Prevalence of mineralocorticoid antagonist prescription after ST-elevation myocardial infarction with impaired left ventricular function: a single centre experience.

Abstract

Background

Evidence suggests long term benefit from angiotensin converting enzyme inhibition (ACE-I) or angiotensin receptor blockade (ARB), beta-adrenoreceptor antagonism and mineralocorticoid antagonism (MRA) in patients with left ventricular dysfunction. After myocardial infarction. However, despite clinical evidence and clearly articulated guidelines, several studies suggest low rates of prescription of some medications like MRA in the target group with post- myocardial infarction left ventricular dysfunction (MI LVD), both in Australia and other countries.

Methods

We studied prescription trends in 152 consecutive STEMI patients between August 2013 and December 2016 admitted to a single referral centre who also had a pre-discharge echo that demonstrated at least moderate left ventricular dysfunction.

Results

The average age was 63 years. Most patients were male (78%) and the average BMI was 28 (±6). 132 patients [87% (80% - 92%)] were prescribed ACE-I/ARBs, 144 patients received beta-adrenoceptor antagonists (95% [90% - 98%]), 147 patients (97%) received DAPT and 146 patients (95%) received statins post-STEMI.

45 eligible patients (30% [23% - 28%]) received an MRA. Younger patients were more likely to be prescribed an MRA (p = 0.008). The MRA prescribed cohort were younger, 59 versus 64 years, had marginally better renal function with average eGFR 108 vs 91 mL/min/1.73m² and lower rates of stage ≥III CKD 11 vs 22 (p <0.05).

Conclusion

Our study shows a substantial treatment gap, in that a majority of patients with impaired LV dysfunction after STEMI with symptoms of heart failure or diabetes are not receiving medications in the MRA class, despite proven benefit. As such, the root causes of this treatment gap require elucidation in a multi-centre context.
Key words

Mineralocorticoid receptor antagonist

Left ventricular dysfunction

Heart failure treatment
Abbreviations

MI Myocardial infarction
LVD Left ventricular dysfunction
ACE-I Angiotensin convertase enzyme-inhibitor
ARB Angiotensin receptor blocker
MRA Mineralocorticoid receptor antagonist
DAPT Dual antiplatelet
LVEF Left ventricular ejection function
STEMI ST elevation myocardial infarction
DM Diabetes mellitus
BMI Basal metabolic index
eGFR estimated glomerular filtration rate
PCI Percutaneous coronary intervention
CABG Coronary artery bypass graft
ACS Acute coronary syndrome
1 Introduction

After myocardial infarction (MI), patients with left ventricular dysfunction (LVD) are at increased risk of recurrent cardiovascular events, arrhythmias, heart failure, and mortality [1]. Specifically, in those with LVD after MI, evidence suggests long-term benefit from angiotensin converting enzyme inhibition (ACE-I) [2, 3] or angiotensin receptor blockade (ARB) [4] beta-adrenoceptor antagonism [5] and mineralocorticoid antagonism (MRA) [6], in addition to the documented benefits of timely reperfusion [7], dual anti-platelet therapy (DAPT) [8, 9] and potent lipid-lowering [10]. Among patients with acute coronary syndrome (ACS), selected on the basis of a left ventricular ejection fraction (LVEF) of ≤40%, with either clinical features of heart failure or diabetes mellitus (DM) and LVEF ≤40%, MRA therapy with eplerenone resulted in an 8% absolute reduction in cumulative of cardiovascular admissions and cardiovascular deaths [6]. This benefit is generally thought to be mediated via additive neurohormonal blockade, with direct effects on cardiac remodelling and fibrosis, evident clinically in several randomised studies utilising cardiac MRI to study LV volumes from 1 to 6 months post-infarction [11-13]. The guidelines of the American Heart Association/American College of Cardiology therefore apply a Level 1 recommendation for MRA prescription in post-MI LVD [14].

However, despite clinical evidence and clearly articulated guidelines, several studies suggest low rates of MRA prescription in the target group with post-MI LVD, both in Australia and other countries [15, 16]. Our aim was therefore to determine the rate discharge prescription and factors determining of MRA therapy in our institution, during initial hospitalisation for ST-elevation MI (STEMI), in a cohort routinely screened for LVD by early echocardiography in addition to clinical examination.

2 Methods

2.1 Study cohort and data source

The Victorian Cardiac Outcomes Registry (VCOR) data set is state-wide, population-based clinical quality registry aiming to improve the quality of care provided to patients with cardiovascular disease in Victoria, Australia. Data from the registry include demographic characteristics, medical history and results of admission laboratory tests. Data are prospectively collected from the medical record and entered by trained personnel. By design, all patients entered into this registry had undergone PCI.

This analysis included STEMI patients admitted to Western Health, Melbourne in between July 2013 to December 2016. Patients who died during hospital admission, or patients with insufficient information regarding prescribed medication at discharge were excluded. The remaining patient data
was collated with inpatient echo data: patients with no inpatient echocardiography and patients with LVEF of >40% were also excluded from the analysis, whilst for patients with LVEF ≤40%, inpatient medical records were searched, in order to ascertain the presence or absence of DM or documented symptoms or signs of heart failure. Thus, the final cohort reflected an appropriate target group for guideline-based criteria for MRA prescription in the post-STEMI context. Within the cohort, patients prescribed MRA were defined as group 1, whereas patients without MRA prescription were defined as group 2. Ethics approval for the study was obtained from the ethics committee of the Western Health, Melbourne (reference QA2017.29).

2.2 Post-MI patient monitoring and echocardiography

All patients were monitored for at least 48 hours in a critical care environment with daily medical review, with assessment for the presence or absence of signs and symptoms of heart failure, including the presence of pulmonary crackles, the presence of the third heart sound and chest radiography showing pulmonary congestion. All medications indicated by guidelines were routinely given, including anticoagulation and dual anti-platelet therapy. As per unit protocol, all patients with STEMI underwent echocardiography in order to assess LV function and exclude an intracardiac thrombus or mechanical complication after MI. LVEF was derived by Simpson's biplane method; in cases in whom 2D planimetry was not possible, a visually estimated LVEF was reported.

2.3 Outcomes and statistical analysis

The primary outcome of the study was guideline-directed prescription of an MRA at the time of discharge. In order to determine the possible co-variates of MRA prescription, the following covariates were included: demographic characteristics (age, sex), body mass index (BMI), vital signs (heart rate, systolic blood pressure), medical history (DM, peripheral vascular disease, prior percutaneous coronary intervention, prior coronary artery bypass grafting), prior stroke, discharge estimated Glomerular Filtration Rate (eGFR), echocardiographically derived LVEF, non-MRA medication prescription on discharge (ACE/ARB, BB) and MRA on admission.

The main outcome of this observational study was the proportion of patients with a prescription for MRA at the time of discharge. The observed proportion and exact 95% confidence intervals were calculated in R, a Language and Environment for Statistical Computing. Baseline characteristics of patients with versus without a prescription for MRA, were compared with Fisher’s exact test and
Welsh independent sample t-test for categorical, respectively continuous variables. All p values represent two-sided tests; no correction for multiple testing was applied.

3 Results

3.1 Study cohort derivation and baseline characteristics

The initial STEMI registry cohort consisted of 741 consecutive patients for this overall STEMI cohort, their length of stay was 2.7 (2.3-3.6) days and inpatient mortality was 2%. In the final cohort, the documented incidence of shock and clinical heart failure on admission were 17% and 18%, respectively, whereas the incidence of DM was 25%. Whilst clinical protocol required that all patients with STEMI underwent echocardiography during their index admission, 9.9% either did not undergo this or the report was not available.

Patient characteristics are summarised in Table 1. The average age was 63 years. Most patients were male (78%) and the average BMI was 28 (±6). Figure 1 shows the derivation of the study cohort, accounting for survivorship, echo availability and presence of LVD, as defined by an LVEF ≤40%. After application of all criteria, the final study cohort included 152 (21 % of STEMI cohort) with post-MI LVD, who were eligible for MRA therapy at discharge.

3.2 Adherence to non-MRA pharmacotherapies at discharge

Figure 2 illustrates the proportions of patients receiving guideline-indicated therapy both at admission and discharge. Of the study cohort, 132 patients [87% (80% - 92%)] were prescribed ACE-I/ARBs, 144 patients received beta-adrenoceptor antagonists (95% [90% - 98%]), 147 patients (97%) received DAPT and 146 patients (95%) received statins post-STEMI. For this analysis, prescription of beta-blockers was further categorised, in order to identify the prescription of agents with documented benefit in LVD, versus those without this. Of interest, of those prescribed a beta-blocker, the majority (73%) received an agent with documented efficacy in chronic heart failure, which included metoprolol succinate, bisoprolol, carvedilol and nebivolol.

3.3 MRA prescription and characteristics according to group

At discharge with reperfused STEMI, 45 eligible patients (30% [23% - 28%]) received an MRA (Group 1). Of these, 40 received eplerenone and 5 received spironolactone. The baseline and clinical characteristics of study patients by MRA prescription at discharge are shown in Table 1. No significant
between-group differences were observed with regard to sex, body mass index (BMI), cardiovascular risk factors and comorbidities, including DM, prior PCI, prior CABG, stroke, or peripheral vascular disease (see Table 1). Younger patients were more likely to be prescribed an MRA (p = 0.008). There was a significant difference in eGFR among patients who received on MRA on discharge (91mL/min/1.73m² vs 108 ml/min/1.73m², p = 0.03) and the presence chronic kidney disease (CKD) of at least stage III (an eGFR <60 mL/min/1.73m²) was associated with a greater proportion of MRA prescription (11% vs 22%, p < 0.05).

MRA therapy did not relate to a greater degree of LVD, comparing patients with an LVEF <35% with those with an LVEF in the range of 35–40%. In terms of haemodynamic measurements obtained during the admission, no relation between heart rate and MRA prescription was detected; however, patients discharged on MRA had a slightly lower BP on discharge, compared to patients discharged without an MRA. The prescription of medications also indicated in post-MI LVD, including ACE-I/ARB and a beta-blocker did not exert a significant effect on MRA prescription at discharge.

4 Discussion

The present study was a single centre assessment of adherence to guideline-based prescription in the context of reperfused STEMI with LVD, with a focus on the MRA class of drugs. Our findings highlight a highly significant treatment gap in this high-risk group. Combining clinical and imaging data, 21% of all comers with STEMI were found to be eligible for MRA prescription prior to discharge, due to resultant LVD. Despite the fact that, in this clinical context, MRA therapy has been associated with significant reductions in morbidity and mortality [6], only 30% of those who were eligible received agents in this class. Notably, this is in contrast to the finding of excellent adherence to other therapies indicated in the presence of LVD, with 87% and 95 %, respectively, receiving ACE-I/ARB and beta-adrenoceptor antagonists, and similar high rates of discharge prescription of DAPT and statins 96 % and 97 % respectively being observed.

In terms of specific reasons for non-adherence, our data provides limited insight. On univariate analysis, older age and renal impairment were the only significant factors apparent in non-prescription. The MRA prescribed cohort were younger, 59 versus 64 years, had marginally better renal function with average eGFR 108 vs 91 mL/min/1.73m² and lower rates of stage ≥III CKD 11 vs 22 (p <0.05). Since the vast majority of patients had normal range renal function would not appear feasible for this to be a driver of non-prescription; only one patient had an eGFR of <30mL/min/1.73m², which excludes eplerenone prescription, according to guidelines [14]. Neither
initial shock, heart rate or blood pressure seemed to explain non-prescription either. Although limited by the power of the sample size, these results suggest the the drivers of non-adherence are beyond the scope of the data which we were able to collect in this study.

4.1 Prescription of MRAs in LVD post-MI and the general heart failure population

High levels of plasma aldosterone concentration are commonly found in patient post MI with LVD and they independently predict less desirable outcomes [17]. This is thought to be due to negative effect of aldosterone on cardiovascular system by preventing myocardial neuronal re-uptake which leads to enhancing the sympathetic drive and also increasing electrolyte and fluid imbalance [18]. Aldosterone also has a direct myocardial effect by promoting myocardial interstitial and perivascular fibrosis [19].

Not surprisingly, inhibiting the production of aldosterone via antagonising mineralocorticoid receptor has shown to have a positive effect. In the EPHESUS trial, patients with post-MI LVD, defined as an LVEF ≤40% and either heart failure symptoms or diabetes, have improved survival and decreased hospitalisation with the addition of MRA therapy between 3 and 14 days post-event [6]. Whereas in the overall cohort, randomisation to eplerenone was associated with a 15% relative reduction in mortality, a greater relative reduction of 26% was observed in the subgroup with reperfused STEMI (45%). Small studies have reported benefits of MRA therapy started immediately after PCI in STEMI patients for the prevention life-threatening arrhythmia [20], prevent LV dilatation [12] and cost effectiveness has been shown [21].

Nevertheless, in the context of ACS, other data suggests reduced prescription rates of MRA therapy. The rate of adherence to MRA after MI also remains poor both in Australia [15] and other countries [16, 22]. Data from Coronary Artery Disease national database in the US have shown that MRA use are increasing slightly over time, however the vast majority of AMI patients eligible for treatment still fail to receive it at hospital discharge with unclear prescribing patterns [23].

A working system for identifying the subgroup of patients with a post-MI indication for an MRA requires adequate and timely access to non-invasive imaging, to detect a reduced LVEF. One possible mechanism is that prescribing decisions may be made early in the course of the admission and not revised in the light of imaging data, particularly if that becomes available late in the admission. Consistent access to echocardiography and communication of results pertinent to prescription is a necessary routine in a system of post-STEMI care. In this regard, our cohort had a median length of stay of 2.7 days and 90% of the cohort underwent echocardiography according to the hospital protocol, at a median of 1.7 days.
As noted, the fact that the majority of patients did receive other medication specifically indicated in post MI with LVD: of particular interest, the fact that the majority of the prescribed beta-adrenoceptor antagonists were agents with proven efficacy in heart failure (i.e., metoprolol succinate, bisoprolol, carvedilol and nebivolol) might suggest awareness in the mind of the prescriber that LVD was present and that therapy should therefore be tailored accordingly.

Although this study does not allow a firm conclusion in regards to non-prescription of MRAs, the reported low rate of MRA prescription in the subgroup most likely to benefit (post-reperfused MI) should provoke further analysis of the problem and an attempt to address practice change focussed on the 3-14 day post-presentation window.

Beyond the immediate context of LVD associated with ACS, low prescription rates of MRAs in the wider context of heart failure have been documented. Aldosterone has an important role in pathophysiology of heart failure [24], according to the neurohumoral model of heart failure. Strong evidence exists that MRA, used in conjunction with an ACE inhibitor, reduces a combined end point of death from cardiac causes or hospitalisation for cardiac causes, with the main mechanisms of benefit thought to relate to reduced death from progressive heart failure and reduced sudden death due to cardiac causes among patients receiving spironolactone, versus placebo [25]. Nevertheless, MRA adherence is also poor in stable heart failure patients and is estimated to be 35 % [26].

4.2 Barriers to MRA utilisation both in ACS and stable heart failure context

Despite the recognition of the treatment gap that exists, there is little empirical evidence regarding the reasons for low MRA utilisation both in post-ACS and chronic heart failure settings. A recent US mixed-methods study, employing a clinician survey and interview to ascertain possible barriers to the optimal use of MRAs, determined that the reasons for the treatment gap are complex and interconnected. The authors suggested that physician knowledge, familiarity, and variable agreement with guidelines were the primary reasons for failure to prescribe MRAs [27]. Participants also described the lack of tools and protocols in place within the system for monitoring patients on MRAs [27]. Data from the “Get with the Guidelines” survey shows that possible explanations for a low MRA prescription rate in the general heart failure population include a concern for safety (mainly hyperkalaemia), the effectiveness of laboratory monitoring, a misunderstanding of aldosterone-blocking benefits as opposed to a potassium sparing diuretic, and plans to initiate therapy in an outpatient setting [28, 29].
Further analysis of the EPHESUS study showed that the use of eplerenone within the dose range of 25 to 50 mg per day in post-ACS infarction patients with LVD results in improved outcomes, without an excess risk of hyperkalaemia [28]. Whilst longitudinal population based studies have not found increased hospital admission secondary to hyperkalaemia or renal failure from starting spironolactone [30], a system of monitoring for the development of hyperkalaemia is certainly needed and would most likely reduced the perceived barriers to prescription of this class of drugs in the post-ACS context, especially in patients above the age of 65 years, due to an increased risk of hyperkalaemia and renal impairment among the elderly [31].

4.3 Limitations

This study was conducted in a single-centre, with a relatively small sample size and 10% of patients post STEMI did not have a detailed inpatient TTE. Whilst the indication for MRA therapy applies to both STEMI and NSTEMI patients with LVD, we elected to study a re-perfused STEMI group, due to an institutional policy of mandatory pre-discharge echocardiography for patients admitted with STEMI, a policy not applied to NSTEMI. As such, this report provides insight into post-STEMI management and is to our knowledge the first to document MRA prescribing post-STEMI.

4.4 Conclusions

Our single centre analysis has demonstrated a substantial treatment gap, in that a significant majority of patients with impaired LV dysfunction after STEMI with symptoms heart failure or diabetes are not receiving medications in the MRA class, despite proven benefit. Given an increasing global burden of heart failure, due in part to increased survival after STEMI, it is possible that reduced utilisation of MRAs contributes to otherwise preventable adverse outcomes, including established heart failure. As such, the root causes of this treatment gap require elucidation in a multi-centre context. Furthermore, specific strategies to drive practice change in the area of post-STEMI prescribing should include a focus on MRA utilisation.
5 References


### Table 1 Patient characteristics according to MRA prescription

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<th>MRA (Group 1)</th>
<th>No MRA (Group 2)</th>
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<td>Age (SD) (years)</td>
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<td>64 (13)</td>
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<td>Female (%)</td>
<td>11</td>
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<td>BMI (SD)</td>
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<td>Inpatient findings</td>
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<td>HR on admission (SD)</td>
<td>86 (22)</td>
<td>86 (20)</td>
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<td>SBP on admission (SD)</td>
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Abbreviation: BMI (Basal Mass Index), DM (Diabetes Mellitus), PVD (Peripheral vascular Disease), PCI (Percutaneous Coronary Intervention), CABG (Coronary Artery Bypass Graft), eGFR (estimated Glomular Filtration Rate), HR (Heart Rate), SBP (Systolic Blood Pressure), LVEF (Left Ventricular Ejection Fraction), MRA (Mineralocorticoid Receptor Antagonist), ACE I (Angiotensin Convertase Enzyme Inhibitor), ARB (Angiotensin Receptor Blocker), BB (Beta Blocker)
**Figure 1 Derivation of study cohort**

**Abbreviations:**
- TTE (Transthoracic Echocardiography)
- LVEF (Left Ventricular Ejection Fraction)
- MRA (Mineralocorticoid Receptor Antagonist)
**Figure 2** Use of guideline-indicated medications in MRA eligible patients on admission and discharge

**Abbreviations:** ACE I (angiotensin convertase enzyme inhibitor), ARB (angiotensin receptor blocker), BB (beta-blocker), MRA (mineralocorticoid receptor antagonist)