Impatto dei nuovi farmaci antidiabetici sul Rischio Cardiovascolare

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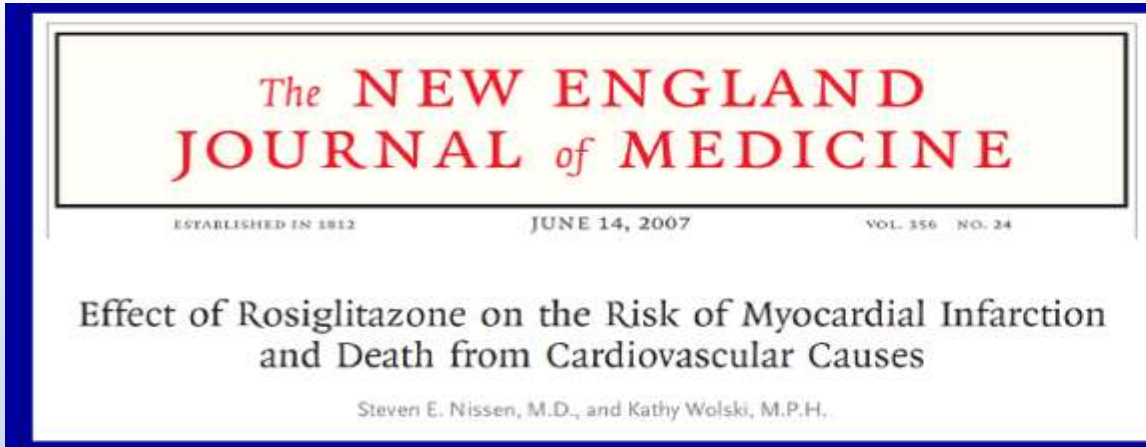
Le linee guida sul diabete di tipo 2 (DM2) continuano a raccomandare **metformina da sola,** o con **insulina** (se HbA1c ≥10% o glicemia ≥300 mg/dl), come **primo** trattamento farmacologico del diabete di tipo 2. Tuttavia:

1. Il DM2 è in continua crescita (stima: da 382 a 592 milioni di pazienti nel mondo dal 2012 al 2025).
2. I pazienti con DM2 muoiono per il 70% per malattie CV (in 50% dei casi: morte improvvisa)
3. Un controllo intensivo della glicemia NON riduce gli eventi CV (studi ACCORD, VADT, ADVANCE), nonostante la netta diminuzione di HBA1c.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Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

Il rosiglitazone aumenta del 30% il rischio di infarto miocardico.

Dato risultato 'poco verosimile' in analisi successive...

FDA U.S. FOOD & DRUG ADMINISTRATION

1. **Studi randomizzati vs placebo** di fase 2 e 3 in pazienti con diabete possibilmente complicato da malattie CV
2. **Major 'hard' CV events** (MACE): morte CV, infarto miocardico, ictus cerebrale, ricovero per SCA, rivascolarizzazione o scompenso cardiaco, etc.
3. **Studi di non inferiorità**: margine superiore dell'IC al 95% per i MACE < 1.80 negli studi di fase 3, ed <1.30 per gli studi di fase 4 per provare non-inferiorità.
4. **Comitati di 'aggiudicazione eventi'** indipendenti e **Protocolli pre-definiti,** idonei per successive meta-analisi

December 2008 FDA Guidance on Evaluating CV Risk in New Antidiabetic Therapies for T2DM


Guidance for Industry

Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

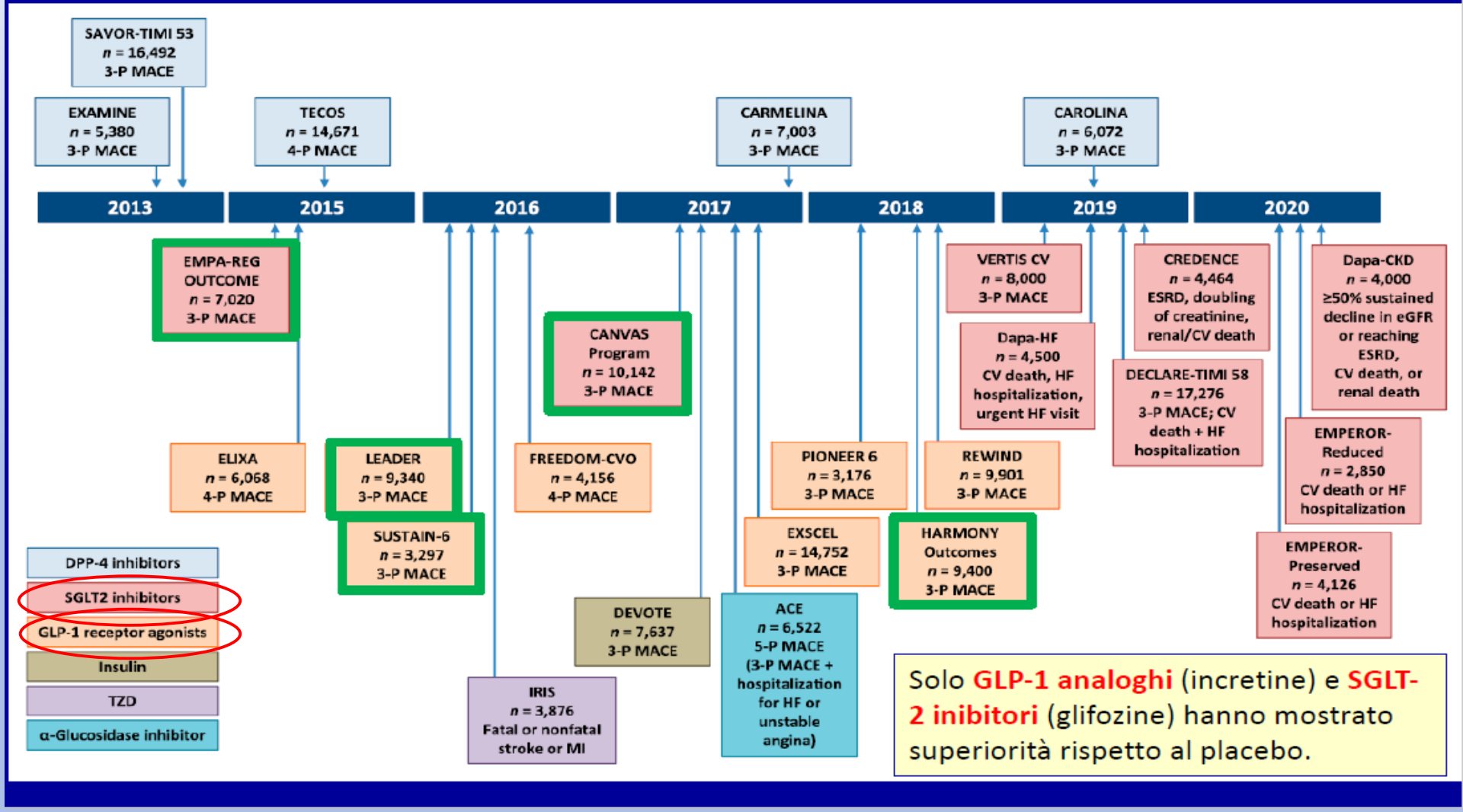

III. RECOMMENDATIONS

Center for Drug Evaluation and Research at the FDA website.

'Registrazione' del farmaco condizionata all'esecuzione, dopo l'entrata in commercio, di uno studio con queste caratteristiche.

SUPERIORITA’

Ongoing and recently completed CV outcome trials in diabetes enrolling about 190,000 patients

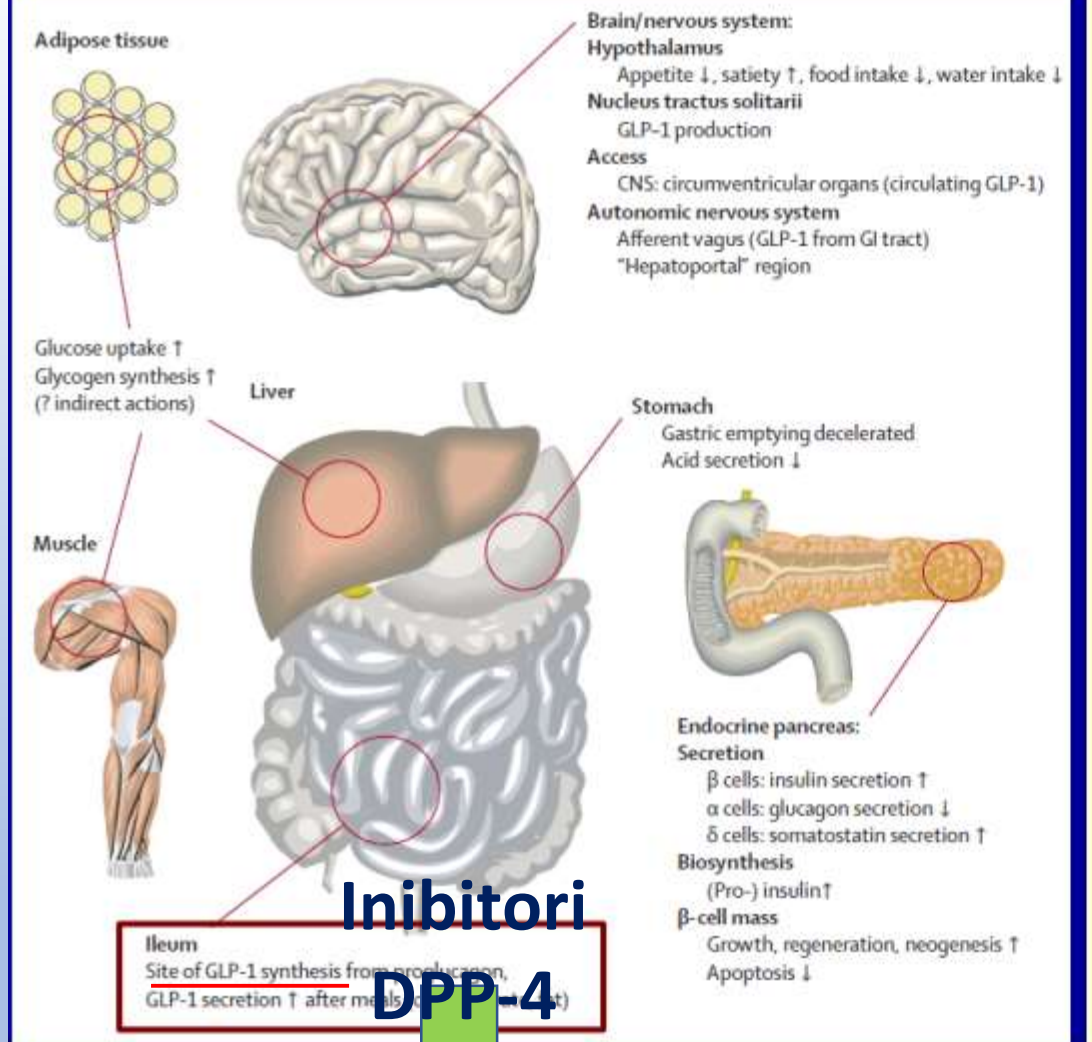


AGONISTI DEL RECETTORE GLP1
(Glucagon Like peptide)

INCRETINE

Ormone prodotto dall'intestino che stimola la secrezione di insulina e inibisce quella del glucagone dal pancreas.

Non causano ipoglicemia



Inibitori DPP-4

Le incretine vengo[illegible] rapidamente ed estensivamente d[illegible]adate da un enzima: la serina peptidasi DDP-4 (presente nel fegato, rene, intestino, endotelio, plasma).

Drucker DJ et al. Lancet 2006;368:1696-1705

Effetti incretine (GLP-1 and GIP)

Pancreas

- **Cellule β:**
  - **Stimolazione secrezione insulina** (glucosio-mediata)
  - **Inibizione apoptosi**
- **Cellule α:**
  - **Inibizione rilascio glucagone**

Stomaco

- **Inibizione svuotamento gastrico** e inibizione secrezione acida

Sistema Nervoso Centrale

- **Inibizione appetito**

Muscoli e Tessuto Adiposo

- **Aumento 'uptake' di glucosio**

Apparato Cardiovascolare

- Miglioramento funzione endoteliale
- **Vasodilatazione** (↓ PA 5/2 mmHg)
- ↑ **FE** (PTCA dopo MI, CHF, CAD)
- ↓ **Peso corporeo**
- ↓ **Grasso viscerale e sottocutaneo**
- ↓ **LDL piccole e dense**

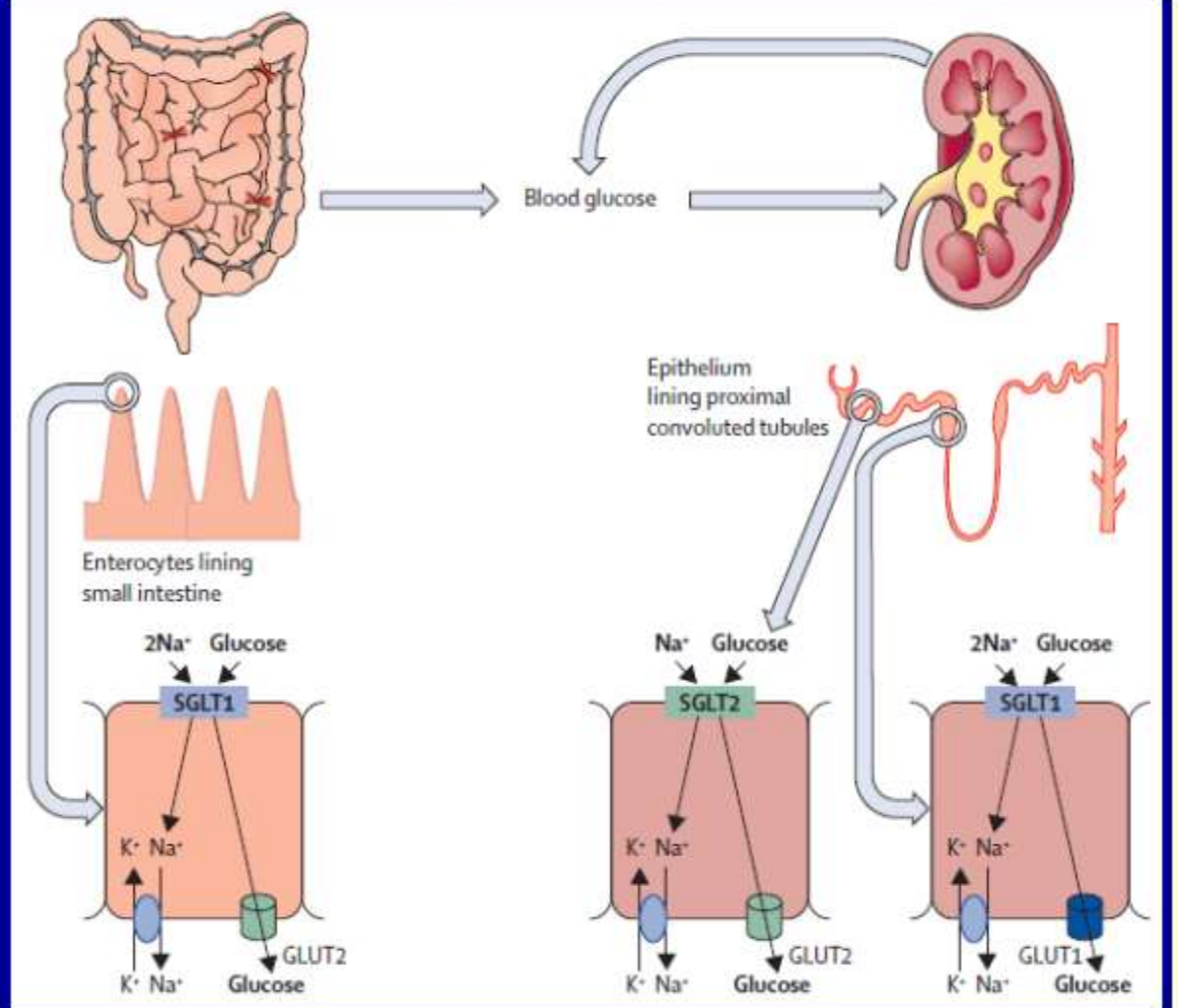
INIBITORI RECETTORIALI SGLT2

(Glicosurici o Glifozine)

Bloccano il riassorbimento del glucosio nel tubulo prossimale renale, determinandone l'eliminazione

SGLT inhibitors in management of diabetes

Abd A Tahrani, Anthony H Barnett, Clifford J Bailey



Inibizione recettori $SGLT_2$ (co-trasporto Na^+/Glucosio) nel tubulo prossimale renale

- ↑ **glicosuria** (a 60-100 g/die) → ↓ **glicemia** e bilancio calorico negativo (→ **calo ponderale** 2-3 kg)
- ↑ **Sodiuria** (anche per diuresi osmotica) → ↓volume extracell. (5-10%)
- ↓ **PA** (4-5/1-2 mmHg)
- ↓ trigliceridi e uricemia, ↑colesterolo HDL e LDL (lievi)

Inibizione Na/H exchanger (miociti e cellule endoteliali):
↓Na e Ca intracellulare → ↓aritmie e vasodilatazione
↑Ca intramitocondriale

Tahrani AA et al. Lancet Diabetes Endocrinol 2013;1:140-51

Che ci dicono i trials che hanno dimostrato una ‘superiorità’ contro placebo ?

Trial	LEADER (N= 9 340)	SUSTAIN-6 (N = 3 297)	HARMONY-OUTCOMES	CANVAS (N=10 142)	EMPAREG-OUTCOME (N= 7 020)
Drug	**Liraglutide** (GLP-1 agonist)	**Semaglutide** (GLP-1 agonist)	**Albiglutide** (GLP-1 agonist)	**Canaglifozin** (SGLT2-inhibitor)	**Empaglifozin** (SGLT2-inhibitor)
Inclusion citeria **HbA_{1c} (%)**	T2D and age>50 and CVD, **or** age>60 and ≥1 CV risk factors; >7%	T2D and age>50 and CVD, **or** age>60 and ≥1 CV risk factors; >7%	T2D **and** CVD (MI, or ≥50% coron. stenosis, revescular. stroke, ≥50% carotid stenosis, revascular, PAD) >7%	T2D and [age>30 and CVD], **or** [age>50 with ≥1 CV risk factors]. 7.0-10.5%	T2D **and** CVD (CVD (MI, ≥50% coronary stenosis, revascularization, unstable angina, stroke, or PAD) 7-10%
Dose	0,6 ->1,2->1,8 mg/die	0,25->0,50->1 mg/week	30->50 mg/week	100 (max 300) mg/die	10 (max 25) mg/die
Duration of trial	3.8 years	2.05 years	1.6 years	3.6 years	3.1 years
Baseline HbA_{1c}	8.7%	8.7%	8.7%	8.2%	8.1%
Primary end-point	**↓ 13% (-3% to -22%)**	**↓ 26% (-5% to -42%)**	**↓ 22% (-10% to -32%)**	**↓ 14% (3% to 25%)**	**↓ 14% (-1% to -26%)**
CV death	**↓ 22% (-7% to -34%)**	↓ 2% (-35% to +48%)	↓ 7% (-27% to 19%)	↓ 13% (-28% to 6%)	**↓ 38% (-23% to -51%)**
Non fatal Myocardial Infarction	↓ 12% (-25% to +3%)	↓ 26% (-49% to +8%)	**↓ 25% (-10% to -39%)**	↓ 15% (-31% to +5%)	↓ 13% (-30% to 9%)
Non fatal Stroke	↓ 11% (-28% to +11%)	**↓ 39% (-62% to -1%)**	↓ 14% (-34% to 14%)	↓ 10% (-29 to +15%)	↑24% (-8% to +67%)
HF Hospitalization	↓ 13% (-27% to 5%)	↑ 11% (**-23% to 61%**)		**↓ 33% (-13 % to -48%)**	**↓ 35% (-15% to -50%)**
All-cause Death	**↓ 15% (-3% to -26%)**	↑ 5% (-26% to 50%)	↓ 5% (-21% to 16%)	↓ 13% (-24% to 1%)	**↓ 32% (-18 % to -43%)**
Important adverse effects	Gallstones, GI side effects	Higher retinophaty rates (3.0 vs 1.8%) and blindness (0.3 vs 0.1%)	Injection site reactions	Genitourinary infections amputations, fractures volume depletion	Genitourinary infections No increase in diabetic ketoacidosis
Possible mechanisms of benefit	Slower effect suggests benefits via **less atherothrombosis** and/or avoidance of hypoglicemia	Slower effect suggests benefits via **less atherothrombosis** and/or avoidance of hypoglicemia	Slower effect suggests benefits via **less athero-thrombosis** and/or avoidance of hypoglicemia	Rapid effects suggest **hemodynamic** or metabolic benefit, although a vascular benefit may also occur	Rapid effects suggest **hemodynamic** or metabolic benefit, although a vascular benefit may also occur

PERSPECTIVE

Is the Mortality Benefit With Empagliflozin in Type 2 Diabetes Mellitus Too Good To Be True?

Circulation 2016

Sanjay Kaul, MD

Signaling a likely end to a long and elusive quest for cardiovascular outcome benefit associated with treatment intervention in type 2 diabetes mellitus, the results of the EMPA-REG OUTCOME trial [BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients] were received with a standing ovation at the European Association for the Study of Diabetes scientific meeting in Stockholm, Sweden, on September 17, 2015.[1] Witnessing the spontaneous applause, I had mixed emotions. Was it time to bring the trumpets out and rejoice that the "holy grail" had finally been achieved? Or, was it more appropriate to curb the enthusiasm and question the "historic milestone," given that the mortality benefit was unexpected and unprecedented?

Examples abound of instances where we have been led astray by implausibly large treatment effects that were not confirmed by subsequent trials. Perhaps the most compelling is the case of perioperative β-blockade with bisoprolol in high-risk vascular surgery.[2] The DECREASE 1 trial (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo) yielded a 91% risk reduction in cardiovascular death or myocardial infarction ($P<0.001$) in 112 patients. These results were widely disseminated and adopted by several practice guidelines, ultimately rising to the status of a performance measure. The positive results of this trial were never replicated. On the contrary, a large, randomized trial (POISE [Perioperative Ischemic Evaluation]) and a meta-analysis pointed to harm, necessitating a downgrading of recommendations a decade after the publication of the original trial results.[3] One systematic review concluded that most large treatment effect estimates should be considered with caution. The vast majority are either spurious findings or represent substantial overestimations, and large mortality benefits are almost entirely nonexistent.[4]

Thus, the key question that lingered in my mind despite the resounding applause was, "Should we simply dismiss these unexpected results to be 'too good to be true' and attribute them to a play of chance?" In answering this question, I wrestled with the following arguments.

First, both all-cause mortality and cardiovascular mortality were prespecified as secondary end points, although they were not included in the statistical hierarchical testing strategy, which included a stepwise evaluation of noninferiority followed by superiority of 3 and 4-point major adverse cardiovascular events (MACE). A purist might argue that because superiority of 4-point MACE was not met ($P=0.079$), the α error had already been spent, and therefore all subsequent analyses, including mortality, must be deemed exploratory, requiring confirmation in subsequent trials. Taken to a logical extreme, this is akin to saying that because Christopher Columbus had prespecified discovering a route to India, America must not exist. There is regulatory precedence of a successful claim of carvedilol reducing the combined incidence of morbidity and mortality in heart failure despite the fact that mortality was not prespecified as a primary or a secondary end point in the pivotal trials.[5]

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Key Words: clinical trial ■ diabetes mellitus ■ mortality

Circulation

American Heart Association.

Is the Mortality Benefit With Empagliflozin in Type 2 Diabetes Mellitus Too Good To Be True?

Sanjay Kaul

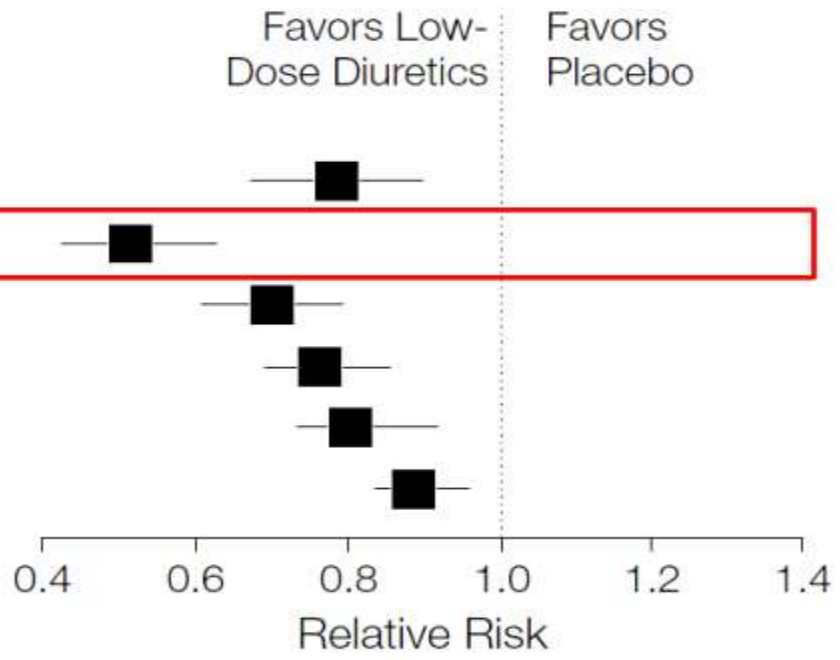
Critics have argued that lack of a clear and biologically plausible mechanism underlying mortality benefit is a major limitation. This is a rather uncharitable criticism because outcome trials are not designed to unravel the potential mechanisms of benefit. What we can say with reasonable confidence from the trial results so far is that mortality benefit is unlikely to be mediated by favorable but very modest effects on cardiometabolic factors such as blood pressure, body weight, or glycemic control, given the rapid onset of treatment effect (curves separate as early as 2–3 months), and it is unlikely to be mediated by an atherothrombotic effect, given the lack of effect on myocardial infarction and stroke. The observations that hospitalization for heart failure was reduced by 35% and that half of the cardiovascular mortality advantage was driven by reduction in worsening heart failure and sudden cardiac death[1] support a possible hemodynamic or antiarrhythmic effect. Future studies aimed at these targets should help yield mechanistic insights.

Thus, the totality of data suggests that the observed magnitude of mortality benefit in EMPA-REG OUTCOME is not likely to be spurious. Nonetheless, because the findings were unexpected and unprecedented and not linked to obvious mechanistic pathway, the results need to be replicated in future investigations. Only then can we be sure beyond any reasonable doubt that the mortality results are highly reliable and that it is time to take the trumpets out to herald the historic milestone.

Effects of low-dose diuretics

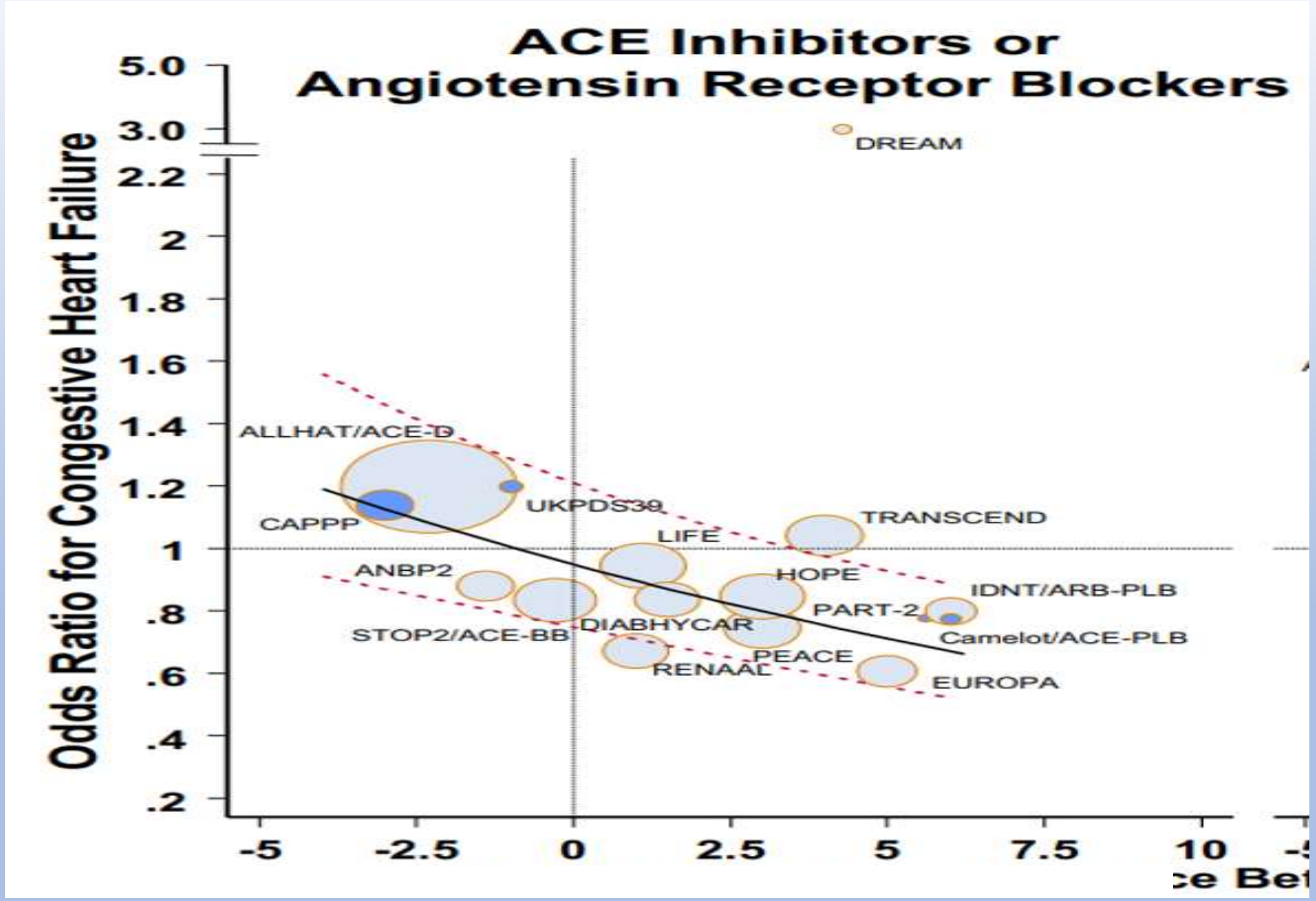
A Low-Dose Diuretics vs Placebo

Outcome	RR (95% CI)	*P* Value
CHD	0.79 (0.69-0.92)	.002
CHF	0.51 (0.42-0.62)	<.001
Stroke	0.71 (0.63-0.81)	<.001
CVD Events	0.76 (0.69-0.83)	<.001
CVD Mortality	0.81 (0.73-0.92)	.001
Total Mortality	**0.90 (0.84-0.96)**	**.002**



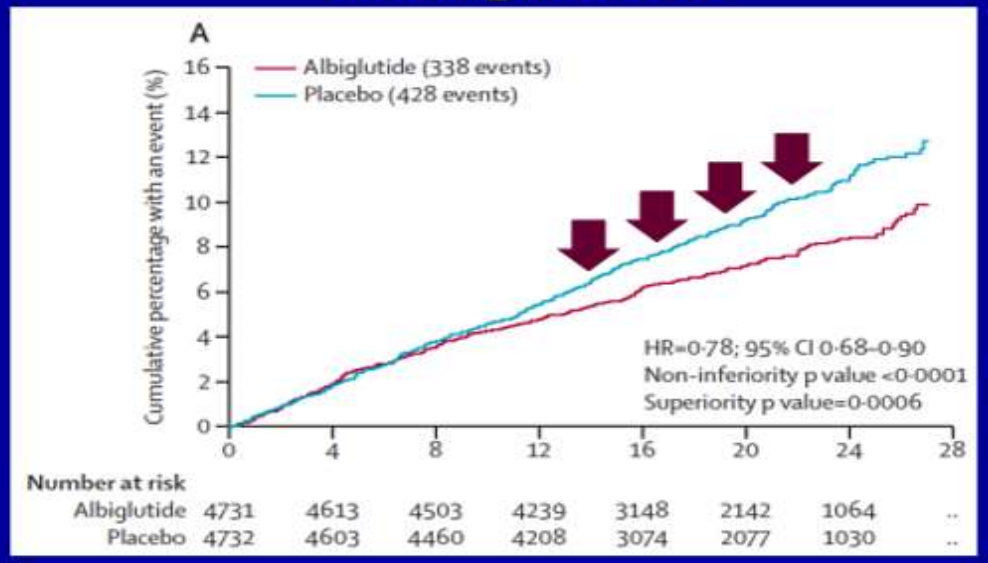
Conclusions Low-dose diuretics are the most effective first-line treatment for preventing the occurrence of cardiovascular disease morbidity and mortality. Clinical practice and treatment guidelines should reflect this evidence, and future trials should use low-dose diuretics as the standard for clinically useful comparisons.

JAMA. 2003;289:2534-2544 **Psaty B et al.** www.jama.com


ACE Inhibitors or
Angiotensin Receptor Blockers
Odds Ratio for Congestive Heart Failure
5.0
3.0
2.2
2
1.8
1.6
1.4
1.2
1
.8
.6
.4
.2
-5
-2.5
0
2.5
5
7.5
10
DREAM
ALLHAT/ACE-D
UKPDS39
CAPPP
LIFE
TRANSCEND
ANBP2
HOPE
IDNT/ARB-PLB
PART-2
DIABHYCAR
STOP2/ACE-BB
Camelot/ACE-PLB
PEACE
RENAAL
EUROPA

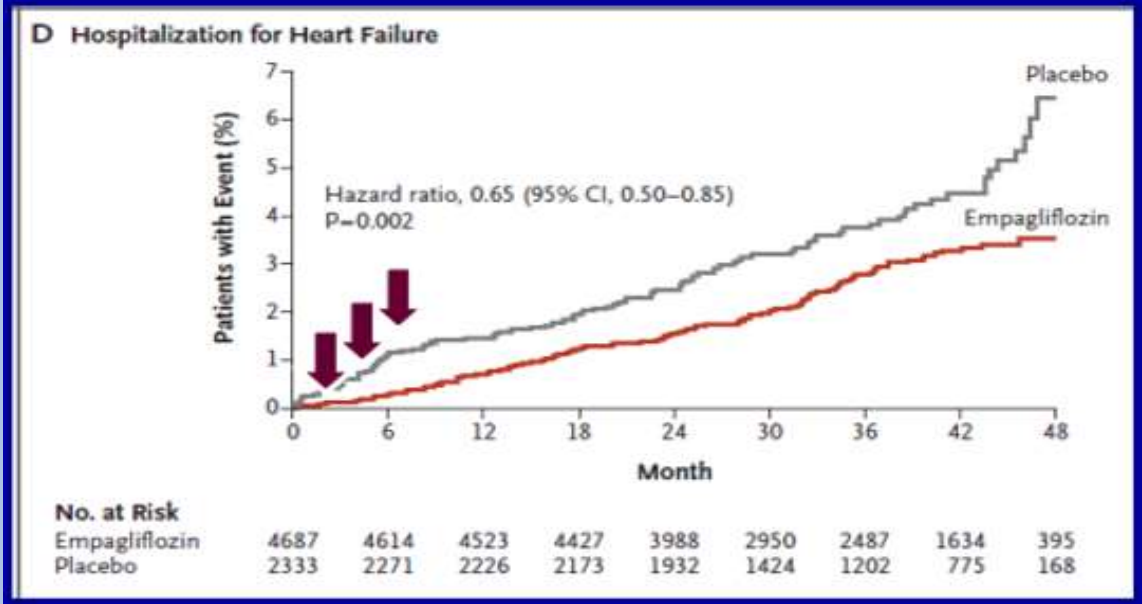
Effetti più 'tardivi' ('antiaterosclerosi'?) per gli analoghi GLP-1

Albiglutide



Effetti più 'precoci' ('emodinamici'?) per gli inibitori $SGLT_2$

Empaglifozin



GLP-1 Analoghi ('incretine')				
Liraglutide	Victoza	Sottocute	0,6 mg → 1,2 mg -→1,8 mg/die	LEADER
Semaglutide	Saxenda	Sottocute	0,25 mg→0,50 mg→1 mg/week	SUSTAIN-6
Albiglutide	Eperzan	Sottocute	30 mg→50 mg/week	HARMONY-OUTCOMES
Lixisenatide	Lyxumia	Sottocute	10 µg/die –(2 weeks)→ 20µg/die	ELIXA
Exenatide	Byetta, Bydureon	Sottocute	5 µg x 2/die→10 µg x 2/die	EXSCEL
Dulaglutide	Trulicity	Sottocute	0,75 mg/week	AWARD 1-9 REWIND

DPP-4 Inibitori				
Linagliptin	Trajenta, Jentadueto	Per os	5 mg/die	CARMELINA CAROLINA
Vidagliptin	Eucreas, Galvus	Per os	50 mg x 2/die	
Saxagliptin	Onglyza	Per os	2,5 mg/die, 5 mg/die	SAVOR-TIMI 52
Sitagliptin	Januvia	Per os	100 mg/die (50 o 25 se IRC)	TECOS
Alogliptin	Vipidia, Nesina	Per os	25 mg/die (6,25 o 12,5 se IRC)	EXAMINE

SGLT-2 inibitori ('gliptine')				
Empaglifozin	Jardiance	Per os	10 mg/die (max 25 mg/die)	EMPAREG-OUTCOME
Canaglifozin	Invokana	Per os	100 mg/die (max 300 mg/die)	CANVAS
Dapaglifozin	Forxiga	Per os	10 mg/die (5 mg se ins. epatica)	DECLARE-TIMI 58

Circulation

ON MY MIND

Are We Ready to Bell The Cat?

A Call for Cardiologists to Embrace Glucose-Lowering Therapies Proven to Improve Cardiovascular Outcomes

Analisi condotta in 313 Ospedali:

1. **Solo il 5%** dei pazienti diabetici con criteri di inclusione EMPA-REG assumeva SGLT-2 inibitori.
2. **Solo il 6%** dei pazienti con criteri di inclusione LEADER assumeva GLP-1 analoghi.
3. I pazienti diabetici con malattie cardiovascolari manifeste o alto rischio di eventi hanno una probabilità **3-8 volte maggiore di ricevere terapie che NON hanno mostrato di ridurre le complicanze cardiovascolari** (insulina, sulfaniluree o DPP-4 antagonisti), rispetto a GLP-1 analoghi o SGLT-2 inibitori.

Quindi, continua a regnare il paradigma **'aggressive glucose lowering and hemoglobin A1c management at the expense of therapies that improve cardiovascular mortality'**

Nassif ME et al. Circulation. 2018;138:4–6

Impariamo a consultare più spesso il diabetologo quando il nostro paziente ha un diabete mellito associato ad almeno una delle condizioni seguenti:

1. Infarto miocardico
2. Procedure di rivascolarizzazione
3. Angina instabile
4. Scompenso cardiaco NYHA II-III
5. Stenosi coronarica >50%
6. Insufficienza renale cronica con eGFR <60 ml min-1 [1.73 m]$^{-2}$).

In queste circostanze, l'uso di un GLP1-analogo o di un SGLT-2 inibitore riduce significativamente il rischio di eventi cardiovascolari maggiori.

I cardiologi dovrebbero essere autorizzati dall'AIFA a compilare i Piani Terapeutici per i nuovi antidiabetici orali.

Ciò migliorerebbe di molto l'assistenza 'integrata' del paziete aumentando l'affluenza verso i diabetologi di un maggior numero di pazienti per tutto quello che concerne gli aspetti diabetologici del follow-up di questi soggetti.

Impatto dei nuovi farmaci antidiabetici sul Rischio Cardiovascolare

GRAZIE PER L' ATTENZIONE