



HAL
open science

MRAs in Elderly HF Patients: Individual Patient-Data Meta-Analysis of RALES, EMPHASIS-HF, and TOPCAT

Joao Pedro Ferreira, Xavier Rossello, Romain Eschalier, John J.V. McMurray, Stuart Pocock, Nicolas Girerd, Patrick Rossignol, Bertram Pitt, Faiez Zannad

► To cite this version:

Joao Pedro Ferreira, Xavier Rossello, Romain Eschalier, John J.V. McMurray, Stuart Pocock, et al.. MRAs in Elderly HF Patients: Individual Patient-Data Meta-Analysis of RALES, EMPHASIS-HF, and TOPCAT. *JACC: Heart Failure*, 2019, 7 (12), pp.1012-1021. 10.1016/j.jchf.2019.08.017. hal-02515938

HAL Id: hal-02515938

<https://hal.univ-lorraine.fr/hal-02515938>

Submitted on 21 Jul 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Mineralocorticoid Receptor Antagonists in Elderly HF patients: Individual Patient-Data Meta-Analysis of RALES, EMPHASIS-HF and TOPCAT

João Pedro Ferreira, MD, PhD¹; Xavier Rossello, MD, PhD^{2,3}; Romain Eschalier, MD, PhD⁴; John J.V. McMurray, MD⁵; Stuart Pocock, PhD⁶; Nicolas Girerd, MD, PhD¹; Patrick Rossignol, MD, PhD¹; Bertram Pitt, MD⁷; Faiez Zannad, MD, PhD¹

¹Université de Lorraine, Centre d'Investigation Clinique- Plurithématique Inserm CIC-P 1433, and Inserm U1116, CHRU Nancy Brabois, F-CRIN INI-CRCT (Cardiovascular and Renal Clinical Trialists), Nancy, France; ²Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC), Madrid, Spain; ³CIBER de enfermedades Cardiovasculares (CIBERCV), Madrid, Spain; ⁴Département de Cardiologie, Hôpital Gabriel Montpied, CHU de Clermont-Ferrand, Clermont-Ferrand, France; ⁵BHF Cardiovascular Research Centre, University of Glasgow, Glasgow, Scotland, UK; ⁶London School of Hygiene and Tropical Medicine, London, United Kingdom; ⁷Department of Medicine, University of Michigan School of Medicine, Ann Arbor, USA.

Address for correspondence:

Dr. João Pedro Ferreira
Centre d'Investigations Cliniques – INSERM CHRU de Nancy
Institut Lorrain du Coeur et des Vaisseaux Louis Mathieu
4 Rue du Morvan, Vandoeuvre lès Nancy 54500, France.
Tel: +33 383157322/20
Fax: +33 383157324
Email: j.ferreira@chu-nancy.fr

Acknowledgments

JPF, PR, FZ are supported by the French National Research Agency Fighting Heart Failure (ANR-15-RHU-0004), by the French PIA project “Lorraine Université d’Excellence” GEENAGE (ANR-15-IDEX-04-LUE) programmes, and the Contrat de Plan Etat Région Lorraine and FEDER IT2MP. X.R. has received support from the SEC-CNIC CARDIOJOVEN fellowship program.

Funding

None.

Disclosures

None.

Abstract

Background: Mineralocorticoid receptor antagonists (MRAs) have shown to reduce morbidity and mortality in HFrEF, and in a subset of patients with HFpEF. Notwithstanding, MRAs are underused, especially in the elderly. Pooling the individual patient-data (IPD) provides more statistical power to assess the efficacy and safety of MRA treatment in this subpopulation.

Aims: To assess the effect of MRA treatment (vs. placebo) in older (≥ 75 years) compared with younger (< 75 years) patients with HF.

Methods: We performed an IPD meta-analysis using Cox proportional hazards models stratified by trial. A total of 1756 patients (853 randomized to placebo and 903 to MRA) aged ≥ 75 , along with 4411 patients (2242 randomized to placebo and 2169 to MRA) aged < 75 years were included. The primary outcome was a composite of death from cardiovascular causes or hospitalization for HF.

Results: The treatment groups were well balanced. The mean age of the patients aged ≥ 75 was 80 years, 61% were male, 30% had diabetes, and the mean eGFR was 59 ml/min. The primary outcome occurred in 331 (38.8%) patients in the placebo group vs. 281 (31.1%) in the MRA group; HR (95%CI)=0.74 (0.63-0.86), $p < 0.001$ (heterogeneity_p=0.52).

Cardiovascular death and all-cause death were also reduced by MRAs without significant between-trial or age (younger vs. older) heterogeneity. Worsening renal function (WRF) and hyperkalemia occurred more frequently in patients taking MRAs (vs. placebo). Compared to younger patients, WRF (but not hyperkalemia) was more frequent in the elderly.

Conclusion: MRAs reduce morbidity and mortality in elderly patients with HF, a beneficial effect that is more marked in HFrEF but homogenous across HFrEF and HFpEF.

Implementation of measures that increase MRA treatment in this population are warranted.

Key-words: mineralocorticoid receptor antagonists; elderly; treatment effects.

Abbreviations list:

MRA, mineralocorticoid receptor antagonist

HFrEF, heart failure with reduced ejection fraction

HFpEF, heart failure with preserved ejection fraction

IPD, individual patient data

eGFR, estimated glomerular filtration rate

WRF, worsening renal function

Introduction

Heart failure (HF) is a common disease in older people with a population prevalence of 10-20% in individuals aged above 75 years¹; and with incidence increasing among the very old².³ In many developed countries the age of patients hospitalised for HF is above 75 years⁴. These older patients are underrepresented in randomized clinical trials and the balance of benefits and risks for standard therapies could differ substantially from the young⁵. Age-related physiological changes, multi-comorbidity, frailty, and polypharmacy, all can alter drug pharmacokinetics and change the effect of treatments in elderly HF patients⁶. Moreover, the prevalence of HF with preserved ejection fraction (HFpEF), is proportionately far greater in the elderly, compared to HF with reduced ejection fraction (HFrEF)⁷.

In patients with HFrEF and severe symptoms enrolled in RALES (The Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure), treatment with spironolactone (vs. placebo) reduced the relative rate of all-cause death by 30%, without evidence of a treatment by age subgroup (median age: <67 vs. ≥67yr) interaction⁸. In patients with HFrEF and mild symptoms enrolled in EMPHASIS-HF (Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms), treatment with eplerenone (vs. placebo) reduced the relative rate of the time-to-first composite of cardiovascular death or HF hospitalization by 37% and all-cause death by 24%, without evidence of a treatment by age subgroup (<65 vs. ≥65yr and <75 vs. ≥75yr) interaction⁹. In TOPCAT (Spironolactone for Heart Failure with Preserved Ejection Fraction) trial, treatment with spironolactone did not reduce the incidence of death due to cardiovascular causes or HF hospitalizations in the overall trial, but the rate of HF hospitalizations was reduced. Due to important heterogeneity in event-rates and treatment effect by geographical region (that have been described in detail¹⁰⁻¹²), subsequent analyses of the TOPCAT trial have been limited to patients from “the Americas”. The 2017 update of the ACC/AHA/HFSA guidelines gave a class IIb indication to spironolactone for treating

HFpEF¹³. In TOPCAT, no treatment by age subgroup (<65 vs. 65-74 vs. ≥75yr) was found¹⁴. Despite the randomized evidence, MRAs continue largely underused, especially in elderly patients¹⁵.

The individual trials were underpowered to assess the treatment effect in the elderly, hence pooling the individual patient data (IPD) provides more statistical power to assess the efficacy and safety of MRA treatment in this subpopulation. We examined the effects of MRA therapy in older (≥75 years), compared with younger (<75 years), participants using IPD from the major randomized trials with morbidity-mortality outcomes: RALES, EMPHASIS-HF, and TOPCAT-Americas.

Methods

Study design, setting, and participants

In RALES, 1663 patients who had HF with severe symptoms and a left ventricular ejection fraction (LVEF) ≤35%, were randomly assigned to spironolactone (up to 50 mg/day) or matching placebo. The primary outcome was all-cause death. In EMPHASIS-HF, 2737 patients who had HF and mild symptoms and a LVEF ≤35% were randomly assigned to eplerenone (up to 50 mg/day) or matching placebo. The primary outcome was a composite of cardiovascular death or HF hospitalization. In TOPCAT, 3445 patients with symptomatic HF and a LVEF ≥45% were randomly assigned to spironolactone (15 to 45 mg daily) or matching placebo. The primary outcome was a composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure¹⁴. As stated in the introduction, due to the major regional variations found in the TOPCAT trial, we report only data regarding patients enrolled in “the Americas” (n =1767)¹⁰.

Each individual randomized controlled trial was conducted in accordance with the Declaration of Helsinki and approved by the site ethics committees. All participants gave written informed consent to participate in the respective studies.

Study outcomes

For consistency across trials the primary outcome was a composite of cardiovascular death or HF hospitalization in the present analysis. Cardiovascular death alone and all-cause death were also assessed.

The major clinical outcomes were centrally adjudicated by endpoint committees and defined by the conventional criteria (definitions have been published in the respective studies).

Statistical analysis

A fixed-effect model for a one-stage IPD meta-analysis was conducted¹⁶. Baseline clinical characteristics of patients were summarised by treatment group with means and standard deviation for continuous variables, with frequencies and percentages for categorical variables, hazard ratios (HRs) with their respective 95% confidence interval (95% CI) for treatment effect estimates. Time-to-first-event curves were obtained using the Kaplan–Meier method and compared using the log-rank test. Univariate Cox proportional hazards' modelling was used to explore the association of the intervention and the outcomes. A Cox model stratified by study was used to obtain the overall HR for this individual patient meta-analysis (assuming equal effects across strata but with a baseline hazard unique to each study)¹⁷. Event-rates, absolute treatment effects and number needed-to-treat to benefit were also computed. Beyond the group of patients aged 75 or more, we also studied patients aged 80 or more as exploratory analysis.

Statistical analyses were performed using the STATA/SE software, version 15.1 (Stata Corp, College Station, TX, USA).

Statistical heterogeneity

The individual effect size for each trial and overall effect size estimations and their 95% CIs are depicted in the **Central Illustration**, and suggest the lack of substantial statistical heterogeneity. To further investigate the variation of primary outcome treatment effect estimates between trials, the Cochran's Q test and the Wald test of the overall interaction were computed.

Results

Patient characteristics

In the present analysis, 1756 patients were aged ≥ 75 years (853 allocated to placebo and 903 to MRA) and 4411 were aged < 75 years (2242 randomized to placebo and 2169 to MRA).

The number (proportion) of patients aged ≥ 75 years in RALES was 352 (21%), in EMPHASIS-HF was 657 (24%), and in TOPCAT-Americas was 747 (42%) (**Supplemental Table 1 & Supplemental Table 2**). The mean age in the older age group was 80 ± 4 years and the mean age in the younger age group was 64 ± 7 years.

The baseline characteristics were well balanced between treatment arms. Patients with HF_rEF (i.e. RALES plus EMPHASIS-HF trials) had some characteristics (beyond ejection fraction) quite different from those with HF_pEF (i.e. TOPCAT-Americas). Patients with HF_pEF were older, more often female, hypertensive, with diabetes, and with peripheral vascular disease; and had less often a previous MI, had lower hemoglobin, and were less often treated with ACEi/ARBs (**Table 1**).

The median (percentile₂₅₋₇₅) follow-up time was 1.8 (0.8-2.6) years in the HF_rEF population, 2.9 (1.9-4.4) years in the HF_pEF population, which gave a median follow-up of 2.2 (1.2-3.1) years in the overall population.

Events and treatment effects

In patients aged ≥ 75 years that participated the HFrEF trials (RALES plus EMPHASIS-HF), the primary outcome of cardiovascular death or HF hospitalization occurred in 215 (43.2%) patients taking placebo and 170 (33.3%) taking a MRA, with a corresponding HR (95%CI) of 0.69 (0.56-0.84), heterogeneity_p between trials =0.70. A similar beneficial MRA effect was observed for the outcomes of cardiovascular and all-cause death. In patients with ≥ 75 years and HFpEF from the TOPCAT-Americas trial, the primary outcome of cardiovascular death or HF hospitalization occurred in 116 (32.7%) patients taking placebo and 111 (28.1%) taking a MRA, with a corresponding HR (95%CI) of 0.83 (0.63-1.08). Cardiovascular and all-cause death were also numerically lower in MRA-treated patients, but also did not reach statistical significance (p-value ≥ 0.1 for all outcomes). In the combined (HFrEF plus HFpEF) population aged ≥ 75 years, the primary outcome of cardiovascular death or HF hospitalization occurred in 331 (38.8%) patients taking placebo and 281 (31.1%) taking a MRA, with a corresponding HR (95%CI) of 0.74 (0.63-0.83), heterogeneity_p between trials =0.52. A similar and homogenous treatment effect was also observed for the outcomes of cardiovascular and all-cause death (**Table 2 & Central Illustration**).

The treatment effect was similar in patients aged < 75 years (compared with those aged ≥ 75 years) without significant statistical interactions by age subgroups (interaction_p > 0.1 for all outcomes). The cumulative hazard curves (MRA vs. placebo) are presented in the **Figure 1**. The adjusted predictions of the treatment effect across the continuum of age is represented in the **Figure 2**. For any given age, treatment with MRA reduces the risk of events associated with ageing. The adjusted predictions of the treatment effect across continuum of age and renal function is represented in the **Figure 3**. For any given age and eGFR, MRAs reduce the event rate.

The absolute event reduction and number needed to treat to benefit was also similar between younger and older patients, and ranged from 8 to 31 patients for the primary composite outcome of cardiovascular or HF hospitalization (**Supplemental Table 3**).

Patients with ≥ 80 years, represented less than 10% of the RALES and EMPHASIS populations, and 24% of the TOPCAT-Americas (**Supplemental Table 2**). The primary outcome HR (95%CI) of the treatment in patients aged 80 or more was 0.86 (0.68-1.08), translating the reduced power to assess the efficacy in this population (**Supplemental Figure 1**).

Event rates

The event rates (per 100 person-years) of the composite of cardiovascular or HF hospitalization and cardiovascular death were nearly 3-fold higher for placebo-treated patients with HFrEF compared to HFpEF: 30.7 (26.8-35.1) vs. 12.5 (10.4-15.0); and 2-fold higher for MRA treated patients with HFrEF compared to HFpEF: 21.1 (18.2-24.6) vs. 10.5 (8.7-12.6). In consequence, the absolute incidence rate difference was higher in HFrEF than in HFpEF: -9.6 (-14.7 to -4.3) vs. -2.0 (-5.0 to 1.0). The rate of CV death was 3-fold higher and all-cause death 2-fold higher in HFrEF compared with HFpEF (**Supplemental Table 4**).

The events rates (per 100 person-years) of the composite of cardiovascular or HF hospitalization and cardiovascular death were similar between patients ≥ 75 vs. < 75 years (primary composite outcome =17.2 [16.3-18.1] in < 75 yr vs. 17.9 [16.5-19.4] in ≥ 75 yr; $p = 0.41$). The rate of all-cause death was higher in elderly patients derived by an increase rate of death from non-cardiovascular causes: 1.7 (1.5-2.0) in < 75 yr vs. 3.4 (2.9-4.1) in ≥ 75 yr; $p < 0.001$ (**Supplemental Table 5**).

Adverse events

Older and younger patients in the placebo group, experienced similar frequency of adverse events (6% for hyperkalemia and 24% for worsening renal function. Older patients (≥ 75

years) taking a MRA experienced more frequently worsening renal function (eGFR drop >30%) during the follow-up compared to those <75 years (39% vs. 31%; interaction_p =0.017), but not hyperkalemia (16% vs. 14%; interaction_p =0.30) (**Table 3**).

Discussion

Our IPD meta-analysis suggests that MRAs are equally beneficial in younger and older HF patients, a beneficial effect that is more marked in HFrEF but homogenous across HFrEF and HFpEF. Compared to the younger, older patients may experience more worsening renal function episodes (but not hyperkalemia ones), in consequence a closer treatment monitoring may be required in this subpopulation.

The great majority of patients with HF are aged above 65 years, and in many contemporary studies a significant proportion of patients are 75 or more. These older patients are often female and have multiple comorbidities^{3, 18}. In contrast, the mean age of the patients participating in each of RALES, EMPHASIS-HF and TOPCAT-Americas was 65, 69 and 72 years and the majority were male, in keeping with most other trials. However, by pooling the three trials we had a sufficient number of patients and events to assess the efficacy and safety of MRAs in truly elderly individuals with HF.

In the elderly (≥ 75 years) HF patients the rate of death from non-cardiovascular causes was overall low (3.4 events per 100 person-years), but higher than in younger patients (1.7 events per 100 person-years), supporting the notion that elderly HF patients are more prone to non-cardiovascular competing-events, on which cardiovascular drugs may fail to act¹⁹; it should be however noted that the relative and absolute reduction in all-cause death with MRAs was marked and similar to that observed in younger patients. Given that MRAs are inexpensive, widely available and overall well-tolerated, they should be given more priority for treating HF patients around the world²⁰. Notwithstanding, a close monitoring and

assessment of serum potassium and renal function are warranted in patients taking MRAs, particularly in the elderly and those with renal impairment²¹; however, it should be stressed out that the beneficial effect of MRAs in reduced major cardiovascular events is preserved across the continuum of age and renal function. Careful dose adjustment may also be required²². For example, in EMPHASIS-HF eplerenone dose was stratified by renal function, whereby patients with an eGFR of 50 ml/min or above received 50 mg/day of eplerenone and those with eGFR below 50 ml/min received 25 mg/day. The effect of eplerenone was similar between the renal function/dose strata²³. In view of this, eplerenone should not be given at a dose above 25 mg/day in patients with renal impairment. Whether elderly patients also require lower MRA dose requires further study, but this possibility underlay the design of TOPCAT, where spironolactone was initiated at a dose of 15 mg/day, which could be increased to 45 mg/day over a period of 4 months.

The anti-fibrotic properties of MRAs may also be of interest in elderly populations, where organ fibrosis (e.g. myocardium, kidney, joints) contribute to the impairment of life-quality, progression of HF, arrhythmias and ultimately death^{24, 25}.

Another note to highlight that the cardiovascular event rates were lower (about 3-fold) in HFpEF patients (i.e. TOPCAT-Americas) compared with HFrEF (RALES plus EMPHASIS-HF), which consistently provided an absolute treatment benefit of higher magnitude in HFrEF; without evidence of relative treatment effect differences. The differences in all-cause death were less marked, suggesting that patients with HFpEF may be at higher risk to die from non-cardiovascular causes. These findings are relevant for the design of future trials, where the cardiovascular and competing non-cardiovascular event-rates should be taken in account.

Overall, our findings strongly support the use of MRAs in elderly HF patients. We hope that this information may serve a “nudge” for a better prescription.

Limitations

The present study has limitations. Our results cannot be extrapolated to patients that were excluded from the RALES, EMPHASIS-HF and TOPCAT trials, particularly patients with “severe” renal impairment (i.e. eGFR <30 ml/min) and hyperkalemia ($K^+ >5.5$ mmol/L). Our results are based on the assumption that both spironolactone and eplerenone provide similar treatment effect; although spironolactone and eplerenone differ in their molecular structure, pharmacokinetics, and pharmacodynamics, it is generally accepted that the benefits of different MRAs represent a “class effect”²⁶. As these are selected trial populations, the rate of safety events may be under-represented when compared to “real world” patients. These are three distinct patient-populations, especially patients with HFpEF, that have more co-morbid conditions and lower cardiovascular event rates. Nonetheless, the treatment effect in the elderly populations from these trials was homogeneous and strongly suggests a beneficial MRA effect. The present study was underpowered to assess the effect of the treatment in patients aged above 80 years, however no signal of harm was observed in this “very elderly” population. The doses and the treatments (spironolactone or eplerenone) could vary between trials and according to the respective dose-adjustment algorithms, but for the purpose of this analysis we assume that MRAs have a “class effect”.

Conclusion

MRAs reduce morbidity and mortality in elderly patients (aged 75 or more) with HF, with a homogenous treatment effect between HFrEF and HFpEF (and between younger and older patients). Compared to the younger patients, the older ones may experience more frequent episodes of worsening renal function when treated with a MRA, warranting close surveillance and dose adaptations in this population.

Clinical Perspectives

The findings presented herein, strongly support the use of MRAs in older HF patients, as they benefit similarly to younger patients without excessive hyperkalemia.

Translational Outlook

Future trials with MRAs could focus on elderly populations, assessing the trade-off between the benefits and risks incorporating quality of life measures.

References

1. Bleumink GS, Knetsch AM, Sturkenboom MC, Straus SM, Hofman A, Deckers JW, Witteman JC and Stricker BH. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure The Rotterdam Study. *Eur Heart J*. 2004;25:1614-9.
2. Zannad F. Rising incidence of heart failure demands action. *Lancet*. 2017.
3. Conrad N, Judge A, Tran J, Mohseni H, Hedgecott D, Crespillo AP, Allison M, Hemingway H, Cleland JG, McMurray JJV and Rahimi K. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. *Lancet*. 2017.
4. Dharmarajan K and Rich MW. Epidemiology, Pathophysiology, and Prognosis of Heart Failure in Older Adults. *Heart Fail Clin*. 2017;13:417-426.
5. Mogensen UM, Ersboll M, Andersen M, Andersson C, Hassager C, Torp-Pedersen C, Gustafsson F and Kober L. Clinical characteristics and major comorbidities in heart failure patients more than 85 years of age compared with younger age groups. *Eur J Heart Fail*. 2011;13:1216-23.
6. Lazzarini V, Mentz RJ, Fiuzat M, Metra M and O'Connor CM. Heart failure in elderly patients: distinctive features and unresolved issues. *Eur J Heart Fail*. 2013;15:717-23.
7. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL and Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med*. 2006;355:251-9.
8. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J and Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med*. 1999;341:709-17.

9. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ and Pitt B. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med.* 2011;364:11-21.
10. Pfeffer MA, Claggett B, Assmann SF, Boineau R, Anand IS, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Heitner JF, Lewis EF, O'Meara E, Rouleau JL, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, McKinlay SM and Pitt B. Regional Variation in Patients and Outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) Trial. *Circulation.* 2015;131:34-42.
11. Ferreira JP, Girerd N, Rossignol P and Zannad F. Geographic differences in heart failure trials. *Eur J Heart Fail.* 2015.
12. de Denus S, O'Meara E, Desai AS, Claggett B, Lewis EF, Leclair G, Jutras M, Lavoie J, Solomon SD, Pitt B, Pfeffer MA and Rouleau JL. Spironolactone Metabolites in TOPCAT - New Insights into Regional Variation. *N Engl J Med.* 2017;376:1690-1692.
13. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Colvin MM, Drazner MH, Filippatos G, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW and Westlake C. 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Am Coll Cardiol.* 2016.
14. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Harty B, Heitner JF, Kenwood CT, Lewis EF, O'Meara E, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, Yang S and McKinlay SM. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med.* 2014;370:1383-92.

15. Pitt B, Pedro Ferreira J and Zannad F. Mineralocorticoid receptor antagonists in patients with heart failure: current experience and future perspectives. *Eur Heart J Cardiovasc Pharmacother.* 2017;3:48-57.
16. da Costa BR and Juni P. Systematic reviews and meta-analyses of randomized trials: principles and pitfalls. *Eur Heart J.* 2014;35:3336-45.
17. Riley RD, Lambert PC and Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. *Bmj.* 2010;340:c221.
18. Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KK, Murabito JM and Vasan RS. Long-term trends in the incidence of and survival with heart failure. *N Engl J Med.* 2002;347:1397-402.
19. Vaduganathan M, Patel RB, Michel A, Shah SJ, Senni M, Gheorghiade M and Butler J. Mode of Death in Heart Failure With Preserved Ejection Fraction. *J Am Coll Cardiol.* 2017;69:556-569.
20. Ferreira JP, Mentz RJ, Pizard A, Pitt B and Zannad F. Tailoring mineralocorticoid receptor antagonist therapy in heart failure patients: are we moving towards a personalized approach? *Eur J Heart Fail.* 2017.
21. Eschalier R, McMurray JJ, Swedberg K, van Veldhuisen DJ, Krum H, Pocock SJ, Shi H, Vincent J, Rossignol P, Zannad F and Pitt B. Safety and efficacy of eplerenone in patients at high risk for hyperkalemia and/or worsening renal function: analyses of the EMPHASIS-HF study subgroups (Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure). *J Am Coll Cardiol.* 2013;62:1585-93.
22. Rossignol P and Ferreira JP. Balancing Benefits and Risks of Spironolactone in HFpEF and Chronic Kidney Disease Patients: Mind the Gap of Biological Monitoring! *JACC Heart Fail.* 2019;7:33-35.

23. Ferreira JP, Abreu P, McMurray JJV, van Veldhuisen DJ, Swedberg K, Pocock SJ, Vincent J, Lins K, Rossignol P, Pitt B and Zannad F. Renal function stratified dose comparisons of eplerenone versus placebo in the EMPHASIS-HF trial. *Eur J Heart Fail.* 2019;21:345-351.
24. Ferreira JP, Barros A, Pitt B, Montalescot G, de Sa EL, Hamm CW, Flather M, Verheugt F, Shi H, Leite-Moreira A, Vincent J, Rossignol P and Zannad F. Collagen biomarker bioprofiles predicting the antifibrotic response to eplerenone in myocardial infarction: findings from the REMINDER trial *Clin Res Cardiol Germany*; 2018(107): 1192-1195.
25. Ferreira JP, Rossignol P, Pizard A, Machu JL, Collier T, Girerd N, Huby AC, Gonzalez A, Diez J, Lopez B, Sattar N, Cleland JG, Sever PS and Zannad F. Potential spironolactone effects on collagen metabolism biomarkers in patients with uncontrolled blood pressure. *Heart.* 2018.
26. Iqbal J, Parviz Y, Pitt B, Newell-Price J, Al-Mohammad A and Zannad F. Selection of a mineralocorticoid receptor antagonist for patients with hypertension or heart failure. *Eur J Heart Fail.* 2014;16:143-50.

Figure 1. Survival curves of the MRA treatment effect (primary outcome of CV death or HF hospitalization)

- (a) Age ≥ 75 years
- (b) Age < 75 years

Log-rank test p-value < 0.001 for both age subgroups; p for interaction with age = 0.39.

Legend: MRA, mineralocorticoid receptor antagonist; CV, cardiovascular; HF, heart failure.

Figure 2. Adjusted predictions of the MRA treatment effect (for the primary outcome of cardiovascular death or heart failure hospitalization) across the continuum of age

Legend: MRA, mineralocorticoid receptor antagonist.

For any given age, MRA treatment reduces the risk of events associated with ageing.

Figure 3. Adjusted predictions of the MRA treatment effect (for the primary outcome of cardiovascular death or heart failure hospitalization) across the continuum of age and renal function

Legend: MRA, mineralocorticoid receptor antagonist; eGFR, estimated glomerular filtration rate.

For any given age and eGFR, MRA treatment reduces the risk of major cardiovascular events

Central Figure. MRA treatment effect on the overall HF population aged ≥ 75 years (primary outcome of CV death or HF hospitalization)

P-value for heterogeneity = 0.52.

Legend: MRA, mineralocorticoid receptor antagonist; CV, cardiovascular; HF, heart failure.

Table 1. Baseline characteristics of the study population.

Patient characteristics	Age \geq 75 years				Age <75 years			
	HF _r EF		HF _p EF		HF _r EF		HF _p EF	
	Placebo	MRA	Placebo	MRA	Placebo	MRA	Placebo	MRA
N. (Total =1756)	498	511	355	392	1716	1675	526	494
Age (years)	79.1 \pm 3.5	79.1 \pm 3.7	80.7 \pm 4.0	80.9 \pm 4.0	63.9 \pm 7.9	63.8 \pm 7.9	64.8 \pm 6.5	64.6 \pm 6.2
Male sex	357 (71.7%)	364 (71.2%)	171 (48.2%)	178 (45.4%)	1329 (77.4%)	1294 (77.3%)	270 (51.3%)	266 (53.8%)
White race	461 (92.6%)	468 (91.6%)	316 (89.0%)	324 (82.7%)	1407 (82.0%)	1371 (81.9%)	379 (72.1%)	365 (73.9%)
Body mass index (kg/m ²)	26.3 \pm 4.0	26.6 \pm 4.3	30.5 \pm 6.2	30.8 \pm 6.7	27.9 \pm 5.0	27.8 \pm 5.1	35.9 \pm 8.6	36.4 \pm 8.3
NYHA class								
II	327 (65.7%)	328 (64.2%)	221 (62.4%)	241 (61.5%)	1047 (61.0%)	1033 (61.8%)	352 (67.3%)	328 (66.5%)
III	122 (24.5%)	138 (27.0%)	133 (37.6%)	151 (38.5%)	460 (26.8%)	456 (27.3%)	171 (32.7%)	165 (33.5%)
IV	48 (9.6%)	45 (8.8%)	0	0	209 (12.2%)	181 (10.8%)	0	0
Systolic blood pressure (mmHg)	124.0 \pm 17.9	126.8 \pm 18.9	126.5 \pm 15.2	128.2 \pm 15.8	122.8 \pm 17.8	122.8 \pm 18.4	128.5 \pm 16.8	126.7 \pm 15.3
Diastolic blood pressure (mmHg)	72.3 \pm 10.0	73.5 \pm 10.8	68.6 \pm 11.4	70.2 \pm 10.8	75.3 \pm 10.7	75.0 \pm 10.9	72.9 \pm 11.5	72.6 \pm 11.6
Heart rate (bpm)	73.4 \pm 13.4	73.4 \pm 12.7	68.4 \pm 10.3	67.8 \pm 11.4	76.0 \pm 14.4	75.9 \pm 14.0	69.8 \pm 11.4	69.4 \pm 12.6
Ejection fraction (%)	26.4 \pm 5.2	26.2 \pm 5.3	58.6 \pm 8.0	58.8 \pm 7.3	25.5 \pm 5.7	25.9 \pm 5.6	57.7 \pm 7.7	57.9 \pm 7.9
Hypertension	290 (58.2%)	303 (59.3%)	315 (88.7%)	350 (89.3%)	818 (47.7%)	801 (47.8%)	473 (90.3%)	450 (91.1%)
Diabetes	133 (26.7%)	141 (27.6%)	122 (34.4%)	123 (31.4%)	461 (26.9%)	492 (29.4%)	275 (52.5%)	268 (54.3%)
Atrial Fibrillation / Flutter	154 (30.9%)	162 (31.7%)	116 (33.1%)	121 (31.3%)	385 (22.4%)	357 (21.3%)	116 (22.4%)	93 (19.1%)
Previous MI	247 (49.6%)	250 (48.9%)	129 (36.3%)	116 (29.6%)	691 (40.3%)	668 (39.9%)	161 (30.7%)	161 (32.6%)

Previous stroke	50 (10.0%)	49 (9.6%)	29 (8.2%)	32 (8.2%)	124 (7.2%)	122 (7.3%)	49 (9.3%)	40 (8.1%)
Peripheral vascular disease	3 (1.8%)	11 (6.1%)	41 (11.5%)	49 (12.5%)	27 (4.0%)	26 (4.1%)	51 (9.7%)	66 (13.4%)
Previous HF hospitalisation	174 (53.2%)	169 (51.2%)	179 (50.4%)	193 (49.2%)	551 (52.7%)	545 (52.8%)	328 (62.6%)	340 (68.8%)
COPD	77 (15.5%)	81 (15.9%)	50 (14.1%)	60 (15.3%)	223 (13.0%)	237 (14.2%)	84 (16.0%)	97 (19.6%)
eGFR (ml/min/1.73m ²)	57.7 ± 17.8	59.2 ± 18.4	59.4 ± 18.7	59.3 ± 17.3	69.9 ± 25.3	70.4 ± 21.7	67.2 ± 22.6	69.3 ± 23.5
Hemoglobin (g/dL)	13.4 ± 1.5	13.4 ± 1.4	12.5 ± 2.4	12.5 ± 2.3	13.9 ± 1.6	13.9 ± 1.5	12.7 ± 2.7	12.7 ± 2.8
Potassium (mmol/L)	4.3 ± 0.4	4.3 ± 0.5	4.2 ± 0.5	4.2 ± 0.4	4.3 ± 0.4	4.3 ± 0.4	4.2 ± 0.4	4.2 ± 0.4
Sodium (mmol/L)	139.7 ± 3.7	139.9 ± 3.7	139.3 ± 8.2	139.9 ± 3.2	139.5 ± 4.0	139.5 ± 4.1	139.7 ± 3.0	139.5 ± 3.2
ACEi/ARBs	453 (91.0%)	473 (92.6%)	255 (71.8%)	293 (74.7%)	1611 (93.9%)	1574 (94.0%)	440 (83.8%)	397 (80.4%)
Beta blockers	292 (58.6%)	301 (58.9%)	273 (76.9%)	289 (73.7%)	986 (57.5%)	964 (57.6%)	417 (79.4%)	400 (81.0%)
Diuretic	455 (91.4%)	461 (90.2%)	319 (89.9%)	343 (87.5%)	1547 (90.2%)	1498 (89.4%)	462 (88.0%)	439 (88.9%)
Lipid lowering drug	212 (42.6%)	210 (41.1%)	227 (63.9%)	241 (61.5%)	706 (41.1%)	688 (41.1%)	336 (64.0%)	338 (68.4%)
Anti thrombotics	362 (72.7%)	377 (73.8%)	190 (53.5%)	213 (54.3%)	1161 (67.7%)	1109 (66.2%)	308 (58.7%)	308 (62.3%)

Legend: HFrEF, heart failure with reduced ejection fraction (RALES+EMPHASIS-HF trials); HFpEF, heart failure with preserved ejection fraction (TOPCAT-Americas); MRA, mineralocorticoid receptor antagonist; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; ACEi/ARBs, angiotensin converting enzyme inhibitors/angiotensin receptor blockers.

Table 2. MRA treatment effect on the study population

Outcome/Events	Placebo	MRA	HR (95% CI)	p-value	Heterogeneity p
Age ≥75 years					
HFrEF (RALES+EMPHASIS-HF); Total n =1009; Placebo n =498; MRA n =511.					
CV death or HF hosp.	215 (43.2%)	170 (33.3%)	0.69 (0.56- 0.84)	<0.001	0.70
CV death	137 (27.5%)	113 (22.1%)	0.74 (0.58- 0.96)	0.020	0.062
All-cause death	160 (32.1%)	134 (26.2%)	0.75 (0.60- 0.95)	0.016	0.059
HFpEF (TOPCAT-Americas); Total n =747; Placebo n =355; MRA n =392.					
CV death or HF hosp.	116 (32.7%)	111 (28.3%)	0.83 (0.63- 1.08)	0.20	-
CV death	61 (17.2%)	50 (12.8%)	0.73 (0.50- 1.06)	0.10	-
All-cause death	105 (29.6%)	102 (26.0%)	0.87 (0.66- 1.14)	0.32	-
Overall population (HFrEF+HFpEF combined); Total n =1756; Placebo n =853; MRA n =903.					
CV death or HF hosp.	331 (38.8%)	281 (31.1%)	0.74 (0.63- 0.86)	<0.001	0.52
CV death	198 (23.2%)	163 (18.1%)	0.74 (0.60- 0.91)	0.005	0.17
All-cause death	265 (31.1%)	236 (26.1%)	0.80 (0.66- 0.95)	0.013	0.13
Age <75 years					
HFrEF (RALES+EMPHASIS-HF); Total n =3391; Placebo n =1716; MRA n =1675.					
CV death or HF hosp.	633 (36.9%)	441 (26.3%)	0.65 (0.57- 0.72)	<0.001	0.75
CV death	386 (22.5%)	282 (16.8%)	0.72 (0.62- 0.84)	<0.001	0.90
All-cause death	439 (25.6%)	323 (19.3%)	0.72 (0.63- 0.83)	<0.001	0.94
HFpEF (TOPCAT-Americas); Total n =1020; Placebo n =526; MRA n =494.					
CV death or HF hosp.	164 (31.2%)	131 (26.5%)	0.81 (0.64- 1.02)	0.069	-
CV death	66 (12.6%)	46 (9.3%)	0.72 (0.50- 1.06)	0.094	-
All-cause death	100 (19.0%)	80 (16.2%)	0.83 (0.62- 1.11)	0.21	-
Overall population (HFrEF+HFpEF combined); Total n =4411; Placebo n =2242; MRA n =2169.					

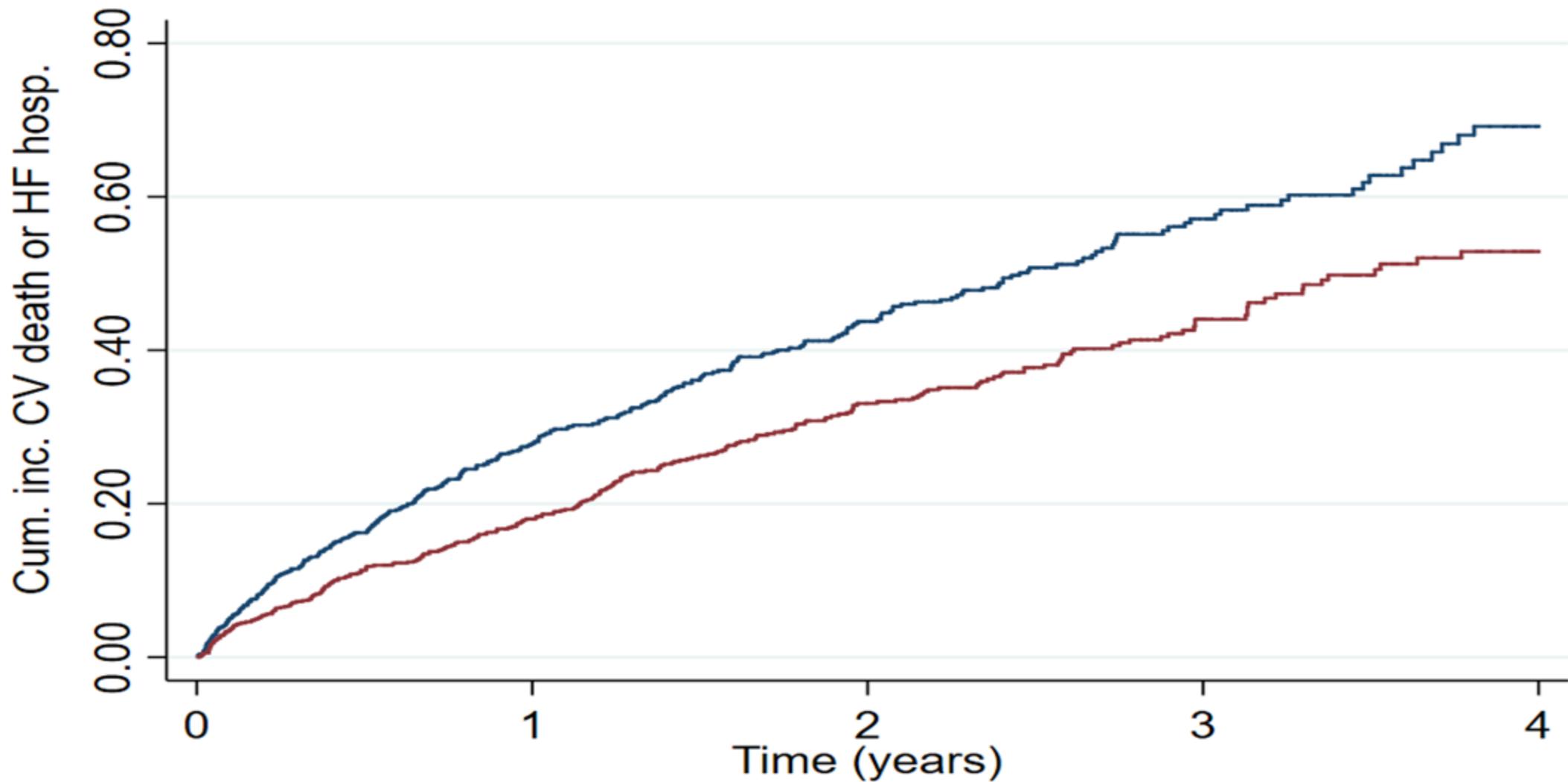
CV death or HF hosp.	797 (35.6%)	572 (26.4%)	0.67 (0.60- 0.75)	<0.001	0.30
CV death	452 (20.2%)	328 (15.1%)	0.71 (0.61- 0.82)	<0.001	0.91
All-cause death	539 (24.0%)	403 (18.6%)	0.74 (0.65- 0.84)	<0.001	0.81
Overall population treatment effect in Older vs. Younger patients					
Outcome/Interaction test	Age dichotomic (<75 vs. ≥75) interaction p		Age continuous interaction p		
CV death or HF hosp.	0.39		0.26		
CV death	0.80		0.37		
All-cause death	0.52		0.69		

Legend: MRA, mineralocorticoid receptor antagonist; CV, cardiovascular; Heterogeneity p, Cochran's Q p-value of treatment effect by study interaction.

Table 3. Side-effects during the follow-up

Side-effects	Placebo	MRA	P-value
Age ≥75 years			
HFrEF (RALES+EMPHASIS-HF); Total n =1009; Placebo n =498; MRA n =511.			
Hyperkalemia	35 (7.0%)	81 (15.9%)	<0.001
Worsening renal function	104 (20.9%)	183 (35.8%)	<0.001
HFpEF (TOPCAT-Americas); Total n =747; Placebo n =355; MRA n =392.			
Hyperkalemia	18 (5.1%)	67 (17.1%)	<0.001
Worsening renal function	110 (31.0%)	172 (43.9%)	<0.001
Overall population (HFrEF+HFpEF combined); Total n =1756; Placebo n =853; MRA n =903.			
Hyperkalemia	54 (6.3%)	148 (16.4%)	<0.001
Worsening renal function	214 (25.1%)	355 (39.3%)	<0.001
Age <75 years			
HFrEF (RALES+EMPHASIS-HF); Total n =3391; Placebo n =1716; MRA n =1675.			
Hyperkalemia	117 (7.0%)	231 (14.1%)	<0.001
Worsening renal function	330 (20.7%)	428 (27.4%)	<0.001
HFpEF (TOPCAT-Americas); Total n =1020; Placebo n =526; MRA n =494.			
Hyperkalemia	27 (5.2%)	74 (15.0%)	<0.001
Worsening renal function	179 (34.0%)	217 (43.9%)	0.001
Overall population (HFrEF+HFpEF combined); Total n =4411; Placebo n =2242; MRA n =2169.			
Hyperkalemia	144 (6.6%)	305 (14.3%)	<0.001
Worsening renal function	509 (24.0%)	645 (31.3%)	<0.001
Overall population side effects in Older vs. Younger patients			
Side-effect/Interaction	Age dichotomic (<75 vs. ≥75) interaction		Age continuous interaction
	p		p
Hyperkalemia	0.30		0.51
Worsening renal function	0.017		0.049

Hyperkalemia was defined as any laboratory value of serum potassium above 5.5 mmol/L during the follow-up and worsening renal function was defined as an estimated glomerular filtration rate drop greater than 30% during the follow-up. P-value from the Chi-square test.



Number at risk

Placebo 852

565

376

183

76

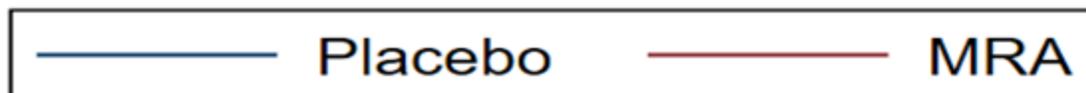
MRA 902

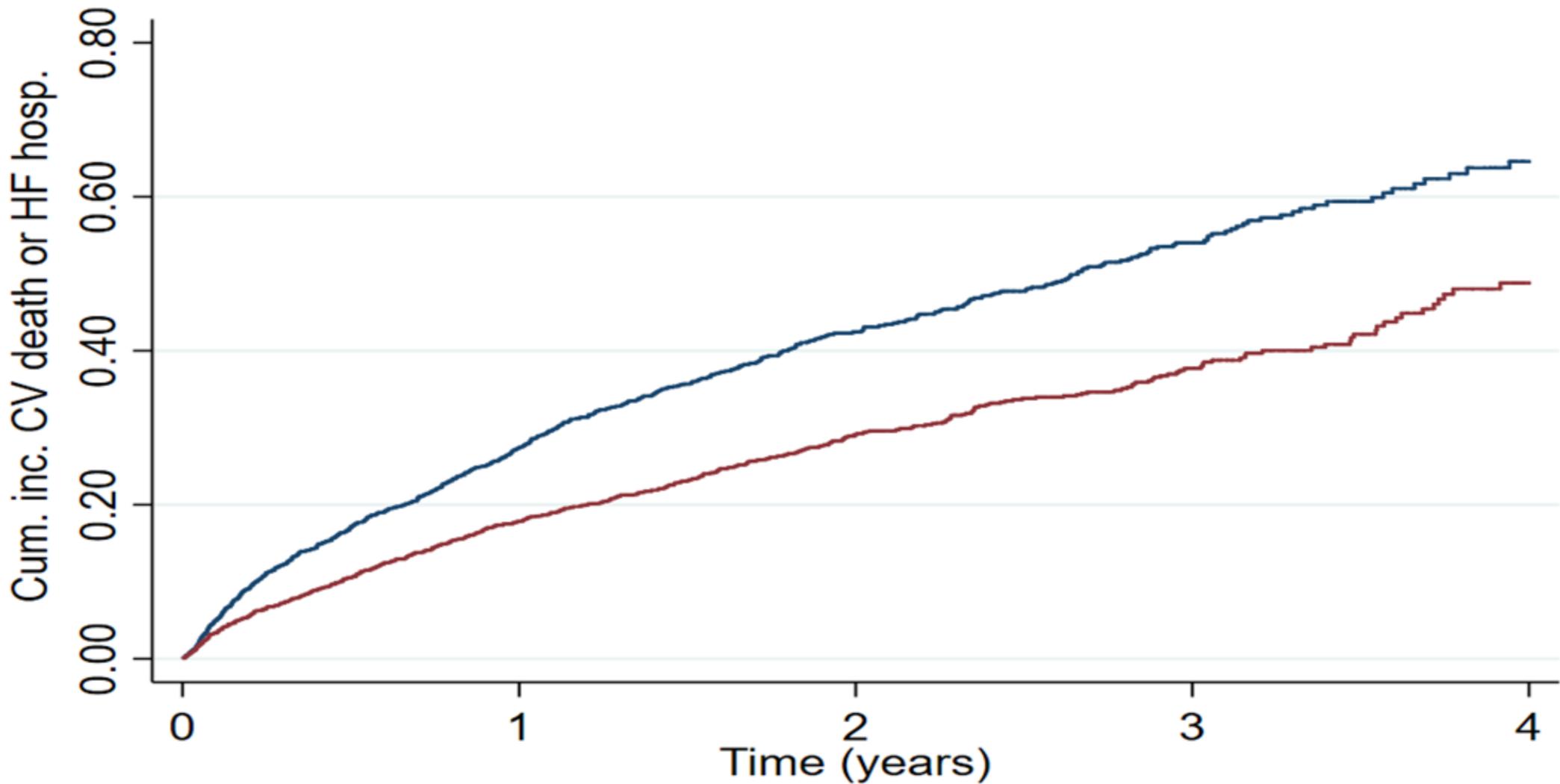
666

416

203

100





Number at risk

Placebo 2242

MRA 2169

1472

1570

906

1006

362

394

106

116

