Tailoring Mineralocorticoid Receptor Antagonist therapy in Heart Failure patients: are we moving towards a Personalized Approach?

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Abstract

The aim of personalized medicine is to offer a tailored approach to each patient in order to provide the most effective therapy, while reducing risks and side effects. The use of mineralocorticoid receptor antagonists (MRAs) has demonstrated major benefits in heart failure with reduced ejection fraction (HF-REF), results with challenging inconsistencies in heart failure with preserved ejection fraction (HF-PEF), and "neutral" preliminary results in acute heart failure (AHF). Data derived from landmark trials are generally applied in a "one size fits all" manner and the development and implementation of more personalized MRA management would offer the potential to improve outcomes and reduce side effects. However, personalization of pharmacotherapy regimens remains poorly defined in the cardiovascular field (in the light of the current knowledge) and until further trials targeting specific sub-populations, MRAs should be provided to the great majority of HF-REF patients in the absence of contra-indication. Spironolactone should be considered for symptomatic HF-PEF patients with elevated natriuretic peptides. In a near future, trials should target HF-REF patients with exclusion criteria from the landmark trials (*e.g.* severe renal impairment), select more homogenous HF-PEF populations (*e.g.* elevated BNP and structural abnormalities on echocardiogram), and determine which patients are likely to benefit from MRAs (*e.g.* prespecified biomarkers).

Key-words: personalized medicine, mineralocorticoid receptor antagonists, heart failure.

Introduction

The aim of personalized medicine is to offer a tailored approach to each patient in order to provide the most effective therapy, while reducing risks and side effects, and also avoiding unnecessary treatments or diagnostic interventions[1, 2].

Treatment of patients with heart failure (HF) with reduced ejection fraction (HF-REF) has improved in recent decades due to data from several large, randomized controlled trials (RCTs). On the other hand, the progress has been much less pronounced in chronic heart failure with preserved ejection fraction (HF-PEF) and in acute heart failure syndromes (AHF), where disease-modifying therapies are urgently needed. For instance, the use of mineralocorticoid receptor antagonists (MRAs) has demonstrated major benefits in HF-REF, results with challenging inconsistencies in heart failure with preserved ejection fraction (HF-PEF) and "neutral" preliminary results in acute heart failure (AHF).

Despite these remarkable advances, data derived from landmark trials are generally applied in a "one size fits all" manner. Broad application of a personalized approach to HF treatment has not become routine. The development and implementation of more personalized management (*e.g.* the creation of multidisciplinary-care teams for high-risk HF patients) offers potential to improve outcomes[3], but personalization of pharmacotherapy regimens remains poorly defined.

Post-hoc analyses from the trial datasets provide insights into disease classification, prognosis and differential treatment effects of guideline-directed medical therapy, which may provide the basis for incremental steps toward personalized HF therapy. However, due to their retrospective nature, these data are prone to bias, and, in general, should be considered as hypothesis-generating[4].

In this review, we aim to analyze which HF subgroups are likely to experience the greatest benefit of MRA therapy, while (ideally) experiencing less side effects and treatment withdrawal. These data may be helpful for better treat patients, for patient-population selection in future MRA trials and to guide inclusion profiles in future platform trials[5].

Methodological Background: Assessing Differential Impacts According to Subgroups

The differential impact of MRA treatment can be assessed by interaction analysis using MRA trial databases. The term "interaction" in the field of biostatistics refers to the impact of a given variable on the effect of another variable. In the present context, such interaction analyses were those that assessed whether MRA treatment has a differential impact in specific subgroups of patients[6]. In addition, we also assessed the absolute risk reduction (ARR) on the primary

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outcome of each major MRA trial, in order to present treatment effects on an absolute scale rather than a relative one, as the former can provide a more clinically useful information[7, 8].

Heart Failure with Reduced Ejection Fraction

MRA therapy for HF-REF has been evaluated in three large randomized controlled trials: 1) the Randomized Aldactone Evaluation Study – RALES[9], 2) the Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms – EMPHASIS[10], and Eplerenone post Myocardial Infarction – EPHESUS[11] (discussed latter in the present manuscript; see acute HF section). These trials showed that MRAs, in addition to standard HF therapy, substantially reduced the risk of both morbidity and mortality among patients with severe, mild and post-myocardial infarction HF-REF. But is this true for all HF-REF patients included in these land-marking trials?

Heart Failure with Reduced Ejection Fraction and Severe Symptoms

In the RALES trial, 1663 patients with HF and severe symptoms and a LVEF d35% were randomized to spironolactone or placebo. There was a 30% reduction in mortality rate in spironolactone group – hazard ratio (HR) =0.70; 95% confidence interval (95%CI), 0.60 to 0.82; p <0.001). The main findings of this trial are summarized in **Table 1**.

In an absolute scale derived from the Kaplan-Meier curves, the ARR of all-cause death at 2 years was H7% which provides a number needed to treat (NNT) of Hl4 patients at 2 years to avoid 1 death – **Figure 1**.

Subgroup Efficacy

The beneficial effect of spironolactone was present across various subpopulations *i.e.* the reduction in the risk of death among patients in the spironolactone group was similar (p for interaction non-significant, NS) in analyses of all prespecified subgroups - **Table 2**. This subgroup consistency increases the internal validity and the overall robustness of the results.

Additional prespecified and exploratory post-hoc analyses were performed in order to provide further insight regarding treatment efficacy, safety and underlying mechanisms – **Table 2**.

Renal Function and Serum Potassium

A post-hoc analysis of the RALES trial provided further insight on the influence of baseline and worsening renal function (WRF; defined as e30% reduction in estimated glomerular filtration rate from baseline through week 12 of follow up) on the efficacy of spironolactone[12]. Patients with baseline estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2 exhibited similar reductions in all-cause death as those with a baseline eGFR e60 ml/min/1.73 m^2. Moreover, WRF was more frequent in spironolactone group, yet these

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patients did not have higher all-cause mortality rates, whereas placebo group of patients with WRF demonstrated increased mortality compared to those without WRF (HR =1.1; 95%CI, 0.8 to 1.5 in spironolactone group vs. 1.9; 95%CI, 1.3 to 2.6 in placebo group; p for interaction =0.009). An additional analysis showed that patients who experienced mild hyperkalemia (up to a potassium of 5.5 mmol/L) derived benefit from spironolactone treatment, whereas patients randomized to placebo had increased death rates[13]. These data suggest that despite lower eGFR and/or the occurrence of WRF/hyperkalemia (up to 5.5 mmol/L of potassium), an effort should be performed to maintain MRA therapy (with adequate dose adjustment) since it associated with improved outcomes in these patients.

Race

Another post-hoc analysis of RALES investigated whether race influenced the effect of spironolactone[14]. Patients were divided in African Americans (AAs; n =120) and non-AAs (n =1543). After adjustment, there were no significant differences between these subgroups in the primary outcome of all-cause death (hazard ratio, HR =0.69; 95% CI, 0.59 to 0.81 in non-AAs vs. 0.91; 95% CI, 0.52 to 1.60 in AAs; p for interaction NS). However, spironolactone reduced the combined end point of death or hospitalization for HF in non-AAs (HR =0.63; 95%CI, 0.55 to 0.73) but not in AAs (HR =1.07; 95%CI, 0.67 to 1.71; p for interaction =0.032), which also did not experience the expected spironolactone side effects, such as mild hyperkalemia – **Table 2**. These data should be interpreted very cautiously. The AAs subgroup is very small and likely to have low power and precision to evaluate significant differences between subgroups. Moreover, these data represent point estimates and do not account for therapeutic adherence. Other potential explanations for these differences have been studied. For example, the aldosterone synthase promoter 344-C allele is linked to higher aldosterone levels and is associated with poorer event-free survival in HF[15]. African Americans without this allele (the majority) are likely to have lower response to MRAs[16]. Other genetic factors have also been identified and associated with renal function decline, which may have an impact in outcomes, MRA indication and response[17].

Subgroup Analysis Resume

Overall the efficacy of spironolactone was consistent across all the studied subgroups. Despite the finding of possible less efficacy in AAs these findings are derived from a retrospective point analysis with unbalanced groups and not accounting for therapeutic compliance. Hence, the benefits of spironolactone can be generalized to all patients with HF and severe symptoms unless formal contraindication.

Predictors of Efficacy

A prespecified analysis of the RALES trial assessed samples of 261 patients to determine their fibrotic status *via* the measurements of serum procollagen type I carboxy-terminal peptide, procollagen type I amino-terminal peptide, and procollagen type III amino-terminal peptide (PIIINP) levels at baseline and at 6 months[18]. Elevated baseline levels of PIIINP were associated with an increased risk of death. At 6 months, markers decreased in the spironolactone group but remained unchanged in the placebo group. The spironolactone effect on outcome was significant only in patients with above-median baseline levels of markers. For example, the HR (95% CI) values for death among patients receiving spironolactone was =0.44 (0.26 to 0.75), p =0.002 in the subgroup of patients with PIIINP levels above the median and =1.11 (0.66 to 1.88), p =0.70 in the subgroup with PIIINP levels below the median (p for interaction <0.05) – **Table 2**. These results show that serum levels of cardiac collagen synthesis were significantly associated with poor outcome, but they could be decreased by spironolactone. Moreover, the morbidity and mortality benefit from spironolactone is greater in patients with the highest (above the median) levels of these markers. These results suggest that limitation of the excessive extracellular matrix turnover may represent one of the various mechanisms contributing to the beneficial effect of spironolactone.

These findings are interesting since they derive from a prespecified randomized analysis and clearly show different response patterns. Hence, these data may help to identify a subgroup of potential "super-responders" - those with high collagen synthesis markers - where an early and well-titrated treatment with spironolactone could provide substantial prognostic benefit. However, spironolactone was not likely to be deleterious in patients with lower collagen synthesis markers levels, thus, until further prospective randomized evidence, spironolactone should still be used in this – lower collagen synthesis – HF-REF subgroup of patients. These findings could also suggest potential for biomarker guided therapy, although would require prospective validation prior to broad application[19].

Safety

There were no significant differences between the spironolactone and placebo treatment groups in serum sodium concentration, blood pressure, or heart rate during the RALES study. However, the median creatinine concentration in the spironolactone group increased by approximately 0.05 to 0.10 mg/dL and the median potassium concentration increased by 0.30 mmol/L during the first year after enrollment, whereas in the placebo group, no changes were detected (p <0.001 for between group difference). Of notice, the increase in potassium and creatinine in the spironolactone group was not associated with increased mortality (as above explained). Overall spironolactone was safe and well tolerated in the context of trial measurements of potassium and creatinine. Importantly, recent real world data highlights that

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these laboratory evaluations are not consistently performed in routine practice, but weather the "regular" potassium and creatinine measurements in the context of MRA treatment are associated with improved outcomes needs further evaluation[20].

Heart Failure with Reduced Ejection Fraction and Mild Symptoms

In the EMPHASIS trial 2737 patients with HF, LVEF d35% and mild symptoms were randomly assigned to receive eplerenone (up to 50 mg daily) or placebo. The primary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure[10]. There was a 37% reduction of the primary outcome in eplerenone group (HR =0.63; 95%CI, 0.54 to 0.74; p <0.001) – **Table 1**.

In an absolute scale derived from the Kaplan-Meier curves the ARR of the primary composite outcome at 2 years was H8% which provides a NNT of H13 patients at 2 years to avoid 1 event – **Figure 1**. Considering all-cause death as outcome (the primary outcome used in RALES) the ARR was H4% providing a NNT of H25 patients at 2 years to avoid 1 death.

These results were also impressive and even more if we consider that the great majority of patients were also receiving angiotensin receptor enzyme inhibitor/angiotensin receptor blocker (ACEi/ARB) and beta-blocker background therapy, which was not the case in RALES in which only H10% of the patients were on beta-blockers.

Subgroup Efficacy

The beneficial effect of eplerenone was consistent across the various studied subpopulations *i.e.* the reduction in the risk of death among patients in the eplerenone group was similar (p for interaction e0.05) in analyses of all prespecified subgroups – **Table 2**. However, the test for interaction is statistically weak and some authorities argue that a larger p-value, *e.g.* d0.1 should be considered as possibly indicative of a true interaction[21]. In this regard, patients with diabetes were likely to experience a greater benefit from eplerenone as compared to patients without diabetes (HR =0.6; 95%CI, 0.5 to 0.8 vs. HR =0.8; 95%CI, 0.6 to 0.9; p for interaction =0.1) and patients receiving an ACEi plus ARB plus beta-blocker were less likely to experience the beneficial eplerenone effects (HR =0.9; 95%CI, 0.3 to 2.2 vs. HR =0.7; 95%CI, 0.6 to 0.9; p for interaction =0.07) – **Table 2**. Despite these weak "interactions" the efficacy was likely to be maintained (HR reduction) across these subgroups, supporting similar use of MRAs in these subpopulations. Additional prespecified and post-hoc analyses were performed in order to provide further insight regarding treatment efficacy, safety and underlying mechanisms.

High-Risk Subgroups

A prespecified analysis of the EMPHASIS trial sought to investigate the safety and efficacy of eplerenone in patients at high risk for hyperkalemia and/or WRF. These prespecified high-risk patients had at least one of the following criteria: age e75 years, diabetes, estimated

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glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2, and systolic blood pressure <123 mmHg (median). The studied endpoints were: hyperkalemia leading to study drug discontinuation or hospitalization, hospitalization for WRF, and the primary outcome of hospitalization for HF or cardiovascular death. Patients treated with eplerenone had an effective reduction in the primary outcome in all high-risk subgroups[22, 23]. The beneficial eplerenone effect was also observed regardless of the presence of atrial fibrillation at baseline[24]. Other post-hoc analysis also documented a maintained survival benefit of eplerenone in patients with WRF and/or hyperkalemia during follow-up[25], in patients with abnormal QRS morphology and duration[26], and in patients taking aspirin[27].

These results are consistent with those of RALES and support the use of MRAs in high-risk subgroups, which are also the populations who are likely to most benefit from disease modifying therapies.

Waist Circumference

Based on experimental data suggesting a better MRA response in the presence of abdominal adiposity[28], HF-REF patients included in the EMPHASIS trial were divided according to their waist circumference (WC) diameter. This post-hoc analysis suggested that patients with "increased" WC derived greater benefits from MRA eplerenone (HR =0.48; 95%CI, 0.37 to 0.63 for WC e102cm in males/88cm in females vs. HR =0.77; 95%CI, 0.61 to 0.98 for WC <102/88cm; p for interaction =0.01) compared to patients with "normal/near normal" WC, with similar safety profile[29]. This observation was not significant when analyzing the benefit derived from eplerenone according to the presence of an obesity defined by body mass index, suggesting that abdominal adiposity that plays a pivotal role in modulating MRA response[28]. Notwithstanding, these data are post hoc and should be interpreted very cautiously. For example, in patients with "normal/near normal" WC a beneficial eplerenone effect was also observed with confidence intervals overlapping those of "increased" WC. Until more replication and prospective confirmation MRA therapy cannot be "tailored" according to WC diameter. However, these data may raise the hypothesis that patients with abdominal obesity may respond better to MRAs. Moreover, future research should try to assess the mechanisms inherent to the "obesity-paradox" findings in HF which has been observed with regards to body mass index (and not waist circumference, which is much less available in datasets)[30, 31]. Nonetheless, if is there a different pattern of response to renin-angiotensin-aldosterone inhibitors in obese patients is a question that is still left to answer.

Safety

Despite mild to moderate hyperkalemia occurring more frequently in patients treated with eplerenone (serum potassium levels >5.5 mmol/L occurred in 11.8% of patients in the

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eplerenone group and 7.2% of those in the placebo group, p <0.001), the rates of severe hyperkalemia did not differ between treatment and placebo groups (serum potassium levels >6.0 mmol/L occurred in 2.5% of patients in the eplerenone group and 1.9% in the placebo group, p =0.29)[10]. Serum creatinine changes were also not significantly different between groups. The safety profile was maintained across high-risk subgroups, with no differences regarding severe hyperkalemia or study drug discontinuation[22].

Overall interpretation of subgroup analysis in Heart Failure with Reduced Ejection Fraction

Mineralocorticoid receptor antagonists (either spironolactone or eplerenone) are effective and safe in HF-REF. Their use should be generalized to this population unless contra-indicated (according to the current guidelines)[32, 33]. A prespecified analysis of the RALES trial identified patients with higher levels of cardiac collagen synthesis markers as potential "super responders" to MRA therapy[18]. However, the use of this approach is not currently recommended to identify HF-REF patients who will respond to therapy (as these data are derived from a small subpopulation of the RALES trial), therefore these data require additional prospective and well powered validation.

One suggestion is that future HF-REF trials prespecify collagen-markers measurements to all included patients at baseline, then the levels of these biomarkers could be measured regularly within the trial (*e.g.* every 6 to 9 months) and plotted against events (*e.g.* hospitalizations, diuretic increase, worsening renal function, hyperkalemia). The time-points to look at the data should also be prespecified (*e.g.* 50% and 75% of the total enrollment). This can allow the evaluation of potential responders (*e.g.* those with elevated collagen markers that decrease over time) vs. non-responders (or with low event risk) who are only experiencing the adverse effects of the treatment (*e.g.* those with persistently low collagen markers). In this case an adaptation of the trial may be required and a sample-size re-calculation performed to include only patients with elevated collagen markers in order to have a robust conclusion about the effect in these patients while limiting the chances of type I error. Early stop of the trial could also be decided in the face of an "unequivocal" benefit in one subgroup[34]. This could clearly change the face of cardiovascular trials and provide compelling indication for MRAs above and beyond usual care.

Heart Failure with Preserved Ejection Fraction

The TOPCAT trial enrolled 3445 patients with symptoms attributable to HF and a LVEF ≥45% to receive either spironolactone (15 to 45 mg daily) or placebo. The primary outcome was a composite of cardiovascular mortality, aborted cardiac arrest, or HF

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hospitalization[35]. Overall, spironolactone did not reduce the primary outcome as compared to placebo (HR =0.89; 95%CI, 0.77 to 1.04; p =0.14) – **Table 1**. Of the components of the primary outcome, only HF hospitalization had a significantly lower incidence in the spironolactone group as compared to the placebo group (HR =0.83; 95%CI, 0.69 to 0.99, p =0.04).

Subgroup Efficacy

Given outcome differences by region and HF entry criterion, the data derived from the TOPCAT trial are complex and several additional post-hoc analyses have been performed to explore these findings – **Table 2**.

Geographical Differences

The TOPCAT trial showed marked geographical differences regarding treatment effect. Patients from "the Americas" (North and South America) showed a marked response to treatment whereas patients from Eastern Europe (Russia and Georgia) did not[36-38]. The HR for the primary outcome of cardiovascular death or HF hospitalization was =0.82; 95%CI, 0.69 to 0.98; p =0.026 in "the Americas" vs. HR =1.10; 95%CI, 0.79 to 1.51, p =0.58 in Eastern Europe, with a p for interaction by treatment region =0.12. Although the p for interaction by treatment region was not <0.05 for the primary outcome we must consider that the test for interaction is statistically weak, and some authorities argue that a larger p-value (*e.g*. d0.1) should be considered as potentially indicative of a significant interaction[21]. Moreover, the HR for cardiovascular mortality was =0.74; 95%CI, 0.57 to 0.97 in "the Americas" vs. 1.31; 95%CI, 0.91 to 1.90 in Eastern Europe; p for interaction =0.01. Although cardiovascular death was a component of the primary outcome (but a prespecified analysis) here the p for interaction is indisputably significant and unlikely to represent a chance finding[39]. Subgroup analysis (which include geographical differences) should be interpreted cautiously and most often they are a consequence of randomness and/or multiple testing[40]. However, the geographical differences in TOPCAT are unlikely to be a product of chance since there is a strong "biological" plausibility for the observed treatment differences. In TOPCAT a huge discrepancy in the baseline characteristics and event rate between patients randomized from Eastern Europe and those enrolled from "the Americas" was observed, with the latter having H4-fold higher event rate. In fact, patients from Eastern Europe had similar event rates to "age-matched" individuals from the general population[36] and spironolactone metabolites were undetectable in these patients, suggesting that the great majority were not taking the study drug[41]. We may assume that patients` baseline characteristics, discrepancy in inclusion criteria, and treatment adherence have played a major role in the treatment effect difference[38]. However, the study was not stratified on regions, neither had an adaptive design that would have allowed to adjust randomization regions along the trial (*i.e*. "the Americas" would have been a "winner") and, unfortunately, in

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international recommendations these data are treated as merely "post-hoc" and no specific recommendations regarding spironolactone in HF-PEF are provided in the current guidelines[32, 33]. However, based on the aforementioned justifications, it is our opinion that the weight of the available evidence favours spironolactone use, and that this treatment is useful and should be considered for morbidity and mortality reduction in symptomatic HF-PEF - which diagnosis can be assessed with more granularity using natriuretic peptides (as below demonstrated) - **Table 2** and **Figure 1**.

Stratification: BNP stratum vs. Hospitalization stratum

Importantly, the TOPCAT trial had a stratification by the entry criteria for HF. Patients were randomized according to BNP strata OR HF hospitalization strata. Those in the BNP strata (NT-pro BNP >360 pg/mL for inclusion) had a positive response to spironolactone treatment with a major primary outcome event rate reduction, whereas those in the hospitalization stratum did not (HR =0.65; 95%CI 0.49 to 0.87 in BNP stratum vs. 1.01; 95%CI, 0.84 to 1.21 in hospitalization stratum; p for interaction =0.01). From a methodological perspective, interactions between pre-specified randomized strata have a higher value than those derived from *post hoc* subgroups. In stratified trials, such as TOPCAT, randomization is performed within each stratum. As a consequence, the results derived within a given stratum are "true" randomized evidence. Despite these data may be limited due to concerns related to multiplicity of testing and type I error we would like to weigh in the possibility that spironolactone is beneficial in HF-PEF patients (and has an acceptable safety profile) with elevated natriuretic peptides[42] – **Table 2**.

Cardiac Structure and Function

A subanalysis of the TOPCAT trial[43] identified echocardiographic variables with prognostic relevance. In particular, left ventricular (LV) hypertrophy, elevated LV filling pressures, and higher pulmonary artery pressure assessed by the tricuspid regurgitation velocity were independently associated with the occurrence of the primary outcome. Additionally, impaired LV systolic function assessed by longitudinal strain (LS, absolute LS value <15.8%) was identified as the strongest echocardiographic predictor of cardiovascular outcomes in TOPCAT. Interestingly, an exploratory analysis in a subset of 131 patients with follow-up LS assessed after 12 to 18 months of trial enrollment, demonstrated a significant improvement (after adjustment for randomization strata and clinical characteristics) in LS associated with spironolactone in patients enrolled in "the Americas" (but not in those from Russia or Georgia)[44]. Despite potential LS improvement in patients randomized to spironolactone, this treatment was not associated to significant differences in measures of LV mass or dimensions in the 239 patients with echocardiographic follow-up at 12-18 month after randomization[45]. A

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meta-analysis of MRA trials on HF-PEF found a potential association with diastolic improvement in patients treated with MRAs as assessed by E/e`, deceleration time and E/A ratio, additionally cardiac collagen markers were also significantly reduced with MRA therapy[46, 47].

The LVEF spectrum in terms of prognosis and treatment effect was also analyzed in TOPCAT[48]. The incidence of the primary endpoint and cardiovascular death was highest in patients at the lower end of the "preserved" LVEF spectrum and spironolactone was likely to provide more benefit to patients with LVEF of 45 to 60% (p for interaction =0.046).

Despite the limitations inherent to post-hoc analysis, these data suggest that patients with HF-PEF but with lower EF and with contractility impairment are likely to experience more benefit out of spironolactone treatment.

Safety

Treatment with spironolactone in TOPCAT was overall safe. While it was associated with increased serum creatinine levels and a doubling of the rate of mild hyperkalemia, there were no significant differences in the incidence of serious hyperkalemia or severe renal dysfunction between spironolactone and placebo[35].

Overall interpretation of subgroup analysis from the HF-PEF trials with MRAs

Patients with HF-PEF and elevated NPs are likely to benefit from spironolactone treatment, since this effect was tested in a truly randomized fashion (within BNP stratum) and is well tolerated if adequately monitored. Patients with the characteristics of those enrolled from "the Americas" in the TOPCAT trial are also likely to benefit from spironolactone treatment. Patients at the lower end of LVEF (45 to 60%) are also more likely to experience more positive effects from spironolactone treatment.

Acute Heart Failure

Data regarding acute heart failure (AHF) are scarce and largely do not result from randomized evidence. With the exception of the EPHESUS trial[11] which included a very particular subtype of patients with AHF (≈90% of the patients presented with signs and symptoms of AHF) – those with acute myocardial infarction (AMI) and LVEF <40% – hence EPHESUS data cannot be generalized to other populations. In the EPHESUS trial the end point of death from cardiovascular causes or hospitalization for cardiovascular events was reduced by 13% in eplerenone group (HR =0.87; 95%CI, 0.79 to 0.95; p = 0.002) – **Table 1**.

In an absolute scale derived from the Kaplan-Meier curves the ARR of the primary composite outcome at 2 years was ≈4% which provides a number NNT of ≈25 patients at 2 years to avoid 1 event – **Figure 1**.

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Subgroup Efficacy

The EPHESUS trial clearly showed that eplerenone is effective in AMI patients with AHF and LVEF <40% as compared to placebo (HR =0.87; 95%CI, 0.79 to 0.95; p =0.002 for the primary outcome of death from cardiovascular causes or hospitalization for cardiovascular events)[49] – **Table 2**. A subanalysis of EPHESUS showed that patients who were randomized to eplerenone or placebo earlier after acute MI (3–7 days) vs. those who were randomized later (8–14 days), experienced a greater benefit from eplerenone treatment (adjusted HR for cardiovascular hospitalization and/or cardiovascular mortality =0.78; 95%CI, 0.67 to 0.90; p =0.001 in early initiation vs. HR =0.94; 95%CI, 0.93 to 1.06; p =0.32 in late initiation; p for interaction =0.03)[50]. Moreover, data from the EMPHASIS trial also suggest that eplerenone also improves survival and prevents re-admission in patient who initiate the drug early after hospital discharge (<42 days)[51]. These data support that the acute setting represents a good opportunity to initiate MRAs.

In acutely decompensated heart failure (ADHF) a small (~100 patient), single-center, open-label, non-randomized study suggested that high-dose spironolactone (~100 mg/day) when initiated in the first 24h of hospitalization was associated with a faster diuretic response and increased spot urine sodium excretion[52-54].

The ATHENA-HF trial (Aldosterone Targeted Neurohormonal Combined with Natriuresis Therapy – Heart Failure trial)[55] was a double-blind, placebo-controlled trial, that randomized 360 patients to "usual care" vs. "usual care plus 100 mg/day of spironolactone for 72h within hospital stay. The hypothesis that treatment with spironolactone would lead to greater reductions in the NT-pro BNP levels at 96h was not met and the ATHENA-HF trial was "neutral" (change in *Log*NT-pro BNP from baseline to 96h = -0.49; 95%CI, -0.98 to -0.14 in "usual care" group vs. -0.55; 95%CI, -0.92 to -0.18 in "spironolactone" group; p =0.57). Other prespecified endpoints of dyspnea relief, clinical congestion, net urine output, weight loss, or clinical events also did not differ between groups. Nonetheless, spironolactone treatment was safe and not associated with higher rates of hyperkalemia (K^+ >5.5 mEq/L) or WRF (results presented at the American Heart Association 2016 congress). However, patients included in the ATHENA-HF trial were relatively young (mean age ± 65 years), were clinically stable and did not have major renal impairment (mean estimated glomerular filtration rate ± 57 ml/min/1.73m^2). Even more striking was the low mortality rate at 30 days, with 3.9% (n=7) deaths in the placebo group vs. 2.7% (n=5) in the spironolactone group; p =0.50, supporting the "low risk" of this ADHF population. It is, therefore, unlikely that these patients had risk for "diuretic resistance" or offered challenges for effective decongestion or for initiation of life saving therapies. In addition, more than 25% of patients in the placebo group already had

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baseline spironolactone treatment and continued it during hospital stay. In this context, ATHENA results are expected. Moreover, spironolactone has an extensive metabolism and slow onset of action (that may take more than 24h), therefore it is not the appropriate drug for the acute setting[56]. A more interesting approach would be the evaluation of intravenous potassium canrenoate in patients with (or prone to) diuretic resistance[57].

Spironolactone shows promising results in AHF after an acute MI, however it did not pointed towards a beneficial effect in patients with ADHF without myocardial infarction, however, as above pointed, there were several limitations in the ATHENA-HF trial and the efficacy and safety of aldosterone antagonists in ADHF should be furtherly explored.

Safety

In AHF MRAs were overall well tolerated. In the EPHESUS trial a non-clinically relevant increase in creatinine levels was observed in eplerenone group (0.06 mg/dL vs. 0.02 mg/dL, p <0.001). Serious hyperkalemia (serum potassium concentration e 6.0 mmol/L) occurred in 5.5% of patients in the eplerenone group vs. 3.9% in placebo group (p =0.002), and there was 1 death attributed to hyperkalemia that occurred in the placebo group. The incidence of hyperkalemia was higher in patients with renal dysfunction at baseline (eGFR <50 ml/min/1.73m^2)[11].

Overall interpretation of subgroup analysis from AHF trials with MRAs

In patients presenting with acute MI plus AHF and systolic dysfunction, eplerenone is effective and safe. Its use should be generalized to the population that meets the EPHESUS criteria. In ADHF the results did not suggest benefit, however other "higher-risk" populations and other aldosterone antagonist formulations (with intravenous administration possibilities) should be tested.

Clinical implications

Heart Failure with Reduced Ejection Fraction

In HF-REF there is currently no sufficient evidence to change guidelines towards a more personalized approach[32, 33]. This is a high-risk population in whom all measures that increase survival, reduce hospitalizations and improve quality of life should be applied. Given the safety and great efficacy of MRAs in this setting there is little place (in the light of the current knowledge) to sub-select HF-REF patients. By the contrary, more patients can benefit from MRA treatment, since many patients are still undertreated[58].

The advent of potassium binding therapies may potentially reassure clinicians to prescribe MRAs to subgroups with high-risk of hyperkalemia[59-62]. However, without adequate prospective evaluation that these potassium binders may actually help to titrate MRA therapy,

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reduce side-effects and improve outcomes, the use of these agents cannot be routinely advocated. Without this evaluation they can have the opposite effect of increasing the fear of hyperkalemia by using MRAs.

Additionally, prospective high-quality evidence should focus on subgroup selection based on patterns of response and side-effects – **Table 3**.

Heart Failure with Preserved Ejection Fraction

In the immediate clinical setting, we have data suggesting that spironolactone could be provided to symptomatic HF-PEF patients (were no therapy is currently available) in symptomatic HF-PEF patients with elevated NPs[36, 42] - **Table 3**.

Acute Heart Failure

All patients with AHF and systolic dysfunction in the context of AMI should be provided MRAs unless contra-indicated. Given their consistent efficacy and safety in this setting there is no place for treatment selection based on sub-groups.

In patients with ADHF, MRA use did not pointed towards a beneficial effect, however other drug formulations (*e.g.* intravenous canrenoate) and higher risk populations should be targeted – **Table 3**.

Research Implications

Implications for future research are of uttermost importance to provide high-quality evidence in RCTs.

Heart Failure with Reduced Ejection Fraction (including post-Myocardial Infarction)

HF-REF is a high-risk condition with elevated event rates (high event incidence) and prone to competing risks such as ageing[63]. MRAs effectively reduce those events without increasing life-threatening adverse effects. The NNT to benefit on an absolute scale is very low (NNT <15 at 2 years), hence MRA treatment in HF-REF should be more inclusive rather than exclusive[64]. In this purpose, treatment effect and safety in high-risk subgroups (*e.g.* patients with severe renal dysfunction) can be improved in order to increase the pool of patients to be treated (*e.g.* with use novel agents such as finerenone and/or use of potassium binders) – **Table 3** and **Figure 2**.

Given the demonstrated event rate reduction, results reproducibility, internal and external validity it is unethical to perform another MRA trial versus placebo in HF-REF. Hence, a novel trial in this setting needs to compare the new MRA versus spironolactone OR eplerenone, in order to demonstrate superiority of the new treatment or, at least, non-inferiority with an improved safety profile. However, the advent of an adaptive MRA trial can help to

determine which patients can thrive more benefit from the novel treatment and the above findings can help to select this patient-population while the trial is ongoing[34, 65].

Heart Failure with Preserved Ejection Fraction

Patients with symptomatic HF-PEF and elevated NPs have similar risk to their HF-REF counterparts. Therefore, future trials should target a more homogeneous population[38]. For example, symptomatic patients with elevated NPs plus structural abnormalities in echocardiogram (LVEF 45 to 60% and/or systolic dysfunction as assessed by LS). As this population is more prone to benefit from MRA therapy – **Table 3** and **Figure 2**. In other words, the target population should have the disease that the study drug aims to treat (in this case HF-PEF) and the patients should have a medium –high risk profile in order to observe a potential treatment effect in an absolute scale (*i.e.* absolute risk reduction). If the population has a very low risk or does not have the disease (as the case of Eastern Europe patients in TOPCAT), the treatment effect will not be apparent as there is little risk to be reduced[23]. Moreover, future HF-PEF trials should have a series of prespecified "rules" (*e.g.* echocardiographic parameters, cardiac collagen markers, natriuretic peptides, drug compliance, potassium levels and renal function, and events monitorization) to help in enrolling patients who have the disease, that adhere to treatment, and that have more chances to respond to therapy (and less harmful effects), as the trial may be adapted in order to select the patients who are likely to benefit more from treatment. However, this possibility must be prespecified before the trial initiation, otherwise we will likely lose more opportunities for "personalized treatments".

Populations "at-risk"

Populations "at-risk" for HF but without overt HF have a lower baseline risk of major cardiovascular events when compared to HF populations[66]. Hence, the risk reduction in an absolute scale will necessarily be lower (as TOPCAT clearly demonstrated on enrolling low-risk Eastern Europe populations with event rates overlapping the age-matched general population)[36] and, in this case, we need to carefully select which patients will benefit ("number needed to treat for benefit" vs. "number needed to treat for harm") from MRA therapy[40]. For this purpose, attention should be provided to pre-specified "response predictors" (as above stated). This approach will possibly avoid overtreatment in lower-risk populations and select patients more prone to respond – **Table 3** and **Figure 2**.

Acutely Decompensated Heart Failure

Preliminary data suggest that MRAs are safe in ADHF but did not point toward potential efficacy. However, improvement in the patient-population selection and study drug formulation should be tested before concluding "futility" – **Table 3**.

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Ongoing Trials on at risk of developing HF patients

HOMAGE

The HOMAGE (Heart OMics in AGEing) project aims to validate specific biomarkers of ageing, fibrosis, cardio-myocyte damage and inflammation allowing HF patients' stratification in order to propose a tailored therapy accordingly to their altered signaling pathways *i.e.* patients biomarker profiles. Thus the project will use an innovative 'omic-based' approach which investigating simultaneously a huge amount of transcripts, proteins and metabolites to set the ground of new ways of preventing HF[67]. This might also allow a repositioning of MRAs as preventive treatment of at risk patients with comorbidities where above-cited signalings are known to be altered (*e.g.* obesity, and chronic kidney disease). In this purpose, a substudy of HOMAGE will randomize patients at risk for HF to spironolactone or "usual care" to identify patients who are likely to respond based on prespecified cardiac collagen marker levels (NCT02556450).

ALCHEMIST

The ALCHEMIST trial is designed to establish the effects of spironolactone vs. placebo on major cardiovascular events on chronic hemodialysis patients (NCT01848639).

Conclusion

In the absence of formal contra-indication and until further RCTs targeting specific sub-populations, MRAs should be provided to the great majority of HF-REF patients in the absence of contra-indication. Spironolactone should be considered for symptomatic HF-PEF patients with elevated natriuretic peptides. Further trials should target HF-REF patients with exclusion criteria from the landmark trials (*e.g.* severe renal impairment), select more homogenous HF-PEF populations (*e.g.* elevated BNP and structural abnormalities on echocardiogram), and determine which patients are more likely to benefit from MRAs (*e.g.* prespecified biomarkers).

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Disclosures

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Aurasense *; (* =stock options); Dr Zannad has received fees for serving on the board of Boston Scientific; consulting fees from Novartis, Takeda, AstraZeneca, Boehringer Ingelheim, GE Healthcare, Relypsa, Servier, Boston Scientific, Bayer, Johnson & Johnson, and Resmed; and speakers' fees from Pfizer and AstraZeneca. He is CardioRenal co-founder (along with Dr Rossignol); Dr Mentz and Pizard declare not to have relevant conflicts of interest to disclose regarding the present manuscript.

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