South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Cardiovascular conditions

MEDICINE REVIEW

1. Executive Summary

Date:3 July 2017
Medicine (INN): Eplerenone (ELN)
Medicine (ATC): C03DA04
Indication (ICD10 code): Congestive cardiac failure (I50.0)
Patient population: Adults with left ventricular systolic dysfunction with clinical evidence of heart failure after acute myocardial infarction (MI)
Prevalence of condition: The prevalence is approximately 1 to 2 % of the adult population in developed countries, rising to more than 10% in the population greater than 70 years of age (1). In the United States, the incidence of new cases is approximately 20 per 1000 individuals in the age category, 65 to 69 years of age, increasing to > 80 per 1000 individuals in the population > 85 years of age (2). There are no population based epidemiological studies for Heart Failure in South Africa; however hospital-based studies suggest that a non-ischaemic aetiologies are predominant in the South African population (3). In the Heart of Soweto study cohort, the most common diagnoses were hypertensive HF (281 [33%]), idiopathic dilated cardiomyopathy (237 [28%]), and, surprisingly, right HF (225 [27%]) (4).
Level of Care: Secondary level of care
Prescriber Level: Doctor, specialist
Current standard of Care: Spironolactone
Efficacy estimates: (preferably NNT) Mean follow-up period was 16 months. A total of 478 patient in the ELN group (14.4%) and 554 patients in the placebo group (16.7%) died (relative risk, 0.85; p = 0.008). The absolute risk reduction (ARR) is 2.3% indicating a number needed-to-treat (NNT) of 44 patients over a 16 month period in order to prevent one additional death from any cause in patients with LVD or heart failure post-acute MI (5).
Kaplan-Meier estimates of mortality at one year were 11.8% in the ELN group vs. 13.6% in the placebo group (5).
Motivator/reviewer name(s): Dr V Mpongoshe, Prof PJ Commerford, Ms T Leong
PTC affiliation: N/a

2. Name of author(s)/motivator(s) :
Dr V Mpongoshe, Prof PJ Commerford, Ms TD Leong

3. Author affiliation and conflict of interest details

- Dr V Mpongoshe: Government Employees Medical Scheme; Adult Hospital Level Committee (2017-2019); no conflicts of interests declared.
- Prof PJ Commerford: University of Cape Town; Adult Hospital Level Committee (2017-2020);McMaster University (PHRI); Bayer: Run COMPASS (with wife) in South Africa and - remunerated by PHRI and travel support to attend study related meetings (COMPASS tests rivaroxaban).
- Ms TD Leong: NDoH; Essential Drugs Programme - Secretariat for the Adult & PHC Technical Sub-Committees of NEMLC; no conflicts of interests declared.

4. Introduction/ Background

Decreased cardiac output, as in the case of heart failure, results in the activation of the renin-angiotensin-aldosterone system (RAAS). This, in turn, increases the concentrations of both angiotensin II and aldosterone. Angiotensin II (AII) is a potent vasoconstrictor while aldosterone is responsible for maintaining a constant circulating blood volume through the retention of salt and water (6).

Elevated aldosterone levels have been linked to the development of heart failure post-MI. Although the use of ACE inhibitors and Angiotensin Receptor Blockers (ARBs) initially reduces aldosterone levels (via the inhibition of AII formation or activity), 'aldosterone escape' (i.e. the increase in aldosterone levels back to baseline) has been seen in the long-term in patients receiving these agents. Agents specifically targeting aldosterone therefore have a useful role to play in managing heart failure post-MI (7).
The co-administration of spironolactone, the current gold standard for aldosterone inhibition, with an ACE inhibitor enhances the beneficial effect of ACE inhibition on mortality in patients with congestive heart failure (1).
Although spironolactone reduces mortality in patients with congestive heart failure, the progestational and anti-androgenic side effects of this non-specific antagonist has tended to limit its use in many instances (1).
Eplerenone (ELN) is a spironolactone derivative and is reported to be a competitive and selective aldosterone blocker (8). In South Africa, ELN is indicated to reduce the risk of cardiovascular death in stable patients with left ventricular dysfunction (ejection fraction $\leq 35\%$ [3]) and acutely for post-myocardial infarction heart failure (9) (10).
A potential advantage associated with this agent is that in animal models, ELN has been shown to have a much lower affinity for progesterone and androgen receptors than spironolactone, thus potentially reducing the side-effect profile in this area.

5. Purpose/Objective i.e. PICO

Questions:

1.) ELN is non-inferior to spironolactone for the treatment of patients with left ventricular systolic dysfunction and clinical evidence of heart failure, after acute MI
2.) ELN has a better safety profile to spironolactone (hormonal side effects)

Population	Adult patients with left ventricular systolic dysfunction and clinical evidence of heart failure, after acute myocardial infarction
Intervention	Eplerenone
Comparison	Spironolactone either as comparison arm or switch study
Outcomes	Mortality, Cardiovascular morbidity; Adverse events

6. Methods:

a. Search strategy

-*Trips database:* "eplerenone" and "spironolactone" and "left ventricular systolic dysfunction" and "heart failure" and "mortality" and "safety" and "morbidity".
One article was retrieved.
-*Cochrane library*: "eplerenone" AND "spironolactone" AND "heart failure".
A total of 21 articles were retrieved.

No "head-to-head" RCTs could be retrieved in the published literature comparing eplerenone to spironolactone.

Excluded studies:

Dos et al, 2013; Iraqi et al, 2009; Struthers et al, 2004; Collier et al, 2013; Weir et al, 2009; Pitt et al, 2005; Deswal et al, 2011; Funder JW et al, 2005; Weir et al, 2011; Popovic B et al, 2016.	Surrogate endpoints and risk scores measurements.
Pitt, B et al, 2015	Finerenone vs eplerenone
Adamopoulus et al, 2009	Timing of initiating eplerenone treatment
Asakura et al, 2015	Japanese RCT of eplerenone with acute decompensated heart failure (n=300)
Coletta et al, 2011	AHA Narrative review
Ito et la, 2015	Population: peritoneal dialysed patients
Chang et al, 2017	Registry study (mineralocorticoid receptor agonists not delineated)
Beygui et al, 2016	Mineralocorticoid receptor agonists grouped
Peters-Klimm F et al, 2010	Case management observational study

b. Evidence synthesis

Author, date	*Type of study*	n	Population	Comparators	Primary outcome	Effect sizes	Comments
(5) Pitt et al 2003(EPHESUS)	Open-label, randomised, placebo controlled, phase III, study	6632	Adults, 3-14 days post acute MI, left ventricular dysfunction (ejection fraction ≤40%); clinical evidence of heart failure, on optimal medical therapy (including angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, diuretics and beta-blockers, as well as coronary reperfusion therapy)	Placebo	Time to death from any cause	A total of 478 patient in the ELN group (14.4%) and 554 patients in the placebo group (16.7%) died (relative risk, 0.85; p = 0.008). The absolute risk reduction (ARR) is 2.3% The second primary endpoint of death from cardiovascular causes or hospitalization for cardiovascular events was reached by 885 patients in the ELN group (26.7%) vs. 993 patients in the placebo group (30.0%) (relative risk, 0.87; p = 0.002). Rates of gynaecomastia in men were similar between treatment arms (0.5% vs 0.6%; p=0.18) After one year of study, safety issues of note included: A mean blood pressure increase of 8/4mmHg in the placebo group vs. 5/3mmHg in the ELN group at one year (p < 0.01) Serum creatinine concentration had increased by 1.8µmol/L in the placebo group vs. 5.3µmol/L in the ELN group (p < 0.001). Serious hyperkalaemia ($K^+ \geq$ 6.0mmol/L) occurred in 5.5% of patients in the ELN group vs. 3.9% of patients in the placebo group (p = 0.002)	Based on the number needed to treat and current cost of eplerenone, the cost of saving one additional life over this 16 month period is: R462,528. A closer analysis of the Kaplan–Meier curves however suggests that for death from any cause, the major benefit occurs within the first three months of therapy. No significant difference in the incidence of hormone related adverse events compared to placebo
(11) Pitt et al 2005 (EPHESUS sub-analysis)	Sub-analysis of the EPHESUS study results 30 days after randomisation	6632	Described above	Placebo	All-cause mortality at 30 days post-randomisation	The primary end-point was improved at 30 days post-randomisation. There were fewer deaths in the EPN group, 107 (3.2%), than the placebo, 153 (4.6%), with an associated HR for death from any cause of 0.69 (95% CI, 0.54-0.89; p=0.004).	Although the study was not powered for this sub-analysis it is of interest because 25% of total deaths occurring over the

						The co-primary endpoint was also improved with a lower rate of events in the ELN arm (8.6%) than the placebo (9.9%) (HR for death from CV causes or hospitalisation for CV events, 0.87; 95% CI 0.74-1.01; p=0.074). Death from CV causes was also reduced (3.0% vs 4.4%, respectively; HR 0.68 95% CI 0.53-0.88; p=0.003), which included a reduction in the rate of sudden cardiac death (0.9% vs 1.4%, respectively)	mean 16-month follow-up in placebo –treated patients in the EPHESUS trial occurred within the first 30 days after randomisation.
(12) Zannard et al 2011 (EMPHASIS-HF)	Double-blind, randomised, placebo-controlled, phase III, study	2737	Acute myocardial infarction, NYHA III or IV heart failure	Placebo	Composite of death from cardiovascular causes or hospitalisation for heart failure.	The primary outcomes occurred in 18.3% of patients in the eplerenone group as compared with 25.9% in the placebo group (HR 0.63; 95% CI 0.54-0.74; p<0.001). A total of 12.5% of patients receiving eplerenone and 15.5% of those receiving placebo died (HR 0.76; 95% CI 0.62-0.93; p=0.008); 10.8% and 13.5%, respectively, died of cardiovascular causes (HR 0.76; 95% CI 0.61-0.94; p=0.01).	Eplerenone treatment was associated with increase in serum creatinine and potassium levels and a slight reduction in blood pressure. There were no other clinically significant differences between the two groups with respect to laboratory variables, reported adverse events, or adverse events leading to permanent withdrawal of the study drug.
(13) Pitt et al 1999 (RALES)	Double-blind, randomised, placebo controlled, phase III, study	1663	Adults, NYHA III or IV.; left ventricular ejection fraction ≤35%.; on ACE-inhibitor and diuretic (if symptoms of congestion)	Placebo	Death from any cause	After a mean follow-up period of 24 months, the total number of deaths amounted to 386 patients in the placebo group (46%) and 284 deaths in the spironolactone group (35%) (p < 0.001) – ARR = 11%, NNT = 9. 314 of the 386 deaths in the placebo group vs. 226 of 284 deaths in the spironolactone group were attributed to cardiovascular causes (p < 0.001).	Of note is that a total of 414 patients (200 in the placebo group and 214 in the spironolactone group) discontinued the study due to reasons including lack of response, adverse events or for administrative reasons.

(14) Le et al 2016	Meta-analysis	19,333 (25 trials)	Prospective randomised controlled trials of aldosterone antagonists in patients with left ventricular dysfunction HF (NYHA class I to IV) and/or post acute MI, with durations of at least 8 weeks, if they included at least one of the following outcomes: sudden cardiac death, all-cause/cardiovascular mortality, all-cause/cardiovascular hospitalisation and common side-effects (hyperkalaemia, renal functions degradation and gynaecomastia)	Placebo or standard treatment	Sudden cardiac death; total mortality and CV mortality	All trials were placebo-controlled, except 3 which compared aldosterone antagonist to routine treatment, 9 assessed effects post-AMI, while the other trials recruited HF patients. Spironolactone (15 studies), ELN (7 studies) and canrenone (3 studies) The meta-analysis concludes that aldosterone antagonist therapy may provide benefit in preventing SCD, as well as all-cause mortality and CV mortality, for selected patients with HF with altered left ventricular function or after a MI Paradoxically their side-effect of hyperkalaemia may induce cardiac arrhythmia and provoke SCD, and there use may be independently associated with increased rates of total mortality and doubled incidence of SCD. Before prescribing careful consideration should be given to the therapeutic benefit and overall safety profile	No head-to-head comparator studies, comparing spironolactone to ELN were identified by the authors of the meta-analysis

c. Evidence quality:
High-quality RCT evidence demonstrating a mortality and morbidity benefit with eplerenone use over placebo in patients with left ventricular dysfunction and evidence of heart failure after acute myocardial infarction.

There is no published RCT evidence directly comparing eplerenone with the standard of care, spironolactone, in this population.

7. Alternative agents:
Spironolactone

8. Other considerations

- In the ELN post-acute myocardial infarction heart failure efficacy and survival study (EPHESUS), the overall incidence of adverse events reported with eplerenone (78.9%) was similar to placebo (79.5%).
- The discontinuation rate due to adverse events in these studies was 4.4% for patients receiving eplerenone and for 4.3% patients receiving placebo.
- Adverse events reported below are those with suspected relationship to treatment and in excess of placebo, taken from EPHESUS. Adverse events are listed by body system and absolute frequency. Frequencies are defined as: common > 1%, ≤ 10%; uncommon > 0.1%, ≤ 1%(15).
    - *Common (*> 1%, ≤ 10%) (15)
        - Autonomic nervous system: hypotension
        - Central and peripheral nervous system: dizziness
        - Gastro-intestinal system: diarrhoea, nausea
        - Metabolic and nutritional: hyperkalemia
        - Urinary system: renal function abnormal

Contra-indications (15):

- ELN should not be administered to patients with clinically significant hyperkalemia or with conditions associated with hyperkalemia.
- ELN should not be co-administered to patients receiving potassium-sparing diuretics or strong inhibitors of CYP 3A4 such as ketoconazole and itraconazole

Warnings (15):

- *Hyperkalemia:* Hyperkalemia may occur with ELN. Serum potassium levels should be monitored in all patients at initiation of treatment and with a change in dosage [15]. Thereafter, periodic monitoring is recommended in patients at risk for the development of hyperkalemia.
- *Impaired renal function:* Potassium levels should be monitored regularly in patients with impaired renal function, including diabetic microalbuminuria. Patients who have serum creatinine levels > 221 µmol/L (>2.5 mg/dL) or creatinine clearance <50 mL/min should be treated with caution. While the data from EPHESUS in patients with type 2 diabetes and microalbuminuria is limited, an increased occurrence of hyperkalemia was observed in this small number of patients. Therefore, these patients should be treated with caution.

- *Impaired hepatic function:* No elevations of serum potassium above 5.5 mmol/L were observed in patients with mild to moderate hepatic impairment. Electrolyte levels should be monitored in patients with mild to moderate hepatic impairment. The use of ELN in patients with severe hepatic impairment has not been evaluated.
- *Non-steroidal anti-inflammatory drugs (NSAIDS):* The administration of other potassium-sparing agents with NSAIDs has been shown to result in hyperkalemia in patients with impaired renal function
- *Lithium:* Lithium toxicity has been reported in patients receiving lithium concomitantly with diuretics and ACE inhibitors. Serum lithium levels should be monitored frequently if INSPRA is administered concomitantly with lithium.

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	**SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS**
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident [X] Not confident [ ] Uncertain [ ]	See evidence synthesis table, above.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms [X] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]	See evidence synthesis table, above.
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes [ ] No [X] List the members of the group: n/a List specific exclusion from the group: n/a	Rationale for therapeutic alternatives included: n/a References: n/a Rationale for exclusion from the group: n/a References: n/a
VALUES & PREFERENCES / ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [ ] Major [ ] Uncertain [x] **Is the option acceptable to key stakeholders?** Yes [ ] No [ ] Uncertain [x]	

<table>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?

More intensive [x] Less intensive [ ] Uncertain [ ]</td><td>Cost of medicines/ month:
<table><tr><th>Medicine</th><th>Cost (ZAR)</th></tr><tr><td>Spironolactone 25mg (56)</td><td>20.71*</td></tr><tr><td>Spironolactone100mg (60)</td><td>111.99*</td></tr><tr><td>Eplerenone 25mg (30)</td><td>370.22**</td></tr><tr><td>Eplerenone 50mg (30)</td><td>370.20**</td></tr></table>* Contract circular: HP09-2016SD
**SEP database, 27 May 2017: 60% of SEP
[Dose equivalency 1:2 - eplerenone:spironolactone; SAMF 2016]
Additional resources:
Note: Neither spironolactone or eplerenone are listed on the MSH International Medical Products Price Guide.(Accessed 24 August 2017: www.http://mshpriceguide.org/en/home/</td></tr>
<tr><td>EQUITY</td><td>Would there be an impact on health inequity?

Yes [ ] No [X] Uncertain [ ]</td><td></td></tr>
<tr><td>FEASIBILITY</td><td>Is the implementation of this recommendation feasible?
Yes [ ] No [X] Uncertain [ ]</td><td></td></tr>
</table>

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	[X]	☐	☐	☐	☐

Recommendation

The Adult Hospital Level Committee recommends that due to the significant price difference between eplerenone and generic spironolactone, and in the absence of high quality evidence demonstrating superior efficacy or safety outcomes with eplerenone over spironolactone, the latter will remain the agent of choice. Eplerenone could be considered in exceptional circumstances where patients cannot tolerate spironolactone due to hormonal side effects (e.g. painful gynaecomastia).

Rationale: There is no direct comparative RCT evidence in terms of efficacy and safety of eplerenone vs. spironolactone. Eplerenone is currently more expensive than current standard of care, spironolactone.

Level of Evidence: I placebo controlled RCT, Expert opinion

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
X		X

VEN status:

Vital	Essential	Necessary

Monitoring and evaluation considerations

Research priorities

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