ACC Emerging Strategies for Heart Failure Roundtable

Prevention of AHA Stage C Heart Failure

Diabetes and heart failure: Do we have an answer?

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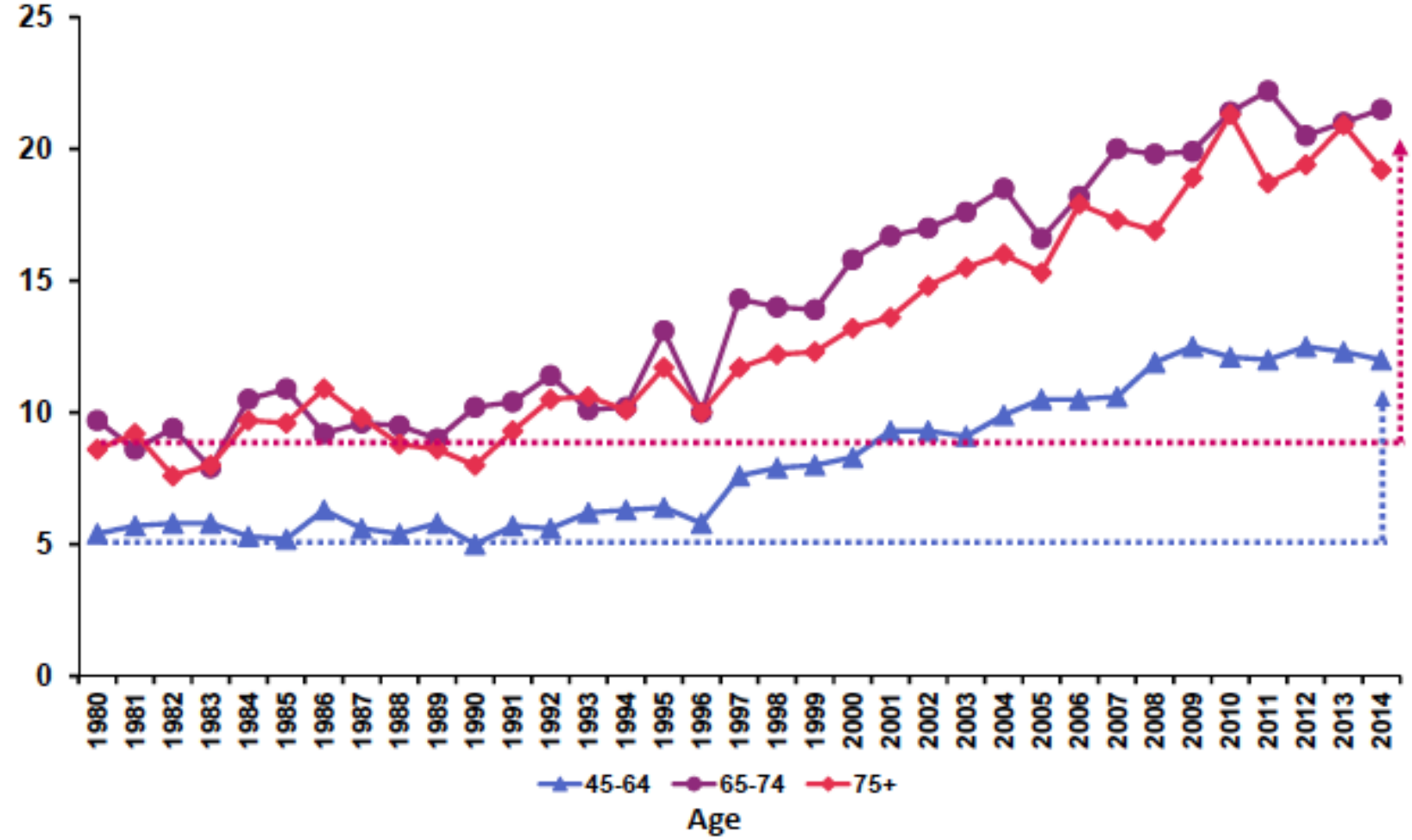
Increasing US Prevalence of Diabetes



Based on data from the National Health Interview Survey. CDC Diabetes Public Health Resource Web Site.

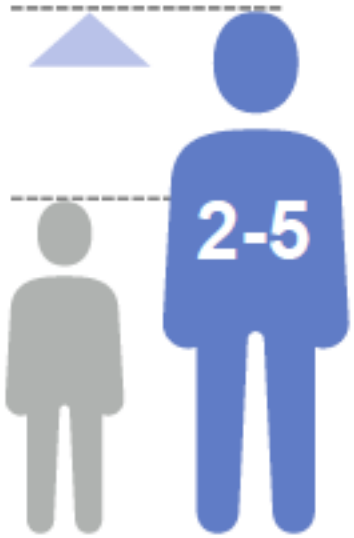
People with diabetes have a 70% higher risk of cardiovascular mortality[1]

Cardiovascular Death: Number 1 Cause of Death in Diabetes

1 in 2 die of heart disease

1. IDF Diabetes Atlas http://www.idf.org/diabetesatlas
2. At least 68% of people >65 years with diabetes die of heart disease; http://www.heart.org/HEARTORG/Conditions/Diabetes/WhyDiabetesMatters/Cardiovascular-Disease-Diabetes_UCM_313085_Article.jsp/ Accessed 16 Sept 2015
3. Centers for Disease Control and Prevention 2011 – National Diabetes fact sheet.
4. http://www.who.int/features/factfiles/diabetes/facts/en/index5.html - accessed 16 sept 2015

Type 2 Diabetes and Heart Failure



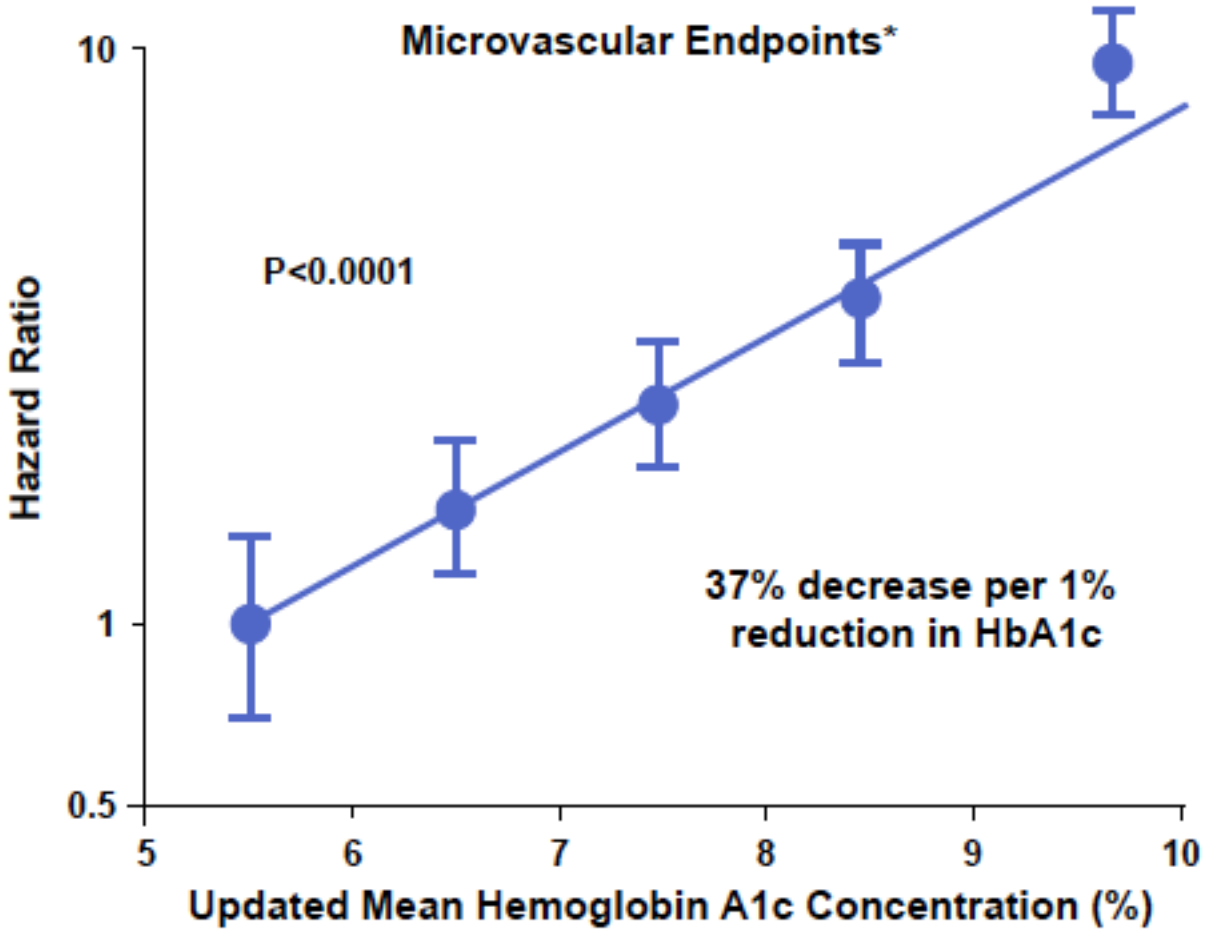
2 to 5 times higher risk of developing heart failure[1]

In diabetes + heart failure 60–80% greater probability of cardiovascular death and all-cause mortality[2,3]

*Synthesised based on data from two clinical studies

1. Kannel WB et al. Am J Cardiol 1974;34:29
2. Cubbon RM et al. Diab Vasc Dis Res 2013;10:330
3. MacDonald MR et al. Eur Heart J 2008;29:1377

HbA1c Lowering: Reduced Microvascular Complications in UKPDS



*Retinopathy requiring photocoagulation, vitreous hemorrhage, and fatal or non-fatal renal failure
HbA1c, hemoglobin A1c
Stratton, Irene M et al. Association of glycemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *British Medical Journal*. 2000; 321:409

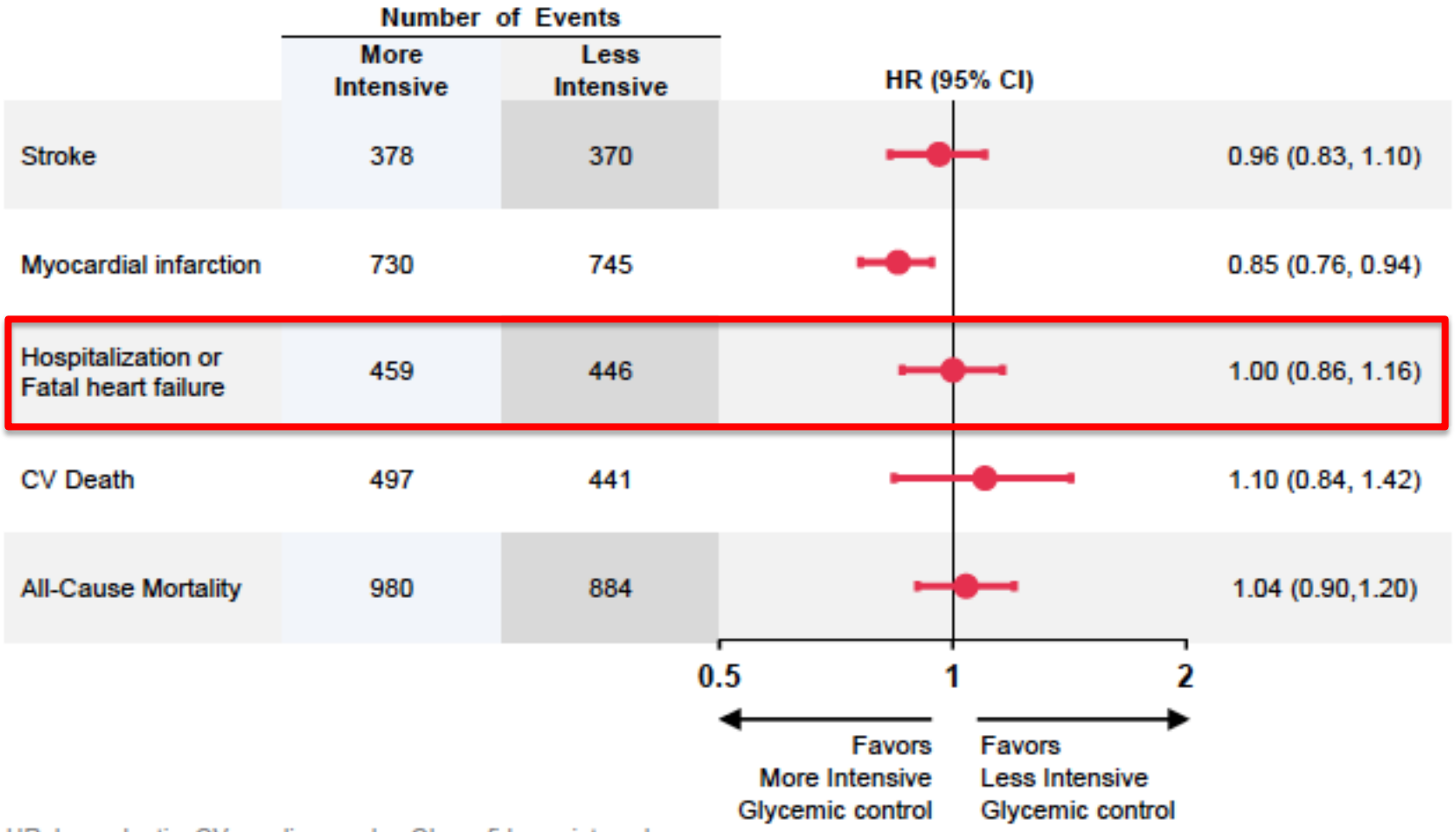
Summary of Glycemic Control Trials

Intensive vs. Less-Intensive Glycemic Control[1]

	Cardiovascular Events	Mortality
ACCORD	↔	↑
ADVANCE	↔	↔
UKPDS	↔	↔
VADT	↔	↔

Effects of glycemic control on cardiovascular events and mortality remain unclear

Impact of Glycemic Control



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

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

8. Cardiovascular Disease and Risk Management

Diabetes Care 2015;38(Suppl. 1):S49–S57 | DOI: 10.2337/dc15-S011

Table 8.1—Recommendations for statin treatment in people with diabetes

Age	Risk factors	Recommended statin dose*	Monitoring with lipid panel
<40 years	None	None	Annually or as needed to monitor for adherence
	CVD risk factor(s)**	Moderate or high	
	Overt CVD***	High	
40–75 years	None	Moderate	As needed to monitor adherence
	CVD risk factors	High	
	Overt CVD	High	
>75 years	None	Moderate	As needed to monitor adherence
	CVD risk factors	Moderate or high	
	Overt CVD	High	

*In addition to lifestyle therapy.
**CVD risk factors include LDL cholesterol ≥100 mg/dL (2.6 mmol/L), high blood pressure, smoking, and overweight and obesity.
***Overt CVD includes those with previous cardiovascular events or acute coronary syndromes.

HYPERTENSION/BLOOD PRESSURE CONTROL

Recommendations

Screening and Diagnosis

- Blood pressure should be measured at every routine visit. Patients found to have elevated blood pressure should have blood pressure confirmed on a separate day. B

Goals

- People with diabetes and hypertension should be treated to a systolic blood pressure (SBP) goal of <140 mmHg. A
- Lower systolic targets, such as <130 mmHg, may be appropriate for certain individuals, such as younger patients, if they can be achieved without undue treatment burden. C
- Individuals with diabetes should be treated to a diastolic blood pressure (DBP) <90 mmHg. A
- Lower diastolic targets, such as <80 mmHg, may be appropriate for certain individuals, such as younger patients, if they can be achieved without undue treatment burden. B

Treatment

- Patients with blood pressure >120/80 mmHg should be advised on lifestyle changes to reduce blood pressure. B
- Patients with confirmed office-based blood pressure higher than 140/90 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely subsequent titration of pharmacological therapy to achieve blood pressure goals. A
- Lifestyle therapy for elevated blood pressure consists of weight loss, if overweight or obese; a Dietary Approaches to Stop Hypertension (DASH)-style dietary pattern including reducing sodium and increasing potassium intake; moderation of alcohol intake; and increased physical activity. B
- Pharmacological therapy for patients with diabetes and hypertension should comprise a regimen that includes either an ACE inhibitor or an angiotensin receptor blocker (ARB). B If one class is not tolerated, the other should be substituted. C
- Multiple-drug therapy (including a thiazide diuretic and ACE inhibitor/ARB, at maximal doses) is generally required to achieve blood pressure targets. B

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8. Cardiovascular Disease and Risk Management

American Diabetes Association

Diabetes Care 2015;38(Suppl. 1):S49–S57 | DOI: 10.2337/dc15-S011

CORONARY HEART DISEASE

Recommendations

Screening

- In asymptomatic patients, routine screening for coronary artery disease (CAD) is not recommended because it does not improve outcomes as long as CVD risk factors are treated. **A**

Treatment

- In patients with known CVD, use aspirin and statin therapy (if not contraindicated) **A** and consider ACE inhibitor therapy **C** to reduce the risk of cardiovascular events.
- In patients with a prior MI, β-blockers should be continued for at least 2 years after the event. **B**
- In patients with symptomatic heart failure, thiazolidinedione treatment should not be used. **A**
- In patients with stable CHF, metformin may be used if renal function is normal but should be avoided in unstable or hospitalized patients with CHF. **B**

ANTIPLATELET AGENTS

Recommendations

- Consider aspirin therapy (75–162 mg/day) as a primary prevention strategy in those with type 1 or type 2 diabetes at increased cardiovascular risk (10-year risk >10%). This includes most men aged >50 years or women aged >60 years who have at least one additional major risk factor (family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria). **C**
- Aspirin should not be recommended for CVD prevention for adults with diabetes at low CVD risk (10-year CVD risk <5%, such as in men aged <50 years and women aged <60 years with no major additional CVD risk factors), since the potential adverse effects from bleeding likely offset the potential benefits. **C**
- In patients in these age-groups with multiple other risk factors (e.g., 10-year risk 5–10%), clinical judgment is required. **E**
- Use aspirin therapy (75–162 mg/day) as a secondary prevention strategy in those with diabetes and a history of CVD. **A**
- For patients with CVD and documented aspirin allergy, clopidogrel (75 mg/day) should be used. **B**
- Dual antiplatelet therapy is reasonable for up to a year after an acute coronary syndrome. **B**

2013 ACCF/AHA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

7.1. Stage A: Recommendations

Class I

1. Hypertension and lipid disorders should be controlled in accordance with contemporary guidelines to lower the risk of HF.[27,94,311–314] *(Level of Evidence: A)*
2. Other conditions that may lead to or contribute to HF, such as obesity, diabetes mellitus, tobacco use, and known cardiotoxic agents, should be controlled or avoided. *(Level of Evidence: C)*

Table 12. Recommendations for Treatment of Stage B HF

Recommendations	COR	LOE	References
In patients with a history of MI and reduced EF, ACE inhibitors or ARBs should be used to prevent HF	I	A	314, 342–345
In patients with MI and reduced EF, evidence-based beta blockers should be used to prevent HF	I	B	346–348
In patients with MI, statins should be used to prevent HF	I	A	104, 349–354
Blood pressure should be controlled to prevent symptomatic HF	I	A	27, 94, 311–313
ACE inhibitors should be used in all patients with a reduced EF to prevent HF	I	A	65, 344
Beta blockers should be used in all patients with a reduced EF to prevent HF	I	C	N/A
An ICD is reasonable in patients with asymptomatic ischemic cardiomyopathy who are at least 40 d post-MI, have an LVEF ≤30%, and on GDMT	IIa	B	355
Nondihydropyridine calcium channel blockers may be harmful in patients with low LVEF	III: Harm	C	N/A

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators*

Table 1. Primary and Secondary Outcomes.*

Outcome	Liraglutide (N=4668)	Incidence Rate	Placebo (N=4672)	Incidence Rate	Hazard Ratio (95% CI)	P Value
	no. of patients (%)	*no. of events/ 100 patient-yr*	*no. of patients (%)*	*no. of events/ 100 patient-yr*		
Primary composite outcome†	608 (13.0)	3.4	694 (14.9)	3.9	0.87 (0.78–0.97)	0.01
Expanded composite outcome‡	948 (20.3)	5.3	1062 (22.7)	6.0	0.88 (0.81–0.96)	0.005
Death from any cause	381 (8.2)	2.1	447 (9.6)	2.5	0.85 (0.74–0.97)	0.02
Death from cardiovascular causes	219 (4.7)	1.2	278 (6.0)	1.6	0.78 (0.66–0.93)	0.007
Death from noncardiovascular causes	162 (3.5)	0.9	169 (3.6)	1.0	0.95 (0.77–1.18)	0.66
Myocardial infarction§	292 (6.3)	1.6	339 (7.3)	1.9	0.86 (0.73–1.00)	0.046
Fatal§	17 (0.4)	0.1	28 (0.6)	0.2	0.60 (0.33–1.10)	0.10
Nonfatal	281 (6.0)	1.6	317 (6.8)	1.8	0.88 (0.75–1.03)	0.11
Silent§	62 (1.3)	0.3	76 (1.6)	0.4	0.86 (0.61–1.20)	0.37
Stroke§	173 (3.7)	1.0	199 (4.3)	1.1	0.86 (0.71–1.06)	0.16
Fatal§	16 (0.3)	0.1	25 (0.5)	0.1	0.64 (0.34–1.19)	0.16
Nonfatal	159 (3.4)	0.9	177 (3.8)	1.0	0.89 (0.72–1.11)	0.30
Transient ischemic attack§	48 (1.0)	0.3	60 (1.3)	0.3	0.79 (0.54–1.16)	0.23
Coronary revascularization	405 (8.7)	2.3	441 (9.4)	2.5	0.91 (0.80–1.04)	0.18
Hospitalization for unstable angina pectoris	122 (2.6)	0.7	124 (2.7)	0.7	0.98 (0.76–1.26)	0.87
Hospitalization for heart failure	218 (4.7)	1.2	248 (5.3)	1.4	0.87 (0.73–1.05)	0.14
Microvascular event	355 (7.6)	2.0	416 (8.9)	2.3	0.84 (0.73–0.97)	0.02
Retinopathy	106 (2.3)	0.6	92 (2.0)	0.5	1.15 (0.87–1.52)	0.33
Nephropathy	268 (5.7)	1.5	337 (7.2)	1.9	0.78 (0.67–0.92)	0.003

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

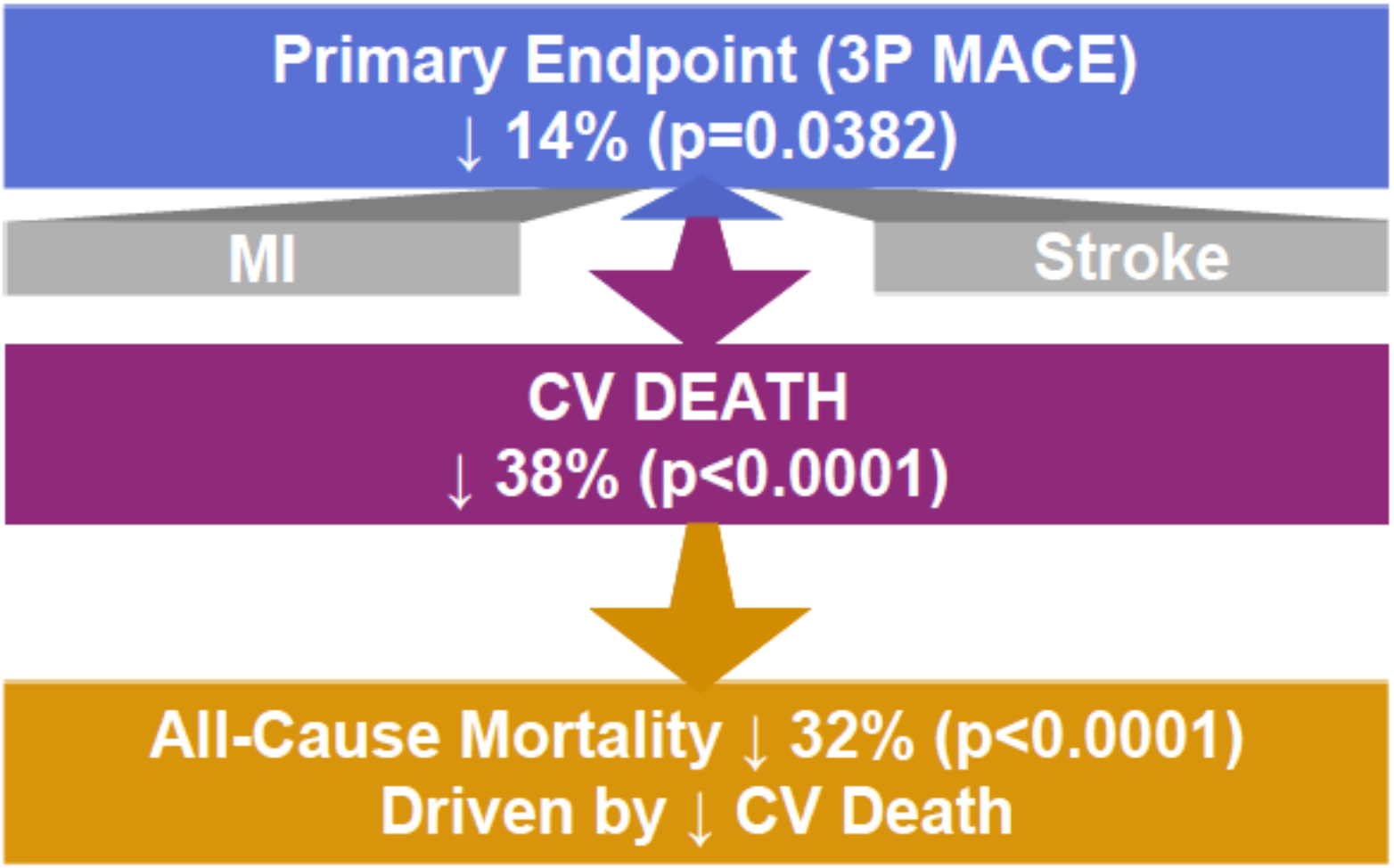
Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME® trial

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

Population with Established Cardiovascular Disease

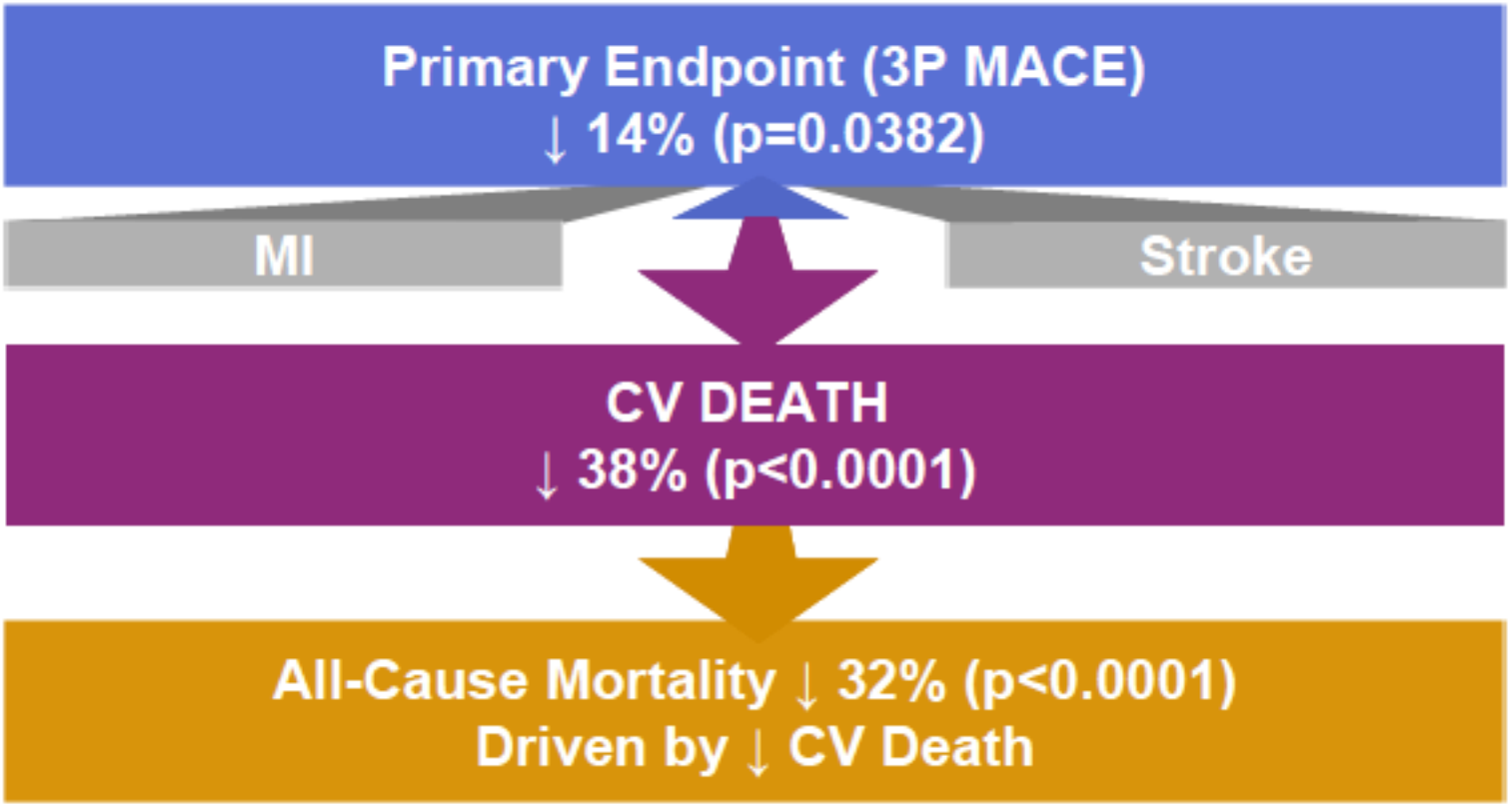
	Placebo N=2333 %	Empagliflozin 10 mg N=2345 %	Empagliflozin 25 mg N=2342 %
Cardiovascular History			
Coronary artery disease	75.6	76.0	75.3
Myocardial infarction	46.4	47.2	46.2
Coronary artery bypass graft	24.1	25.3	24.8
Stroke	23.7	22.8	23.4
Cardiac failure	10.5	10.2	9.5

EMPA-REG OUTCOME Trial: Key Results



MACE, major adverse cardiovascular events; MI, myocardial infarction; CV, cardiovascular
Zinman et al. *N Engl J Med.* 2015

EMPA-REG OUTCOME Trial: Key Results

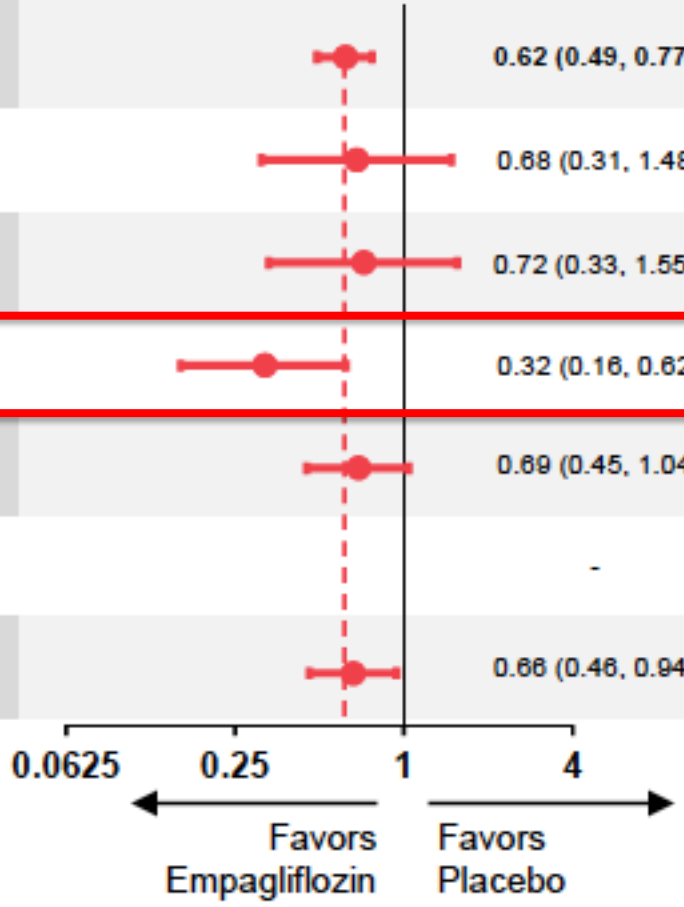


Heart Failure

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

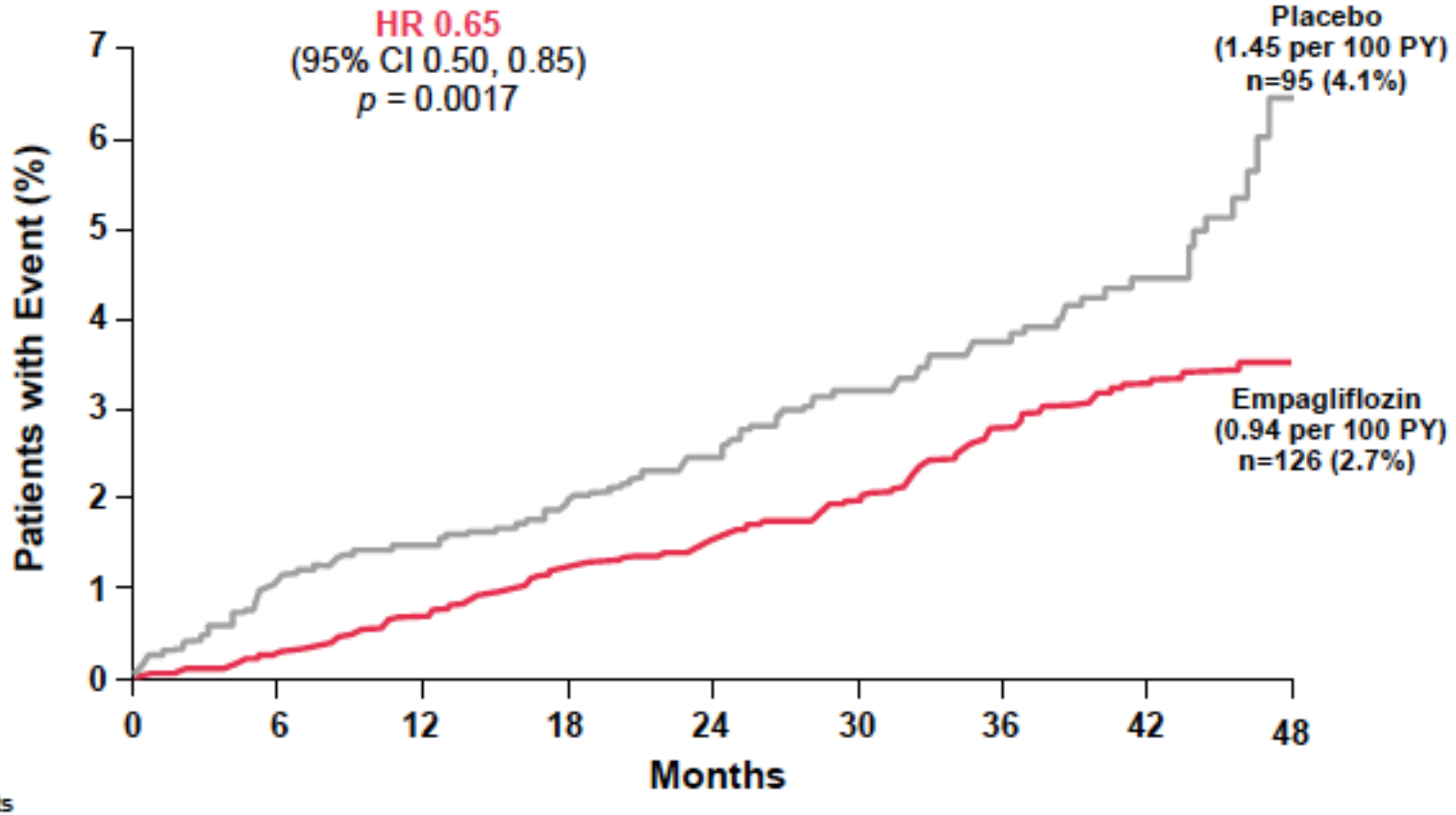
Modes of Cardiovascular Death

	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



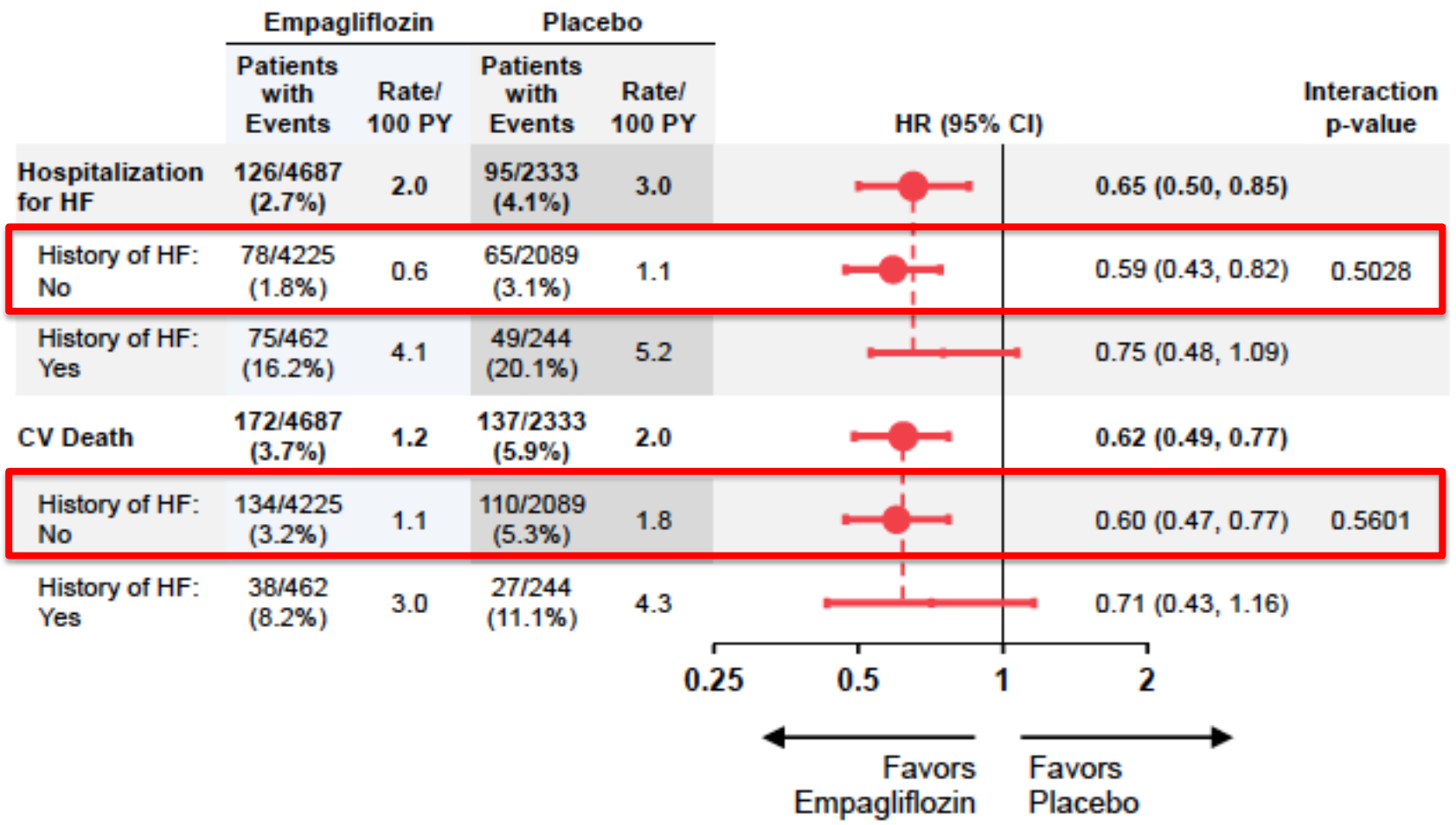
#Death due to worsening of heart failure or cardiogenic shock
*Due to CV causes other than MI, Stroke, HF or sudden death
CV, cardiovascular; MI, myocardial infarction
PY, patient years; CI, confidence interval; HR, hazard ratio

Hospitalization for Heart Failure



No. of patients									
Empagliflozin	4687	4614	4523	4427	3988	2950	2487	1634	395
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

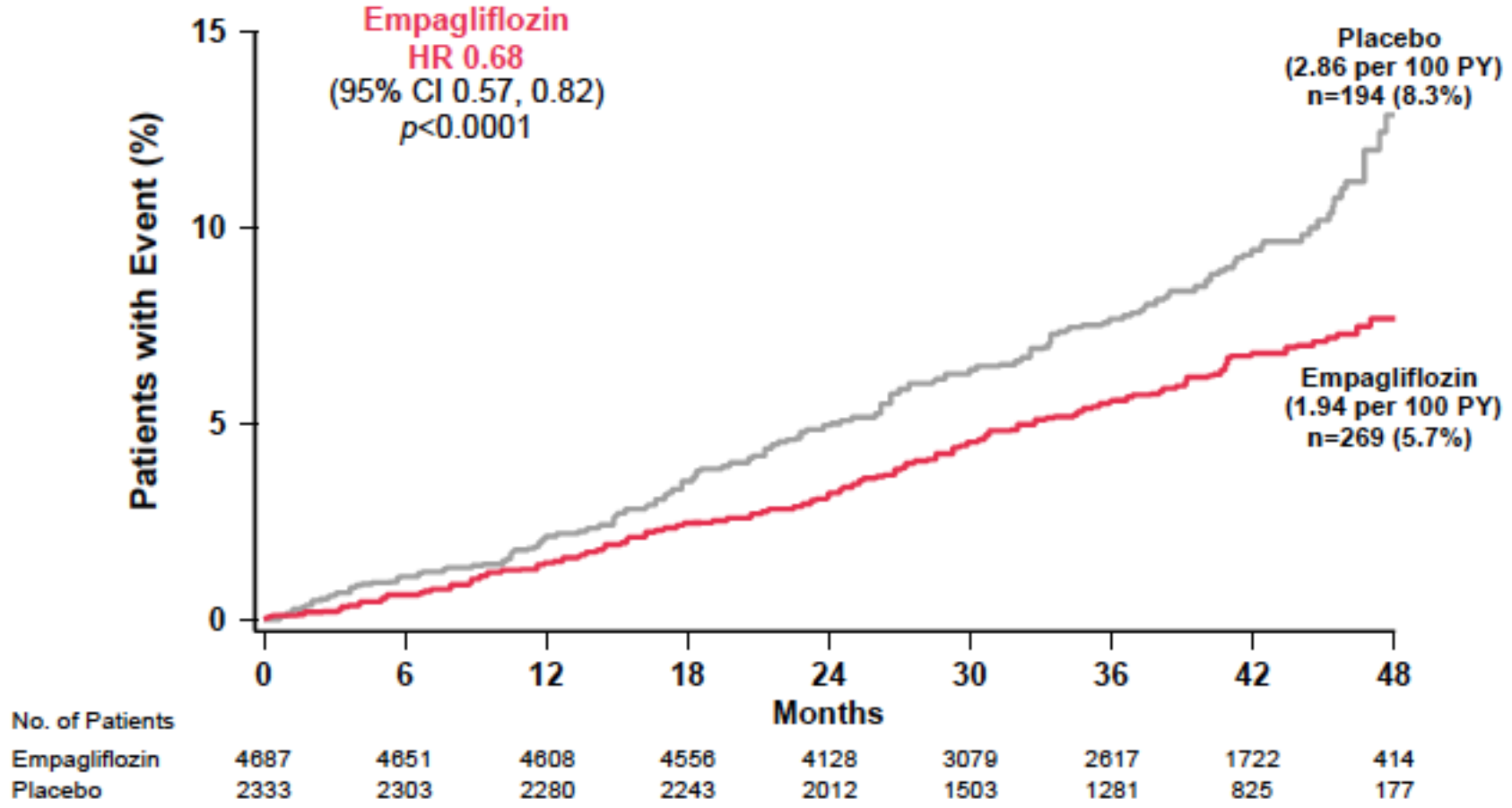
Hospitalization for HF or CV Death: Subgroups by History of Heart Failure



Cox regression analysis (intent-to-treat population)

HF, heart failure; CV, cardiovascular; PY, patient years; HR, hazard ratio; CI, confidence interval.

All-Cause Mortality

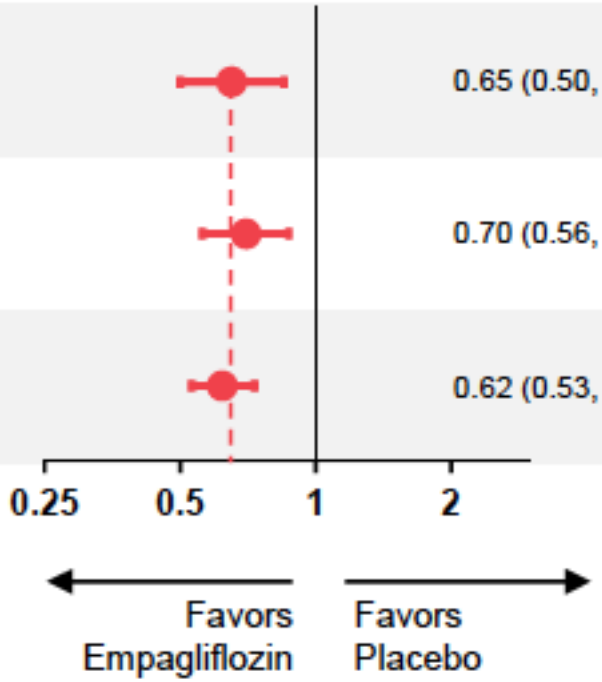


PY, patient years; CI, confidence interval; HR, hazard ratio

HF was a secondary endpoint

Hospitalization for Heart Failure

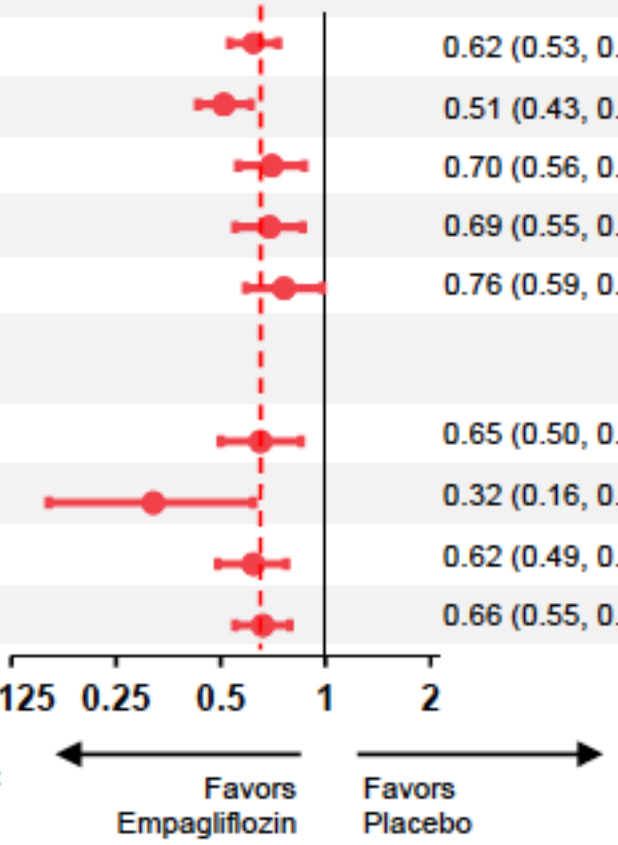
	Empagliflozin		Placebo		HR (95% CI)	*p*-value
	Patients with Events	Rate/ 100 PY	Patients with Events	Rate/ 100 PY		
Adjudicated HHF	126/4687 (2.7%)	0.94	95/2333 (4.1%)	1.45	0.65 (0.50, 0.85)	0.0017
Investigator Reported HF	204/4687 (4.4%)	1.53	143/2333 (6.1%)	2.20	0.70 (0.56, 0.87)	0.0010
Initiation of Loop Diuretics	340/3962 (8.6%)	3.07	262/1969 (13.3%)	4.96	0.62 (0.53, 0.73)	<0.0001



Cox regression analysis (intent-to-treat population)
HHF, hospitalisation for heart failure; HF, heart failure
PY, patient years; CI, confidence interval; HR, hazard ratio

Robustness of Heart Failure Results Across Multiple Outcomes

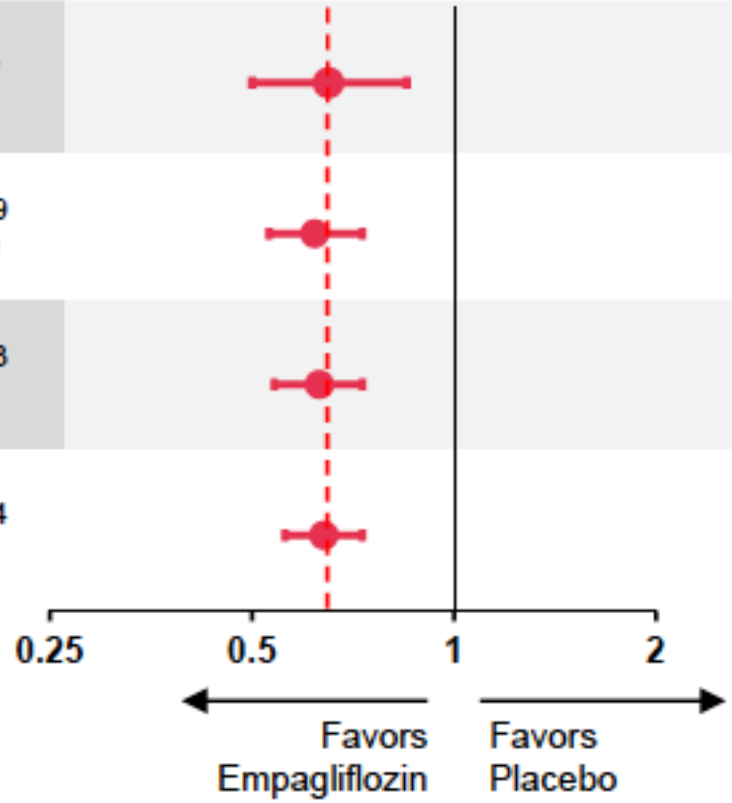
Time to First:	Empagliflozin Patients with Events	Placebo Patients with Events	HR (95% CI)	*p*-value
Investigator reported:				
Loop Diuretic	340 (8.6)	262 (13.3)	0.62 (0.53, 0.73)	p<0.0001
Edema AE	251 (5.4)	235 (10.1)	0.51 (0.43, 0.61)	p<0.0001
HF* AE	204 (4.4)	143 (6.1)	0.70 (0.56, 0.87)	p=0.001
HF† 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.

Time to Introduction of Loop Diuretics: Sensitivity Analyses

	Patients with Event/Analyzed		HR (95% CI)
	Empagliflozin	Placebo	
All Patients: HHF	126/4687 (2.7%)	95/2333 (4.1%)	0.65 (0.50, 0.85)
Introduction of Loop Diuretic	340/3962 (8.6%)	262/1969 (13.3%)	0.62 (0.53, 0.73)
Introduction of Loop Diuretic or HHF	411/4027 (10.2%)	313/2013 (15.5%)	0.63 (0.54, 0.73)
Introduction of Loop Diuretic, HHF, or CV death	532/4066 (13.1%)	399/2044 (19.5%)	0.64 (0.56, 0.73)



Cox regression analysis in the treated set.
HR, hazard ratio. CI, confidence interval; HHF, hospitalization for heart failure.

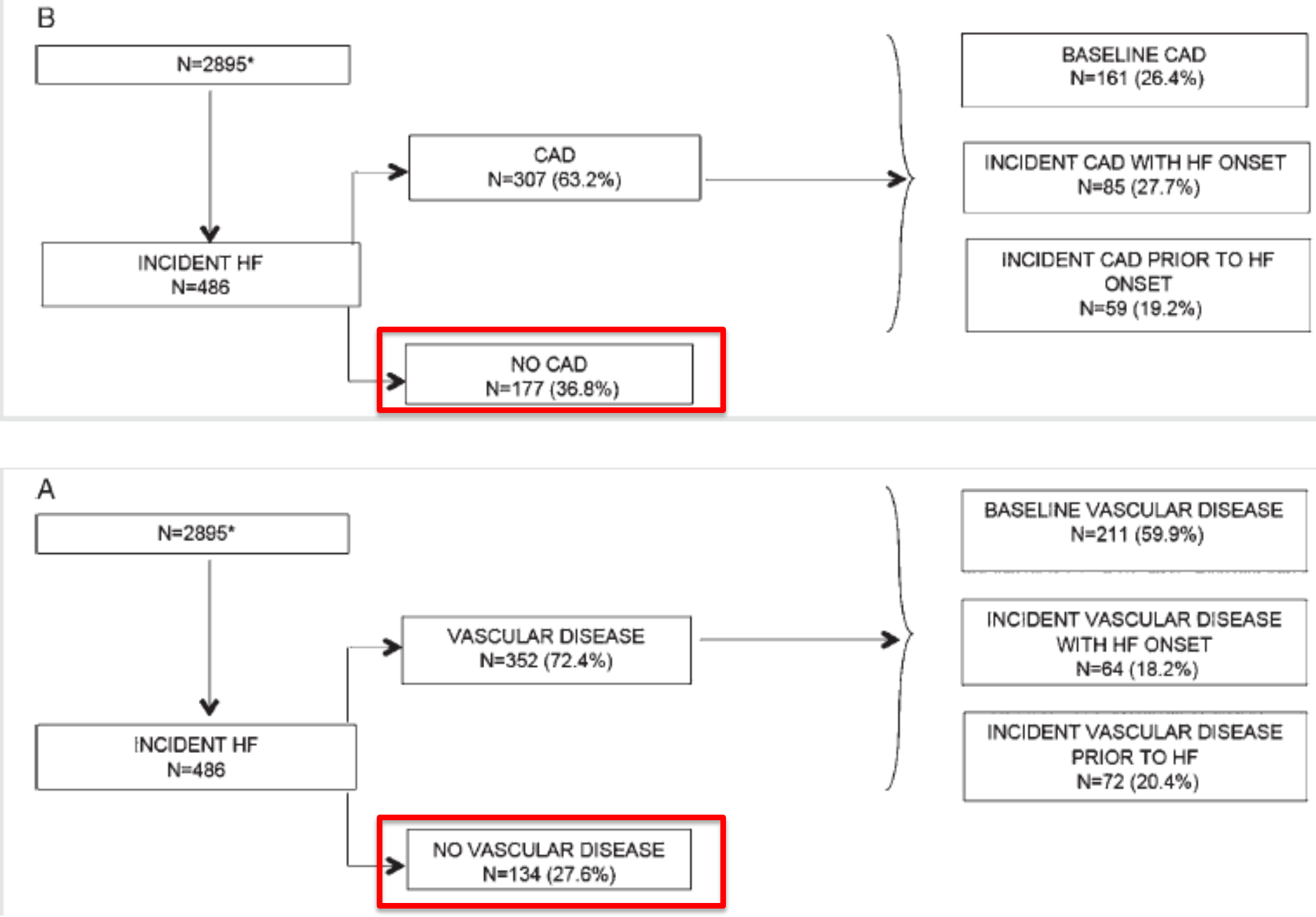
How can HF risk be reduced without reducing coronary events?

EUROPEAN SOCIETY OF CARDIOLOGY®

European Journal of Heart Failure (2014) 16, 526–534
doi:10.1002/ejhf.69

Incident heart failure in relation to vascular disease: Insights from the Health, Aging, and Body Composition Study

Hassan Khan[1], Andreas P. Kalogeropoulos[2], Faiez Zannad[3], Catherine N. Marti[2], Peter W. F. Wilson[2], Vasiliki V. Georgiopoulou[2], Alka M. Kanaya[4], Anne B. Newman[5], Erik Schelbert[6], Tamara B. Harris[7], Stephen Kritchevsky[8], Clyde Yancy[9], Mihai Gheorghiade[10], Gregg C. Fonarow[11], and Javed Butler[2]*, for the Health ABC Study


B
N=2895*
INCIDENT HF
N=486
CAD
N=307 (63.2%)
NO CAD
N=177 (36.8%)
BASELINE CAD
N=161 (26.4%)
INCIDENT CAD WITH HF ONSET
N=85 (27.7%)
INCIDENT CAD PRIOR TO HF ONSET
N=59 (19.2%)
A
N=2895*
INCIDENT HF
N=486
VASCULAR DISEASE
N=352 (72.4%)
NO VASCULAR DISEASE
N=134 (27.6%)
BASELINE VASCULAR DISEASE
N=211 (59.9%)
INCIDENT VASCULAR DISEASE WITH HF ONSET
N=64 (18.2%)
INCIDENT VASCULAR DISEASE PRIOR TO HF
N=72 (20.4%)

Heart Failure Not Phenotyped

- Ejection fraction and NP etc. not known

- Does it matter for prevention?
- Hypertension trials
- Do we know subclinical CAD in CAD prevention trials?

What is the mechanism of action?

Curr Cardiovasc Risk Rep (2015) 9:38
DOI 10.1007/s12170-015-0467-0

HEART FAILURE PREVENTION (W TANG, SECTION EDITOR)

SGLT-2 Inhibitors: Potential Novel Strategy to Prevent Congestive Heart Failure in Diabetes?

Frederik H. Verbrugge[1,2,3] · Roman Vangoitsenhoven[4,5] · Wilfried Mullens[2,6] · Bart Van der Schueren[4,5] · Chantal Mathieu[4,5] · W. H. Wilson Tang[1]

Diuretic
Volume
Sodium
Glucose
Weight loss
Blood pressure

Insulin sensitivity
Oxidative stress
Metabolism
Renal function

Other unknown MOA

Conclusion

- Importance of HF prevention
  - Recognized but understudied
- Despite high risk for developing HF and subsequent adverse outcomes in patients with DM
  - No targeted interventions recommended to reduce HF
- EMPAREG trial data on HF prevention
  - New option
  - Compelling data
  - Next steps?
  - Data from other SGLT2i forthcoming