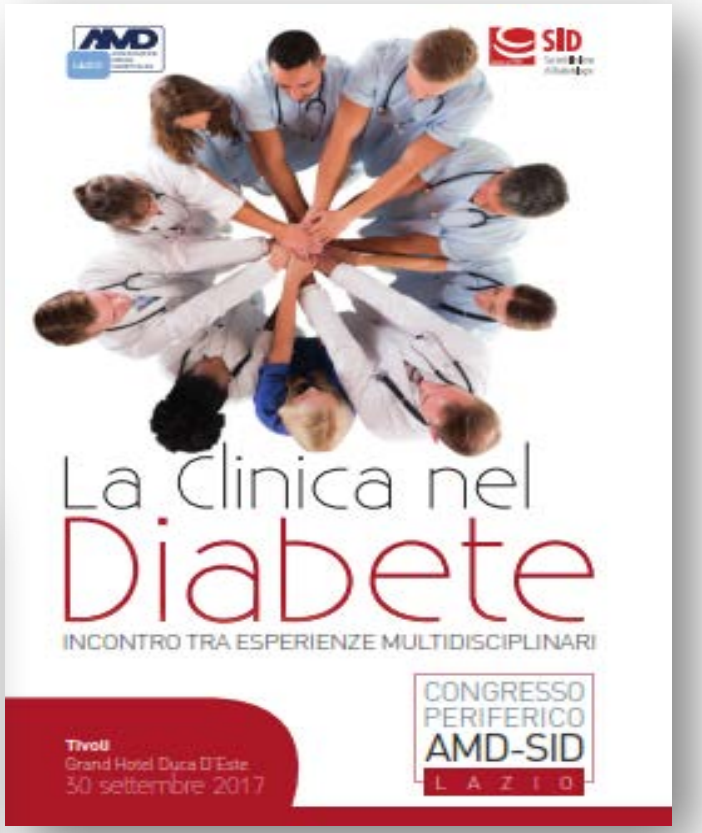
Farmaci Antidiabetici e Rischio Cardio-Nefro-Vascolare



Il Verdetto

F. Tuccinardi

CONGRESSO PERIFERICO AMD - SID

LA CLINICA DEL DIABETE INCONTRO TRA ESPERIENZE MULTIDISCIPLINARI

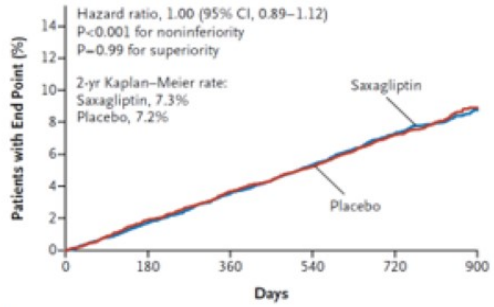
Tivoli, 30 settembre 2017

Il dr. Tuccinardi dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- ASTRAZENECA, MSD, NOVO NORDISK, LILLY, ABBOTT, SIGMA-TAU, BOEHRINGER, ROCHE

DPP-4 Inhibitors
CV Outcomes

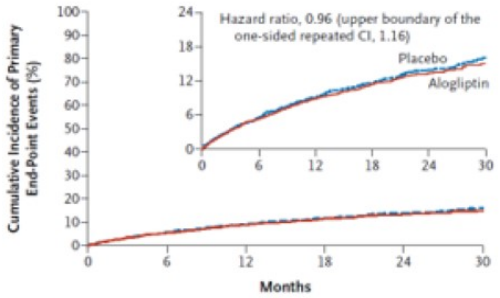
Saxagliptin
(SAVOR-TIMI 53 Trial)[a]
N=16,492



No. at Risk						
Placebo	8212	7983	7761	7267	4855	851
Saxagliptin	8280	8071	7836	7313	4920	847

Composite of CV death, nonfatal MI, or nonfatal ischemic stroke

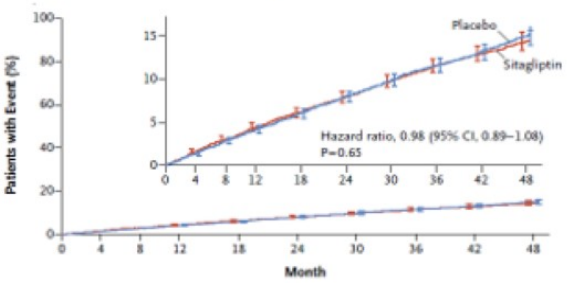
Alogliptin
(EXAMINE Trial)[b]
N=5380



No. at Risk						
Placebo	2679	2299	1891	1375	805	286
Alogliptin	2701	2316	1899	1394	821	296

Composite of CV death, nonfatal MI, or nonfatal stroke

Sitagliptin
(TECOS Trial)[c]
N=14,671



No. at Risk										
Sitagliptin	7332	7131	6937	6777	6579	6386	4525	3346	2058	1248
Placebo	7339	7146	6902	6751	6512	6292	4411	3272	2034	1234

Composite of CV death, nonfatal MI, nonfatal stroke, or hospitalization for UA

a. From N Engl J Med, Scirica BM, et al, Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus, 369, 1317-1326, Copyright © 2013 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.; b. From N Engl J Med, White WB, et al, Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes, 369, 1327-1335. Copyright © 2013 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.;
c. From N Engl J Med, Green JB, et al, Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes, 373., 232-242. Copyright © 2015 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Now 4 CVOTs Demonstrate CV Benefit

EMPA-REG OUTCOME[a] Endpoint, n (%)	Empagliflozin (n = 4687)	Placebo (n = 2333)	HR (95% CI)
CV death, nonfatal MI, or nonfatal stroke	490 (10.5)	282 (12.1)	0.86 (0.74, 0.99) *P* = .04
LEADER[b] Endpoint, n (%)	Liraglutide (n = 4668)	Placebo (n = 4672)	HR (95% CI)
CV death, nonfatal MI, or nonfatal stroke	608 (13.0)	694 (14.9)	0.87 (0.78, 0.97) *P* = .001
SUSTAIN-6[c] Endpoint, n (%)	Semaglutide* (n = 1648)	Placebo (n = 1649)	HR (95% CI)
CV death, nonfatal MI, or nonfatal stroke	108 (6.6)	146 (8.9)	0.74 (0.58, 0.95) *P* = .02
CANVAS[d] Endpoint, participants with event per 1000 patient years (%)	Canagliflozin (n = 4795)	Placebo (n = 4347)	HR (95% CI)
CV death, nonfatal MI, or nonfatal stroke	26.9	31.5	0.86 (0.75 0.97) *P* = .02

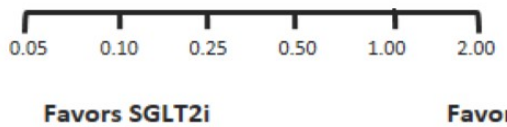
*The FDA has not yet approved this medication for use.

a. Zinman B, et al. *N Engl J Med*. 2015;373:2117-2128; b. Marso SP, et al. *N Engl J Med*. 2016;375:311-322; c. Marso SP, et al. *N Engl J Med*. 2016;375:1834-1844; d. Neal B, et al. *N Engl J Med*. 2017. [Epub ahead of print]

CVD-REAL Study: SGLT2 Inhibitors Are Associated With a Significantly Reduced Risk for hHF

- Primary outcome: Risk for hHF in patients with T2D newly initiated on SGLT2 inhibitors vs other glucose-lowering drugs

Database	N	No. of events	HR (95% CI)
USA	233,798	298	0.55 (0.44, 0.69)
Norway	25,050	278	0.62 (0.49, 0.79)
Denmark	18,468	167	0.77 (0.59, 1.01)
Sweden	18,378	191	0.61 (0.45, 0.82)
UK	10,462	16	0.36 (0.12, 1.13)
Germany	2900	11	0.14 (0.03, 0.68)
Total	309,056	961	0.61 (0.51, 0.73)



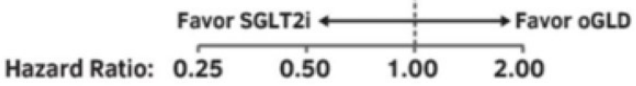
***P* value for SGLT2i vs oGLD: < .001**

Kosiborod M, et al. Circulation. 2017. [Epub ahead of print] With permission from Wolters Kluwer Health.

CVD-REAL Study: SGLT2 Inhibitors are Associated With a Significantly Reduced Risk for All-Cause Mortality

- Secondary outcome: risk of all-cause mortality between treatment groups

Database	N	# of events	HR (95% CI)
US	143,264	250	0.38 (0.29, 0.50)
Norway	25,050	364	0.55 (0.44, 0.68)
Denmark	18,468	323	0.46 (0.37, 0.57)
Sweden	18,378	317	0.47 (0.37, 0.60)
UK	10,462	80	0.73 (0.47, 1.15)
Total	215,622	1334	0.49 (0.41, 0.57)



P-value for SGLT2i vs oGLD: <0.001

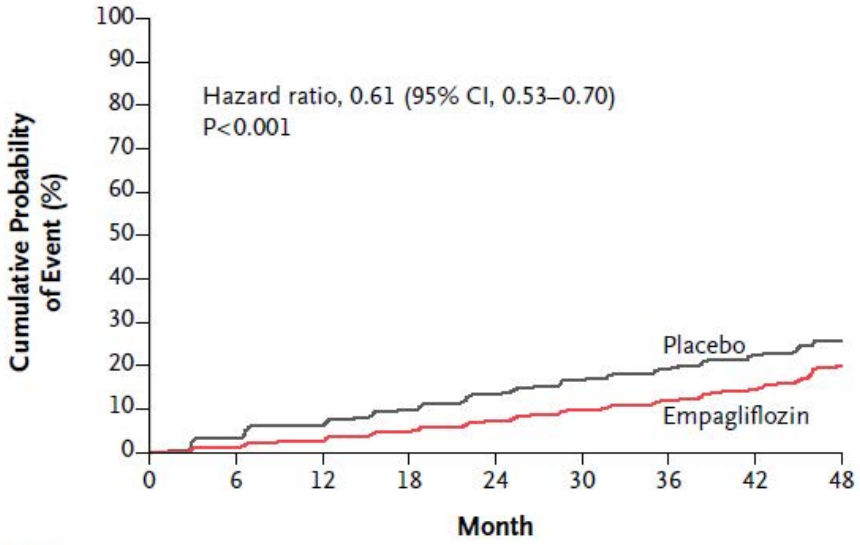
Heterogeneity p-value: 0.09

Kosiborod M, et al. Circulation. 2017. [Epub ahead of print] With permission from Wolters Kluwer Health.

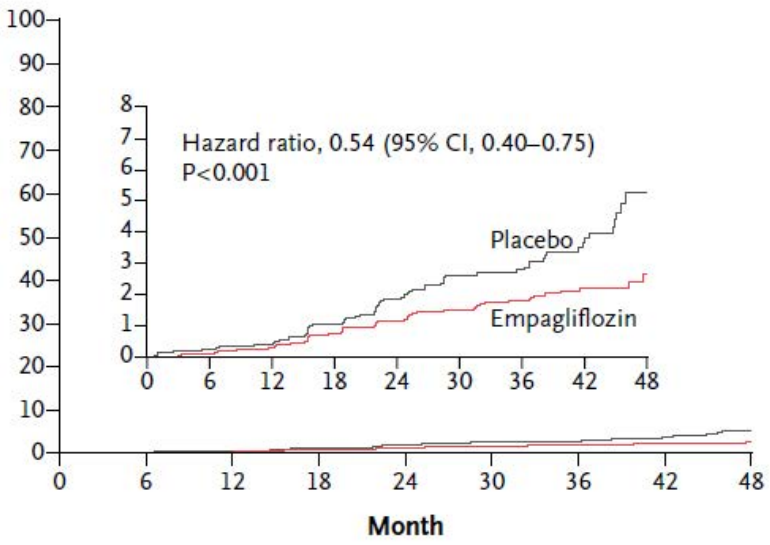
Renal Outcomes with Empagliflozin

EMPA-REG RENAL
(N=7020)

Incident or Worsening Nephropathy



Post-hoc Renal Composite Outcome*

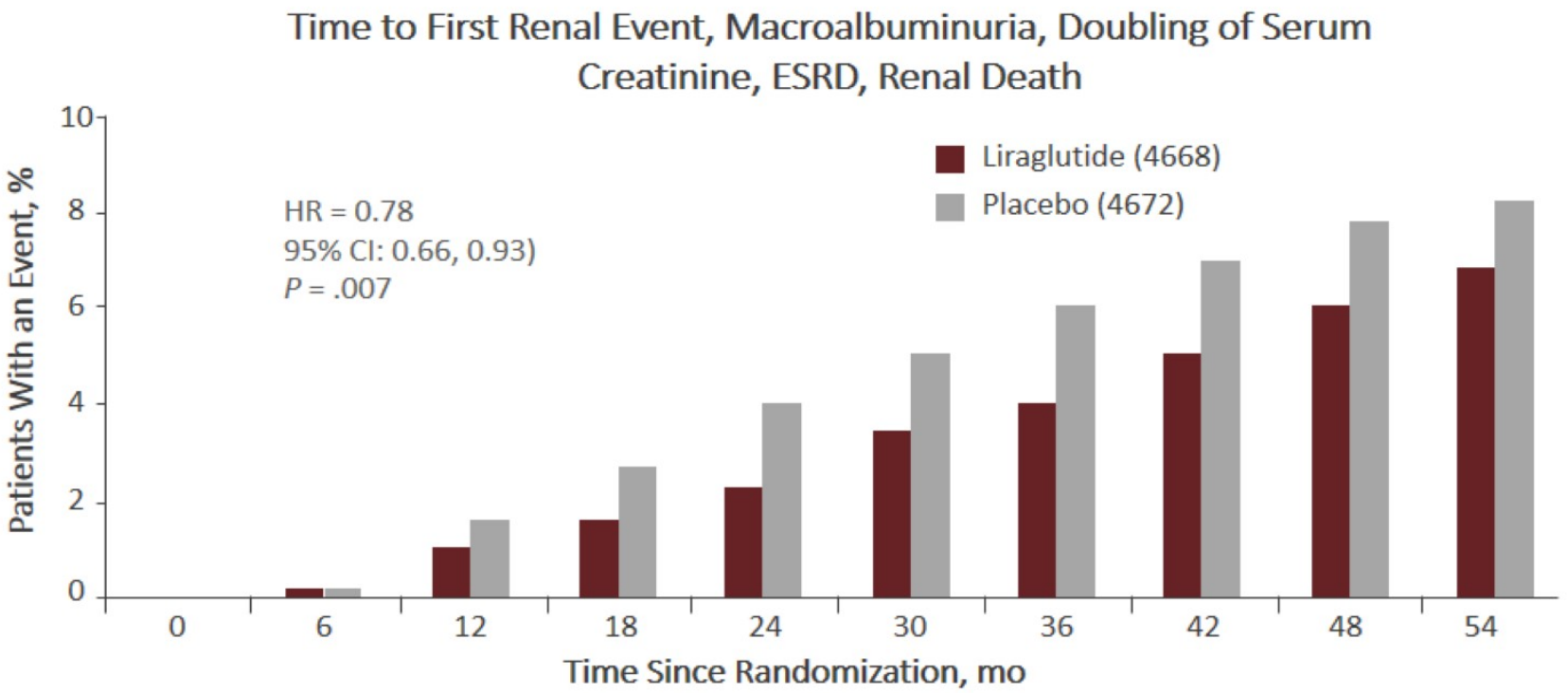


No. at Risk

Empagliflozin	4124	3994	3848	3669	3171	2279	1887	1219	290	4645	4500	4377	4241	3729	2715	2280	1496	360
Placebo	2061	1946	1836	1703	1433	1016	833	521	106	2323	2229	2146	2047	1771	1289	1079	680	144

*Doubling of SCr + eGFR ≤45 mL/min/1.73 m^2, initiation of renal replacement therapy, or death from renal disease. CI, confidence interval; eGFR, estimated glomerular filtration rate; SCr, serum creatinine.Wanner C, et al. *N Engl J Med*. 2016 Jun 14. [Epub ahead of print]

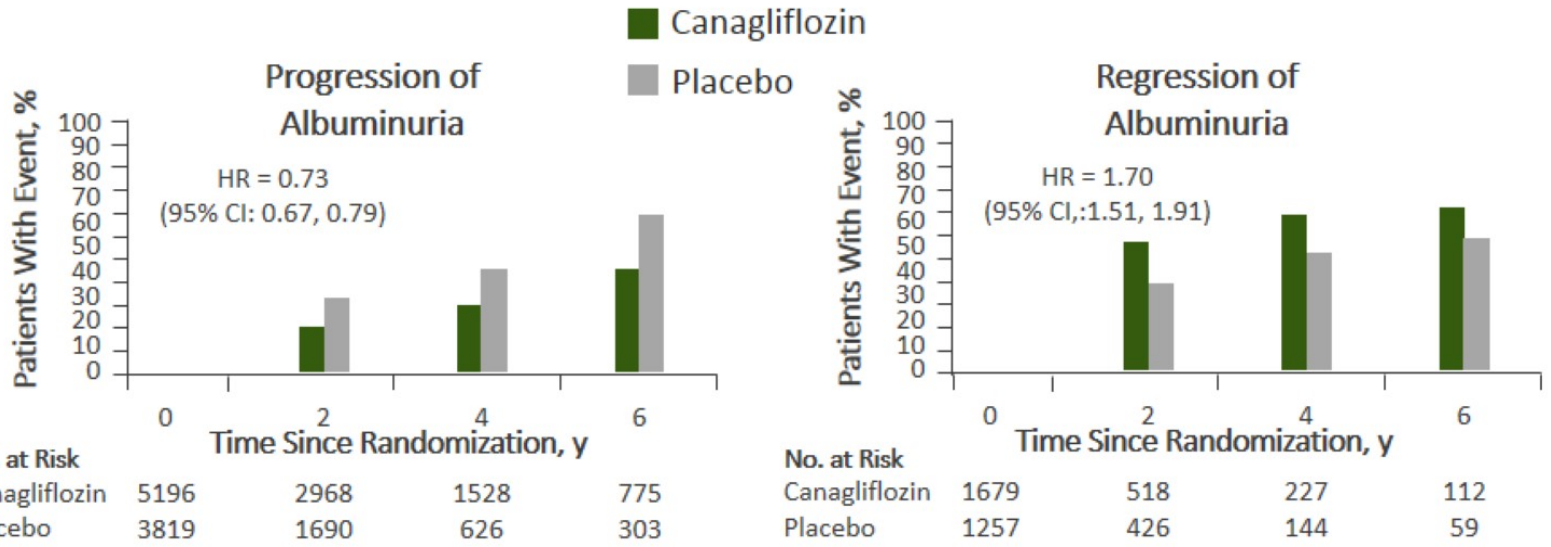
LEADER: Time to First Renal Event



The data analyses are truncated at 54 months, because fewer than 10% of the patients had an observation time beyond 54 months.

Marso SP, et al. *N Engl J Med*. 2016;375:311-322.

Exploring the Potential Renal Benefits of Canagliflozin



~70% of the patients in CANVAS had normal renal function and not micro- or macro-albuminuria

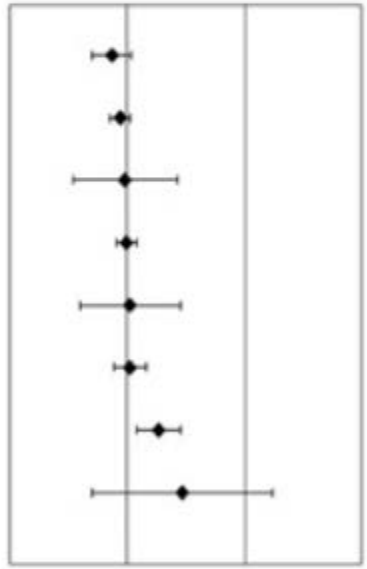
Neal B, et al. *N Engl J Med*. 2017. [Epub ahead of print]

SU and MACE

Meta-analysis of available RCTs

Major CV 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

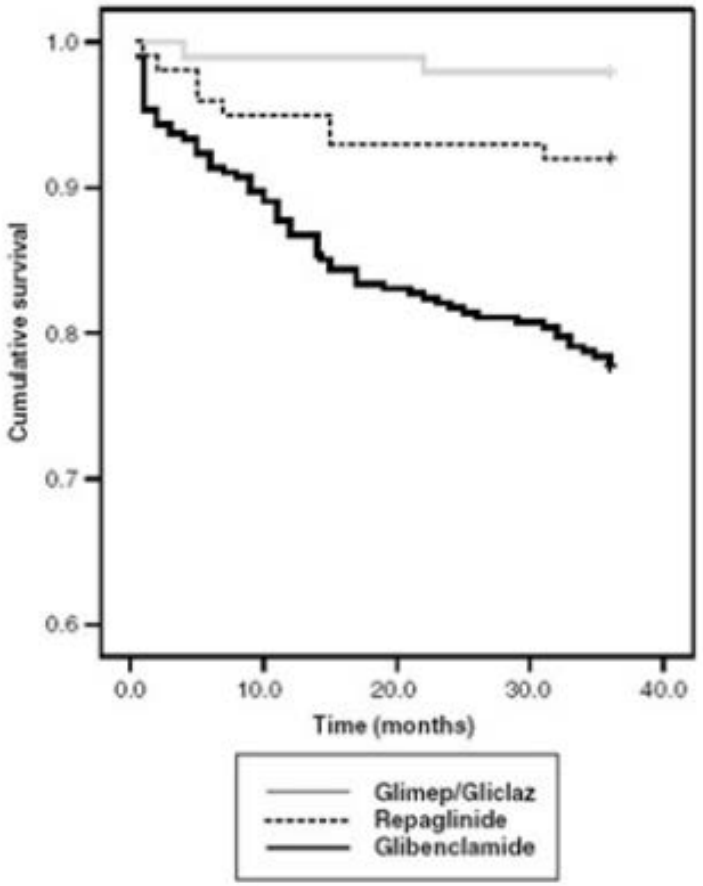


All-cause mortality: **1.22 [1.01–1.49] P=0.047**

Monami M, Genovese S, Mannucci E.
Diabetes Obes Metab 2013; 15:938-53,

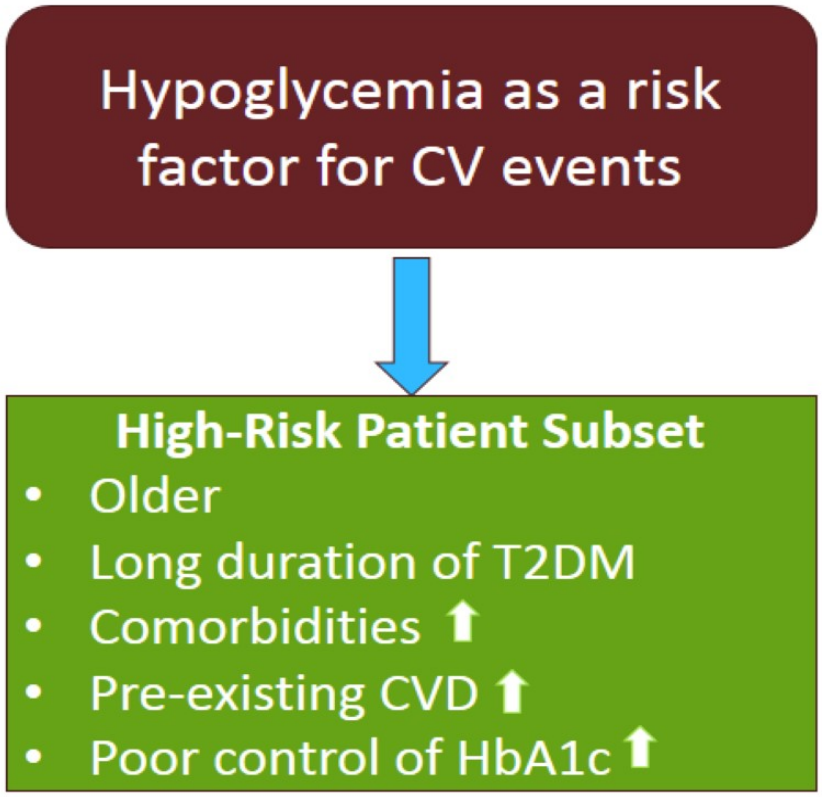
SU and all-cause mortality

Cohort study



Monami M et al., *Diabetes Metab Res Rev* 2006

Hypoglycemia and CV Risk in Patients With T2DM



Sanon VP, et al. *Clin Cardiol*. 2014;37:499-504.

Roma, 3 aprile 2015

Chiar. mo Prof. Luca Pani
Direttore Generale
Agenzia Italiana del Farmaco (AIFA)
Via del Tritone 181 - 00187 Roma (RM)

Oggetto: Glibenclamide e Gliclazide

Gentilissimo Prof. Pani,

scriviamo perché riteniamo opportuno che AIFA prenda una posizione ufficiale in merito a due farmaci della categoria delle sulfoniluree che sono usati per il trattamento del diabete. Questa categoria di farmaci, nella quale potrebbe essere inserita anche repaglinide, che possiede identico meccanismo di azione (1,2), è ancora largamente utilizzata in Italia (quasi il 50% dei diabetici tipo 2)(3,4). Le sulfoniluree, che determinano un significativo e non desiderabile incremento ponderale, stimolano la secrezione di insulina con meccanismo glucosio-indipendente e per questo motivo possono causare ipoglicemia, anche severa e prolungata e talora fatale (5-10).

Standard Italiani AMD-SID 2016[1]

	MET	ACARB	GLP-1 RA	SGLT-2 inib	DPP-4 inib	PIO	SU/ REP	INS BAS	INS BAS/BOL
Riduzione HbA1c a breve termine (3-6 mesi)*	+++	+	+++	++	++	+	+++	+++	++++
Riduzione HbA1c a medio termine (1-2 anni)*	++	+	+++	++	++	++	++	+++	++++
Riduzione HbA1c a lungo termine (oltre 2 anni)*	++	+	+++	++	ND	+++	+	+++	++++
Riduzione peso corporeo	+/-	+/-	+++	++	-	-	-	-	-
Riduzione pressione arteriosa	+/-	-	+	++	-	+	-	-	-
Riduzione CVD**	++	-	++	+++	-	++	-	-	-

* Derivata da studi di comparazione diretta con altri farmaci attivi

** A parità di obiettivo glicemico perseguito

ND: dato non disponibile

Drug Benefits

[1] http://www.standarditaliani.it/

Perché i CAD prescrivono un Numero Elevato di «Vecchie Molecole»?

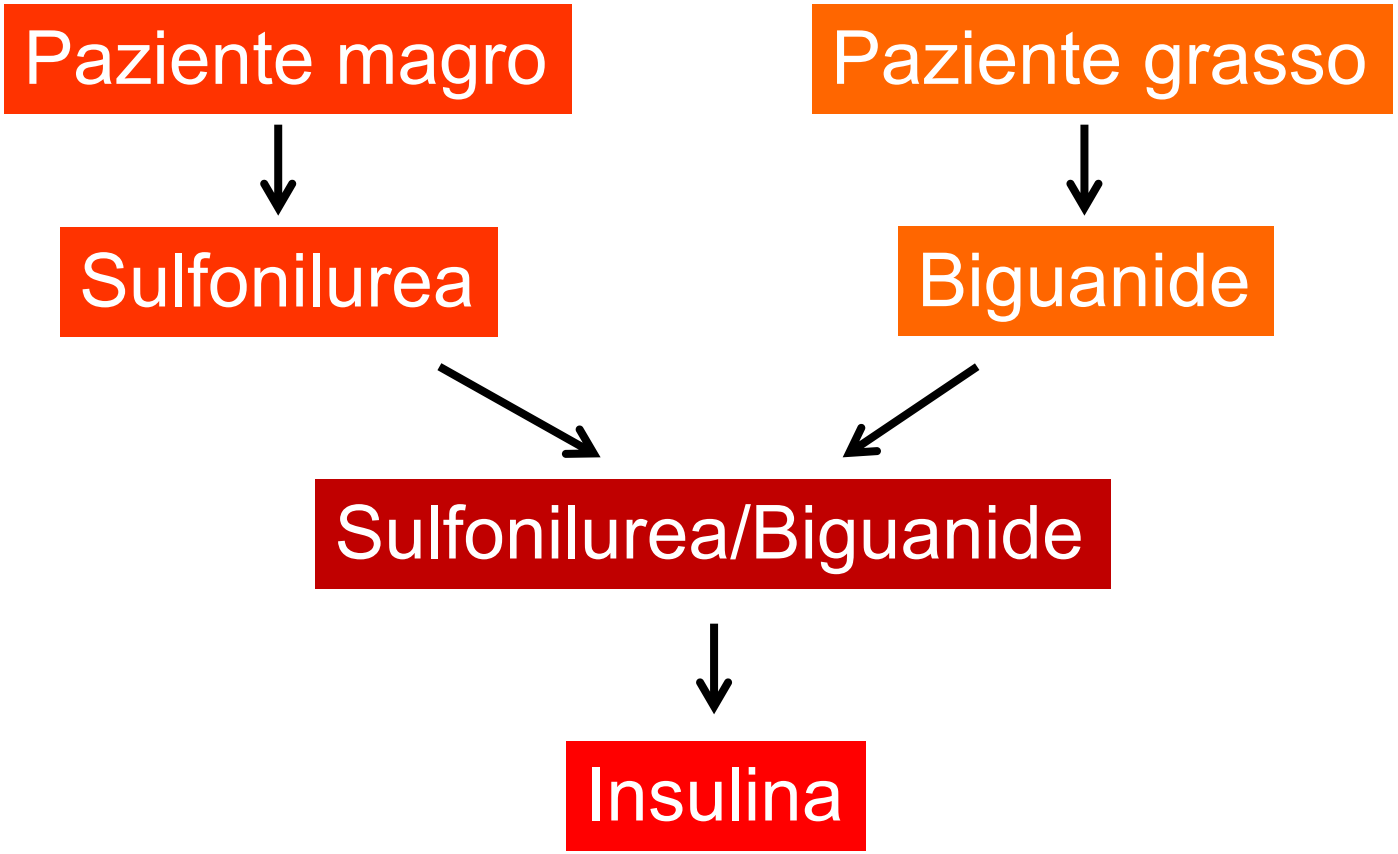
- Inerzia Terapeutica Specialista (Prevale la Semplicità di Prescrizione)

- Limitazioni nel Formulare un Piano Terapeutico per i Nuovi Farmaci? (tempi tecnici in termini di digitazioni)
- Impossibilità Burocratica nell'Associare «Nuove Molecole»

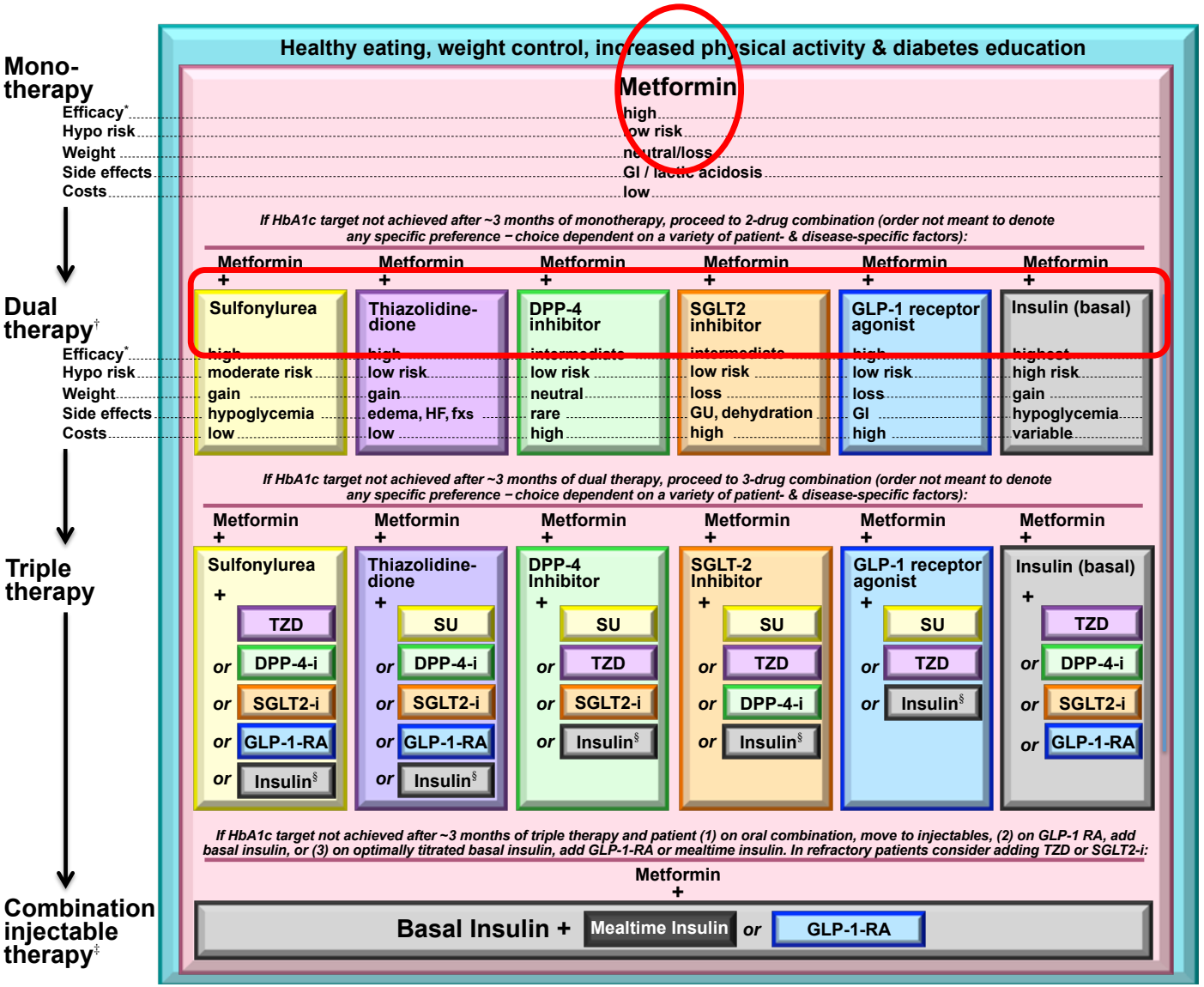
- Inapplicabilità di Schemi Complessi in Pazienti Complessi e Snellimento degli Schemi in Pazienti Complessi

- Superiorità Ipoglicemizzante dei Segretagoghi e/o Effetti Collaterali delle Molecole di Nuova Generazione???

APPROPRIATEZZA IERI….

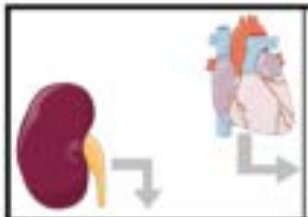


APPROPRIATEZZA OGGI…



Diabetes Care 2015;38:140-149; *Diabetologia* 2015;58:429-442

FENOTIPIZZAZIONE APPROPRIATA

	Normal or subclinical **ENDOTHELIAL DYSFUNCTION**	**ESTABLISHED ATHERO-SCLEROSIS**	**ACUTE CORONARY SYNDROME**	**HEART FAILURE**
Stage I-II CKD **eGFR 90-60 ml/min/1.73 m²**	Metformin[a], Pioglitazone[b] DPP4-I[c-e], GLP-1 RA[f], SGLT2-I[g], Insulin[1h] SUs[1]	Metformin, SGLT2-I[g], GLP-1RA[f], Pioglitazone[b], DPP4-I[c-e], Insulin[h], Gliclazide[k]	Insulin[m] DPP4-I[e], GLP-1RA[j],	SLGT2-I[g] DPP4-I[d,e], GLP-1RA[f], Insulin[h]
Stage III CKD **eGFR 59-30 ml/min/1.73 m²**	Metformin[2], Pioglitazone[3b], SLGT2-I[4g], GLP-1RA[f], DPP4-I[2c-e], Gliclazide[2k], Insulin[h]	Metformin[2], GLP-1RA[f], SGLT2-I[4g], Pioglitazone[3b], DPP4-I[2c-e], Insulin[h], Gliclazide[2k]	Insulin[m] DPP4-I[e], GLP-1RA[j],	SLGT2-I[g] DPP4-I[d,e], GLP-1RA[f], Insulin[h]
Stage IV CKD **eGFR 29-15 ml/min/1.73 m²**	Pioglitazone[3], DPP4-I[2], Insulin[2]	Pioglitazone[3], DPP4-I[2], Insulin[2]	DPP4-I[2], Insulin[2]	DPP4-I[2], Insulin[2]
Stage V CKD **eGFR <15 ml/min/1.73 m²**	Pioglitazone[3], DPP4-I[2], Insulin[2]	Pioglitazone[3], DPP4-I[2], Insulin[2]	DPP4-I[2], Insulin[2]	DPP4-I[2], Insulin[2]

Evidence of efficacy **Evidence of safety** **Author consensus**

The challenge…

Translating CVOTs data into clinical practice !

2017 ADA Standards of Medical Care in Diabetes

"In patients with long-standing suboptimally controlled type 2 diabetes and established atherosclerotic cardiovascular disease, **empagliflozin** or **liraglutide** should be considered as they have been shown to reduce cardiovascular and all-cause mortality when added to standard care."

- Level of evidence B

ADA. *Diabetes Care*. 2017;40(Suppl 1):S64-S74.

Nuovi farmaci per il diabete : nuovi profili di appropriatezza

Dal “Treat to target” al….”Treat to benefit”

…efficacia duratura ottenuta in sicurezza e impatto favorevole sulle complicanze e sulla mortalità cv……

IL VERDETTO

Condanna

l'uso ancora così diffuso delle SU di vecchia generazione
no demonizzazione su tutte le SU

Pena

Imparare la corretta fenotipizzazione del paziente per il miglior utilizzo dei nuovi farmaci

ASSOCIAZIONE MEDICI DIABETOLOGI

1974
ANNO DI FONDAZIONE

SHARING EVENTS

Impact of diabetes drugs on cardiovascular and renal disease in type 2 diabetes

Roma 2-3 Febbraio 2018

grazie