New Trials

Iain Squire
Professor of Cardiovascular Medicine
University of Leicester

Chair, BSH

BSH Heart Failure Day for Revalidation and Training 2017

Presentation title: New Trials

Speaker: Iain Squire

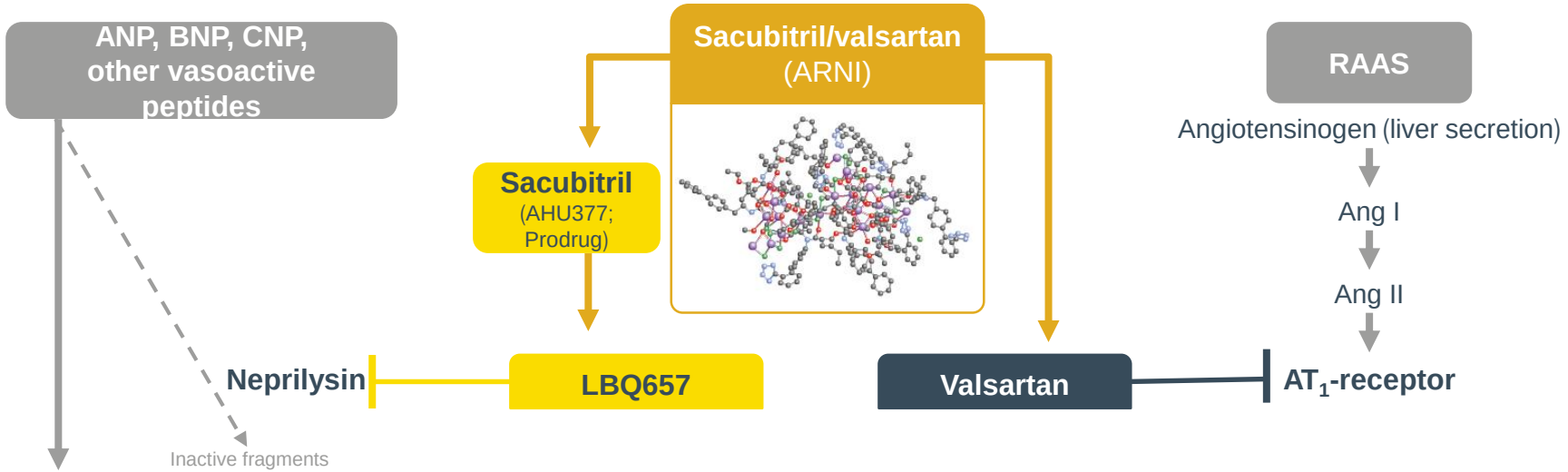
Conflicts of interest: Honoraria from Novartis; Research funding from Novartis / Amgen / Boehringer Ingelheim

ORIGINAL ARTICLE

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*

Sacubitril/valsartan – the first angiotensin receptor neprilysin inhibitor (ARNI)[1–9]



Enhancing cGMP-mediated effects of natriuretic peptides

- ↑ Vasodilatation
- ↑ Natriuresis/diuresis
- ↓ Proliferation
- ↑ Hypertrophy
- ↑ SNS outflow/sympathetic tone
- ↑ Aldosterone secretion
- ↑ Detrimental effects of vascular remodeling

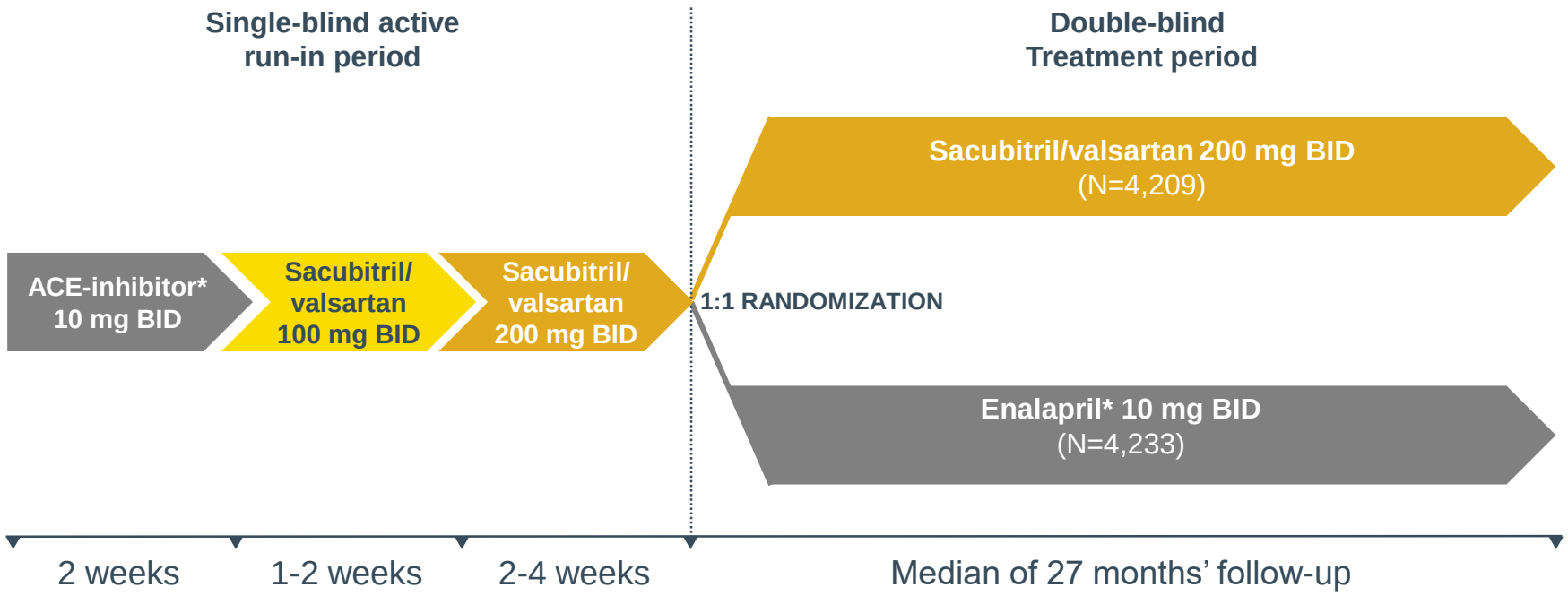
Suppressing RAAS-mediated effects

- ↓ Vasoconstriction
- ↓ Sodium and water retention
- ↓ Ventricular hypertrophy/remodeling
- ↓ Aldosterone secretion
- ↓ Cardiac fibrosis
- ↓ Sympathetic tone
- ↓ Systemic vascular resistance

ANP=atrial natriuretic peptide; BNP=B-type natriuretic peptide; CNP=C-type natriuretic peptide; AT_1=angiotensin II type1; RAAS=renin-angiotensin aldosterone system; ARNI=Angiotensin-Receptor-Neprilysin-Inhibitor

1. Highlights of prescribing information (Sacubitril/valsartan); http://www.pharma.us.novartis.com/product/pi/pdf/entresto.pdf Accessed 19 May 2016;
2. Langenickel and Dole. Drug Discov Today: Ther Strateg 2012;9:e131–9;
3. Gu et al. J Clin Pharmacol 2010;50:401–14; 4. Levin et al. N Engl J Med 1998;339:321–8; 5. Gardner et al. Hypertension 2007;49:419–26;
6. Molkentin. J Clin Invest 2003;111:1275–7; 7. Nishikimi et al. Cardiovasc Res 2006;69:318–28; 8. Volpe et al. Int J Cardiol 2014; 176:630–9;
9. Von Lueder et al. Circ Heart Fail 2013;6:594–605

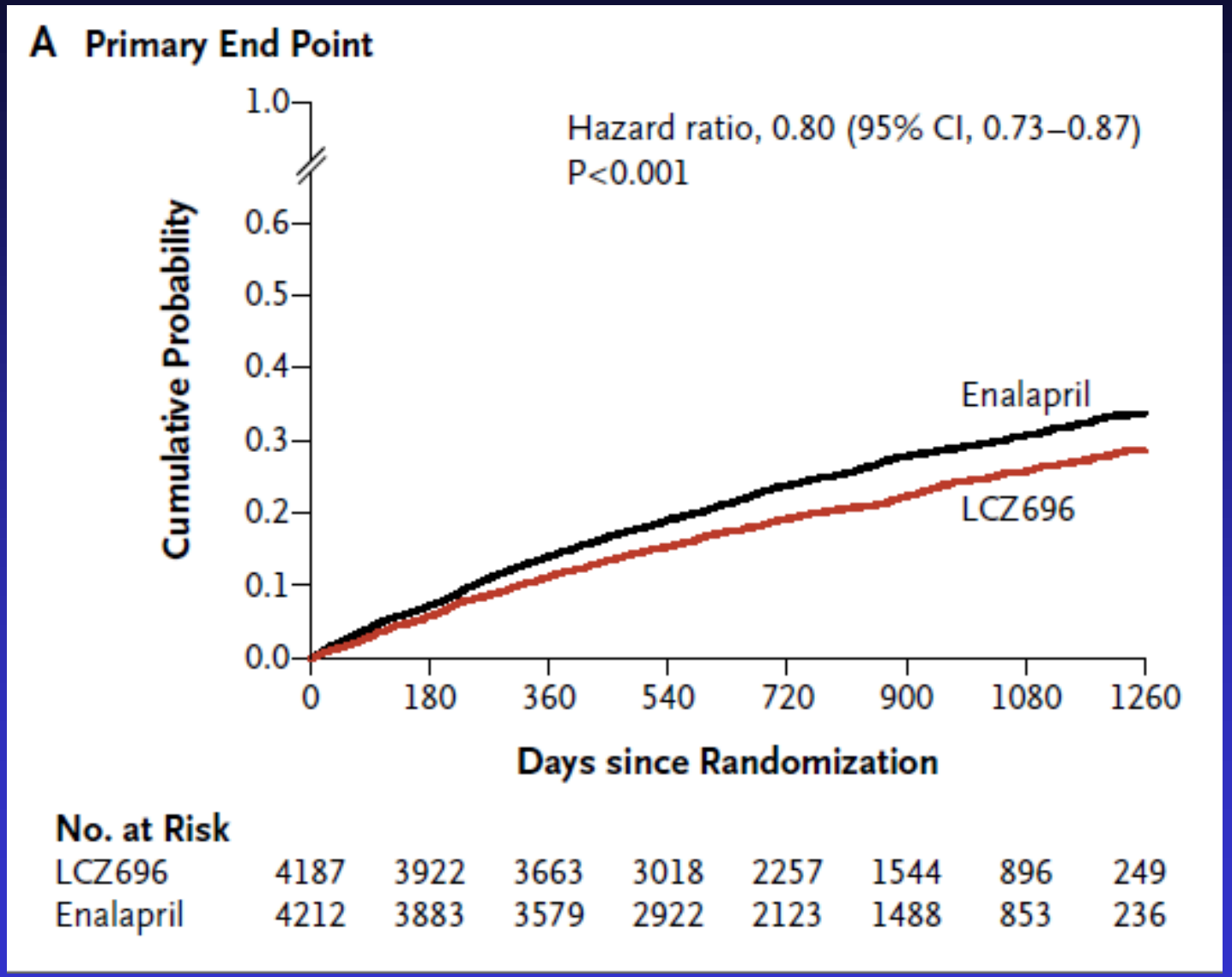
PARADIGM-HF: study design



*Enalapril 5 mg BID (10 mg TDD) for 1–2 weeks followed by enalapril 10 mg BID (20 mg TDD) as an optional starting run-in dose for those patients who are treated with ARBs or with a low dose of ACEI

ACE=angiotensin-converting enzyme; ARB=angiotensin-receptor-blocker; BID=twice daily; NYHA=New York Heart Association; LVEF=left ventricular ejection fraction; TDD=total daily dose

McMurray et al. Eur J Heart Fail 2013;15:1062–73


A Primary End Point
Hazard ratio, 0.80 (95% CI, 0.73–0.87)
P<0.001
Cumulative Probability
1.0
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Enalapril
LCZ696
0
180
360
540
720
900
1080
1260
Days since Randomization
No. at Risk
LCZ696 4187 3922 3663 3018 2257 1544 896 249
Enalapril 4212 3883 3579 2922 2123 1488 853 236

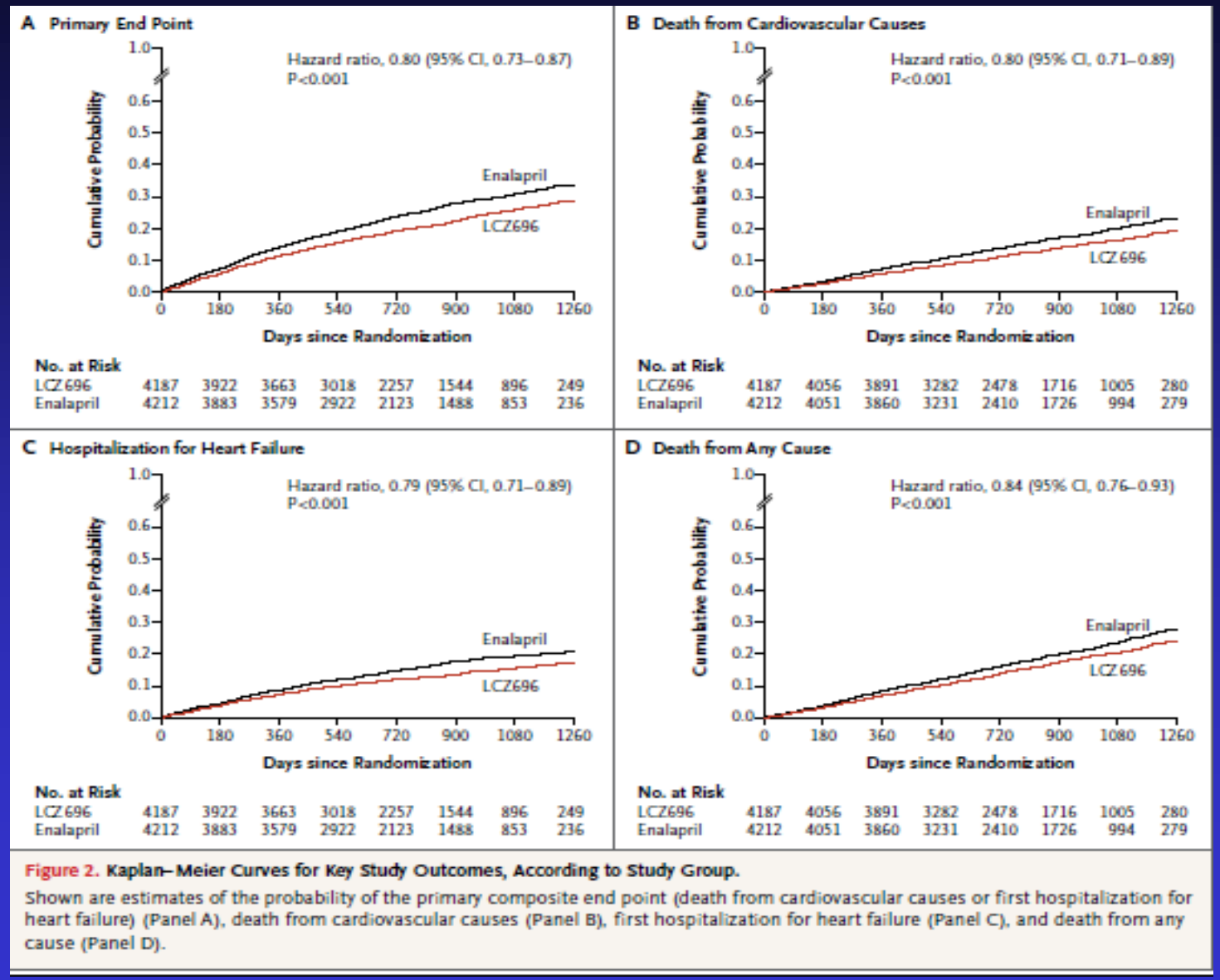


Figure 2. Kaplan–Meier Curves for Key Study Outcomes, According to Study Group.

Shown are estimates of the probability of the primary composite end point (death from cardiovascular causes or first hospitalization for heart failure) (Panel A), death from cardiovascular causes (Panel B), first hospitalization for heart failure (Panel C), and death from any cause (Panel D).

The RELAX-AHF Trial

THE LANCET

Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial

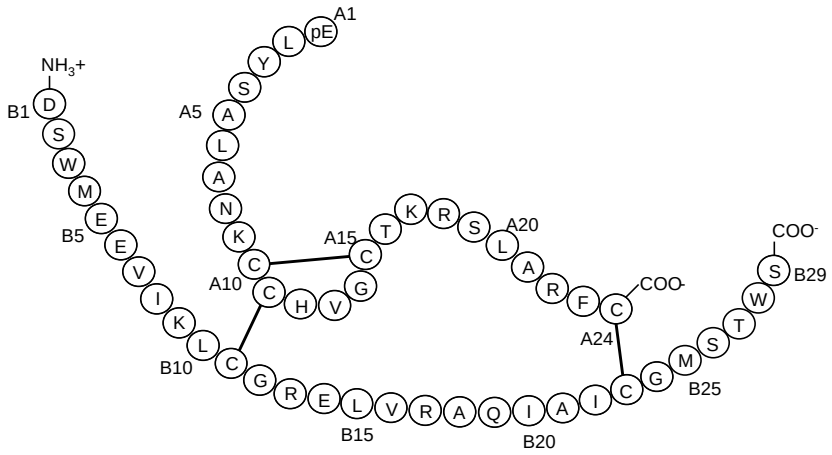
John R Teerlink, Gad Cotter, Beth A Davison, G Michael Felker, Gerasimos Filippatos, Barry H Greenberg, Piotr Ponikowski, Elaine Unemori, Adriaan A Voors, Kirkwood F Adams Jr, Maria I Dorobantu, Liliana R Grinfeld, Guillaume Jondeau, Alon Marmor, Josep Masip, Peter S Pang, Karl Werdan, Sam L Teichman, Angelo Trapani, Christopher A Bush, Rajnish Saini, Christoph Schumacher, Thomas M Severin, Marco Metra, for the RELAXin in Acute Heart Failure (RELAX-AHF) Investigators

Published online 06.November, 2012
http://dx.doi.org/10.1016/S0140-6736(12)61855-8

NOVARTIS

Serelaxin is a recombinant form of human relaxin-2

Structure of native and manufactured human relaxin-2

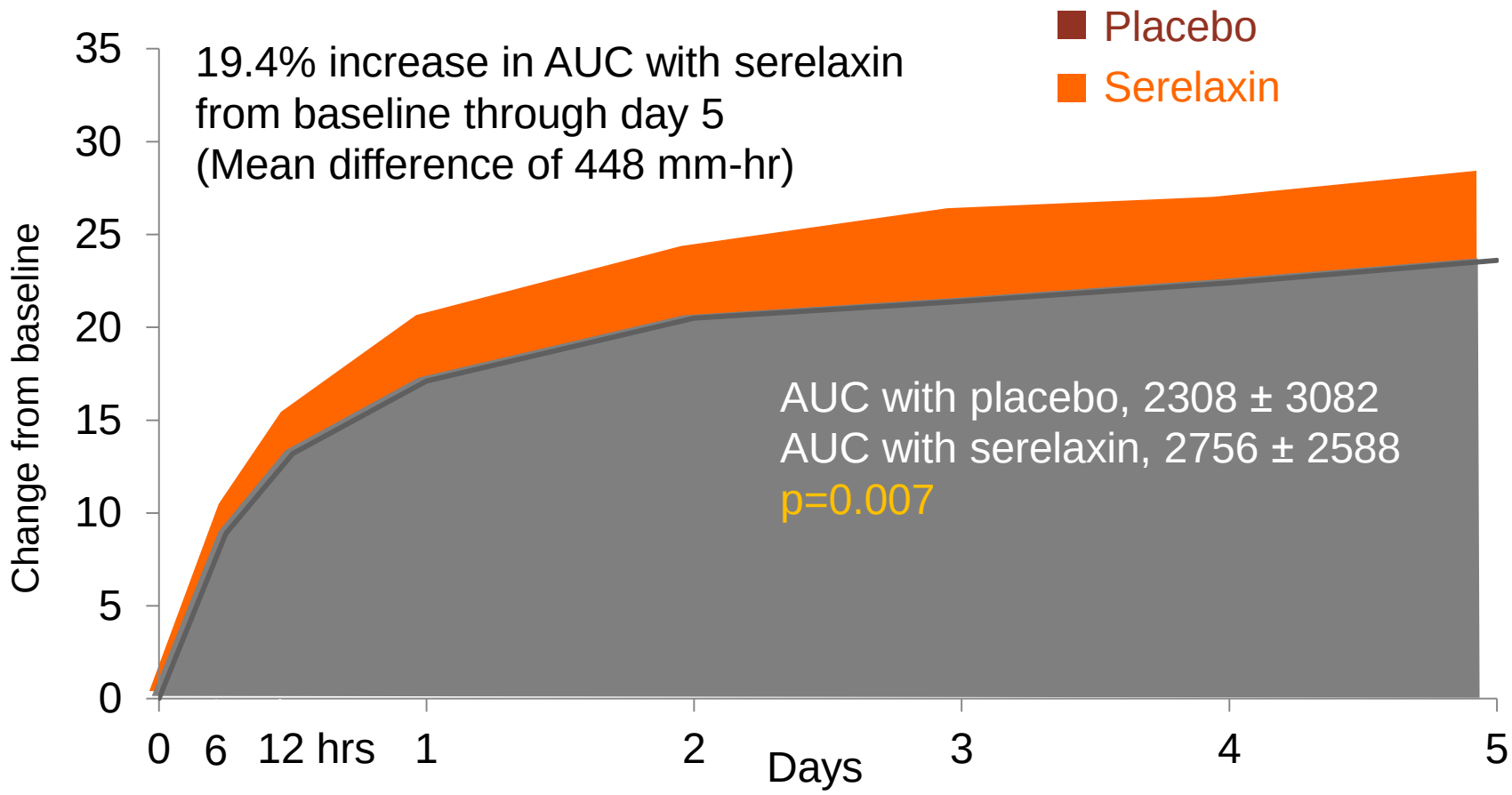


- Relaxin-2 is a naturally occurring peptide hormone which mediates systemic hemodynamic and renal adaptive changes during pregnancy
- Structure of human relaxin-2:
  53 amino acids (2 chains connected by 2 disulphide bonds)
- Human relaxin-2 is one of seven peptides in the relaxin family of hormones
- Each of these seven peptides is structurally and functionally distinct
- Relaxin-2 mediates its effects via specific G-protein-coupled receptors: RXFP1 (LGR7) and RXFP2 (LGR8)
- Relaxin-2 receptors are localized in many blood vessels

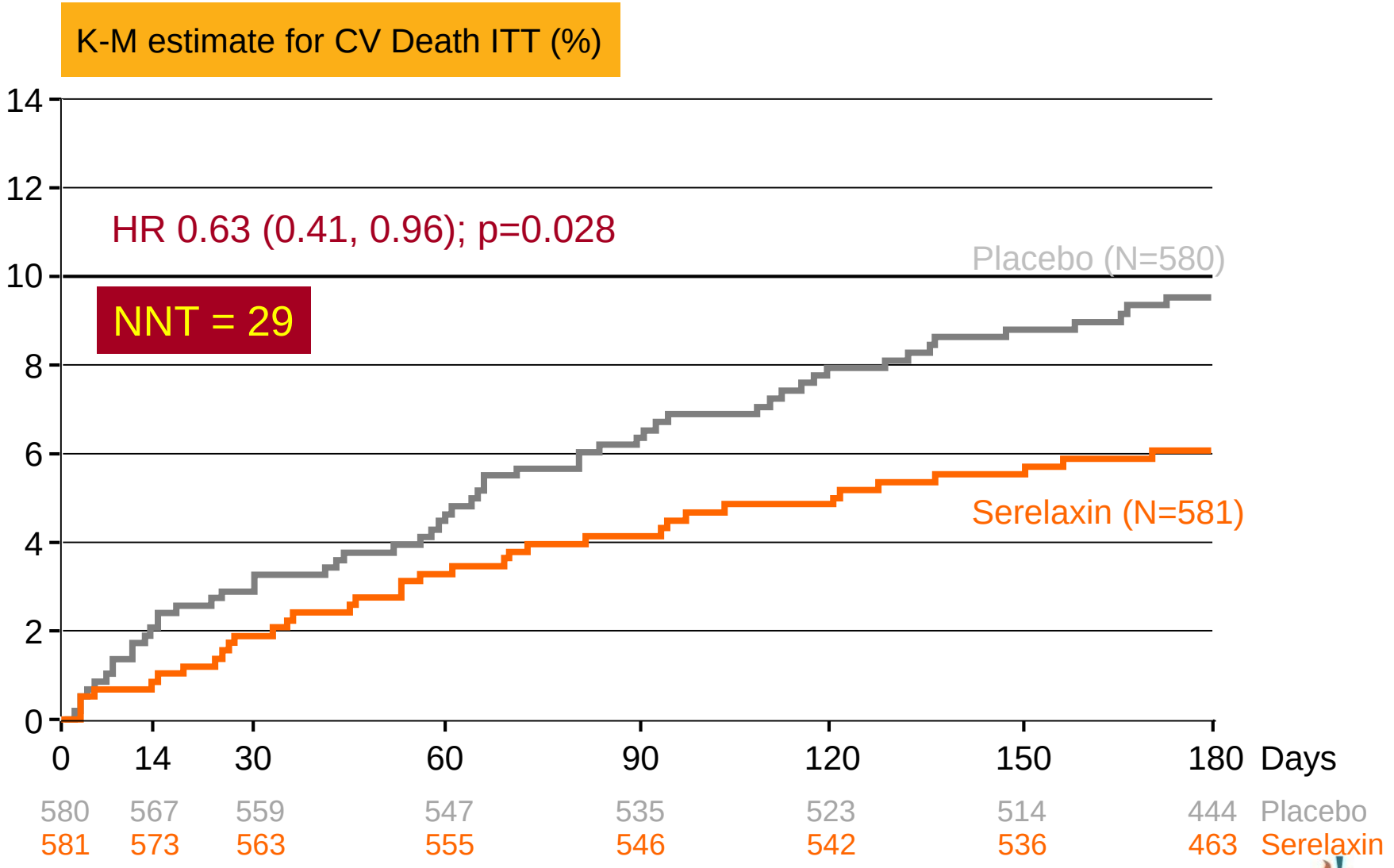
Teichman et al. Heart Fail Rev 2009;14:321–9; Jeyabalan et al. Adv Exp Med Biol 2007;612:65–87
Kong et al. Moll Cell Endocrinol 2010;320:1–15

NOVARTIS

1°Endpoint: Dyspnoea Relief (VAS AUC)



CV Death through Day 180



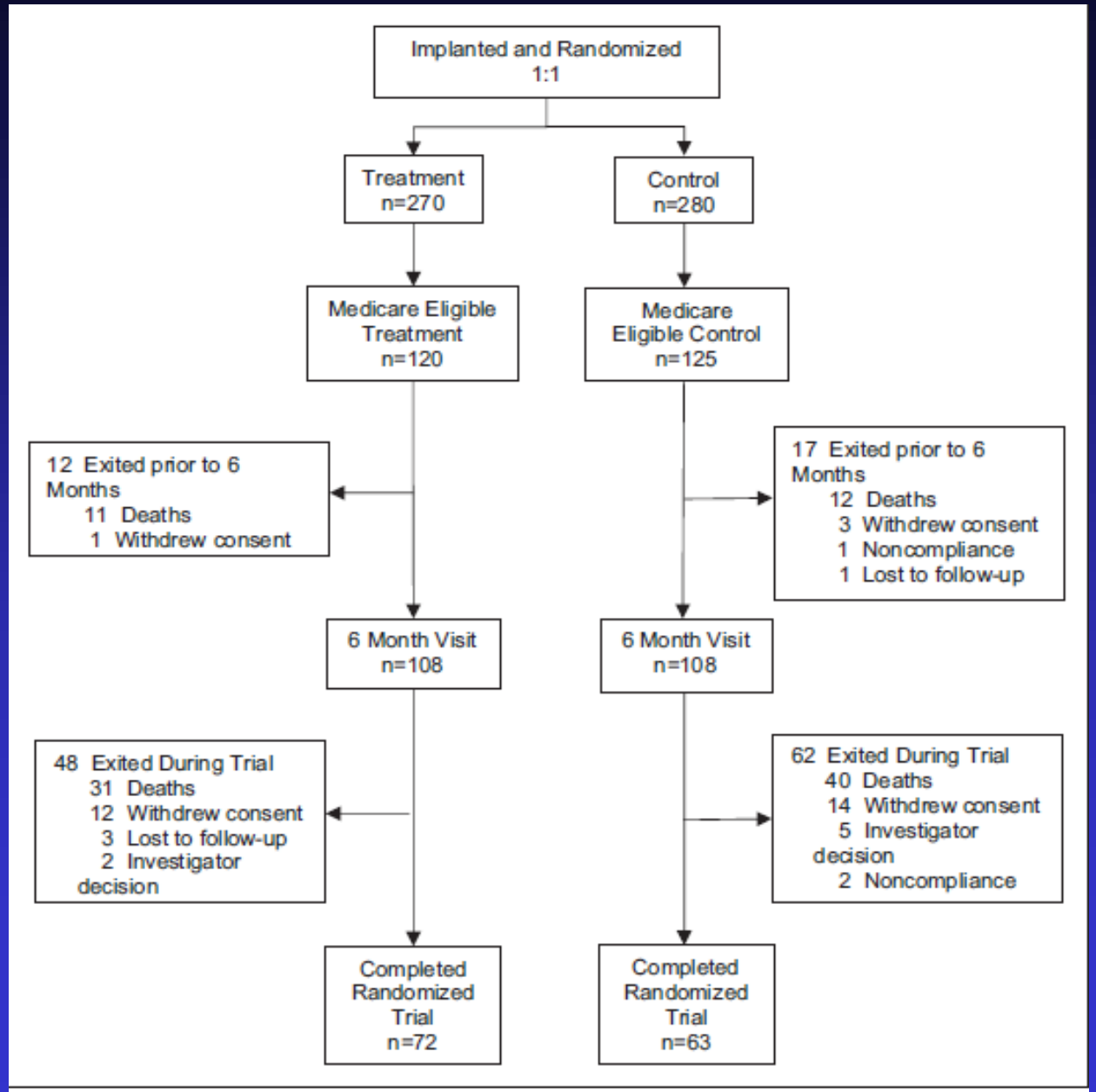
NOVARTIS

Pulmonary Artery Pressure–Guided Heart Failure Management Reduces 30-Day Readmissions

Philip B. Adamson, MD; William T. Abraham, MD; Lynne Warner Stevenson, MD;
Akshay S. Desai, MD, MPH; JoAnn Lindenfeld, MD; Robert C. Bourge, MD; Jordan Bauman, MS

Background—This study examines the impact of pulmonary artery pressure–guided heart failure (HF) care on 30-day readmissions in Medicare-eligible patients.

CardioMicroElectroMechanicalSystem


Implanted and Randomized 1:1
Treatment n=270
Control n=280
Medicare Eligible Treatment n=120
Medicare Eligible Control n=125
12 Exited prior to 6 Months
11 Deaths
1 Withdrew consent
17 Exited prior to 6 Months
12 Deaths
3 Withdrew consent
1 Noncompliance
1 Lost to follow-up
6 Month Visit n=108
6 Month Visit n=108
48 Exited During Trial
31 Deaths
12 Withdrew consent
3 Lost to follow-up
2 Investigator decision
62 Exited During Trial
40 Deaths
14 Withdrew consent
5 Investigator decision
2 Noncompliance
Completed Randomized Trial n=72
Completed Randomized Trial n=63

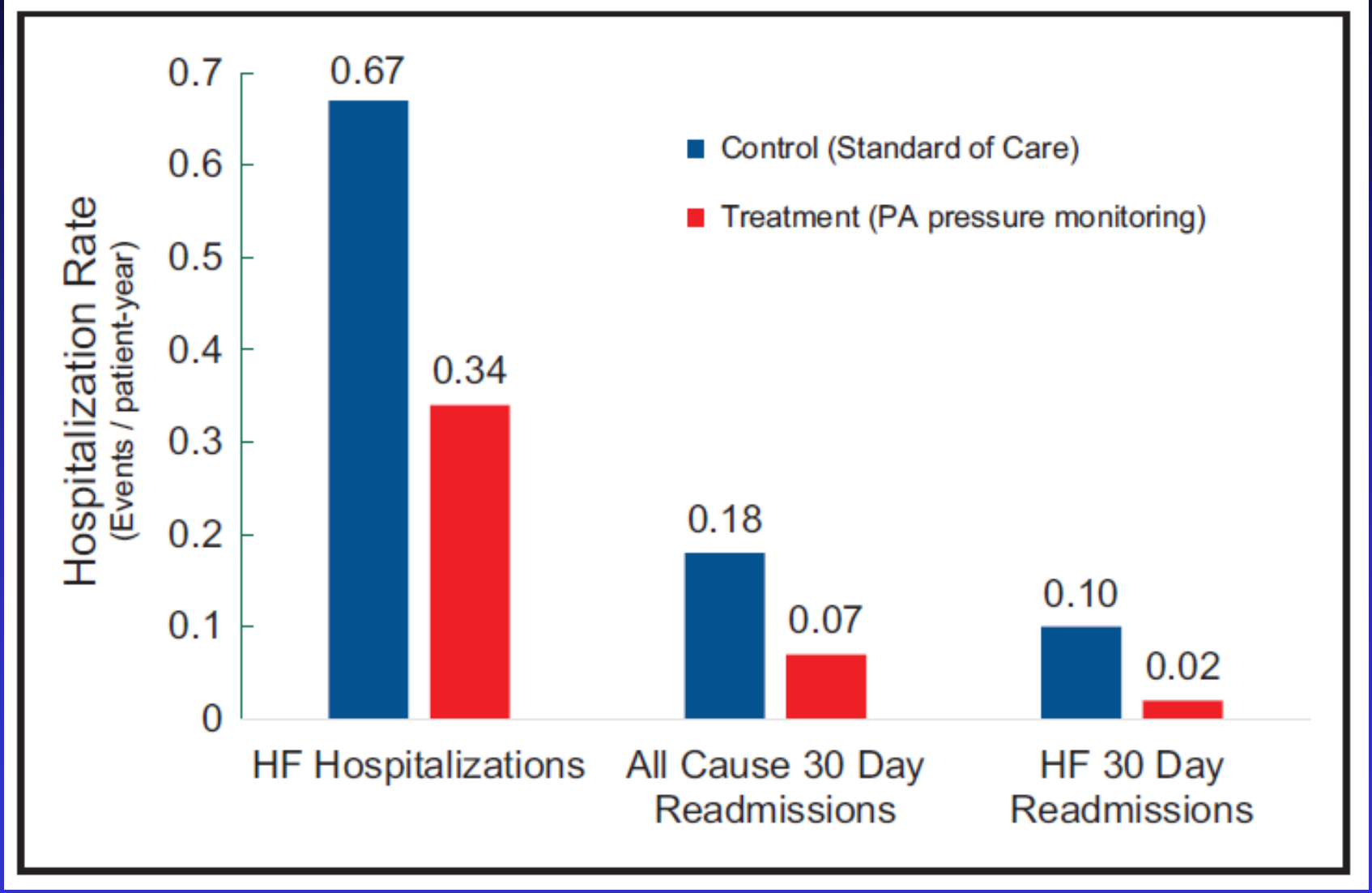

Hospitalization Rate
(Events / patient-year)
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.67
0.34
0.18
0.07
0.10
0.02
Control (Standard of Care)
Treatment (PA pressure monitoring)
HF Hospitalizations
All Cause 30 Day Readmissions
HF 30 Day Readmissions

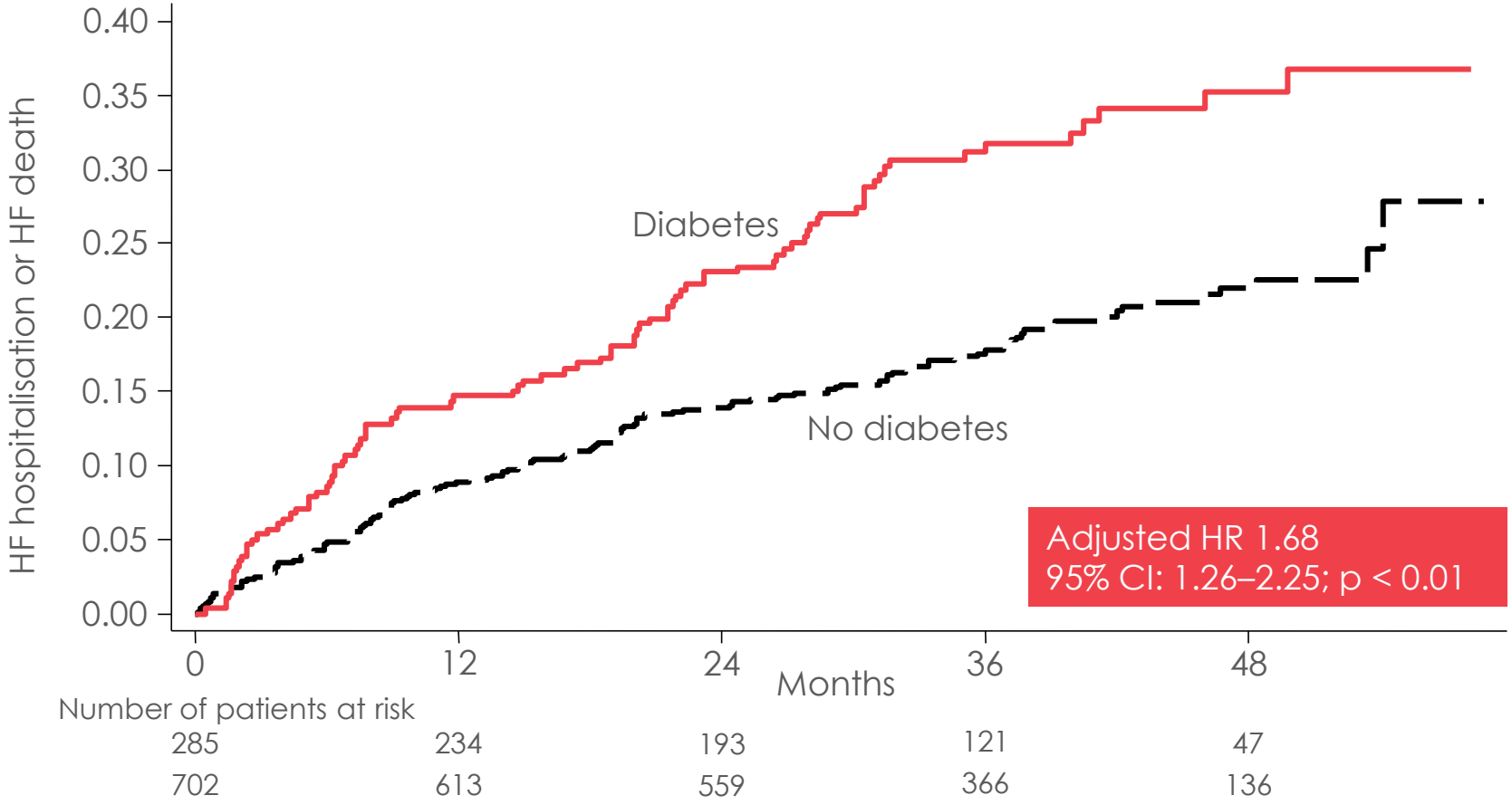
Table 5. Frequency of Heart Failure Drug Therapy Changes at 6 Months

Drug	Treatment Group (n=120)			Control Group (n=125)			*P* Value*
	Total	Increases	Decreases	Total	Increases	Decreases	
Diuretic	679	348	215	273	148	78	<0.0001
ACE/ARB	138	92	38	59	34	26	0.0017
Nitrate/ hydralazine	123	101	24	41	33	6	0.0007
Beta blocker	101	64	28	63	36	26	0.0269
Aldosterone antagonist	40	33	5	19	14	4	0.0198
All changes	1081	638	310	455	265	140	<0.0001

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

The presence of diabetes increases the risk of hospitalisation or death in patients with heart failure



Aguilar D, et al. *Am J Cardiol*. 2010;105:373–377.

Empagliflozin

- **Virtually all glucose filtered by the kidney is reclaimed in the proximal tubule.[1] Sodium glucose cotransporter 2** (SGLT2) **is responsible for 90% of this reabsorption[2]**
- **Empagliflozin is a highly selective inhibitor of SGLT2[3]**
- **By reducing renal glucose reabsorption, empagliflozin increases urinary glucose excretion[2]**
- **In patients with type 2 diabetes, empagliflozin leads to[4]:**
  - Significant reductions in HbA_{1c}
  - Weight loss
  - Reductions in BP *without* increases in heart rate

Empagliflozin is not licenced for weight loss or blood pressure reduction

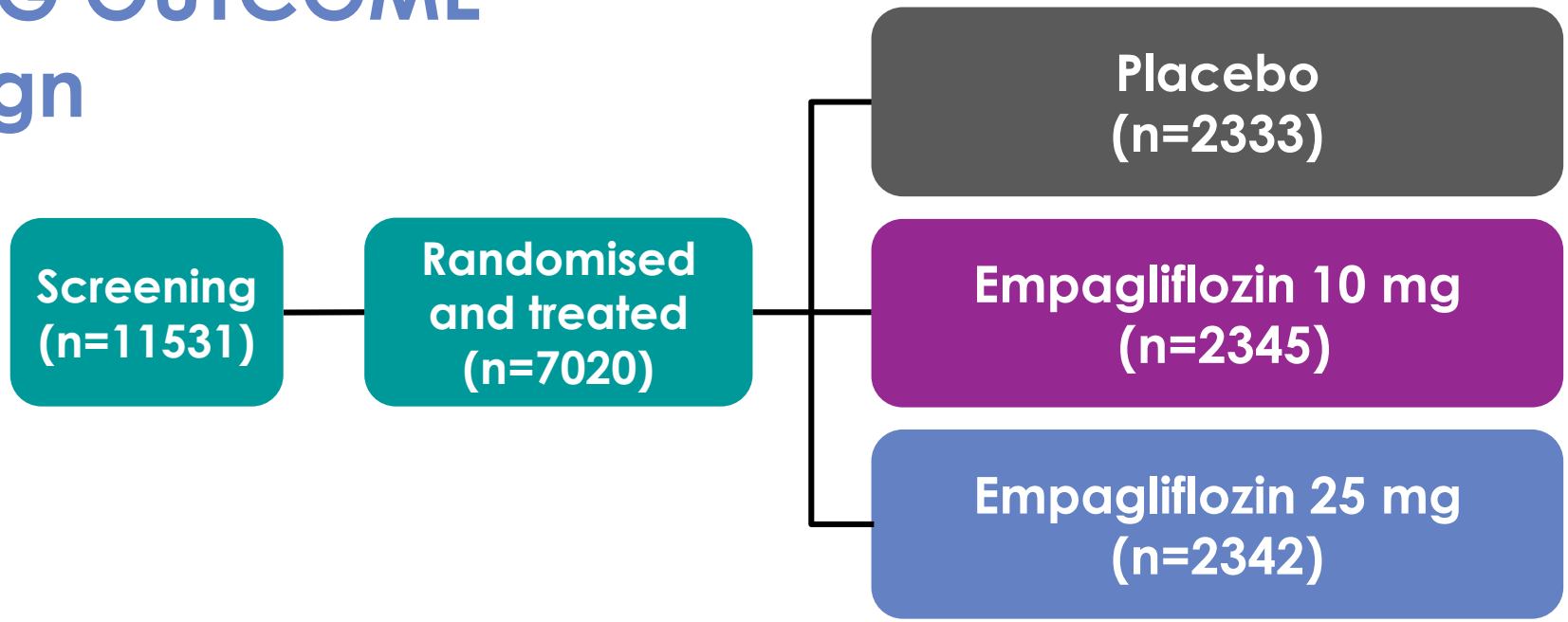
1. Abdul-Ghani et al. Curr Diab Rep. 2012;12:230-8.
2. Heise T et al. Diabetes Obes Metab 2013;15:613-21.
3. Grempler et al. Diabetes Obes Metab.2012 ;14:83-90.
4. Liakos A et al. Diabetes Obes Metab 2014;16:984-93.

Empa-Reg population

- Type 2 DM
- Established cardiovascular disease
- BMI <45
- eGFR ≥ 30ml/min/1.73m^2

- Composite primary outcome
  - CV death
  - Non-fatal MI
  - Non-fatal CVA

EMPA-REG OUTCOME®
Trial design



- **Study medication was given in addition to standard of care.**
- **The trial was to continue until ≥ 691 patients experienced an adjudicated primary outcome event.**
- **Key inclusion criteria:**
  - Adults with type 2 diabetes and established CVD
  - BMI ≤45 kg/m^2; HbA_{1c} 7–10%; eGFR ≥30 mL/min/1.73m^2 (MDRD)

CV, cardiovascular; BMI, body mass index; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.

Zinman B et al. N Engl J Med. 2015;373:2117–28.

New Trials

- RELAX-AHF 2 results

- PARAGON-HF
- PARADISE AMI

- EMPEROR HF
  - HFrEF
  - HFpEF

- Dapagliflozin HF

- IDEAA HF (Elamipretide)