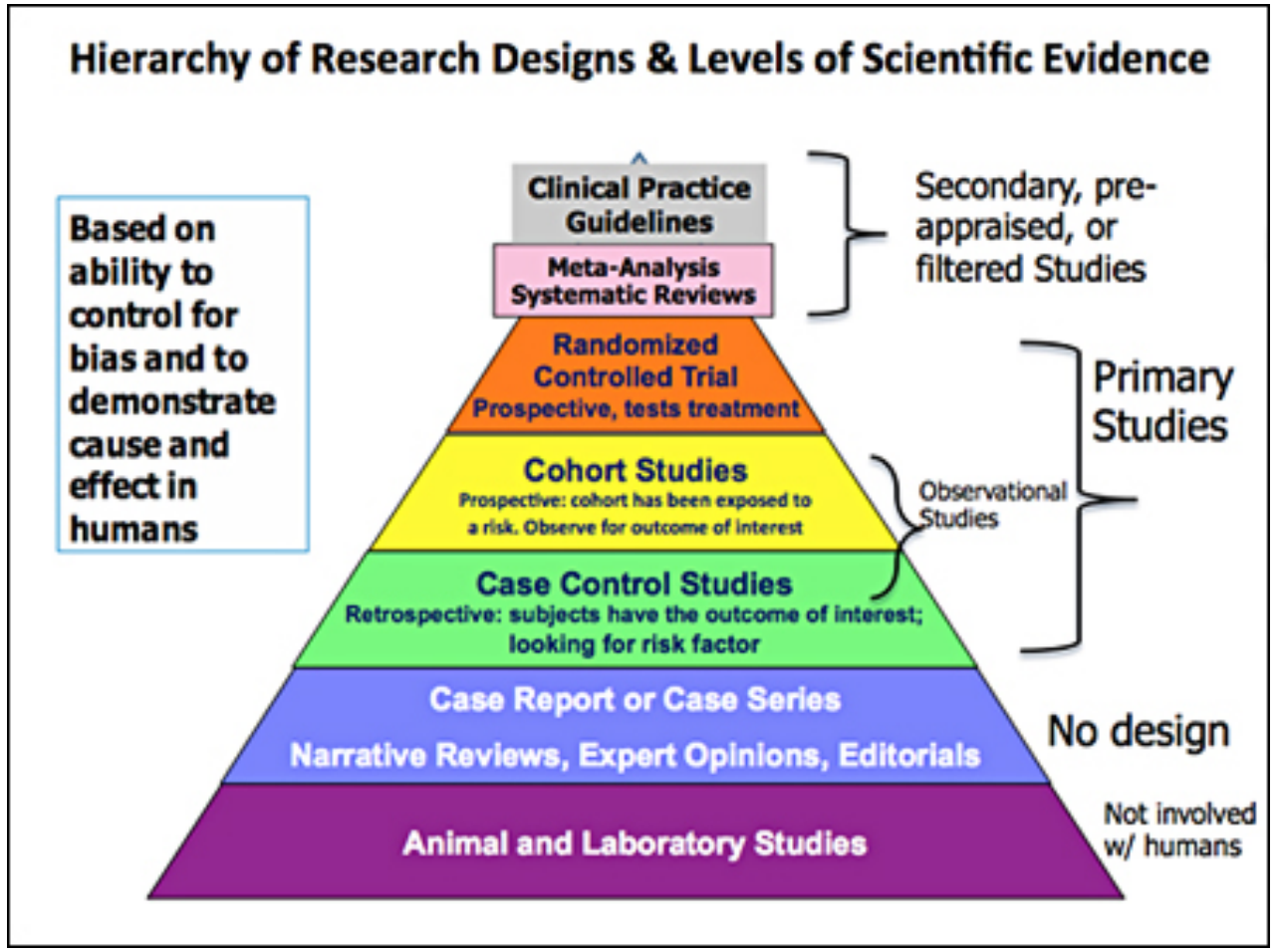
La gerarchia delle evidenze in Diabetologia:
Trials, Studi Osservazionali, Linee Guida

Ilaria Dicembrini

Grosseto, 30 novembre 2018

Conflitti di interessi

Negli ultimi due anni, I. Dicembrini ha ricevuto:
compensi per consulenze da ***Movi e Roche.***
compensi da agenzie in eventi sponsorizzati da ***Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Menarini, Merck, Novo Nordisk, Sanofi*** e ***Takeda***


Hierarchy of Research Designs & Levels of Scientific Evidence
Based on ability to control for bias and to demonstrate cause and effect in humans
Clinical Practice Guidelines
Meta-Analysis Systematic Reviews
Secondary, pre-appraised, or filtered Studies
Randomized Controlled Trial
Prospective, tests treatment
Cohort Studies
Prospective: cohort has been exposed to a risk. Observe for outcome of interest
Observational Studies
Case Control Studies
Retrospective: subjects have the outcome of interest; looking for risk factor
Primary Studies
Case Report or Case Series
Narrative Reviews, Expert Opinions, Editorials
No design
Animal and Laboratory Studies
Not involved w/ humans

Effects of remote, retroactive intercessory prayer on outcomes in patients with bloodstream infection: randomised controlled trial

Leibovici L et al. *BMJ* 323: 1450-1451, 2001

Retrospective intercessory prayer: effect on sepsis

Results of a RCT

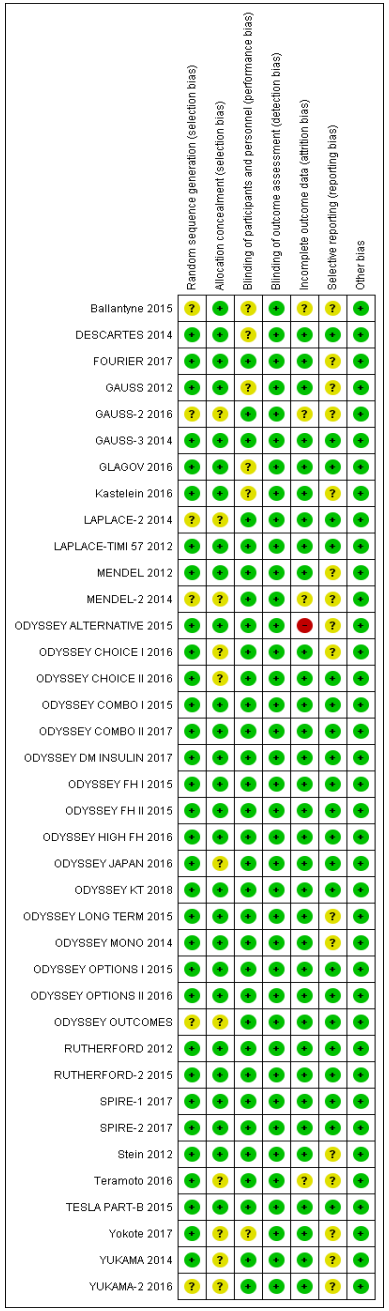
Table 2 Numbers of days' stay in hospital and duration of fever

	Minimum	Lower quartile	Median	Upper quartile	Maximum	P
Stay in hospital:						
Intervention	0	4	7	13	165	0.01
Control	0	4	8	16	320	
Duration of fever:						
Intervention	0	1	2	4	49	0.04
Control	0	1	2	5	50	

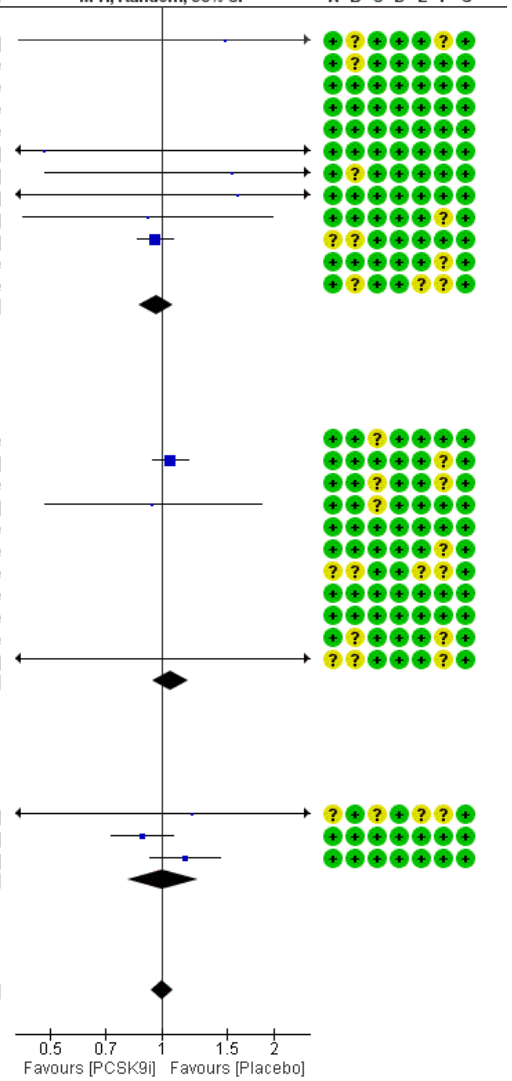
Principal endpoint:
Duration of hospital stay

3,393 patients admitted for sepsis

Leibovici L et al. *BMJ* 323: 1450-1451, 2001



Study or Subgroup	PCSK9 inhibitors Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.37.1 Alirocumab						
ODYSSEY CHOICE I 2016	11	573	3	230	0.3%	1.48 [0.41, 5.36]
ODYSSEY CHOICE II 2016	0	173	0	58		Not estimable
ODYSSEY COMBO I 2015	0	209	0	107		Not estimable
ODYSSEY FH I 2015	0	322	0	163		Not estimable
ODYSSEY FH II 2015	0	167	0	81		Not estimable
ODYSSEY HIGH FH 2016	1	72	1	35	0.1%	0.48 [0.03, 7.89]
ODYSSEY JAPAN 2016	12	144	4	72	0.3%	1.55 [0.48, 4.97]
ODYSSEY KT 2018	3	97	2	102	0.1%	1.60 [0.26, 9.76]
ODYSSEY LONG TERM 2015	18	1553	10	788	0.8%	0.91 [0.42, 1.99]
ODYSSEY OUTCOMES	648	9462	676	9462	37.5%	0.96 [0.85, 1.07]
Stein 2012	0	62	0	15		Not estimable
Teramoto 2016	0	75	0	25		Not estimable
Subtotal (95% CI)		**12909**		**11138**	**39.1%**	**0.96 [0.86, 1.07]**
Total events	693		696			
Heterogeneity: Tau² = 0.00; Chi² = 1.63, df = 5 (P = 0.90); I² = 0%						
Test for overall effect: Z = 0.68 (P = 0.49)						
1.37.2 Evolocumab						
DESCARTES 2014	0	599	0	302		Not estimable
FOURIER 2017	663	13784	631	13780	37.5%	1.05 [0.94, 1.18]
GAUSS 2012	0	30	0	32		Not estimable
GLAGOV 2016	17	484	18	484	1.0%	0.94 [0.48, 1.85]
LAPLACE-TIMI 57 2012	0	475	0	156		Not estimable
MENDEL 2012	0	228	0	91		Not estimable
MENDEL-2 2014	0	306	0	154		Not estimable
RUTHERFORD-2 2015	0	221	0	110		Not estimable
TESLA PART-B 2015	0	33	0	16		Not estimable
YUKAMA 2014	0	205	0	102		Not estimable
YUKAMA-2 2016	1	202	0	202	0.0%	3.01 [0.12, 74.45]
Subtotal (95% CI)		**16567**		**15429**	**38.6%**	**1.05 [0.94, 1.17]**
Total events	681		649			
Heterogeneity: Tau² = 0.00; Chi² = 0.52, df = 2 (P = 0.77); I² = 0%						
Test for overall effect: Z = 0.89 (P = 0.37)						
1.37.3 Bocucizumab						
Ballantyne 2015	1	253	0	101	0.0%	1.21 [0.05, 29.85]
SPIRE-1 2017	199	8409	225	8408	12.5%	0.88 [0.73, 1.07]
SPIRE-2 2017	177	5309	154	5312	9.7%	1.16 [0.93, 1.44]
Subtotal (95% CI)		**13971**		**13821**	**22.3%**	**1.00 [0.80, 1.25]**
Total events	377		379			
Heterogeneity: Tau² = 0.01; Chi² = 3.30, df = 2 (P = 0.19); I² = 39%						
Test for overall effect: Z = 0.02 (P = 0.98)						
Total (95% CI)		**43447**		**40388**	**100.0%**	**1.00 [0.94, 1.07]**
Total events	1751		1724			
Heterogeneity: Tau² = 0.00; Chi² = 6.71, df = 11 (P = 0.82); I² = 0%						
Test for overall effect: Z = 0.08 (P = 0.94)						
Test for subgroup differences: Chi² = 1.24, df = 2 (P = 0.54), I² = 0%						



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Debolezze dei trial

- Errori nei Metodi
- Pubblicazione selettiva di risultati favorevoli casuali

EBM richiede più trial concordanti su un determinato quesito

Contromisure per contrastare i limiti dei trial

Criticità	Contromisura
Pubblicazione selettiva dei trial con risultati favorevoli	EMA e FDA pubblicano report su tutti i trial registrativi presentati su nuovi farmaci Per i trial post immissione in commercio creazione di registri di trial clinici e disclosure dei risultati anche senza pubblicazione estesa.
Trial di fase IV non registrati	Richiesta di registrazione da parte delle principali riviste
Non inclusione nelle analisi sistematiche di trial non pubblicati	Le Systematic review devono includere anche questi trial
Endpoint secondari non favorevoli definiti non significativi	Richiesta di pubblicazione completa del protocollo e degli endpoint secondari.

Debolezze dei trial

- Errori nei Metodi
- Pubblicazione selettiva di risultati casuali

EBM richiede più trial concordanti su un determinato quesito

- Limitata generalizzabilità dei risultati

Alogliptin: effect on major cardiovascular events

Results of the EXAMINE trial

Patients were eligible for enrollment if they had received a diagnosis of type 2 diabetes mellitus, were receiving antidiabetic therapy (other than a DPP-4 inhibitor or GLP-1 analogue), and had had an acute coronary syndrome within 15 to 90 days before randomization. Further criteria for the diagnosis of type 2 diabetes included a glycated hemoglobin level of 6.5 to 11.0% at screening, or if the antidiabetic regimen included insulin, a glycated hemoglobin level of 7.0 to 11.0%.

Principal endpoint:
3-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death)

5380 T2DM patients with recent acute coronary syndrome, alogliptin vs placebo 1:1.
Follow-up: 1.5 y

White et al. *N Engl J Med* 369:1327-35, 2013

Debolezze dei trial

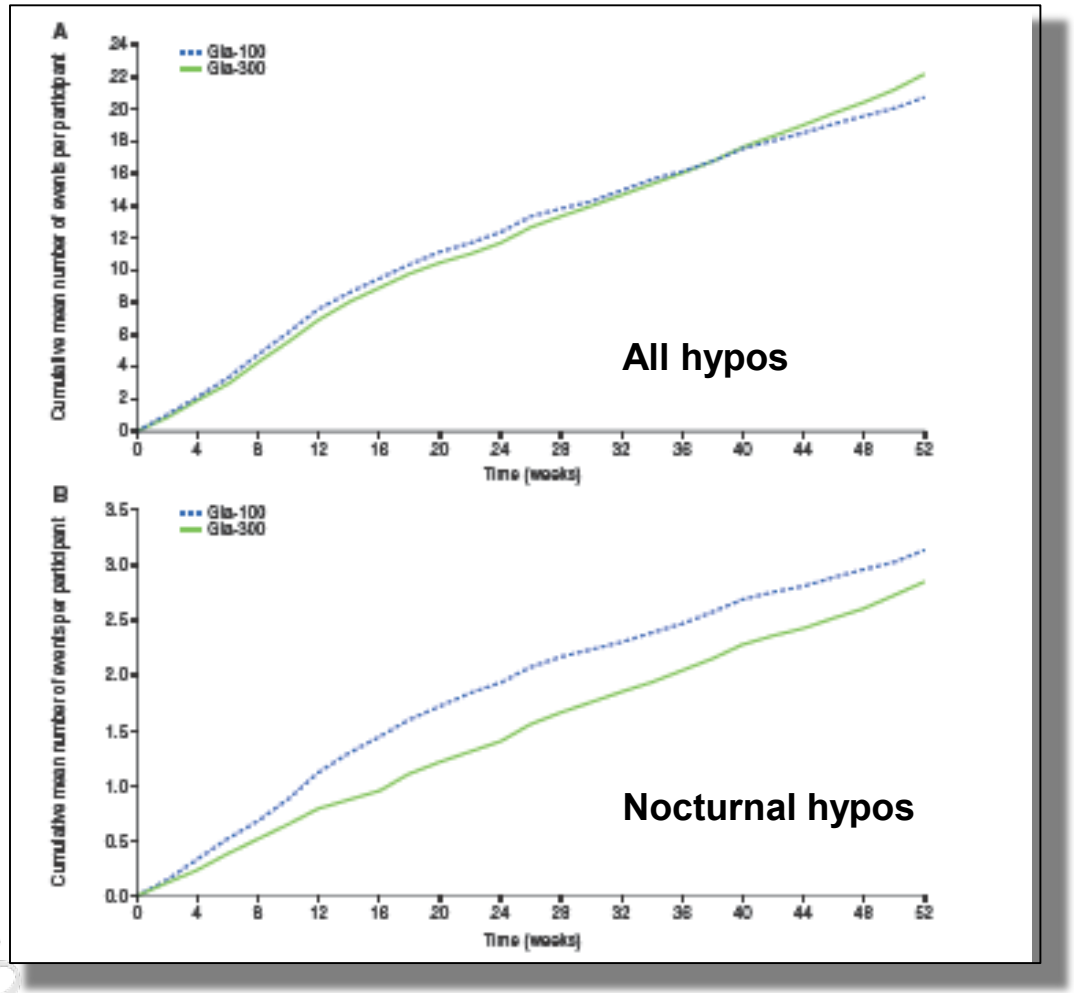
- Errori nei Metodi
- Pubblicazione selettiva di risultati casuali

EBM richiede più trial concordanti su un determinato quesito

- Limitata generalizzabilità dei risultati
- Setting e modalità di trattamento e titolazione diversi dalle realtà clinica

Glargine U-300 vs Glargine U-100

Results of the EDITION-1 trial



52-wk trial on T2DM patients on basal-bolus therapy

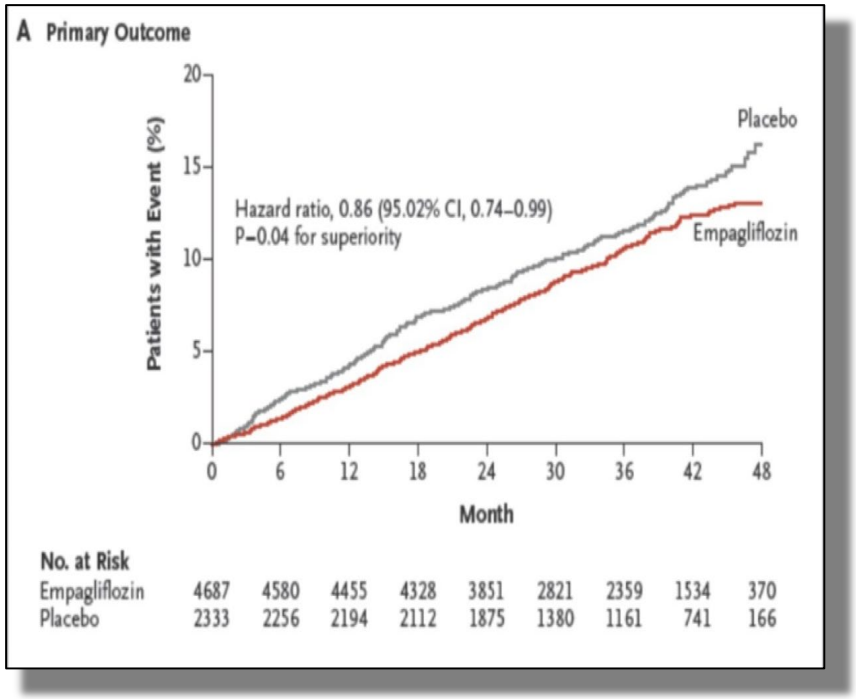
Riddle MC, et al. *Diabet Obes Metab*. 17: 835–842, 2015

Altri limiti dei trial

- Selezione della popolazione (criteri di inclusione, esclusione, selezione di sani e ipercomplianti)
- La dimensione del campione inadeguata per eventi avversi rari
- Durata dei trial relativamente breve

Empagliflozin: effect on major cardiovascular events

Results of the EMPAREG-OUTCOME trial

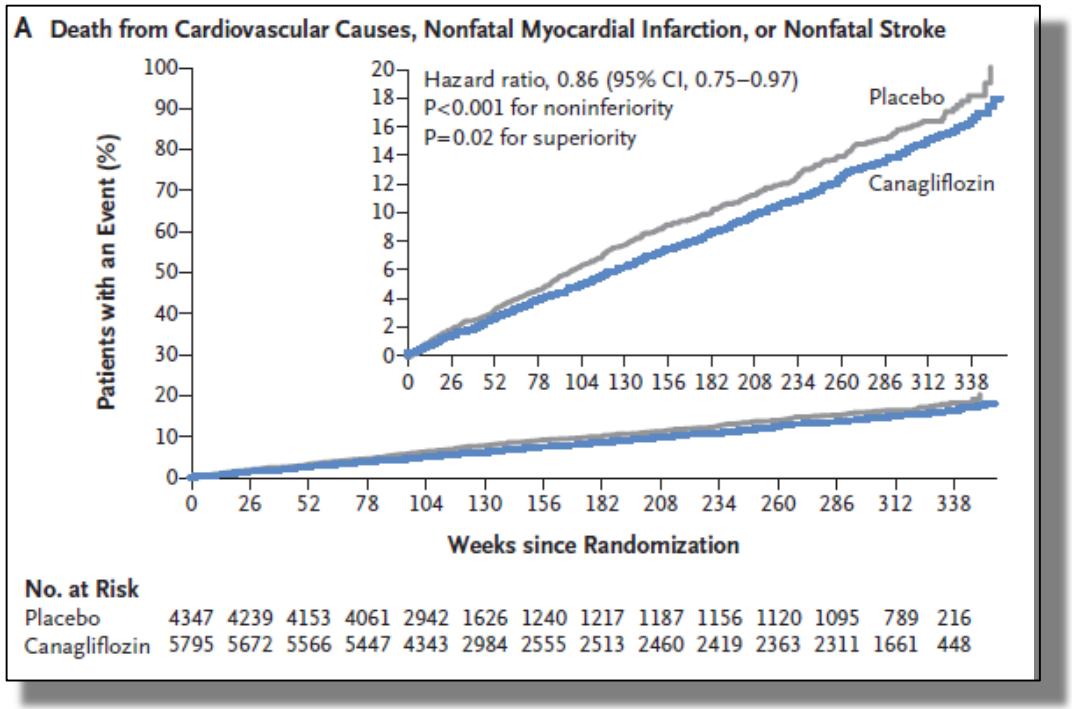


9,340 T2DM patients with prior CVD, Empagliflozin vs placebo
Follow-up: 3 y

Zinman B et al. *N Engl J Med* 373: 2117-28, 2015

Canagliflozin: effect on major cardiovascular events

Results of the CANVAS and CANVAS-R trial



10,142 T2DM patients with prior CVD or multiple risk factors, Canagliflozin vs placebo
Follow-up: 3.6 y

Neal et al. *N Engl J Med* 377: 644-57, 2017

Dapagliflozin and CV risk

Results of a UK retrospective cohort study

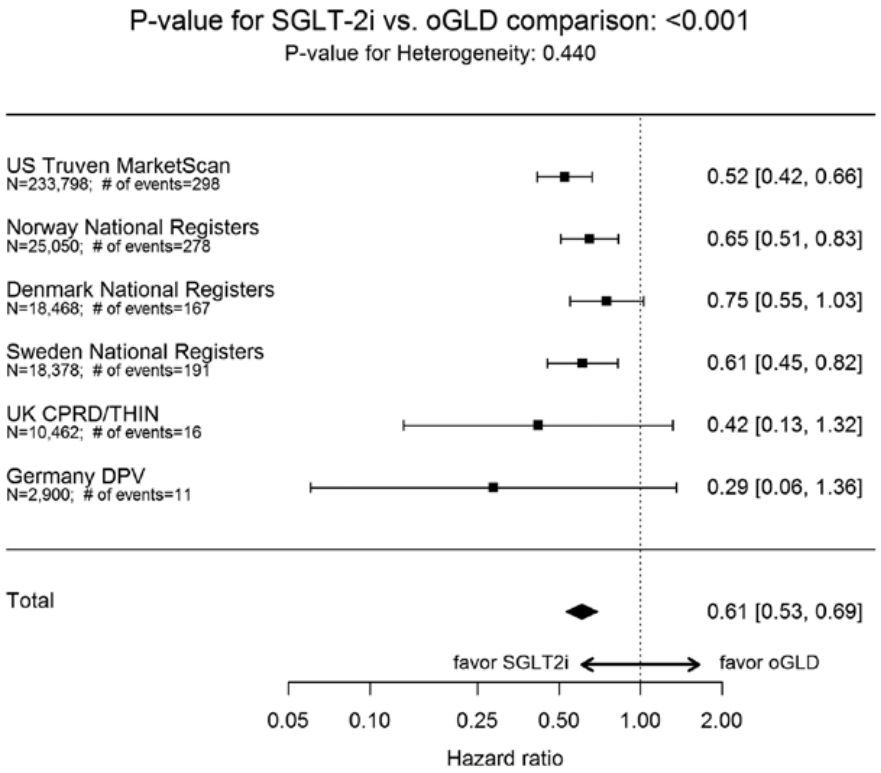
Table 2. Risk of Death From Any Cause and Incident CVD in Dapagliflozin Cohort Compared With Unexposed (Standard Treatment) Cohort

	Exposed to Dapagliflozin	Unexposed	Crude IRR (95%CI)	*P* Value	Adjusted IRR[a] (95%CI)	*P* Value
Total population						
Person-years	3456	13,129	—	—	—	—
Death from any cause	29	226	—	—	—	—
Incidence rate (deaths per 1000 person-years)	8.39	17.2	0.49 (0.33–0.72)	0.0001	0.50 (0.33–0.75)	0.001
Low-risk population						
Person-years	2842	10,514	—	—	—	—
Death from any cause	15	128	—	—	—	—
Incidence rate (deaths per 1000 person-years)	5.27	12.17	0.43 (0.25–0.74)	0.002	0.44 (0.25–0.78)	0.005
Person-years (CVD)	2839	10,488	—	—	—	—
Incident CVD	38	141	—	—	—	—
Incidence rate (CVD per 1000 person-years)	13.38	13.43	1.00 (0.70–1.42)	0.981	0.89 (0.61–1.30)	0.546

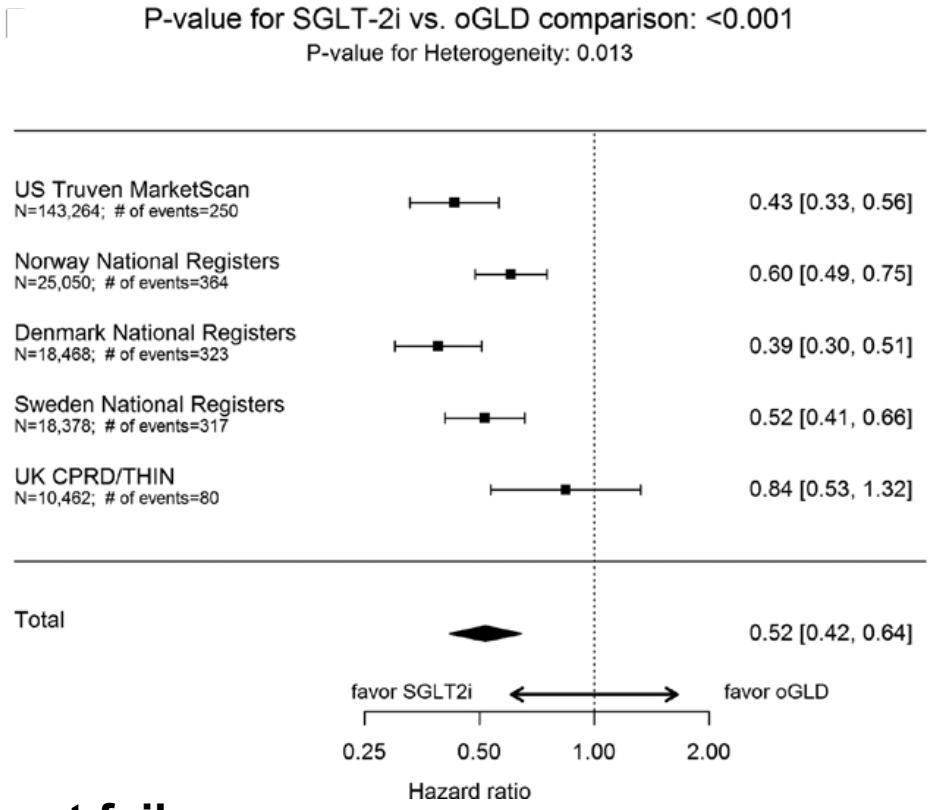
Toulis KA et al. *J Clin Endocrinol Metab* 102:1719-1725, 2018

SGLT2 inhibitors and CV risk

Results of the CVD REAL retrospective cohort study



All-cause death



Heart failure

Kosiborod M et al. *Circulation* 136:249–259, 2017

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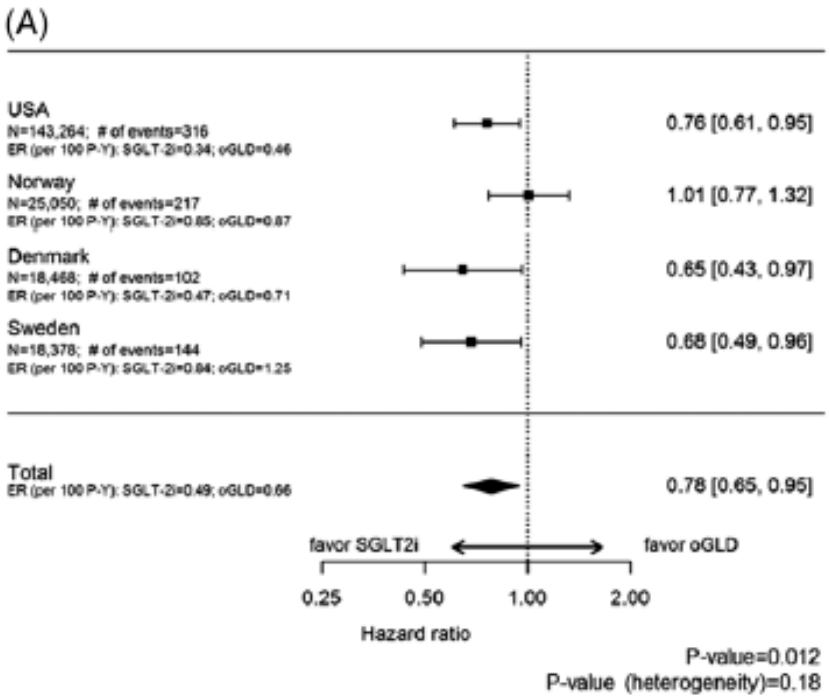

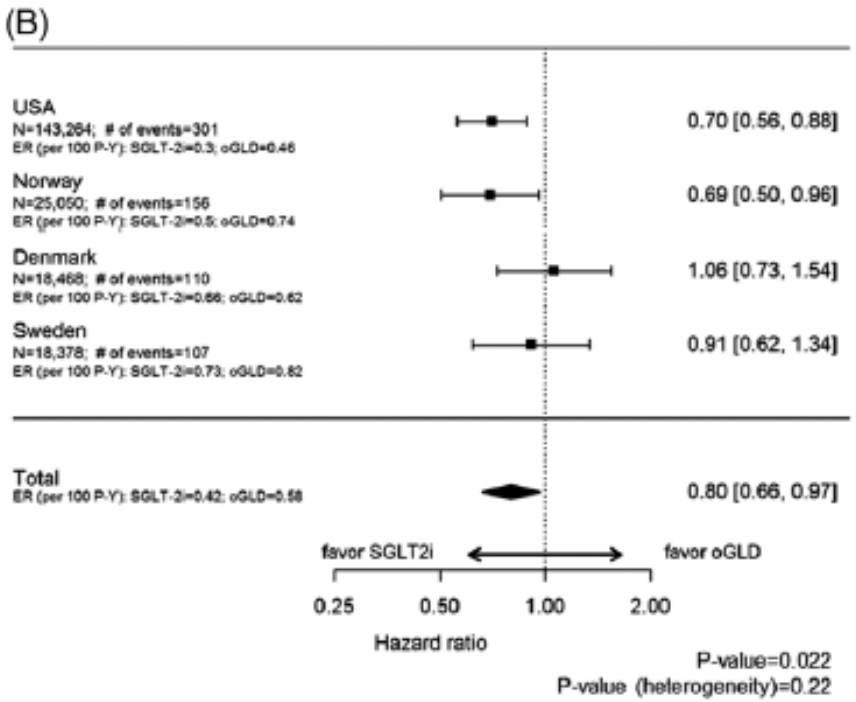

Myocardial Infarction

Stroke

Kosiborod M et al. *Diabetes Obes Metab* 20:1983-1987, 2018

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The Charlson comorbidity index was not used as a covariate in incident CVD outcomes.

Toulis KA et al. *J Clin Endocrinol Metab* 102:1719-1725, 2018

Dapagliflozin and CV risk

Results of a UK retrospective cohort study

Table 1. Baseline Characteristics of the Study Population on the Basis of Exposure to Dapagliflozin

	Exposed to Dapagliflozin	Unexposed Cohort
Charlson comorbidity index		
1	1941 (43.7)	7526 (42.6)[a]
2	889 (20.0)	3582 (20.3)[a]
3	959 (21.6)	3558 (20.1)[a]
4	395 (8.9)	1624 (9.2)[a]
5 or more	260 (5.9)	1390 (8.0)[a]

[a]Statistically significant at the level of 0.05.

Toulis KA et al. *J Clin Endocrinol Metab* 102:1719-1725, 2018

Limiti degli studi osservazionali

- Errori nei metodi
- Pubblicazione selettiva di risultati casuali
- Effetto di confounders non controllabili (prescription bias)

Insulin therapy and CV risk

Results of observational studies

TABLE 1 Association of insulin therapy with major cardiovascular events and all-cause mortality in selected observational studies and available randomized trials in patients with type 2 diabetes

Study [Ref.]	Comparator/Reference	HR [95% CI][a]	
		Major CV events	All-cause mortality
Observational studies			
Currie et al. 2010[1]	Oral agents	1.31 [1.22-1.42]	1.46 [1.34-1.59]
Vallarino et al. 2013[2]	Pioglitazone	2.27 [2.00-2.56]	NR
Roumie et al. 2014[3]	Sulfonylureas	1.30 [1.07-1.58]	1.44 [1.15-1.79]
Nijjar et al. 2014[4]	No treatment	1.25 [1.13-1.39]	1.31 [1.17-1.42]
Paul et al. 2015[5]	Exenatide BID	2.00 [1.26-3.12]	NR

Mannucci E, Ferrannini E. *Diabetes Obes Metab* 19:1201-1204, 2017

Quali sono i vantaggi degli studi osservazionali su coorte singola

- Identificare pattern di trattamento
- Valutare la reale prevalenza di eventi avversi in un setting real life
- Esplorare le risposte ai diversi trattamenti come predittori per efficacia e tollerabilità

Studi osservazionali matchati versus RCT

Osservazionali vs RCT	
No RCT disponibili	Posso generare ipotesi - Disegnando specifici RCT per efficacia - Possono far emergere problemi di sicurezza.

Observational studies with treatment comparisons vs RCTs

Osservazionali vs RCT	
No RCT disponibili	Posso generare ipotesi - Disegnando specifici RCT per efficacia - Possono far emergere problemi di sicurezza
RWD discordanti rispetto agli RCT	Dobbiamo credere agli RCT

Studi osservazionali vs RCT

Osservazionali vs RCT	
No RCT disponibili	Posso generare ipotesi - Disegnando specifici RCT per efficacia - Possono far emergere problemi di sicurezza
RWD discordanti rispetto agli RCT	Dobbiamo credere agli RCT
RWD concordanti con RCT	- Conferma di RCT sulla stessa popolazione e stessa terapia - Possibile estensione a popolazioni diverse (?)

From trials to the real world: i trial pragmatici

Studi randomizzati che confrontano due trattamenti:

- Criteri di inclusione: indicazioni
- Criteri di esclusione: contraindicazioni
- Procedure: standard clinical practice

Jones WS, et al. *J Am Coll Cardiol* 68:1898-1907, 2016

Altri limiti dei trial randomizzati vs trial pragmatici

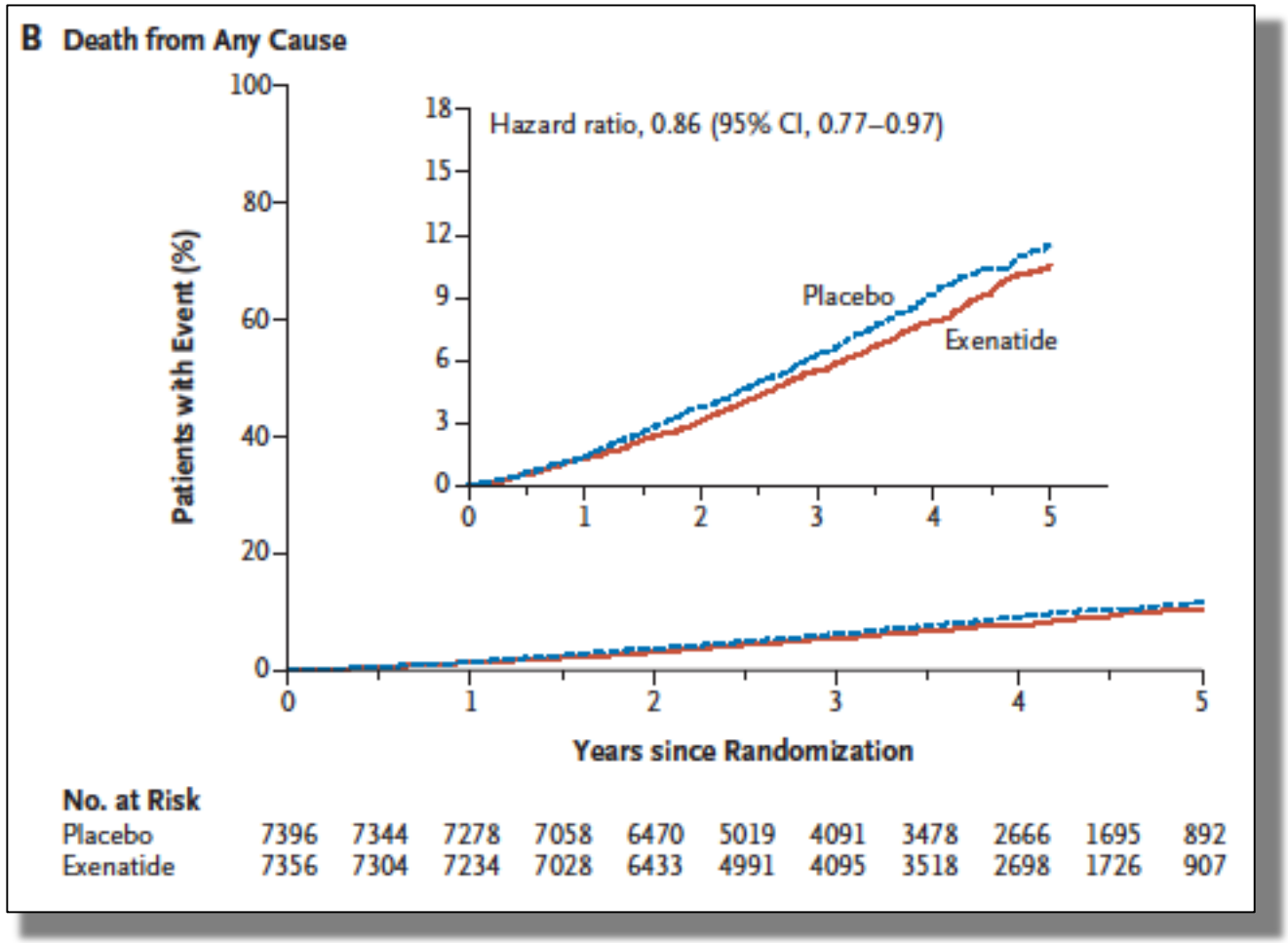
- Selezione della popolazione (criteri di inclusione, esclusione, selezione di sani e ipercomplianti)
- Setting e modalità di trattamento
- La dimensione del campione inadeguata per eventi avversi rari
- Durata dei trial relativamente breve

Altri limiti dei trial randomizzati vs trial pragmatici in diabetologia

- **Selezione della popolazione (criteri di inclusione, esclusione, selezione di sani e ipercomplianti)**
- **Setting e modalità di trattamento**
- **La dimensione del campione inadeguata per eventi avversi rari**
- **Durata dei trial relativamente breve**

Exenatide LAR: effect on all-cause mortality

Results of the EXSCEL trial



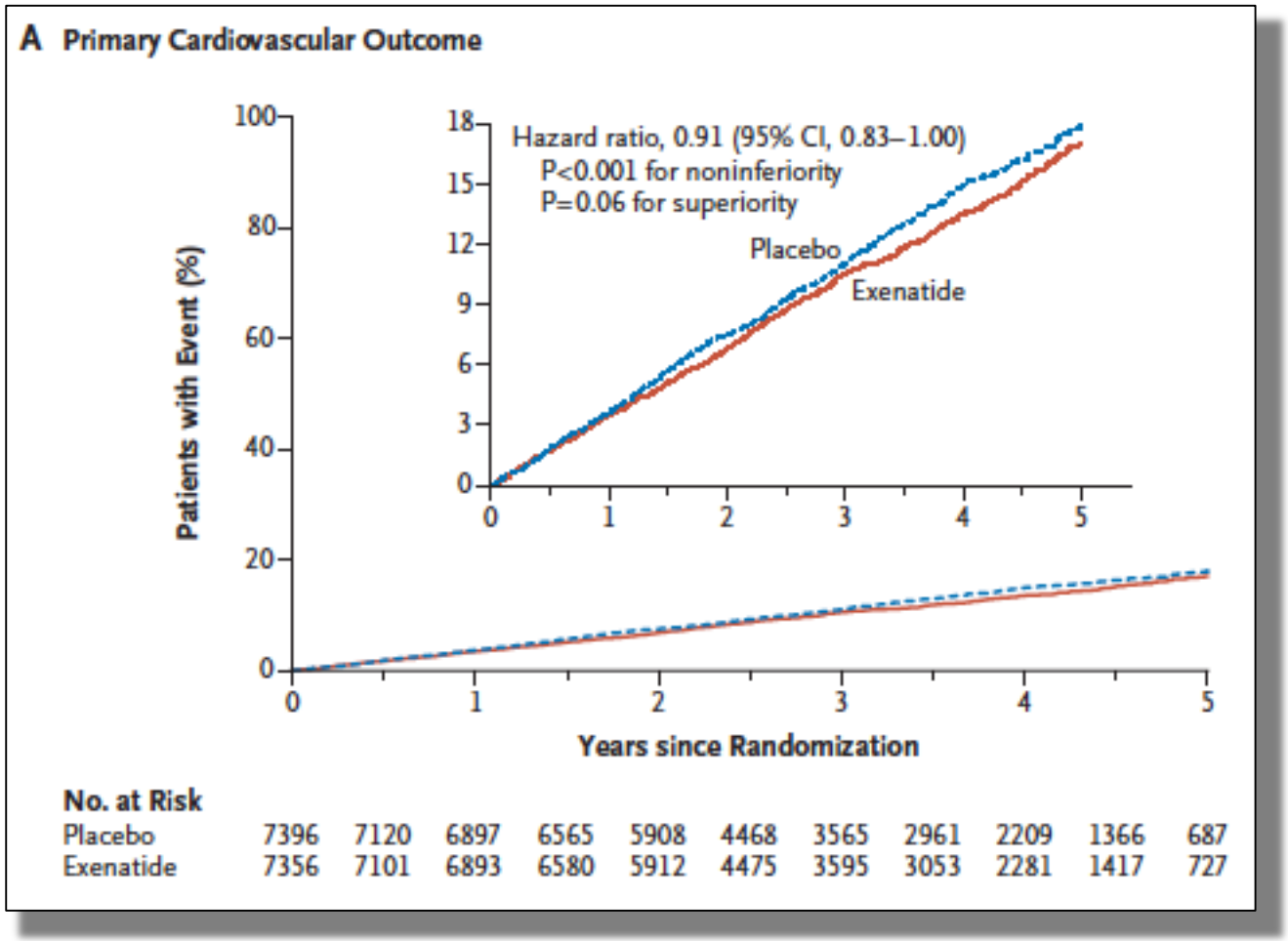
Principal endpoint:
3-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death)

14,752 T2DM patients with prior cardiovascular disease and/or high CV risk, exenatide LAR vs placebo 1:1. Follow-up: 3.2 y

Holman RR et al. *N Engl J Med* 377: 1228-39, 2016

Exenatide LAR: effect on major cardiovascular events

Results of the EXSCEL trial



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Exenatide LAR: effect on major cardiovascular events

Results of the EXSCEL trial

Subgroup	Exenatide	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
	no. of events/total no. (%)			
Antihyperglycemic oral agent therapy				0.37
Yes	660/6213 (10.6)	703/6278 (11.2)	0.93 (0.84–1.04)	
No	179/1143 (15.7)	202/1118 (18.1)	0.84 (0.69–1.03)	
Insulin therapy				0.45
Yes	467/3397 (13.7)	519/3439 (15.1)	0.89 (0.78–1.00)	
No	372/3959 (9.4)	386/3957 (9.8)	0.95 (0.83–1.10)	
DPP-4 inhibitor therapy				0.17
Yes	126/1118 (11.3)	113/1085 (10.4)	1.08 (0.84–1.39)	
No	713/6238 (11.4)	792/6311 (12.5)	0.89 (0.80–0.99)	

Holman RR et al. *N Engl J Med* 377: 1228-39, 2016

Limiti dei trial pragmatici

- Popolazioni eterogenee: necessità di ampie popolazioni
- Costo
- Richiesta di tempo

Jones WS, et al. *J Am Coll Cardiol* 68:1898-1907, 2016

E le Linee guida…..