True rate of mineralocorticoid receptor antagonists-related hyperkalemia in placebo-controlled trials: A meta-analysis

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Background Mineralocorticoid receptor antagonists (MRA) improve survival in heart failure with reduced ejection fraction but are often underused, mostly due to concerns of hyperkalemia. Because hyperkalemia occurs also on placebo, we aimed to determine the truly MRA-related rate of hyperkalemia.

Methods We performed a meta-analysis including randomized, placebo-controlled trials reporting hyperkalemia on MRAs in patients after myocardial infarction or with chronic heart failure. We evaluated the truly MRA-related rate of hyperkalemia that represents hyperkalemia on MRA, corrected for hyperkalemia on placebo (Pla), according to the equation: True MRA (%) = (MRA (%) – Pla (%))/MRA (%).

Results A total number of 16,065 patients from 7 trials were analyzed. Hyperkalemia was more frequently observed on MRA (9.3%) vs placebo (4.3%) (risk ratio 2.17, 95% CI 1.92-2.45, $P < .0001$). Truly MRA-related hyperkalemia was 54%, whereas 46% were non–MRA related. In trials using eplerenone, hyperkalemia was documented in 5.0% on eplerenone and in 2.6% on placebo ($P < .0001$). In spironolactone trials, hyperkalemia was documented in 17.5% and in 7.5% of patients on placebo ($P = .0001$). Hypokalemia occurred less frequently in patients on MRA (9.3%) compared with placebo (14.8%) (risk ratio 0.58, CI 0.47-0.72, $P < .0001$).

Conclusion This meta-analysis shows that in clinical trials, 54% of hyperkalemia cases were specifically related to the MRA treatment and 46% to other reasons. Therefore, non–MRA-related rises in potassium levels might be underestimated and should be rigorously explored before cessation of the evidence-based therapy with MRAs. (Am Heart J 2017;188:99-108.)

Aldosterone contributes to potassium excretion, sodium retention, and fluid overload by binding to the mineralocorticoid receptor in the kidney[1] and promotes remodeling and fibrosis in chronic heart failure (CHF).[2,3] Mineralocorticoid receptor antagonists (MRAs) such as eplerenone and spironolactone reduced mortality in large randomized, placebo-controlled trials,[4,5] and are strongly recommended in the current heart failure guidelines.[6,7] This applies also for the patients with left ventricular dysfunction (ejection fraction ≤40%) after acute myocardial infarction.[8] Mineralocorticoid receptor antagonists are associated with hyperkalemia as well as renal function decline.[9] Concerns about these adverse effects are common reasons why physicians are reluctant to use MRAs at recommended doses, because potassium values greater than 5.1 mmol/L were associated with increased mortality.[10] Registry data showed that the use of MRAs among eligible patients varies from 9% to 55%, which demonstrates a remarkable underuse of this lifesaving therapy.[11-17] In a considerable number of patients included in controlled clinical trials, hyperkalemia occurred also on placebo. On the other side, low potassium values have been also associated with adverse outcome[10,18] and MRA might prevent the occurrence of hypokalemia. We addressed the question whether the rates of hyperkalemia due to MRA treatment are overestimated or non–MRA-related causes are underestimated, because the numbers of placebo-related hyperkalemia have not been taken into consideration. This is of particular clinical importance because withholding or interruption of MRA application may be associated with a worse prognosis, particularly in heart failure.

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Methods

Study protocol

The meta-analysis is in accordance with the PRISMA statement for meta-analysis.[19] The primary analysis was carried out according to a predefined protocol. We included articles reporting hyperkalemia and/or hypokalemia as adverse effects of MRA therapy in randomized, placebo-controlled studies in patients with arterial hypertension, coronary heart disease, and heart failure. Trials included had to have a minimum of 100 patients in each arm and follow-up of at least 4 weeks. Only trials with the approved MRAs spironolactone and eplerenone were further analyzed. We included only published peer-reviewed articles.

Literature search, selection strategy, and data extraction

We searched PubMed database for articles published until December 2015 and Cochrane library database for articles published until January 2017, using the terms "aldosterone receptor antagonist" and/or "mineralocorticoid receptor antagonist" in combination with "placebo-controlled." To avoid any relevant study to be missed, we crosschecked the identified studies with those referenced in the current European Association of Cardiology guidelines for arterial hypertension, acute myocardial infarction with and without ST-segment elevation, and heart failure.

We performed an additional search for clinical registries reporting hyperkalemia as adverse effects of MRA. These data were used in a sensitivity analysis. We searched in PubMed and Cochrane library database for articles published until January 2017, using the terms "aldosterone receptor antagonist" and/or "mineralocorticoid receptor antagonist" in combination with "registry," as well as using a systematic review regarding this issue as source for relevant articles.[20]

The investigator (D.V.) screened the search results for relevance accordingly to their title and abstract and reviewed the full-text articles considered for study inclusion. Two investigators (D.V., D.L.) extracted data independently from included articles. Any disagreement has been resolved through consultation of a third investigator (M.B.). Authors of the included studies were contacted for further information as needed. We extracted the following items from included articles: data about hyperkalemia and hypokalemia, population (patients with myocardial infarction or heart failure, New York Heart Association (NYHA) functional class when reported, ejection fraction, age, study size), substance (MRA type), duration of average follow-up, and outcome.

Truly MRA-related hyperkalemia

Truly MRA-related hyperkalemia rate presents the attributable fraction of total hyperkalemia among exposed individuals that can be attributed specifically to the exposure.[21,22] Taking the rate of incident hyperkalemia in the MRA groups and in the placebo groups of randomized trials, truly MRA-related hyperkalemia rate (%) was calculated as the difference between the rates of hyperkalemia in patients on MRA and those on placebo (Pla), divided by the total rate of hyperkalemia on MRA:

Truly MRA-hyperkalemia = (MRA-hyperkalemia − Pla-hyperkalemia)/MRA-hyperkalemia.

Statistical analysis

We conducted a meta-analysis of the summary statistics from the individual trials that investigated the effect of MRA treatment compared with placebo. Differences in the occurrence of hyperkalemia and hypokalemia among groups were determined and presented as risk ratios (RRs) with corresponding 95% CIs for each trial. We used RR as a measure of relative risk. The results from each trial were pooled using fixed- or random-effects model as appropriate. Heterogeneity between the trials was assessed using Cochran Q test and I^2 statistic. Relevant statistical heterogeneity was considered as Cochran Q test $P < .05$ and $I^2 > 50\%$. In this case, we used random-effects model. Without relevant statistical heterogeneity between trials, we used the fixed-effects model to estimate combined RR. A potential presence of publication bias was assessed using the Egger regression asymmetry test by estimating the presence of asymmetry in Funnel plot. Study-specific and summary RR and corresponding 95% CIs together with the corresponding p value are figured in the Forest plots. We used Fisher exact test analysis to determine whether there was a difference in the rate of hyperkalemia or hypokalemia between the drug and the placebo arm in each study. To normalize the data for the different length of follow-up in the trials, we calculated the incidence rate ratio. Trials were standardized by multiplying the number of patients in each trial (separately in MRA and placebo groups) with the number of months of follow-up, determining person-month as a person-time data. We also performed a sensitivity analysis to evaluate specific impact of data from individual study on the final results. To evaluate if and to what extent the hyperkalemia on MRA from noninterventional studies match the results obtained from clinical trials, we performed sensitivity analysis by estimating the RR from combined data, that is, by adding the data from registries to data from clinical trials. All statistical analyses were conducted by using StatsDirect version 3.0.150 (Cheshire, UK). All P values were 2-sided, with $P < .05$ considered as significant.

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Results

Initially, we identified 682 potentially appropriate trials. After reviewing the titles and abstracts, 665 trials were