Prossimità e organizzazione delle cure: la medicina generale di domani tra demografia e cronicità

Il diabete e il rischio CV

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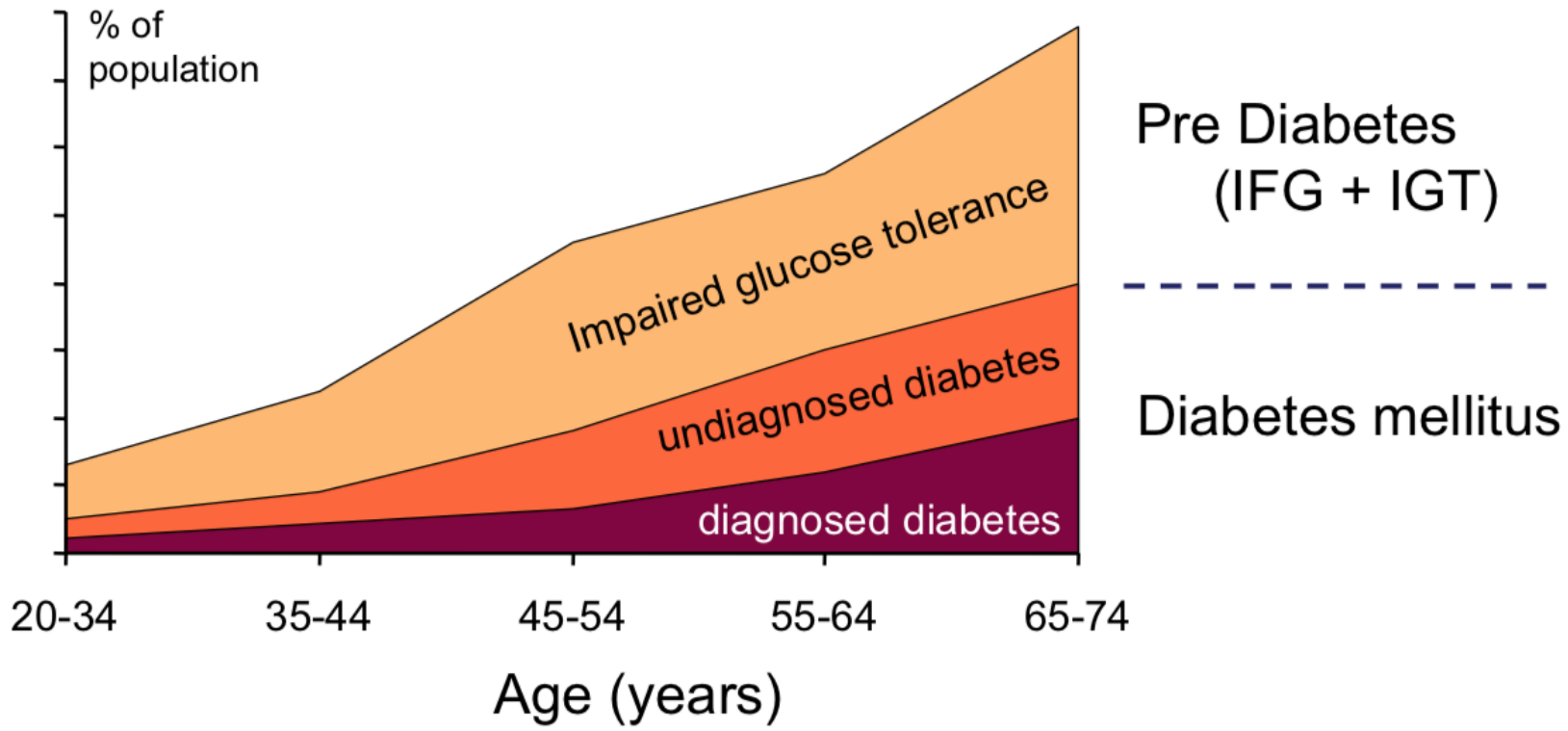
IRCCS San Raffaele

Roma

76° CONGRESSO NAZIONALE | 7-12 ottobre 2019 | Tanka Village - Villasimius (CA)

Spectrum of glucose metabolism disturbances



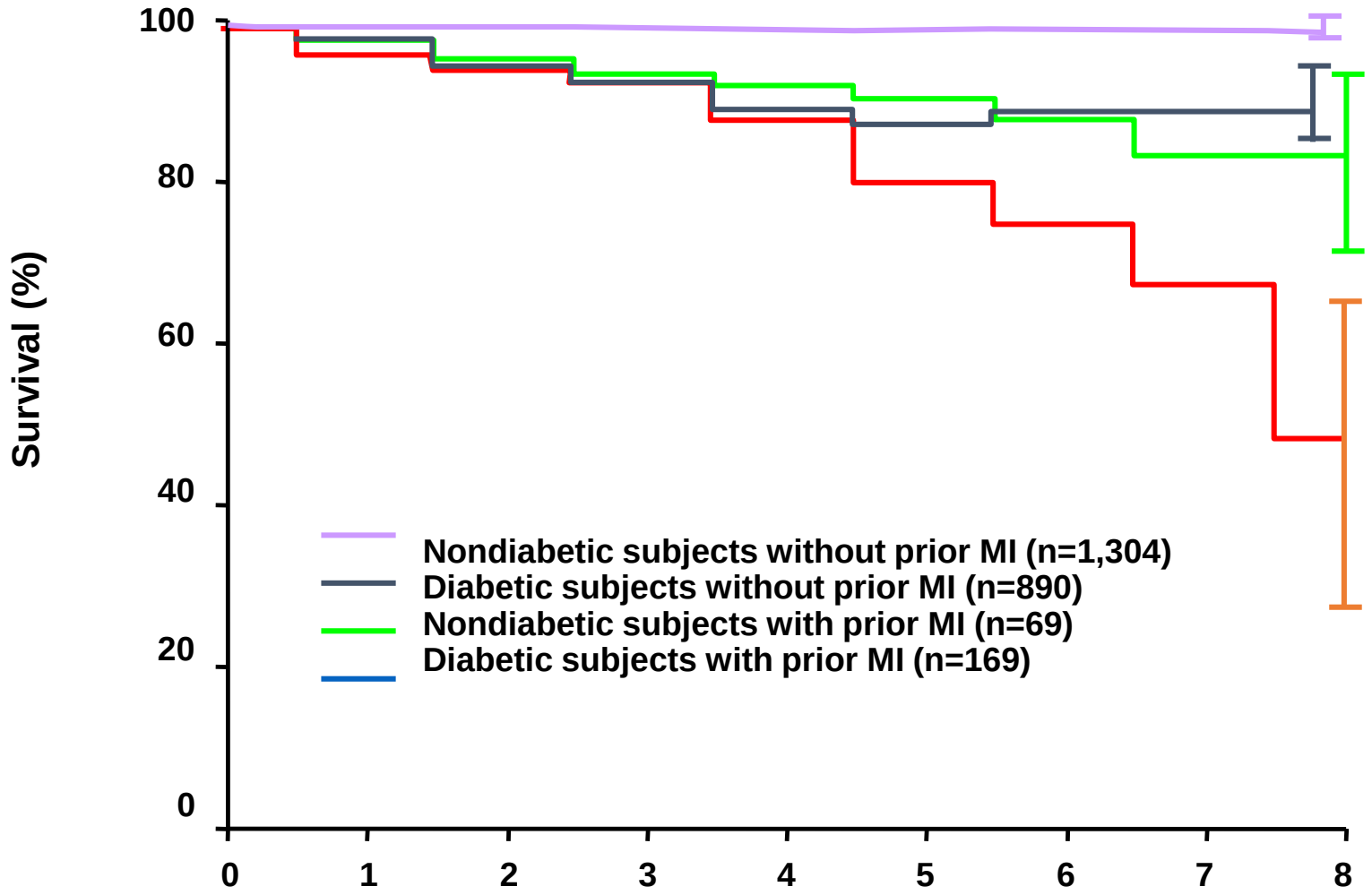
Cardiovascular risk categories in patients with DM

Very high-risk	Patients with DM **and** established CVD **or** other target organ damage[a] **or** three or more major risk factors[b] **or** early onset T1DM of long duration (>20 years)
High-risk	Patients with DM duration ≥10 years without target organ damage[a] plus any other additional risk factor[b]
Moderate-risk	Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors

[a] proteinuria, renal impairment defined as eGFR≥30mL/min/1.73m^2.
[b] age, hypertension, dyslipidemia, smoking, obesity.

ESC Guidelines on Diabetes, pre-diabetes and cardiovascular diseases in collaboration with EASD (European Heart Journal 2019 - doi/10.1093/eurheartj/ehz486)

Risk Similar in Pts With Type 2 Diabetes and No Prior MI vs Nondiabetic With Prior MI



Diabetes and CVD - key points

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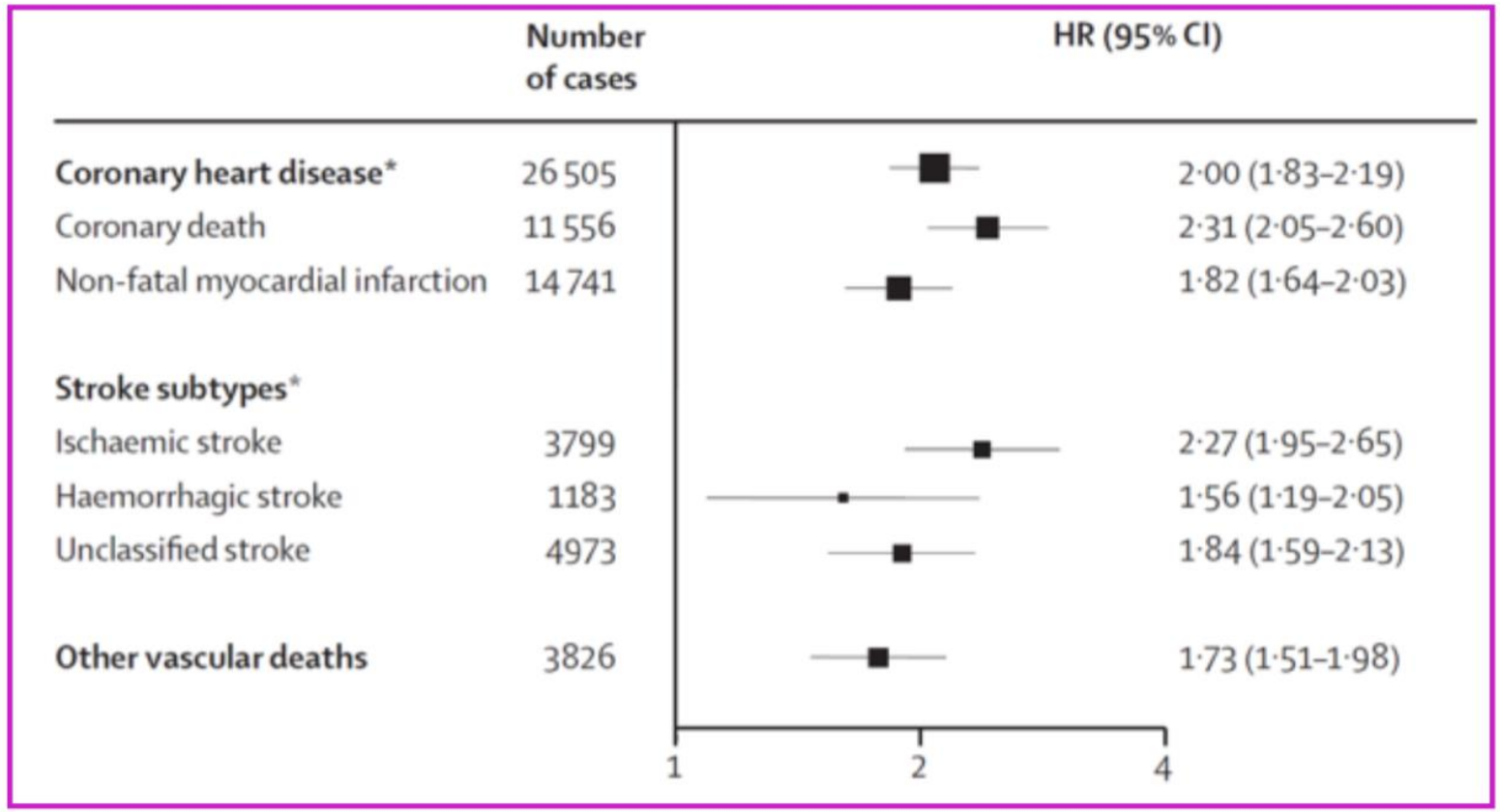
DM: double CVD risk <u>on average</u>

Hazard ratios for vascular outcomes DM vs. no DM



ERFC, *Lancet* 2010

ESC Guidelines on Diabetes, pre-diabetes and cardiovascular diseases in collaboration with EASD (European Heart Journal 2019 - doi/10.1093/eurheartj/ehz486)

Impact of diabetes on mortality after CABG vs PCI

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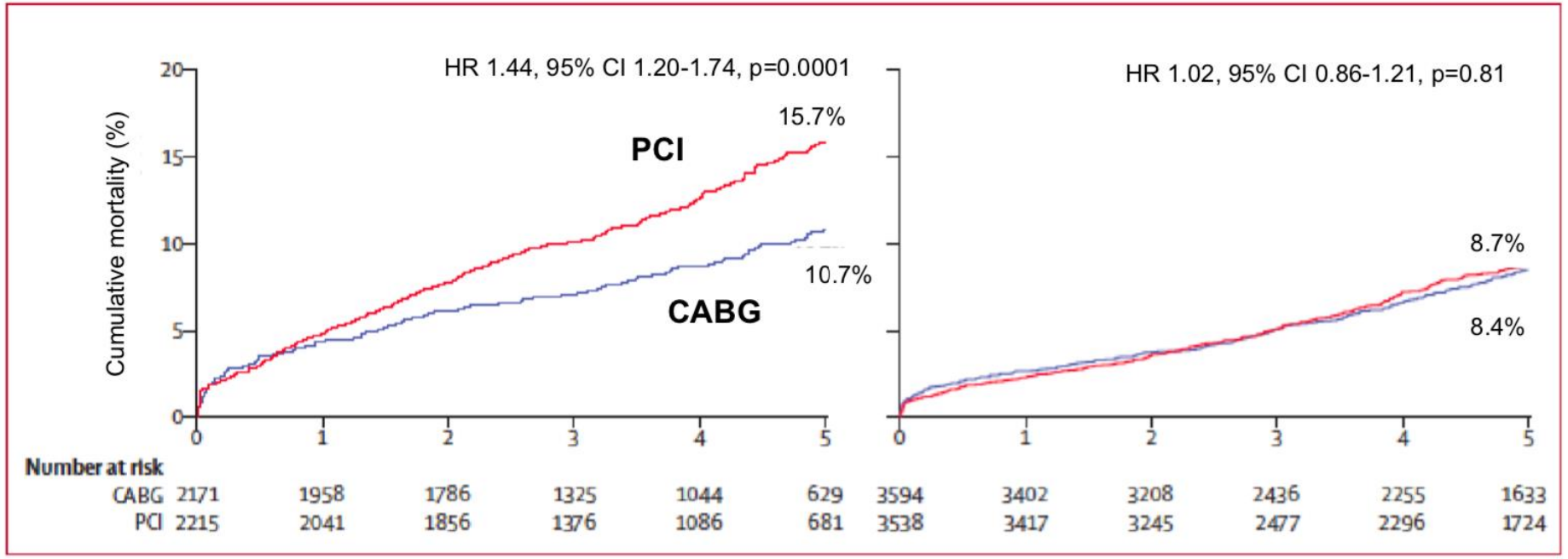
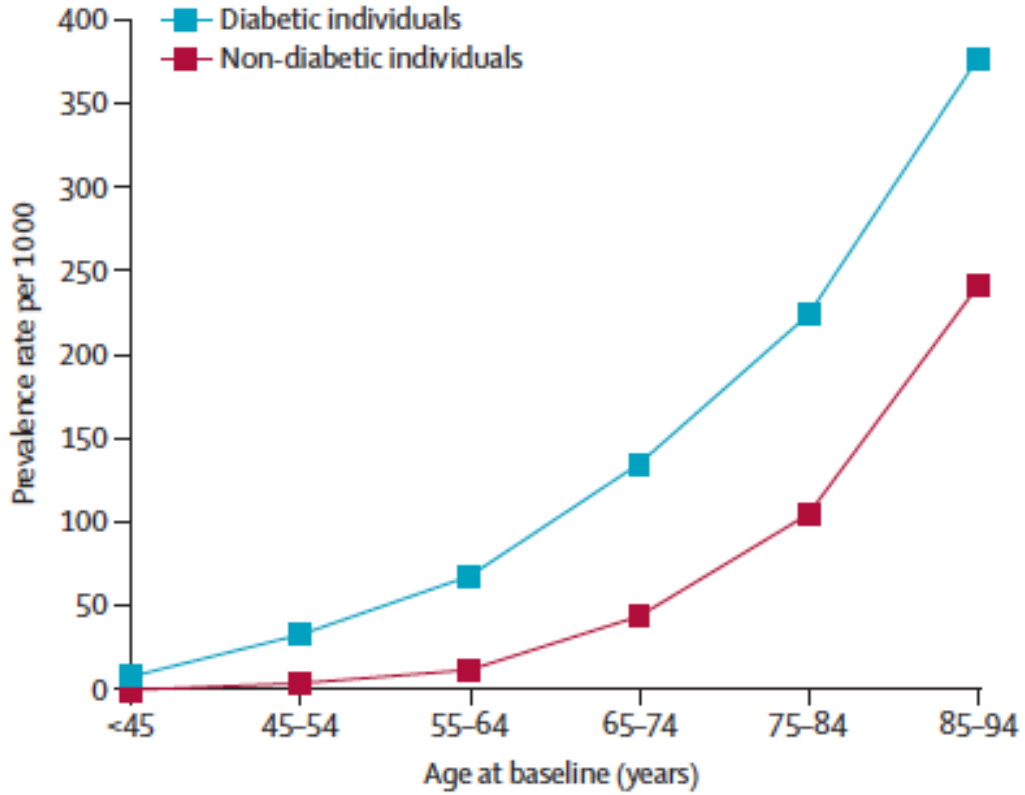
Pooled analysis of individual patient data from 11 trials

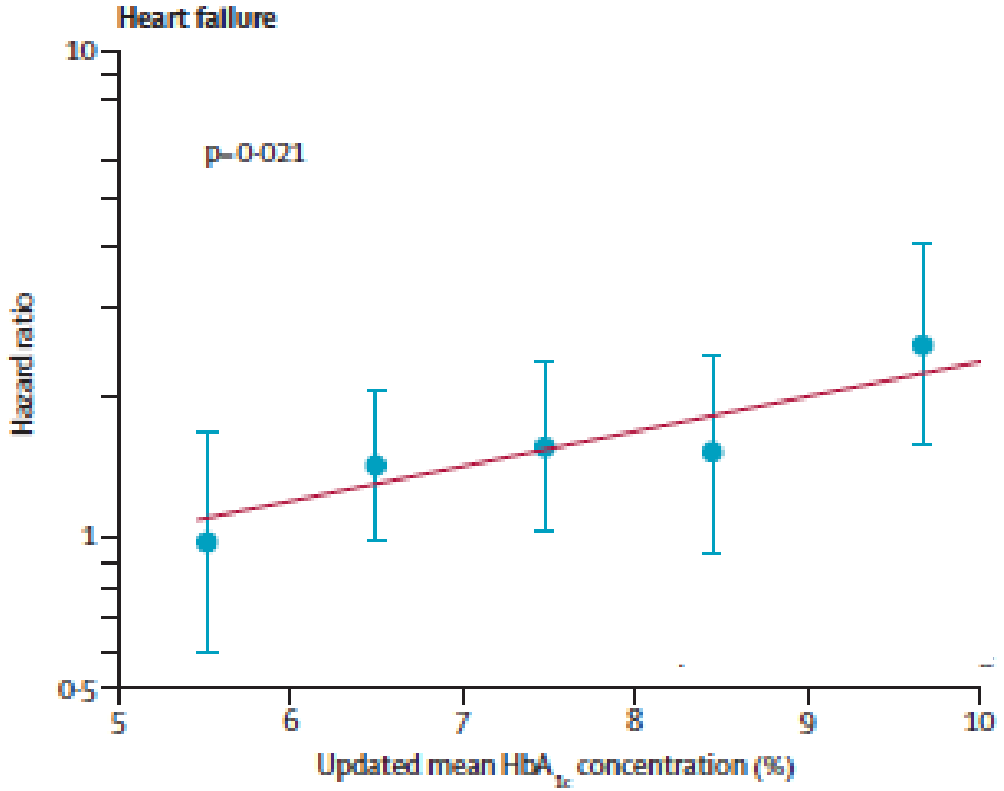


Head SJ et al. Lancet 2018

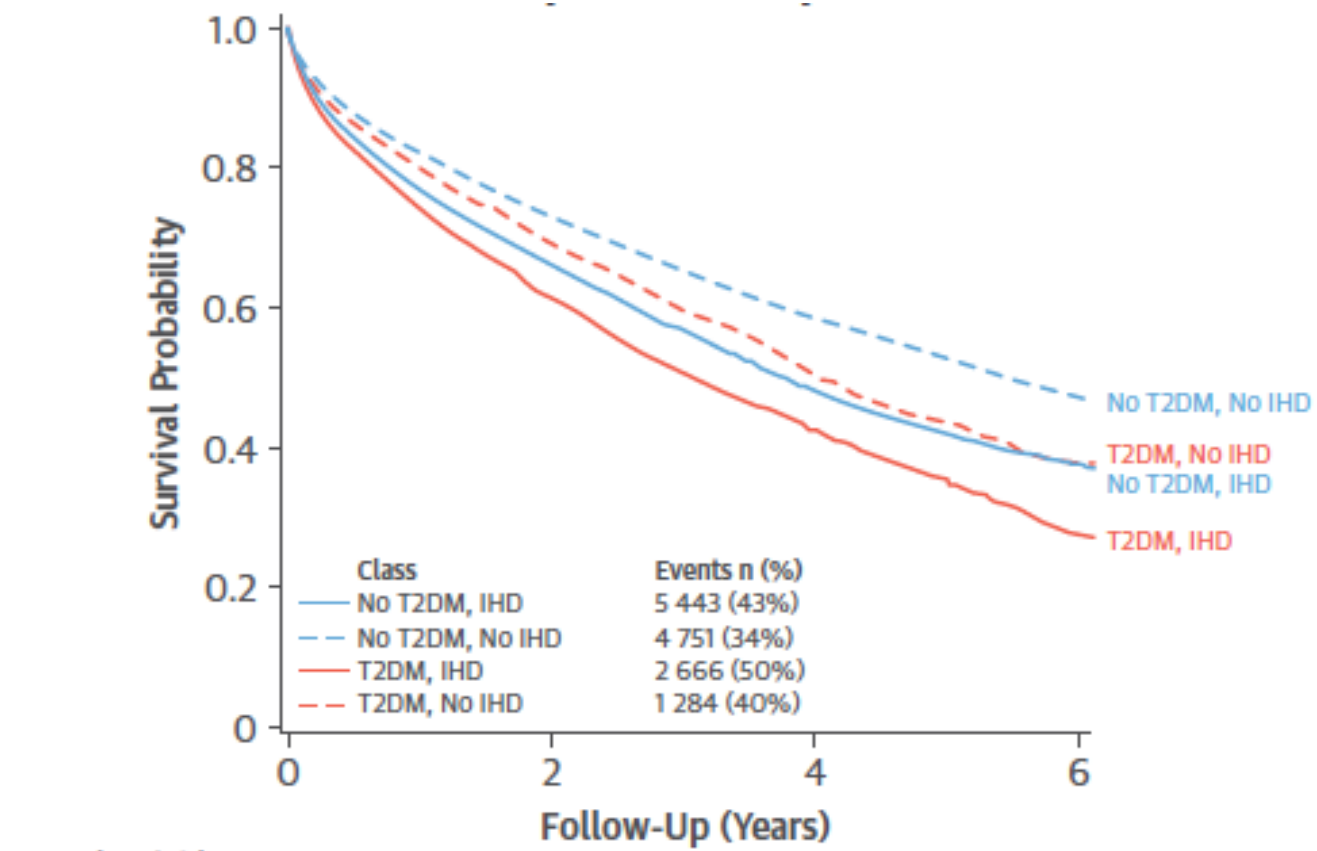
ESC Guidelines on Diabetes, pre-diabetes and cardiovascular diseases in collaboration with EASD (European Heart Journal 2019 - doi/10.1093/eurheartj/ehz486)

Diabetes mellitus and risk of heart failure





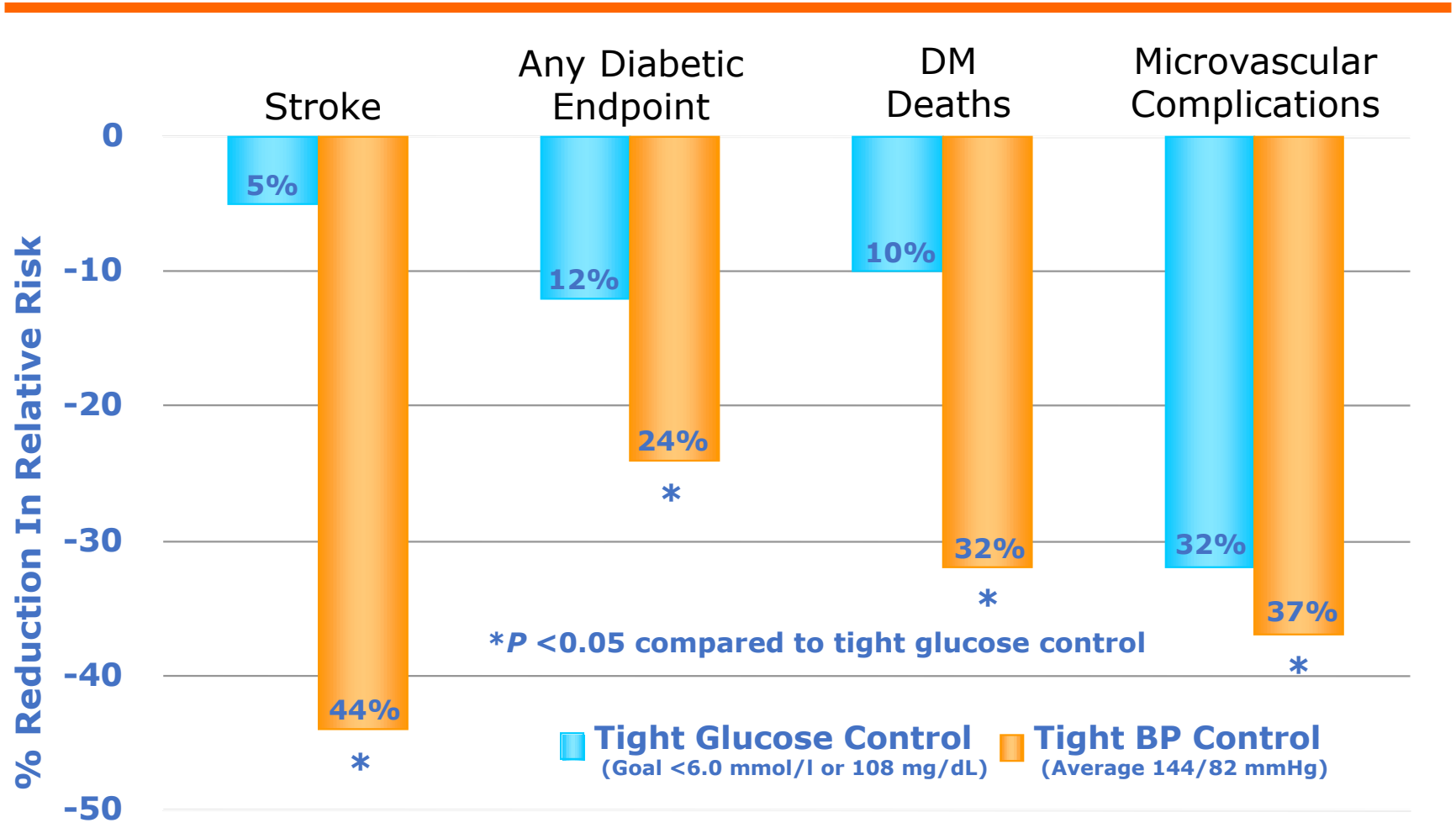
Prognosis in patients with heart failure and diabetes



Number at risk				
No T2DM, IHD	12574	5791	2158	537
No T2DM, No IHD	14029	6943	2535	688
T2DM, IHD	5317	2391	845	183
T2DM, No IHD	3243	1565	499	119

Johansson I J Am Coll Cardiol. 2016 Sep 27;68(13):1404-16

Diabetes: Tight Glucose vs Tight BP Control and CV Outcomes in UKPDS



Bakris GL, et al. Am J Kidney Dis. 2000;36(3):646-661

Recommendations for the management of dyslipidaemia with lipid-lowering drugs (I)

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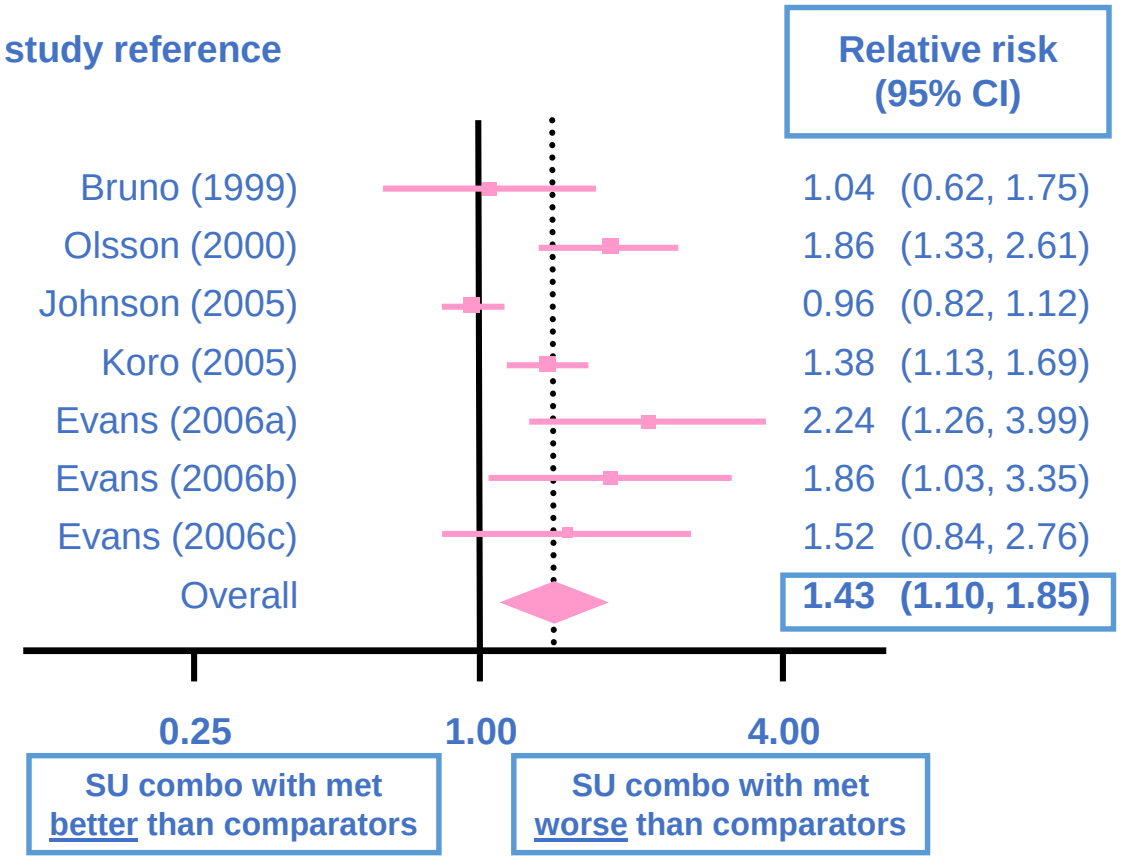
Recommendations	Class	Level
Targets		
In patients with T2DM at moderate CV risk, an LDL-C target of <2.5 mmol/L (<100 mg/dL) is recommended.	I	A
In patients with T2DM at high CV risk, an LDL-C target of <1.8 mmol/L (<70 mg/dL) or an LDL-C reduction of at least 50% is recommended.	I	A
In patients with T2DM at very high CV risk, an LDL-C target of <1.4 mmol/L (<55 mg/dL) or an LDL-C reduction of at least 50%	I	B
In patients with T2DM, a secondary goal of a non–HDL-C target of <2.2 mmol/L (<85 mg/dL) in very high CV risk patients, and <2.6 mmol/L (<100 mg/dL) in high CV risk patients, is recommended.	I	B

aboration
tj/ehz486)

Diabetes Therapy and CV Risk

Combination of SUs and Metformin may be Linked to Higher Risk for CVD and All-cause Mortality*

Meta-analysis data from 9 clinical studies



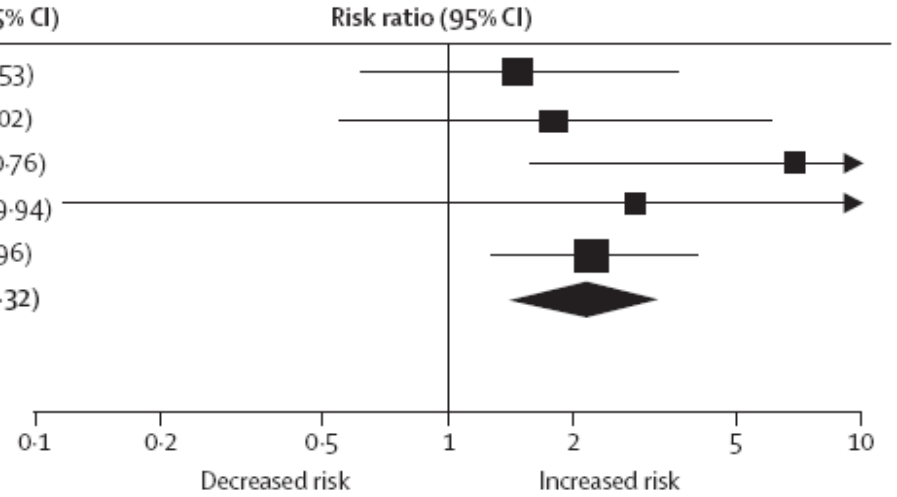
CI=confidence interval; CVD=cardiovascular disease; met=metformin; NS=not specified; SU=sulfonylurea.
*Composite end point of CVD hospitalizations or CVD mortality – only statistically significantly increased end point.
Rao A, et al. *Diabetes Care*. 2008; 31: 1672–1678.

Concerns About the Safety of Diabetic Therapy

TZDs and Heart failure

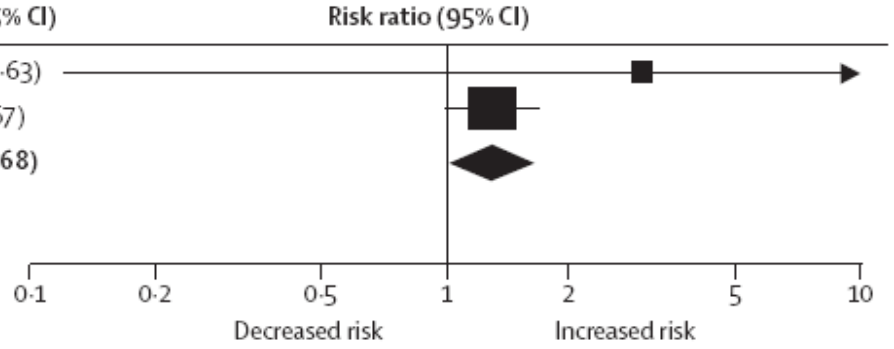
Rosiglitazone

	Weight	Risk ratio (95% CI)
Rosiglitazone *vs* control[19]	23·7%	1·49 (0·62, 3·53)
Rosiglitazone *vs* placebo[10]	12·2%	1·81 (0·55, 6·02)
Rosiglitazone *vs* placebo[18]	8·0%	7·00 (1·59, 30·76)
Rosiglitazone *vs* placebo[21]	1·7%	2·88 (0·12, 69·94)
Rosiglitazone *vs* metformin and sulfonylurea[20]	54·4%	2·24 (1·27, 3·96)
Total	**100·0%**	**2·18 (1·44, 3·32)**
Test for heterogeneity: χ^2=3·33, df=4 (p=0·50), I^2=0%		
Test for overall effect: Z=3·65 (p=0·0003)		



Pioglitazone

C	Weight	Risk ratio (95% CI)
Pioglitazone *vs* glimepiride[8]	0·6%	2·97 (0·12, 72·63)
Pioglitazone *vs* placebo[7]	99·4%	1·31 (1·03, 1·67)
Total	**100·0%**	**1·32 (1·04, 1·68)**
Test for heterogeneity: χ^2=0·25, df=1 (p=0·62), I^2=0%		
Test for overall effect: Z=2·24 (p=0·02)		



Lago, Lancet 2007

Recommendations for the treatment of diabetes in patients with HF

Diabetes		
Thiazolidinediones (glitazones) are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization.	III	A

Regulatory Obligations for All New Diabetes Medications – 2008

- Demonstrate effective HbA1c reduction
- *Exclude excess risk in Phase II/III (FDA)*
  - *More patients in Phase II/III*
  - *Higher risk population (CVD, CKD)*
  - *Longer follow-up (minimum 2-years)*
  - *Pre-defined CV endpoints with independent blind adjudication*
  - *Statistical plan to perform meta-analysis of CV events in Phase II/III program*
- *Post-Approval CV safety study (EMA)*

Cardiovascular outcome trials with newer glucose-lowering agents

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	SGLT2 inhibitors				GLP-1 RAs							DPP-IV inhibitors				
Trial	**EMPA-REG OUTCOME**[206]	**CANVAS**[209]	**DECLARE–TIMI 58**[211]	**CREDENCE**[213]	**ELIXA**[297]	**LEADER**[176]	**SUSTAIN-6**[299]	**EXSCEL**[158]	**Harmony Outcomes**[301]	**REWIND**[303]	**PIONEER 6**[300]	**SAVOR–TIMI 53**[291]	**EXAMINE**[292]	**TECOS**[293]	**CARMELINA**[294]	**CAROLINA**[277]
Baseline	**Empagliflozin vs. placebo**	**Canagliflozin vs. placebo**	**Dapagliflozin vs. placebo**	**Canaglifozin vs. placebo**	**Lixisenatide vs. placebo**	**Liraglutide vs. placebo**	**Semaglutide vs. placebo**	**Exenatide vs. placebo**	**Albiglutide vs. placebo**	**Dulaglutide vs. placebo**	**Oral Semaglutide vs. placebo**	**Saxagliptin vs. placebo**	**Alogliptin vs. placebo**	**Sitagliptin vs. placebo**	**Linagliptin vs. placebo**	**Linagliptin vs. glimiperide**
n	7020	10 142	17160	4401	6068	9340	3297	14 752	9463	9901	3182	16 492	5400	14 671	6979	6033
Age (years)	63	63	63	63	60	64	64	62	64	66	66	65	61	66	65	64
DM (years)	57% >10	13.5	11.8	15.8	9.3	12.8	13.9	12.0	14.1	10.5	14.9	10	7.2	9.4	14.7	6.2
Body mass index (kg/m^2)	30.6	32.0	32.1	31.3	30.1	32.5	32.8	31.8	32	32.3	32.3	31	29	30	31.3	30.1
Insulin (%)	48	50	~40	65	39	44	58	46	60	24	61	41	30	23	58	0
HbA1c (%)	8.1	8.2	8.3	8.3	7.7	8.7	8.7	8.0	8.7	7.2	8.2	8.0	8.0	7.3	7.9	7.2
Previous CVD (%)	99	65	40	50.4	100	~81	~83	73	100	31	35	78	100	100	57	42
CV risk inclusion criteria	**MI, CHD, CVD, or PVD**	**MI, CHD, CVD, or PVD**	**CVD or at least one CVRF**	**CKD**	**ACS <180 days**	**Age ≥50 years and CVD,[b] or CKD, or age ≥60 years and at least one CVRF**		**CHD, CVD, or PVD27% no previous CV event**	**MI, CHD, CVD, or PVD**	**Age ≥50 years and CVD or CVRFs**	**Age ≥50 years and CVD, or CKD, or age ≥60 years and CVRFs**	**Age ≥40 years and CVD (CHD, CVD, or PVD), or age ≥55 years and at least one CVRF**	**ACS<90 days**	**CHD, CVD, or PVD**	**CVD and/or CKD**	**CVD or evidence of vascular-related end-organ damage, or age ≥70 years, or at least two CVRFs**
Hypertension (%)	94	89	89	96.8	76	92	92	90	86	93	94	81	83	86	95	90
Follow-up (years)	3.1	2.4	4.5	2.6	2.1	3.8	2.1	3.2	1.6	5.4	1.3	2.1	1.5	2.8	2.2	6.3

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CVOTs with DPP-IV inhibitors
(MACE endpoint and hospitalisation for heart failure)

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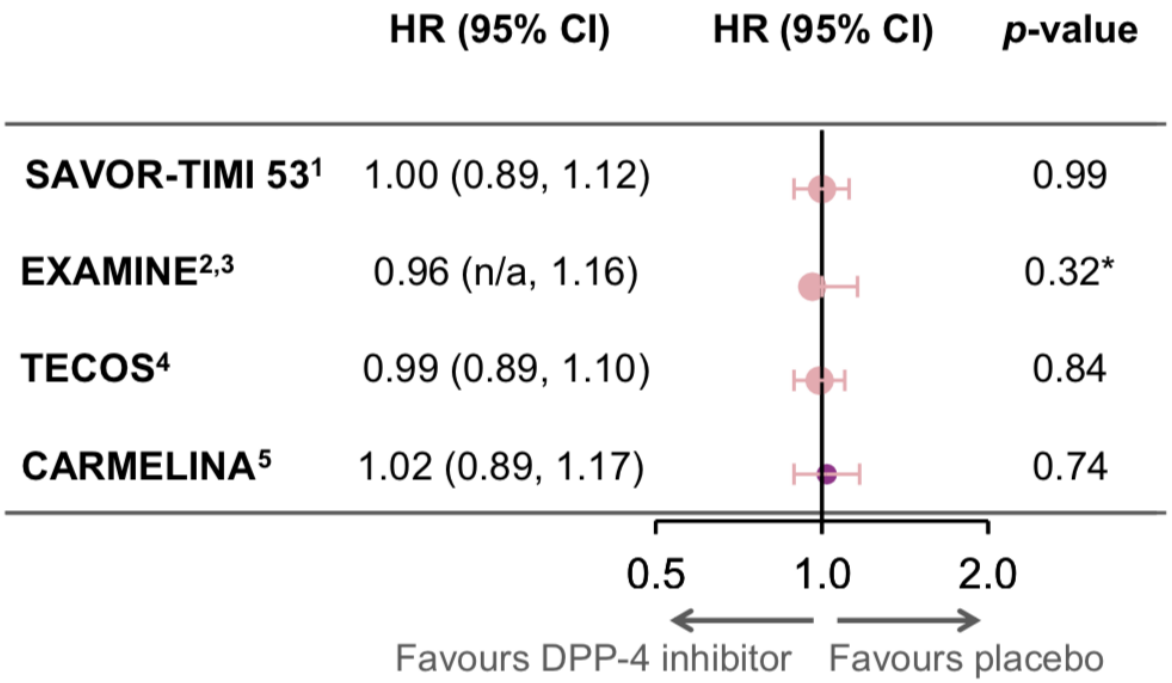
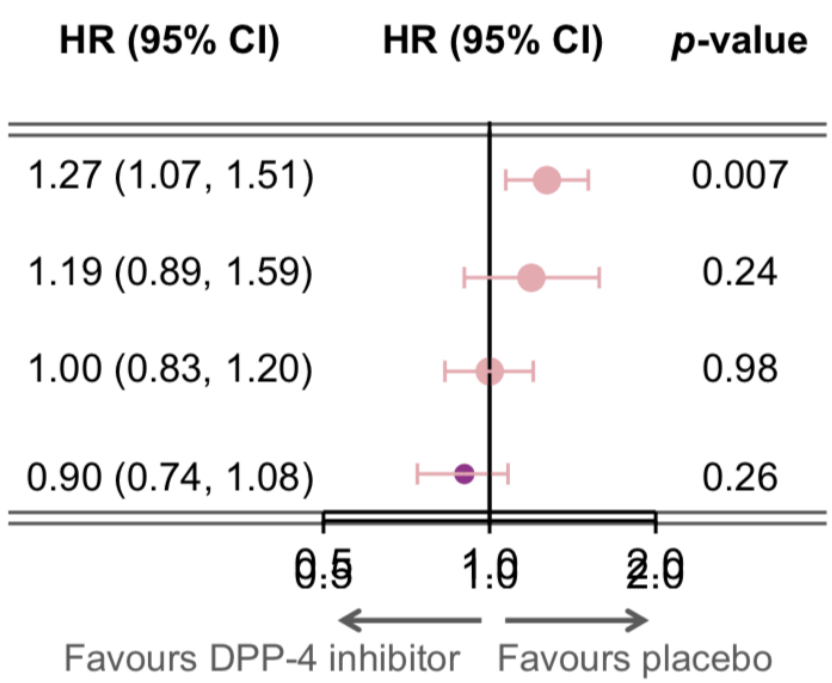
3P-MACE



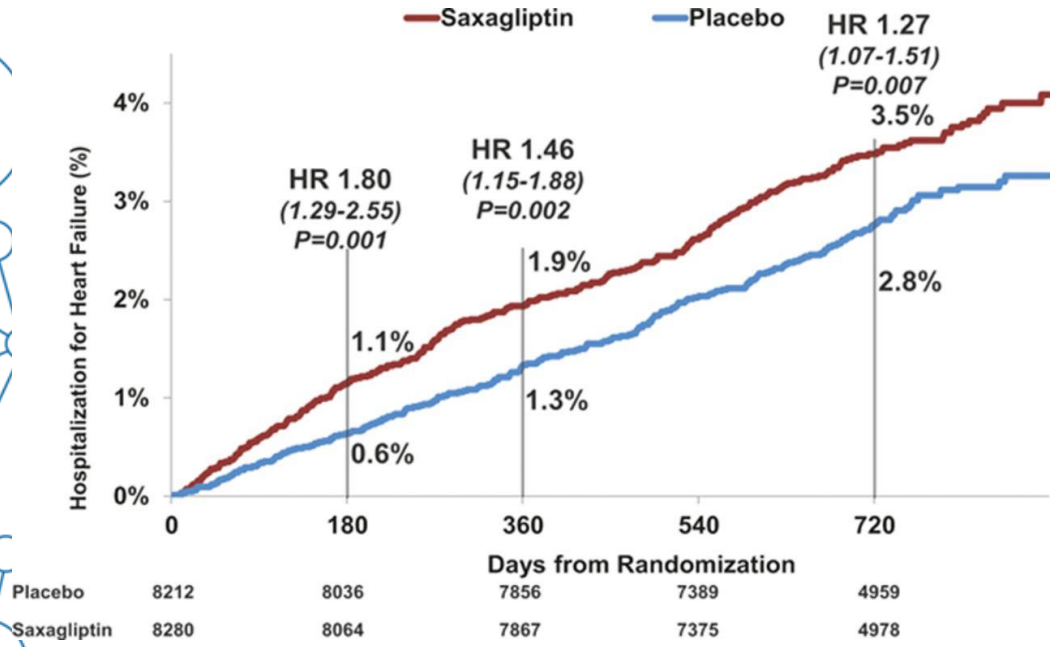
Hospitalisation for heart failure[5,6]



1. Scirica BM *et al. N Engl J Med* 2013;369:1317; 2. White WB *et al. N Engl J Med* 2013;369:1327; 3. Zannad F *et al. Lancet* 2015;385;2067-76;
4. Green JB *et al. N Engl J Med* 2015;373:232; 5. Rosenstock J *et al. JAMA* 2018; doi: 10.1001/jama.2018.18269; 6. McGuire D. *et al. JAMA Cardiol* 2016;1:126

DPP4i and risk of heart failure

Saxagliptin and hospitalization for heart failure



Cardiovascular effects of dipeptidyl peptidase-4 inhibitors in diabetic patients: A meta-analysis

Gianluigi Savarese [a,b,1], Pasquale Perrone-Filardi [a,1], Carmen D'Amore [a], Cristiana Vitale [b], Bruno Trimarco [a], Luca Pani [c], Giuseppe M.C. Rosano [b,d,*]

G. Savarese et al. / International Journal of Cardiology 181 (2015) 239–244

Outcome	Long term follow-up		
	RR	95% CI	p
All-cause death	1.012	0.909 to 1.126	0.829
Cardiovascular death	0.962	0.843 to 1.098	0.565
Myocardial infarction	0.939	0.835 to 1.056	0.290
Stroke	0.953	0.794 to 1.144	0.605
New onset of HF	1.158	1.011 to 1.326	0.034

Scirica B M et al. Circulation. 2014;130:1579-1588

CVOTs with GLP-1 receptor agonists
(3P-MACE endpoint)

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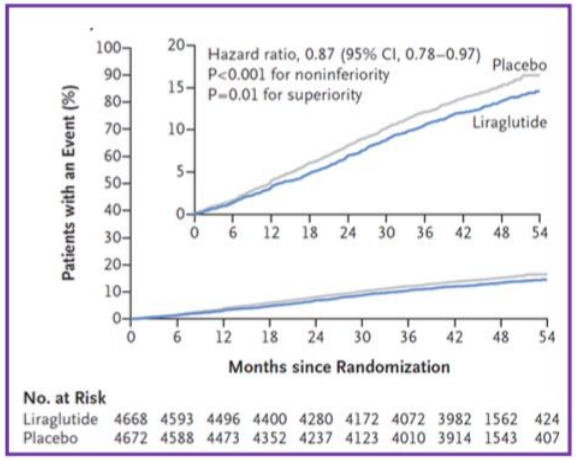
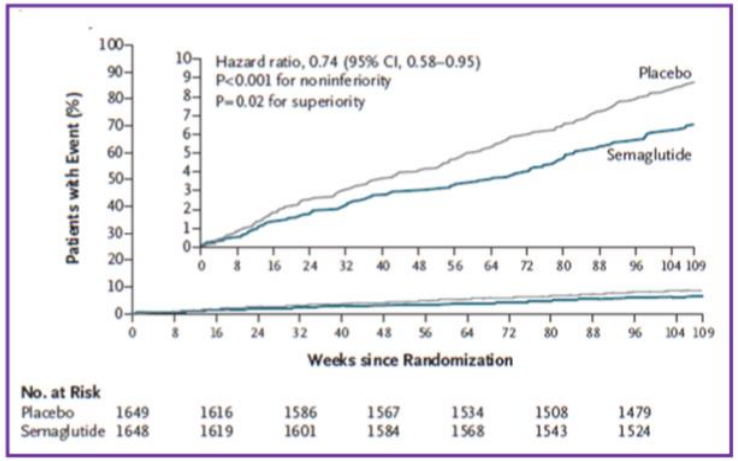
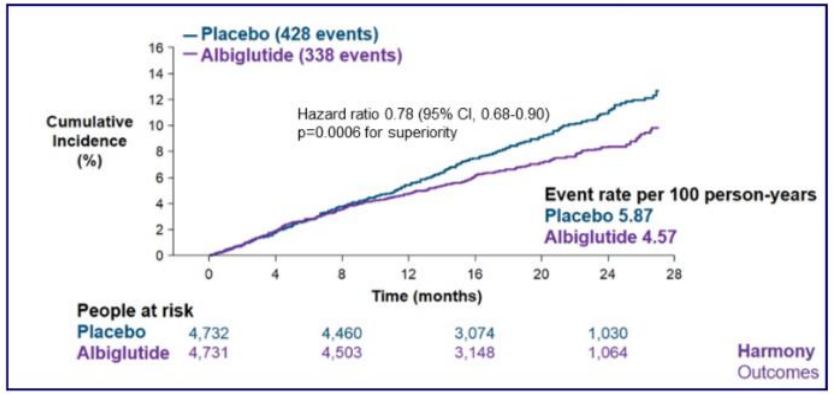
LEADER[1]



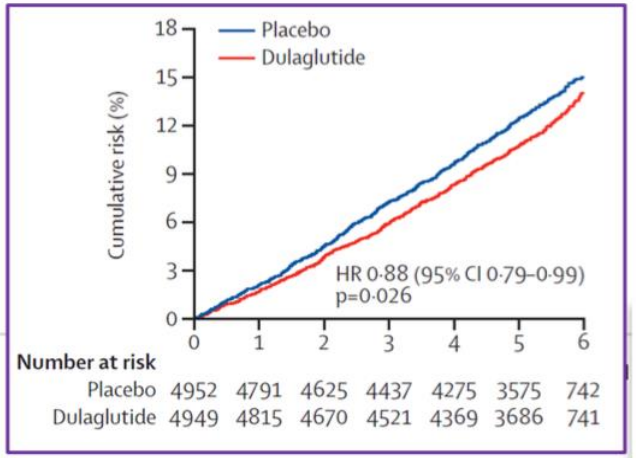
SUSTAIN-6[2]



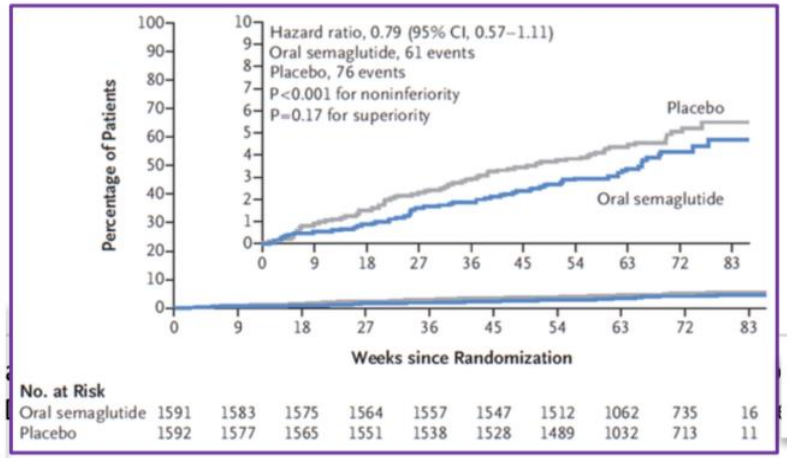
HARMONY[3]



REWIND[4]



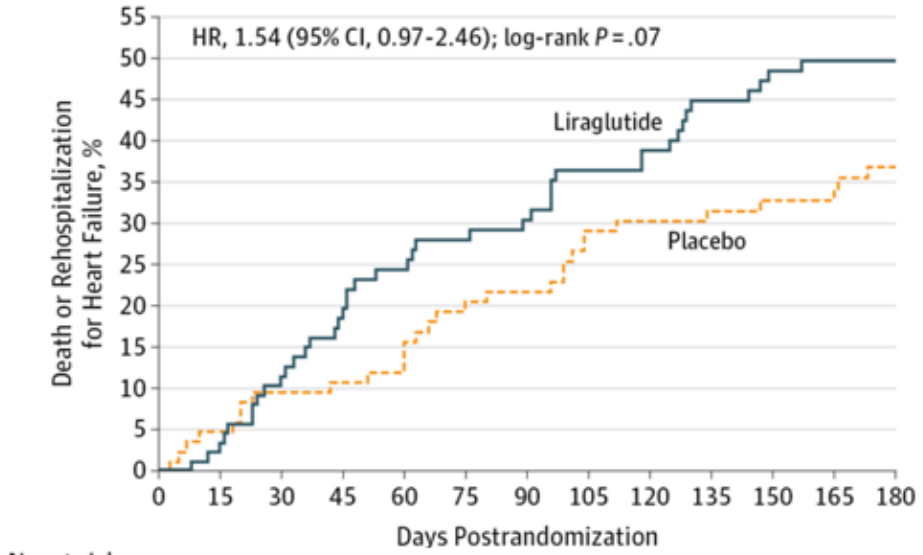
PIONEER-6[5]



1. Marso et al. *N Engl J Med.* 2016
2. Marso SP et al. *N Engl J Med.* 2016
3. Hernandez AF et al. *Lancet* 2018
4. Gerstein H et al. *Lancet* 2019
5. Husain M et al. *N Engl J Med* 2019

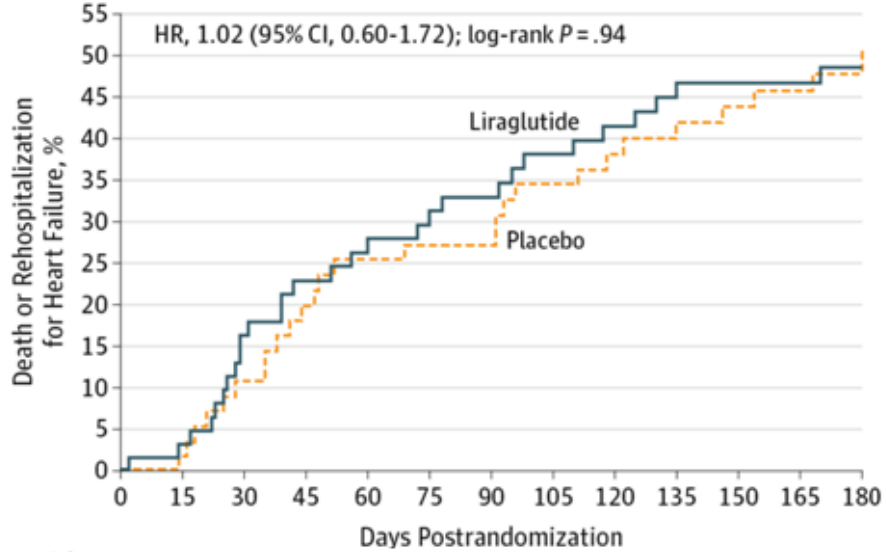
Liraglutide in patients with acutely decompensated heart failure

Patients with diabetes



No. at risk													
Liraglutide	91	86	77	69	63	60	58	53	51	46	43	41	24
Placebo	87	80	75	73	72	66	64	58	57	56	52	50	31

Patients without



No. at risk													
Liraglutide	63	60	51	46	44	42	40	36	34	32	31	29	16
Placebo	59	55	49	44	41	40	40	36	33	31	29	28	16

Margulies, KB, JAMA. 2016;316(5):500-508. doi:10.1001/jama.2016.10260

CVOTs with SGLT2 inhibitors
(3P-MACE endpoint)

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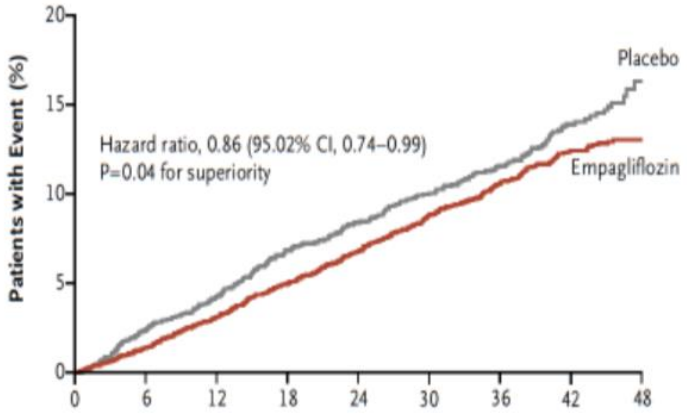
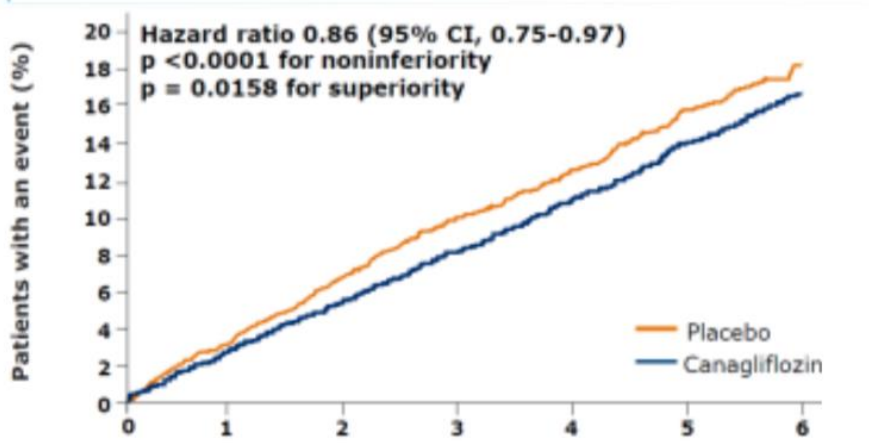
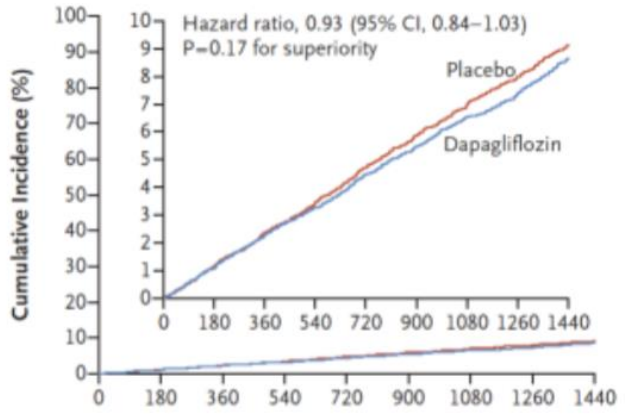
EMPA-REG Outcome[1]



CANVAS Program[2]



DECLARE[3]



1. Zinman B et al. N Engl J Med. 2015
2. Neal B et al. N Engl J Med 2017
3. Wiviott SD et al. N Engl J Med 2018

CVOTs with SGLT2 inhibitors
(HF hospitalization and CV death)

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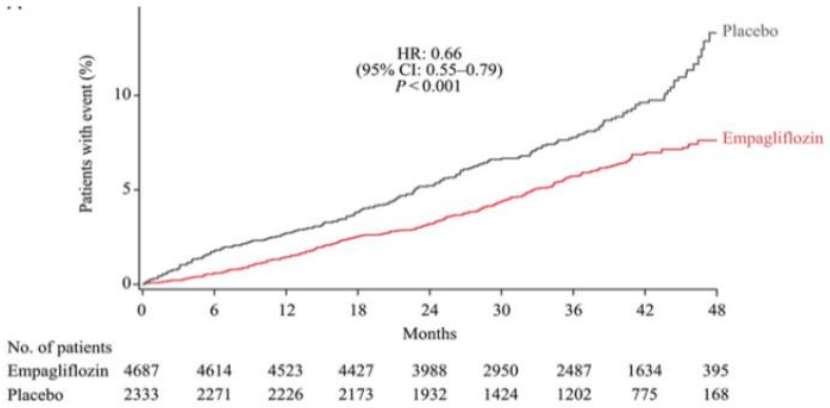
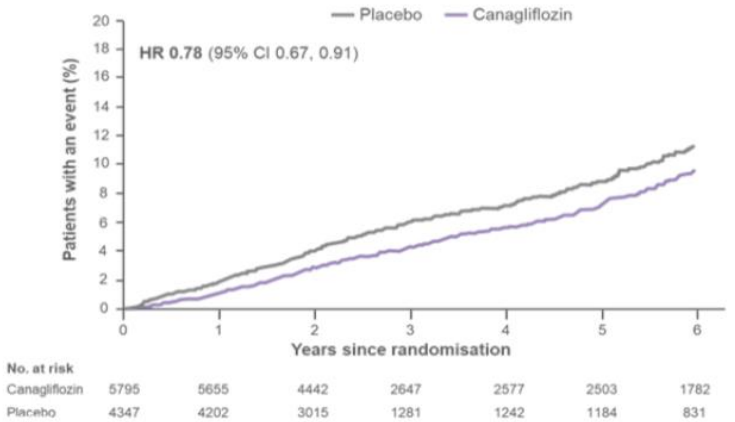
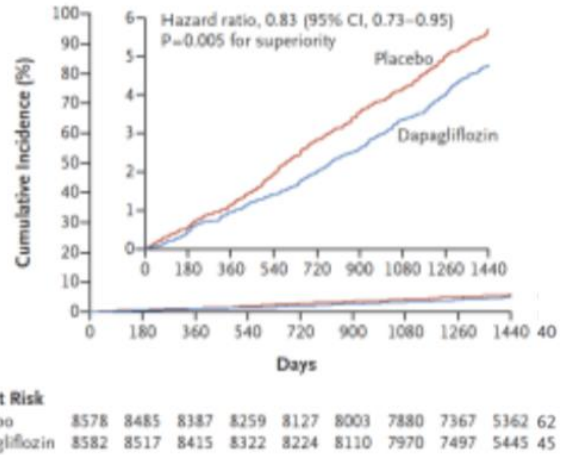
EMPA-REG Outcome[1]



CANVAS Program[2]



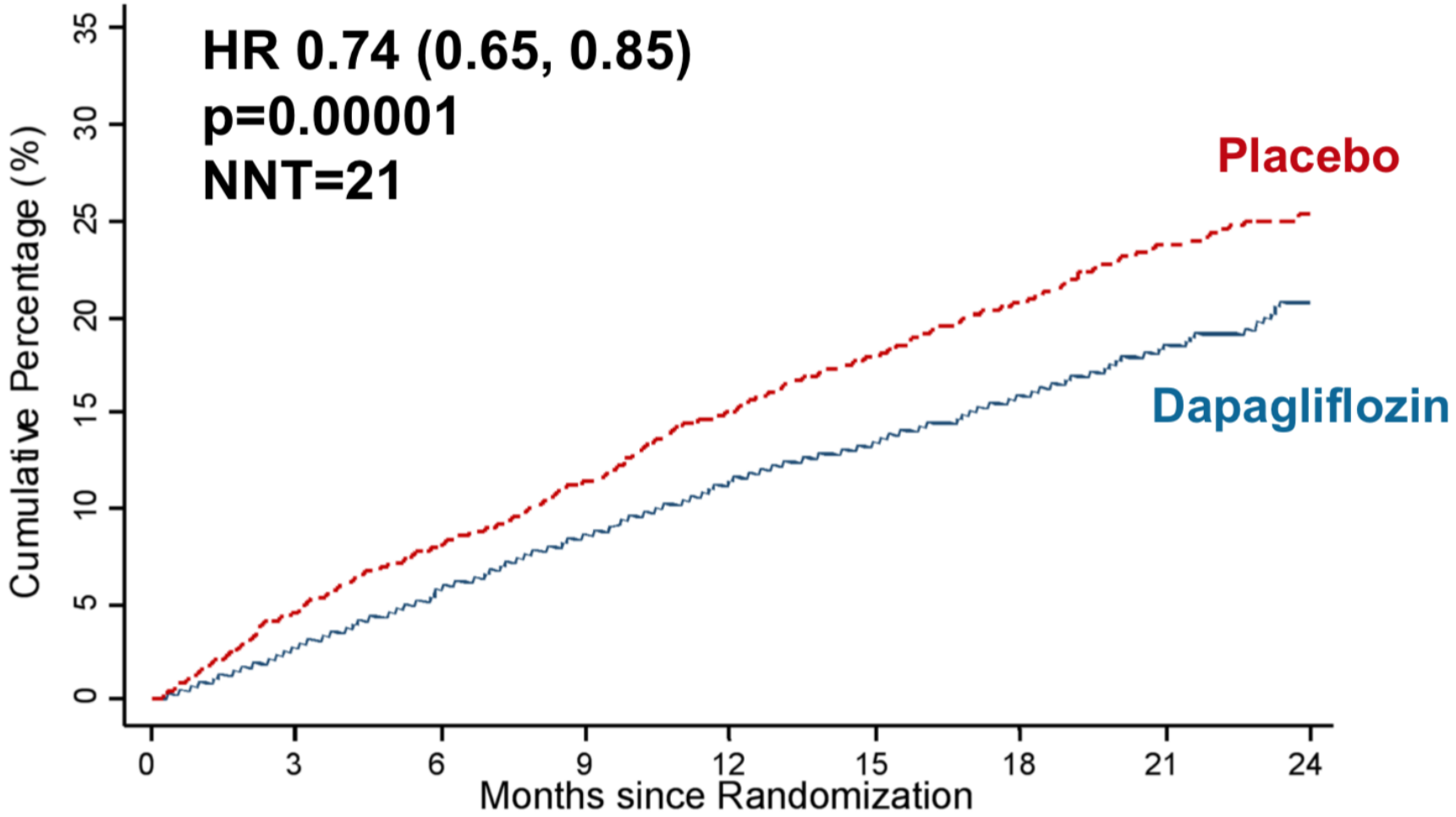
DECLARE[3]



1. Zinman B et al. N Engl J Med. 2015
2. Neal B et al. N Engl J Med 2017
3. Wiviott SD et al. N Engl J Med 2018

Primary composite outcome

CV Death/HF hospitalization/Urgent HF visit

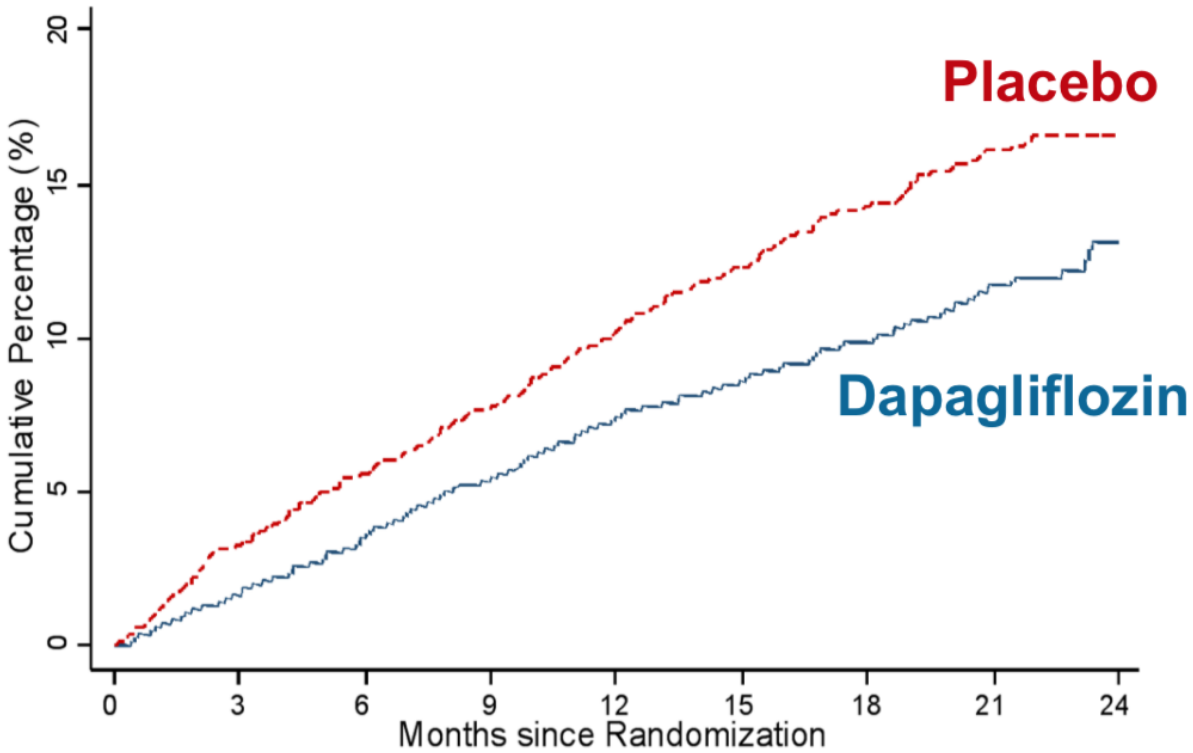


Number at Risk									
Dapagliflozin	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

Components of primary outcome

Worsening HF event

HR 0.70 (0.59, 0.83); p=0.00003

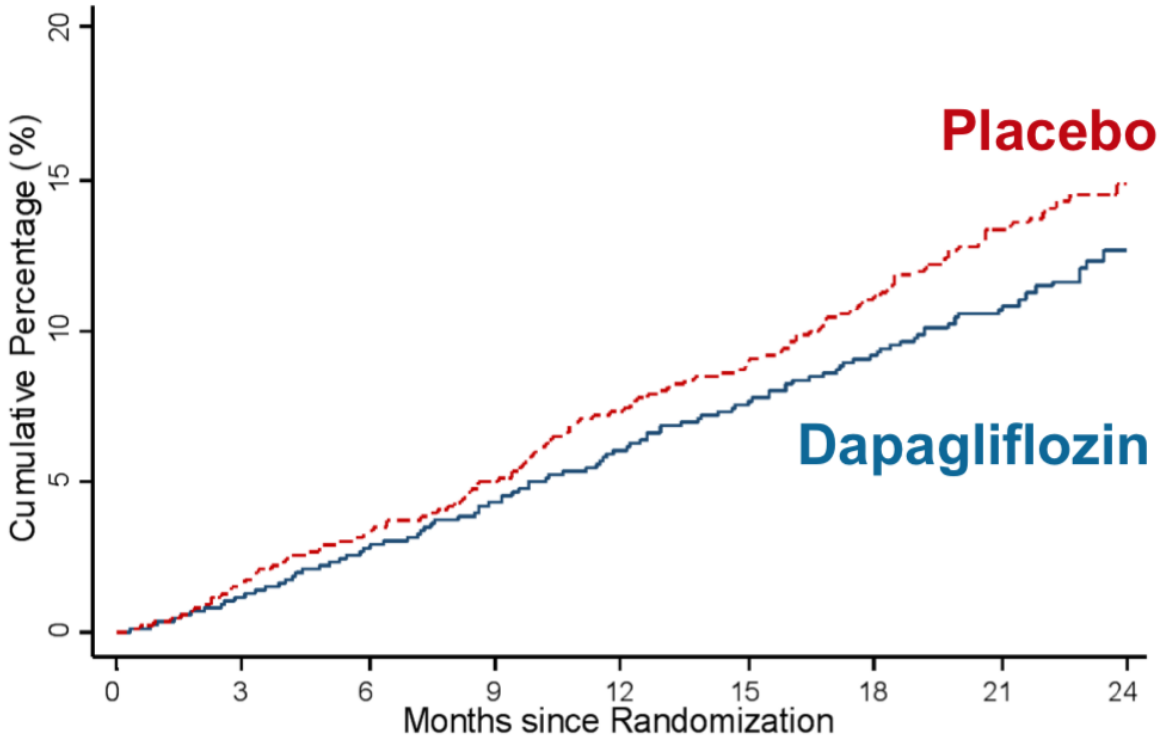


Number at Risk

Dapagliflozin	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

Cardiovascular death

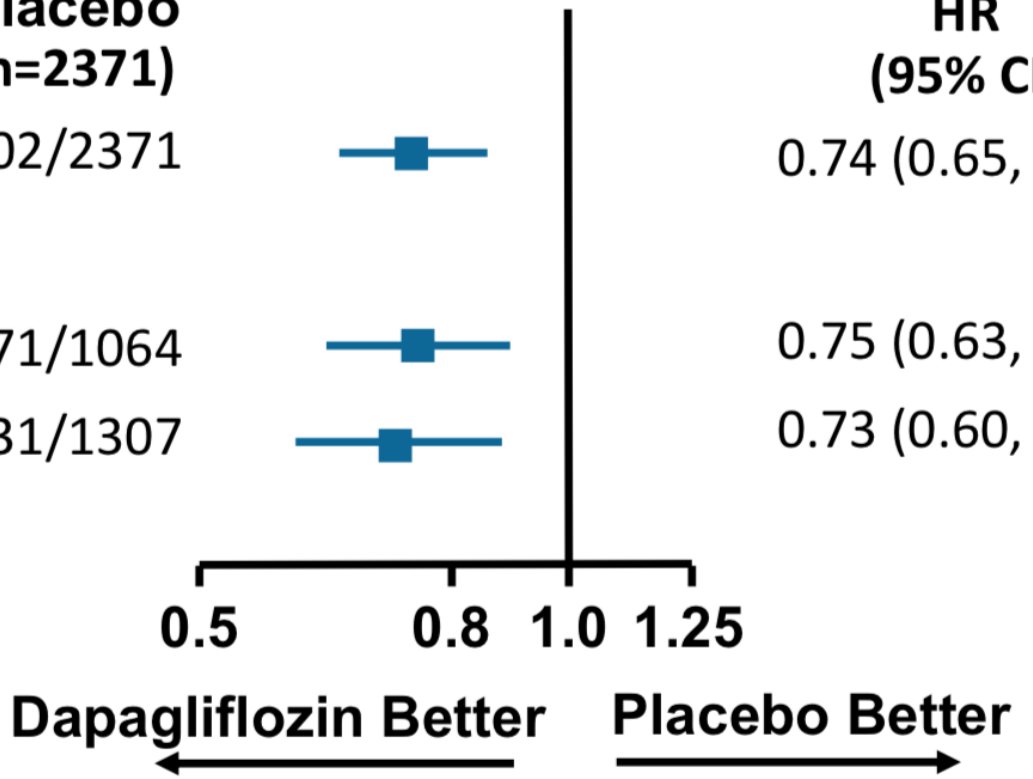
HR 0.82 (0.69, 0.98); p=0.029



	2373	2339	2293	2248	2127	1664	1242	671	232
	2371	2330	2279	2230	2091	1636	1219	664	234

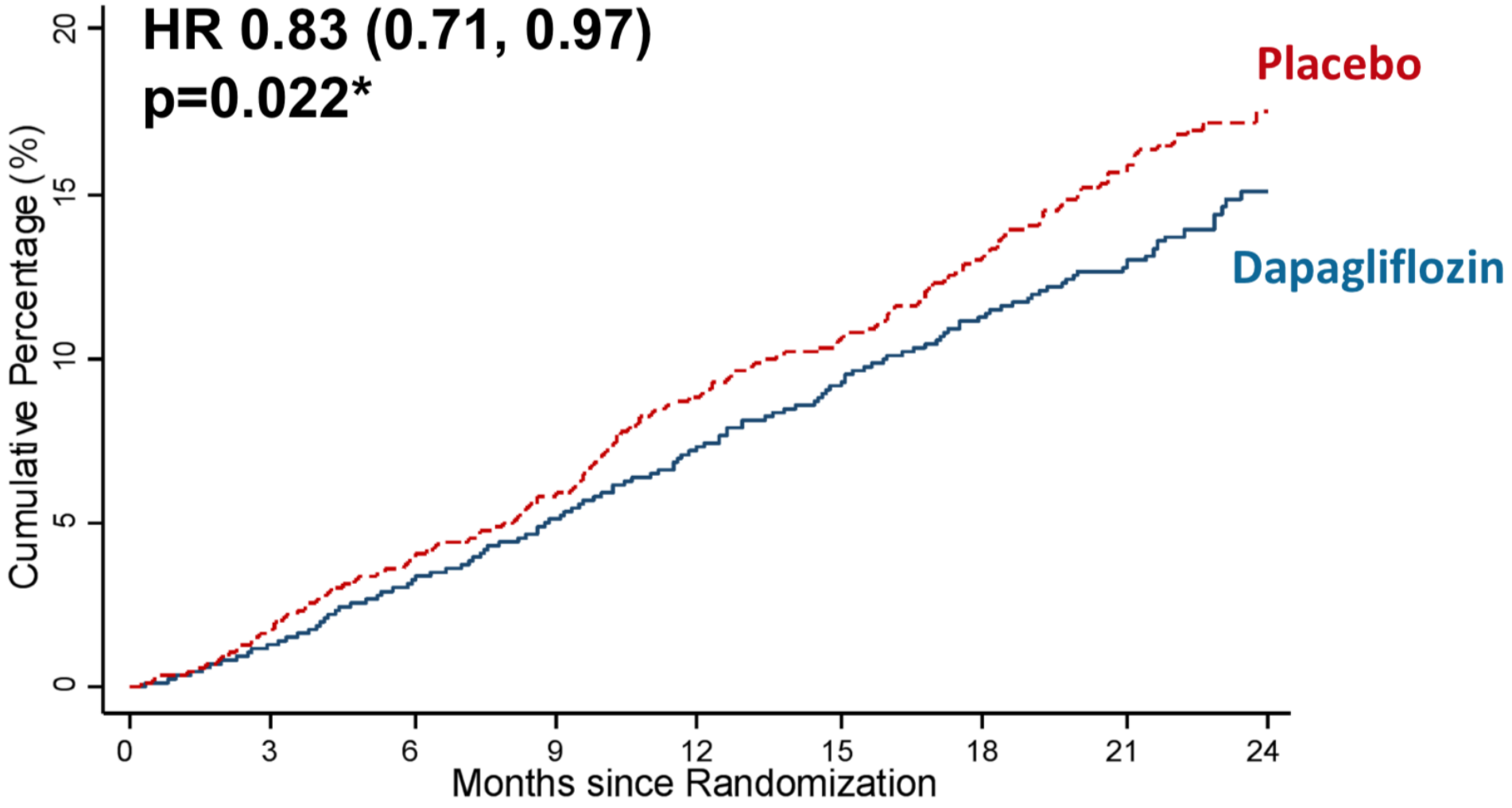
No diabetes/diabetes subgroup: Primary endpoint

	Dapagliflozin (n=2373)	Placebo (n=2371)	HR (95% CI)
All patients	386/2373	502/2371	0.74 (0.65, 0.85)
Type 2 diabetes at baseline*			
Yes	215/1075	271/1064	0.75 (0.63, 0.90)
No	171/1298	231/1307	0.73 (0.60, 0.88)



*Defined as history of type 2 diabetes or HbA1c ≥6.5% at both enrollment and randomization visits.

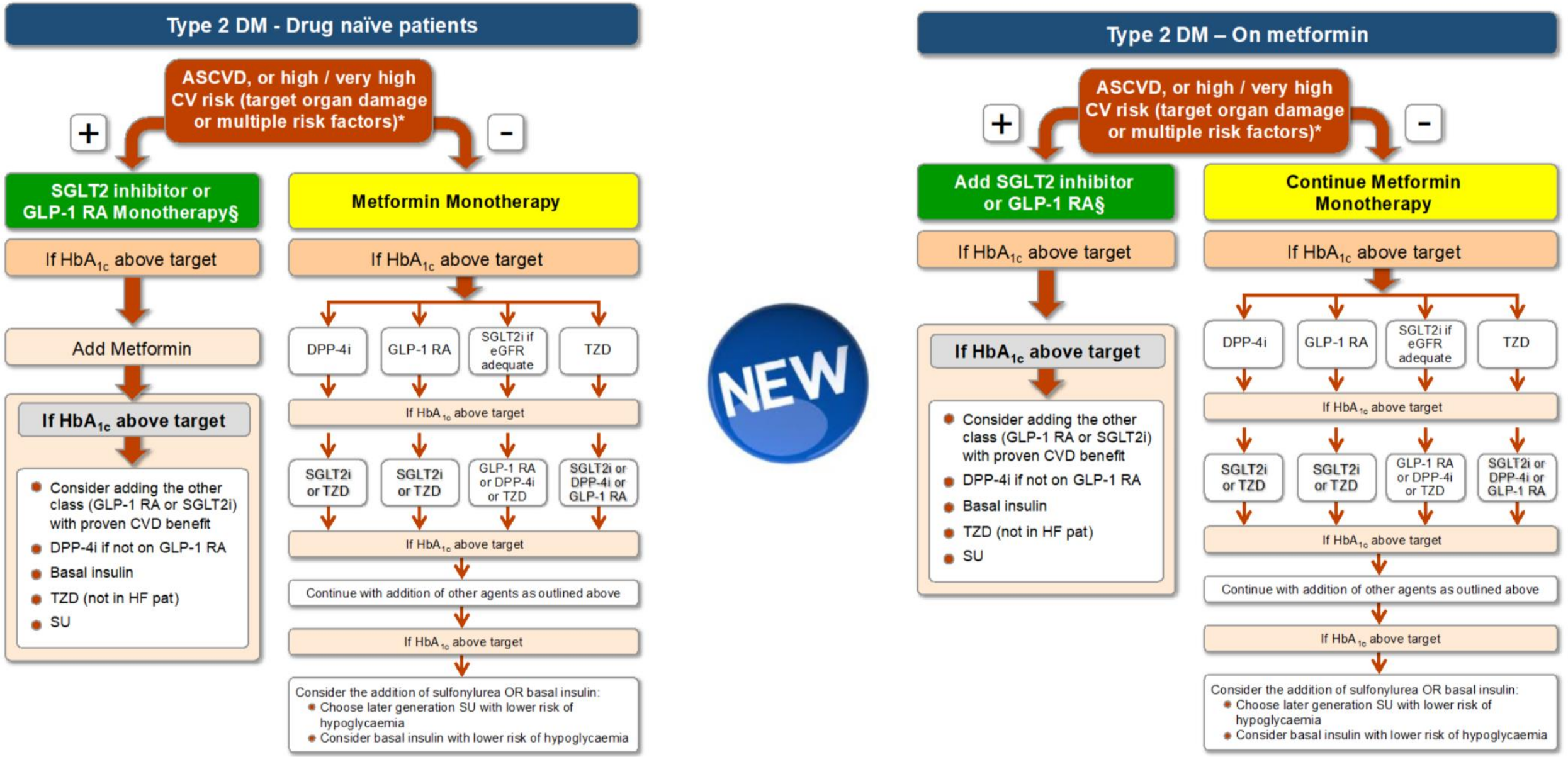
All-cause death



Number at Risk									
Dapagliflozin	2373	2342	2296	2251	2130	1666	1243	672	233
Placebo	2371	2330	2279	2231	2092	1638	1221	665	235

*Nominal p value

New treatment algorithms



A Randomised Trial of Aspirin versus Placebo for Primary Cardiovascular Prevention in 15,480 people with Diabetes (ASCEND)

- Aspirin 100 mg/day vs placebo
- Serious vascular events (SVE) followed for 7.4 years
- Safety assessed by bleeding
- Small reduction in SVE
- Hazard ratio 1.3 for major bleeding
- Aspirin not warranted in primary prevention in diabetes

Bowman L, et al N Engl J Med. 2018; 379(16):1529-1539.

Recommendations for antiplatelet therapy in primary prevention in DM

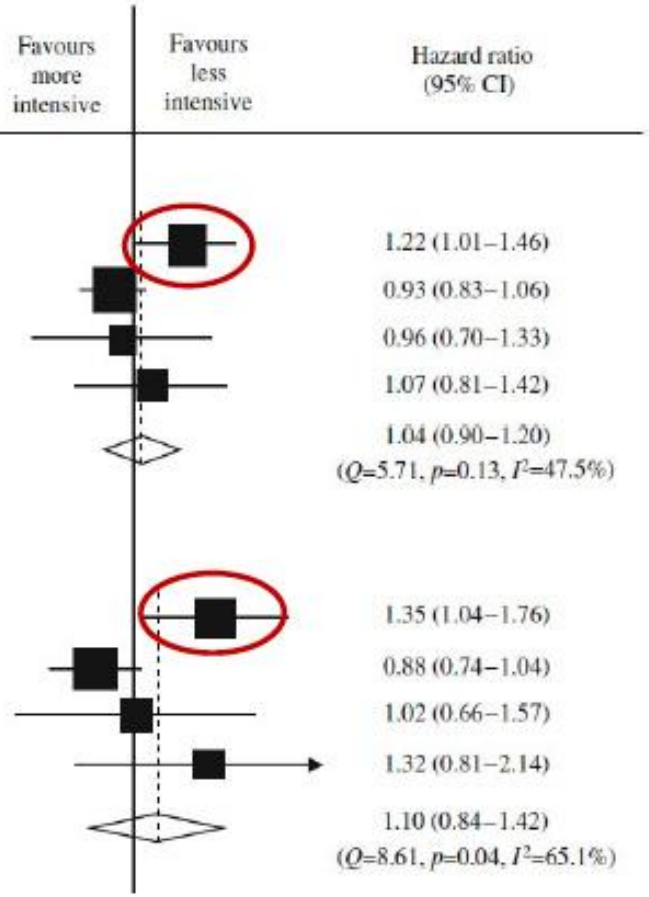
ESC European Society of Cardiology

Recommendations	Class	Level
In patients with DM at high/very high risk, aspirin (75–100 mg/day) may be considered in primary prevention in the absence of clear contraindications.	IIb	A
In patients with DM at moderate CV risk, aspirin for primary prevention is not recommended.	III	B
Gastric protection		
When low-dose aspirin is used, proton pump inhibitors should be considered to prevent gastrointestinal bleeding.	IIa	A

ESC Guidelines on Diabetes, pre-diabetes and cardiovascular diseases in collaboration with EASD (European Heart Journal 2019 - doi/10.1093/eurheartj/ehz486)

Meta-analysis: Intensive glucose control & mortality

Trials	Number of events (annual event rate, %) More intensive	Less intensive	ΔHbA_{1c} (%)	Hazard ratio (95% CI)
All-cause mortality				
ACCORD	257 (1.41)	203 (1.14)	−1.01	1.22 (1.01–1.46)
ADVANCE	498 (1.86)	533 (1.99)	−0.72	0.93 (0.83–1.06)
UKPDS	123 (0.13)	53 (0.25)	−0.66	0.96 (0.70–1.33)
VADT	102 (2.22)	95 (2.06)	−1.16	1.07 (0.81–1.42)
Overall	980	884	−0.88	1.04 (0.90–1.20) (Q=5.71, p=0.13, I^2=47.5%)
Cardiovascular death				
ACCORD	135 (0.79)	94 (0.56)	−1.01	1.35 (1.04–1.76)
ADVANCE	253 (0.95)	289 (1.08)	−0.72	0.88 (0.74–1.04)
UKPDS	71 (0.53)	29 (0.52)	−0.66	1.02 (0.66–1.57)
VADT	38 (0.83)	29 (0.63)	−1.16	1.32 (0.81–2.14)
Overall	497	441	−0.88	1.10 (0.84–1.42) (Q=8.61, p=0.04, I^2=65.1%)



Diabetologia (2009); 52:2288-98

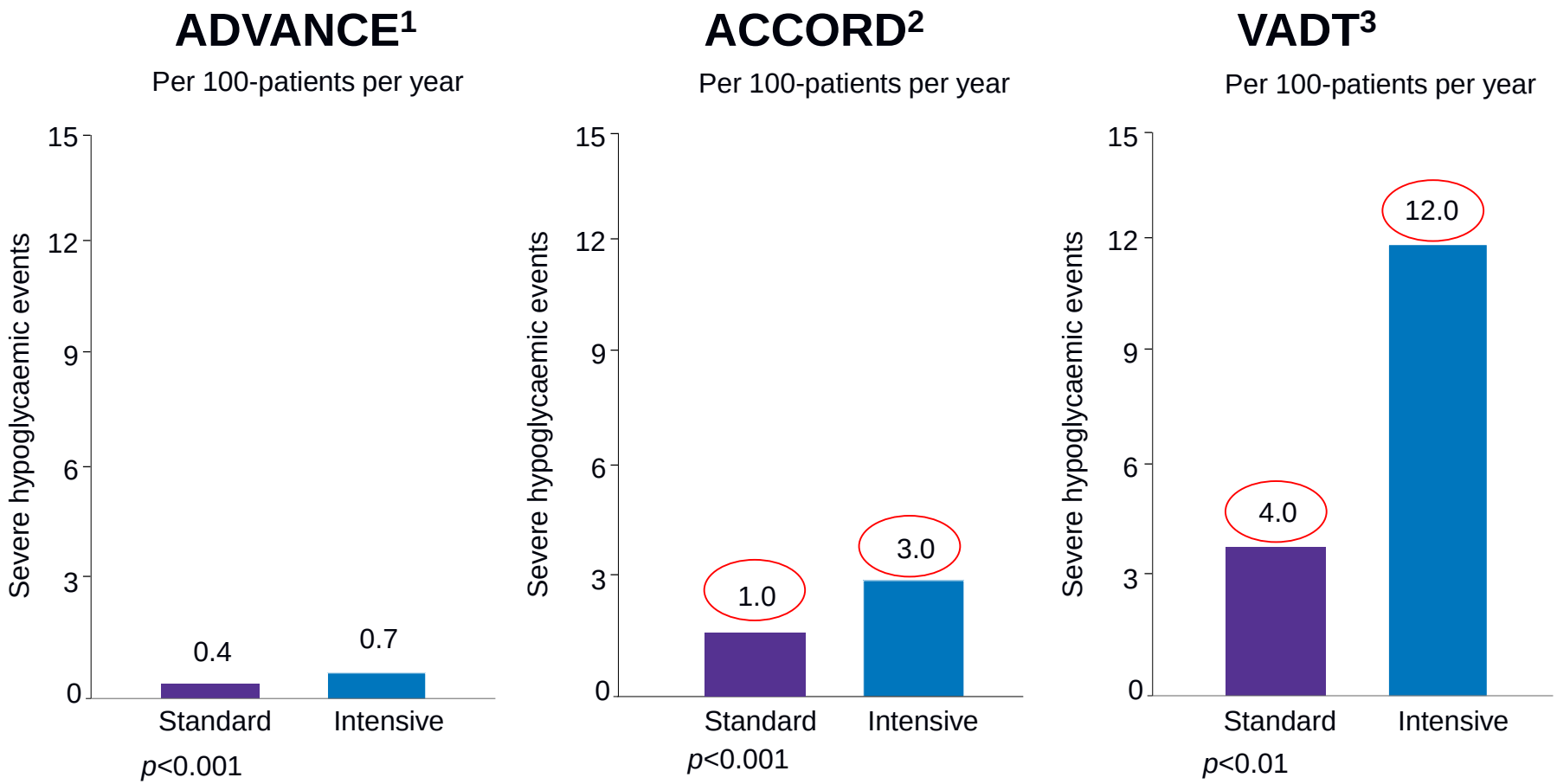
Summary of Outcomes from Mega-trials:

	ACCORD*	ADVANCE	VADT
A1C (%) (Intensive vs. Std)	< 6.0 vs. 7.0-7.9	6.4 vs. 7.0 †	6 4 †
Nonfatal MI (%) (Intensive vs. Std)	3.6 vs 4.6% †	2.7 vs 3	s. 6.1
CV Death (%) (Intensive vs. Std)	2.6 vs. 1.8 † (1.35 Haz P		2.1 vs.1.7
Microvascul		nephropathy ↓ 21% retinopathy ↓ 5% NS	-
Take	↑ risk death in intensive arm	Glucose control has no impact on CV events, but ↓ Microvascular risk	Glucose control has no impact on CV events

No clear evidence of CV benefits
Concerns about safety!

ACCORD Study Group, *NEJM* 2008, 358:2545-2559; ADVANCE Collaborative Group, *NEJM* 2008, 358:2560-2572;
VADT: N Engl J Med 2009;360:129–39

Intensive glucose lowering is associated with increased incidence of Severe Hypoglycemia

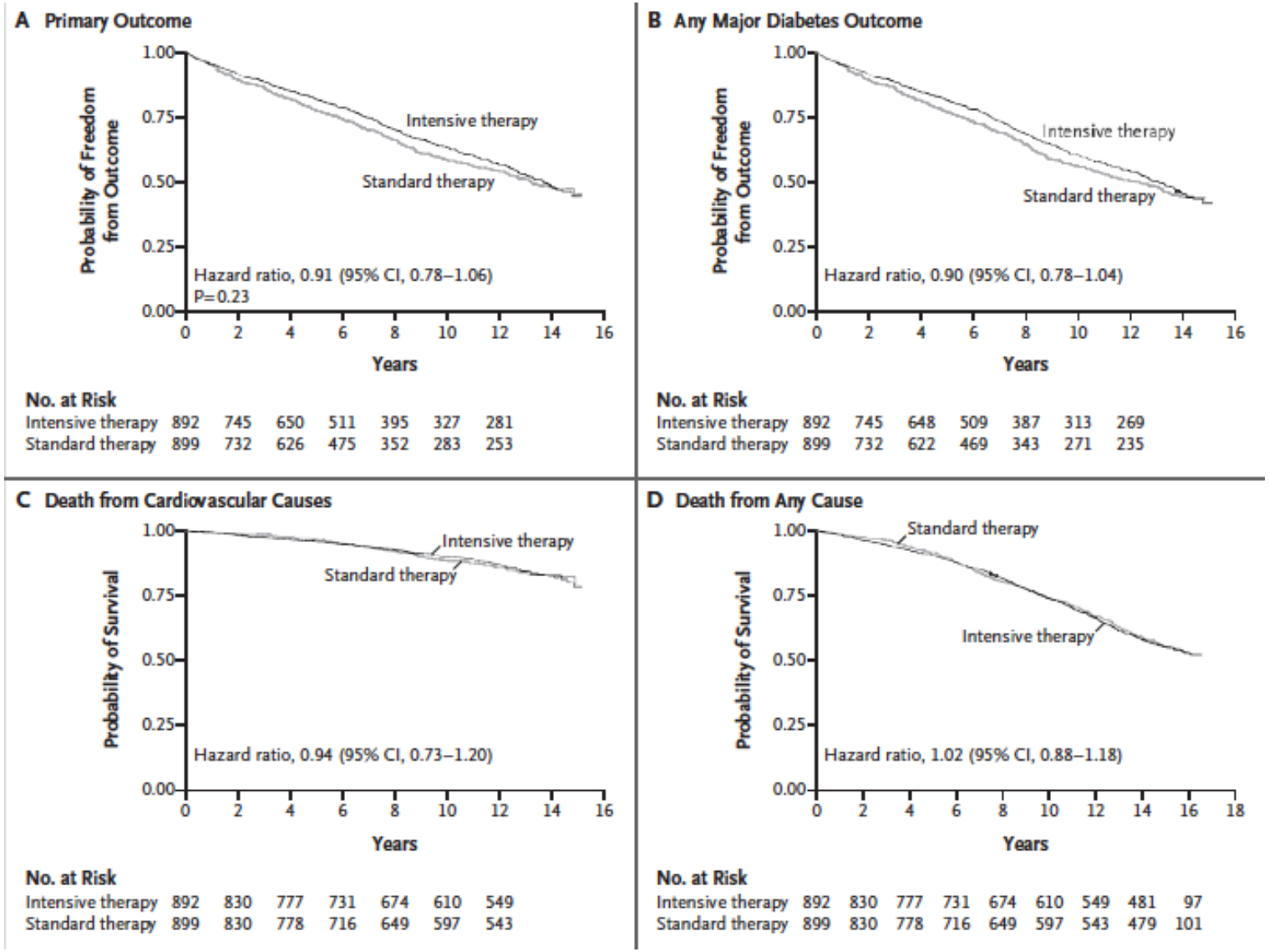


Intensive glucose lowering contributes to an increased risk of hypoglycemia by 2- to 3-fold, particularly in advanced type 2 diabetes

ACCORD Study Group, *NEJM* 2008, 358:2545-2559; ADVANCE Collaborative Group, *NEJM* 2008, 358:2560-2572; VADT: N Engl J Med 2009;360:129–39

Speaker

Intensive vs less intensive glucose control : 15 year FU of the VADT study

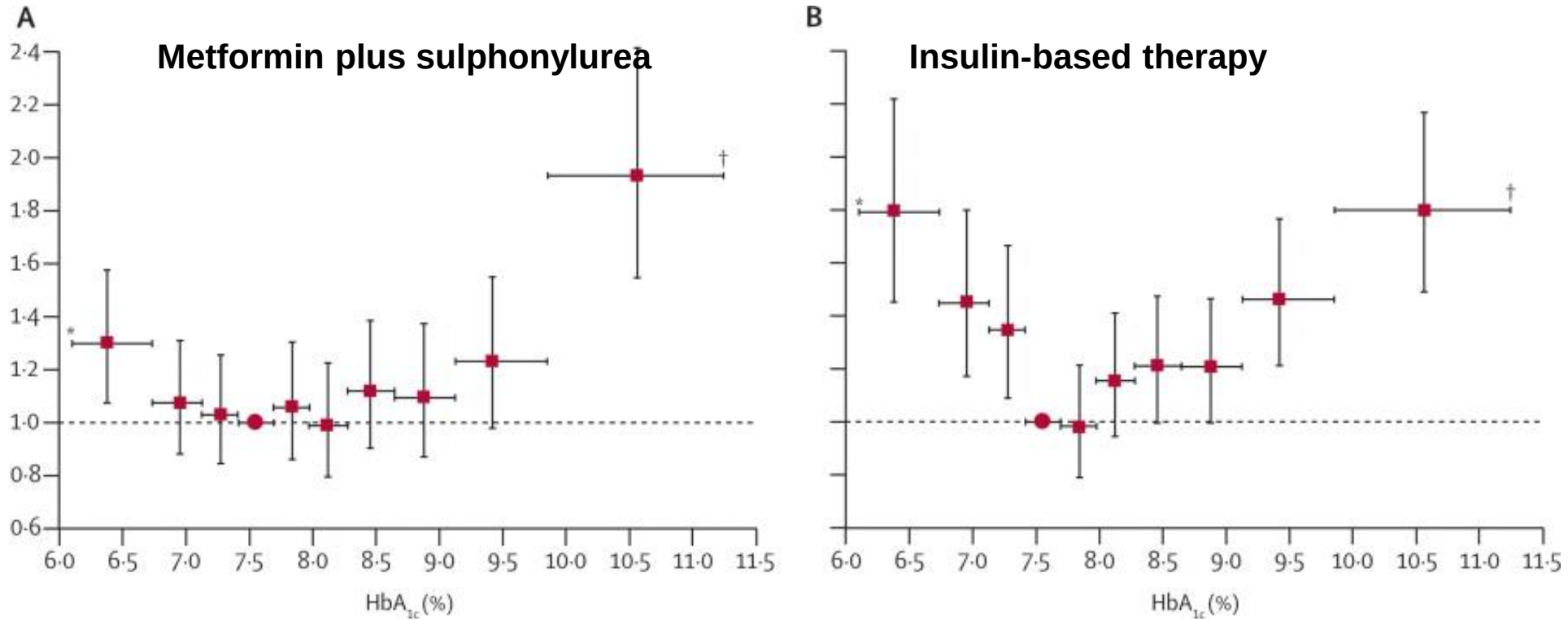


The Goldilocks effect

Blood glucose lowering: not too little, not too much

Observational study: HbA1c of about 7.5% associated with lowest risk of all-cause mortality (increase above or decrease below this associated with greater risk)

Adjusted hazard ratios for all-cause mortality by HbA1c deciles in people given metformin plus sulphonylurea (A) and insulin-based therapy (B)



Currie CJ, et al. Lancet 2010;375:481–9, MeReC Rapid Review No. 101

Conclusion

Diabetes is a CVD and as such should be managed by cardiologists using an holistic approach the includes BP and Lipid management

CVD management in diabetic patients should be tailored to the degree of risk

- GLP1a-based therapy reduce macrovascular end-point
- SGLT2 inhibitors reduce heart failure events in patients with diabetes
- Dapagliflozin reduces mortality and hospitalisations in patients with heart failure with and without diabetes mellitus