Diabetes and Heart Failure: Challenges and Opportunities

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Diabetes and Heart Failure

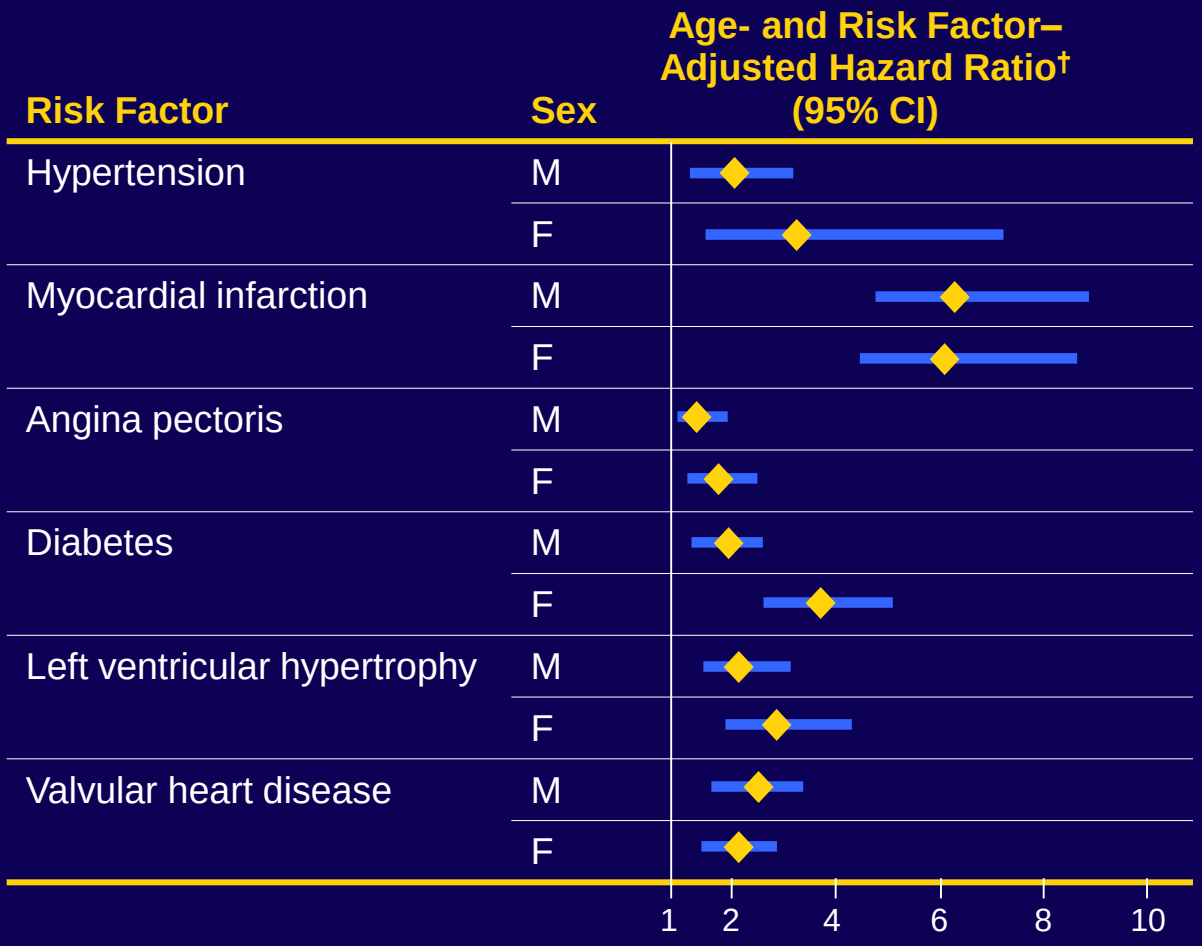
- The two diseases entities are highly co-prevalent
- Diabetes contributes to disease progression in HF and is associated with substantially worse prognosis, even when conventional HF therapies are applied
- The relationship between HbA1c and outcome in patients with diabetes and heart failure is complex
- The choice of pharmacologic glycemic management can markedly impact heart failure outcomes
  - Certain therapies are neutral or associated with harm
  - Certain therapies markedly improve outcomes
- Pharmacologic glycemic management is a critical component of HF management

Diabetes and Incident Heart Failure in the US

- Framingham study (risk of HF in diabetics)
  - 2x diabetic males
  - 5x diabetic females
  - 4x young diabetic males
  - 8x young diabetic females
- US HMO prevalence study
  - With diabetes, incident HF developed at a rate of 3.3% per year
- Each 1% elevation in HbA_{1c} leads to a 15% increase in frequency of HF

Kannel WB et al. *JAMA*. 1979;241:2035–2038. Nichols GA. *Diabetologia*. 2000;43(suppl A2):7. Chue CU et al. *Circulation.* 1998;98(suppl 1):721.

Risk Factors for the Development of Heart Failure



* Based on dynamic model with reclassification of hypertension and risk factors at each follow-up examination. CI indicates confidence interval.

† Adjusted for angina pectoris, myocardial infarction, diabetes, left ventricular hypertrophy, and valvular heart disease.

‡ Levy D et al. *JAMA.* 1996;275:1557–1562.

Prevalence of Diabetes in Patients with Heart Failure

Clinical Trial	Diabetics
SOLVD	25.8%
MERIT	24.5%
Val HEFT	25.4%
EMPHASIS-HF	31.4%
PARADIGM-HF	34.7%
OPTIME (hospitalized)	44.2%
VMAC (hospitalized)	47.0%

Diabetes in Patients Hospitalized with Heart Failure: GWTG-HF

Temporal trends and factors associated with diabetes mellitus among patients hospitalized with heart failure: Findings from Get With The Guidelines–Heart Failure registry

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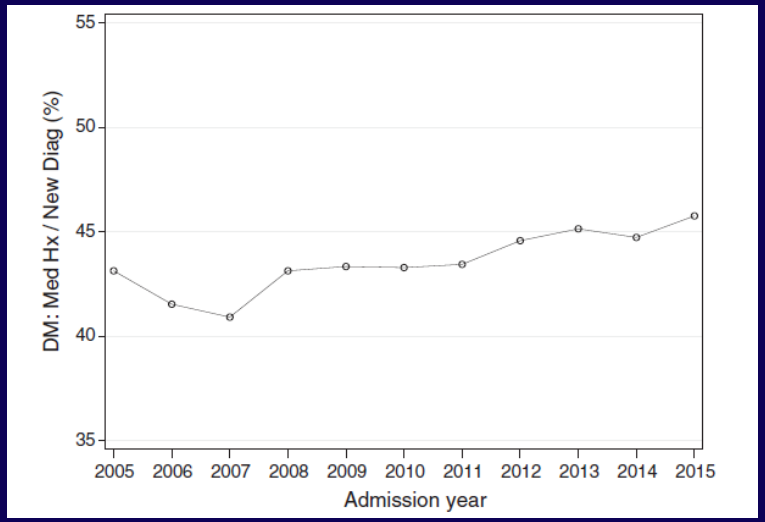
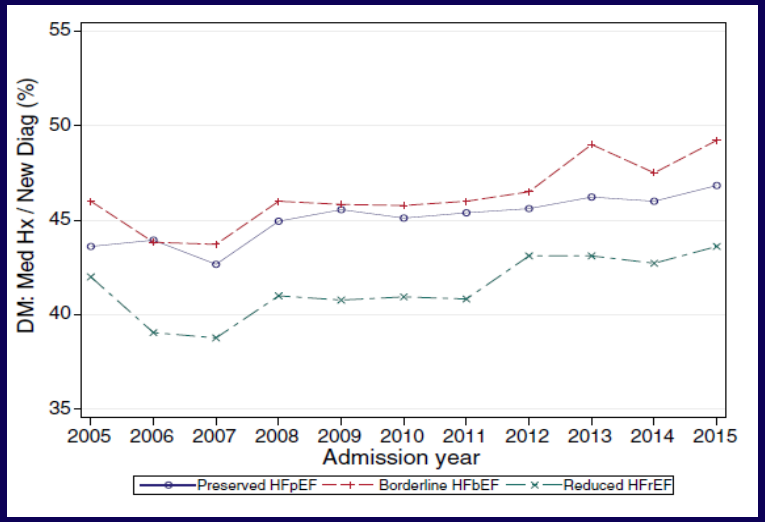
Background The contribution of diabetes to the burden of heart failure (HF) remains largely undescribed. Assessing diabetes temporal trends among US patients hospitalized with HF and their relation with quality measures in real-world practice can help to define this burden.

Methods Using data from the Get With the Guidelines–Heart Failure registry, we assessed temporal trends in diabetes prevalence among patients with HF and in subgroups with reduced ejection fraction (HFrEF; EF < 40%), borderline EF (HFbEF; 40% ≤ EF < 50%), or preserved EF (HFpEF; EF ≥ 50%), hospitalized between 2005 and 2015. Logistic regression was used to assess whether in-hospital outcomes and HF quality of care were related to trends.

Results Among 364,480 HF hospitalizations, 160,171 had diabetes (44.0% overall, 41.8% in HFrEF, 46.7% in HFbEF, 45.5% in HFpEF). There was a temporal increase in diabetes frequency in HF patients (43.2%-45.8%; $P_{trend} < .0001$), including among those with HFrEF (42.0%-43.6%; $P_{trend} < .0001$), HFbEF (46.0%-49.2%; $P_{trend} < .0001$), or HFpEF (43.6%-46.8%, $P_{trend} < .0001$). Diabetic patients had a longer hospital stay (adjusted odds ratio 1.14, 95% CI 1.12-1.16), but lower in-hospital mortality (adjusted odds ratio 0.93 [0.89-0.97]) compared with those without diabetes, with limited differences in quality measures. Temporal trends in diabetes were not associated with in-hospital mortality or length of stay. There were no temporal interactions of most HF quality measures with diabetes status.

Conclusions Approximately 44% of hospitalized HF patients have diabetes, and this proportion has been increasing over the past 10 years, particularly among those patients with new-onset HFpEF. (Am Heart J 2016;182:9-20.)

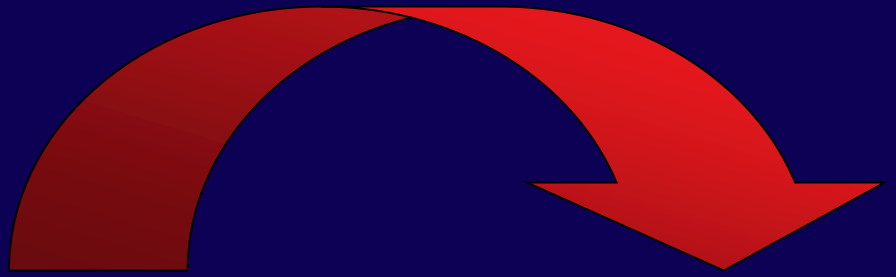




Am Heart J 2016;182:9-20

Relationship Between DM and HF

Incidence of HF: 13 / 1000 person-years in non-diabetics vs. 31 / 1000 person-years in diabetics



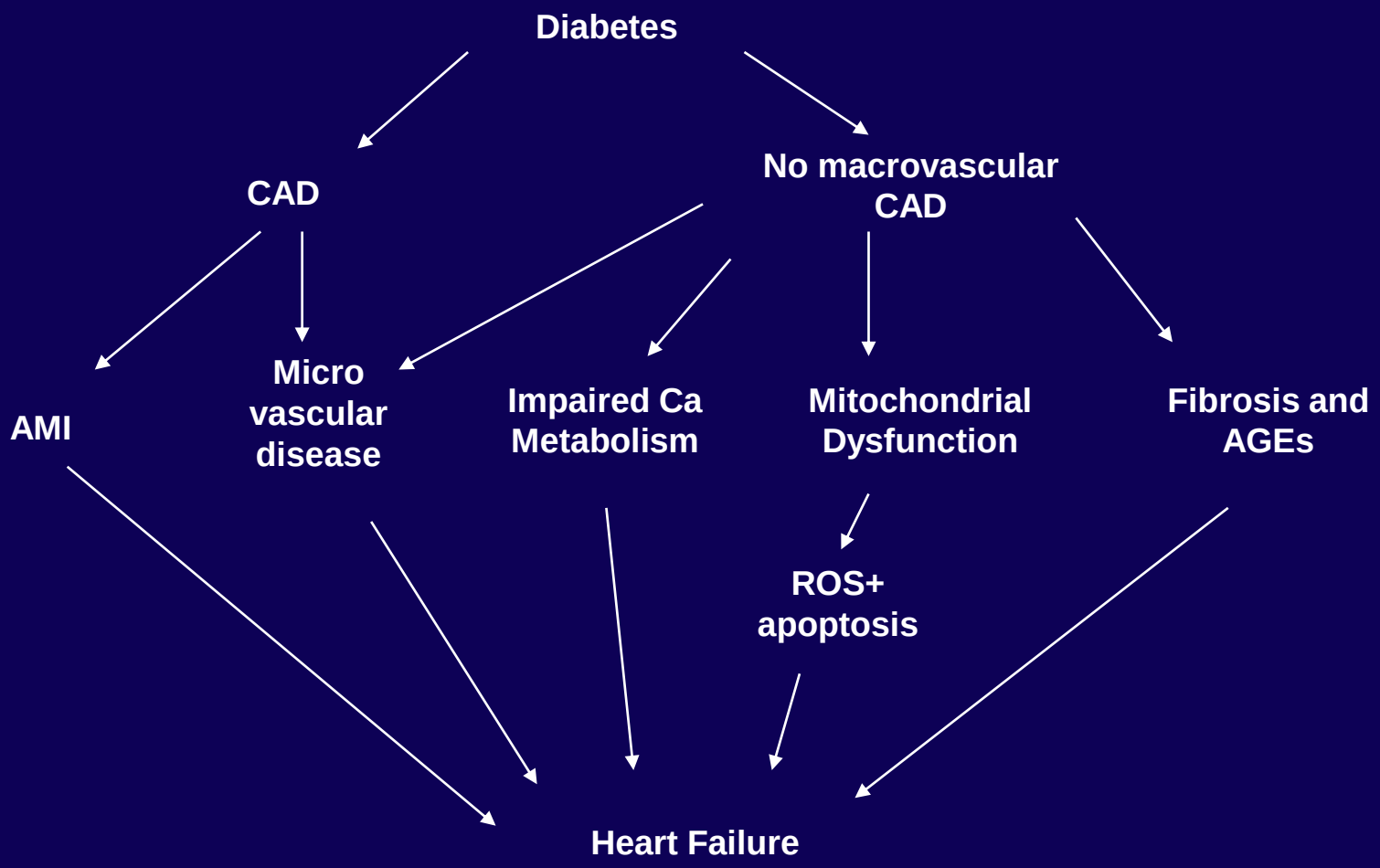
Diabetes Mellitus

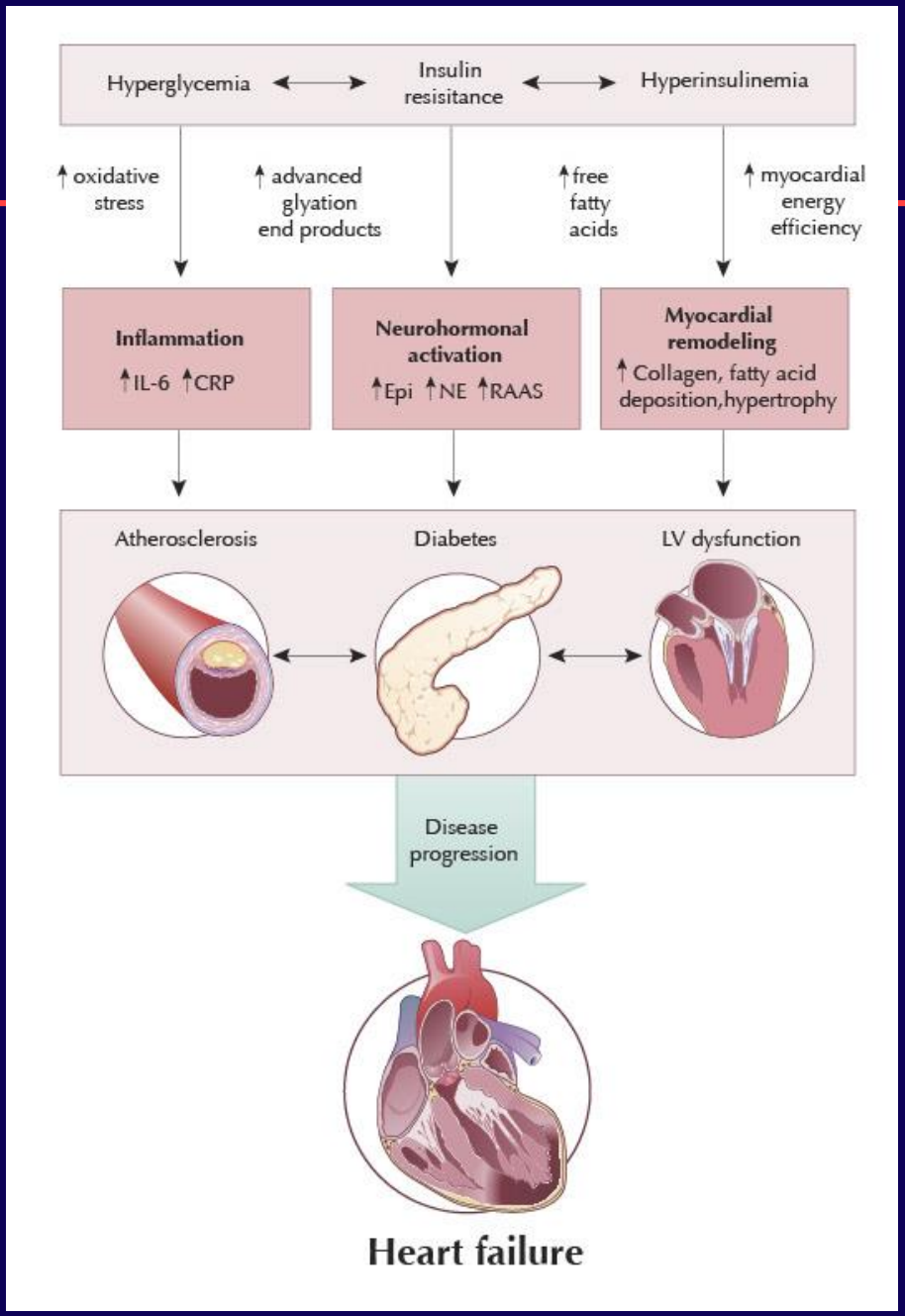
Heart Failure

Insulin Resistance, Hyperglycemia, and Heart Failure

- Hyperglycemia
  - oxidative stress
  - altered intracellular signaling
  - decreased vascular endothelial growth factor
  - altered gene expression
- Insulin
  - Myocardial hypertrophy
- Advanced Glycosylation Endproduct s (AGEs)
  - sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase
  - collagen cross-linking and reduce ventricular distensibility and vascular compliance
- Myocardial metabolism may become more dependent on free fatty acids
  - uncoupling of oxidative phosphorylation

Diabetes Leading to HF
Potential Mechanisms





Multiple Pathogenetic Mechanisms Involved in the Relationship Between Diabetes, Metabolic Disease, and Heart Failure

Horwich and Fonarow.

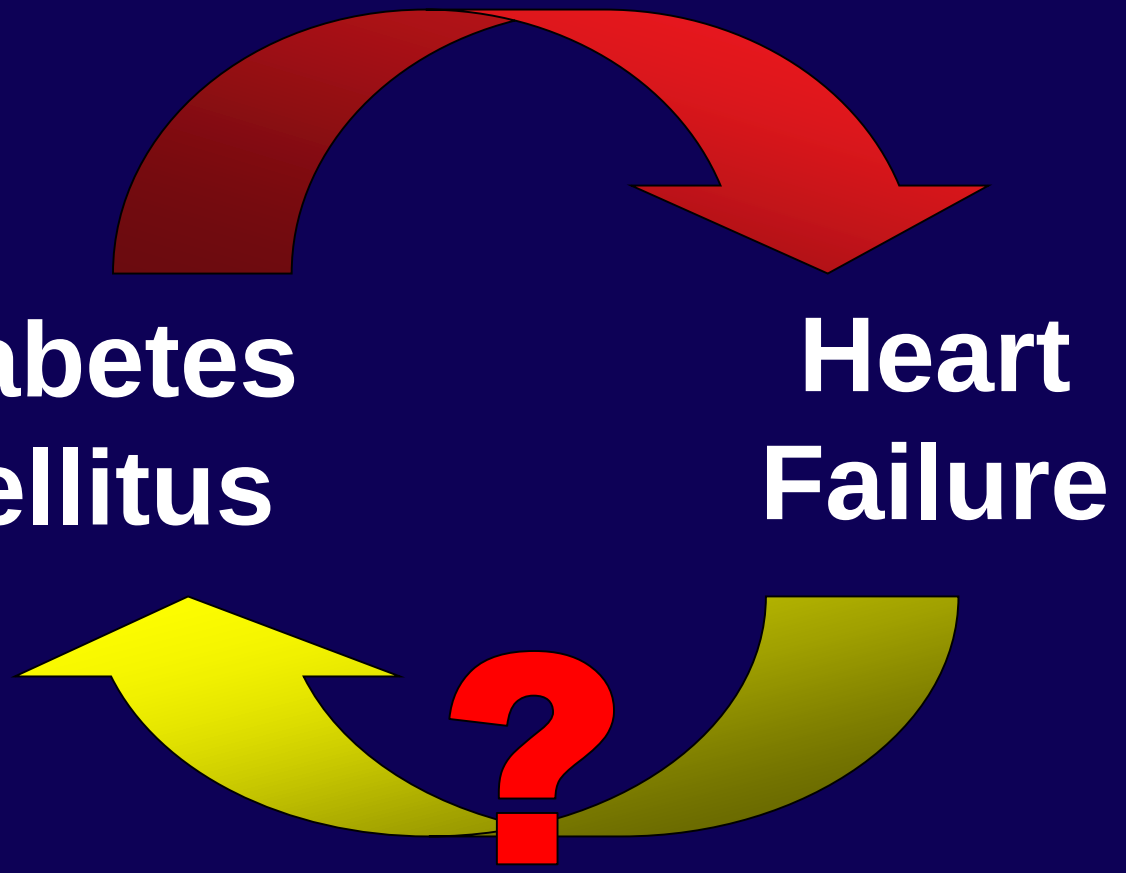
J Am Coll Cardiol 2010.

Etiology of HF in Patients with Diabetes

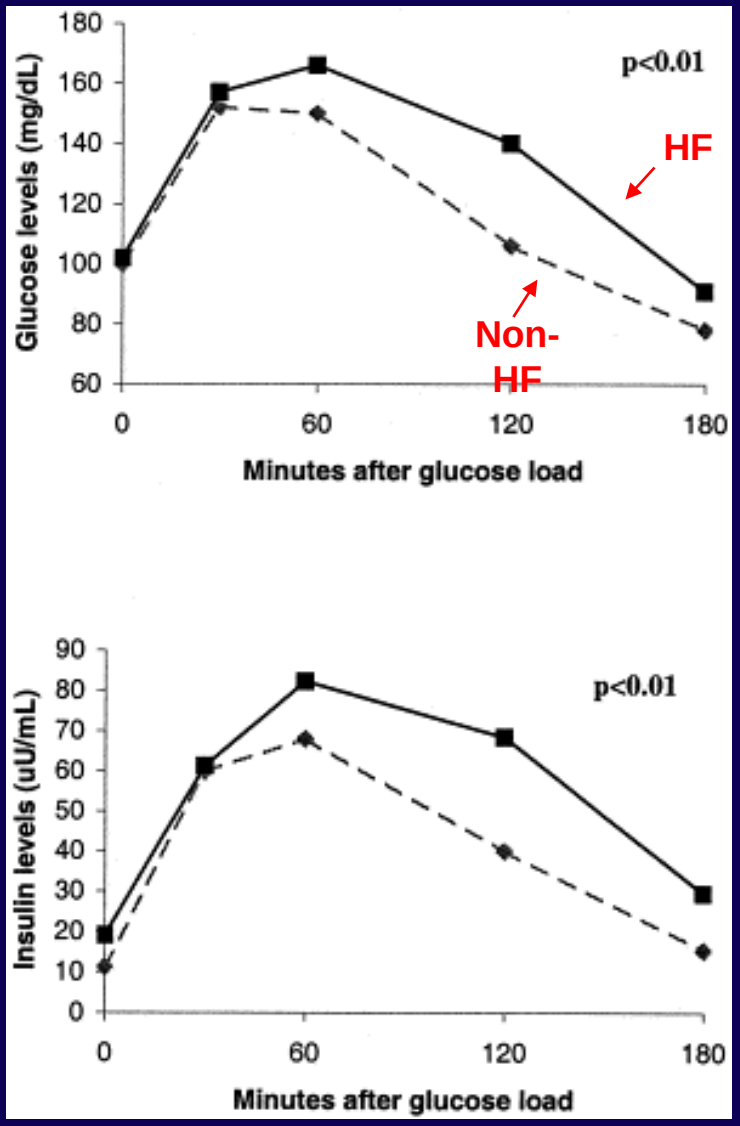
- Comorbidities
  - Ischemic Heart Disease
  - Hypertension
- Diabetic Cardiomyopathy
  - Direct Myocardial Effects of hyperglycemia and Advanced glycation end products
    - Fibrosis, diastolic dysfunction
    - Altered calcium homeostasis, systolic dysfunction
    - Free-radicals, oxidation, inflammation
    - Lipotoxicity of myocardium
    - Altered myocardial energetics
- Variable Combinations of above factors

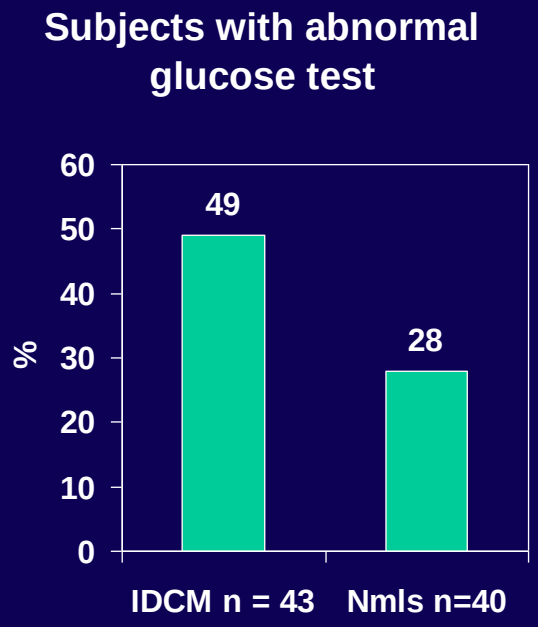
Bell, Diabetes Care 2003; 26: 2948-50.

Relationship Between DM and HF



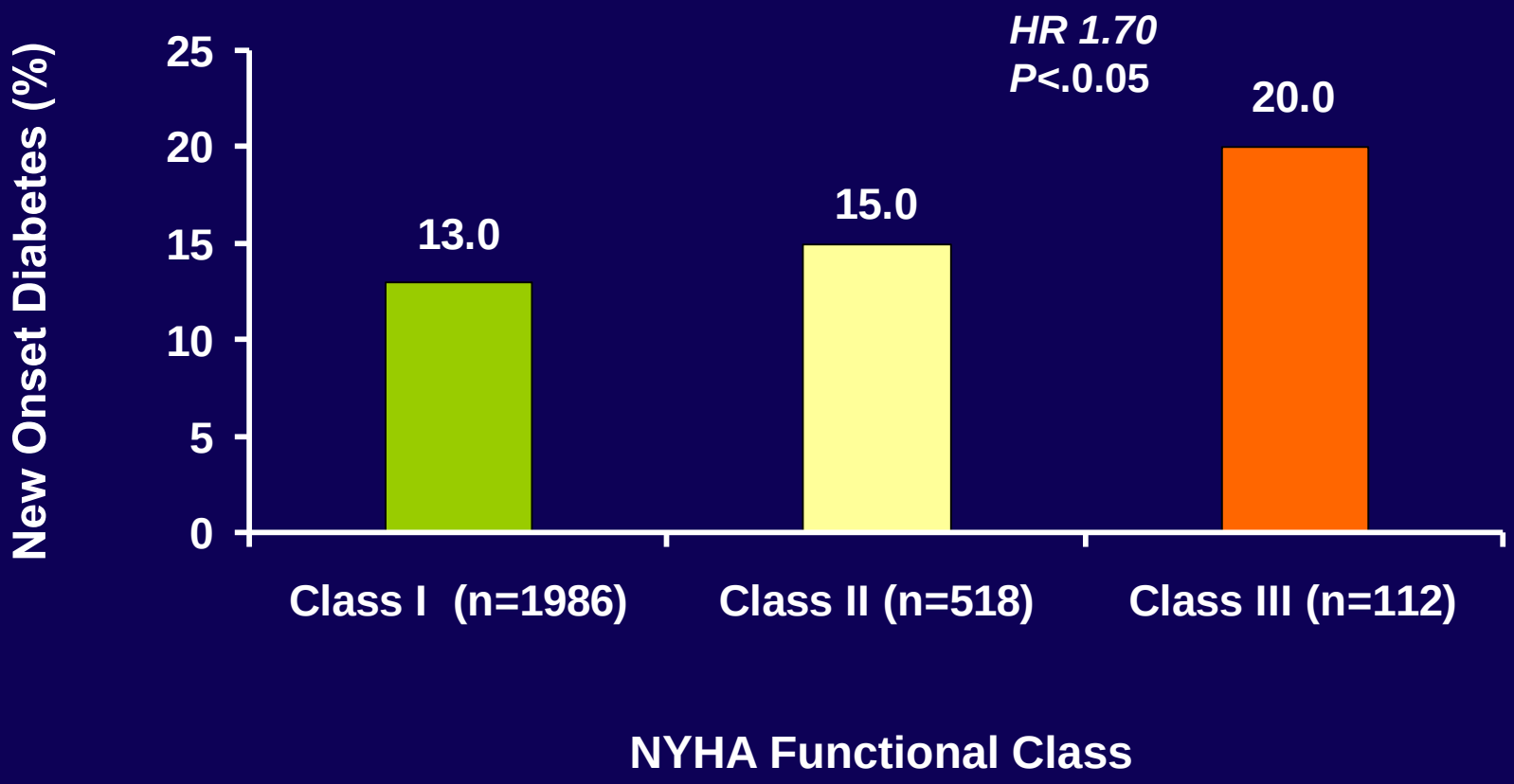
Insulin Resistance in Idiopathic Dilated Cardiomyopathy vs. Age, Sex, BMI-matched Controls





Witteles et al. *J Am Coll Cardiol*.2004;44:78-81.

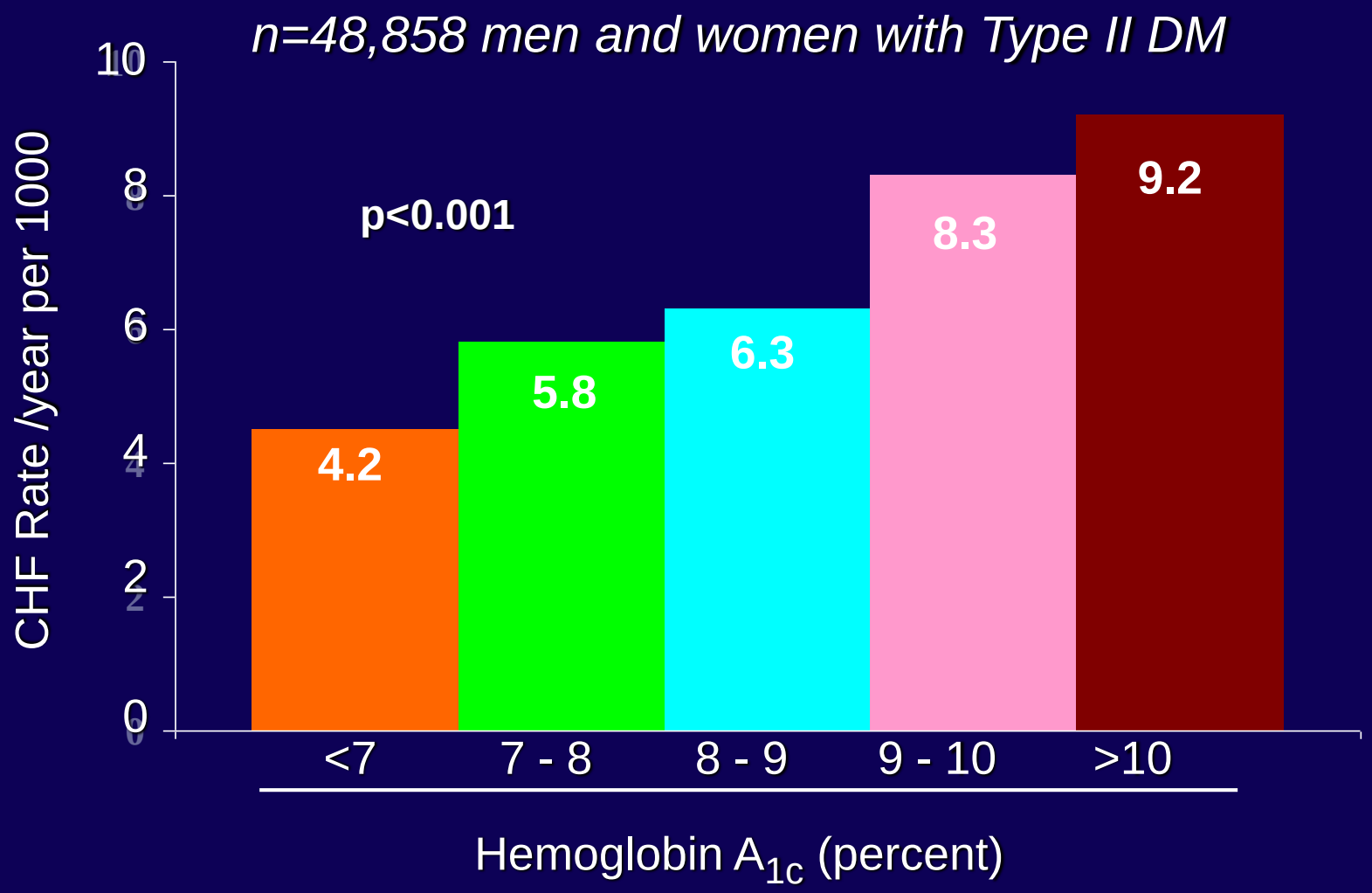
Advanced Heart Failure Associated with Increased Risk of Developing Diabetes



BIP Trial 2616 non-diabetics at baseline, prior MI during 7.7 years of follow-up

Tenenbaum et al. Am J Med 2003;114:271-275.

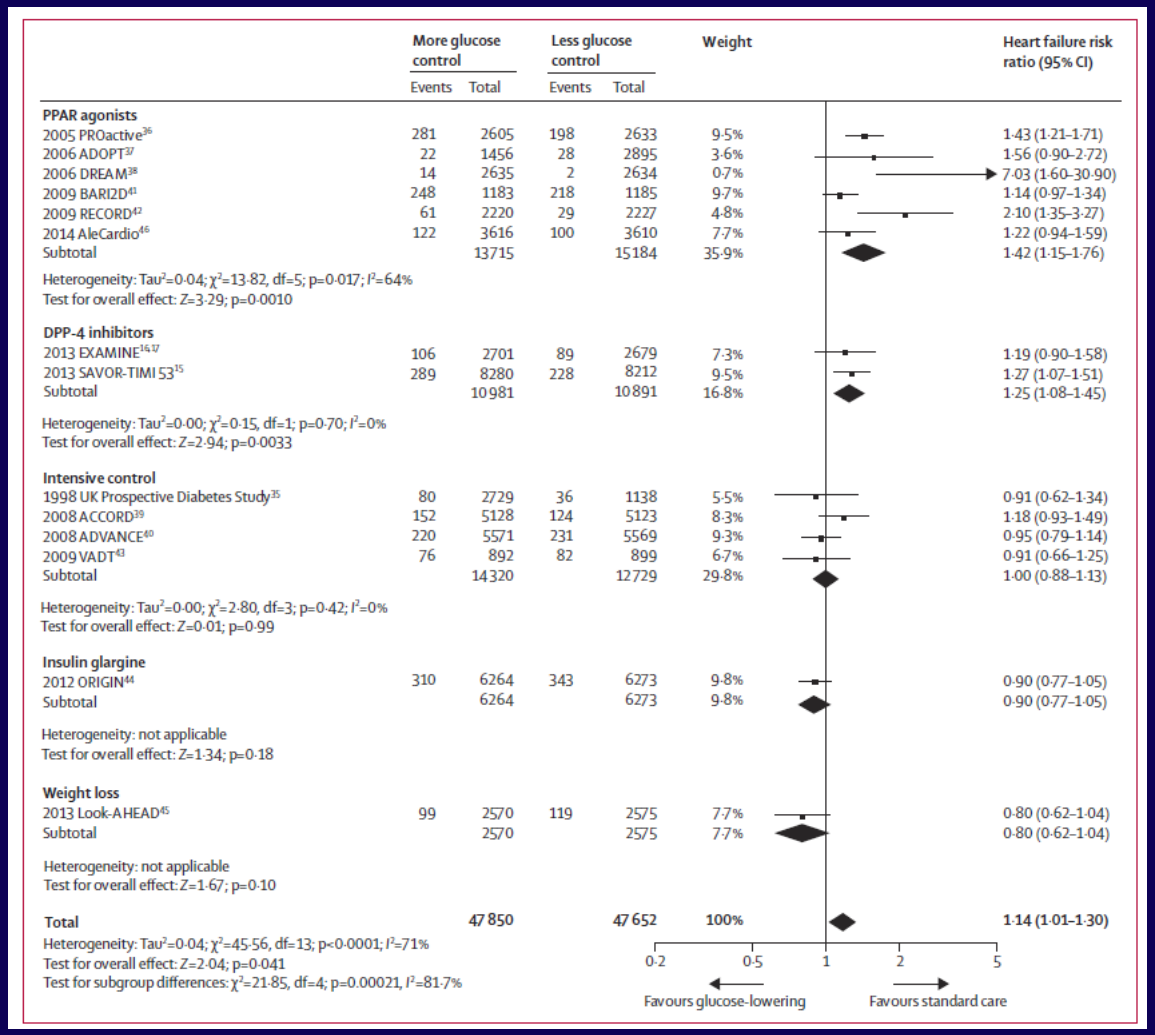
Poor Glycemic Control in DM is Independently Associated with Increased HF Risk



Iribarren et al. *Circulation* 2001;103:2668-2673

Heart Failure Rates in Diabetes Glucose Control Trials

Risk of HF events with glucose-lowering drugs or strategies versus standard care



PPAR Agonists

DPP-4 Inhibitors

Intensive Control

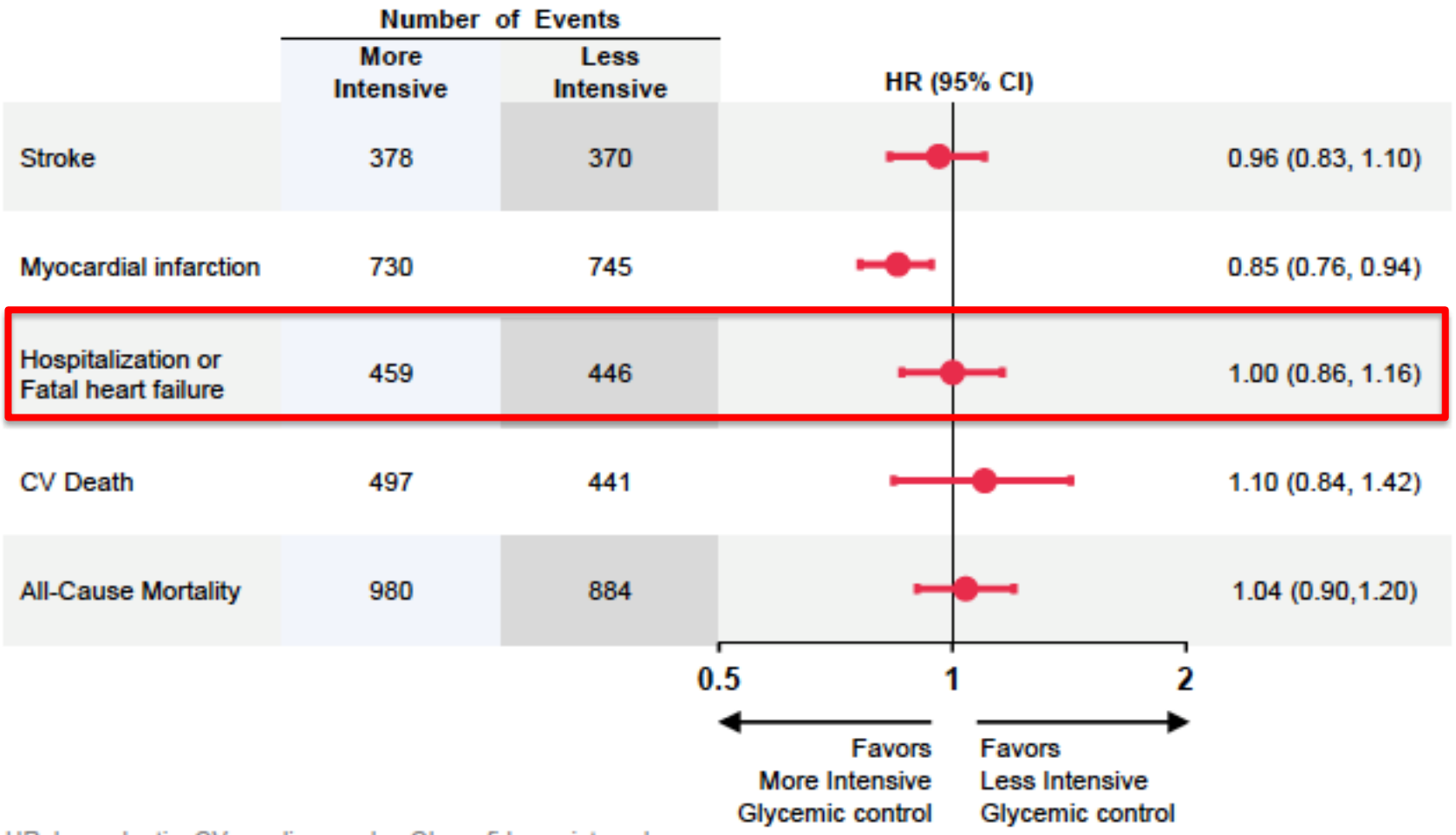
Insulin

Weight loss

Lancet Diabetes Endocrinol 2015 March 17, 2015 http://dx.doi.org/10.1016/S2213-8587(15)00044-3

Effect of Glycemic Control in Type 2 DM on Cardiovascular Outcomes

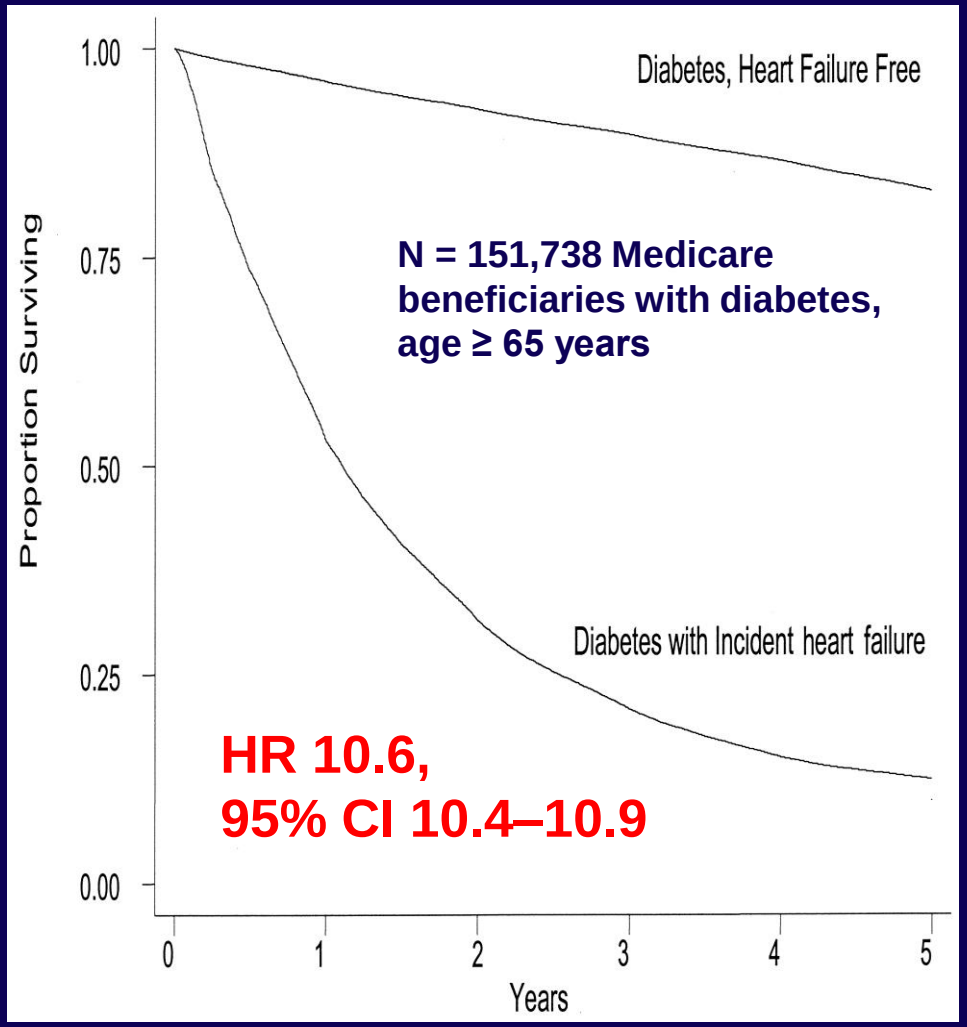
Impact of Glycemic Control



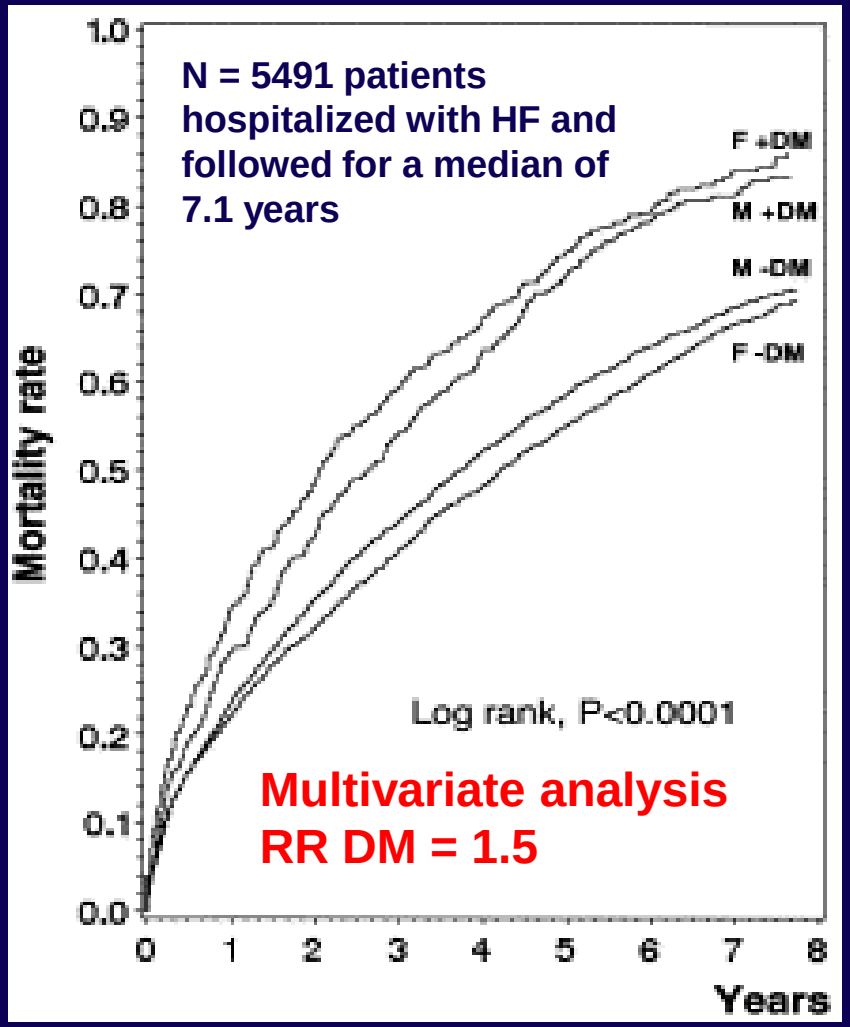
HR, hazard ratio; CV, cardiovascular, CI, confidence interval

Turnbull FM et al. Diabetologia 2009;52:2288–2298

Diabetics and Heart Failure: Poor Prognosis

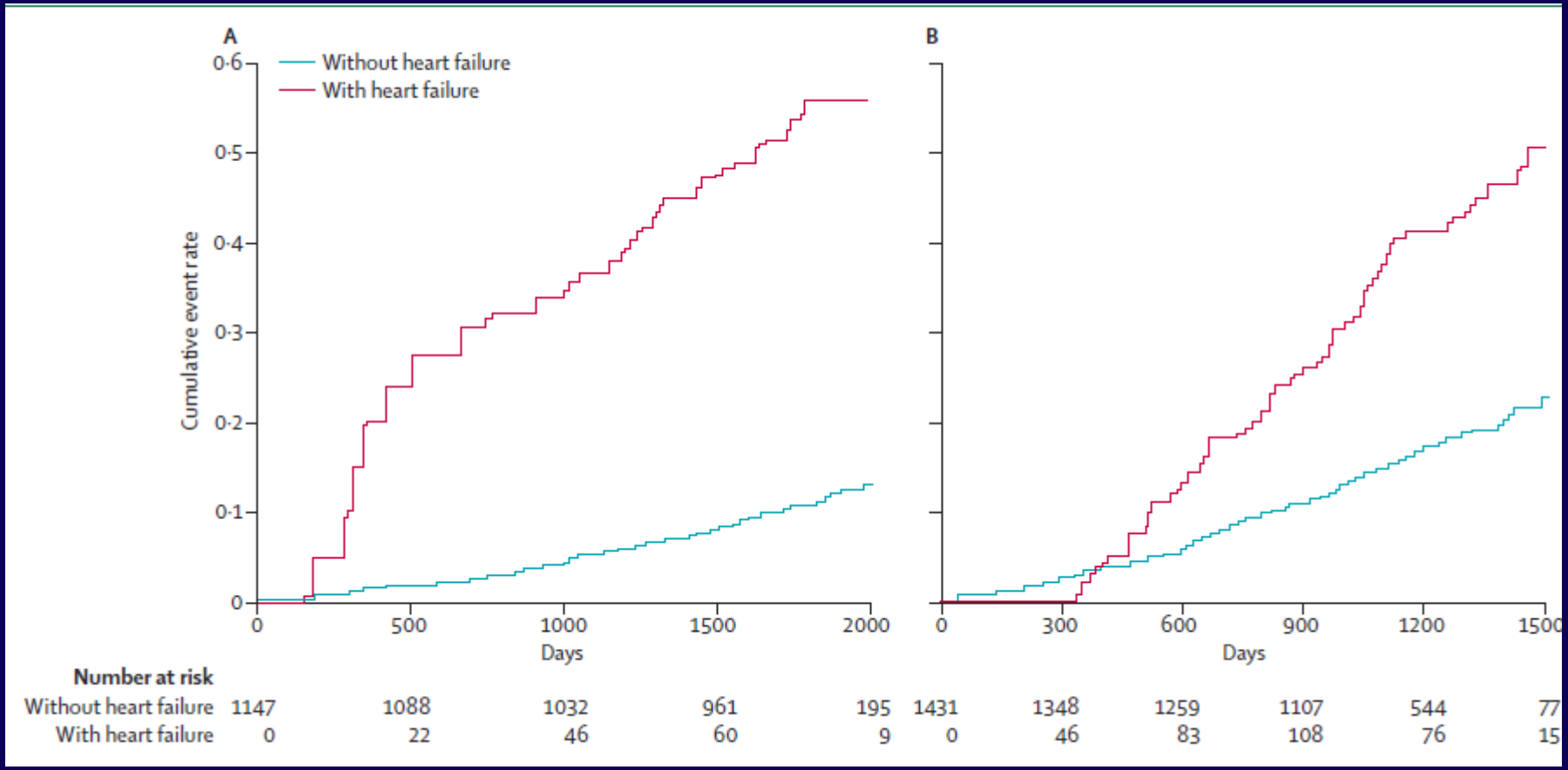


Bertoni et al. *Diabetes Care* 27:699–703, 2004



Gustafsson et al. JACC 2003; 43: 771-777.

Mortality in Patients with Diabetes with and without HF in LIFE and RENAAL



The heart failure:no heart failure hazard ratio for mortality was 5.98 (95% CI 3..90–9.17, p<0.0001) in LIFE and 3.99, 95% CI 3.02–5.25, p<0 · 0001) in RENAAL.

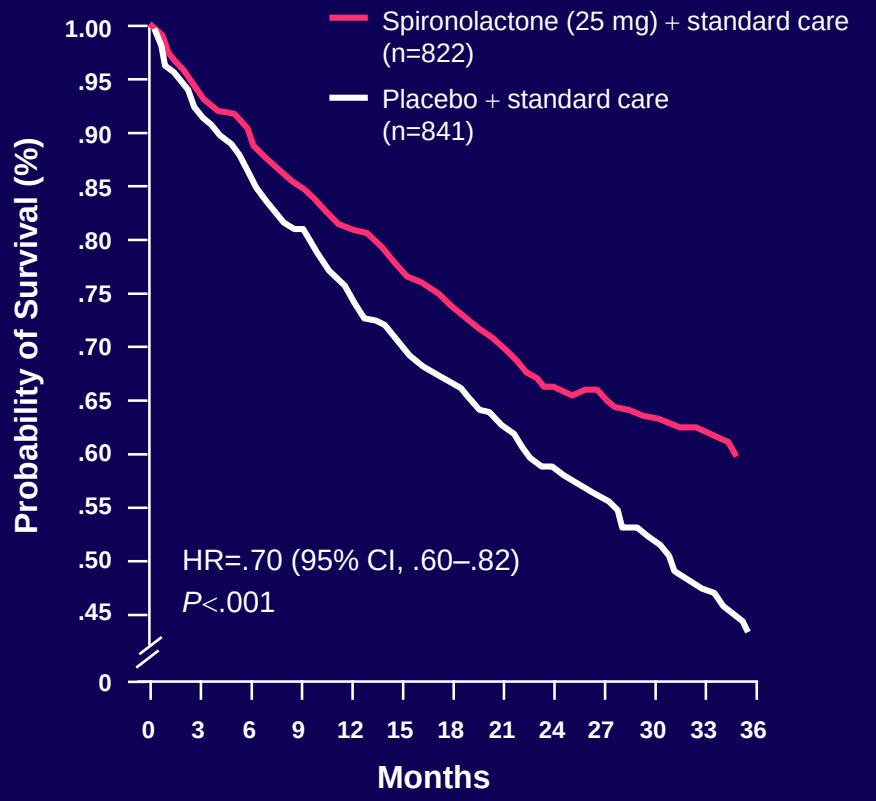
Optimal Heart Failure Therapy in Heart Failure Patients with Diabetes

ACE Inhibitors in Patients with HF with and without Diabetes

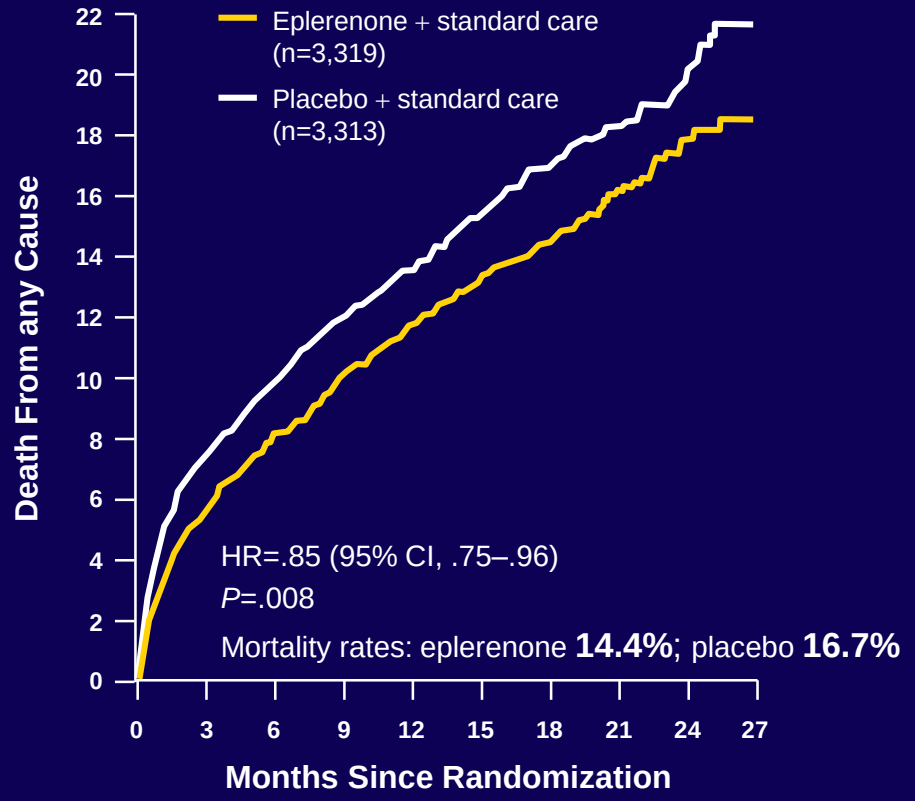
Relative Risks Analysis						
Study Name	Total N	Nondiabetic N=10188	Diabetic N=2398	Relative Risk, Nondiabetic (95% CI)	Relative Risk, diabetic (95% CI)	Ratio of Relative Risks (95% CI)
CONSENSUS	253	197	56	0.64 (0.46, 0.88)	1.06 (0.65, 1.74)	1.67 (0.93, 3.01)
SAVE	2231	1739	492	0.82 (0.68, 0.99)	0.89 (0.68, 1.16)	1.09 (0.79, 1.50)
SMILE	1556	1253	303	0.79 (0.54, 1.15)	0.44 (0.22, 0.87)	0.56 (0.25, 1.22)
SOLVD-prevention	4228	3581	647	0.97 (0.83, 1.15)	0.75 (0.55, 1.02)	0.77 (0.54, 1.09)
SOLVD-treatment	2569	1906	663	0.84 (0.74, 0.95)	1.01 (0.85, 1.21)	1.21 (0.97, 1.50)
TRACE	1749	1512	237	0.85 (0.74, 0.97)	0.73 (0.57, 0.94)	0.87 (0.65, 1.15)
Random Effects Pooled Estimate		10188	2398	0.85 (0.78, 0.92)	0.84 (0.70, 1.00)	1.00 (0.80, 1.25)

Shekelle P et al. *J Am Coll Cardiol*. 2003;41:1529-38.

Aldosterone Antagonists Reduce All-Cause Mortality in Chronic HF



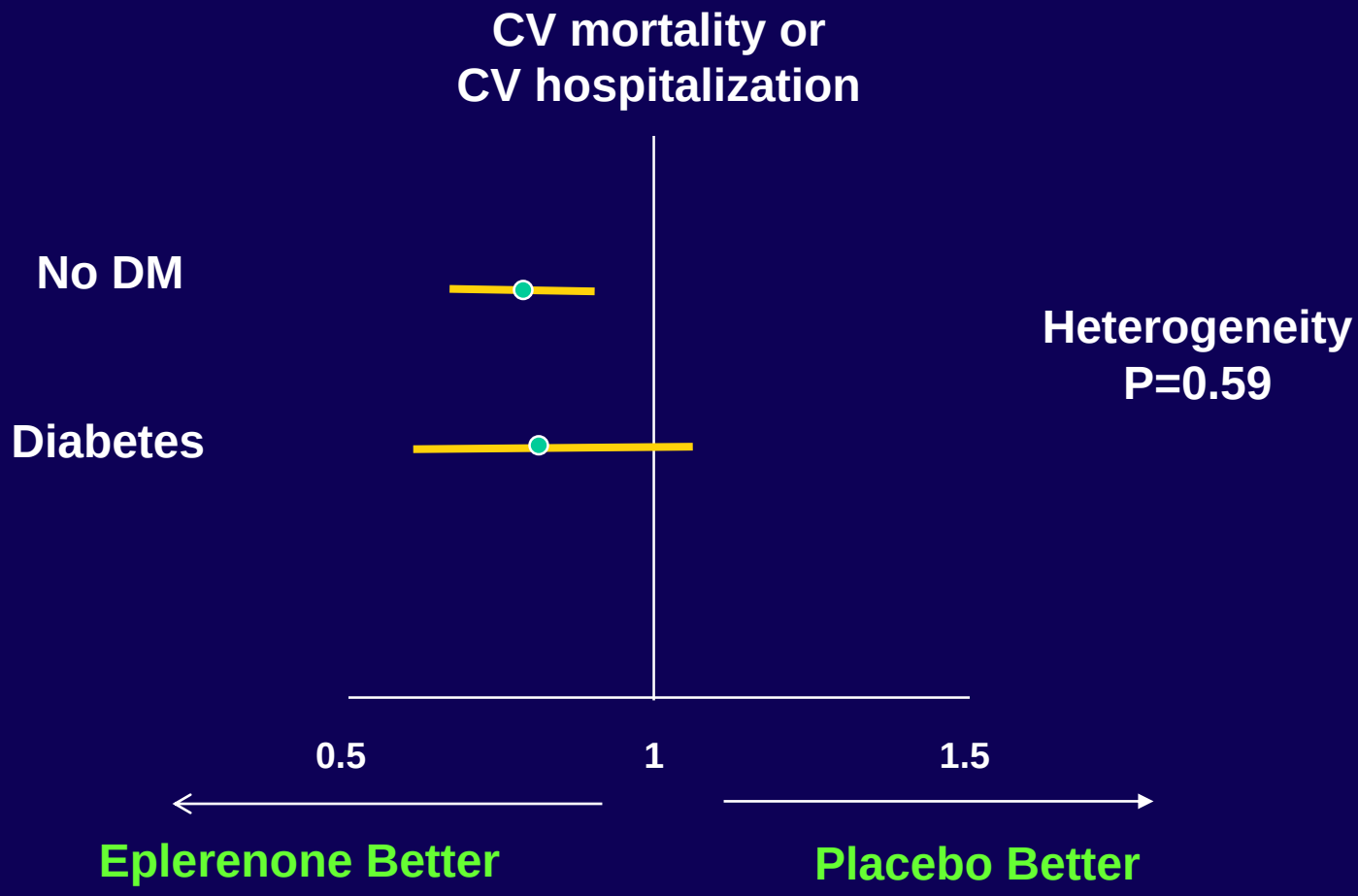
RALES (Randomized Aldactone Evaluation Study): 822 patients with severe HF and LVEF<35% randomized to receive spironolactone 25 mg QD or placebo and followed for 24 months.



EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study): 6,642 patients with acute MI and LVD randomized to eplerenone started at 25 mg and titrated to 50 mg QD or placebo in addition to optimal medical therapy and followed for 16 months.

Pitt B et al. *N Engl J Med*. 1999;341:709–717. Pitt B et al. *N Engl J Med.* 2003;348:1309–1321.

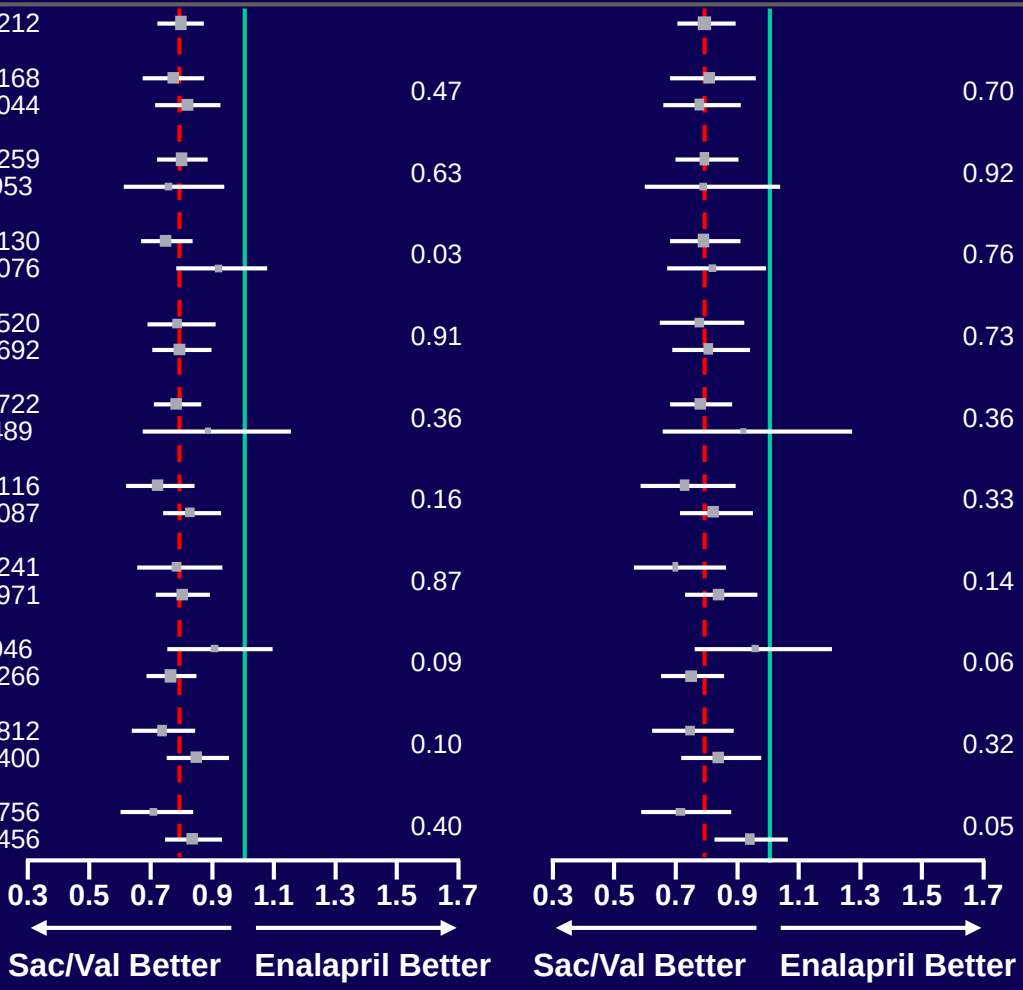
Effect of Eplerenone on Mortality Post-MI in Diabetes and no-Diabetes



N=6632, 32% diabetic
Pitt NEJM 2003;348:1309-21

Sac/Val vs. Enalapril on Primary Endpoint and on CV Death by Subgroups: PARADIGM-HF

Subgroup	No. Sac/Val	No. Enalapril	Primary Endpoint Hazard Ratio (95% CI)	Primary Endpoint *p*-Value for Interaction	Death from Cardiovascular Causes Hazard Ratio (95% CI)	Death from Cardiovascular Causes *p*-Value for Interaction
All Patients	4187	4212				
Age						
<65 years	2111	2168		0.47		0.70
≥65 years	2076	2044				
Sex						
Male	3308	3259		0.63		0.92
Female	879	953				
NYHA Class						
I or II	3187	3130		0.03		0.76
III or IV	1002	1076				
Estimated GFR						
<60 mL/min/1.73 m^2	1541	1520		0.91		0.73
≥60 mL/min/1.73 m^2	2646	2692				
Ejection fraction						
≤35%	3715	3722		0.36		0.36
>35%	472	489				
NT-proBNP						
≤Median	2079	2116		0.16		0.33
>Median	2103	2087				
Hypertension						
No	1218	1241		0.87		0.14
Yes	2969	2971				
Prior use of ACE inhibitor						
No	921	946		0.09		0.06
Yes	3266	3266				
Prior use of aldosterone antagonist						
No	1916	1812		0.10		0.32
Yes	2271	2400				
Diabetes						
No	2736	2756		0.40		0.05
Yes	1451	1456				



McMurray JJV, et al. *N Engl J Med.* 2014;371:993-1004.

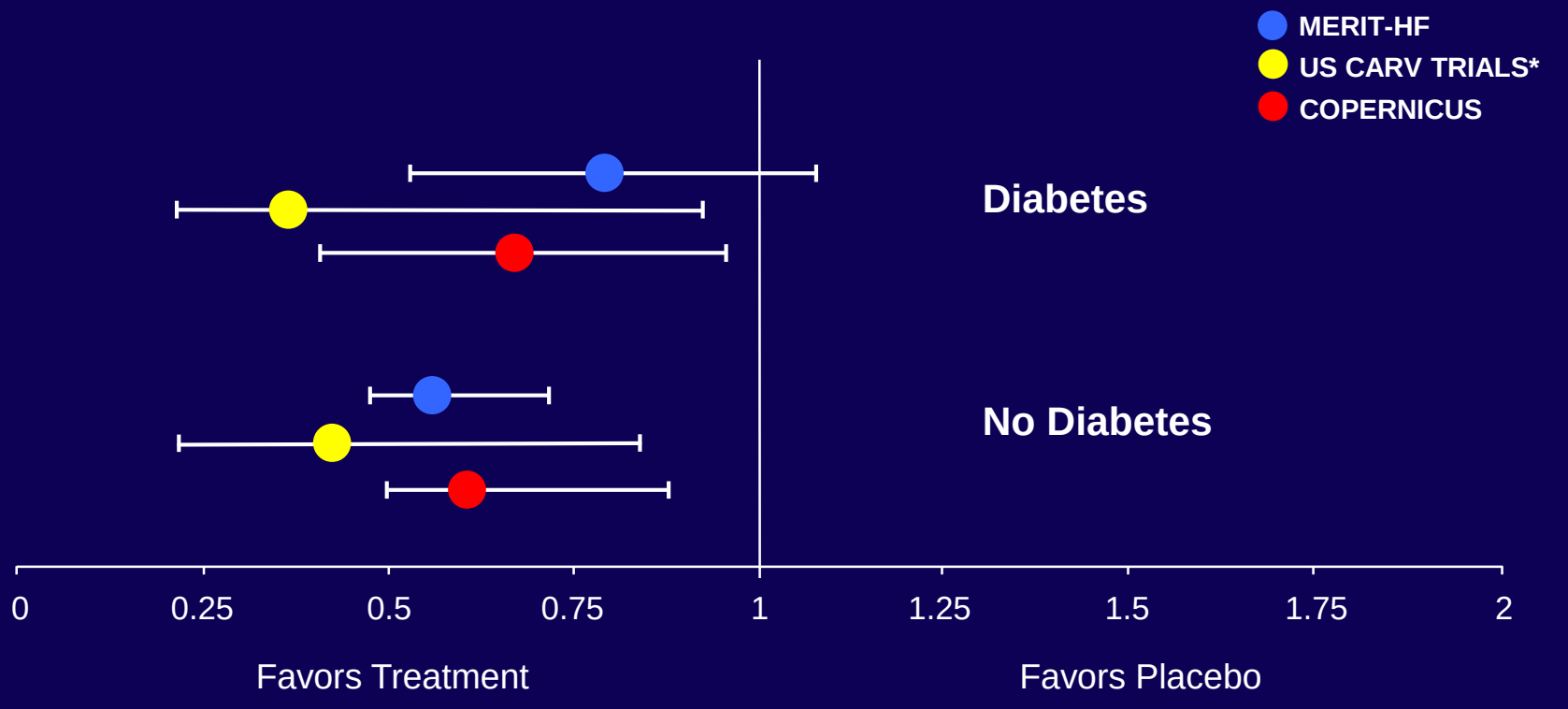
Effect of β-Blockade on Mortality in HF

Study	Drug	HF Severity	Target Dosage (mg/day)	Effect on Mortality
US Carvedilol[1]	carvedilol	mild/ moderate	6.25 to 25* bid	↓65% mortality† (*P*=.0001)
CIBIS-II[2]	bisoprolol†	moderate/ severe	10 qd	↓34% mortality (*P*<.0001)
MERIT-HF[3]	metoprolol succinate	mild/ moderate	200 qd	↓34% mortality (*P*=.0062)
COPERNICUS[4]	carvedilol	severe	25 bid	↓35% mortality (*P*=.0014)

*50 mg bid if >85 kg.
†Not a planned end point.

[1]Packer M et al. *N Engl J Med*. 1996;334:1349–1355.
[2]CIBIS II Investigators and Committees. *Lancet*. 1999;353:9–13.
[3]MERIT-HF Study Group. *Lancet.* 1999;353:2001–2007.
[4]Packer M et al. *N Engl J Med.* 2001;344:1651–1658.

Effect of β-Blockade in HF By Diabetes Status: All-Cause Mortality

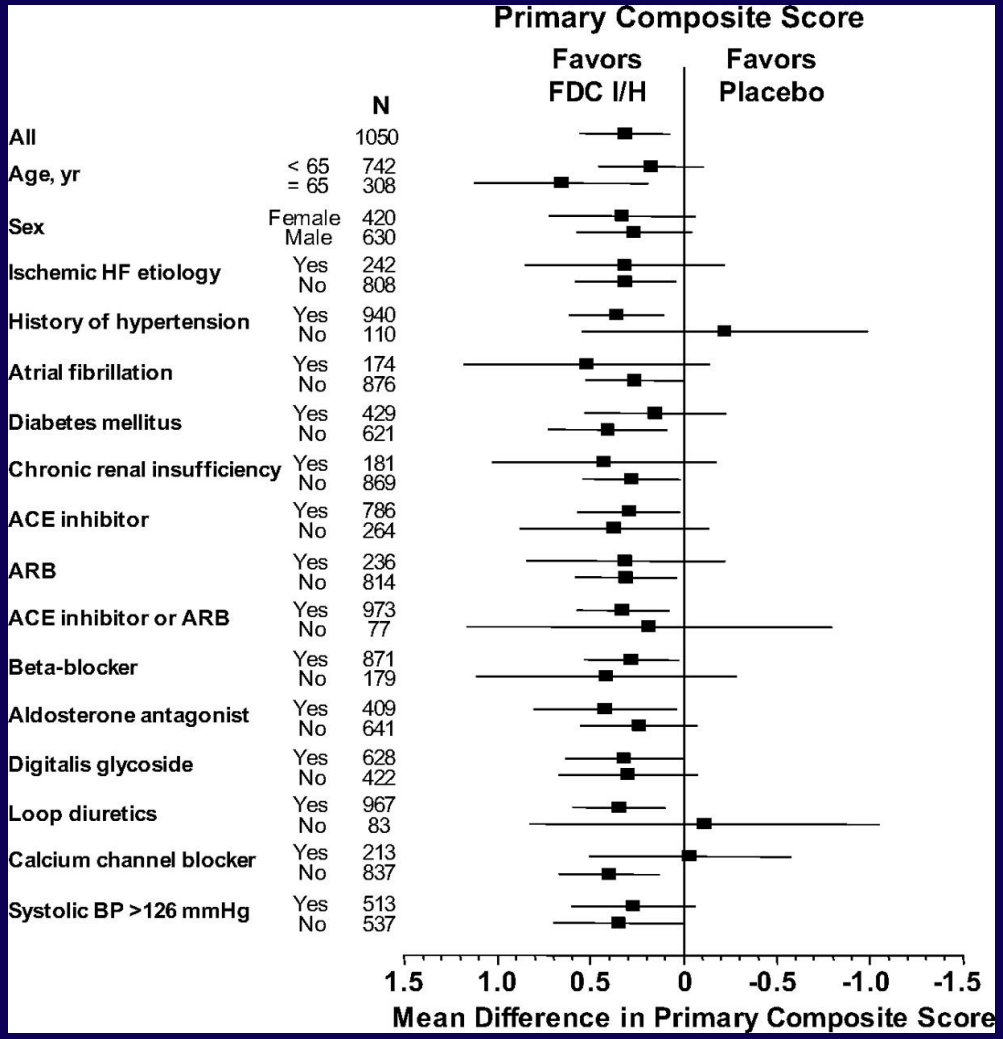


	Metoprolol CR/XL/placebo	US carvedilol/placebo	COPERNICUS/placebo
Diabetics:	495/1990 (25%)	195/696 (28%)	302/1156 (26%)
Nondiabetics	489/2001 (24%)	112/398 (28%)	287/1133 (25%)

*Not a planned end point.

Wedel H et al. *Am Heart J.* 2001;142:502–511.
MERIT-HF Study Group. *Lancet.* 1999;353:2001–2007.

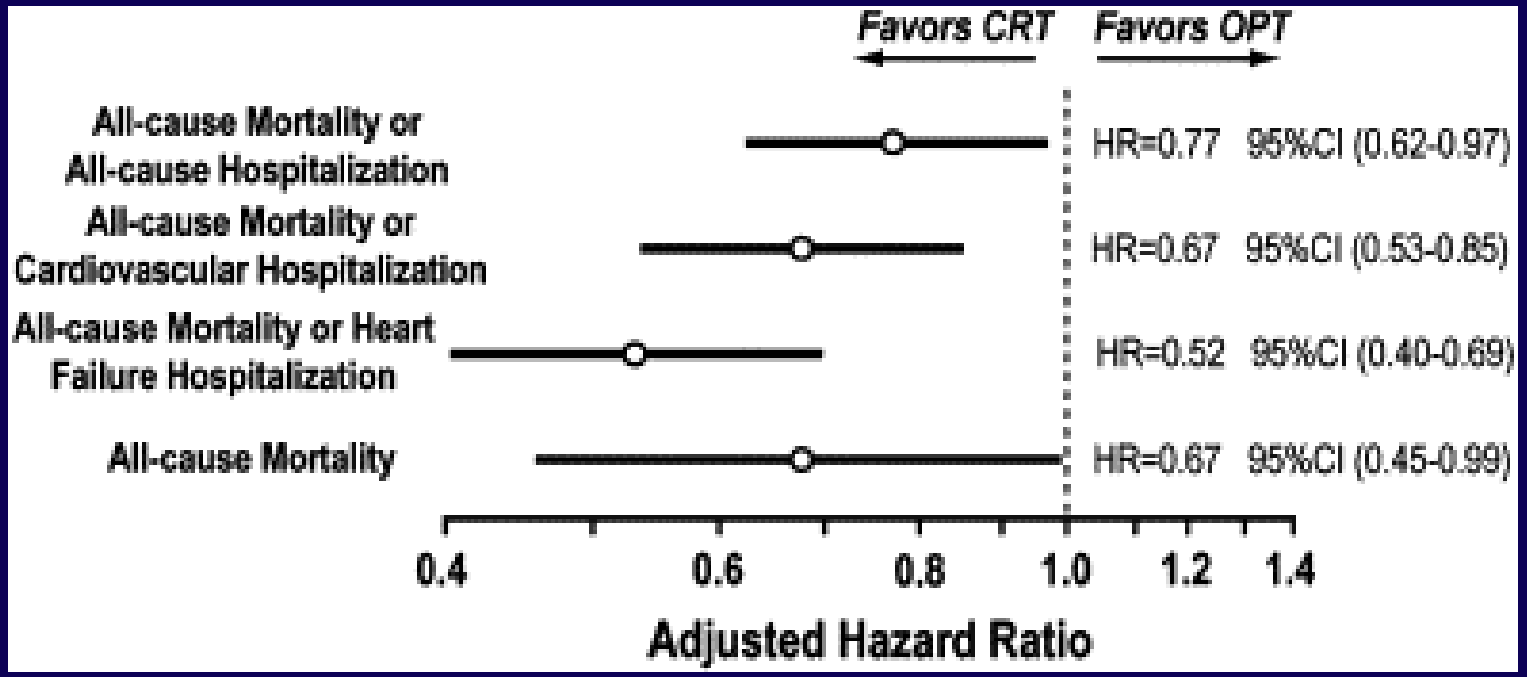
AHEFT: Subgroup Analyses of Primary Outcome No Significant Interaction by Diabetes



Anne L. Taylor et al. Circulation. 2007;115:1747-1753

Influence of Diabetes on CRT With or Without Defibrillator in Patients With Advanced HF

COMPANION Trial



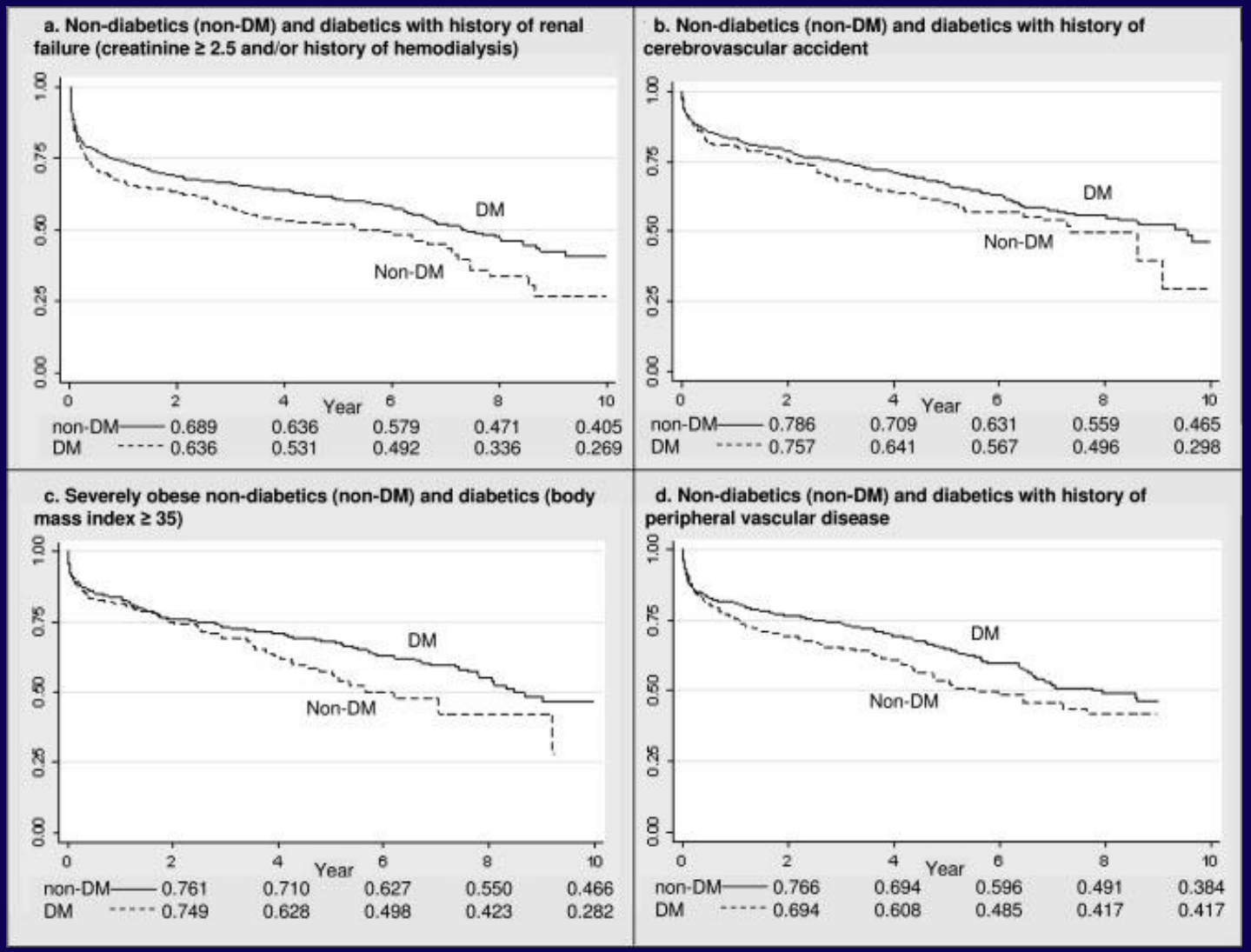
Diabetes mellitus was reported at the time of enrollment in 622 of 1520 patients (41%). Patients were randomized in a 1:2:2 ratio to OPT, CRT-P, and CRT-D,

Ghali JK et al. J Card Fail. 2007 Nov;13(9):769-73.

TABLE 1 Major Clinical Trials in Patients With Heart Failure and Subgroup Analyses With Concomitant Diabetes Mellitus

Trial	Primary Outcome	Subgroup of Patients With or Without DM	Average Follow-up (months)	Treatment	Results	Reference
SOLVD	Mortality and hospitalization for worsening HF	HF patients with EF <35%	41.4	Enalapril vs. placebo	RR of 0.84 (0.74–0.95) in no DM vs. 1.01 (0.85–1.21) in DM	35
SAVE	CV mortality	Recent survivors of MI with EF ≤40%	42	Captopril vs. Placebo	RR of 0.82 (0.68–0.99) in no DM vs. 0.89 (0.68–1.16) in DM	36
TRACE	All-cause mortality	Patients with LVEF <35% after acute MI	26	Trandalapril vs. placebo	RR of 0.82 (0.69–0.97) in no DM vs. 0.64 (0.45–0.91) in DM (interaction analysis p = 0.3)	37
SMILE	Progression to HF	Patients with anterior acute MI not eligible for thrombolytic treatment	12	Zofenopril vs. Placebo	RR of 0.79 (0.54–1.15) in no DM vs. 0.44 (0.22–0.87) in DM	38
ATLAS	All-cause mortality	High-risk HF patients	46	Lisinopril high dose (32.5–35 mg day^{-1}) vs. low-dose (2.5–5 mg day^{-1})	↓6% RR in no DM patients vs. ↓14% RR in DM high-dose vs. low dose (interaction analysis p = 0.3)	39
CHARM	CV death or hospitalization for HF	NYHA functional class II–IV patients (LVEF <40%)	40	Candesartan vs. placebo	RR not significant in no DM vs. that in DM (interaction analysis p = 0.12)	41
Val-HeFT	Combined endpoint of CV mortality and morbidity	NYHA functional class II–IV patients	23	Valsartan vs. Placebo	↓RR in no DM vs. that in DM (although not significant)	42
EPHESUS	Mortality and CV morbidity	Postacute MI patients with LVEF ≤40% and clinical HF	16	Eplerenone vs. Placebo	↓RR in no DM vs. that in DM (although not significant; p = 0.59)	43
Subgroup analysis	All-cause mortality	NYHA functional class III–IV patients with LVEF <35%	24	Spironolactone vs. Placebo	RR of 0.70 (0.60–0.82) in non-DM vs. HR of 0.70 (0.52–0.94) in DM	44
BEST	All-cause mortality	NYHA functional class III–IV patients with EF ≤35%	24	Bucindolol vs. Placebo	RR of 0.91 (0.74–1.13) in no DM vs. HR of 0.87 (0.73–1.03) in DM	29
MERIT-HF	Risk of hospitalization for HF	NYHA functional class III–IV patients with EF <40%	12	Metoprolol vs. Placebo	↓37% RR in DM vs. ↓35% in no DM; test of diabetes by treatment interaction was nonsignificant	30
CIBIS II	All-cause mortality	NYHA functional class III–IV patients with EF ≤35%	16	bisoprolol vs. Placebo	RR 0.66 (95% CI 0.54–0.81) in no DM vs. RR 0.81 (95% CI 0.51–1.28) in DM (heterogeneity test for interaction p = 0.48)	32
COPERNICUS	Combined endpoint All-cause mortality or hospitalization for HF	NYHA functional class IV patients with EF <25%	10.4	Carvedilol vs. Placebo	RR of 0.67 (0.52–0.85) in no DM vs. 0.68 (0.47–1.00) in DM	31
ASTRONAUT	CV death or HF rehospitalization	Hemodynamically stable patients hospitalized for HF	11.3	Aliskiren vs. Placebo	HR of 0.80 (0.64–0.99) in no DM vs. 1.16 (0.91–1.47) in DM ; test for interaction p = 0.03	2

Survival After Heart Transplantation Is Not Diminished Among Recipients With Uncomplicated Diabetes Mellitus



20,412 first-time heart transplant recipients, 19% with diabetes

No increased risk for mortality with 0 or 1 end organ complications

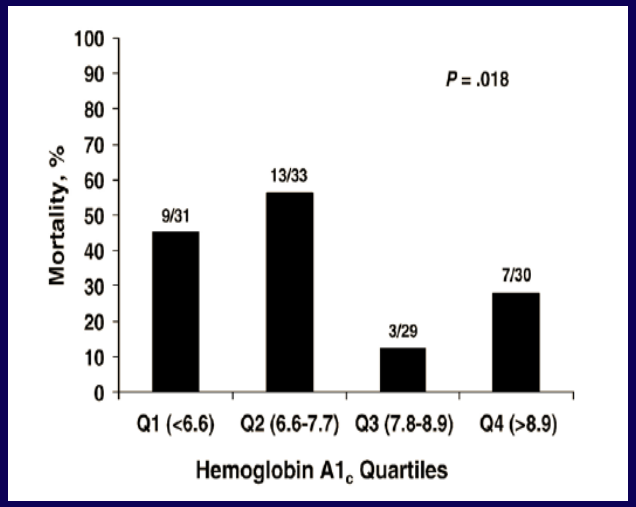
Increased mortality with 2 or 3 or more factors

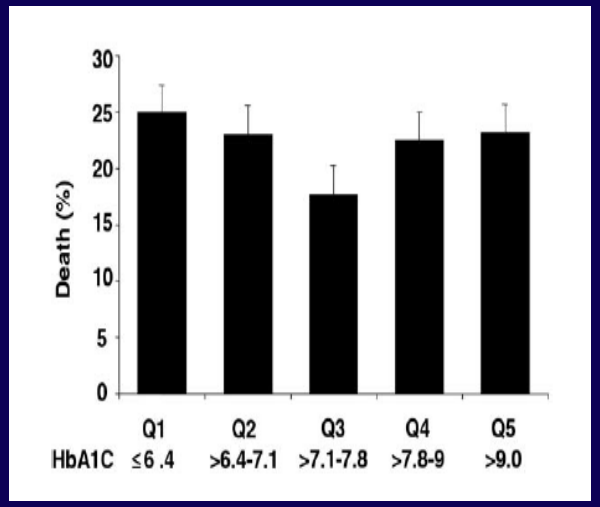
Circulation. 2006;114:2280-2287

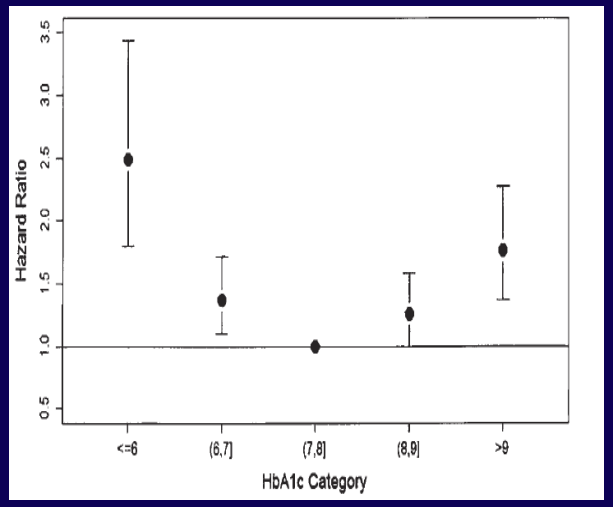
Optimal Diabetes Therapy in Heart Failure Patients with Diabetes

Hemoglobin A1C and Mortality in Heart Failure Patients With Diabetes

All Cause Mortality in HF Patients with Diabetes as a Function of HbA1c







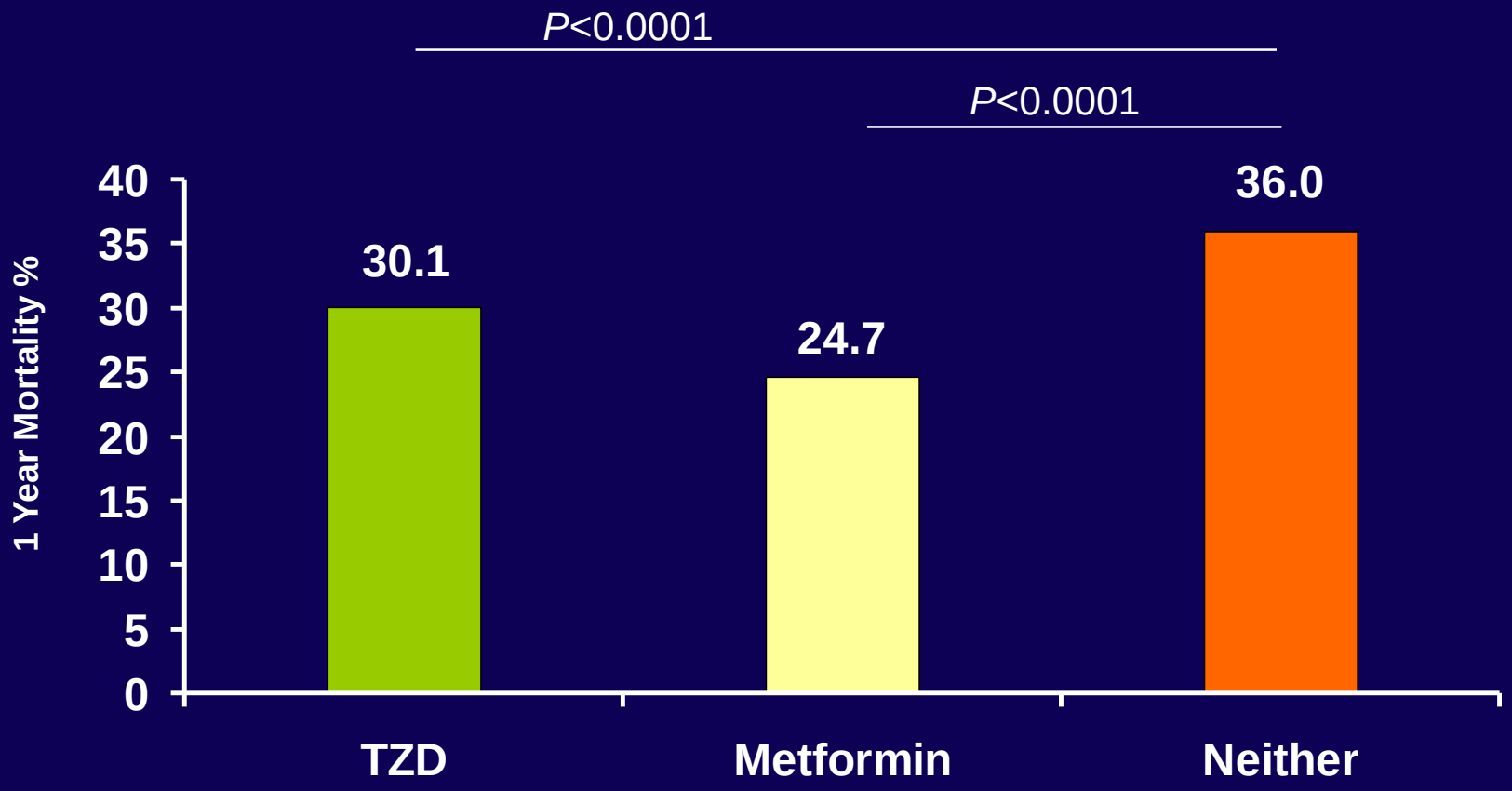
Am Heart J 2006;151:91.e1-91.e6 *J. Am. Coll. Cardiol.* 2009;54;422-428 European JHF (2016) **18**, 94–102

Glycemic Management Medications: Possible Mechansims Impacting HF

Table 2. Cellular mechanisms and possible cellular effects in HF of the commercially available antidiabetic agents

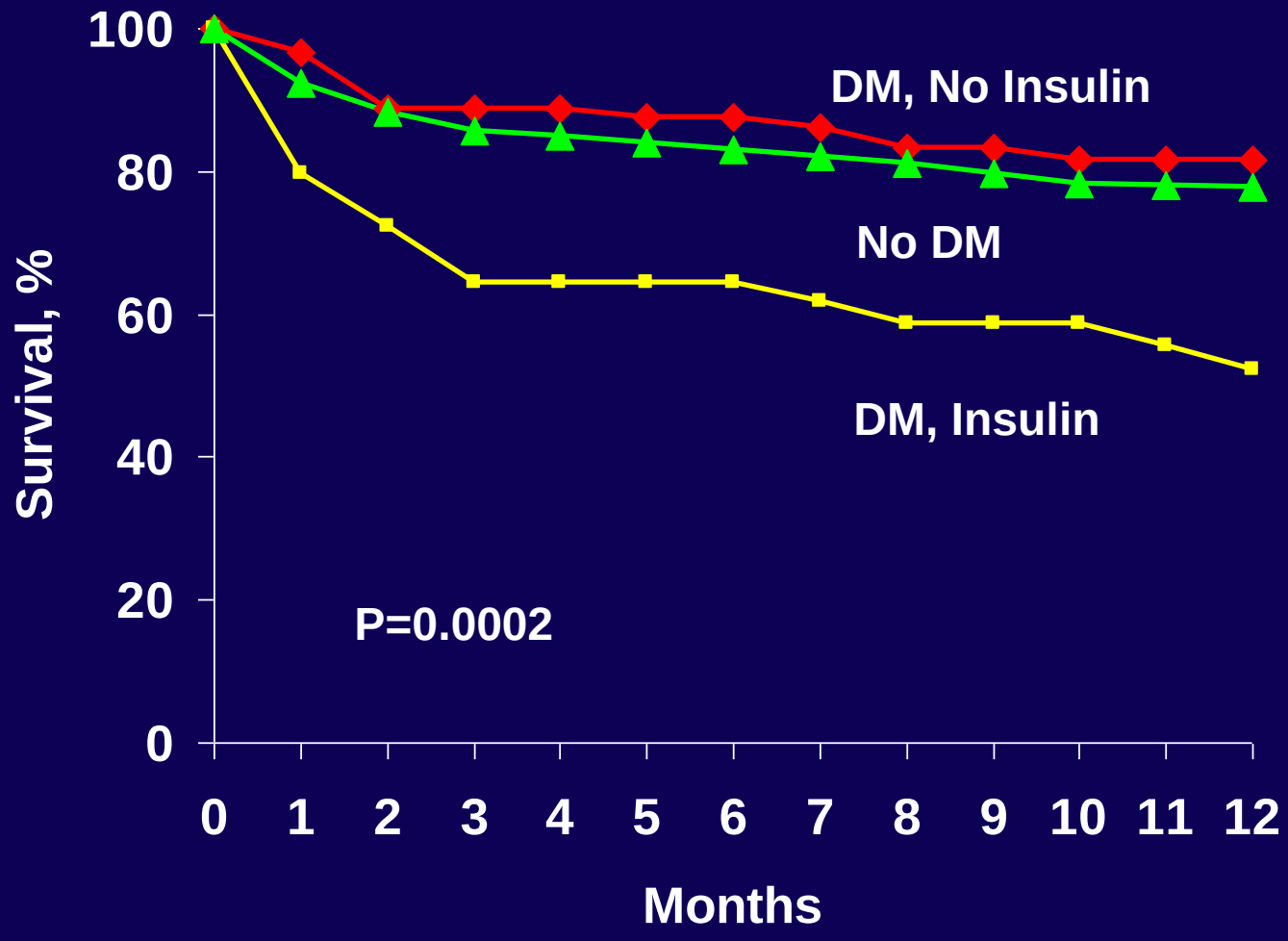
Agent	Cellular mechanism	Possible cellular effects in CAD/HF
Metformin	AMP-kinase activation	↓ Activity of carnitine palmitoyltransferase-1, a key regulator of FFA uptake in the mitochondria, ↑ Myocardial glucose uptake and glycolysis
Thiazolidinediones	Nuclear transcription factor PPARγ activation	↑ Fluid retention and edema ↓ Angiotensin II levels ↓ Blood pressure, ↑ Endothelial function ↓ Inflammation ↑ HDL and ↓ TG and LDLox
Sulfonylureas	KATP channels closure on β-cell membranes	Possible implication of closure of cardiac potassium-sensitive ATP channels ↑ Body weight
Insulin	Insulin receptor activation	↑ MAPK activation mediating proinflammatory and mitogenic effects ↑ PI-3K activation mediating myocardial glucose uptake and glycolysis, NO production and anti-inflammatory effects ↑ Body weight
GLP-1 agonists	GLP-1 receptor activation	Possible implication of the binding to cardiomyocytes and VSMCs receptors in the heart ↑ Glucose myocardial uptake via cAMP production ↓ Body weight ↓ Blood pressure ↑ Inotropic effect
DPP-4 inhibitors	DPP-4 activity inhibition	↑ BNP levels
SGLT-2 inhibitors	Kidney SGLT-2 inhibition	↓ Fluid retention and edema ↓ Blood pressure

Glycemic Control Medications and Outcomes in Older Patients with Diabetes and HF



16,417 Medicare beneficiaries with diabetes discharged after hospitalization with the principal diagnosis of HF. 2226 patients treated with a thiazolidinedione, 1861 treated with metformin, 12,069 treated with neither
Masoudi FA et al. Circulation 2005;111:583-90

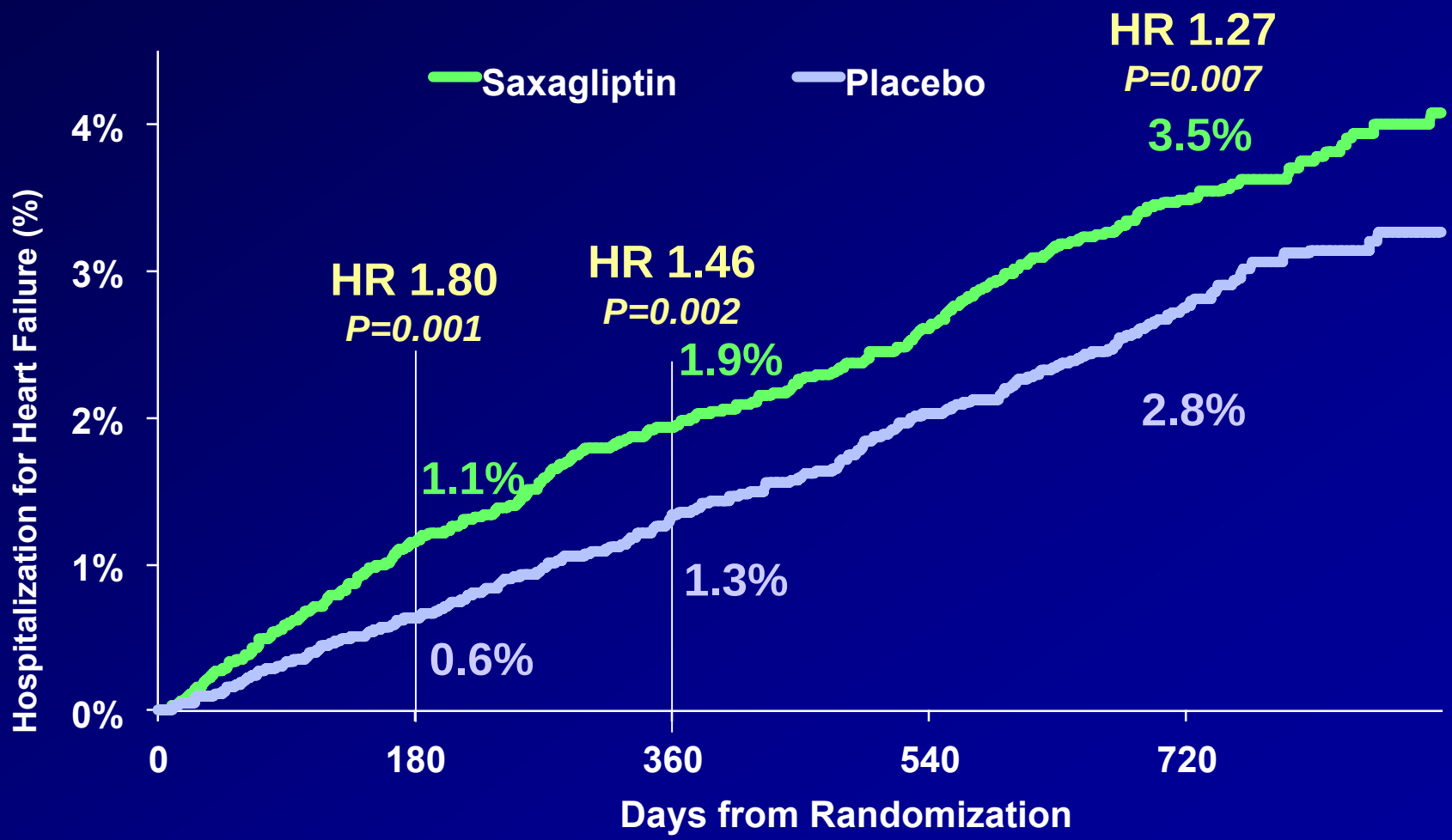
Insulin Treatment is Associated With Increased Mortality In Patients With Advanced HF



624 patients with advanced HF, systolic dysfunction
Smooke, Horwich, andFonarow, AHJ 2005;149:168-74.

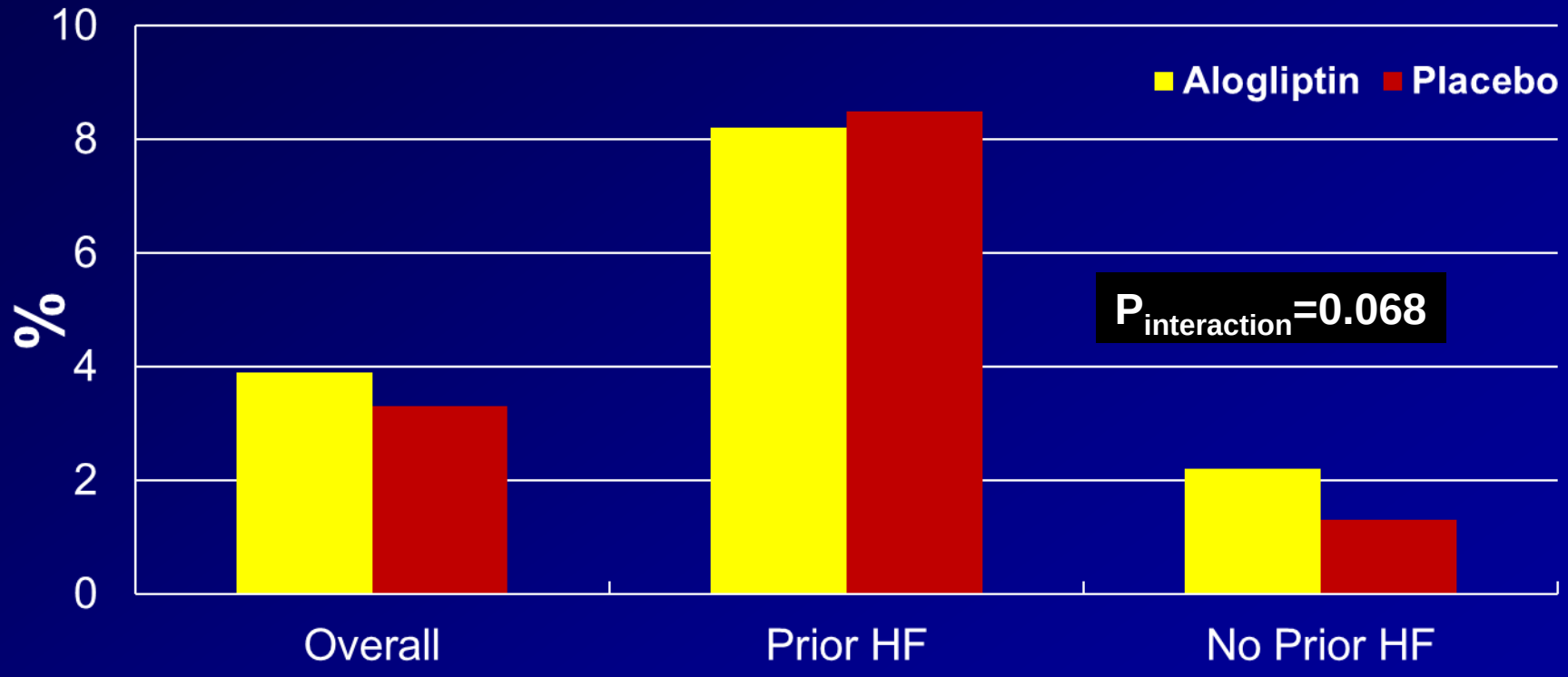
SAVOR TIMI 53-Hospitalization for Heart Failure: DPP-4

Time to the 1st occurrence of any hospitalization for heart failure; 517 events



Scirica BM, et al. Circulation 2014; 130:1579-88.

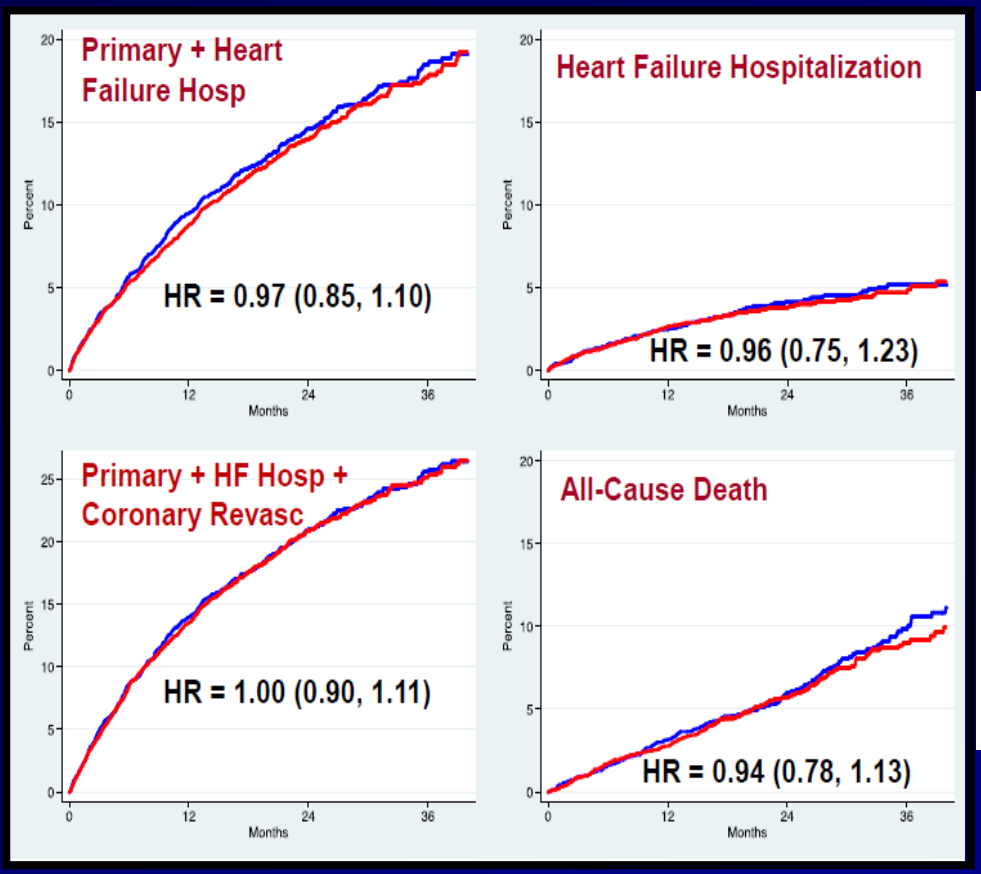
Hospitalization for HF with Alogliptin: Observations from EXAMINE



	Overall	Prior HF	No Prior HF
HR:	**1.19**	**1.00**	**1.76**
95% CI:	**0.90-1.58**	**0.71-1.42**	**1.07-2.90**
P-value:	**p=0.22**	**p=0.99**	**p=0.026**

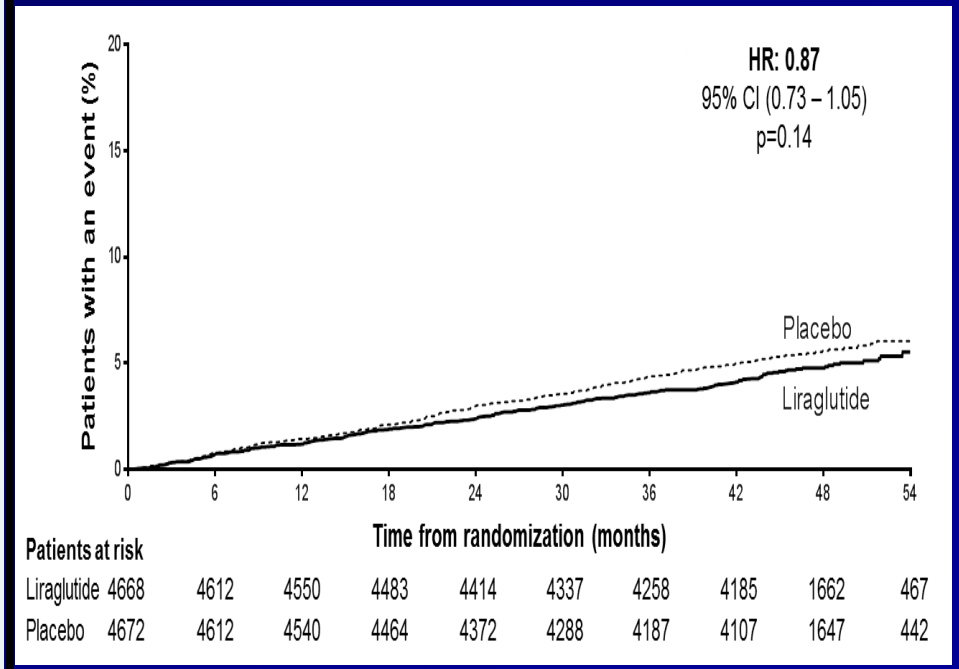
Zannad F. et al. **Lancet 2015: 385** : 2067-2076

CV Effects of Lixisenatide: ELIXA Trial Results

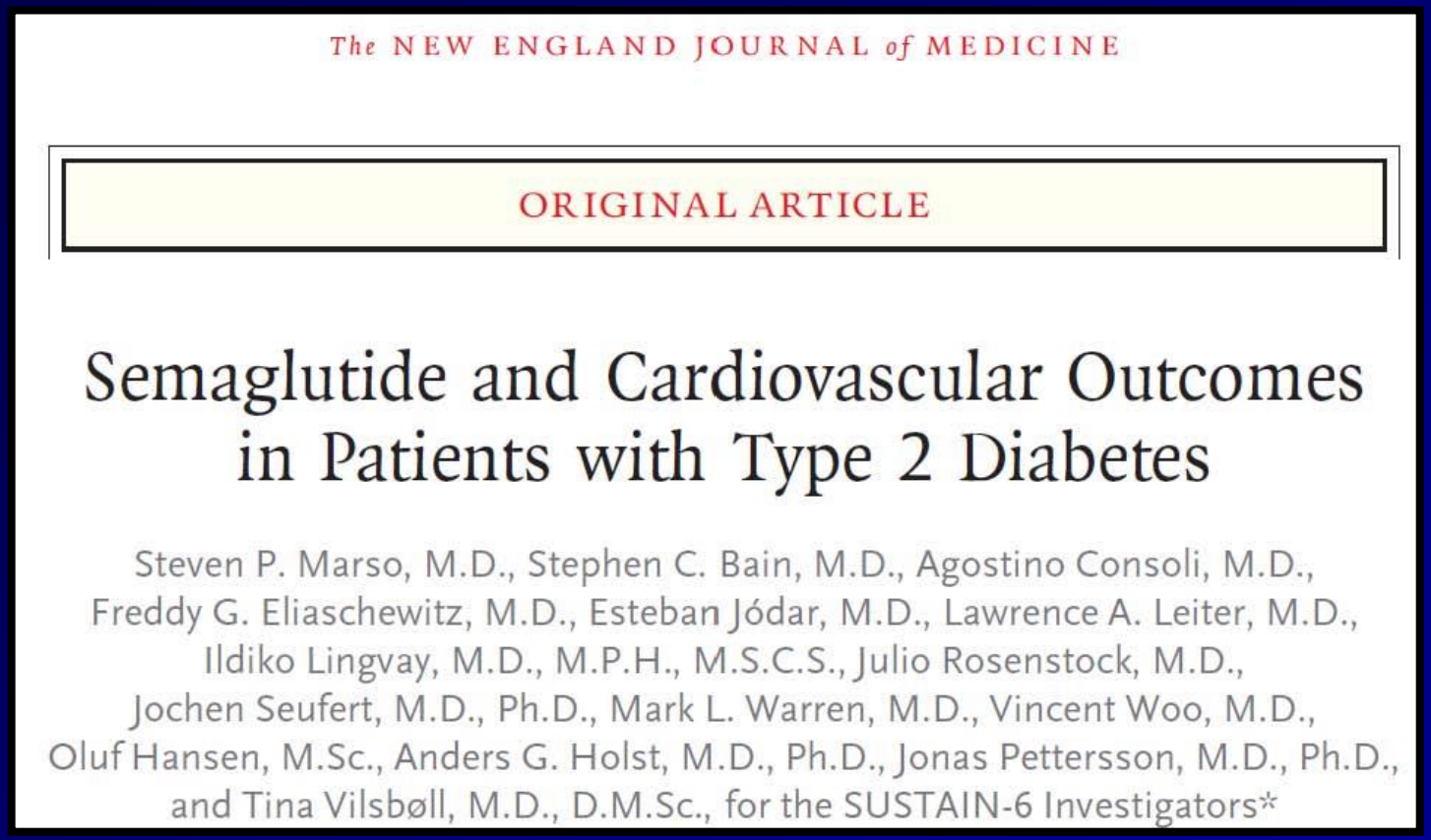


Pfeffer, M. A., et al. N Engl J Med 2015 373: 2247-2257

LEADER: Hospitalization for heart failure



Marso SP et al. N Engl J Med. 2016;375:311-22.



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Steven P. Marso, M.D., Stephen C. Bain, M.D., Agostino Consoli, M.D., Freddy G. Eliaschewitz, M.D., Esteban Jódar, M.D., Lawrence A. Leiter, M.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Julio Rosenstock, M.D., Jochen Seufert, M.D., Ph.D., Mark L. Warren, M.D., Vincent Woo, M.D., Oluf Hansen, M.Sc., Anders G. Holst, M.D., Ph.D., Jonas Pettersson, M.D., Ph.D., and Tina Vilsbøll, M.D., D.M.Sc., for the SUSTAIN-6 Investigators*

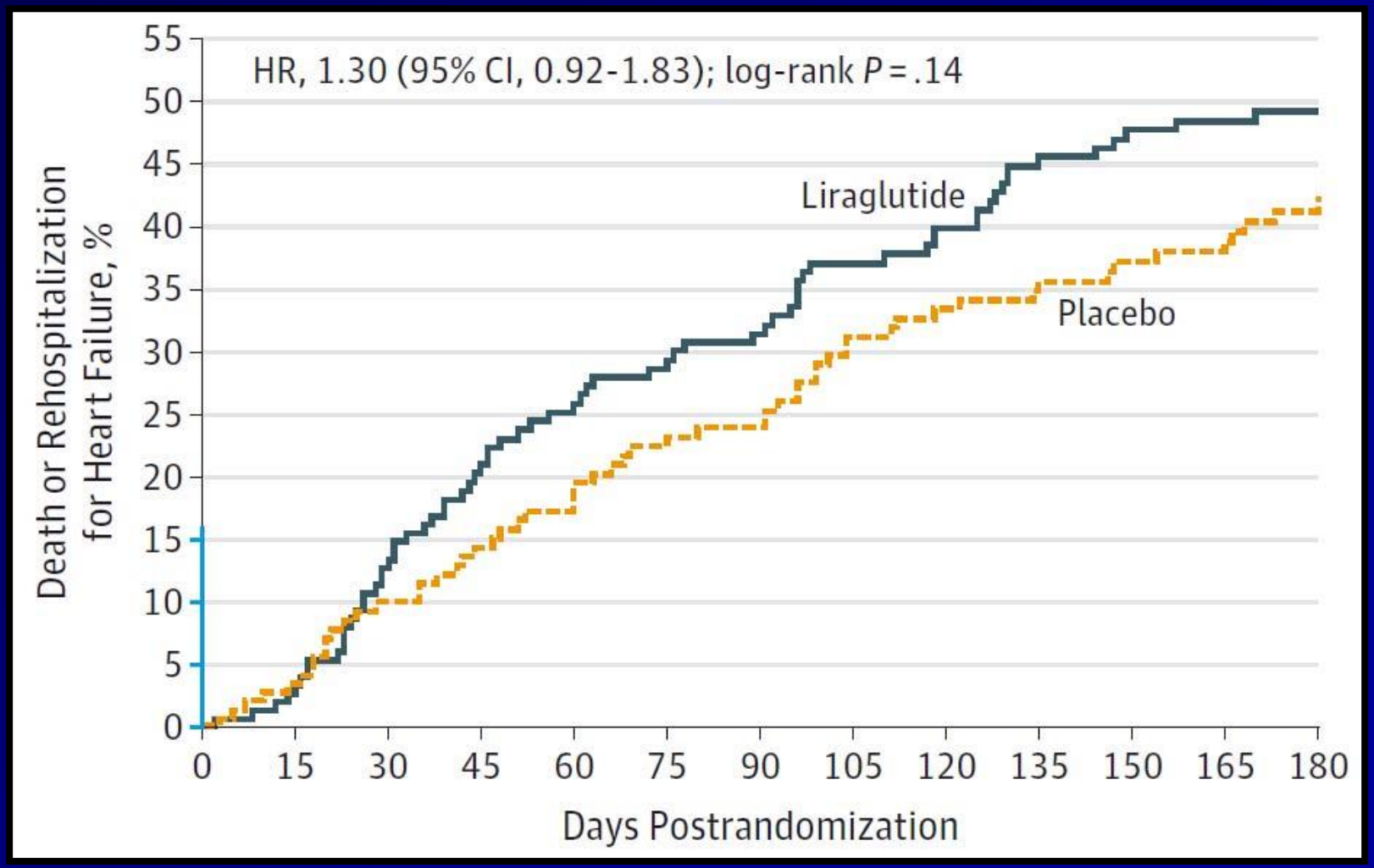
N=3297 T2DM w/ CVD/CV risk
Semaglutide 0.5 or 1.0mg vs. placebo once weekly
104 Weeks

Outcome	# of events semaglutide vs placebo	HR	95%CI
CV Death/MI/Stroke	108 vs 146	0.74	0.58-0.95
HF hospitalization	59 vs 54	1.11	0.77-1.61

Marso SP, et al. NEJM 2016; DOI: 10.1056/NEJMoa1607141

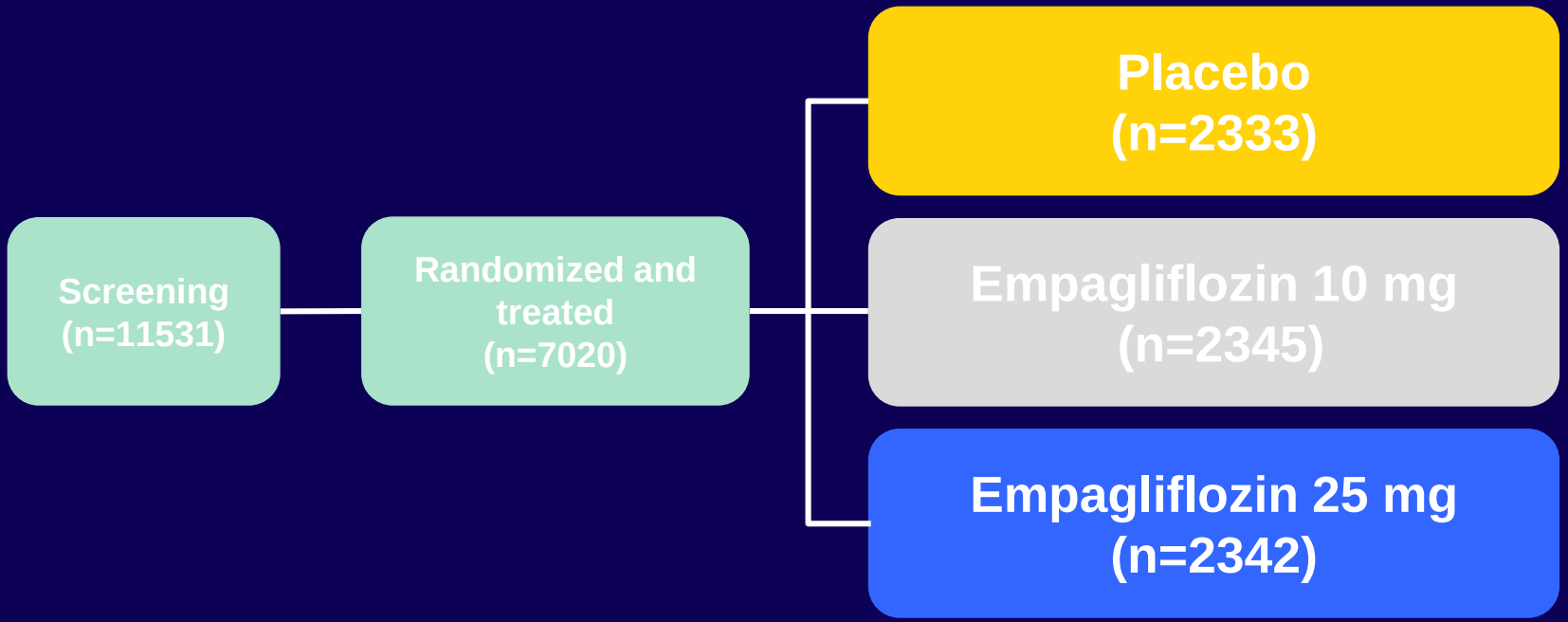
Liraglutide in Systolic Heart Failure: The FIGHT Trial

N=300: liraglutide (n = 154) vs. placebo (n = 146)



Margulies KB et al. JAMA. 2016;316:500-508.

EMPA-REG OUTCOME
Trial design: SGLT2 Inhibitor

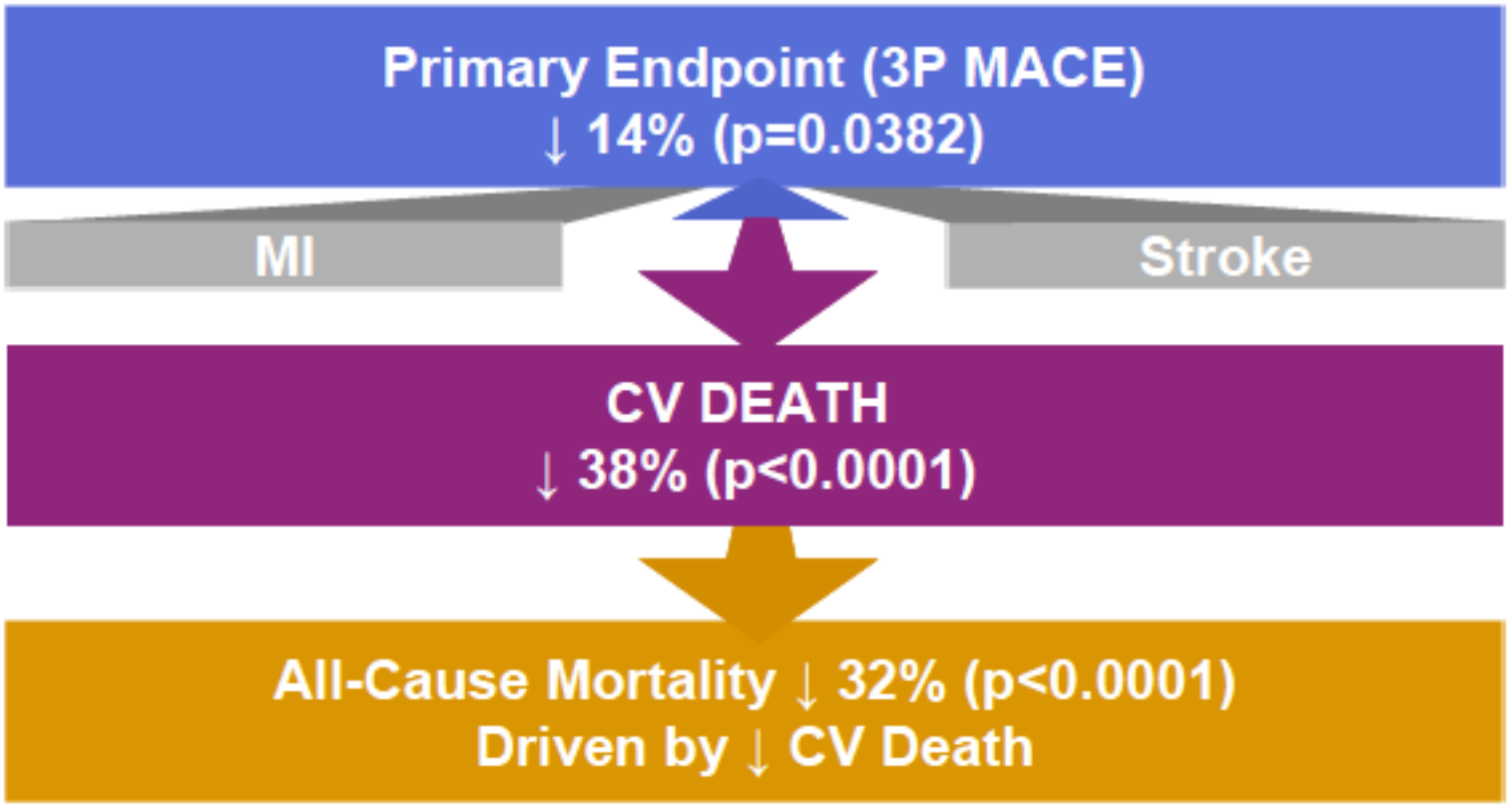


- **Key inclusion criteria:**
  - Adults with type 2 diabetes and established CVD
  - BMI ≤45 kg/m^2; HbA1c 7–10%; eGFR ≥30 mL/min/1.73m^2 (MDRD)
  - 10.2% of patients enrolled with pre-existing heart failure

Zinman B et al. N Engl J Med 2015 [Epub ahead of print].

EMPA-REG OUTCOME Trial

EMPA-REG OUTCOME Trial: Key Results

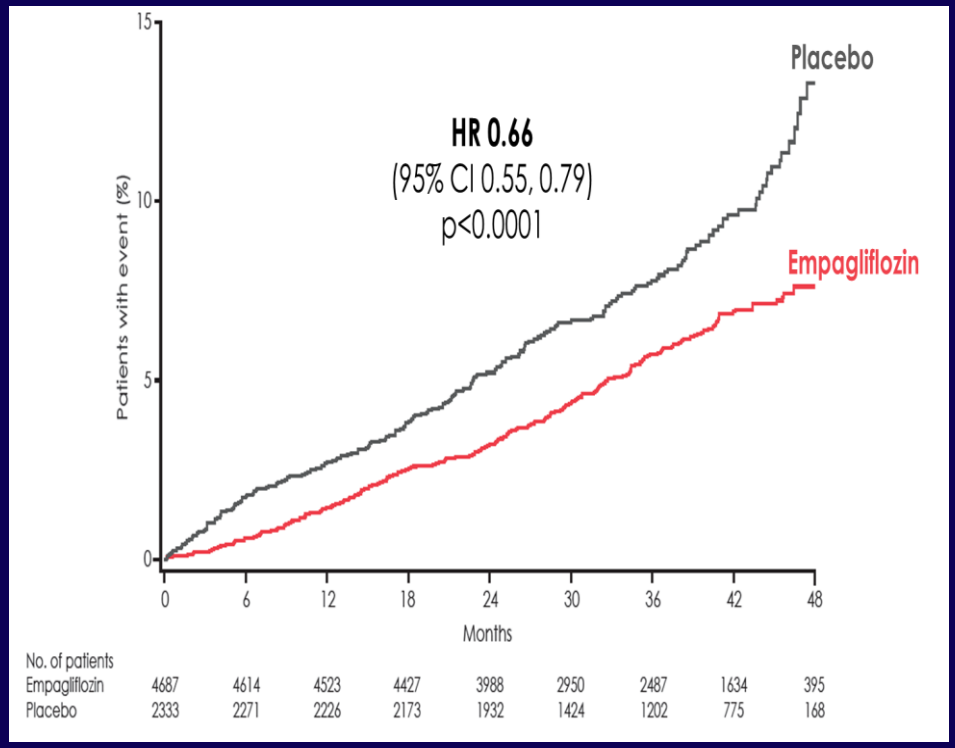


Heart Failure

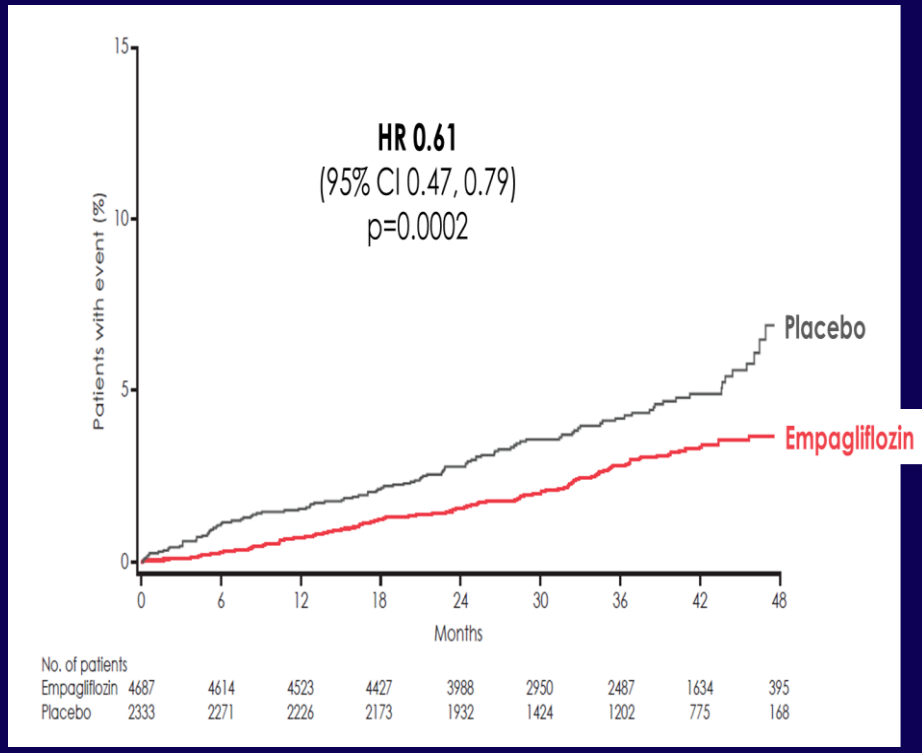
- Hospitalization for Heart Failure ↓ 35% (p=0.0017)
- Hospitalization for Heart Failure or CV Death ↓ 34% (p<0.0001)

EMPA-REG OUTCOME Study

HF Hospitalization or CV Death



HF Hospitalization or HF Death



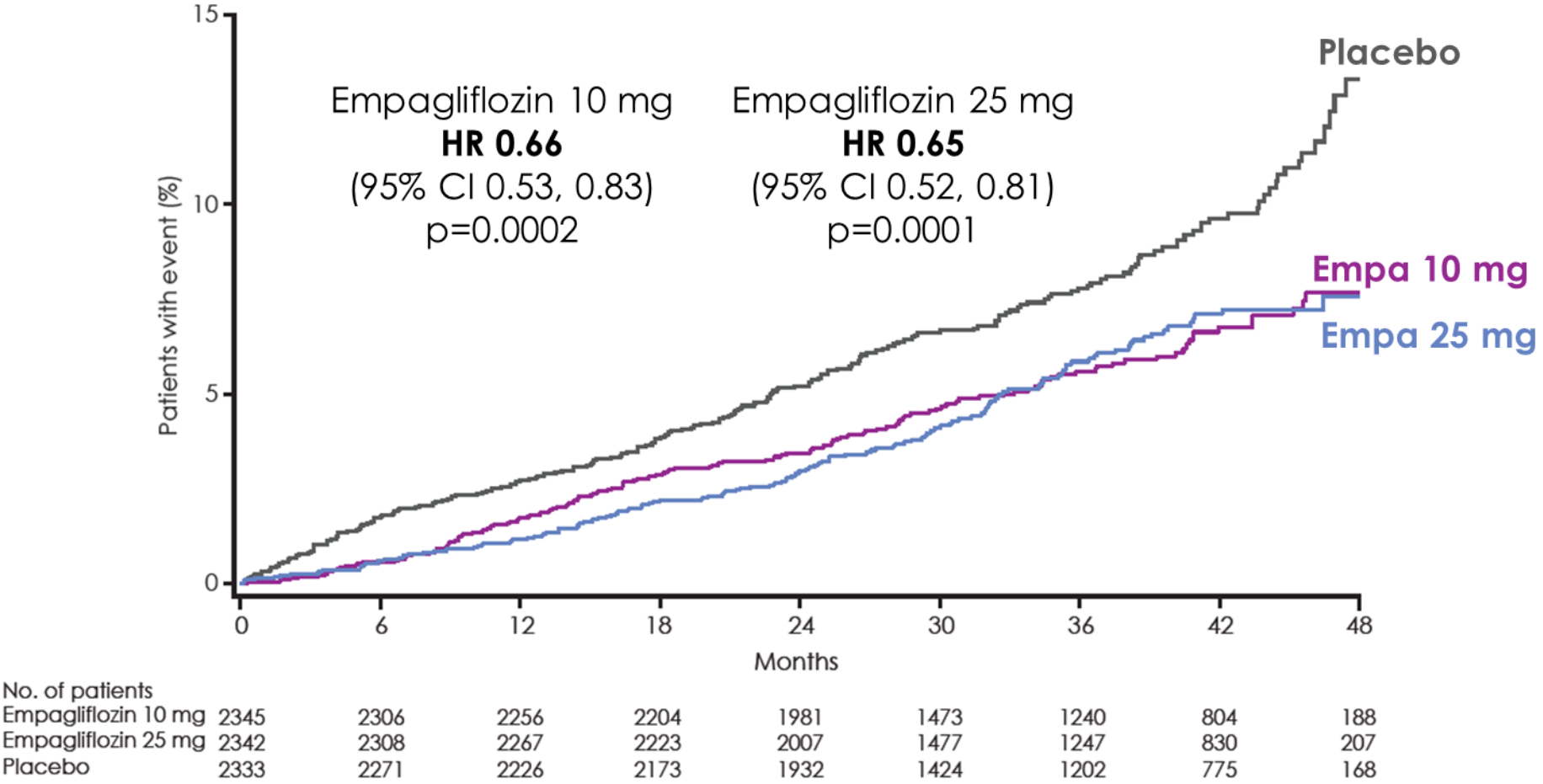
Empagliflozin is a highly selective inhibitor of Sodium-Glucose Cotransporter-2

7020 adults with type 2 diabetes and established CVD

BMI ≤45 kg/m^2; HbA1c 7–10%; eGFR ≥30 mL/min/1.73m^2 (MDRD)

Zinman B et al. N Engl J Med 2015 [Epub ahead of print].

Heart Failure Hospitalization or CV death

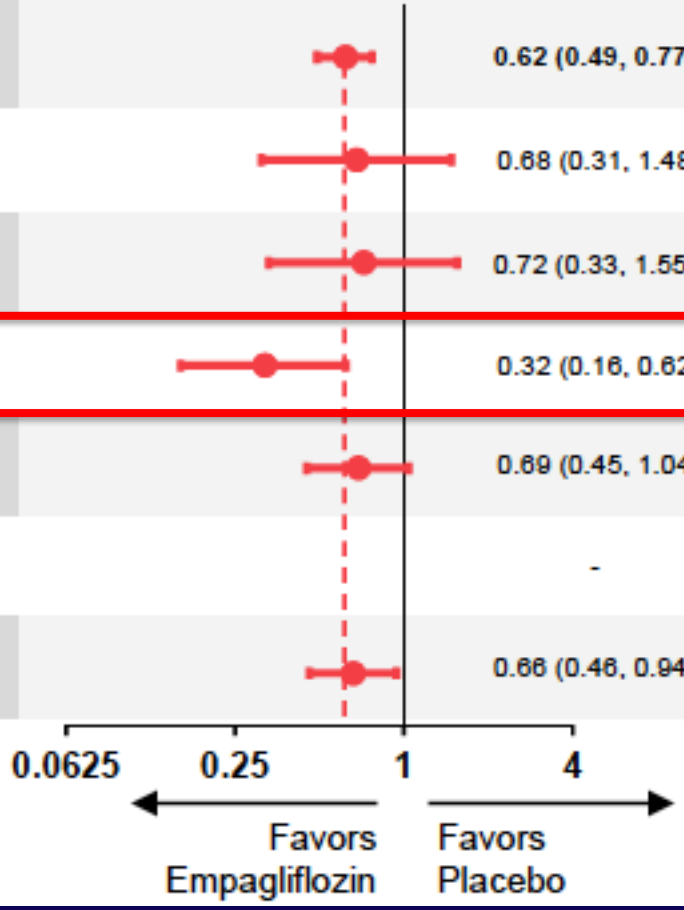


Cumulative incidence function. CV, cardiovascular; HR, hazard ratio; CI, confidence interval.

European Heart Journal doi:10.1093/eurheartj/ehv728

Modes of Cardiovascular Death

	Empagliflozin		Placebo			
	Patients with Events	Rate/ 100 PY	Patients with Events	Rate/ 100 PY	HR (95% CI)	*p*-value
All CV Deaths	172/4687 (3.7%)	1.24	137/2333 (5.9%)	2.02	0.62 (0.49, 0.77)	<0.0001
Fatal MI	15/4687 (0.3%)	0.11	11/2333 (0.5%)	0.16	0.68 (0.31, 1.48)	0.3271
Fatal Stroke	16/4687 (0.3%)	0.12	11/2333 (0.5%)	0.16	0.72 (0.33, 1.55)	0.4015
Death due to Heart Failure#	14/4687 (0.3%)	0.10	22/2333 (0.9%)	0.32	0.32 (0.16, 0.62)	0.0008
Sudden death	53/4687 (1.1%)	0.38	38/2333 (1.6%)	0.56	0.69 (0.45, 1.04)	0.0766
Other CV Causes*	3/4687 (0.06%)	-	2/2333 (0.09%)	-	-	-
Presumed CV Death	71/4687 (1.5%)	0.51	53/2333 (2.3%)	0.78	0.66 (0.46, 0.94)	0.0218

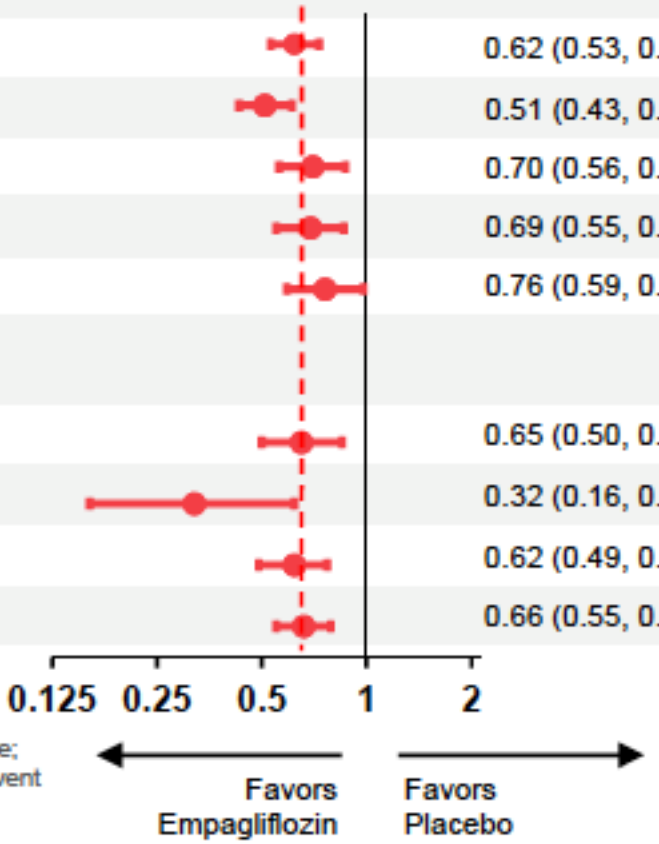


#Death due to worsening of heart failure or cardiogenic shock
*Due to CV causes other than MI, Stroke, HF or sudden death
CV, cardiovascular; MI, myocardial infarction
PY, patient years; CI, confidence interval; HR, hazard ratio

European Heart Journal doi:10.1093/eurheartj/ehv728

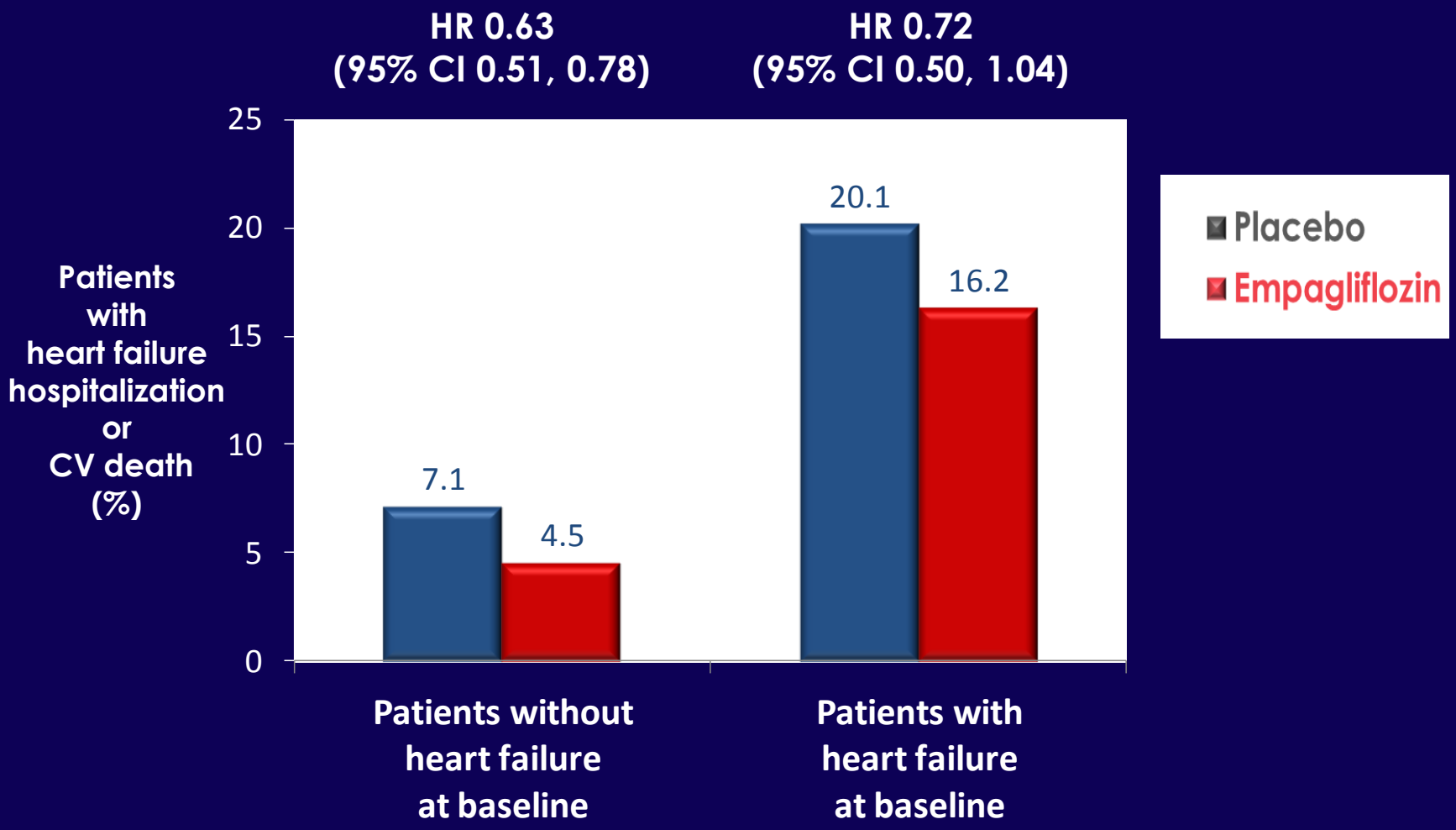
Robustness of Heart Failure Results Across Multiple Outcomes

Time to First:	Empagliflozin Patients with Events	Placebo Patients with Events	HR (95% CI)	*p*-value
Investigator reported:				
Loop Diuretic	340 (8.6)	262 (13.3)	0.62 (0.53, 0.73)	p<0.0001
Edema AE	251 (5.4)	235 (10.1)	0.51 (0.43, 0.61)	p<0.0001
HF* AE	204 (4.4)	143 (6.1)	0.70 (0.56, 0.87)	p=0.001
HF† Serious AE	192 (4.1)	136 (5.8)	0.69 (0.55, 0.86)	p=0.001
HHF	151 (3.2)	98 (4.2)	0.76 (0.59, 0.98)	p=0.035
Central Adjudication Committee confirmed:				
HHF	126 (2.7)	95 (4.1)	0.65 (0.50, 0.85)	p=0.002
Death Due to HF	14 (0.3)	22 (0.9)	0.32 (0.16, 0.62)	p=0.0008
CV Death	172 (3.7)	137 (5.9)	0.62 (0.49, 0.77)	p<0.0001
HHF or CV Death	265 (5.7)	198 (8.5)	0.66 (0.55, 0.79)	p<0.0001



Cox regression analysis, ITT population.
HR, hazard ratio; CI, confidence interval; AE, adverse event; HF, heart failure; HHF, hospitalization for HF; CV, cardiovascular; Death Due to HF, clinical event committee confirmed death due to worsening of HF or cardiogenic shock.
*Based on narrow HF Standard MedRA query (SMQ) of adverse events.

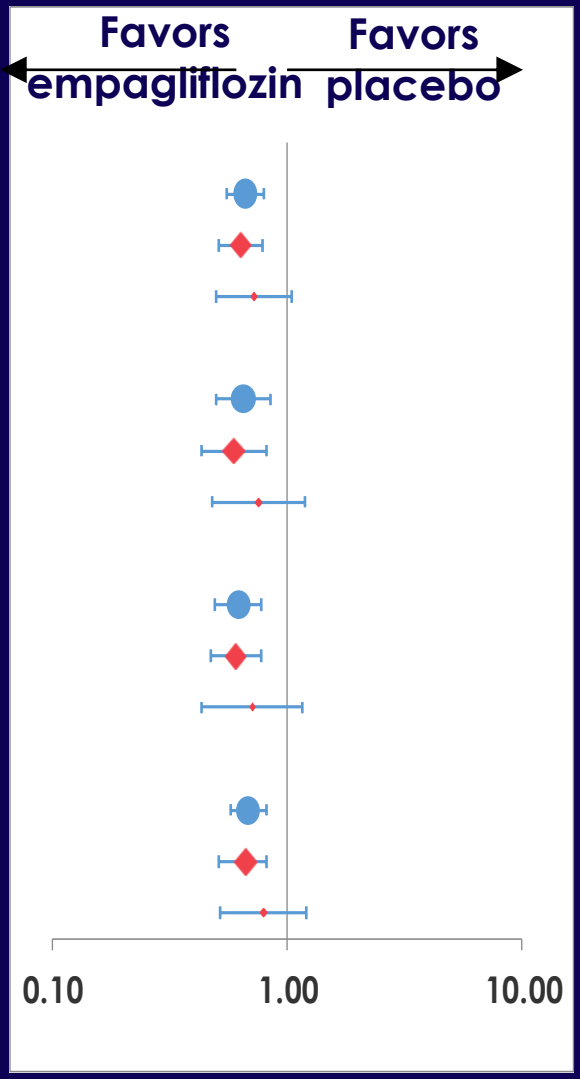
Heart Failure Hospitalization or CV Death in Patients with vs without HF at Baseline



Zinman B et al. N Engl J Med 2015 [Epub ahead of print].

Outcomes in Patients with vs without Heart Failure at Baseline

	Patients with event/analyzed			
	Empagliflozin	Placebo	HR	(95% CI)
HF hospitalization or CV death				
All patients	265/4687	198/2333	**0.66**	(0.55, 0.79)
Baseline HF: **No**	190/4225	149/2089	**0.63**	(0.51, 0.78)
Baseline HF: **Yes**	75/462	49/244	**0.72**	(0.50, 1.04)
Hospitalization for HF				
All patients	126/4687	95/2333	**0.65**	(0.50, 0.85)
Baseline HF: **No**	78/4225	65/2089	**0.59**	(0.43,0.82)
Baseline HF: **Yes**	48/462	30/244	**0.75**	(0.48, 1.19)
CV death				
All patients	172/4687	137/2333	**0.62**	(0.49, 0.77)
Baseline HF: **No**	134/4225	110/2089	**0.60**	(0.47, 0.77)
Baseline HF: **Yes**	38/462	27/244	**0.71**	(0.43, 1.16)
All-cause mortality				
All patients	269/4687	194/2333	**0.68**	(0.57, 0.82)
Baseline HF: **No**	213/4225	159/2089	**0.66**	(0.54, 0.81)
Baseline HF: **Yes**	56/462	35/244	**0.79**	(0.52, 1.20)



Cox regression analysis.

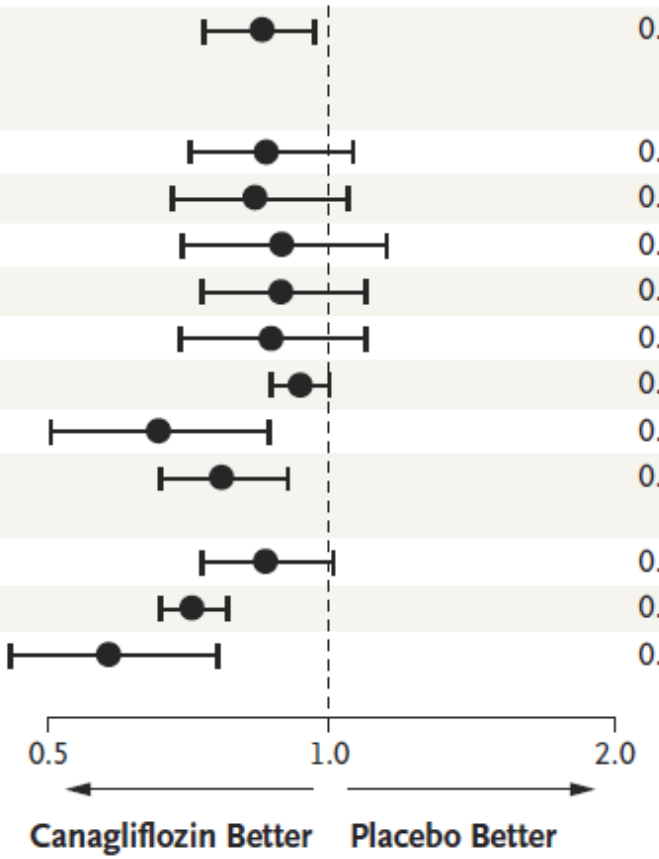
European Heart Journal doi:10.1093/eurheartj/ehv728

SGLT2 Inhibitors

		Empagliflozin[1]	Dapagliflozin[2]	Canagliflozin[3]
	Launch year	2014(EU/US)	2012 (EU) 2014 (US)	2013 (EU/US)
MoA	Molecular class	C-glycoside	C-glycoside	C-glycoside
	Metabolism	Dual renal and hepatic 50:50	Mainly hepatic 97:3	Mainly hepatic, no details reported
Dosing	Administration	Oral	Oral	Oral
	Regimen	Once daily	Once daily	Once daily
	Doses	10 mg and 25 mg	5 mg and 10 mg	100 mg and 300 mg

Canagliflozin and Cardiovascular Events in Type 2 Diabetes: CANVAS

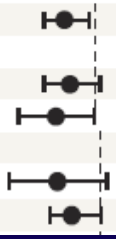
Outcome	Canagliflozin (N=5795)	Placebo (N=4347)	Hazard Ratio (95% CI)
	no. of participants per 1000 patient-yr		
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	26.9	31.5	0.86 (0.75–0.97)
Death from cardiovascular causes	11.6	12.8	0.87 (0.72–1.06)
Nonfatal myocardial infarction	9.7	11.6	0.85 (0.69–1.05)
Nonfatal stroke	7.1	8.4	0.90 (0.71–1.15)
Fatal or nonfatal myocardial infarction	11.2	12.6	0.89 (0.73–1.09)
Fatal or nonfatal stroke	7.9	9.6	0.87 (0.69–1.09)
Hospitalization for any cause	118.7	131.1	0.94 (0.88–1.00)
Hospitalization for heart failure	5.5	8.7	0.67 (0.52–0.87)
Death from cardiovascular causes or hospitalization for heart failure	16.3	20.8	0.78 (0.67–0.91)
Death from any cause	17.3	19.5	0.87 (0.74–1.01)
Progression of albuminuria	89.4	128.7	0.73 (0.67–0.79)
40% reduction in eGFR, renal-replacement therapy, or renal death	5.5	9.0	0.60 (0.47–0.77)



DOI: 10.1056/NEJMoa1611925

Canagliflozin and Cardiovascular Events in Type 2 Diabetes: CANVAS

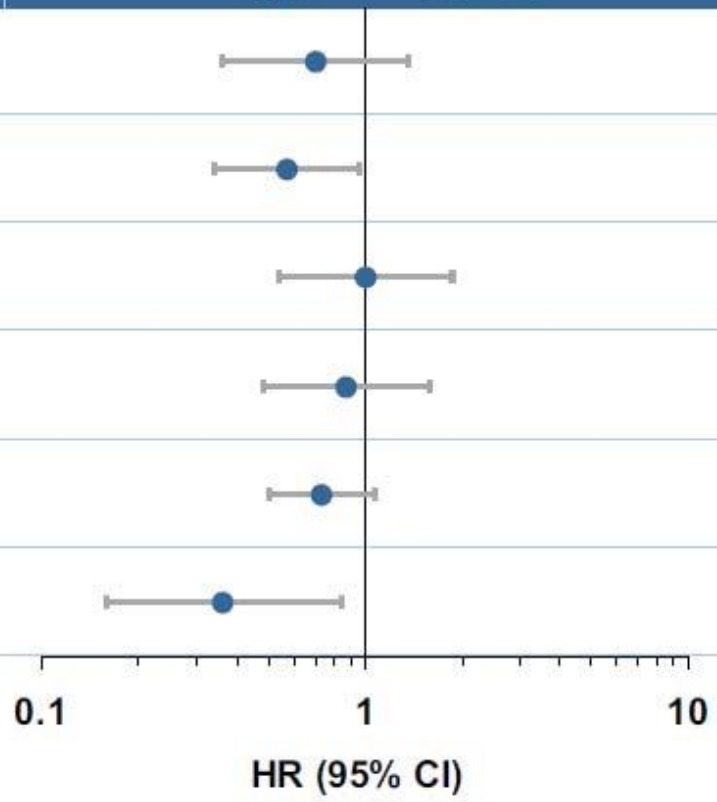
Subgroup	Canagliflozin	Placebo	Hazard Ratio (95% CI)	P Value
	no. of participants per 1000 patient-yr			
All patients	26.9	31.5	0.86 (0.75–0.97)	
Study				0.60
CANVAS	26.9	30.4	0.88 (0.75–1.03)	
CANVAS-R	27.1	33.0	0.82 (0.66–1.01)	
History of heart failure				0.51
Yes	42.2	51.4	0.80 (0.61–1.05)	
No	24.8	28.3	0.87 (0.76–1.01)	



DOI: 10.1056/NEJMoa1611925

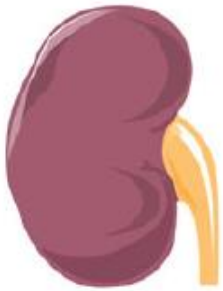
Component Analyses of MACE Events: Dapagliflozin

Event	Pts with Event: Dapa N=5936	Pts with Event: Control N=3403	Hazard Ratio vs. Control (95% CI)
CV Death	20 / 3825	18 / 2200	0.70 (0.36, 1.36)
MI	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 Revasc	58 / 5525	55 / 3153	0.73 (0.50, 1.07)
Hosp. for Heart Failure	10 / 2576	16 / 1780	0.36 (0.16, 0.84)



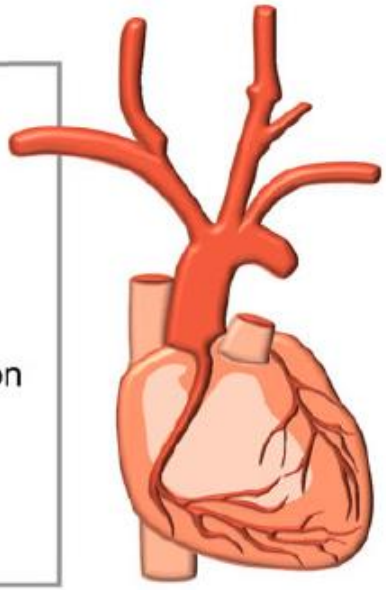
Http://www.Fda.Gov/DOWNLOADS/ADVISORYCOMMITTEES/COMMITTEESMEETINGMATERIALS/DRUGS/ENDOCRINOLOGICANDMETABOLICDRUGSADVISORYCOMMITTEE/UCM262994.Pdf

Potential Mechanisms Involved in the Reduction of Cardiovascular Events



Potential mechanisms

- blood pressure ↓
- body weight ↓
- arterial stiffness ↓
- cardiac function ↑
- cardiac oxygen demand ↓
- lack of sympathetic nerve activation
- sodium depletion
- oxidative stress ↓
- glucagon secretion ↑
- additional unknown mechanisms



SGLT2 inhibition (Empagliflozin)

Reduction of

- **CV death**
- **overall mortality**
- **HF hospitalization**

EMPA-REG OUTCOME

CV Outcome Trials with SGLT2 Inhibitors

Table I Cardiovascular outcome trials with sodium glucose cotransporter-2-inhibitors

Trial	EMPA-REG OUTCOME	CANVAS	DECLARE-TIMI 58	VERTIS
Clinicaltrials.gov	NCT01131676	NCT01032629	NCT01730534	NCT01986881
Intervention	Empagliflozin vs. Placebo (2:1)	Canagliflozin vs. Placebo (2:1)	Dapagliflozin vs. Placebo (1:1)	Ertugliflozin vs. Placebo (2:1)
Primary outcome measure	CV death, non-fatal MI, non-fatal stroke	CV death, non-fatal MI, non-fatal stroke	CV death, non-fatal MI, non-fatal ischaemic stroke	CV death, non-fatal MI, non-fatal stroke
Patient number	7020	4417	17 276	3900
Patients	T2D; established CV disease	T2D; high CV risk	T2D; high CV risk	T2D; established CV disease
Follow-up (estimated)	3 years	6–7 years (estimated)	4–5 years (estimated)	5–7 years (estimated)
Reporting (estimated)	2015	2017 (estimated)	2019 (estimated)	2020 (estimated)

EMPA-REG OUTCOME, (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; CANVAS, CANagliflozin cardioVascular Assessment Study; DECLARE-TIMI 58, Dapagliflozin Effect on CardiovascuLAR Events-TIMI 58. VERTIS: Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Assess Cardiovascular Outcomes Following Treatment With Ertugliflozin in Subjects With Type 2 Diabetes Mellitus and Established Vascular Disease.

T2D, type 2 diabetes mellitus; CV, cardiovascular.

Diabetes Medications, HF Outcomes, and Patterns of Care

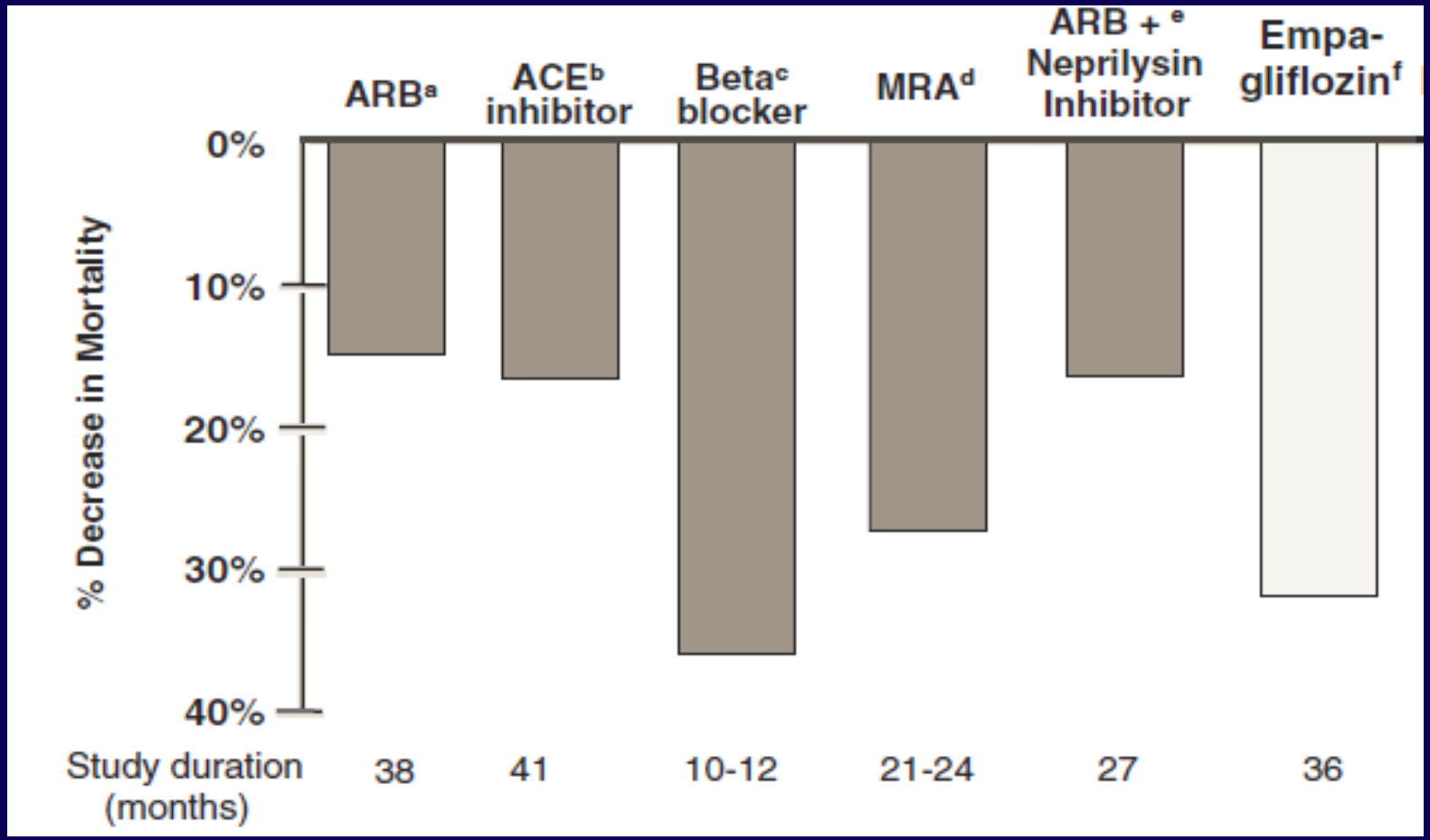
- Antihyperglycemic therapies/strategies influence risk for heart failure
  - Increased risk:
    - Intensification of glucose control
    - Thiazolidinediones
    - Saxagliptin and alogliptin
  - Neutral risk:
    - Glargine insulin; sitagliptin; lixisenatide; liraglutide, semaglutide
  - Decreased risk:
    - Empagliflozin; perhaps metformin
- Effects on HF risk of selected therapies appear independent of glycemic effects
    - Empagliflozin (and potentially other SGLT2i's)

Antihyperglycemic Medication Use Patterns In HF

Variable	Overall
Therapy	
Metformin	17.0
Sulfonylurea	32.4
Meglitinide	3.7
DPP-4 inhibitor	5.1
Thiazolidinedione	6.6
Insulin	39.5
GLP-1 agonist	0.4
α-Glucosidase inhibitor	0.5
Amylin analog	0.1

Circ Heart Fail. 2016;9:e002638

Comparison of Mortality Reduction in HF Trials with EMPA-REG Trial in Patients with Diabetes



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2016 ESC Guidelines for the Diagnosis and Treatment of Acute & Chronic HF

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

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Conclusions: Diabetes and HF

- The two diseases entities are highly co-prevalent
- Diabetes contributes to disease progression in HF and is associated with a worse prognosis
- Standard HF therapies (ARNI, ACEI, or ARB, BB, MRA, ICD/CRT) should be instituted in eligible HFrEF patients with diabetes
- More needs to be done to prevent HF in patients with diabetes

Conclusions: Diabetes and HF

- Until 2015, no known diabetes therapy demonstrated in RTCs to improve CV outcomes in general or for HF
- Most diabetes medications worsened outcomes in HF patients or at best were neutral
- EMPA-REG Outcome and CANVAS trial data
  - New option to reduce CV death and HF in patients with diabetes with and without HF
  - Compelling data
- Pharmacological glycemic management is an essential component of HF therapy
- It is critical for cardiologists and HF specialists to play an active role in this management as choice of therapy is key determinate of outcomes, including survival

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