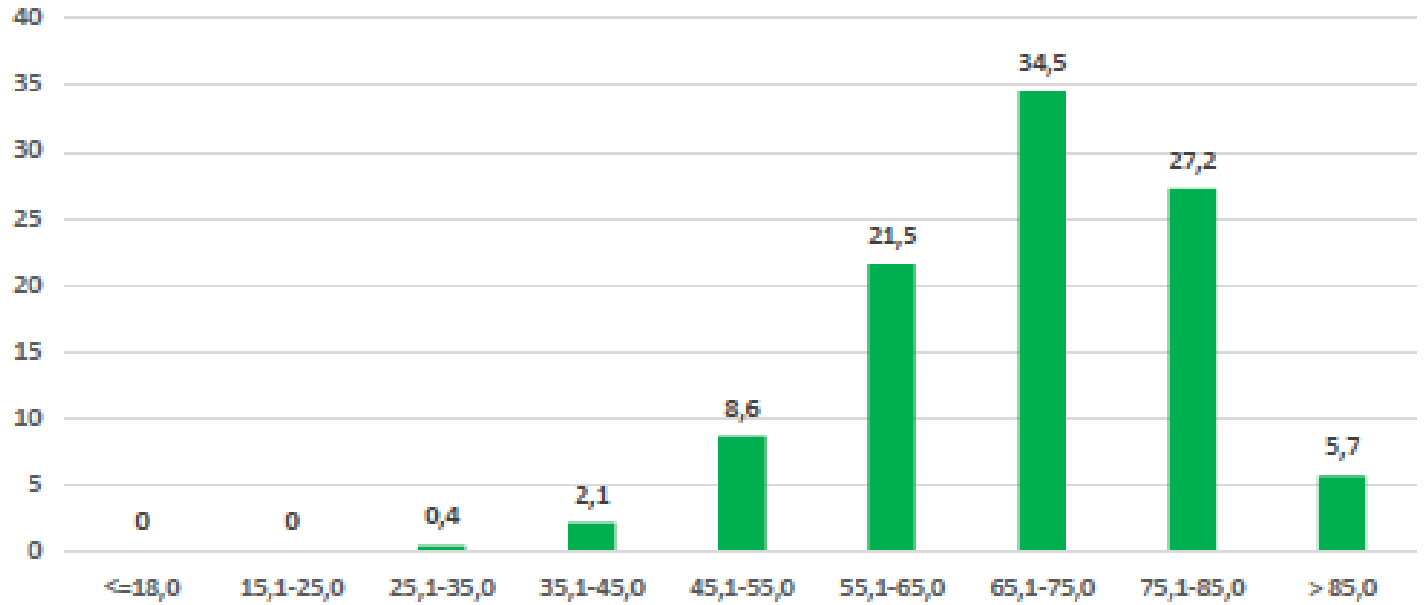




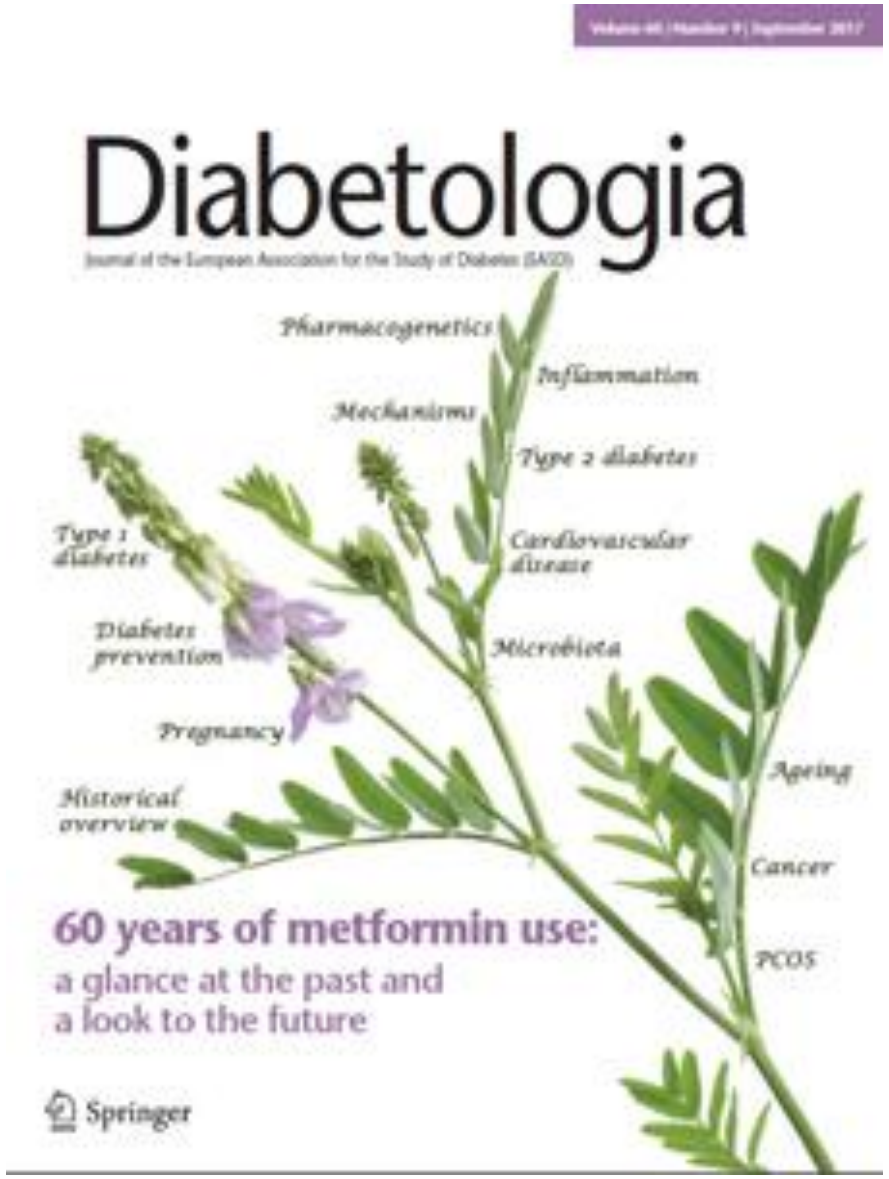
Contesto epidemiologico

- La distribuzione per genere conferma, nel 2018, la maggior prevalenza di diabete negli uomini, in aumento rispetto ai dati precedenti.
- **L'età media** della popolazione diabetica è di **69,2±11.1 anni**.
- E' stabile la quota di soggetti di età <55 anni, mentre cresce quella dei pazienti over 85 anni.
- Complessivamente, il 67,4% dei soggetti con diabete ha una età >65 anni.





Metformina


Diabetologia
Journal of the European Association for the Study of Diabetes (EASD)
Pharmacogenetics
Inflammation
Mechanisms
Type 2 diabetes
Type 1 diabetes
Cardiovascular disease
Diabetes prevention
Microbiota
Pregnancy
Historical overview
Ageing
Cancer
PCOS
60 years of metformin use:
a glance at the past and a look to the future
Springer

Metformina: meccanismo d'azione

- **Riduce la produzione epatica di glucosio**
- **Inibisce la gluconeogenesi**
- **⇓ Insulino resistenza**
- **Migliora l'uptake periferico del glucosio (muscolo, tessuto adiposo)**

Mediata dall'attivazione della

5'AMP-activated protein kinase (AMPK)

negli epatociti e nei muscoli

Metformina: meccanismo d’azione

- **Non aumenta la secrezione insulinica**
- **Livelli d’insulina invariati o ridotti**
- **Non produce ipoglicemie gravi**
- **Riduzione dei FFA (acidi grassi liberi)**
- **Favorevoli effetti sui lipidi**
  - ⇓ **trigliceridi**
  - ⇓ **colesterolo totale**
  - ⇓ **LDL**
  - ⇑ **HDL**

DIABETES RESEARCH AND CLINICAL PRACTICE 160 (2020) 108001

Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

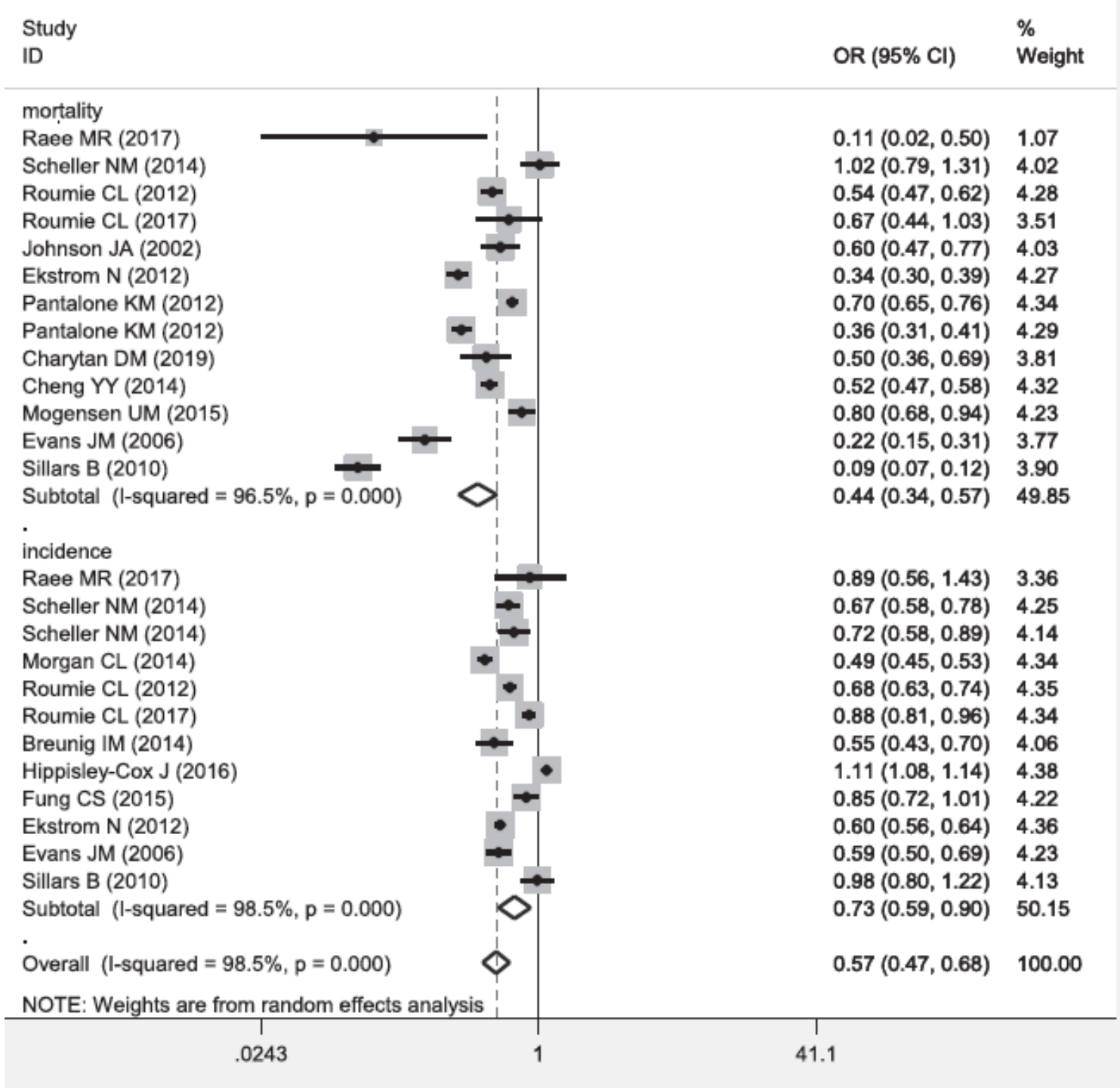
Cardiovascular risk following metformin treatment in patients with type 2 diabetes mellitus: Results from meta-analysis

Kui Zhang [a,1], *Wenxing Yang* [b,1], *Hao Dai* [a], *Zhenhua Deng* [a,*]

MORTALITA' CVD: -56%

INCIDENZA CVD: -27%

RISCHIO CVD COMPLESSIVO: -43%



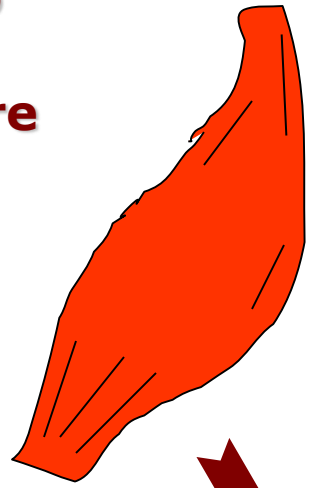
Metformina: effetti collaterali

- **Disturbi gastrointestinali (epigastralgie, nausea e diarrea nel 10-30% dei pazienti)**
- **Riduzione effetti indesiderati con formulazioni a lento rilascio**
- **Acidosi lattica (0.03 casi/1000 pazienti-anno)**

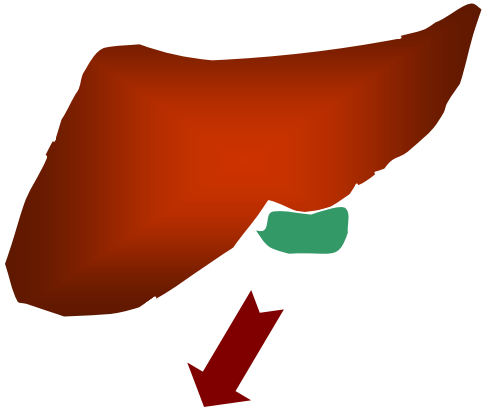
Biguanidi ed Acidosi Lattica

Biguanidi

Aumento glicolisi muscolare



Inibizione gluconeogenesi epatica

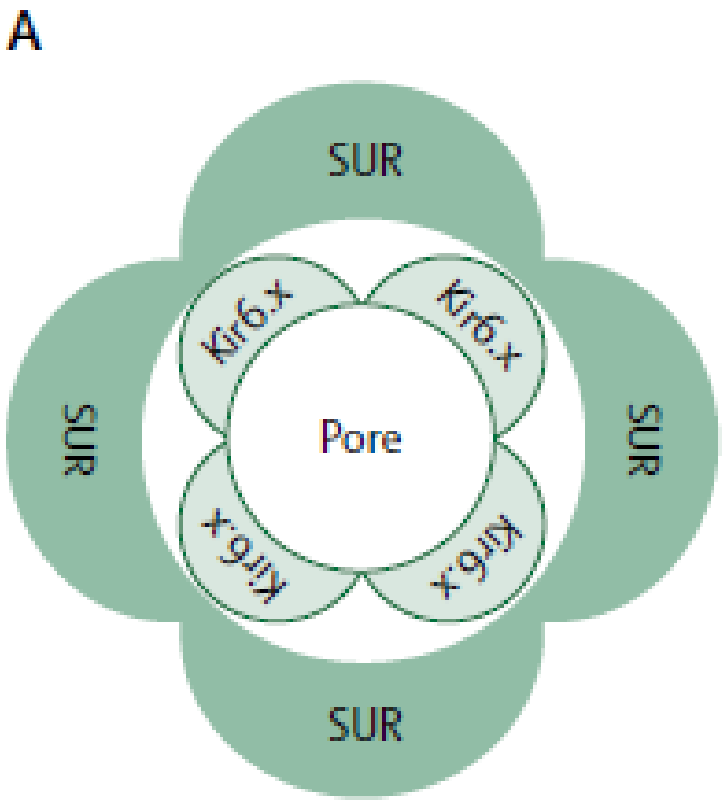


Aumento lattato

Metformina: controindicazioni

- **Insufficienza renale : con eGFR >45ml/min proseguire**
  - **Se eGFR >30 ml/min: ridurre la dose**
  - **Se eGFR <30ml/min: sospendere**
- **Insufficienza epatica grave**
- **Insufficienza cardiorespiratoria ed IMA recente**
- **Intervento chirurgico**
- **Uso di m.d.c. organo-jodato**
- **Gravi stati infettivi**
- **Disidratazione**

Sulfaniluree e Glinidi

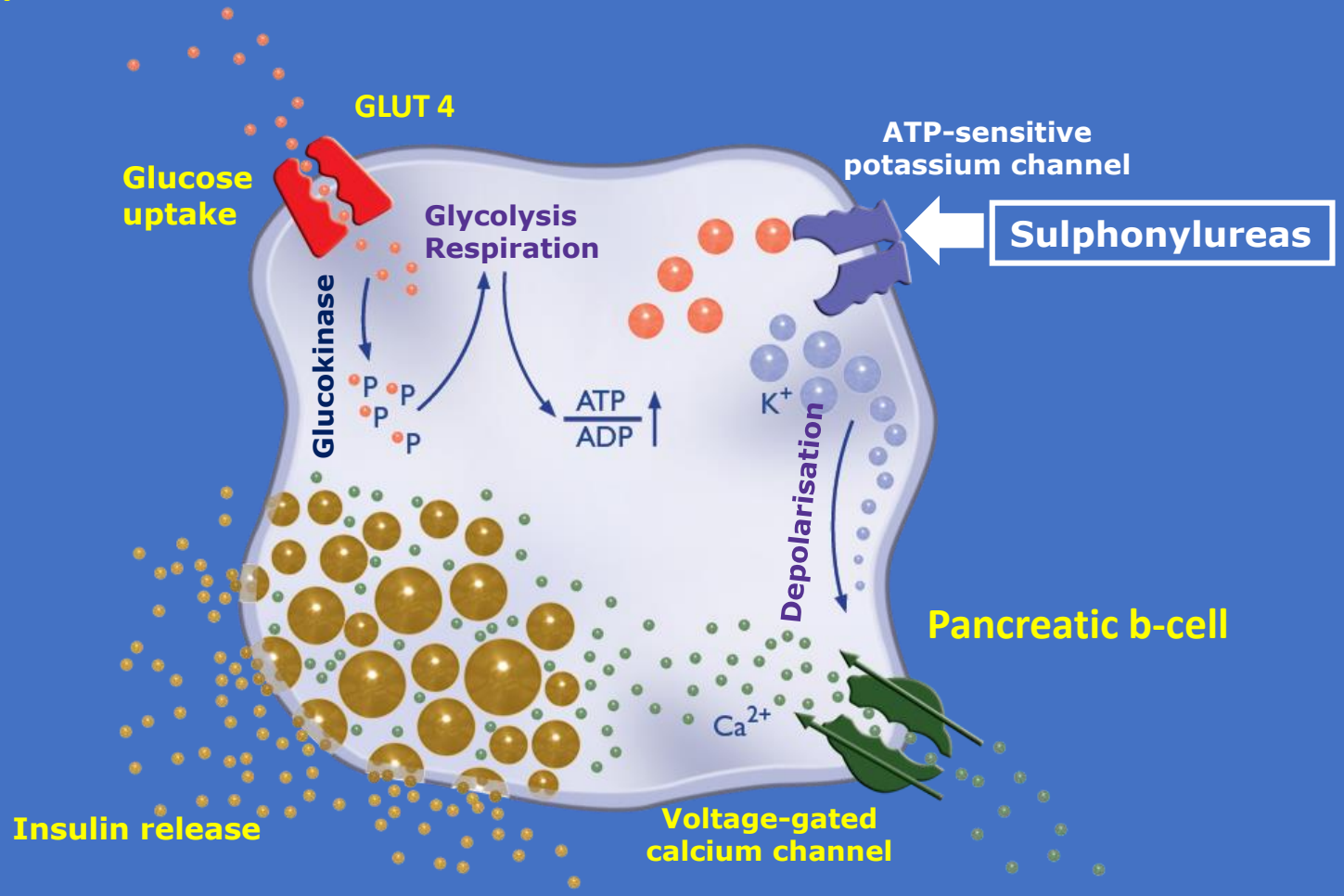


Sulfoniluree

Farmaco Anno produz.	Dose *mg/die*	Somministr/ die	Emivita *h*	Durata azione *h*
Clorpropamide 1957	100-500	1	35 (25-60)	24-72
Glibenclamide 1969	2.5-20	1-3	10	16
Gliclazide 1972	40-240	1-3	10-12	8-16
Glimepiride 1999	1-6	1	5-8	24

Sulfaniluree: meccanismo d'azione

Incrementano la secrezione di insulina endogena legandosi alle β-cellule pancreatiche e innescando una cascata di eventi intracellulari [1-3]

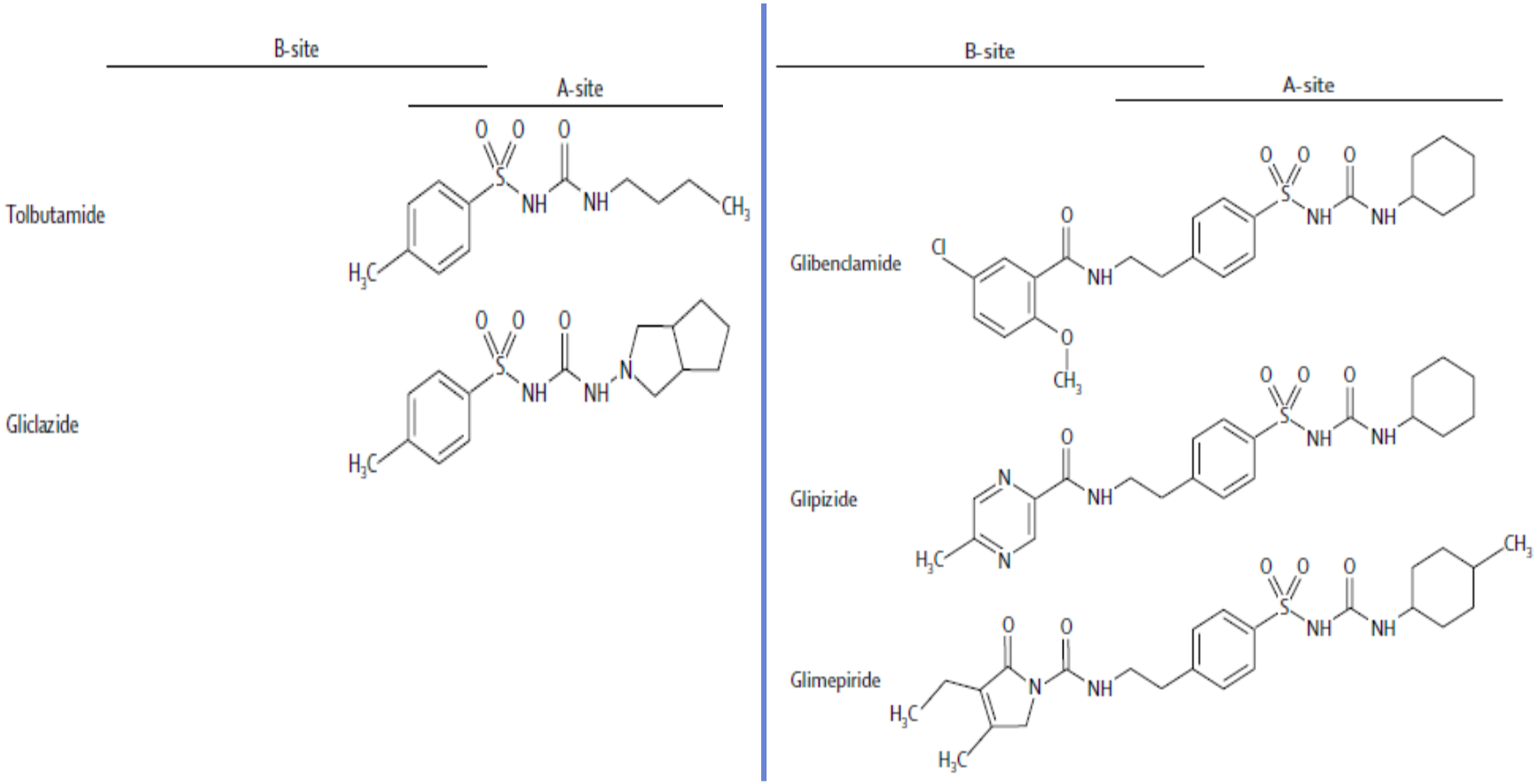


1. Gallwitz B, Haring H-U. Diabetes Obes Metab. 2010;12:1-11.
2. Schuit FC, et al. Diabetes .2001;50:1-11.
3. Krentz AJ, Bailey CJ. Drugs. 2005;65:385-411.

Do sulphonylureas still have a place in clinical practice?

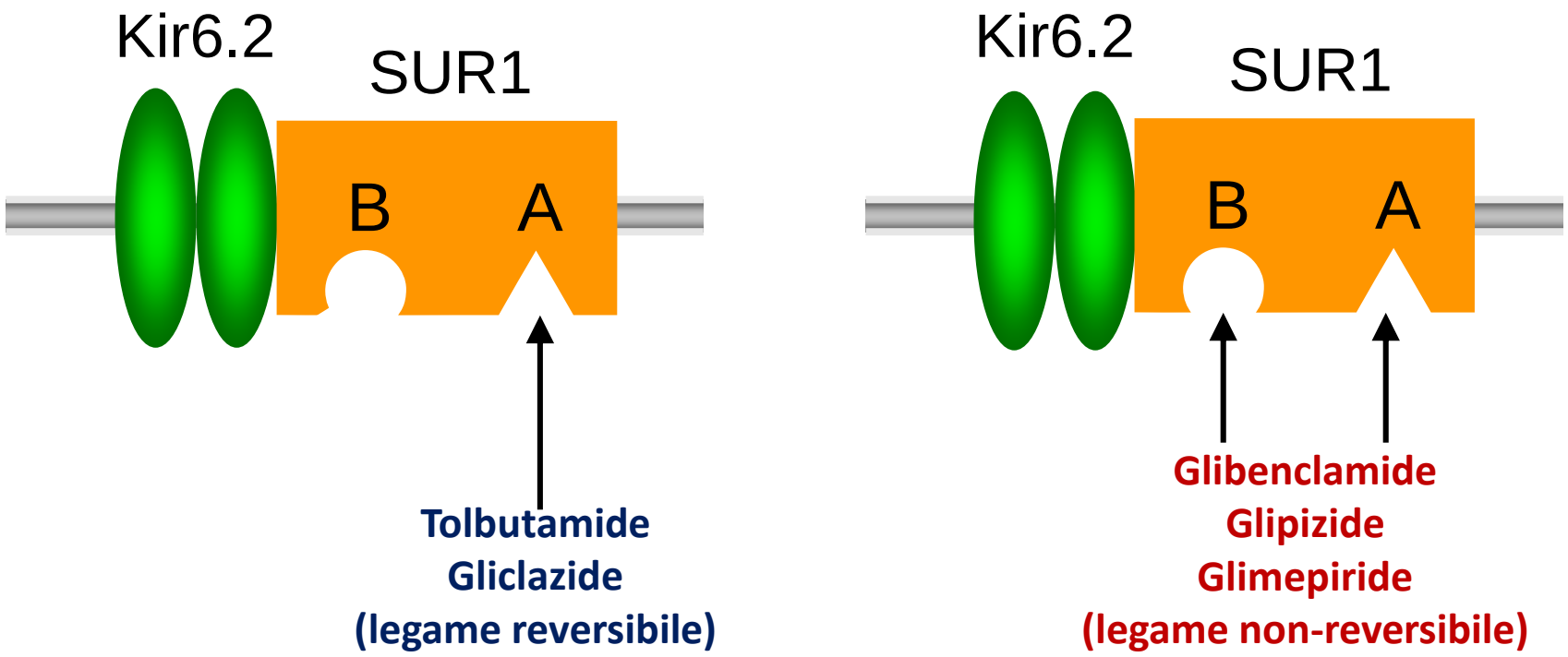
Kamlesh Khunti, Sudesna Chatterjee, Hertzel C Gerstein, Sophia Zoungas, Melanie J Davies

Lancet Diabetes Endocrinol 2018



Published Online February 28, 2018 http://dx.doi.org/10.1016/S22138587(18)30025-1

Legame di SU e Glinidi al canale K-ATP delle β-cellule



A: Sito di legame del gruppo Sulfamidico

B: Sito di legame del gruppo Benzamidico

Sulfoniluree e repaglinide: effetti collaterali

- **Ipoglicemia**
- **Incremento ponderale**
- **Disturbi gastrointestinali**
- **Manifestazioni cutanee**
- **Alterazioni della crasi ematica**

Cardiovascular Implications of Hypoglycemia in Diabetes Mellitus

Kim A. Connelly, MBBS, PhD; Andrew T. Yan, MD; Lawrence A. Leiter, MD; Deepak L. Bhatt, MD, MPH; Subodh Verma, MD, PhD

Table 2. Rates of Hypoglycemia in the ACCORD, VADT, and ADVANCE Clinical Trials

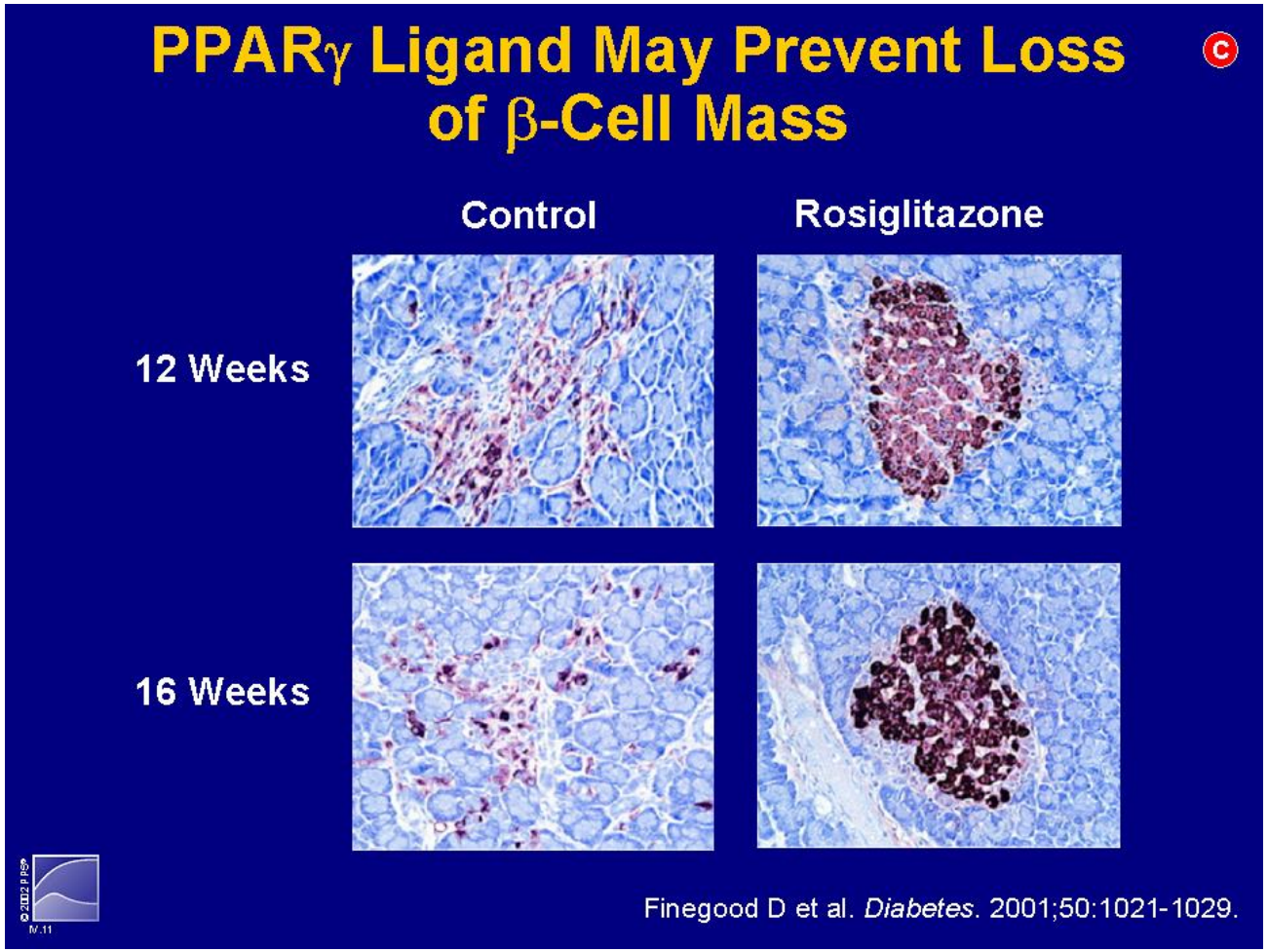
	Standard Glucose Control Arm, %	Intensive Glucose Control Arm, %	*P* Value
ACCORD	5.1	16.2	<0.001
ADVANCE	1.5	2.7	<0.001
VADT	9.9	21.2	<0.001

Circulation. 2015;132:2345-2350

Sulfoniluree:
Controindicazioni

- **Diabete mellito di tipo 1**
- **Diabete mellito secondario a patologia pancreatica**
- **Interventi chirurgici**
- **Insufficienza renale, insufficienza epatica**
- **Gravidanza, allattamento**
- **Ipersensibilità al farmaco**

Pioglitazone



TZD: meccanismo d'azione

Sono dei ligandi dei PPAR:

peroxisome proliferator-activated receptor

- **Appartengono alla superfamiglia dei recettori nucleari**
- **Regolano la trascrizione genica**

- **Ligandi naturali (con bassa affinità)**
  - **Prostanoidi, es. 15-deoxy$\Delta^{12,14}$PG J2**
  - **Acidi grassi polinsaturi, es. acido linoleico e acido arachidonico**

PPAR γ

- **Regolano la differenziazione del tessuto adiposo (da preadipociti ad adipociti maturi) e la sua proliferazione**

- **Stimolano l'accumulo di acidi grassi negli adipociti**

- **Stimolano l'espressione e l'azione del GLUT4**

TZD: meccanismo d’azione

- Effetto ipoglicemizzante
- Non aumentano la secrezione di insulina
- Aumentano la sensibilità all’insulina nel fegato e nel muscolo
- Migliorano l’uptake di glucosio insulino-stimolato nei tessuti periferici
- Riducono l’output epatico di glucosio
- Migliorano il profilo lipidico

TZD: effetti collaterali

- Incremento ponderale
- Ritenzione idrica e espansione del volume ematico
- Edema arti inferiori
- Edema retinico (specie se in associazione con insulina)

TZD: controindicazioni

- Scompenso cardiaco cronico
- Terapia insulinica
- Insufficienza epatica grave
- Insufficienza renale grave

Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial

Endpoint Primario composito: mortalità per tutte le cause, IMA non fatale, Ictus, Amputazioni maggiori, SCA, PTCI, CABG o rivascolarizzazione periferica.

Endpoint Principale secondario:
mortalità per tutte le cause, IMA non fatale (escluso IMA silente), ictus

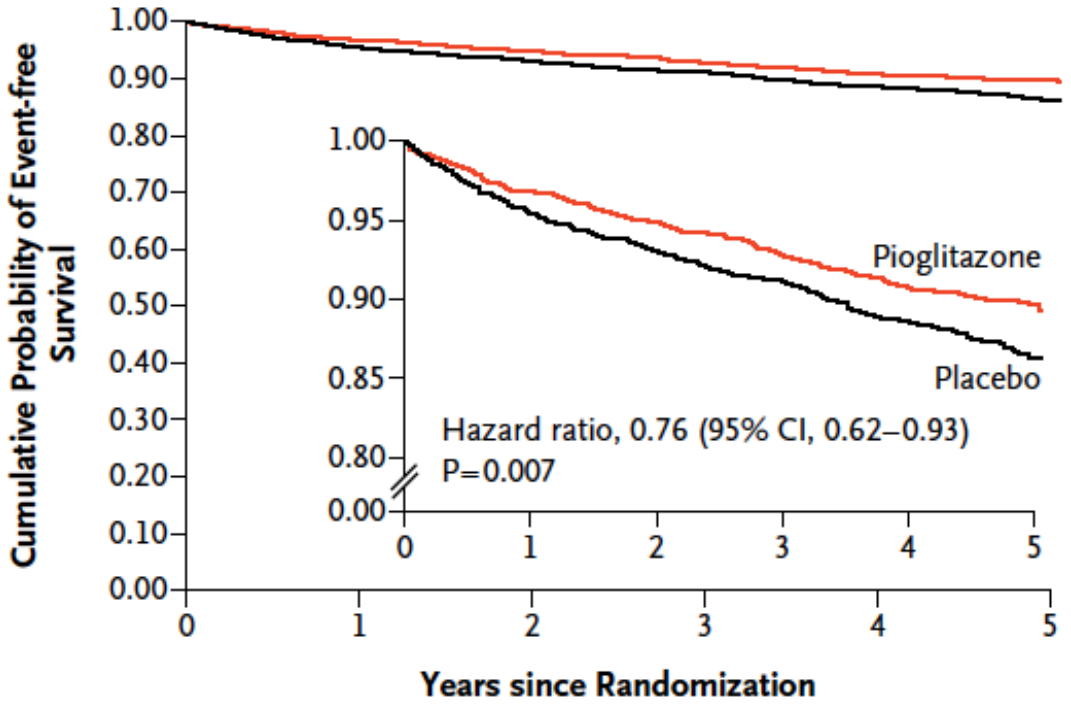
Summary of Results

	3-year Kaplan-Meier estimate			
	Pioglitazone %	Placebo %	RR %	p
Primary endpoint	21.0	23.5	10	0.095
Principal secondary endpoint	12.3	14.4	16	0.027

Dormandy JA et al. Lancet 2005; 366: 1279–89

Pioglitazone after **I**schemic **S**troke or Transient Ischemic Attack (the IRIS trial)**:** riduzione dell'outcome primario

Ictus fatale o non-fatale o MI



No. at Risk						
Pioglitazone	1939	1793	1701	1491	1196	481
Placebo	1937	1778	1690	1476	1182	459

Kernan WN et al. February 17, 2016, NEJM.org

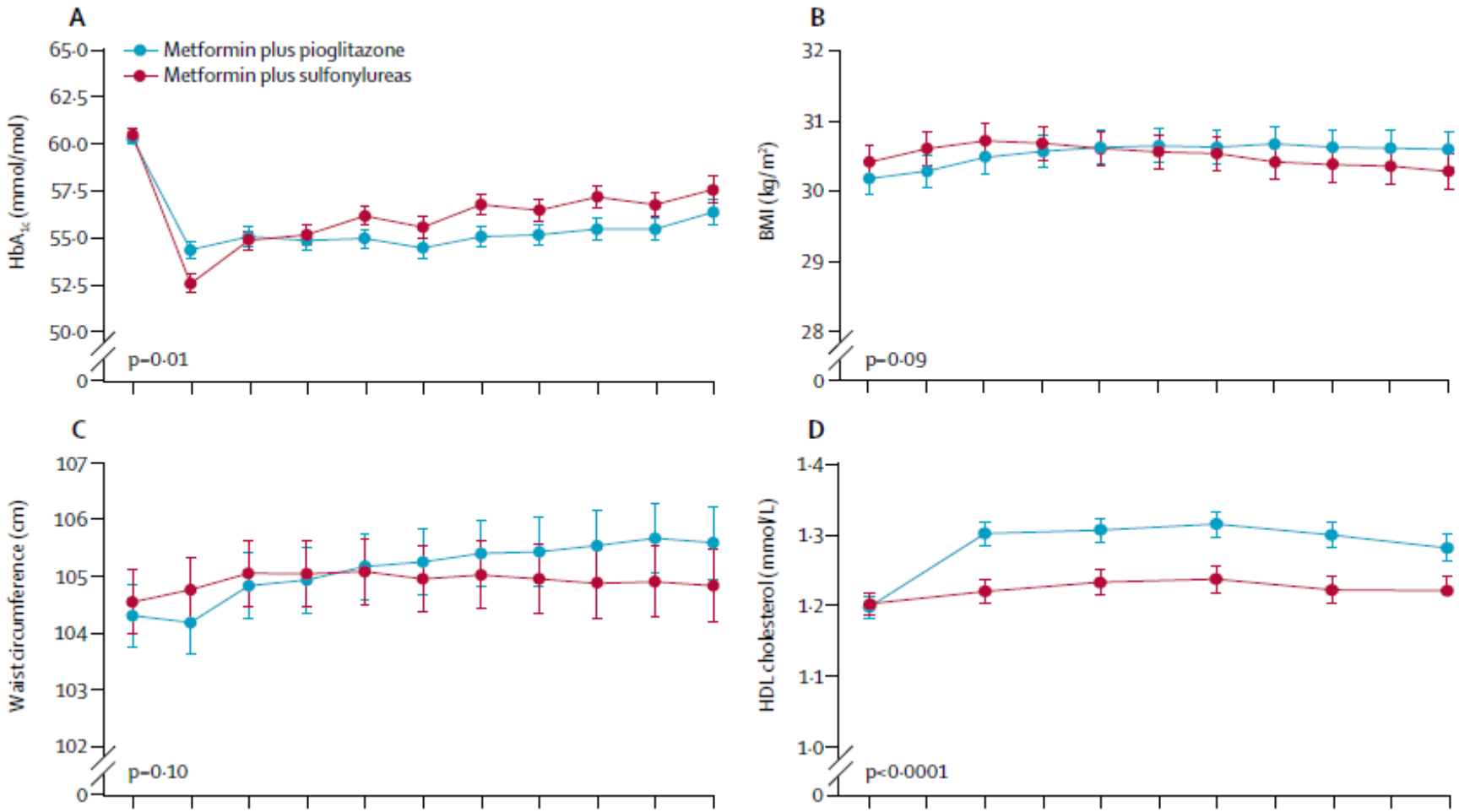
Effects on the incidence of cardiovascular events of the addition of pioglitazone versus sulfonylureas in patients with type 2 diabetes inadequately controlled with metformin (TOSCA.IT): a randomised, multicentre trial

Olga Vaccaro, Maria Masulli*, Antonio Nicolucci, Enzo Bonora, Stefano Del Prato, Aldo P Maggioni, Angela A Rivellese, Sebastiano Squatrito, Carlo B Giorda , Giorgio Sesti, Paolo Mocarelli, Giuseppe Lucisano, Michele Sacco, Stefano Signorini, Fabrizio Cappellini, Gabriele Perriello, Anna Carla Babini, Annunziata Lapolla, Giovanna Gregori, Carla Giordano, Laura Corsi, Raffaella Buzzetti, Gennaro Clemente, Graziano Di Cianni, Rossella Iannarelli, Renzo Cordera, Olga La Macchia, Chiara Zamboni, Cristiana Scaranna, Massimo Boemi, Ciro Iovine, Davide Lauro, Sergio Leotta, Elisabetta Dall'Aglio, Emanuela Cannarsa, Laura Tonutti, Giuseppe Pugliese, Antonio C Bossi, Roberto Anichini, Francesco Dotta, Antonino Di Benedetto, Giuseppe Citro, Daniela Antenucci, Lucia Ricci, Francesco Giorgino, Costanza Santini, Agostino Gnasso, Salvatore De Cosmo, Donatella Zavaroni, Monica Vedovato, Agostino Consoli, Maria Calabrese, Paolo di Bartolo, Paolo Fornengo, Gabriele Riccardi, for the Thiazolidinediones Or Sulfonylureas Cardiovascular Accidents Intervention Trial (TOSCA.IT) study group† under the mandate of the Italian Diabetes Society*

3.028 DMT2 patients (Metformin treated) from 57 diabetes clinics in Italy.
- 1535 were assigned to pioglitazone (15-45mg die).
- 1493 to sulfonylureas (glibenclamide 2%, glimepiride 48%, gliclazide 50%).
At baseline, 335 (11%) participants had a previous CV event.
The study was stopped early on the basis of a futility analysis after a median follow-up of 57,3 months.

*Lancet Diabetes Endocrinol 2017;*5: 887–97 Published Online September 13, 2017
http://dx.doi.org/10.1016/S2213-8587(17)30317-0

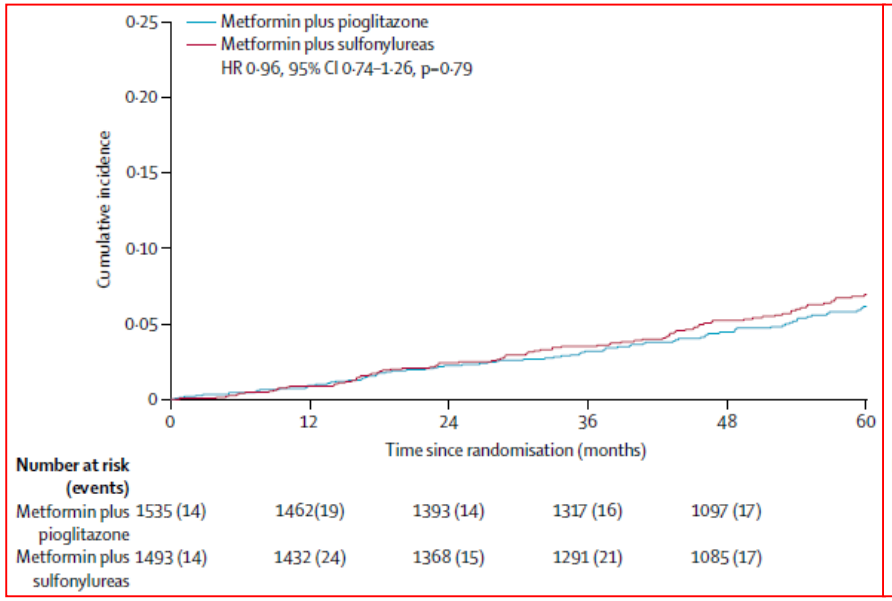
Effects on the incidence of cardiovascular events of the addition of pioglitazone versus sulfonylureas in patients with type 2 diabetes inadequately controlled with metformin (TOSCA.IT): a randomised, multicentre trial



Effects on the incidence of cardiovascular events of the addition of pioglitazone versus sulfonylureas in patients with type 2 diabetes inadequately controlled with metformin (TOSCA.IT): a randomised, multicentre trial

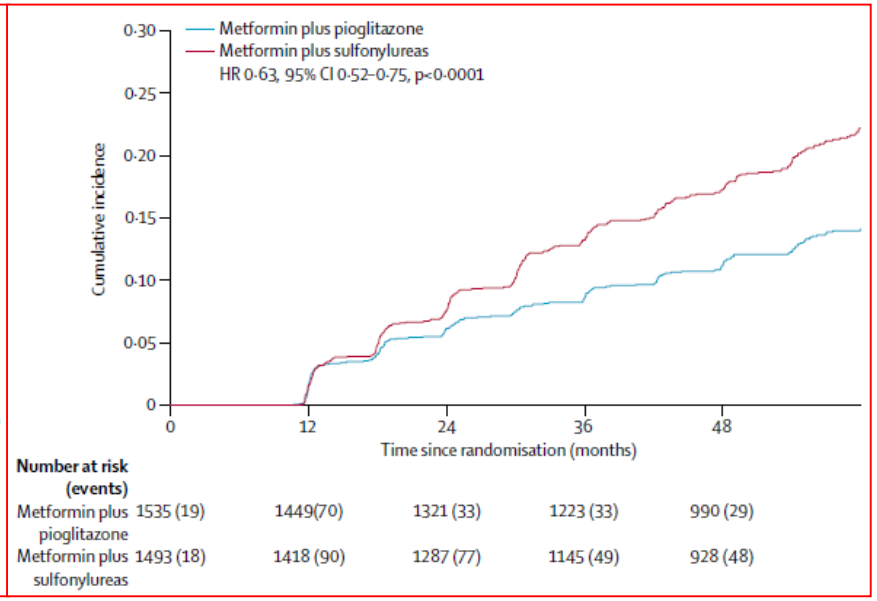
Composite primary outcome

(first occurrence of all-cause death, non-fatal MI, non-fatal stroke, or urgent coronary revascularisation)



Number at risk (events)					
Metformin plus pioglitazone	1535 (14)	1462(19)	1393 (14)	1317 (16)	1097 (17)
Metformin plus sulfonylureas	1493 (14)	1432 (24)	1368 (15)	1291 (21)	1085 (17)

Incidence of treatment failure



Number at risk (events)					
Metformin plus pioglitazone	1535 (19)	1449(70)	1321 (33)	1223 (33)	990 (29)
Metformin plus sulfonylureas	1493 (18)	1418 (90)	1287 (77)	1145 (49)	928 (48)

MET+SU

MET+PIO

*Lancet Diabetes Endocrinol 2017;*5: 887–97 Published Online September 13, 2017
http://dx.doi.org/10.1016/S2213-8587(17)30317-0

Effects on the incidence of cardiovascular events of the addition of pioglitazone versus sulfonylureas in patients with type 2 diabetes inadequately controlled with metformin (TOSCA.IT): a randomised, multicentre trial

Moderate weight gain occurred in both groups.
Rates of heart failure, bladder cancer, and fractures were not significantly different between treatment groups.

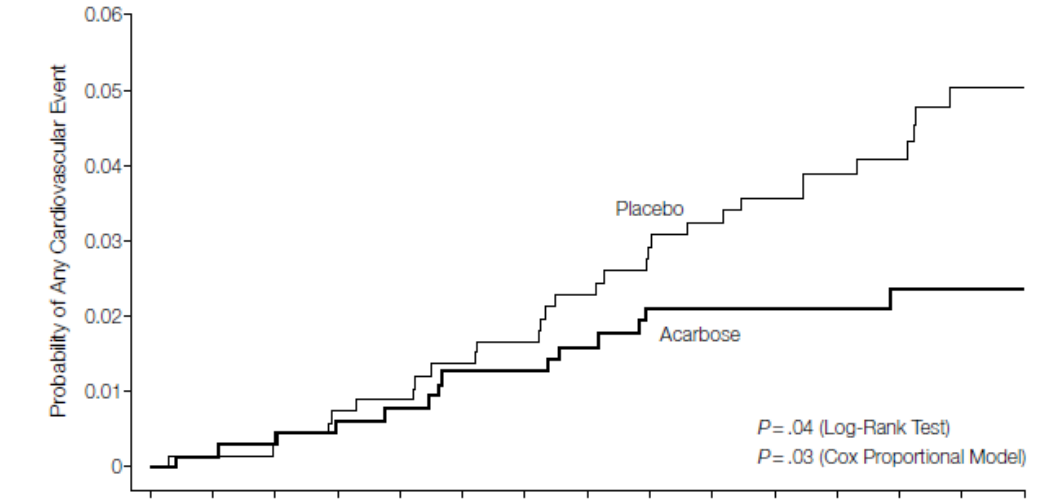
	Metformin plus pioglitazone (n=1535)		Metformin plus sulfonylurea (n=1493)		Incidence rate ratio (95% CI)	p value
	Patients	Events	Patients	Events		
Severe hypoglycaemic events	1 (<1%)	2	24 (2%)	33	0·06 (0·01–0·25)	<0·0001
Moderate hypoglycaemic events	147 (10%)	515	484 (32%)	1868	0·27 (0·24–0·30)	<0·0001

Data are n (%) or n, unless otherwise specified. Hypoglycaemic events were defined as a glucose value lower than 3·3 mmol/L and graded as moderate (not requiring help for treatment) or severe (requiring assistance for treatment). Data are shown for patients who received at least one dose of assigned study drugs.

*Lancet Diabetes Endocrinol 2017;*5: 887–97 Published Online September 13, 2017
http://dx.doi.org/10.1016/S2213-8587(17)30317-0

Acarbose

Figure 2. Effect of Acarbose on the Probability of Remaining Free of Cardiovascular Disease



No. at Risk															
Placebo	686	675	667	658	643	638	633	627	615	611	604	519	424	332	232
Acarbose	682	659	635	622	608	601	596	590	577	567	558	473	376	286	203

Acarbose: meccanismo d’azione

- **Inibitore delle α glucosidasi dell’orletto a spazzola degli enterociti (es. saccaridasi, maltasi, destrinasi, lattasi)**
- **Meccanismo competitivo e reversibile**
- **Ritarda digestione ed assorbimento dei CHO**

Acarbose: meccanismo d’azione

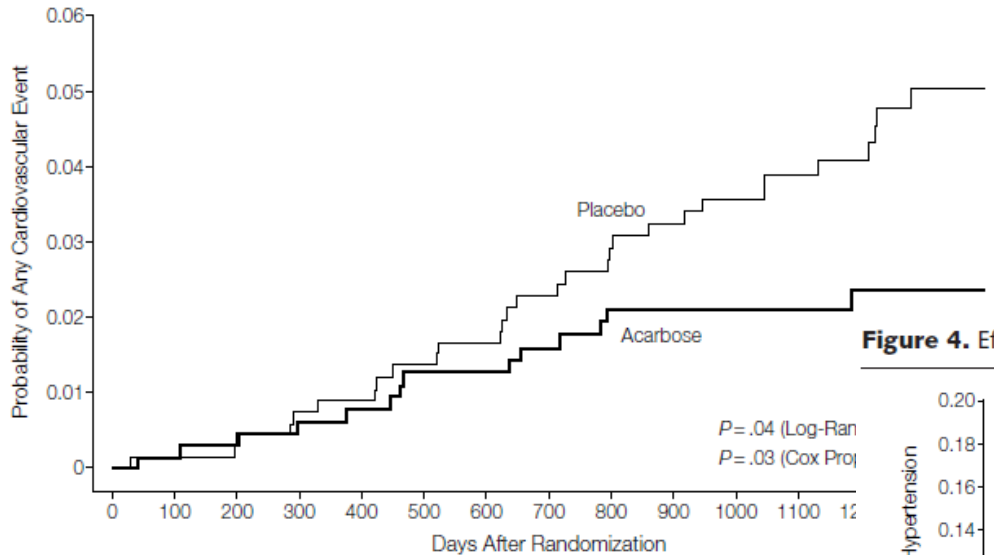
- **Ridotto incremento glicemico postprandiale**
- **Non stimola la secrezione di insulina**
- **Non causa ipoglicemie né acidosi lattica né incremento ponderale**

Acarbose Treatment and the Risk of Cardiovascular Disease and Hypertension in Patients With Impaired Glucose Tolerance

The STOP-NIDDM Trial

JL Chiasson et Al. JAMA 2003;290, 486-490

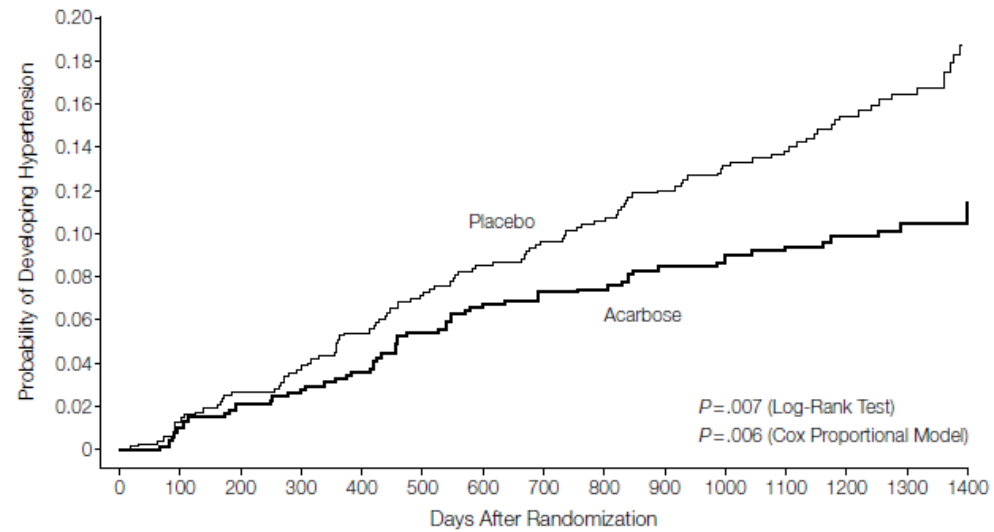
Figure 2. Effect of Acarbose on the Probability of Remaining Free of Cardiovascular Disease



No. at Risk

Placebo	686	675	667	658	643	638	633	627	615	611	604	519	4
Acarbose	682	659	635	622	608	601	596	590	577	567	558	473	3

Figure 4. Effect of Acarbose on the Probability of Remaining Free of Hypertension

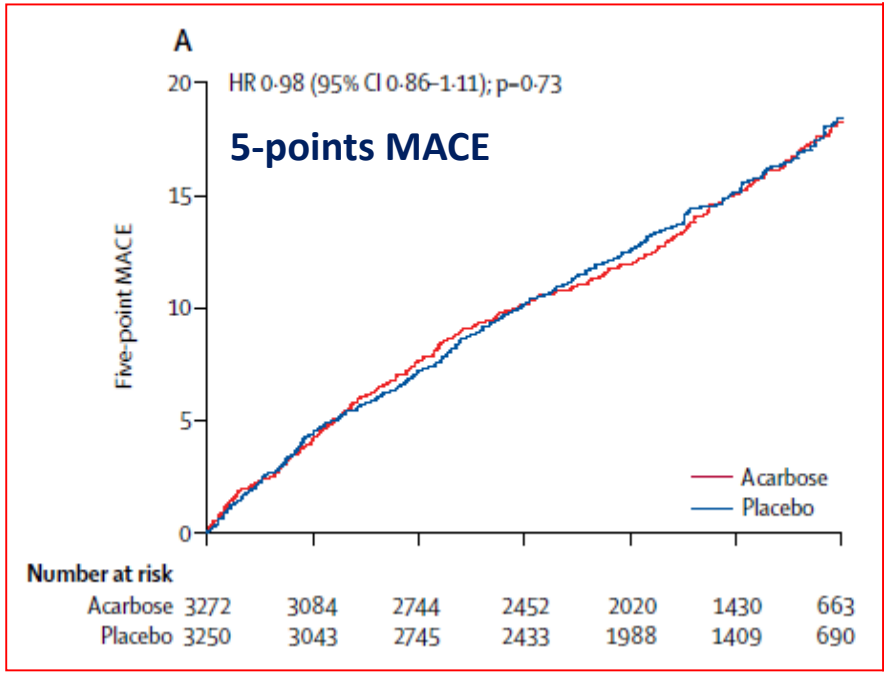


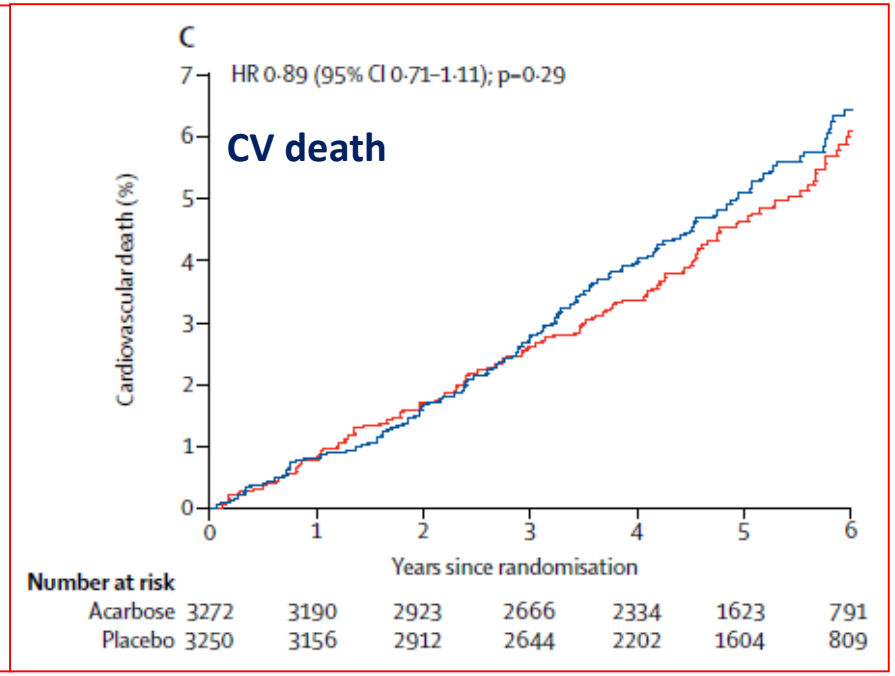
No. at Risk

Placebo	686	663	646	632	607	593	581	573	562	550	538	458	368	287	196
Acarbose	682	645	617	601	585	570	559	559	552	524	514	435	342	254	178

Effects of acarbose on cardiovascular and diabetes outcomes in patients with coronary heart disease and impaired glucose tolerance (ACE): a randomised, double-blind, placebo-controlled trial

Rury R Holman, Ruth L Coleman, Juliana C N Chan, Jean-Louis Chiasson, Huimei Feng, Junbo Ge, Hertzel C Gerstein, Richard Gray, Yong Huo, Zhihui Lang, John J McMurray, Lars Rydén, Stefan Schröder, Yihong Sun, Michael J Theodorakis, Michal Tendera, Lynne Tucker, Jaakko Tuomilehto, Yidong Wei, Wenying Yang, Duolao Wang, Dayi Hu, Changyu Pan*, for the ACE Study Group†*





Lancet Diabetes Endocrinol 2017; 5: 877–86
Published Online September 13, 2017
http://dx.doi.org/10.1016/
S2213-8587(17)30309-1

Effects of acarbose on cardiovascular and diabetes outcomes in patients with coronary heart disease and impaired glucose tolerance (ACE): a randomised, double-blind, placebo-controlled trial

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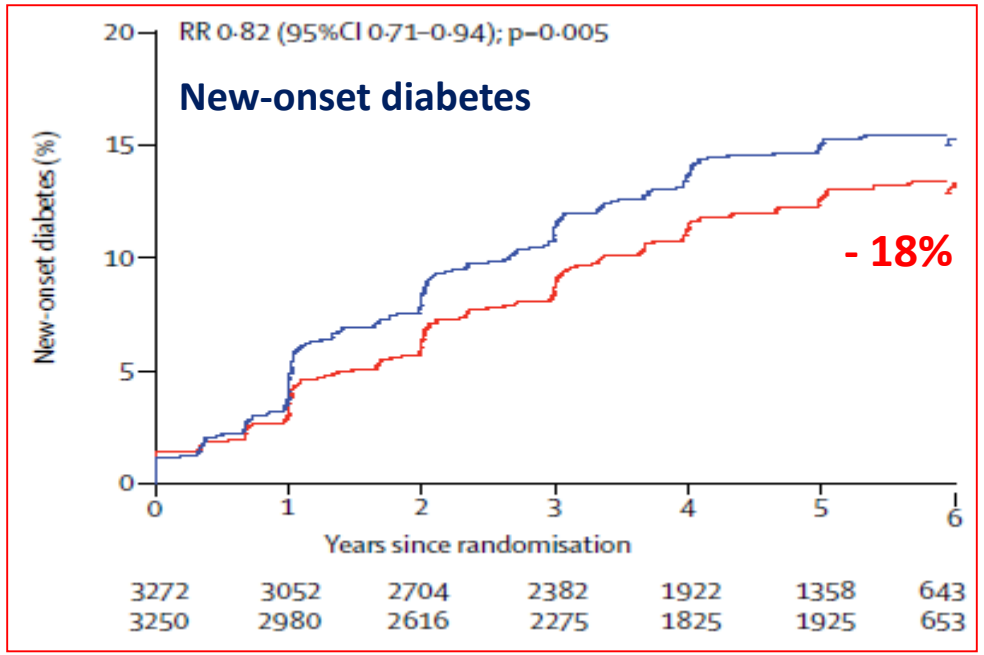

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