Heart Failure 2019- The world has changed

A/Prof Gautam Vaddadi

Head of Heart Failure- Northern Health

Director of Cardiac Services, Cabrini Health

Disclosures

- Gautam Vaddadi has received honoraria from Novartis

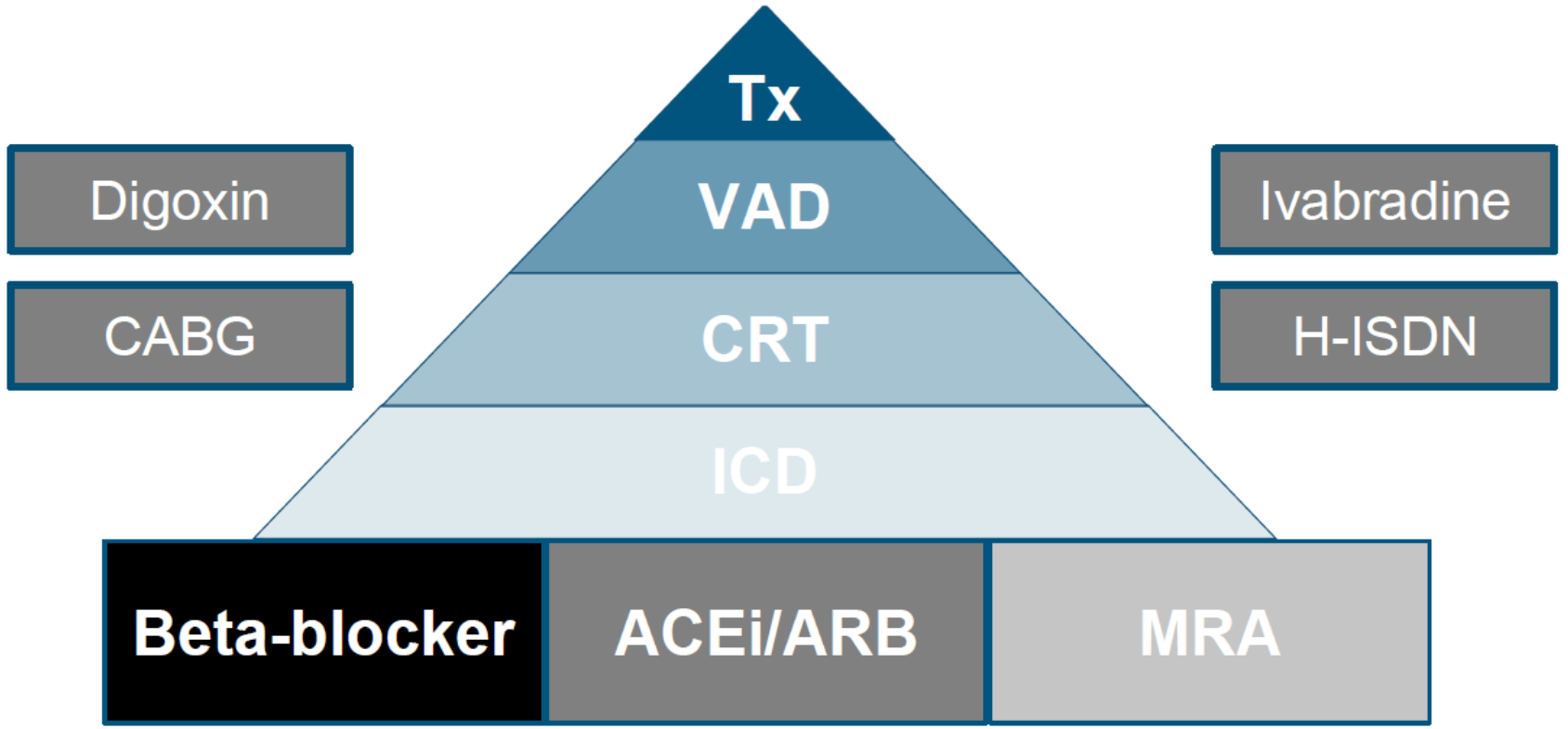
Heart failure- What are we talking about?

- Heart failure reduced ejection fraction (HFrEF)

EF < 40%

- Not heart failure preserved ejection fraction (HFpEF)

HF-REF: The building blocks of therapy

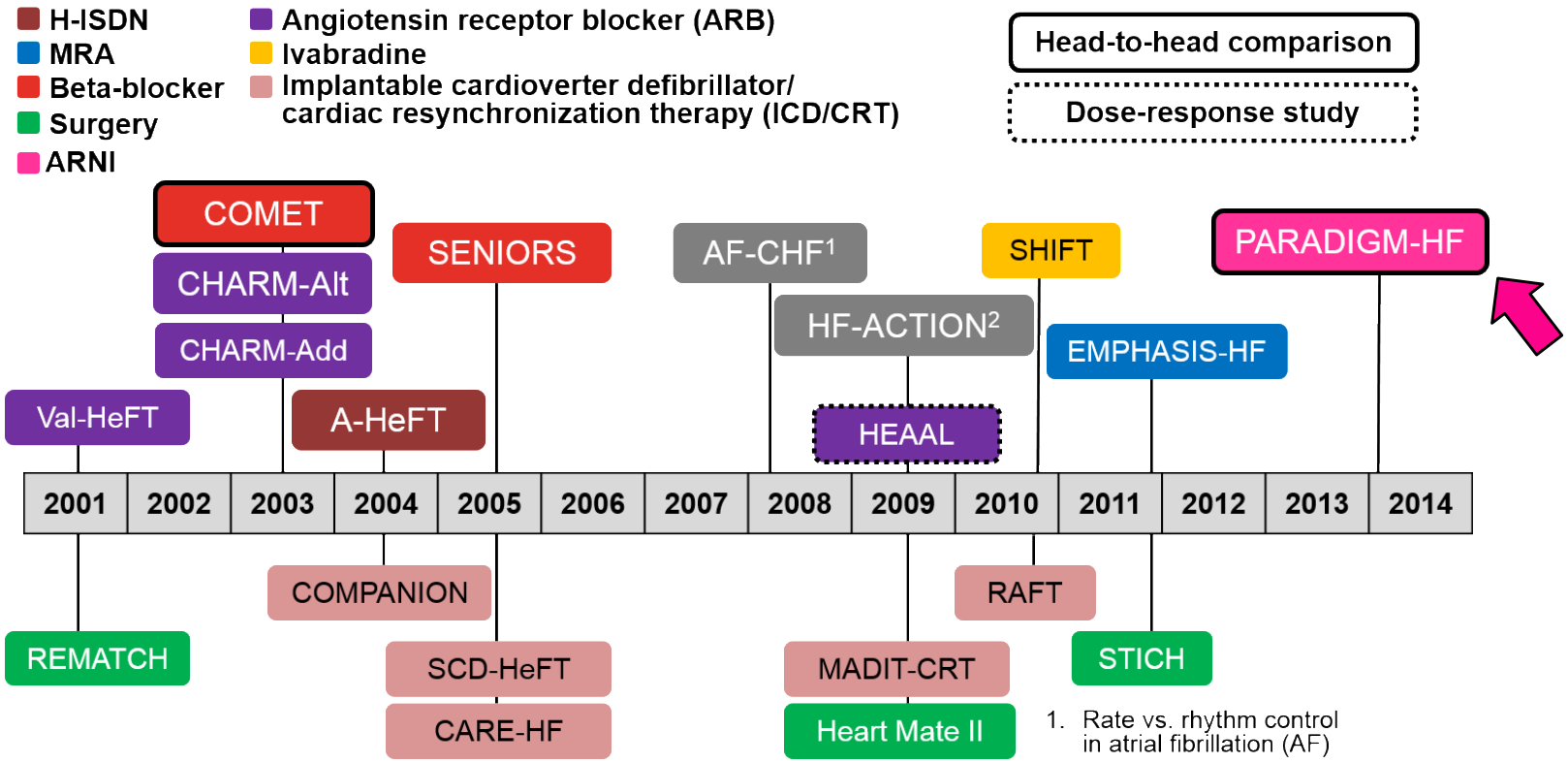


ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft surgery; CRT, cardiac resynchronisation therapy; HF-REF, heart failure with reduced ejection fraction; H-ISDN, hydralazine/isosorbide dinitrate; ICD, implantable cardioverter defibrillator; MRA, mineralocorticoid (aldosterone) receptor antagonist; VAD, ventricular assist device

McMurray et al. Eur Heart J 2012;33:1787–1847

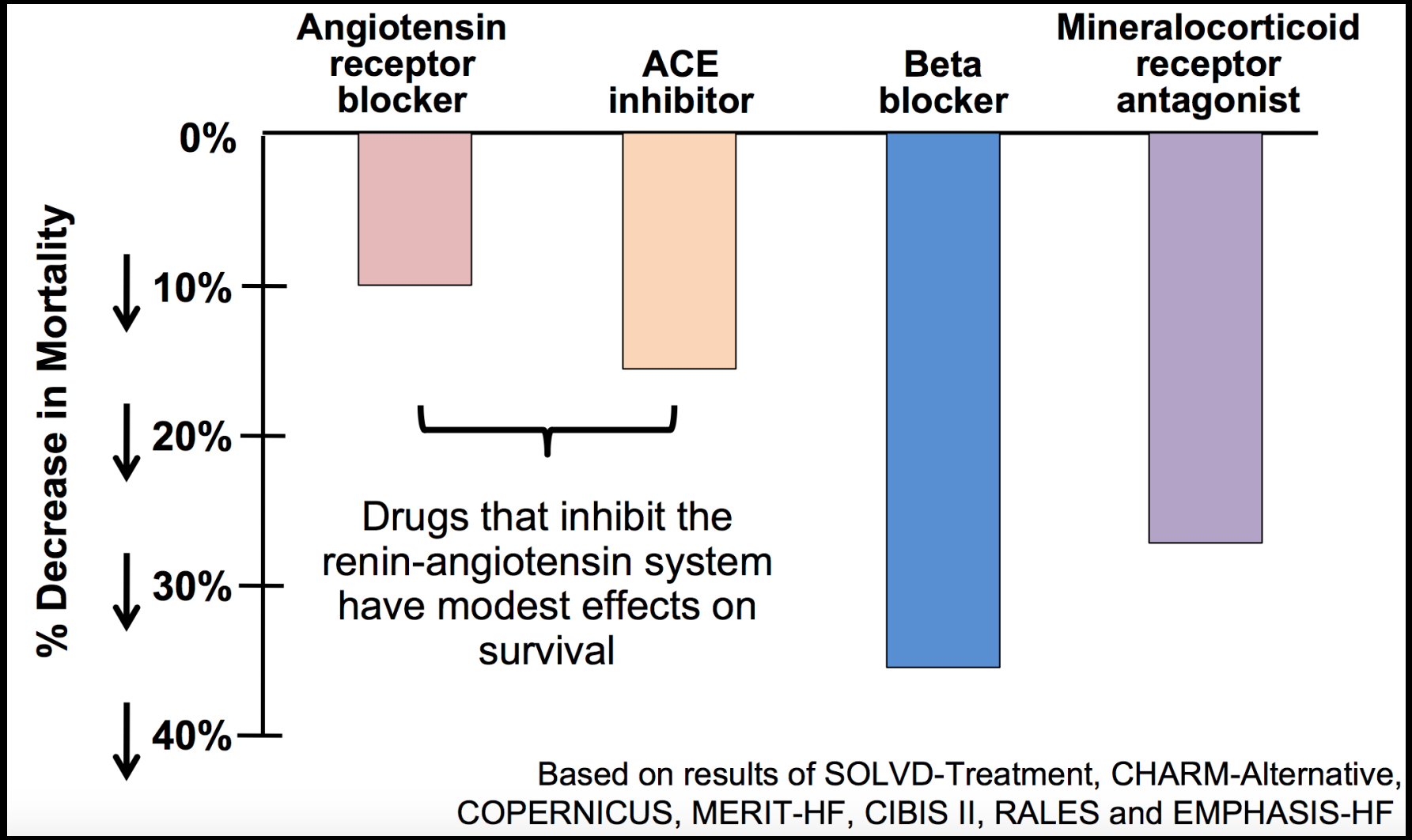
The old paradigm

Do we really need more HF therapy? Positive trials 2001 - 2016



McMurray JJV. Eur J Heart. 2015;36:3467-7(

Mortality benefit of current HF therapy



Presented by Milton Packer, ESC 2014

Do we really need more treatments for HF?

Despite evidence-based pharmacologic therapy, morbidity and mortality associated with HF-rEF remain high,[1] leaving opportunity for further improvement in care

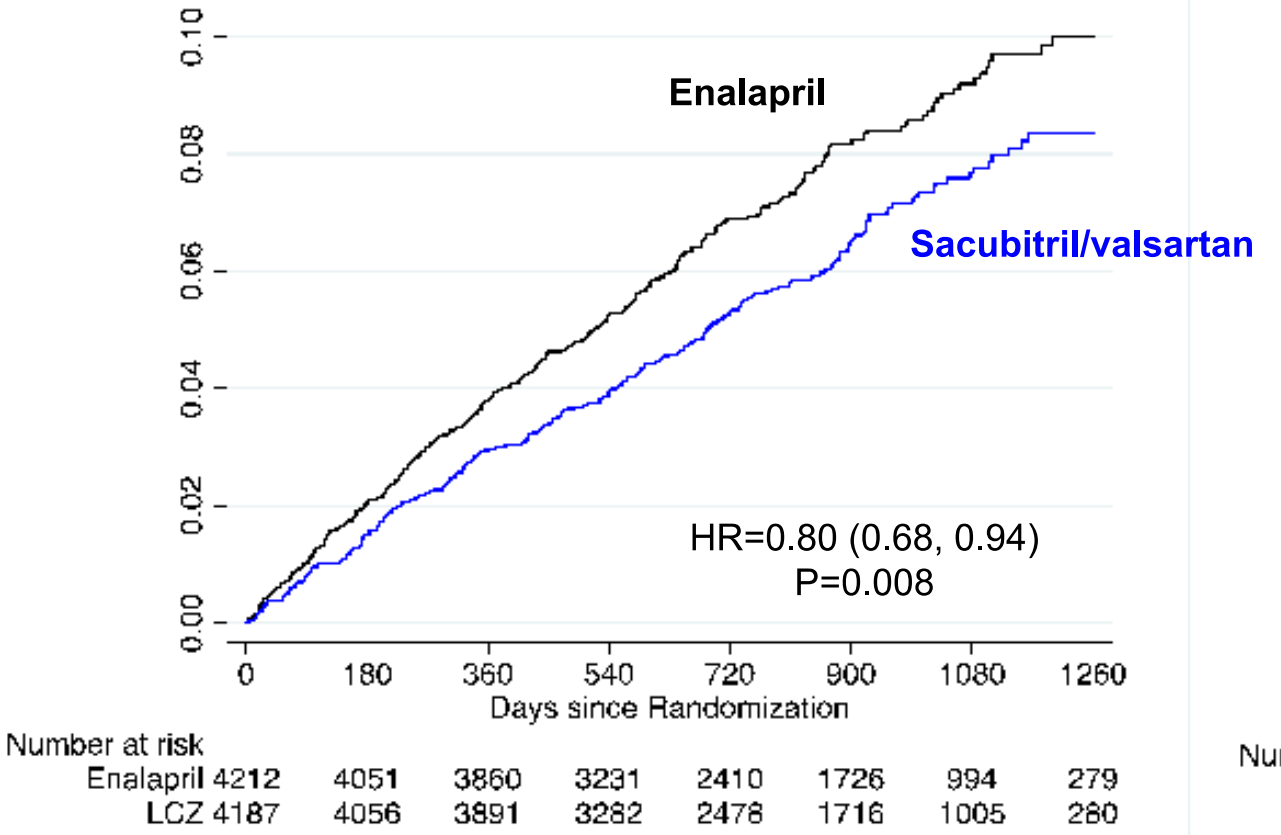
5 year mortality 30% – 50%

HF-rEF: heart failure with reduced ejection fraction

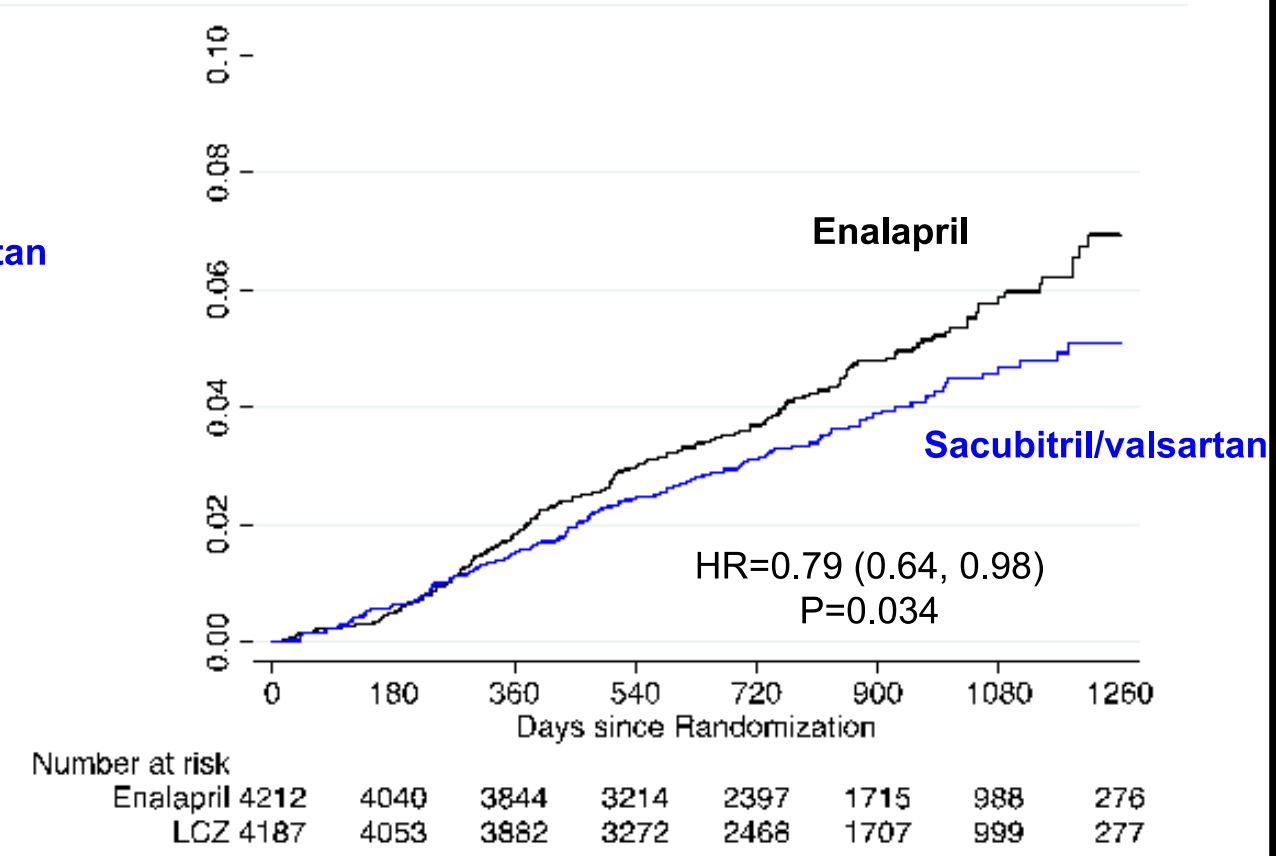
1. Yancy CW *et al. J Am Coll Cardiol* 2013;62(16)e147–239

The two major modes of death in HF

Sudden death

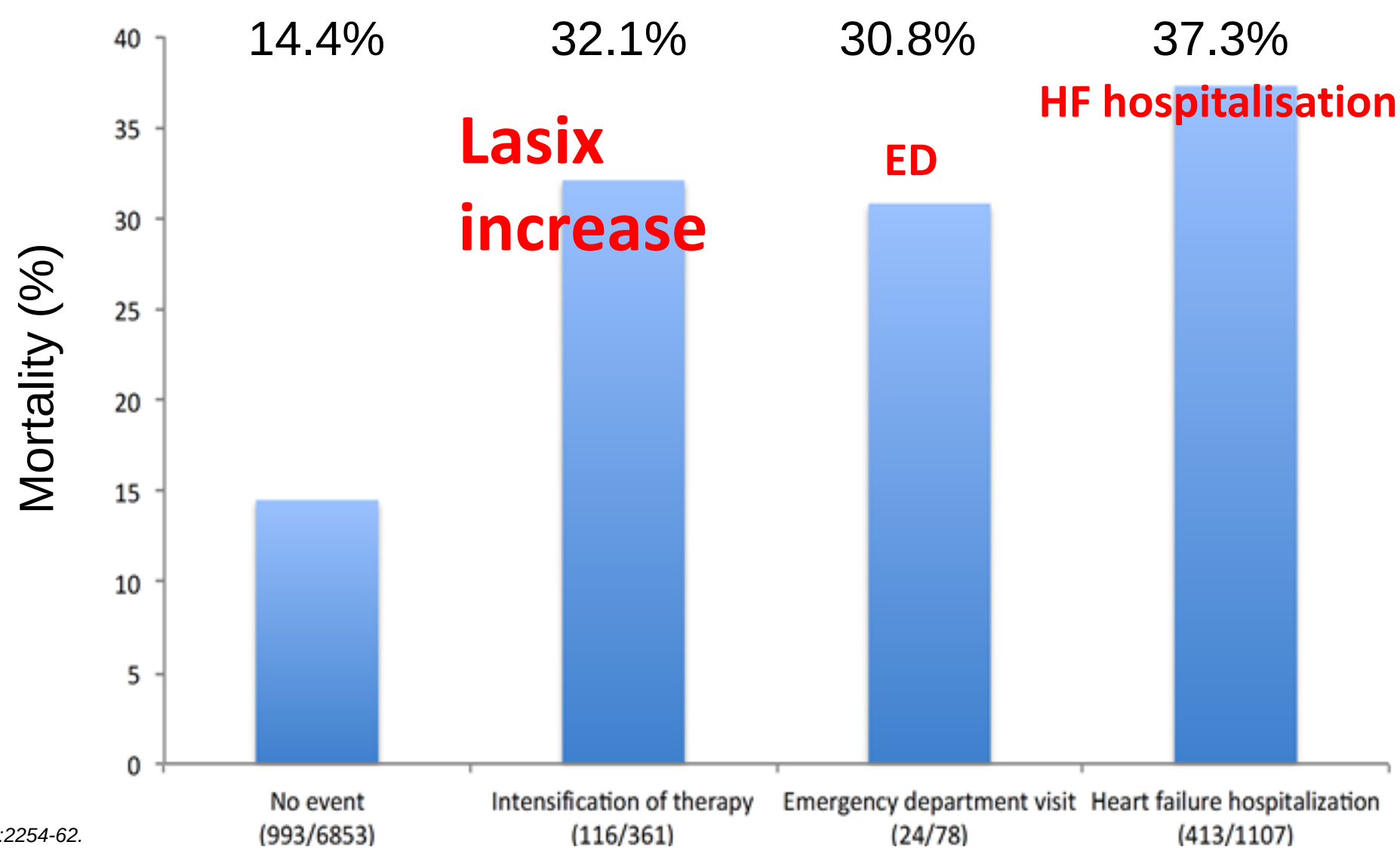


Death due to worsening HF



Desai et al. Eur Heart J 2015;36:1990-7

All-cause mortality (%) after a first event (or in patients with no event)



Okumura et al. Circulation 2016;133:2254-62.

“Stability” is a MYTH

Mrs IZ- 71yo at original presentation

- 2009 “DCM” + LBBB
- Normal coronary angiogram

- “stabilized on medical therapy”

- Further HF exacerbations- 2010. treated with BiV-ICD
- 2010-2016- stable with recovery of LV function

Mrs IZ- 2016

- Recurrent admissions to hospital with APO and cardiogenic shock- treated with adrenaline on 2 separate occasions….
- Severe functional decline
- Repeat left and right heart cath- “low filling pressures” and normal pulmonary artery pressure

Mrs IZ- multiple admissions continue

- Echo: Blown/dilated LV, severe LV dysfunction
- Severe MR- functional/poor coaptation

- TOE- “not suitable for mitral clip”

- BiV system and lead upgraded- new LV lead more lateral- QRS further narrowed….

Mrs IZ- referred to HF service for further medical management….

- NYHA class 3+
- Terrified to leave her house

- Meds:, bicor 2.5mg/d, spironolactone 25mg/d, Lasix 80mg bd, crestor, aropax, ivabradine 7.5mg bd, GTN patch 25mg

- Drugs recently down titrated due to hypotension….

- BP 90/60mmHg. Hr 75

Bloods

Date	28/12/16	29/12/16	07/01/17	**14/02/17**		
S SODIUM	137	144	136	**139**	mmol/L	(135-145)
S POTASSIUM	4.9	3.8	3.7	**3.2 L**	mmol/L	(3.5-5.5)
S CHLORIDE	89 L	95	92 L	**95**	mmol/L	(95-110)
S BICARB.	32	34 H	30	**31**	mmol/L	(20-32)
S UREA	15.0 H	13.7 H	10.3 H	**5.6**	mmol/L	(3.5-9.5)
S CREAT.	107 H	74	79	**74**	umol/L	(45-90)
eGFR	44	68	63	**68**		
S T-BIL.			21 H	**12**	umol/L	(3-15)
S ALP			80	**70**	U/L	(30-115)
S GGT			103 H	**35**	U/L	(5-35)
S ALT			47 H	**16**	U/L	(5-30)
S AST			26	**21**	U/L	(10-35)
S T-PROTEIN			68	**70**	g/L	(63-80)
S ALBUMIN			36	**40**	g/L	(33-44)
S GLOBULIN			32	**30**	g/L	(26-41)

NT-proBNP

Date	21/06/10	20/12/16	07/01/17	**14/02/17**		
S NT-proBNP	18	1244 H	221 H	**385 H**	pmol/L	(<35)

Progress

- Feb 14th 2017: sacubitril/valsartan 24/26… BP 90/60
- Feb 27th 2017: sacubitril/valsartan 24/26 1 bd BP 85-90/60
- March 6th 2017 bloods:

S SODIUM	137	
S POTASSIUM	4.7	
S CHLORIDE	94	L
S BICARB.	28	
S UREA	10.7	H
S CREAT.	96	H
eGFR	50	

S NT-proBNP	129	H

Functional capacity- April 2017

- Improving
- NYHA 2
- Out in the garden
- Some postural dizziness

- GTN patch ceased March 2017

May 2017

- Feeling well. No admissions to hospital

Date:		18/05/17		30/03/17
Coll. Time:		NS		11:20
Lab Number:		5395573		4429515
Sodium		141		140
Potassium		4.6	*	**5.3**
Chloride		103		99
Bicarbonate		30	*	**34**
Urea		7.1		7.2
Creatinine	*	**109**	*	**93**
eGFR		43		52

2017 – Feb 2018 Progress

- No admissions, independent out of the house

- Frusemide reduced to 80mg/d
- Sacubitril/valsartan 24/26 bd
- Spironolactone 25mg/d
- Bicor 2.5 mg /d
- Ivabradine 7.5mg bd
- Frusemide 80mg /daily

BP 110/70mmHg
Hr 55bpm
Echo: Severe LV dysfunction + mod MR. 6cm LV

Feb 2018 – January 2019

- Sacubitril/valsartan gradually uptitrated to 97/103mg bd
- Frusemide gradually reduced to and ceased

- **NYHA class 1…..**

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 11, 2014 VOL. 371 NO. 11

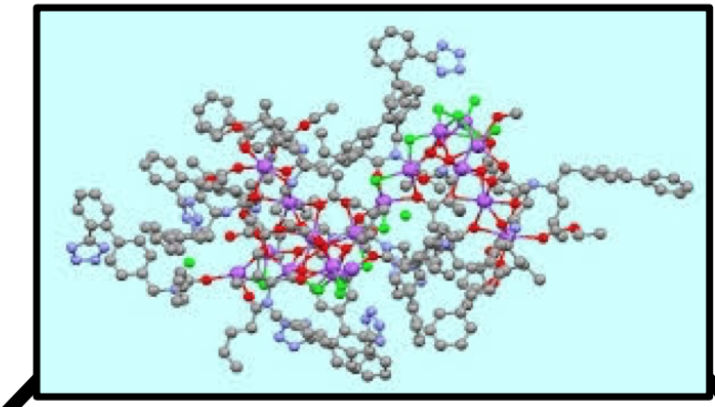
Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees*

What is Neprilysin?

- Protease inactivates many peptides
- Ubiquitous expression
- Membrane protease
- Exists as a soluble active form

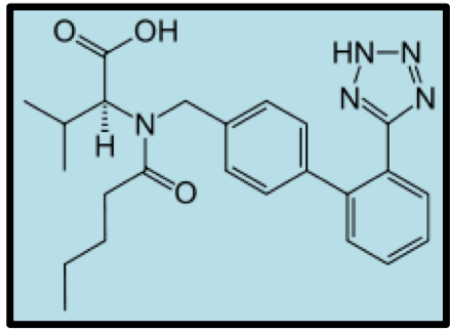
ARNI-
sacubitril/
valsartan

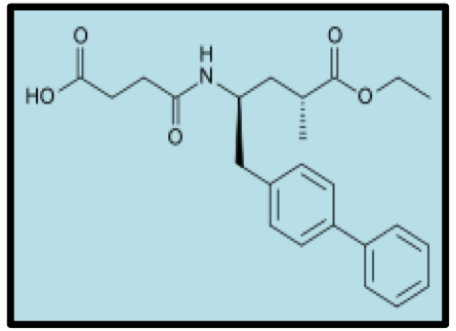


Angiotensin receptor blocker

+

Inhibition of neprilysin





Valsartan

Sacubitril

PARADIGM- HF- what are we looking at?

Sacubitril/Valsartan + all best optimal guideline based therapy

Vs

Enalapril 20mg + all best optimal guideline based therapy

- HFrEF
- EF <40%
- NYHA class II/III (71.6%/23%)

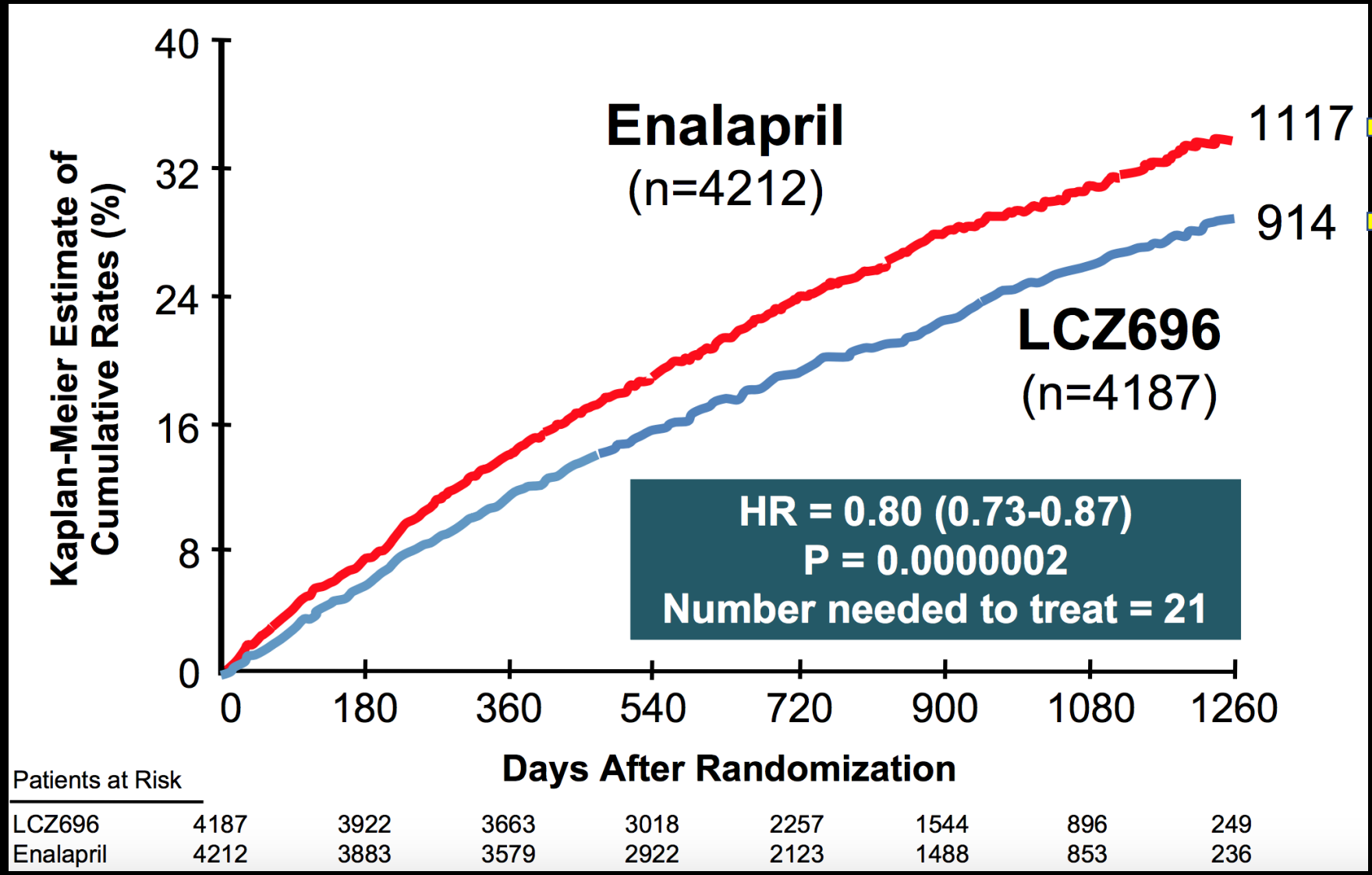
PARADIGM-HF: Endpoints

- Primary endpoint- Cardiovascular death or heart failure hospitalisation
- Designed and powered to be a cardiovascular mortality trial

PARADIGM-HF

- Study stopped early
- Overwhelming benefit of Sacubitril/Valsartan
- 27 months

PARADIGM-HF: CV death and Heart Failure hospitlisation



NNT = 21

PARADIGM-HF- Well treated HF patients

Table 1. (Continued.)

Characteristic	LCZ696 (N = 4187)	Enalapril (N = 4212)
Treatments at randomization — no. (%)		
Diuretic	3363 (80.3)	3375 (80.1)
Digitalis	1223 (29.2)	1316 (31.2)
Beta-blocker	3899 (93.1)	3912 (92.9)
Mineralocorticoid antagonist	2271 (54.2)	2400 (57.0)
Implantable cardioverter–defibrillator	623 (14.9)	620 (14.7)
Cardiac resynchronization therapy	292 (7.0)	282 (6.7)

Beta blocker use >90%

PARADIGM-HF: Adverse Events

Increase in hypotension

Better for renal function and potassium

Less cough	LCZ696 (n=4187)	Enalapril (n=4212)	P Value
Prospectively identified adverse events			
Symptomatic hypotension	588	388	< 0.001
Serum potassium > 6.0 mmol/l	181	236	0.007
Serum creatinine ≥ 2.5 mg/dl	139	188	0.007
Cough	474	601	< 0.001

What about angioedema?

	LCZ696 (n=4187)	Enalapril (n=4212)	P Value
Angioedema (adjudicated)			
Medications, no hospitalization	16	9	NS
Hospitalized; no airway compromise	3	1	NS
Airway compromise	0	0	----

No significant difference

Discontinuation for adverse events

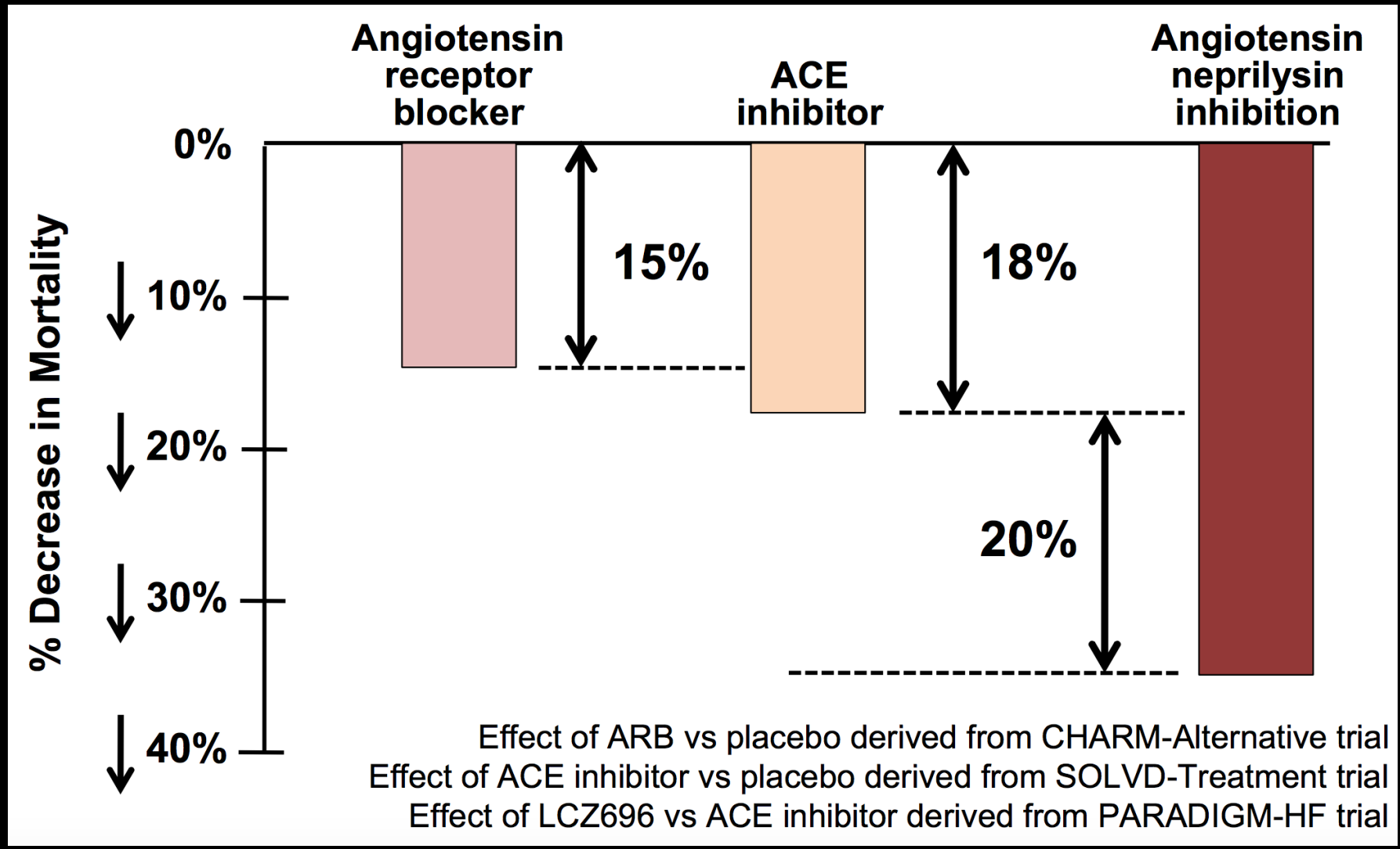
Significantly more patients in the Enalapril arm discontinued due to renal dysfunction

	LCZ696 (n=4187)	Enalapril (n=4212)	P Value
Discontinuation for adverse event	**449**	**516**	**0.02**
Discontinuation for hypotension	36	29	NS
Discontinuation for hyperkalemia	11	15	NS
Discontinuation for renal impairment	29	59	0.001

PARADIGM-HF: Summary

- In heart failure reduced ejection fraction on optimal medical therapy Sacubitril/Valsartan was significantly more effective than Enalapril
  - Reduce CV death and HF hospitalisation
  - Reduce all-cause mortality
  - Improved symptoms and physical limitations
  - Better tolerated than Enalapril

20% more benefit with ARNI over standard care



PARADIGM-HF: Secondary endpoints

	LCZ696 (n=4187)	Enalapril (n=4212)	Treatment effect	P Value
KCCQ clinical summary score at 8 months	– 2.99 ± 0.36	– 4.63 ± 0.36	1.64 (0.63, 2.65)	0.001
New onset atrial fibrillation	84/2670 (3.2%)	83/2638 (3.2%)	Hazard ratio 0.97 (0.72,1.31)	0.84
Protocol-defined decline in renal function	94/4187 (2.3%)	108/4212 (2.6%)	Hazard ratio 0.86 (0.65, 1.13)	0.28

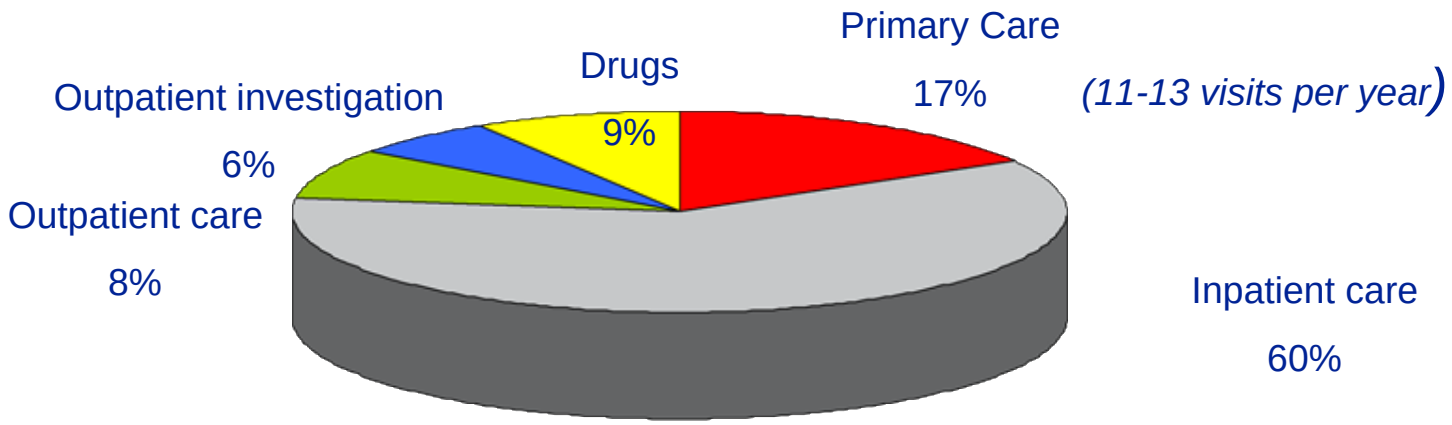
Improved symptoms and quality of life

Hospitalisation


ACROSS VICTORIA
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
WITHIN 30 DAYS OF BEING DISCHARGED
1 in 4
PATIENTS WITH HEART FAILURE
WILL BE READMITTED TO HOSPITAL[1]
25.3%

Burden of Heart Failure Costs

The cost of heart failure is driven by hospitalisation



Total cost > GBP 1 billion (1% of annual NHS budget)

British Heart Foundation, 2002 (updated to 2014)

ARNI- Heart failure hospitalisation

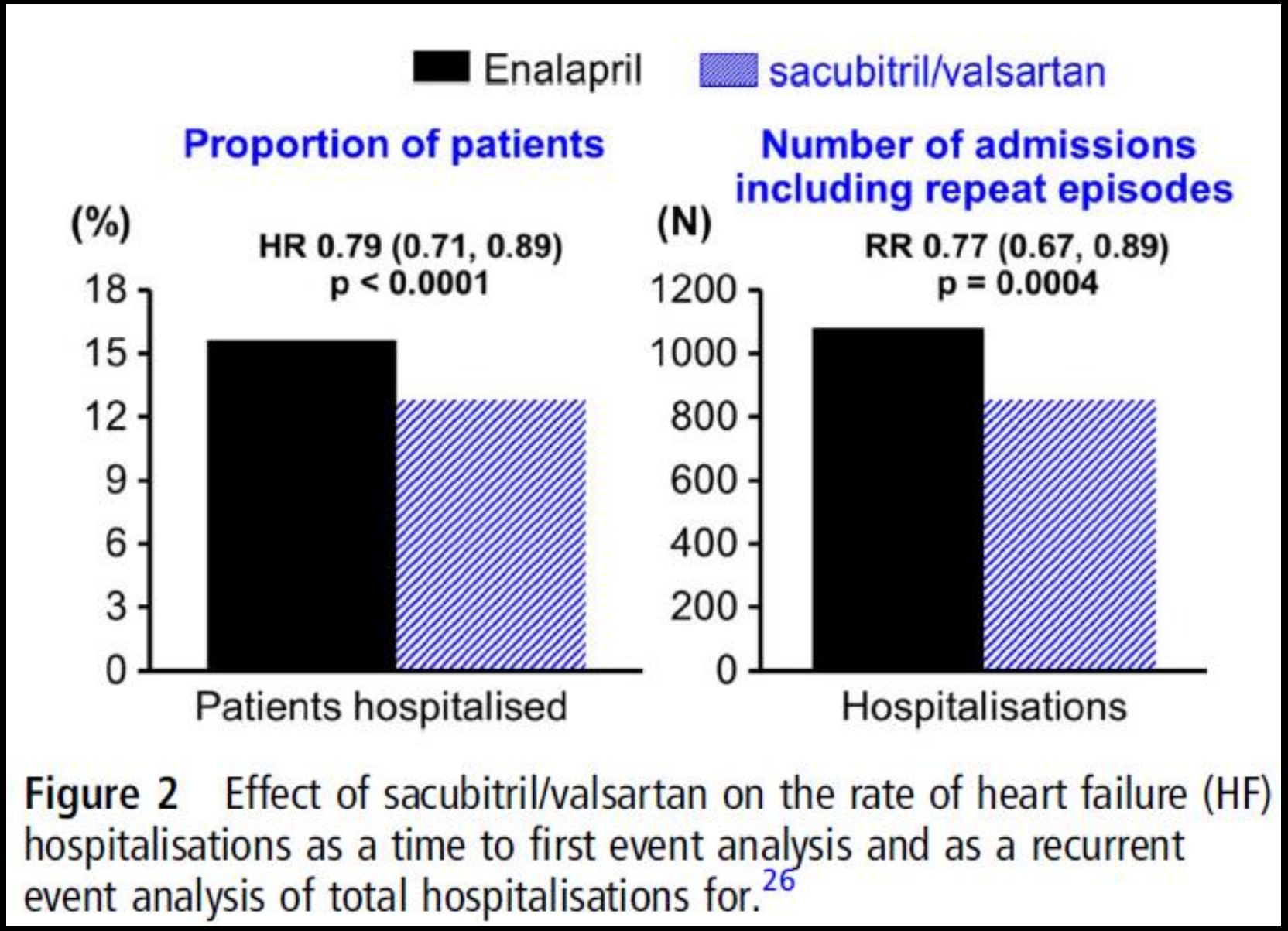
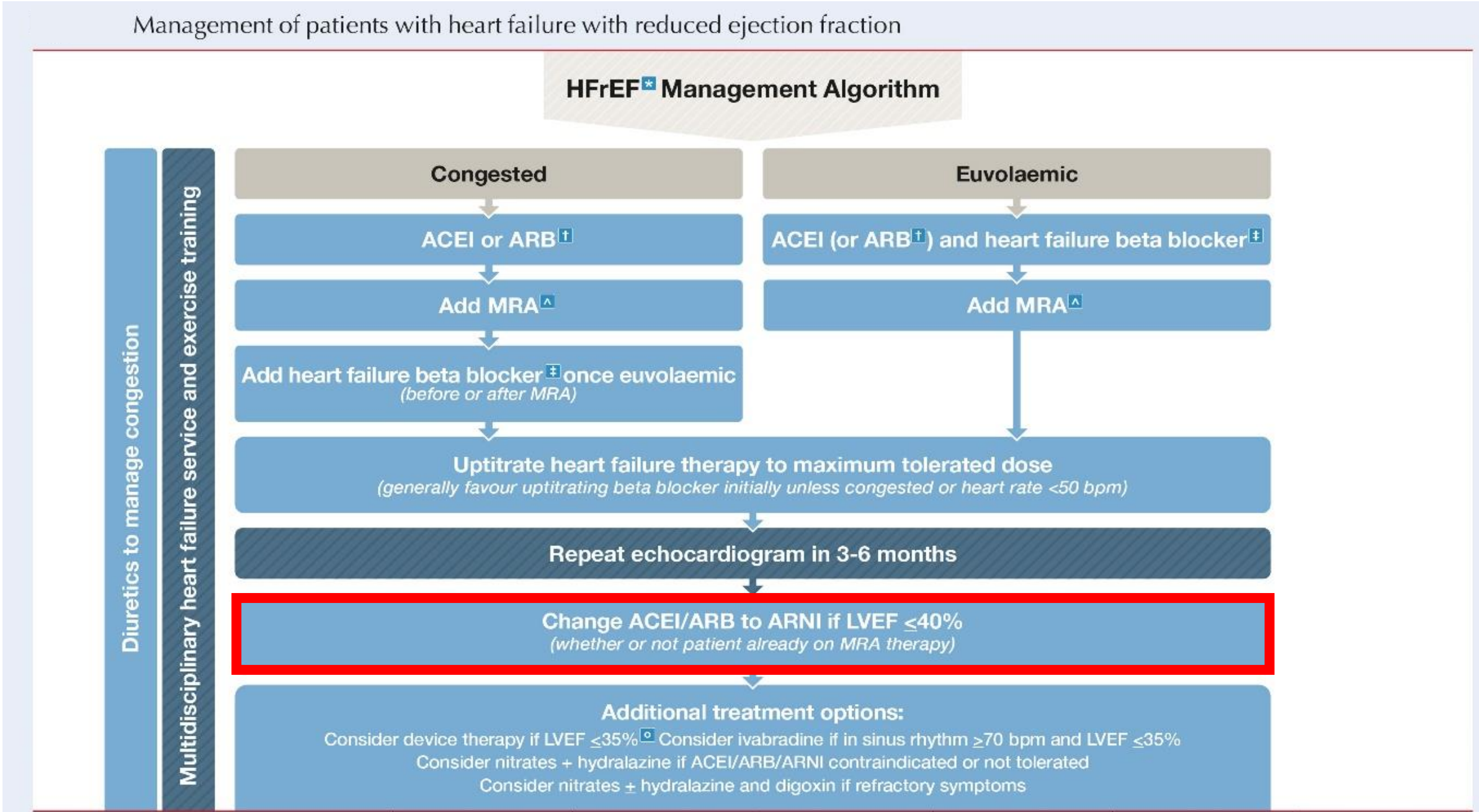


Figure 2 Effect of sacubitril/valsartan on the rate of heart failure (HF) hospitalisations as a time to first event analysis and as a recurrent event analysis of total hospitalisations for.[26]

Jhund PS, McMurray JJV;
The neprilysin pathway in heart failure: a review and guide on the use of sacubitril/valsartan
Heart 2016;102:1342-1347.


FOLLOW THE
GUIDELINES

2018 CSANZ / Heart Foundation Australian Guidelines



Pharmacological management (HF with EF ≤35-40%)

Recommendation	GRADE strength of recommendation	GRADE quality of evidence
An angiotensin receptor blocker (ARB) is recommended in patients with HFrEF associated with an LVEF less than or equal to 40% if an ACE inhibitor is contraindicated or not tolerated, to decrease the combined endpoint of cardiovascular mortality and HF hospitalisation.[1]	Strong	Moderate
An angiotensin receptor neprilysin inhibitor (ARNI) is recommended as a replacement for an ACE inhibitor (with at least a 36-hour washout window) or an ARB in patients with HFrEF associated with an LVEF of less than or equal to 40% despite receiving maximally tolerated or target doses of an ACE inhibitor (or ARB) and a beta-blocker (unless contraindicated), with or without an MRA, to decrease mortality and decrease hospitalisation.[2]	Strong	High
Ivabradine should be considered in patients with HFrEF associated with an LVEF of less than or equal to 35% and with a sinus rate of 70 bpm and above, despite receiving maximally tolerated or target doses of an ACE inhibitor (or ARB) and a beta-blocker (unless contraindicated), with or without an MRA, to decrease the combined endpoint of cardiovascular mortality and HF hospitalisation.[3]	Strong	High

1.Granger CB, et al. Lancet. 2003;362(9386):772-6.
2.McMurray JJ, et al. N Engl J Med. 2014;371(11):993-1004.
3.Swedberg K et al. Lancet. 2010;376(9744):875-885.

Case 1: Switching to an ARNI

Case 1: 63yo HFrEF- ischaemic

- CAGS 4 years ago
- HTN
- Gout

- Meds:

Carvedilol 12.5mg bd
Ramipril 10mg/d
Spironolactone 12.5mg d

aspirin 100mg/d
allopurinol 300mg/d
frusemide 40mg bd

Case 1- The switch

- Cease ACE-I
- Wait 36 hours
- Commence sacubitril/valsartan 24/26mg bd

Watch for increased diuresis

Advise about hypotension

Case 1: Up titrate- every 2 -4 weeks?

- Aim for BP no < 100mmHg
- Sacubitril/valsartan 49/51mg bd

- Likely to reduce diuretic need-
- Scope to increase spironolactone

Aim for maximum dose sacubitril/valsartan 97/103mg bd

Aim- discontinue loop diuretics

Issues to discuss

- Managing hypotension
- Echo requirements
- Using BNP or NT-Pro BNP levels
- Renal dysfunction
- Should patient have an optimal MRA before starting ARNI?

Sacubitril/Valsartan: What to Do in Case of Hypotension?

- Treatment must not be initiated unless SBP is ≥ 100 mmHg
  - Cases of symptomatic hypotension have been reported
  - Especially in patients ≥ 65 years old, patients with renal disease and patients with low SBP
  - When initiating therapy or during dose titration with sacubitril/valsartan, blood pressure should be monitored routinely
- Dose reduction, if systolic BP < 100 mmHg*
- Dose reduction of other antihypertensives (if present)
- Look for over-diuresis and correct it

*Consult prescribing information for additional details

Summary of prescribing characteristics for sacubitril/valsartan

How Is Sacubitril/Valsartan Used in Patients With Renal Insufficiency?

- Normal dosing scheme if eGFR > 30ml/min
- eGFR < 30ml/min – There is limited clinical experience; start with lower dose of 24/26 mg twice daily and consult prescribing information for additional details
- Reduce dose if renal function worsens during treatment (drop in eGFR by > 10ml/min)
- Careful in patients with renal artery stenosis (close follow-up; check for increase in creatinine / BUN)

Renal dysfunction can be very volume dependent- NT-pro BNP valuable clinical aid

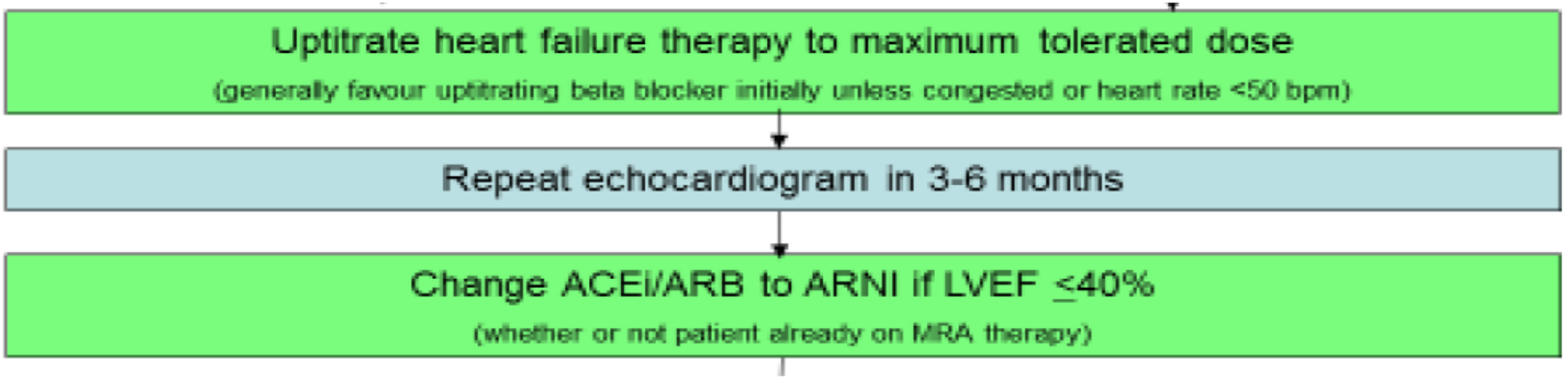
Summary of prescribing characteristics for sacubitril/valsartan.

Sacubitril/Valsartan: What to Do in Case of Hyperkalemia?

- Treatment should not be initiated if the serum potassium level is > 5.4 mmol/l
- Monitoring of serum potassium is recommended especially in patients with:
  - Renal impairment
  - Diabetes mellitus
  - On mineralocorticoid antagonists
- Adjust concomitant medication
- If patients experience clinically significant hyperkalemia adjustment of concomitant medicinal products, or temporary down–titration or discontinuation is recommended
- Stop sacubitril/valsartan if serum potassium level is > 5.4 mmol/l

Summary of prescribing characteristics for sacubitril/valsartan

Do Patients Need a Repeat Echocardiogram Before Starting Sacubitril/Valsartan?



1. If a patient has improved on ACE/ARB + Beta-blocker +/- MRA and you think that their LVEF has improved to > 40%, then repeat echo
2. If a patient is on ACE/ARB + Beta-blocker +/- MRA and they are still symptomatic, then *two options* could be taken:

   a) repeat the echo if you think that something else has occurred, eg worsening valvular regurgitation, pericardial effusion, new wall motion abnormality

Or

   b) change the ACE/ARB to ARNI in the knowledge that this will improve the patient's survival, symptoms, left ventricular function and reduce heart failure hospitalisations

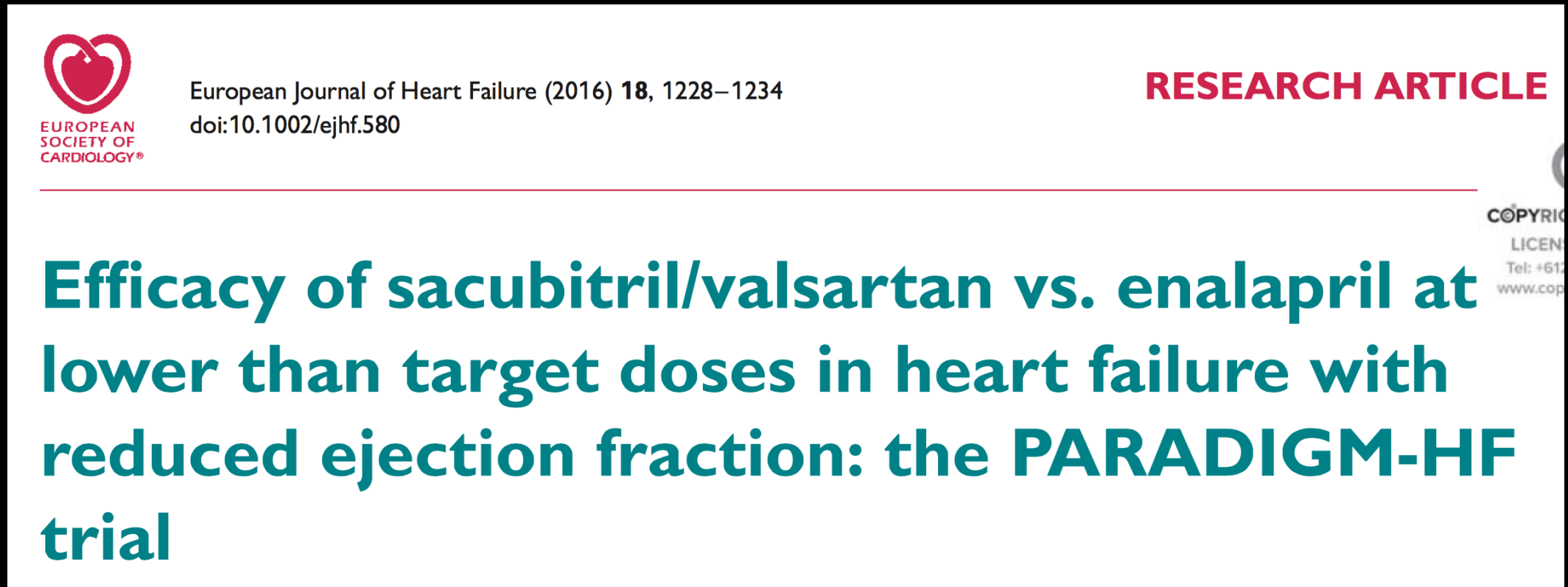
Discussion....

Beyond PARADIGM-HF

A/Prof Gautam Vaddadi

Does Sac/Val work at low dose?

- Post hoc analysis of PARADIGHM-HF
- 43% (Enalapril) and 42% (Sac/Val) reduced dose during the study



EUROPEAN SOCIETY OF CARDIOLOGY®

European Journal of Heart Failure (2016) **18**, 1228–1234
doi:10.1002/ejhf.580

RESEARCH ARTICLE

Efficacy of sacubitril/valsartan vs. enalapril at lower than target doses in heart failure with reduced ejection fraction: the PARADIGM-HF trial

Dose reduction is associated with higher rates of CV death and HF hospitalization

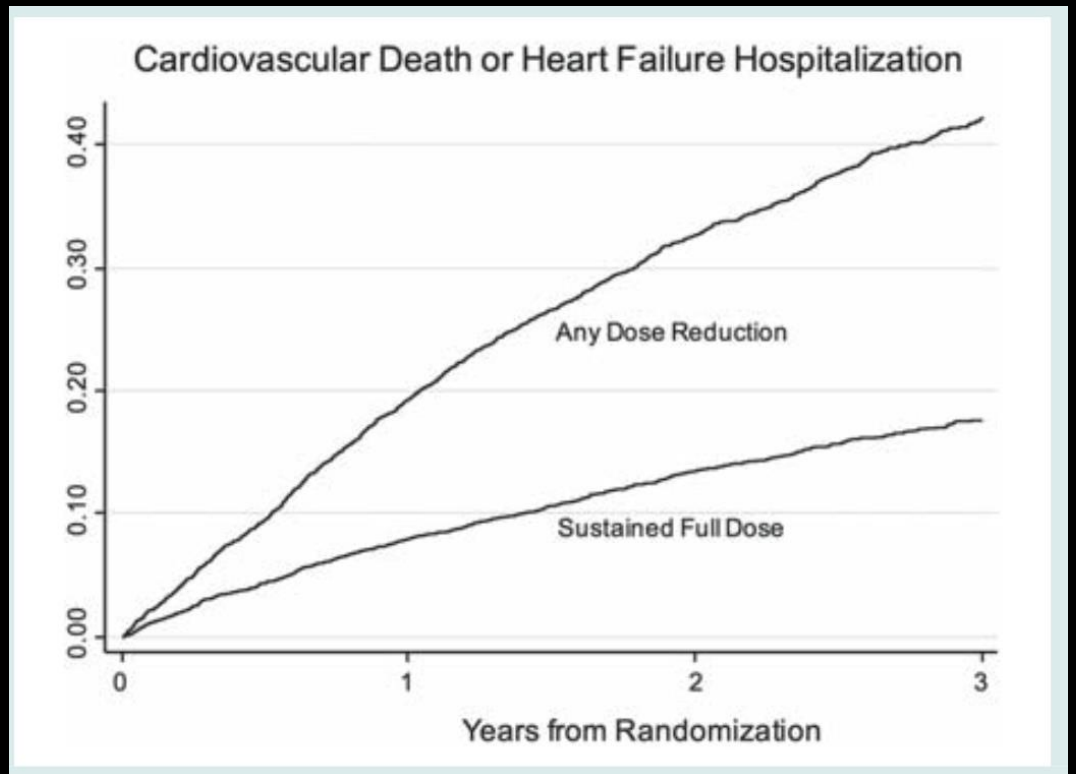
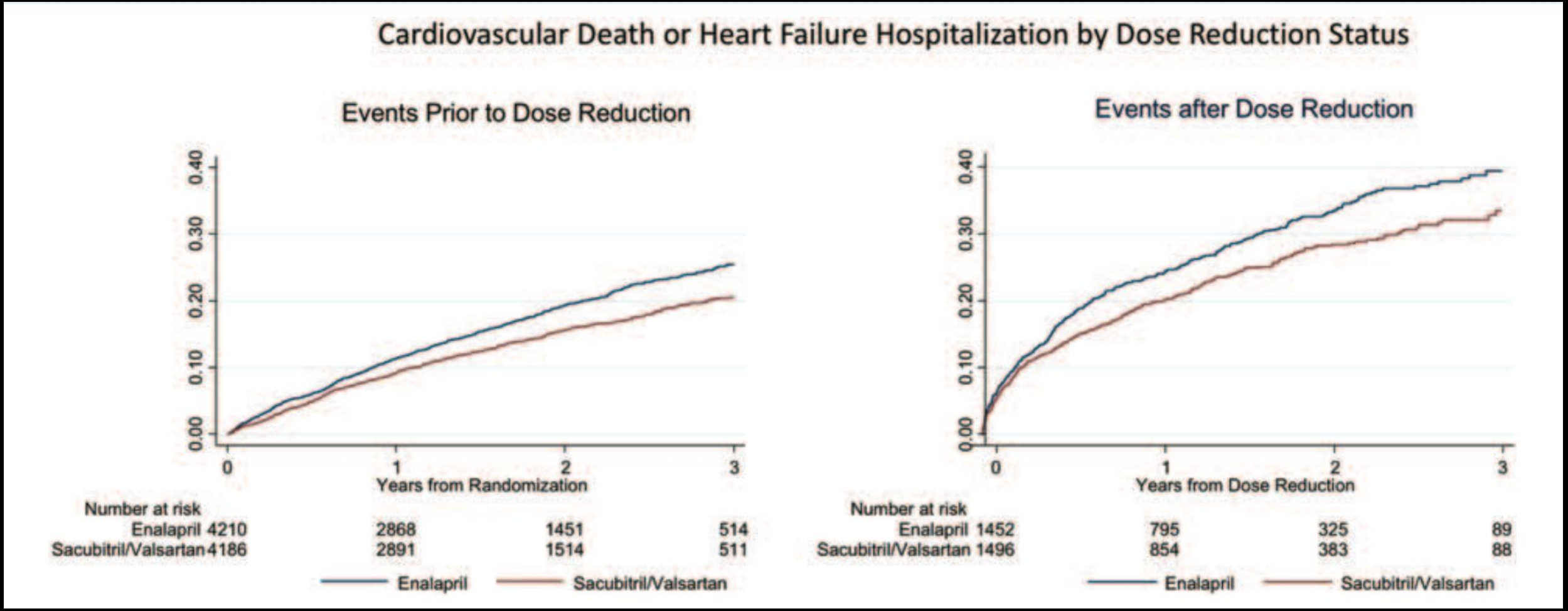


Figure 1 Kaplan–Meier curves showing primary outcome events by dose reduction status. Participants with a dose reduction had a higher risk of the primary event compared with those who remained on full study medication doses.

Sac/Val better than Enalapril in dose reduced patients- CV death and HF hospitlisation



PIONEER –HF: Sac/Val in acute decompensated HF- 8 week trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Angiotensin–Neprilysin Inhibition in Acute Decompensated Heart Failure

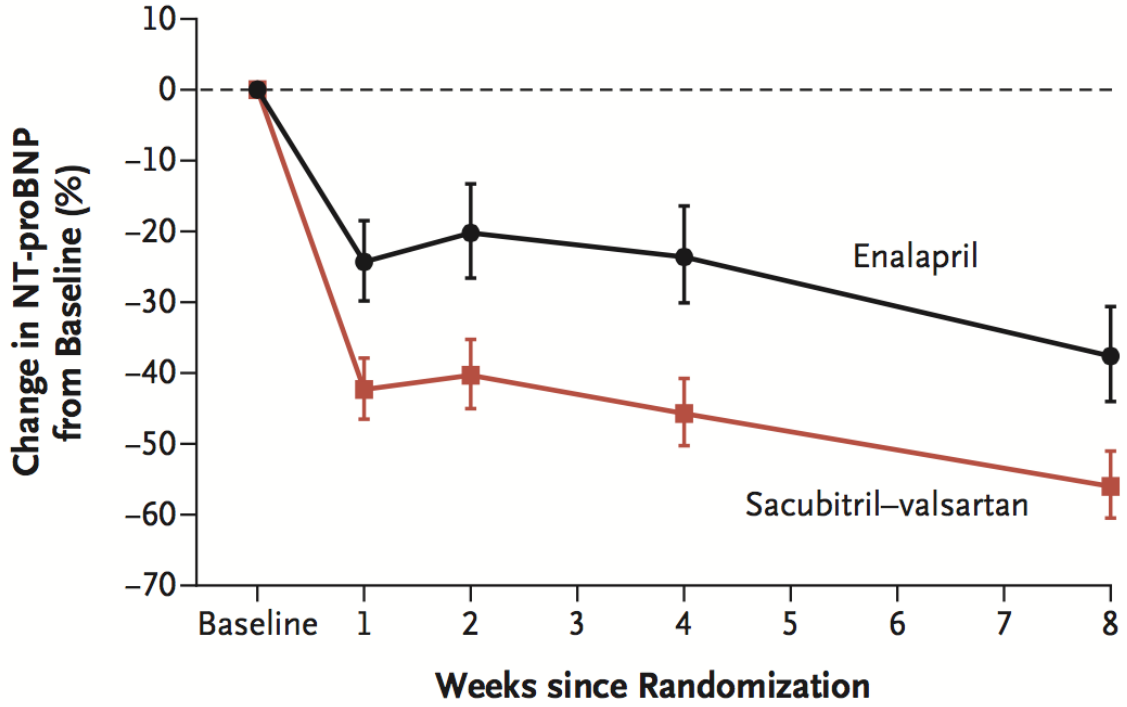
Eric J. Velazquez, M.D., David A. Morrow, M.D., M.P.H., Adam D. DeVore, M.D., M.H.S., Carol I. Duffy, D.O., Andrew P. Ambrosy, M.D., Kevin McCague, M.A., Ricardo Rocha, M.D., and Eugene Braunwald, M.D., for the PIONEER-HF Investigators*

PIONEER-HF: key points of study design

- N=440 in each arm
- 65%- prior heart failure
- Admitted for ADHF- randomized after haemodynamic stabilization

- Sac/Val vs Enalapril

- MRA use was low at 10%



No. at Risk

Enalapril	394	359	351	350	348
Sacubitril–valsartan	397	355	363	365	349

Figure 2. Change in the NT-proBNP Concentration.

The time-averaged reduction in the N-terminal pro–B-type natriuretic peptide (NT-proBNP) concentration was significantly greater in the sacubitril–valsartan group than in the enalapril group; the ratio of the geometric mean of values obtained at weeks 4 and 8 to the baseline value was 0.53 in the sacubitril–valsartan group as compared with 0.75 in the enalapril group (percent change, −46.7% vs. −25.3%; ratio of change with sacubitril–valsartan vs. enalapril, 0.71; 95% CI, 0.63 to 0.81; P<0.001).

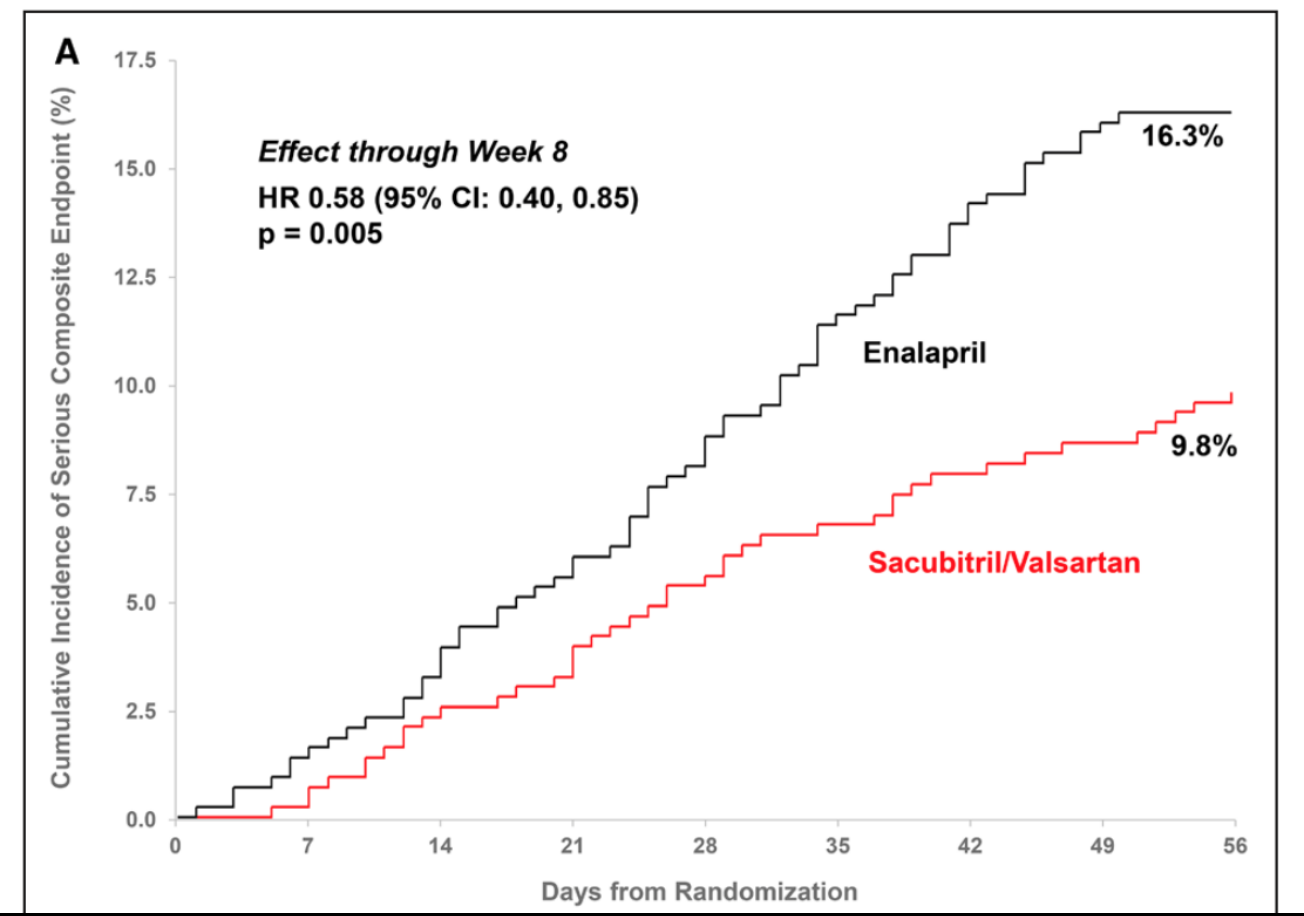
End point of the trial was reduction in NT-proBNP

PIONEER-HF: Safety

- No difference in the following

- Worsening renal function
- Symptomatic hypotension
- Hyperkalaemia
- Angioedema

PIONEER-HF: Sac/Val better than Enalapril for CV death and HF hospitalization

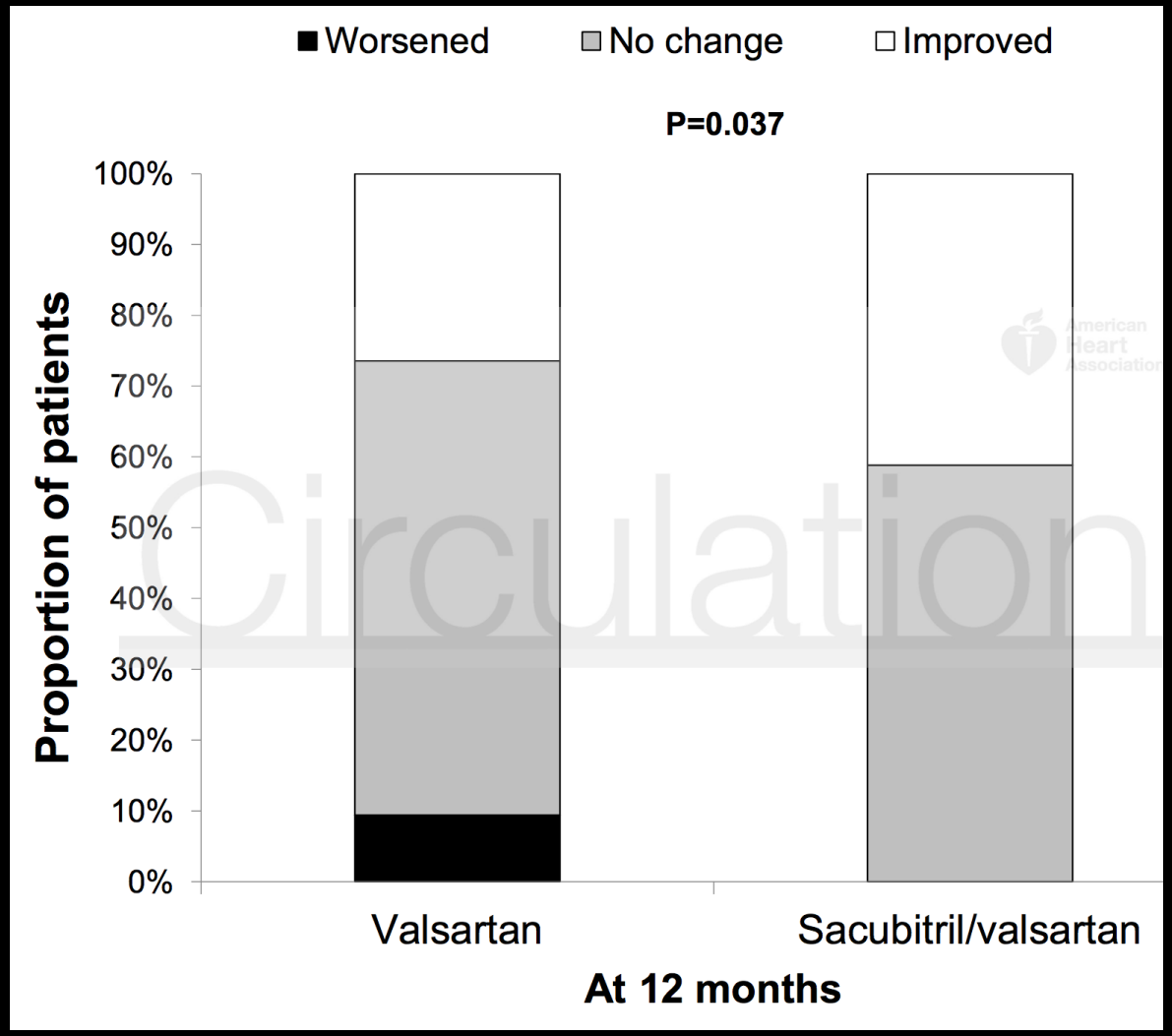


Circulation

RESEARCH LETTER

Clinical Outcomes in Patients With Acute Decompensated Heart Failure Randomly Assigned to Sacubitril/Valsartan or Enalapril in the PIONEER-HF Trial

Functional Mitral Regurgitation Improves with Sacubitril/Valsartan



118 patients randomised to valsartan or sac/val for ”significant” functional MR

90%- NYHA 2

EF- 25-50%

Angiotensin Receptor Neprilysin Inhibitor for Functional Mitral Regurgitation

PRIME Study

Duk-Hyun Kang, Sung-Ji Park, Sung-Hee Shin, Geu-Ru Hong, Sahmin Lee, Min-Seok Kim, Sung-Cheol Yun, Jong-Min Song, Seung-Woo Park, Jae-Joong Kim

Originally published 12 Mar 2019 | https://doi.org/10.1161/CIRCULATIONAHA.118.037077 | Circulation. 2018;139:1354–1365


SUGAR


HaHaStop.com

Case 1: with diabetes…His HbA1c is 8%

- Metformin 1g bd

- BP 105/70mmHg. Hr 65 sinus
- Euvolemic
- Mild-moderate CKD (eGFR 50ml/min)

What's the plan?

Heart failure reduced EF

Ischaemic

Sacubitril/valsartan 97/103mg bd
Carvedilol 25mg bd
Frusemide 40mg d
Aspirin, statin
Spironolactone 25mg/d

European Heart Journal (2008) 29, 1377–1385
doi:10.1093/eurheartj/ehn153

CLINICAL RESEARCH
Heart failure/cardiomyopathy

Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure

An analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme

Michael R. MacDonald[1], Mark C. Petrie[1], Fumi Varyani[2], Jan Östergren[3], Eric L. Michelson[4], James B. Young[5], Scott D. Solomon[6], Christopher B. Granger[7], Karl Swedberg[8], Salim Yusuf[9], Marc A. Pfeffer[6], John J.V. McMurray[2*], and for the CHARM Investigators

Diabetics have higher HF hospitalization rates and all cause death

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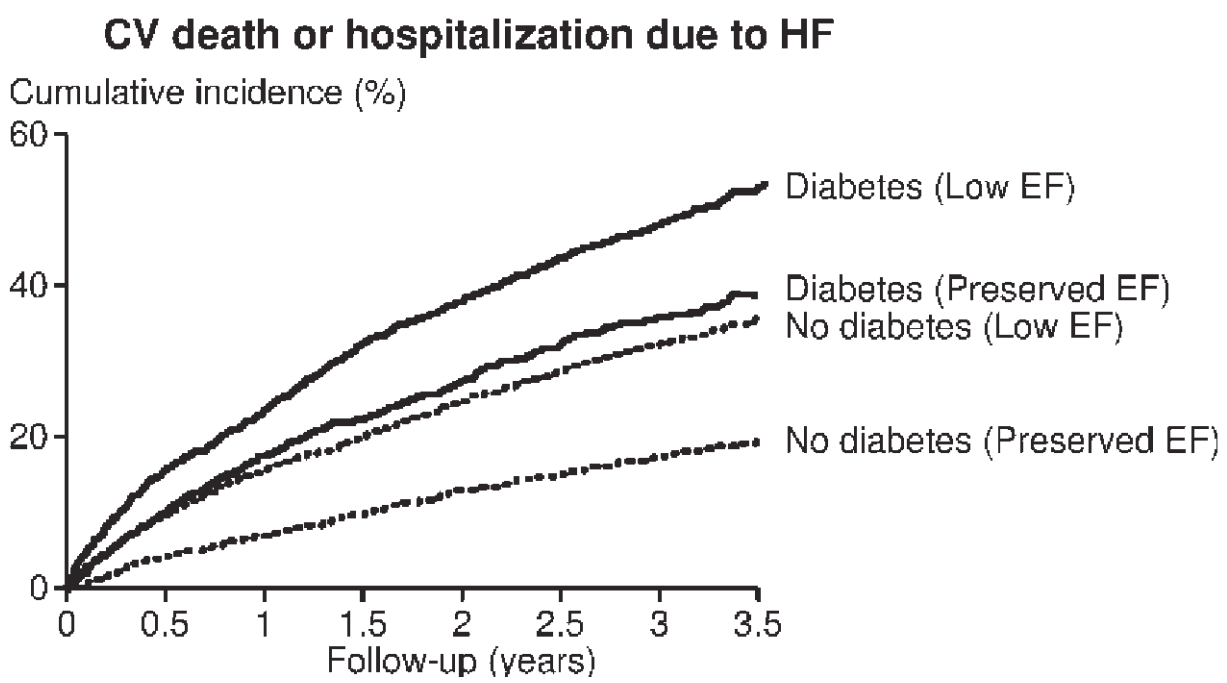
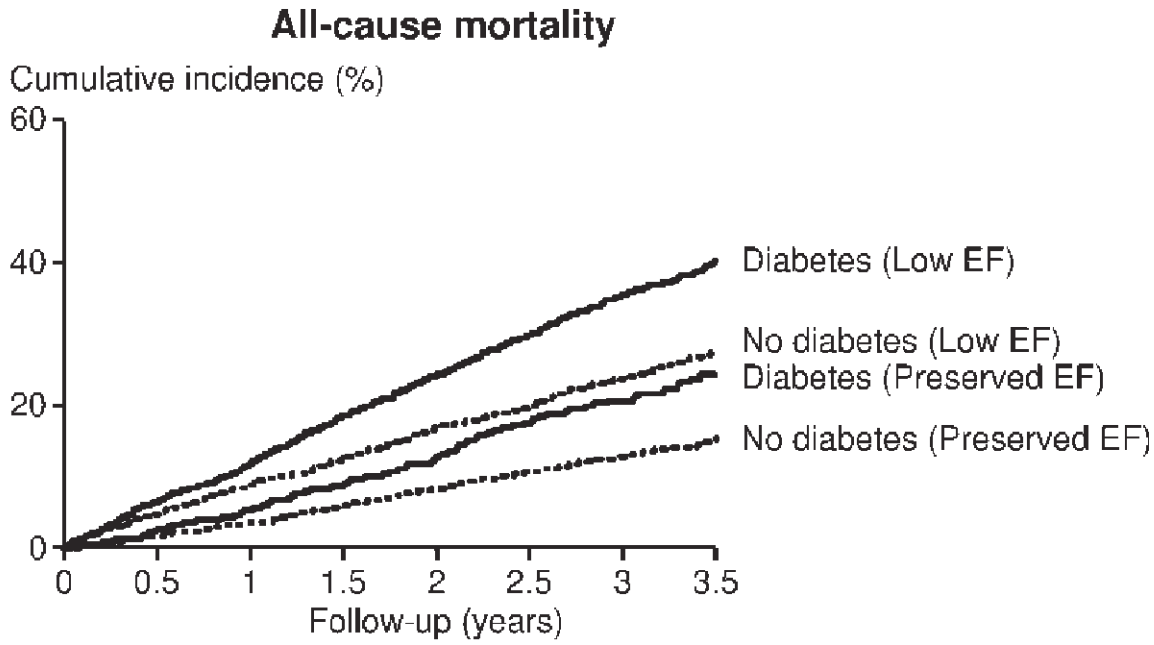




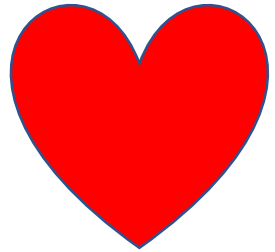
Glucose lowering drugs and HF- A new era?

Lower the HbA1c

↓ Eye disease

↓ neuropathy

?CV disease



Impact of Intensive Glucose-Lowering Therapy in DM: Summary of Major RCTs

Study	Microvasc	CVD	Mortality
UKPDS 33 (7.0 vs. 7.9%)	↓	↔	↔
DCCT / EDIC* (7.2 vs. 9.1%)	↓	↔	↔
ACCORD (6.4% vs. 7.5%)	↓	↔	↑
ADVANCE (6.3% vs. 7.0%)	↓	↔	↔
VADT (6.9% vs. 8.4%)	↓	↔	↔

UKPDS Group. *Lancet* 1998;352:854; Holman RR. *NEJM* 2008;359:1577; DCCT Group. *NEJM* 1993;329;977; Nathan DM. *NEJM* 2005;353:2643. Gerstein HC. *NEJM* 2008;358:2545; Patel A. *NEJM* 2008;358:2560; Duckworth W. *NEJM* 2009;360:129. (*erratum*:361:1024); DCCT Group. JAMA 2015:313:45

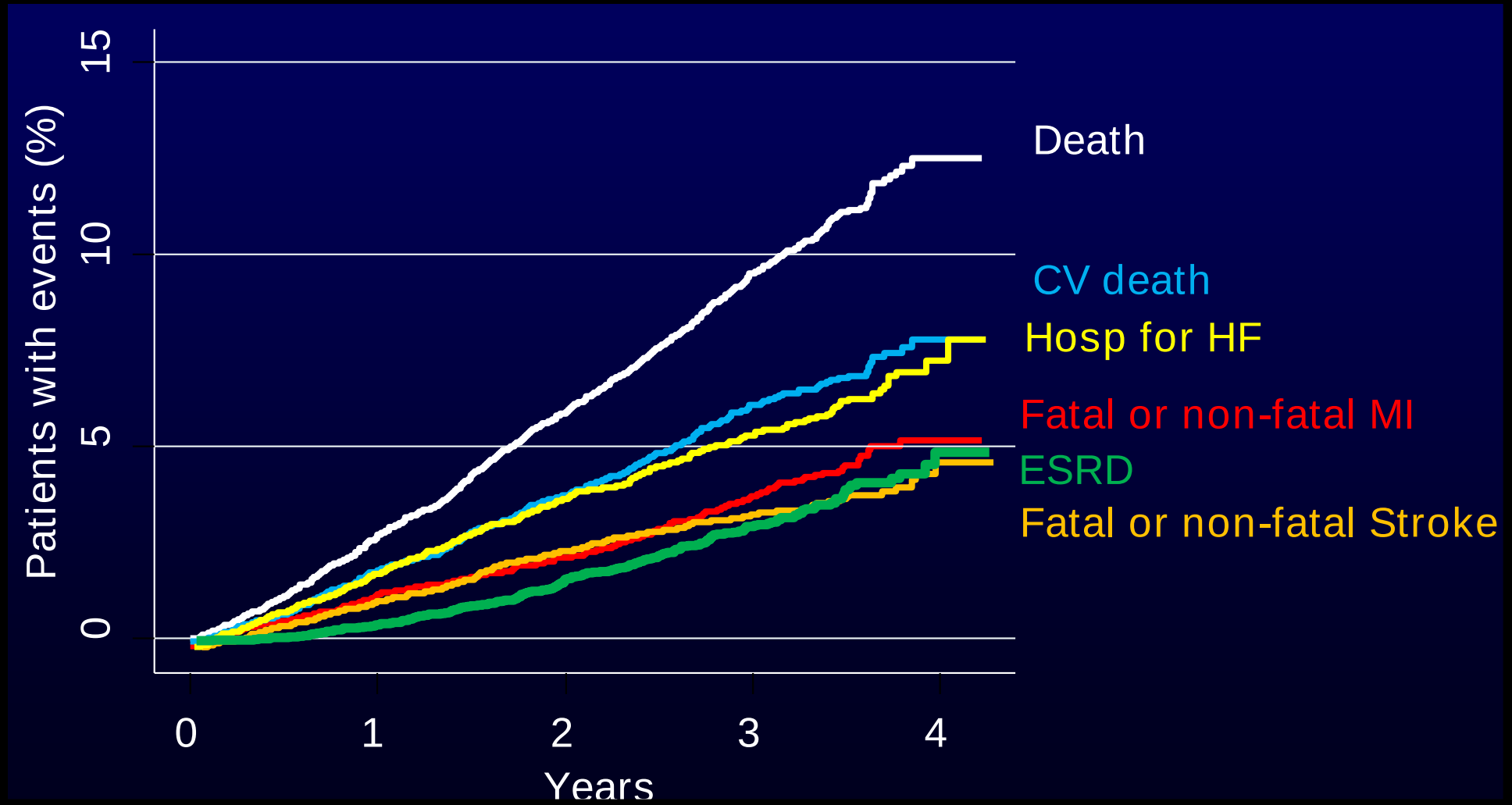
* in T1DM

Heart failure not primary endpoint in any diabetic drug trial….

CV Outcome Trials by drug class

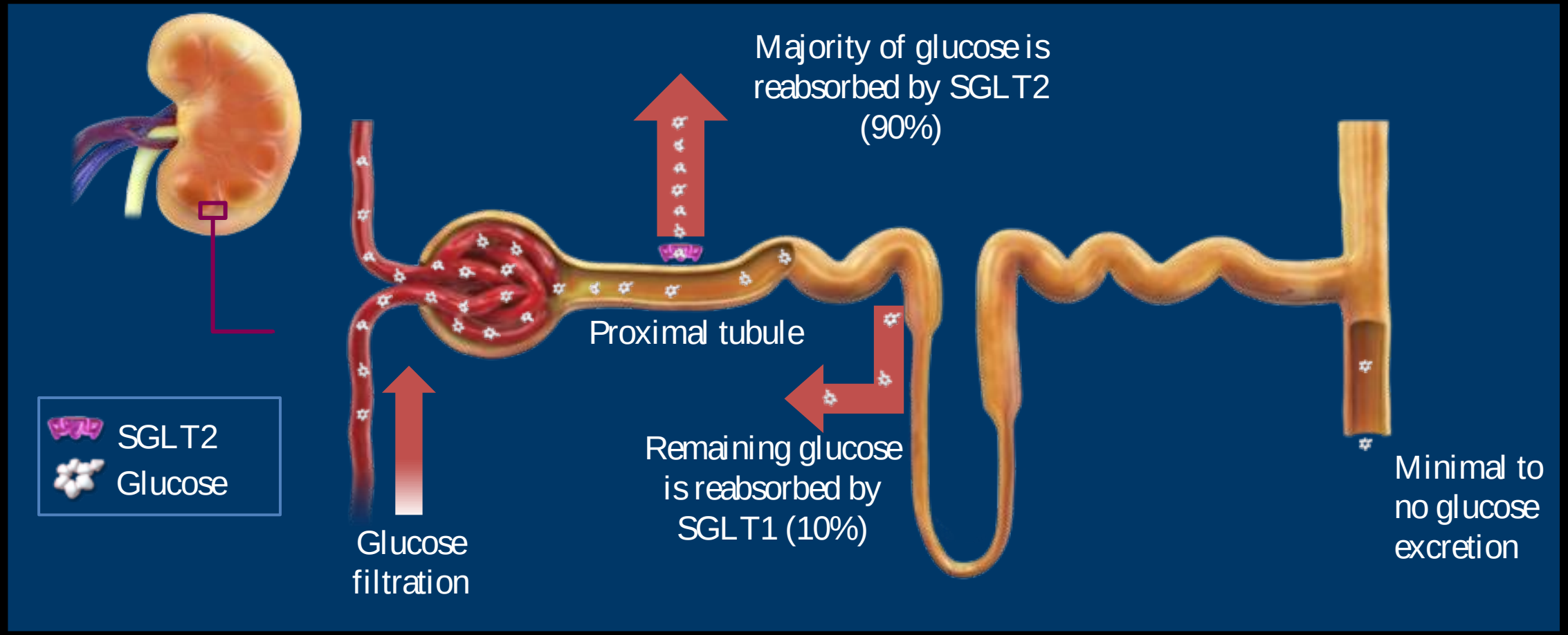
Agent	Trial	Additional factors	N	CV Death in 1°	MI/ACS in 1°	Stroke in 1°	HF in 1°
Saxagliptin	SAVOR-TIMI 53	CVD and/or RFs, A1C ≥6.5%	16,496	✔	✔	✔	✘
Sitagliptin	TECOS	Pre-existing CVD, A1C 6.5-8%	14,671	✔	✔	✔	✘
Linagliptin	CAROLINA	CVD or end-organ damage or RFs A1C 6.5-8.5%	6,000	✔	✔	✔	✘
Alogliptin	EXAMINE	ACS, A1C 6.5-11%	5,380	✔	✔	✔	✘
MK-3102	MK-3102-018 AM5	Pre-existing CVD	4,202	✔	✔	✔	✘
Liraglutide	LEADER	CVD risk or age/RFs, A1C ≥7%,	9,340	✔	✔	✔	✘
Lixisenatide	ELIXA	ACS, A1C 5.5-11%	6,068	✔	✔	✔	✘
Dulaglutide QW	REWIND	High CV risk, A1C ≤9.5%	9,622	✔	✔	✔	✘
Exenatide QW	EXSCEL	A1C 6.5-10% and CVD	14,000	✔	✔	✔	✘
Semaglutide	SUSTAIN	Pre-existing CVD	3,297	✔	✔	✔	✘
Canagliflozin	CANVAS	High CV risk, A1C 7-10.5%	4,411	✔	✔	✔	✘
Dapagliflozin	DECLARE-TIMI 58	High CV risk	17,150	✔	✔	✔	✘
Empagliflozin	C-SCADE 8	Pre-existing CV	7,097	✔	✔	✔	✘
Aleglitazar	ALEPREVENT	CVD + T2D or glucose abnormality	19,000	✔	✔	✔	✘
	ALECARDIO	ACS + T2D	7,226	✔	✔	✔	✘
Insulin degludec	Not known	Criteria not known	7,637	✔	✔	✔	✘
All trials			**151,597**	✔	✔	✔	ZERO

Heart failure is the top non-fatal event in diabetic trials



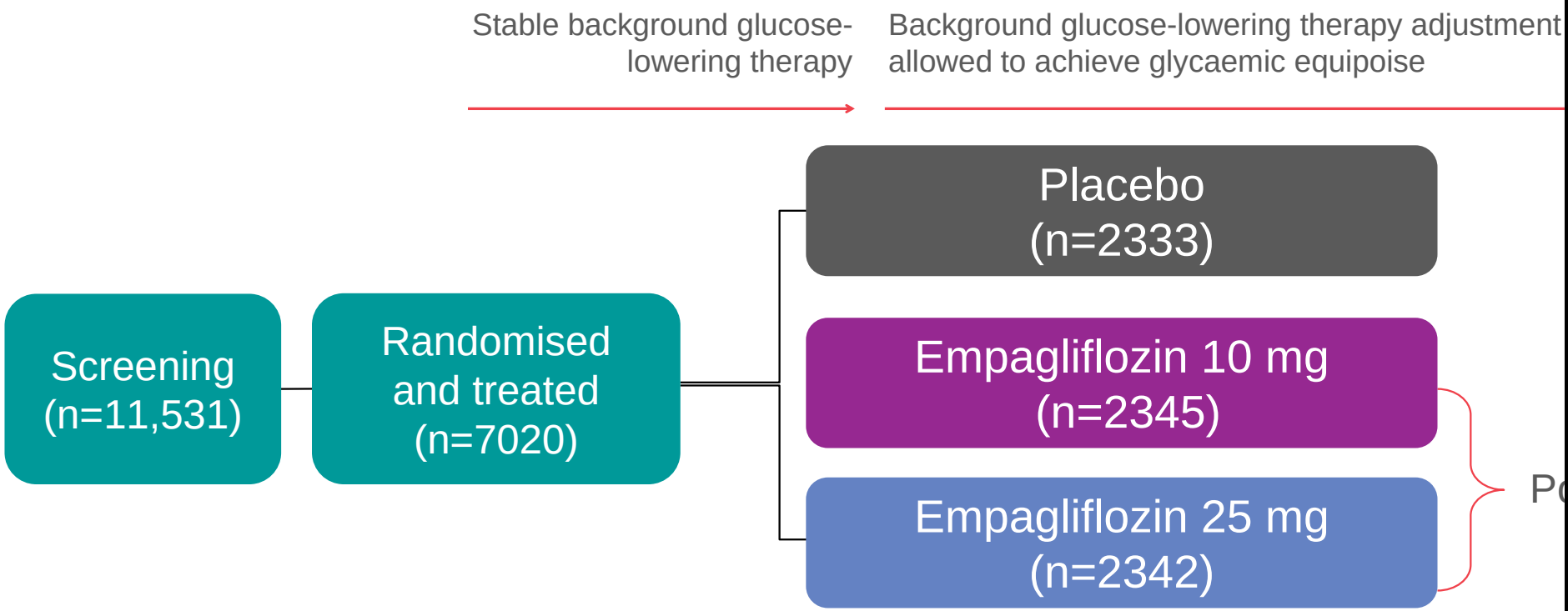
M Pfeffer, 2017 HFA meeting Paris Data from NEJM 2012- Trial of direct renin inhibitor in T2DM

SGLT-2 inhibition: Focus on EMPA REG CV outcome study



Empaglifozin: WOW!!!

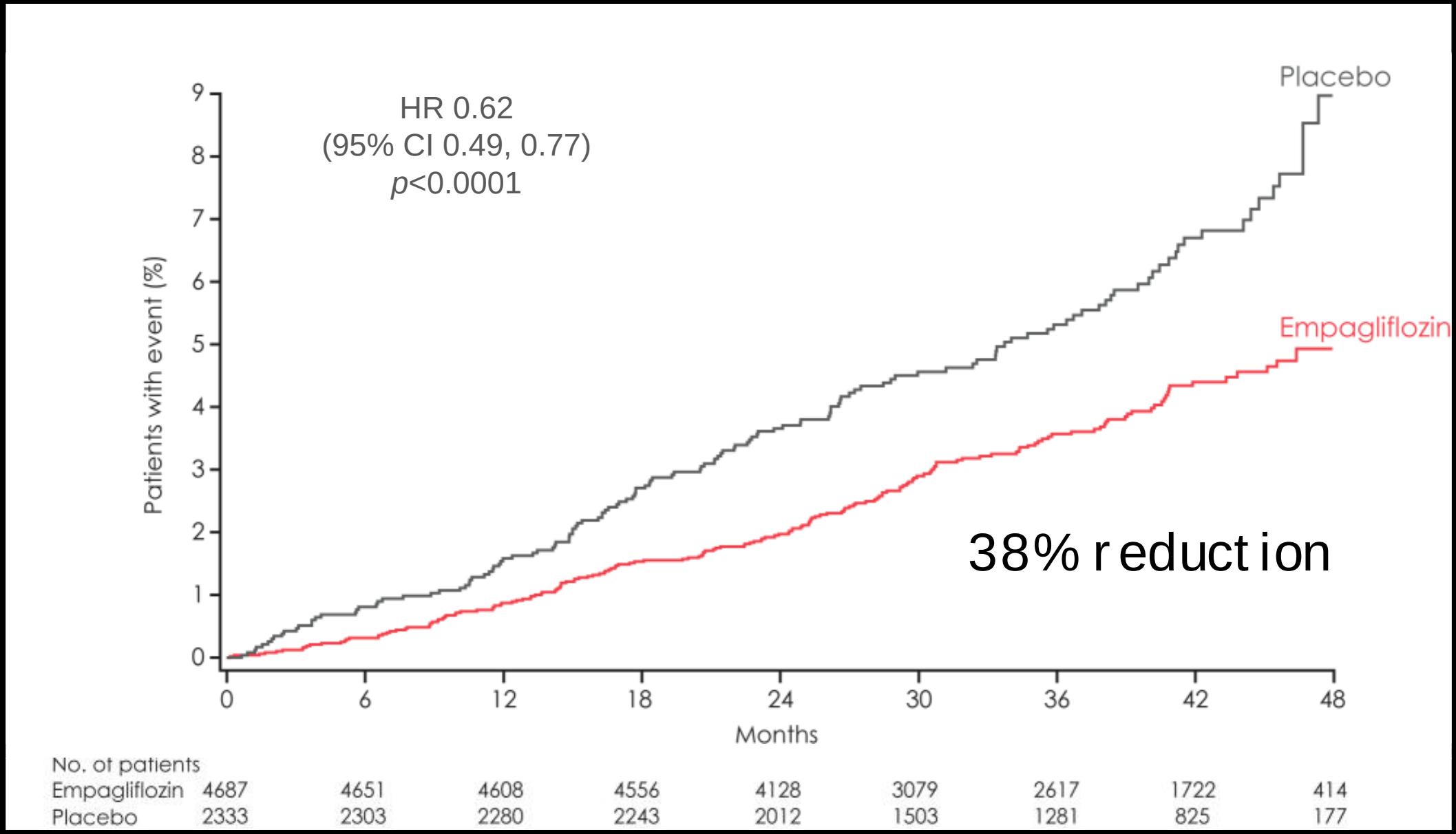
EMPA REG OUTCOME: Trial design



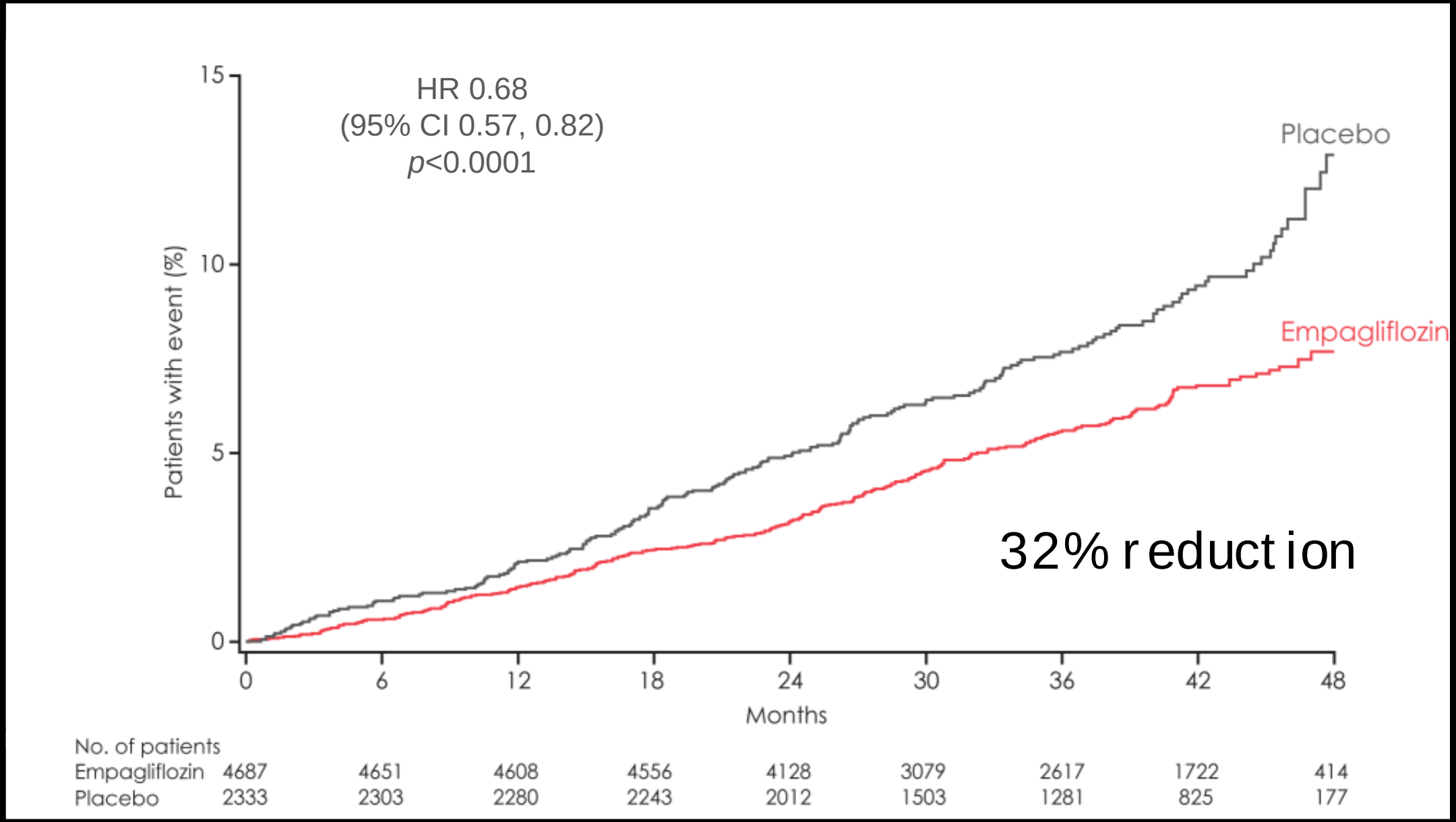
- Study medication was given in addition to standard of care
  - Glucose-lowering therapy was to remain unchanged for first 12 weeks
- Treatment assignment double-blinded
- The trial was to continue until at least 691 patients experienced an adjudicated primary outcome event

Zinman B *et al. N Engl J Med* 2015;doi:10.1056/NEJMoa1504720

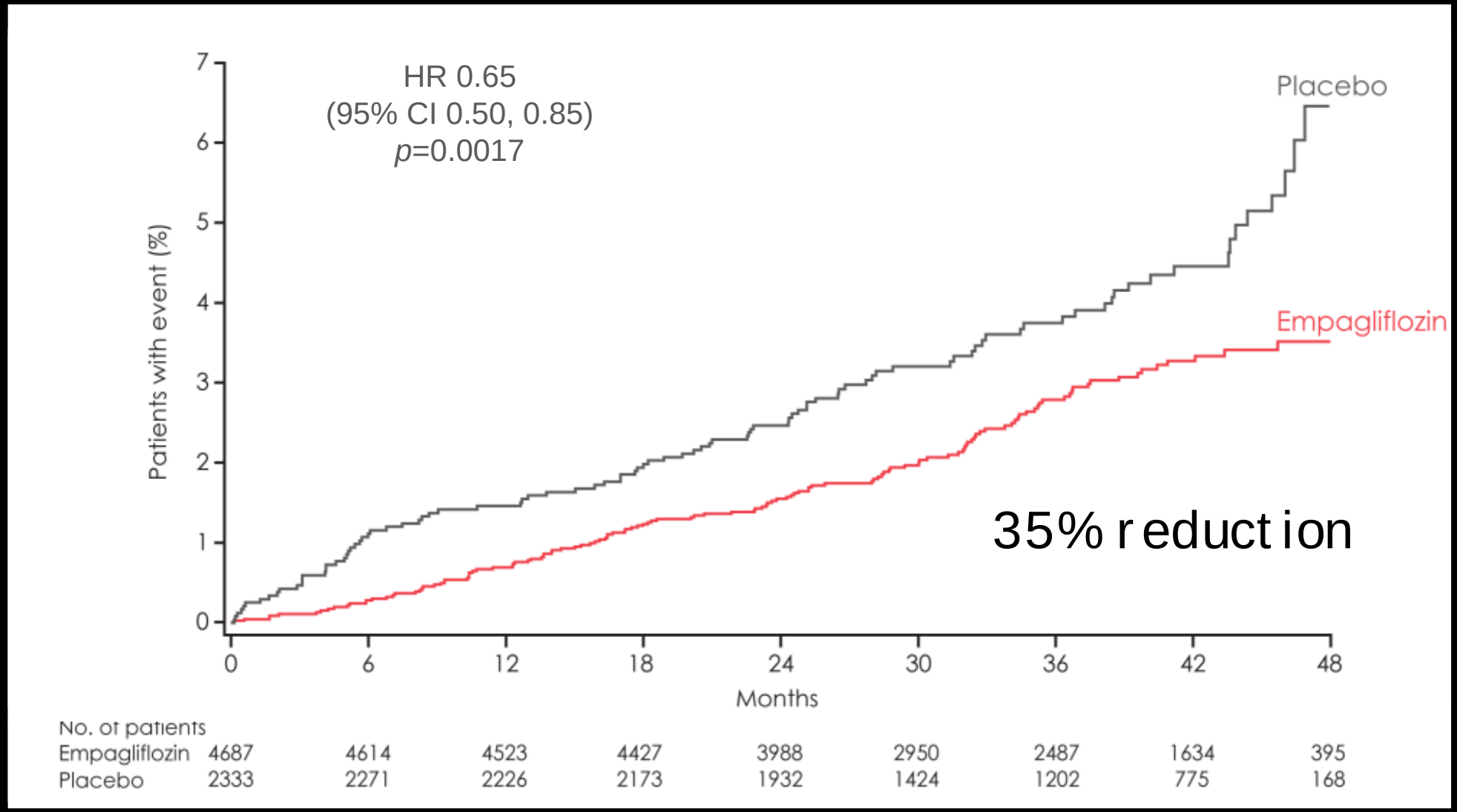
CV Death


HR 0.62
(95% CI 0.49, 0.77)
p<0.0001
Placebo
Empagliflozin
38% reduction
Patients with event (%)
0
1
2
3
4
5
6
7
8
9
0
6
12
18
24
30
36
42
48
Months
No. of patients
Empagliflozin 4687 4651 4608 4556 4128 3079 2617 1722 414
Placebo 2333 2303 2280 2243 2012 1503 1281 825 177

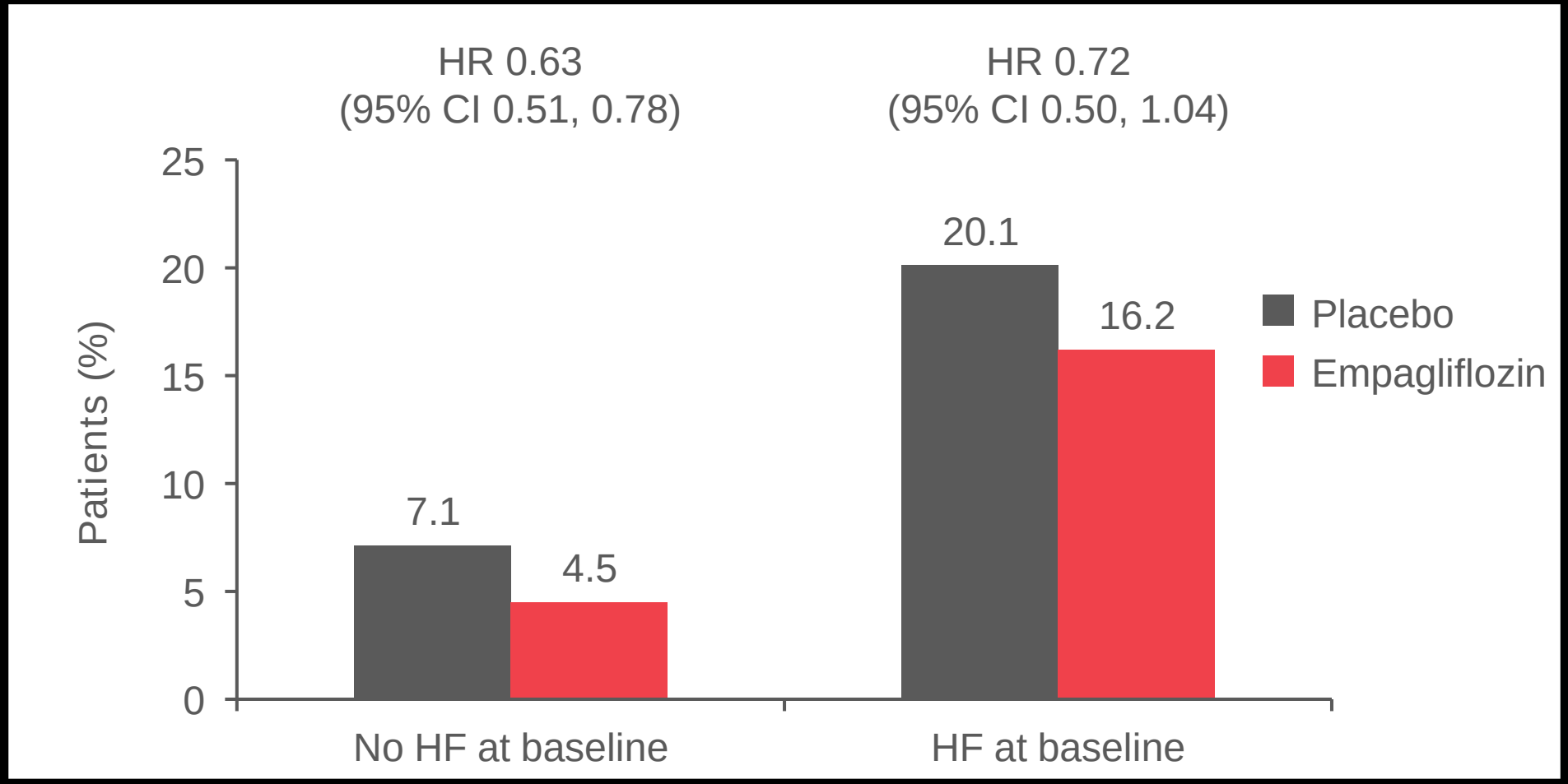
All Cause mortality



HF hospitalisation



HF hospitalisation and CV death with or without HF at baseline



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Frusemide 40mg d
Aspirin, statin
Spironolactone 25mg/d

Let’s chat….

PRESCRIPTION MEDICINE. Entresto® 24mg/26mg, 49mg/51mg, 97mg/103mg (sacubitril/valsartan) film coated tablets. Consult full Data Sheet before prescribing, available from www.medsafe.govt.nz. Entresto is fully funded under Special Authority Criteria, please refer to www.pharmac.health.nz.

Indication: Treatment of chronic heart failure (NYHA Class II-IV) with reduced ejection fraction. Contraindications: Hypersensitivity to sacubitril, valsartan, or excipients. ACE inhibitors (ACEi). Do not administer within 36 hours of switching from or to an ACEi. Angioedema related to previous ACEi or ARB therapy. Use with aliskiren in Type 2 diabetes (T2D). Severe hepatic impairment, biliary cirrhosis and cholestasis. Pregnancy.

Precautions: Caution switching from ACEi or while co-administering with aliskiren in T2D (see Contraindications). Should not be co-administered with an ARB. May cause symptomatic hypotension, especially in those ≥75 years old, renal disease and systolic BP <112 mmHg or patients with an activated RAAS. Initiation not recommended in systolic BP <100 mmHg. Monitor BP when initiating therapy or during dose titration. If hypotension occurs, dose adjustment of diuretics, antihypertensives, and consider treatment of other causes of hypotension. If hypotension persists, consider dose reduction or temporary interruption. Correct sodium and/or volume depletion before starting treatment. May be associated with decreased renal function; assess renal function before initiation and during treatment. Monitor serum creatinine, and down-titrate or interrupt if a clinically significant decrease in renal function develops. May increase urea and creatinine levels in patients with renal artery stenosis. Not recommended with end-stage renal disease. Should not be initiated and consider discontinuation if the serum potassium level is >5.4 mmol/L. Monitor serum potassium periodically and treat appropriately, especially in patients with risk factors, dosage reduction or interruption may be required. Caution with medications known to raise potassium levels. If clinically significant hyperkalaemia occurs, consider adjusting the dose of concomitant medications. If angioedema occurs, immediately discontinue, and provide appropriate therapy and monitoring until complete and sustained resolution; black patients or patients with a prior history of angioedema may be at higher risk. Caution in NYHA Class IV or in moderate hepatic impairment or with AST/ALT >2X ULN. Use in lactation not recommended. Use contraception during treatment and for 1 week after last dose.

Interactions: Aliskiren in T2D, ACEi/ARB. Caution with statins, sildenafil, lithium, potassium-sparing diuretics including mineralocorticoid antagonists, potassium supplements, or salt substitutes containing potassium, NSAIDs including selective COX-2 Inhibitors, frusemide, inhibitors of OATP1B1/B3, OAT3 or MPR2 and metformin.

Dosage: Target dose one tablet of 97 mg/103 mg twice daily. Starting dose one tablet of 49 mg/51 mg twice daily. Starting dose one tablet of 24 mg/26 mg taken twice daily recommended for ACEi/ARB naive patients, those with severe renal impairment, moderate hepatic impairment, and in those ≥ 75 years old. Double every 2-4 weeks to the target dose.

Adverse effects: Very common (≥ 10%): Hyperkalaemia, hypotension, renal impairment. Common (1 to 10%): Cough, dizziness, renal failure, diarrhoea, hypokalaemia, fatigue, headache, syncope, nausea, asthenia, orthostatic hypotension, vertigo. Uncommon (0.1 to 1%): Angioedema, dizziness postural. Unknown: Hypersensitivity (including rash, pruritus, and anaphylaxis).

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