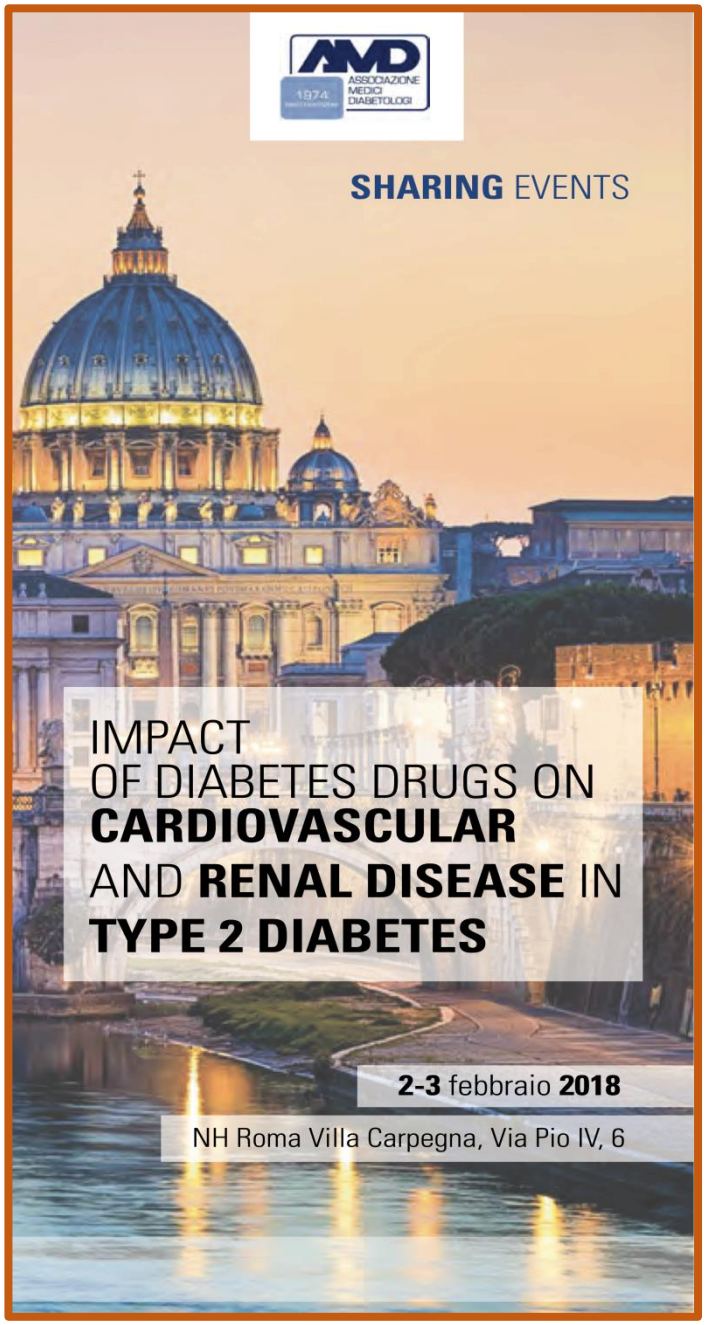


Impatto dei farmaci antidiabetici sullo scompenso cardiaco

Riccardo Candido
S.S.D. Gestione Rete Diabetologica Aziendale
Azienda Sanitaria Universitaria Integrata di Triste

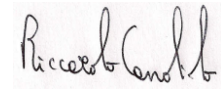
Il sottoscritto Riccardo Candido

DICHIARA

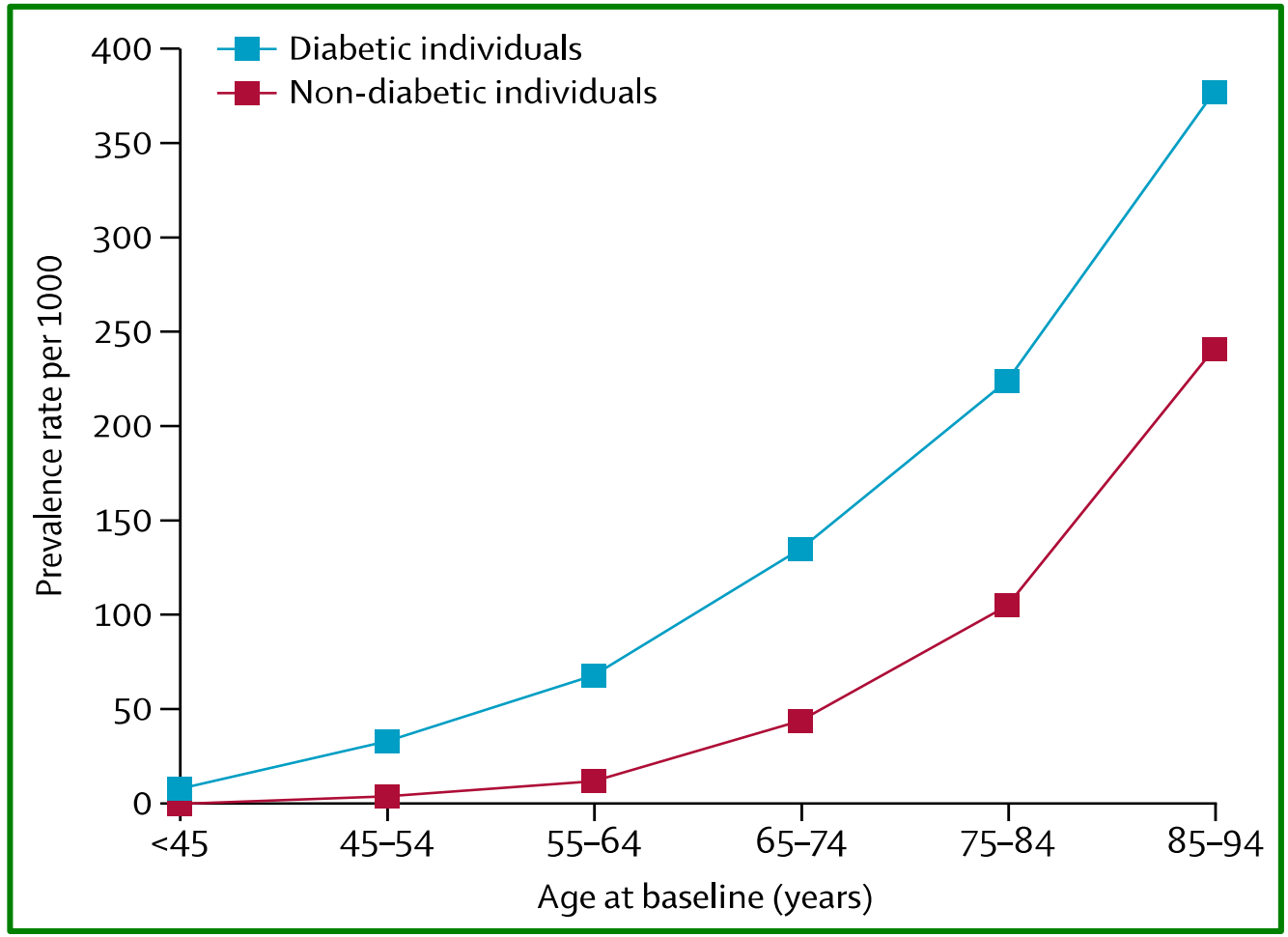
che negli ultimi 2 anni ha avuto i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:

Novo Nordisk, Roche Diagnostics, Johnson & Johnson Medical, Eli Lilly Italy, Boehringer Ingelheim, Merck Sharp & Dohme, Sanofi-Aventis, Takeda

In fede
Riccardo Candido

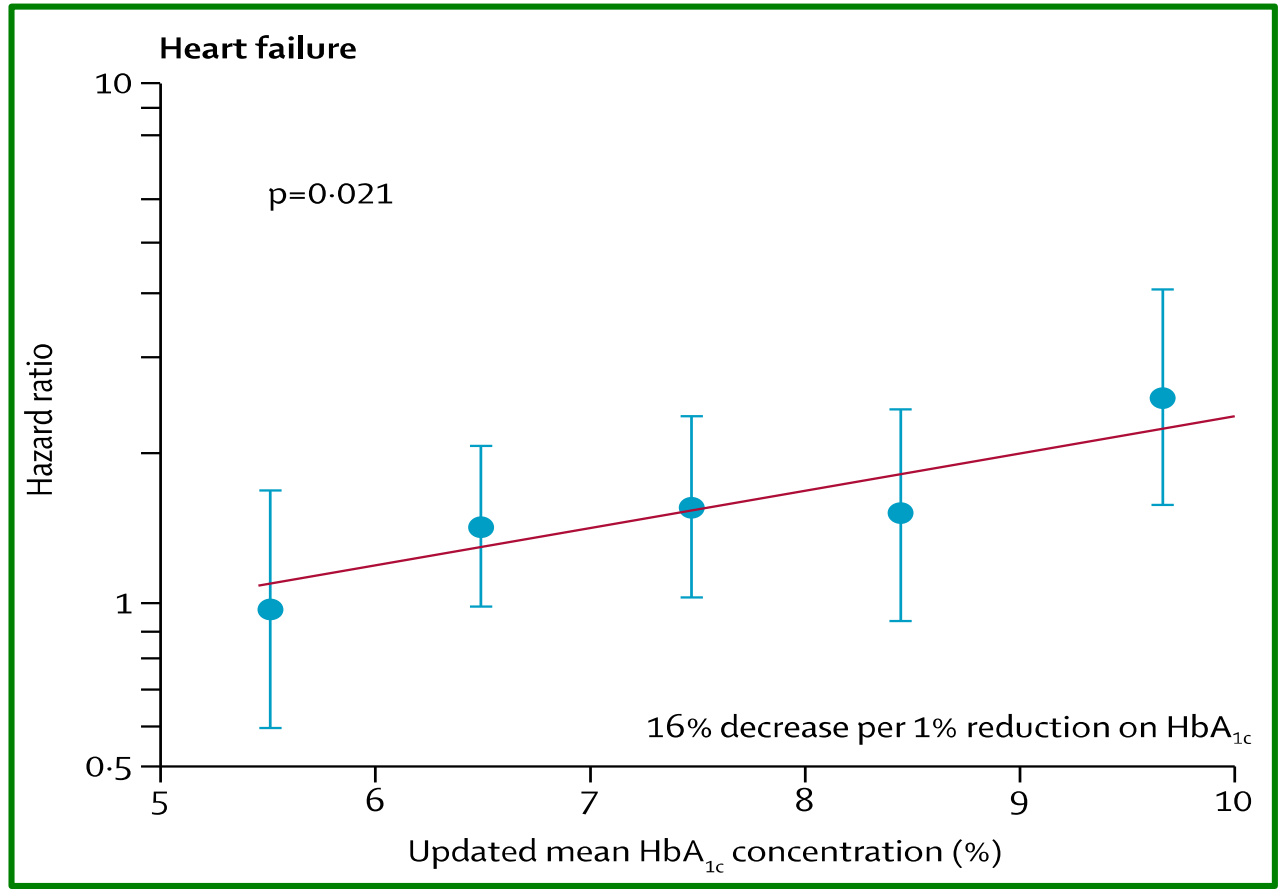


Age-associated prevalence of heart failure in diabetic and non-diabetic individuals



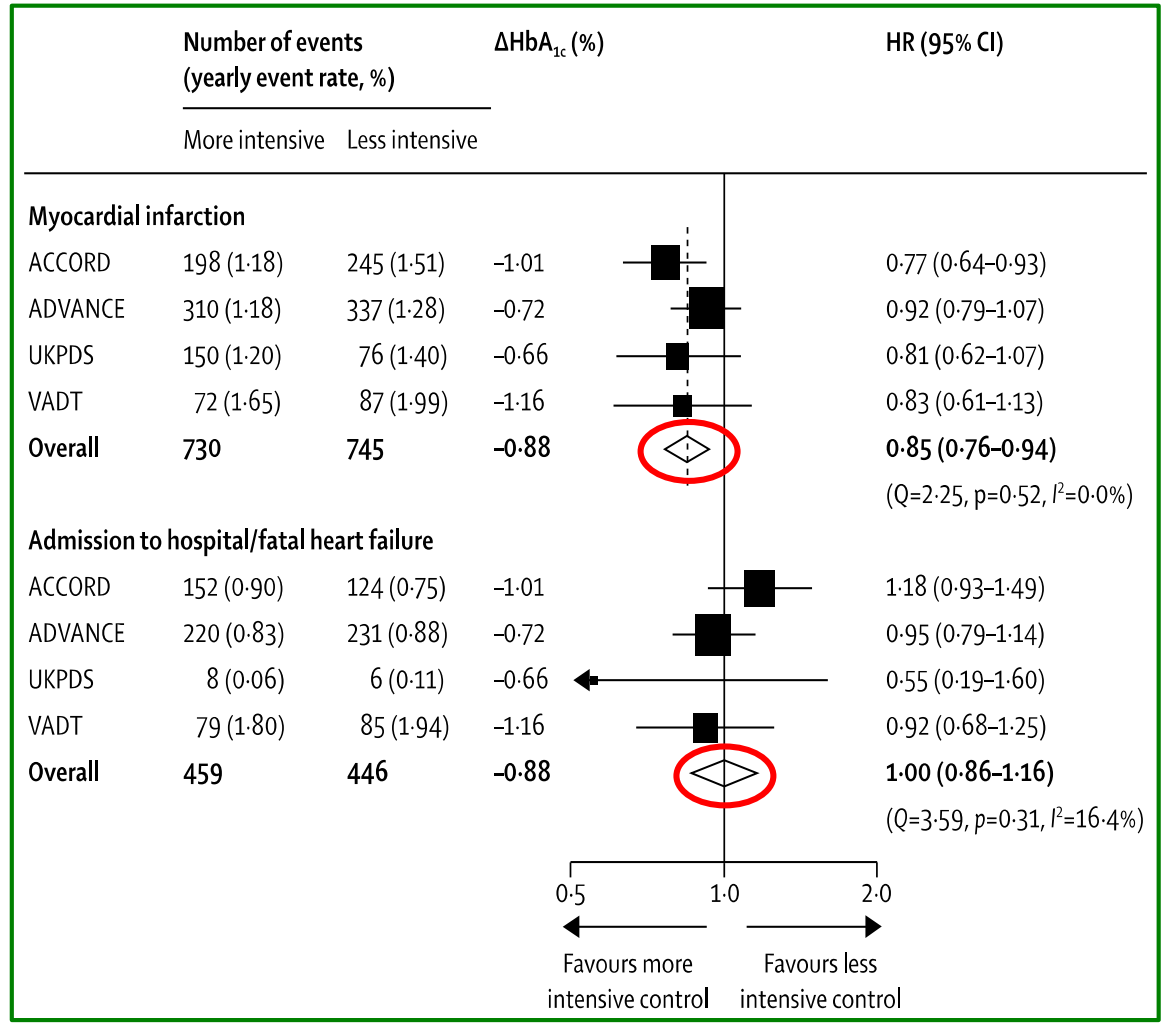
Nichols GA et al. Diabetes Care 2001; 24: 1614–19.

Hazard ratios (HRs), with 95% CIs as floating absolute risks, as an estimate of association between category of updated mean haemoglobin A1c (HbA1c) concentration and heart failure



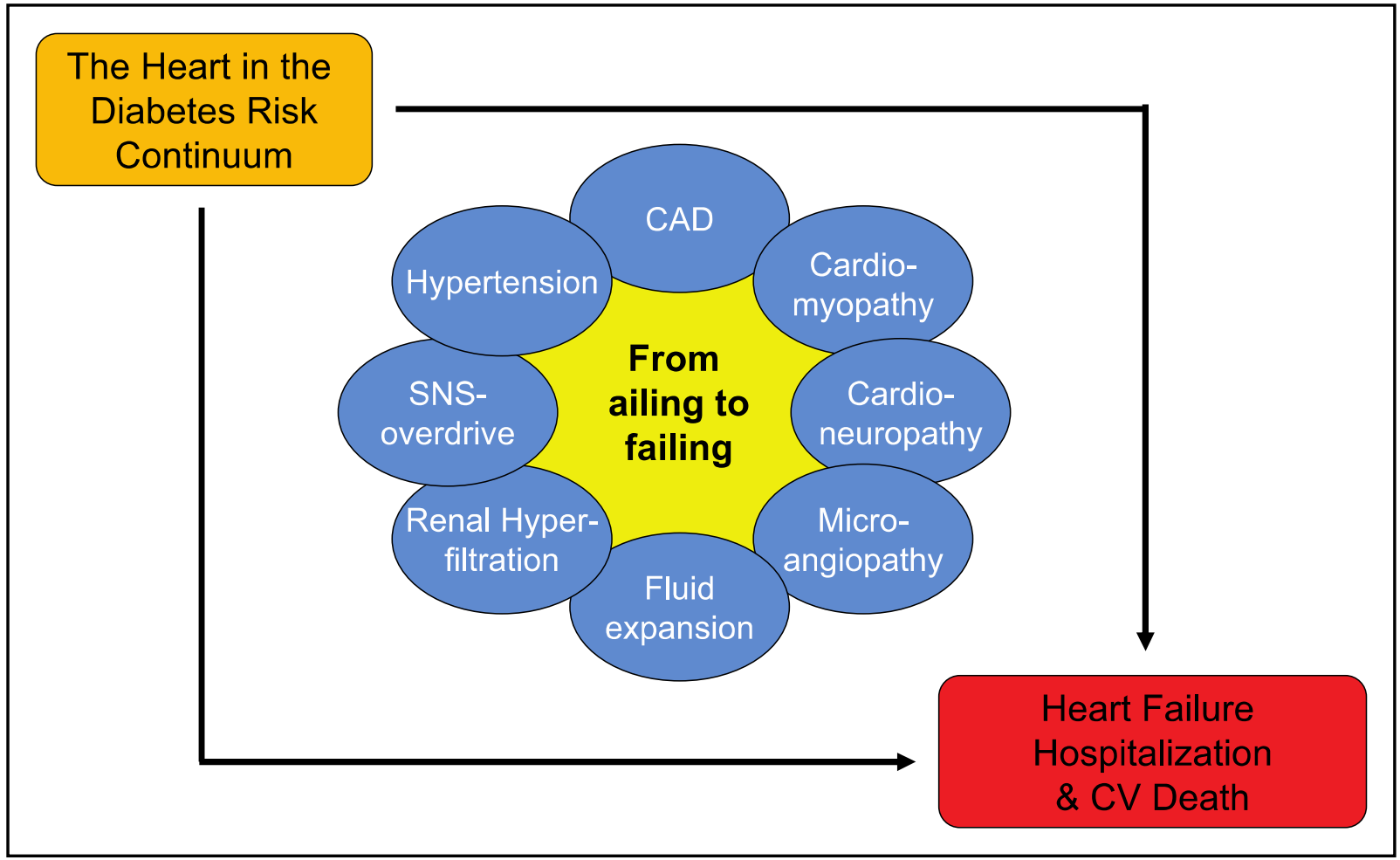
Stratton IM et al. BMJ 2000; 321: 405–12.

Effects in trials of more versus less intensive glycaemic control on myocardial infarction (fatal or non-fatal) and heart failure resulting in admission to hospital or death



Turnbull FM et al. Diabetologia 2009; 52: 2288–98

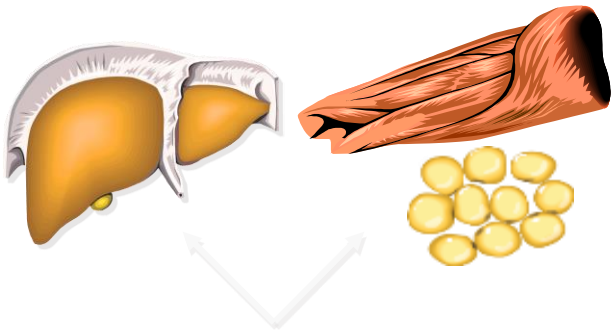
Heart failure in type 2 diabetes mellitus: the ominous octet



Standl E. et al. *Circ Res*. 2016;118:1830-1843

Options for Antidiabetic Treatment

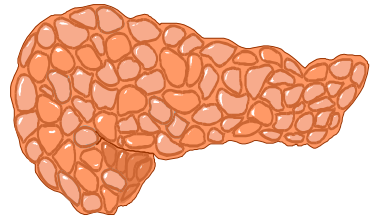
Insulin Resistance



Metformin

Pioglitazone

Insulin Secretion



Glucose independent

Sulfonylurea

Glinides

Exogenous Insulin

Glucose dependent

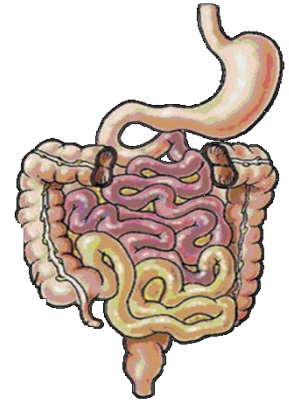
DPP-4 Inhibitors

Sitagliptin, Vildagliptin, Saxagliptin, Linagliptin, Alogliptin

GLP-1 Mimetics

Exenatide, Liraglutide, Lixisenatide Dulaglutide

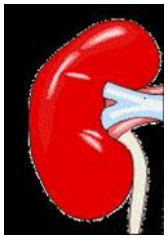
Inhibtion of Glucose Reabsorption



α-Glucosidase Inhibitors

Acarbose

Inhibition of Renal Glucose Reabsorption

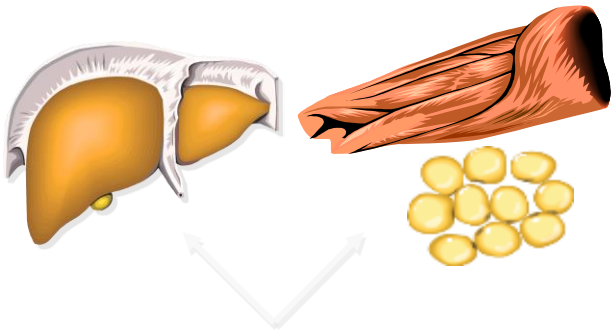


SGLT2-Inhibitors

Dapagliflozin, Canagliflozin Empagliflozin

Options for Antidiabetic Treatment

Insulin Resistance



Metformin

Pioglitazone

Original Article

Circ Heart Fail. 2013;6:395-402

Comparative Safety and Effectiveness of Metformin in Patients With Diabetes Mellitus and Heart Failure

Systematic Review of Observational Studies Involving 34 000 Patients

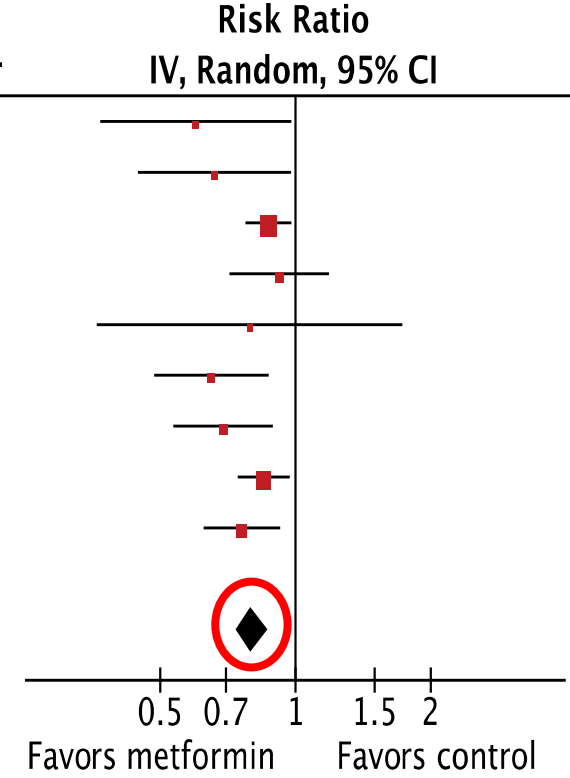
Dean T. Eurich, PhD; Daniala L. Weir, BSc; Sumit R. Majumdar, MD, MPH; Ross T. Tsuyuki, PharmD, MSc; Jeffrey A. Johnson, PhD; Lisa Tjosvold, MLIS; Saskia E. Vanderloo, MSc; Finlay A. McAlister, MD, MSc

Pooled adjusted risk ratios for metformin compared with other treatments for all-cause mortality

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI	Year
Evans	-0.5108	0.25	2.6%	0.60 [0.37, 0.98]	2005
Eurich	-0.4156	0.2	4.1%	0.66 [0.45, 0.98]	2005
Masoudi	-0.1393	0.06	29.0%	0.87 [0.77, 0.98]	2005
Inzucchi	-0.0834	0.13	8.9%	0.92 [0.71, 1.19]	2005
Shah	-0.2357	0.4	1.1%	0.79 [0.36, 1.73]	2010
MacDonald	-0.4308	0.15	6.9%	0.65 [0.48, 0.87]	2010
Roussel	-0.3711	0.13	8.9%	0.69 [0.53, 0.89]	2010
Andersson	-0.1625	0.0682	24.6%	0.85 [0.74, 0.97]	2010
Aguilar	-0.2744	0.1	13.9%	0.76 [0.62, 0.92]	2011
Total (95% CI)			**100.0%**	**0.80 [0.74, 0.87]**	

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 9.45$, df = 8 (P = 0.31); $I^2 = 15\%$

Test for overall effect: Z = 5.35 (P < 0.00001)



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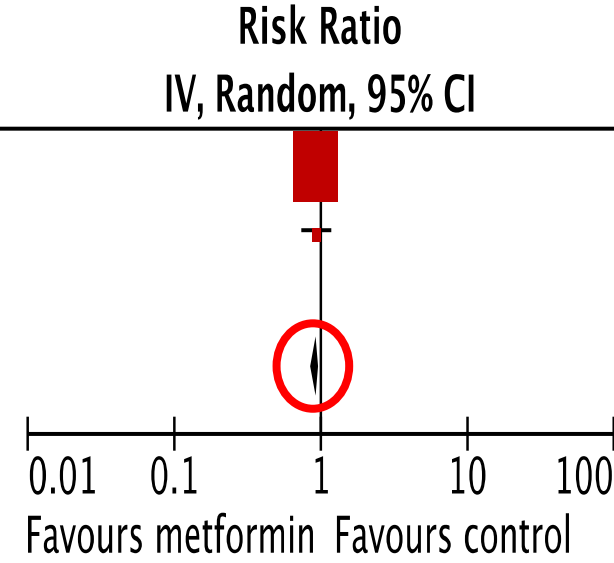
Pooled adjusted risk ratio for metformin compared with other treatments for HF admission

Study or Subgroup	Weight	Risk Ratio IV, Random, 95% CI	Year
Masoudi	92.2%	0.92 [0.86, 0.99]	2005
Aguilar	7.8%	0.93 [0.74, 1.18]	2011
Total (95% CI)	**100.0%**	**0.92 [0.86, 0.98]**	

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.01$, df = 1 (P = 0.93); $I^2 = 0\%$

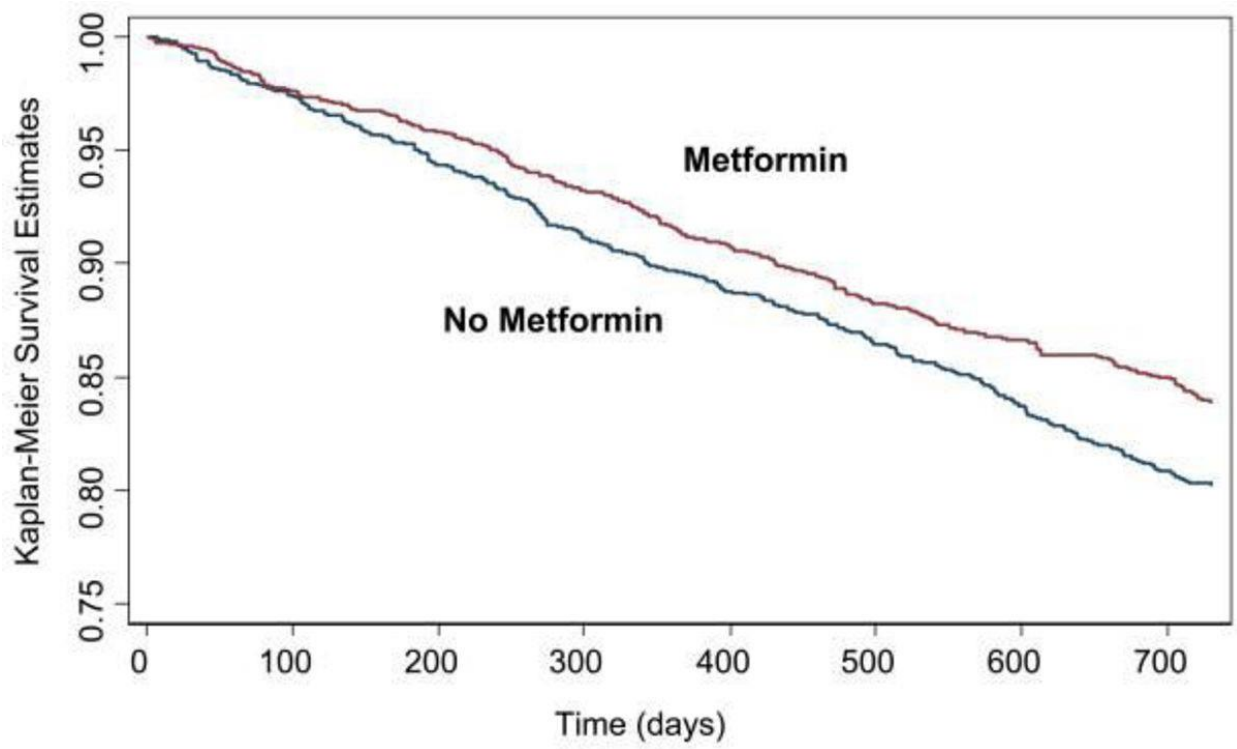
Test for overall effect: Z = 2.46 (P = 0.01)



Published in final edited form as:
Curr Cardiovasc Risk Rep. 2013 December 1; 7(6): 417–422. doi:10.1007/s12170-013-0355-4.

Metformin in Diabetic Patients with Heart Failure: Safe and Effective?

Ijeoma Ananaba Ekeruo, MD, **Amirreza Solhpour, MD**, and **Heinrich Taegtmeyer, MD, DPhil**



Changes in labelling for metformin use in patients with type 2 diabetes and heart failure: documented safety outweighs theoretical risks

Dean T Eurich, Sumit R Majumdar, Finlay A McAlister, Ross T Tsuyuki, Jeffrey A Johnson

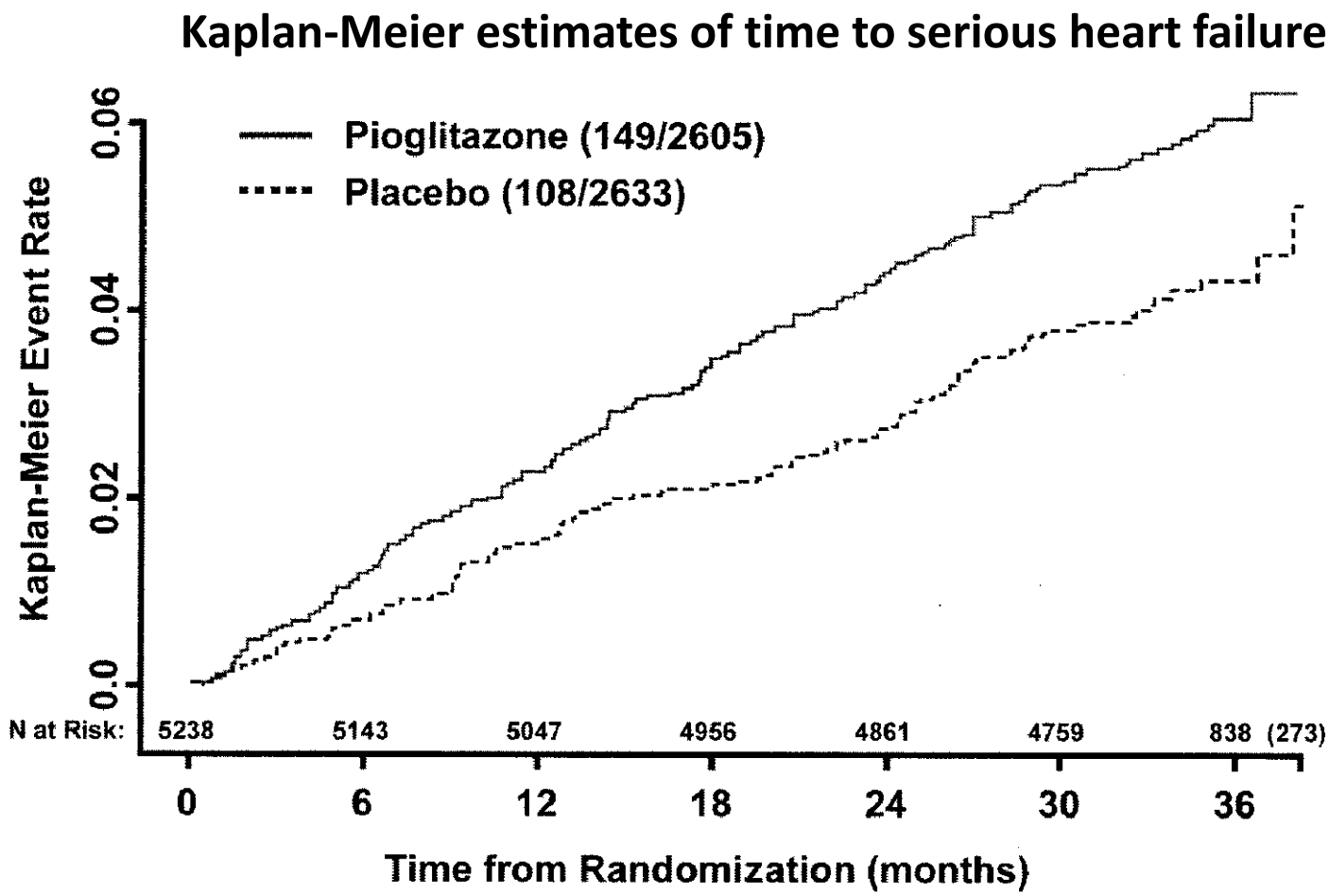
We hope that these formal regulatory changes, in conjunction with support within clinical practice guidelines, **will alleviate any lingering concerns clinicians may have about continuing or starting metformin in patients with both diabetes and heart failure**.

Open Med 2011;5(1):e33-e34.

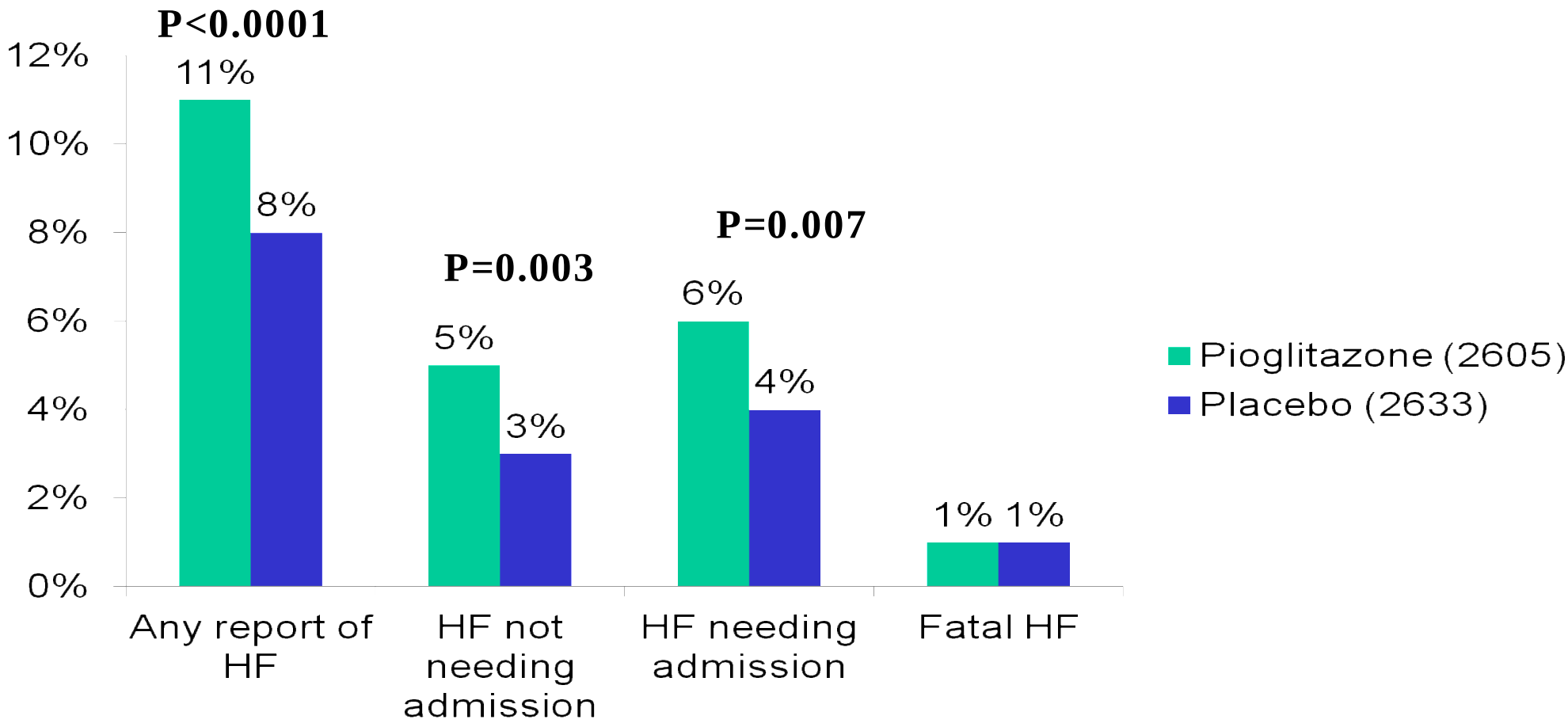
Pioglitazone Use and Heart Failure in Patients With Type 2 Diabetes and Preexisting Cardiovascular Disease

Data from the PROactive Study (PROactive 08)

Diabetes Care 30:2773–2778, 2007



Pioglitazone and Heart Failure



PROACTIVE Trial. Lancet 2005;366:1279

Pioglitazone Use and Heart Failure in Patients With Type 2 Diabetes and Preexisting Cardiovascular Disease

Data from the PROactive Study (PROactive 08)

Diabetes Care 30:2773–2778, 2007

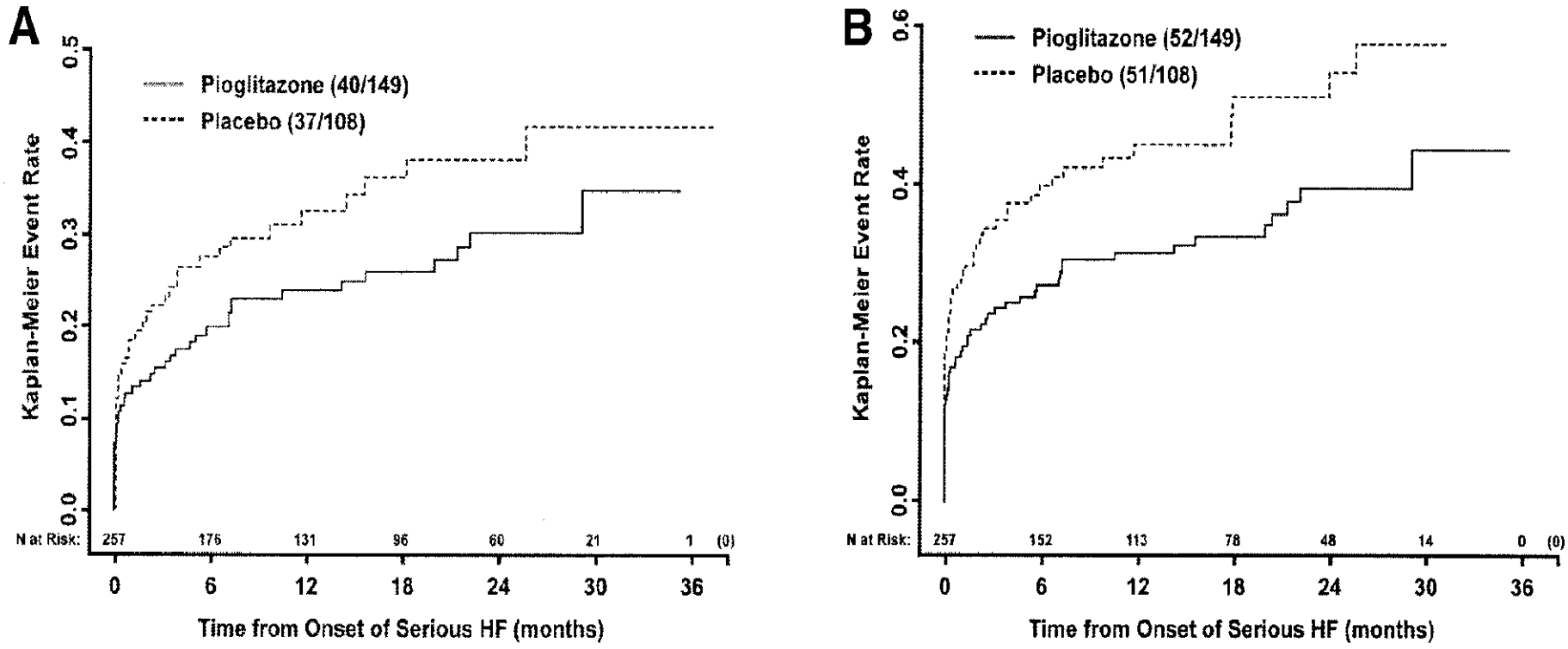
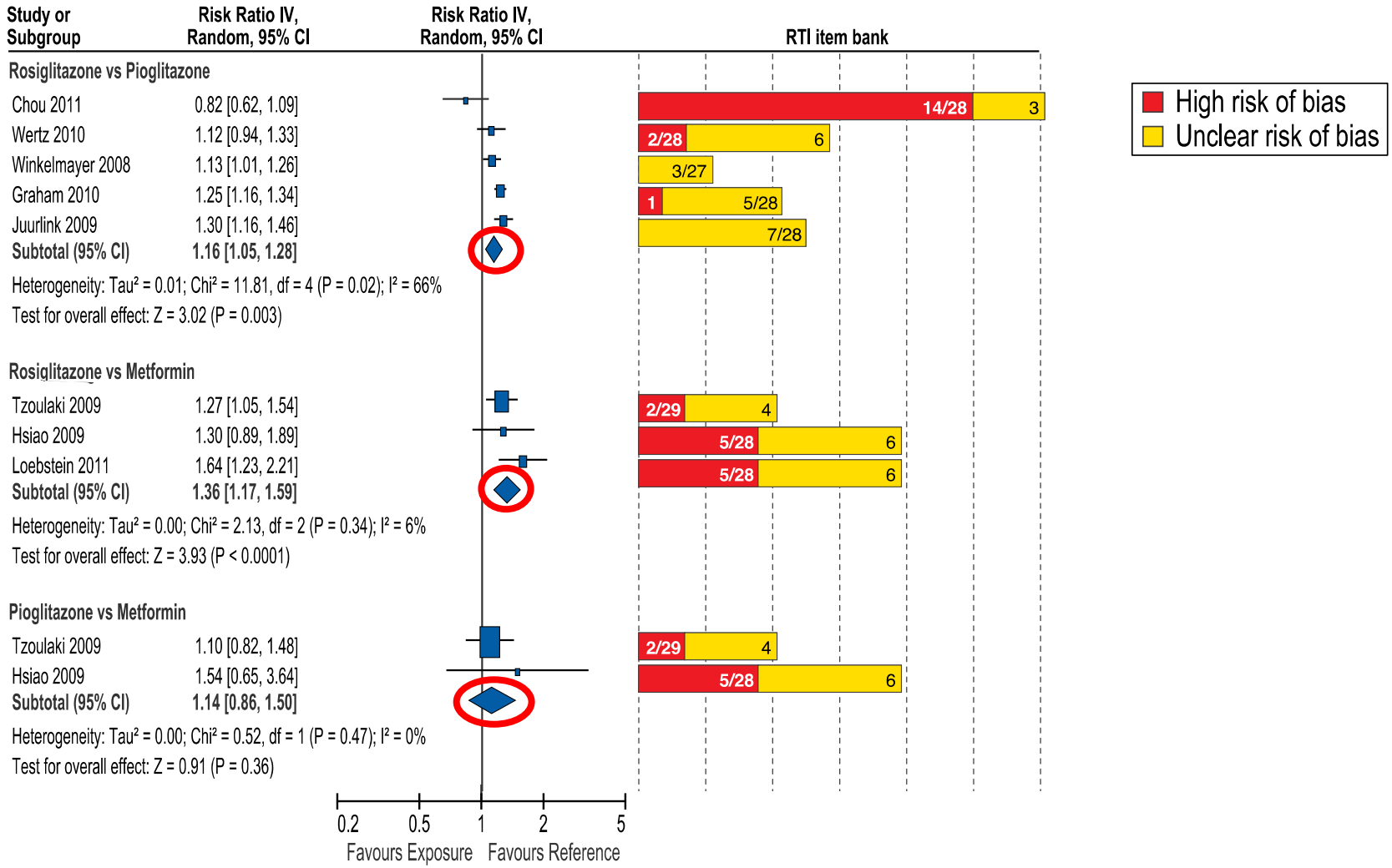


Figure 2—*Kaplan-Meier estimates of time from serious heart failure to all-cause mortality (A) and the main secondary end point (B). HF, heart failure.*

RESEARCH ARTICLE Open Access

The risk of heart failure associated with the use of noninsulin blood glucose-lowering drugs: systematic review and meta-analysis of published observational studies

Varas-Lorenzo et al. BMC Cardiovascular Disorders 2014, 14:129



European Heart Journal (2015) 36, 2454–2462
doi:10.1093/eurheartj/ehv301

Risk of hospitalization for heart failure in patients with type 2 diabetes newly treated with DPP-4 inhibitors or other oral glucose-lowering medications: a retrospective registry study on 127,555 patients from the Nationwide OsMed Health-DB Database

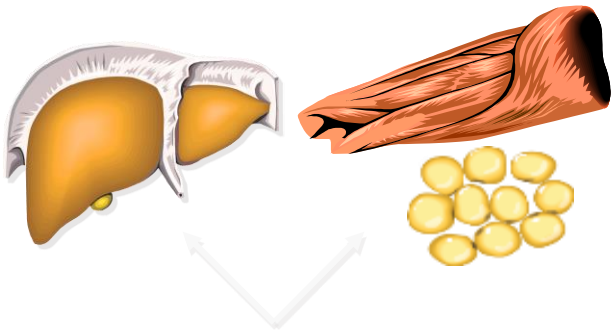
Gian Paolo Fadini[1], Angelo Avogaro[1*], Luca Degli Esposti[2], Pierluigi Russo[3], Stefania Saragoni[2], Stefano Buda[2], Giuseppe Rosano[3,4,5], Sergio Pecorelli[3,6], and Luca Pani[3], on behalf of the OsMed Health-DB Network[†]

Table 4 Results of the Cox proportional hazard multiple regression analysis in the whole study population including hospitalization episodes with a primary or secondary HF diagnosis

Variable	Before propensity matching		After propensity matching	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Glucose-lowering medications				
Sulphonylureas (reference)	1.000		1.000	
Glitazones	0.926 (0.807–1.063)	0.277	0.777 (0.635–0.950)	0.014
DPP-4 inhibitors	0.751 (0.630–0.895)	0.001	0.642 (0.510–0.808)	<0.001

Options for Antidiabetic Treatment

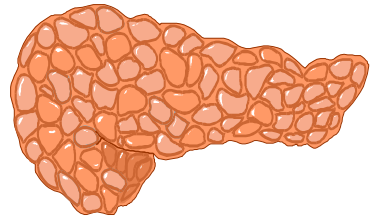
Insulin Resistance



Metformin

Pioglitazone

Insulin Secretion



Glucose independent

Sulfonylurea

Glinides

Exogenous Insulin

RESEARCH ARTICLE Open Access

The risk of heart failure associated with the use of noninsulin blood glucose-lowering drugs: systematic review and meta-analysis of published observational studies

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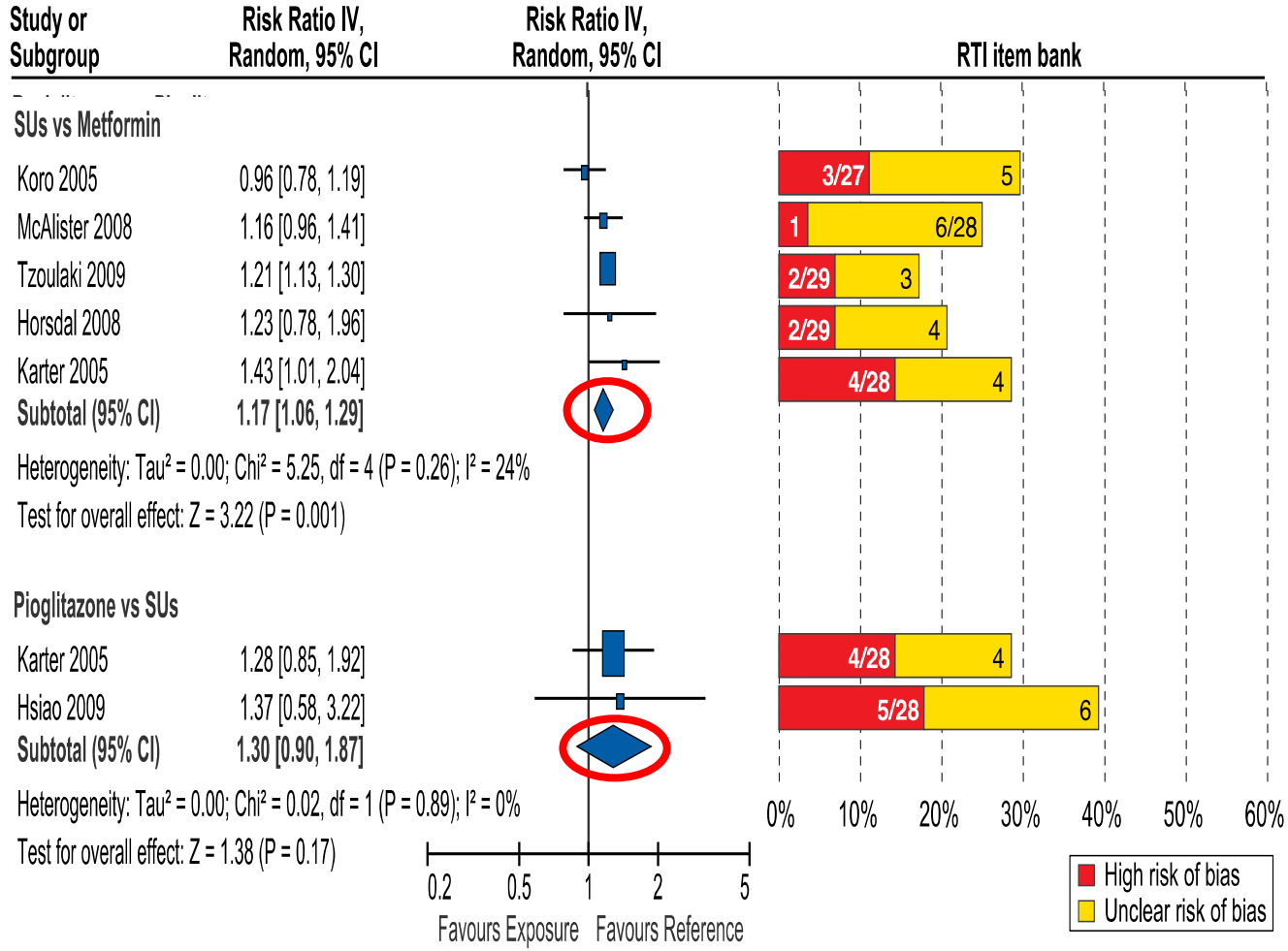


Adjudicated Serious Events

	Pioglitazone (N=1535)	*Sulfonylurea (N=1493)*	*P value*
	N (%)	N (%)	
Any serious adverse events	208 (13.6)	195 (13.1)	0.69
Heart Failure	19 (1.2)	12 (0.8)	0.11
Any fracture	*27 (1.8)*	*36 (2.4)*	*0.24*
Pathological fractures	6 (0.4)	4 (0.3)	0.75
- Male (1774)	3 (0.3)	1 (0.1)	0.61
- Female (1254)	3 (0.5)	3 (0.5)	1.00
Macular edema	7 (0.5)	3 (0.2)	0.34

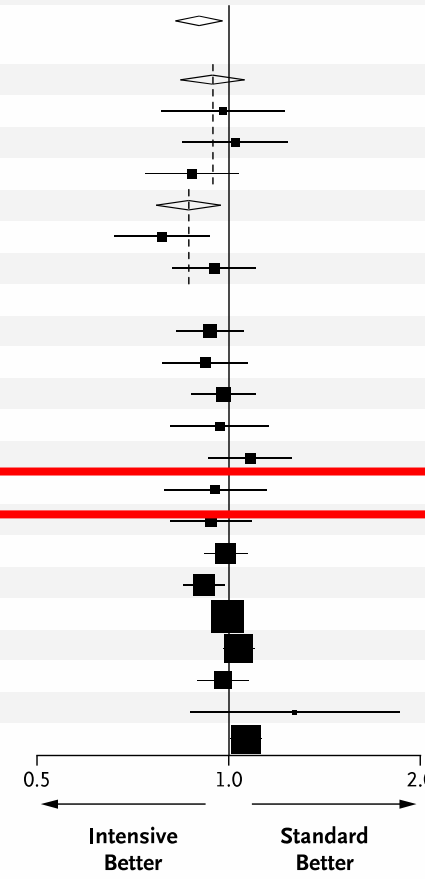
Lancet Diabetes Endocrinol 2017;5(11):887-897

Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes

N Engl J Med 2008;358:2560-72

The ADVANCE Collaborative Group*

Subgroup	Intensive Control (N=5571)	Standard Control (N=5569)	Relative Risk Reduction (95% CI)
	number of patients (percent)		*percent*
Primary End Points			
Combined major macrovascular and microvascular events	1009 (18.1)	1116 (20.0)	10 (2 to 18)
Major macrovascular events	557 (10.0)	590 (10.6)	6 (–6 to 16)
Nonfatal MI	153 (2.7)	156 (2.8)	2 (–23 to 22)
Nonfatal stroke	214 (3.8)	209 (3.8)	–2 (–24 to 15)
Death from cardiovascular causes	253 (4.5)	289 (5.2)	12 (–4 to 26)
Major microvascular events	526 (9.4)	605 (10.9)	14 (3 to 23)
New or worsening nephropathy	230 (4.1)	292 (5.2)	21 (7 to 34)
New or worsening retinopathy	332 (6.0)	349 (6.3)	5 (–10 to 18)
Secondary End Points			
Death from any cause	498 (8.9)	533 (9.6)	7 (–6 to 17)
Major coronary events	310 (5.6)	337 (6.1)	8 (–7 to 21)
All coronary events	560 (10.1)	572 (10.3)	2 (–10 to 13)
Major cerebrovascular events	238 (4.3)	246 (4.4)	3 (–16 to 19)
All cerebrovascular events	352 (6.3)	327 (5.9)	–8 (–26 to 7)
Heart failure	220 (3.9)	231 (4.1)	5 (–14 to 21)
Peripheral vascular events	345 (6.2)	366 (6.6)	6 (–9 to 19)
All cardiovascular events	1232 (22.1)	1249 (22.4)	1 (–7 to 9)
New-onset microalbuminuria	1318 (23.7)	1434 (25.7)	9 (2 to 5)
Visual deterioration	3033 (54.4)	3015 (54.1)	0 (–5 to 5)
New or worsening neuropathy	2353 (42.2)	2311 (41.5)	–4 (–10 to 2)
Cognitive decline	895 (16.1)	911 (16.4)	2 (–7 to 11)
Dementia	61 (1.1)	48 (0.9)	–27 (–86 to 13)
Hospitalization	2501 (44.9)	2381 (42.8)	–7 (–13 to –1)



Insulin-treated diabetes is associated with a marked increase in mortality in patients with advanced heart failure

RESULTS

- Survival at 1 year was:
  - ✓ 89.7% for nondiabetic patients
  - ✓ 85.8% for non-insulin-treated diabetic patients
  - ✓ 62.1% for insulin-treated diabetic patients

- Insulin-treated diabetes was found to be an independent predictor of mortality (hazard ratio 4.30, 95% CI 1.69-10.94) whereas non-insulin-treated diabetes was not (hazard ratio 0.95, 95% CI 0.31-2.93).

Am Heart J. 2005;149(1):168-74

BMJ Open

Hospitalisation for heart failure and mortality associated with dipeptidyl peptidase 4 (DPP-4) inhibitor use in an unselected population of subjects with type 2 diabetes: a nested case–control study

Table 2 Matched ORs of different outcomes associated with exposure to DPP-4i in the 6 months before index date

	Any admission for HF		Incident HF		Re-admission for HF		All-cause mortality	
	Unadjusted OR (95% CI); p value	Adjusted OR (95% CI); p value	Unadjusted OR (95% CI); p value	Adjusted OR (95% CI); p value	Unadjusted OR (95% CI); p value	Adjusted OR (95% CI); p value	Unadjusted OR (95% CI); p value	Adjusted OR (95% CI); p value
DPP-4i use	0.99 (0.92 to 1.05); p=0.6383	1.00 (0.94 to 1.07); p=0.9832	1.01 (0.92 to 1.11); p=0.8867	1.01 (0.92 to 1.11); p=0.7808	1.01 (0.84 to 1.22); p=0.8944	1.02 (0.84 to 1.22); p=0.8745	0.93 (0.89 to 0.97); p=0.0005	0.94 (0.90 to 0.98); p=0.0021
Previous disorders or treatments								
Ischaemic heart disease (in the past 5 years)	1.36 (1.31 to 1.40); p=<0.0001	1.34 (1.29 to 1.38); p=<0.0001	1.09 (1.04 to 1.14); p=0.0003	1.08 (1.03 to 1.13); p=0.0014	1.03 (0.96 to 1.11); p=0.4455	1.02 (0.95 to 1.10); p=0.6067	1.11 (1.09 to 1.14); p=<0.0001	1.09 (1.07 to 1.12); p=<0.0001
Glimepiride or glibenclamide (in the past 6 months)	0.99 (0.96 to 1.02); p=0.3555	1.01 (0.98 to 1.04); p=0.4844	1.02 (0.98 to 1.06); p=0.3520	1.03 (0.99 to 1.08); p=0.0998	1.00 (0.92 to 1.09); p=0.9614	1.02 (0.93 to 1.11); p=0.6751	0.96 (0.95 to 0.98); p=<0.0001	0.98 (0.97 to 1.00); p=0.0540
Insulin (in the past 6 months)	1.21 (1.18 to 1.24); p=<0.0001	1.19 (1.17 to 1.22); p=<0.0001	1.13 (1.10 to 1.17); p=<0.0001	1.13 (1.10 to 1.17); p=<0.0001	1.12 (1.06 to 1.19); p=0.0001	1.12 (1.06 to 1.19); p=0.0002	1.20 (1.19 to 1.22); p=<0.0001	1.20 (1.18 to 1.21); p=<0.0001

HF, heart failure.

Giorda CB, et al. BMJ Open 2015;5:e007959.

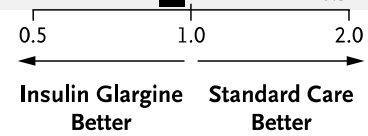
ORIGINAL ARTICLE

N Engl J Med 2012;367:319-28

Basal Insulin and Cardiovascular and Other Outcomes in Dysglycemia

The ORIGIN Trial Investigators*

Outcome	Insulin Glargine (N=6264)		Standard Care (N=6273)		Hazard Ratio (95% CI)	P Value
	no. (%)	*no./100 patient-yr*	*no. (%)*	*no./100 patient-yr*		
First coprimary outcome	1041 (16.6)	2.94	1013 (16.1)	2.85	1.02 (0.94–1.11)	0.63
Second coprimary outcome	1792 (28.6)	5.52	1727 (27.5)	5.28	1.04 (0.97–1.11)	0.27
Microvascular outcomes	1323 (21.1)	3.87	1363 (21.7)	3.99	0.97 (0.90–1.05)	0.43
Total mortality	951 (15.2)	2.57	965 (15.4)	2.60	0.98 (0.90–1.08)	0.70
Total myocardial infarctions	336 (5.4)	0.93	326 (5.2)	0.90	1.02 (0.88–1.19)	0.75
Total strokes	331 (5.3)	0.91	319 (5.1)	0.88	1.03 (0.89–1.21)	0.69
Death from cardiovascular causes	580 (9.3)	1.57	576 (9.2)	1.55	1.00 (0.89–1.13)	0.98
Hospitalization for congestive heart failure	310 (4.9)	0.85	343 (5.5)	0.95	0.90 (0.77–1.05)	0.16
Revascularization	908 (14.5)	2.69	860 (13.7)	2.52	1.06 (0.96–1.16)	0.24
Angina	709 (11.3)	2.07	743 (11.8)	2.17	0.95 (0.85–1.05)	0.29
Unstable	238 (3.8)	0.66	261 (4.2)	0.72	0.91 (0.76–1.08)	0.28
New	100 (1.6)	0.27	138 (2.2)	0.38	0.72 (0.56–0.93)	0.01
Worsening	455 (7.3)	1.29	446 (7.1)	1.26	1.02 (0.89–1.16)	0.80
Limb or digit amputation	47 (0.8)	0.13	53 (0.8)	0.14	0.89 (0.60–1.31)	0.55
Cardiovascular hospitalization	2081 (33.2)	6.98	2071 (33.0)	6.91	1.00 (0.94–1.07)	0.90
Noncardiovascular hospitalization	2339 (37.3)	7.90	2349 (37.4)	7.93	0.99 (0.94–1.05)	0.85
Any cancer	476 (7.6)	1.32	477 (7.6)	1.32	1.00 (0.88–1.13)	0.97
Death from cancer	189 (3.0)	0.51	201 (3.2)	0.54	0.94 (0.77–1.15)	0.52



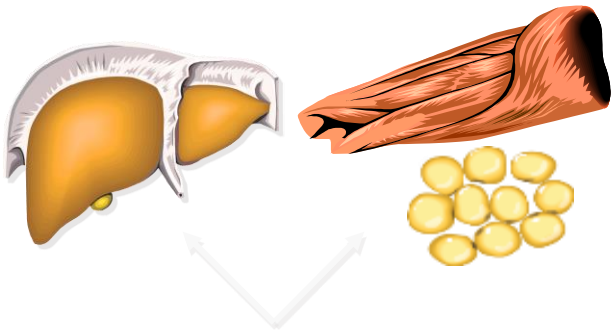
Incidence and predictors of hypoglycaemia in type 2 diabetes – an analysis of the prospective DiaRegis registry

Table 1 Patient characteristics, risk factors, laboratory values

	Incident hypo 12 months FU Median (quartiles) or % (n=473)	No hypo 12 months FU Median (quartiles) or % (n=2874)	p-value / OR (95%CI)
Age (years)	66.8 (57.8-74.1)	65.9 (57.6-72.7)	0.08
Female gender (%)	43.8	47.5	0.14
Diabetes duration (years)	6.4 (3.0-10.5)	5.5 (2.9-9.2)	<0.01
Blood glucose			
HbA1c (%)	7.6 (6.8-8.8)	7.4 (6.8-8.1)	<0.0001
HbA1c ≥ 7.5%	55.9	46.2	<0.001
FPG (mg/dl)	142 (115–174)	140 (119–168)	0.83
PPG (mg/dl)	183 (156–222)	183 (155–220)	0.39
Blood glucose self measurement (%)	87.7	73.9	<0.0001
Prior smoker (%)	20.9	14.2	<0.001
Bodyweight (kg)	87 (78–98)	89 (78–100)	0.09
Coronary artery disease (%)	22.0	17.5	<0.05
Stroke / TIA (%)	5.7	4.5	0.23
PAD (%)	8.6	5.7	<0.05
Heart failure (%)	13.1	9.3	<0.05

Options for Antidiabetic Treatment

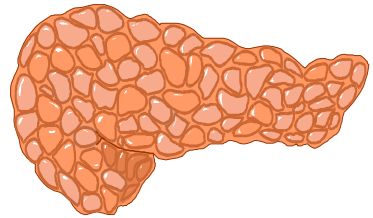
Insulin Resistance



Metformin

Pioglitazone

Insulin Secretion



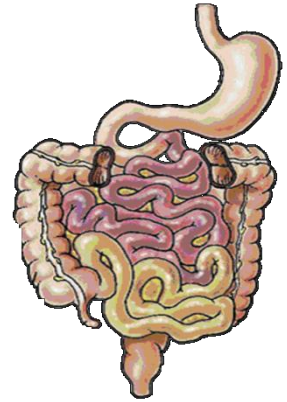
Glucose independent

Sulfonylurea

Glinides

Exogenous Insulin

Inhibtion of Glucose Reabsorption



α-Glucosidase Inhibitors

Acarbose

Comparing the risks of hospitalized heart failure associated with glinide, sulfonylurea, and acarbose use in type 2 diabetes.

- A significantly higher risk of HHF was found for glinide (adjusted HR, 1.53; 95% CI, 1.24-1.88)…
- … but not for sulfonylurea (adjusted HR, 0.94; 95% CI, 0.80-1.11), as compared with acarbose
- The elevated risk remained consistent across different subgroups of patients as well as several sensitivity analyses including exploring the impact of potential unmeasured confounding.

Lee YC et al. Int J Cardiol. 2017;228:1007-1014

Acarbose reduces the risk for myocardial infarction in type 2 diabetic patients: meta-analysis of seven long-term studies

Whereas a significant reduc- tion of any cardiovascular event and of MI was found in the group of 1248 patients randomized to acarbose versus 932 patients randomized to placebo, **no significant difference was noted in terms of HF outcomes**.

Eur Heart J. 2004;25(1):10-6.

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

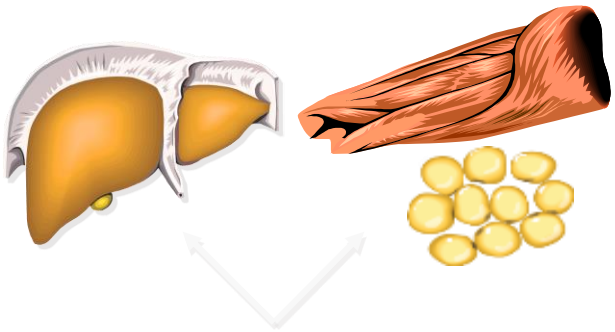
RESULTS

No significant differences were seen between treatment groups for the secondary three-point composite outcome, death from any cause, cardiovascular death, fatal or non-fatal myocardial infarction, fatal or non-fatal stroke, hospital admission for unstable angina, **hospital admission for heart failure**, or impaired renal function.

Lancet Diabetes Endocrinol. 2017;5(11):877-886

Options for Antidiabetic Treatment

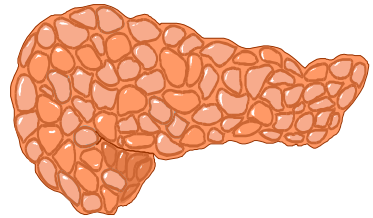
Insulin Resistance



Metformin

Pioglitazone

Insulin Secretion



Glucose independent

Sulfonylurea

Glinides

Exogenous Insulin

Glucose dependent

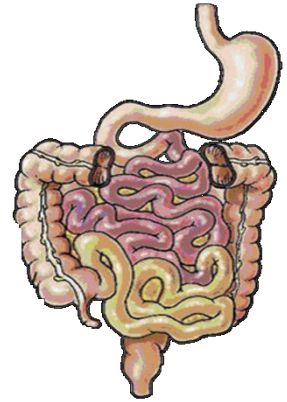
DPP-4 Inhibitors

Sitagliptin, Vildagliptin, Saxagliptin, Linagliptin, Alogliptin

GLP-1 Mimetics

Exenatide, Liraglutide, Lixisenatide Dulaglutide

Inhibtion of Glucose Reabsorption



α-Glucosidase Inhibitors

Acarbose

Summary of the clinical outcomes of the recent randamized large cohort trials for DPP4 inhibitors.

Trial components	SAVOR-TIMI-53	EXAMINE	TECOS
Clinical outcomes			
CV death, nonfatal MI/ CAD	HR 1.00 (NS)	HR 1.00 (NS)	HR0.98 (NS)
Death from any cause	HR 1.11 (NS)	HR 0.88 (NS)	HR 1.01 (NS)

Bando YK and Murohara T. J Atheroscler Thromb, 2016; 23: 147-154

Summary of the clinical outcomes of the recent randamized large cohort trials for DPP4 inhibitors

			Heart Failure		
	Primary outcome	Secondary outcome(s)	Total	History of HF	No history of HF
DPP–4 inhibitors					
SAVOR-TIMI 53 [5–8]	1.00 (0.89–1.12)	1.02 (0.94–1.11)	1.27 (1.07–1.51)	1.21 (0.93–1.58)	1.32 (1.04–1.66)
EXAMINE [9–11]	0.96 (≤1.16)[c]	0.95 (≤1.14)[c]	1.07 (0.79–1.46)	1.00 (0.71–1.42)	1.76 (1.07–2.90)
TECOS [12–15]	0.98 (0.89–1.08)	0.99 (0.89–1.10)	1.00 (0.83–1.20)	1.05 (0.79–1.39)	0.96 (0.76–1.23)

Secrest MH et al. Trends in Cardiovasc Med 2017; 27:194–202

Circulation. 2014 Oct 28;130(18):1579-88

Heart Failure, Saxagliptin and Diabetes Mellitus: Observations from the SAVOR - TIMI 53 Randomized Trial.

Scirica BM, Braunwald E, Raz I, Cavender MA, Morrow DA, Jarolim P, Udell JA, Mosenzon O, Im K, Umez-Eronini AA, Pollack PS, Hirshberg B, Frederich R, Lewis BS, McGuire DK, Davidson J, Steg PG, Bhatt DL; for the SAVOR-TIMI 53 Steering Committee and Investigators

CONCLUSIONS:

- Saxagliptin treatment was associated with an increased risk for hospitalization for heart failure.

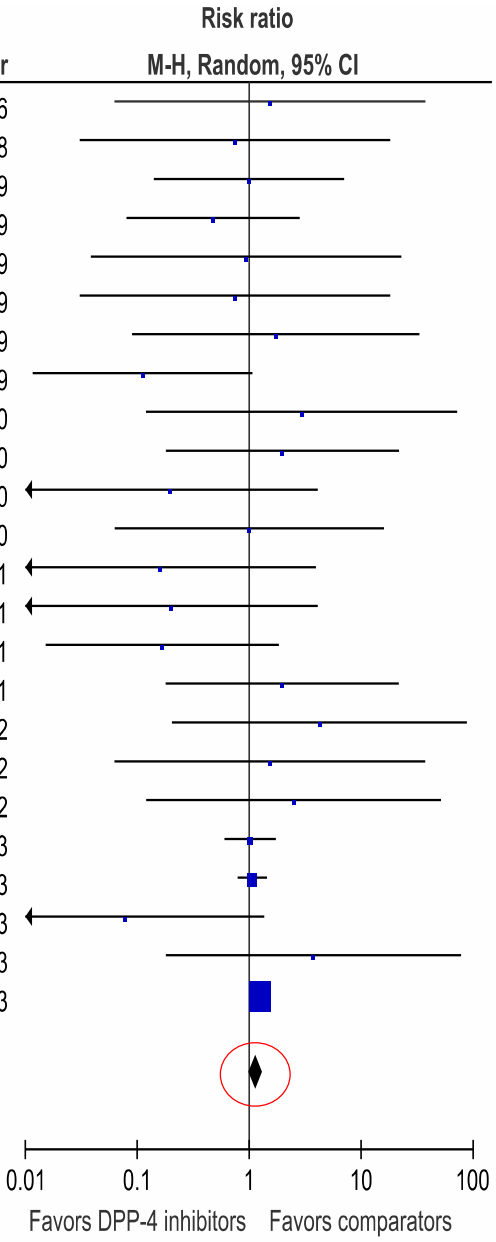
- This increase in risk was highest among patients:
  - with elevated levels of natriuretic peptides
  - prior heart failure,
  - chronic kidney disease.

Heart failure in trials of patients receiving a DPP4 inhibitor versus all comparators

Study or subgroup	DPP-4 inhibitors Events	Total	All comparators Events	Total	Weight	Risk ratio M-H, Random, 95% CI	Year
Charbonnel et al. 2006	1	464	0	237	0.2%	1.54 [0.06, 37.55]	2006
Nauck et al. 2009	1	420	0	104	0.2%	0.75 [0.03, 18.24]	2008
Ferrannini et al. 2009	2	1396	2	1393	0.5%	1.00 [0.14, 7.07]	2009
DeFronzo et al. 2009	3	564	2	179	0.6%	0.48 [0.08, 2.83]	2009
Rosenstock (1) 2009	1	306	0	95	0.2%	0.94 [0.04, 22.84]	2009
Pratley et al. (2) 2009	1	401	0	99	0.2%	0.75 [0.03, 18.18]	2009
Pratley et al. (1) 2009	3	396	0	97	0.2%	1.73 [0.09, 33.18]	2009
Jadzinsky et al. 2009	1	978	3	328	0.4%	0.11 [0.01, 1.07]	2009
Williams-Herman 2010	1	551	0	540	0.2%	2.94 [0.12, 72.02]	2010
Seck et al. 2010	2	588	1	584	0.3%	1.99 [0.18, 21.85]	2010
Vilsboll et al. 2010	0	322	2	319	0.2%	0.20 [0.01, 4.11]	2010
Goke et al. 2010	1	428	1	430	0.3%	1.00 [0.06, 16.01]	2010
Hollander et al. 2011	0	381	1	184	0.2%	0.16 [0.01, 3.94]	2011
Nowicki et al. 2011	0	85	2	85	0.2%	0.20 [0.01, 4.10]	2011
Pfutzner et al. 2011	1	978	2	328	0.3%	0.17 [0.02, 1.84]	2011
Bosi et al. 2011	2	404	1	399	0.3%	1.98 [0.18, 21.70]	2011
Haak et al. 2012	2	428	0	363	0.2%	4.24 [0.20, 88.08]	2012
Kawamori et al. 2012	1	319	0	162	0.2%	1.53 [0.06, 37.30]	2012
Barnett et al. (2) 2012	2	304	0	151	0.2%	2.49 [0.12, 51.58]	2012
McMurray et al. 2013	23	128	22	125	6.9%	1.02 [0.60, 1.73]	2013
White et al. 2013	85	2701	79	2679	21.3%	1.07 [0.79, 1.44]	2013
NCT00509262	0	211	6	212	0.2%	0.08 [0.00, 1.36]	2013
NCT00722371	2	922	0	693	0.2%	3.76 [0.18, 78.18]	2013
Scirica et al. 2013	289	8280	228	8212	66.2%	1.26 [1.06, 1.49]	2013
Total (95% CI)		**21,955**		**17,998**	**100.0%**	**1.16 [1.01, 1.33]**	
Total events	424		352				

Heterogeneity: Tau² = 0.00; Chi² = 19.02, df = 23 (*P* = 0.70); I² = 0%

Test for overall effect: Z = 2.08 (*P* = 0.04)



Wu S et al. Cardiovascular Therapeutics 32 (2014) 147–158

BMJ Open

Hospitalisation for heart failure and mortality associated with dipeptidyl peptidase 4 (DPP-4) inhibitor use in an unselected population of subjects with type 2 diabetes: a nested case–control study

Table 2 Matched ORs of different outcomes associated with exposure to DPP-4i in the 6 months before index date

	Any admission for HF		Incident HF		Re-admission for HF		All-cause mortality	
	Unadjusted OR (95% CI); p value	Adjusted OR (95% CI); p value	Unadjusted OR (95% CI); p value	Adjusted OR (95% CI); p value	Unadjusted OR (95% CI); p value	Adjusted OR (95% CI); p value	Unadjusted OR (95% CI); p value	Adjusted OR (95% CI); p value
DPP-4i use	0.99 (0.92 to 1.05); p=0.6383	1.00 (0.94 to 1.07); p=0.9832	1.01 (0.92 to 1.11); p=0.8867	1.01 (0.92 to 1.11); p=0.7808	1.01 (0.84 to 1.22); p=0.8944	1.02 (0.84 to 1.22); p=0.8745	0.93 (0.89 to 0.97); p=0.0005	0.94 (0.90 to 0.98); p=0.0021
Previous disorders or treatments								
Ischaemic heart disease (in the past 5 years)	1.36 (1.31 to 1.40); p=<0.0001	1.34 (1.29 to 1.38); p=<0.0001	1.09 (1.04 to 1.14); p=0.0003	1.08 (1.03 to 1.13); p=0.0014	1.03 (0.96 to 1.11); p=0.4455	1.02 (0.95 to 1.10); p=0.6067	1.11 (1.09 to 1.14); p=<0.0001	1.09 (1.07 to 1.12); p=<0.0001
Glimepiride or glibenclamide (in the past 6 months)	0.99 (0.96 to 1.02); p=0.3555	1.01 (0.98 to 1.04); p=0.4844	1.02 (0.98 to 1.06); p=0.3520	1.03 (0.99 to 1.08); p=0.0998	1.00 (0.92 to 1.09); p=0.9614	1.02 (0.93 to 1.11); p=0.6751	0.96 (0.95 to 0.98); p=<0.0001	0.98 (0.97 to 1.00); p=0.0540
Insulin (in the past 6 months)	1.21 (1.18 to 1.24); p=<0.0001	1.19 (1.17 to 1.22); p=<0.0001	1.13 (1.10 to 1.17); p=<0.0001	1.13 (1.10 to 1.17); p=<0.0001	1.12 (1.06 to 1.19); p=0.0001	1.12 (1.06 to 1.19); p=0.0002	1.20 (1.19 to 1.22); p=<0.0001	1.20 (1.18 to 1.21); p=<0.0001

HF, heart failure.

Giorda CB, et al. BMJ Open 2015;5:e007959.

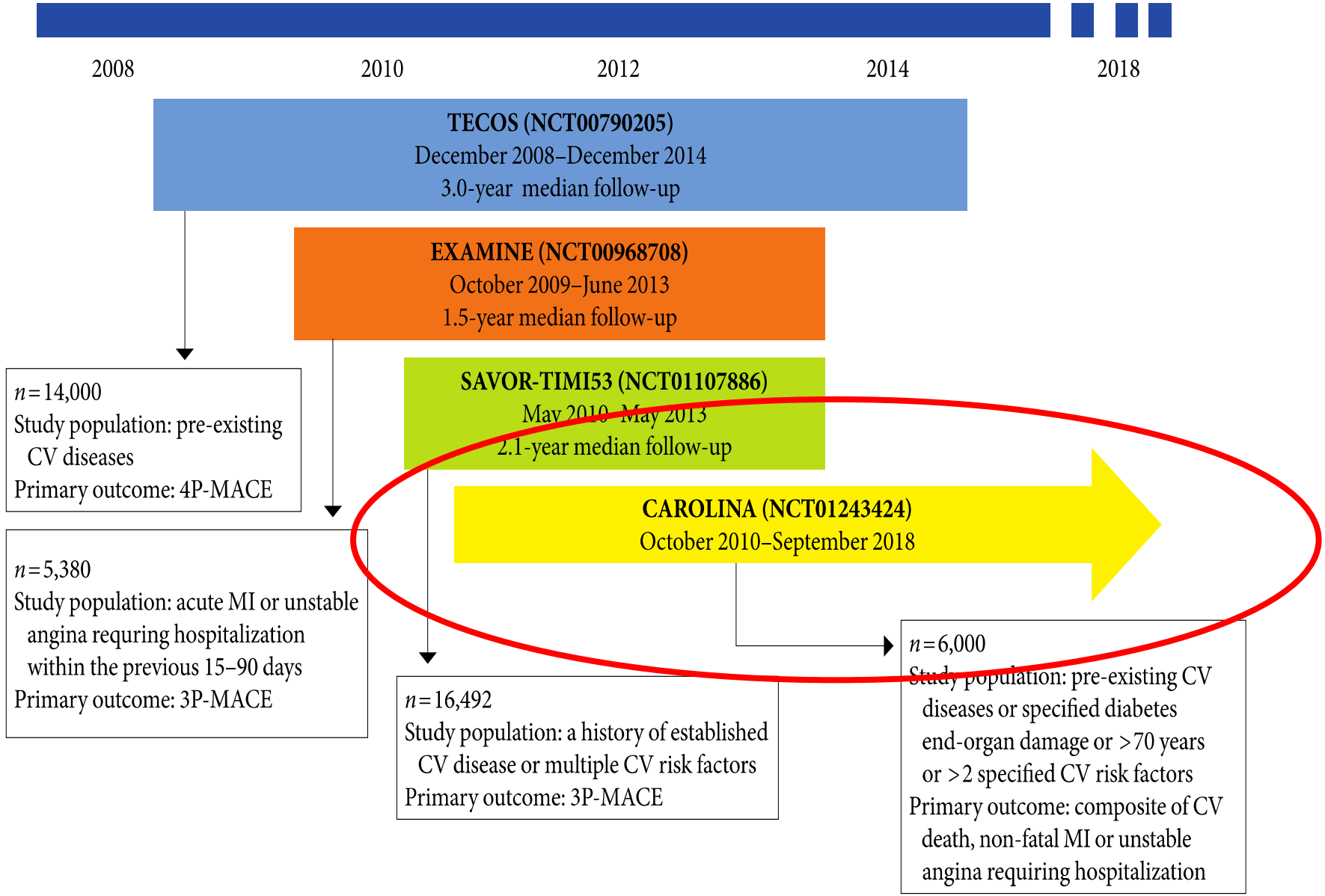
European Heart Journal (2015) 36, 2454–2462
doi:10.1093/eurheartj/ehv301

Risk of hospitalization for heart failure in patients with type 2 diabetes newly treated with DPP-4 inhibitors or other oral glucose-lowering medications: a retrospective registry study on 127,555 patients from the Nationwide OsMed Health-DB Database

Gian Paolo Fadini[1], Angelo Avogaro[1*], Luca Degli Esposti[2], Pierluigi Russo[3], Stefania Saragoni[2], Stefano Buda[2], Giuseppe Rosano[3,4,5], Sergio Pecorelli[3,6], and Luca Pani[3], on behalf of the OsMed Health-DB Network[†]

Table 4 Results of the Cox proportional hazard multiple regression analysis in the whole study population including hospitalization episodes with a primary or secondary HF diagnosis

Variable	Before propensity matching		After propensity matching	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Glucose-lowering medications				
Sulphonylureas (reference)	1.000		1.000	
Glitazones	0.926 (0.807–1.063)	0.277	0.777 (0.635–0.950)	0.014
DPP-4 inhibitors	0.751 (0.630–0.895)	0.001	0.642 (0.510–0.808)	<0.001



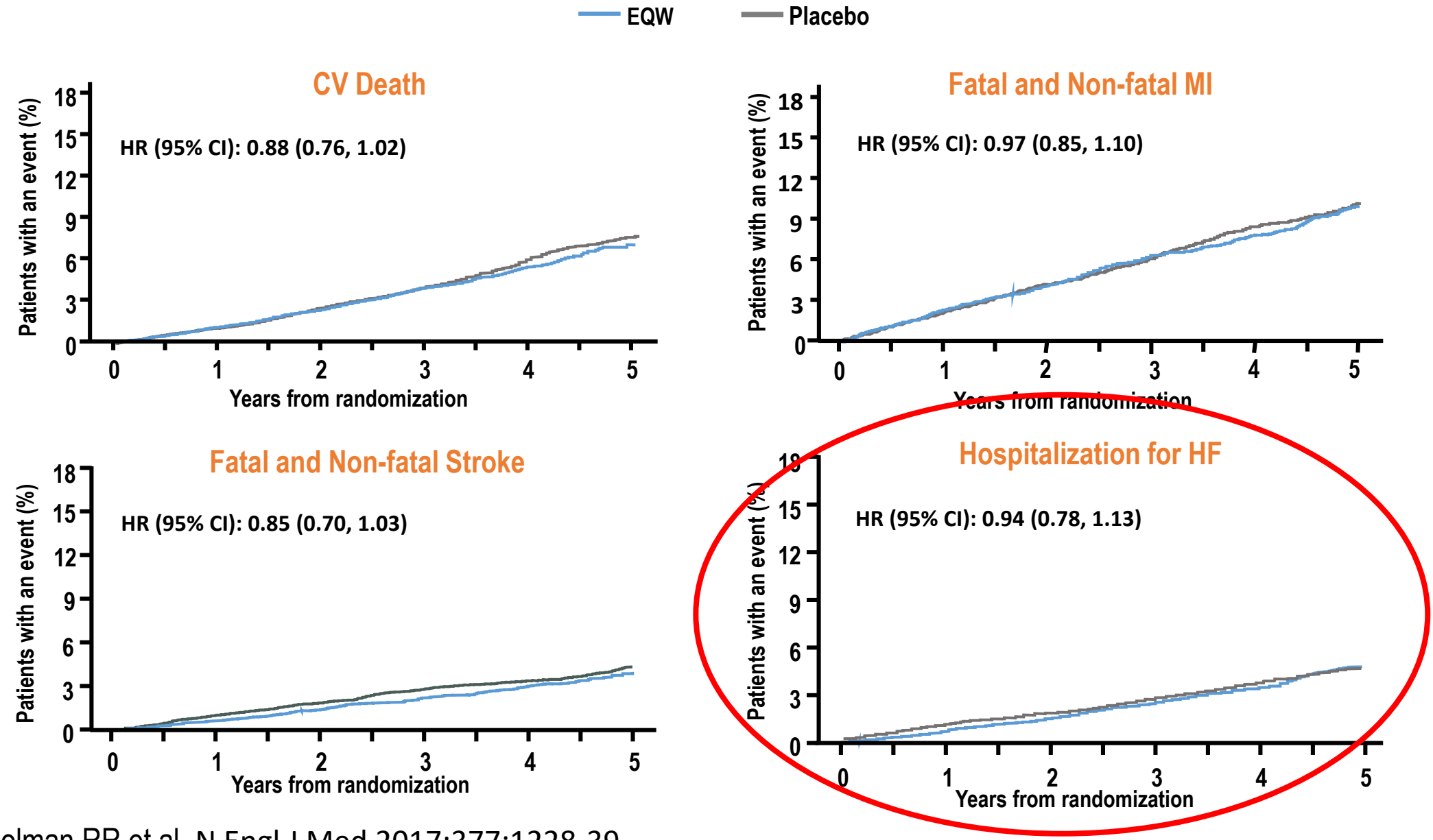
Diabetes Metab J 2015;39:373-383

Summary of the clinical outcomes of the recent randamized large cohort trials for GLP-1 agonists

	Primary outcome	Secondary outcome(s)	Heart Failure		
			Total	History of HF	No history of HF
GLP–1 agonists					
ELIXA [22,23]	1.02 (0.89–1.17)	1) 0.97 (0.85–1.10) 2) 1.00 (0.90–1.11)	0.96 (0.75–1.23)	0.93 (0.66–1.30)	0.97 (0.67–1.40)
LEADER [24,25]	0.87 (0.78–0.97)	0.88 (0.81–0.96)	0.87 (0.73–1.05)	Not reported	Not reported
SUSTAIN–6 [26]	0.74 (0.58–0.95)	1) 0.74 (0.62–0.89) 2) 0.77 (0.61–0.97)	1.11 (0.77–1.61)	Not reported	Not reported

Secrest MH et al. Trends in Cardiovasc Med 2017; 27:194–202

EXSCEL Study: Additional Secondary Endpoints

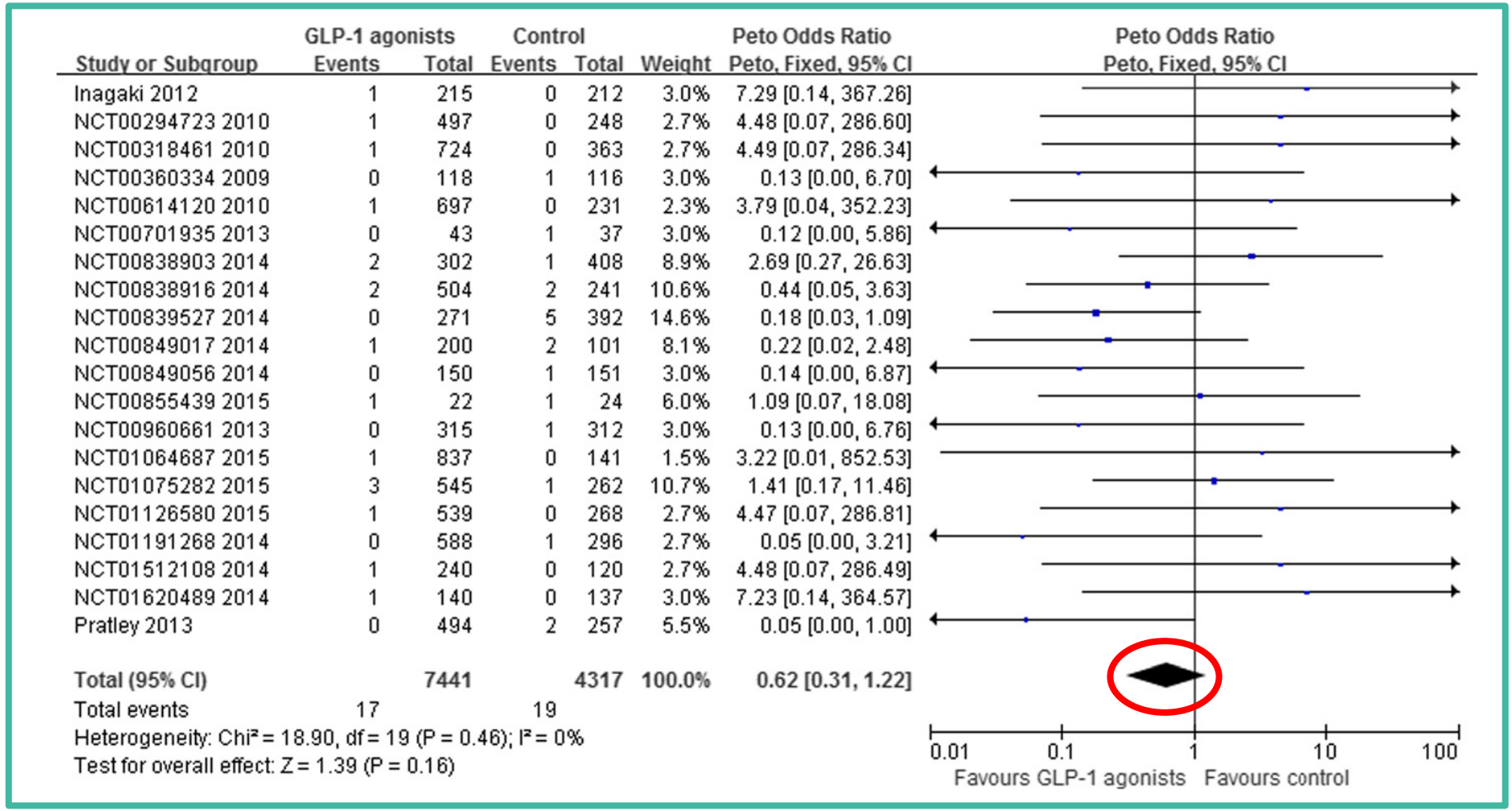


Holman RR et al. N Engl J Med 2017;377:1228-39.

Li et al. BMC Cardiovascular Disorders (2016) 16:91

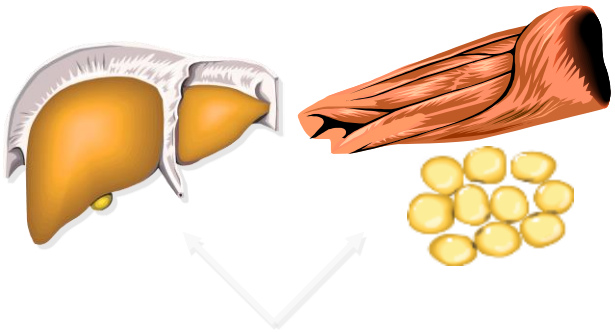
RESEARCH ARTICLE Open Access

Glucagon-like peptide-1 receptor agonists and heart failure in type 2 diabetes: systematic review and meta-analysis of randomized and observational studies



Options for Antidiabetic Treatment

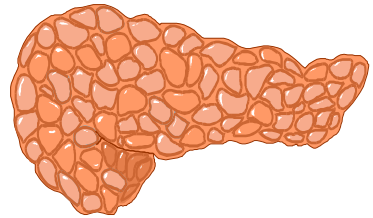
Insulin Resistance



Metformin

Pioglitazone

Insulin Secretion



Glucose independent

Sulfonylurea

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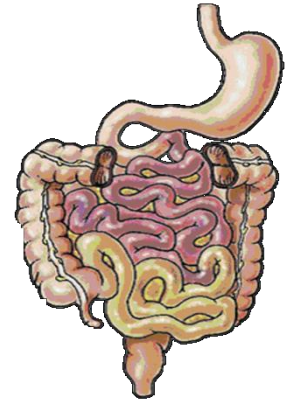
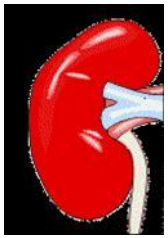


α-Glucosidase Inhibitors

Acarbose

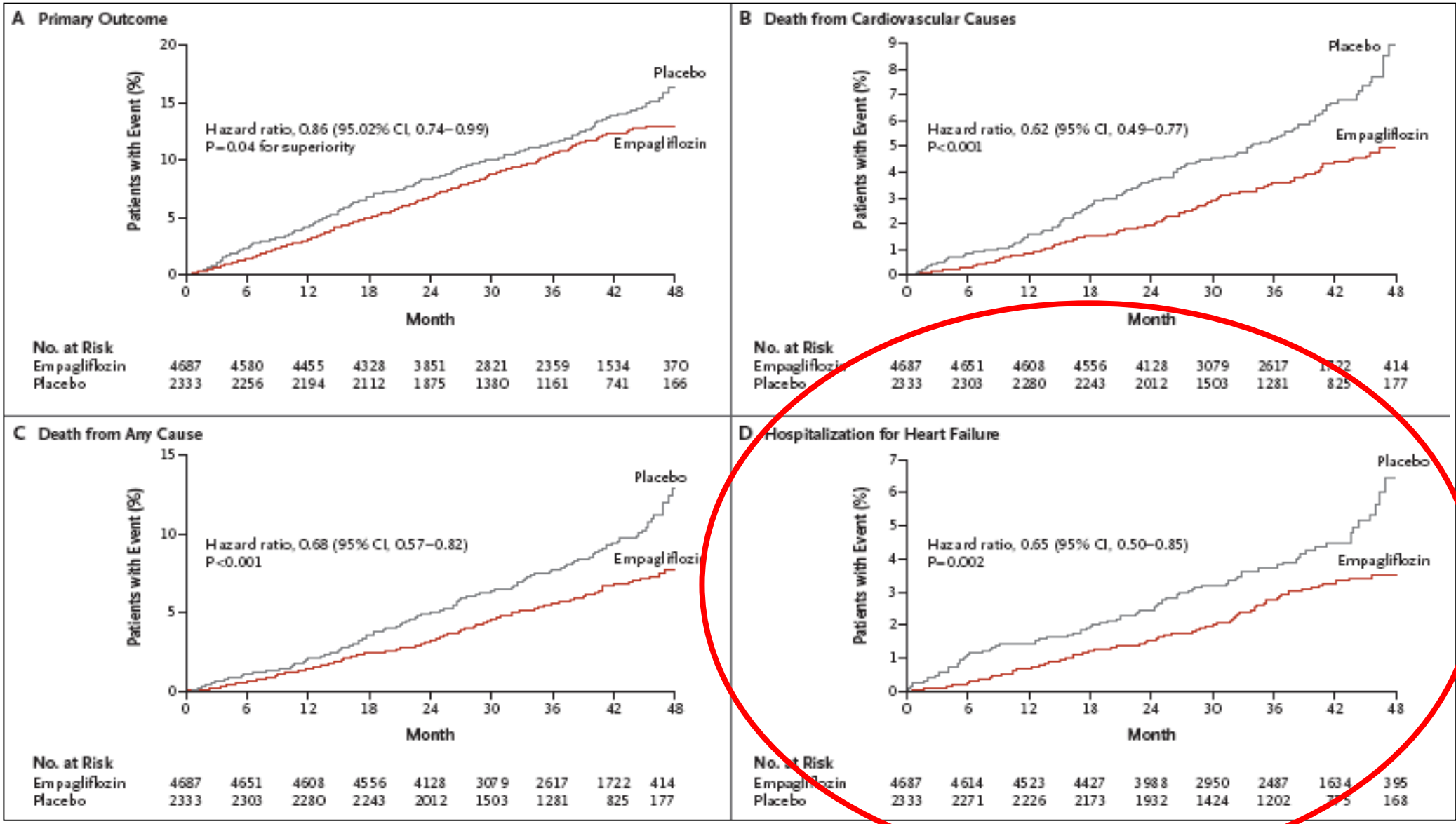
Inhibition of Renal Glucose Reabsorption



SGLT2-Inhibitors

Dapagliflozin, Canagliflozin Empagliflozin

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes



Zinman B et al. N Engl J Med. 2015;373(22):2117-28

European Heart Journal Advance Access published January 26, 2016

European Heart Journal
doi:10.1093/eurheartj/ehv728

AHA
Heart failure/cardiomyopathy

Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME[W] trial

David Fitchett[1*], Bernard Zinman[2,3], Christoph Wanner[4], John M. Lachin[5], Stefan Hantel[6], Afshin Salsali[7], Odd Erik Johansen[8], Hans J. Woerle[9], Uli C. Broedl[9], and Silvio E. Inzucchi[10], on behalf of the EMPA-REG OUTCOME[W] trial investigators

Table I Heart failure outcomes and all-cause hospitalization

Outcome	Placebo (*N* = 2333)		Empagliflozin (*N* = 4687)		HR (95% CI)	*P*-value
	n (%)	Rate/1000 patient-years	*n* (%)	Rate/1000 patient-years		
Heart failure hospitalization or cardiovascular death	198 (8.5)	30.1	265 (5.7)	19.7	0.66 (0.55–0.79)	<0.001
Hospitalization for or death from heart failure	104 (4.5)	15.8	129 (2.8)	9.6	0.61 (0.47–0.79)	<0.001
Hospitalization for heart failure	95 (4.1)	14.5	126 (2.7)	9.4	0.65 (0.50–0.85)	0.002
Investigator-reported heart failure[a]	143 (6.1)	22.0	204 (4.4)	15.3	0.70 (0.56–0.87)	0.001
Investigator-reported serious heart failure[a,b]	136 (5.8)	20.9	192 (4.1)	14.4	0.69 (0.55–0.86)	0.001
All-cause hospitalization	925 (39.6)	183.3	1725 (36.8)	161.9	0.89 (0.82–0.96)	0.003

CI, confidence interval; HR, hazard ratio; MedDRA, Medical Dictionary for Regulatory Activities.

[a]Based on narrow standardized MedDRA query 'cardiac failure', which comprised these preferred terms: acute pulmonary oedema; cardiac failure; cardiac failure, acute; cardiac failure, chronic; cardiac failure, congestive; cardiogenic shock; cardiopulmonary failure; left ventricular failure; pulmonary oedema; right ventricular failure.

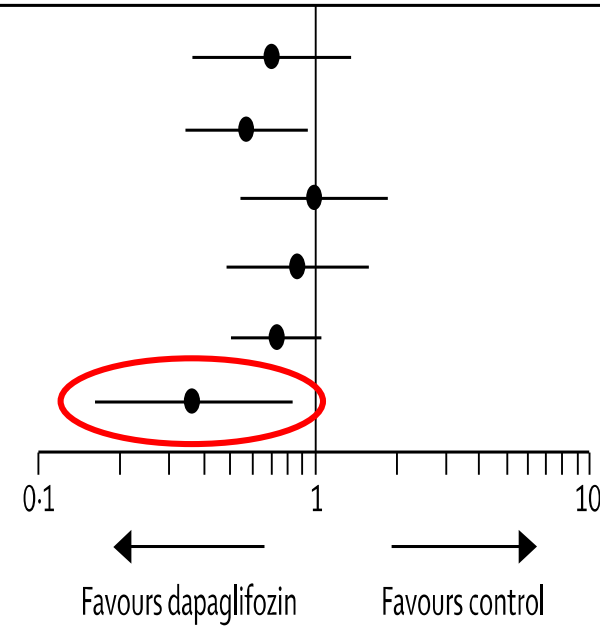
[b]Adverse events reported as serious adverse events by investigator. Patients treated with at least one dose of study drug.

Heart failure in diabetes: effects of anti-hyperglycaemic drug therapy

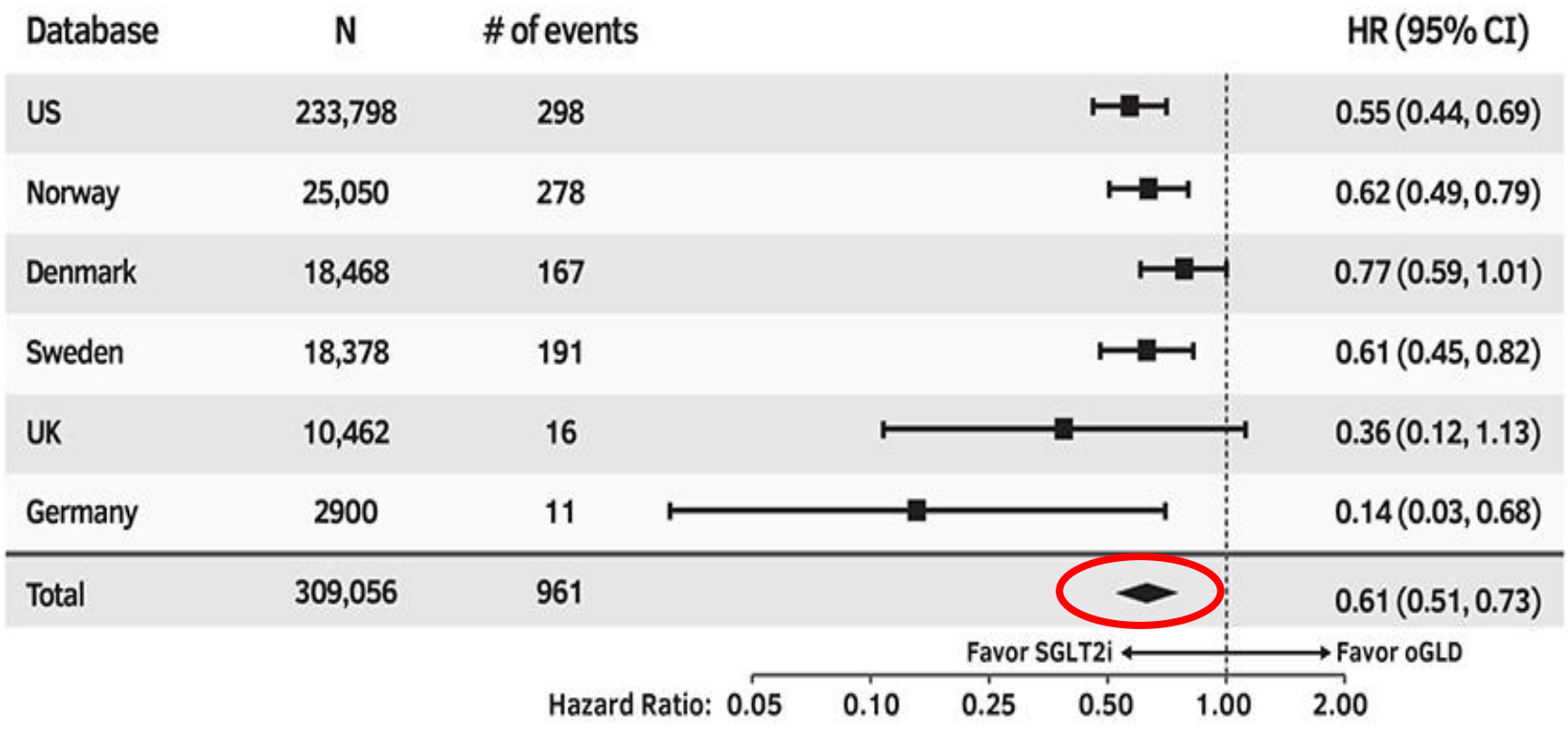
Lancet 2015; 385: 2107–17

Richard E Gilbert, Henry Krum

	Patients with event		HR (95% CI)	HR *vs* control (95% CI)
	Dapaglifozin (n=5936)	Control (n=3403)		
Cardiovascular death	20/3825	18/2200		0·70 (0·36–1·36)
Myocardial infarction	30/5244	33/3014		0·57 (0·34–0·95)
Stroke	25/4227	18/2412		1·00 (0·54–1·86)
Unstable angina	26/4592	20/2697		0·87 (0·48–1·59)
Unplanned coronary revascularisation	58/5525	55/3153		0·73 (0·50–1·07)
Admission to hospital for heart failure	10/2576	16/1780		0·36 (0·16–0·84)



The CVD-REAL Study: Hospitalization for heart failure primary analysis



Heterogeneity p-value: 0.169

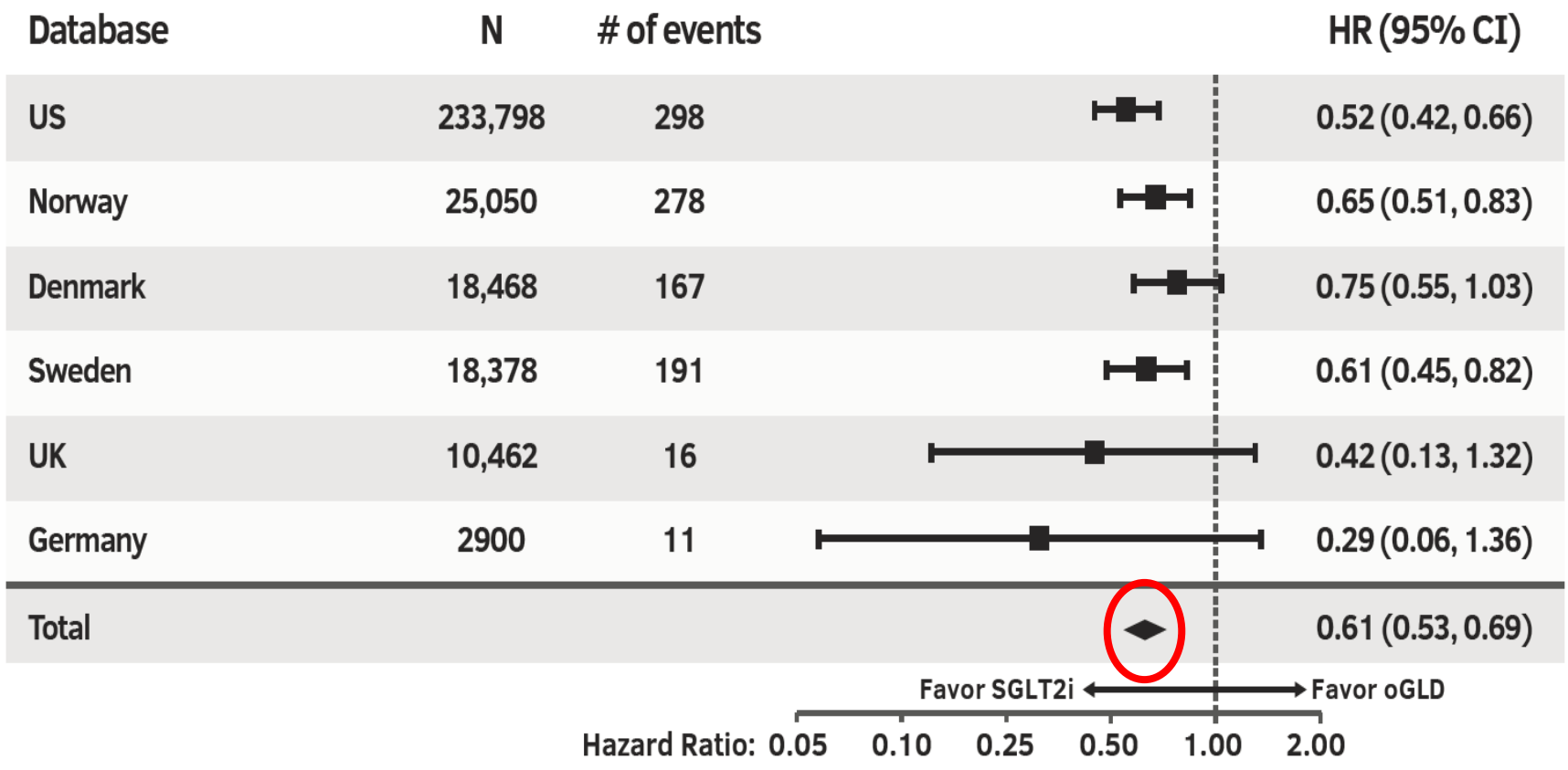
P-value for SGLT2 inhibitor vs other glucose-lowering drug: <0.001

Data are on treatment, unadjusted.

Kosiborod M ei al. Circulation. 2017;136:249–259

The CVD-REAL Study

Hospitalization for heart failure sensitiviy analysis: On treatment, adjusted*



P-value for SGLT2i vs other glucose-lowering drug: <0.001

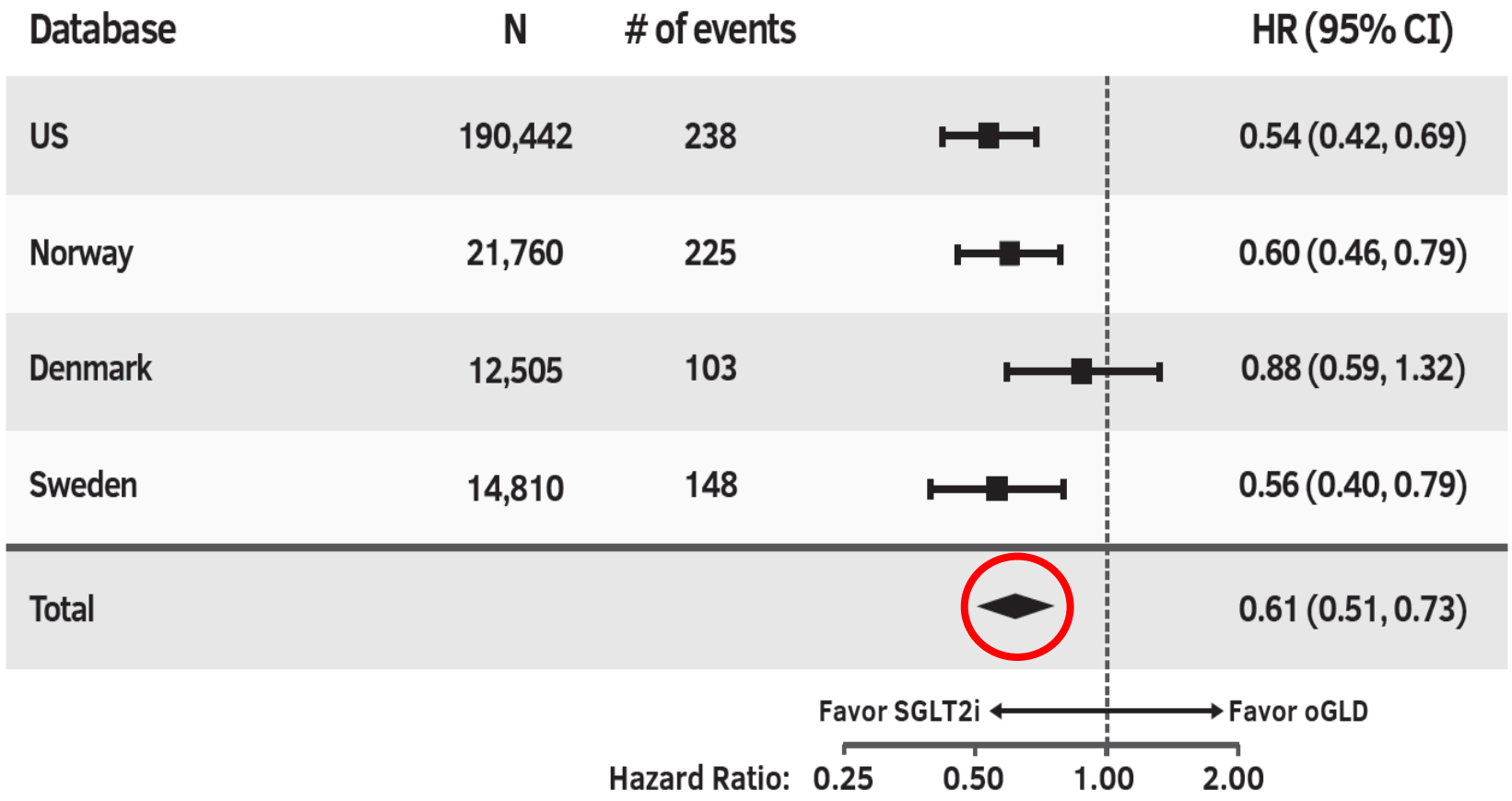
Heterogeneity p-value: 0.440

*Model adjusted for history of heart failure, age, gender, frailty, history of myocardial infarction, history of atrial fibrillation, hypertension, obesity / body mass index, duration of diabetes, ACE inhibitor or ARB use; β-blocker or α-blocker use, Ca+-channel blocker use, loop diuretic use, thiazide diuretic use

Kosiborod M ei al. Circulation. 2017;136:249–259

The CVD-REAL Study

Hospitalization for heart failure sensitivity analysis: Removal of patients with GLP-1 receptor agonists at baseline



P-value for SGLT2i vs other glucose-lowering drug: <0.001

Heterogeneity p-value: 0.229

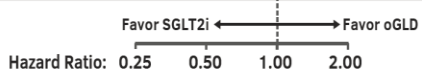
Kosiborod M ei al. Circulation. 2017;136:249–259

The CVD-REAL Study

Hospitalization for heart failure: Stepwise removal of other glucose-lowering drugs

TZD removed

Database	N	# of events	HR (95% CI)
US	226,844	268	0.53 (0.42, 0.67)
Norway	24,680	277	0.65 (0.51, 0.83)
Denmark	18,468	167	0.75 (0.55, 1.03)
Sweden	18,244	190	0.62 (0.46, 0.84)
Total			0.62 (0.54, 0.71)



Heterogeneity p-value: 0.357

TZD and insulin removed

N	# of events	HR (95% CI)
188,315	198	0.62 (0.47, 0.83)
16,698	172	0.64 (0.47, 0.86)
11,046	78	0.54 (0.34, 0.86)
9942	86	0.70 (0.46, 1.08)
		0.63 (0.53, 0.75)

Heterogeneity p-value: 0.879

TZD, insulin and SU removed

N	# of events	HR (95% CI)
167,590	179	0.56 (0.41, 0.77)
12,360	118	0.83 (0.56, 1.22)
9124	63	0.44 (0.26, 0.74)
7728	63	0.43 (0.25, 0.73)
		0.57 (0.42, 0.76)

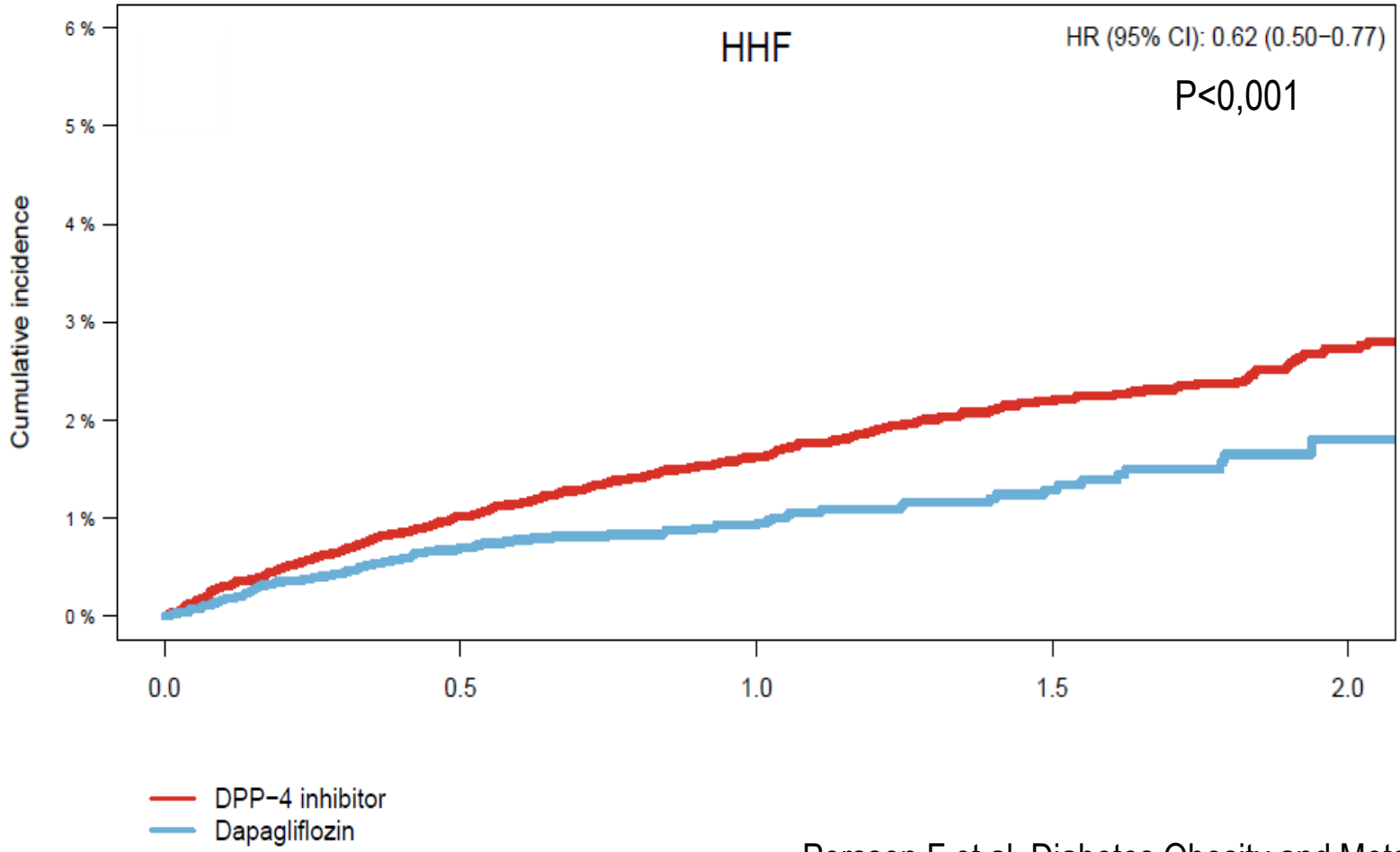
Heterogeneity p-value: 0.133

P-value for SGLT2i vs other glucose-lowering drug: <0.001 for all

Kosiborod M ei al. Circulation. 2017;136:249–259

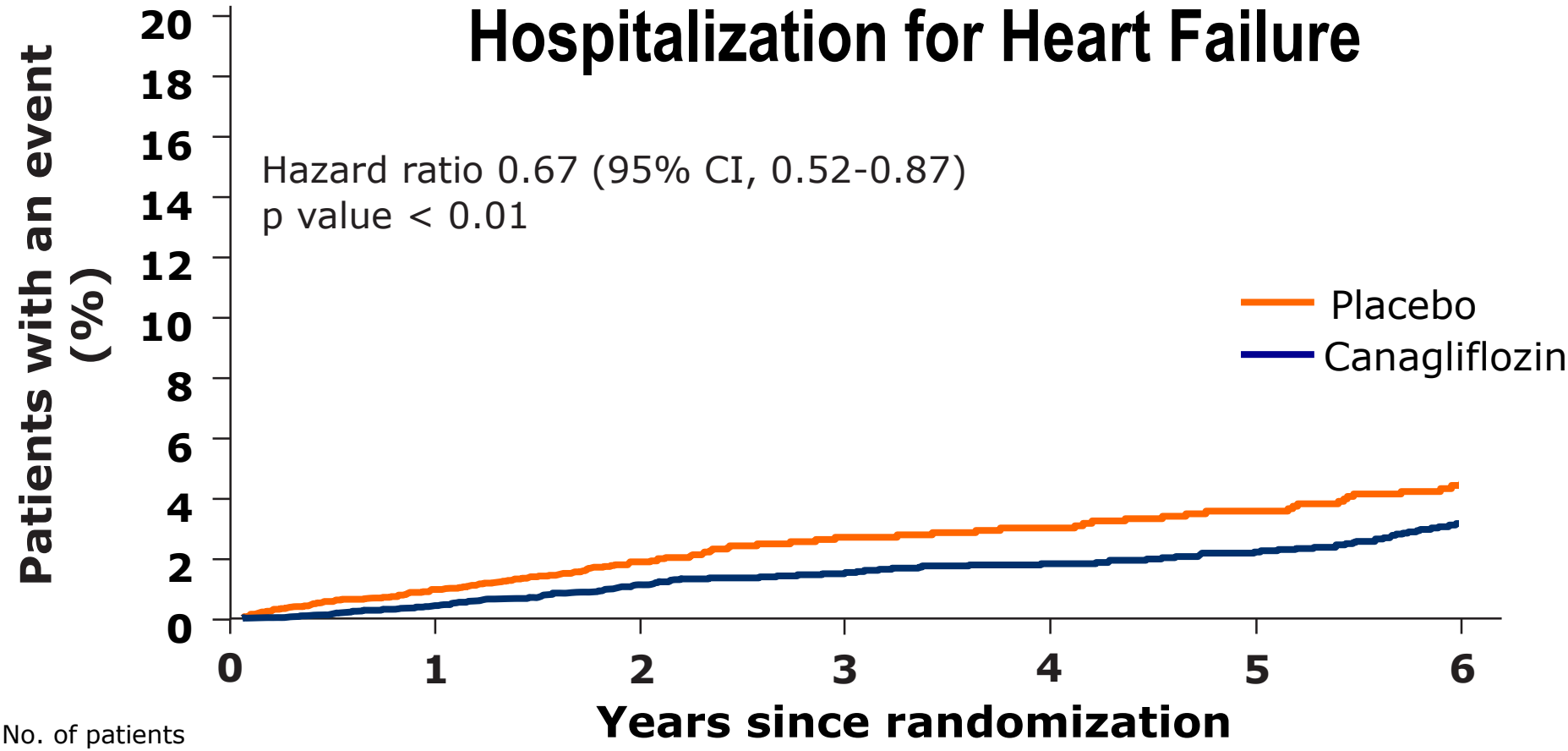
CVD-REAL Nordic
Dapagliflozin Compared to DPP-4 inhibitors

Pooled Kaplan–Meier curves for HHF



Persson F et al. Diabetes Obesity and Metabolism 2017;1–8

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes



No. of patients							
Placebo	4347	4198	3011	1274	1236	1180	829
Canagliflozin	5795	5653	4437	2643	2572	2498	1782

N Engl J Med. 2017;377(7):644-657

European Journal of Heart Failure (2016)
doi:10.1002/ejhf.633

Heart failure outcomes in clinical trials of glucose-lowering agents in patients with diabetes

David H. Fitchett[1]*, Jacob A. Udell[2], and Silvio E. Inzucchi[3]

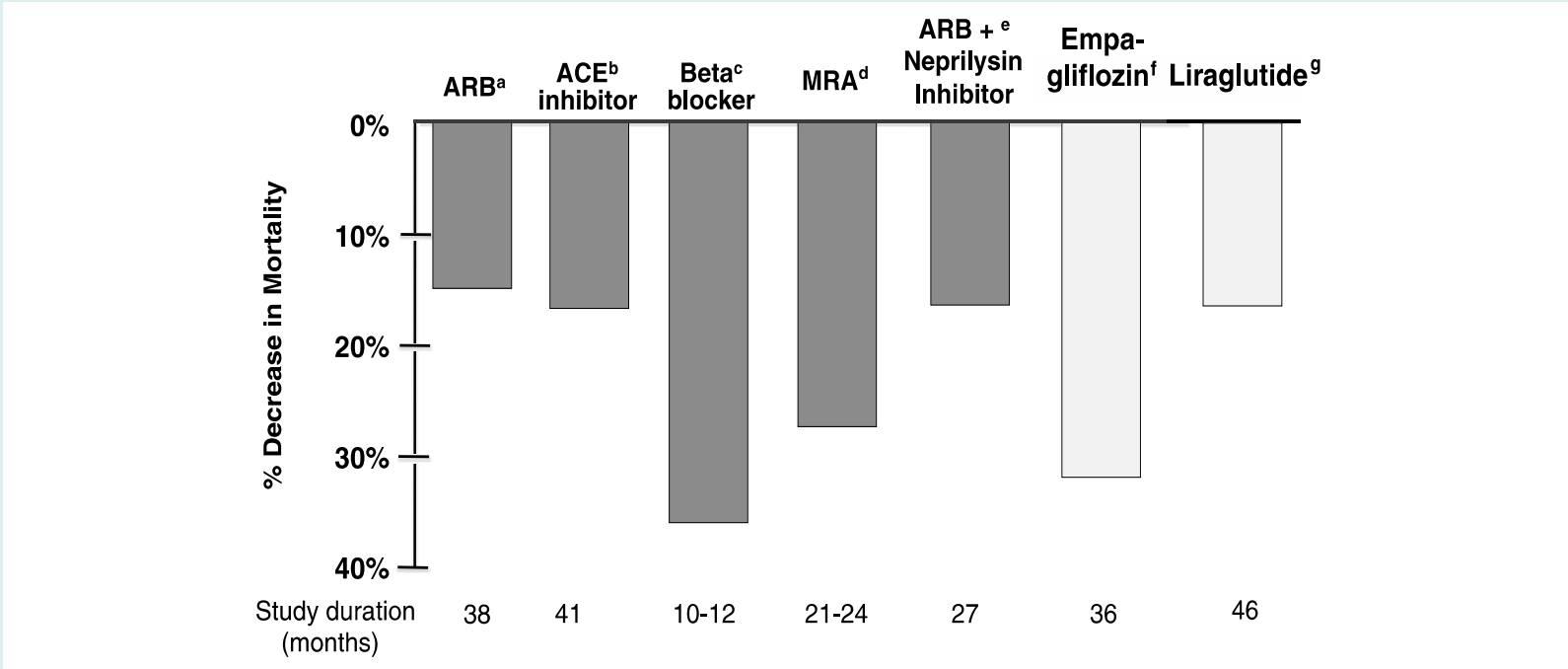


Figure 5 Comparison of all-cause mortality reduction observed in heart failure trials with the EMPA-REG OUTCOME and LEADER cardiovascular outcome trials in patients with diabetes. [a]SOLVD Treatment[69], [b]CHARM Alternative[70], [c]COPERNICUS[71] and MERIT-HF[72], [d]RALES[73] and EMPHASIS-HF[74], [e]PARADIGM[75], [f]EMPA-REG OUTCOME[65], [g]LEADER.[51]

European Journal of Heart Failure (2016) 18, 891–975
doi:10.1002/ejhf.592

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Recommendations to prevent or delay the development of overt heart failure or prevent death before the onset of symptoms

Recommendations	Class [a]	Level [b]	Ref [c]
Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life.	I	A	126, 129, 150, 151
Treatment with statins is recommended in patients with or at high-risk of CAD whether or not they have LV systolic dysfunction, in order to prevent or delay the onset of HF and prolong life.	I	A	137–140, 152
Counselling and treatment for smoking cessation and alcohol intake reduction is recommended for people who smoke or who consume excess alcohol in order to prevent or delay the onset of HF.	I	C	131–134
Treating other risk factors of HF (e.g. obesity, dysglycaemia) should be considered in order to prevent or delay the onset of HF.	IIa	C	130, 141, 153–155
Empagliflozin should be considered in patients with type 2 diabetes in order to prevent or delay the onset of HF and prolong life.	IIa	B	130
ACE-I is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction in order to prevent or delay the onset of HF and prolong life.	I	A	5, 144, 145
ACE-I is recommended in patients with asymptomatic LV systolic dysfunction without a history of myocardial infarction, in order to prevent or delay the onset of HF.	I	B	5
ACE-I should be considered in patients with stable CAD even if they do not have LV systolic dysfunction, in order to prevent or delay the onset of HF.	IIa	A	142
Beta-blocker is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction, in order to prevent or delay the onset of HF or prolong life.	I	B	146
ICD is recommended in patients: a) with asymptomatic LV systolic dysfunction (LVEF ≤30%) of ischaemic origin, who are at least 40 days after acute myocardial infarction, b) with asymptomatic non-ischaemic dilated cardiomyopathy (LVEF ≤30%), who receive OMT therapy, in order to prevent sudden death and prolong life.	I	B	149, 156–158

Impact of glucose-lowering drugs on major adverse CV outcome, and HF hospitalization

	MACE outcome	HF Outcome	Use in HF
Insulin	↔	↔	✓
Metformin	↔	↔	✓
SU	?↔	?↔	✓
TZD	Rosiglitazone ↔ Pioglitazone ↓	↑	✖
GLP-1 A	Lixisenatide ↔ Liraglutide ↓	↔	✓
DPP4-i	↔	Saxagliptin ↑ Alogliptin ↑ns Sitagliptin ↔	Caution Caution ✓
SGLT2-i	↓	↓	✓

↔ Unchanged, ↓ Decreased, ↑ Increased.
DPP4-i, dipeptidyl peptidase 4 inhibitor; GLP-1 A, glucagon-like peptide 1 agonist; HF, heart failure; MACE, major adverse cardiac event; SGLT2-i, sodium–glucose co-transporter 2 inhibitor; SU, sulphonylurea; TZD, thiazolidinedione.

Fitchett DH et al. European Journal of Heart Failure (2016)