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Eplerenone in Post Myocardial Infarction Patients

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Abstract

Background: Eplerenone is a mineralocorticoid receptor antagonist (MRA), which is currently used in patients post myocardial infarction (MI) with symptoms of heart failure and left ventricular systolic dysfunction. NICE guidelines 2013 sets out the use of Eplerenone in a post-MI setting.

Aim: The aim of this guideline review is to analyse recent literature (2013 onwards) to valuate if NICE guideline is still relevant to clinical practice.

Method: Literature search was conducted to find articles from 2013-present, in English, and contained the key words "Eplerenone" and "myocardial infarction" in the subject title.

Results: Seven articles were found. They were read and evaluated to see how Eplerenone effects clinical outcomes in a variety of settings.

Conclusion: The NICE guideline is still relevant in light of evidence from more recently published literature. However further research is suggested to be completed in future to assess the effect of Eplerenone in patients without heart failure post-MI as in REMINDER trial.

Keywords: Heart failure; Myocardial infarction; Cardiovascular; Pharmacology

Introduction

Cardiovascular disease (CVD) is a prevalent problem amongst the UK population. CVD encompasses a variety of cardiovascular related problems including stroke and coronary heart disease. Mortality from CVD therefore makes up a large proportion of deaths in the population, causing approximately 27.4% of deaths in men and 25.2% in women in 2015 [1].

Coronary heart disease was the most common single cause of CVD deaths [1]. A frequent consequence as a result of coronary heart disease (CHD) are myocardial infarctions (MI), with 194,506 patients in 2015/16 being admitted as an inpatient due to an acute myocardial infarction [1]. In the days and months following a MI; left ventricular systolic dysfunction and heart failure (even if transient) independently increase the risk of cardiac death by 2-6 fold; and both together increase the risk by 8 fold -from 3% to 26% [2].

Cost burden to the UK economy from CHD was estimated 26 billion (euros) in 2015 [1], demonstrating not only is this a large-scale problem but it is also an economic strain to the NHS. Therefore, managing patients' appropriately post MI is a priority; to improve cardiac function, reduce mortality and prevent further cardiovascular events occurring.

When managing patients post MI, several pharmacological treatments can be initiated. Eplerenone is a drug which can be prescribed in a post MI setting, in patients who have signs and symptoms of heart failure. Recommendations for clinical practice in the management of post MI patients are outlined in NICE guidelines.

Background

Eplerenone is an aldosterone antagonist or mineralocorticoid-receptor antagonists (MRA) [3], used mainly for its diuretic properties. Aldosterone is a mineralocorticoid secreted by glomerulosa cells in the adrenal cortex [4]. It acts on principle cells found in the kidneys which are located on the thick ascending limb, late distal tubule and collecting duct of a nephron [3].

The parts of the nephron which are most sensitive to aldosterone are those which not only have mineralocorticoid receptors but also have the presence of 11β-hydroxysteroid dehydrogenase 2 [4]. This enzyme is essential as it metabolises glucocorticoids, preventing them from binding to the receptor [4].

Aldosterone is most sensitive in the distal nephron (late distal tubule and collecting duct), where it increases the NaCl symporters in the apical membrane of cells [4]. This allows sodium reabsorption to be increased which in turns increases the reabsorption of water. It also stimulates potassium secretion in the later distal tubule and collecting duct [4].

Eplerenone antagonises aldosterone receptor so sodium and therefore water is secreted. With aldosterone blocked, it also means that potassium secretion reduces, hence why it is also known as potassium sparing diuretic.

The use of Eplerenone in a post-MI setting was evaluated in the 2003 EPHESUS trial [5]. This was a double-blind, placebo-controlled study which evaluated the effect of Eplerenone on morbidity and mortality. It studied a total of 6642 patients who post MI had a left ventricular ejection fraction of 40% or lower and symptoms of heart failure.

It found that in the group being treated with Eplerenone there was a decrease in the number of patients who were hospitalised for cardiovascular events and less deaths also due to cardiovascular causes, compared to the placebo group.

Results produced also demonstrated a reduction in all-cause mortality with 14.4% dying in the Eplerenone group compared to 16.7% in placebo group [5]. This formed the evidence base for the use of Eplerenone in post-MI patients who had left ventricular systolic dysfunction (LVSD).

Further to this, the EMPHASIS trial studied the use of Eplerenone in patients with New York Heart Association class II and ejection fraction no more than 35% [6]. This further demonstrated that Eplerenone reduced mortality and hospitalisation rates, and therefore should be added to therapy even if patients have only mild symptoms of heart failure.

Guidelines

NICE clinical guideline CG 172 published in 2013 outlines the management of myocardial infarction in terms of CVD prevention and cardiac rehabilitation [7]. Furthermore, it summarises the use of aldosterone antagonists in this setting.

It states that patients who have had acute MI and who have signs of heart failure and left ventricular systolic dysfunction (LVSD) should have an aldosterone antagonist initiated within 3-14 days post MI [7].

From this guidance therefore, Eplerenone should be initiated post MI but only in patients with heart failure. However, due to this guideline being written five years previous, it would be interesting to see if more recent literature would still indicate the same.

Aim

The aim of this guideline review is to examine the evidence on the use of Eplerenone post MI, since the EPHESUS trial was conducted, and NICE guidance was published. By evaluating more recent evidence on the drug, conclusions can be made as to whether the guideline is still relevant in current clinical practice.

Methods

A literature search on Scopus database was conducted using the terms "Eplerenone" and "Myocardial Infarction". This produced 509 results and therefore required filtering. The search was limited to results containing the keywords in the article title, to year published from 2013 to present and in English language. Results from this demonstrated 7 appropriate articles. The Figure 1 below demonstrates the search pathway;

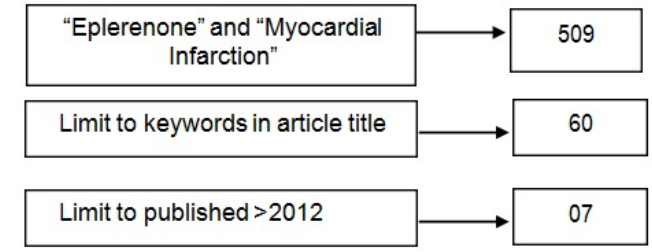

Figure 1: Demonstrates the search pathway.

Results

All seven articles were accessible and dated from 2014-2018 (Table 1). Of the seven articles found on SCOPUS, four were sub studies/sub-analysis of the EPHESUS [5] trail. They used the same patients recruited from the EPHESUS study to evaluate specific topic and areas in postacute MI patients.

Number	Article Title	Authors
1	Eplerenone Modulates Interleukin-33/sST2 Signaling and IL-1b in Left Ventricular Systolic Dysfunction After Acute Myocardial Infarction [8].	Bo Chen, Jing Geng, Shao-xi Gao, Wen-wei Yue, and Qiang Liu
2	Effect of eplerenone on extracellular cardiac matrix biomarkers in patients with acute ST elevation myocardial infarction without heart failure: insights from the randomized double blind REMINDER Study [9]	João Pedro Ferreira[1,2], Kévin Duarte1, Gilles Montalescot[3], Bertram Pitt[4], Esteban Lopez de Sa[5], Christian W Hamm[6], Marcus Flather[7], Freek Verheugt[8], Harry Shi[9], Eva Turgonyi[10], Miguel Orri[10], Patrick Rossignol[1], John Vincent[9], Faiez Zannad[1]
3	Combined baseline and one-month changes in big endothelin-1 and brain natriuretic peptide plasma concentrations predict clinical outcomes in patients with left ventricular dysfunction after acute myocardial infarction: Insights from the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) study [10]	A Olivier[a,b,c,d,*], N Girerd[a,b,c], JBMichel [e], JM Ketelslegers[f], R Fay[a,b,c], J Vincent [g], P Bramlage[h], B Pitt[i], F Zannad[a,b,c,d], P Rossignol[a,b,c], for the EPHESUS Investigators
4	Early eplerenone treatment in patients with acute ST-elevation myocardial infarction without heart failure: The Randomized Double-Blind Reminder Study [11]	Gilles Montalescot[1*], Bertram Pitt[2], Esteban Lopez de Sa[3], ChristianW. Hamm[4], Marcus Flather[5], Freek Verheugt[6], Harry Shi[7], Eva Turgonyi[8], Miguel Orri[8], John Vincent[7], and Faiez Zannad[9], for the REMINDER Investigators
5	Effect of eplerenone in percutaneous coronary intervention-treated post-myocardial infarction patients with left ventricular systolic dysfunction: a subanalysis of the EPHESUS trial [12]	Javaid Iqbal[1*], Renaud Fay[2], David Adlam[3], Iain Squire[3], Yasir Parviz[1], Julian Gunn[1], Bertram Pitt[4], and Faiez Zannad[2]

6	Opposite Predictive Value of Pulse Pressure and Aortic Pulse Wave Velocity on Heart Failure With Reduced Left Ventricular Ejection Fraction Insights From an Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) Substudy [13]	Veronique Regnault*, Jérémy Lagrange*, Anne Pizard*, Michel E. Safar, Renaud Fay, Bertram Pitt, Pascal Challande, Patrick Rossignol, Faiez Zannad, Patrick Lacolley
7	Heart failure with systolic dysfunction complicating acute myocardial infarction- differential outcomes but similar eplerenone efficacy by ST-segment or non-ST-segment elevation: A post hoc substudy of the EPHESUS trial [14]	Sylvain Carillo [a*], Yan Zhang[b], Renaud Fay[a], Michael Angioi[c], John Vincentd, Santosh C. Sutradhor[d], Ali Ahmed[b], Bertram Pitt [e], Faiez Zannada

Table 1: The following articles were used to evaluate whether the NICE guidelines on the use of Eplerenone post MI are still appropriate.

The REMINDER study published in 2014 [11], was a randomised, placebo controlled, double blind trial, using 1012 participants. Another article [9] was a sub-study used the data collected in this to provide insights on a specific focus area.

The final article collected was a laboratory experiment published in 2018 [8]. This study was conducted to see how Eplerenone effects interleukin pathways following an acute MI, in rats.

Discussion

There is approximately a 20% reduction in all-cause mortality with the use of aldosterone blockade post MI in a heterogeneous group of patients with left ventricular dysfunction. There is also a 3.1% improvement in ejection fraction; although there was significant statistical heterogeneity. A post-hoc analysis of EPHESUS showed that early initiation of Eplerenone reduced the mortality rate as early as 30 days post MI.

Effect of eplerenone on specific biomarkers of cardiac function

Following EPHESUS study, three papers have demonstrated the effect of Eplerenone on specific cardiac biomarkers and inflammatory markers. A sub study [10] conducted evaluated the effect Eplerenone had on a specific biomarker big endothelin-1 (BigET-1) and brain natriuretic peptide (BNP). BigET-1 is increased in congestive heart failure and is a pre-cursor for ET-1 which is a vasoconstrictor stimulating hypertrophy in the myocardial tissue. In this sub-study it was demonstrated that using Eplerenone decreased the levels of BNP but not BigET-1. It was suggested that the reninaldosterone-angiotensin system did not have a role in BigET-1 system.

In addition to this, another study [8] conducted assessed the role of Eplerenone on specific inflammatory markers Interleukin (IL)-33/sST2 pathway and interleukin-1β. This study demonstrated that in the group treated with Eplerenone, there was a reduction in IL-1β. A reduction in IL-1β is useful as this is essential for activating inflammatory and fibrogenic pathways, and effects cardiac remodelling of the myocardium post MI. Thus, reducing this interleukin will help to improve cardiac function and reduce fibrosis.

Another sub study [9], but from the REMINDER trial, was published in 2018 which evaluated the effect of the drug on biomarkers of collagen turnover. It measured the following extra cellular collagen matrix markers (ECMM); PIIINP, ICTP, PINP and Galectin-3, which all have a role in cardiac remodelling. It found PIIINP and PINP levels were reduced when the patient was taking Eplerenone. This revealed that the drug also helps to reduce "pro-fibrotic ECCM deposition" and suggested that it limits "adverse cardiac remodelling".

It can be concluded from these three studies that Eplerenone post MI, has been shown to work at a cellular level to decrease inflammation and improve cardiac function. These pleiotropic effects are poorly understood; and include anti-inflammatory effects, favourable effects on endothelial function, vascular remodelling through actions on collagen synthesis and fibrosis.

Eplerenone efficacy in ST elevation vs. Non-ST elevation myocardial infarction

A further sub study [14] of the EPHESUS trial was conducted to compare the use of Eplerenone in patients with ST elevation myocardial infarction (STEMI) to patients with Non-ST elevation myocardial infarction (NSTEMI).

This study revealed that over a 30 month follow up period, NSTEMI patients experienced more adverse outcomes. All-cause death was higher in the group who had a NSTEMI compared to STEMI, at 19% and 13% respectively. Furthermore, it was reported that cardiovascular death specifically, was 16% in NSTEMI compared to 12% in STEMI.

However, it found that the beneficial effects of Eplerenone, on cardiac function, did not differ depending on the ST segment status. Demonstrating that it should be used in a post-MI setting, in both STEMI and NSTEMI patients if they develop signs and symptoms of heart failure.

Using Eplerenone in patients without known heart failure

The REMINDER study [11], assessed the early use of Eplerenone treatment inpatients post STEMI without known heart failure or left ventricular ejection fraction <40%. Eplerenone should usually be initiated within 3-14 days post MI usually after ACE-Inhibitor initiation, however in this trial, it was given within 24 hours of the onset of symptoms. 1012 patients were recruited, and computer randomised to receive Eplerenone or placebo. BNP and NTpro BNP elevation occurred less frequently in the group receiving Eplerenone when this was assessed at 1,6,12 and 18 months post MI, with 16% of patients treated having elevated BNP at 1 month compared to 25.9% in the placebo group.

Therefore, demonstrating it can improve cardiac outcomes in patients without previous known heart failure. However, it was stated that further study is required to assess the use of MRA's in patients after acute STEMI, which is then not complicated by heart failure.

Eplerenone in patients post Percutaneous Coronary Intervention (PCI)

A sub study [12] of the EPHESUS trial looked at the effects of Eplerenone use in patients who were treated with PCI post MI. It

compared outcomes between non-PCI and PCI treated groups. It discovered that Eplerenone was similarly effective whether being treated with PCI or not, to lower mortality, reduce hospitalisation and cardiovascular events. Although it stated that using both PCI and Eplerenone demonstrated better clinical outcomes.

However, the cohorts compared did have differing clinical characteristics, with the PCI treated group were younger, had less co-morbidities and a better renal function.

Cardiovascular mortality was thus lower than the non-PCI treated patients. Despite this, from the sub study, it has been shown that Eplerenone should be used in patients whether they have been treated with PCI or not, as it still aids in reducing adverse outcomes.

Eplerenone compare to other MRAs

Spironolactone is the other most common MRA used in heart failure settings. The efficacy of using spironolactone in patients with heart failure was studies in the 1999 RALES trial [15]. This double-blind study looked at the effect of spironolactone on patients with severe heart failure and ejection fraction of no more than 35%. The risk of all-cause mortality demonstrated in the trail was reduced by 30% in those treated with spironolactone compare to placebo. Hospitalisation due to worsening HF was reduced by 35%. Comparing this to results from the EPHESUS trail [5], it demonstrated 15% risk reduction all-cause mortality in the treatment group.

However, when looking at the incidence adverse events, in particular gynaecomastia and impotence in male patients, this did not differ from placebo group. This was not demonstrated in the RALES trial, where there were incidents of gynaecomastia on spironolactone. This is explained due Eplerenone having greater selectivity, therefore it binds less to androgen and progesterone receptors [5].

Further studies have also demonstrated that Eplerenone is more cost-effective compared to spironolactone for the treatment of post-MI heart failure [16]. During a period where the NHS budget is being squeezed, cost effectiveness becomes an important factor in deciding what drugs to use.

Therefore, a conclusion can be drawn from reading these studies, that Eplerenone is superior to Spironolactone in treating heart failure in post MI patients, as it is more cost effective and has less risk of adverse events.

Conclusion

From analysing evidence of recent literature, post publication of the guidelines, it can be concluded that Eplerenone should be used in patients post MI with symptoms of heart failure and LVSD. Therefore, the NICE guidance on this subject should remain unchanged.

An area for further research into the use of Eplerenone, would be to see whether it should be used post MI in patients where it is not complicated by heart failure. The use of Eplerenone could be analysed to see whether adding this to standard therapy in patients who do not develop heart failure, would reduce mortality and reduce risk of further hospitalisation. Another study to replicate the results of REMINDER would be useful to expand on the licensed indication of Eplerenone.

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