



Controllo metabolico e piede diabetico

Tra nuovi farmaci e tecnologie

Edoardo Mannucci

Conflitti di interessi

Negli ultimi due anni, E. Mannucci ha ricevuto:

compensi per consulenze da ***AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck e Novo Nordisk***

compensi per relazioni a corsi/convegni da ***Abbott e Eli Lilly***

compensi da agenzie in simposi sponsorizzati da ***Abbott, Allergan, AstraZeneca, Boehringer Ingelheim, Bruno, Eli Lilly, Menarini, Merck, Novo Nordisk, Sanofi e Takeda***

La struttura diretta da E. Mannucci ha ricevuto:

finanziamenti per attività di ricerca e/o educative da ***AstraZeneca, Bayer, Boehringer Ingelheim, Molteni e Novo Nordisk***

compensi per trial clinici da:

AstraZeneca, Eli Lilly, Genentech, Janssen, Novartis e Novo Nordisk.

Predictors of incident foot ulcers

Results of the Seattle Diabetic Foot study

Table 2—Final multivariable model predicting the occurrence of foot ulcer

Characteristic	HR (95% CI)	P value
A1C*	1.10 (1.06–1.15)	<0.001
Vision poorer than 20/40	1.48 (1.00–2.18)	0.05
History of foot ulcer	2.18 (1.61–2.95)	<0.001
History of amputation	2.57 (1.60–4.12)	<0.001
Monofilament insensitivity	2.03 (1.50–2.76)	<0.001
Tinea pedis	0.73 (0.54–0.98)	0.035
Onychomycosis	1.58 (1.16–2.16)	0.004

*HR shown for a 1% increase in A1C level.

N=1,245 patients
with DM.

Cohort study,
Follow-up 3.3 y

Glycemic control and complications in T2DM

Results of the the UKPDS trial

AGGREGATE ENDPOINT	Patients with clinical endpoints		Absolute risk events per 1000 patient-years		Log-rank p	RR for intensive policy (CI)	Favours intensive	Favours conventional
	Intensive (n=2729)	Conventional (n=1138)	Intensive	Conventional				
Any diabetes-related endpoint	563	438	40.9	46.0	0.029	0.88 (0.79-0.99)		
Diabetes-related deaths	285	129	10.4	11.5	0.34	0.90 (0.73-1.11)		
All-cause mortality	489	213	17.9	18.9	0.44	0.94 (0.80-1.10)		
Myocardial infarction	387	186	14.7	17.4	0.052	0.84 (0.71-1.00)		
Stroke	148	55	5.6	5.0	0.52	1.11 (0.81-1.51)		
Amputation or death from PVD	29	18	1.1	1.6	0.15	0.65 (0.36-1.18)		
Microvascular	225	121	8.6	11.4	0.0099	0.75 (0.60-0.93)		
SINGLE ENDPOINTS								
Fatal myocardial infarction	207	50	7.6	8.0	0.63	0.94 (0.68-1.30)		
Non-fatal myocardial infarction	197	101	7.5	9.5	0.057	0.79 (0.58-1.06)		
Fatal: sudden death	24	18	0.9	1.6	0.047	0.54 (0.24-1.21)		
Heart failure	80	36	3.0	3.3	0.63	0.91 (0.54-1.52)		
Angina	177	72	6.8	6.7	0.91	1.02 (0.71-1.46)		
Fatal stroke	43	15	1.6	1.3	0.60	1.17 (0.54-2.54)		
Non-fatal stroke	114	44	4.3	4.0	0.72	1.07 (0.68-1.66)		
Death from peripheral vascular disease	2	8	0.1	0.3	0.12	0.26 (0.03-2.77)		
Amputation	27	18	1.0	1.6	0.059	0.61 (0.28-1.33)		

Long-term effects of glycemic control in T1DM

30-y results of the EDIC follow-up of the DCTT trial

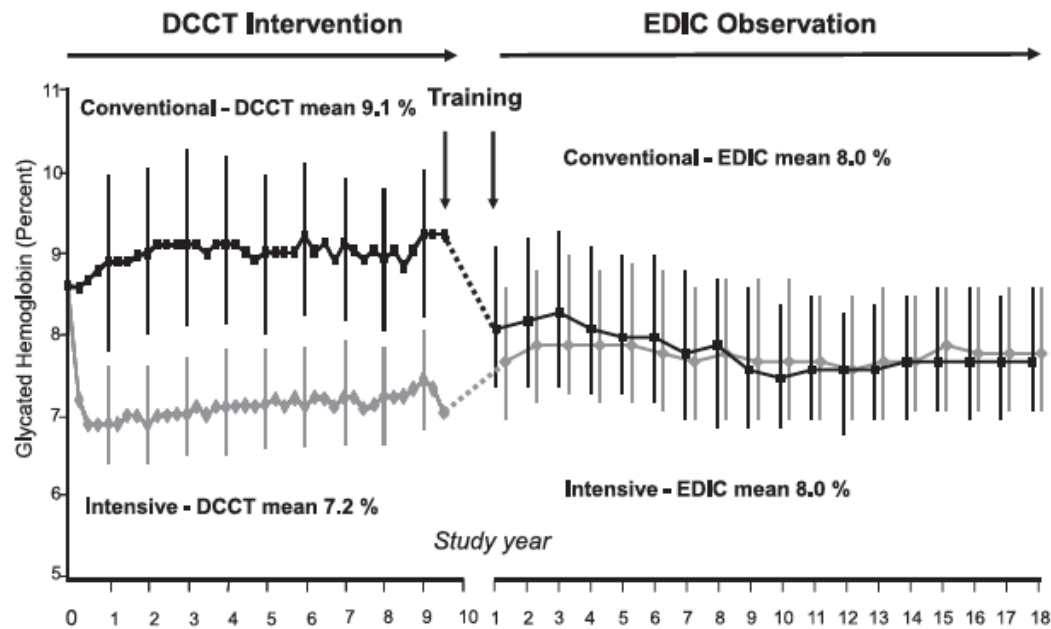


Figure 1—Median HbA_{1c} concentrations during DCCT, the “training” period between DCCT and EDIC, and EDIC. $P < 0.001$ for INT vs. CON during entire DCCT and for the first 3 years during EDIC. Reprinted and modified with permission from Nathan et al. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study at 30 years: advances and contributions. *Diabetes* 2013;62:3976–3986.

DCCT
1983-93

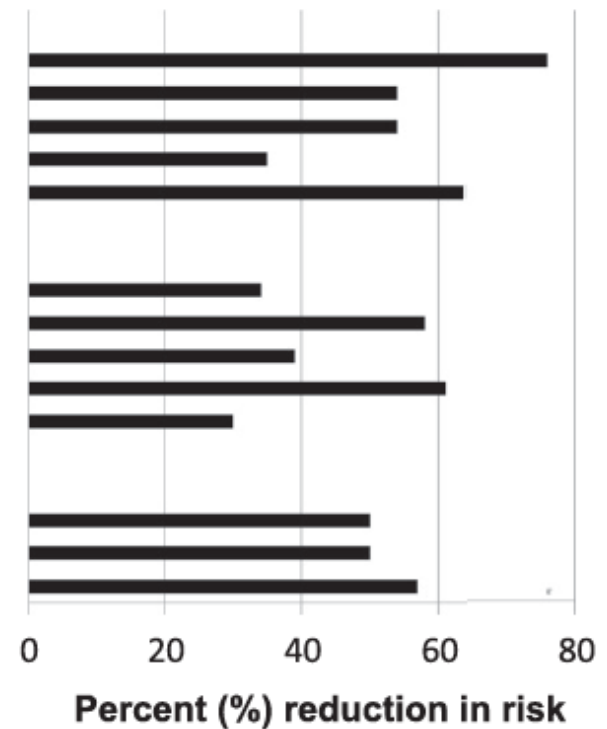
3+step devel, Prim
3+step progression, Scnd
Microalb
Macroalb
Neuropathy

EDIC
1994-2011

Further 3+ step prog, Prim
Further 3+step prog, Scnd
New Microalb
New Macroalb
New Neuropathy(2007-08)

DCCT
+
EDIC

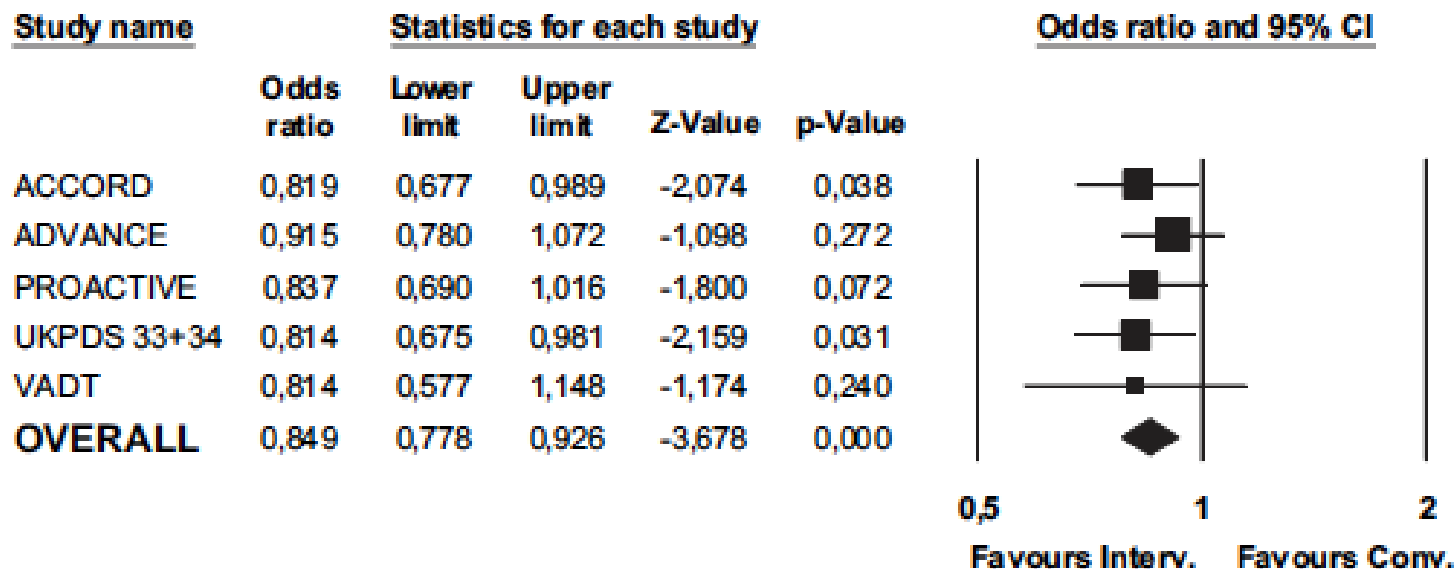
Severe eye
Reduced GFR
CVD events



Glycemic control and risk of MI in T2DM

Meta-analysis of RCTs on intensification of therapy

Myocardial infarction



Conclusions (1)

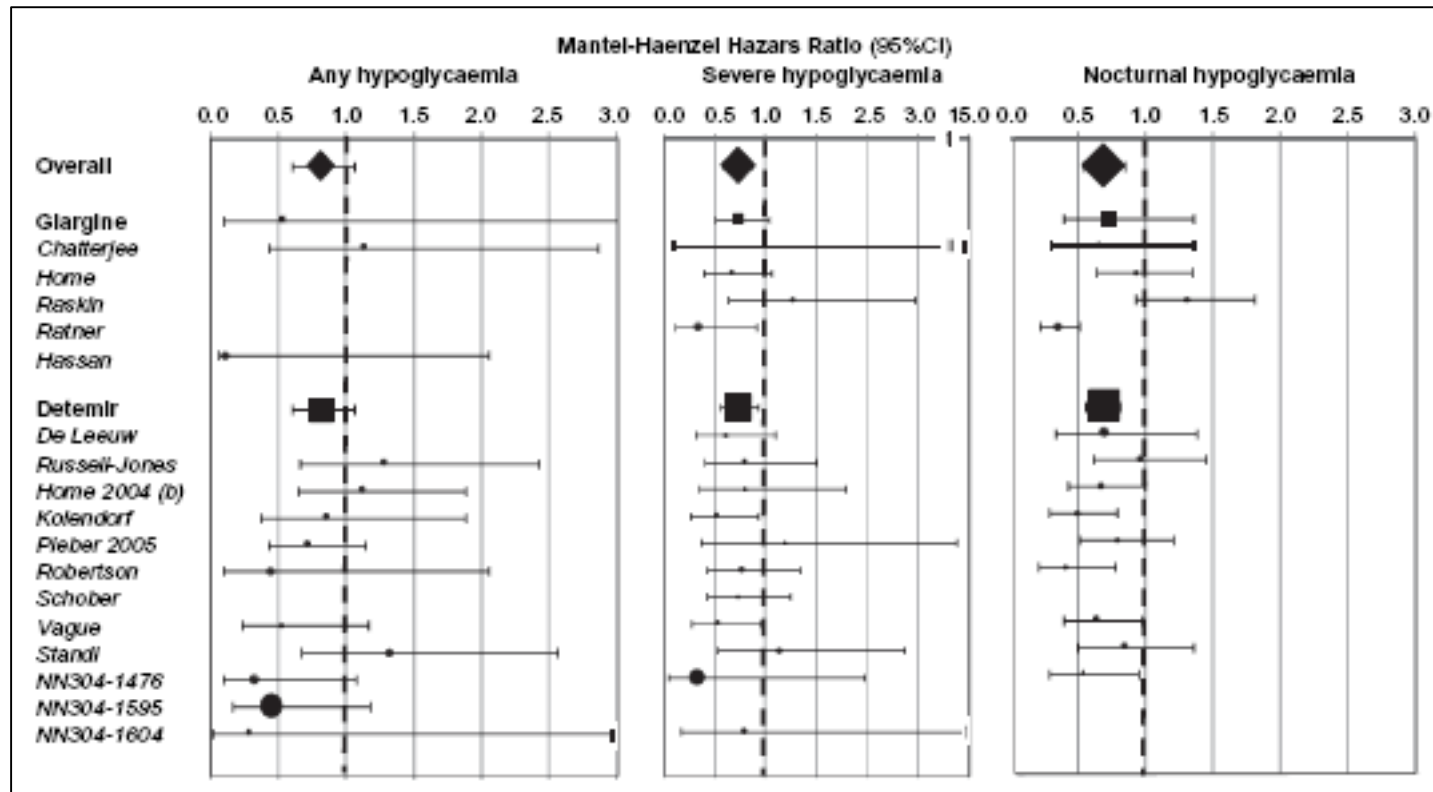
- There are strong clues, but no definitive evidence, that hyperglycemia increases the risk of foot ulcers and lower limb amputations in patients with diabetes.
- Therefore, it is advisable to maintain as good metabolic control as possible, in order to prevent ulcers and amputations

Improvements in the management of type 1 diabetes

- New insulin formulations

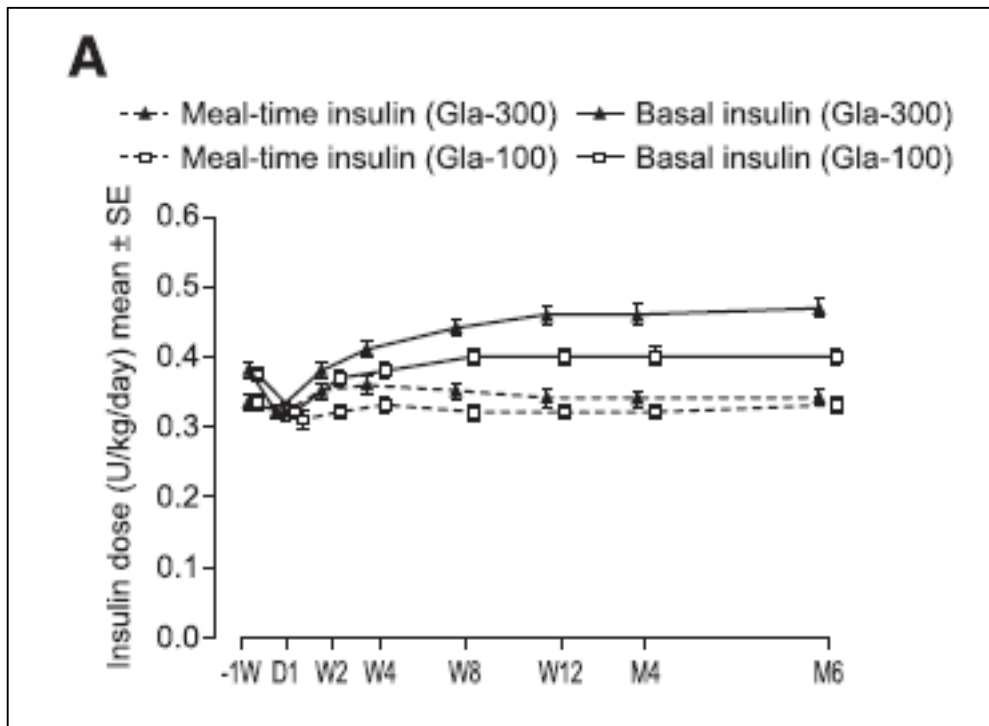
Long-acting analogues vs NPH insulin in T1DM

Meta-analysis of RCTs



Glargine U-300 vs Glargine U-100 in T1DM

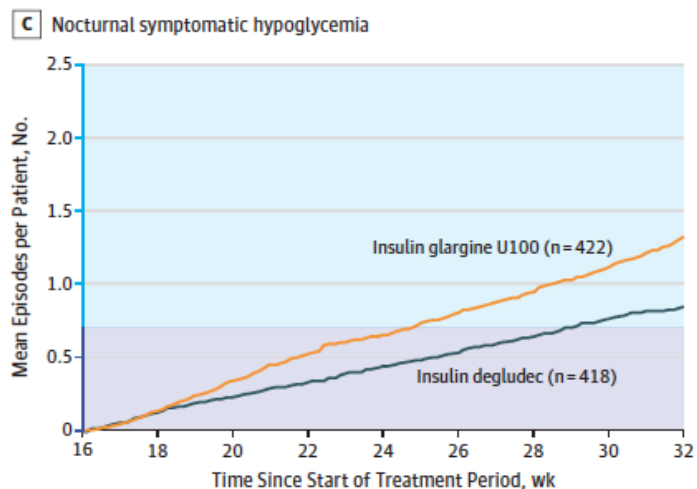
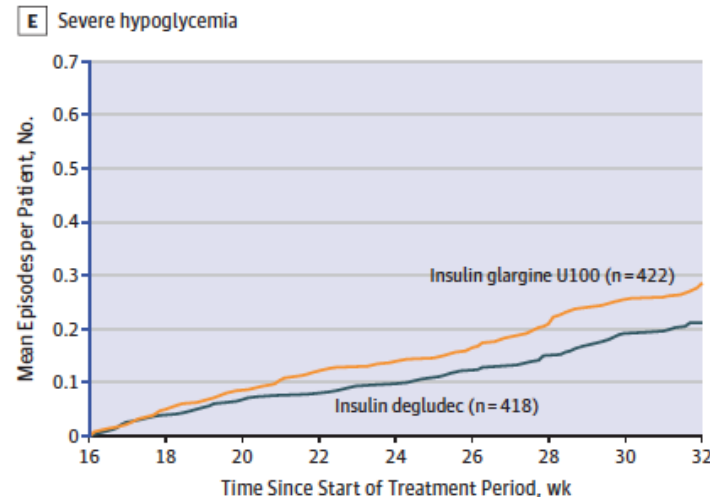
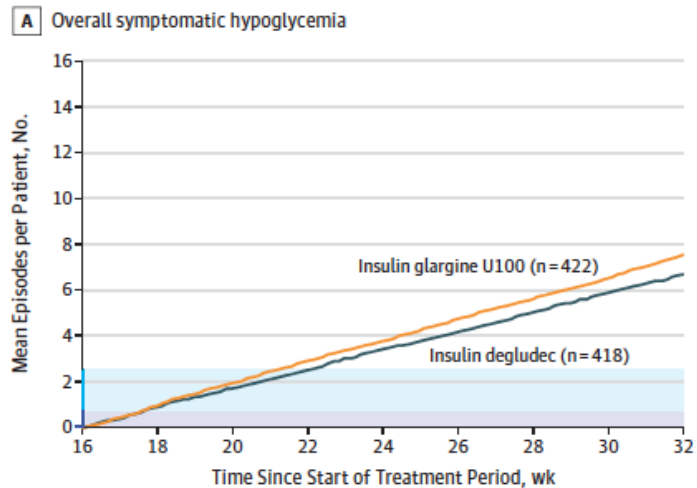
Results of the EDITION-4 trial



N=549 patients with T1DM
28-wk trial on T2DM patients on
basal-bolus therapy

Degludec vs Glargine U-100 in T1DM

Results of the SWITCH trial



Principal endpoint:

Non-inferiority for symptomatic hypoglycemia in the maintenance phase (wk 16-32)

N=501 patients with T1DM

Cross-over trial (32 wk for each treatment, 16 wk for titration and 16 for maintenance)

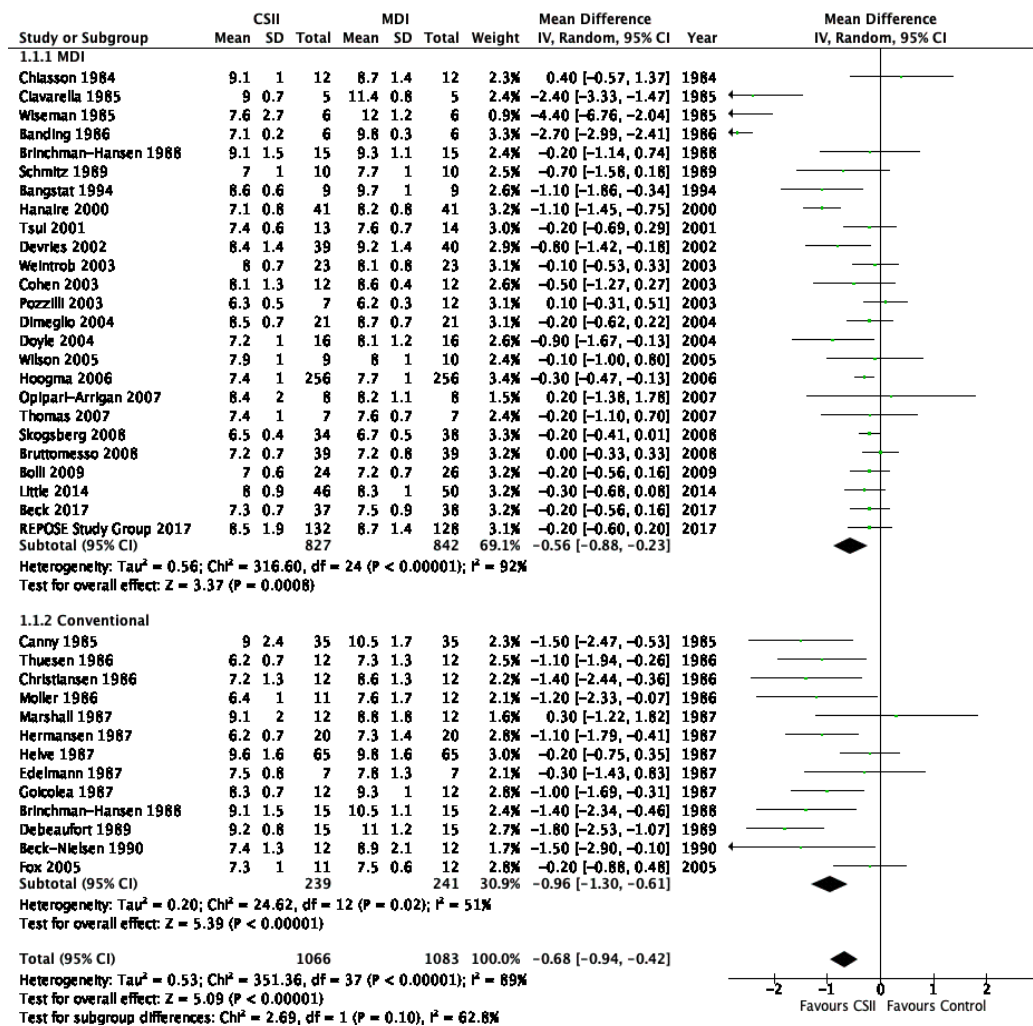
Improvements in the management of type 1 diabetes

- New insulin formulations
- New insulin pumps
- New glucose sensors
- Sensor-augmented pumps

CSII vs traditional injections in T1DM

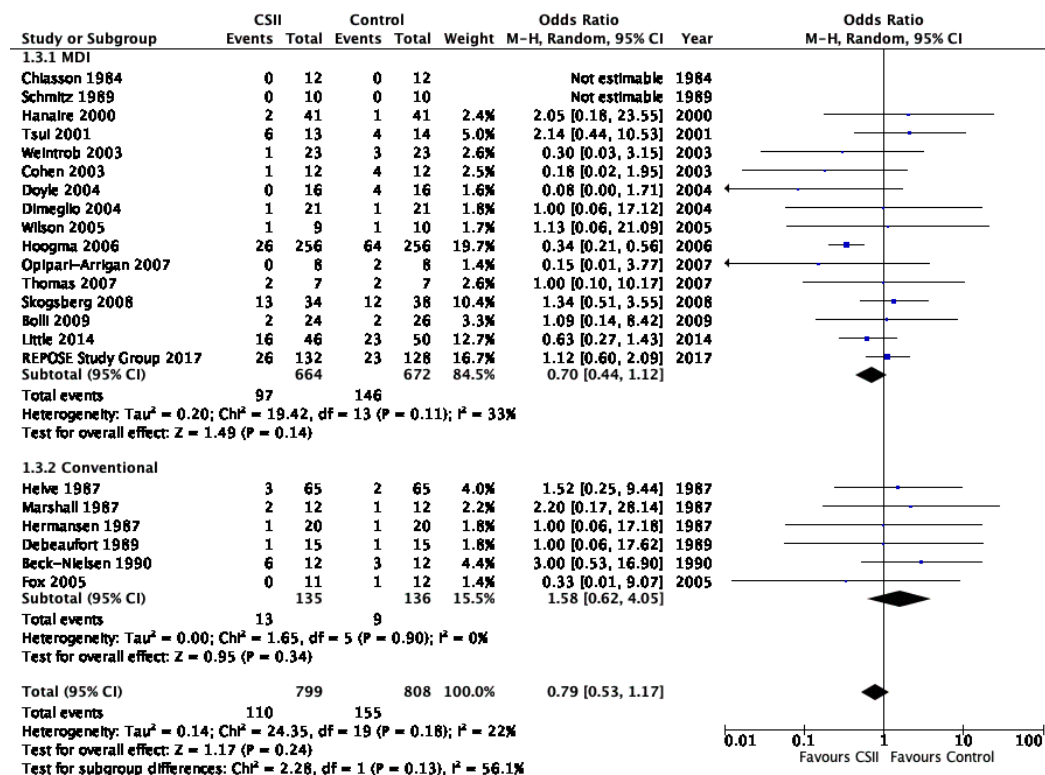
Meta-analysis of RCTs

HbA1c



RCTs with a duration of at least 12 wk,
Comparing with CSII with either MDI or
conventional insulin therapy

Severe hypo



CGM in T1DM: effect on HbA1c

Meta-analysis of RCTs

RCTs with a duration of at least 12 wk

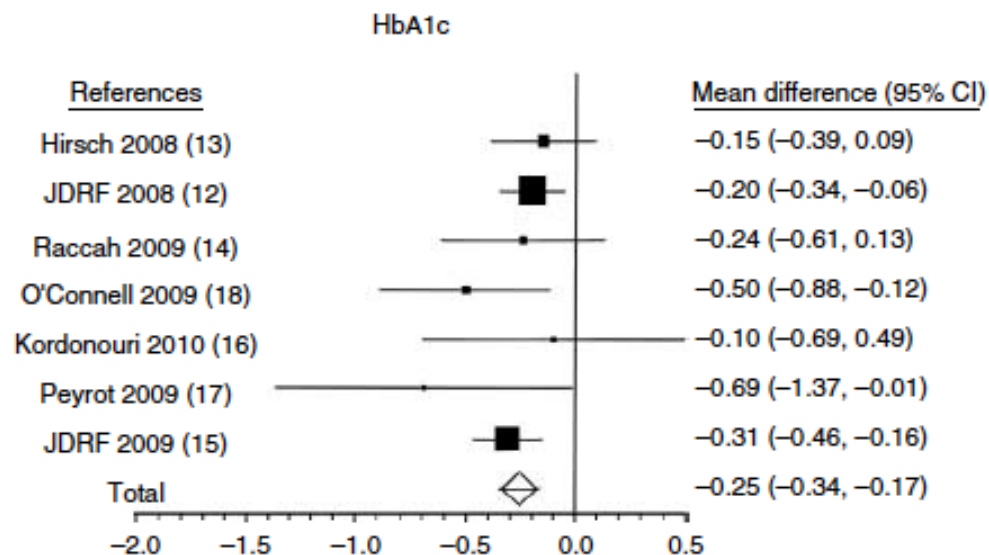


Figure 2 Mean difference and 95% CI of change in HbA1c (%) of patients treated with CSII or MDI in whom the RT-CGM and SBGM were compared with SBGM alone in the management of T1DM. Fixed-effect model. Heterogeneity $I^2=0\%$.

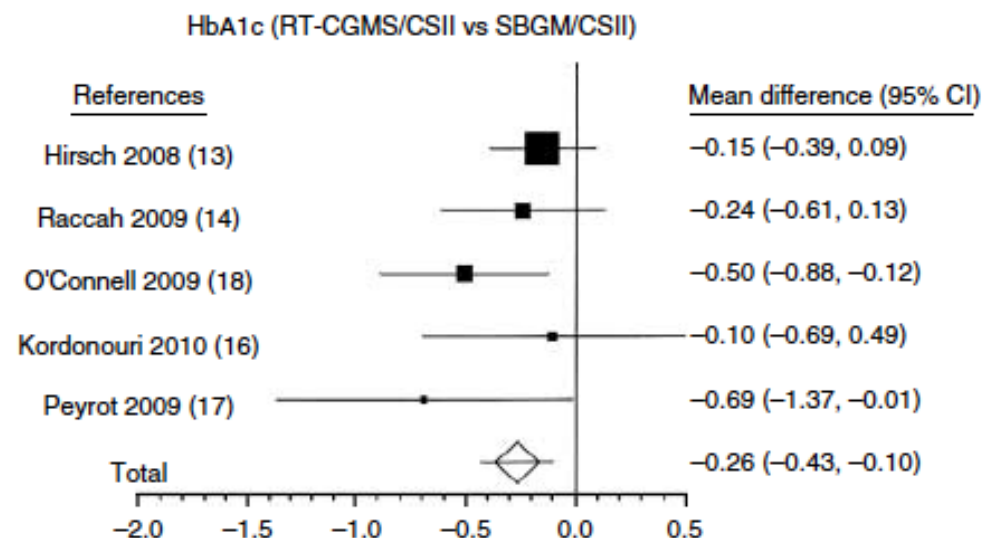
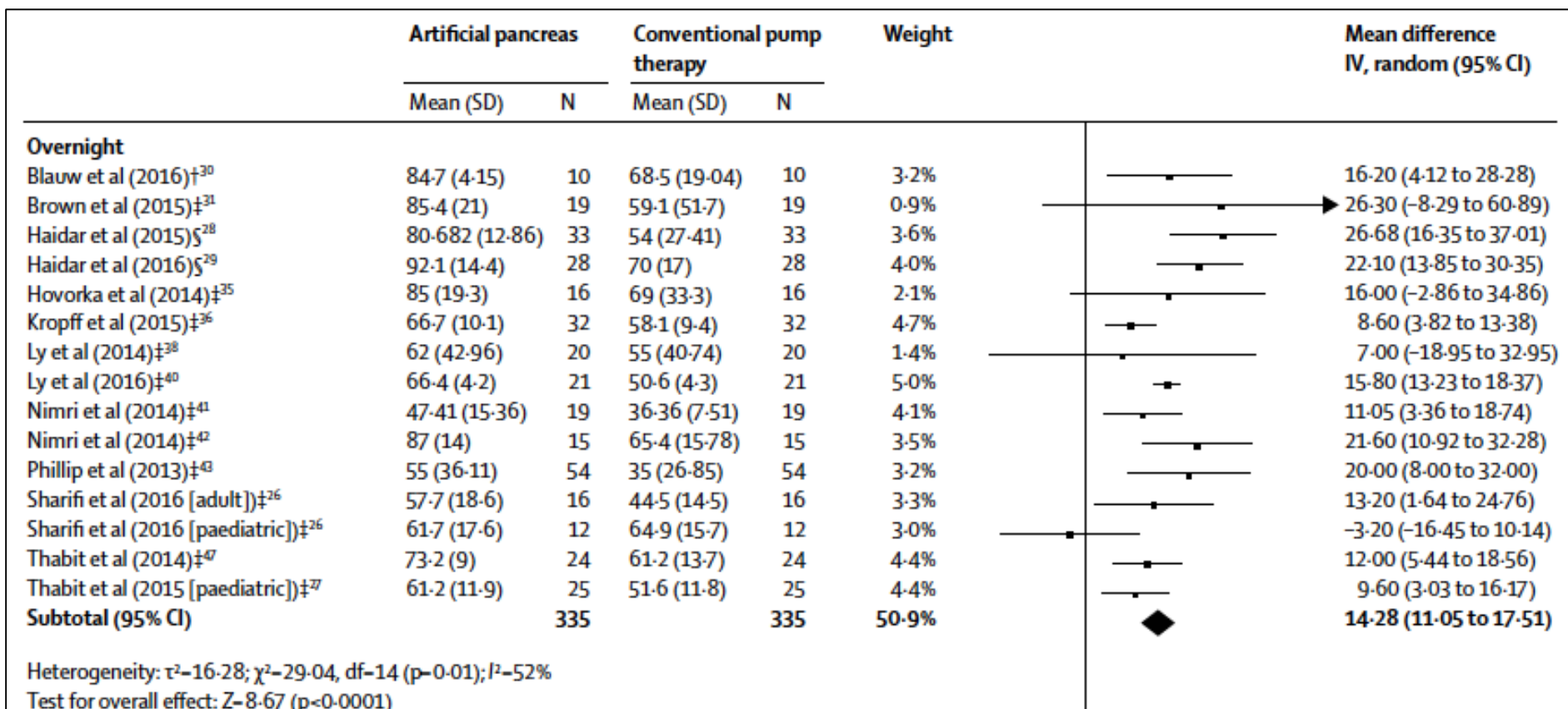


Figure 3 Mean difference and 95% CI of change in HbA1c (%) of patients managed with insulin pump combined with RT-CGM and SBGM in comparison with subjects treated with insulin pump and monitored with SBGM alone. Fixed-effect model. Heterogeneity $I^2=4\%$.

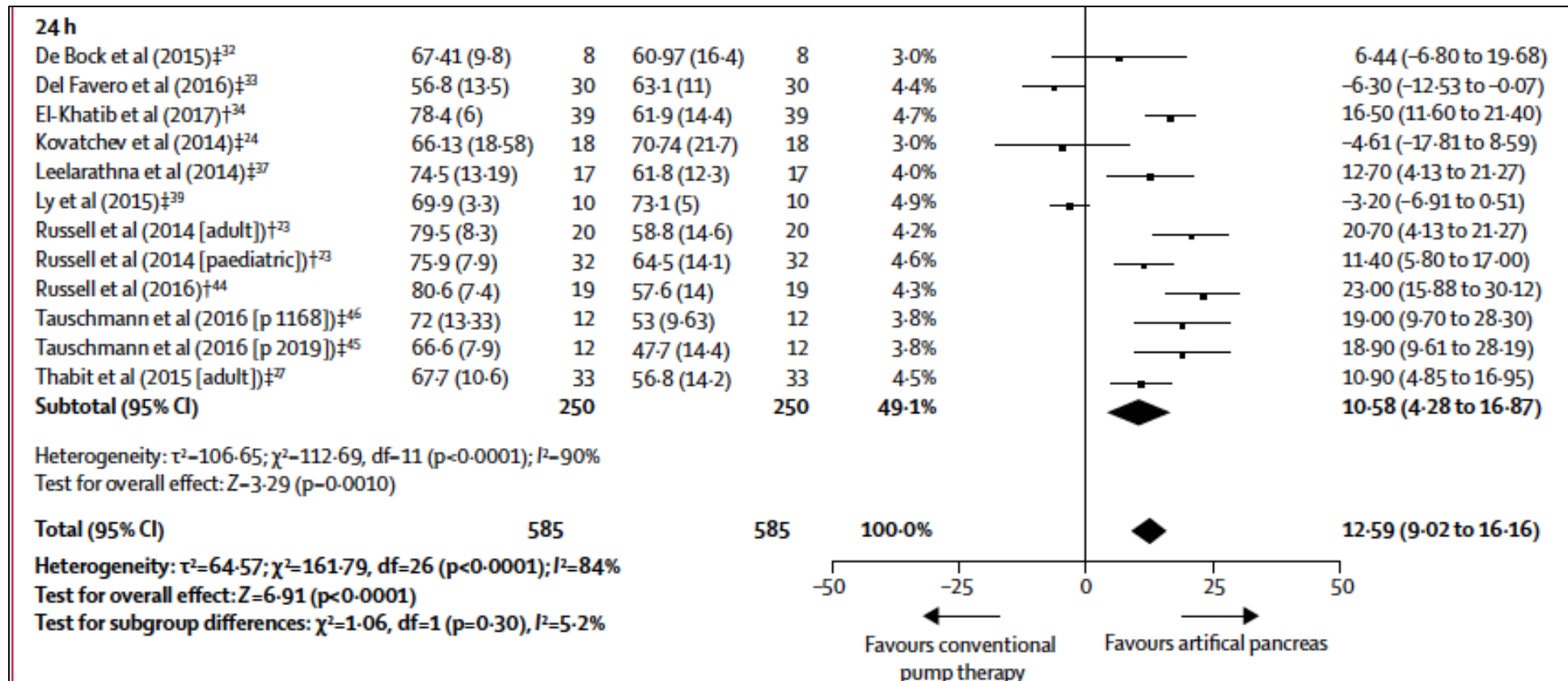
Artificial pancreas in T1DM: effect on time in target

Meta-analysis of RCTs



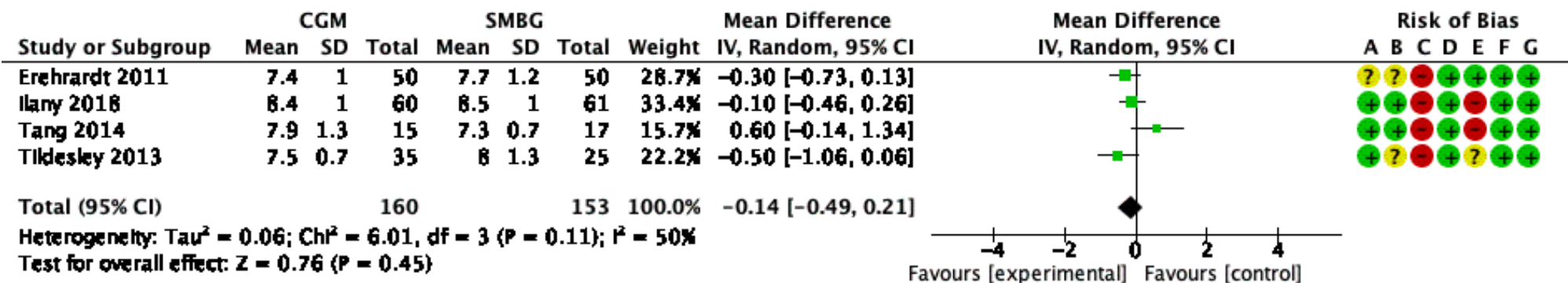
Artificial pancreas in T1DM: effect on time in target

Meta-analysis of RCTs



CSII vs MDI in T2DM on basal-bolus insulin therapy: HbA1c

Meta-analysis of RCTs

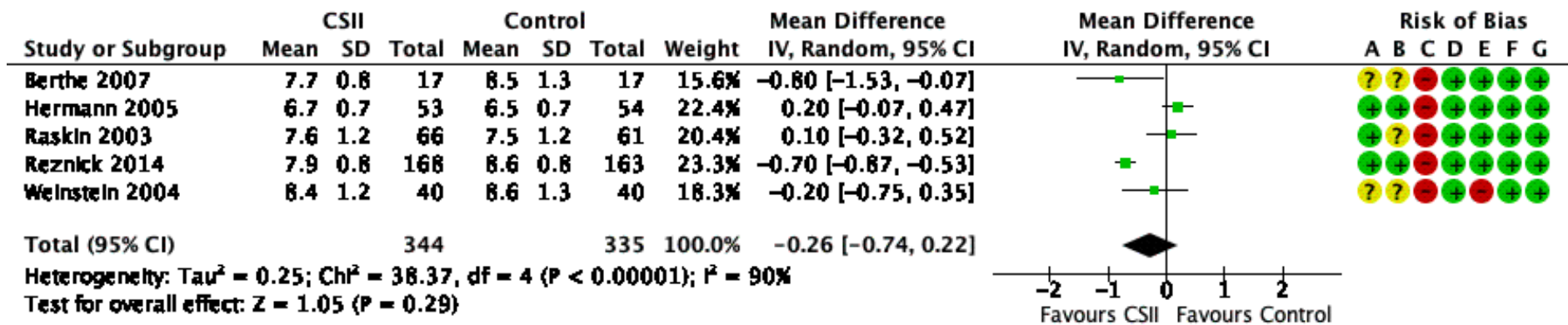


Risk of bias legend

- (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

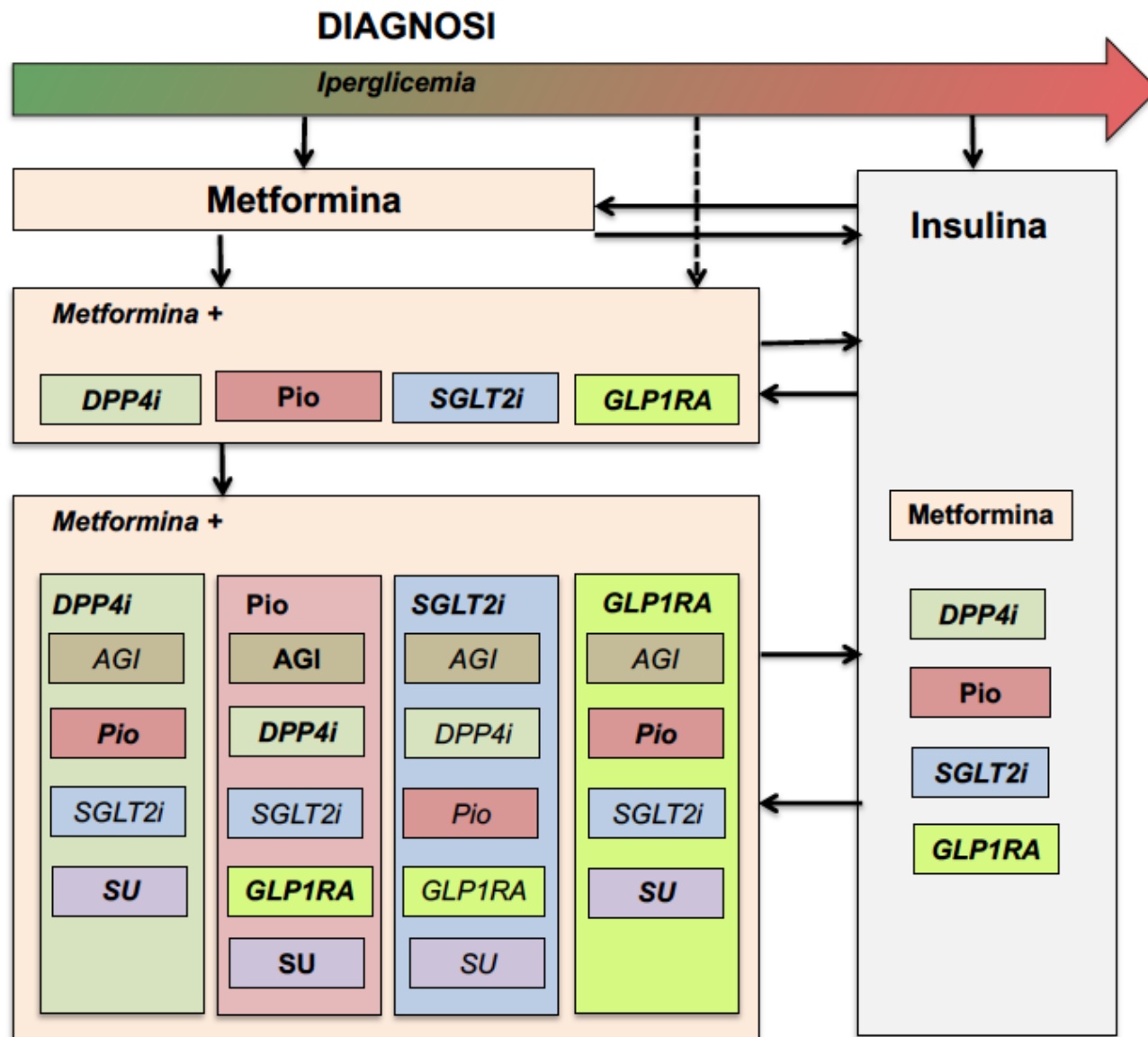
CSII vs MDI in T2DM on basal-bolus insulin therapy: HbA1c

Meta-analysis of RCTs



Risk of bias legend

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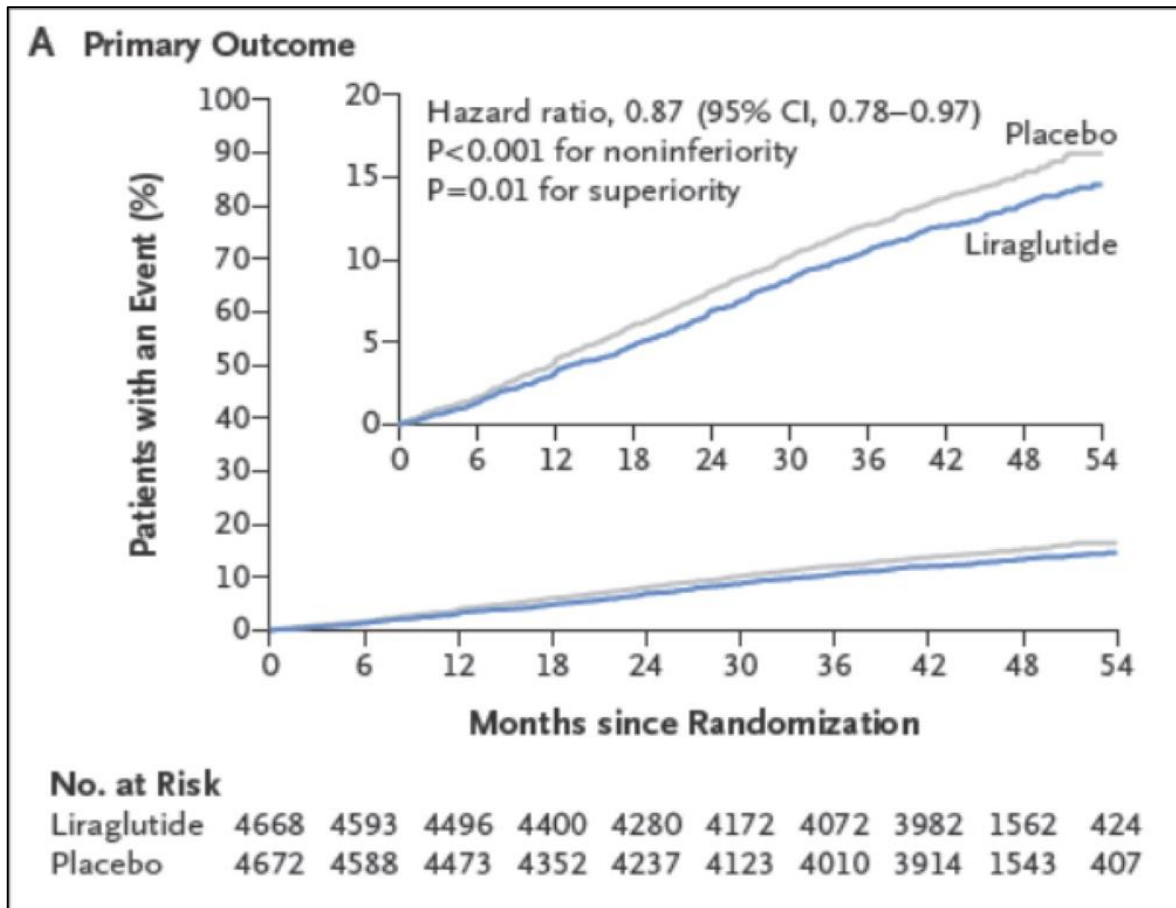


Target di emoglobina glicata

Pazienti	mmol/mol	42	48	53	58	64	69	75
Target generale								
<i>Trattamento con sulfaniluree/glinidi/insulina</i>								
Anziani o comorbilità con aspettativa di vita ridotta								
<i>Trattamento con sulfaniluree/glinidi/insulina</i>								
<i>con fragilità/comorbilità/decadimento cognitivo</i>								
	%	6.0	6.5	7.0	7.5	8.0	8.5	9.0

Liraglutide: effect on major cardiovascular events

Results of the LEADER trial



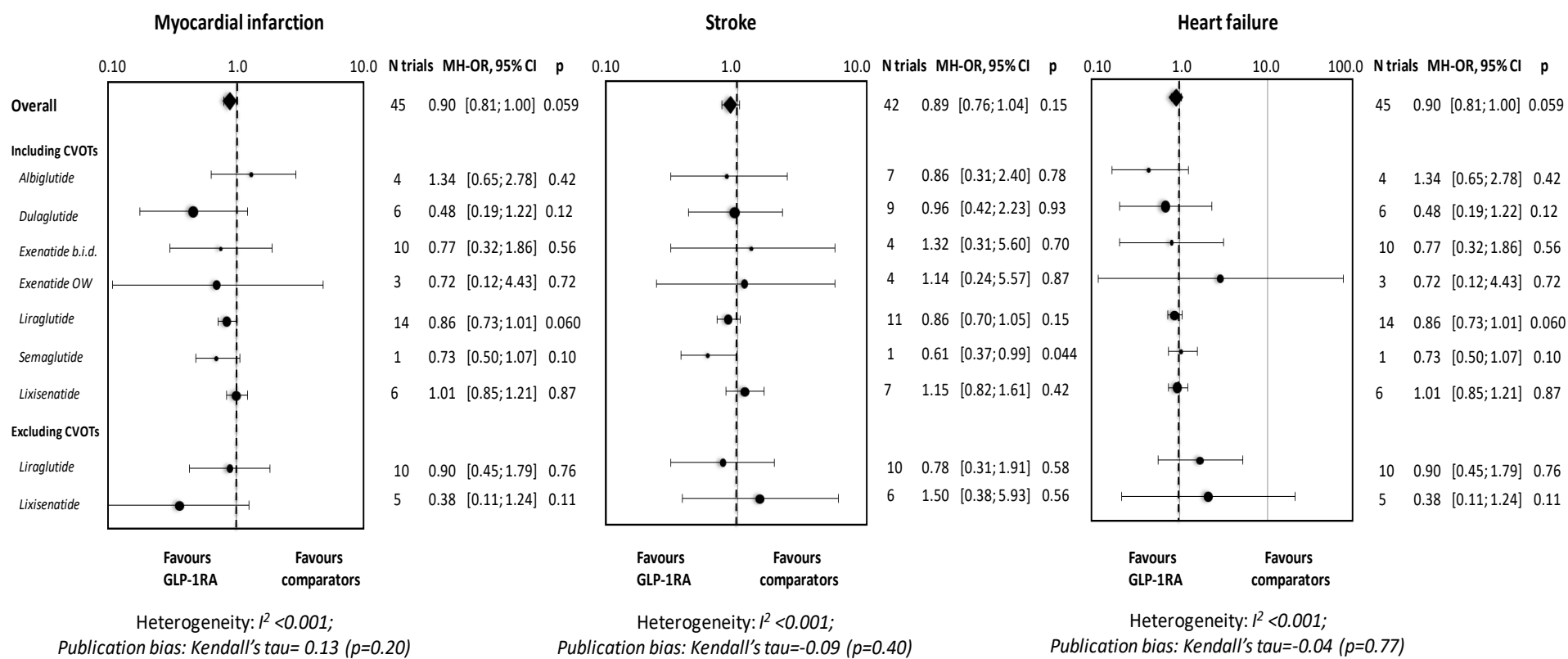
Principal endpoint:

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

9,340 T2DM patients with prior cardiovascular disease and/or high CV risk, Liraglutide vs placebo 1:1. Follow-up: 4 y

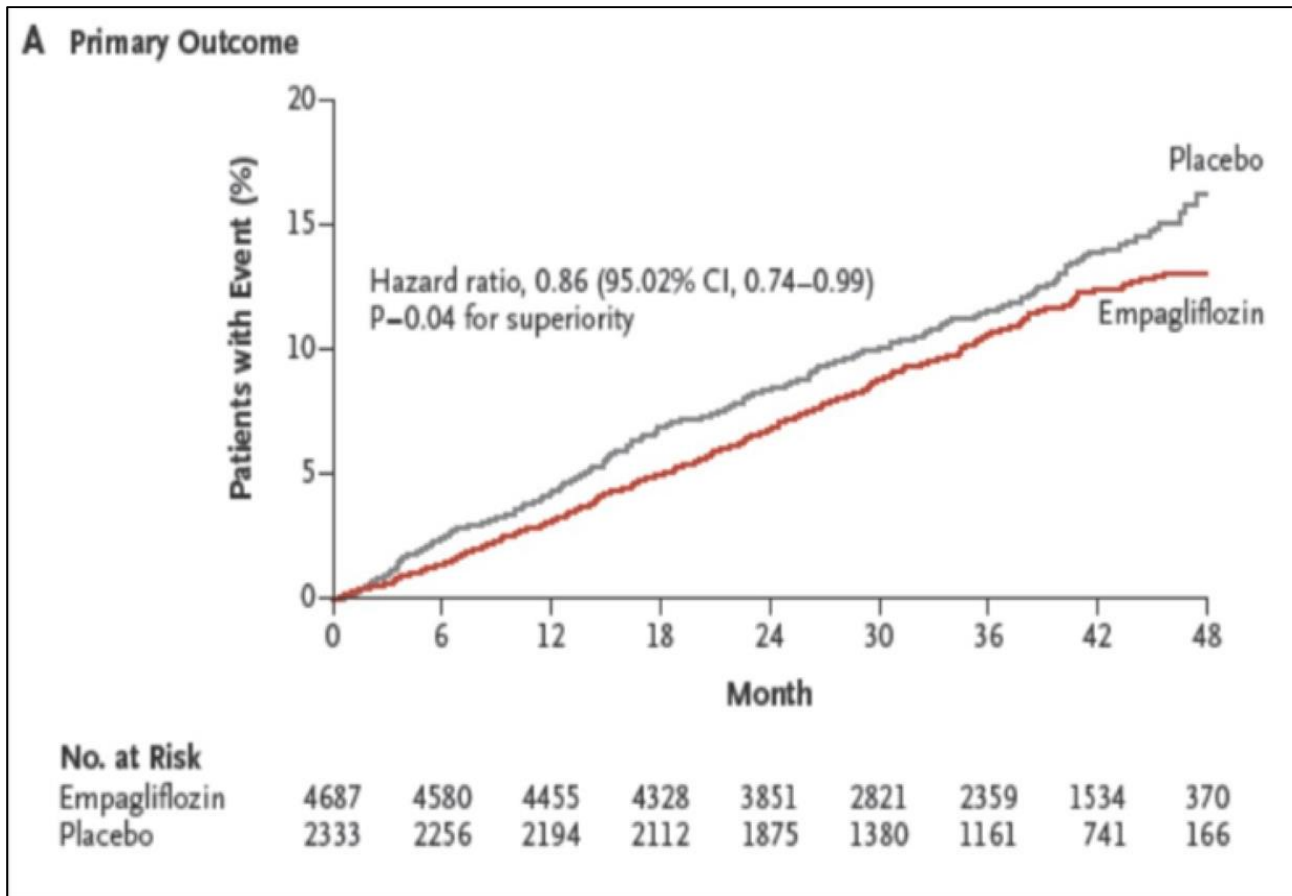
GLP1RA: effect on major cardiovascular events

Metanalysis of available RCTs



Empagliflozin: effect on major cardiovascular events

Results of the EMPAREG-OUTCOME trial



Principal endpoint:

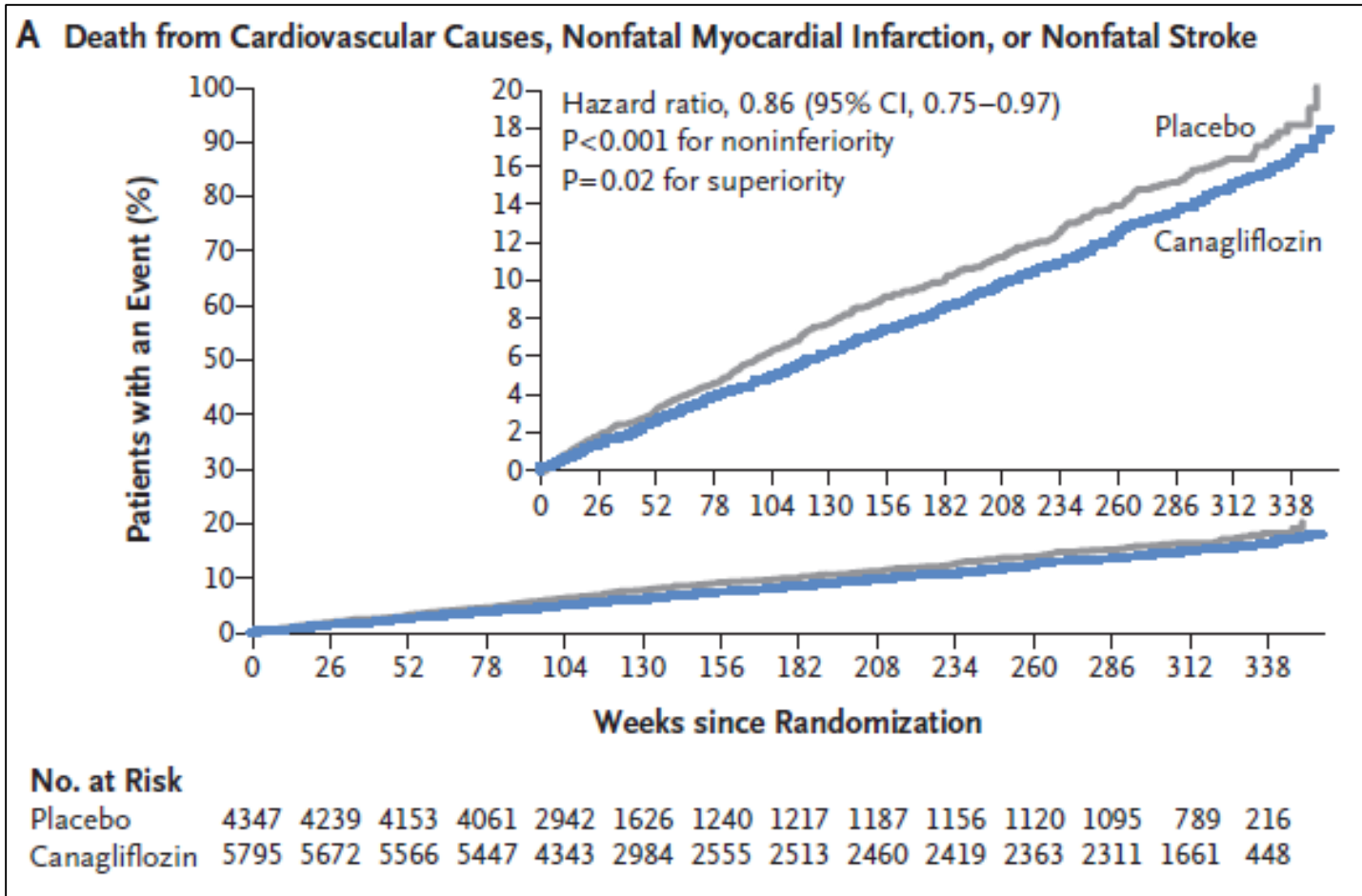
3-point MACE

(nonfatal MI, nonfatal stroke, and cardiovascular death)

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

Canagliflozin: effect on major cardiovascular events

Results of the CANVAS and CANVAS-R trial



Principal endpoint:

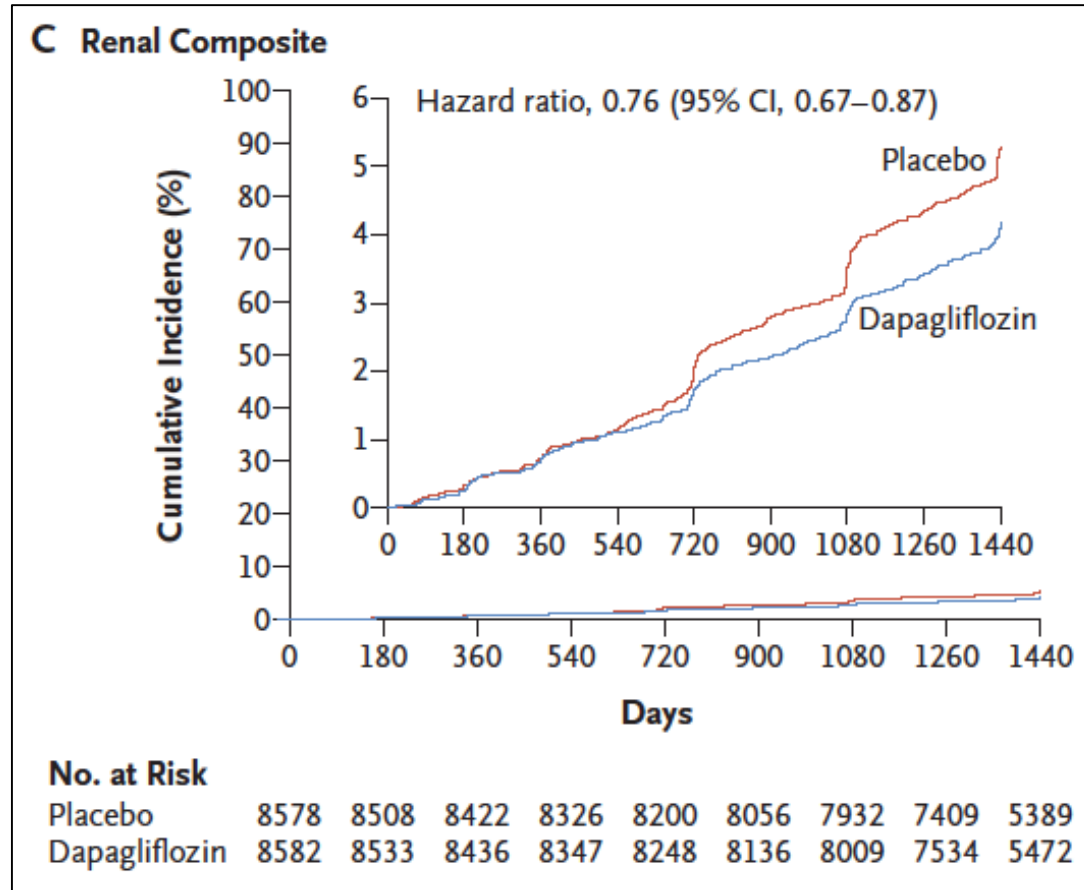
3-point MACE

(nonfatal MI, nonfatal stroke, and cardiovascular death)

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

Dapagliflozin: effect on renal outcomes*

Results of the DECLARE trial



Principal endpoints:

- 3-point MACE (nonfatal MI, nonfatal stroke, and cardiovascular death)
- Composite of HHF and CV death

17,160 T2DM patients with prior CVD (40.6%) or high CV risk, dapagliflozin vs placebo 1:1. Follow-up: 4.2 y

* Composite of decrease >40% of GFR, end-stage renal disease, renal death

Canagliflozin: effect on renal outcomes

Results of the CANVAS and CANVAS-R trial

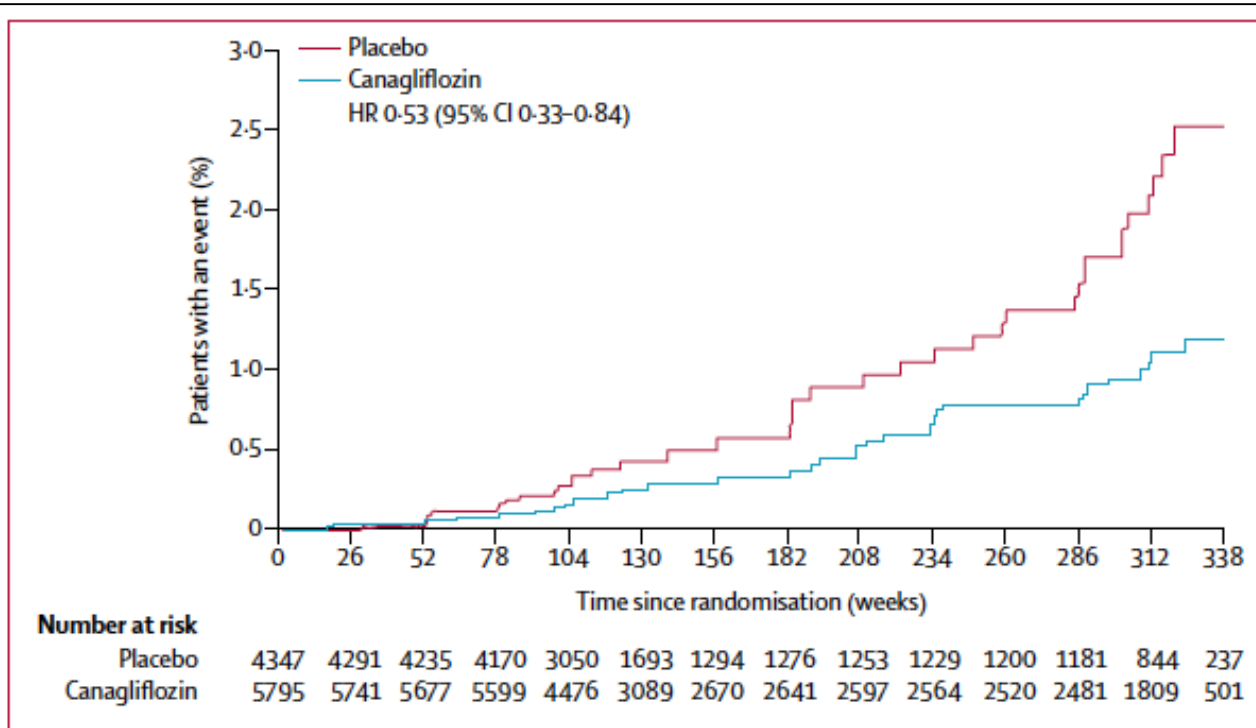


Figure 1: Effects of canagliflozin versus placebo on the composite outcome of doubling of serum creatinine, ESKD, or death from renal causes in the CANVAS Program

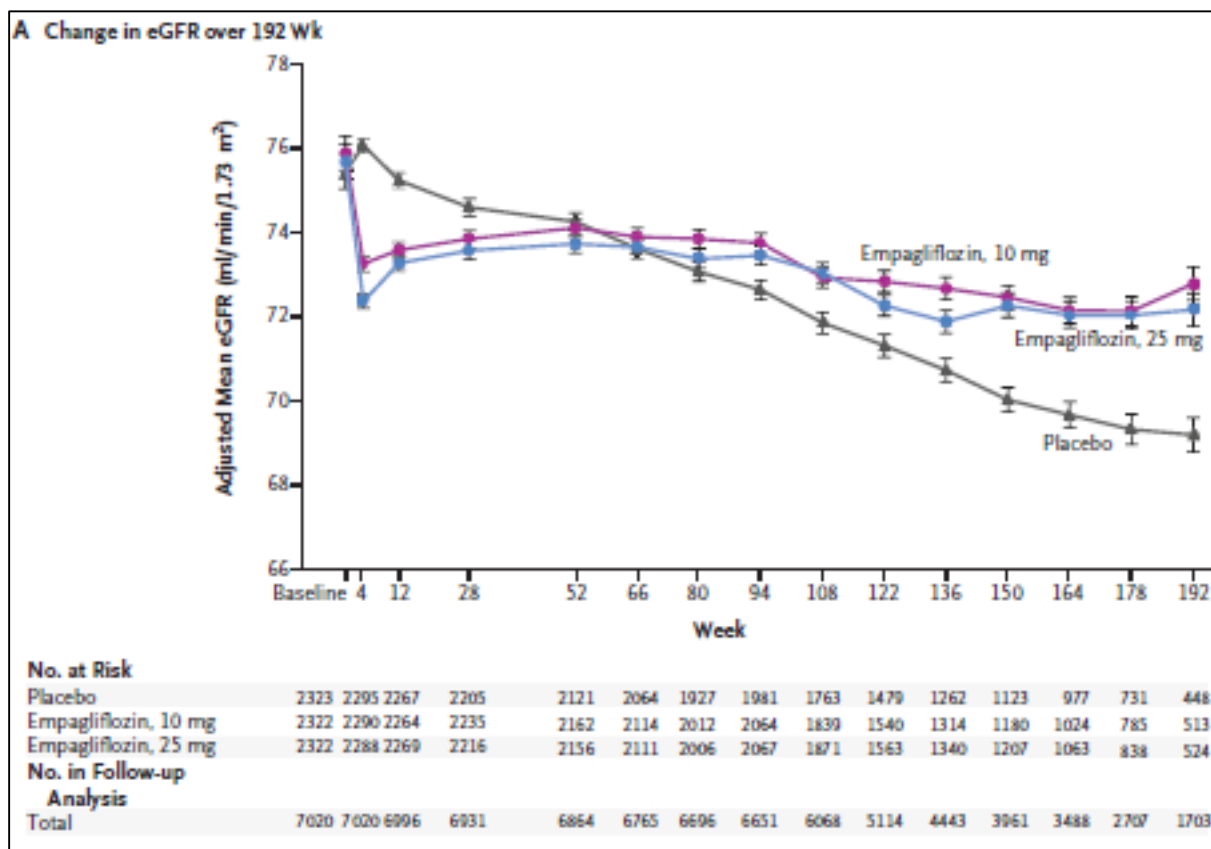
Principal endpoint:

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

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

Empagliflozin: effect on renal function

Results of the EMPAREG-OUTCOME trial



Principal endpoint:

3-point MACE

(nonfatal MI, nonfatal stroke, and cardiovascular death)

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

Canagliflozin: adverse events

Results of the CANVAS and CANVAS-R trial

Event	Canagliflozin <i>event rate per 1000 patient-yr</i>	Placebo	P Value†
All serious adverse events	104.3	120.0	0.04
Adverse events leading to discontinuation	35.5	32.8	0.07
Serious and nonserious adverse events of interest recorded in the CANVAS Program			
Acute pancreatitis (adjudicated)	0.5	0.4	0.63
Cancer			
Renal cell	0.6	0.2	0.17
Bladder	1.0	1.1	0.74
Breast	3.1	2.6	0.65
Photosensitivity	1.0	0.3	0.07
Diabetic ketoacidosis (adjudicated)	0.6	0.3	0.14
Amputation	6.3	3.4	<0.001

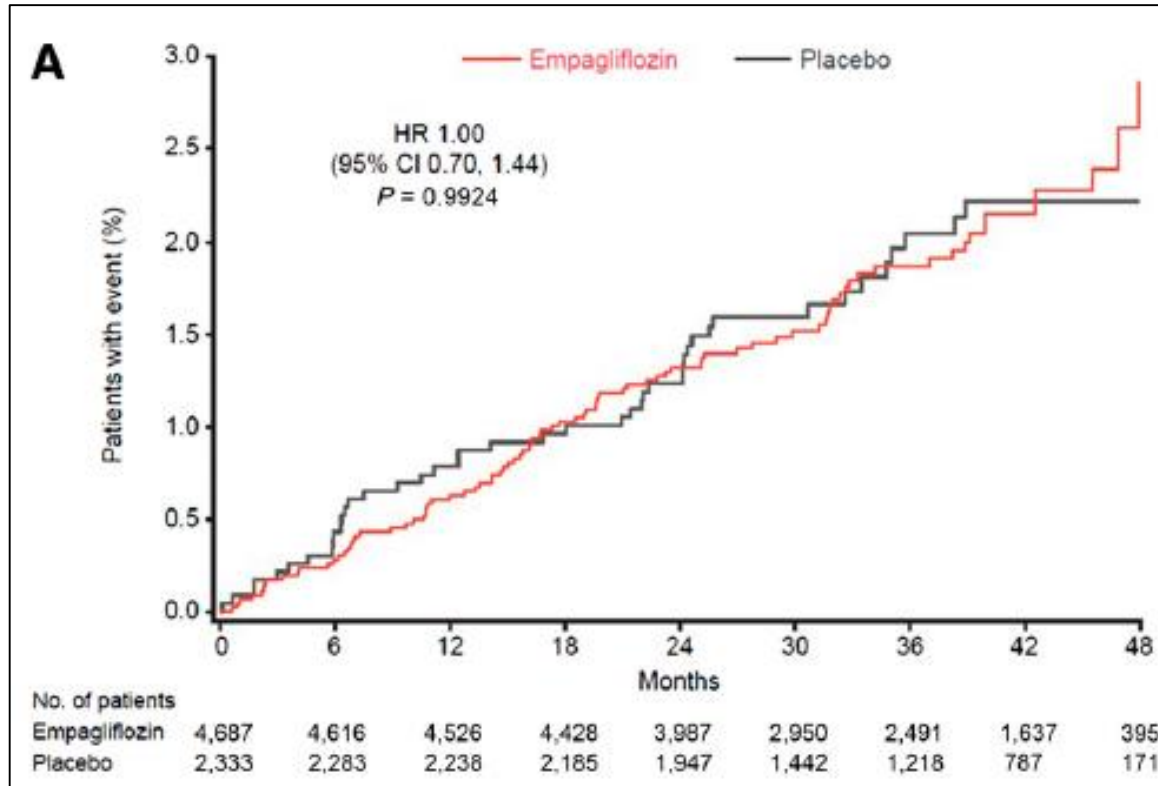
Principal endpoint:

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

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

Empagliflozin: effect on amputations

Results of the EMPAREG-OUTCOME trial



Principal endpoint:

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

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

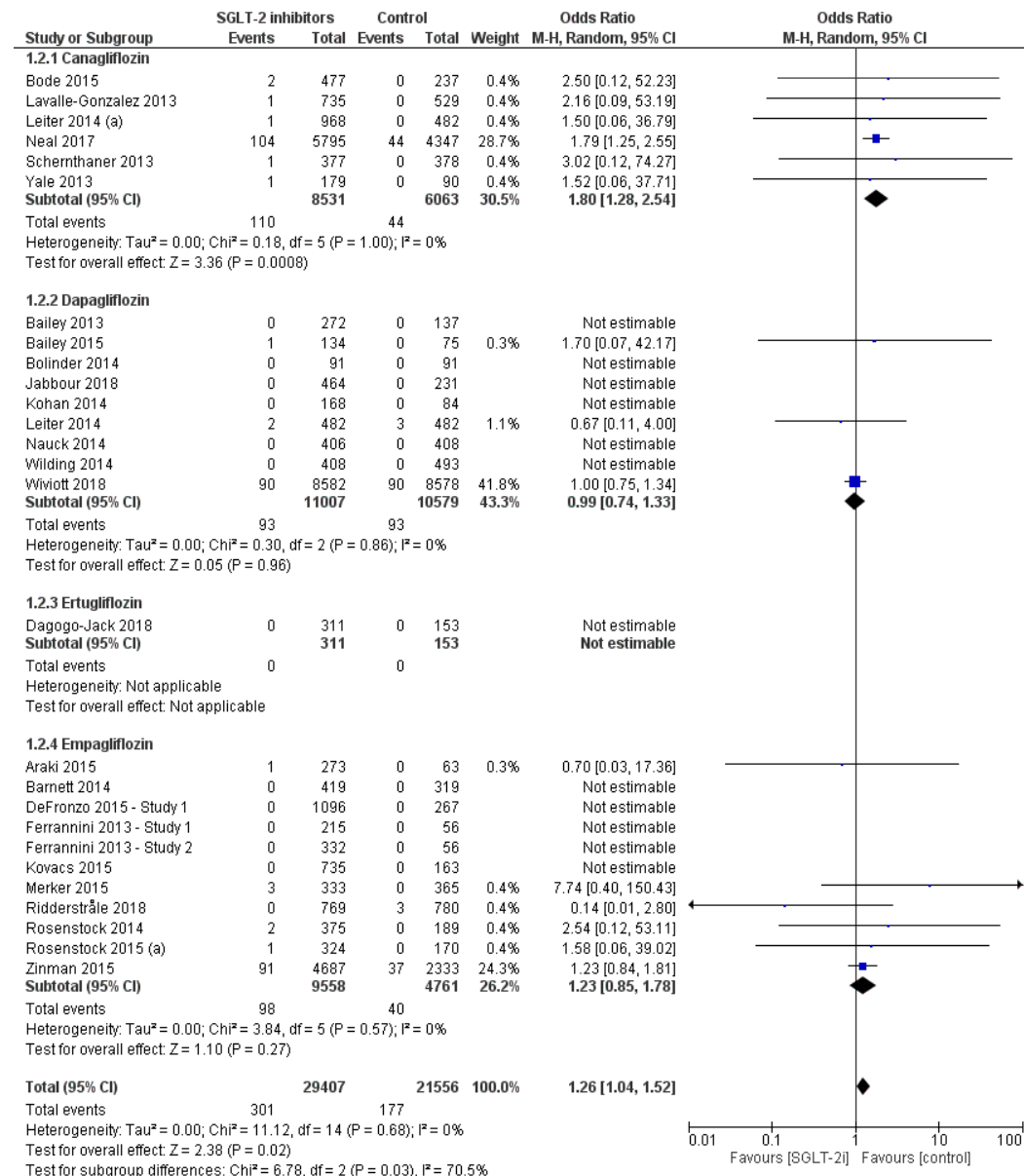
Dapagliflozin: effect on renal outcomes*

Results of the DECLARE trial

Event	Dapagliflozin (N = 8574)	Placebo (N = 8569)	Hazard Ratio (95% CI)	P Value
	no. (%)			
Serious adverse event	2925 (34.1)	3100 (36.2)	0.91 (0.87–0.96)	<0.001
Adverse event leading to discontinuation of trial regimen	693 (8.1)	592 (6.9)	1.15 (1.03–1.28)	0.01
Major hypoglycemic event	58 (0.7)	83 (1.0)	0.68 (0.49–0.95)	0.02
Diabetic ketoacidosis	27 (0.3)	12 (0.1)	2.18 (1.10–4.30)	0.02
Amputation	123 (1.4)	113 (1.3)	1.09 (0.84–1.40)	0.53

SGLT2 inhibitors: effect on amputations

Meta-analysis of RCTs



Dicembrini I, et al. *Submitted*

Conclusions (2)

- New technologies and new treatments allow a stricter glycemic control with lower hypoglycemic risk
- Some treatments can have additional benefits on cardiovascular and renal outcomes beyond glycemic control
- There are clues, but no definitive evidence, that new technologies and some new treatments can reduce the risk of ulcers and amputations.
- The safety of new treatments for lower limb outcomes needs to be carefully assessed.