European Journal of Heart Failure (2017) **19**, 974–986
doi:10.1002/ejhf.814

REVIEW

Tailoring mineralocorticoid receptor antagonist therapy in heart failure patients: are we moving towards a personalized approach?

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Received 2 November 2016; revised 30 December 2016; accepted 21 February 2017; online publish-ahead-of-print 12 April 2017

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 (HFrEF), results with challenging inconsistencies in heart failure with preserved ejection fraction (HFpEF), and 'neutral' preliminary results in acute heart failure. 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, the personalization of pharmacotherapy regimens remains poorly defined in the cardiovascular field (in light of current knowledge) and until further trials targeting specific subpopulations have been conducted, MRAs should be provided to the great majority of HFrEF patients in the absence of contraindication. Spironolactone should be considered for symptomatic HFpEF patients with elevated natriuretic peptides. In the near future, trials should target HFrEF patients using exclusion criteria sourced from landmark trials (e.g. severe renal impairment), select more homogeneous HFpEF populations (e.g. with elevated BNP and structural abnormalities on echocardiography), and determine which patients are likely to benefit from MRAs (e.g. according to prespecified biomarkers).

Keywords 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]

The treatment of patients with heart failure with reduced ejection fraction (HFrEF) has improved in recent decades as a result of data sourced from several large randomized controlled trials (RCTs). In contrast, progress has been much less pronounced in chronic heart failure with preserved ejection fraction (HFpEF) and in acute heart failure (AHF) syndromes, in which disease-modifying therapies are urgently needed. For instance, the use of mineralocorticoid receptor antagonists (MRAs) has demonstrated major benefits in HFrEF, results with challenging inconsistencies in HFpEF, and 'neutral' preliminary results in AHF.

Despite these remarkable advances, data derived from landmark trials are generally applied in a 'one size fits all' manner. The broad application of a personalized approach to heart failure (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 the 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 towards personalized HF therapy. However,

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Table 1 Main findings of trials of treatment with mineralocorticoid receptor antagonists in heart failure

Variable	RALES	EMPHASIS	EPHESUS	TOPCAT
Population	HFrEF Severe symptoms	HFrEF Mild symptoms	HFrEF Post-MI	HFpEF Symptomatic
Drug (vs. placebo)	Spironolactone	Eplerenone	Eplerenone	Spironolactone
Dose	~25 mg/day	~50 mg/day	~50 mg/day	15–45 mg/day
Primary endpoint	ACM	CO	CO	CO
HR (95% CI) for TTx	0.70 (0.60–0.82)	0.63 (0.54–0.74)	0.87 (0.79–0.95)	0.89 (0.77–1.04)

ACM, all-cause mortality; CI, confidence interval; CO, composite outcome of death from cardiovascular causes or hospitalization for heart failure in EMPHASIS and TOPCAT and death from cardiovascular causes or hospitalization for cardiovascular events in EPHESUS; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; MI, myocardial infarction; TTx, treatment.

in view of 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 analyse which HF subgroups are likely to experience the greatest benefit of MRA therapy, while (ideally) experiencing fewer side effects and less treatment withdrawal. These data may be helpful in supporting the better treatment of patients, in the selection of patient populations in future MRA trials and in guiding inclusion profiles in future platform trials.[5]

Methodological background: assessing differential impacts according to subgroups

The differential impacts 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 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 more clinically useful information.[7,8]

Heart failure with reduced ejection fraction

Therapy with MRAs for HFrEF has been evaluated in three large RCTs: (i) the Randomized Aldactone Evaluation Study (RALES);[9] (ii) the Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms Study (EMPHASIS);[10] and (iii) the Eplerenone Post-Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS)[11] (discussed later in the present manuscript; see AHF section). These trials showed that MRAs, in addition to standard HF therapy, substantially reduced the risk for both morbidity and mortality among patients with severe, mild and post-myocardial infarction (MI) HFrEF. However, is this true for all HFrEF patients included in these landmark trials?

Heart failure with reduced ejection fraction and severe symptoms

In the RALES trial, 1663 patients with HF and severe symptoms and a left ventricular ejection fraction (LVEF) of ≤35% were randomized to spironolactone or placebo. There was a 30% reduction in mortality in the spironolactone group [hazard ratio (HR) 0.70, 95% confidence interval (CI) 0.60–0.82; $P < 0.001$]. The main findings of this trial are summarized in *Table 1*.

In an absolute scale derived from Kaplan–Meier curves, the ARR of all-cause death at 2 years was ≈7%, which provides a number needed to treat (NNT) of ≈14 patients at 2 years to avoid one death (*Figure 1*).

Subgroup efficacy

The beneficial effect of spironolactone was present across various subpopulations [i.e. the reduction in the risk for death among patients in the spironolactone group was similar; *P*-value 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 into the influence of baseline and worsening renal function [WRF; defined as a ≥30% reduction in estimated glomerular filtration rate (eGFR) from baseline to week 12 of follow-up] on the efficacy of spironolactone.[12] Patients with a baseline eGFR of <60 mL/min/1.73 m^2 exhibited reductions in all-cause death similar to those in patients with a baseline eGFR of ≥60 mL/min/1.73 m^2. Moreover, WRF was more frequent in the spironolactone group, yet these patients did not have higher all-cause mortality rates, whereas in the placebo group, patients with WRF demonstrated increased mortality compared with those without WRF (HR 1.1, 95% CI 0.8–1.5 in the spironolactone group; HR 1.9, 95% CI 1.3–2.6 in the placebo group; $P = 0.009$ for interaction). An additional analysis showed that patients who experienced mild

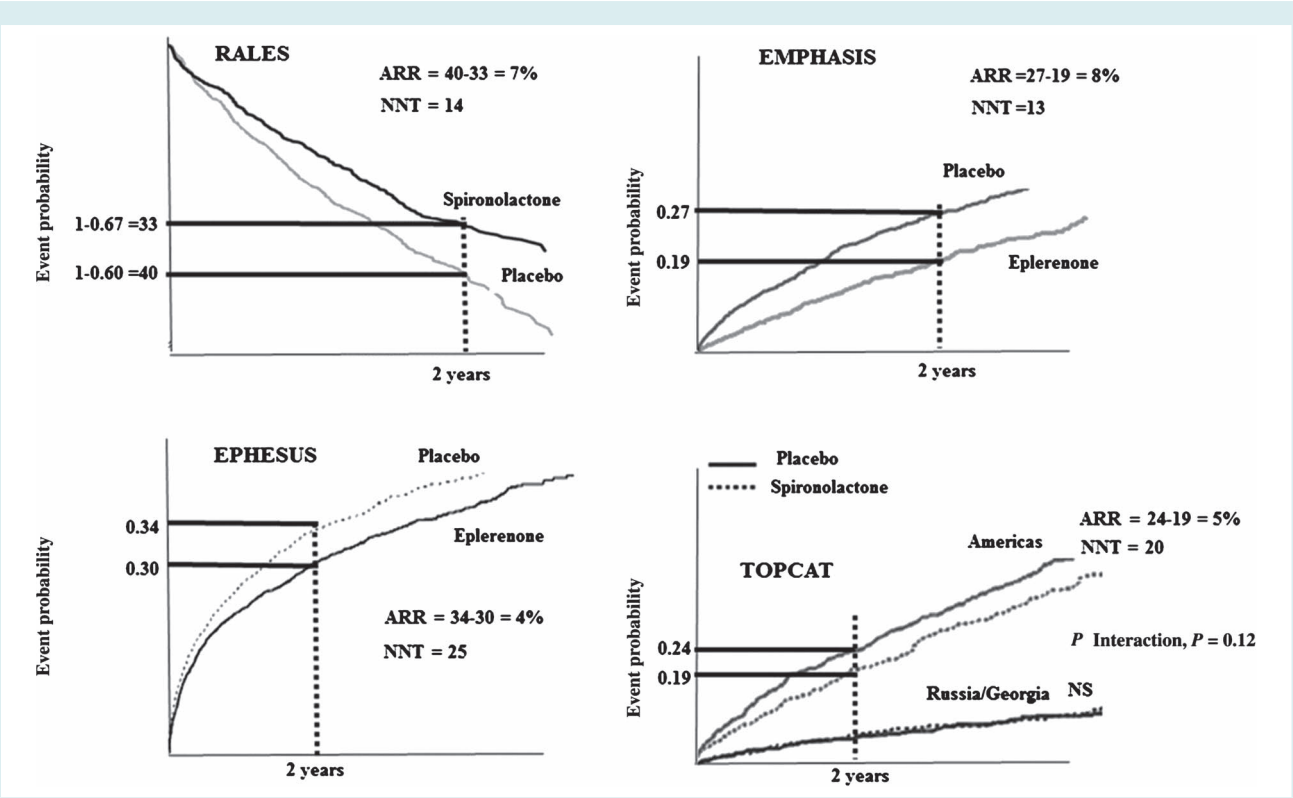

Figure 1 Comparison of absolute risk reduction (ARR) and number needed to treat (NNT) to benefit between trials of mineralocorticoid receptor antagonists. The primary outcome of each trial was used in the present interpretation. NS, non-significant.

hyperkalaemia (up to a potassium level 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 or hyperkalaemia (up to a potassium level of 5.5 mmol/L), an effort should be made to maintain MRA therapy (with adequate dose adjustment) as it is 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 into 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 (HR 0.69, 95% CI 0.59–0.81 in non-AAs; HR 0.91, 95% CI 0.52–1.60 in AAs; *P*-value for interaction: NS). However, spironolactone reduced the combined endpoint of death or hospitalization for HF in non-AAs (HR 0.63, 95% CI 0.55–0.73) but not in AAs (HR 1.07, 95% CI 0.67–1.71; $P = 0.032$), who also did not experience the expected spironolactone side effects, such as mild hyperkalaemia (*Table 2*). These data should be interpreted very cautiously. The AA subgroup is very small and likely to have low power and insufficient 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 a lower response to MRAs.[16] Other genetic factors have also been identified and associated with renal function decline, which may have an impact on outcomes, MRA indication and response.[17]

Summary of subgroup analysis

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

Predictors of efficacy

A prespecified analysis of the RALES trial assessed samples of 261 patients to determine their fibrotic status through 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

Table 2 Differences between patient subgroups in treatment effect in major trials of treatment with mineralocorticoid receptor antagonists in heart failure

Variable	RALES	EMPHASIS	EPHESUS	TOPCAT
Age (above vs. below median) HR (95% CI), *P*-value for interaction	NS	NS	0.93 (0.82–1.05) 0.78 (0.70–0.92) $P = 0.08$	—
Sex (male vs. female) HR (95% CI), *P*-value for interaction	NS	NS	0.82 (0.72–0.93) 0.95 (0.71–1.11) $P = 0.08$	—
Race (non-AA vs. AA) HR (95% CI), *P*-value for interaction	0.6 (0.6–0.7) 1.1 (0.7–1.7) $P = 0.03$	—	—	—
LVEF (above vs. below median) HR (95% CI), *P*-value for interaction	NS	NS	0.98 (0.82–1.15) 0.81 (0.71–0.90) $P = 0.07$	—
Pulse pressure (above vs. below median) HR (95% CI), *P*-value for interaction	—	NS	0.79 (0.70–0.90) 0.93 (0.81–1.08) $P = 0.08$	—
Waist circumference (≥102 cm in males/≥ 88 cm in females vs. <102/88 cm) HR (95% CI), *P*-value for interaction	—	0.48 (0.37–0.63) 0.77 (0.61–0.98) $P = 0.01$	—	—
Atrial fibrillation (yes vs. no)	—	NS	—	—
Diabetes mellitus (yes vs. no) HR (95% CI), *P*-value for interaction	—	0.6 (0.5–0.8) 0.8 (0.6–0.9) $P = 0.10$	NS	—
Hypertension (yes vs. no)	—	NS	NS	—
QRS interval (≤130 ms vs. >130 ms)		NS	—	—
Potassium levels (above vs. below median) HR (95% CI), *P*-value for interaction	NS	—	0.95 (0.85–1.10) 0.77 (0.70–0.90) $P = 0.02$	—
Creatinine or eGFR (above vs. below median)	NS	NS	NS	—
Collagen synthesis markers (above vs. below median) HR (95% CI), *P*-value for interaction	0.4 (0.3–0.8) 1.1 (0.7–1.9) $P < 0.05$		—	—
Enrolment stratum (NPs vs. hospitalization) HR (95% CI), *P*-value for interaction		NS	—	0.7 (0.5–0.9) 1.0 (0.8–1.92) $P = 0.01$
Geographical region (west vs. east) HR (95% CI), *P*-value for interaction	—	NS	—	0.7 (0.6–1.0) 1.3 (0.9–1.9) $P = 0.01$
Digitalis use (yes vs. no)	NS	—	—	—
ACEi/ARBs (yes vs. no)	NS	NS	NS	—
Beta-blockers (yes vs. no)	NS	NS	—	—
ACEi + ARBs + beta-blockers (yes vs. no) HR (95% CI), *P*-value for interaction		0.9 (0.3–2.2) 0.7 (0.6–0.9) $P = 0.07$	NS	—

AAs, African Americans; ACEi, angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blockers; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LVEF, left ventricular ejection fraction; NPs, natriuretic peptides; NS, non-significant.
The test for interaction was considered statistically significant at a *P*-value of ≤0.1 for the primary outcome of each trial.[21]

with an increased risk for 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 values for death among patients receiving spironolactone were 0.44 (95% CI 0.26–0.75; $P = 0.002$) in the subgroup of patients with PIIINP levels above the median and 1.11 (95% CI 0.66–1.88; $P = 0.70$) in the subgroup with PIIINP levels below the median ($P < 0.05$ for interaction) (*Table 2*). These results show that serum levels of cardiac collagen synthesis were significantly associated with poor outcome, but could be decreased by spironolactone. Moreover, the morbidity

and mortality-related benefits to be derived from spironolactone are 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 because 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' represented by patients with high collagen synthesis markers, in whom 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 marker levels and thus, until further prospective randomized evidence is available, spironolactone should still be used in this (lower collagen synthesis) HFrEF subgroup of patients. These findings may also suggest potential for biomarker-guided therapy, although this 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 0.05–0.10 mg/dL and median potassium concentration increased by 0.30 mmol/L during the first year after enrolment, whereas in the placebo group, no changes were detected (between-group difference, $P < 0.001$). Of note, the increases in potassium and creatinine in the spironolactone group were not associated with increased mortality (as explained above). Overall, spironolactone was safe and well tolerated in the context of trial measurements of potassium and creatinine. Importantly, recent real-world data highlight that these laboratory evaluations are not consistently performed in routine practice, and the question of whether '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 of ≤35% and mild symptoms were randomly assigned to receive eplerenone (up to 50 mg/day) or placebo. The primary outcome was a composite of death from cardiovascular causes or hospitalization for HF.[10] There was a 37% reduction in the primary outcome in the eplerenone group (HR 0.63, 95% CI 0.54–0.74; $P < 0.001$) (*Table 1*).

In an absolute scale derived from the Kaplan–Meier curves, the ARR of the primary composite outcome at 2 years was ≈8%, which provides an NNT of ≈13 patients at 2 years to avoid one event (*Figure 1*). Considering all-cause death as the outcome (the primary outcome used in RALES), the ARR was ≈4%, providing an NNT of ≈25 patients at 2 years to avoid one death.

These results were also impressive and even more so if we consider that the great majority of patients were also receiving ACE inhibitor (ACEi)/angiotensin receptor blocker (ARB) and beta-blocker background therapy, which was not the case in RALES, in which only ≈10% of patients were on beta-blockers.

Subgroup efficacy

The beneficial effect of eplerenone was consistent across the various subpopulations studied in that the reduction in the risk for death among patients in the eplerenone group was similar ($P \geq 0.05$ for interaction) 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, such as ≤0.1, should be considered as possibly indicative of a true interaction.[21] In this regard, patients with diabetes were likely to experience greater benefit from eplerenone than patients without diabetes (HR 0.6, 95% CI 0.5–0.8 vs. HR 0.8, 95% CI 0.6–0.9; $P = 0.10$ for interaction) and patients receiving an ACEi plus ARB plus beta-blocker were less likely to experience the beneficial effects of eplerenone (HR 0.9, 95% CI 0.3–2.2 vs. HR 0.7, 95% CI 0.6–0.9; $P = 0.07$ for interaction) (*Table 2*). Despite these weak interactions, efficacy was likely to be maintained (HR reduction) across these subgroups, which supports the similar use of MRAs in these subpopulations. Additional prespecified and post hoc analyses were performed in order to generate further insight into 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 hyperkalaemia and/or WRF. These prespecified high-risk patients fulfilled at least one of the following criteria: age ≥75 years; a diagnosis of diabetes; an eGFR of <60 mL/min/1.73 m^2, and systolic blood pressure of <123 mmHg (median). The studied endpoints were hyperkalaemia 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 showed an effective reduction in the primary outcome in all high-risk subgroups.[22,23] The beneficial effect of eplerenone was also observed regardless of the presence of atrial fibrillation at baseline.[24] Other post hoc analyses also documented the maintenance of a survival benefit of eplerenone in patients with WRF and/or hyperkalaemia 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 also represent the populations 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] HFrEF patients included in the EMPHASIS trial were divided according to their waist circumference (WC). This post hoc analysis suggested that patients with 'increased' WC derived greater benefits from MRA eplerenone (HR 0.48, 95% CI 0.37–0.63 for subjects with a WC of ≥102 cm in males or ≥88 cm in females vs. HR 0.77, 95% CI 0.61–0.98 for subjects with a WC of <102 cm in males or <88 cm in females; $P = 0.01$ for interaction) compared with patients with a 'normal/near normal' WC with a similar safety profile.[29] This observation was not significant in analyses of the benefit derived from eplerenone according to the presence of obesity defined by body mass index (BMI), which suggests that abdominal adiposity plays a pivotal role in modulating MRA response.[28] However, these data represent post hoc findings and should be interpreted very cautiously. For example, in patients with a 'normal/near normal' WC, a beneficial effect of eplerenone for which the 95% CIs overlapped those applying to patients with an 'increased' WC was also observed. Not until further replication has been carried out and prospective confirmation obtained can MRA therapy be tailored according to WC. 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 in the 'obesity paradox' findings in HF, which has been observed with regard to BMI (and not WC, details of which are much less available in datasets).[30,31] Nonetheless, the question of whether there is a different pattern of response to renin–angiotensin–aldosterone inhibitors in obese patients remains to be answered.

Safety

Although mild to moderate hyperkalaemia occurred more frequently in patients treated with eplerenone [serum potassium levels of >5.5 mmol/L occurred in 11.8% of patients in the eplerenone group and 7.2% of those in the placebo group ($P < 0.001$)], rates of severe hyperkalaemia did not differ between the treatment and placebo groups [serum potassium levels of >6.0 mmol/L occurred in 2.5% of patients in the eplerenone group and 1.9% of those in the placebo group ($P = 0.29$)].[10] Changes in serum creatinine did not differ significantly between the groups. The safety profile was maintained across high-risk subgroups, with no differences with respect to severe hyperkalaemia or study drug discontinuation.[22]

Overall interpretation of subgroup analysis in heart failure with reduced ejection fraction

The use of MRAs (either spironolactone or eplerenone) is effective and safe in HFrEF. Use of these therapies should be generalized to this population unless contraindicated (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, this approach is not currently recommended to identify HFrEF patients who will respond to therapy (as these data are derived from a small subpopulation of the RALES trial), and therefore these data require additional prospective and well powered validation.

One suggestion is that future HFrEF trials prespecify measurements of collagen markers in all patients included at baseline and then measure levels of these biomarkers regularly within the trial (e.g. every 6–9 months) and plot the resultant data against events (e.g. hospitalizations, diuretic increase, WRF, hyperkalaemia). The time-points at which the data are examined should also be prespecified (e.g. 50% and 75% of the total enrolment). This would allow the evaluation of potential responders (e.g. those with elevated collagen markers that decrease over time) vs. non-responders (or those with low event risk) who experience only the adverse effects of the treatment (e.g. those with persistently low collagen markers). In this context, the trial may require some adaptation and a recalculation of sample size to include only patients with elevated collagen markers in order to support a robust conclusion about the effects of treatment in these patients while limiting the chances of type I error. An early termination of the trial could also be decided in the face of an 'unequivocal' benefit in one subgroup.[34] Clearly, this might change the face of cardiovascular trials and provide compelling indications for the use of MRAs above and beyond usual care.

Heart failure with preserved ejection fraction

The TOPCAT trial enrolled 3445 patients with symptoms attributable to HF and an LVEF of ≥45% to receive either spironolactone (15–45 mg/day) or placebo. The primary outcome was a composite of cardiovascular mortality, aborted cardiac arrest and HF hospitalization.[35] Overall, spironolactone did not reduce the primary outcome in comparison with placebo (HR 0.89, 95% CI 0.77–1.04; $P = 0.14$) (*Table 1*). Of the components of the primary outcome, only hospitalization for HF occurred at a significantly lower incidence in the spironolactone group than in the placebo group (HR 0.83, 95% CI 0.69–0.99; $P = 0.04$).

Subgroup efficacy

Given differences in outcomes by region and HF entry criteria, 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 HRs for the primary outcome of cardiovascular death or HF hospitalization were 0.82 (95% CI 0.69–0.98; $P = 0.026$) for subjects in the Americas and 1.10 (95% CI 0.79–1.51; $P = 0.58$) for subjects in Eastern Europe (interaction by treatment

region, $P = 0.12$). Although the *P*-value for interaction by treatment region was not <0.05 for the primary outcome, it should be noted that the test for interaction is statistically weak, and some authorities argue that a larger *P*-value (e.g. of ≤0.1) should be considered as potentially indicative of a significant interaction.[21] Moreover, HRs for cardiovascular mortality were 0.74 (95% CI 0.57–0.97) in the Americas and 1.31 (95% CI 0.91–1.90) in Eastern Europe ($P = 0.01$ for interaction). Although cardiovascular death was a component of the primary outcome (but a prespecified analysis), here the *P*-value for interaction is indisputably significant and is unlikely to represent a chance finding.[39] Subgroup analyses (that include geographical differences) should be interpreted cautiously and very often represent a consequence of randomness and/or multiple testing.[40] However, the geographical differences in TOPCAT are unlikely to be a product of chance as there is strong 'biological' plausibility for the treatment differences observed. In TOPCAT, huge discrepancies in baseline characteristics and event rate were observed between patients randomized from Eastern Europe and those enrolled from the Americas, whereby the latter showed an approximately four-fold higher event rate. In fact, rates of events in patients from Eastern Europe were similar to those in age-matched individuals from the general population[36] and spironolactone metabolites were undetectable in these patients, which suggests that the great majority were not taking the study drug.[41] We may assume that patients' baseline characteristics, discrepancies in inclusion criteria and treatment adherence played major roles in the difference in treatment effect.[38] However, the study was not stratified by region and did not feature an adaptive design that would have allowed for the adjusting of randomization regions along the trial (i.e. 'the Americas' would have been a 'winner') and, unfortunately, in international recommendations these data are treated as merely 'post hoc' and current guidelines provide no specific recommendations regarding spironolactone in HFpEF.[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 the purposes of reducing morbidity and mortality in symptomatic HFpEF, the diagnosis of which can be assessed with more granularity using natriuretic peptides (NPs; as demonstrated below) (*Table 2* and *Figure 1*).

Stratification: BNP stratum vs. hospitalization stratum

Importantly, the TOPCAT trial was stratified according to the entry criteria for HF. Patients were randomized according to BNP *or* HF hospitalization strata. Those in the BNP stratum (NT-proBNP >360 pg/mL for inclusion) showed a positive response to spironolactone treatment and a major reduction in primary outcome event rate, whereas those in the hospitalization stratum did not (HR 0.65, 95% CI 0.49–0.87 in the BNP stratum vs. HR 1.01, 95% CI 0.84–1.21 in the hospitalization stratum; $P = 0.01$ for interaction). From a methodological perspective, interactions between prespecified 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 concerns that these data may be limited as a result of multiplicity of testing and type I error, we would like to propose that spironolactone is beneficial in HFpEF patients (and has an acceptable safety profile) with elevated NPs[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 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 12–18 months of trial enrolment 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 with significant differences in measures of LV mass or dimensions in the 239 patients with echocardiographic follow-up at 12–18 months after randomization.[45] A meta-analysis of MRA trials in HFpEF found a potential association with diastolic improvement in patients treated with MRAs as assessed by E/E′, deceleration time and E/A ratio, and, in addition, cardiac collagen markers were significantly reduced with MRA therapy.[46,47]

The LVEF spectrum in terms of prognosis and treatment effect was also analysed 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 45–60% ($P = 0.046$ for interaction).

Despite the limitations inherent in post hoc analysis, these data suggest that patients with HFpEF but with lower EF and with impaired contractility are likely to derive more benefit from spironolactone treatment.

Safety

Overall, treatment with spironolactone in TOPCAT was safe. Although the treatment was associated with increased serum creatinine levels and a doubling of the rate of mild hyperkalaemia, there were no significant differences in incidences of severe hyperkalaemia or severe renal dysfunction between the spironolactone and placebo groups.[35]

Overall interpretation of subgroup analysis from heart failure with preserved ejection fraction trials with mineralocorticoid receptor antagonists

Patients with HFpEF and elevated NPs are likely to benefit from spironolactone treatment because this effect was tested in a truly

randomized fashion (within the BNP stratum) and the drug 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 (45–60%) are also more likely to experience positive effects from spironolactone treatment.

Acute heart failure

Data regarding AHF are scarce and largely are not based on randomized evidence. 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) comprising those with acute MI and LVEF of <40%, represents an exception to this, and hence EPHESUS data cannot be generalized to other populations. In the EPHESUS trial, the endpoint of death from cardiovascular causes or hospitalization for cardiovascular events was reduced by 13% in the eplerenone group (HR 0.87, 95% CI 0.79–0.95; P = 0.002) (*Table 1*).

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

Subgroup efficacy

The EPHESUS trial clearly showed that eplerenone is effective in acute MI patients with AHF and LVEF of <40% in comparison with placebo (HR 0.87, 95% CI 0.79–0.95; P = 0.002 for the primary outcome of death from cardiovascular causes or hospitalization for cardiovascular events)[49] (*Table 2*). A subanalysis of EPHESUS data 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 0.67–0.90; P = 0.001) in early initiation and 0.94 (95% CI 0.93–1.06; P = 0.32) in late initiation (P = 0.03 for interaction)].[50] Moreover, data from the EMPHASIS trial also suggest that eplerenone improves survival and prevents readmission in patients in whom the drug is initiated soon after hospital discharge (<42 days).[51] These data support the claim that the acute setting represents a good context in which to initiate MRAs.

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

The ATHENA-HF (Aldosterone Targeted Neurohormonal Combined with Natriuresis Therapy–Heart Failure) trial[55] was a double-blind, placebo-controlled trial, in which 360 patients were randomized to 'usual care' vs. 'usual care' plus 100 mg/day of spironolactone for 72 h within the hospital stay. The hypothesis that treatment with spironolactone would lead to greater reductions in NT-proBNP levels at 96 h was not met and the findings of the ATHENA-HF trial were 'neutral' [change in logNT-proBNP from baseline to 96 h: −0.49 (95% CI −0.98 to −0.14) in the 'usual care' group vs. −0.55 (95% CI −0.92 to −0.18) in the spironolactone group (P = 0.57)]. Other prespecified endpoints of dyspnoea relief, clinical congestion, net urine output, weight loss and clinical events also did not differ between the groups. Nonetheless, spironolactone treatment was found to be safe and not associated with higher rates of hyperkalaemia (K^+ >5.5 mEq/L) or WRF (Butler J., unpublished data). 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 eGFR: 57 mL/min/1.73 m^2). Even more striking were the low mortality rates at 30 days, which amounted to 3.9% (n = 7 deaths) in the placebo group and 2.7% (n = 5 deaths) in the spironolactone group (P = 0.50), supporting the 'low risk' profile of this ADHF population. It is, therefore, unlikely that these patients were at risk of 'diuretic resistance' or offered challenges for effective decongestion or for the initiation of life-saving therapies. In addition, more than 25% of patients in the placebo group had already received baseline spironolactone treatment and continued it during their hospital stay. In this context, the results of the ATHENA-HF trial are as expected. Moreover, spironolactone has an extensive metabolism and slow onset of action (which may take >24 h), and therefore is not an appropriate drug in the acute setting.[56] A more interesting approach would involve the evaluation of i.v. potassium canrenoate in patients with (or prone to) diuretic resistance.[57]

Spironolactone shows promising results in AHF after an acute MI, but did not demonstrate beneficial effects in patients with ADHF without MI. However, as noted above, the ATHENA-HF trial was subject to several limitations and the efficacy and safety of aldosterone antagonists in ADHF should be further explored.

Safety

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

Overall interpretation of subgroup analysis from acute heart failure trials with mineralocorticoid receptor antagonists

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 i.v. administration possibilities) should be tested.

Table 3 Clinical and research implications of subgroup analysis in trials of angiotensin receptor blockers (ARBs) and mineralocorticoid receptor antagonists (MRAs) in heart failure

Clinical implications	Research implications
In heart failure with reduced ejection fraction	
Administer MRAs ideally to all patients (unless contraindicated)	Include higher-risk subgroups (e.g. severe renal dysfunction)
Treat more patients (validate potassium binders/novel MRAs)	Test novel MRAs in populations excluded from previous trials
	Test the management of MRA-induced hyperkalaemia with novel potassium binders in a randomized fashion
	Evaluate prospectively the role of biomarkers (e.g. collagen markers) for a 'personalized approach'
In heart failure with preserved ejection fraction	
Provide MRAs to symptomatic patients with elevated NPs	Test MRAs in more homogeneous populations (e.g. elevated NPs/structural abnormalities on echocardiography)
	Evaluate prospectively the role of biomarkers (e.g. collagen markers) for a 'personalized approach'
In acute heart failure	
Initiate early administration of MRAs	Test higher-risk populations and use aldosterone antagonists in i.v. formulations
Use MRAs for congestion improvement?	
In populations 'at risk'	
Treat risk factors according to current recommendations	Evaluate prospectively the role of biomarkers (e.g. collagen markers) for a 'personalized approach'

NPs, natriuretic peptides.

Clinical implications

Heart failure with reduced ejection fraction

In HFrEF there is at present insufficient evidence to change current guidelines towards a more personalized approach.[32,33] This is a high-risk population in which all measures that increase survival, reduce hospitalization and improve quality of life should be applied. Given the safety and great efficacy of MRAs in this setting, there is little reason (in light of current knowledge) to sub-select HFrEF patients. In contrast, more patients can benefit from MRA treatment as many patients are still undertreated.[58]

The advent of potassium-binding therapies may potentially reassure clinicians about prescribing MRAs to subgroups of patients at high risk for hyperkalaemia.[59–62] However, without adequate prospective evaluation that these potassium binders may actually help to titrate MRA therapy, reduce side effects and improve outcomes, the use of these agents cannot be routinely advocated. Hence, the lack of such evaluation may increase concerns related to risk for hyperkalaemia associated with the use of 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, current data suggest that spironolactone could be provided to symptomatic HFpEF patients (for whom no therapy is currently available) with elevated NPs[36,42] (*Table 3*).

Acute heart failure

All patients with AHF and systolic dysfunction in the context of acute MI should be treated with MRAs unless their use is contraindicated. Given their consistent efficacy and safety in this setting, there is no place for treatment selection based on subgroups.

In patients with ADHF, MRA use did not point towards a beneficial effect. However, other drug formulations (e.g. i.v. canrenoate) and higher-risk populations should be targeted (*Table 3*).

Research implications

Implications for future research are of the utmost importance in the provision of high-quality evidence in RCTs.

Heart failure with reduced ejection fraction (including post-myocardial infarction)

Heart failure with reduced EF is a high-risk condition in which event rates are elevated (high event incidence) and patients are prone to competing risks imposed by factors such as ageing.[63] The use of MRAs effectively reduces those events without increasing life-threatening adverse effects. The NNT to benefit on an absolute scale is very low (NNT: <15 at 2 years) and hence MRA treatment in HFrEF should be inclusive rather than exclusive.[64] To this

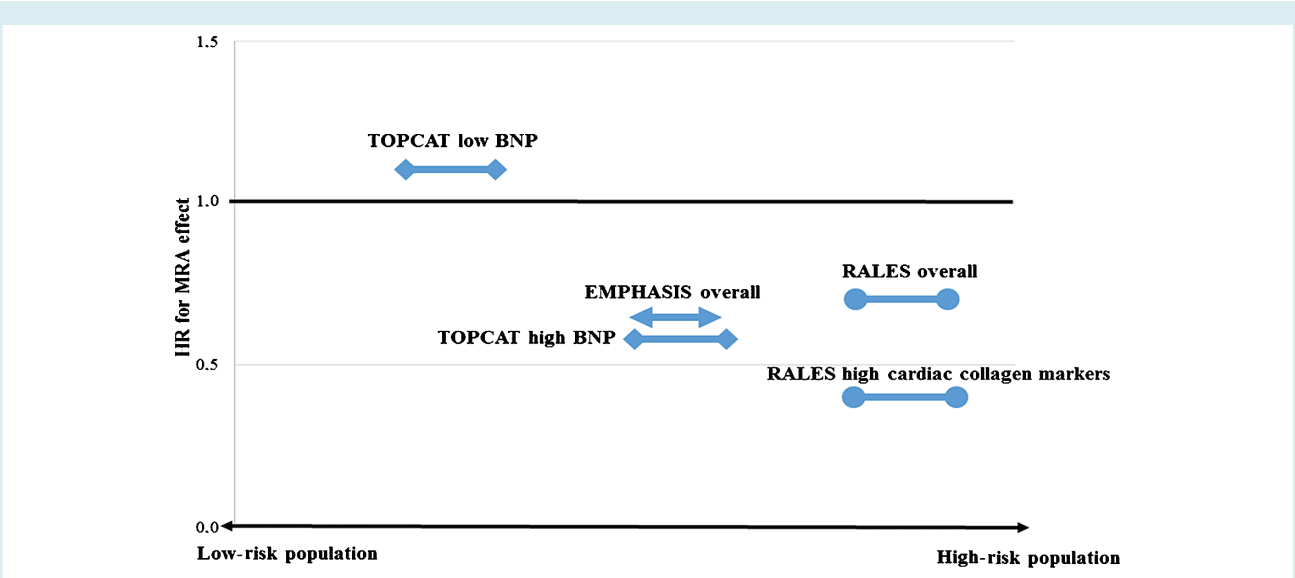

Figure 2 Hazard ratio (HR) for mineralocorticoid receptor antagonist (MRA) treatment according to a population's baseline risk. Estimation of a population's risk is based on event rates in the placebo groups of the respective trials. BNP, brain natriuretic peptide.

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 the use of novel agents such as finerenone and/or the use of potassium binders) (*Table 3* and *Figure 2*).

Given the demonstrated reduction in event rates, and the reproducibility of results, and internal and external validity, it would be unethical to perform another trial of treatment with MRAs vs. placebo in HFrEF. Hence, a novel trial in this setting might compare the new MRA vs. spironolactone or eplerenone in order to demonstrate the superiority of the new treatment or, at least, its non-inferiority and improved safety profile. However, the advent of an adaptive MRA trial may help to determine which patients will derive more benefit from the novel treatment and the findings outlined can help to select this patient population while the trial is ongoing.[34,65]

Heart failure with preserved ejection fraction

Patients with symptomatic HFpEF and elevated NPs are subject to levels of risk similar to those of their HFrEF counterparts. Therefore, future trials should target a more homogeneous population,[38] comprising, for example, symptomatic patients with elevated NPs plus structural abnormalities on echocardiography (LVEF 45–60% 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 HFpEF) and the patients should have a medium–high risk profile in order to allow the observation of a potential treatment effect on an absolute scale (i.e. absolute risk reduction). If the population has a very low level of risk or does not have the disease (as in the case of the Eastern European patients in TOPCAT), the treatment effect will not be apparent as there is little risk to be reduced.[23] Moreover, future HFpEF trials should apply a series of prespecified 'rules' (e.g. echocardiographic parameters, cardiac collagen markers, NP levels, drug compliance, potassium levels and renal function, and monitoring of events) in order to help enrol patients who have the disease, who adhere to treatment, and who have more opportunity to respond to therapy (and suffer less harmful effects) as the trial may be adapted in order to select patients who are likely to benefit more from treatment. However, unless this protocol is prespecified before the trial is initiated, we are likely to lose more opportunities for the development of 'personalized treatments'.

Populations at risk

Populations at risk for HF but without overt HF have a lower baseline risk for major cardiovascular events in comparison with HF populations.[66] Hence, the risk reduction in an absolute scale will necessarily be lower (as TOPCAT clearly demonstrated by enrolling low-risk Eastern European populations in which event rates overlapped those of the age-matched general population[36]) and, in this case, patients likely to benefit from MRA therapy must be carefully selected ('NNT for benefit' vs. 'NNT for harm').[40] For this purpose, attention should focus on prespecified 'response predictors' (as stated above). This approach will possibly avoid overtreatment in lower-risk populations and select patients who are more prone to respond (*Table 3* and *Figure 2*).

Acutely decompensated heart failure

Preliminary data suggest that MRAs are safe in ADHF, but do not point towards potential efficacy. However, improvement in patient population selection and the formulation of the study drug should

be tested before the administration of MRAs is concluded to be futile (*Table 3*).

Ongoing trials in patients at risk of developing heart failure

HOMAGE

The HOMAGE (Heart OMics in AGEing) project aims to validate specific biomarkers of ageing, fibrosis, cardio-myocyte damage and inflammation that allow the stratification of HF patients in order to support the proposition of therapy tailored according to altered signalling pathways (i.e. patients' biomarker profiles). Hence the project will use an innovative 'omic-based' approach that enables the simultaneous investigation of a huge amount of transcripts, proteins and metabolites to set the basis for new ways of preventing HF.[67] This might also allow for the repositioning of MRA therapy as preventive treatment in at-risk patients with co-morbidities in whom the signalling pathways cited above are known to be altered (e.g. patients with obesity and/or chronic kidney disease). To this purpose, a sub-study of HOMAGE will randomize patients at risk for HF to spironolactone or 'usual care' in order to identify those 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 in chronic haemodialysis patients (NCT01848639).

Conclusions

In the absence of formal contraindications and until further RCTs targeting specific subpopulations have been conducted, MRAs should be provided to the great majority of HFrEF patients. Spironolactone should be considered for use in symptomatic HFpEF patients with elevated NP levels. Further trials should target HFrEF patients using the exclusion criteria applied in landmark trials (e.g. severe renal impairment), select more homogeneous HFpEF populations (e.g. with elevated BNP and structural abnormalities on echocardiography), and determine which patients are more likely to benefit from MRAs (e.g. according to prespecified biomarkers).

Acknowledgements

The authors would like to acknowledge the Global CardioVascular Clinical Trialists (CVCT) Forum, 4–6 December 2015, Washington, DC, for providing an opportunity to discuss and develop the contents of the present manuscript.

Conflict of interest: J.P.F. has received board membership fees from Novartis. B.P. is a consultant for Bayer, Merck, AstraZeneca, Takeda, Relypsa, SC Pharmaceuticals, PharMain, KBP Pharmaceuticals, Tricida, Stealth Peptides, DaVinci Therapeutics, Sarfez Pharmaceuticals and Aurasense, and holds stock options in Relypsa, SC Pharmaceuticals, PharMain, KBP Pharmaceuticals, Tricida, DaVinci Therapeutics, Sarfez Pharmaceuticals and Aurasense. F.Z. 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 speaker's fees from Pfizer and AstraZeneca. He is a co-founder of the Cardiorenal Forum. R.J.M. and A.P. have nothing to disclose.

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