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Gap between clinical-guidelines and practice: The case of aldosterone-antagonists in patients with Myocardial Infarction

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The use of aldosterone-antagonists among patients with acute myocardial infarction (AMI) with ejection fraction<40% and symptomatic heart failure (HF) and/or diabetes mellitus (DM) is currently a class I recommendation[1, 2]. A recent report described low utilization rates (9.1%) of aldosterone-antagonists at discharge among eligible AMI patients[3]. However, this study did not assess aldosterone-antagonist utilization post-discharge where patients may be routinely initiated on or taken-off medications. Accordingly, our objective was to assess aldosterone-antagonist utilization at discharge and during longitudinal follow-up in a cohort of AMI patients.

We utilized PREMIER and TRIUMPH multi-center registries that capture detailed longitudinal data on AMI patients. They are unique among existing AMI registries as they follow enrolled patients prospectively and include extensive data on patient's socioeconomic and psychological status, collected using validated instruments at discharge and follow-up. Both these registries have been previously described[4, 5].

We included 6,329 AMI patients from 31 U.S. hospitals between 1/1/2003 through 12/31/2008 who were (i) aldosterone-antagonist naïve (ii) survived index hospitalization and

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(iii) had data on ejection fraction (EF), serum creatinine and potassium at discharge. AMI patients were classified as eligible for aldosterone-antagonists if they met the following criteria based on enrollment criteria for the EPHESUS trial[6]:

- a. EF<40% with HF (defined as presence of HF signs prior to or after index AMI or discharge on loop-diuretics) or DM (defined as documented history, hemoglobinA1c $\geq 6.5\%$ or discharge on glucose-lowering medications).
- b. Serum potassium $<5\text{mEq/L}$ and creatinine $<2.5\text{mg/dL}$.

Patients not meeting any of these criteria were classified as ineligible for aldosterone-antagonist.

We also evaluated factors (specified *a priori*) associated with aldosterone-antagonist non-utilization among eligible patients. A hierarchical-logistic regression model was fitted with selected patient-level covariates to identify factors associated with aldosterone-antagonist non-utilization. These covariates included GRACE score (per 10 units increment), serum potassium at discharge (per 0.5 mEq/L increment), DM, receipt of other guideline-concordant therapies (composite of aspirin, statins, beta-blockers and angiotensin-antagonists), insurance status, absence of primary care provider, patient reported lack of difficulty in obtaining medical care and financial difficulty obtaining medications.

We then assessed new initiation of aldosterone-antagonists at 1, 6 and 12 months post-discharge among eligible patients not prescribed the medication at discharge. We also assessed medication persistence amongst eligible patients prescribed therapy at discharge. These were based on patient-reported use by telephone follow-up at 1,6 and 12-months post-discharge.

Overall, 678 AMI patients ($n=6,329$; 10.7%) were eligible for aldosterone-antagonists. Mean age among eligible patients was 62 years, 68% were males and 62% were Caucasian. Only 15.2% ($n=678/6,329$) eligible patients received treatment at discharge, whereas among ineligible patients $<2\%$ ($113/5,651$) received it at discharge. Table 1 displays baseline characteristics of eligible patients stratified by receipt of aldosterone-antagonists at discharge. Compared to eligible patients receiving therapy at discharge, eligible patients not receiving therapy at discharge were older (63 ± 12 vs. 60 ± 11 years, $p=0.034$) without significant differences in gender, race and insurance status. Eligible patients not receiving therapy had a higher mean EF ($28\pm 7\%$ vs. $24\pm 8\%$, $p<0.001$) without significant differences in other co-morbidities including chronic kidney disease. In addition, eligible patients not receiving aldosterone-antagonists were less likely to receive other guideline-concordant therapies (OR 0.64, 95% CI 0.37–1.10). None of the other clinical or patient-reported psychosocial and economic factors were associated with discharge on aldosterone-antagonist.

Interestingly, amongst all post-AMI patients with EF<40%, those with HF were more likely to receive aldosterone-antagonists compared to those with DM (OR 0.60; 95% CI 0.37–0.98) despite a similar class 1 recommendation to use aldosterone-antagonists in both these groups.

Follow-up interviews at 1, 6 and 12 months were available on 322 ($n=575$, 56%), 323 (56%) and 289 (50%) eligible patients not discharged on aldosterone-antagonists. Only an additional 7.5% ($24/322$) of these patients reported new initiation within first month post-discharge with non-significant increase in further utilization on subsequent follow-ups at 6 (2.1%) or 12-months (0.8%).

Furthermore, persistence to therapy among eligible patients prescribed therapy at discharge was also low. Follow-up interviews at 1, 6 and 12 months were available on 55 (n=103, 53%), 51 (50%) and 47 (46%) eligible patients discharged on aldosterone-antagonists. At 1-month, 27% (n=15/55) discontinued treatment and at 6 and 12-months, discontinuation rates increased to 41% (21/51) and 53% (25/47) respectively (Figure 1).

Our results demonstrate significant underutilization of aldosterone-antagonists and poor persistence during longitudinal follow-up in a real-world cohort of AMI patients. Compared to EPHEsus trial (~85% persistence over 16 months) we observed lower persistence rates (47%). Furthermore, our observed persistence rates of 47% are lower than those described for statins and other medications[7]. Inherent differences in patients recruited and closer oversight in clinical-trials compared to real-world cohorts can partly explain these differences. Other potential reasons for lower persistence in a real-world setting include higher incidence of hyperkalemia, renal dysfunction, gynecomastia (with spironolactone) or financial concerns (with eplerenone).

To our knowledge, this is the first report assessing aldosterone-antagonist use in AMI patients post-discharge. Rassi et al reported similar aldosterone-antagonist utilization rates at discharge[3], but our report suggests worsening use of aldosterone-antagonists after discharge as well. Prior reports in AMI patients have suggested that higher-risk patients are less likely to receive guideline-concordant therapy (so-called “risk-treatment paradox”)[8]. Eligible patients not receiving aldosterone-antagonists in our cohort were also less likely to receive other guideline-concordant therapies. Therefore, it can be postulated that this phenomenon of “risk-treatment paradox” might be contributing towards our findings because AMI patients eligible for aldosterone-antagonists are higher-risk as well (e.g. EF<40% with DM). Another consideration is a persistent fear of hyperkalemia with these agents especially with prior reports suggesting increased morbidity and mortality from hyperkalemia with these agents in HF patients[9].

Limitations with this analysis include our relatively small sample size and potential for recall bias in data collected on follow-up patient interviews. Additionally, we could not evaluate reasons behind discontinuation of aldosterone-antagonists. Despite these limitations, TRIUMPH and PREMIER are unique in affording opportunities to assess follow-up care patterns from a representative, real-world, diverse sample amongst US patients with proven high-quality dataset.

These results highlight low rates of aldosterone-antagonist use and need for concerted efforts to improve the use of aldosterone-antagonists among eligible post-AMI patients.

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Figure 1.

Flowchart showing longitudinal utilization of aldosterone antagonists in eligible patients with acute myocardial infarction (AMI)

Table 1

Baseline characteristics of patients eligible for aldosterone antagonists stratified by receipt of therapy at discharge

Patient characteristics	Patients eligible for aldosterone antagonists (N=678)		p value
	Aldosterone antagonists received at discharge (n=103)	Aldosterone antagonists not received at discharge (n=575)	
Age, years (mean $\pm$ SD)	59.8 $\pm$ 11.0	62.6 $\pm$ 12.6	0.03
Race, n(%)			0.41
Caucasian	58 (57.4)	361 (63.2)	
Afro-american	36 (35.6)	166 (29.1)	
Other	7 (6.9)	44 (7.7)	
Male sex, n(%)	70 (68.0)	392 (68.2)	0.97
Lack of insurance, n(%)	20 (19.8)	105 (19.0)	0.86
Patient-reported lack of difficulty in obtaining medications, n(%)	65 (63.7)	384 (67.7)	0.43
Lack of designated primary care provider, n(%)	13 (12.6)	87 (15.4)	0.47
Never avoiding medication due to cost, n(%)	77 (74.8)	426 (75.0)	0.96
Hypertension, n(%)	67 (65.0)	425 (73.9)	0.06
Hyperlipidemia, n(%)	49 (47.6)	288 (50.1)	0.64
Diabetes, n(%)	56 (54.5)	363 (63.1)	0.09
Congestive heart failure, n(%)	39 (37.9)	169 (29.4)	0.09
Chronic renal failure, n(%)	6 (5.8)	54 (9.4)	0.24
Prior MI, n(%)	17 (16.5)	112 (19.5)	0.48
Current medications or counselling for depression, n(%)	16 (15.7)	65 (11.4)	0.22
Presenting with STEMI, n(%)	47 (45.6)	214 (37.2)	0.11
Ejection Fraction during admission (% , mean $\pm$ SD)	23.8 $\pm$ 8.1	28.3 $\pm$ 6.9	<0.001
GRACE score at discharge (mean $\pm$ SD)	116.1 $\pm$ 31.8	120.4 $\pm$ 31.7	0.20
Aspirin at discharge, n(%)	92 (92.0)	525 (93.4)	0.60
Beta blocker at discharge, n(%)	89 (90.8)	501 (90.0)	0.97
Statin at discharge, n(%)	81 (82.7)	473 (83.7)	0.79
Angiotensin antagonists at discharge, n(%)	94 (96.9)	448 (83.3)	<0.001

Legend: MI - myocardial infarction, STEMI – ST segment elevation myocardial infarction, SD – standard deviation