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Timing of Statistical Benefit of Mineralocorticoid Receptor Antagonists Among Patients With Heart Failure and Post-Myocardial Infarction

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1 **Timing of Statistical Benefit of Mineralocorticoid Receptor Antagonists Among Patients**
2 **with Heart Failure and Post-Myocardial Infarction**

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- 43 Non-standard Abbreviations and Acronyms:
- 44 CI confidence interval
- 45 HF Heart failure
- 46 HFpEF Heart failure with preserved ejection fraction
- 47 HFrEF Heart failure with reduced ejection fraction
- 48 HR hazard ratio
- 49 LVEF Left ventricular ejection fraction
- 50 MI myocardial infarction
- 51 MRA mineralocorticoid receptor antagonist
- 52 NYHA New York Heart Association
- 53

54 Heart failure (HF) with reduced ejection fraction (HFrEF) and preserved ejection fraction
55 (HFpEF), and myocardial infarction (MI) complicated with systolic dysfunction have a poor
56 prognosis. Mineralocorticoid-receptor antagonists (MRAs) reduce morbidity or mortality in these
57 syndromes, but MRAs remain underutilized. Understanding the timing of benefit may help
58 clinicians better understand the treatment effect and motivate them to prescribe MRAs.
59 Therefore, we investigated the treatment effect of MRAs over time by conducting a post-hoc
60 analysis of four trials in three clinical scenarios: 1) HFrEF: pooled cohort of Randomized
61 Aldactone Evaluation Study (RALES)¹ and Eplerenone in Patients with Systolic Heart Failure
62 and Mild Symptoms (EMPHASIS-HF),² 2) HFpEF: Spironolactone for Heart Failure with
63 Preserved Ejection Fraction (TOPCAT)-Americas,³ and 3) post-MI complicated by LV
64 dysfunction: the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and
65 Survival Study (EPHESUS).⁴

66 The clinical characteristics of these trials were as follows: RALES (n=1,663;
67 spironolactone vs placebo; New York Heart Association [NYHA] class III–IV with left
68 ventricular ejection fraction [LVEF] $\leq 35\%$); EMPHASIS-HF (n=2,737; eplerenone vs. placebo;
69 NYHA class II with LVEF $\leq 35\%$); TOPCAT-Americas (n=3,445; spironolactone vs. placebo;
70 HF signs and symptoms with LVEF $\geq 45\%$); and EPHESUS (n=6,632; eplerenone vs placebo; 3-
71 14 days post-MI with diabetes or complicated by HF signs/symptoms or LVEF $\leq 40\%$). While
72 RALES and EMPHASIS-HF enrolled patients with more and less severe HF symptoms
73 (respectively), they were pooled together as they both enrolled patients with HFrEF. Hazard
74 ratios (HR) were calculated on each day following randomization until the last observation of the
75 last patient using the Cox proportional hazards model. All events until the respective day were
76 considered. Patients without any events were censored at the respective day. We assessed the

77 treatment effect of MRAs over time from initiation and assessed when the HR and the 95%
78 confidence interval (CI) for the treatment effect of MRA versus placebo first crossed unity and
79 reached and maintained statistical significance based on a p-value of <0.05. Our primary
80 outcome was the composite of cardiovascular (CV) death or HF hospitalization (HHF). We also
81 evaluated time to statistically significant benefit for HHF and all-cause death. Data supporting
82 this study will not be available from the corresponding author.

83
84 The pooled cohort of RALES and EMPHASIS-HF included a total of 2,186 participants
85 in the MRA arms and 2,214 participants in the placebo arms. TOPCAT-Americas included 886
86 participants in the MRA arm and 881 in the placebo arm. EPHESUS included 3319 in the MRA
87 arm and 3313 in the placebo arm. The median age of the pooled cohort of patients with HFrEF
88 was 68 (IQR 12), 24.0% were female, and the median LVEF was 27%. In TOPCAT-Americas,
89 the median age was 72 (IQR 15), 49.9% were female, and the median LVEF was 58%. In
90 EPHESUS, the median age was 65.0 (18.0) and 28.9% were female, and the median LVEF was
91 33%.

92 For the pooled HFrEF cohort, significant statistical reduction in cardiovascular death or
93 hospitalization was observed after 19 days (Figure 1). The timing of significant statistical
94 reduction for HHF was 11 days, 122 days for all-cause death, and 332 for CV death. In
95 TOPCAT-Americas, statistical reduction was observed later: on day 208 for the primary
96 outcome and day 224 for HHF. For EPHESUS, the timing of statistical reduction for the primary
97 outcome was seen on day 7, 84 days for HHF, 10 days for all-cause death, and 9 days for CV
98 death (Figure 1).

99

100 This study is one of the first to determine the timing of significant reduction in mortality
101 and hospitalizations after MRA initiation in HFrEF and HFpEF. A Pitt et al. study on timing to
102 benefit in EPHEBUS found a 13% reduction within 30 days after randomization.⁵ These
103 differences are due to contrasting approaches to the study question; Pitt et al adopted a pre-
104 specified analysis studying the effect at the 30 day mark, whereas we analyzed the treatment
105 effect until the point of statistical significance.

106
107 We present evidence of early significant benefit of MRA initiation in patients with
108 HFrEF and those who are post-MI complicated by systolic dysfunction, heart failure or diabetes.
109 Our analysis suggests a longer time horizon of statistical significance in the HFpEF population
110 compared to HFrEF. While this may reflect differences in pathophysiology between HFrEF and
111 HFpEF, this more likely reflects differences in event rates seen across trials.

112
113 Our study has a few limitations to consider, namely those inherent to post-hoc analyses.
114 With the available sample size and event rates, the TOPCAT-Americas cohort is likely
115 underpowered, thereby showing a more delayed achievement of statistical significance. Our
116 analysis is also not powered to determine time interactions with response to therapy over time
117 and we did not adjust for multiple comparisons.

118
119 Understanding when treatment benefits become statistically significant may motivate
120 clinicians to introduce MRAs in the treatment course of people (both in the in- and out-patient
121 setting) with HFrEF, HFpEF, and those who are post-MI with systolic dysfunction, HF, or
122 diabetes.

123
124

125 FIGURES

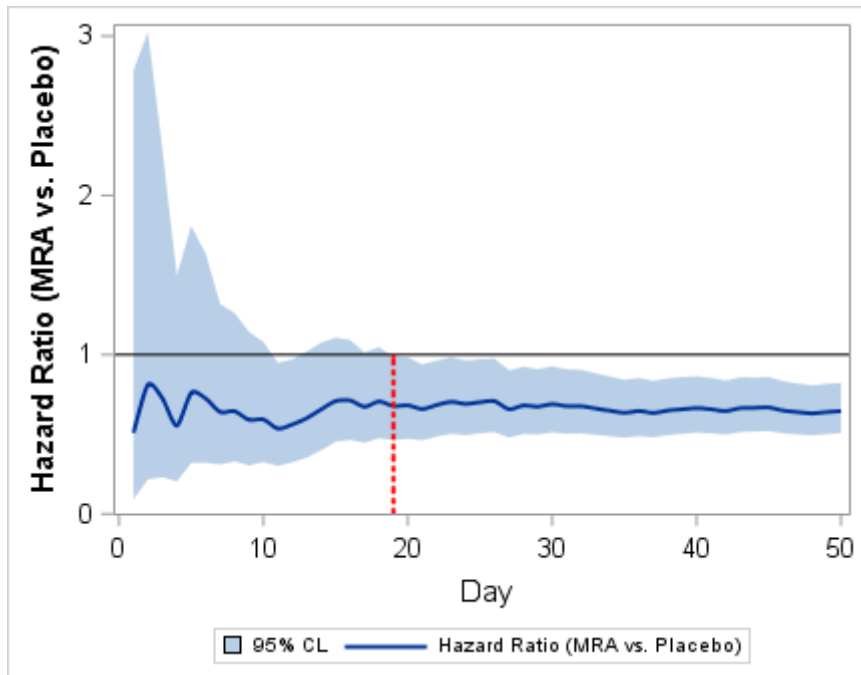
126

127 Figure 1: Timing of statistical demonstration of benefit of mineralocorticoid receptor antagonist
128 versus placebo for cardiovascular mortality or hospitalization for heart failure

129

130 A. Pooled cohort of the Randomized Aldactone Evaluation Study (RALES) and Eplerenone in
131 Patients with Systolic Heart Failure and Mild Symptoms (EMPHASIS-HF).

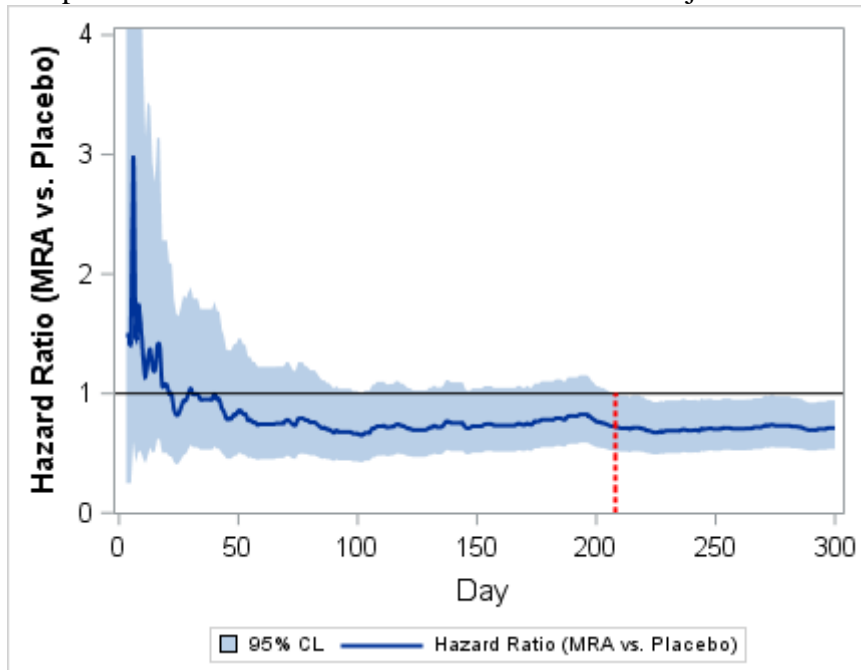
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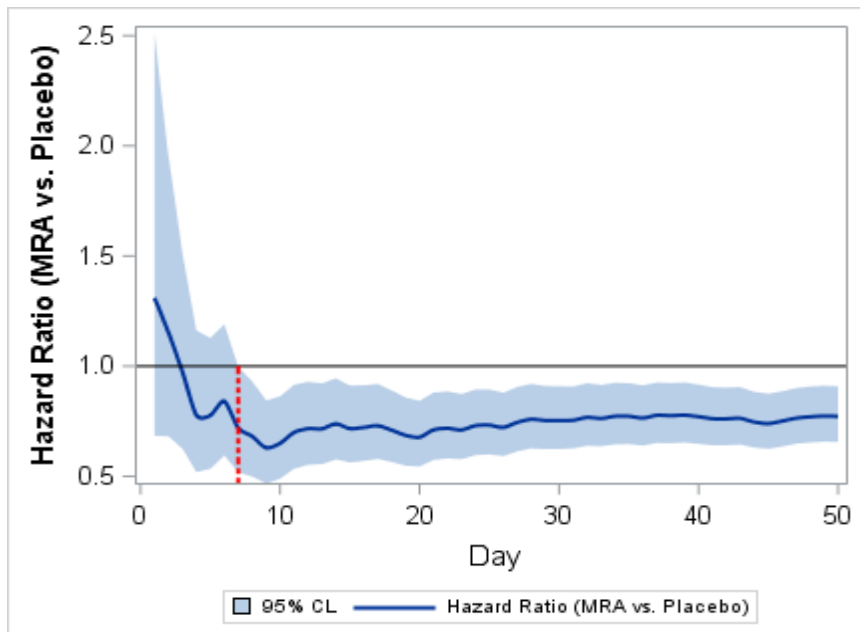
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135 B. Spironolactone for Heart Failure with Preserved Ejection Fraction (TOPCAT-Americas)



136

137 C. Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study
138 (EPHESUS) trial
139



140
141
142 Legend: The primary outcome for this analysis was CV death or HHF. CV cardiovascular. HHF
143 Heart failure hospitalization. In the pooled-cohort, benefit was seen by day 19. In TOPCAT-
144 Americas., the benefit for CV death or HHF was seen on day 208. In the EPHESUS trial benefit
145 was seen on by day 7. Follow-up truncated at day 50 for the pooled cohort (RALES and
146 EMPHASIS-HF) and EPHESUS. (MRA) Mineralocorticoid receptor antagonist; (CI);
147 Confidence Interval
148
149
150

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167 patent for site-specific delivery of eplerenone to the myocardium (US patent 9931412) and a
168 provisional patent for histone-acetylation–modulating agents for the treatment and prevention of
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218
219
220 The other authors report no conflicts of interest.

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222
223
224 REFERENCES

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