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DIABETE
OBESITÀ

XVI CONGRESSO NAZIONALE

29-31 Marzo 2017

NH VITTORIO VENETO

ROMA



Dr Giovanni Maria Polizzi
Direttore
U.O.C. Cardiologia-UTIC

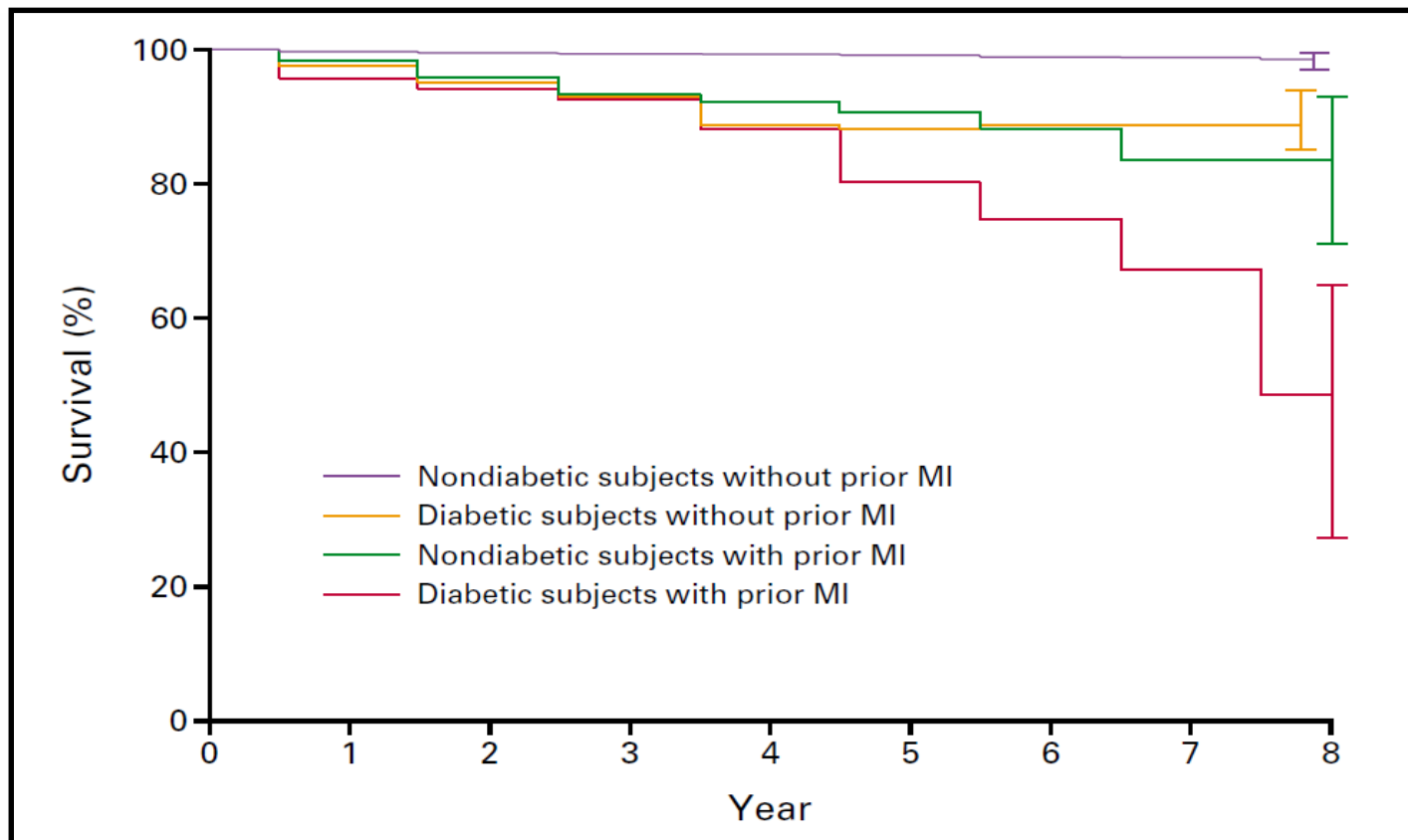
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SESSIONE CONGIUNTA SIMDO - ANMCO

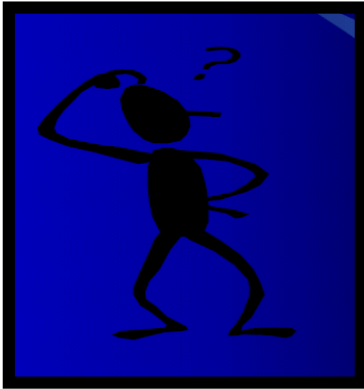
Scompenso cardiaco, Cardiomiopatie e Diabete

MORTALITY FROM CORONARY HEART DISEASE IN SUBJECTS WITH TYPE 2 DIABETES AND IN NONDIABETIC SUBJECTS WITH AND WITHOUT PRIOR MYOCARDIAL INFARCTION

STEVEN M. HAFFNER, M.D., SEppo LEHTO, M.D., TAPANI RÖNNEMAA, M.D., KALEVI PYÖRÄLÄ, M.D.,
AND MARKKU LAAKSO, M.D.



Sul rapporto tra DM ed HF abbiamo 2 annosi problemi:

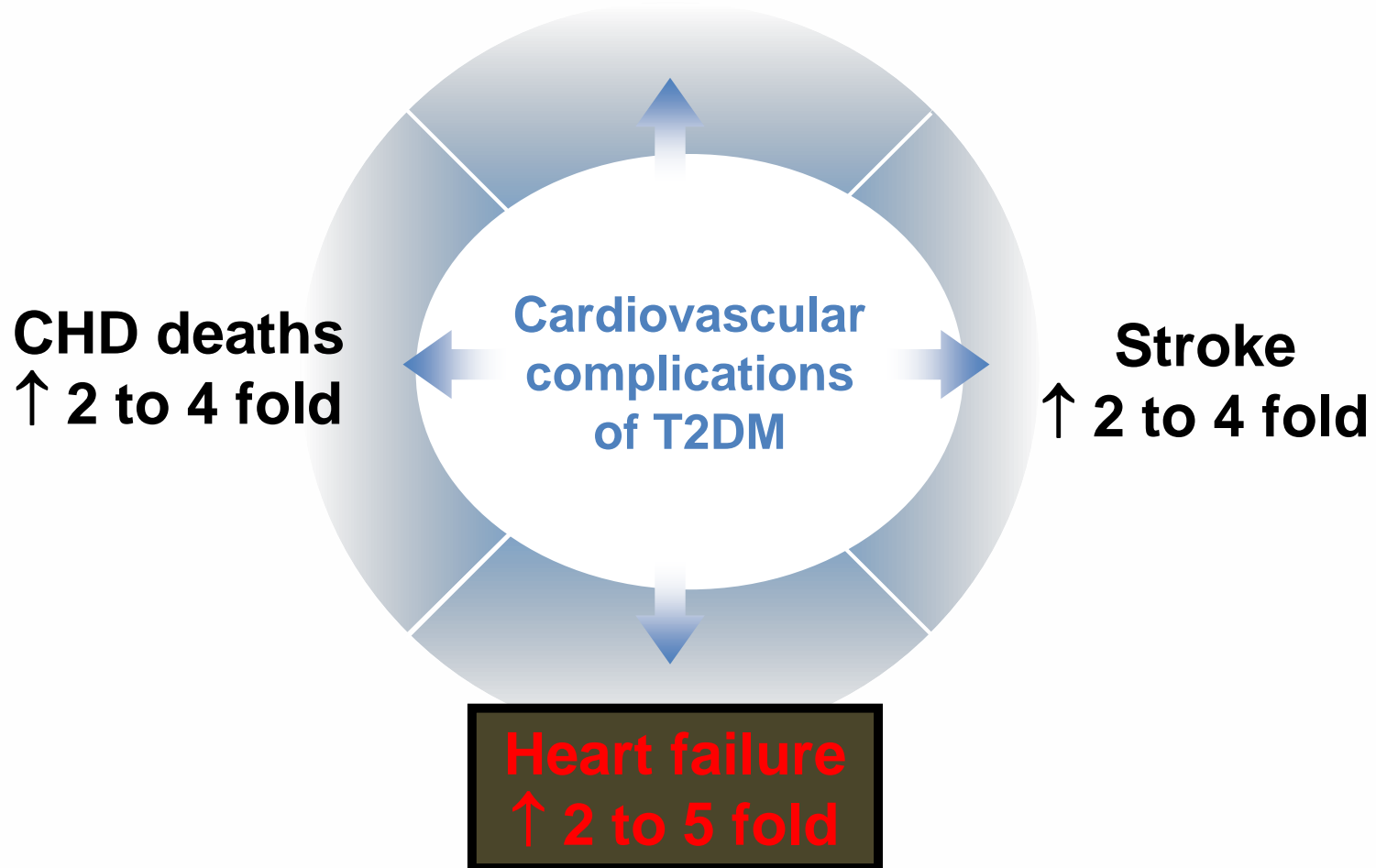


Nella scala gerarchica per importanza delle complicanze del DM abbiamo sempre tenuto nella massima considerazione quelle **micro** – e **macro vascolari** e **neurologiche** poco considerando lo **HF** nonostante la sua immensa rilevanza per incidenza, prevalenza, morbilità e mortalità;

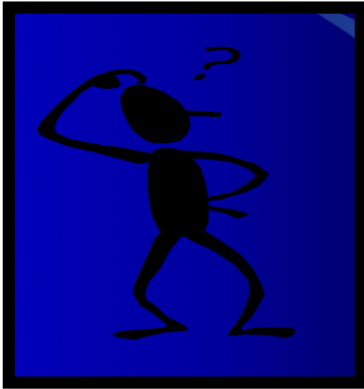


Cardiovascular disease and diabetes

~ 65% of deaths are due to CVD



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Abbiamo prestato, per troppo tempo, la massima attenzione agli effetti dei farmaci sulla glicemia piuttosto che sulla loro abilità a ridurre le complicanze a lungo termine.

ROADMAP

- Dati epidemiologici ed impatto prognostico
- Fisioterapia
- Terapia

HF e DM

Dati epidemiologici ed impatto prognostico



DUE CATTIVI COMPAGNI

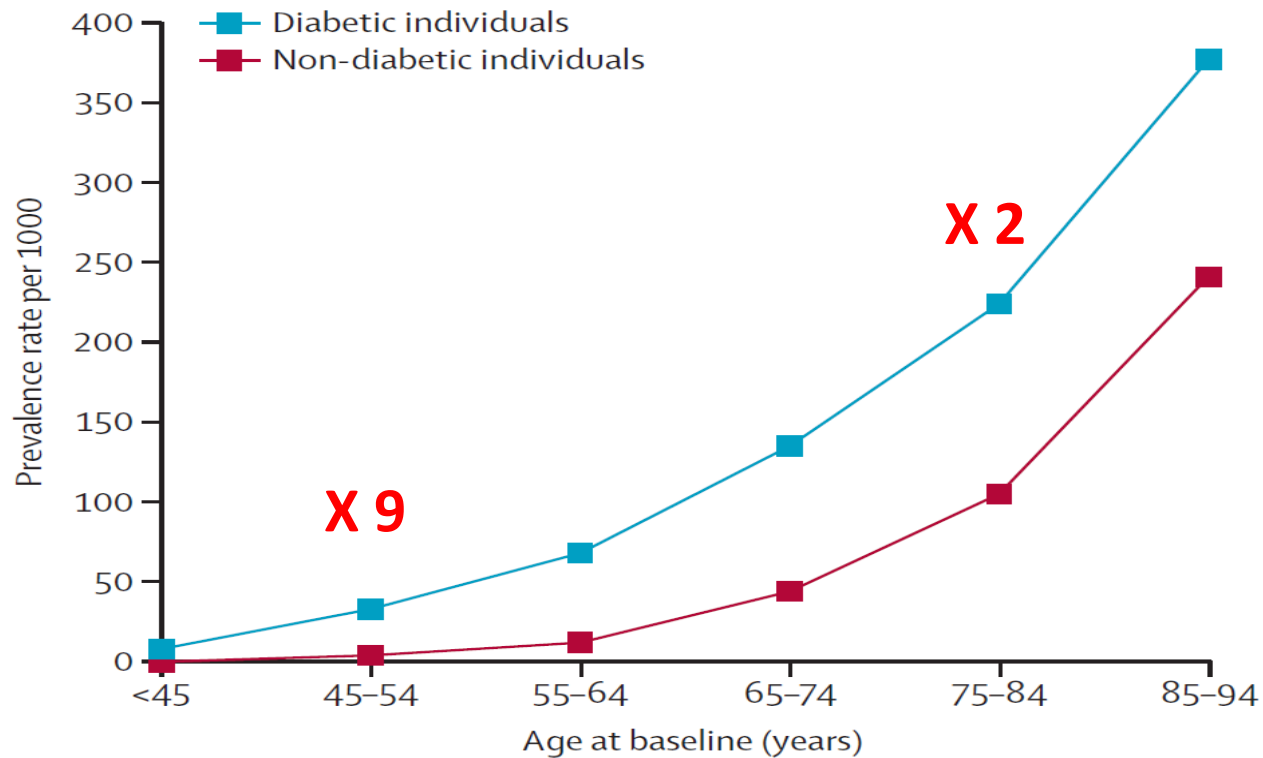
PUNTO DI VISTA DEL DIABETOLOGO

Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. *Am J Cardiol* 1974; 34: 29–34.

DM: rischio di HF

X 2 Uomini -- X 5 Donne

Prevalenza di HF in DM



Studi che hanno esaminato l'associazione tra DM ed HF

Table 1: Studies Examined the Association between Diabetes Mellitus and Heart Failure

Study/Author	Design	Subjects	Results
Nichols et al. 2004 ¹⁰	Retrospective cohort	8,231 patients with DM and 8,845 non-DM patients	The incidence rate of HF in DM subjects was 3 times that of non-DM
Iribarren et al. 2001 ¹¹	Prospective cohort (2.2 years follow-up)	49.000 DM patients	Increased levels were associated with greater risk of HF
Stratton et al. 2000 (UKPDS 35) ¹²	Prospective observational study	4,585 DM patients	In type 2 DM patients the risk of diabetic complications and HF was strongly associated with previous hyperglycaemia
Matsushita et al. 2010 (ARIC study) ¹³	Prospective cohort (14.1 years follow-up)	11.000 subjects free of DM or HF at baseline	Elevated HbA1c (≥ 5.5 –6.0 %) was associated with incident HF
He et al. 2001 (NHANES I) ¹⁴	Prospective cohort (19 years follow-up)	13.643 subjects without HF	DM is an independent risk factor for HF (relative risk 1.85)
Boonman-de Winter et al. 2012 ¹⁵	Cross-sectional study	605 patients with type 2 DM	HF (28 %) and left ventricular dysfunction (23 %) are highly prevalent in DM patients
Vasiliadis et al. 2014 ⁸	Cross-sectional	200 HF patients	From HF subjects 27 % had type 2 DM and 10 % type 1 DM
Bertoni et al. 2004 ¹⁶	Prospective cohort study (5 years follow-up)	151.000 DM subjects over 65 years old	The incidence rate of HF was estimated at 12.6 per 100 person-years

ARIC = Atherosclerosis Risk in Community; DM = diabetes mellitus; HbA1c = glycated haemoglobin; HF = heart failure; NHANES I = First National Health and Nutrition Examination Survey Epidemiologic Follow-up Study; UKPDS = UK Prospective Diabetes Study.

Nella scala gerarchica per importanza delle complicanze del DM abbiamo sempre tenuto nella massima considerazione quelle **micro** – e **macro vascolari** e **neurologiche** poco considerando lo **HF** nonostante la sua immensa rilevanza per incidenza, prevalenza, morbilità e mortalità;

Inciden

with
h

Il per

IMA + STROKE

VS

HF



PUNTO DI VISTA DEL CARDIOLOGO

Diabetes, left ventricular systolic dysfunction, and chronic heart failure

The prevalence of DM in general populations with and without HF

Study	Year of publication	Number of participants	Age range	Mean age (years)	Prevalence of HF	Prevalence of DM in population with HF	Prevalence of DM in population without HF
Rotterdam ¹²⁴	2001	5255	55-94	69	n = 181 (3.4%)	n = 32 (17.5%)	n = 523 (10.3%)
Italy ¹⁷	1997	1339	>65	74	n = 125 (9.5%)	n = 37 (29.6%)	n = 160 (13.2%)
Rekjavik ¹	2005	19 381	33-84	-	n = 733 (3.8%)	n = 85 (11.6%)	n = 635 (3.4%)
Olmsted ²⁷	2006	655	>45	77	Random sample of patients from general population study, all with HF	1979-1984: 13% 1990-1999: 11%	

X 2 - X 3

DM and mortality in HF: non-clinical trial populations



Location	Year of publication	Type of study	Number of patients	Mortality risk of DM (HR)
Rotterdam ¹²⁴	2001	Population-based cohort study	5540	3.19 (1.80–5.65)
Framingham ¹²⁵	1993	Population-based cohort study	9405	Women: 1.70 (1.21–2.38) Men: 0.99 (0.70–1.40)
Scotland ³⁰	2000	Retrospective cohort study	66 547	Men: 1.55 (1.41–1.70) Women: 1.50 (1.38–1.62)
USA ¹²⁶	1999	Retrospective cohort study	170 239	Black: 1.11 (1.06–1.16) White: 1.22 (1.24–1.25)
USA ¹²⁷	2005	HF clinic	495	1.71 (1.16–2.51)
USA ⁸⁵	2005	HF clinic	554	Patients not treated with insulin: 0.95(0.31–2.93) Patients treated with insulin: 4.30 (1.69–10.9)
France ²⁶	2004	HF clinic	1246	HF secondary to CHD: 1.54 (1.13–2.09) HF secondary to other aetiologies: 0.65 (0.39–1.07)
Olmsted, USA ²⁷	2006	Population-based cohort study	665	Overall: (RR) 1.48(1.20 to 1.82) HF secondary to CHD: (RR) 1.11 (0.81–1.51) HF secondary to other aetiologies: (RR) 1.79 (1.33–2.41)
Italy ³⁵	2003	HF Registry 'BRING-UP'	2843	(RR) 1.44 (1.16–1.78)

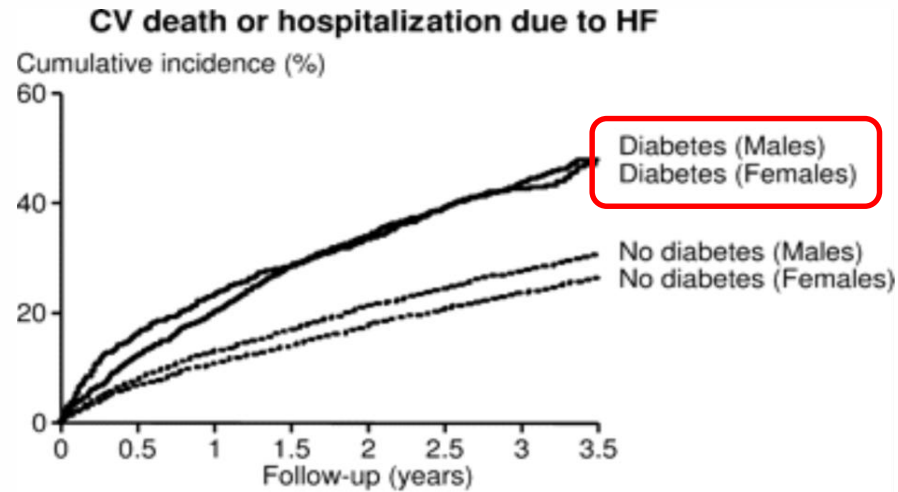
X 1.5 - X 3

Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart

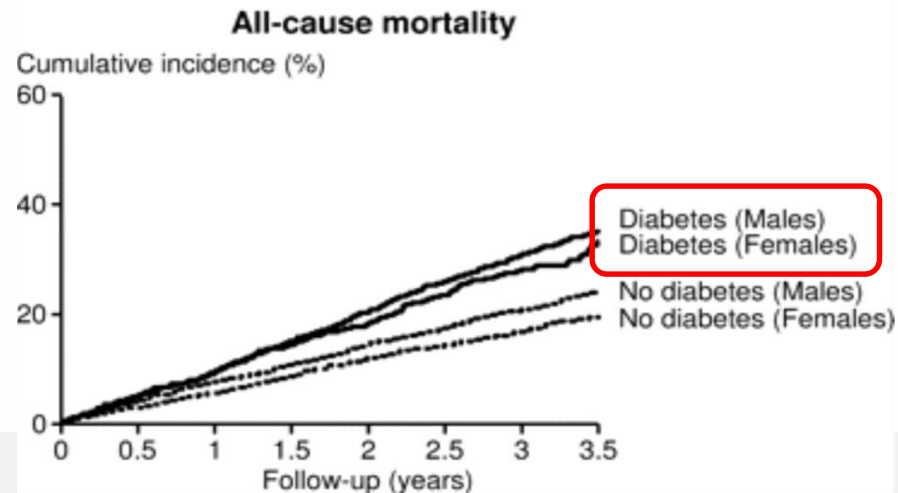


CHARM

Outcomes in diabetic and non-diabetic patients.



X 2



X 2

Despite these compelling statistics,
heart failure is often omitted from textbook lists
of diabetes complications and from major trials
that focus on **cardiovascular outcomes**.



Heart Failure:
the frequent, forgotten, and often
fatal complication of diabetes

DAVID S.H. BELL, MB, FACE

Effects of Intensive Glucose Lowering in Type 2 Diabetes

The Action to Control Cardiovascular Risk in Diabetes Study Group*

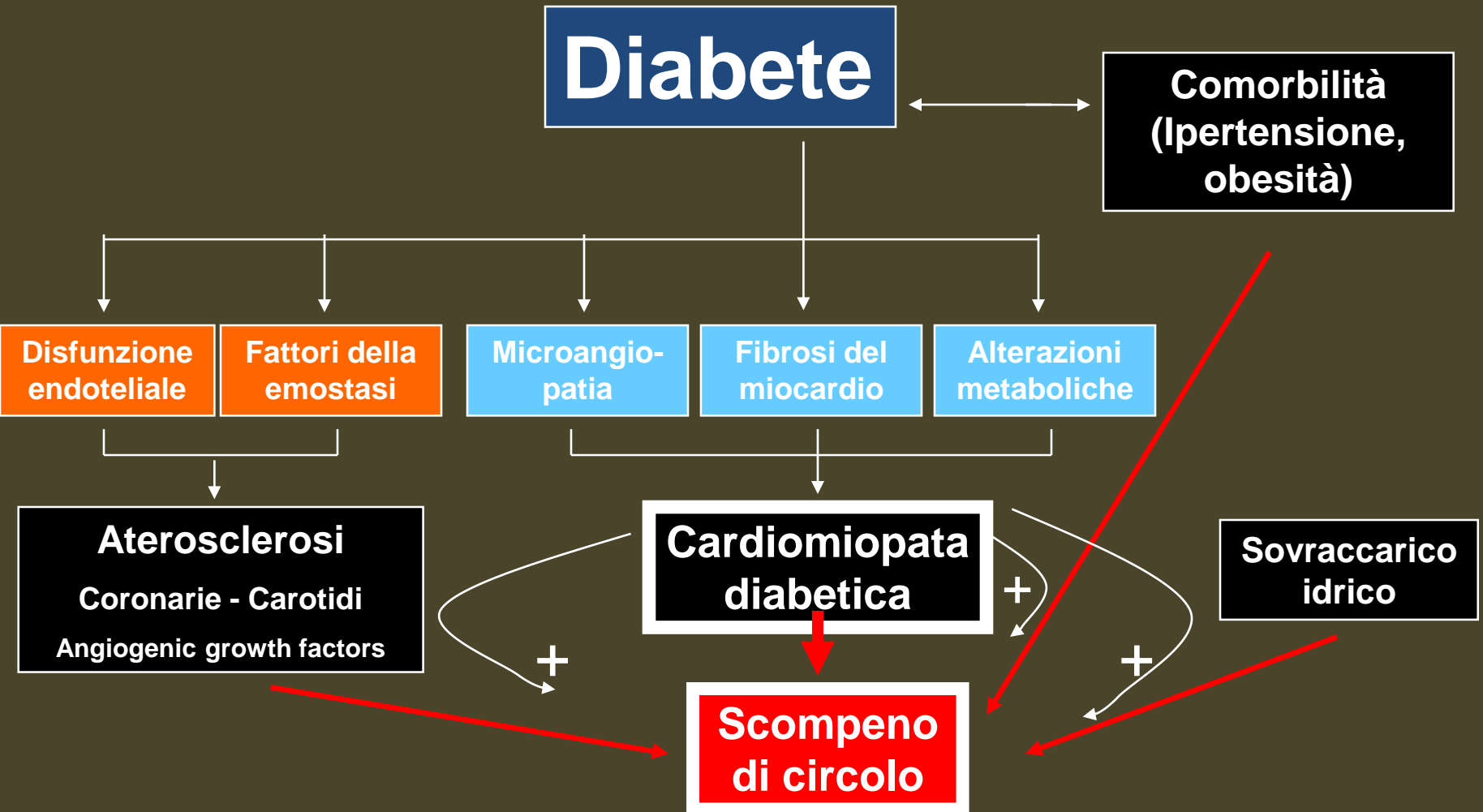
Primary Outcomes

Outcome	Intensive Therapy (N=5128)		Standard Therapy (N=5123)		Hazard Ratio (95% CI)	P Value
	<i>no. of patients (%)</i>	<i>% per yr</i>	<i>no. of patients (%)</i>	<i>% per yr</i>		
Primary outcome	352 (6.9)	2.11	371 (7.2)	2.29	0.90 (0.78–1.04)	0.16
Secondary outcome						
Death						
Any cause	257 (5.0)	1.41	203 (4.0)	1.14	1.22 (1.01–1.46)	0.04
Cardiovascular causes	135 (2.6)	0.79	94 (1.8)	0.56	1.35 (1.04–1.76)	0.02
Nonfatal myocardial infarction	186 (3.6)	1.11	235 (4.6)	1.45	0.76 (0.62–0.92)	0.004
Nonfatal stroke	67 (1.3)	0.39	61 (1.2)	0.37	1.06 (0.75–1.50)	0.74

Etiopatogenesi

Patogenesi dell'insufficienza cardiaca nel diabete

"LA TETRADE CARDIOTOSSICA"



Lundbaek K.

Diabetic angiopathy. A specific vascular disease.

Lancet 1954;263:377–379.

Diabetes mellitus directly causing myocardial dysfunction.
Myocardial dysfunction to be a common DM-related complication present in two-thirds of elderly DM patients: **Diabetes mellitus-related cardiomyopathy (DMCMP).**

Rubler S and coll.

A new type of cardiomyopathy associated with diabetic glomerulosclerosis.

Am J Cardiol 1972; 30:595–602.

Cardiomyopathic dysfunction could indeed directly result from DM and not merely indirectly from concomitant coronary artery disease.

A **cardiomyopathy** is defined as a heart muscle disease in which the myocardium is structurally and/or functionally abnormal in the absence of **coronary artery disease** as well as **hypertensive** or **valvular deseas**.

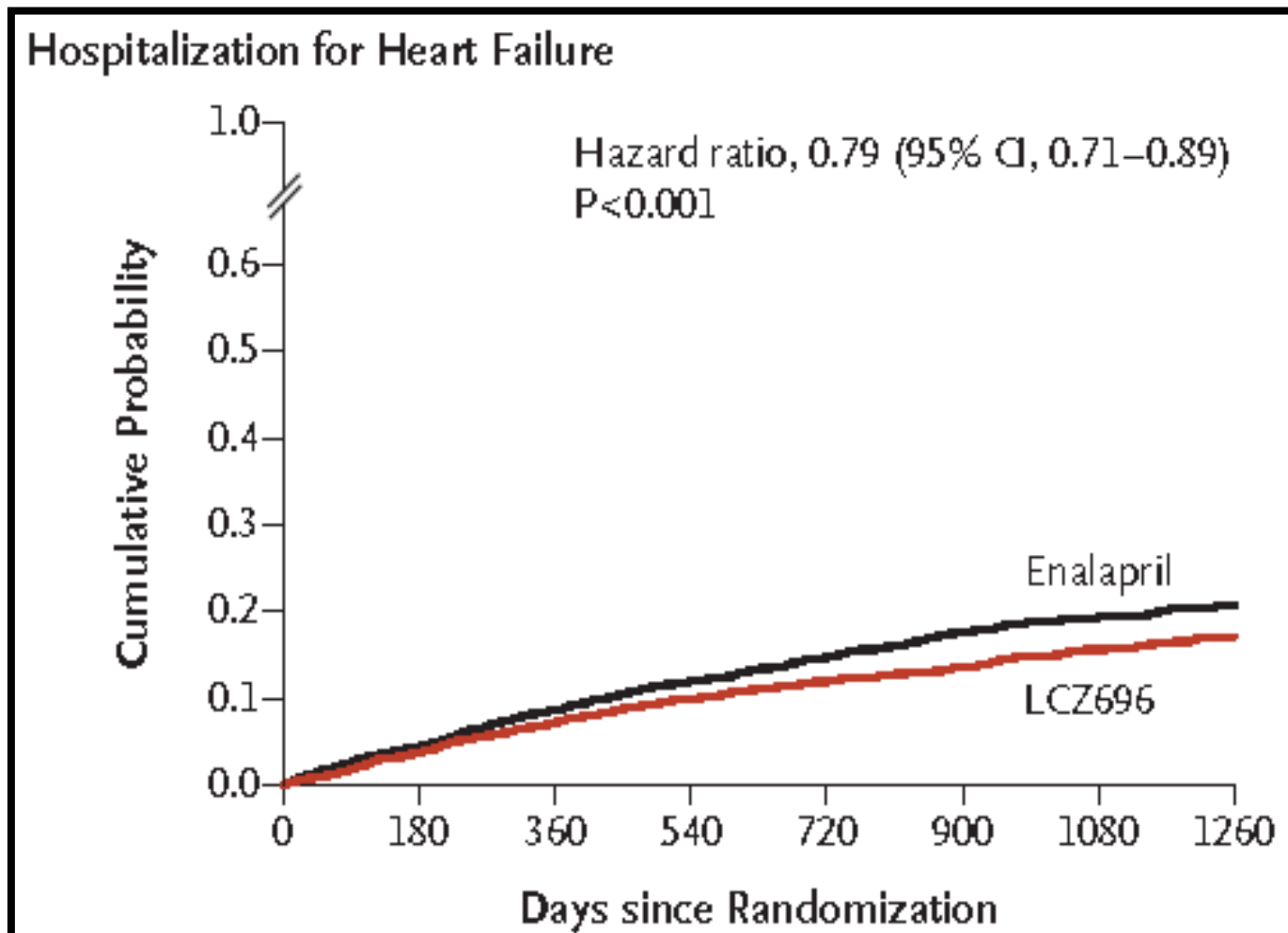
Terapia

Dalla prospettiva
cardiologica “no problem”
visto che tutte le classi di
farmaci che

.....

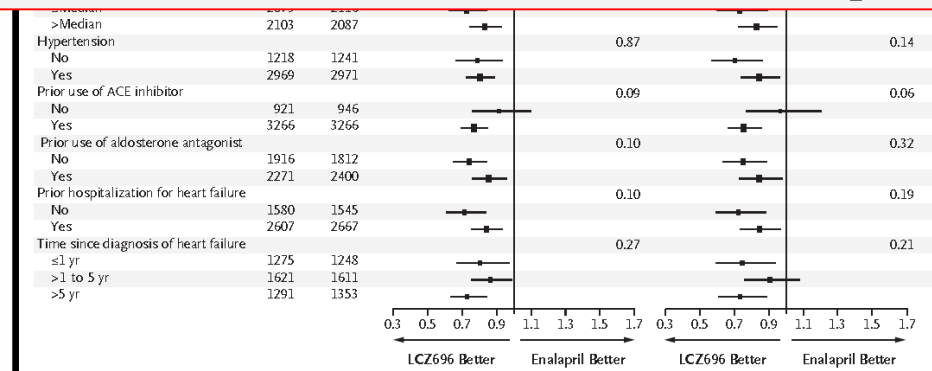
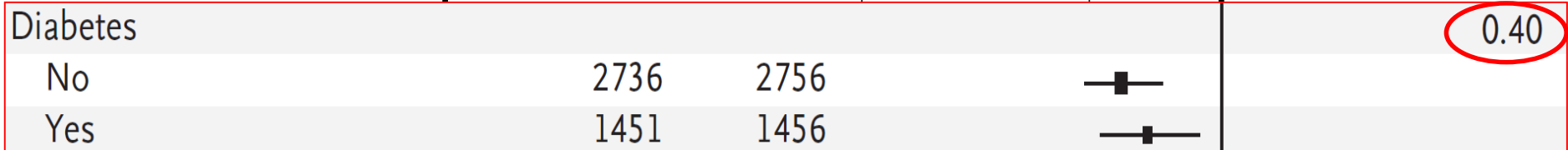
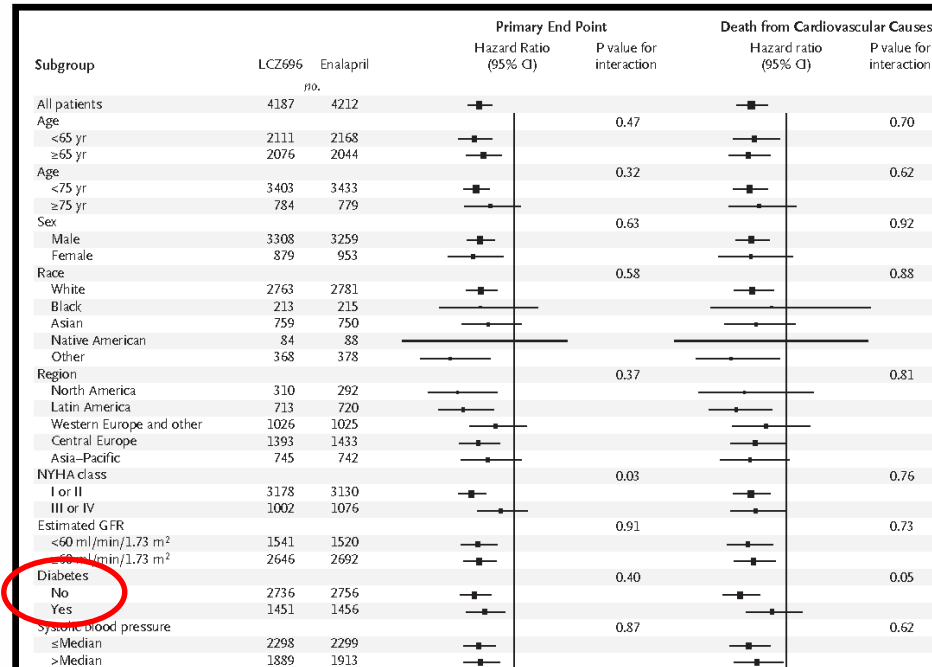
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Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure PARADIGM-HF



Medical history — no. (%)

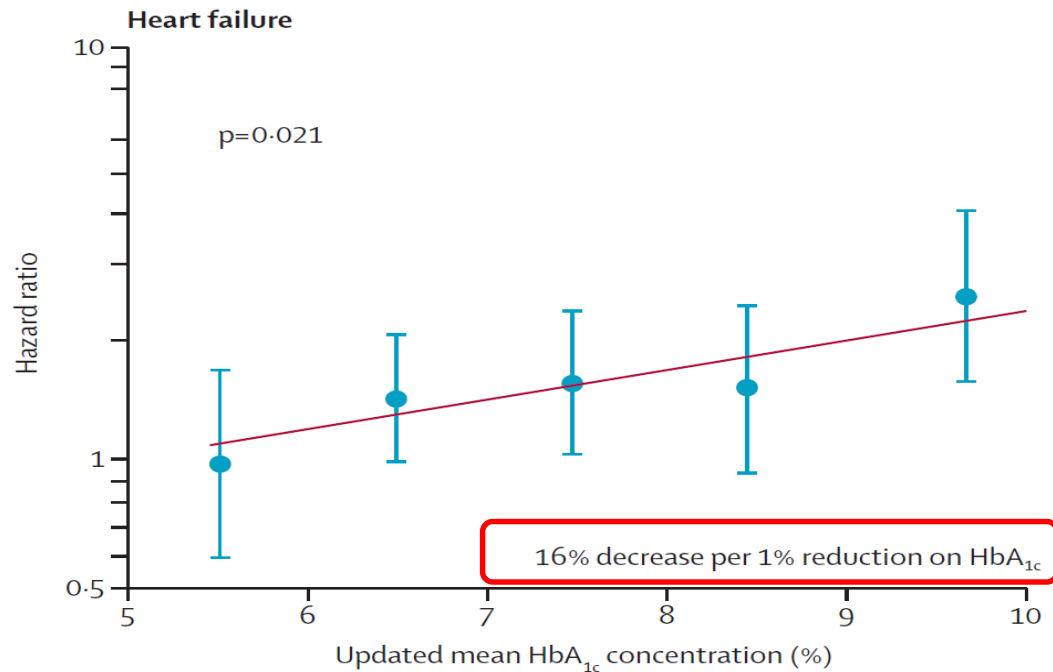
Hypertension	2969 (70.9)	2971 (70.5)
Diabetes	1451 (34.7)	1456 (34.6)
Atrial fibrillation	1517 (36.2)	1574 (37.4)
Hospitalization for heart failure	2607 (62.3)	2667 (63.3)
Myocardial infarction	1818 (43.4)	1816 (43.1)
Stroke	355 (8.5)	370 (8.8)
Pretrial use of ACE inhibitor	3266 (78.0)	3266 (77.5)
Pretrial use of ARB	929 (22.2)	963 (22.9)



Dalla prospettiva
diabetologica

Rapporto tra controllo glicemico ed HF

Osservazione epidemiologica

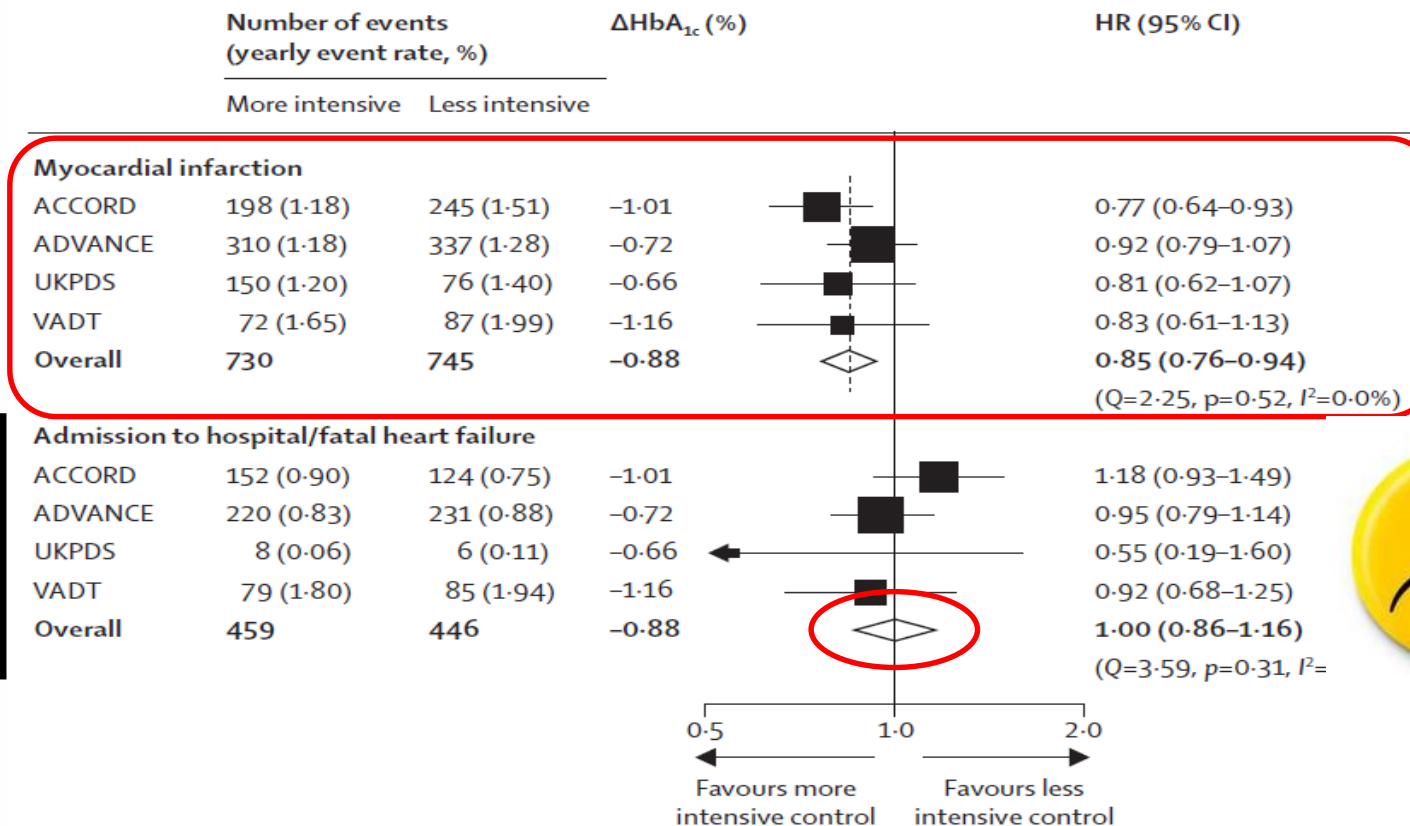


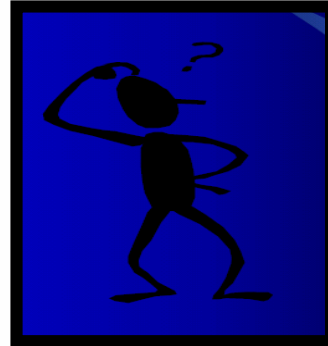
Stratton (UKPDS 35)

BMJ 2000; 321: 405–12

Rapporto tra controllo glicemico ed HF

Trial d'intervento "storici"





Confounding the issue of glycaemic control and heart failure prognosis is the role of antihyperglycaemic therapy ?

- Sulfaniluree
- Metformina
- Tiazolodinedioni
- GLP-1 receptor agonists
- DPP-IV inhibitors
- Glifozine
- Insulina

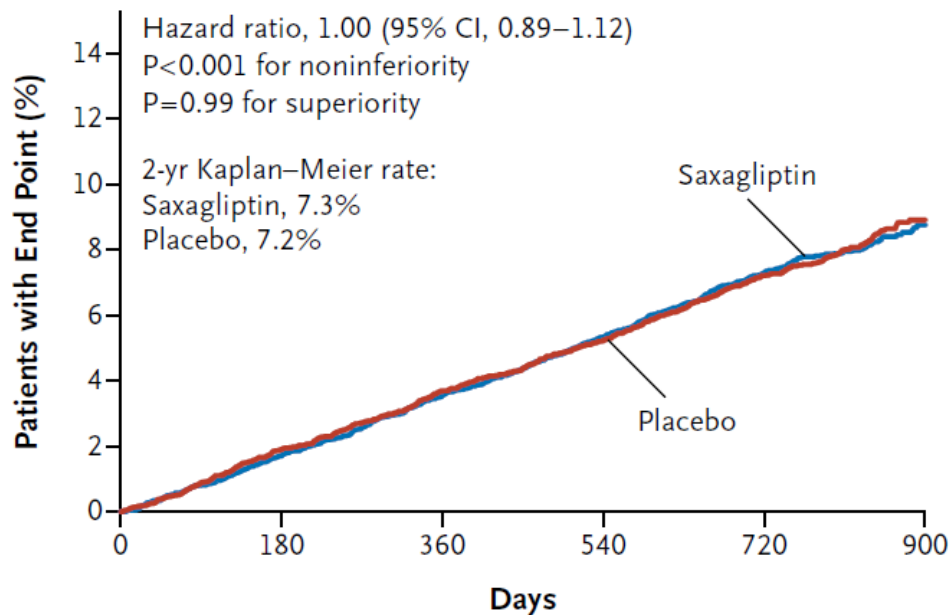
- Sulfaniluree
- Metformina
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- GLP-1 receptor agonists
- **DPP-IV inhibitors**
- **Glifozine**
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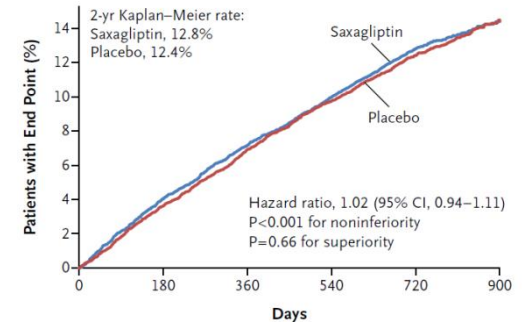
Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus

SAVOR-TIMI 53

A Primary End Point

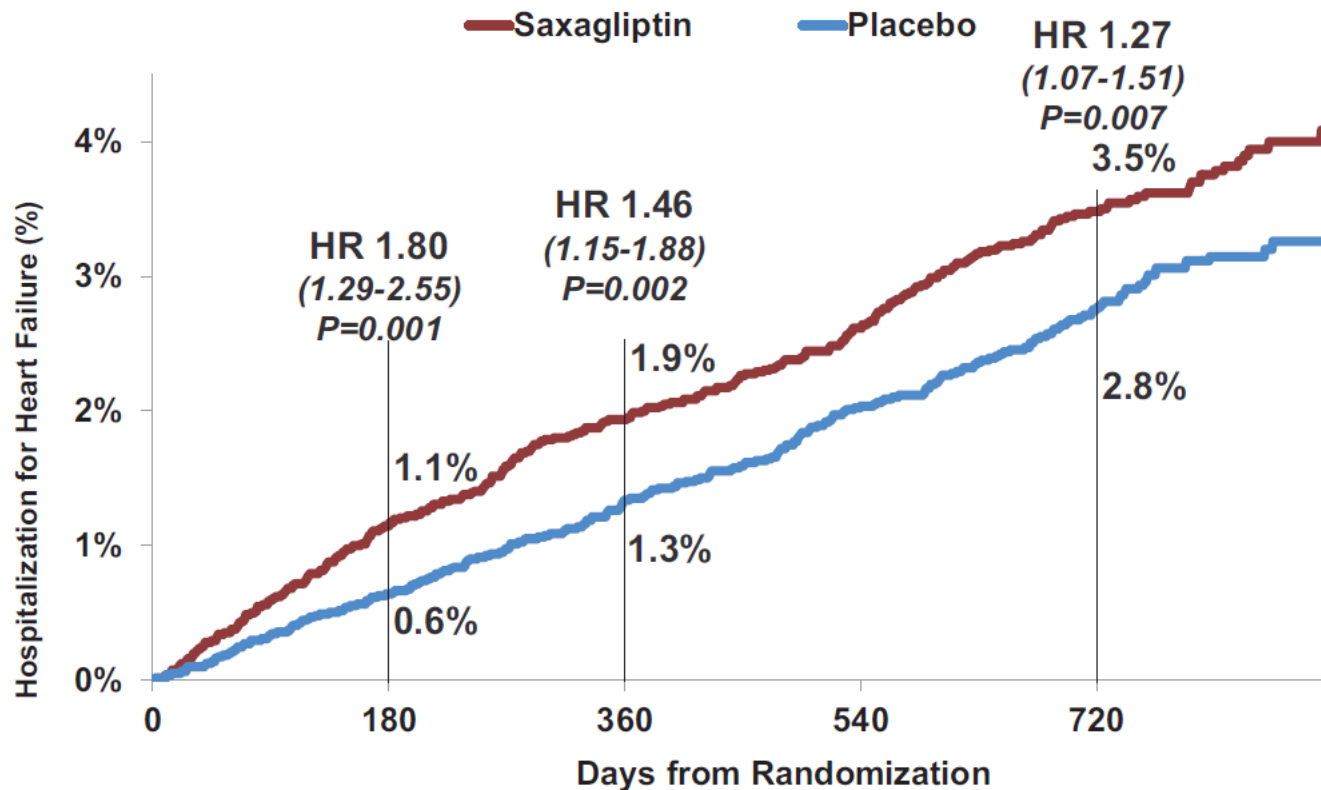


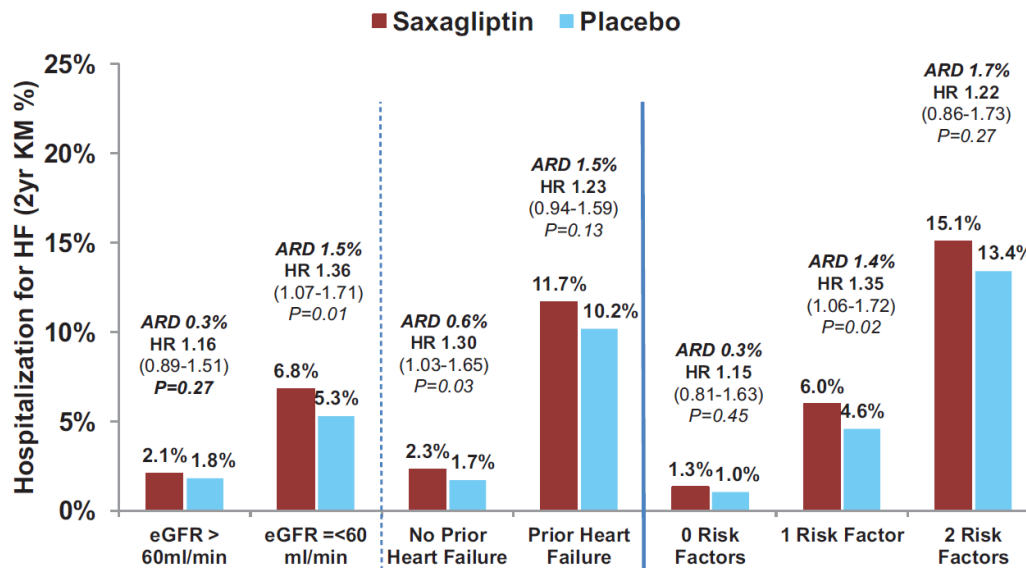
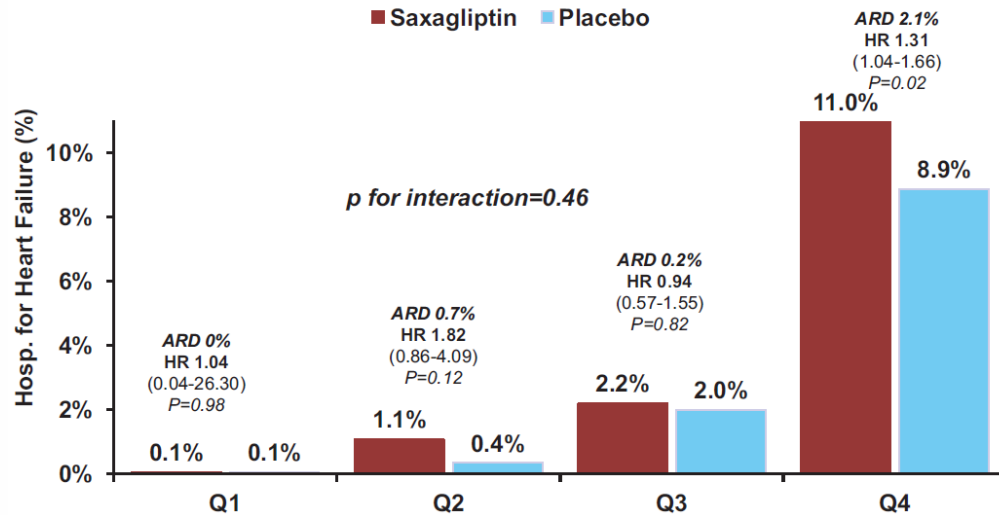
B Secondary End Point



End Point	Saxagliptin (N = 8280)	Placebo (N = 8212)	Hazard Ratio (95% CI)	P Value
	<i>no. (%)</i>			
Cardiovascular death, myocardial infarction, or stroke: primary efficacy end point	613 (7.3)	609 (7.2)	1.00 (0.89–1.12)	0.99
Cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, heart failure, or coronary revascularization: secondary efficacy end point	1059 (12.8)	1034 (12.4)	1.02 (0.94–1.11)	0.66
Death from any cause	420 (4.9)	378 (4.2)	1.11 (0.96–1.27)	0.15
Death from cardiovascular causes	269 (3.2)	260 (2.9)	1.03 (0.87–1.22)	0.72
Myocardial infarction	265 (3.2)	278 (3.4)	0.95 (0.80–1.12)	0.52
Ischemic stroke	157 (1.9)	141 (1.7)	1.11 (0.88–1.39)	0.38
Hospitalization for unstable angina	97 (1.2)	81 (1.0)	1.19 (0.89–1.60)	0.24
Hospitalization for heart failure	289 (3.5)	228 (2.8)	1.27 (1.07–1.51)	0.007
Hospitalization for coronary revascularization	423 (5.2)	459 (5.6)	0.91 (0.80–1.04)	0.18
Doubling of creatinine level, initiation of dialysis, renal transplantation, or creatinine >6.0 mg/dl (530 μ mol/liter)	194 (2.2)	178 (2.0)	1.08 (0.88–1.32)	0.46
Hospitalization for hypoglycemia	53 (0.6)	43 (0.5)	1.22 (0.82–1.83)	0.33

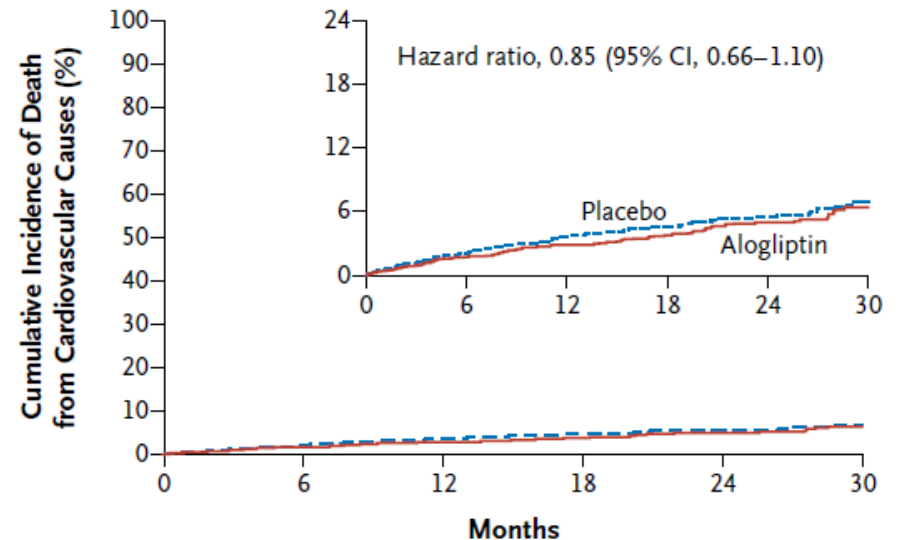
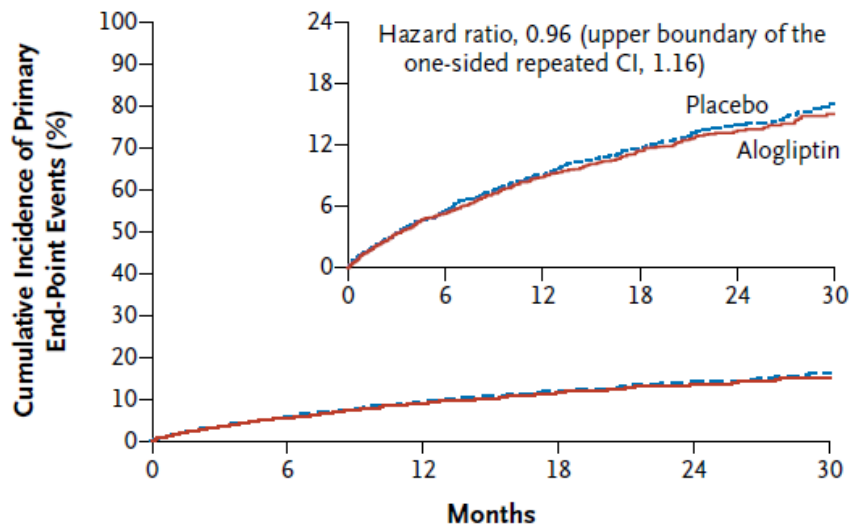
Heart Failure, Saxagliptin, and Diabetes Mellitus: Observations from the SAVOR-TIMI 53 Randomized Trial





Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes

EXAMINE



Zannad F, Cannon CP, Cushman WC, et al.
Heart failure and mortality outcomes in patients with type 2
diabetes taking alogliptin versus placebo in EXAMINE.
Lancet 2015



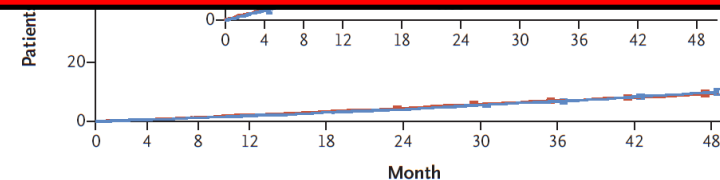
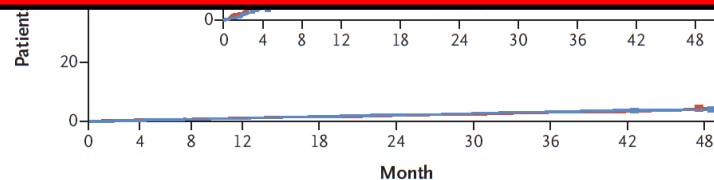
Although
not reported in the initial manuscript, admission to
hospital for heart failure was a **predefined exploratory
endpoint** that was independently adjudicated whereby
3.9% of alogliptin-treated vs **3.3 % of placebo-treated**
patients were admitted to hospital for heart failure
(**HR 1.19**, 95% CI **0.89–1.58**, $p = 0.220$)

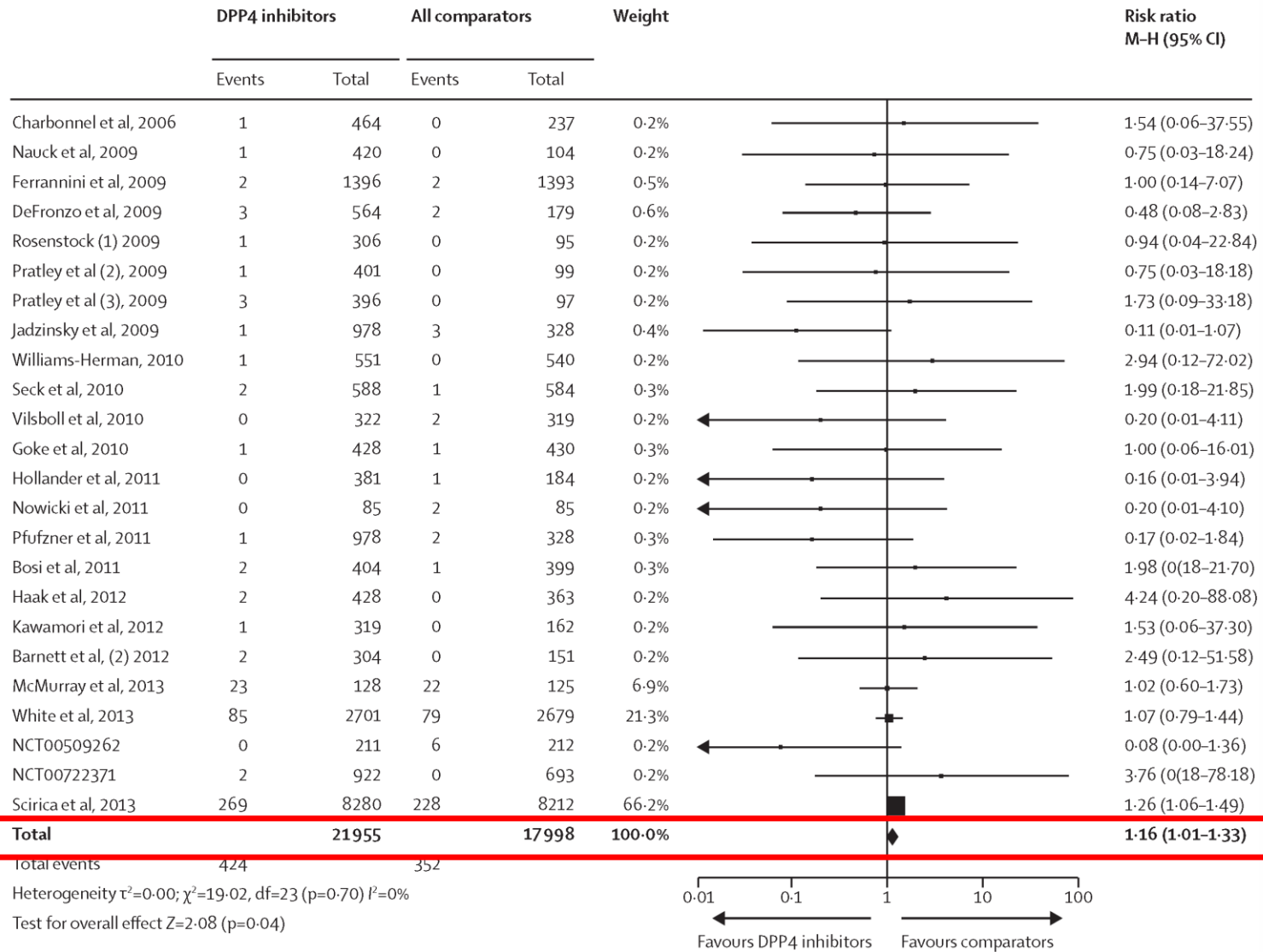
Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes

TECOS

Secondary outcome

Cardiovascular death	380 (5.2)	1.72	366 (5.0)	1.67	1.03 (0.89–1.19)
Hospitalization for unstable angina	116 (1.6)	0.54	129 (1.8)	0.61	0.90 (0.70–1.16)
Fatal or nonfatal myocardial infarction	300 (4.1)	1.42	316 (4.3)		(0.81–1.11)
Fatal or nonfatal stroke	178 (2.4)	0.83	183 (2.5)		(0.79–1.19)
Death from any cause	547 (7.5)	2.48	537 (7.3)	2.43	1.01 (0.90–1.14)
Hospitalization for heart failure†	228 (3.1)	1.07	229 (3.1)	1.09	1.00 (0.83–1.20)

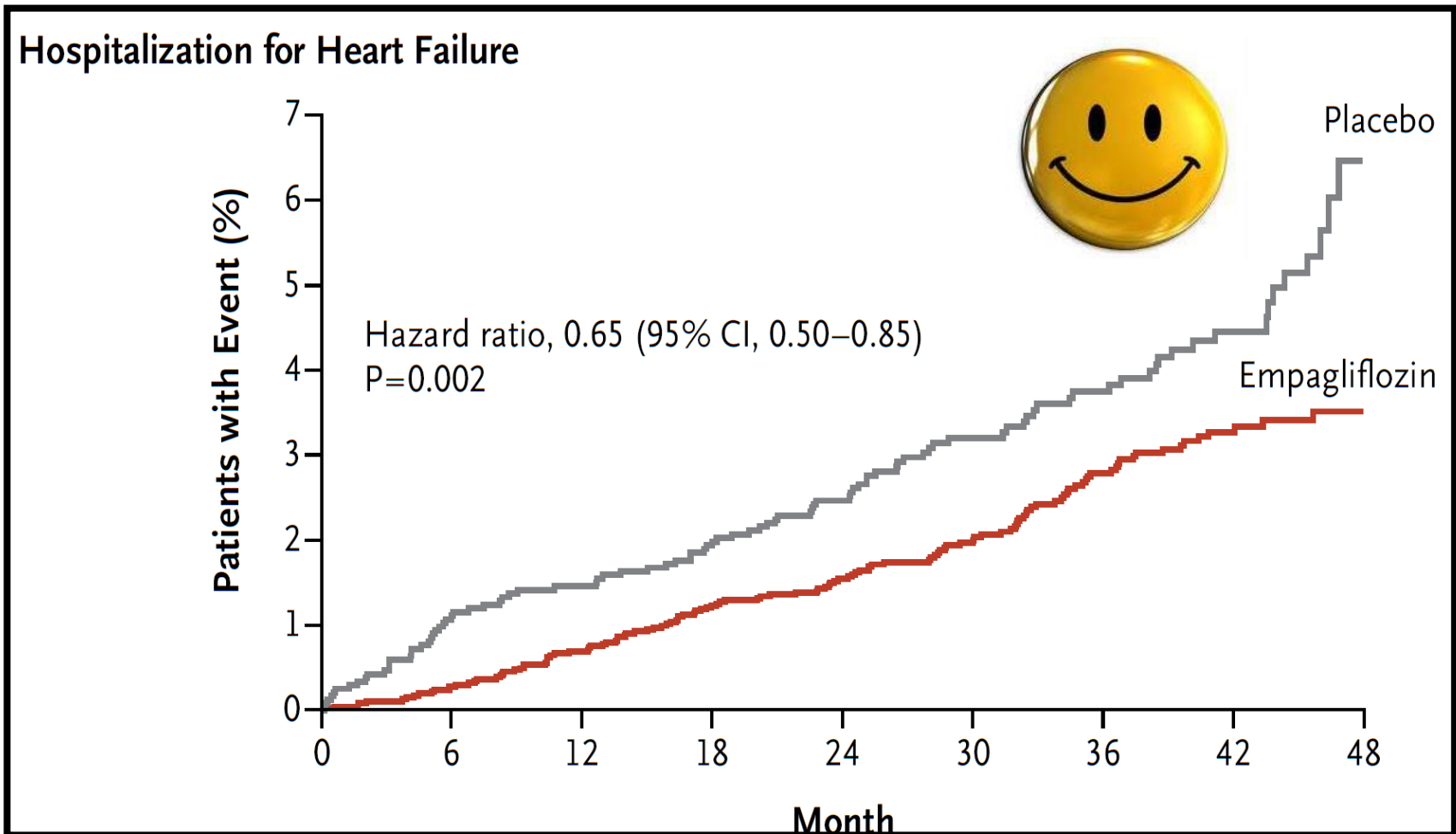




- Sulfaniluree
- Metformina
- Tiazolodinedioni
- GLP-1 receptor agonists
- DPP-IV inhibitors
- **Glifozine**
- Insulina

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

EMPA-REG



Perspective

Is the Mortality Benefit With Empaglifozin in Typo 2 DM Too Good To Be True ?

Sanjai Kaul, MD

Use of SGLT 2i in the Hands of Cardiologists.

With Great Power Comes Great Responsibility

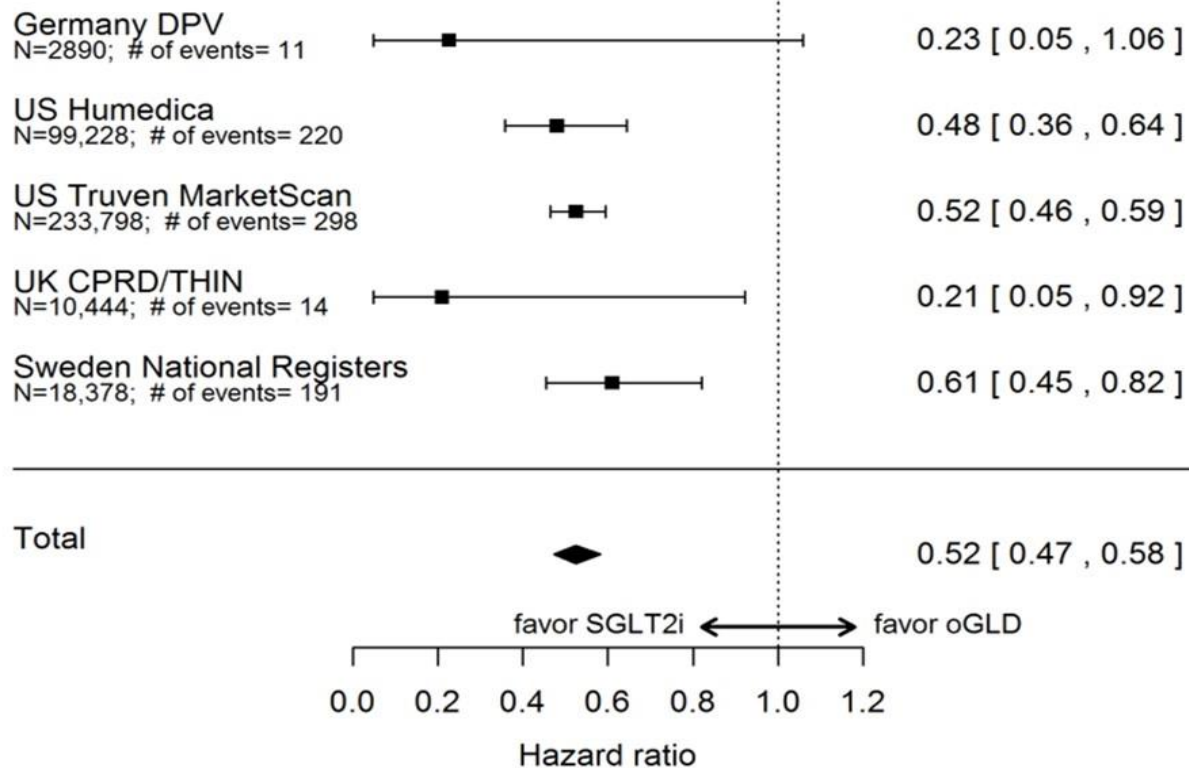
David Z.I. Cherney, MD

Lower Rates of Hospitalization for Heart Failure and All-Cause Death in New Users of SGLT-2 Inhibitors: The CVD-REAL Study

[ACC 2017 Scientific Session Program Planner Home](#)

March 19, 2017, 2:45 - 2:55 PM

Figure: Hazard ratios for hospitalization for heart failure by country/database and pooled estimate from meta-analysis.



Canaglifozin
(CANVAS)
and
Dapagliflozin
(DECLARE-TIMI58)

