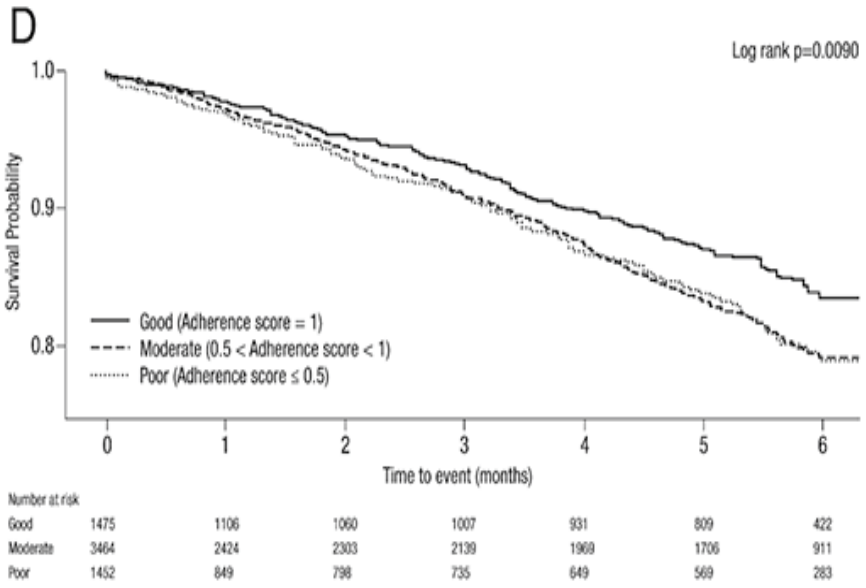
# HF - Simplistic Assumptions

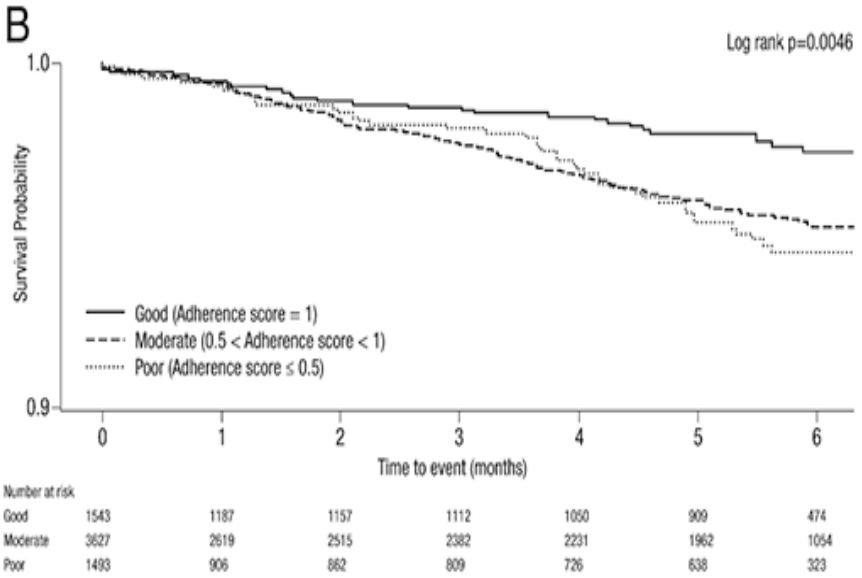
- All HFs are the same;
- Pathophysiology of HF is always the same
- HF remains the same for each patient throughout natural history of the disease
- Pharmacokinetics and pharmacodynamics is the same for each patient
- Clinical Trial Dose is always appropriate

# Physicians' guideline adherence and prognosis in HFrEF: QUALIFY international registry

Cardiovascular (CV) mortality

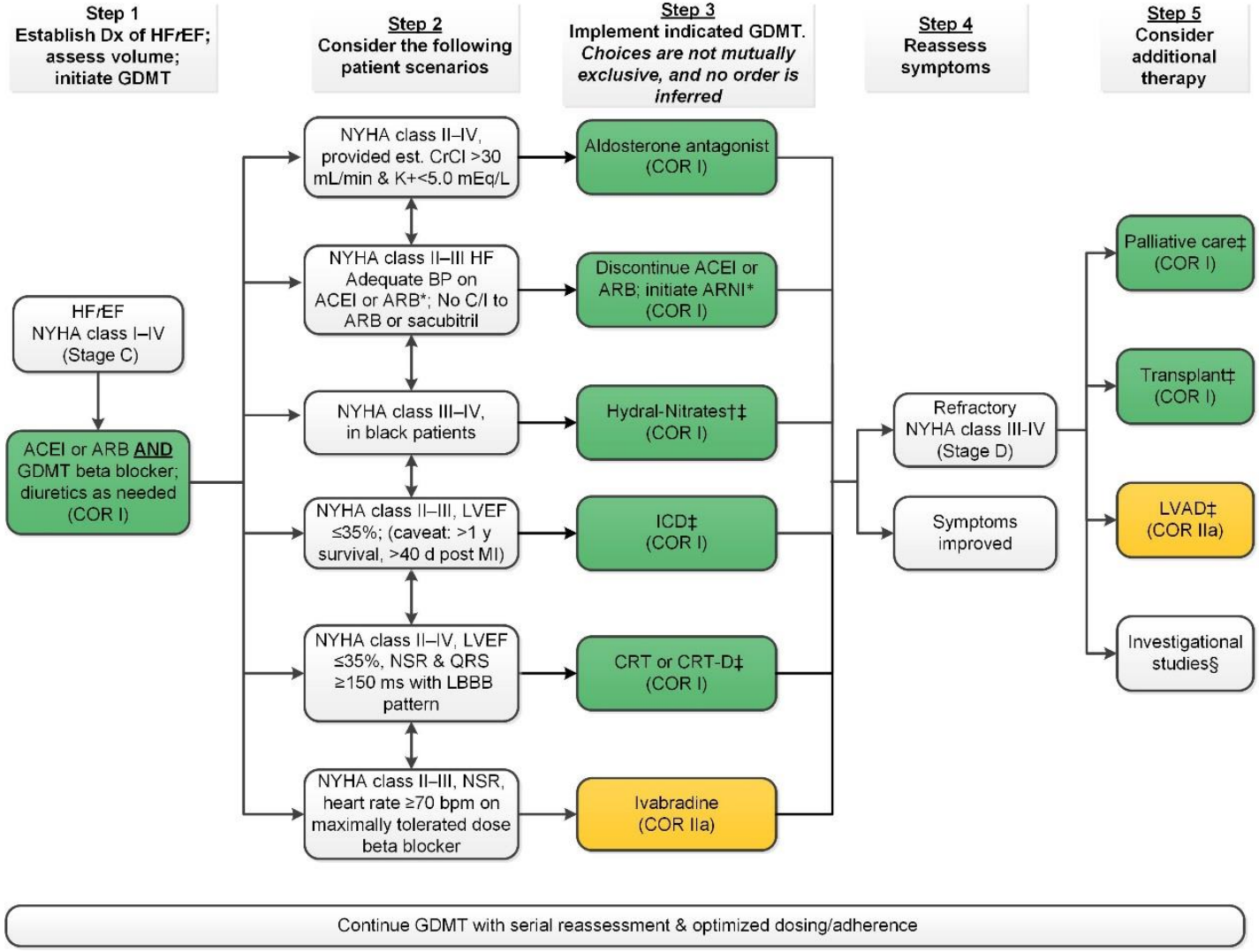



CV hospitalization or CV death




Komajda et al. European Journal of Heart Failure 30 APR 2017 DOI: 10.1002/ejhf.887

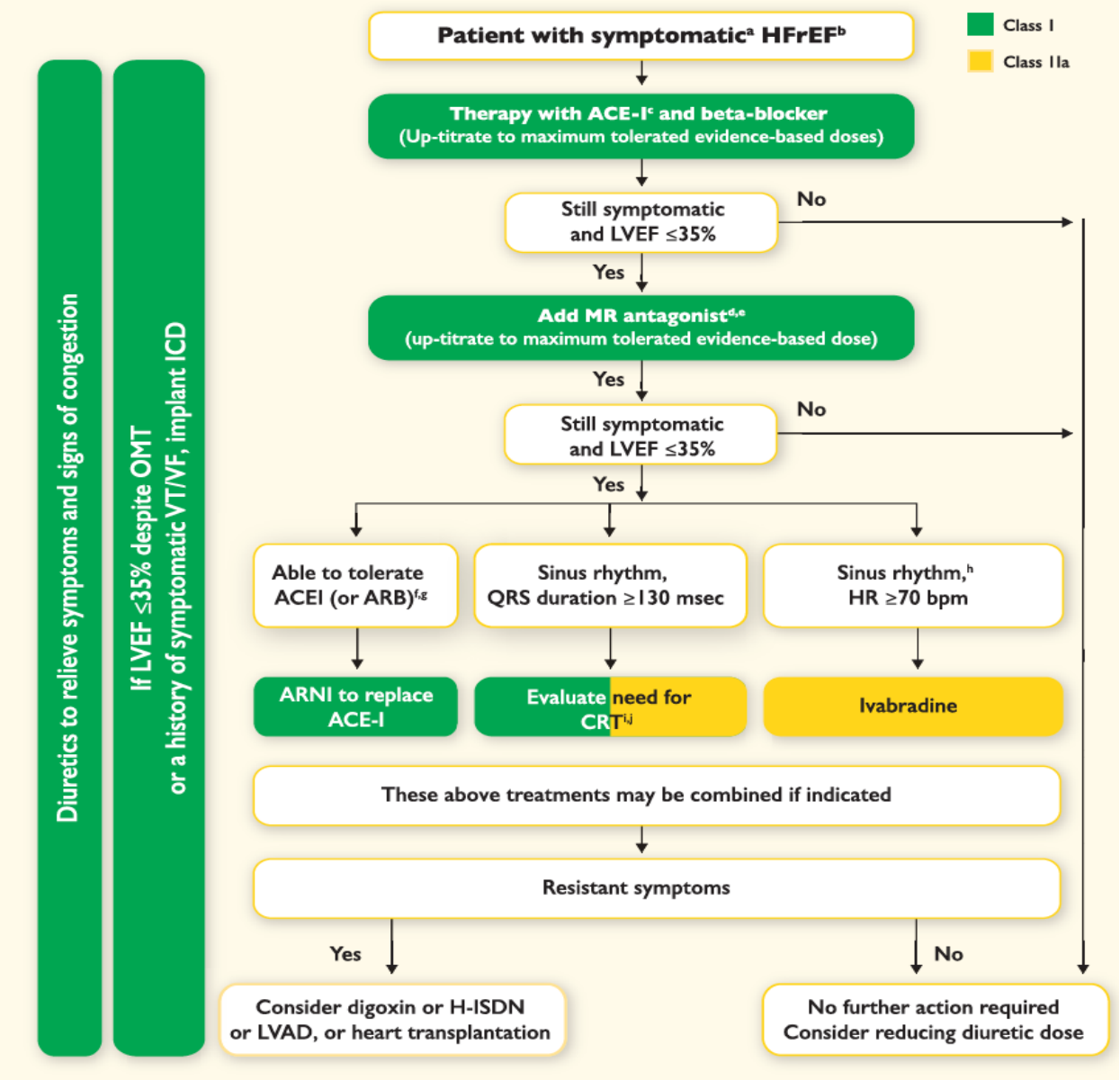
# Treatment of HFrEF Stage C and D



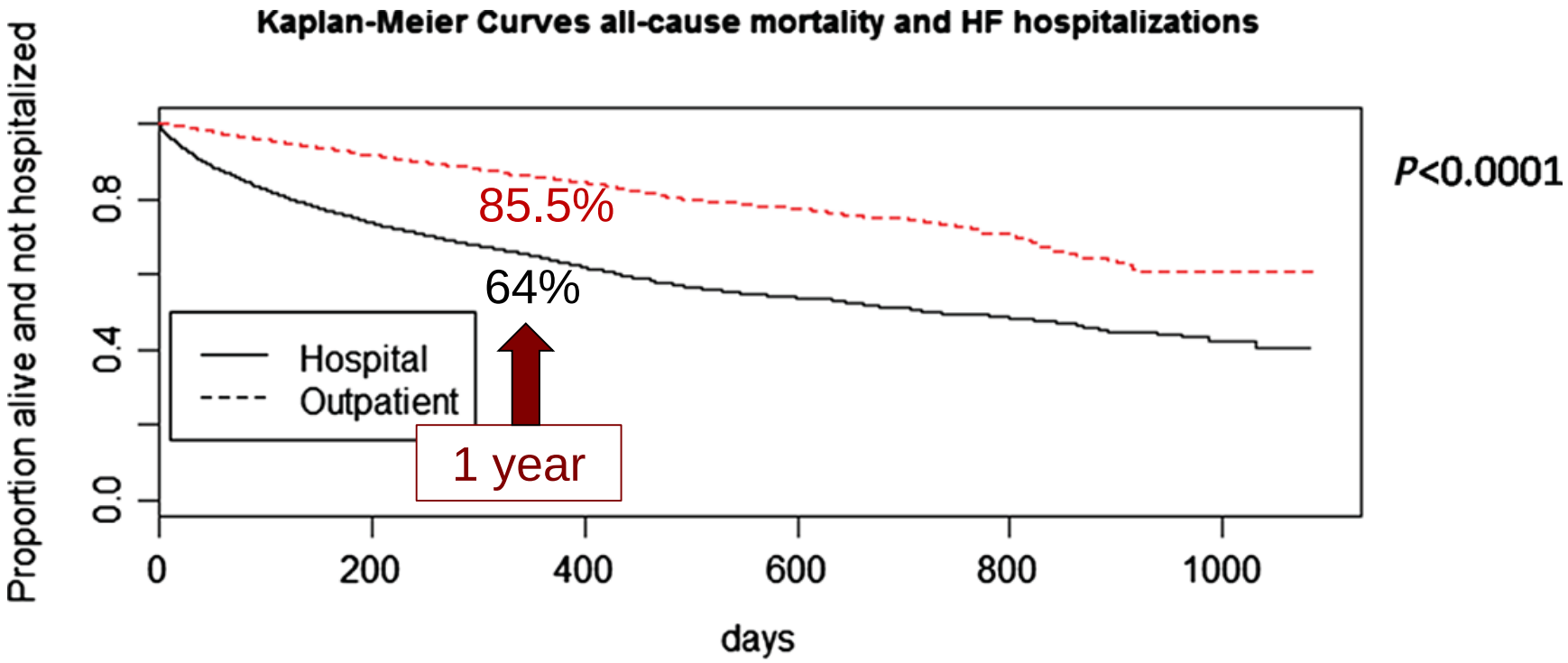
# 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

EUROPEAN SOCIETY OF CARDIOLOGY®

ESC GUIDELINES



# ESC Heart Failure Long-Term Registry: All-cause Mortality and HF Hospitalizations



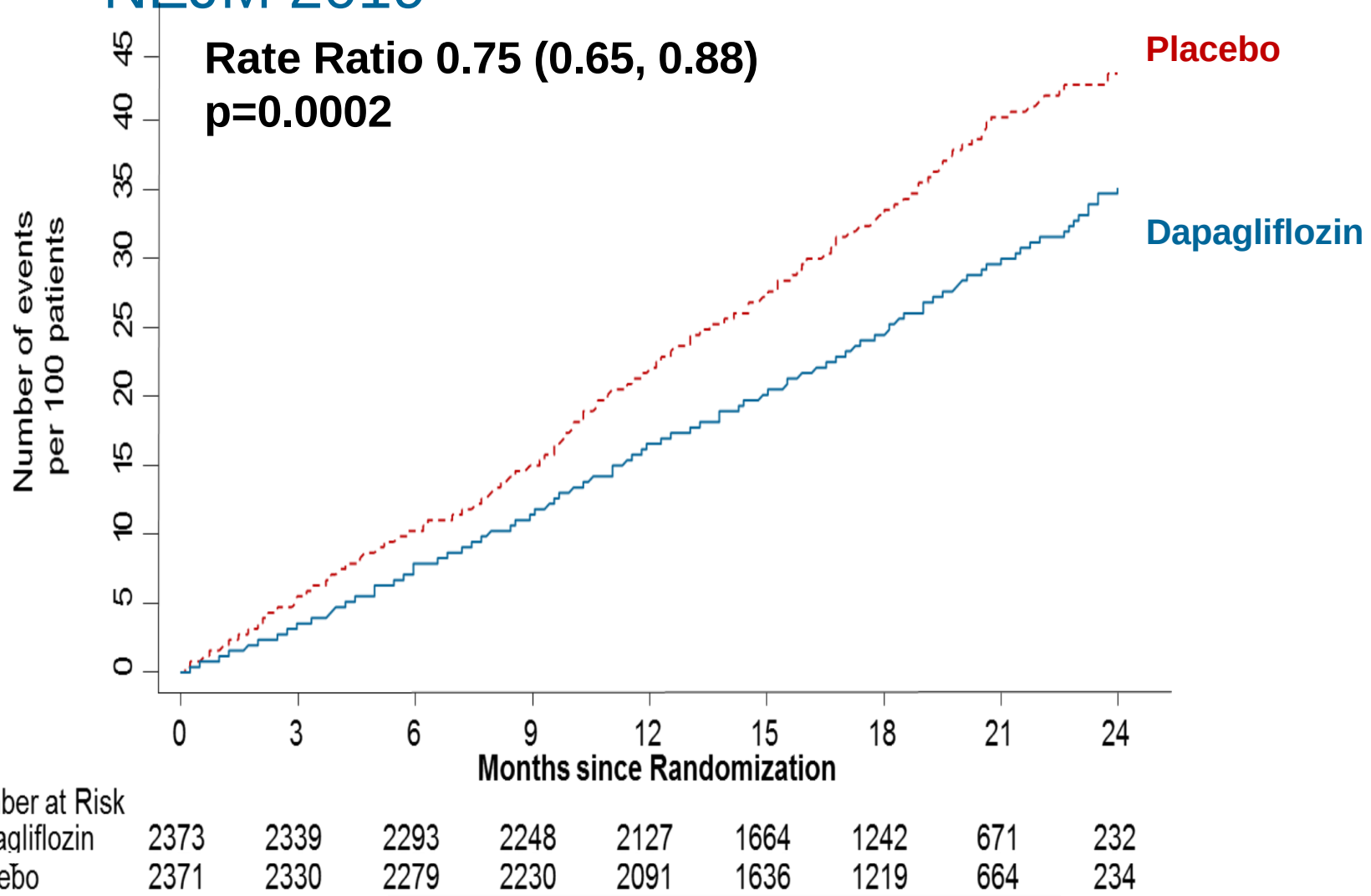

Number of Patients at Risk:

| | | | | | | |
|---|---|---|---|---|---|---|
| Hospital | 4958 | 3369 | 1457 | 708 | 336 | 52 |
| Outpatient | 7378 | 6513 | 2221 | 684 | 242 | 67 |

Crespo-Leiro et al. Eur J Heart Fail 2016; 18, 613–625

# Total HF hospitalizations and CV death

## Including first and repeat hospitalizations NEJM 2019



# SCC: l'importanza della personalizzazione della terapia

- 35 aa, maschio, NYHA III , CMPD, BBsin; FEVsin 30 %

- 78 aa, maschio, NYHA III, post-IMA, BBsin; FEVsin 30%

# SCC: l'importanza della personalizzazione della terapia

- 35 aa, maschio, NYHA (II)-III , CMPD, BBsin (QRS 160 msec), RS; FEVsin 30 %; Hb 13.5 g/dl; ferritina 350 mcg/L; GFR 87 ml/min
- 78 aa, maschio, NYHA III-(IV), post-IMA, BBsin (QRS 120 msec); FA; FEVsin 30%; Hb 11.8 g/dl; ferritina 78 mcg/L; DM (HbA1C 9%); GFR 45 ml/min; estesa cicatrice posteriore; H recidivanti per SCC e necessità supporto inotropo

STATE-OF-THE-ART REVIEW

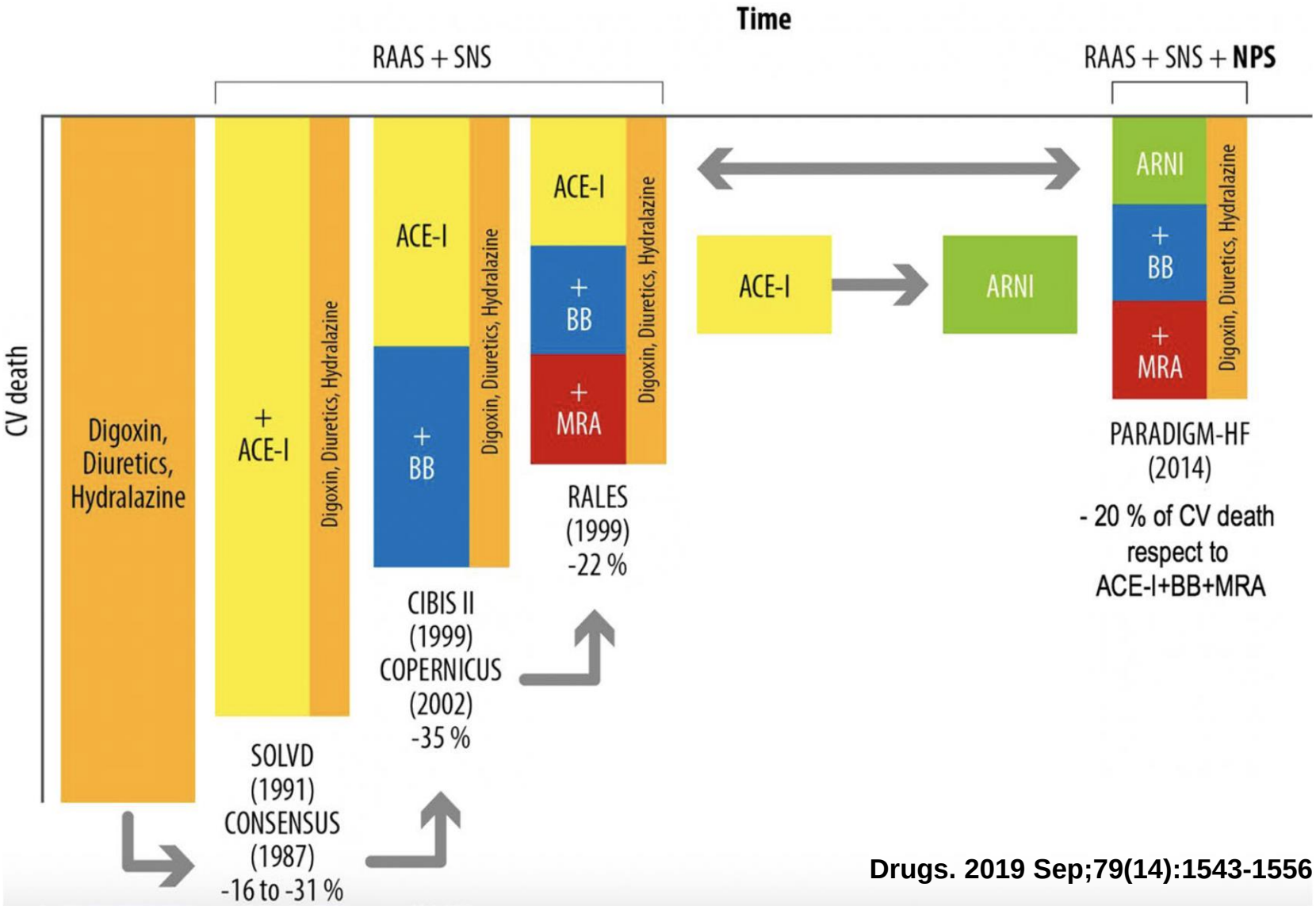
# Noncardiac Comorbidities in Heart Failure With Reduced Versus Preserved Ejection Fraction

| COMORBIDITY | BIDIRECTIONAL IMPACT ON DISEASE PROGRESSION | HEART FAILURE SPECIFICS |
|---|---|---|
| Chronic obstructive pulmonary disease | Inflammation; hypoxia; parenchymal changes; airflow limitation, leading to pulmonary congestion; abnormal left ventricular (LV) diastolic filling; inhaled beta-agonist cardiovascular effects<br>Elevated LV end-diastolic pressure and beta-blocker use may compromise lung function | More prevalent in preserved ejection fraction (HFpEF), compared to reduced (HFrEF)<br>Higher mortality risk in HFpEF |
| Anemia | Adverse LV remodeling; adverse cardiorenal effects; increased neurohormonal and inflammatory cytokines<br>Inflammation; hemodilution; renal dysfunction; metabolic abnormalities exacerbate | More prevalent in HFpEF<br>Similar increased risk for mortality in both groups |
| Diabetes | Diabetic cardiomyopathy; mitochondrial dysfunction; abnormal calcium homeostasis; oxidative stress; renin-angiotensin-aldosterone system (RAAS) activation; atherosclerosis; coronary artery disease<br>Incident and worsening diabetes mellitus via sympathetic and RAAS activation | More prevalent in HFpEF<br>Similar increased risk for mortality in both groups |
| Renal dysfunction | Sodium and fluid retention; anemia; inflammation; RAAS and sympathetic activation<br>Cardiorenal syndrome through low cardiac output; accelerated atherosclerosis; inflammation; increased venous pressure | Similar prevalence in both groups<br>Similar increased risk for mortality in both groups |
| Sleep-disordered breathing | Hypoxia; systemic inflammation; sympathetic activation; arrhythmias; hypertension (pulmonary and systemic); RV dysfunction; worsening congestion<br>Rostral fluid movement may worsen pharyngeal obstruction; instability of ventilatory control system | Similar prevalence in both groups<br>Unknown mortality differential associated with HFpEF vs. HFrEF |
| Obesity | Inflammation; reduced physical activity and deconditioning; hypertension; metabolic syndrome; diabetes mellitus<br>Fatigue and dyspnea may limit activity; spectrum of metabolic disorders including nutritional deficiencies | More prevalent in HFpEF<br>Obesity paradox; potential for a U-shaped association with mortality |

***Streng KW et al. Int J Card 2018;2***

# Sacubitril/Valsartan: Updates and Clinical Evidence for a Disease-Modifying Approach

Enrico Fabris[1] · Marco Merlo[1] · Claudio Rapezzi[2] · Roberto Ferrari[3,4] · Marco Metra[5] · Maria Frigerio[6] · Gianfranco Sinagra[1]




Drugs. 2019 Sep;79(14):1543-1556

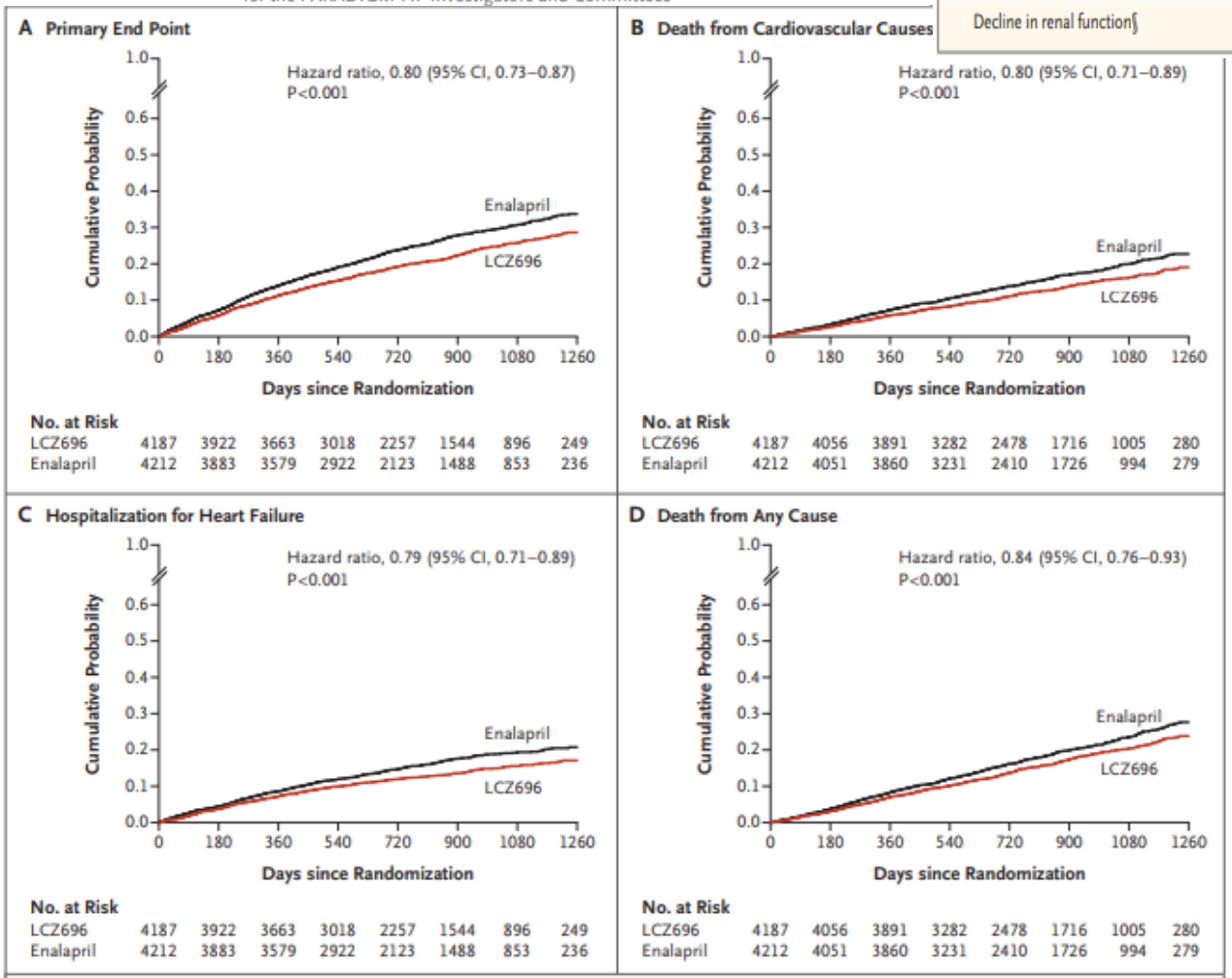
The NEW ENGLAND JOURNAL of MEDICINE

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

# Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

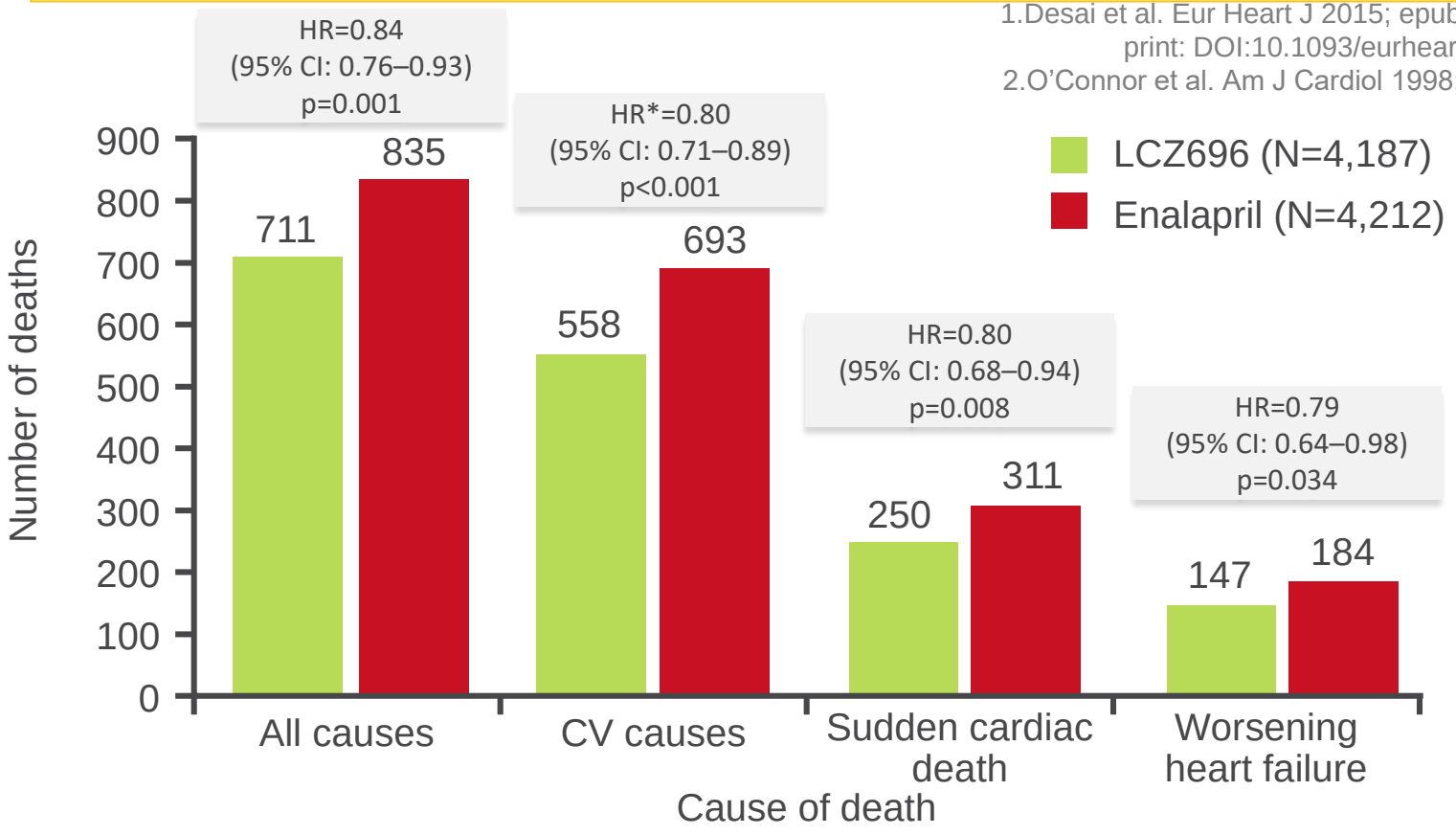
John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators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

| Outcome | LCZ696 (N=4187) | Enalapril (N=4212) | Hazard Ratio or Difference (95% CI) | P Value |
|---|---|---|---|---|
| Primary composite outcome — no. (%) | | | | |
| Death from cardiovascular causes or first hospitalization for worsening heart failure | 914 (21.8) | 1117 (26.5) | 0.80 (0.73–0.87) | <0.001 |
| Death from cardiovascular causes | 558 (13.3) | 693 (16.5) | 0.80 (0.71–0.89) | <0.001 |
| First hospitalization for worsening heart failure | 537 (12.8) | 658 (15.6) | 0.79 (0.71–0.89) | <0.001 |
| Secondary outcomes — no. (%) | | | | |
| Death from any cause | 711 (17.0) | 835 (19.8) | 0.84 (0.76–0.93) | <0.001 |
| Change in KCCQ clinical summary score at 8 mo† | −2.99±0.36 | −4.63±0.36 | 1.64 (0.63–2.65) | 0.001 |
| New-onset atrial fibrillation‡ | 84 (3.1) | 83 (3.1) | 0.97 (0.72–1.31) | 0.83 |
| Decline in renal function§ | 94 (2.2) | 108 (2.6) | 0.86 (0.65–1.13) | 0.28 |



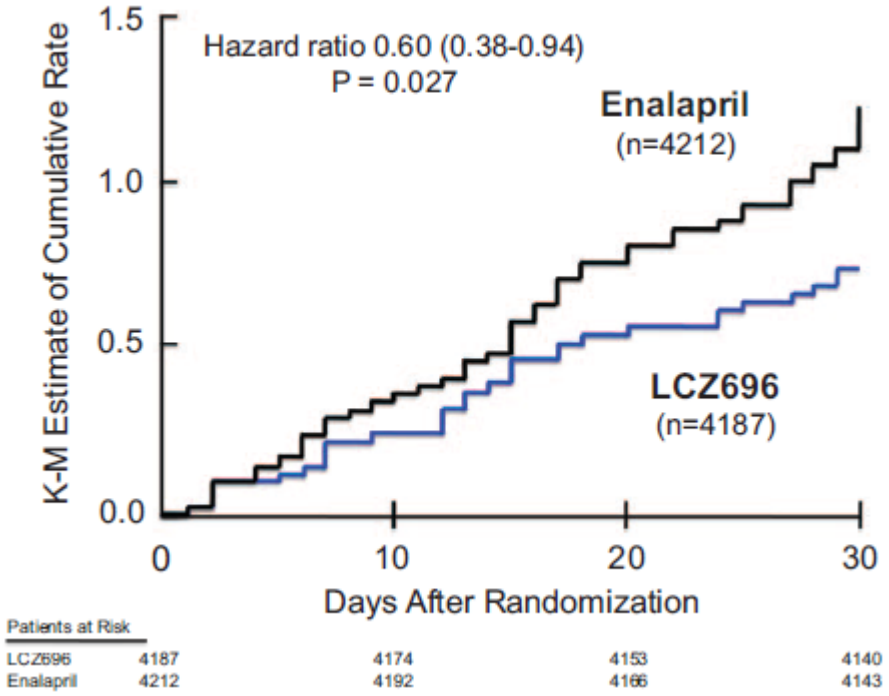
# Effect of the angiotensin-receptor-neprilysin inhibitor LCZ696 compared with enalapril on mode of death in heart failure patients

1.Desai et al. Eur Heart J 2015; epub ahead of print: DOI:10.1093/eurheartj/ehv186;
2.O'Connor et al. Am J Cardiol 1998;82:881–7

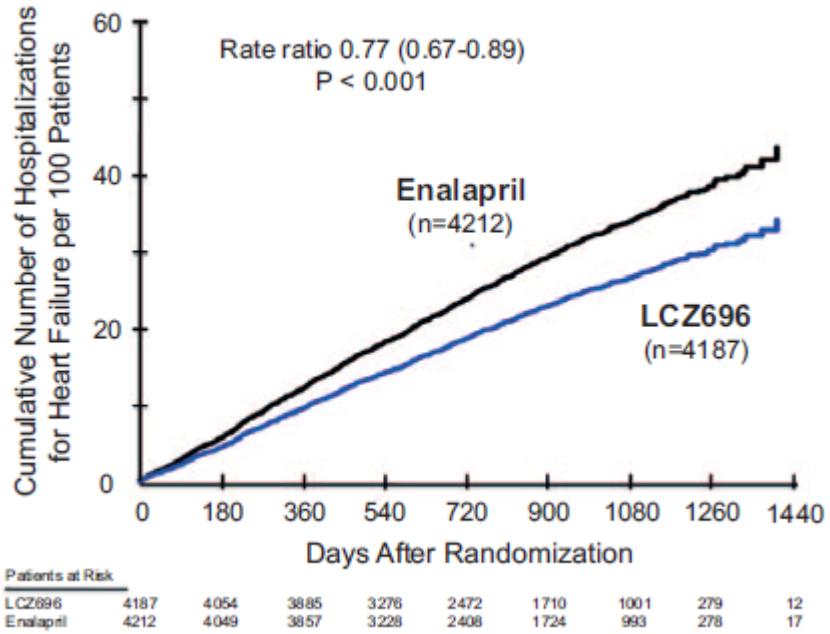


# Angiotensin Receptor Neprilysin Inhibition Compared With Enalapril on the Risk of Clinical Progression in Surviving Patients With Heart Failure

**Time to first hospitalization for HF during the first 30 days**




**Cumulative number of hospitalizations for HF**




Packer M et al, Circulation 2015

# Effect of the angiotensin-receptor-neprilysin inhibitor LCZ696 compared with enalapril on mode of death in heart failure patients

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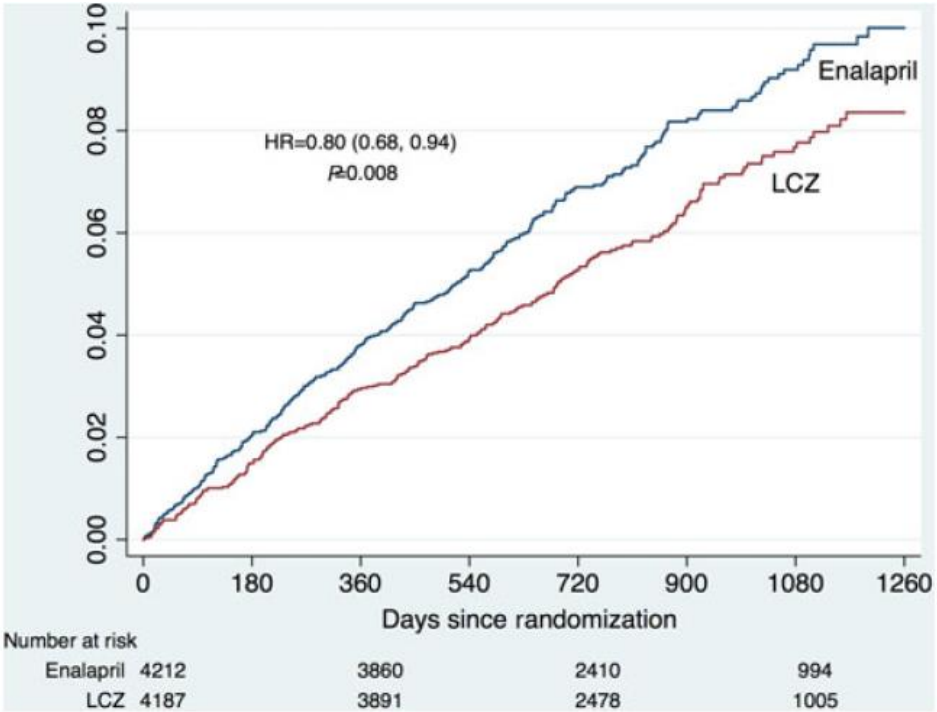
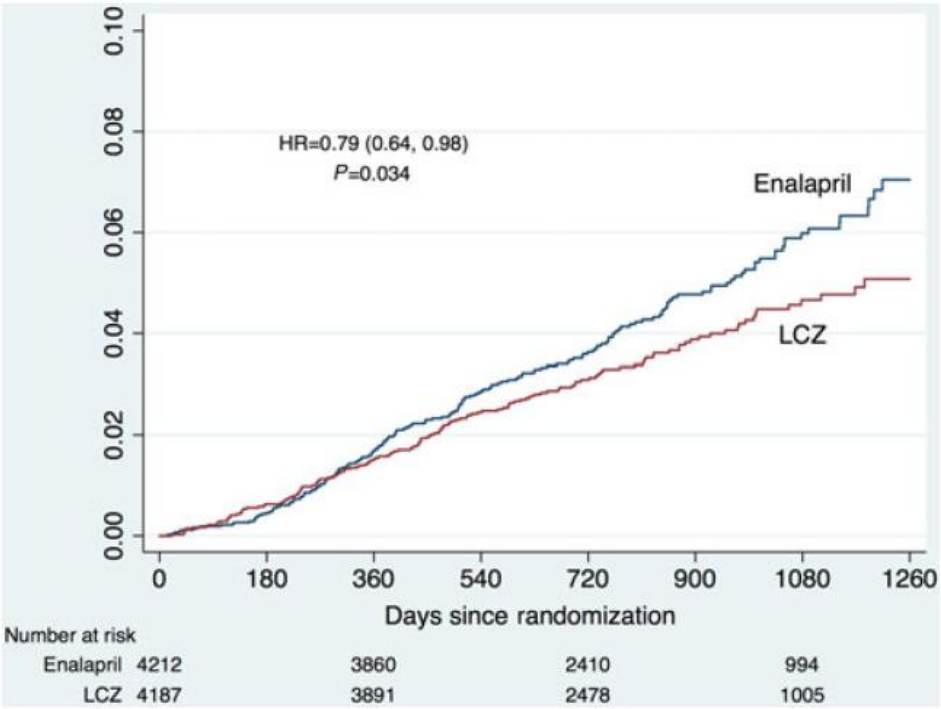
Sudden death




Worsening HF




European Heart Journal (2015) **36**, 1990–1997

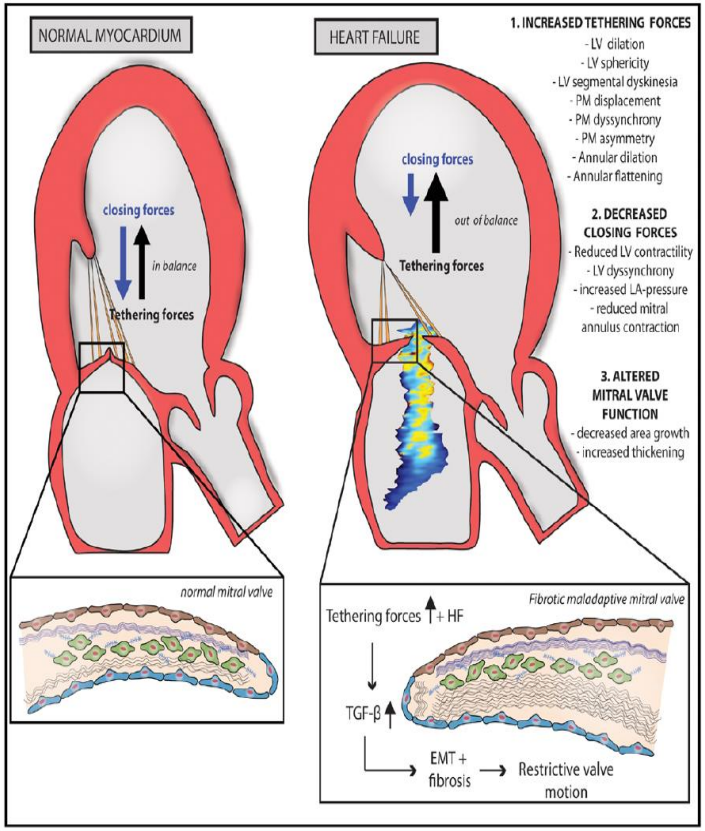
Circulation

EDITORIAL

# Sacubitril/Valsartan to Reduce Secondary Mitral Regurgitation

## Refinement of Guideline-Directed Medical Therapy?

**A** Pathophysiologic basis of secondary MR




**B** Comparison of included patients in COAPT, MITRA-FR and PRIME-study

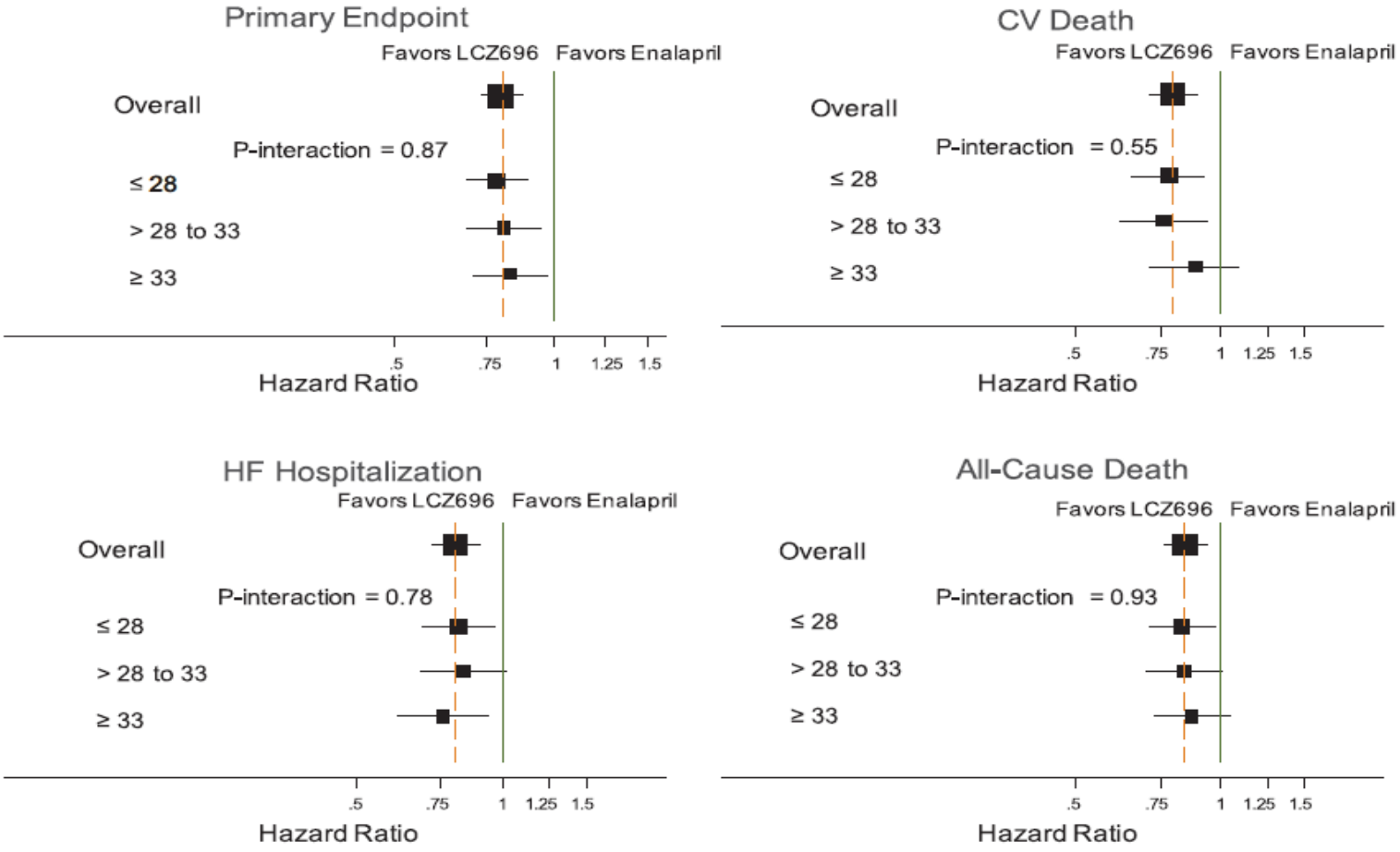
| | COAPT | MITRA-FR | PRIME |
|---|---|---|---|
| Number of patients | 614 | 304 | 118 |
| Age , years | 72.3 ± 11.2 | 70.4 ± 10.0 | 62.6 ± 11.2 |
| Ischemic etiology HF | 61% | 59% | 36% |
| NYHA-class II/III/IV in % | 39% / 52% / 9% | 33% / 59% / 8% | 88% / 12% / 0% |
| Baseline ACE-I/ARB/(ARNI)° | 67% | 83% | 100% |
| Baseline Beta-blocker | 90% | 89% | 88% |
| Baseline MRA | 50% | 55% | 43% |
| Baseline loop diuretic | 89% | 99% | 88% |
| LVEF, % | 31 ± 9 | 33 ± 7 | 34 ± 7 |
| LVEDVi (ml/m²) | 101 ± 34 | 135 ± 35 | 116 ± 39 |
| Mean EROA, cm² | 0.41 ± 0.15 | 0.31 ± 0.10 | 0.20 ± 0.10 |
| EROA < 0.40 cm² | 59% | 84% | 94% |
| EROA > 0.40 cm² | 41% | 16% | 6% |
| Follow-up duration trial | 2y* | 1y | 1y |
| Primary endpoint | Recurrent HF | HF or death | Change in EROA |
| Annualized mortality rate | 19% | 23% | 0.8% |

# Influence of Ejection Fraction on Outcomes and Efficacy of Sacubitril/Valsartan (LCZ696) in Heart Failure with Reduced Ejection Fraction

## The Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) Trial

Circulation
Heart Failure
*Circ Heart Fail.* 2016;9:e002744.

Treatment effect of LCZ696 by tertile of left ventricular ejection fraction for all outcomes




***Conclusions***—In patients with HF and reduced EF enrolled in PARADIGM-HF, LVEF was a significant and independent predictor of all outcomes. Sacubitril/valsartan was effective at reducing cardiovascular death and HF hospitalization throughout the LVEF spectrum.

# Systolic blood pressure, cardiovascular outcomes and efficacy and safety of sacubitril/valsartan (LCZ696) in patients with chronic heart failure and reduced ejection fraction: results from PARADIGM-HF

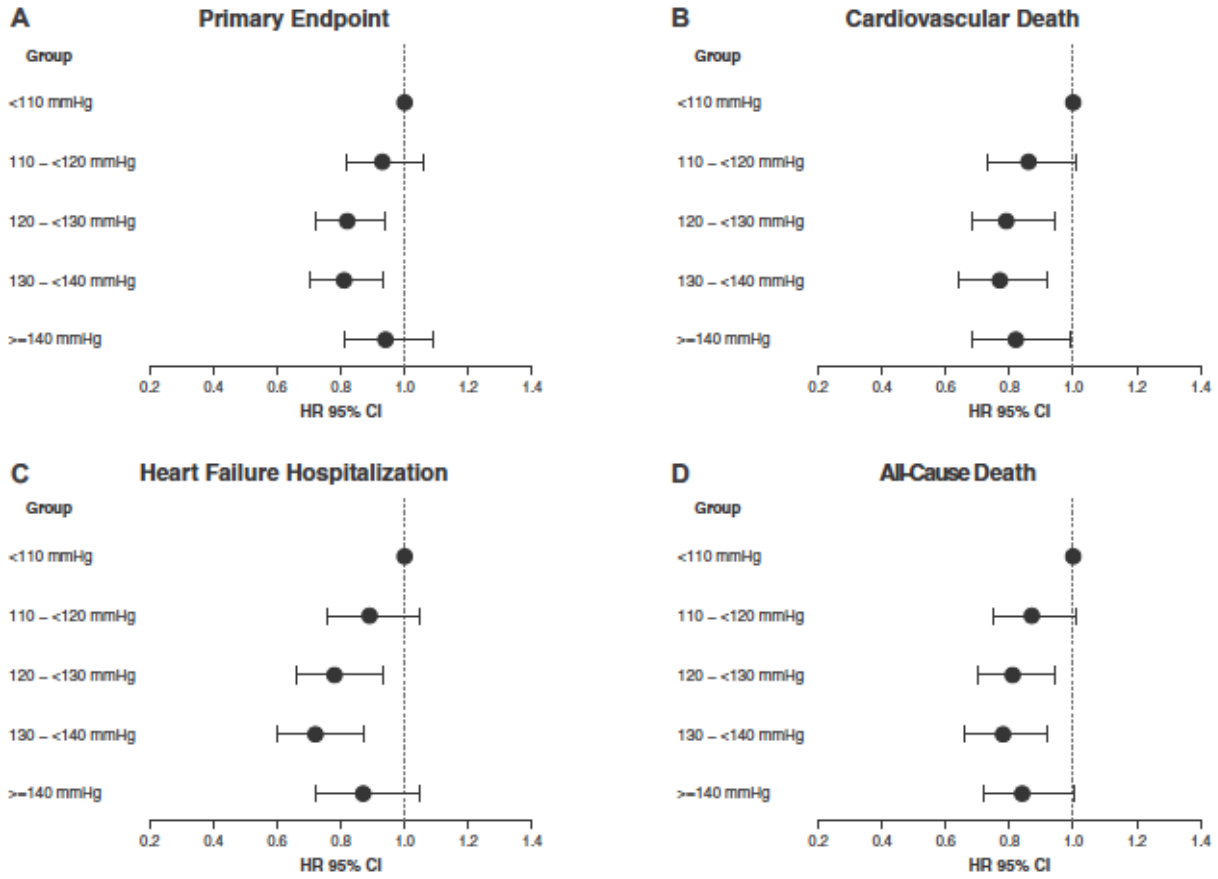


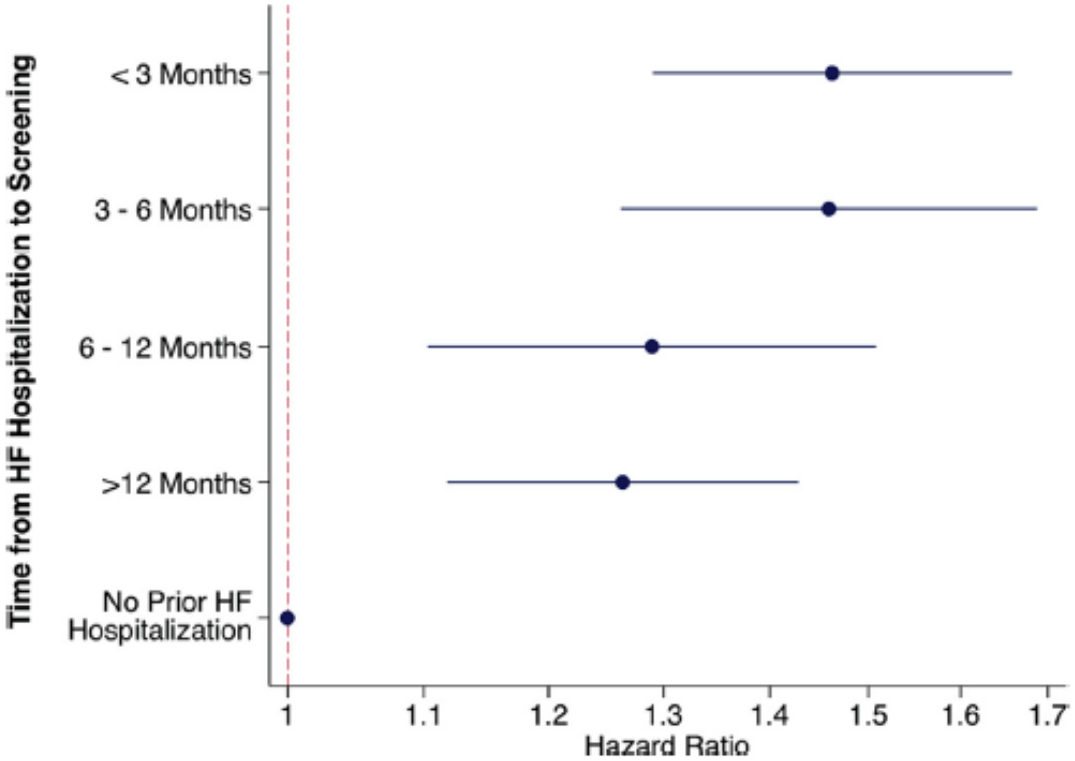

**Figure 2** Adjusted hazard ratios for the (*A*) primary endpoint, (*B*) cardiovascular death, (*C*) heart failure hospitalization and (*D*) all-cause death according to systolic blood pressure at baseline in all patients. The group with systolic blood pressure < 110 mmHg is given as a reference (=1).

European Heart Journal (2017) **38**, 1132–1143
doi:10.1093/eurheartj/ehw570

# Efficacy of Sacubitril/Valsartan Relative to a Prior Decompensation

## The PARADIGM-HF Trial

**FIGURE 1** Hazard Ratio for Primary Endpoint

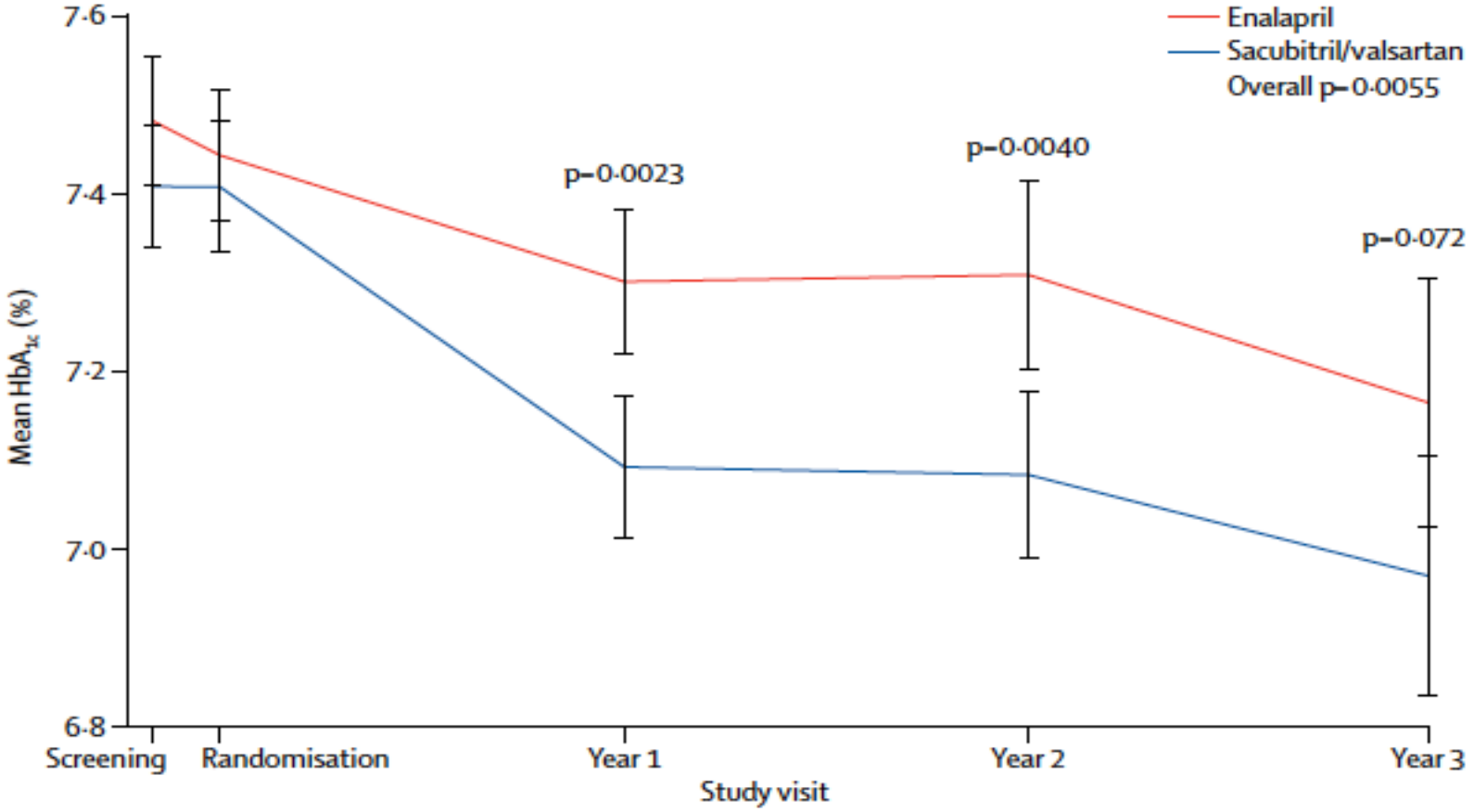



Hazard ratio for primary endpoint (cardiovascular death or HF hospitalization) based on the presence of and time from a HF hospitalization prior to screening, adjusted for baseline characteristics which significantly differed across groups. HF = heart failure.

VOL. 4, NO. 10, 2016
ISSN 2213-1779/$36.00
http://dx.doi.org/10.1016/j.jchf.2016.05.002

# 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

**Changes in mean HbA1c and confidence intervals by treatment group at screening, randomisation, 1-year, 2-year, and 3-year visits**




**Interpretation** Patients with diabetes and HFrEF enrolled in PARADIGM-HF who received sacubitril/valsartan had a greater long-term reduction in $HbA_{1c}$ than those receiving enalapril. These data suggest that sacubitril/valsartan might enhance glycaemic control in patients with diabetes and HFrEF.

Seferovic et al. *Lancet Diabetes Endocrinol* 2017

ESC European Society of Cardiology
European Journal of Heart Failure (2018)
doi:10.1002/ejhf.1342

RESEARCH ARTICL

# Effects of sacubitril/valsartan on neprilysin targets and the metabolism of natriuretic peptides in chronic heart failure: a mechanistic clinical study

Hélène Nougué[1,2†], Théo Pezel[1,3†], François Picard[4], Malha Sadoune[1], Mattia Arrigo[5], Florence Beauvais[3], Jean-Marie Launay[1,6,7], Alain Cohen-Solal[1,3,8‡], Nicolas Vodovar[1*‡], and Damien Logeart[1,3,8*‡]

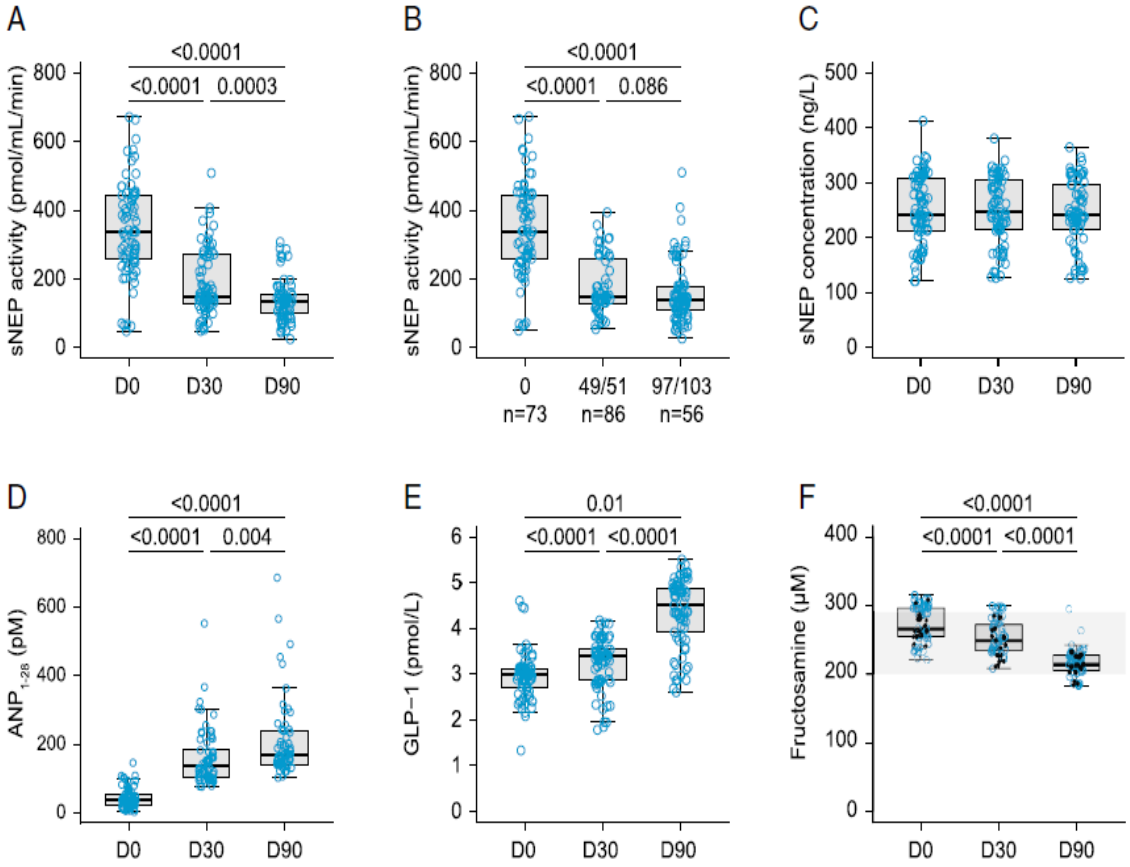
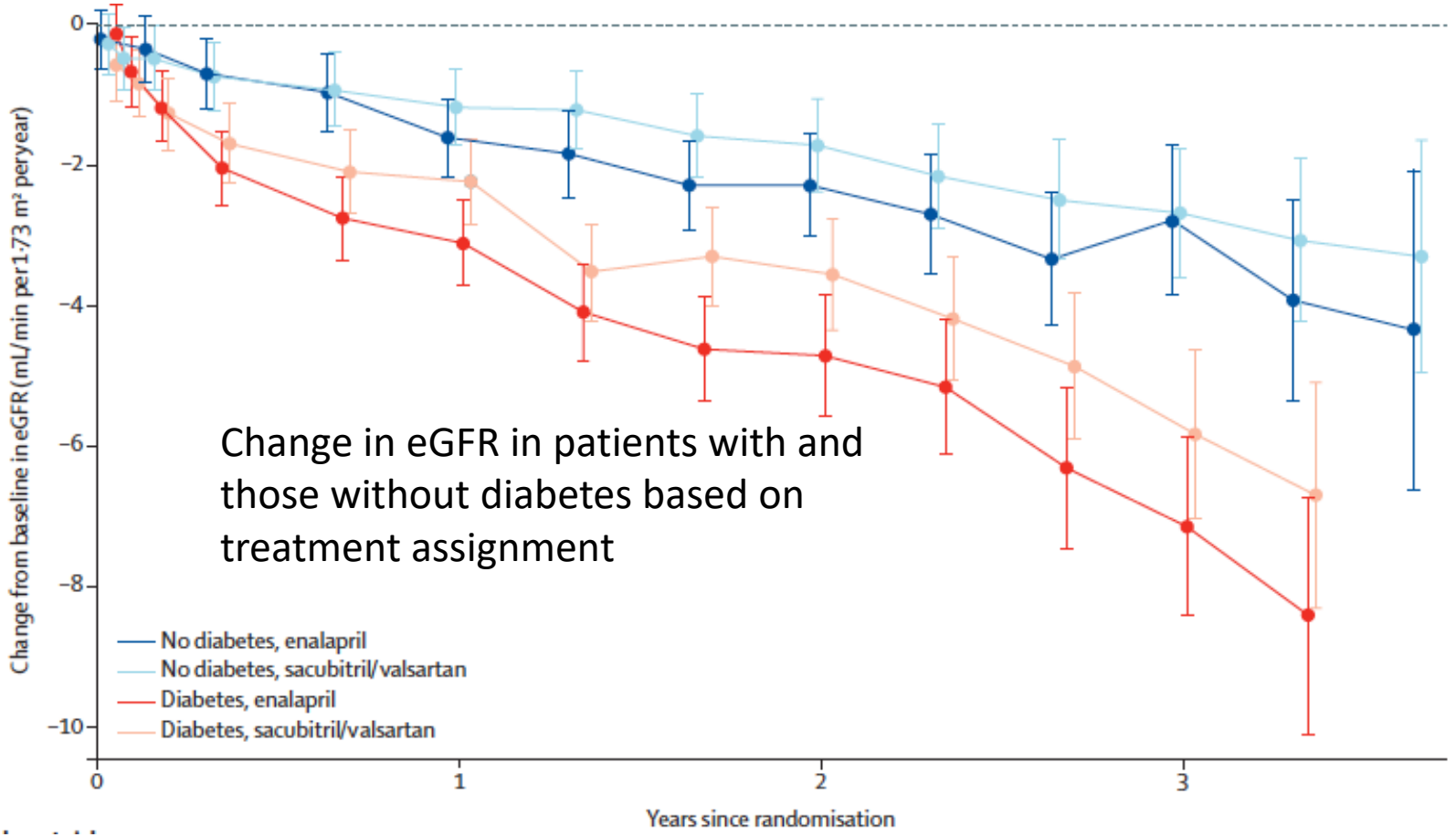



**Table 1** Baseline characteristics of the study population ($n = 73$)

| | |
|---|---|
| **Patient characteristics** | |
| Age (years) | 65 [56–72] |
| Male sex | 61 (84%) |
| Body mass index (kg/m$^2$) | 25.1 [23.0–28.0] |
| Diabetes | 16 (22%) |
| Atrial fibrillation | 25 (34%) |
| Ischaemic heart disease | 40 (55%) |
| Last decompensation (months) | 6 [3–25] |
| Systolic blood pressure (mmHg) | 114 [102–125] |
| Diastolic blood pressure (mmHg) | 67 [60–77] |
| eGFR (mL/min/1.73 m$^2$) | 62 [48–84] |
| NYHA classification | |
| I | 2 (3%) |
| II | 36 (49%) |
| III | 33 (45%) |
| IV | 2 (3%) |
| **Medication** | |
| Furosemide | 62 (85%) |
| ACEi or ARB | 72 (98%) |
| Beta-blocker | 68 (73%) |
| MRA | 58 (73%) |
| **Plasma biomarkers** | |
| Creatinine (µmol/L) | 103 [87–124] |
| BNP (ng/L) | 370 [193–702] |
| NT-proBNP (ng/L) | 1201 [571–1997] |
| hsTnI (ng/L) | 14.3 [9.4–20.7] |
| sNEP activity (pmol/mL/min) | 340 [254–445] |
| sNEP concentration (pg/mL) | 241 [205–303] |
| $ANP_{1-28}$ (pM) | 37.4 [23.5–55.0] |
| GLP-1 (pmol/L) | 3.0 [2.6–3.1] |
| Substance P (ng/L) | 36 [27–44] |
| Fructosamine (µM) | 265 [255–296] |
| sST2 (ng/mL) | 27.3 [21.3–38.4] |
| sCD146 (ng/mL) | 403 [317–560] |

# Effect of neprilysin inhibition on renal function in patients with type 2 diabetes and chronic heart failure who are receiving target doses of inhibitors of the renin-angiotensin system: a secondary analysis of the PARADIGM-HF trial




Change in eGFR in patients with and those without diabetes based on treatment assignment

**Interpretation** In patients in whom the renin-angiotensin system is already maximally blocked, the addition of neprilysin inhibition attenuates the effect of diabetes to accelerate the deterioration of renal function that occurs in patients with chronic heart failure.

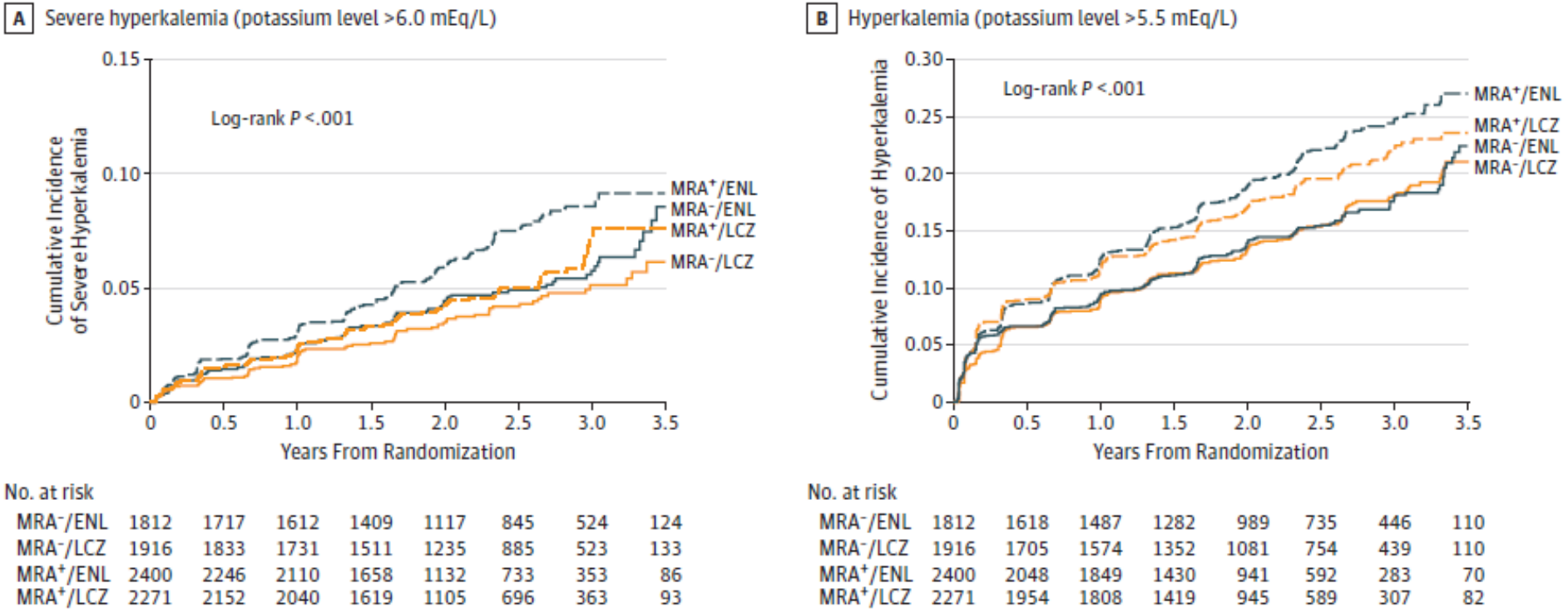
Packer et al. Lancet Diabetes Endocrinol 2018

# Reduced Risk of Hyperkalemia During Treatment of Heart Failure With Mineralocorticoid Receptor Antagonists by Use of Sacubitril/Valsartan Compared With Enalapril

## A Secondary Analysis of the PARADIGM-HF Trial

JAMA Cardiology

**Figure 3. Time to Development of Severe Hyperkalemia (A) and Hyperkalemia (B) According to Mineralocorticoid Receptor Antagonist (MRA) Use at Baseline and Treatment Assignment**




No. at risk

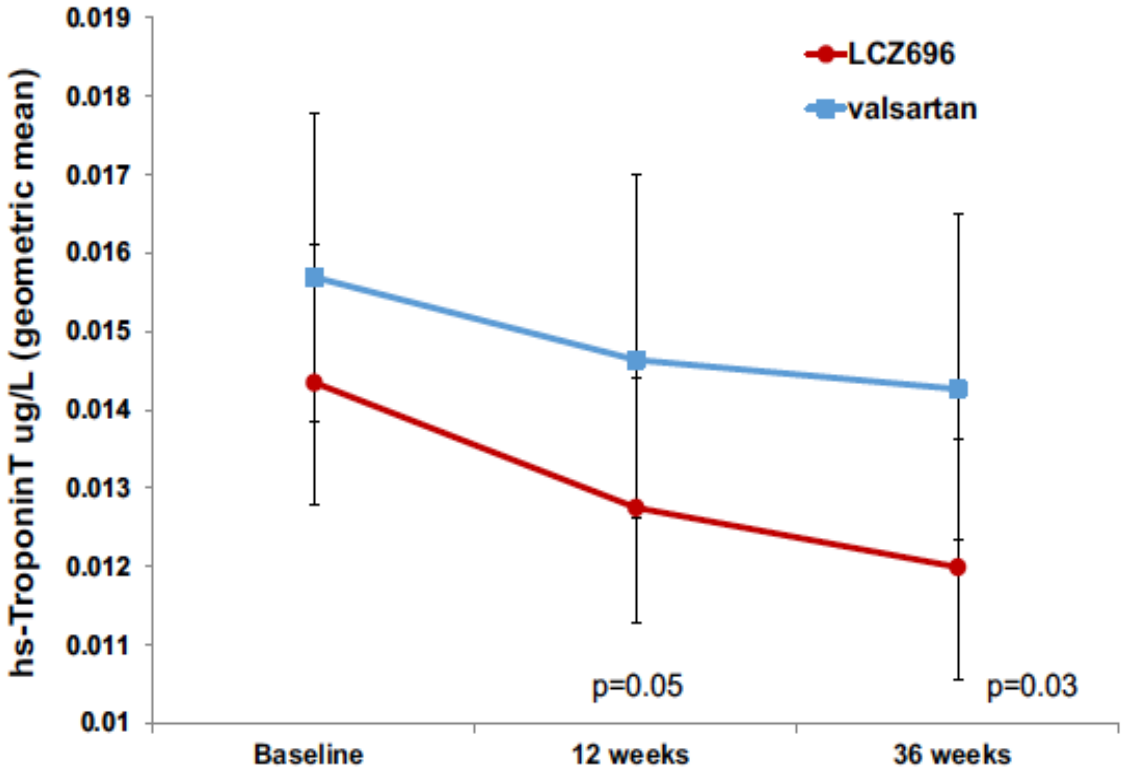
| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| MRA⁻/ENL | 1812 | 1717 | 1612 | 1409 | 1117 | 845 | 524 | 124 |
| MRA⁻/LCZ | 1916 | 1833 | 1731 | 1511 | 1235 | 885 | 523 | 133 |
| MRA⁺/ENL | 2400 | 2246 | 2110 | 1658 | 1132 | 733 | 353 | 86 |
| MRA⁺/LCZ | 2271 | 2152 | 2040 | 1619 | 1105 | 696 | 363 | 93 |

No. at risk

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| MRA⁻/ENL | 1812 | 1618 | 1487 | 1282 | 989 | 735 | 446 | 110 |
| MRA⁻/LCZ | 1916 | 1705 | 1574 | 1352 | 1081 | 754 | 439 | 110 |
| MRA⁺/ENL | 2400 | 2048 | 1849 | 1430 | 941 | 592 | 283 | 70 |
| MRA⁺/LCZ | 2271 | 1954 | 1808 | 1419 | 945 | 589 | 307 | 82 |

# Elevation in High-Sensitivity Troponin T in Heart Failure and Preserved Ejection Fraction and Influence of Treatment With the Angiotensin Receptor Neprilysin Inhibitor LCZ696

Circulation
Heart Failure
JOURNAL OF THE AMERICAN HEART ASSOCIATION




High-sensitivity troponin T (hs-TnT) levels by treatment group

Decreases in hs-TnT with LCZ696 in parallel with improvement in N-terminal pro-brain natriuretic peptide and left atrial size suggest that the angiotensin receptor neprilysin inhibitor LCZ696 may reduce this measure of myocardial injury in heart failure with preserved ejection fraction.

(*Circ Heart Fail.* 2014;7:953-959.)

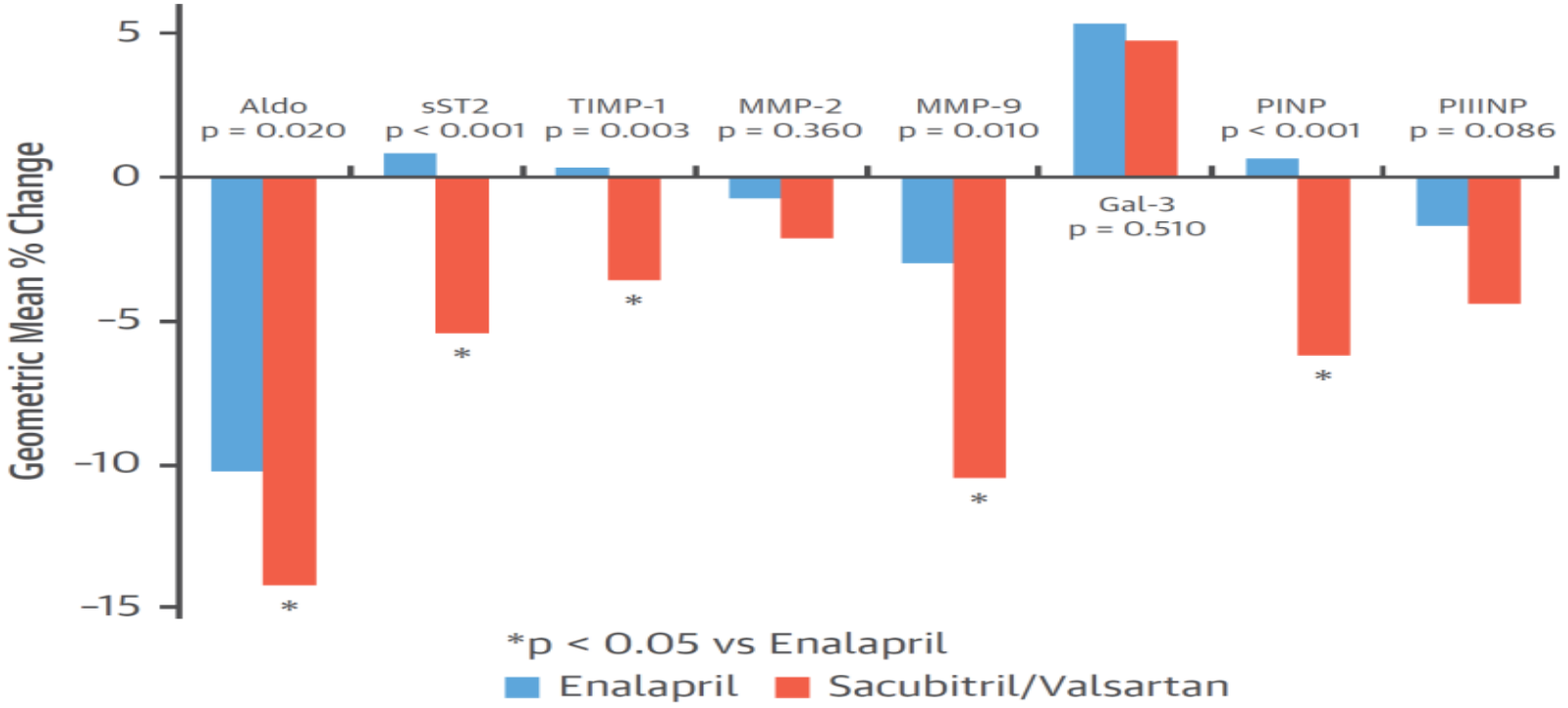
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 73, NO. 7, 2019

PUBLISHED BY ELSEVIER

# Effects of Sacubitril/Valsartan on Biomarkers of Extracellular Matrix Regulation in Patients With HFrEF

Michael R. Zile, MD,[a] Eileen O'Meara, MD,[b] Brian Claggett, PhD,[c] Margaret F. Prescott, PhD,[d] Scott D. Solomon, MD,[c] Karl Swedberg, MD,[e] Milton Packer, MD,[f] John J.V. McMurray, MD,[g] Victor Shi, MD,[d] Martin Lefkowitz, MD,[d] Jean Rouleau, MD[b]

**FIGURE 1 Effects of Treatment on the Geometric Mean Percent Change in Biomarkers From Baseline to 8 Months After Randomization**



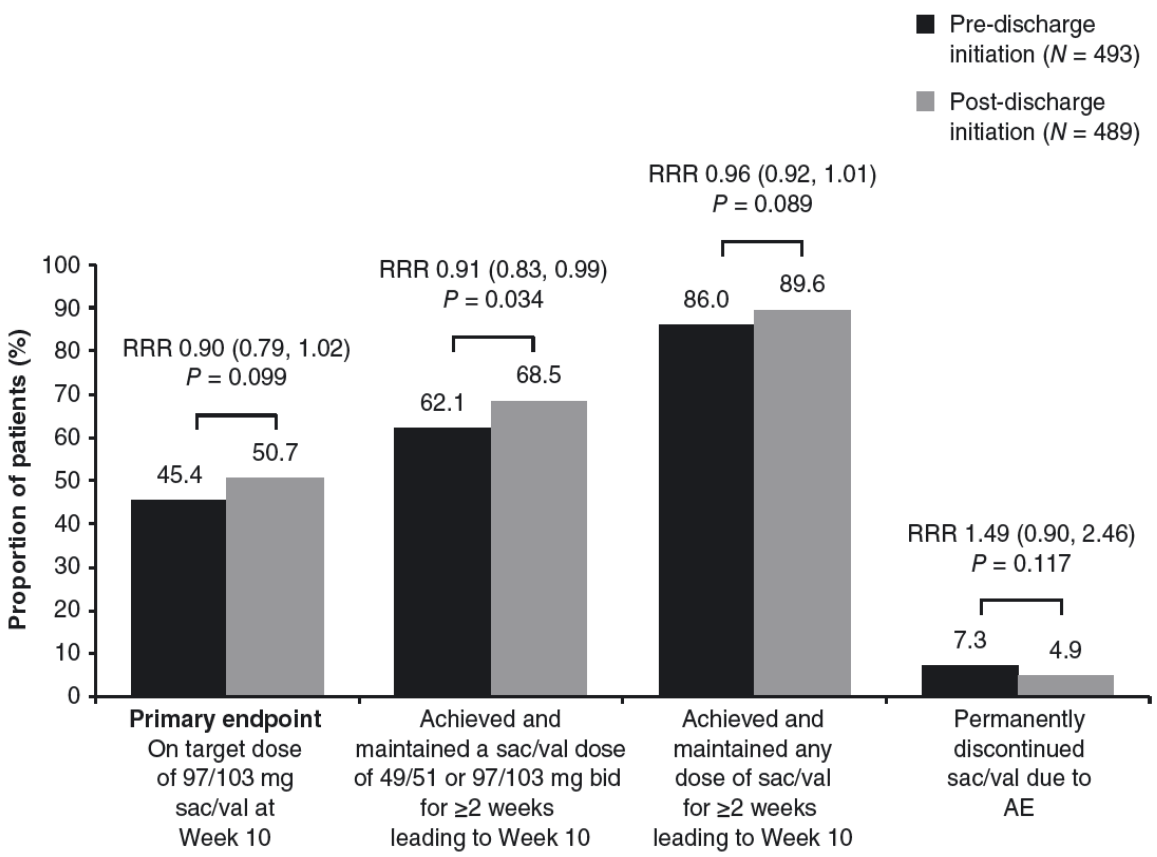



**Figure 3** Primary and secondary endpoints during pre-discharge and post-discharge initiation of sacubitril/valsartan. AE, adverse event; bid, twice daily; RRR, relative risk ratio; sac/val, sacubitril/valsartan.

**Conclusions** Initiation of sacubitril/valsartan in a wide range of heart failure with reduced ejection fraction patients stabilised after an AHF event, either in hospital or shortly after discharge, is feasible with about half of the patients achieving target dose within 10 weeks.

# 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*

This article was published on November 11, 2018, at NEJM.org.

DOI: 10.1056/NEJMoa1812851



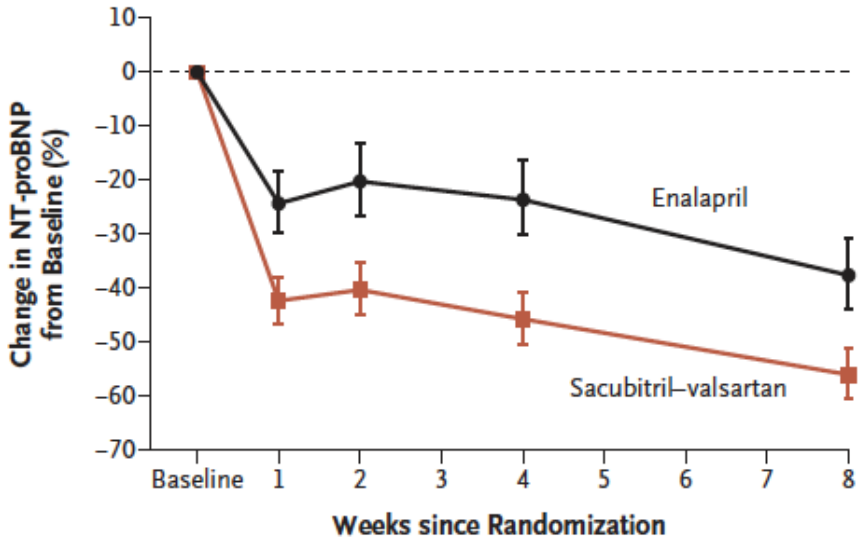



**Figure 2. Change in the NT-proBNP Concentration.**

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).

ORIGINAL ARTICLE

# Angiotensin–Neprilysin Inhibition in Acute Decompensated Heart Failure

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**Table 2. Secondary Efficacy and Safety Outcomes.***

| Outcome | Sacubitril–Valsartan (N=440) | Enalapril (N=441) | Sacubitril–Valsartan vs. Enalapril |
|---|---|---|---|
| **Key safety outcomes — no. (%)** | | | **Relative risk (95% CI)** |
| Worsening renal function† | 60 (13.6) | 65 (14.7) | 0.93 (0.67 to 1.28) |
| Hyperkalemia | 51 (11.6) | 41 (9.3) | 1.25 (0.84 to 1.84) |
| Symptomatic hypotension | 66 (15.0) | 56 (12.7) | 1.18 (0.85 to 1.64) |
| Angioedema | 1 (0.2) | 6 (1.4) | 0.17 (0.02 to 1.38) |
| **Secondary biomarker outcomes — % (95% CI)‡** | | | **Ratio of change (95% CI)** |
| Change in high-sensitivity troponin T concentration | −36.6 (−40.8 to −32.0) | −25.2 (−30.2 to −19.9) | 0.85 (0.77 to 0.94) |
| Change in B-type natriuretic peptide concentration | −28.7 (−35.5 to −21.3) | −33.1 (−39.5 to −25.9) | 1.07 (0.92 to 1.23) |
| Change in ratio of B-type natriuretic peptide to NT-proBNP | 35.2 (28.8 to 42.0) | −8.3 (−3.6 to −12.7) | 1.48 (1.38 to 1.58) |
| **Exploratory clinical outcomes — no. (%)** | | | **Hazard ratio (95% CI)§** |
| Composite of clinical events | 249 (56.6) | 264 (59.9) | 0.93 (0.78 to 1.10) |
| Death | 10 (2.3) | 15 (3.4) | 0.66 (0.30 to 1.48) |
| Rehospitalization for heart failure | 35 (8.0) | 61 (13.8) | 0.56 (0.37 to 0.84) |
| Implantation of left ventricular assist device | 1 (0.2) | 1 (0.2) | 0.99 (0.06 to 15.97) |
| Inclusion on list for heart transplantation | 0 | 0 | NA |
| Unplanned outpatient visit leading to use of intravenous diuretics | 2 (0.5) | 2 (0.5) | 1.00 (0.14 to 7.07) |
| Use of additional drug for heart failure | 78 (17.7) | 84 (19.0) | 0.92 (0.67 to 1.25) |
| Increase in dose of diuretics of >50% | 218 (49.5) | 222 (50.3) | 0.98 (0.81 to 1.18) |
| Composite of serious clinical events¶ | 41 (9.3) | 74 (16.8) | 0.54 (0.37 to 0.79) |

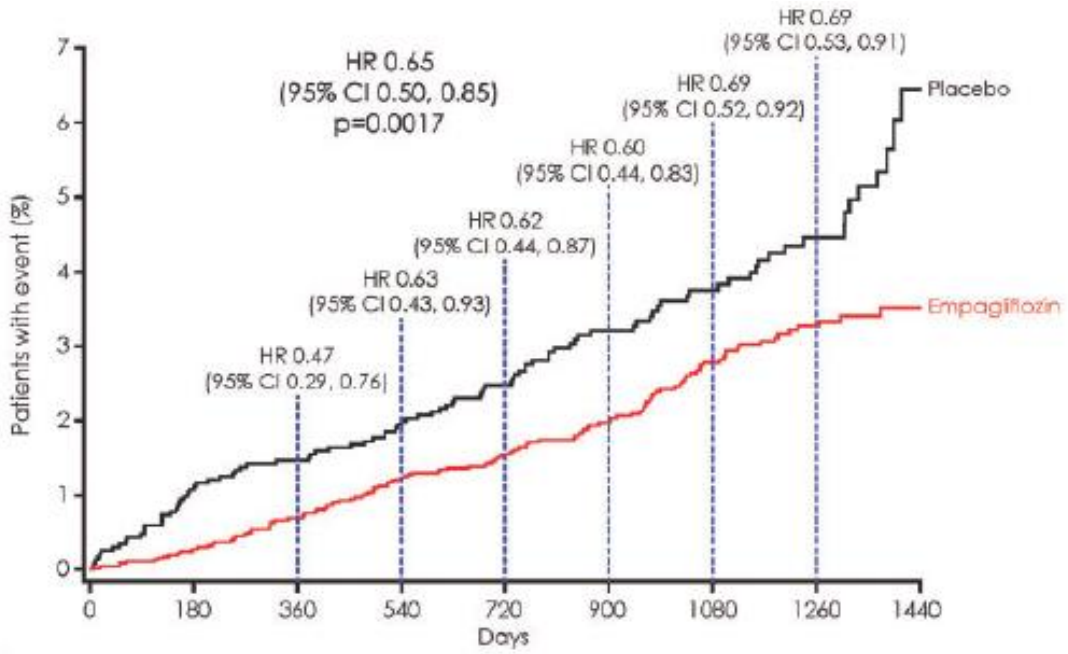
# PARADIGM-HF: Pre-specified safety endpoints

| | LCZ696 (n=4187) | Enalapril (n=4212) | P value |
|---|---|---|---|
| **Hypotension (%)** | | | |
| symptoms | **14.0** | **9.2** | <0.001 |
| symptoms and SBP <90mmHg | **2.7** | **1.4** | <0.001 |
| **Renal impairment (%)** | | | |
| Cr ≥2.5mg/dl | **3.3** | **4.5** | 0.007 |
| Cr ≥3.0mg/dl | **1.5** | **2.0** | 0.10 |
| **Hyperkalaemia (%)** | | | |
| $K_+$ >5.5mmol/l | **16.2** | **17.4** | 0.15 |
| $K_+$ >6.0mmol/l | **4.3** | **5.6** | 0.007 |
| **Cough (%)** | **11.3** | **14.3** | <0.001 |
| **Angioedema: not hospitalised** | | | |
| No treatment/antihistamines n, (%) | **10 (0.2)** | **5 (0.1)** | 0.19 |
| Catecholamines/corticosteroids n, (%) | **6 (0.1)** | **4 (0.1)** | 0.52 |
| **Angioedema: hospitalised** | | | |
| No airway compromise n, (%) | **3 (0.1)** | **1 (0.0)** | 0.31 |
| Airway compromise n, (%) | **0 (0.0)** | **0 (0.0)** | - |

*McMurray et al. N Engl J Med 2014;371(11):993-1004*

# Effects of empagliflozin on risk for cardiovascular death and heart failure hospitalization across the spectrum of heart failure risk in the EMPA-REG OUTCOME® trial

ESC European Society of Cardiology
European Heart Journal (2018) **39**, 363–370
doi:10.1093/eurheartj/ehx511




Cumulative incidence curve, HRs, and 95% CIs. (Cox regression analysis in patients treated with ≥1 dose of study drug). CI, confidence interval; HR, hazard ratio.

## Time trajectory of benefit for heart failure hospitalization

Reductions in the risk for HF hospitalization with empagliflozin vs. placebo were observed by the first month and persisted for the duration of the trial (*Figure 2A*). The HR stabilized as the number of patients with events increased over time (*Figure 2B*).

# DAPA-HF Trial Design

- **Key inclusion criteria:** Symptomatic HF; EF ≤40%; NT-proBNP ≥600 pg/ml (if hospitalized for HF within last 12 months ≥400 pg/mL; if atrial fibrillation/flutter ≥900 pg/mL)
- **Key exclusion criteria:** eGFR <30 ml/min/1.73 $m^2$; symptomatic hypotension or SBP <95 mmHg; type 1 diabetes mellitus
- **Primary endpoint:** Worsening HF event or cardiovascular death (worsening HF event = unplanned HF hospitalization or an urgent heart failure visit requiring intravenous therapy)

*For full details see McMurray JJV et al Eur J Heart Fail. 2019;21:665-675*

# Key baseline characteristics

| Characteristic | Dapagliflozin (n=2373) | Placebo (n=2371) |
|---|---|---|
| Mean age (yr) | 66 | 67 |
| Male (%) | 76 | 77 |
| NYHA class II/III/IV (%) | 68/31/1 | 67/32/1 |
| Mean LVEF (%) | 31 | 31 |
| Median NT pro BNP (pg/ml) | 1428 | 1446 |
| Mean systolic BP (mmHg) | 122 | 122 |
| Ischaemic aetiology (%) | 55 | 57 |
| Mean eGFR (ml/min/1.73m$^2$) | 66 | 66 |
| Prior diagnosis T2D (%) | 42 | 42 |
| Any baseline T2D (%)* | 45 | 45 |

*includes 82 dapagliflozin and 74 placebo patients with previously undiagnosed diabetes i.e. two HbA1c ≥6.5% (≥48 mmol/mol)

# Baseline treatment

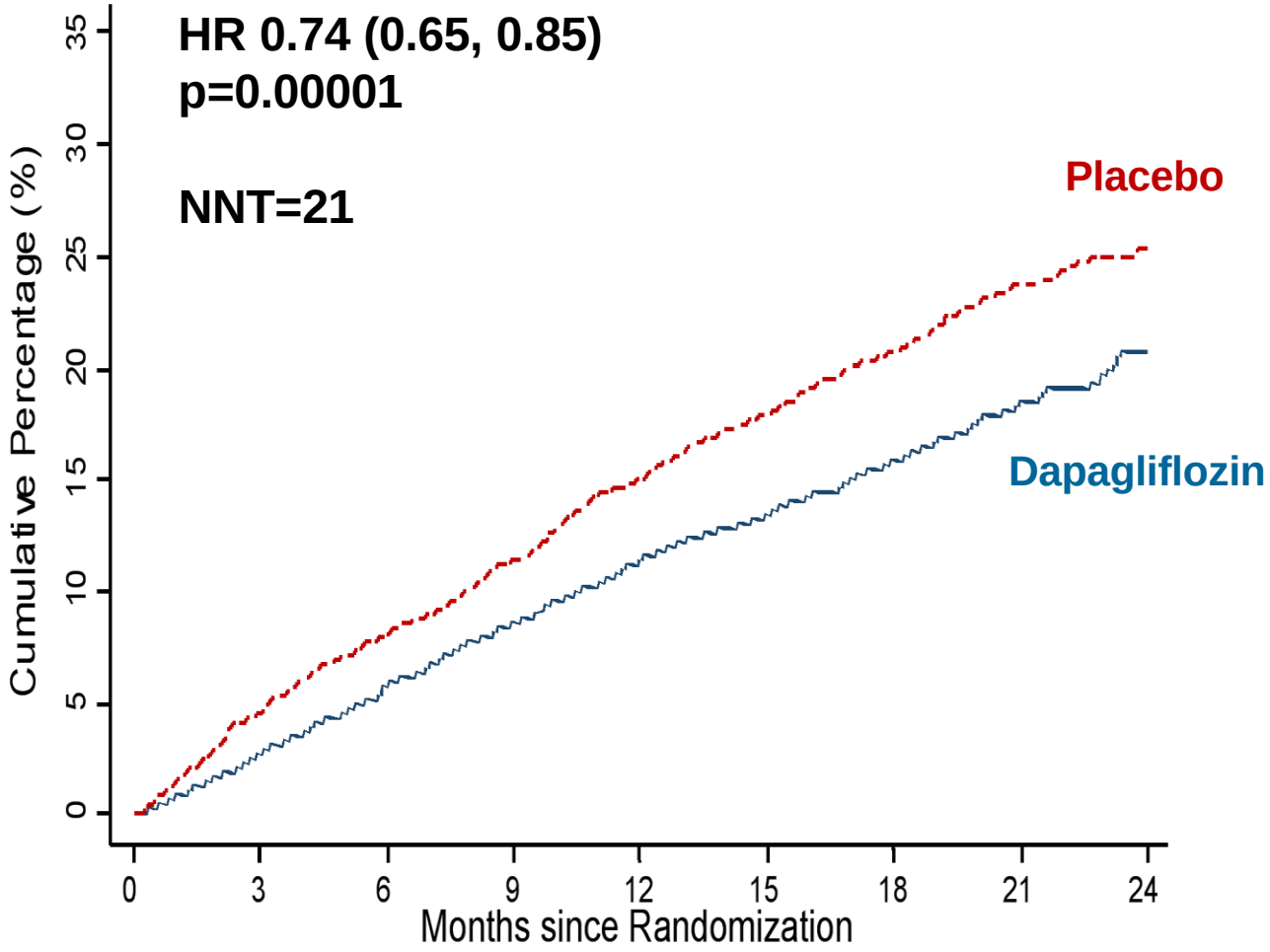
| Treatment (%) | Dapagliflozin (n=2373) | Placebo (n=2371) |
|---|---|---|
| Diuretic | 93 | 94 |
| ACE-inhibitor/ARB/ARNI+ | 94 | 93 |
| ACE inhibitor | 56 | 56 |
| ARB | 28 | 27 |
| Sacubitril/valsartan | 11 | 11 |
| Beta-blocker | 96 | 96 |
| MRA | 71 | 71 |
| ICD* | 26 | 26 |
| CRT** | 8 | 7 |

+ARNI = angiotensin receptor neprilysin inhibitor
*ICD or CRT-D **CRT-P or CRT-D

*For full details see McMurray JJV et al*
*Eur J Heart Fail.2019 Jul 15. doi: 10.1002/ejhf.1548*

# Primary composite outcome

CV Death/HF hospitalization/Urgent HF visit



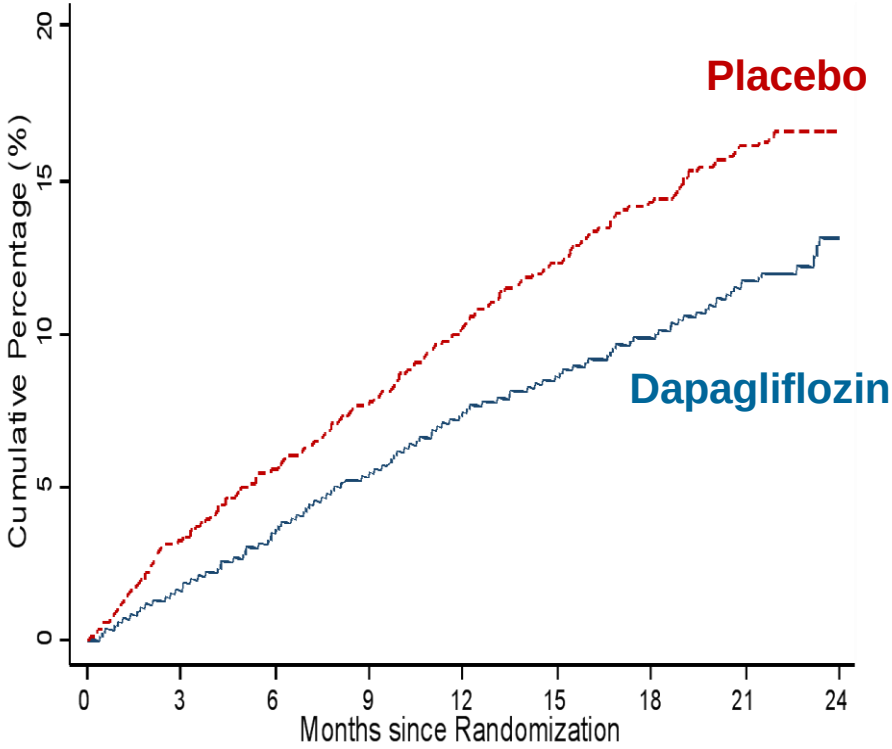

Number at Risk

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Dapagliflozin | 2373 | 2305 | 2221 | 2147 | 2002 | 1560 | 1146 | 612 | 210 |
| Placebo | 2371 | 2258 | 2163 | 2075 | 1917 | 1478 | 1096 | 593 | 210 |

# Components of primary outcome

## Worsening HF event

**HR 0.70 (0.59, 0.83); p=0.00003**

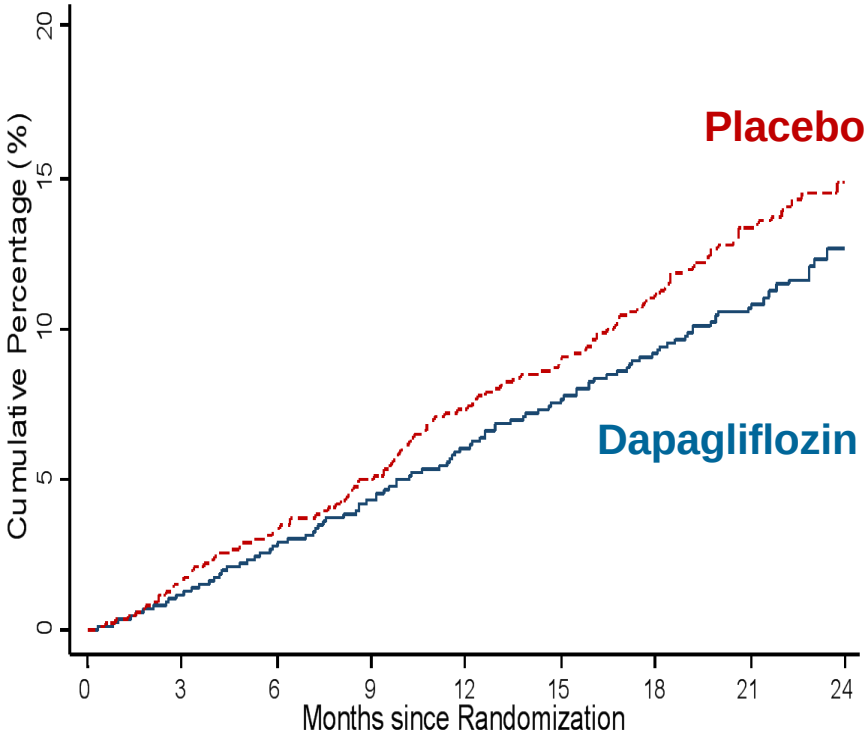



Number at Risk

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Dapagliflozin | 2373 | 2305 | 2221 | 2147 | 2002 | 1560 | 1146 | 612 | 210 |
| Placebo | 2371 | 2258 | 2163 | 2075 | 1917 | 1478 | 1096 | 593 | 210 |

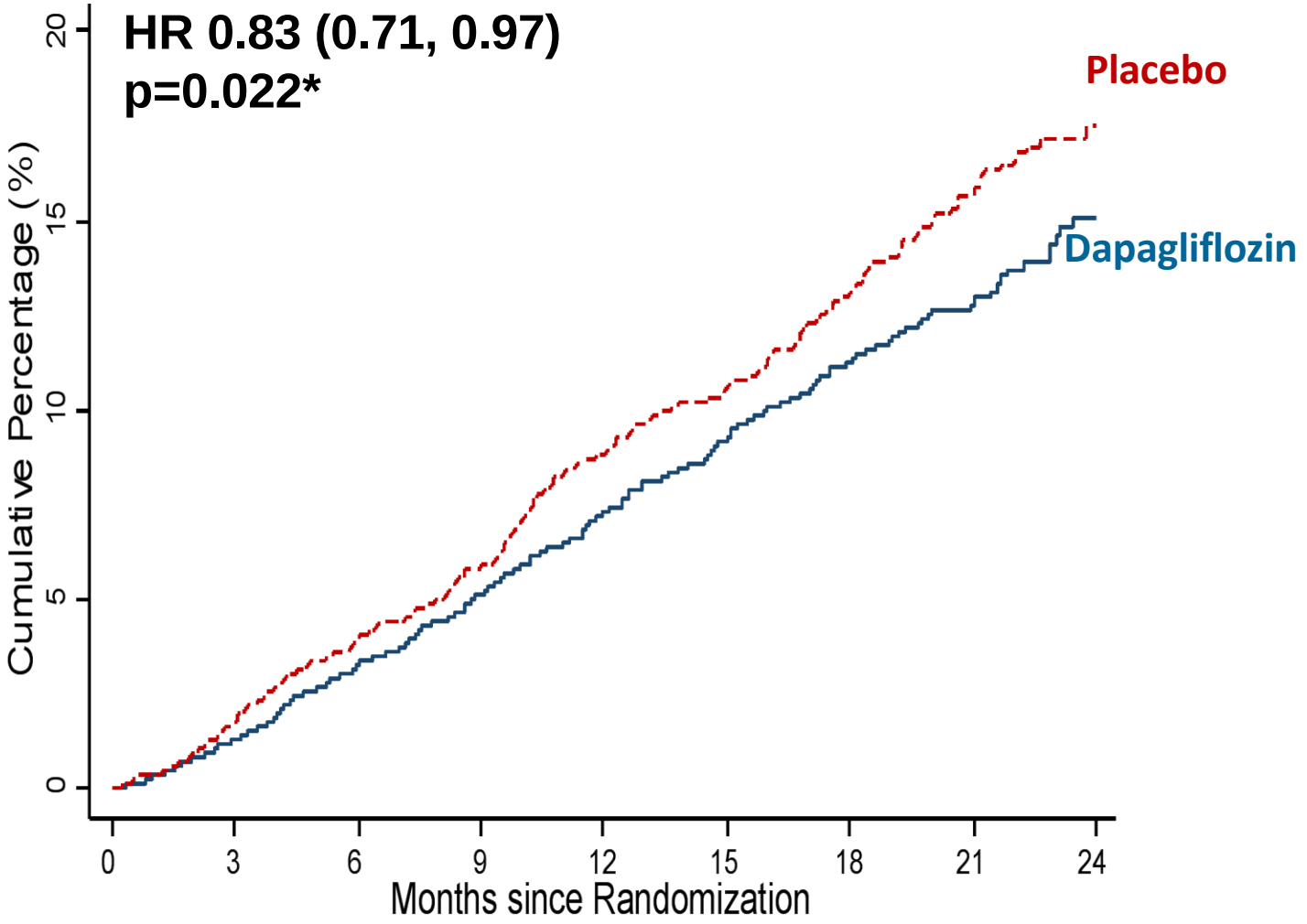
## Cardiovascular death

**HR 0.82 (0.69, 0.98); p=0.029**




| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 2373 | 2339 | 2293 | 2248 | 2127 | 1664 | 1242 | 671 | 232 |
| | 2371 | 2330 | 2279 | 2230 | 2091 | 1636 | 1219 | 664 | 234 |

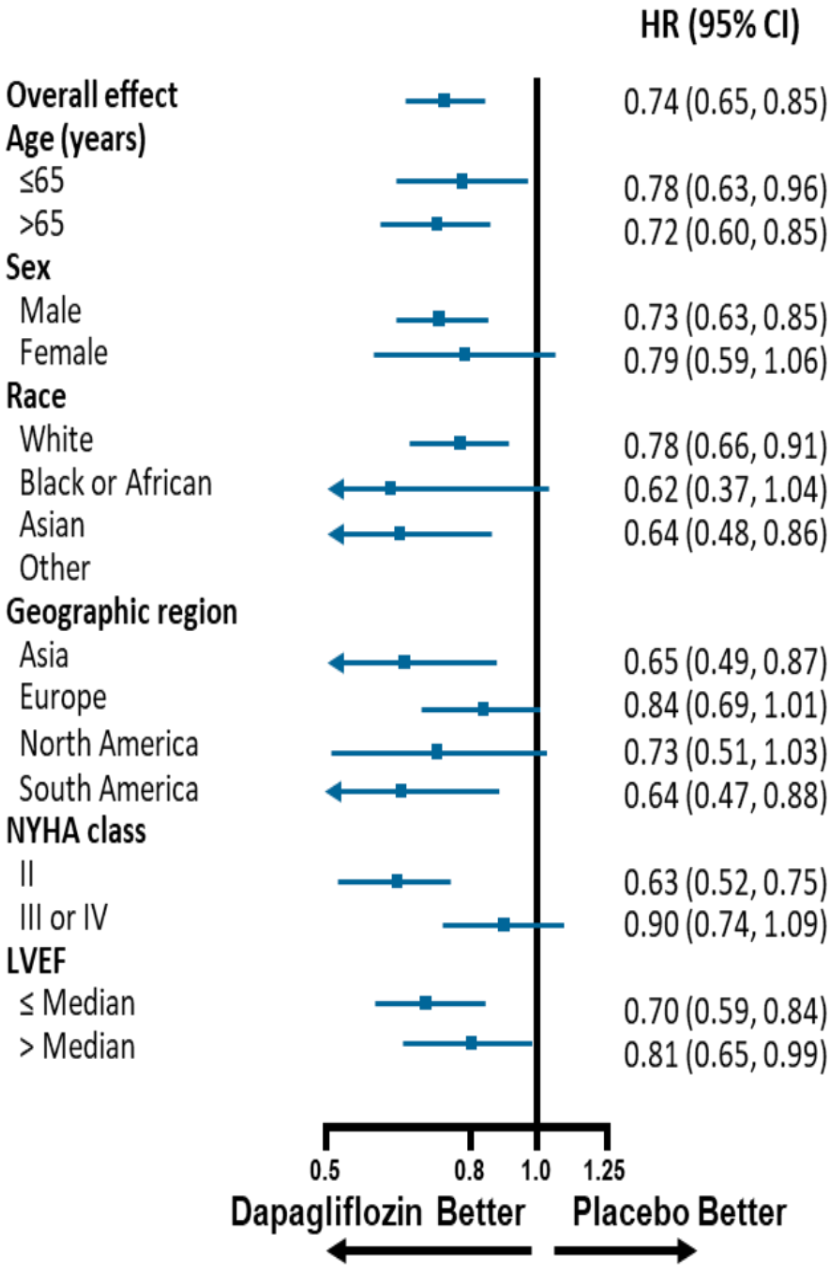
# All-cause death

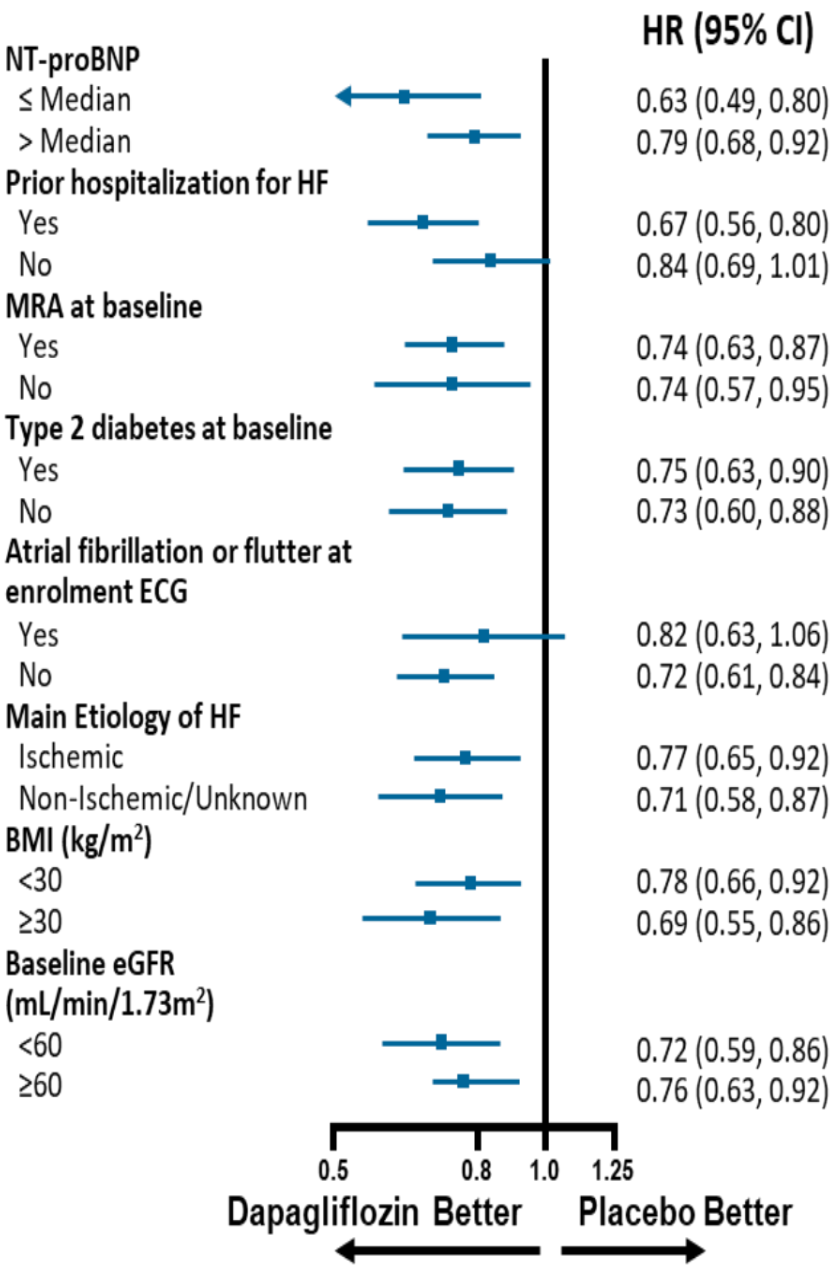



| Number at Risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Dapagliflozin | 2373 | 2342 | 2296 | 2251 | 2130 | 1666 | 1243 | 672 | 233 |
| Placebo | 2371 | 2330 | 2279 | 2231 | 2092 | 1638 | 1221 | 665 | 235 |

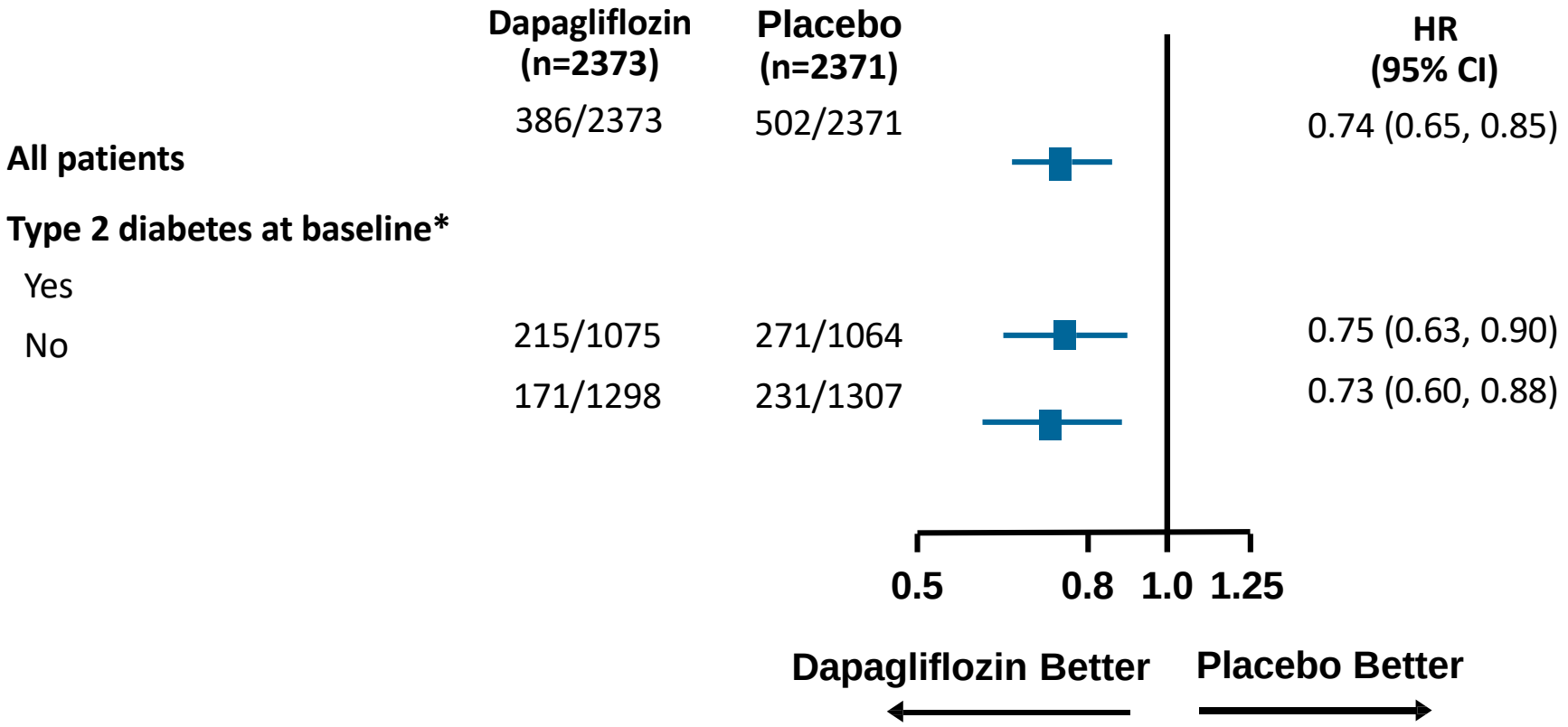
*Nominal p value

# Primary Endpoint: Prespecified subgroups



# No diabetes/diabetes subgroup: Primary endpoint




*Defined as history of type 2 diabetes or HbA1c ≥6.5% at both enrollment and randomization visits.

# Safety/adverse events

| Patients exposed to at least one dose of study drug | Dapagliflozin (n=2368) | Placebo (n=2368) | p-value |
|---|---|---|---|
| **Adverse events (AE) of interest (%)** | | | |
| Volume depletion[+] | 7.5 | 6.8 | 0.40 |
| Renal AE[‡] | 6.5 | 7.2 | 0.36 |
| Fracture | 2.1 | 2.1 | 1.00 |
| Amputation | 0.5 | 0.5 | 1.00 |
| Major hypoglycaemia | 0.2 | 0.2 | - |
| Diabetic ketoacidosis | 0.1 | 0.0 | - |
| **AE leading to treatment discontinuation (%)** | 4.7 | 4.9 | 0.79 |
| **Any serious adverse event (incl. death) (%)** | 38 | 42 | <0.01 |

[+] Volume depletion serious AEs in 29 dapagliflozin patients (1.2%) and 40 placebo patients (1.7%), p=0.23

[‡] Renal serious AEs in 38 dapagliflozin patients (1.6%) and 65 placebo patients (2.7%), p=0.009

# Incident Hyperkalemia

(Any Occurrence of Serum Potassium>5.5 mmol/L)
According to Background Dose of Key Neurohormonal Agents

| | Eplerenone, % | Placebo, % | *P* Value by Fisher Exact Test |
|---|---|---|---|
| ACEi≥50% dose (n=1530) | 12.6 | 7.0 | 0.0003 |
| ACEi<50% dose (n=1207) | 10.8 | 7.4 | 0.043 |
| BB≥50% dose(n=1081) | 10.8 | 7.9 | 0.14 |
| BB<50% dose (n=1656) | 12.5 | 6.7 | <0.0001 |
| ACEi and BB≥50% dose (n=736) | 11.2 | 6.5 | 0.027 |
| At least one of ACEi or BB<50% dose (n=2001) | 12.1 | 7.4 | 0.0006 |

ACEi indicates angiotensin-converting enzyme inhibitor; and BB, β-blocker.

- greater incidence of hyperkalemia in the eplerenone group compared with placebo.
- little evidence of **greater absolute rate of hyperkalemia** events in patients receiving **high doses versus low doses of background agents**.

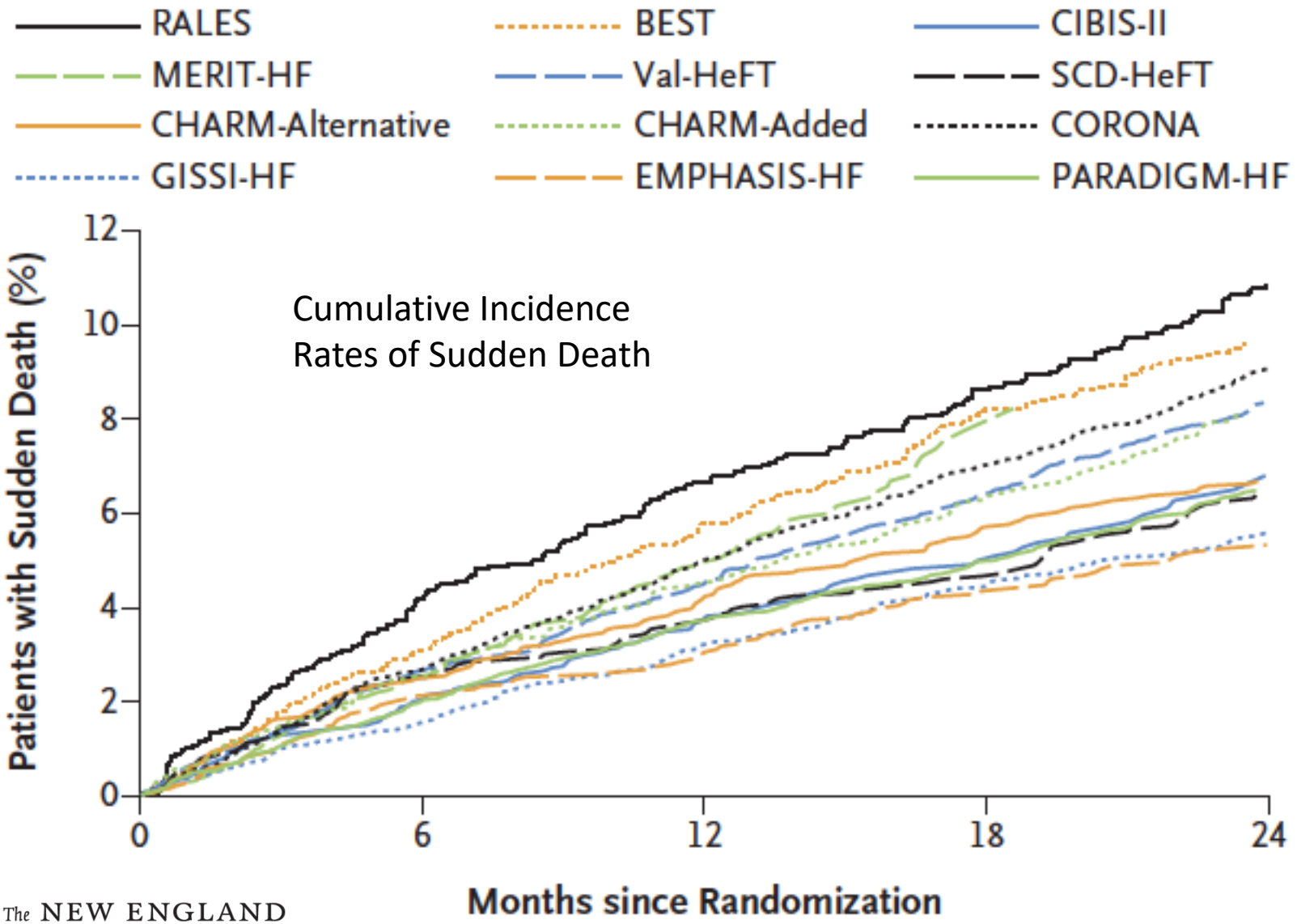
(*Circ Heart Fail*. 2013;6:711-718.)

# Mineralocorticoid receptor antagonist pattern of use in heart failure with reduced ejection fraction: findings from BIOSTAT-CHF


(n=1049); changes in MRA prescription between baseline and 9 months

*Ferreira et al. European Journal of Heart Failure (2017).19:1284*

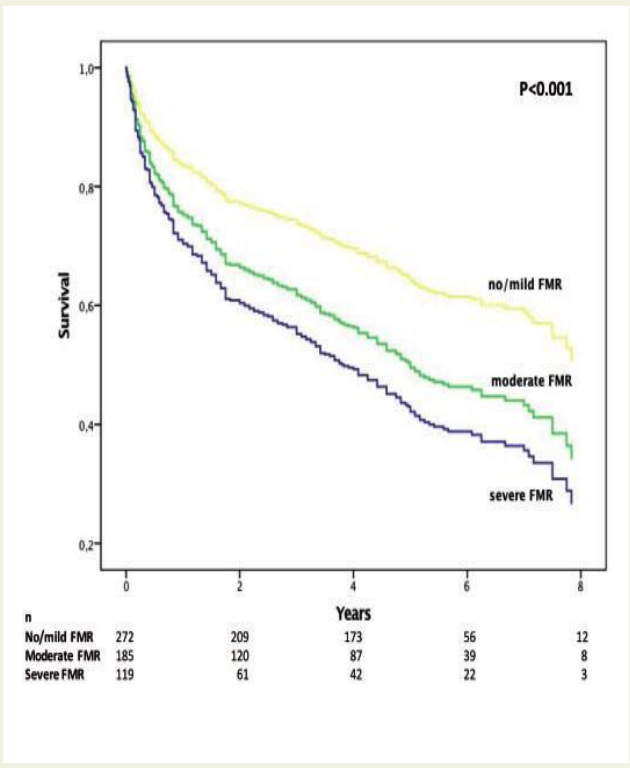
# Declining Risk of Sudden Death in Heart Failure




The NEW ENGLAND JOURNAL of MEDICINE

Shen et al. N Engl J Med 2017;377:41-51

# Refining the prognostic impact of functional mitral regurgitation in chronic heart failure




Adjusted for age, sex, ischaemic aetiology of heart failure, serum creatinine, and NT-proBNP

**Table 3** Impact of severe mitral regurgitation on outcome compared with the remaining study population by various subgroups of heart failure defined functionally by New York Heart Association stage, biochemically by quartiles of NT-proBNP, and echocardiographically by left ventricular ejection fraction

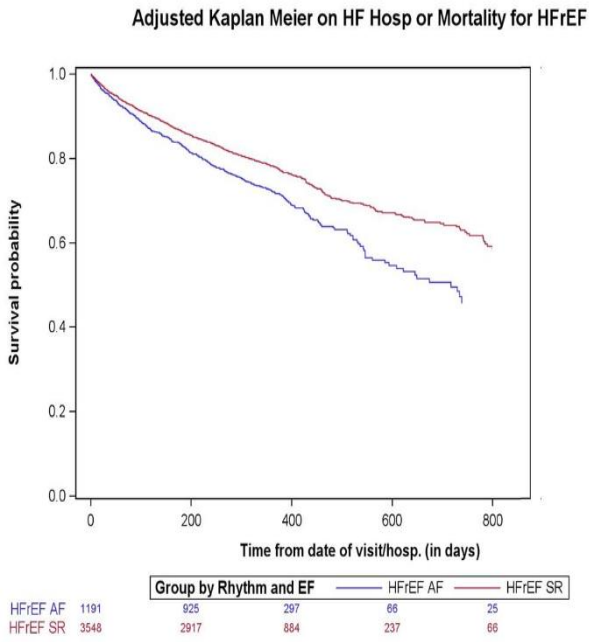
| Subgroups | Patients/events | Crude HR (95% CI) | *P*-value | Adjusted HR (95% CI)[a] | *P*-value |
|---|---|---|---|---|---|
| NYHA functional class | | | | | |
| NYHA I | 66/22 | 1.20 (0.40–3.55) | 0.75 | 0.83 (0.27–2.49) | 0.73 |
| NYHA II | 153/58 | 1.89 (0.95–3.77) | 0.07 | 2.17 (1.07–4.44) | **0.03** |
| NYHA III | 236/110 | 1.81 (1.18–2.79) | **0.007** | 1.80 (1.17–2.77) | **0.008** |
| NYHA IV | 121/81 | 1.02 (0.65–1.60) | 0.93 | 1.09 (0.69–1.72) | 0.71 |
| Echocardiographic LV function | | | | | |
| Moderately reduced (LVEF 30–40%) | 159/76 | 2.15 (1.25–3.69) | **0.006** | 2.37 (1.36–4.12) | **0.002** |
| Severely reduced (LVEF <30%) | 325/171 | 1.29 (0.94–1.79) | 0.12 | 1.31 (0.95–1.81) | 0.10 |
| Quartiles of NT-proBNP (pg/mL) | | | | | |
| 1st quartile (<863 pg/mL) | 144/39 | 0.43 (0.06–3.17) | 0.41 | 0.56 (0.07–4.05) | 0.56 |
| 2nd quartile (871–2360 pg/mL) | 145/64 | 2.07 (1.19–3.62) | **0.01** | 2.16 (1.22–3.86) | **0.009** |
| 3rd quartile (2368–5159 pg/mL) | 143/67 | 1.33 (0.78–2.26) | 0.30 | 1.36 (0.79–2.32) | 0.26 |
| 4th quartile (>5167 pg/mL) | 144/101 | 1.17 (0.78–1.76) | 0.45 | 1.18 (0.78–1.77) | 0.43 |

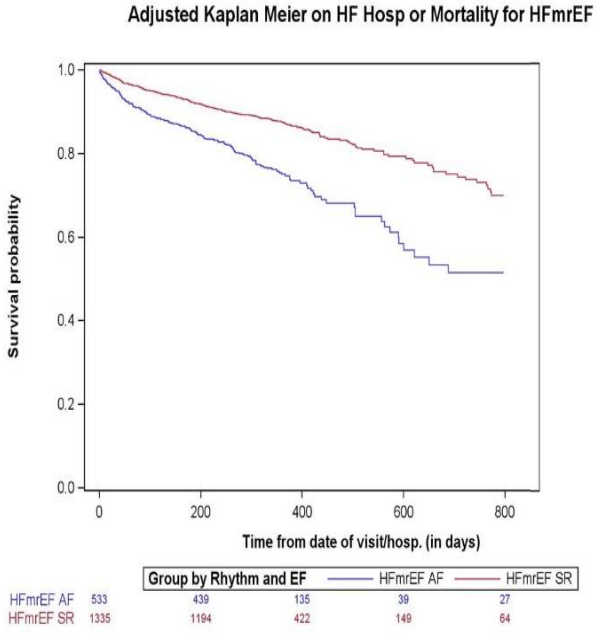
Severe MR exerted the largest impact in patients with intermediate severity of HF

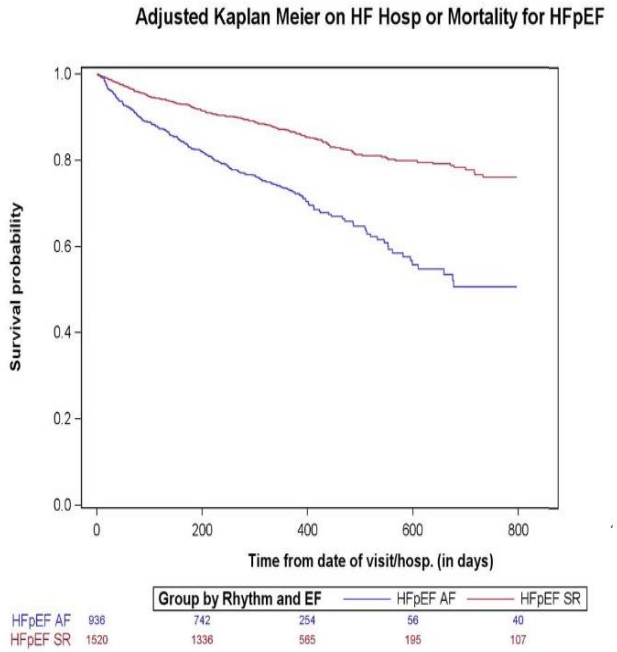
G. Goliasch *et al.*

European Heart Journal (2017) **0**, 1–8
doi:10.1093/eurheartj/ehx402

# Prognostic implications of atrial fibrillation in heart failure with reduced, mid-range, and preserved ejection fraction: a report from 14 964 patients in the European Society of Cardiology Heart Failure Long-Term Registry




*Zafrir et al. Eur Heart J 2018;39:4277-4284*

# 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

ESC GUIDELINES

EUROPEAN SOCIETY OF CARDIOLOGY®

Candidates to LVAD

| Patients with >2 months of severe symptoms despite optimal medical and device therapy and more than one of the following: |
|---|
| LVEF <25% and, if measured, peak $VO_2$ <12 mL/kg/min. |
| ≥3 HF hospitalizations in previous 12 months without an obvious precipitating cause. |
| Dependence on i.v. inotropic therapy. |
| Progressive end-organ dysfunction (worsening renal and/or hepatic function) due to reduced perfusion and not to inadequate ventricular filling pressure (PCWP ≥20 mmHg and SBP ≤80–90 mmHg or CI ≤2 L/min/$m^2$). |
| Absence of severe right ventricular dysfunction together with severe tricuspid regurgitation. |

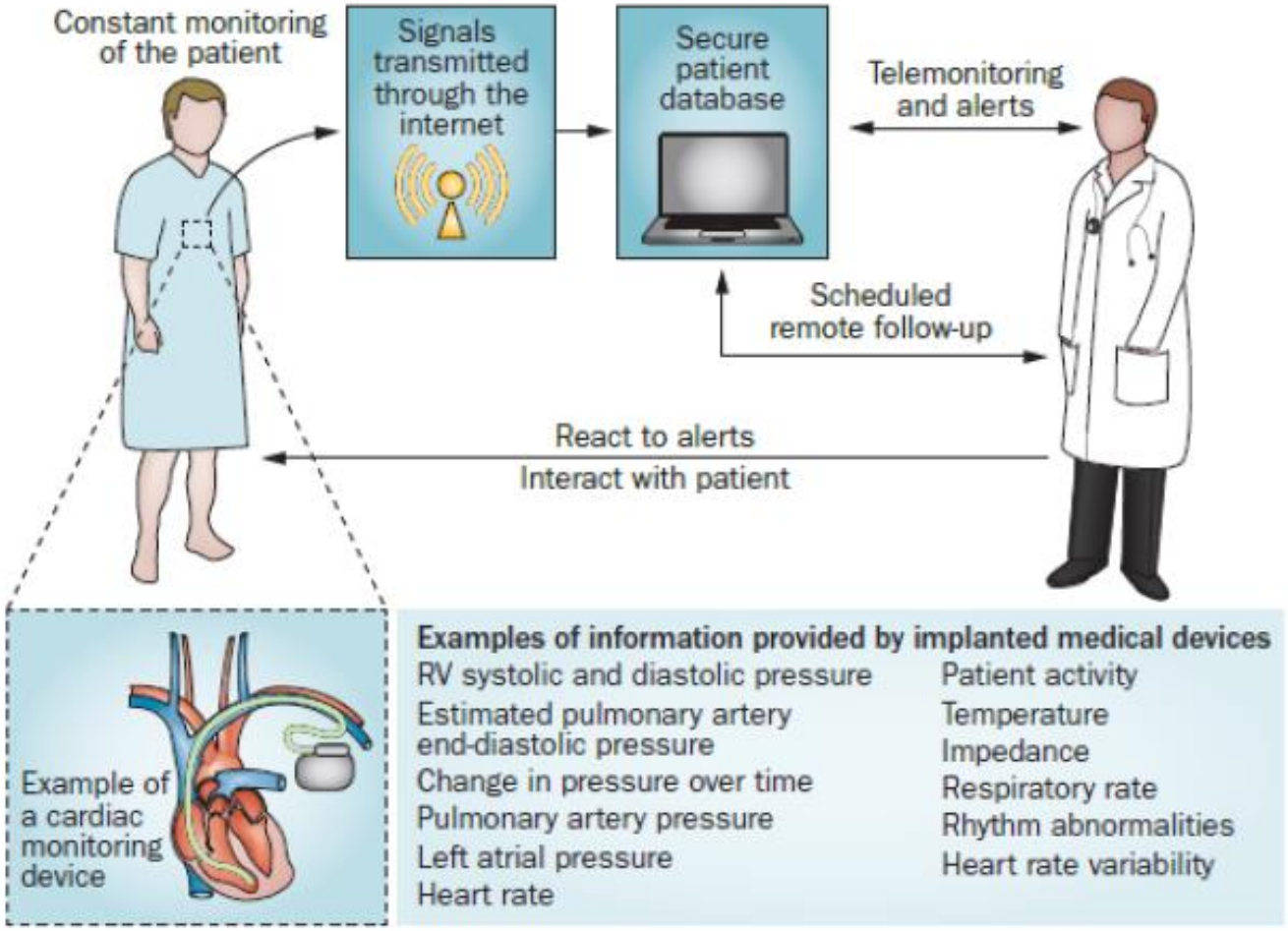
| Recommendations | Class [a] | Level [b] |
|---|---|---|
| An LVAD should be considered in patients who have end- stage HFrEF despite optimal medical and device therapy and who are eligible for heart transplantation in order to improve symptoms, reduce the risk of HF hospitalization and the risk of premature death (Bridge to transplant indication). | IIa | C |
| An LVAD should be considered in patients who have end-stage HFrEF despite optimal medical and device therapy and who are not eligible for heart transplantation to, reduce the risk of premature death. | IIa | B |

EHJ. 2016;37:2129-200

nature REVIEWS CARDIOLOGY

# Trials of implantable monitoring devices in heart failure: which design is optimal?

*William T. Abraham, Wendy G. Stough, Ileana L. Piña, Cecilia Linde, Jeffrey S. Borer, Gaetano M. De Ferrari, Roxana Mehran, Kenneth M. Stein, Alphons Vincent, Jay S. Yadav, Stefan D. Anker and Faiez Zannad*



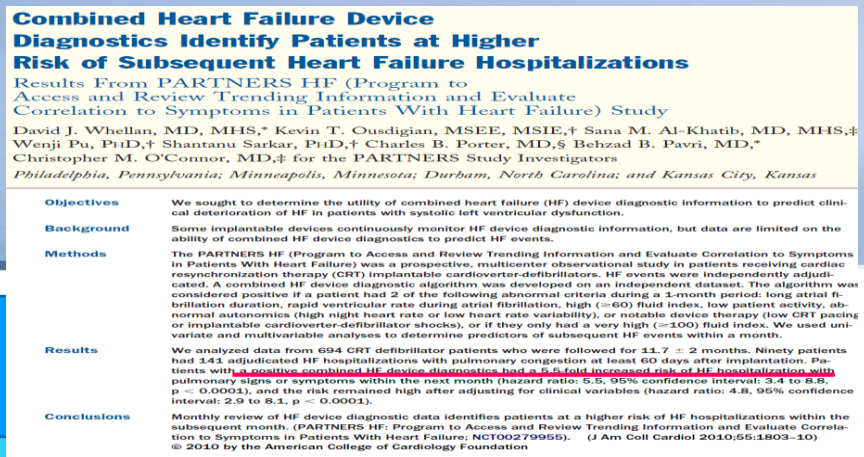

Abraham, W. T. et al. Nat. Rev. Cardiol. 11, 576–585 (2014)

# Può la diagnostica del dispositivo aiutare il medico nella gestione del paziente scompensato?

- **<u>Riconoscere l'insorgenza di uno stato di scompenso</u> prima dei sintomi:**

  - ✓ **Variazioni FC diurna-notturna**
  - ✓ **Variazioni  Heart Rate Variability**
  - ✓ **Presenza di aritmie atriali/ventricolari**
  - ✓ **Osservazione attività pz**
  - ✓ **Effetti componente liquida nei polmoni**
  - ✓ **Misurazione  parametri emodinamici**
  - ✓ **Valutazione apnee notturne/indici respiratori**

# PARTNER-HF



**Combined Heart Failure Device Diagnostics Identify Patients at Higher Risk of Subsequent Heart Failure Hospitalizations**

Results From PARTNERS HF (Program to Access and Review Trending Information and Evaluate Correlation to Symptoms in Patients With Heart Failure) Study

David J. Whellan, MD, MHS,* Kevin T. Ousdigian, MSEE, MSIE,† Sana M. Al-Khatib, MD, MHS,‡ Wenji Pu, PHD,† Shantanu Sarkar, PHD,† Charles B. Porter, MD,§ Behzad B. Pavri, MD,* Christopher M. O'Connor, MD,‡ for the PARTNERS Study Investigators

*Philadelphia, Pennsylvania; Minneapolis, Minnesota; Durham, North Carolina; and Kansas City, Kansas*

**Objectives** We sought to determine the utility of combined heart failure (HF) device diagnostic information to predict clinical deterioration of HF in patients with systolic left ventricular dysfunction.

**Background** Some implantable devices continuously monitor HF device diagnostic information, but data are limited on the ability of combined HF device diagnostics to predict HF events.

**Methods** The PARTNERS HF (Program to Access and Review Trending Information and Evaluate Correlation to Symptoms in Patients With Heart Failure) was a prospective, multicenter observational study in patients receiving cardiac resynchronization therapy (CRT) implantable cardioverter-defibrillators. HF events were independently adjudicated. A combined HF device diagnostic algorithm was developed on an independent dataset. The algorithm was considered positive if a patient had 2 of the following abnormal criteria during a 1-month period: long atrial fibrillation duration, rapid ventricular rate during atrial fibrillation, high (≥60) fluid index, low patient activity, abnormal autonomics (high night heart rate or low heart rate variability), or notable device therapy (low CRT pacing or implantable cardioverter-defibrillator shocks), or if they only had a very high (≥100) fluid index. We used univariate and multivariable analyses to determine predictors of subsequent HF events within a month.

**Results** We analyzed data from 694 CRT defibrillator patients who were followed for 11.7 ± 2 months. Ninety patients had 141 adjudicated HF hospitalizations with pulmonary congestion at least 60 days after implantation. Patients with a positive combined HF device diagnostics had a 5.5-fold increased risk of HF hospitalization with pulmonary signs or symptoms within the next month (hazard ratio: 5.5, 95% confidence interval: 3.4 to 8.8, $p < 0.0001$), and the risk remained high after adjusting for clinical variables (hazard ratio: 4.8, 95% confidence interval: 2.9 to 8.1, $p < 0.0001$).

**Conclusions** Monthly review of HF device diagnostic data identifies patients at a higher risk of HF hospitalizations within the subsequent month. (PARTNERS HF: Program to Access and Review Trending Information and Evaluate Correlation to Symptoms in Patients With Heart Failure; NCT00279955). (J Am Coll Cardiol 2010;55:1803–10)



| Parameter | Criterion |
|---|---|
| Fluid Index | ≥60 ohm/days |
| AT/AF Duration | ≥6 hours & not persistent AT/AF |
| V. rate during AT/AF | AT/AF ≥24 hrs & V. ≥ 90 bpm |
| Patient Activity | Avg. <1 hr over 1 week |
| Night Heart Rate | ≥85 bpm for 7 consecutive days |
| HRV | <60 ms for 7 consecutive days |
| CRT % Pacing | < 90% for 5 of 7 days |
| Shock(s) | 1 or more shocks |

Approccio multiparametrico.

L'algoritmo era considerato positivo quando almeno 2 dei criteri erano soddisfatti.

Ospedali Riuniti di Trieste

Whellan et al. JACC Vol. 55, No. 17, April 27, 2010:1803–10

JACC: HEART FAILURE
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# A Multisensor Algorithm Predicts Heart Failure Events in Patients With Implanted Devices

## Results From the MultiSENSE Study

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**ABSTRACT**

**OBJECTIVES** The aim of this study was to develop and validate a device-based diagnostic algorithm to predict heart failure (HF) events.

**BACKGROUND** HF involves costly hospitalizations with adverse impact on patient outcomes. The authors hypothesized that an algorithm combining a diverse set of implanted device-based sensors chosen to target HF pathophysiology could detect worsening HF.

**METHODS** The MultiSENSE (Multisensor Chronic Evaluation in Ambulatory Heart Failure Patients) study enrolled patients with investigational chronic ambulatory data collection via implanted cardiac resynchronization therapy defibrillators. HF events (HFEs), defined as HF admissions or unscheduled visits with intravenous treatment, were independently adjudicated. The development cohort of patients was used to construct a composite index and alert algorithm (HeartLogic) combining heart sounds, respiration, thoracic impedance, heart rate, and activity; the test cohort was sequestered for independent validation. The 2 coprimary endpoints were sensitivity to detect HFE >40% and unexplained alert rate <2 alerts per patient-year.

**RESULTS** Overall, 900 patients (development cohort, n = 500; test cohort, n = 400) were followed for up to 1 year. Coprimary endpoints were evaluated using 320 patient-years of follow-up data and 50 HFEs in the test cohort (72% men; mean age 66.8 ± 10.3 years; New York Heart Association functional class at enrollment: 69% in class II, 25% in class III; mean left ventricular ejection fraction 30.0 ± 11.4%). Both endpoints were significantly exceeded, with sensitivity of 70% (95% confidence interval [CI]: 55.4% to 82.1%) and an unexplained alert rate of 1.47 per patient-year (95% CI: 1.32 to 1.65). The median lead time before HFE was 34.0 days (interquartile range: 19.0 to 66.3 days).

**CONCLUSIONS** The HeartLogic multisensor index and alert algorithm provides a sensitive and timely predictor of impending HF decompensation. (Evaluation of Multisensor Data in Heart Failure Patients With Implanted Devices [MultiSENSE]; NCT01128166) (J Am Coll Cardiol HF 2017;5:216–25) © 2017 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

# Examples of longitudinal indices
## Known association with wHF

| | | |
|---|---|---|
| Mean Heart Rate | ⇨ | 1.8% increased risk of wHF per 1 bpm increase of mean heart rate[6] |
| Atrial Arrhythmias | ⇨ | Well assessed predictor of wHF [7] |
| PVC frequency | ⇨ | Associated with 5.5-fold increased risk of cardiovascular death [8] |
| Exercise and daily activity | ⇨ | Inability to maximal exercise for at least 4 minutes predicts death and wHF[9] |
| Heart Rate variability | ⇨ | HRV reduction is associated with wHF[10] |
| Thoracic Impedance | ⇨ | 40% sensitivity [11] |


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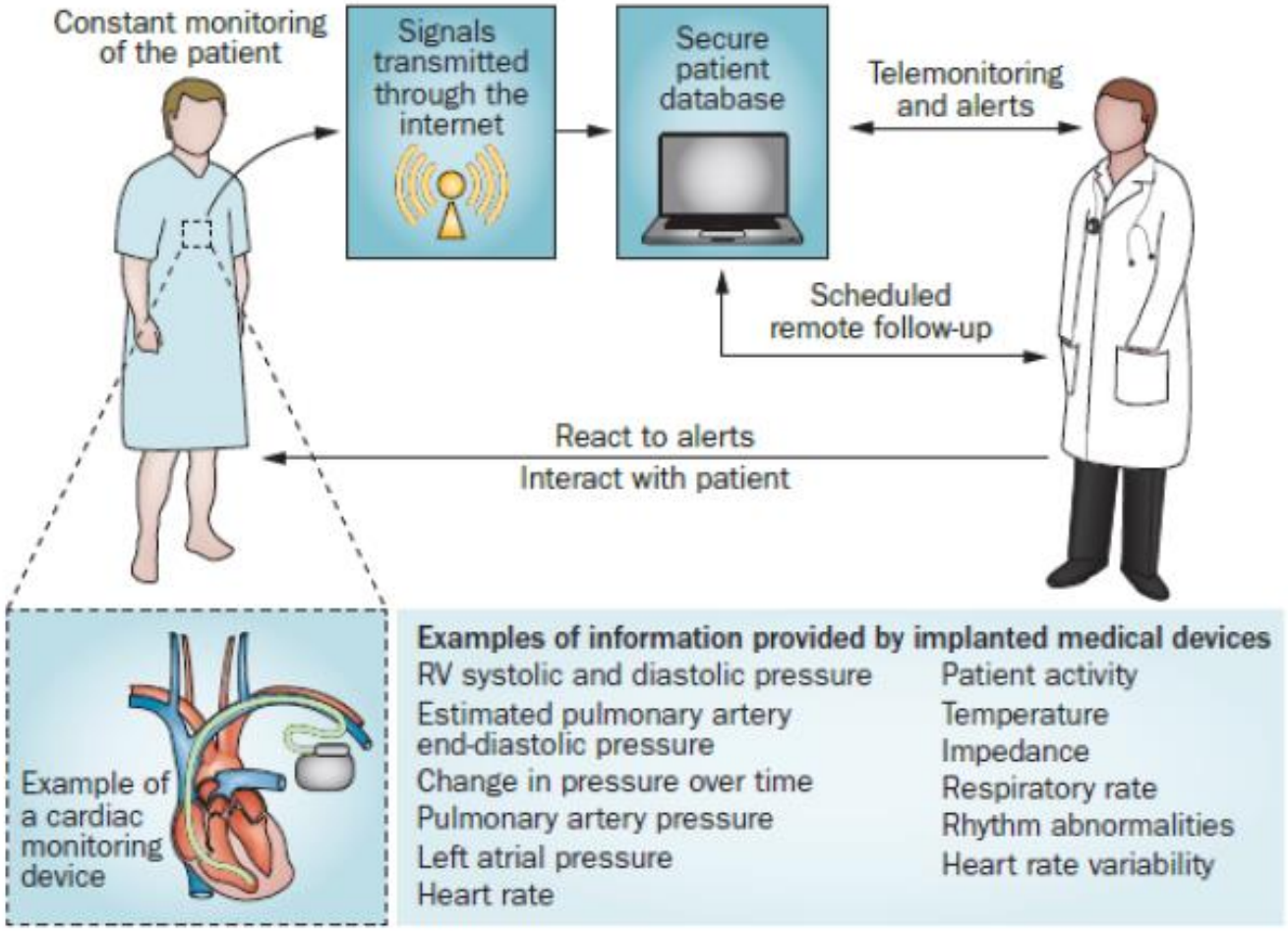
nature REVIEWS CARDIOLOGY

# Trials of implantable monitoring devices in heart failure: which design is optimal?

*William T. Abraham, Wendy G. Stough, Ileana L. Piña, Cecilia Linde, Jeffrey S. Borer, Gaetano M. De Ferrari, Roxana Mehran, Kenneth M. Stein, Alphons Vincent, Jay S. Yadav, Stefan D. Anker and Faiez Zannad*

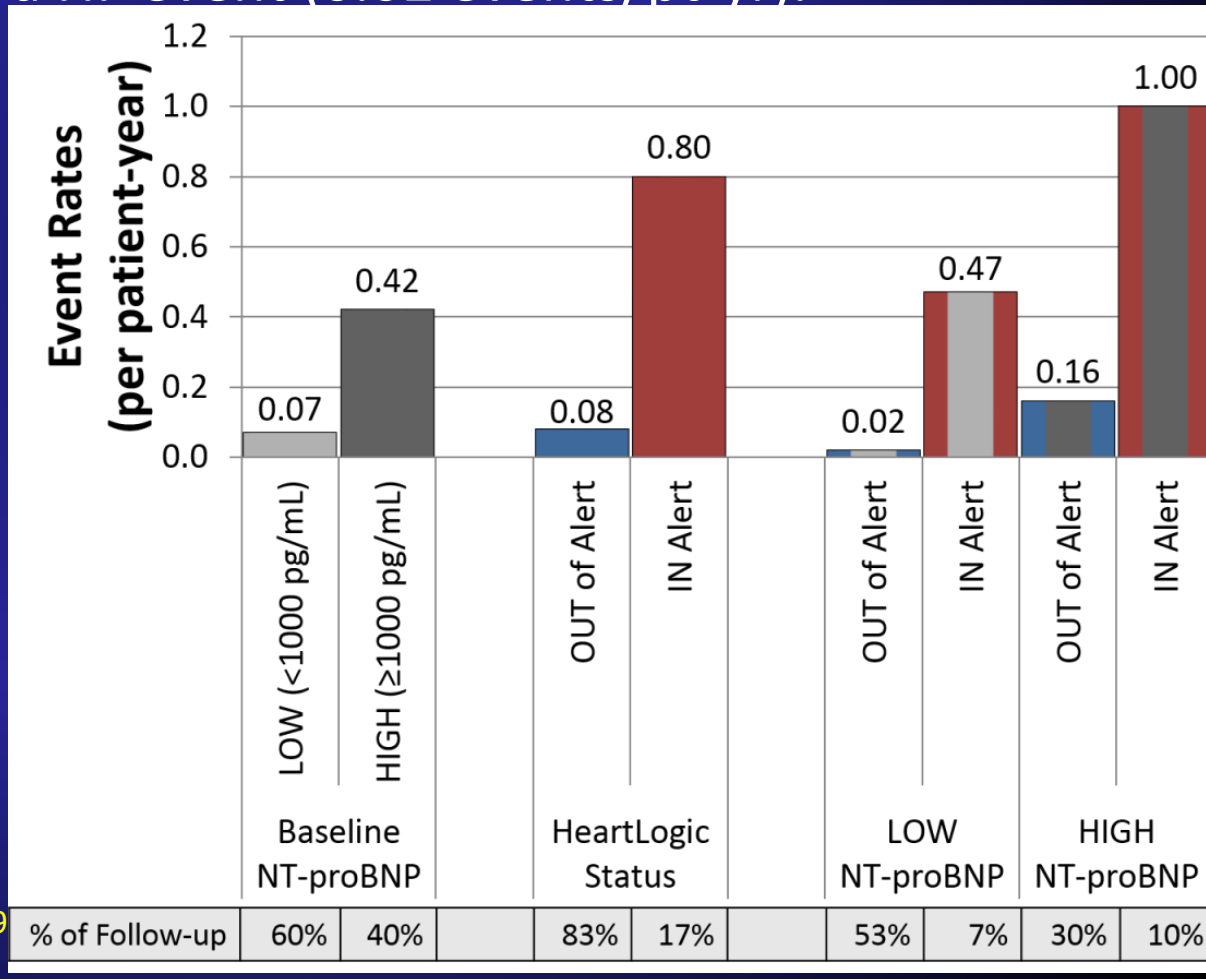



Abraham, W. T. et al. Nat. Rev. Cardiol. 11, 576–585 (2014)

# HeartLogic Event Rate Ratio

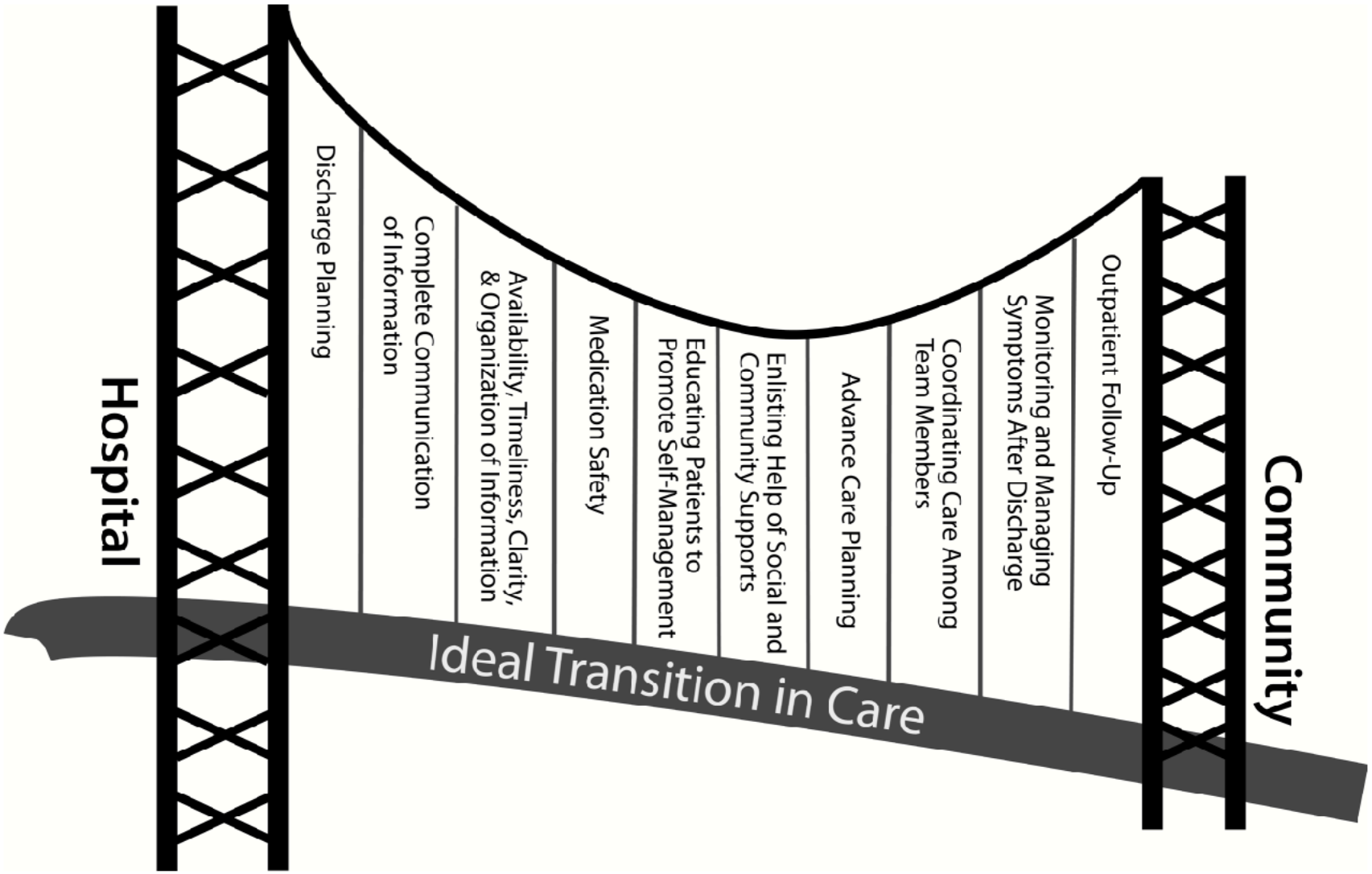
Combining the HeartLogic Index and a baseline NT-proBNP measurement sub-stratified a majority (53%) of patient follow-up into very low risk for a HF event (0.02 events/pt-yr).

- An active HeartLogic alert increased the patient event risk 23.5x in patients with NT-proBNP < 1000pg/mL
- Patients in a HeartLogic alert with high NT-proBNP (≥1000 pg/mL) had 50x increased risk of an event than the lowest risk patients.




Gardner RS et al. Circ Heart Fail. 2018;11:e004669

# What are the Ideal Components in the Transition in Care?




Burke RE, *et al. J Hosp Med* 2013;8:102-9.

JCM 200182

Editorial

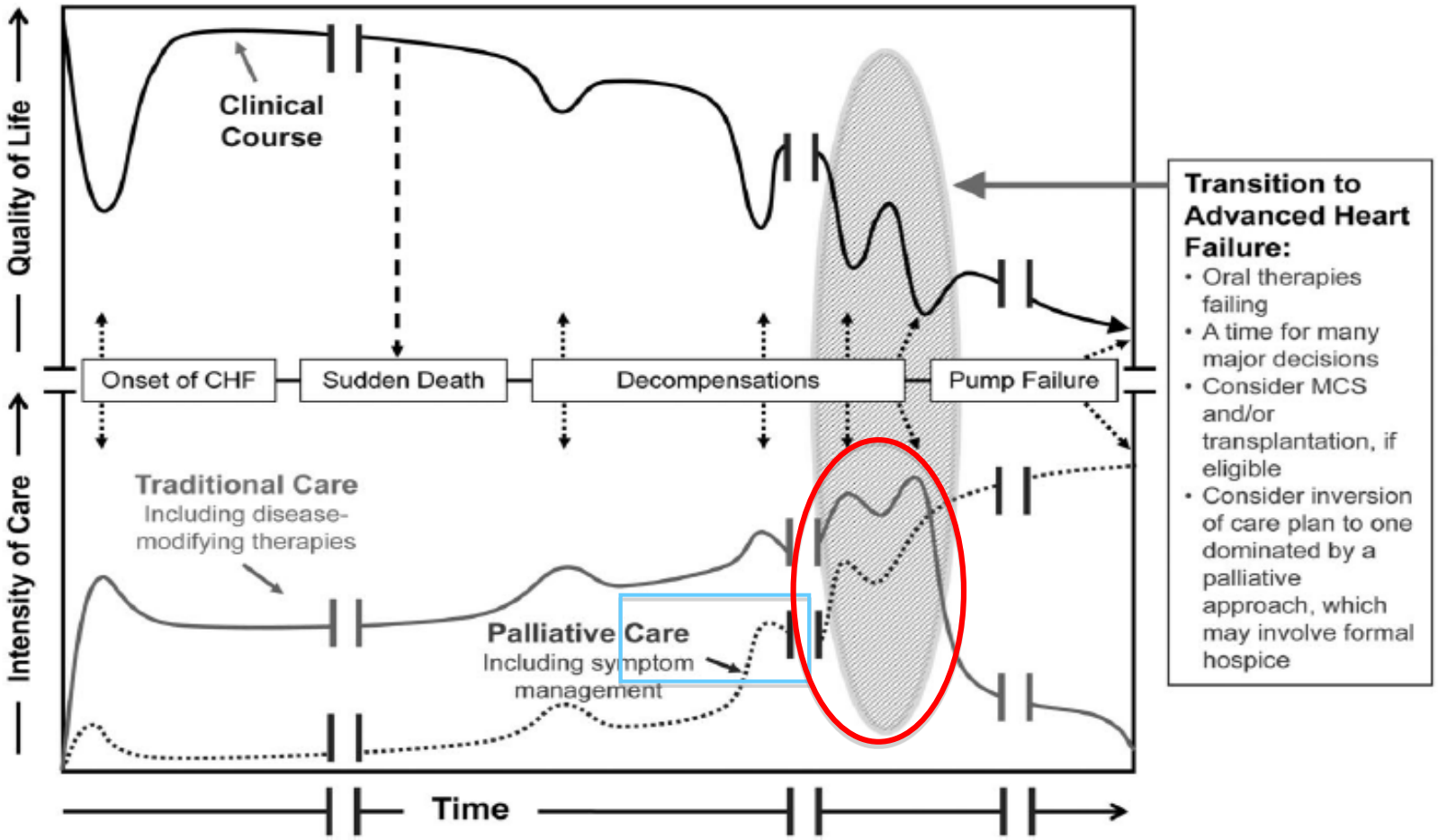
# The evolving care of the elderly with heart failure: from the "high-tech" to the "high-touch" approach

Giovanni Pulignano[a], Donatella Del Sindaco[b], Andrea Di Lenarda[c] and Gianfranco Sinagra[c]

Journal of Cardiovascular Medicine 2006, 7:

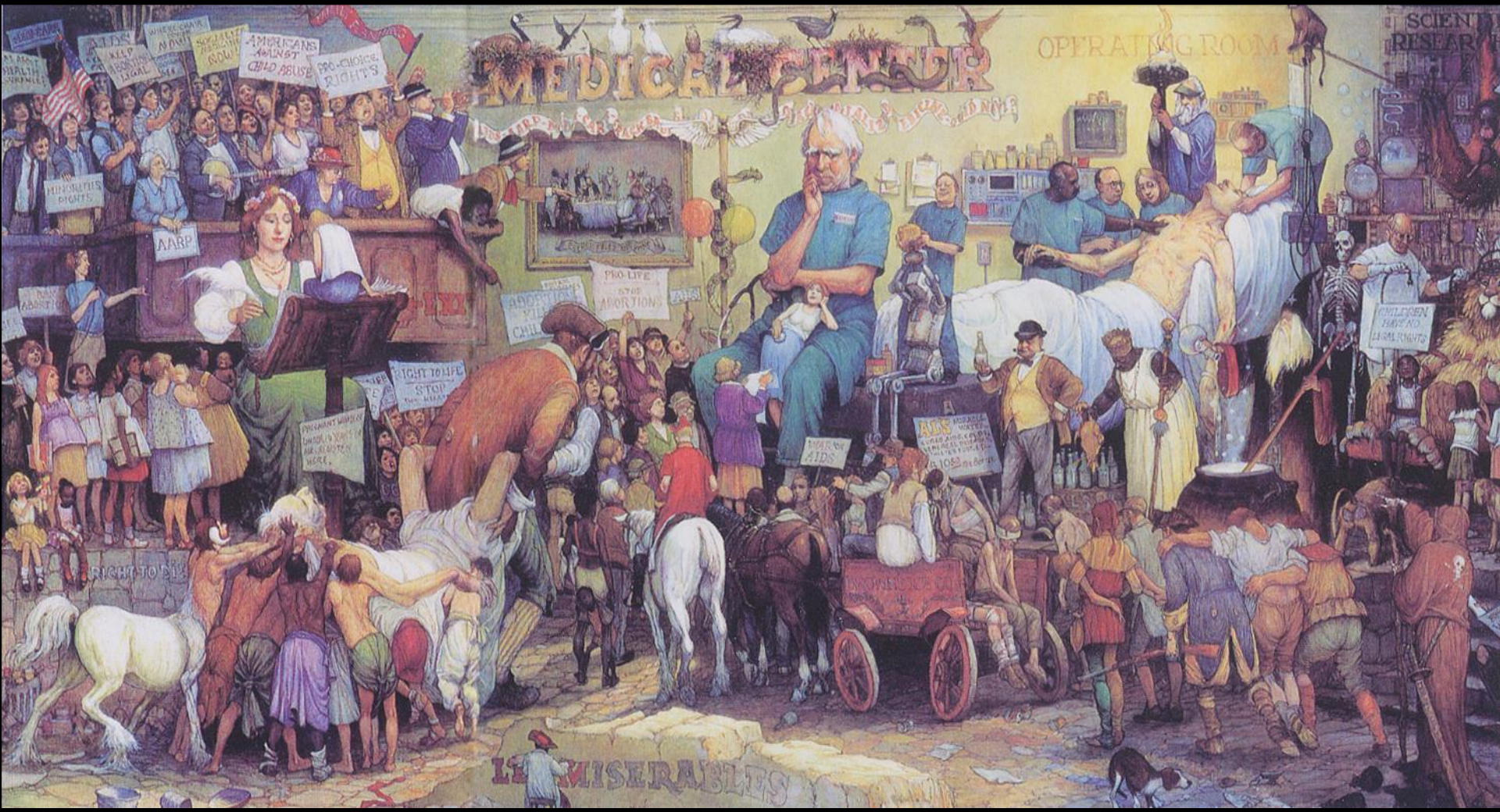
**Decision Making in Advanced Heart Failure : A Scientific Statement From the American Heart Association**

Larry A. Allen, Lynne W. Stevenson, Kathleen L. Grady, Nathan E. Goldstein, Daniel D. Matlock, Robert M. Arnold, Nancy R. Cook, G. Michael Felker, Gary S. Francis, Paul J. Hauptman, Edward P. Havranek, Harlan M. Krumholz, Donna Mancini, Barbara Riegel and John A. Spertus




(*Circulation*. 2012;125:1928-1952.)

***"…. specializzazione che spesso frammenta i contesti, la globalità, la complessità. …. La specializzazione "as-trae" ossia estrae un oggetto dal suo insieme, ne rifiuta i legami e le interconnesioni con l'ambiente, lo inserisce in un settore concettuale astratto che è quello della disciplina compartimentata, in cui le frontiere spezzano arbitrariamente la sistemicità e la multidimensionalità dei fenomeni…" (Edgar Morin 2003)***




**Josè Perez. Un giorno in ospedale, 1929**