Heart Failure and Diabetes Mellitus: Update 2019

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Disclosures

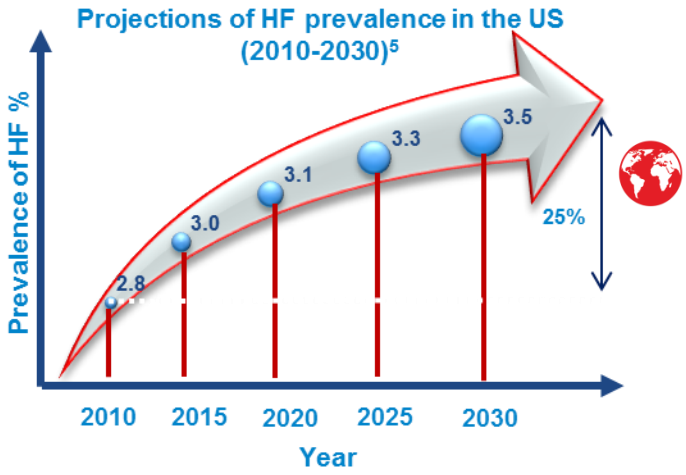
- **Grants: ALARM investigator received research grants by Abbott US and Orion Pharma**
- **Horonaria: received horonaria for advisory boards and lectures from Novartis, Pfizer, Menarini, Servier, MSD, ASTRA, Sanofi,**

  Boerhninger and Roche diagnostics
- **Journals: Associate Editor of EJHF**
- **ESC HF GLs: Member of task force**

HF is common and the prevalence is growing

- 1 in 5 people aged 40 years and over will develop heart failure in their lifetime[1]

- It is the most rapidly growing cardiovascular condition[2]. This is primarily driven by deteriorating lifestyles and ageing populations[3]



- The prevalence of HF is predicted to increase in developed countries because of ageing populations: in the US is estimated to increase by 25% between 2010-2030[4]

1Lloyd-Jones et al. Circulation. 2002 10;106(24):3068-72.; [2]McMurray et al., Eur. Heart J. Suppl. (2002) 4 (Supplement D), D50-D58; [3]Cowie et al., Recommendations of Heart Failure Association of the ESC.2014; [4]Heidenreich et al., Circulation. 2011;123(8):933-44.

Heart failure leads to frequent hospitalizations

HF is one of the most common causes of hospitalization for patients aged **>65 years** in developed countries[216]

Nearly **44%** of all HF patients are readmitted for any cause within **1 year** after discharge[217a]

- **Length of stay** for HF hospitalization ranges between **5–10 days**[218]
- In the USA, **30-day** re-admission rates are **>25%**[219]
- In Europe, **re-admission rates** are **~24%** at 12 weeks[220]

216. Bui et al. Nat Rev Cardiol 2011;8:30–41; 217a. Maggioni et al. Eur J Heart Fail 2013;15:808–17; 218. Ponikowski et al. ESC Heart Fail 2014;1:4-25; 219. Kociol et al. Am Heart J 2013;165:987–94; 220. Cleland et al. Eur Heart J 2003;24:442–63

Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) & reduced ejection fraction (HFrEF)

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%
	3	–	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).

Ponikowski P et al. Eur Heart J. 21 May 2016.
doi:10.1093/eurheartj/ehw128

ACCF/AHA HF stages and NYHA functional classes

ACCF/AHA Stages and NYHA Functional Classifications: Comparison[1]

ACCF/AHA Stages of HF		NYHA Functional Classification	
A	At high risk for HF but without structural heart disease or symptoms of HF.	None	
B	Structural heart disease but without signs or symptoms of HF.	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
C	Structural heart disease with prior or current symptoms of HF.	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
		II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF.
		III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.
		IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.
D	Refractory HF requiring specialized interventions.		

At risk of developing HF[2]

Existing HF[2]

The first 2 stages (A and B) are not HF but help identify patients who are at risk for developing HF because of comorbidities like coronary artery disease, hypertension, or **diabetes mellitus**.[1,2]

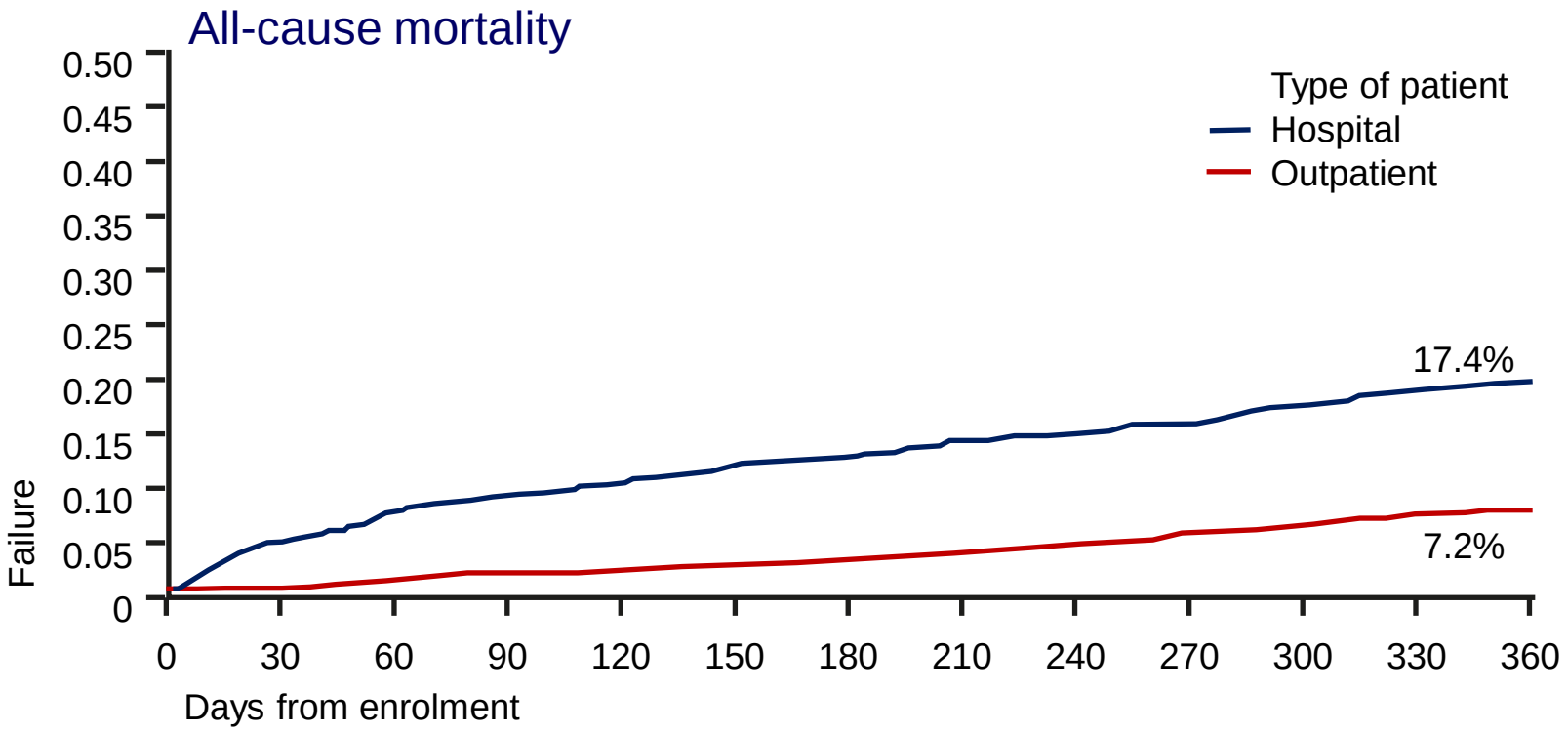
This suggests therapeutic interventions introduced even before the appearance of LV dysfunction or symptoms can reduce the population morbidity and mortality of HF.[2]

1. Yancy CW et al. *J Am Coll Cardiol.* 2013;62:e147-239; 2. Hunt SA et al. *Circulation.* 2009;119:e391-479.

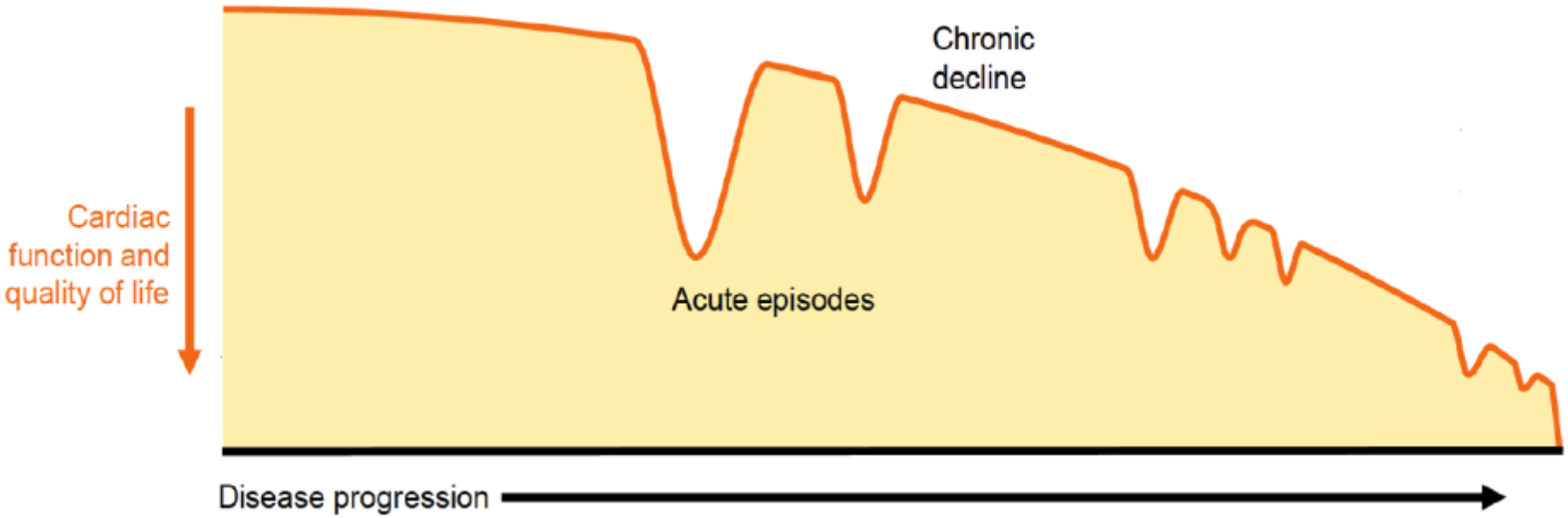
European Journal of Heart Failure (2013) 15, 808–817
doi:10.1093/eurjhf/hft050

EURO*bservational* Research Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot)

Aldo P. Maggioni[1*], Ulf Dahlström[2], Gerasimos Filippatos[3], Ovidiu Chioncel[4], Marisa Crespo Leiro[5], Jaroslaw Drozdz[6], Friedrich Fruhwald[7], Lars Gullestad[8], Damien Logeart[9], Gianna Fabbri[1], Renato Urso[1], Marco Metra[10], John Parissis[11], Hans Persson[12], Piotr Ponikowski[13], Mathias Rauchhaus[14], Adriaan A. Voors[15], Olav Wendelboe Nielsen[16], Faiez Zannad[17], and Luigi Tavazzi[18] on behalf of the Heart Failure Association of the European Society of Cardiology (HFA)[†]



HF is a progressive disease

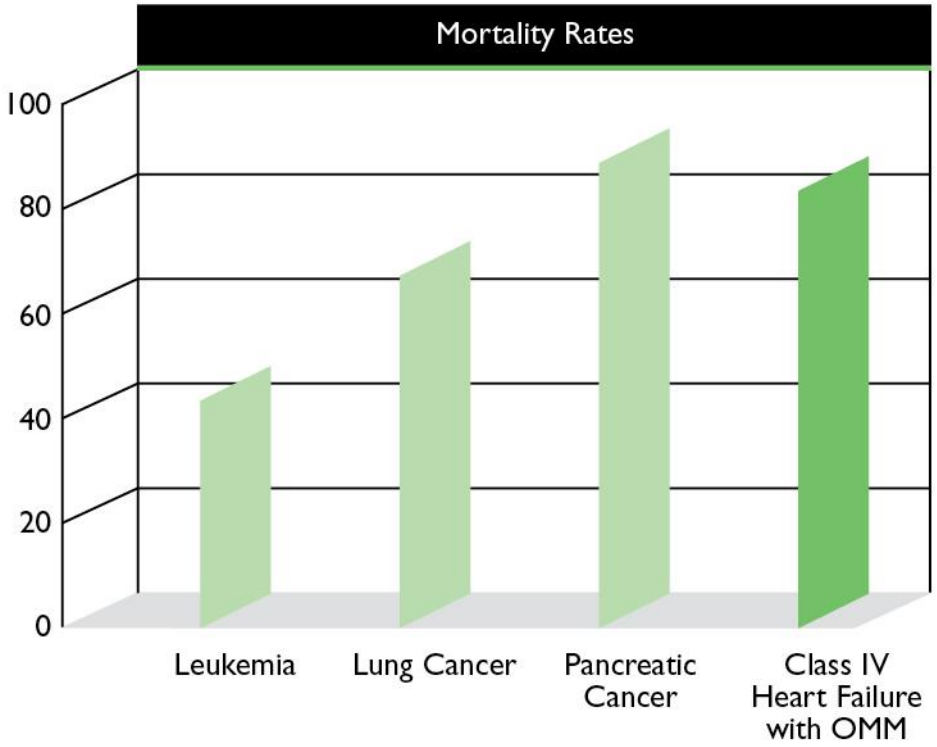


Adapted from Gheorghiade M, et al. Am J Cardiol. 2005;96:11G-17G

Advanced Heart Failure Has A High Mortality Rate Similar To Aggressive Malignancies

Medical therapy alone can be a poor long-term treatment option for many in the more advanced stages of heart failure.

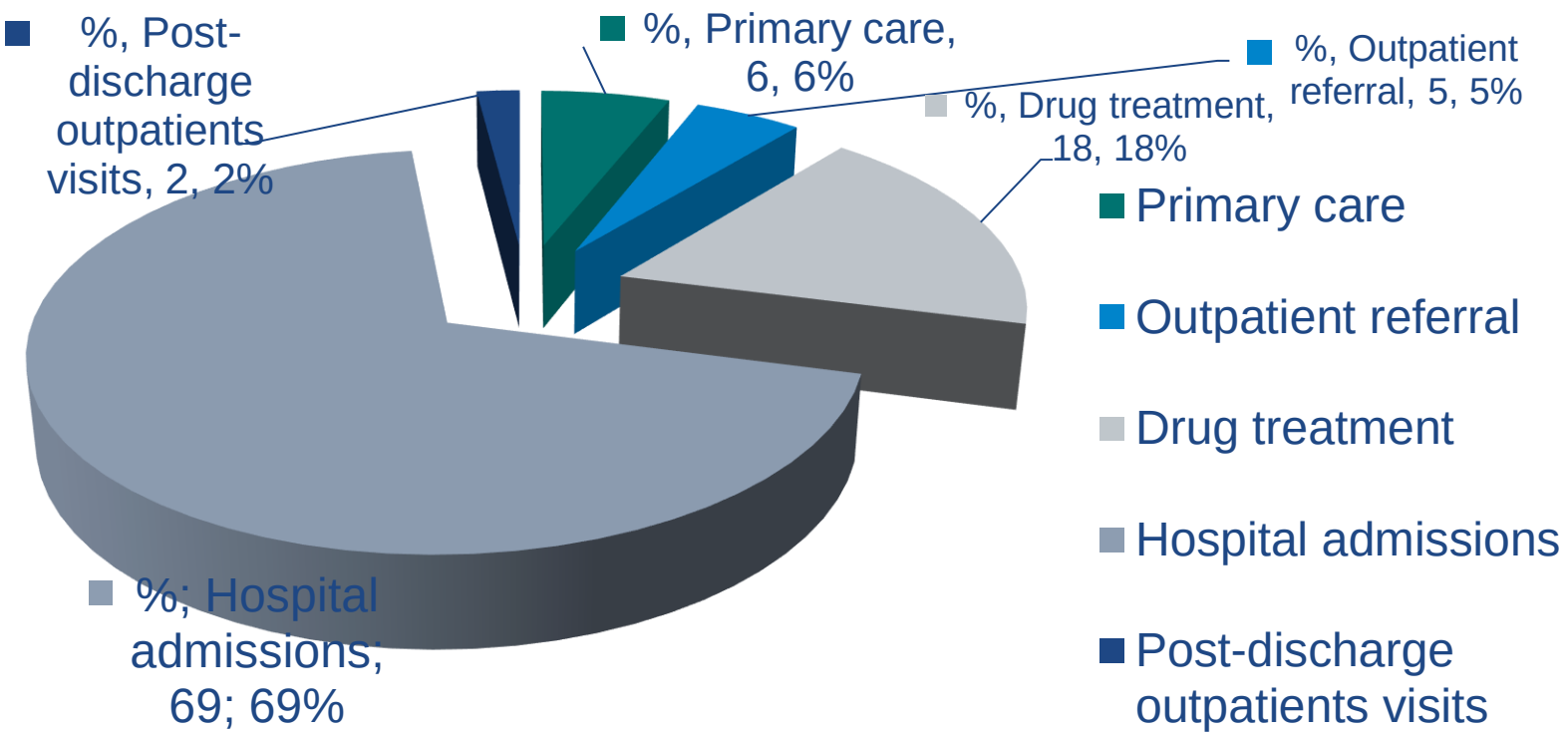
Many publications show the mortality risk associated with NYHA Class IV heart failure is high, with a 1-year mortality between 60 and 94 percent.[1-4]



Class IV heart failure patients treated with medical therapy alone have mortality rates similar to or greater than aggressive forms of cancer.[5]

[1] Rose, Gelijns, Moskowitz, et al. *NEJM*. 345:1435-43, 2001.
[2] Rogers, Butler, Lansman, et al. *J Am Coll Cardiol.* 50:741-47, 2007.
[3] Hershberger, Nauman, Walker, et al. *J Card Fail.* 22:616-24, 2003.
[4] Gorodeski, Chu, Reese, et al. *Circ Heart Fail.* 2:320-24, 2009.
[5] Data on file. Pleasanton, Calif: Thoratec Corp.

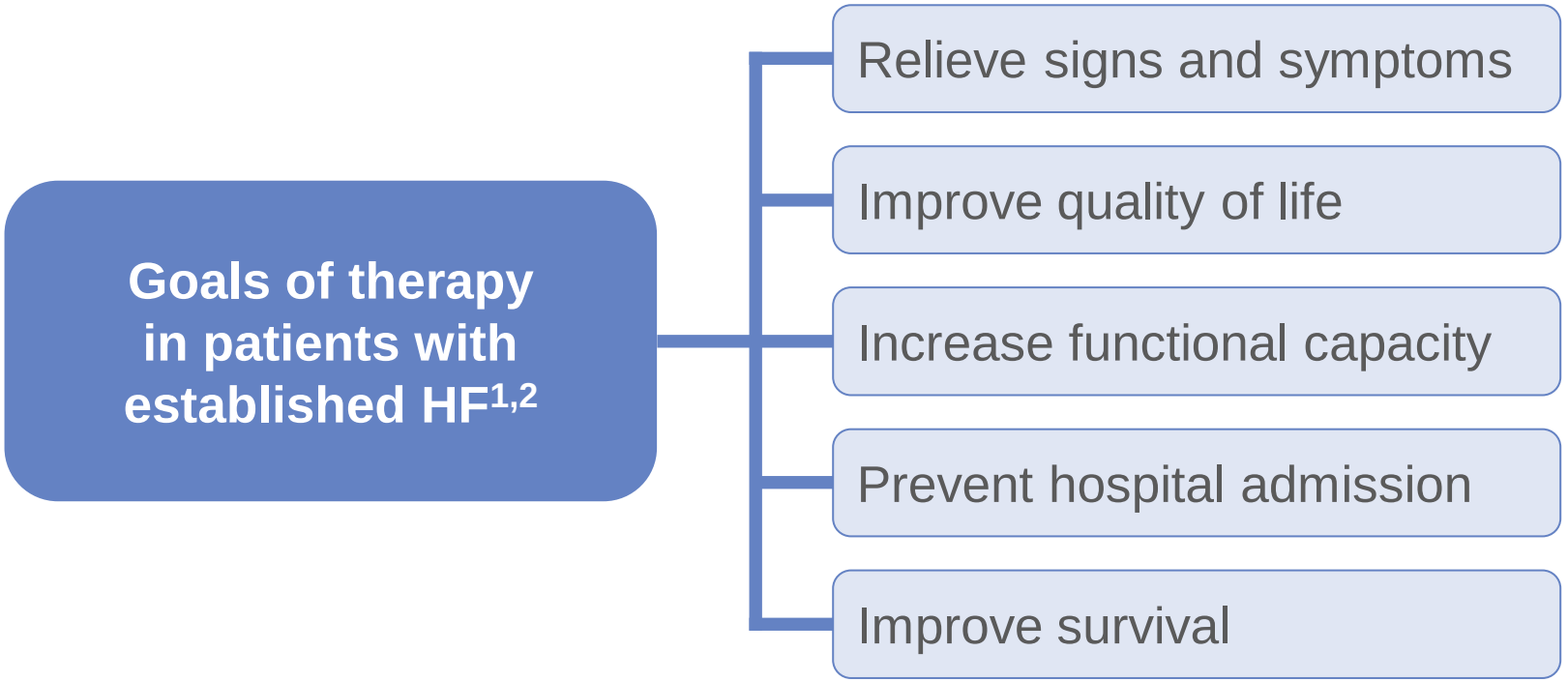
Economic burden of chronic HF



Hospitalization accounts for most CHF-associated costs

Stewart S et al. *Eur J Heart Fail* 2002;4:361–71

Στόχοι της θεραπείας Καρδιακής Ανεπάρκειας

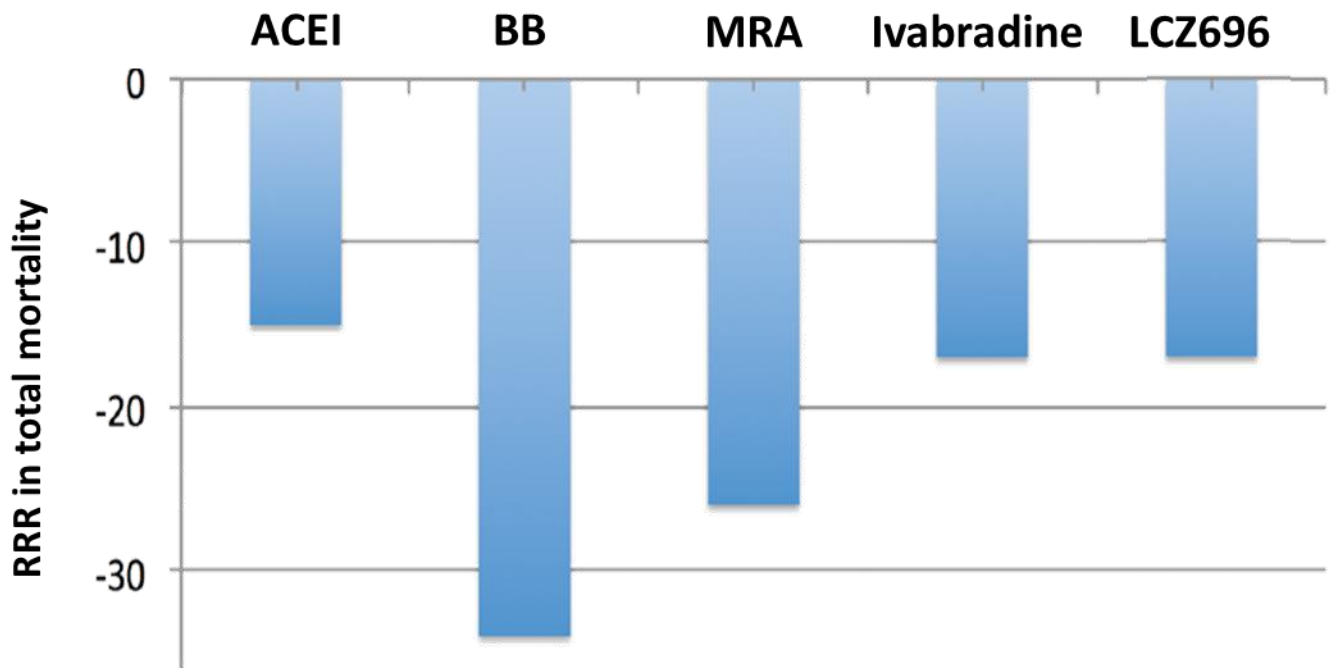


- Drug therapy is the mainstay of treatment but only evidence-based for HF*r*EF[3]
- Reductions in mortality and hospitalisation reflect ability of therapies to slow or prevent progressive worsening[1]

HF, heart failure; HF*r*EF, heart failure with reduced ejection fraction

1. McMurray JJ *et al. Eur Heart J* 2012;33:1787; 2. Yancy CW *et al*. *Circulation* 2013;128:e240; 3. McMurray JJ, Pfeffer MA. *Lancet* 2005;365:1877

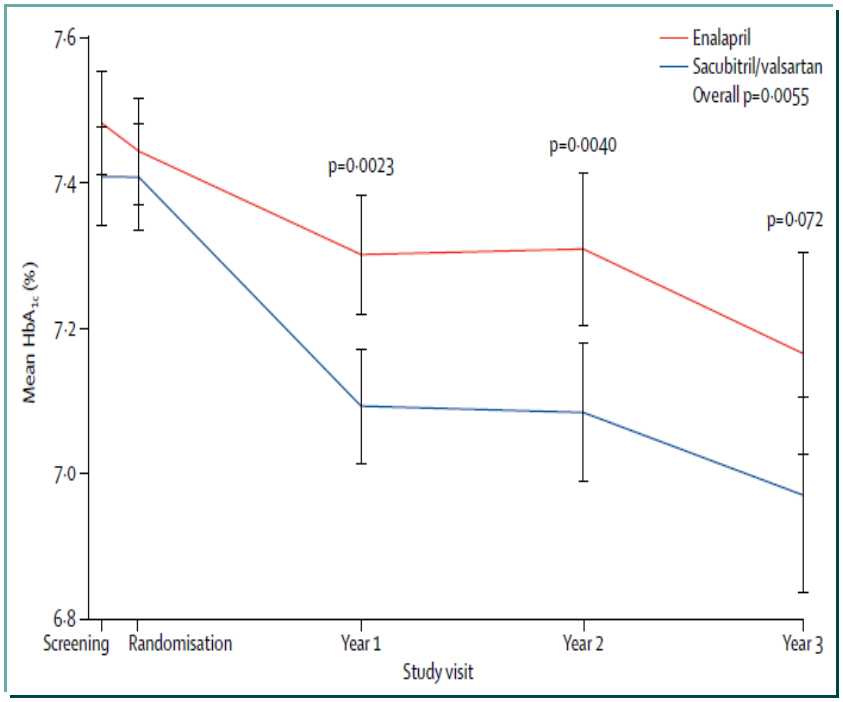
ΟΙ ΒΑΣΙΚΕΣ ΦΑΡΜΑΚΕΥΤΙΚΕΣ ΘΕΡΑΠΕΙΕΣ ΠΟΥ ΒΕΛΤΙΩΝΟΥΝ ΤΗΝ ΠΡΟΓΝΩΣΗ ΤΩΝ ΑΣΘΕΝΩΝ ΜΕ ΚΑ

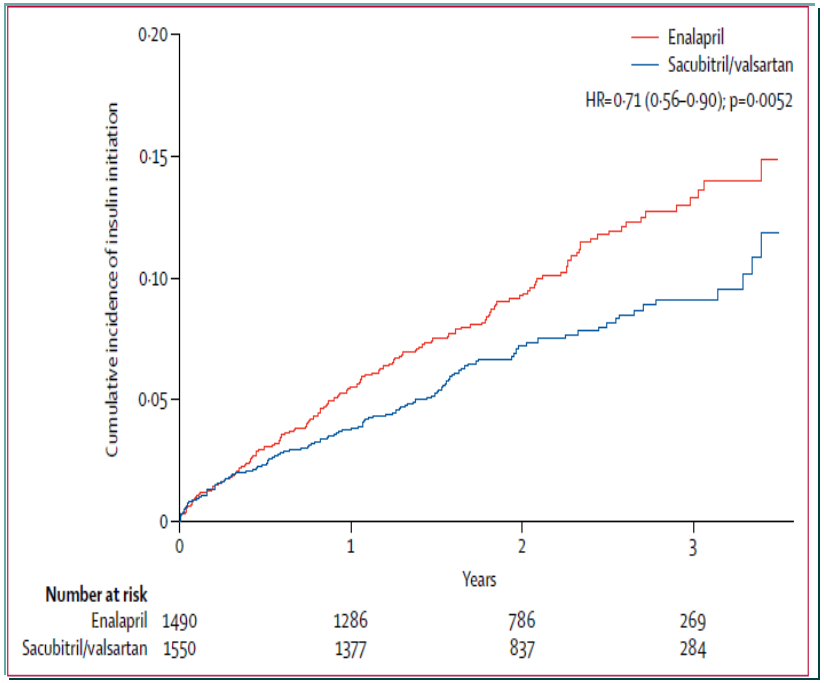


CHF population	Symptomatic HFrEF	Symptomatic HFrEF	Symptomatic HFrEF	Symptomatic HFrEF, SR, HR≥75 bpm	Symptomatic HFrEF with elevated NP levels
Background therapy	vs placebo	ACEI vs placebo	ACEI, BB vs placebo	ACEI, BB, MRA vs placebo	BB, MRA vs enalapril

Ponikowski et al. Eur Heart J. 21 May 2016.

Effect of sacubitril/valsartan versus enalapril on glycaemic control in patients with heart failure and diabetes: a post-hoc analysis from the PARADIGM-HF trial

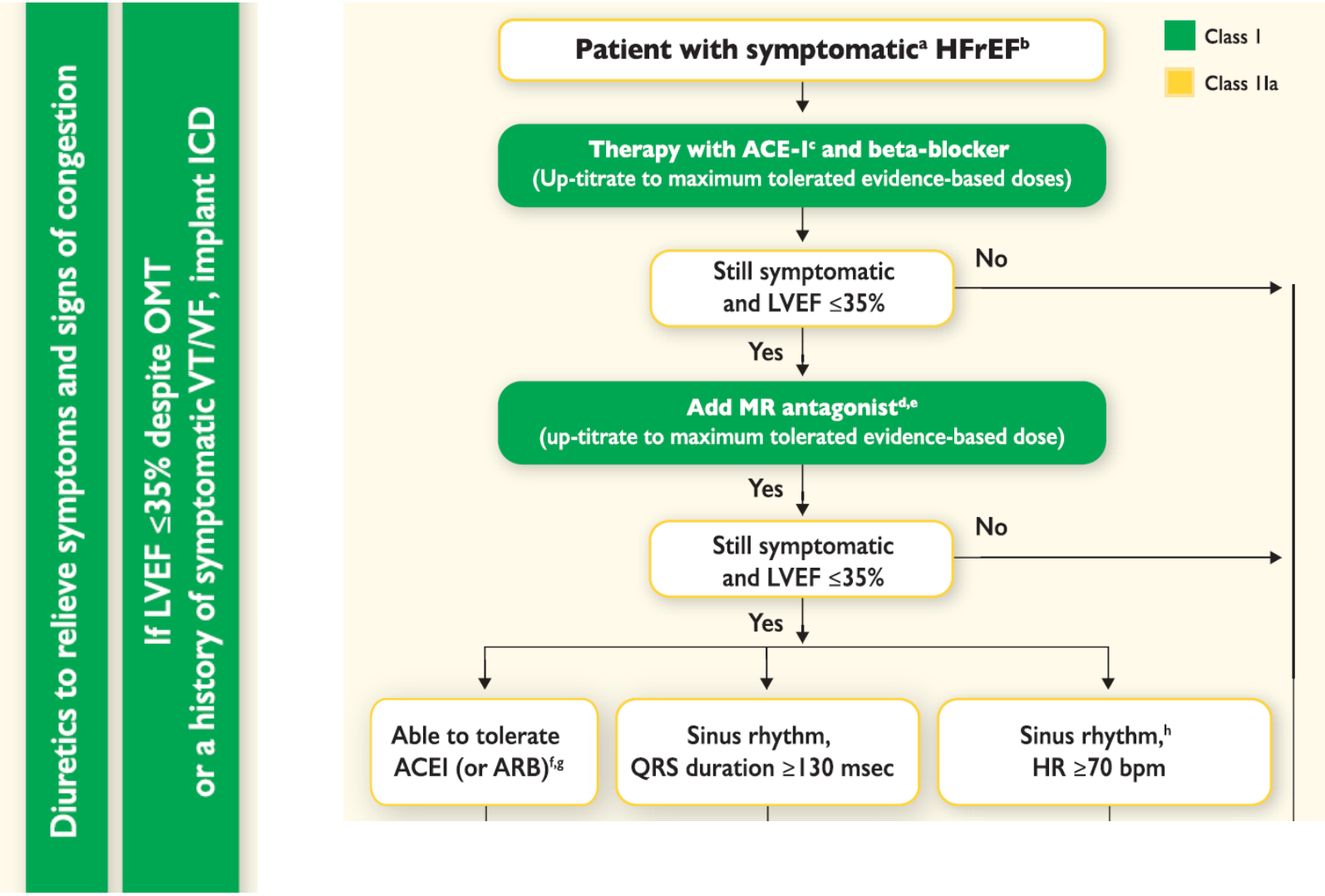




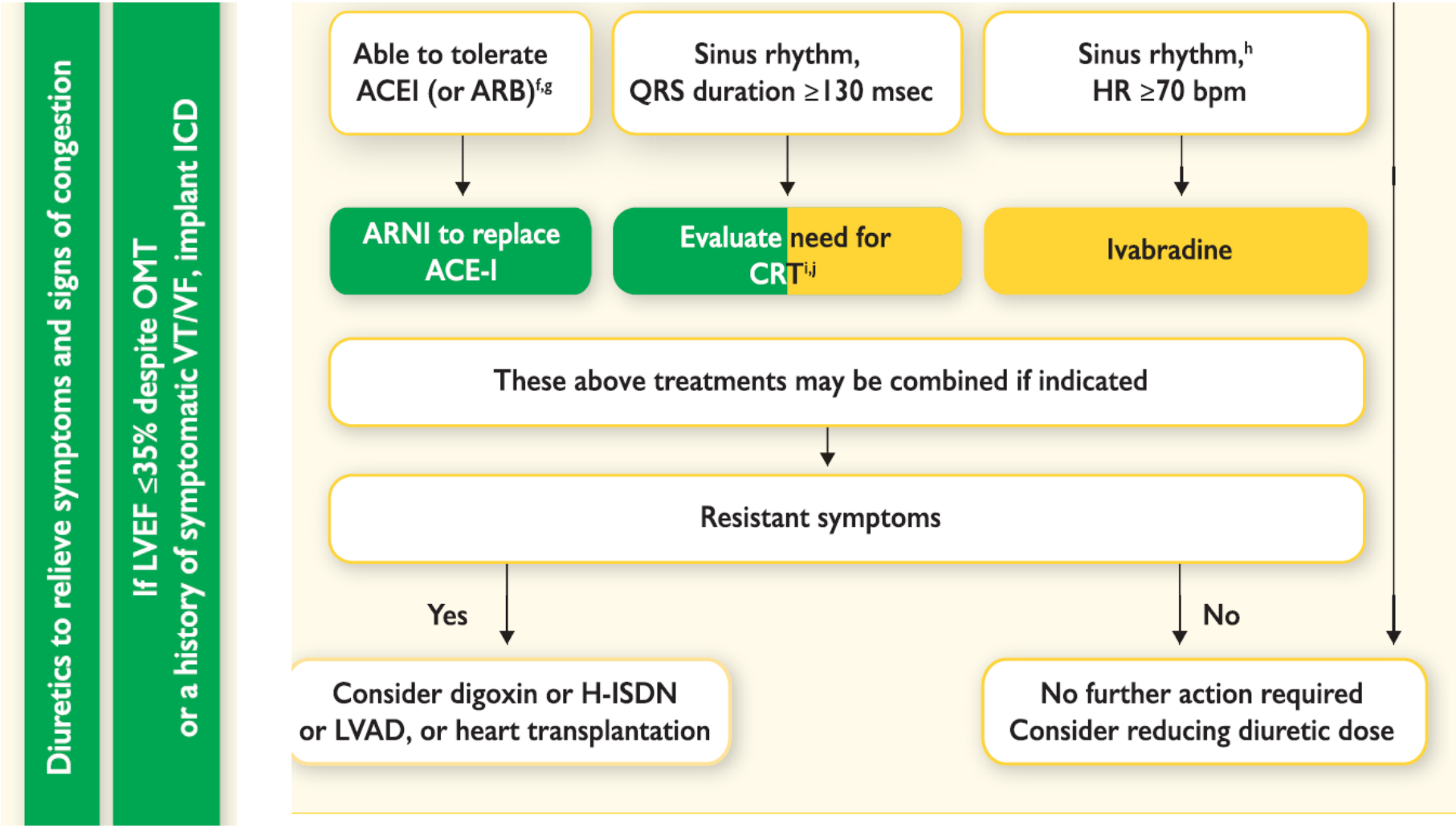
Lancet Diabetes Endocrinol 2017

Published Online
March 18, 2017
http://dx.doi.org/10.1016/
S2213-8587(17)30087-6

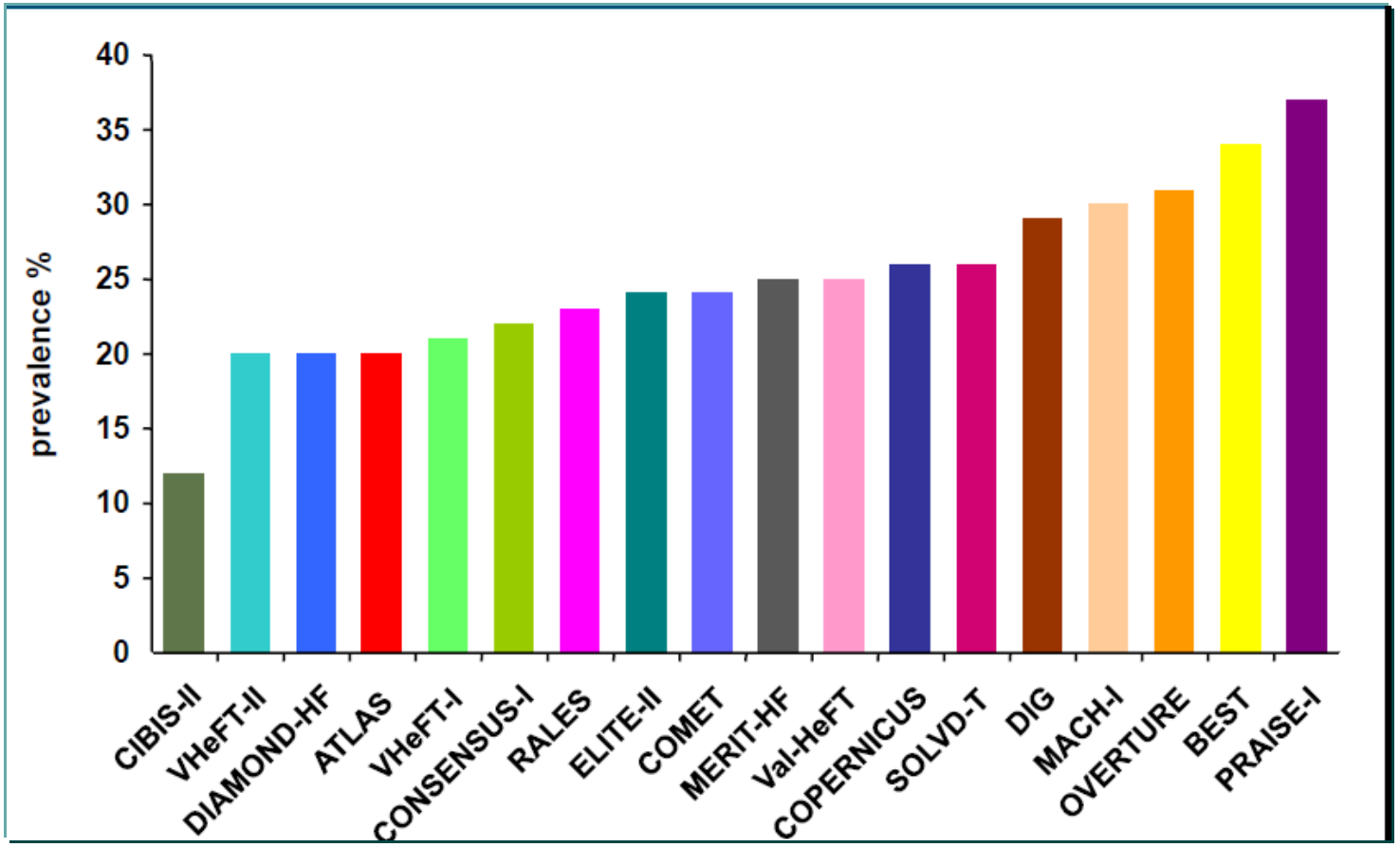
Therapeutic algorithm for a patient with symptomatic HF with reduced ejection fraction.(ESC HF GLs 2016)



Therapeutic algorithm for a patient with symptomatic HF with reduced ejection fraction. (cont..)



Heart failure trials: Prevalence of diabetes



Physicians' adherence to evidence-based pharmacotherapy in systolic heart failure: data from the international QUALIFY survey

Baseline characteristics (3)

	Total N=7092
Diabetes mellitus, %	34.3
Hypertension, %	64.6
Atrial fibrillation, flutter, %	28.7
Peripheral artery disease, %	9.5
Stroke or TIA, %	11
Chronic kidney disease, %	17.8
Asthma or COPD, %	14.1
Mean serum creatinine *, µmol/L (SD)	110.3 (71.5)
Median outpatient values BNP*, pmol/L, [Q1;Q3]	113.1 [39.0;235]
Median outpatient values NTproBNP* (pmol/L), [Q1;Q3]	232.5 [90.4;482.6]

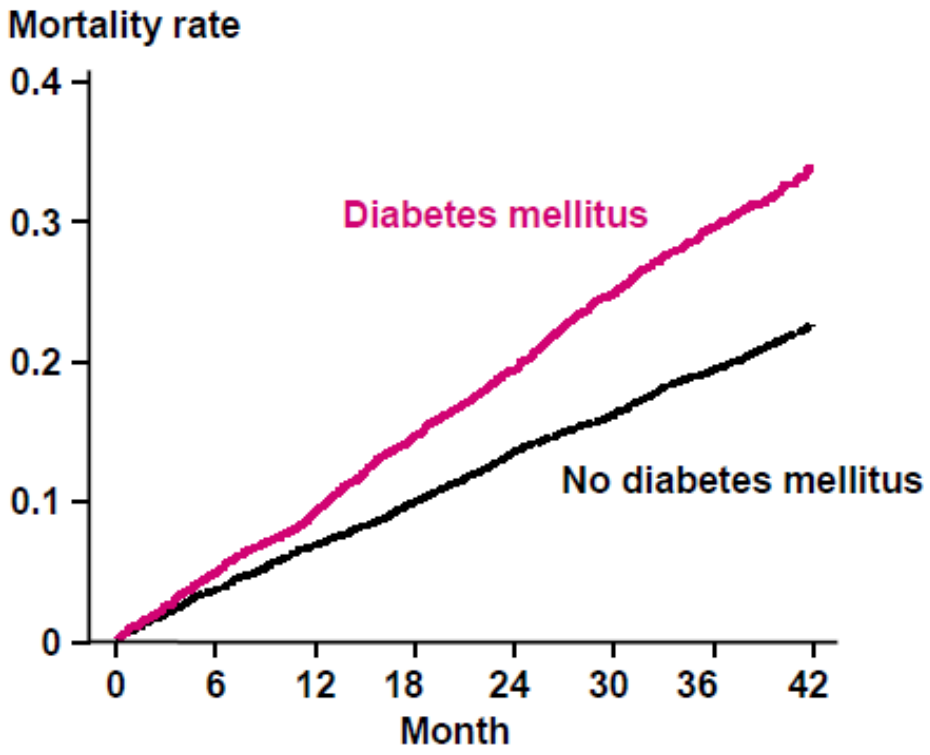
* Laboratory data within the last 12 months

Komajda et al. Eur J Heart fail 2016;18:514-522

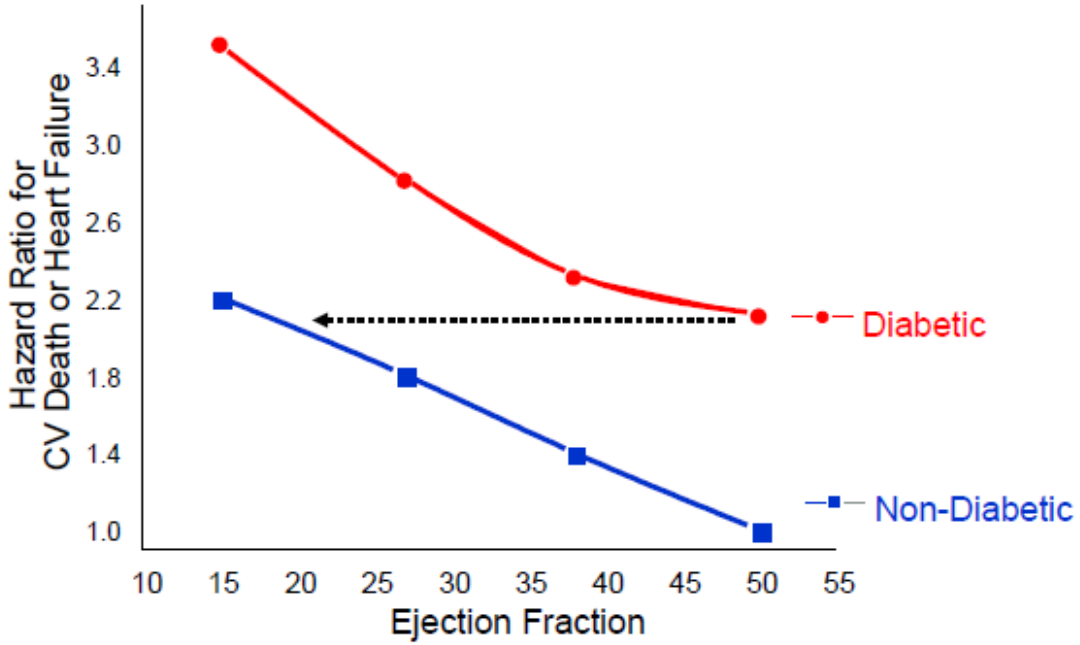
PATHOPHYSIOLOGIC IMPLICATIONS OF DIABETES IN HF

- Worse symptom/functional status
- Worse renal function
- More autonomic dysfunction
- More pulmonary dysfunction
- Impaired arterial vasodilatation
- Greater LV “diastolic dysfunction”
- Abnormal myocardial metabolism

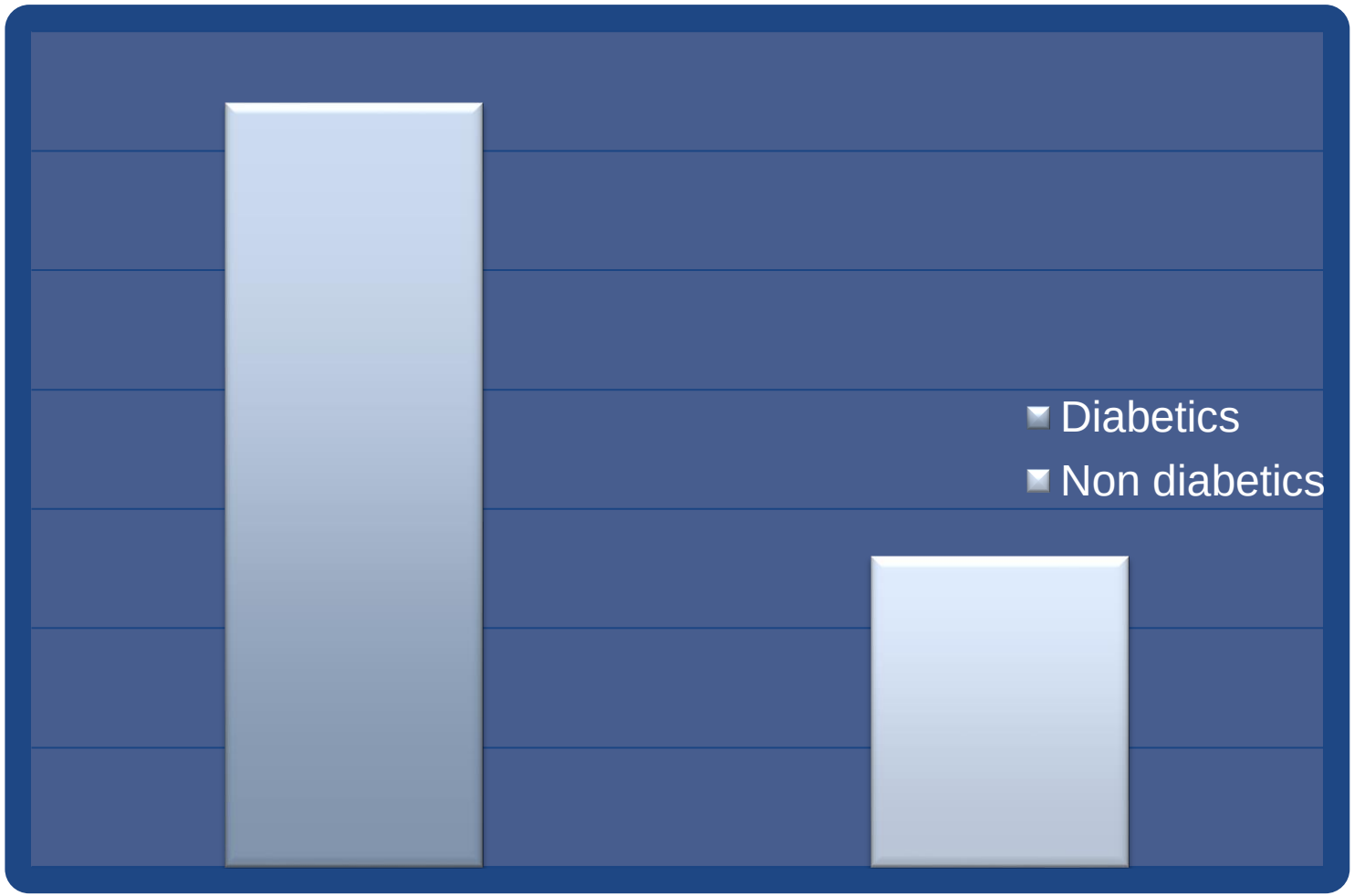
CHARM-Overall: Prognostic impact of diabetes



CHARM: Diabetes modifies relationship between ejection fraction and outcome



In-hospital Mortality of Diabetics vs Non-Diabetics With AHF (ALARM-HF)



Parissis et al. Int J Cardiol 2012

ESC 2016: Management of specific comorbidities

Recommendations	Class [a]	Level [b]
Iron deficiency		
Intravenous FCM should be considered in symptomatic patients with HFrEF and iron deficiency (serum ferritin <100 µg/L, or ferritin between 100–299 µg/L and transferrin saturation <20%) in order to alleviate HF symptoms, and improve exercise capacity and quality of life.	IIa	A
Diabetes		
Metformin should be considered as a first-line treatment of glycaemic control in patients with diabetes and HF, unless contra-indicated.	IIa	C

Ponikowski P et al. Eur Heart J. 21 May 2016. doi:10.1093/eurheartj/ehw128

Treatments not recommended for co-morbidities 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	209, 210
Arthritis			
NSAIDs or COX-2 inhibitors are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization.	III	B	211–213

Ponikowski P et al. Eur Heart J. 21 May 2016. doi:10.1093/eurheartj/ehw128

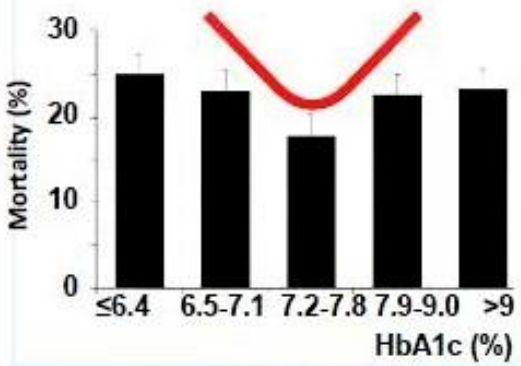
HbA1c for outcome prediction in HF ?

Is there an *optimum HbA1c* for CHF patients with DM ?

Unclear association between glycaemia (HbA1c) and mortality in CHF

not suitable as therapy target in CHF

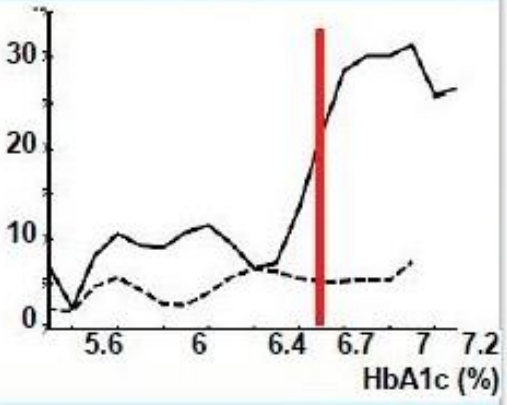
U - shaped relation



N=5,815
CHF + DM

Aguilar et al., JACC 2009

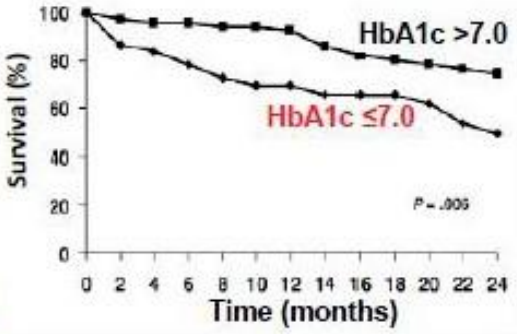
J – shaped relation



N=436
CHF, LVEF≤45%

Goode et al., Heart 2009

inverse relation

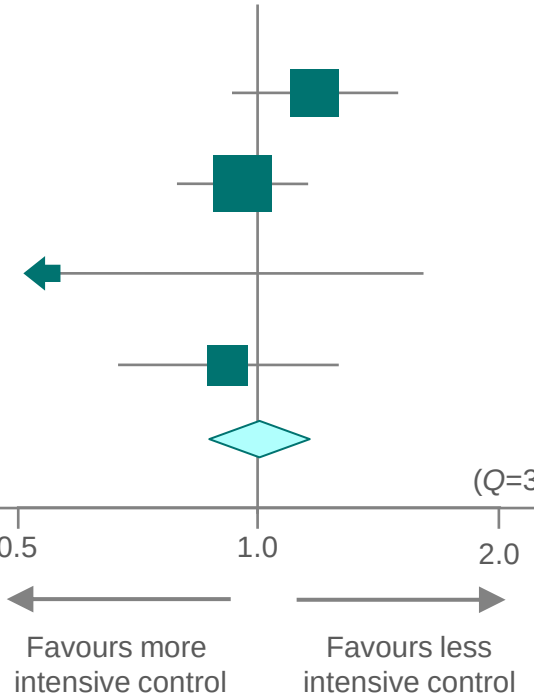


N=123
CHF +DM
LVEF 25±7%

Eshaghian et al., AHJ 2006

Ο εντατικός γλυκαιμικός έλεγχος* δεν απέδειξε να επηρεάζει σημαντικά τον κίνδυνο για Καρδιακή Ανεπάρκεια

	Number of events (yearly rate, %)		ΔHbA1c (%)	Hazard ratio (95% CI)
	More intensive	Less intensive		
Admission to hospital/fatal HF				
ACCORD	152 (0.90)	124 (0.75)	–1.01	1.18 (0.93, 1.49)
ADVANCE	220 (0.83)	231 (0.88)	–0.72	0.95 (0.79, 1.14)
UKPDS	8 (0.06)	6 (0.11)	–0.66	0.55 (0.19, 1.60)
VADT	79 (1.80)	85 (1.94)	–1.16	0.92 (0.68, 1.25)
Overall	**459**	**446**	**–0.88**	1.00 (0.86, 1.16)
				(Q=3.59, p=0.31, I^2=16.4%)



*Versus less-intensive glycaemic control
HbA1c, glycated haemoglobin; HF, heart failure
Turnbull FM *et al. Diabetologia* 2009;52:2288

Type 2 diabetes mellitus and heart failure: a position statement from the Heart Failure Association of the European Society of Cardiology

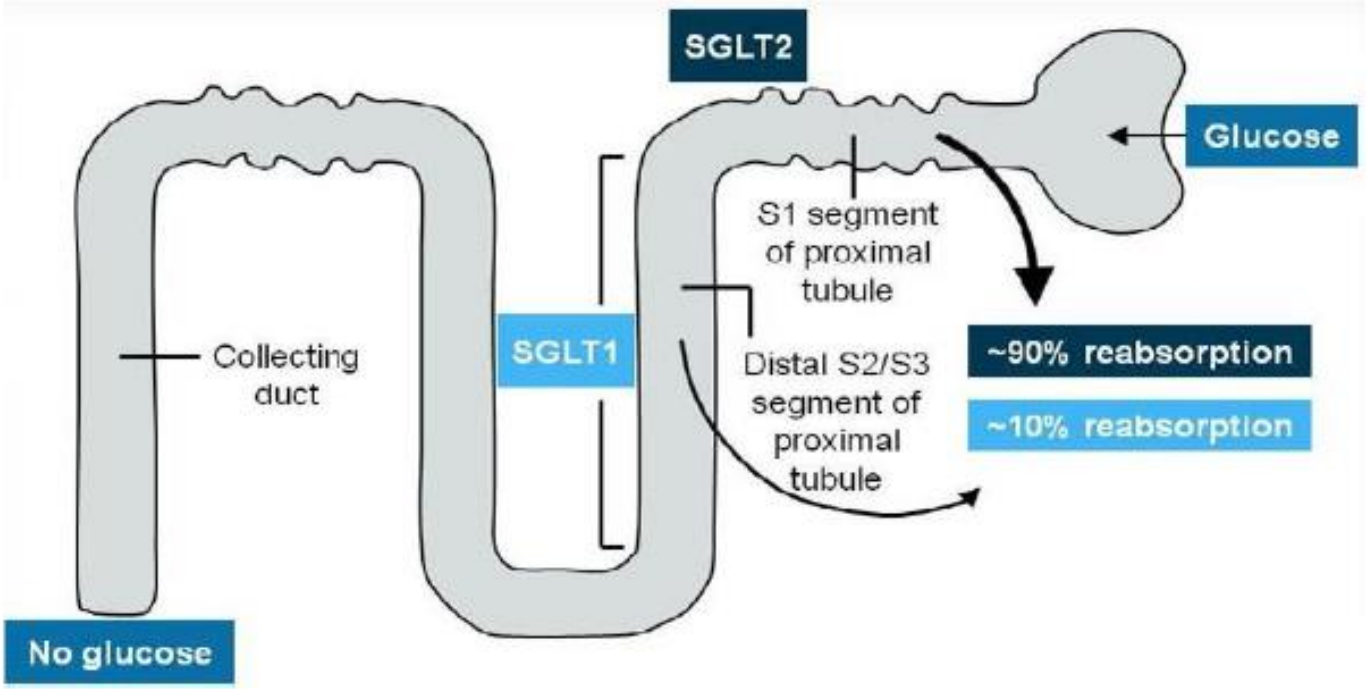
Table 7 Summary of evidence for type 2 antidiabetic drugs in patients with prevalent heart failure

Class of drug	Evidence
SGLT2 inhibitors (e.g. empagliflozin, canagliflozin)	No RCTs in HF. Large RCTs in patients with HF with an without T2DM are underway
Metformin	No RCTs in HF. In observational studies in HF, metformin is associated with lower mortality rates than sulphonylureas or insulin.[179] Benefit/risk ratio unknown.
GLP-1 receptor antagonists (e.g. liraglutide, albiglutide)	No large RCTs. Liraglutide - two small RCTs reported no effect on (i) LV function,[180] (ii) hierarchical composite of death/HF hospitalization/BNP change.[181] Benefit/risk ratio unknown.
Sulphonylureas	No RCTs in HF. Data equivocal. Some observational data suggest an increased mortality risk with sulphonylureas compared with metformin.[179,182]
Insulin	No RCTs in HF. In observational studies in HF, insulin was associated with higher mortality rates than metformin.[179] Benefit/risk ratio unknown.
DPP4 inhibitors	No RCTs in HF (saxagliptin contraindicated in HF[16,17]). Benefit/risk ratio unknown.

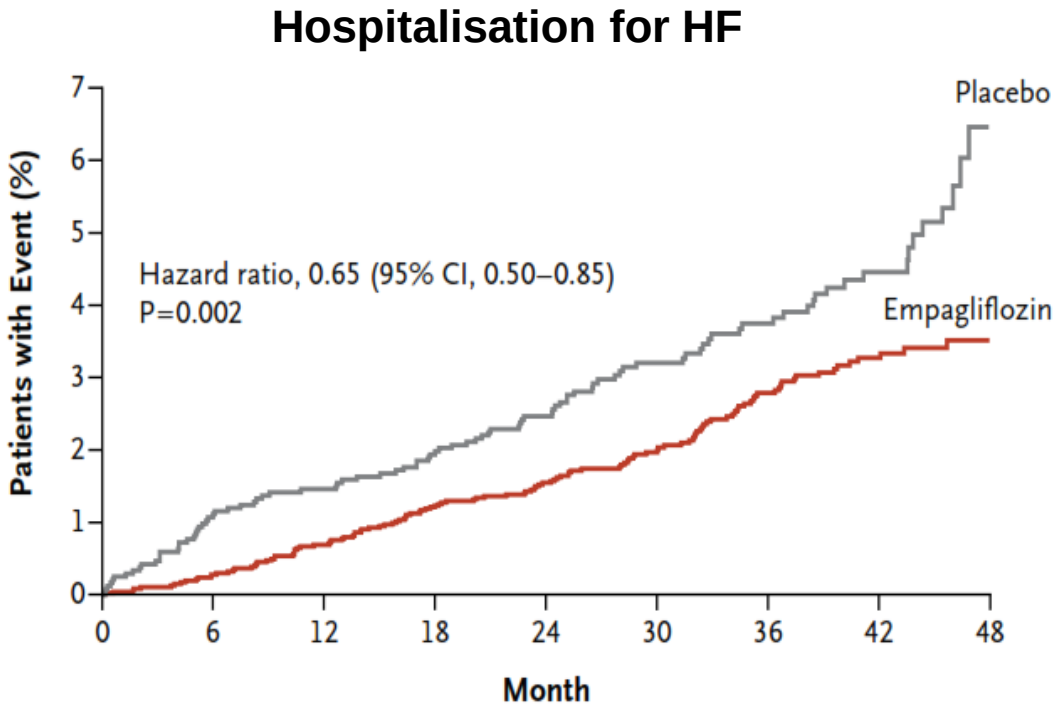
European Journal of Heart Failure (2018)
doi:10.1002/ejhf.1170

SGLT-2 inhibitors

Inhibit proximal tubular glucose reabsorption, cause diuresis and natriuresis, lower BP and reduce weight. Also renoprotective (in diabetes)?



Empagliflozin reduced the rate of HF hospitalisation versus placebo



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

Empagliflozin reduced hospitalisation for heart failure by 35%

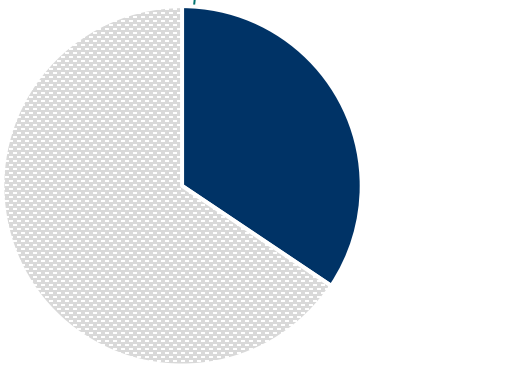
Zinman B, et al. N Engl J Med 2015;373:2117–2128.

Η DECLARE έχει το μεγαλύτερο ποσοστό ένταξης ασθενών χωρίς εγκατεστημένη ΚΔ νόσο μεταξύ των μελετών ΚΔ έκβασης με SGLT2i

- Η πλειοψηφία των ασθενών με ΣΔτ2 δεν έχει εγκατεστημένη αθηροσκληρωτική ΚΔ νόσο[1]

EMPA-REG OUTCOME[2]
(N=7.020)

CANVAS[3]
(N=10.142)

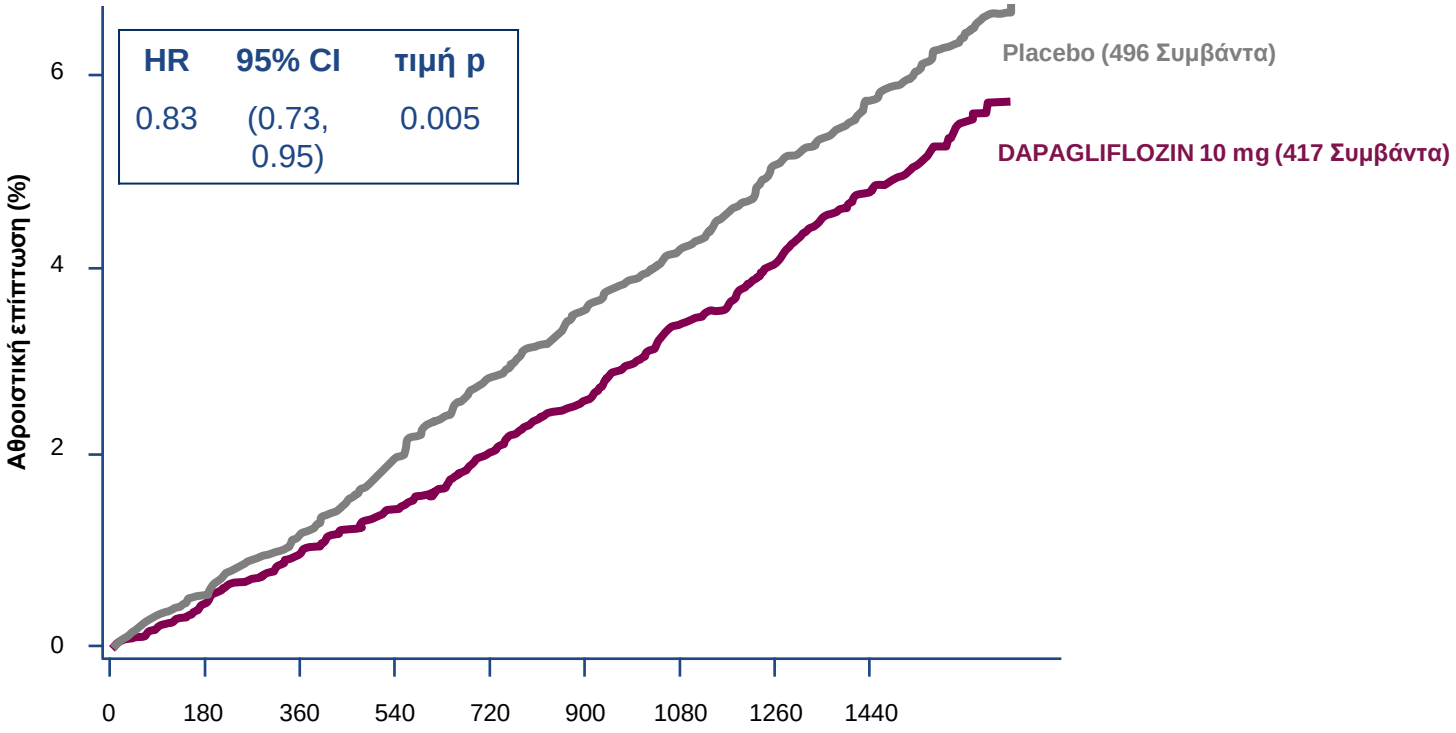


DECLARE[4]
(N=17.160)

SGLT2i: Αναστολέας συμμεταφορέα Γλυκόζης – Νατρίου 2, ΚΔ: Καρδιαγγειακά, ΣΔτ2: Σακχαρώδης Διαβήτης τύπου 2.

1. Einarson TR, et al. *Cardiovasc Diabetol* 2018;17:83; 2. Zinman B, et al. *N Engl J Med* 2015;373:2117–2128; 3. Neal B, et al. *N Engl J Med* 2017;377:644–657;
4. Raz I, et al. *Diabetes Obes Metab* 2018;20:1102–1110

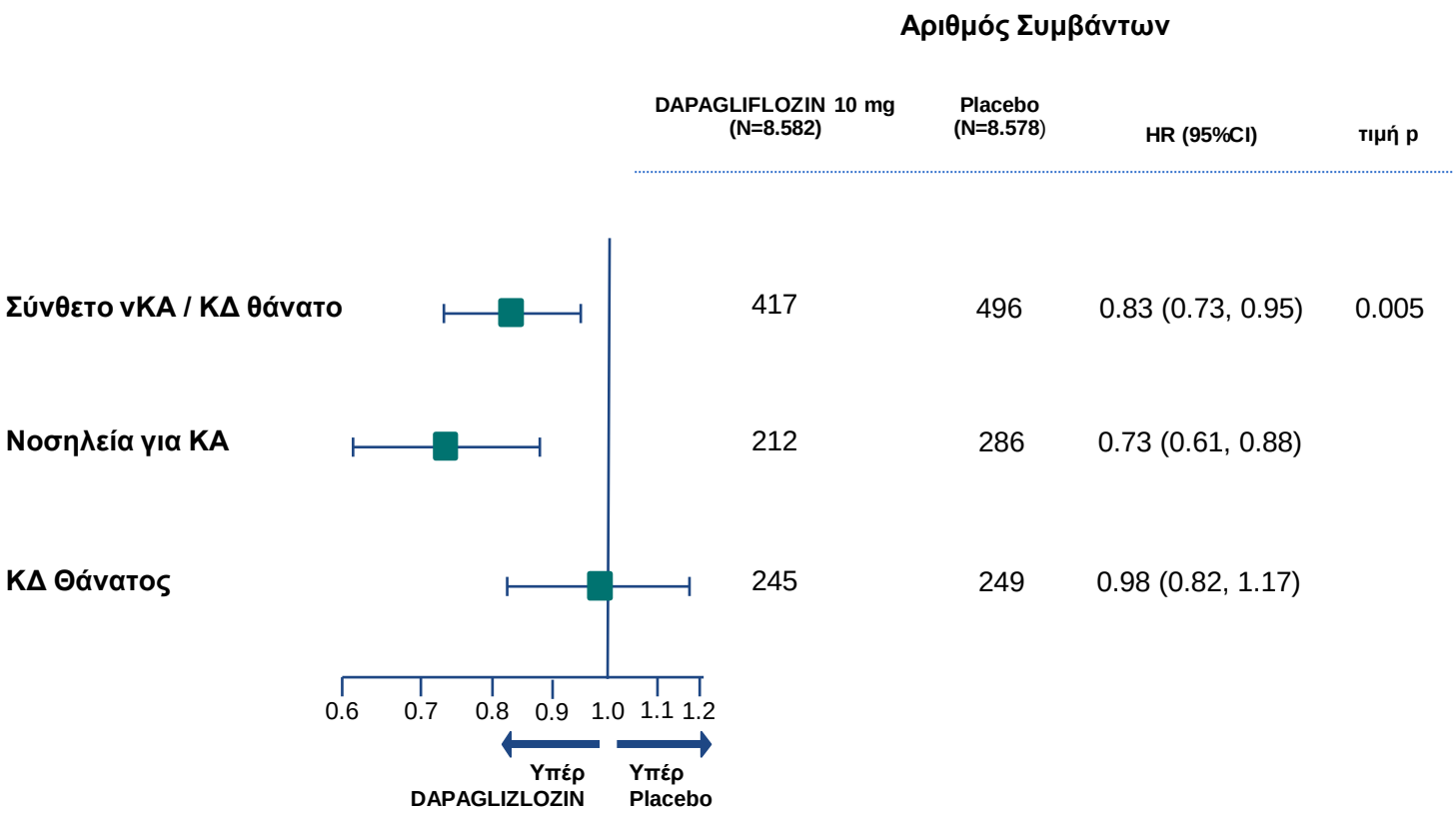
Κύριο τελικό σημείο: Σύνθετο νοσηλείας για Καρδιακή Ανεπάρκεια ή ΚΔ θάνατο



Ν σε κίνδυνο									
DAPAGLIFLOZIN 10 mg	8582	8517	8415	8322	8224	8110	7970	7497	5445
Placebo	8578	8485	8387	8259	8127	8003	7880	7367	5362

Ν σε κίνδυνο είναι ο αριθμός των ασθενών υπό κίνδυνο εκδήλωσης συμβάντος κατά την έναρξης της περιόδου παρακολούθησης.
ΚΔ, καρδιαγγειακός, HR, αναλογία κινδύνου, CI, διάστημα εμπιστοσύνης
Wiviott SD et al. Online ahead of print. *New Engl J Med.* 2018.

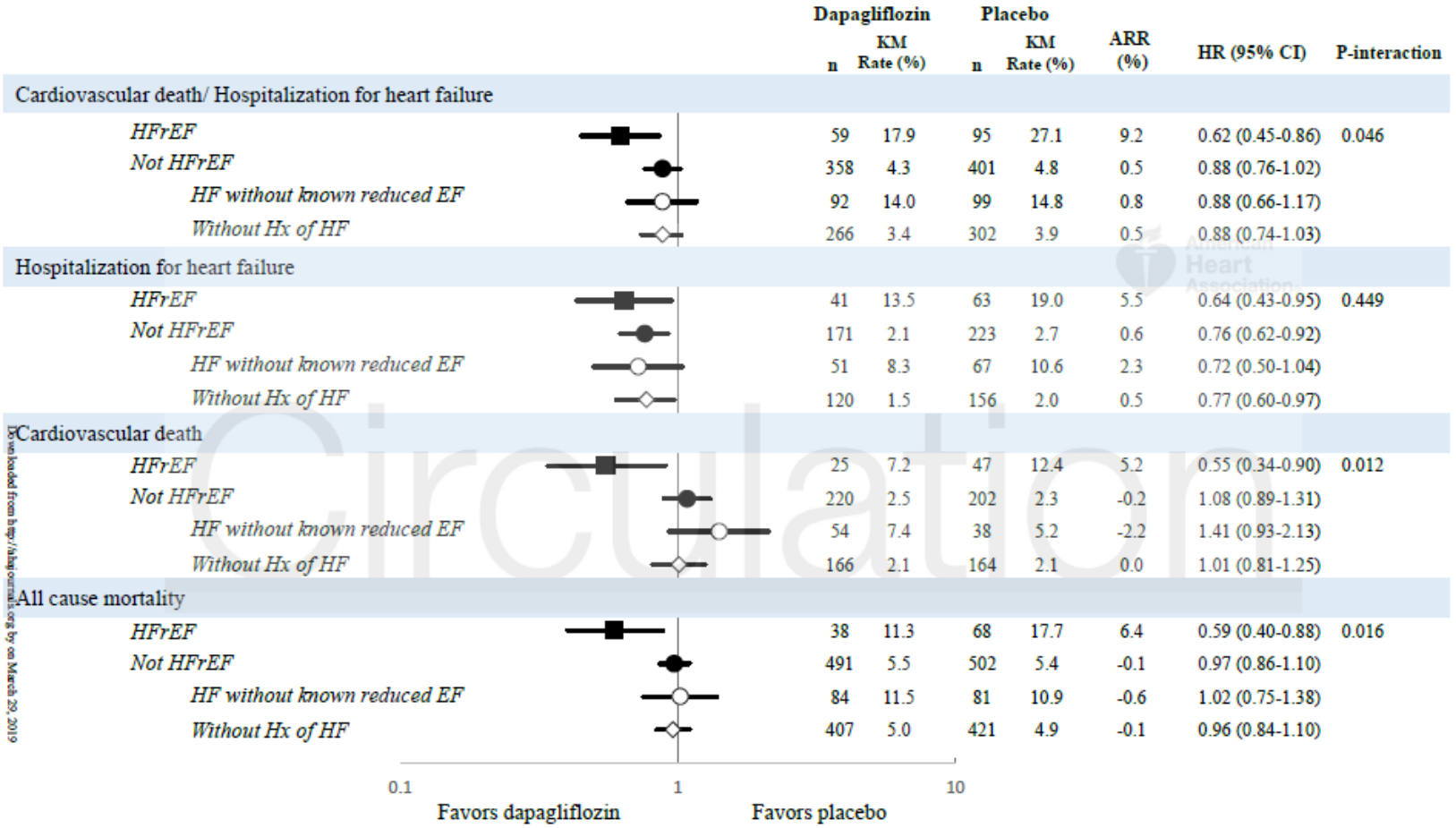
Κύριο τελικό σημείο: Σύνθετο νοσηλείας για Καρδιακή Ανεπάρκεια ή ΚΔ θάνατο και επιμέρους στοιχεία



Η τιμή-p αμφίπλευρου ελέγχου παρουσιάζεται για το πρωτεύον καταληκτικό σημείο αποτελεσματικότητας του ΚΔ θανάτου ή νοσηλείας για ΚΑ.
ΚΔ, καρδιαγγειακός, νΚΑ, νοσηλεία για καρδιακή ανεπάρκεια; ΚΑ, καρδιακή ανεπάρκεια; HR, αναλογία κινδύνου, CI, διάστημα εμπιστοσύνης
Wiviott SD et al. Online ahead of print. New Engl J Med. 2018.

Effect of Dapagliflozin on Heart Failure and Mortality in Type 2 Diabetes Mellitus

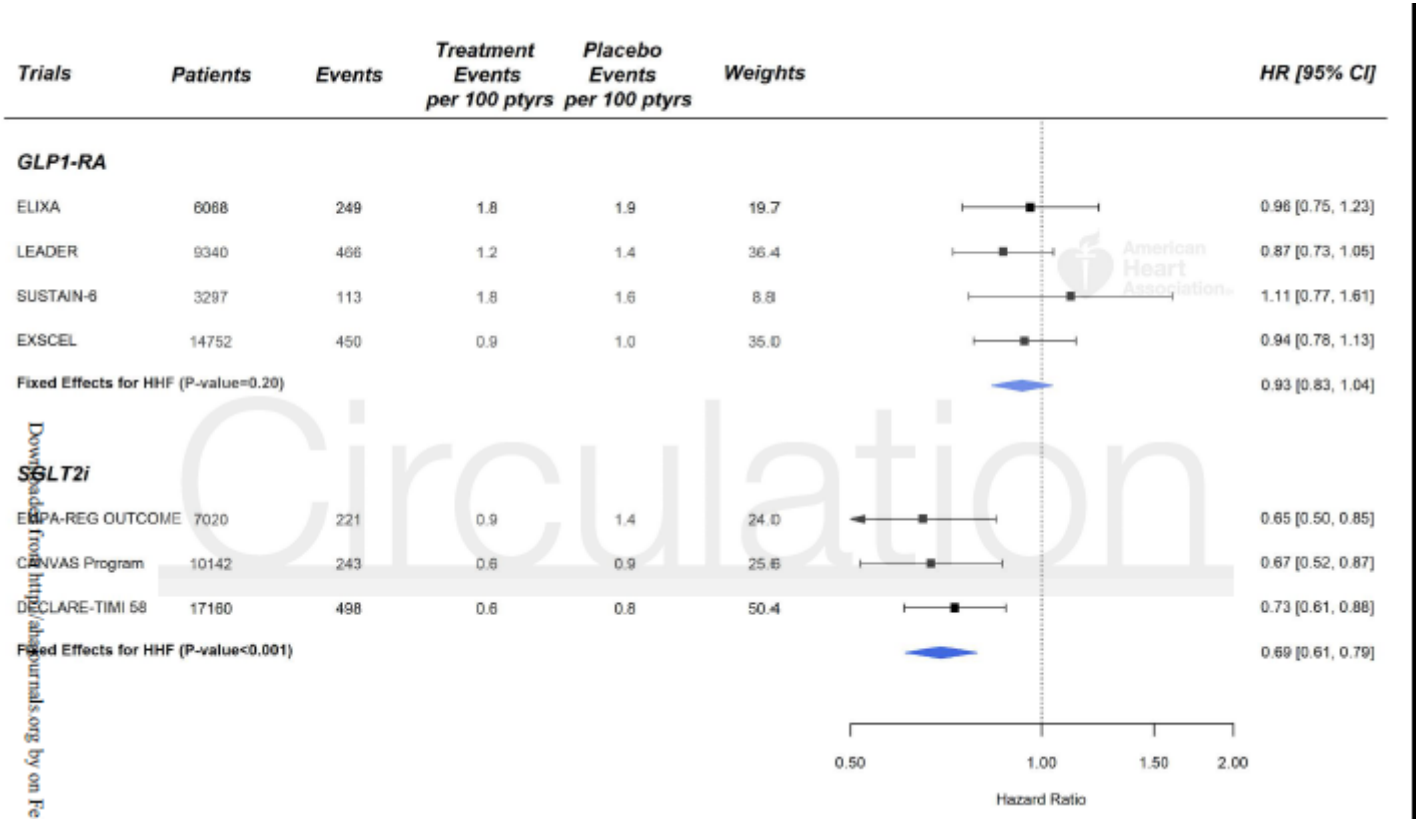
Of 17,160 patients, 671 (3.9%) had HFrEF, 1316 (7.7%) had HF without known reduced EF and 15,173 (88.4%) had no history of HF at baseline



	Dapagliflozin n	Dapagliflozin KM Rate (%)	Placebo n	Placebo KM Rate (%)	ARR (%)	HR (95% CI)	P-interaction
Cardiovascular death/ Hospitalization for heart failure							
HFrEF	59	17.9	95	27.1	9.2	0.62 (0.45-0.86)	0.046
Not HFrEF	358	4.3	401	4.8	0.5	0.88 (0.76-1.02)	
HF without known reduced EF	92	14.0	99	14.8	0.8	0.88 (0.66-1.17)	
Without Hx of HF	266	3.4	302	3.9	0.5	0.88 (0.74-1.03)	
Hospitalization for heart failure							
HFrEF	41	13.5	63	19.0	5.5	0.64 (0.43-0.95)	0.449
Not HFrEF	171	2.1	223	2.7	0.6	0.76 (0.62-0.92)	
HF without known reduced EF	51	8.3	67	10.6	2.3	0.72 (0.50-1.04)	
Without Hx of HF	120	1.5	156	2.0	0.5	0.77 (0.60-0.97)	
Cardiovascular death							
HFrEF	25	7.2	47	12.4	5.2	0.55 (0.34-0.90)	0.012
Not HFrEF	220	2.5	202	2.3	-0.2	1.08 (0.89-1.31)	
HF without known reduced EF	54	7.4	38	5.2	-2.2	1.41 (0.93-2.13)	
Without Hx of HF	166	2.1	164	2.1	0.0	1.01 (0.81-1.25)	
All cause mortality							
HFrEF	38	11.3	68	17.7	6.4	0.59 (0.40-0.88)	0.016
Not HFrEF	491	5.5	502	5.4	-0.1	0.97 (0.86-1.10)	
HF without known reduced EF	84	11.5	81	10.9	-0.6	1.02 (0.75-1.38)	
Without Hx of HF	407	5.0	421	4.9	-0.1	0.96 (0.84-1.10)	

10.1161/CIRCULATIONAHA.119.040130

Comparison of the Effects of Glucagon-Like Peptide Receptor Agonists and Sodium-Glucose Co-Transporter 2 Inhibitors for Prevention of Major Adverse Cardiovascular and Renal Outcomes in Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis of Cardiovascular Outcomes Trials

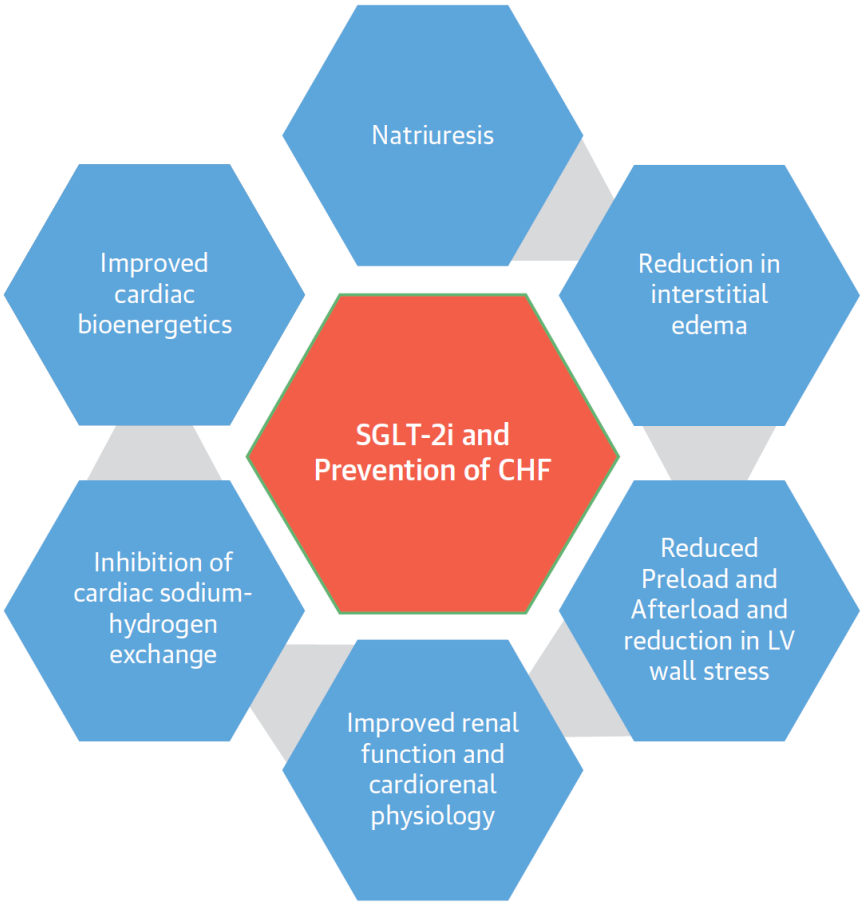


Conclusions: In trials reported to date, GLP1-RA and SGLT2i reduce atherosclerotic MACE to a similar degree in patients with established ASCVD, whereas SGLT2i have a more marked effect on preventing HHF and progression of kidney disease. Their distinct clinical benefit profiles should be considered in the decision-making process when treating patients with T2DM.

10.1161/CIRCULATIONAHA.118.038868

Prevention of Heart Failure With SGLT-2 Inhibition

FIGURE 1 Proposed Mechanisms of Benefit of SGLT-2i in Heart Failure



CHF = congestive heart failure; LV = left ventricular; SGLT-2i = sodium-dependent glucose cotransporter-2 inhibitor(s).

JACC VOL. 71, NO. 22, 2018
JUNE 5, 2018:2507–10

Η μελέτη DAPA-HF θα αξιολογήσει την επίδραση της δαπαγλιφλοζίνης σε ασθενείς με HFrEF με ή χωρίς ΣΔτ2

Ασθενείς με HFrEF:

- NYHA Class II-IV
- LVEF ≤40%
- Αυξημένο NT-proBNP
- Σταθερή SoC HF αγωγή
- Με ή χωρίς ΣΔτ2
- eGFR ≥30 mL/min/1.73 m^2

1:1 Διπλά τυφλή

Δαπαγλιφλοζίνη (10 mg ή 5 mg ανά ημέρα)

Εικονικό φάρμακο

- **Επιπρόσθετα στην SoC για HFrEF**
- **Διάρκεια μελέτης ~33 months**
- **Εκτιμώμενη ημερομηνία ολοκλήρωσης της μελέτης: Δεκέμβριος 2019**

Τελικά σημεία

Πρωτεύον καταληκτικό σημείο

Σύνθετο καταληκτικό σημείο:

- **ΚΔ θάνατος**
- **vKA**
- **Επείγουσα επίσκεψη για HF**

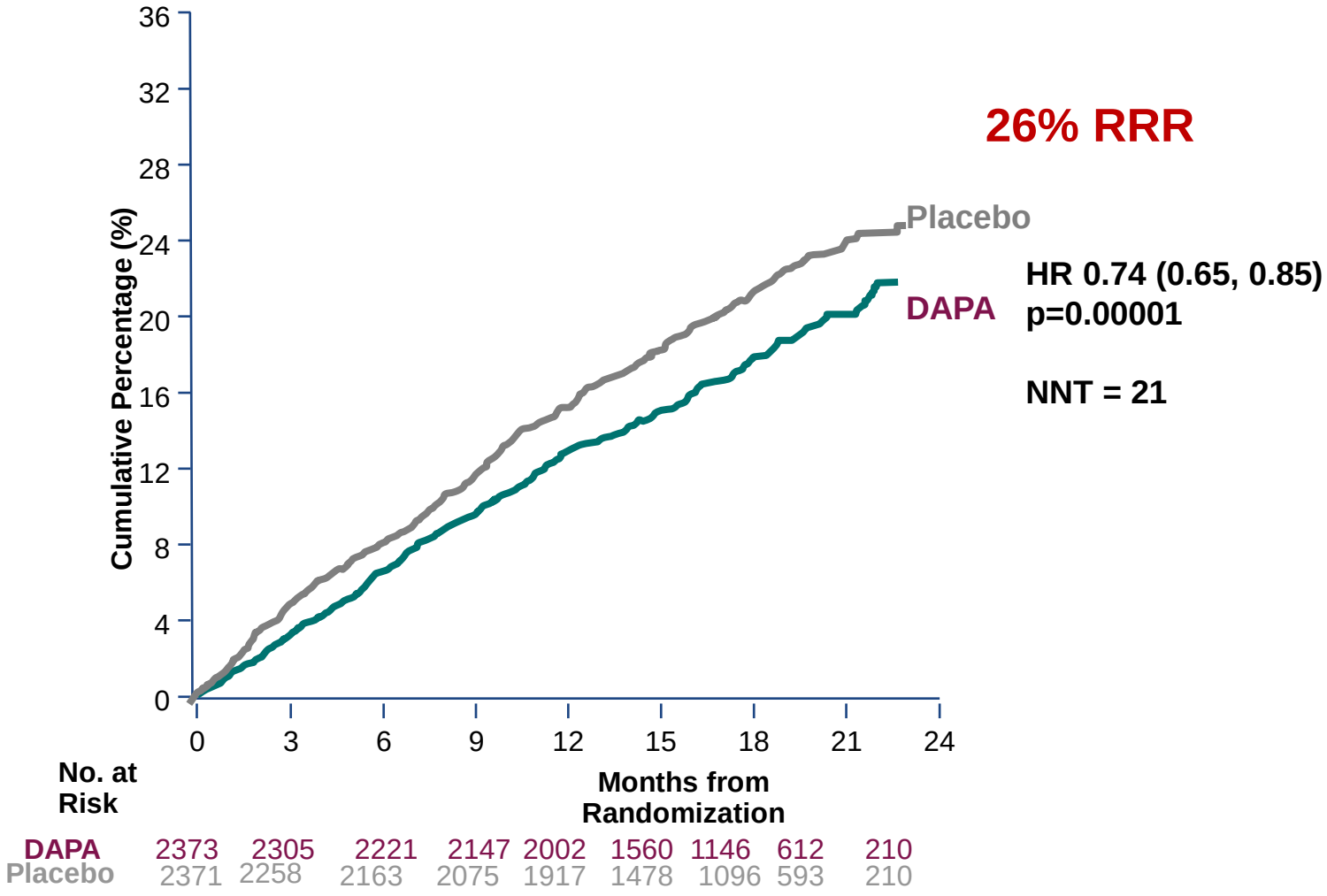
Δευτερεύοντα καταληκτικά σημεία

- **ΚΔ θάνατος και θάνατος κάθε αιτιολογίας**
- **Συνολικός αριθμός ΚΔ θανάτου και νοσηλειών για ΚΑ**
- **Νεφρικό τελικό σημείο**
- **Σκορ συμπτωμάτων ΚΑ**

ΚΔ = καρδιαγγειακός; eGFR = εκτιμώμενος ρυθμός σπειραματικής διήθησης; HFrEF = καρδιακή ανεπάρκεια με μειωμένο κλάσμα εξώθησης; ΚΑ = καρδιακή ανεπάρκεια, vKA = νοσηλεία για καρδιακή ανεπάρκεια; LVEF = κλάσμα εξώθησης αριστερής κοιλίας; NT-proBNP = N-τερματικό pro B τύπου νατριουρητικό πεπτίδιο; NYHA = New York Heart Association; SoC = καθιερωμένη θεραπεία; ΣΔτ2 = σακχαρώδης διαβήτης τύπου 2.

Study NCT03036124. ClinicalTrials.gov website.

Primary Endpoint: CV Death or hHF or an Urgent HF Visit[1,2]

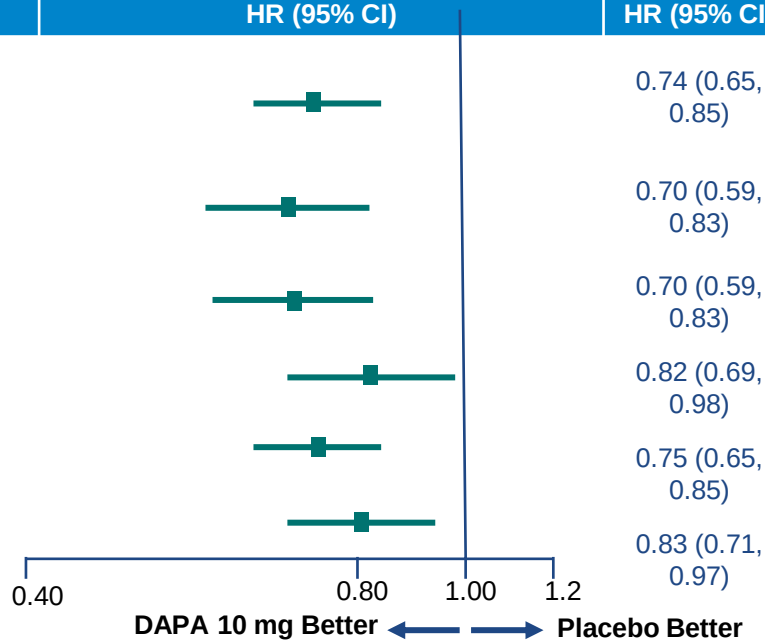


DAPA = dapagliflozin; HF = heart failure; hHF = hospitalization for heart failure; HR = hazard ratio; NNT = number needed to treat; RRR = relative risk reduction

1. McMurray JJV et al. *N Engl J Med*. 2019. https://doi.org/10.1056/NEJMoa1911303. Accessed September 19, 2019. 2. McMurray J. Presentation at: European Society of Cardiology Congress. September 1, 2019; Paris, France.

Effects of Dapagliflozin on Worsening Heart Failure and Mortality[1-3]

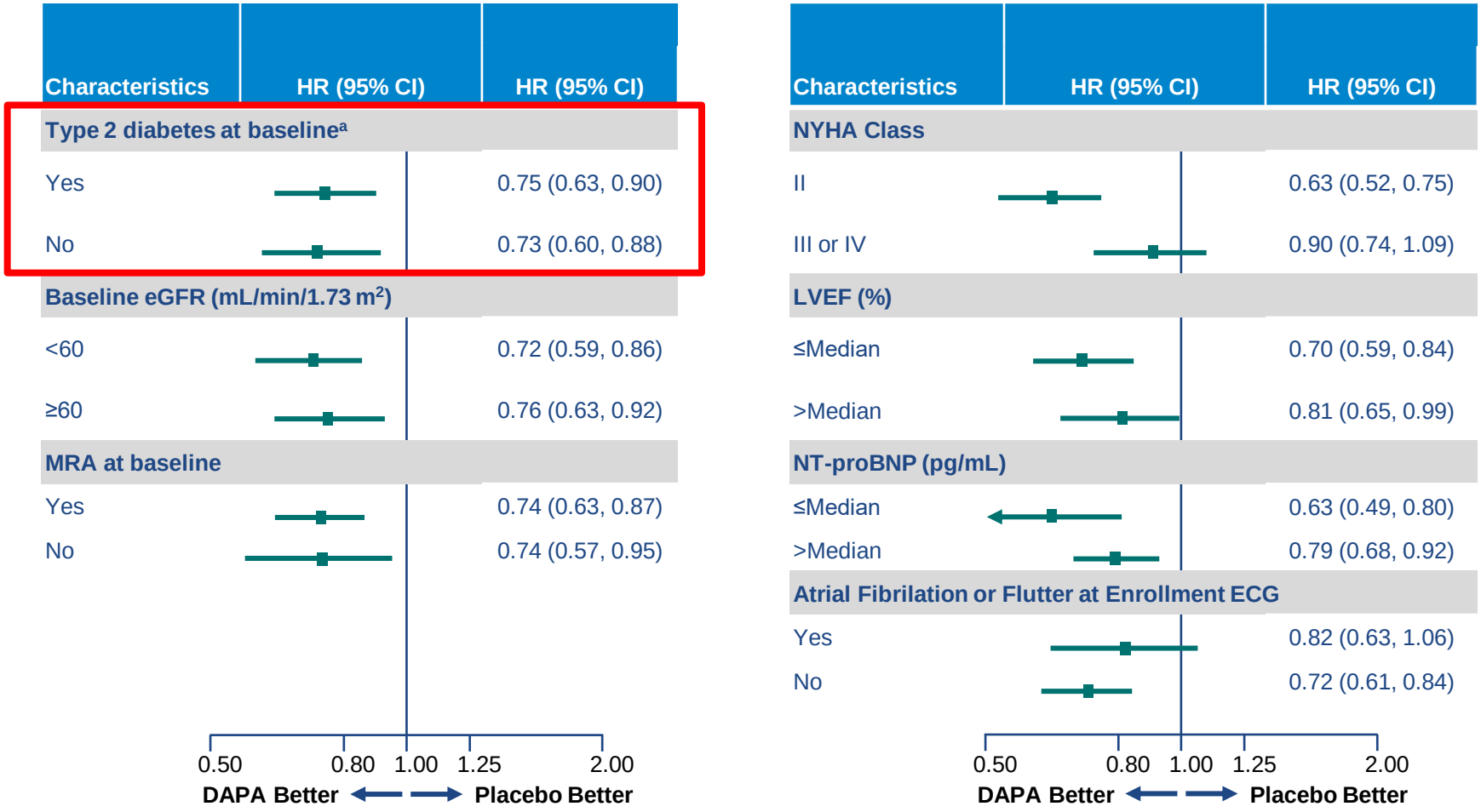
Outcome	Dapagliflozin 10 mg (n=2373)	Placebo (n=2371)	HR (95% CI)	P value
Cardiovascular death, hospitalization for heart failure or urgent heart failure visit	386 (16.3)	502 (21.2)	0.74 (0.65, 0.85)	0.00001[2]
Hospitalization for heart failure or urgent heart failure visit	237 (10.0)	326 (13.7)	0.70 (0.59, 0.83)	0.00003[2]
Hospitalization for heart failure	231 (9.7)	318 (13.4)	0.70 (0.59, 0.83)	0.0001[3]
Cardiovascular death	227 (9.6)	273 (11.5)	0.82 (0.69, 0.98)	0.029[2]
Cardiovascular death or hospitalization for heart failure	382 (16.1)	495 (20.9)	0.75 (0.65, 0.85)	0.00002[2]
Death from any cause	276 (11.6)	329 (13.9)	0.83 (0.71, 0.97)	0.022*[2]



*Nominal p-value.

1. McMurray JJV et al. Supplementary material. *N Engl J Med*. 2019. https://doi.org/10.1056/NEJMoa1911303. Accessed September 19, 2019. 2. McMurray J. Presentation at: European Society of Cardiology Congress. September 1, 2019; Paris, France. 3. In House Data, AstraZeneca Pharmaceuticals LP. CSP D1699C00001.

Primary Endpoint: Prespecified Subgroups



A selection of subgroups is presented above.

[a]Defined as history of T2DM or HbA1c ≥6.5% at both enrollment and randomization visits.

DAPA = dapagliflozin; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HR = hazard ratio; MRA = mineralocorticoid receptor antagonist; NT pro BNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; LVEF = left ventricular ejection fraction.

McMurray JJV et al. *N Engl J Med*. 2019. https://doi.org/10.1056/NEJMoa1911303. Accessed September 19, 2019.

Safety Outcomes

Variable	Dapagliflozin (n=2368)	Placebo (n=2368)	p-value
AE leading to treatment discontinuation, n (%)	111 (4.7)	116 (4.9)	0.79
Adverse Events of Interest, n (%)			
Volume depletion†	178 (7.5)	162 (6.8)	0.40
Renal AE‡	153 (6.5)	170 (7.2)	0.36
Fracture	49 (2.1)	50 (2.1)	1.00
Amputation	13 (0.5)	12 (0.5)	1.00
Major hypoglycemia‖	4 (0.2)	4 (0.2)	-
Diabetic ketoacidosis§	3 (0.1)	0.0	-
Fournier's gangrene	0	1 (<0.1)	-

*

McMurray JJV et al. *N Engl J Med*. 2019. https://doi.org/10.1056/NEJMoa1911303. Accessed September 19, 2019.

Type 2 diabetes mellitus and heart failure: a position statement from the Heart Failure Association of the European Society of Cardiology

Table 9 Selected ongoing randomized clinical trials of SGLT2 inhibitors in patients with prevalent heart failure

Clinical trial	Brief description of the trial
Empagliflozin	
EMPEROR-Reduced (NCT03057977)	Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction • Study population: HFrEF, with and without T2DM. • Estimated enrolment: *n*=2850. • Treatment: empagliflozin vs. placebo on top of guideline-based medical therapy. • Primary outcome: CV death or HF hospitalization (time frame: up to 38 months).
EMPEROR-Preserved (NCT03057951)	Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction • Study population: HFpEF, with and without T2DM. • Estimated enrolment: *n*=4126. • Treatment: empagliflozin vs. placebo on top of guideline-based medical therapy. • Primary outcome: CV death or HF hospitalization (time frame: up to 38 months).
Empire HF (NCT03198585)	Empagliflozin in Heart Failure Patients With Reduced Ejection Fraction • Study population: HFrEF, with and without T2DM. • Estimated enrolment: *n*=189. • Treatment: empagliflozin vs. placebo on top of guideline-based medical therapy. • Primary outcome: change in plasma concentrations of NT-proBNP (time frame: 90 days) as a measure of treatment impact on HF.
EMMY (NCT03087773)	Impact of Empagliflozin on Cardiac Function and Biomarkers of Heart Failure in Patients With Acute Myocardial Infarction • Study population: patients with acute MI with and without T2DM. • Estimated enrolment: *n*=476. • Treatment: empagliflozin vs. placebo. • Primary outcome: change in plasma concentrations of NT-proBNP (time frame: 26 weeks) as a measure of treatment impact on HF.
RECEDE-CHF (NCT03226457)	SGLT2 Inhibition in Combination With Diuretics in Heart Failure • Study population: HFrEF with T2DM. • Estimated enrolment: *n*=34. • Treatment: empagliflozin vs. placebo. • Primary outcome: the effect on the change in urine output from baseline (time frame: 6 weeks).
Canagliflozin	
(NCT02920918)	Treatment of Diabetes in Patients With Systolic Heart Failure • Study population: HFrEF with T2DM. • Estimated enrolment: *n*=88. • Treatment: canagliflozin vs. sitagliptin. • Primary outcome: change in aerobic exercise capacity and ventilator efficiency (time frame: baseline and 12 weeks).
Dapagliflozin	
Dapa-HF (NCT03036124)	Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure • Study population: HFrEF with and without T2DM • Estimated enrolment: *n*=4500. • Treatment: dapagliflozin vs. placebo. • Primary outcome: CV death or hospitalization for HF, or an urgent HF visit (time frame: from randomization up to approximately 3 years).
DEFINE-HF (NCT02653482)	Dapagliflozin Effect on Symptoms and Biomarkers in Diabetic Patients With Heart Failure • Study population: HFrEF with T2DM. • Estimated enrolment: *n*=250. • Treatment: dapagliflozin vs. placebo. • Primary outcome: change in plasma concentrations of NT-proBNP (time frame: 12 weeks) as a measure of treatment impact on HF.

European Journal of Heart Failure (2018)
doi:10.1002/ejhf.1170

Diabetes in Heart Failure Checklist

- ✓ Treat heart failure in people with diabetes the SAME as you would a person without diabetes
- ✓ METFORMIN recommended if eGFR >30 mL/min/1.73 m^2
- ✓ If eGFR <60 mL/min, use Renin Angiotensin Aldosterone system or sacubitril/valsartan blockade carefully
- ✓ Do NOT use thiazolidinediones
- ✓ Avoid saxagliptin in patients with heart failure and diabetes
- ✓ SGLT2 inhibitors should be preferable treatment in diabetic HF pts
- ✓ An SGLT2 inhibitor should be the preferable anti-diabetic agent in patients with risk factors in order to prevent HF