ACC Middle East Conference 2018

In partnership with:

Diabetes and the Heart

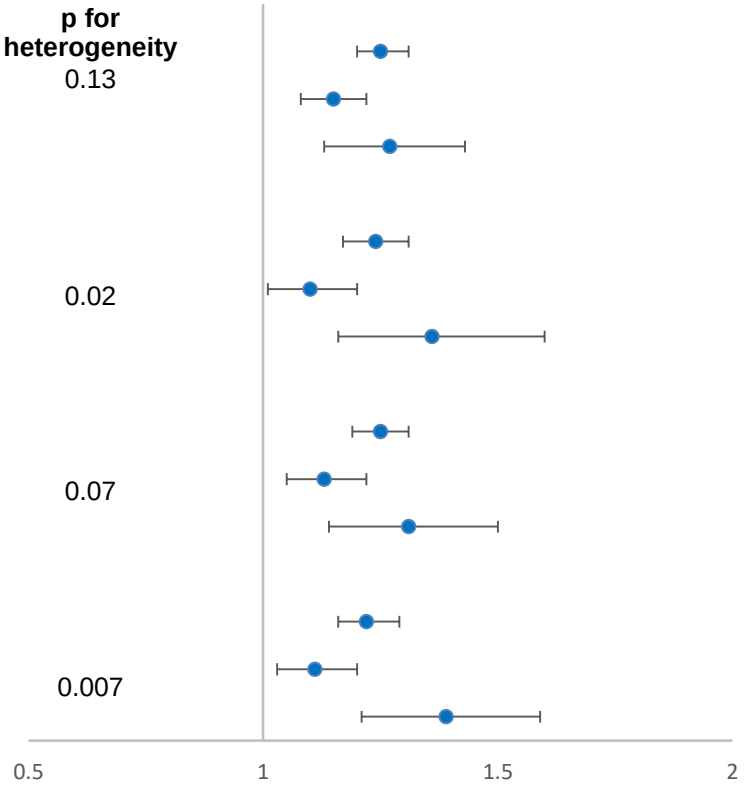
Waleed AlHabeeb, MD, MHA

President of the Saudi Heart Failure Working Group

Increased HbA1c is an independent risk factor for CV events in patients with HF

- For every 1% increase in HbA1c, the risk of CV events or death increases by approximately 25% in patients with HF[2]

	HR (95% CI)	p for heterogeneity
CV death or HF hospitalization		
All (N=2412)	1.25 (1.20–1.31)	0.13
Diabetes (n=907)	1.15 (1.08–1.22)	
No diabetes (n=1505)	1.27 (1.13–1.43)	
CV death		
All (N=2412)	1.24 (1.17–1.31)	0.02
Diabetes (n=907)	1.10 (1.01–1.20)	
No diabetes (n=1505)	1.36 (1.16–1.60)	
Worsening HF		
All (N=2412)	1.25 (1.19–1.31)	0.07
Diabetes (n=907)	1.13 (1.05–1.22)	
No diabetes (n=1505)	1.39 (1.14–1.50)	
Death		
All (N=2412)	1.25 (1.19–1.31)	0.007
Diabetes (n=907)	1.13 (1.05–1.22)	
No diabetes (n=1505)	1.39 (1.14–1.50)	

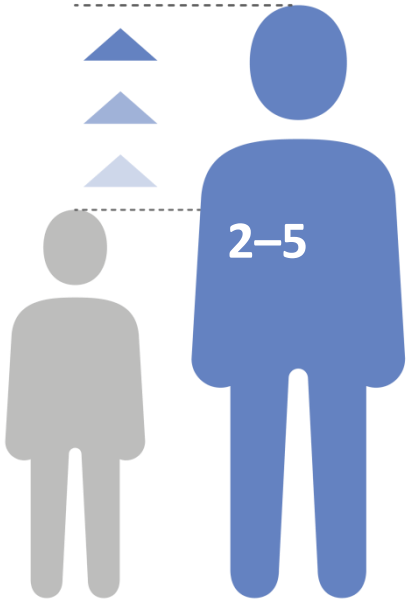


Data from CHARM trial program

DM=diabetes mellitus; CI=confidence interval; CV=cardiovascular; HbA1c=glycated hemoglobin; HF=heart failure; HR=hazard ratio

1. Kristensen et al. Circ Heart Fail 2016; 9(1). pii: e002560; 2. **Gerstein et al. Arch Intern Med. 2008;168(15):1699-1704**

People with diabetes are at increased risk of heart failure



People with diabetes have a 2- to 5-fold higher risk of developing HF[1]

Diabetes confers a 60–80% greater probability of CV death and all-cause mortality in those with established HF[2,3]*

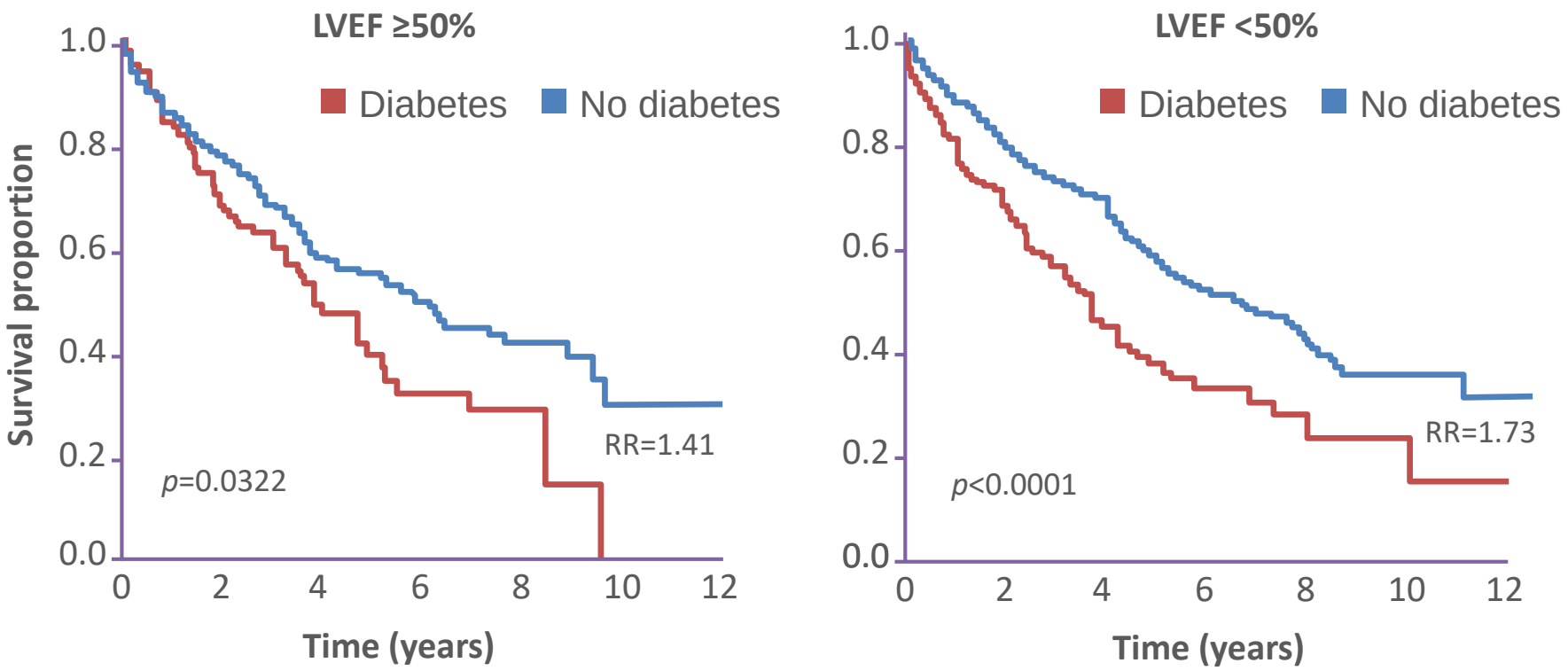
*Synthesised based on data from two clinical studies – see Notes for details

CV, cardiovascular; HF, heart failure

1. Kannel WB *et al. Am J Cardiol* 1974;34:29; 2. Cubbon RM *et al. Diab Vasc*

Diabetes worsens heart failure prognosis

Poorer HF survival with diabetes than without diabetes



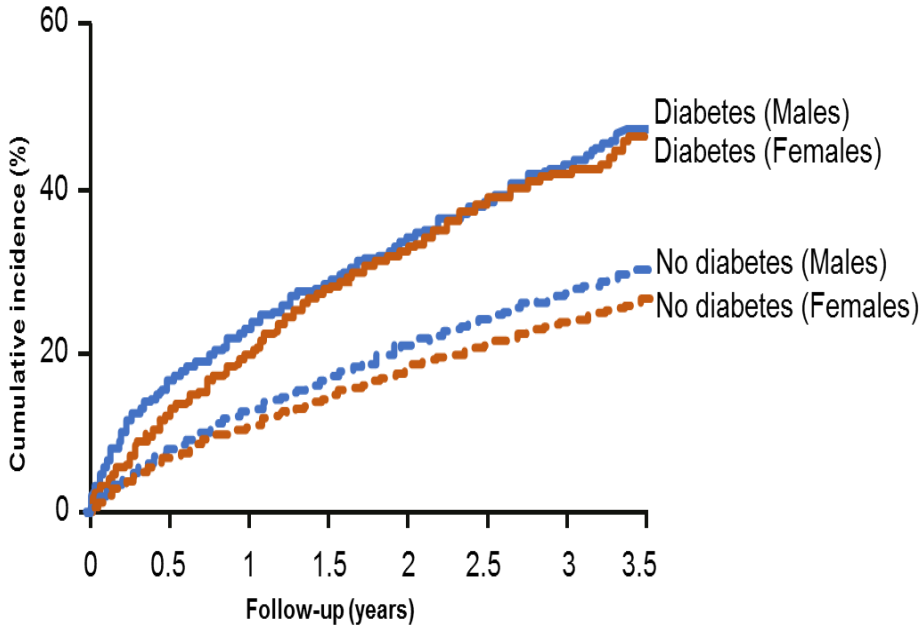
- Kaplan–Meier survival curves of HF patients hospitalised with LVEF ≥50% (n=498) and <50% (n=754)

HF, heart failure; LVEF, left ventricular ejection fraction

Varela-Roman A *et al. Eur J Heart Failure* 2005;7:859

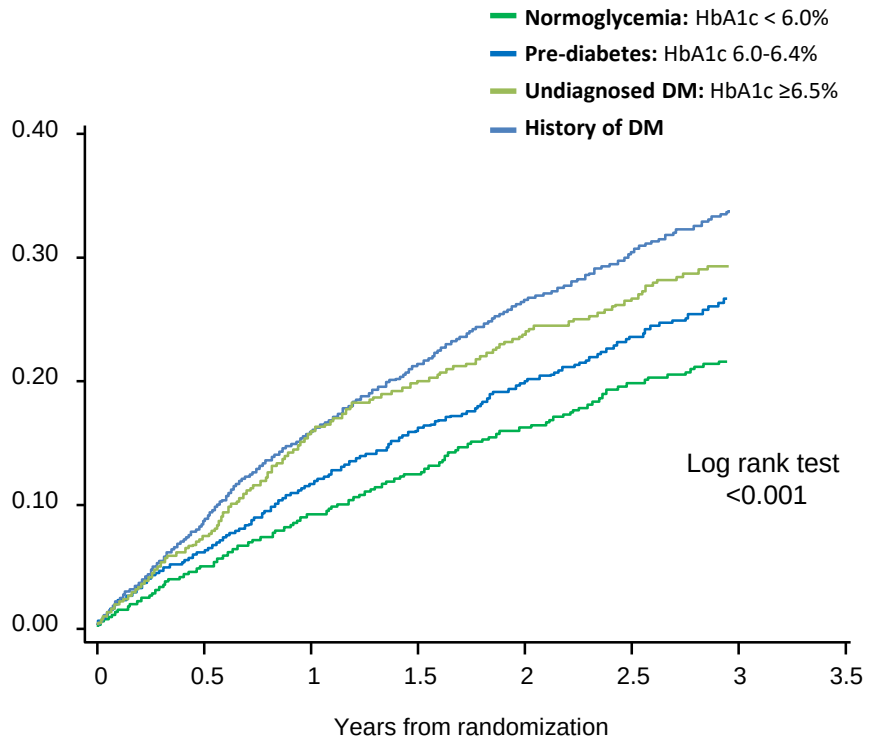
Association of HF and DM predicts worse outcomes than either disease would alone

CV death or HF hospitalization by DM status in patients with HF[3]



Data from CHARM trial program;

CV death or HF hospitalization by degree of dysglycemia in patients with HFrEF[2]



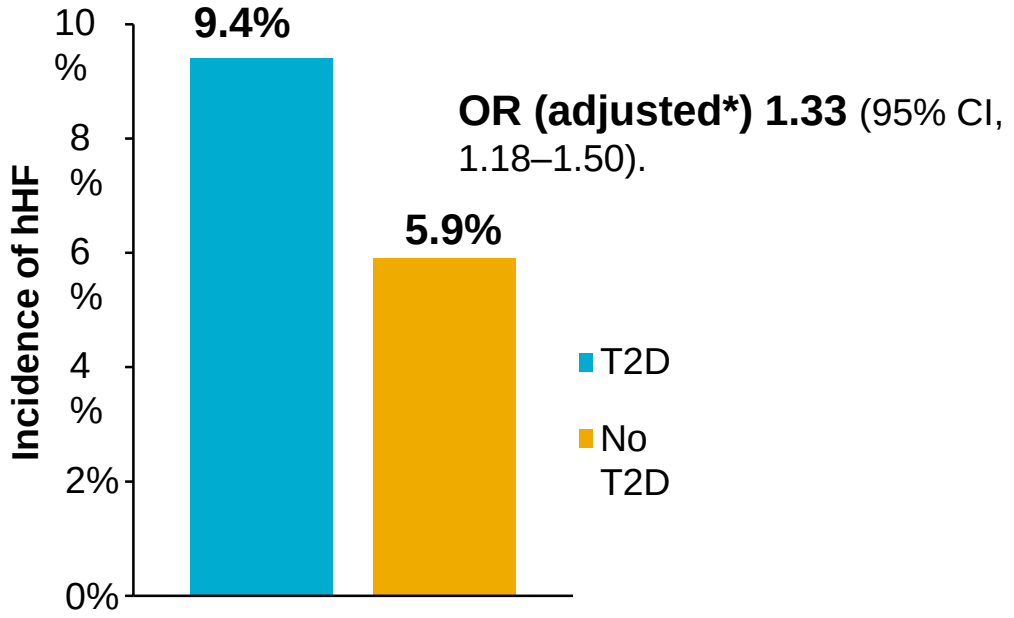
Data from PARADIGM-HF trial

DM=diabetes mellitus; HbA!c=glycated hemoglobin;
HF=heat failure; HFrEF=HF with reduced ejection fraction

1. Dei Cas A et al. Curr Probl Cardiol. 2015 Jan;40(1):7-43; **2.** Kristensen et al. Circ Heart Fail 2016; 9(1). pii: e002560; 3. MacDonald et al. Eur Heart J 2008; 29:1377–1385

Type 2 diabetes is a potent, independent risk factor for HF

Four year follow up of a cohort with and without T2D (n-45,227) and either eCVD or CV risk factors



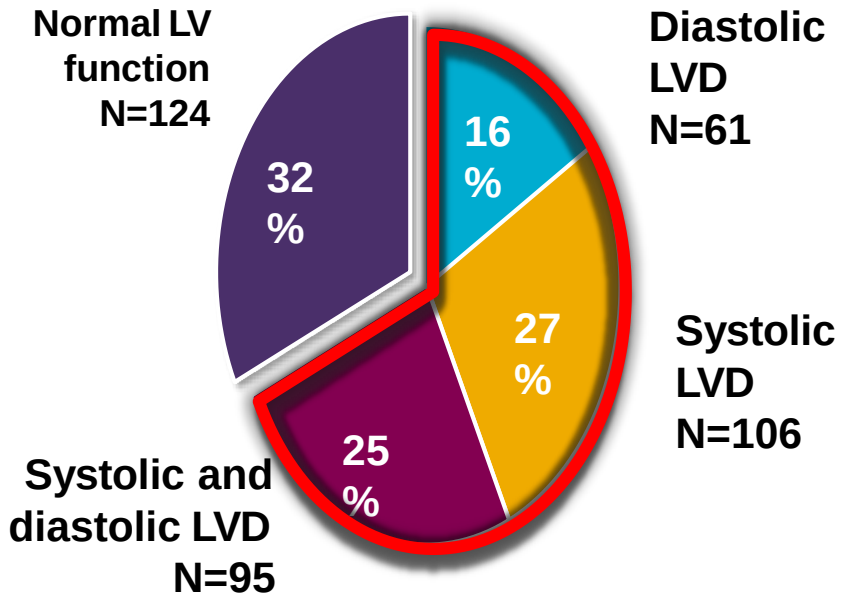
Diabetes mellitus was associated with a 33% greater risk of hospitalization for heart failure

hHF, hospitalization for heart failure Cavender *Circulation*. 2015;132:923-931.

* sex, age, geographic region , cardiovascular risk factors; ischemic event, renal dysfunction, known vascular disease, congestive heart failure, atrial fibrillation, and

Left ventricular dysfunction is an early complication of T2DM

68% of patients with T2D had evidence of LV dysfunction 5 years after T2D diagnosis



Patients had no evidence of inducible ischemia by stress testing at baseline

LV, left ventricular; LVD, LV dysfunction

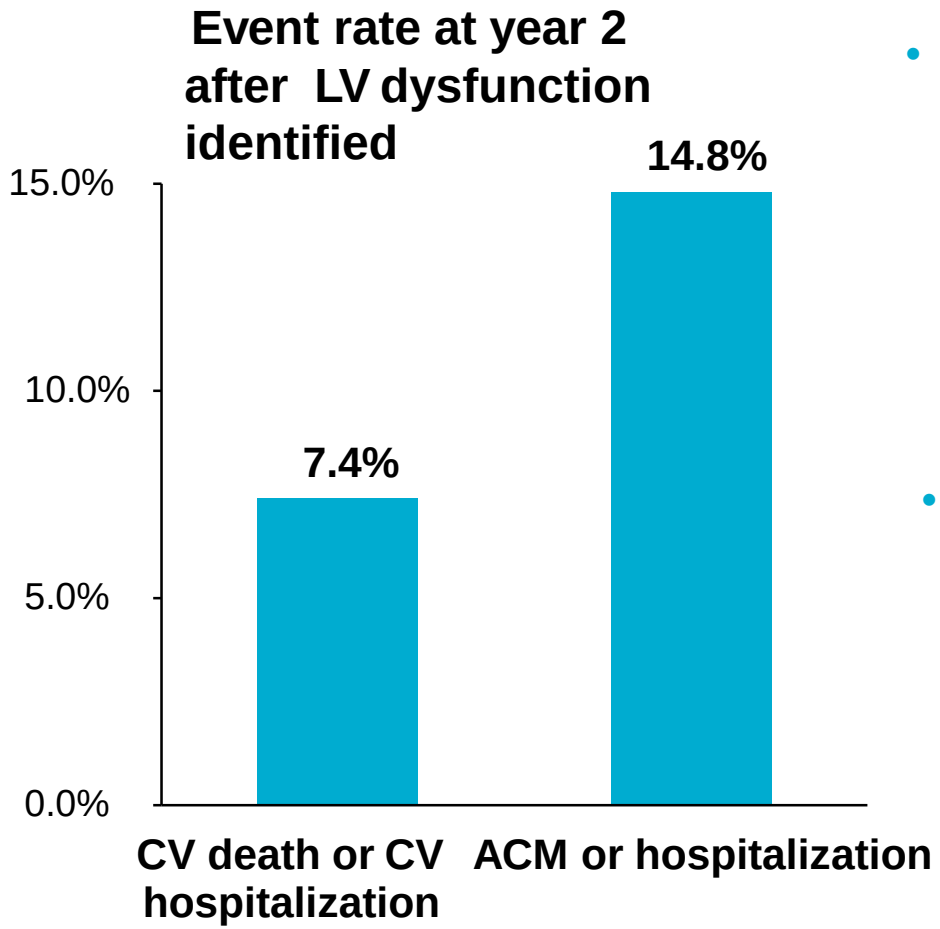
Faden Diabetes and Clinical Research 2013; Seferović PM, Paulus WJ. *Eur Heart J*. 2015;36:1718-27, 1727a-1727c

Two distinct phenotypes of diabetes-related cardiomyopathy exist

HFpEF (earliest)	HFrEF
▪ Cardiomyocyte hypertrophy ▪ Cardiomyocyte fibrosis ▪ Increased cardiomyocyte stiffness	▪ Cardiomyocyte apoptosis ▪ Cardiomyocyte necrosis ▪ Decreased cardiomyocyte shortening

This suggests the earliest defect in the diabetic heart is that of diastolic dysfunction not atherothrombosis

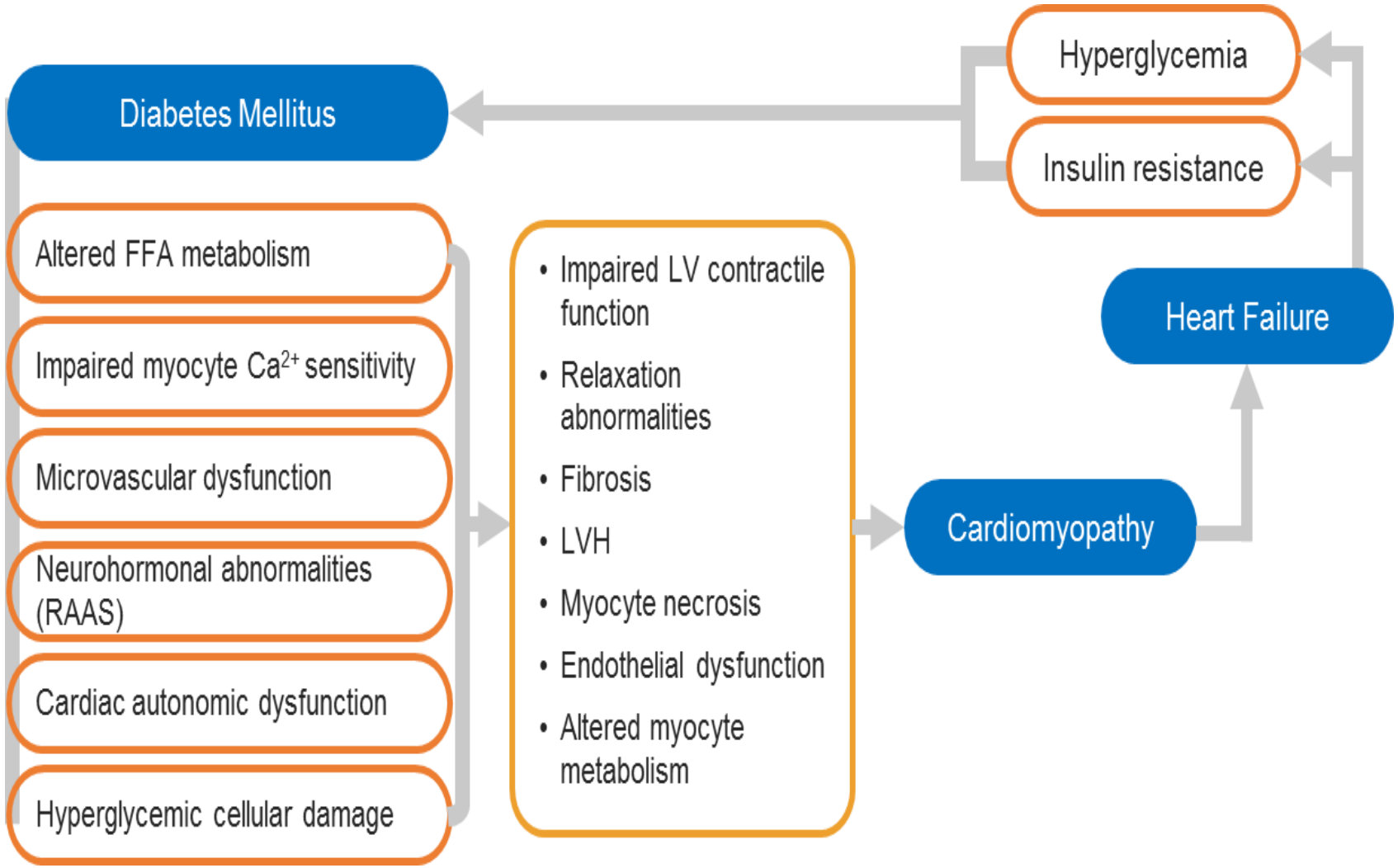
Quick Progression from Asymptomatic LVD to a CV event



- Patients with T2D and no evidence of coronary disease in the DYDA study who had LV dysfunction identified by transthoracic echocardiography were assessed for the incidence of clinical events at a 2-year follow-up
- The incidence of a combined outcome measure of all-cause death and hospitalizations at 2-year follow-up was 14.8%

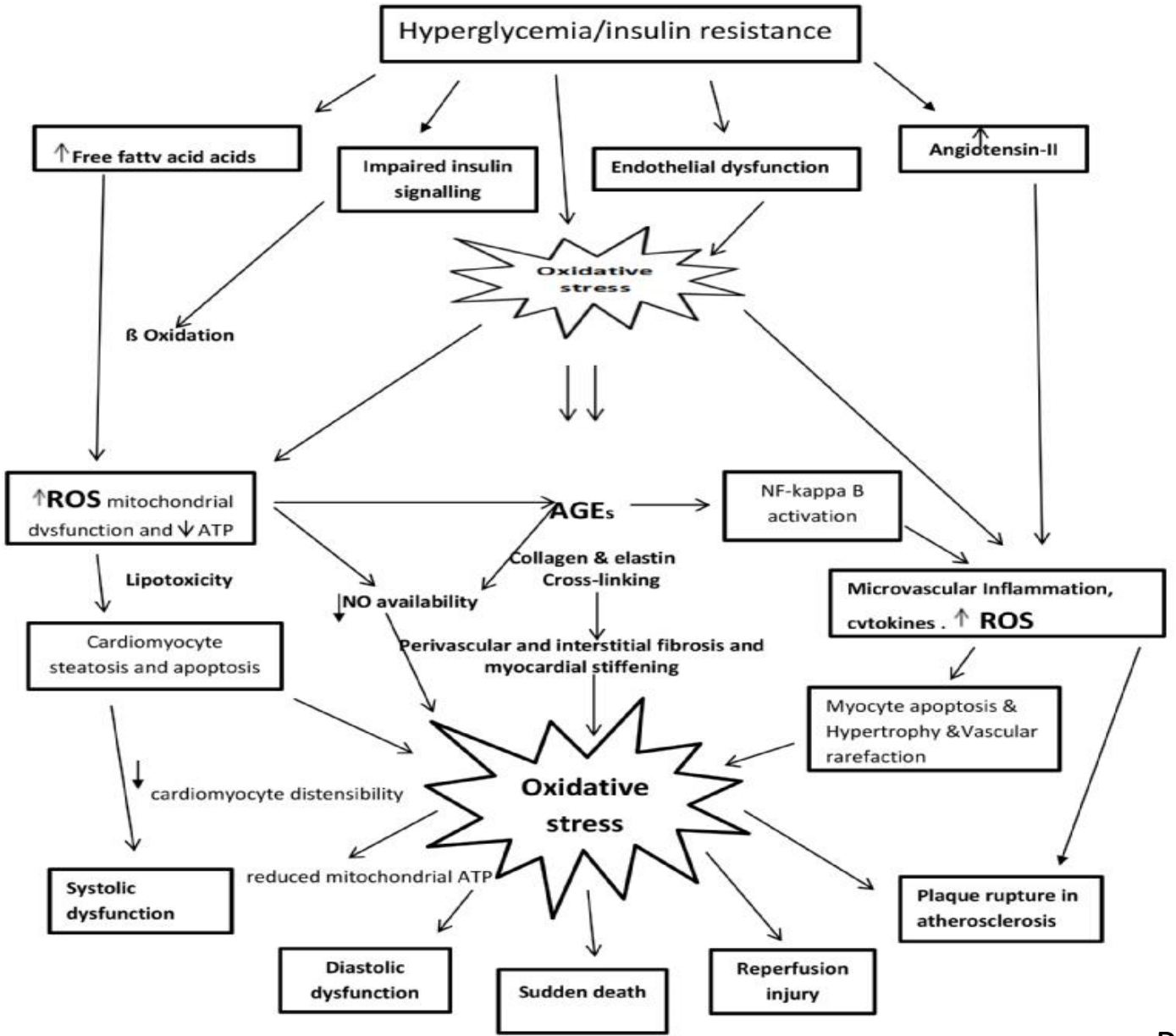
LV, left ventricular;
Cioffi, Diabetes Research and Clinical Practice 2013; 236-242

Potential pathophysiological link between HF and DM

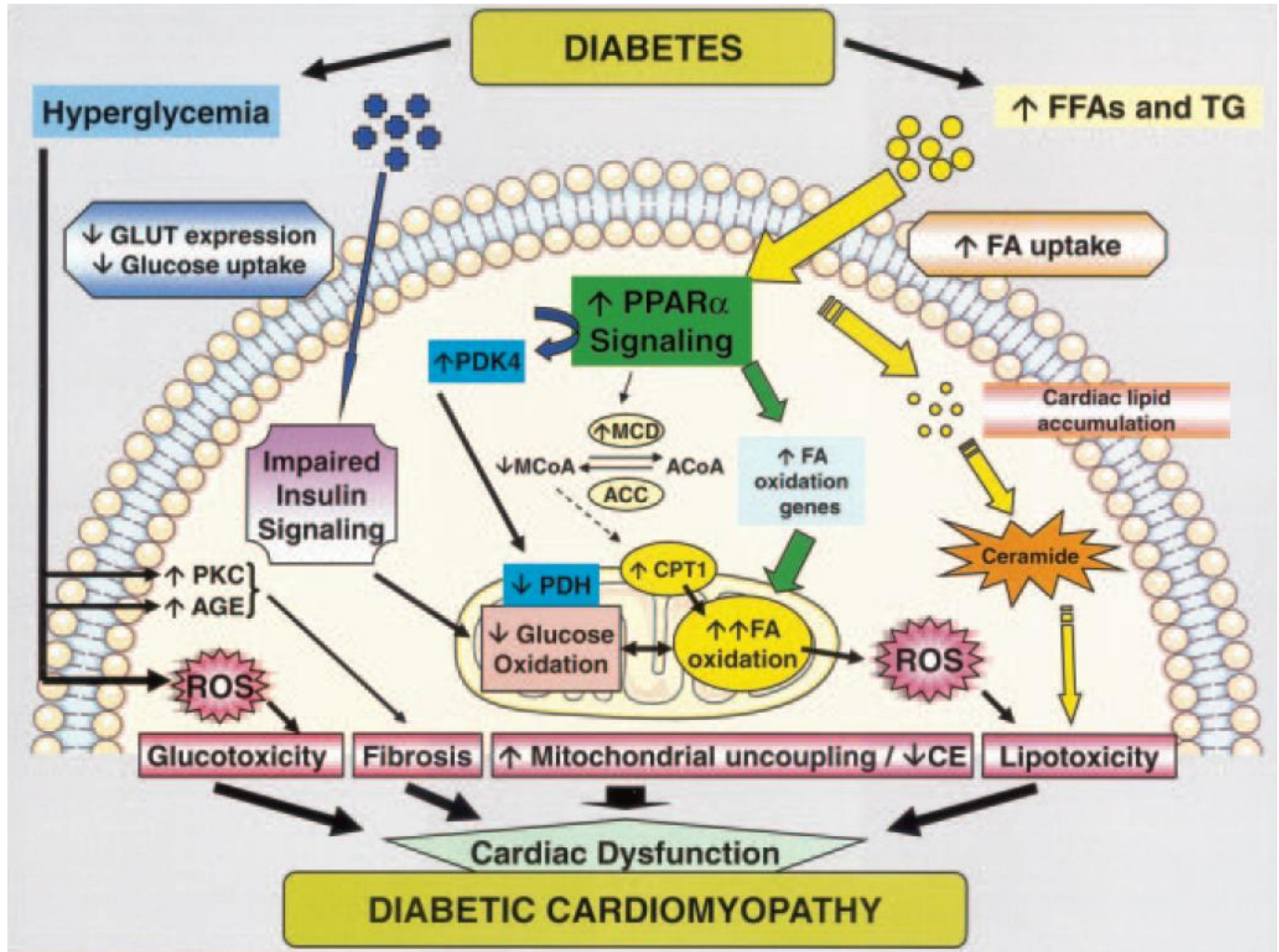


DM=diabetes mellitus; FFA=free fatty acid; LV=left ventricular; LVH=left ventricular hypertrophy; RAAS=renin–angiotensin–aldosterone system

1. Dei Cas A et al. Curr Probl Cardiol. 2015 Jan;40(1):7-43; **2.** Campbell et al. Cardiac Failure Review, 2015;1(1):8–10



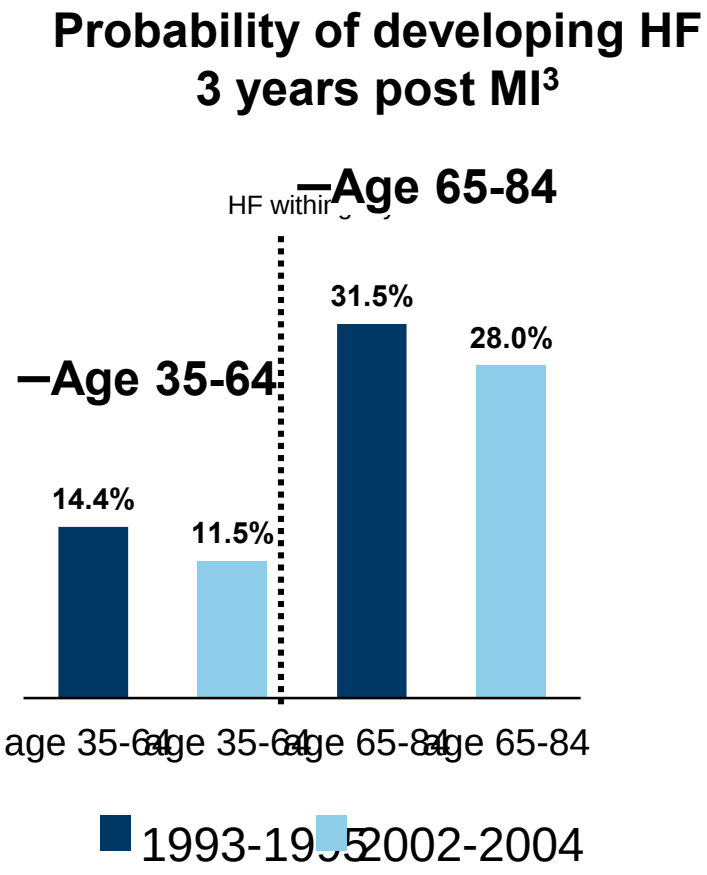
Prof. Datshana P. Naidoo
Vol.14,N°14 - 21 Jun 2016



Circulation. **2007;115:3213-3223.)**

Ischemic heart disease is a common cause of HF, although due to post-MI care its contribution is declining

- Acute MI results in loss of functioning myocytes, development of myocardial fibrosis and subsequent LV remodeling[1]
- In a pooled analysis of 37 studies, ischemic heart disease was a risk factor for HF in >50% of patients with HF in western high income and eastern and central Europe regions and 30-40% in East Asia, Asia Pacific high income, Latin America and Caribbean regions[2]
- Introduction of new medical and interventional treatments have improved the prognosis in patients with acute MI[3]
- Therefore the incidence of HF post-MI is declining[3]
- This suggests modification of additional risk factors for HF will become increasingly important



LV, left ventricular; MI, myocardial infarction.

1. Gheorghiade M, Bonow R, *Circulation*. 1998;97:282-289; 2. Khatibzadeh S, *International Journal of Cardiology.* 2013;168:1186–1194; 3. Shafazhand M, *Eur Journal of Heart Failure*. 2011;13:135–141.

Diabetic Cardiomyopathy

- DM appears to contribute directly to the development of CMP, rather than solely *via coronary atherosclerosis* and hypertension
- Changes occur in LV structure and cardiac function
- Diabetics tend to have greater cardiac mass, particularly LV mass

- Patients with DM also tend to have a slightly diminished diastolic function due to increased myocardial triglyceride content
- Abnormalities in systolic function have also been observed and may be related to impaired myocardial sympathetic innervation and impaired contractile reserve
- Interstitial fibrosis with increased collagen deposition has been observed

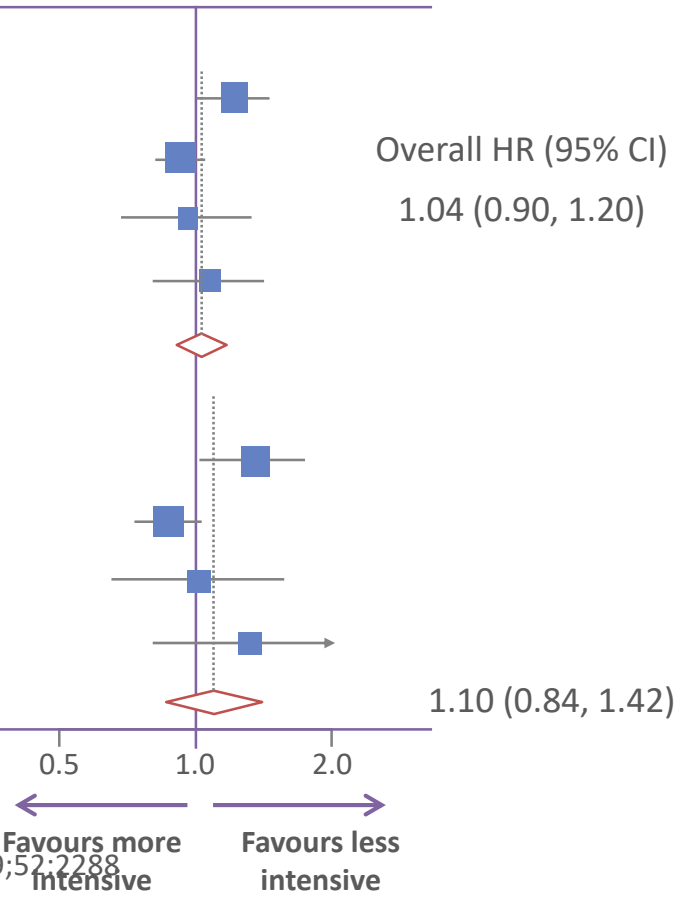
Cardiovascular Autonomic Neuropathy

- Common among patients with DM and is correlated with an increased 5-year mortality rate from CVD
- Clinical manifestations are resting tachycardia, postural hypotension, exercise intolerance, abnormal coronary vasomotor regulation, increased QT interval, and perioperative instability
- Related to an increased risk of renal disease, stroke, CVD and sudden death

No evidence from prospective trials that more intensive glycaemic control reduces mortality

Meta-analysis including 27,049 participants and 2370 major vascular events

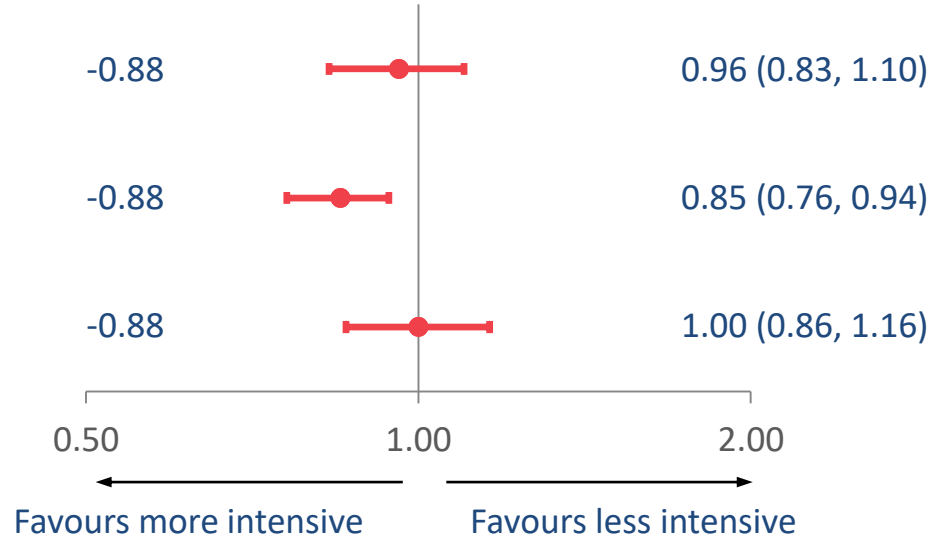
Trials	Number of events (annual event rate, %)		ΔHbA1c (%)
	More intensive	Less intensive	
All-cause mortality			
ACCORD	257 (1.41)	203 (1.14)	-1.01
ADVANCE	498 (1.86)	533 (1.99)	-0.72
UKPDS	123 (0.13)	53 (0.25)	-0.66
VADT	102 (2.22)	95 (2.06)	-1.16
Overall	980	884	-0.88
Cardiovascular death			
ACCORD	137 (0.79)	94 (0.56)	-1.01
ADVANCE	253 (0.95)	289 (1.08)	-0.72
UKPDS	71 (0.53)	29 (0.52)	-0.66
VADT	38 (0.83)	29 (0.63)	-1.16
Overall	497	441	-0.88



Turnbull FM *et al. Diabetologia* 2009;52:2288

Meta-analysis of intensive glucose control in T2DM: major CV events including heart failure

	Number of events			
	More intensive	Less intensive	Difference in HbA1c (%)	HR (95% CI)
Stroke	378	370	-0.88	0.96 (0.83, 1.10)
Myocardial infarction	730	745	-0.88	0.85 (0.76, 0.94)
Hospitalisation for or death from heart failure	459	446	-0.88	1.00 (0.86, 1.16)

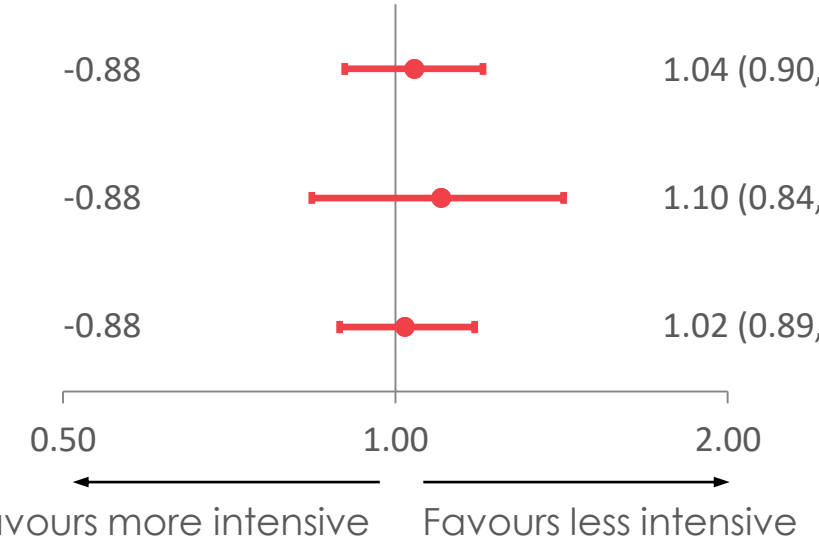


- Meta-analysis of 27,049 participants and 2370 major vascular events from:
  - ADVANCE
  - UKPDS
  - ACCORD
  - VADT

HR, hazard ratio; CV, cardiovascular
Turnbull FM et al. Diabetologia 2009;52:2288–2298

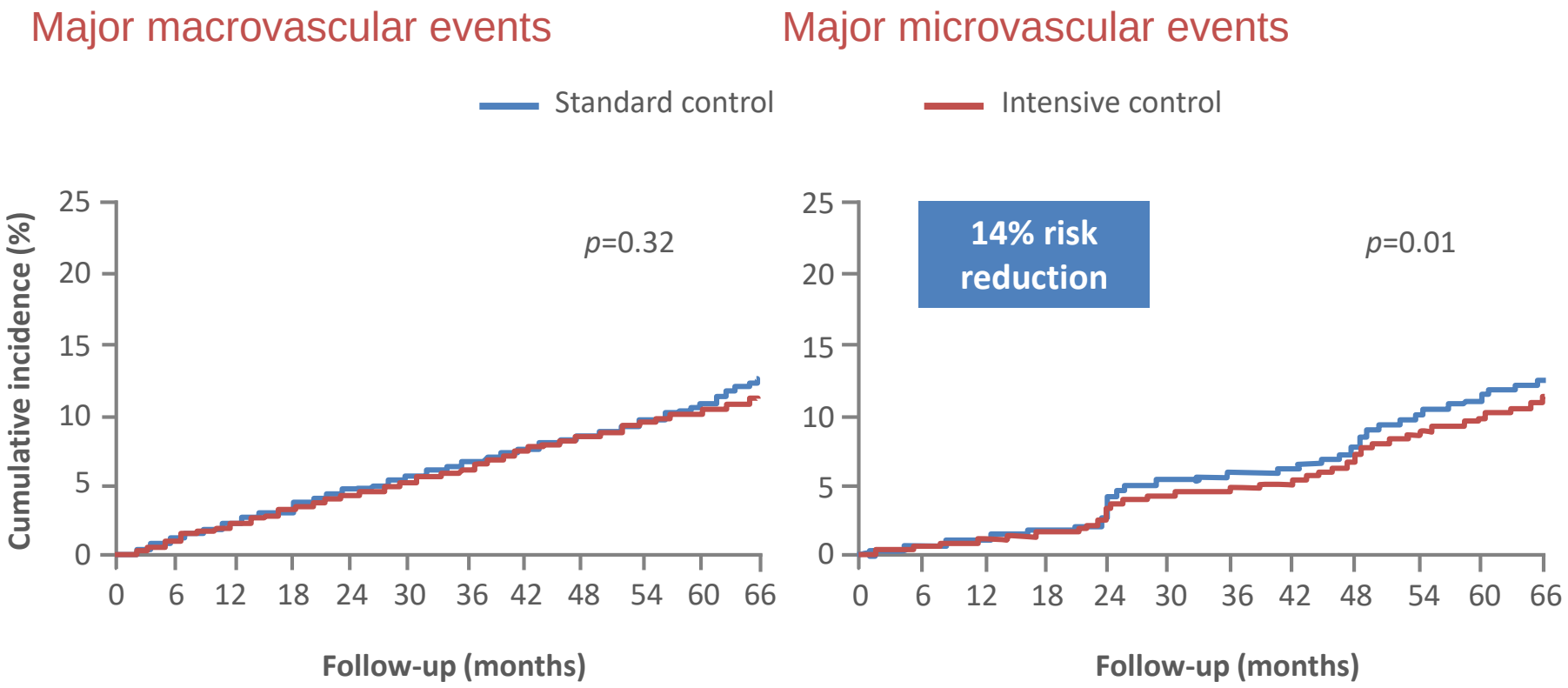
Meta-analysis of intensive glucose control in T2DM: mortality

	Number of events			
	More intensive	Less intensive	Difference in HbA1c (%)	HR (95% CI)
All-cause mortality	980	884	-0.88	1.04 (0.90,1.20)
CV death	497	441	-0.88	1.10 (0.84,1.42)
Non-CV death	476	432	-0.88	1.02 (0.89,1.18)



- Meta-analysis of 27,049 participants and 2370 major vascular events from
  - ADVANCE
  - UKPDS
  - ACCORD
  - VADT

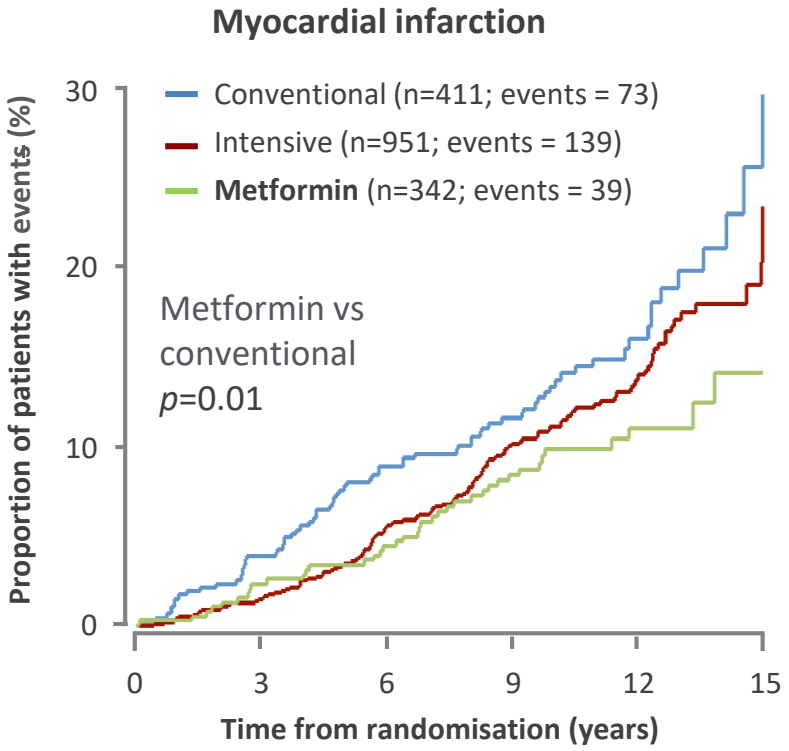
ADVANCE: intensive glycaemic control reduced microvascular but not macrovascular events



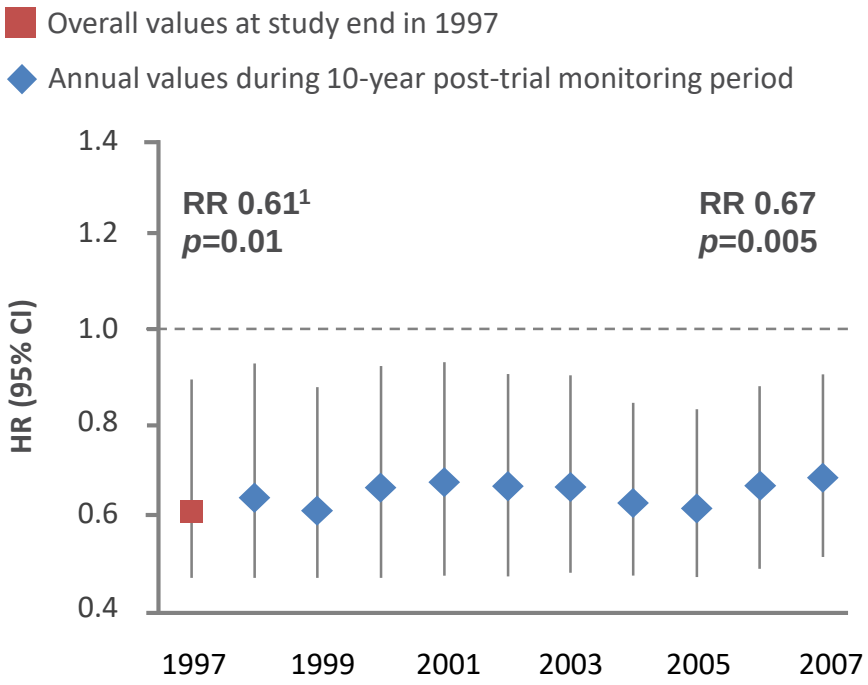
Patel A *et al. N Engl J Med* 2008;358:2560

UKPDS provides some evidence for beneficial CV effects of metformin in overweight patients

Risk of MI is 39% lower with metformin vs conventional therapy in obese patients[1,2]



Significant reduction in MI maintained over 10 years' follow-up[3]

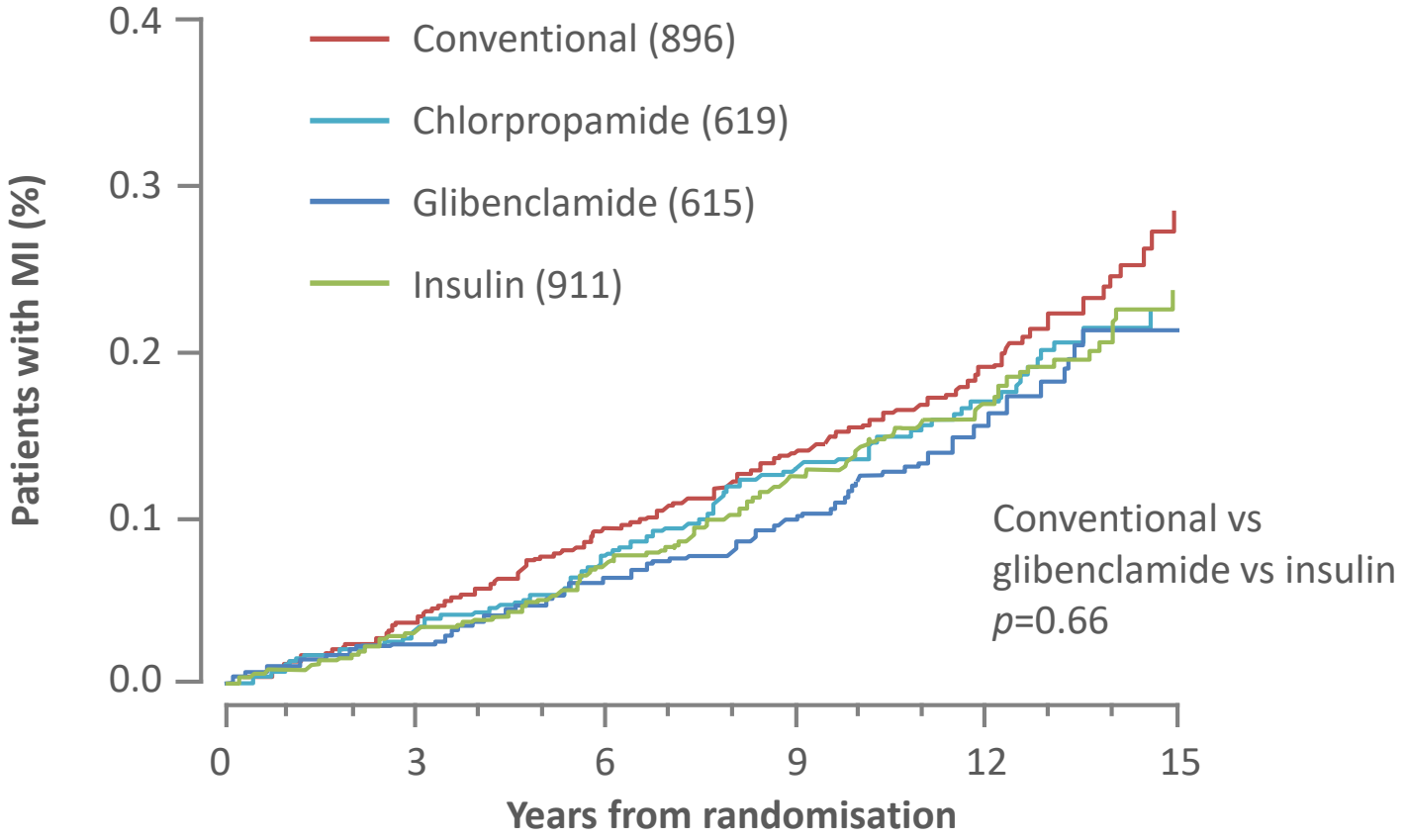


No. of events:						
Conventional therapy	73	83	92	106	118	126
Metformin	39	45	55	64	68	81

CV, cardiovascular; MI, myocardial infarction; RR, relative risk; UKPDS, United Kingdom Prospective Diabetes Study

1. UKPDS 34. *Lancet* 1998;352:854; 2. http://www.medicines.org.uk/emc/medicine/23244/SPC; 3. Holman RR *et al. N Engl J Med* 2008;359:1577

No deleterious CV effect of SUs vs insulin or conventional therapy observed in UKPDS 33[1]



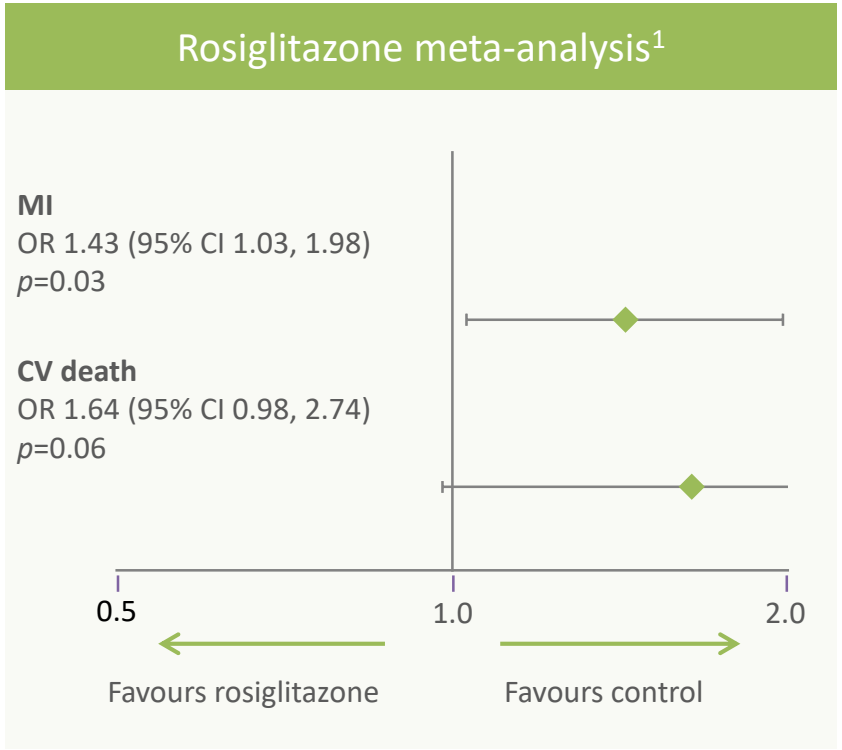
In addition, in the ADVANCE study, intensive glucose control involving gliclazide was not associated with deleterious CV effects[2]

CV, cardiovascular; MI, myocardial infarction; SU, sulphonylurea; UKPDS, UK Prospective Diabetes Study

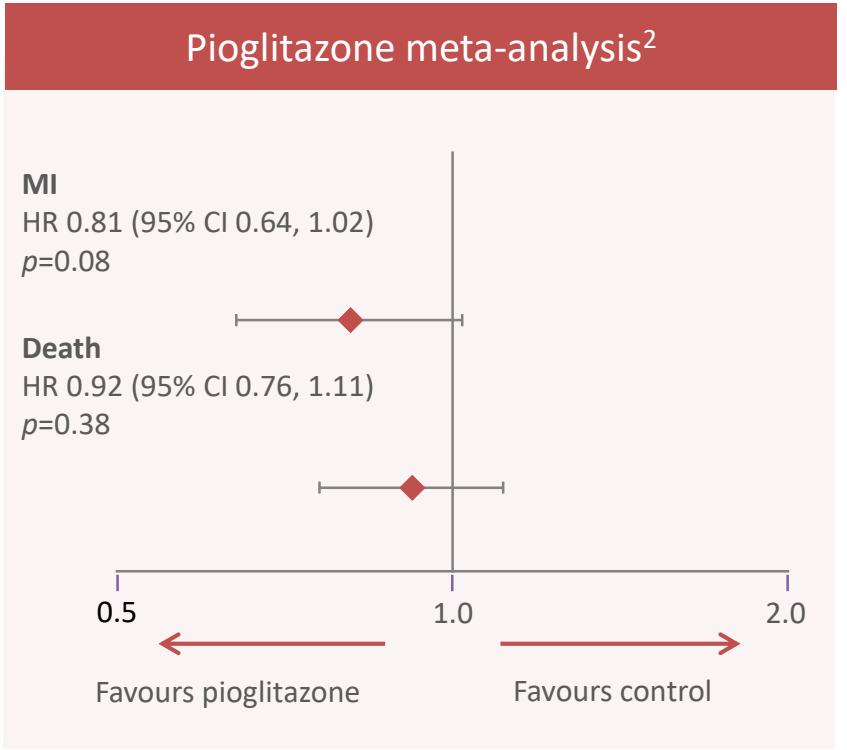
1. UKPDS33. *Lancet* 1998;352:837; 2. Patel A *et al. N Engl J Med* 2008;358:2560

In 2007, separate meta-analyses suggested differing CV effects of drugs within the TZD class

Rosiglitazone meta-analysis[1]



Pioglitazone meta-analysis[2]



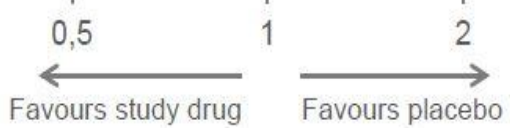
No clinical trial directly compares the CV effects of pioglitazone and rosiglitazone

CV, cardiovascular; MI, myocardial infarction; OR, odds ratio; TZD, thiazolidinedione

1. Nissen SE & Wolski K. *N Engl J Med* 2007;356:2457; 2. Lincoff AM *et al. JAMA* 2007;298:1180

Primary outcomes from completed DPP-4 inhibitor CVOTs

Trial	Primary endpoint	Number of events, n (%) Study drug + usual care	Number of events, n (%) Placebo + usual care	HR (95% CI)	*p*-value
SAVOR-TIMI 53[1] (saxagliptin)	3P-MACE	613 (7.3)	609 (7.2)	1.00 (0.89, 1.12)	0.99
EXAMINE[2] (alogliptin)	3P-MACE	305 (11.3)	316 (11.8)	0.96 (≤1.16*)	0.32
TECOS[3] (sitagliptin)	4P-MACE	695 (9.6)	695 (9.6)	0.98 (0.88, 1.09)	0.65



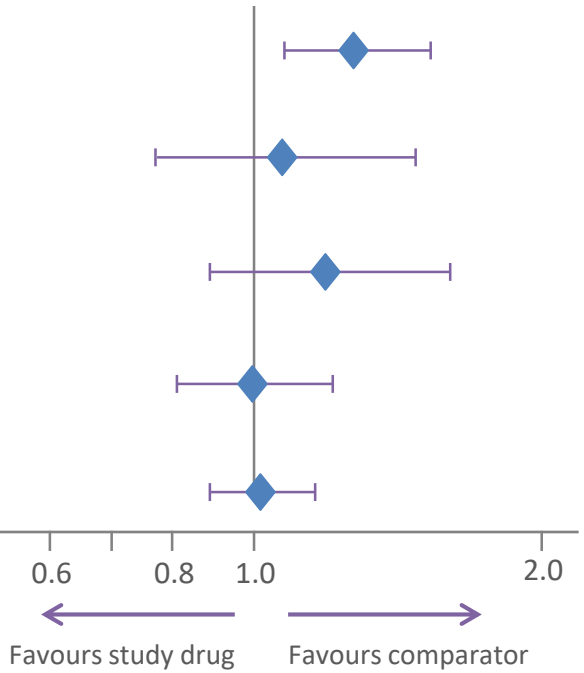
Note: data are from different trials and cannot be directly compared *Upper boundary of the one-sided repeated CI

3P-MACE, 3-point major adverse cardiovascular events; 4P-MACE, 4-point major cardiovascular events; CVOT, cardiovascular outcomes trial; DPP-4, dipeptidyl peptidase-4

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. Green JB *et al. N Engl J Med* 2015;373:232

Hospitalisation for heart failure data for previously completed CVOTs with DPP-4 inhibitors

	Number of events (%)		
	Placebo + standard of care	Comparator + standard of care	HR (95% CI)
SAVOR-TIMI 53 (HHF)[1]	228 (2.8)	289 (3.5)	
EXAMINE (HHF analysis 1)[2]	79 (2.9)	85 (3.1)	
EXAMINE (HHF analysis 2)[2]	89 (3.3)	106 (3.9)	
TECOS (HHF)[3]	229 (3.1)	228 (3.1)	
TECOS (HHF + CV death)[3]	525 (7.2)	538 (7.3)	

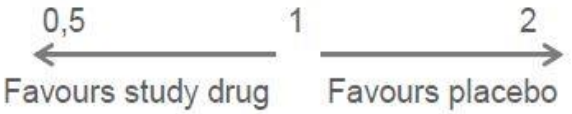


Analysis 1 = as component of expanded MACE
Analysis 2 = as component of post hoc composite of CV death and HHF
Refer to slide notes for abbreviations

1. Scirica BM *et al. N Engl J Med* 2013;369:1317; 2. Zannad F *et al. Lancet* 2015;385:2067; 3. Green JB *et al. N Engl J Med* 2015;73:232

CV death outcomes from completed GLP-1 receptor agonist CVOTs

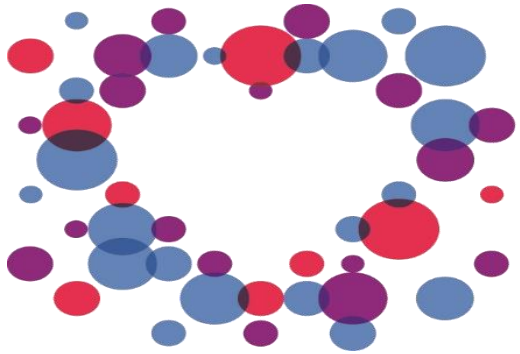
Trial	Patients with event/analysed: Comparator + usual care	Patients with event/analysed: Placebo + usual care	HR (95% CI)	*p*-value
ELIXA[1] (lixisenatide)	156/3034	158/3034	0.98 (0.78, 1.22)	0.85
LEADER[2] (liraglutide)	219/4668	278/4672	0.78 (0.66, 0.93)	0.007
SUSTAIN-6[3] (semaglutide)	44/1648	46/1649	0.98 (0.65, 1.48)	0.92
EXSCEL[4] (exenatide)	340/7356	383/7396	0.88 (0.76, 1.02)	NR



Note: data are from different trials and cannot be directly compared

1. Pfeffer MA *et al. N Engl J Med* 2015;373:2247; 2. Marso SP *et al. N Engl J Med* 2016;375:311; 3. Marso SP *et al. N Engl J Med* 2016;375;1834; 4. Holman RR *et al. N Engl J Med* 2017;377:1228 (supplementary appendix)

EMPA-REG OUTCOME®



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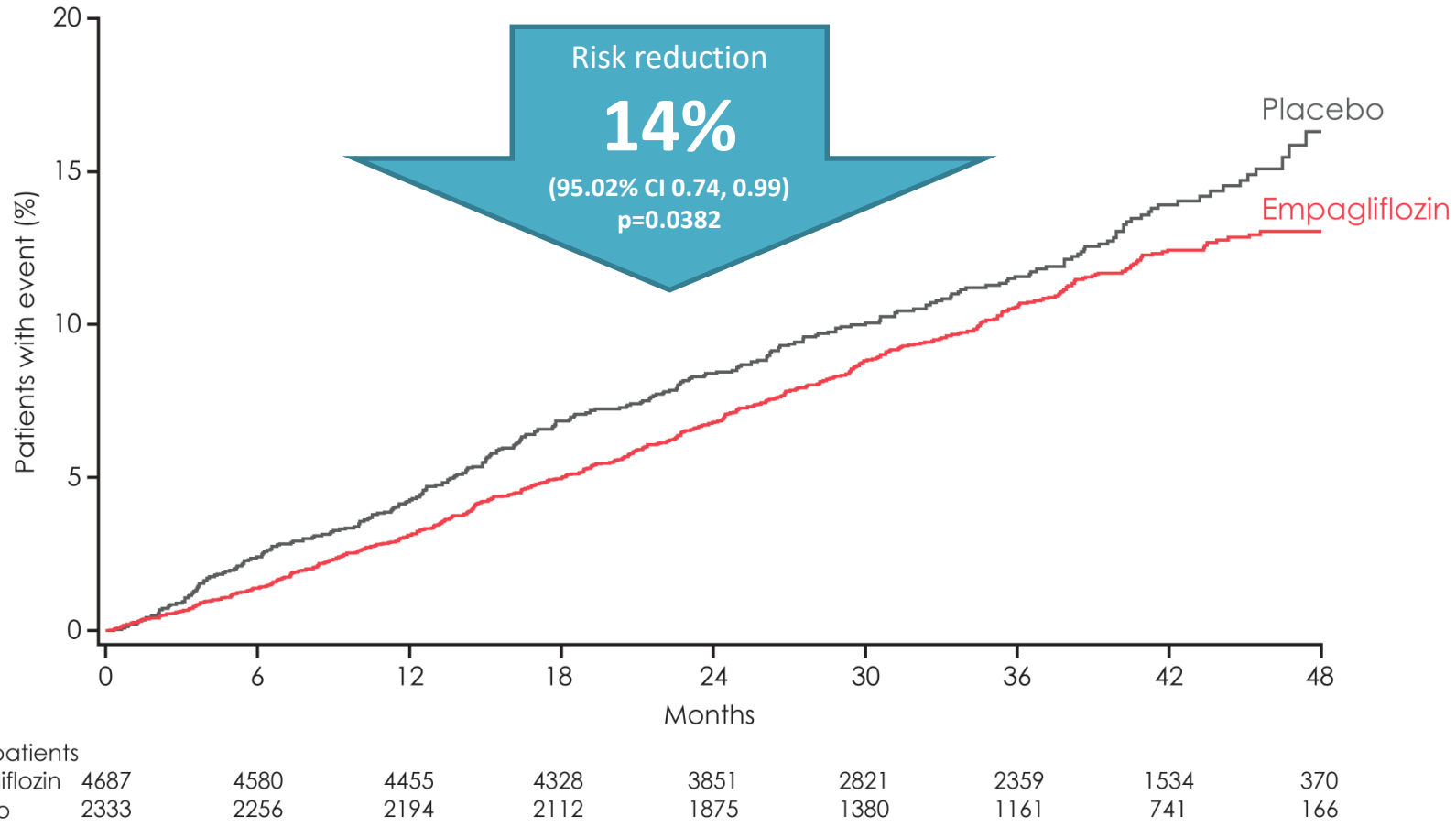
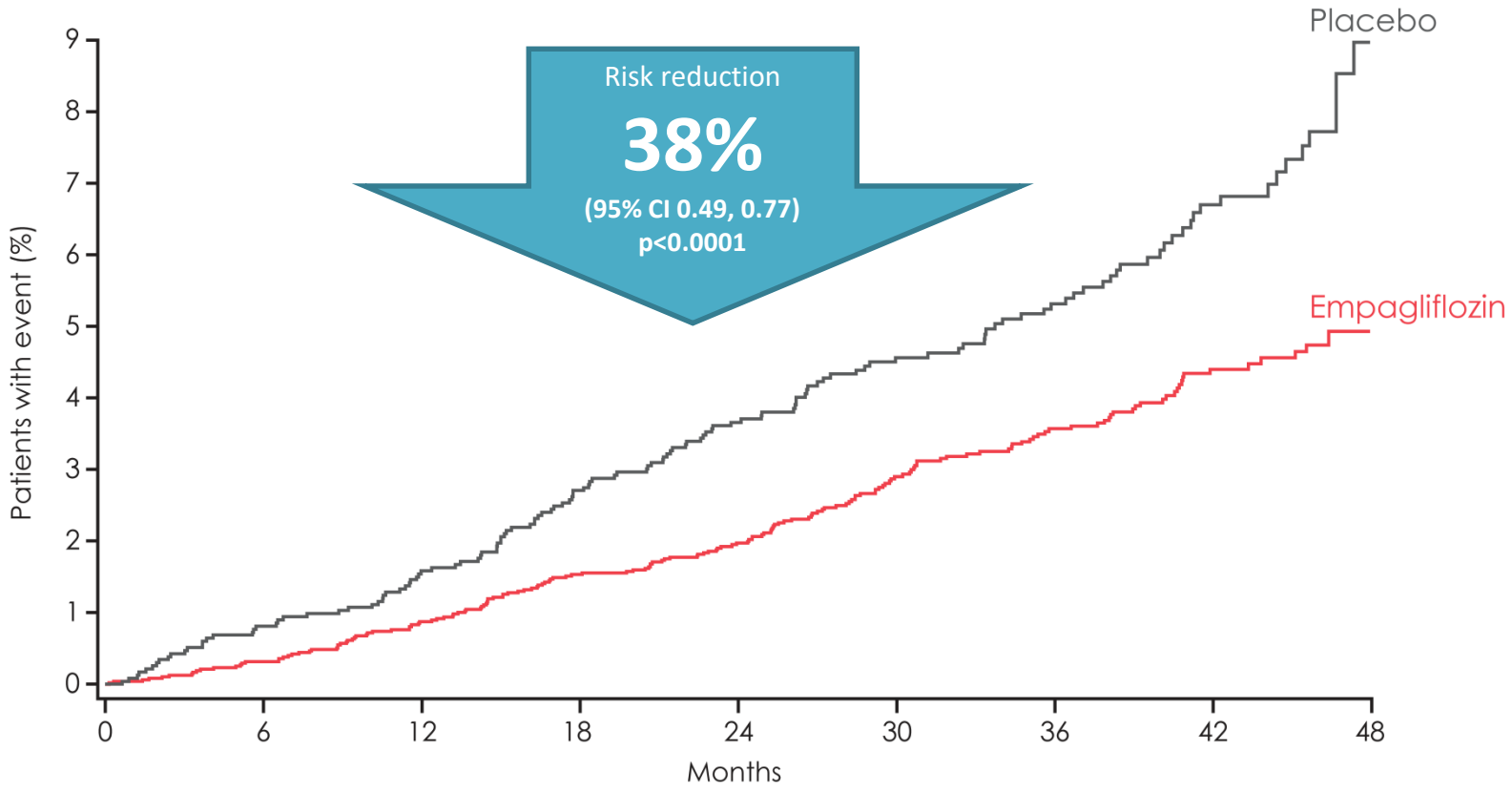
Primary outcome:
3-point MACE



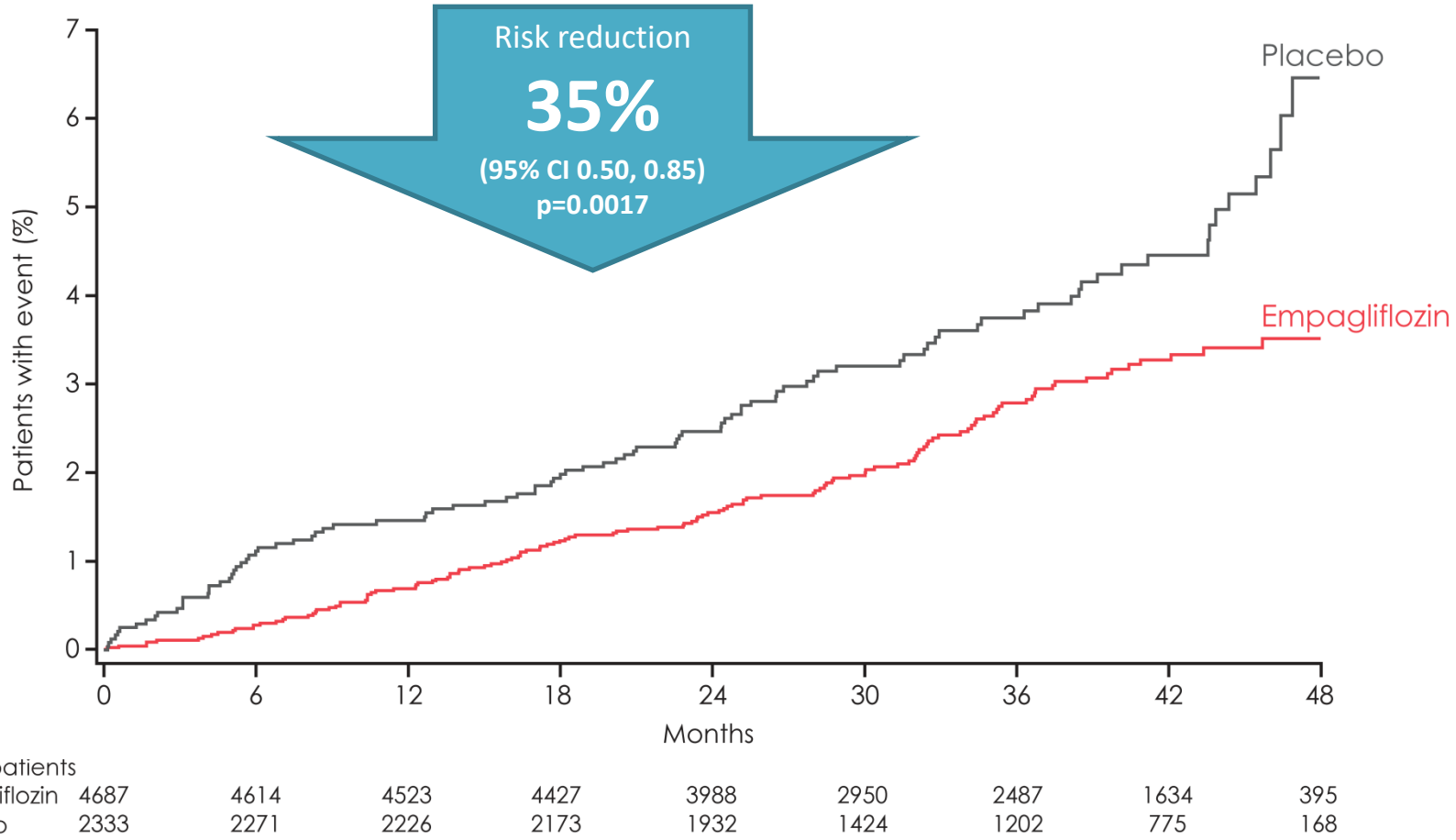
Cumulative incidence function. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio.
* Two-sided tests for superiority were conducted (statistical significance was indicated if p≤0.0498)

CV death



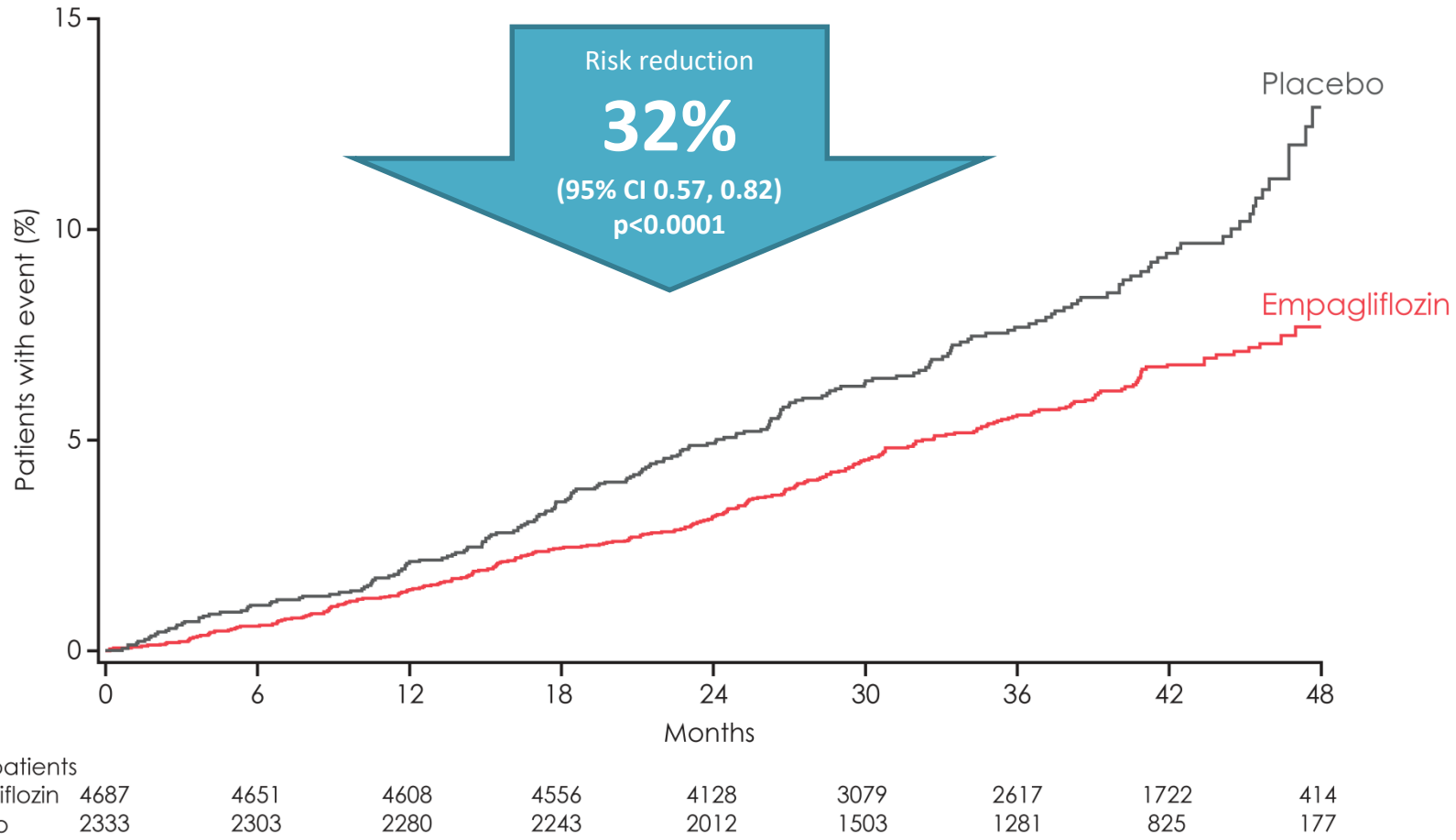
Cumulative incidence function. HR, hazard ratio

Hospitalisation for heart failure



Cumulative incidence function. HR, hazard ratio

All-cause mortality



Kaplan-Meier estimate. HR, hazard ratio

Lower Rates of Hospitalization for Heart Failure and All-Cause Death in New Users of SGLT2 Inhibitors: The CVD-REAL Study

Data presented at the 66th Annual Scientific Session of the ACC, Washington, March 17–19, 2017

Summary of positive outcomes

	PRIMARY OUTCOME	SECONDARY OUTCOMES			
	CV Death, Nonfatal MI, Nonfatal Stroke	CV Death	Nonfatal MI	Nonfatal Stroke	Hospitalization for Heart Failure
EMPA-REG OUTCOME[1] HR (95% CI)	0.86 (0.74, 0.99)	0.62 (0.49, 0.77)	NS	NS	0.65 (0.50, 0.85)
CANVAS[2] HR (95% CI)	0.86 (0.75, 0.97)	NS	NS	NS	0.67 (0.52, 0.87)
LEADER[3] HR (95% CI)	0.87 (0.78, 0.97)	0.78 (0.66, 0.93)	NS	NS	NS
SUSTAIN-6[4] HR (95% CI)	0.74 (0.58, 0.95)	NS	NS	0.61 (0.38, 0.99)	NS

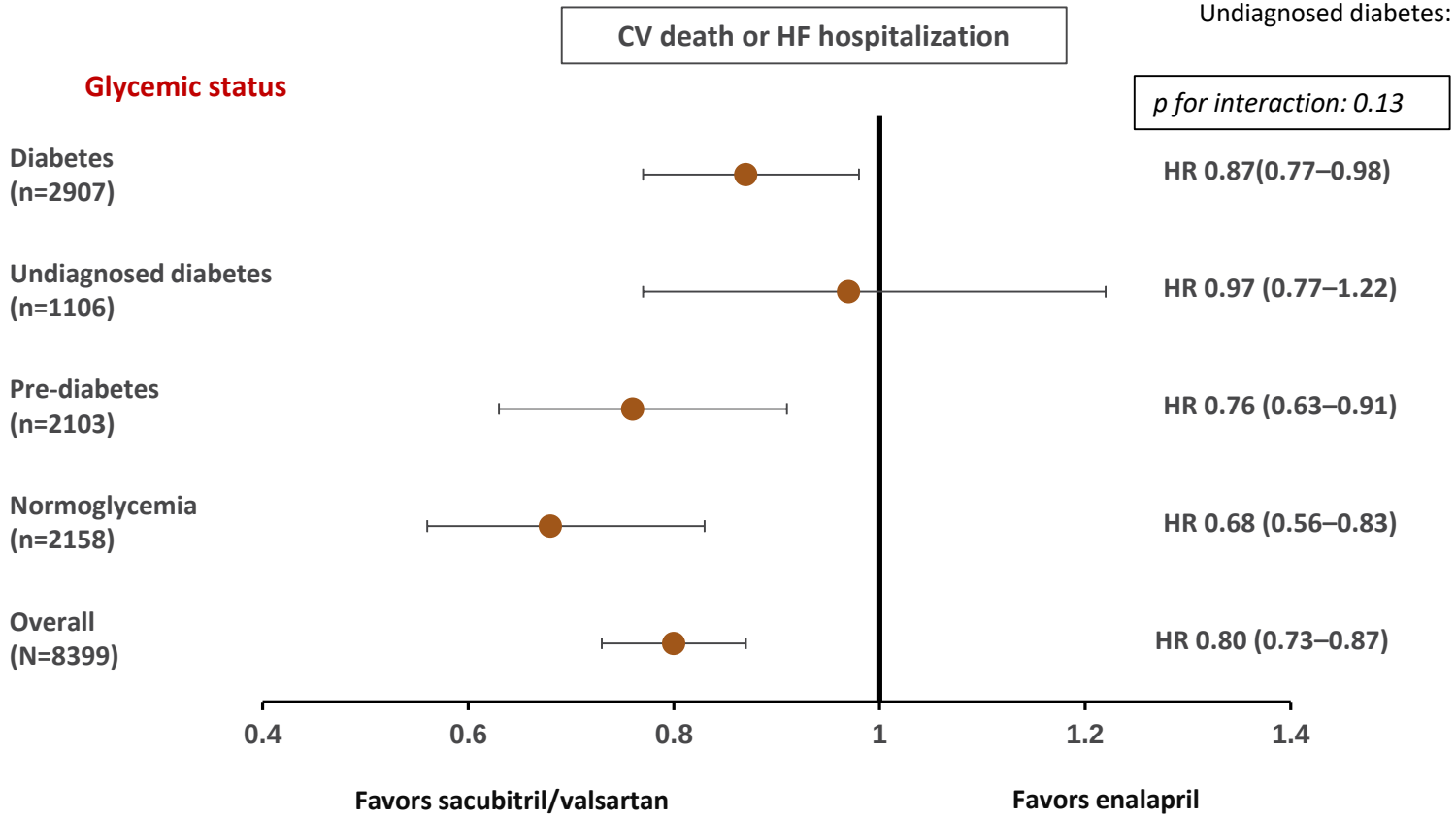
CV: cardiovascular; NS: not significant; MI: myocardial infarction

1 Z… *Med* Sep 17, 2015. 10.1056/NEJMoa1504720; 2 Neal B., Perkovic V, Mahaffey KW et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes, *N Engl J Med* Jun 12, 2017. doi: 10.1056/NEJMoa1611925

3 Marso S et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes *N Engl J Med* June 2016 doi: 10.1056/NEJMoa160382; 4 Marso S et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes *N Engl J Med* September 2016 doi: 10.1056/NEJMoa1607141

PARADIGM-HF: Treatment with sacubitril/valsartan reduced the risk of primary outcome as compared to enalapril across all glycemic states (post hoc analysis)

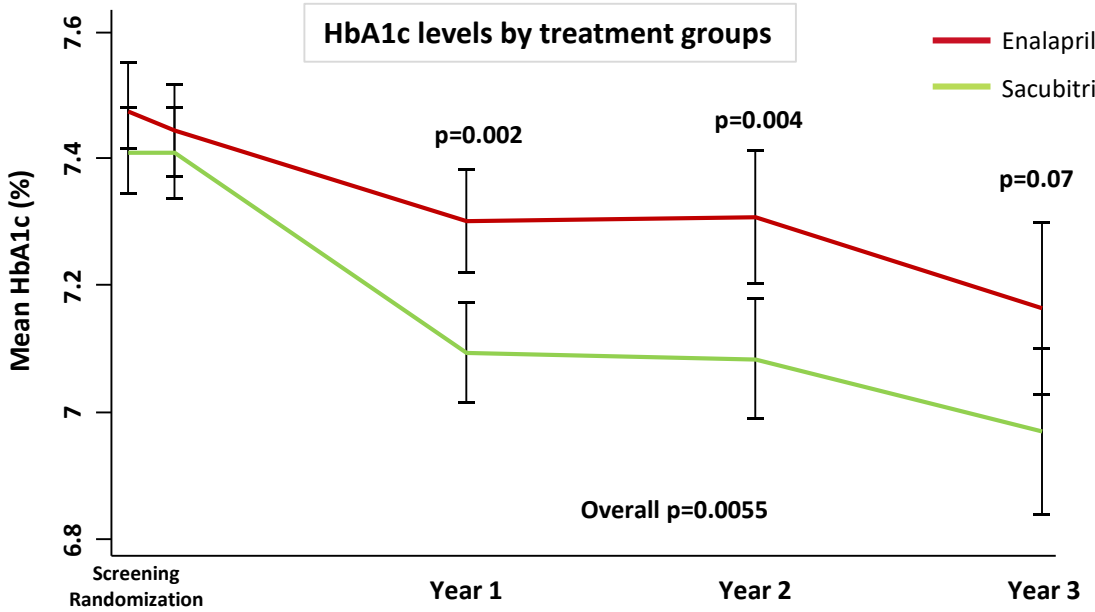
Normoglycemia: HbA1c < 6.0%
Pre-diabetes: HbA1c 6.0-6.4%
Undiagnosed diabetes: HbA1c ≥6.5%



CV=cardiovascular; HbA1c=glycated hemoglobin; HF=heart failure; HR=hazard ratio

Kristensen et al. Circ Heart Fail 2016; 9(1). pii: e002560

Sacubitril/valsartan significantly reduced HbA1c compared to enalapril in patients with HFrEF and DM (post hoc analysis)



Analysis was conducted in a subset of randomized patients who reported a history of DM and/or a HbA1c level ≥6.5% at screening (n= 3778/8399 44.9%)

HbA1c, %		Year 1	Year 2	Year 3	Overall*
Sac/Val (n=1904)	7.41 ± 1.51	7.09 ± 1.60	7.08 ± 1.61	6.97 ± 1.58	
Enalapril (n=1874)	7.48 ± 1.58	7.30 ± 1.66	7.31 ± 1.78	7.16 ± 1.61	
Difference (95% CI) (Adjusted for screening values)		−0.13 (−0.22 to −0.05) p=0.0023	−0.17 (−0.28 to −0.05) p=0.0040	−0.15 (−0.32 to −0.01) p=0.072	−0.14 (−0.23 to −0.06) p=0.0055

In a landmark analysis at 1 year considering the change in HbA1c and the screening value, there was no significant relationship between change in HbA1c and the composite primary outcome of CV death or first HF hospitalization in the entire cohort of patients with diabetes (HR, 0.99, 95% CI 0.91–1.06 per HbA1c unit, p=0.70), suggesting that the potential benefit on HF outcomes and on HbA1c were independent of one another.

Data is presented as means ± SD; *longitudinal model; CI=confidence interval; CV=cardiovascular; DM=diabetes mellitus; HbA1C= glycated hemoglobin; HF=heart failure; HFrEF=HF with reduced ejection fraction; Sac/Val=sacubitril/valsartan

Seferovic et al. Lancet Diabetes Endocrinol. 2017;5(5):333-340

At diagnosis, initiate lifestyle management, set A1C target, and initiate pharmacologic therapy based on A1C:

A1C is less than 9%, **consider Monotherapy.**

A1C is greater than or equal to 9%, **consider Dual Therapy.**

A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy** (See Figure 8.2).

Monotherapy — Lifestyle Management + Metformin

Initiate metformin therapy if no contraindications* (See Table 8.1)

A1C at target after 3 months of monotherapy?

Yes: - Monitor A1C every 3–6 months

No: - Assess medication-taking behavior
- Consider Dual Therapy

Dual Therapy — Lifestyle Management + Metformin + Additional Agent

ASCVD?

Yes: – Add agent proven to reduce major adverse cardiovascular events and/or cardiovascular mortality (see recommendations with * on p. S75 and **Table 8.1**)

No: – Add second agent after consideration of drug-specific effects and patient factors (See Table 8.1)

A1C at target after 3 months of dual therapy?

Yes: - Monitor A1C every 3–6 months

No: - Assess medication-taking behavior
- Consider Triple Therapy

Triple Therapy — Lifestyle Management + Metformin + Two Additional Agents

Add third agent based on drug-specific effects and patient factors[#] (See Table 8.1)

A1C at target after 3 months of triple therapy?

Yes: - Monitor A1C every 3–6 months

No: - Assess medication-taking behavior
- Consider Combination Injectable Therapy (See Figure 8.2)

Combination Injectable Therapy (See Figure 8.2)

European Heart Journal
doi:10.1093/eurheartj/ehw128

ESC GUIDELINES

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)

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

Diabetes			
Metformin should be considered as a first-line treatment of glycaemic control in patients with diabetes and HF, unless contra-indicated.	IIa	C	440 ,441
Diabetes			
Thiazolidinediones (glitazones) are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization.	III	A	209, 210

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