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**Routine Spironolactone in Acute Myocardial Infarction - the CLEAR Trial**

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**Abstract**

**Background:** Mineralocorticoid receptor antagonists have been shown to reduce mortality in patients post myocardial infarction with congestive heart failure. It is uncertain if routine spironolactone use is beneficial post myocardial infarction.

**Methods:** Using a 2-by-2 factorial design at 104 centers in 14 countries, we randomly assigned 7,062 patients post-myocardial infarction to receive either spironolactone or placebo (reported here) and colchicine or placebo. The co-primary outcomes were co-primary 1: the total number of cardiovascular deaths or new or worsening heart failure events or co-primary 2: the composite of the first occurrence of cardiovascular death, myocardial infarction, stroke or new or worsening heart failure.

**Results:** Out of 7,062 participants, only 45 (0.6%) had an unknown vital status, . For co-primary outcome 1, there were 183 events (1.7 per 100 patient years) in the spironolactone group and 220 events (2.1 per 100 patient years) in the placebo group over a median follow-up of three years (competing risk hazard ratio 0.91; 95% confidence interval (CI) 0.69-1.21, p=0.51). The co-primary outcome 2 occurred in 280 of 3537 patients (7.9%) in the spironolactone group and 294 of 3525 patients (8.3%) in the placebo group (hazard ratio 0.95; 95% CI 0.80-1.12, p=0.52). Serious adverse events were reported in 7.2% of patients in the spironolactone group and 6.8% in the placebo group.

**Conclusion:** Post myocardial infarction, spironolactone, did not reduce either co-primary outcomes.

**Trial registration:** ClinicalTrials.gov number NCT03048825

Inhibition of the renin-angiotensin-aldosterone system with an angiotensin converting enzyme inhibitor improves outcomes in post-myocardial infarction patients.[1,2] Higher aldosterone levels have been associated with increased mortality after a myocardial infarction.[3] Aldosterone antagonism with spironolactone has been shown to reduce mortality in patients with chronic heart failure with reduced ejection fraction, and is a cornerstone of therapy.[4] Aldosterone antagonism also reduces heart failure in patients with preserved ejection fraction and heart failure. [5]

Aldosterone antagonism with eplerenone has been shown to improve outcomes in acute myocardial infarction patients in heart failure with reduced ejection fraction, but it remains uncertain whether aldosterone antagonism is beneficial in all post-myocardial infarction patients.[6] Recent attempts to improve outcomes with intensified renin-angiotensin-aldosterone inhibition have not shown improvements in outcomes.[7,8] A trial of routine aldosterone antagonism with spironolactone in addition to standard therapy in 1603 post-myocardial infarction patients without heart failure showed no improvement in outcomes.[9] However, there was a significant reduction of mortality in the ST-elevation myocardial infarction subgroup (n=1229), identifying the need for a large trial. Finally, an additional randomized trial in STEMI patient without heart failure showed eplerenone reduced B-Type Natriuretic peptide levels.[10]

We conducted the CLEAR trial to evaluate if routine spironolactone use is beneficial in patients post myocardial infarction.

## Methods

### Study Design

The CLEAR trial was an international, investigator-initiated, multicenter, prospective, randomized placebo-controlled, 2x2 factorial design trial of spironolactone versus placebo and colchicine versus placebo in patients with acute myocardial infarction. We previously published details of the trial design.[11] This report focuses on comparisons of spironolactone and placebo; the results of comparisons of colchicine and placebo were reported separately.[12] All participants, investigators, healthcare providers, data collectors and outcome adjudicators were blinded to treatment allocation. A stent registry for SYNERGY stents in ST-elevation myocardial infarction (STEMI) was embedded within the trial (N=733) and has been published.[13]

Initially, patients were only eligible if they had STEMI and underwent percutaneous coronary intervention (PCI). To increase recruitment, the steering committee modified the protocol on April 5, 2020, to enroll patients with large non-ST-elevation myocardial infarction (NSTEMI) who had PCI plus one or more of the following risk criteria: (1) left ventricular ejection fraction ≤45%, (2) diabetes mellitus, (3) multivessel coronary artery disease defined as a ≥50% stenosis in a second major epicardial vessel, (4) prior myocardial infarction, or (5) age >60 years. The detailed eligibility criteria are provided in Table S1.

Ethics committees of participating centers and national regulatory authorities approved the trial. All patients provided written informed consent. The Population Health Research Institute at McMaster University and Hamilton Health Sciences in Hamilton, Canada, coordinated the trial, collected and held all trial data, and conducted all analyses. The steering committee designed the trial protocol and vouched for the integrity and completeness of data and analyses. The trial funders had no role in the design and conduct of the trial. An independent Data and Safety Monitoring Committee monitored the accumulating safety and efficacy data.

**Randomization**

Patients were randomized as soon as possible after the index PCI, in a factorial 1:1:1:1 allocation to receive spironolactone/colchicine, spironolactone placebo/colchicine, spironolactone/colchicine placebo or spironolactone placebo/ colchicine placebo, as soon as possible after the index PCI. Randomization was performed using permuted blocks within a 24-hour computerized central system at the Population Health Research Institute. Randomization was stratified by study center and whether the patient had a STEMI or NSTEMI.

**Outcomes**

The co-primary efficacy outcomes were total events of cardiovascular death or new or worsening heart failure (co-primary 1) and time-to-first occurrence

of the composite of cardiovascular death, myocardial infarction, stroke or new or worsening heart failure (co-primary 2). Total events look at the totality of intervention as they include recurrent events. Key secondary outcomes were 1) time-to-first occurrence of the composite of cardiovascular death, new or worsening heart failure or significant ventricular arrhythmia, 2) time-to-first occurrence of cardiovascular death and 3) time-to-first occurrence of the composite of cardiovascular death or new worsening heart failure.

A committee of clinicians blinded to the treatment allocation adjudicated all the primary outcome events, major bleeding, and stent thromboses. A blinded angiographic core laboratory at the Population Health Research Institute reviewed all ischemia-driven revascularizations and stent thromboses. The detailed definitions of outcomes are available in the supplementary appendix (Table S2).

**Trial interventions**

Study drugs were spironolactone tablets of 25 mg and colchicine tablets of 0.5 mg with matching placebos for each. Tiofarma, The Netherlands, provided both study drugs with raw materials produced by Indena S.p.A., Milan, Italy.

**Statistical Considerations**

The initial sample size calculation for cardiovascular death or new or worsening heart failure was based on a time-to-event analysis with an anticipated control event rate of 15% at three years, 80% power, a 2-sided type 1 error level

of 5%, a 2% loss to follow-up in both arms, study drug discontinuation of 12.5%, and the assumption of no interaction with colchicine. Based on the above assumptions, it was estimated that 4,000 participants (an expected 512 events) were needed to detect a 25% relative risk reduction using a log-rank test. In April 2020, an interim analysis of blinded event rates by SFL showed a 3% per year event rate and modelled that event rate to 9% at 3 years, which was consistent with several recent trials.[14] As a result, the sample size was increased from 4,000 to 7,000 patients to maintain study power of 80%, which would result in an estimated 546 events, which would be sufficient to detect a 25% relative risk reduction at 80% power. The sample size was increased without knowledge of any treatment effects.

In October 2023, blinded analysis showed an overall event rate of time to first event for composite of cardiovascular death and new or worsening heart failure of 4%. As a result, in December 2023, given the lower-than-expected event rates, we decided to proceed with co-primary outcomes but preserve the type 1 error rate at 5%. The type 1 error rate was partitioned to 4% for co-primary 1 and 1.85% for coprimary 2, considering the overlap of 57% based on the overall blinded data between the two co-primary outcomes. With 7,000 study participants, we estimated power of 84% to detect a relative risk reduction of 31.5%, assuming a control rate of 6% (357 events) over three years using the Prentice-Williams-Peterson model for co-primary 1. Furthermore, we estimated power of 80% to

detect a 26% relative risk reduction, assuming a control rate of 10.5% (644 events) over three years, using a log-rank test for co-primary 2.

The pre-specified primary analysis was performed using the intention-to-treat principle. Co-primary 1 (cardiovascular death or new or worsening heart failure) was analyzed as total events using the Prentice-Williams-Peterson conditional gap model. Co-primary 2 (cardiovascular death, myocardial infarction, stroke or new or worsening heart failure) was analyzed as a time-to-first-event using the log-rank test for the P-value and a stratified (by allocation to colchicine and MI type) and Cox proportional hazards model for the effect size and 95% confidence intervals. A post hoc analysis requested by the journal using the Ghosh and Lin for the total events and the Fine-Gray sub distribution hazard model for the time-to first were used to account for competing risks and are reported in the manuscript. Secondary outcomes were analyzed using the same approach. The widths of the confidence intervals have not been adjusted for multiplicity, and that the intervals may not be used in place of hypothesis testing. An interaction between factorial treatment groups was not expected but was tested to be tested at a 5% significance level. The safety outcomes were analyzed with on-treatment analysis.

The data monitoring committee reviewed unblinded data for two interim analyses for efficacy on Oct 12, 2021 and Oct 17, 2022 (see supplement for further details).

In addition, the systolic blood pressure and diastolic blood pressure were analyzed using a linear mixed model with repeated measures, adjusted for the baseline value, and the least square (LS) mean with standard error (SE) and mean difference (MD) with 95% CI were reported.

**Subgroup Analyses**

The pre-specified subgroups were analyzed using the Cox regression model with an interaction term for the subgroup. The pre-specified subgroups were i) age ≥65 versus <65 years (hypothesized consistent effect), ii) female versus male (hypothesized consistent effect), iii) anterior STEMI versus other MI (hypothesized greater benefit in anterior STEMI), iv) baseline serum potassium concentration <4 mmol/L and ≥4 mmol/L (hypothesized greater benefit <4 mmol/L), v) history of hypertension versus no history of hypertension (hypothesized greater benefit for hypertension), vi) pre, during and post-Covid pandemic phases (hypothesized reduced effect during Covid pandemic). Geographic region (North America versus Europe versus Other) was added as a post hoc subgroup to demonstrate consistency. We did not collect information about left ventricular ejection fraction (LVEF) and are not able to report results of subgroups based on LVEF.

**Sensitivity analyses**

We undertook a pre-specified on-treatment analyses excluding patients who discontinued the study drug on the same day of randomization and censored patients seven days after permanent study drug discontinuation.

**Results**

Between February 1, 2018 and November 8, 2022, 7062 participants were enrolled from 104 centers in 14 countries. Of these, 3537 were randomized to spironolactone and 3525 to placebo (figure S1). Out of 7,062 participants, only 45 (0.6%) had an unknown vital status. Given that the missing data was rare and evenly distributed between the spironolactone and placebo groups the missingness is likely to be at random. Baseline characteristics were well balanced between the groups, with mean age was 61 years and 20.4% of patients were female (Table 1). Approximately 9% had prior myocardial infarction, 0.8% had a history of heart failure, and 19% had diabetes mellitus. Most randomized patients had STEMI (95%), and 5% had NSTEMI.

The median time from onset of myocardial infarction to randomization was 26.8 hours (interquartile range [IQR], 15.9 – 42.4), and the median time from randomization to the first dose of the study drug was 2.1 hours (IQR, 0.7 – 9.2). The discharge medications were similar in the two groups (Table 1).

The median duration of therapy was three years (IQR, 2.14 – 3.71), and the study drug was discontinued in 28.0% of patients allocated to spironolactone and

24.4% to placebo. Open label spironolactone was used instead of study drug by treating physician was prescribed in 140 (4.0%) in spironolactone group and 166 (4.7%) in the placebo group.

### Blood Pressure

The LS mean (SE) of the SBP at year 1, adjusted for baseline, was 126.9 (0.3) in 2724 patients randomized to Spironolactone and 129.7 (0.3) in 2672 patients randomized to Placebo, with a MD (95% CI) of -2.8 (-3.6, -2.0). The LS mean (SE) of the DBP at year 1, adjusted for baseline, was 77.5 (0.2) in 2717 patients randomized to Spironolactone and 78.9 (0.2) in 2660 patients randomized to Placebo, with a MD (95% CI) of -1.3 (-1.8, -0.8). A similar trend was observed at all time points.

## Efficacy

For co-primary outcome 1, there were 183 events (1.7 per 100 patient years) in the spironolactone group compared with 220 events (2.1 per 100 patient years) in the placebo group (hazard ratio [HR], 0.89; 95% CI 0.73-1.08; P=0.23,) (Table 2, Figure 1a, Table S3). Co-primary outcome 2 occurred in 280 of 3537 patients (7.9%) in the spironolactone group compared with 294 of 3525 patients (8.3%) in the placebo group (hazard ratio [HR], 0.95; 95% CI 0.80-1.12; P=0.52, competing risks HR 0.96; 95% CI 0.81-1.13) (Table 2, Figure 1b, table S3). The

colchicine factorial had no significant effect on the spironolactone versus placebo co-primary outcome 1 or 2 (P=0.23 and 0.80 for interactions, respectively).

Cardiovascular mortality was similar (3.2% spironolactone versus 3.3% placebo; HR, 0.98; 95% CI 0.76-1.27, competing risks HR 0.98, 95% CI 0.76-1.27) (Table 2). New or worsening heart failure occurred in 58 (1.6%) in the spironolactone group, compared with 84 (2.4% in the placebo group (HR, 0.69; 95% CI 0.49-0.96, competing risk HR 0.77; 95% CI 0.51-1.16).

The baseline characteristics for on-treatment analyses for both groups were well balanced and shown in table S4. The on-treatment analyses for spironolactone co-primary 1 had 131 events in the spironolactone group versus 179 events in the placebo group, (HR 0.79; 95% CI 0.63-1.00) and co-primary 2 outcome occurred in 204 (5.8%) spironolactone versus 250 (7.2%) placebo, (HR 0.83; 95% CI 0.69-1.00) supplementary online appendix (Table S5). The co-primary outcomes were consistent across all pre-specified subgroups (figure S1 and S2).

**Safety**

Hyperkalemia (serum potassium >5.5 mmol/L), leading to discontinuation of the study drug, occurred in 39 (1.1%) of the spironolactone group and 20 (0.6%) of the placebo group (table 3). Renal death, dialysis, transplant or sustained ≥40% drop in eGFR occurred in 37 (1.0%) spironolactone patients and 44 (1.2%) placebo patients (odds ratio 0.84; 95% CI 0.54-1.30).

(Table 2) Sustained ≥40% drop in eGFR occurred in 32 (0.9%) spironolactone patients and 38 (1.1%) placebo patients (odds ratio 0.84; 95% CI 0.52-1.34)(Table 2), The mean glomerular filtration rate (eGFR) during follow-up was lower in the spironolactone group than in the placebo group (89.0 [SD 16.8] ml per minute per 1.73 $m^2$ versus 90.6 [SD 16.1] ml per minute per 1.73 $m^2$, $p<0.001$). Gynecomastia was more common with spironolactone 81 (2.3%) compared with placebo 19 (0.5%), $p<0.001$. (Table 3)

**DISCUSSION**

In post-myocardial infarction patients, spironolactone, as compared to placebo, did not reduce the total events of cardiovascular death or new or worsening heart failure and the composite of cardiovascular death, recurrent MI, stroke or new or worsening heart failure over a median follow-up of three years.

The RALES trial randomized 1,663 patients with NYHA 3 or 4 chronic heart failure and reduced ejection fraction (≤35%) to spironolactone versus placebo.[4] There was a 30% reduction in all-cause mortality (primary outcome) and a 35% reduction in hospitalization for heart failure. The EPHESUS trial randomized 6,642 patients post myocardial infarction who had an ejection fraction less than 40% and either heart failure or diabetes mellitus to eplerenone versus placebo.[6] Eplerenone use resulted in a 15% relative risk reduction for both all-cause mortality and hospitalization for heart failure. In contrast, the ALBATROSS trial randomized 1,603 post-MI patients without heart failure to spironolactone versus

placebo and did not show a reduction in events with spironolactone. Finally, an additional randomized trial in STEMI patient without heart failure showed eplerenone reduced B-Type Natriuretic peptide levels and a meta-analysis suggested benefit in patients post myocardial infarction without heart failure.[10,15,16]

A recent trial with angiotensin- neprilysn inhibitors post myocardial infarction (N=5661) did not show significant reductions in the primary outcome of time to first cardiovascular death or heart failure.[8] However, an exploratory analysis showed a reduction in total events.[17] A recent trial of empagliflozin post myocardial infarction (N=3620) did not show a reduction in death or hospitalization for heart failure but did show a reduction in heart failure events.[18] These findings are similar to our trial and highlight the challenges in improving outcomes in the modern era post myocardial infarction. We did not demonstrate a reduction in mortality with spironolactone.,Our results are consistent with the findings of prior trials of a point estimate for areduction in heart failure events with spironolactone. The lack of a statistically significant impact on mortality may relate to improvements in clinical care over the last two decades, resulting in overall lower mortality post myocardial infarction and a reduction in study power. Furthermore, trials of mineralocorticoid antagonists in patients with heart failure and preserved ejection fraction showed similar findings with reductions in heart failure but no impact on mortality.[5]

The on treatment analysis is hypothesis generating that with increased compliance and less discontinuation, a benefit may exist that should be tested in future trials.

The newer selective non-steroidal mineralocorticoid antagonist finerenone has been examined in several trials. In a pooled analysis of two trials examining finerenone in chronic kidney disease (N = 13,026), finerenone, compared to placebo, reduced the composite of CV death, MI, stroke or hospitalization for heart failure (HR 0.86; 95% CI 0.78-0.95) driven primarily by a reduction in hospitalization for heart failure (HR 0.78; 95% CI 0.66-0.92).[19] Furthermore, finerenone, has been shown in a randomized trial of 5734 patients to prevent the composite of kidney failure, a sustained decrease of at least 40% in the eGFR from baseline, or death from renal causes in patients with established renal disease (hazard ratio, 0.82; 95% confidence interval [CI], 0.73 to 0.93).[20] These findings suggests that a selective non-steroidal mineralocorticoid antagonist can be renally protective and reduce heart failure.

**Limitations**

First, based on the 95% CI of the primary outcome results, we cannot exclude a beneficial relative risk reduction of 27% or smaller that could be clinically important. Second, despite the increases in sample size, the event rates were lower than planned and we cannot rule out type 2 error due to reduced power. Third, women and visible minorities were underrepresented in the trial

compared to the incidence of disease worldwide. Fourth, our discontinuation rate was higher than anticipated, which may have reduced our power, especially given the findings of the on-treatment analysis. Fifth, we cannot rule out that the side effects of colchicine in the factorial may have adversely affected the discontinuation of the spironolactone study drug in the factorial design.

In conclusion, in patients post myocardial infarction, spironolactone did not reduce a broad composite of cardiovascular outcomes;

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**Table 1. Baseline and procedural characteristics**

| | Spironolactone N= 3537 | | Placebo N= 3525 | |
|---|---|---|---|---|
| **Demographics** | | | | |
| Age, years (mean ±SD) | 60.9 | (10.3) | 60.4 | (10.3) |
| Age > 75 yr (%) | 294 | (8.3) | 277 | (7.9) |
| Female (%) | 760 | (21.5) | 678 | (19.2) |
| Killip ≥2 Heart failure at randomization (%) | 24 | (0.7) | 24 | (0.7) |
| Geographic Region | | | | |
| North America | 1009 | (28.5) | 1013 | (28.7) |
| Europe | 2366 | (66.9) | 2349 | (66.4) |
| Other | 162 | (4.6) | 163 | (4.6) |
| NSTEMI at presentation | 168 | (4.7) | 181 | (5.1) |
| STEMI at presentation | 3369 | (95.3) | 3344 | (94.9) |
| **Location of STEMI** | | | | |
| Anterior (%) | 1315 | (39.0) | 1315 | (39.3) |
| Inferior (%) | 1942 | (57.6) | 1890 | (56.5) |
| Lateral (%) | 434 | (12.9) | 423 | (12.6) |
| Posterior (%) | 328 | (9.7) | 332 | (9.9) |
| **History** | | | | |
| Previous heart failure (%) | 24 | (0.7) | 35 | (1.0) |
| Current smoker (%) | 1440 | (40.7) | 1444 | (41.0) |
| Hypertension (%) | 1600 | (45.2) | 1633 | (46.3) |

| | | | | |
|---|---|---|---|---|
| Diabetes Mellitus (%) | 630 | (17.8) | 673 | (19.1) |
| Prior myocardial infarction (%) | 321 | (9.1) | 312 | (8.9) |
| Prior percutaneous coronary intervention (%) | 356 | (10.1) | 353 | (10.0) |
| **Medications at discharge** | | | | |
| Aspirin | 3417 | (96.6) | 3416 | (96.9) |
| Clopidogrel | 1499 | (42.4) | 1476 | (41.9) |
| Ticagrelor | 1596 | (45.1) | 1586 | (45.0) |
| Prasugrel | 393 | (11.1) | 401 | (11.4) |
| ACE inhibitor or ARB | 2745 | (77.6) | 2773 | (78.7) |
| Statin | 3408 | (96.4) | 3416 | (96.9) |
| SGLT2 inhibitor | 113 | (3.2) | 98 | (2.8) |
| **Initial PCI procedure** | | | | |
| Bare-metal stent* | 11 | (0.2) | 9 | (0.2) |
| ≥1 drug-eluting stent* | 4667 | (96.1) | 4646 | (96.0) |
| Angioplasty only* | 149 | (3.1) | 162 | (3.3) |
| Multivessel coronary disease | 1725 | (48.8) | 1752 | (49.7) |
| Intra-aortic balloon pump (%) | 46 | (1.3) | 48 | (1.4) |

***Total number of stents 9695 with 4854 for Spironolactone vs. 4841 for Placebo.**

**Table 2: Primary and Secondary Outcomes analysis using competing risks**

| | Spironolactone (n=3537) (%) | Placebo (n=3525) (%) | Competing risk Hazard Ratio | 95% CI | P Value |
|---|---|---|---|---|---|
| **Co-Primary outcomes** | | | | | |
| Co-primary 1*:CV death or new or worsening heart failure | 183 (1.7) | 220 (2.1) | 0.91 | (0.69-1.21) | 0.51 |
| Co-Primary 2: CV death, MI, stroke or new or worsening heart failure | 280 (7.9) | 294 (8.3) | 0.96 | (0.81-1.13) | 0.60 |
| Components of primary outcome | | | | | |
| CV death | 114 (3.2) | 116 (3.3) | 0.98 | (0.76-1.27) | |
| Recurrent MI | 106 (3.0) | 107 (3.0) | 1.02 | (0.77-1.35) | |
| Stroke | 51 (1.4) | 42 (1.2) | 1.15 | (0.72-1.84) | |
| New or worsening heart failure | 58 (1.6) | 84 (2.4) | 0.77 | (0.51-1.16) | |
| Other outcomes | | | | | |
| CV death, new or worsening heart failure or significant arrythmia | 173 (4.9) | 186 (5.3) | 0.95 | (0.77-1.17) | |
| Significant arrythmia | 20 (0.6) | 17 (0.5) | 1.45 | (0.67-3.12) | |
| All cause death | 166 (4.7) | 175 (5.0) | 0.95 | (0.77-1.17) | |
| Renal outcome**# | 37 (1.1) | 44 (1.2) | 0.84 | (0.54-1.30) | |
| Renal death | 4 (0.1) | 4 (0.1) | | | |
| Dialysis or renal transplant | 1 (0.03) | 2 (0.1) | | | |

| | | | | |
|---|---|---|---|---|
| Peristent drop in eGFR ≥40%** | 32 (0.9) | 38 (1.1) | 0.84 | (0.52-1.34) |
| Atrial Fibrillation | 93 (2.6) | 87 (2.5) | 1.14 | (0.84-1.55) |

***Co-primary 1 is total events with number of event per 100 patient years**

**** logistic regression; odds ratio reported instead of HR**

******* widths of the intervals have not been adjusted for multiplicity and may not be used in place of hypothesis testing

#Renal outcome was defined as: death related to renal causes, dialysis, renal transplant or a sustained drop ≥40% eGFR

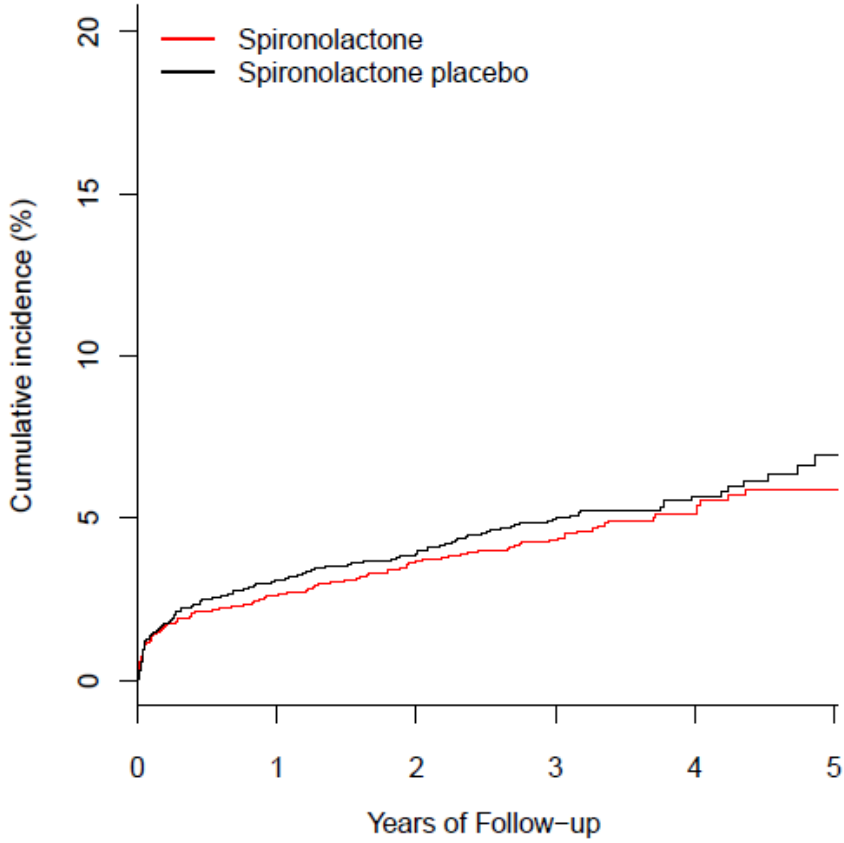
**Table 3: Adverse Events**

| | Spironolactone (n=3537) (%) | Placebo (n=3525) (%) | P value |
|---|---|---|---|
| Serious Adverse Events | 255 (7.2) | 241 (6.8) | 0.54 |
| Hyperkalemia K>5.5 mmol/L leading to study | 39 (1.1) | 20 (0.6) | 0.01 |

| | | | |
|---|---|---|---|
| drug discontinuation | | | |
| Adverse events | 1157 (32.7) | 1086 (30.8) | 0.09 |
| Hypotension | 38 (1.1) | 29 (0.8) | 0.28 |
| Orthostatic hypotension | 16 (0.5) | 7 (0.2) | 0.06 |
| Breast tenderness | 20 (0.6) | 2 (0.1) | <0.001 |
| Gynecomastia | 81 (2.3) | 19 (0.5) | <0.001 |

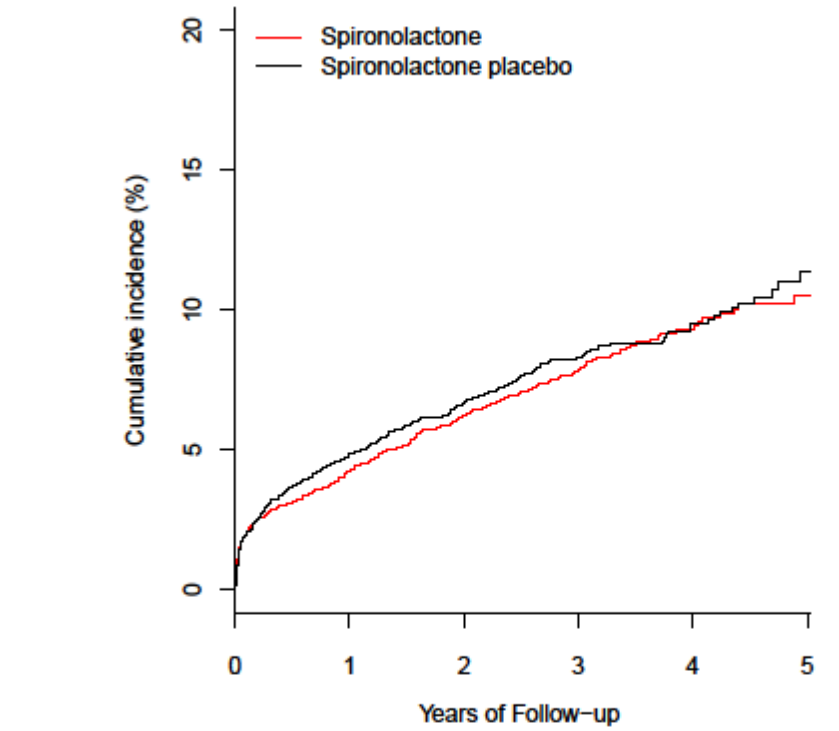
Figure Legends

**Figure 1a:** Kaplan Meier event curves for CV death, new or worsening heart failure (total events)




| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Spironolactone | 3537 | 3422 | 2788 | 1778 | 704 | 183 |
| Placebo | 3525 | 3392 | 2785 | 1754 | 735 | 194 |

**Figure 1b: Kaplan Meier curves for CV death, MI, stroke or new or worsening heart failure**




| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Spironolactone | 3537 | 3365 | 2712 | 1721 | 681 | 173 |
| Placebo | 3525 | 3331 | 2707 | 1695 | 707 | 184 |

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