# Common Drug Review

*Clinical Review Report*

**October 2014**

| | |
|---|---|
| **Drug** | Eplerenone (Inspra) (25 mg tablet and 50 mg tablet) |
| **Indication** | As an adjunct to standard therapy to reduce the risk of cardiovascular mortality and hospitalization for heart failure in patients with NYHA class II systolic chronic heart failure and left ventricular systolic dysfunction |
| **Listing request** | As per indication |
| **Manufacturer** | Pfizer Canada Inc. |

This report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). Through the Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update — Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

The information in this report is intended to help Canadian health care decision-makers, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. The information in this report should not be used as a substitute for the application of clinical judgment with respect to the care of a particular patient or other professional judgment in any decision-making process, nor is it intended to replace professional medical advice. While CADTH has taken care in the preparation of this document to ensure that its contents are accurate, complete, and up-to-date as of the date of publication, CADTH does not make any guarantee to that effect. CADTH is not responsible for the quality, currency, propriety, accuracy, or reasonableness of any statements, information, or conclusions contained in the source documentation. CADTH is not responsible for any errors or omissions or injury, loss, or damage arising from or relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the information in this document or in any of the source documentation.

This document is intended for use in the context of the Canadian health care system. Other health care systems are different; the issues and information related to the subject matter of this document may be different in other jurisdictions and, if used outside of Canada, it is at the user's risk. This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse) of this document will be governed by and interpreted in accordance with the laws of the Province of Ontario and the laws of Canada applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of the Province of Ontario, Canada.

CADTH takes sole responsibility for the final form and content of this document, subject to the limitations noted above. The statements and conclusions in this document are those of CADTH and not of its advisory committees and reviewers. The statements, conclusions, and views expressed herein do not necessarily represent the views of Health Canada or any Canadian provincial or territorial government. Production of this document is made possible by financial contributions from Health Canada and the governments of Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Northwest Territories, Nova Scotia, Nunavut, Prince Edward Island, Saskatchewan, and Yukon.

# TABLE OF CONTENTS

**Tables**



**Figures**

# ABBREVIATIONS

| | |
|---|---|
| **ACEI** | angiotensin-converting enzyme inhibitor |
| **AE** | adverse event |
| **AF** | atrial fibrillation |
| **ARB** | angiotensin receptor blocker |
| **BB** | beta blocker |
| **BNP** | brain natriuretic peptide |
| **CADTH** | Canadian Agency for Drugs and Technologies in Health |
| **CDR** | Common Drug Review |
| **CI** | confidence interval |
| **CRT** | cardiac resynchronization therapy |
| **CV** | cardiovascular |
| **EF** | ejection fraction |
| **eGFR** | estimated glomerular filtration rate |
| **EMPHASIS-HF** | Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure |
| **EPHESUS** | Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study |
| **EPL** | eplerenone |
| **FAS** | full analysis set |
| **Hgb** | hemoglobin |
| **HF** | heart failure |
| **HR** | hazard ratio |
| **ICD** | implantable cardioverter-defibrillator |
| **K+** | serum potassium |
| **LV** | left ventricular |
| **LVEF** | left ventricular ejection fraction |
| **MI** | myocardial infarction |
| **MRA** | mineralocorticoid receptor antagonist |
| **NNT** | number needed to treat |
| **NR** | not reported |
| **NT-p-BNP** | amino terminal pro-brain natriuretic peptide |
| **NYHA** | New York Heart Association |
| **PL** | placebo |
| **PCI** | percutaneous coronary intervention |
| **PP** | per-protocol |

| | |
|---|---|
| **RALES** | Randomized Aldactone Evaluation Study |
| **SAE** | serious adverse event |
| **SBP** | systolic blood pressure |
| **SD** | standard deviation |
| **SPI** | spironolactone |
| **WDAE** | withdrawal due to adverse event |

# EXECUTIVE SUMMARY

## Introduction

Heart failure (HF) is a condition that results from an inability of the heart to meet the body's metabolic demands for oxygen because of a structural or functional abnormality of the heart.[1] According to 2006 statistics from the Heart and Stroke Foundation, 500,000 Canadians were living with HF while 50,000 new cases were being diagnosed each year.[2] This was associated with an annual mortality rate of 5% to 50% and a five-year survival rate of 50%.[2] In Canada, 54,333 hospitalizations for HF were recorded between 2005 and 2006.[3]

Half of all HF patients have systolic HF characterized by reduced ejection fraction (EF) (≤ 40%). The 2012 Canadian Cardiovascular Society Heart Failure Management Guidelines[4] recommend initial combination therapy with an angiotensin-converting enzyme inhibitor (ACEI) (or angiotensin receptor blocker [ARB], in case of intolerance to ACEI) plus a beta blocker in patients with chronic (systolic) HF with reduced EF, titrated to target or maximally tolerated doses; these medications have individually shown a beneficial effect on survival in clinical trials.[4] In parallel, diuretics may be used as needed for symptomatic relief of dyspnea or edema. Addition of a mineralocorticoid receptor antagonist (MRA) is recommended based on persistence of symptoms consistent with New York Heart Association (NYHA) class II-IV.[4]

Eplerenone is the second MRA to be marketed in Canada after spironolactone.[5] Eplerenone has a Health Canada indication as an adjunct to standard therapy to reduce the risk of cardiovascular (CV) mortality and hospitalization for HF in patients with NYHA class II systolic chronic HF and left ventricular systolic dysfunction.[6] Reimbursement is being sought by the manufacturer in accordance with this indication. Previously, eplerenone was granted an indication by Health Canada as an adjunct to standard therapy to reduce the risk of mortality and hospitalization for HF following myocardial infarction (MI) in clinically stable adult patients who have evidence of HF and left ventricular systolic dysfunction (EF ≤ 40%).[6]

The objective of this systematic review was to evaluate the beneficial and harmful effects of eplerenone 25 mg to 50 mg daily for the treatment of patients with NYHA class II systolic chronic HF and left ventricular systolic dysfunction.

## Results and Interpretation

### Included Studies

The evidence for this review was drawn from one phase III (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure [EMPHASIS-HF]) double-blind, randomized (1:1), placebo-controlled trial comprising 2,737 patients with NYHA class II chronic systolic heart failure and left ventricular systolic dysfunction, during which patients received either eplerenone 25 mg daily (increasing to 50 mg daily after four weeks) or matching placebo. The primary efficacy outcome in EMPHASIS-HF was a composite of death from CV causes or a first hospitalization for heart failure. Designed as an event-driven trial, EMPHASIS-HF was originally designed to run approximately 48 months until 813 primary efficacy end points had occurred. However, the trial was stopped early after a median of 21 months of follow-up when an interim analysis revealed that the pre-specified stopping rules for efficacy had been met.

While the trial was largely representative of class II HF patients in Canada, North American (< 10%) and Black patients (2.5%) were under-represented. As well, there was some concern that the trial enrolled patients at higher risk for CV events, which could affect generalizability of results to Canadian clinical practice. Although there is a paucity of evidence regarding the efficacy and safety of spironolactone in

class II HF, it is used in clinical practice in this population, according to the clinical expert consulted on this review. The decision to exclusively use a placebo comparator in EMPHASIS-HF leaves considerable uncertainty regarding the comparative efficacy and safety of eplerenone and spironolactone in milder HF.

**Efficacy**

The primary efficacy outcome of EMPHASIS-HF was a composite of death from CV causes or a first hospitalization for HF. This occurred in 249 (18.3%) patients in the eplerenone group compared with 356 (25.9%) patients in the placebo group, favouring eplerenone (hazard ratio [HR] 0.63; 95% CI, 0.54 to 0.74). An examination of the individual components of the composite suggests that the primary driver was the reduction in first hospitalization for HF (eplerenone [EPL] 164 [12.0%] versus placebo [PL] 253 [18.4%]); by comparison, the magnitude of the reduction in risk over time was smaller for CV death (EPL 147 [10.8%] versus PL 185 [13.5%]). The number needed to treat (NNT) to prevent one primary composite event per year of follow-up was reported to be 19 (95% CI, 15 to 27).[7] Death from all causes was also less frequent in the eplerenone group (171 [12.5%]) than in the placebo group (213 [15.5%]) (HR 0.76; 95% CI, 0.62 to 0.93); the NNT to postpone one death per year of follow-up was 51 (95% CI, 32 to 180).[7] A statistically significant difference favouring eplerenone was likewise observed among the following secondary outcomes identified within the systematic review protocol: death from CV causes (HR 0.76; 95% CI, 0.61 to 0.94), all-cause hospitalizations (HR 0.77; 95% CI, 0.67 to 0.88), HF hospitalizations (HR 0.58; 95% CI, 0.47 to 0.70), CV hospitalization (HR 0.69; 95% CI, 0.60 to 0.81), and development of atrial fibrillation (AF) or flutter (HR 0.59; 95% CI, 0.38 to 0.91). However, the composite of fatal and non-fatal MI did not favour eplerenone (HR 1.32; 95% CI, 0.84 to 2.06). The findings from subgroup analyses of the primary composite efficacy outcome were generally consistent with the overall results.

**Harms**

Because the trial was stopped early for efficacy reasons, the risk of adverse events conferred by eplerenone in the population studied may be underestimated as a consequence of the shorter period during which patients were exposed to treatment. In addition, the interpretation of adverse event data is complicated by the overlap between clinical (efficacy) event and adverse event data, where efficacy outcomes such as CV events were included in the reporting of the overall incidence of adverse events.

The overall frequency of adverse events was similar between eplerenone (72.0%) and placebo (73.6%) groups. Except for cardiac failure, most individual adverse events occurred at low frequencies between both groups without a particular pattern of concentration. Hyperkalemia was twice as frequent with eplerenone treatment as with placebo (EPL 8.0% versus PL 3.7%); renal impairment and hypotension were similar between groups. Gynecomastia or other breast disorders were uncommon and not more frequently observed in the eplerenone group. Except for cardiac failure, serious adverse events were similarly infrequent and comparable in the two treatment arms. Withdrawals due to adverse events (WDAEs) were similar between groups. An open-label extension trial of 12 months' duration was carried out following the early completion of the double-blind phase. No additional safety signals were identified from these observational data. It is unclear, however, why only fewer than half of patients were taking an ACEI (or ARB) during the open-label phase. (APPENDIX 6: SUMMARY OF OTHER STUDIES for summary of data.)

## Other Considerations

### Potential Off-label Uses

Based on discussion with the clinical expert consulted for this review, the following potential off-label uses of eplerenone were identified:

- HF with preserved left ventricular ejection fraction (LVEF)
- Acute decompensated HF
- Asymptomatic (NYHA class I) HF with reduced LVEF
- HF patients with reduced LVEF:
  - < 55 years old
  - > 75 years old
  - with renal failure
- Treatment of hypertension
- Treatment of non-cardiac peripheral edema.

## Pharmacoeconomic Summary

### Summary of Economic Analysis

The manufacturer stated that a cost-utility analysis was conducted using a discrete event simulation method, which was then used to populate an Excel workbook. The target population was the Health Canada indication. The manufacturer indicated that on entry to the model, patients could have events that allowed the patient to remain in the model (CV hospitalization, HF hospitalization, AF, adverse events, discontinuation), or events that remove them from the model (CV mortality, non-CV mortality, device implantation). The manufacturer stated that patient-level data from the EMPHASIS-HF trial were used to determine risk equations for events by fitting a distribution to the time to each event, with these distributions providing a basis for the simulated model cohort. Cost elements included in the study were drug costs, hospitalization, adverse events and device implantation costs, and disease management and monitoring costs. Primary utility values were obtained from a subpopulation of the earlier Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) trial, with various alterations to these values as well as disutility values (from a variety of sources) stated to have been used to determine overall utility values for each patient throughout the model. The time horizon for the analysis was set at the patient lifetime; however, the life expectancy of these patients has not been presented. The results of the manufacturer's economic evaluation indicated that eplerenone plus standard optimal therapy was more costly than standard optimal therapy alone ($51,378 versus $44,576), but led to more quality-adjusted life-years (5.29 versus 4.36), resulting in an incremental cost-utility ratio of $7,347 per quality-adjusted life-year gained.

### Interpretations and Key Limitations

The key limitations with the manufacturer's economic evaluation are:

**Lack of transparency with the model:** The lack of transparency and the ability of the Common Drug Review (CDR) to independently assess the model logic did not allow CDR to verify the model.

**Patients included in the modelled population:** The manufacturer did not specify what happens to patients once they move out of NYHA class II disease within the model. Based on CDR clinical feedback, it was suggested that NYHA classes are subjective and transient states, and thus modelling other NYHA classes and including spironolactone would have been an appropriate scenario analysis. The CDR Clinical

Review Report found uncertainty regarding the extent to which the studied patients are reflective of the typical NYHA class II HF patient population seen in clinical practice.

**Modelling and assumptions for subsequent hospitalizations:** Given the lack of transparency with the submitted model, it is unclear what approach was used to model subsequent events (hospitalizations and adverse events). The validity of assuming treatment effects beyond two hospitalizations given the small number of events in the clinical trial, especially as subsequent hospitalizations were not an established end point, was also questioned. The inclusion of patients with multiple subsequent hospitalizations could reflect those who are no longer in class II and may have various comorbidities, potentially overestimating the benefit of eplerenone.

**Results of Common Drug Review Analysis**

CDR analyses were not conducted, given the issues with transparency and the ability to run analyses of interest independently.

## Conclusions

Although CDR was unable to fully assess the manufacturer's economic evaluation, the CDR Clinical Review Report indicates that eplerenone appears to reduce the number of initial hospitalizations for patients with NYHA class II HF and an LVEF ≤ 35%. How this translates to the incremental cost-effectiveness of eplerenone using the manufacturer's economic model could not be fully assessed.

At the submitted price, eplerenone costs $2.61 daily (25 mg and 50 mg) or approximately $955 annually.

In one, adequately designed randomized controlled trial, eplerenone was shown to reduce the risk of a composite outcome event (death from CV causes or a first hospitalization for HF) compared with placebo in patients with NYHA class II systolic chronic HF. The individual components of the composite outcome occurred at a lower rate in the eplerenone group compared with placebo and the difference was statistically significant. The number of deaths from any cause was lower in the eplerenone group (12.5%) than the placebo group (15.5%). Quality of life data were not collected during the trial; nor was there an analysis of changes in NYHA class over time. The safety profile of eplerenone appeared similar to placebo, although hyperkalemia occurred about twice as frequently with eplerenone. Serious adverse events (other than cardiac failure) were infrequent, while WDAEs were similar between groups. Because the trial was stopped early for efficacy reasons after a median of only 21 months, the long-term risk of adverse events may be underestimated. There was no evidence to inform the comparative efficacy and safety of eplerenone and spironolactone in patients with NYHA class II systolic chronic HF.

**TABLE 1: SUMMARY OF RESULTS**

| Outcome | EMPHASIS-HF[8] | |
|---|---|---|
| | Eplerenone (n = 1,364) | Placebo (n = 1,373) |
| **CV Death or HF Hospitalization** | | |
| n (%) | 249 (18.3) | 356 (25.9) |
| HR (95% CI) | 0.63 (0.54 to 0.74) | |
| *P* Value | < 0.0001 | |
| **CV Mortality** | | |
| n (%) | 147 (10.8) | 185 (13.5) |
| HR (95% CI) | 0.76 (0.61 to 0.94) | |
| *P* value | 0.012 | |
| **HF Hospitalization** | | |
| n (%) | 164 (12.0) | 253 (18.4) |
| HR (95% CI) | 0.58 (0.47 to 0.70) | |
| *P* value | < 0.0001 | |
| **All-Cause Mortality** | | |
| n (%) | 171 (12.5) | 213 (15.5) |
| HR (95% CI) | 0.76 (0.62 to 0.93) | |
| *P* value | 0.0081 | |
| **All-Cause Hospitalization** | | |
| n (%) | 408 (29.9) | 491 (35.8) |
| HR (95% CI) | 0.77 (0.67 to 0.88) | |
| *P* value | < 0.0001 | |
| **AEs** | | |
| n (%) | 979 (72.0) | 1007 (73.6) |
| **SAEs** | | |
| n (%) | 509 (37.4) | 614 (44.9) |
| **WDAEs** | | |
| n (%) | 188 (13.8) | 222 (16.2) |
| **Notable Harms** | | |
| Hyperkalemia[7] | 109 (8.0) | 50 (3.7) |
| Hypotension[7] | 46 (3.4) | 37 (2.7) |
| Renal impairment[7] | 57 (4.2) | 36 (2.6) |

AE = adverse event; CV = cardiovascular; EMPHASIS-HF = Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; HF = heart failure; HR = hazard ratio; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

# 1. INTRODUCTION

## 1.1 Disease Prevalence and Incidence

Heart failure (HF) is a condition that results from an inability of the heart to meet the body's metabolic demands for oxygen because of a structural or functional abnormality of the heart.[1] Depending on the severity of dysfunction and use of diuretics, patients may or may not experience classic symptoms of HF, namely shortness of breath, swelling in the ankles, or fatigue.[1,4] Because such symptoms are neither sensitive nor specific for HF, identifying an underlying cardiovascular (CV) etiology is essential to making the diagnosis of heart failure and guiding subsequent treatment decisions.[1]

According to 2006 statistics from the Heart and Stroke Foundation, 500,000 Canadians were living with HF, while 50,000 new cases were being diagnosed each year;[2] this was associated with an annual mortality rate of 5% to 50% (average of 10%) — depending on disease and symptom severity, age, and other factors — and a five-year survival rate of 50%.[2] Within five years of HF diagnosis, 40% to 50% of patients were expected to die.[2] In Canada, 54,333 hospitalizations for HF were recorded between 2005 and 2006.[3]

Primarily a disease of ageing, the estimated incidence of HF in the US in 2005 was 10 per 1,000 population after the age of 65;[9] consequently, it is this same age group that comprises around 80% of HF hospitalizations in the US.[9] By ethnicity, the risk for heart failure is highest among Black people.[9] Half of all HF patients have systolic HF characterized by reduced ejection fraction ([EF] i.e., EF $\leq$ 40%), for which the evidence base regarding treatment is more well established than diastolic HF where EF is preserved (i.e., EF $\geq$ 50%).[1,9] Major risk factors for the development of systolic HF include coronary artery disease (which accounts for two-thirds of cases), hypertension, and diabetes.[1]

The New York Heart Association (NYHA) functional classification provides a means to classify patients with HF according to functional capacity, as described in Table 2.

**TABLE 2: NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION**

| Class | Description |
|---|---|
| I | No limitations of physical activity |
| II | Slight limitation of physical activity, but no symptoms at rest |
| III | Marked limitation of physical activity, but no symptoms at rest |
| IV | Inability to perform any physical activity without discomfort; symptoms may be present at rest |

Source: UpToDate.com[10]

## 1.2 Standards of Therapy

The 2012 Canadian Cardiovascular Society Heart Failure Management Guidelines[4] recommend initial combination therapy with an angiotensin-converting enzyme inhibitor (ACEI) (or angiotensin receptor blocker [ARB], in case of intolerance to ACEI) plus beta blocker in patients with chronic (systolic) heart failure with reduced EF (HF-REF) titrated to target or maximally tolerated doses; these medications have individually shown a beneficial effect on survival in clinical trials.[4] In parallel, diuretics — particularly loop diuretics — may be used as needed for symptomatic relief of dyspnea or edema.[1,4,9] US guidelines make similar treatment recommendations.[9] European guidelines[1] differ somewhat in that they recommend a stepped approach starting with initial ACEI (or ARB) therapy, followed by the addition of a beta blocker. However, all three guideline groups[1,4,9] recommend a stepped approach when it comes to the addition of a mineralocorticoid receptor antagonist (MRA) based on persistence of symptoms

consistent with NYHA class II-IV.[1,4,9] The recommendations regarding when to use adjunctive device therapy, such as an implantable cardioverter-defibrillator (ICD) to reduce the risk of sudden cardiac death, or cardiac resynchronization therapy (CRT), vary according to clinical criteria (e.g., NYHA class, left ventricular ejection fraction [LVEF], QRS duration and morphology [CRT], presence of normal sinus rhythm [CRT], ischemic or non-ischemic etiology [ICD]) and intended purpose (i.e., primary or secondary prevention).[1,4,9]

## 1.3 Drug

Eplerenone is the second MRA to be marketed in Canada after spironolactone.[5] Eplerenone has a Health Canada indication as an adjunct to standard therapy to reduce the risk of CV mortality and hospitalization for HF in patients with NYHA class II systolic chronic HF and left ventricular systolic dysfunction.[6] Reimbursement is being sought by the manufacturer in accordance with this indication. Previously, eplerenone was granted an indication by Health Canada as an adjunct to standard therapy to reduce the risk of mortality and hospitalization for HF following myocardial infarction (MI) in clinically stable adult patients who have evidence of HF and left ventricular systolic dysfunction (EF $\leq$ 40%).[6]

| Indication under review |
| --- |
| As an adjunct to standard therapy to reduce the risk of cardiovascular mortality and hospitalization for heart failure in patients with NYHA class II systolic chronic heart failure and left ventricular systolic dysfunction |
| **Listing criteria requested by sponsor** |
| As per indication |

**TABLE 3: KEY CHARACTERISTICS OF EPLERENONE AND SPIRONOLACTONE**

| | Eplerenone[6] | Spironolactone[5] |
|---|---|---|
| **Mechanism of Action** | Binds to the mineralocorticoid receptor and blocks the binding of aldosterone<br>Eplerenone is a second-generation MRA that has less affinity than spironolactone for progesterone and androgen receptors[11] | Binds to the mineralocorticoid receptor and blocks the binding of aldosterone<br>Spironolactone is a non-selective MRA that also binds to progesterone and androgen receptors[11] |
| **Health Canada Indication** | Reduce the risk of CV mortality and hospitalization for HF in patients with NYHA class II systolic chronic HF and left ventricular systolic dysfunction.<br><br>Adjunct to standard therapy to reduce the risk of mortality and hospitalization for HF following MI in clinically stable adult patients who have evidence of HF and left ventricular systolic dysfunction (EF ≤ 40%) | Management of edema and sodium retention when the patient is only partially responsive to, or is intolerant of, other therapeutic measures (e.g., congestive HF)<br><br>Cirrhosis of the liver accompanied by edema and/or ascites<br><br>Patients with nephrotic syndrome who are not responsive to glucocorticoid therapy and who do not respond to other diuretics<br><br>In patients with essential hypertension in whom other measures are considered inadequate or inappropriate |
| **Route of Administration** | Oral | Oral |
| **Recommended Dose** | 25 mg to 50 mg daily | 50 mg to 100 mg |
| **Serious Side Effects/ Safety Issues** | Conditions that may increase the risk of hyperkalemia and/or dehydration<br><br>No studies in pregnant women | Conditions that may increase the risk of hyperkalemia and/or dehydration<br><br>No studies in pregnant women<br><br>In chronic toxicity studies, has been shown to be a tumorigen in rats. Breast cancer and other neoplasms (intestinal, pancreas, etc.) have been reported in post-market surveillance<br><br>Gynecomastia<br><br>Negative sexual or reproductive effects in animal studies |

CV = cardiovascular; EF = ejection fraction; HF = heart failure; MI = myocardial infarction; MRA = mineralocortoid receptor antagonist; NYHA = New York Heart Association.

# 2. OBJECTIVES AND METHODS

## 2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of eplerenone 25 mg to 50 mg daily for the treatment of patients with NYHA class II systolic chronic HF and left ventricular systolic dysfunction.

## 2.2 Method

Studies were selected for inclusion in the systematic review based on the selection criteria presented in Table 4.

**TABLE 4: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW**

| | |
|---|---|
| **Patient Population** | NYHA class II systolic HF with LV systolic dysfunction<br><br>Subgroups: LVEF (< 30%, ≥ 30%); age (< 75 years, ≥ 75 years); baseline eGFR; diabetes; country/region; daily dosage (25 mg, 50 mg); refractory to or intolerant of spironolactone |
| **Intervention** | Eplerenone 25 mg to 50 mg daily added onto ACEI (or ARB) + BB |
| **Comparators** | Placebo added to ACEI (or ARB) + BB<br>• Spironolactone added to ACEI (or ARB) + BB<br>• ARB added to ACEI + BB |
| **Outcomes** | **Key efficacy outcomes:**<br>All-cause mortality<br><br>**Other efficacy outcomes:**<br>Death from CV causes<br>Sudden cardiac death<br>Fatal or non-fatal MI<br>Fatal or non-fatal stroke<br>All-cause hospitalizations<br>• HF-related<br>• CV-related<br>Development of new or worsening AF<br>ICD or CRT device insertion<br>LVEF<br>Quality of Life<br>Change in NYHA class<br><br>**Harms outcomes:**<br>AEs, SAEs, WDAEs, mortality, notable harms (hyperkalemia, hypotension, renal impairment; gynecomastia, new diabetes) |
| **Study Design** | Published and unpublished RCTs |

ACEI = angiotensin-converting enzyme inhibitor; AE = adverse event; AF = atrial fibrillation; ARB = angiotensin receptor blocker; BB = beta blocker; CRT = cardiac resynchronization therapy; CV = cardiovascular; eGFR = estimated glomerular filtration rate; HF = heart failure; ICD = implantable cardioverter-defibrillator; LV = left ventricular; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

The literature search was performed by an information specialist using a peer-reviewed search strategy. Published literature was identified by searching the following bibliographic databases: MEDLINE (1946– ) with in-process records and daily updates through Ovid; Embase (1974– ) through Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was Inspra (eplerenone).

Methodological filters were applied to limit retrieval to randomized controlled trials, controlled clinical trials, and safety data. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See APPENDIX 2: LITERATURE SEARCH STRATEGY for the detailed search strategies.

The initial search was completed on August 30, 2013. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee on January 15, 2014. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites of the Grey Matters checklist (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters), including websites of regulatory agencies, health technology assessment agencies, and clinical guideline repositories. Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies. See APPENDIX 2: LITERATURE SEARCH STRATEGY for more information on the grey literature search strategy.

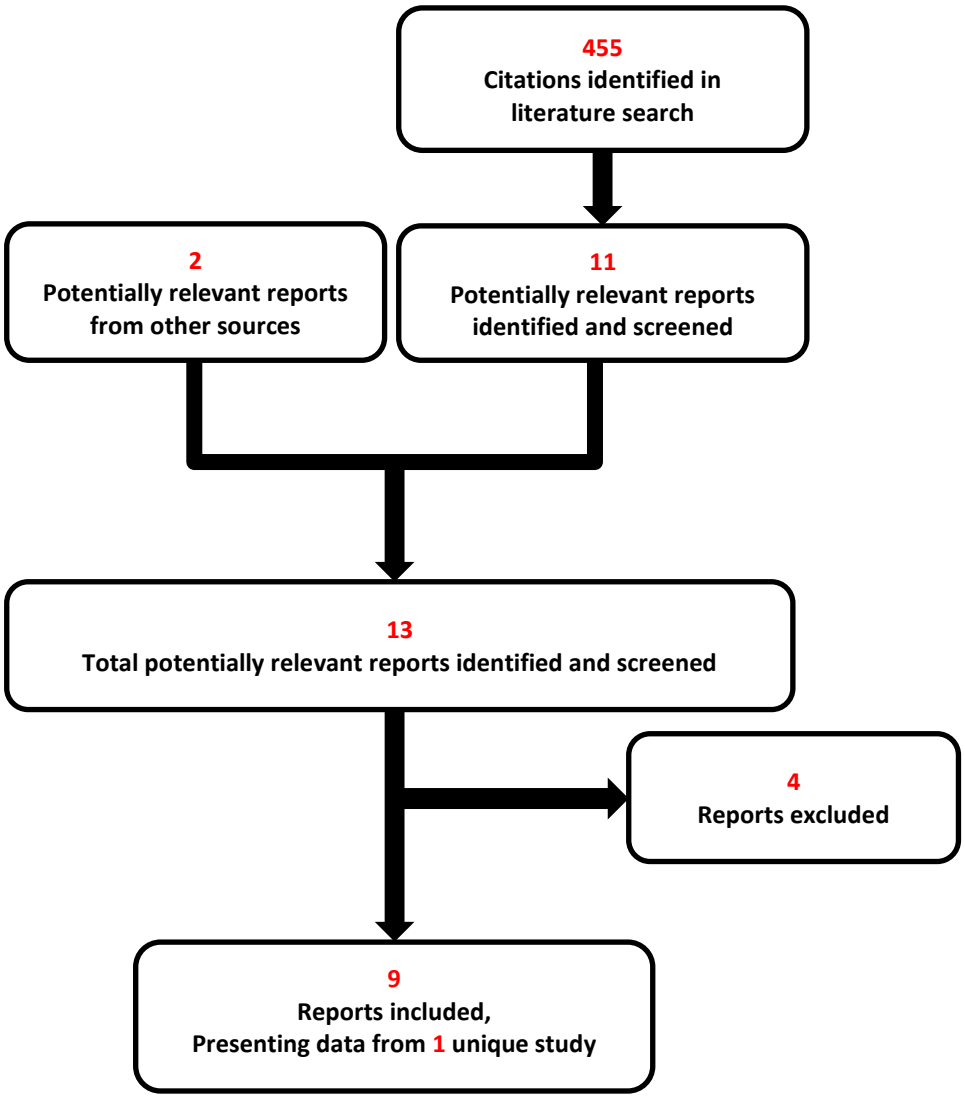
Two Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 5; excluded studies (with reasons) are presented in APPENDIX 3: EXCLUDED STUDIES.

# 3. RESULTS

## 3.1 Findings from the Literature

A total of 455 studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 2 and described in Section 3.2. A list of excluded studies is presented in APPENDIX 3: EXCLUDED STUDIES.

**FIGURE 1: QUOROM FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES**




QUOROM = Quality of Report of Meta-Analyses.

**TABLE 5: DETAILS OF INCLUDED STUDIES**

| | | EMPHASIS-HF[8] |
|---|---|---|
| DESIGNS AND POPULATIONS | **Study Design** | Multinational (29 countries), double-blind, placebo-controlled, event-driven RCT |
| | **Locations** | Five continents including Western and Eastern Europe; Canada |
| | **Randomized (N)** | N = 2,737 |
| | **Inclusion Criteria** | Age ≥ 55 years; chronic systolic HF of ischemic or non-ischemic etiology (duration: > 4 weeks; LVEF ≤ 30% or LVEF ≤ 35% + QRS duration ≥ 130 ms; NYHA II); treated with maximally tolerated doses of ACEI and/or ARB + BB, diuretic if clinically indicated); K+ ≤ 5 mmol/L; eGFR ≥ 30 mL/min/1.73 $m^2$; randomization not more than 6 months from date of CV hospitalization[b], or if no recent CV hospitalization, BNP ≥ 250 pg/mL or NT-p-BNP ≥ 500 pg/mL (males) or ≥750 pg/mL (females) ≤ 15 days of randomization. Entry was permitted if no history of hyperkalemia or renal impairment in cases of previous MRA use > 7 days, in which MRA was discontinued for ≥ 3 months before randomization. Patients with inoperable valve disease as primary cause of HF were also eligible. |
| | **Exclusion Criteria** | Severe chronic systolic HF (i.e., symptoms at rest despite optimal therapy); K+ > 5.0 mmol/L or eGFR < 30 mL/min/1.73 $m^2$ ≤ 24 hours of randomization; any of the following within 30 days prior to randomization: AMI complicated by LV systolic dysfunction and clinical HF, stroke, cardiac surgery, or PCI; previous treatment with MRA for > 7 consecutive days, in which permanent cessation of therapy did not occur ≥ 3 months prior to randomization or with clinically important hyperkalemia or renal impairment during a previous MRA exposure; required eplerenone, spironolactone, or potassium canrenoate and had either prior NYHA IV HF with LVEF ≤ 35% **or** HF or diabetes with LVEF < 40% after AMI; uncontrolled hypertension (i.e., SBP > 180 mm Hg or DBP > 110 mm Hg); symptomatic hypotension or SBP < 85 mm Hg; cardiogenic shock; primary cause of HF amenable to surgery; use of mechanical assist device; concurrent use of potent CYP3A4 inhibitors or inducers; Hgb < 10 g/dL; pre-existing hepatic disease; life expectancy < 3 years; pregnant or lactating |
| DRUGS | **Intervention** | Eplerenone 25 mg to 50 mg orally once daily added to standard[a] HF therapy |
| | **Comparator(s)** | Matching placebo orally once daily added to standard[a] HF therapy |
| DURATION | Run-in | ≥ 30 days |
| | Double-blind | (event-driven: until 813 events achieved) |
| | Follow-up | (planned: 48 months, but stopped early for efficacy: median follow-up was 21 months; then 12-month open-label extension) |
| OUTCOMES | **Primary End Point** | Composite of CV mortality or HF hospitalization |
| | **Other End Points** | Secondary: Composite of all-cause mortality or HF hospitalization<br><br>Other secondary:<br>All-cause mortality; CV mortality; all-cause hospitalization; HF hospitalization; all-cause mortality or all-cause hospitalization; HF mortality or HF hospitalization; CV hospitalization; fatal/non-fatal MI; fatal/non-fatal stroke; implantation of cardioverter-defibrillator; implantation of a CRT; new-onset AF/flutter[c]; new-onset diabetes[c]; worsening renal function (if it results in hospitalization); hospitalization for hyperkalemia |

| | | EMPHASIS-HF[8] |
|---|---|---|
| NOTES | **Publications**[d] | Zannad et al. (2011),[7] Eschalier et al. (2013),[12] Krum et al. (2013),[13] Preiss et al. (2012),[14] Rogers et al. (2012),[15] Swedberg et al. (2012),[16] Zannad et al. (2010)[17] |

ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; AMI = acute myocardial infarction; ARB = angiotensin receptor blocker; BB = beta blocker; BNP = brain natriuretic peptide; CRT = cardiac resynchronization therapy; CV = cardiovascular; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; EMPHASIS-HF = Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; HF = heart failure; Hgb = hemoglobin; K+ = serum potassium; LV = left ventricular; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist;
MRA = mineralocorticoid receptor antagonist; NT-p-BNP = amino terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; SBP = systolic blood pressure.
[a]"Standard HF therapy included ACEIs and/or ARBs and beta blockers at the optimal target or maximally tolerated doses (unless contraindicated), and diuretics, if clinically indicated to minimize fluid retention" (CSR, p. 25/3290).[8]
[b]CV hospitalization was defined as hospitalization for first or subsequent HF; AMI; unstable angina pectoris; cardiac arrhythmia; stroke; other CV reasons (e.g., hypotension, peripheral vascular disease). Unless hospitalized for implantation of cardioverter-defibrillator or CRT, elective CV hospitalization was not included in the definition (CSR, p. 30/3290).[8]
[c]Non-adjudicated events.
[d]One additional report was included.[6]
Source: Clinical Study Report (CSR).[8]

## 3.2 Included Studies

### 3.2.1 Description of Studies

Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) was a multinational, double-blind, placebo-controlled, event-driven randomized controlled trial. It comprised 29 clinical centres including sites in North America, and Canada specifically. EMPHASIS-HF was designed to run until 813 primary efficacy end point events had been recorded, which corresponded to an expected median follow-up of approximately 48 months; however, the trial was halted early (median of 21 months) due to pre-specified stopping rules for the primary efficacy outcome being met.

Patients were randomized to receive eplerenone 25 mg once daily or matching placebo; after four weeks, the dose of eplerenone was increased to 50 mg once daily, if indicated by the K+ level.

### 3.2.2 Populations

**a) Inclusion and exclusion criteria**

EMPHASIS-HF enrolled patients with mild (NYHA class II) chronic heart failure, who were aged $\geq$ 55 years old with reduced EF (LVEF $\leq$ 30%, or $\leq$ 35% with QRS $\geq$ 130 ms). Patients were receiving standard treatments of combination ACEI (or ARB) and beta blocker therapy. The trial did not permit the enrolment of patients with severe HF or renal impairment, hyperkalemia, or acute cardiovascular event (i.e., within 30 days of randomization). Additional eligibility criteria required patients to have had either a recent hospitalization for a CV event (within the last six months preceding randomization) or an elevated brain natriuretic peptide level (within 15 days of randomization).

**b) Baseline characteristics**

Baseline characteristics were generally well balanced between groups. Patients enrolled in EMPHASIS-HF were predominantly male (78%), white (83%), NYHA class II (> 99%), with a mean age of 69 years and body mass index of 27.5 kg/m$^2$. Approximately one-quarter of enrolled patients were $\geq$ 75 years of age. Mean LVEF was 26%, with 70% of patients having a LVEF < 30%. HF was of ischemic etiology in 70% of patients. Medical history included previous MI (50%), diabetes mellitus (31%), atrial fibrillation (AF) or flutter (31%), hypertension (66%), and previous hospitalization for congestive HF (53%). One-third of

patients had an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 $m^2$, half of whom (17%) had an eGFR from 30 to < 50 mL/min/1.73 $m^2$. Most patients were receiving an ACEI (80%) and beta blocker (88%); device therapy use was infrequent, with 13% of patients having an implantable cardioverter-defibrillator (ICD).

**TABLE 6: SUMMARY OF BASELINE CHARACTERISTICS IN EMPHASIS-HF (FAS)**

| Characteristic | Eplerenone (n = 1,364) | Placebo (n = 1,373) |
|---|---|---|
| **Age (years)** | | |
| Mean (SD) | 68.7 (7.7) | 68.6 (7.6) |
| Proportion ≥ 75 years, n (%) | 330 (24.2) | 327 (23.8) |
| **Sex, n (%)** | | |
| Male | 1,055 (77.3) | 1,072 (78.1) |
| Female | 309 (22.7) | 301 (21.9) |
| **Race, n (%)** | | |
| Caucasian | 1,127 (82.6) | 1,141 (83.1) |
| Black | 37 (2.7) | 30 (2.2) |
| Asian | 158 (11.6) | 158 (11.5) |
| Other | 42 (3.1) | 44 (3.2) |
| **Weight (kg)** | | |
| Mean (SD) | 79.2 (16.9) | 79.4 (16.9) |
| **Body Mass Index (kg/$m^2$)** | | |
| Mean (SD) | 27.5 (4.9) | 27.5 (4.9) |
| **Blood Pressure (mm Hg)** | | |
| Systolic/Diastolic Mean (SD) | 124.3 (17.2) / 74.6 (10.3) | 123.9 (16.6) / 74.7 (10.2) |
| **LVEF (%)** | | |
| Mean (SD) | 26.2 (4.6) | 26.1 (4.7) |
| **LVEF Classification, n (%)** | | |
| < 30% | 934 (68.5) | 978 (71.2) |
| ≥ 30% to ≤ 35% | 424 (31.1) | 392 (28.6) |
| > 35% | 1 (0.1) | 2 (0.1) |
| Missing | 5 (0.4) | 1 (0.1) |
| **NYHA Heart Functional Classification, n (%)** | | |
| I | 1 (0.1) | 0 |
| II | 1356 (99.4) | 1372 (99.9) |
| III | 2 (0.1) | 1 (0.1) |
| IV | 0 | 0 |
| Missing | 5 (0.4) | 0 |
| **HF Etiology** | | |
| Ischemic, n (%) | 951 (69.7) | 935 (68.1) |
| Non-ischemic, n (%) | 410 (30.1) | 436 (31.8) |
| **Duration of HF (years)** | | |
| Ischemic, Mean (SD) | 5.4 (6.3) | 5.3 (5.9) |
| Non-ischemic, Mean (SD) | 3.4 (4.8) | 3.2 (4.4) |

| Characteristic | Eplerenone (n = 1,364) | Placebo (n = 1,373) |
|---|---|---|
| **Smoking Classification, n (%)** | | |
| Never Smoked | 603 (44.2) | 620 (45.2) |
| Current Smoker | 147 (10.8) | 146 (10.6) |
| Ex-smoker | 614 (45.0) | 607 (44.2) |
| **Serum Potassium (mmol/L)** | | |
| Mean (SD) | 4.3 (0.4) | 4.3 (0.4) |
| **Device Therapy, n (%)** | | |
| ICD | 178 (13.0) | 184 (13.4) |
| Pacemaker Implanted | 193 (14.1) | 200 (14.6) |
| Conventional Pacemaker | 90 (6.6) | 85 (6.2) |
| CRT[c] | 38 (2.8) | 22 (1.6) |
| ICD with CRT | 74 (5.4) | 99 (7.2) |

CRT = cardiac resynchronization therapy; ECG = electrocardiogram; EMPHASIS-HF = Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; HF = heart failure; FAS = full analysis set; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SD = standard deviation.
Source: Study CSR.[8]
[a]Includes ischemic, hemorrhagic, embolic, and "other" stroke.
[b]In non-paced baseline ECG.
[c]Biventricular pacing.

### 3.2.3 Interventions

Patients were randomized (1:1) to either eplerenone 25 mg orally once daily or placebo added to standard therapy (i.e., ACEI [and/or ARB] plus beta blocker), with the initial 25 mg dose of eplerenone up-titrated to 50 mg daily after one month, depending on K+ levels. Aside from standard therapy, permitted concomitant treatments included diuretics, digoxin, vasodilators, and inotropes. Potassium supplements were permitted on a case-by-case basis, according to the clinical judgment of the investigator. MRAs (i.e., spironolactone, potassium canrenoate), potassium-sparing diuretics, and potent CYP3A4 inhibitors or inducers were not permitted as concomitant therapies. Standard therapy was modified at the investigator's discretion, but centres were encouraged to treat patients with target or maximally tolerated doses of ACEI (and/or ARB) and beta blocker.

### 3.2.4 Outcomes

The primary efficacy outcome in EMPHASIS-HF was a composite of death from CV causes or first hospitalization for HF (Table 7). Other secondary end points included:

- composite of the first occurrence of all-cause mortality or a first hospitalization for HF
- first occurrence of any of the following:
  - all-cause mortality
  - CV mortality
  - all-cause hospitalization
  - hospitalization for HF
  - all-cause mortality or all-cause hospitalization
  - HF mortality or HF hospitalization
  - CV hospitalization
  - fatal or non-fatal MI
  - fatal or non-fatal stroke
  - implantation of cardiac defibrillator
  - implantation of a CRT device
  - new-onset AF or flutter (not an adjudicated event)
  - new-onset diabetes (not an adjudicated event)
  - worsening renal function (if it results in hospitalization)
  - hospitalization for hyperkalemia.

**TABLE 7: PRIMARY EFFICACY OUTCOME DEFINITIONS**

| Efficacy Outcome | Definition |
|---|---|
| CV mortality | Death due to HF, MI, cardiac arrhythmia, stroke/CVA, or other CV cause (e.g., aneurysm or pulmonary embolism) |
| Hospitalization for HF | An overnight stay, or longer, in a hospital environment (emergency room, observation unit or in-patient care, or similar facility, including admission to a day facility) with a discharge diagnosis that included a CV reason for hospitalization |

CV = cardiovascular; CVA = cerebrovascular accident; HF = heart failure; MI = myocardial infarction.
Source: CSR.[8]

There was no collection of quality of life data during EMPHASIS-HF. Likewise, there were no questionnaires (e.g., symptom scales) administered during the trial.

Safety data including adverse events, serious adverse events, and withdrawals due to adverse events (WDAEs) were collected according to regulatory requirements throughout the trial.

### 3.2.5 Statistical Analysis

EMPHASIS-HF was an end point-driven trial. It was initially estimated that 2,584 patients and a total of 813 primary events would be required to have at least 80% power to detect an 18% risk reduction in the primary efficacy end point (i.e., composite of death from CV causes or a first hospitalization for HF). Sample size estimations were based on a two-sided log-rank test for the between-treatment comparison in the time to first occurrence of the primary outcome at a 5% level of significance. The protocol was amended during the trial because the event rate was lower than expected, so the sample size was increased to 3,100 patients. EMPHASIS-HF was a trial with three planned equal interval efficacy looks (i.e., two interim analyses and the final analysis at the completion of the trial).

Interim analyses examining the primary efficacy end point were performed after a total of approximately 271 and 542 primary events had occurred. Statistical decisions on early trial termination for efficacy were based on the analysis of time to the composite primary end point. Upon accrual of 271 primary end points, the trial could be recommended for termination (by the Data Safety Monitoring Committee) if either an overwhelming benefit (two-sided *P* value < 0.0001 in favour of eplerenone), or an overwhelming harm (two-sided *P* value < 0.001 against eplerenone), was observed. Upon accrual of 542 primary end points, the trial could be recommended for termination if either an overwhelming benefit (two-sided *P* value < 0.001 in favour of eplerenone), or an overwhelming harm (two-sided *P* value < 0.01 against eplerenone), was observed. In addition, the trial could be recommended for termination for an excess of all-cause mortality on eplerenone (*P* value < 0.01), at any of the two interim looks to examine efficacy. Using an adaptation of the Haybittle-Peto stopping criterion, the *P* value for the final primary analysis was compared with alpha = 0.049. No adjustment in alpha was made for any looks on parameters/end points other than the primary composite end point.

**TABLE 8: THRESHOLDS FOR STOPPING THE TRIAL**

| Timing of Interim Look | End Points | | |
|---|---|---|---|
| | CV Mortality/ HF Hospitalization (Primary End Point) | | All-Cause Mortality |
| | Eplerenone superior | Eplerenone inferior | Eplerenone inferior |
| **At 271 Events** | *P* < 0.0001 | *P* < 0.001 | *P* < 0.01 |
| **At 542 Events** | *P* < 0.001 | *P* < 0.01 | *P* < 0.01 |

CV = cardiovascular; HF = heart failure.

The enrolment for the double-blind phase of the trial was stopped after the second interim analysis. At that time, the data and safety monitoring committee reported that the pre-specified stopping boundary for benefit had been crossed. Eligible patients in the trial were transitioned to receive open-label eplerenone as part of the open-label extension trial. (APPENDIX 5: OPEN-LABEL EXTENSION STUDY SUMMARY for details.)

Available data from all randomized patients were analyzed according to the patients' original treatment assignment. Time-to-event analyses were modelled using Cox's proportional hazards approach. The regression model was adjusted for the following baseline characteristics: age, eGFR, LVEF, body mass index, hemoglobin, heart rate, systolic blood pressure, diabetes mellitus (yes or no), history of hypertension (yes or no), prior MI (yes or no), baseline left bundle branch block or baseline QRS > 130 ms (yes or no), AF. Treatment effects in the incidence rates of binary outcomes were assessed by the Cochran–Mantel-Haenszel general association test, stratified by region.

Pre-specified subgroup analyses were analyzed using the log-rank test without any baseline covariate adjustment. These subgroups were gender, age (< 65/≥ 65; < 75/≥ 75), region, baseline systolic blood pressure and pulse pressure, baseline heart rate, baseline eGFR, baseline NYHA class (I and II versus III and IV), etiology of HF (ischemic/non-ischemic), prior beta blocker plus ACEI plus ARB use, prior beta blocker use, LVEF (< 30% and ≥ 30%), AF, diabetes mellitus, history of hypertension, patients with prior hospitalization, prior CRT or ICD insertion procedures, QRS >130 ms, and left bundle branch block.

Serious adverse events, adverse events, and adverse events leading to permanent study-drug withdrawal were tabulated according to randomized group assignment and analyzed by means of Fisher's exact test.[7]

### a) Analysis Populations

The primary analysis set for performing efficacy analyses in EMPHASIS-HF was the full analysis set (FAS), which included all randomized patients; there was no per-protocol analysis set defined. The safety analysis set included all randomized patients who received at least one dose of study drug. Data from both the FAS and safety analysis sets were analyzed according to randomized treatment assignment, irrespective of actual treatment received.

## 3.3 Patient Disposition

In EMPHASIS-HF, a total of 2,737 patients were randomized: 1,364 to eplerenone and 1,373 to placebo; the randomized set comprised the FAS. Four patients from each group never received treatment. Median follow-up was 21 months, for a total of 4,783 patient-years of follow-up.[7] The number of patients who discontinued treatment prematurely for reasons other than death was similar between eplerenone (222 [16.3%]) and placebo (228 [16.6%]) groups. The most common reason for discontinuation (other than death) was reported as the patient being no longer willing to participate in the trial (eplerenone: 101 [7.4%]; placebo: 113 [8.3%]). At the end of the double-blind phase, follow-up

for clinical end points was nearly complete in both groups (98.8% versus 98.9% respectively). See Table 9.

**TABLE 9: PATIENT DISPOSITION**

| | EMPHASIS-HF[8] | |
|---|---|---|
| | **EPL** | **PL** |
| **Screened, N** | 3,027 | |
| **Randomized, N (%)** | 1,364 (45.1) | 1,373 (45.4) |
| **Discontinued,[a] N (%)** | 222 (16.3) | 228 (16.6) |
| *Most common reason[a]* | | |
| No longer willing to participate in the trial | 101 (7.4) | 113 (8.3) |
| **WDAEs, N (%)** | 188 (13.8) | 222 (16.2) |
| **Lost to follow-up, N (%)** | 17 (1.2) | 15 (1.1) |
| **FAS, N** | 1,364 (100.0) | 1,373 (100.0) |
| **PP, N** | NR | NR |
| **Safety, N** | 1,360 (99.7) | 1,369 (99.7) |

EMPHASIS-HF = Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; EPL = eplerenone; FAS = full analysis set; NR = not reported; PL = placebo; PP = per-protocol; WDAE = withdrawal due to adverse event.
Source: Study CSR.[8]
[a]Does not include discontinuations due to death.

## 3.4 Exposure to Study Treatments

At month 5, 61.3% of eplerenone-treated patients were successfully up-titrated to the 50 mg dose compared with 66.3% in the placebo group. At the end of the trial cut-off, 54.4% of eplerenone-treated patients were taking the 50 mg dose, while the mean daily dose (SD) was 37.4 (14.2) mg; the corresponding values in the placebo group were 60.1% and 39.2 (13.6) mg.

Median study follow-up duration (i.e., from randomization until study end or cut-off date) was 646 days (range: 0 to 1504) in the eplerenone group and 603 days (range: 0 to 1,499) in the placebo group.

## 3.5 Critical Appraisal

### 3.5.1 Internal Validity

Overall, the trial was adequately designed and executed with appropriate blinding, allocation concealment, randomization (by permuted block design), and centralized event adjudication for primary and secondary efficacy outcomes (except for new-onset AF or flutter or new-onset diabetes). Participant follow-up was nearly complete at the end of the double-blind phase.

Although investigators were encouraged to treat patients using evidence-based or maximally tolerated doses of standard therapies (i.e., ACEIs, ARBs, beta blockers), such prescribing decisions were left to the discretion of the individual site investigators. Given that less than half of patients were taking an ACEI or ARB concomitantly with eplerenone during the open-label extension phase (APPENDIX 5: OPEN-LABEL EXTENSION STUDY SUMMARY), it is uncertain to what extent these therapies may have been discontinued during the double-blind phase of the trial under the auspices of clinical judgment. It is also uncertain whether ACEI, ARB, or beta blocker discontinuation rates differed between treatment arms, which could bias the observed effect estimates.

Patients with diabetes often have comorbid HF with more severe symptoms; they are also at higher risk than non-diabetic patients for hospitalizations due to HF.[18] AF is also a common comorbidity in HF and its development quite often signals a worsening in HF symptoms.[18] New diabetes or new AF or flutter cases were not adjudicated events; rather, they were determined and reported by individual clinical centres. These events may therefore have been under- or over-reported due to variations in clinical practice guidelines or practice patterns between countries or regions.

### 3.5.2 External Validity

The primary efficacy outcome in EMPHASIS-HF was a hard clinical end point — the composite of CV death or hospitalization for HF, analyzed as time to first event, the individual components of which are considered clinically meaningful end points.[19]

EMPHASIS-HF enrolled primarily older, Caucasian, male patients; female and Black patients were under-represented. However, the consulting clinical expert indicated that the profile of the enrolled population was not inconsistent with the type of patient treated in clinical practice in Canada. It should be noted that US guidelines[9] cite epidemiologic data that showed both a higher incidence and higher five-year mortality rate of HF in Black men; by comparison, the incidence rate of HF was lowest in Caucasian women and five-year mortality rate lower among Caucasian patients overall than Black patients.

Most clinical practice guidelines[1,4,9] recommend an ACEI or ARB plus beta blocker as initial therapy in chronic systolic HF, but not triple combination therapy. Likewise, the consulting clinical expert confirmed that a triple combination strategy was uncommon in clinical practice. Nonetheless, patients taking a combination of ACEI, ARB, and beta blocker were potentially eligible for enrolment at baseline, although it is unclear what percentage of patients used all three therapies.

Recent hospitalization or elevated brain natriuretic peptide were additional inclusion criteria in EMPHASIS-HF, both of which likely served to elevate the baseline CV risk in the trial population. As a result of this excess CV risk, it is possible that the level of CV risk of the trial cohort was higher than typically encountered among patients with NYHA class II HF in clinical practice.[18]

According to the European Society of Cardiology,[1] patients with chronic heart failure are considered to be clinically stable if signs and symptoms of HF have remained unchanged for at least one month. In EMPHASIS-HF, NYHA functional class was assessed at the screening visit, but not again until the first visit post-randomization. Although the interval between screening and randomization visits could have extended beyond one month, the manufacturer reports that 90% and 95% of patients had their screening NYHA class determined three days and six days, respectively, prior to randomization.[20] It can therefore be assumed that the screening NYHA class was still reflective of the patient's prevailing NYHA classification at the time of randomization.

North American patients represented less than 10% of the trial population, within which Canadian patients numbered just 38 (1.4%). In the trial's regional subgroup analyses, North America was combined with South America. Although this was likely done for pragmatic reasons (i.e., balancing numbers of participants per subgroup), from a socioeconomic perspective, grouping North America with Western Europe and Australia may have been more reasonable, owing to these regions' similar levels of prosperity, health care resources, and agreement in the clinical management of HF. Examining how North America fared as a region in EMPHASIS-HF with respect to consistency of results compared with the main trial population was identified as a subgroup analysis of interest in the systematic review protocol; however, this was complicated by the relatively small number of participants recruited into

the trial from North America and its subgroup pairing with South America, an economically diverse region whose prosperity, health care resources, and practice patterns may diverge substantially from North America's.

Although a surrogate marker, LVEF is a recognized prognostic indicator in HF.[1] Beyond the availability of hard, clinical end point data in EMPHASIS-HF, the consulting clinical expert considered LVEF a relevant supplemental outcome that could influence the treatment decisions made by clinicians; however, LVEF was not measured during the EMPHASIS-HF trial. It should be noted that serial measurement of LVEF is not routinely recommended by Canadian and US clinical practice guidelines.[4,9] Without a compelling reason to test sooner (e.g., change in clinical status), Canadian and US guidelines[4,9] suggest reserving echocardiographic reassessment for annual intervals. European guidelines are less clear on the matter.[1]

## 3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 4). See APPENDIX 4: DETAILED OUTCOME DATA for detailed efficacy data.

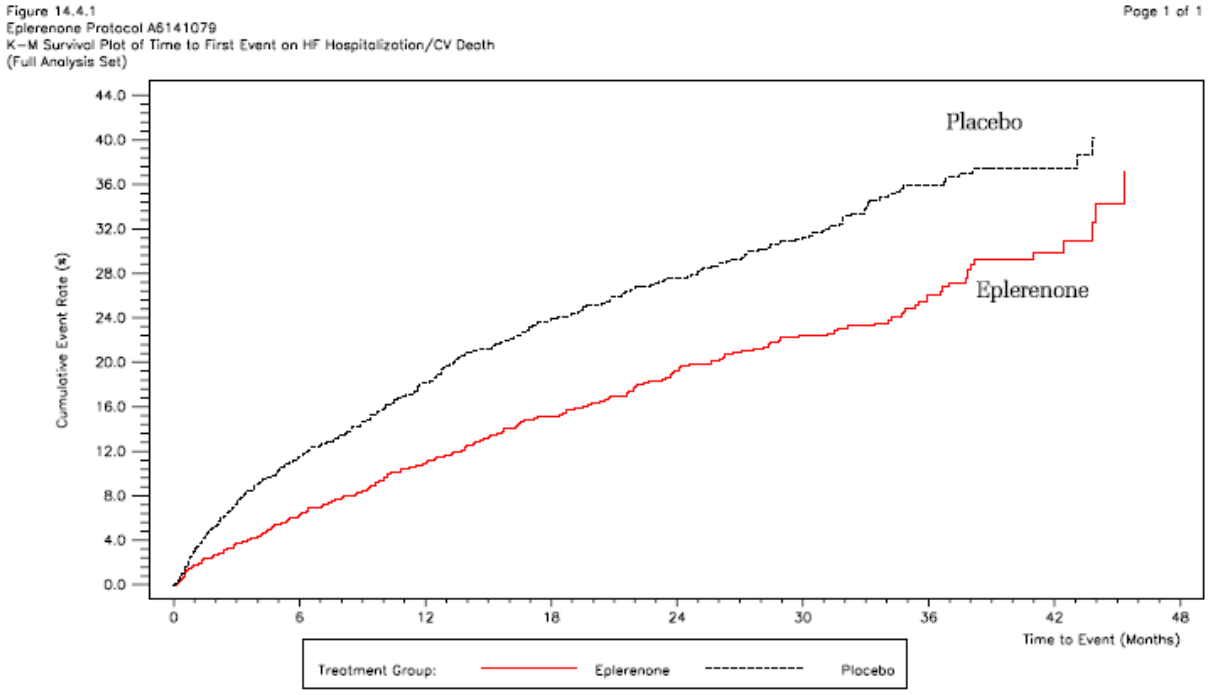
### 3.6.1 Mortality

**a) Composite of cardiovascular death or heart failure hospitalization (primary efficacy end point)**

The primary efficacy end point occurred in 249 (18.3%) patients in the eplerenone group compared with 356 (25.9%) patients in the placebo group; this translated into a statistically significant difference in the time to the composite primary end point of CV death or first HF hospitalization favouring eplerenone (HR 0.63; 95% CI, 0.54 to 0.74) (Figure 2) (Table 10).

The following subgroups identified as being of interest in the systematic review protocol were examined in the trial: LVEF (< 30%, ≥ 30%), age (< 75 years, ≥ 75 years), baseline eGFR, diabetes, and geographical region. However, no data were available for two of the subgroups of interest: daily dose of eplerenone (25 mg, 50 mg); refractory to, or intolerant of, spironolactone (Table 14). In these subgroups, results were consistent with those of the main trial findings in that eplerenone was favoured compared with placebo on the primary composite outcome; there were therefore no treatment-by-subgroup interactions observed.

**FIGURE 2: KAPLAN–MEIER SURVIVAL PLOT OF TIME TO FIRST EVENT OF HEART FAILURE HOSPITALIZATION OR CARDIOVASCULAR DEATH**




Source: Study CSR.[8]

### b) All-cause mortality

All-cause mortality was a secondary efficacy outcome, which occurred in 171 (12.5%) patients in the eplerenone group compared with 213 (15.5%) in the placebo group; this translated into a statistically significant difference in time to all-cause mortality favouring eplerenone (HR 0.76; 95% CI, 0.62 to 0.93) (Table 10) (Figure 6).

### c) Death from cardiovascular causes

CV mortality as an individual end point was a secondary efficacy outcome, which occurred in 147 (10.8%) patients in the eplerenone group compared with 185 (13.5%) in the placebo group; this translated into a statistically significant difference in time to CV death favouring eplerenone (HR 0.76; 95% CI, 0.61 to 0.94) (Table 10) (Figure 5).

Of note, the eplerenone product monograph[21] indicates that a benefit on CV mortality — a secondary efficacy outcome in EMPHASIS-HF — was not observed in patients aged $\geq$ 75 years. In the trial, the results for this subgroup were reported as 51 (15.5%) CV deaths in the eplerenone group compared with 51 (15.6%) in the placebo group with an associated HR of 0.98 (95% CI, 0.67 to 1.45).

### d) Sudden cardiac death

Sudden cardiac death was a secondary efficacy outcome, which occurred in 60 (4.4%) patients in the eplerenone group compared with 76 (5.5%) in the placebo group; however, there was no statistically significant difference between groups in the time to this event (HR 0.76; 95% CI, 0.54 to 1.07) (Table 13).

### 3.6.2 Morbidity

**a) Fatal or non-fatal myocardial infarction**

Fatal or non-fatal MI was a secondary efficacy outcome, which occurred in 45 (3.3%) patients in the eplerenone group compared with 33 (2.4%) in the placebo group; however, there was no statistically significant difference between groups in the time to this event (HR 1.32; 95% CI, 0.84 to 2.06) (Table 13).

**b) Fatal or non-fatal stroke**

Fatal or non-fatal stroke was a secondary efficacy outcome, which occurred in 21 (1.5%) patients in the eplerenone group compared with 26 (1.9%) in the placebo group; however, there was no statistically significant difference between groups in the time to this event (HR 0.79; 95% CI, 0.44 to 1.41) (Table 13).

**c) All-cause hospitalization**

All-cause hospitalization was a secondary efficacy outcome, which occurred in 408 (29.9%) patients in the eplerenone group compared with 491 (35.8%) in the placebo group; this translated into a statistically significant difference in the time to all-cause hospitalization favouring eplerenone (HR 0.77; 95% CI, 0.67 to 0.88) (Table 10) (Figure 4).

**Heart failure-related hospitalizations**

HF-related hospitalization, as an individual end point, was a secondary efficacy outcome, which occurred in 164 (12.0%) patients in the eplerenone group compared with 253 (18.4%) in the placebo group; this translated into a statistically significant difference in the time to HF-related hospitalization favouring eplerenone (HR 0.58; 95% CI, 0.47 to 0.70) (Table 10) (Figure 3).

**Cardiovascular-related hospitalizations**

CV-related hospitalization was a secondary efficacy outcome, which occurred in 304 (22.3%) patients in the eplerenone group compared with 399 (29.1%) in the placebo group; this translated into a statistically significant difference in time to CV-related hospitalization favouring eplerenone (HR 0.69; 95% CI, 0.60 to 0.81) (Table 10).

### 3.6.3 Other Efficacy Outcomes

**a) Development of new atrial fibrillation or flutter**

Development of new AF or flutter was a secondary outcome that was a non-adjudicated event; instead, it was assessed and reported directly by the clinical sites. Worsening AF, although identified as an outcome of interest in the systematic review protocol, was not reported.

Of the 1,887 (68.9%) patients included in the analysis, 32 of 950 (3.4%) patients in the eplerenone group compared with 52 of 937 (5.5%) in the placebo group developed new AF or flutter; this was associated with an HR of 0.59 (95% CI, 0.38 to 0.91) favouring eplerenone (Table 13).

**b) Implantation of cardioverter-defibrillator or cardiac resynchronization therapy device**

Implantation of a cardioverter-debrillator or a cardiac resynchronization therapy device was an individual secondary outcome. Implantation of a cardioverter-defibrillator occurred in 61 (4.5%) patients in the eplerenone group compared with 59 (4.3%) in the placebo group (HR 0.99; 95% CI, 0.69 to 1.42) while cardiac resynchronization device implantation occurred in 33 (2.4%) and 41 (3.0%) patients, respectively (HR 0.77; 95% CI, 0.49, 1.22) (Table 13).

**c) Quality of life**

There were no quality of life data collected during the trial.

### d) Change in New York Heart Association class

There were no analyses available on the change in NYHA class during the trial.

**TABLE 10: KEY EFFICACY OUTCOMES**

| | EMPHASIS-HF[8] | |
|---|---|---|
| **Primary: CV Death or HF Hospitalization[a]** | **EPL** | **PL** |
| N (%) | **249 (18.3)** | **356 (25.9)** |
| HR[b] | **0.63** | |
| 95% CI | **0.54 to 0.74** | |
| *P* value | **< 0.0001** | |
| **All-Cause Mortality** | | |
| N (%) | 171 (12.5) | 213 (15.5) |
| HR | 0.76 | |
| 95% CI | 0.62 to 0.93 | |
| *P* value | 0.0081 | |
| **CV Mortality** | | |
| N (%) | 147 (10.8) | 185 (13.5) |
| HR | 0.76 | |
| 95% CI | 0.61 to 0.94 | |
| *P* value | 0.012 | |
| **All-Cause Hospitalization** | | |
| N (%) | 408 (29.9) | 491 (35.8) |
| HR | 0.77 | |
| 95% CI | 0.67 to 0.88 | |
| *P* value | < 0.0001 | |
| **HF Hospitalization** | | |
| N (%) | 164 (12.0) | 253 (18.4) |
| HR | 0.58 | |
| 95% CI | 0.47 to 0.70 | |
| *P* value | < 0.0001 | |
| **CV Hospitalization** | | |
| N (%) | 304 (22.3) | 399 (29.1) |
| HR | 0.69 | |
| 95% CI | 0.60 to 0.81 | |
| *P* value | < 0.0001 | |

CI = confidence interval; CV = cardiovascular; EMPHASIS-HF = Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; EPL = eplerenone; HF = heart failure; HR = hazard ratio; PL = placebo.
[a]Outcomes identified as important to the review (Section 2.2.1 for review protocol).
[b]Adjusted HRs presented.
Source: Study CSR[8], Zannad et al., 2011.[7]

## 3.7 Harms

Only those harms identified in the review protocol are reported below (2.2.1 Protocol). See APPENDIX 4: DETAILED OUTCOME DATA for detailed harms data.

Because the trial was stopped early for efficacy reasons, the risk of adverse events conferred by eplerenone in the population studied may be underestimated, as a consequence of the shorter period during which patients were exposed to treatment. In addition, the interpretation of adverse events data

is complicated by the overlap between clinical (efficacy) event and adverse event data, where efficacy outcomes such as CV events were included in the reporting of the overall incidence of adverse events.

### 3.7.1 Adverse Events

Adverse events occurred with similar frequency in the eplerenone (72.0%) and placebo (73.6%) groups. Except for cardiac failure (EPL 17.4% versus PL 21.8%) and hyperkalemia (EPL 8.0% versus PL 3.7%), individual adverse events occurred at low frequencies in both groups without particular patterns of concentration.

### 3.7.2 Serious Adverse Events

SAEs — except cardiac failure (EPL 13.8% versus PL 17.8%) — were infrequent and unremarkable in distribution, including the frequencies of renal impairment (EPL 1.8% versus PL 1.3%), hyperkalemia (EPL 1.2% versus PL 0.5%), and hypotension (EPL 0.2% versus PL 0.4%).

### 3.7.3 Withdrawals due to Adverse Events

WDAEs occurred in 188 (13.8%) patients in the eplerenone group and 222 (16.2%) in the placebo group, while temporary discontinuations or dose reductions due to adverse events occurred in 229 (16.8%) and 185 (13.5%) patients, respectively. The most common reason for permanent WDAE was hyperkalemia (EPL 1.1% versus 0.9%).[7]

### 3.7.4 Notable Harms

The clinical expert consulted by CDR identified three harms of interest: hyperkalemia (EPL 8.0% versus PL 3.7%), renal impairment (EPL 4.2% versus PL 2.6%), and hypotension (EPL 3.4% versus PL 2.7%), of which hyperkalemia was the most frequently occurring. The incidence of hyperkalemia was additionally reported according to K+ threshold (> 5.5 mEq/L, > 6 mEq/L): 158 (11.8%) patients in the eplerenone group and 96 (7.2%) in the placebo group had a serum K+ level > 5.5 mEq/L while 33 (2.5%) and 25 (1.9%), respectively, had a serum K+ > 6 mEq/L.

Two other harms of interest were gynecomastia and new diabetes diagnosis. A reduction in the incidence of gynecomastia, a known adverse effect of spironolactone,[5] is a proposed advantage of eplerenone therapy.[18] Likewise, perturbations in blood glucose have been reported previously with spironolactone;[18] thus, examining the risk of iatrogenic dysglycemia from eplerenone therapy is a relevant safety outcome given that patients with heart failure often co-present with diabetes.[18] In EMPHASIS-HF, “gynecomastia or other breast disorders” occurred in 10 (0.7%) patients in the eplerenone group and 14 (1.0%) in the placebo group.[7] New-onset diabetes was a non-adjudicated, secondary efficacy outcome in the trial. There was no difference in the incidence of new diabetes diagnosis between patients taking eplerenone (34/904 [3.8%]) or those taking placebo (40/973 [4.1%]) (HR 0.89; 95% CI, 0.56 to 1.40).

**TABLE 11: HARMS**

| | EMPHASIS-HF[8] | |
|---|---|---|
| **AEs[a]** | **EPL** | **PL** |
| Patients with ≥1 AEs, N (%) | 979 (72.0) | 1007 (73.6) |
| **Most common AEs (≥2%)** | | |
| Cardiac failure | 236 (17.4) | 298 (21.8) |
| Hyperkalemia | 109 (8.0) | 50 (3.7) |
| Dyspnea | 58 (4.3) | 70 (5.1) |
| Renal impairment | 57 (4.2) | 36 (2.6) |
| Dizziness | 55 (4.0) | 60 (4.4) |
| Bronchitis | 52 (3.8) | 53 (3.9) |
| Cough | 51 (3.8) | 41 (3.0) |
| Chest pain | 50 (3.7) | 56 (4.1) |
| Atrial fibrillation | 48 (3.5) | 63 (4.6) |
| Hypotension | 46 (3.4) | 37 (2.7) |
| Nasopharyngitis | 45 (3.3) | 42 (3.1) |
| Peripheral edema | 44 (3.2) | 62 (4.5) |
| Fatigue | 38 (2.8) | 47 (3.4) |
| Upper respiratory tract infection | 36 (2.6) | 32 (2.3) |
| Syncope | 34 (2.5) | 28 (2.0) |
| Diarrhea | 33 (2.4) | 42 (3.1) |
| Pneumonia | 32 (2.4) | 36 (2.6) |
| Back pain | 31 (2.3) | 35 (2.6) |
| Constipation | 28 (2.1) | 13 (0.9) |
| Diabetes mellitus | 29 (2.1) | 25 (1.8) |
| Gout | 29 (2.1) | 32 (2.3) |
| Headache | 29 (2.1) | 29 (2.1) |
| Hypertension | 28 (2.1) | 39 (2.8) |
| Myocardial infarction | 29 (2.1) | 29 (2.1) |
| Nausea | 29 (2.1) | 38 (2.8) |
| Pruritus | 29 (2.1) | 15 (1.1) |
| Urinary tract infection | 29 (2.1) | 28 (2.0) |
| Pain in extremity | 27 (2.0) | 25 (1.8) |
| Death | 26 (1.9) | 35 (2.6) |
| Renal failure | 26 (1.9) | 32 (2.3) |
| Angina pectoris | 24 (1.8) | 31 (2.3) |
| Ventricular tachycardia | 25 (1.8) | 31 (2.3) |
| Hypokalemia | 16 (1.2) | 30 (2.2) |
| **SAEs** | | |
| Patients with ≥1 SAEs, N (%) | 509 (37.4) | 614 (44.9) |
| Most common SAEs (≥1%) | | |
| Cardiac failure | 187 (13.8) | 243 (17.8) |
| Myocardial infarction | 29 (2.1) | 29 (2.1) |
| Death | 26 (1.9) | 34 (2.5) |
| Renal impairment | 25 (1.8) | 18 (1.3) |
| Syncope | 25 (1.8) | 21 (1.5) |
| Unstable angina | 24 (1.8) | 23 (1.7) |
| Atrial fibrillation | 22 (1.6) | 30 (2.2) |
| Pneumonia | 22 (1.6) | 29 (2.1) |

| | EMPHASIS-HF[8] | |
|---|---|---|
| **AEs[a]** | **EPL** | **PL** |
| Chest pain | 21 (1.5) | 28 (2.0) |
| Ventricular tachycardia | 17 (1.3) | 27 (2.0) |
| Hyperkalemia | 16 (1.2) | 7 (0.5) |
| Cerebrovascular accident | 15 (1.1) | 19 (1.4) |
| Cardiac arrest | 13 (1.0) | 15 (1.1) |
| Congestive cardiac failure | 13 (1.0) | 19 (1.4) |
| Dyspnea | 14 (1.0) | 28 (2.0) |
| Sudden death | 10 (0.7) | 24 (1.8) |
| **WDAEs[b]** | | |
| WDAEs, N (%) | 188 (13.8) | 222 (16.2) |
| Most common reasons | | |
| Hyperkalemia[7] | 15 (1.1) | 12 (0.9) |
| Hypokalemia[7] | 0 | 3 (0.2) |
| Renal failure[7] | 4 (0.3) | 6 (0.4) |
| Hypotension[7] | 0 | 3 (0.2) |
| Gynecomastia or other breast disorders[7] | 2 (0.1) | 2 (0.1) |
| **Notable Harms** | | |
| Hyperkalemia | 109 (8.0) | 50 (3.7) |
| Hypotension | 46 (3.4) | 37 (2.7) |
| Renal impairment | 57 (4.2) | 36 (2.6) |
| Gynecomastia or other breast disorders[7] | 10 (0.7) | 14 (1.0) |
| New diabetes diagnosis | 34 (3.8) | 40 (4.1) |

AE = adverse event; EMPHASIS-HF = Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; EPL = eplerenone; PL = placebo; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
[a]Outcomes identified as important to the review (Table 2 for review protocol).
[b]Only the top five reasons were reported.

# 4. DISCUSSION

## 4.1 Summary of Available Evidence

The evidence for this review was drawn from one phase III (EMPHASIS-HF) double-blind, randomized (1:1), placebo-controlled trial comprising 2,737 patients with NYHA class II chronic systolic heart failure and left ventricular systolic dysfunction, during which patients received either eplerenone 25 mg daily (increasing to 50 mg daily after four weeks) or matching placebo. The primary efficacy outcome in EMPHASIS-HF was a composite of death from CV causes or a first hospitalization for heart failure. Designed as an event-driven trial, EMPHASIS-HF was originally planned to run approximately 48 months until 813 primary efficacy end points had occurred. However, the trial was stopped early after a median of 21 months of follow-up when an interim analysis revealed that the pre-specified stopping rules for efficacy had been met.

## 4.2 Interpretation of Results

### 4.2.1 Efficacy

The primary efficacy outcome of EMPHASIS-HF was a composite of death from CV causes or a first hospitalization for HF. This occurred in 249 (18.3%) patients in the eplerenone group compared with 356 (25.9%) patients in the placebo group, favouring eplerenone (HR 0.63; 95% CI, 0.54 to 0.74). An examination of the individual components of the composite suggests that the primary driver was the

reduction in first hospitalization for HF (HR 0.58; 95% CI, 0.47 to 0.70); by comparison, the magnitude of the reduction in risk over time was smaller for CV death (HR 0.76; 95% CI, 0.61 to 0.94). The number needed to treat (NNT) to prevent one primary outcome event per year of follow-up was reported to be 19 (95% CI, 15 to 27) while the NNT to postpone one death per year of follow-up was reported to be 51 (95% CI, 32 to 180).[7] Mechanistically, the reduction in the risk of hospitalizations for HF from eplerenone treatment has been postulated to arise from its blood pressure lowering and diuretic effects, which are pharmacologic properties of the MRA class.[22]

Although the systematic review protocol identified all-cause mortality as the key efficacy outcome, all-cause mortality was studied only as a secondary outcome in EMPHASIS-HF. The investigators indicated that a cause-specific end point was justified on the basis that eplerenone was not expected to have an effect on non-CV death.[17] Nonetheless, during the trial, death from all causes was less frequent in the eplerenone group (171 [12.5%]) than in the placebo group (213 [15.5%]) (HR 0.76; 95% CI, 0.62 to 0.93). This pattern of a statistically significant difference favouring eplerenone was repeated for the following secondary efficacy outcomes identified in the systematic review protocol (although it should be noted that there was no statistical adjustment for multiple testing):

- Death from CV causes (HR 0.76; 95% CI, 0.61 to 0.94).
- All-cause hospitalizations (HR 0.77; 95% CI: 0.67 to 0.88).
- HF hospitalizations (HR 0.58; 95% CI, 0.47 to 0.70).
- CV hospitalization (HR 0.69; 95% CI, 0.60 to 0.81).
- Development of AF or flutter (HR 0.59; 95% CI, 0.38 to 0.91).

For the remaining secondary outcomes identified in the systematic review protocol, there were no statistically significant differences between groups:

- Sudden cardiac death (HR 0.76; 95% CI, 0.54 to 1.07).[7]
- Fatal or non-fatal MI (HR 1.32; 95% CI: 0.84 to 2.06).
- Fatal or non-fatal stroke (HR 0.79; 95% CI, 0.44 to 1.41).
- Insertion of ICD (HR 0.99; 95% CI: 0.69 to 1.42) or CRT device (HR 0.77; 95% CI, 0.49 to 1.22).

It is interesting to note that the direction of the estimate of the treatment effect for the composite secondary outcome of fatal or non-fatal MI went against eplerenone; although the result was not statistically significant, it was nonetheless a unique finding among the outcomes examined in this review.

The findings from the subgroups of interest identified in the systematic review protocol (i.e., LVEF < 30%, $\geq$ 30%; age < 75 years, $\geq$ 75 years; baseline eGFR; diabetes; geographical region) were consistent with the main trial findings in that eplerenone was favoured compared with placebo. There were no treatment-by-subgroup interactions noted. There were no subgroup data available for eplerenone dosing (i.e., 25 mg, 50 mg) or for patients refractory to, or intolerant of, spironolactone. As stated in the product monograph,[21] no benefit on CV mortality (secondary outcome) was observed in the subgroup of patients $\geq$ 75 years old, creating some uncertainty with respect to the interpretation of the primary (composite) outcome in this patient group.

At baseline, 93% of patients were taking an ACEI and/or ARB and 87% of patients were taking a beta blocker; these usage rates were similar at the end of the double-blind phase of the trial.[20] It is therefore unclear why, upon entry into the open-label extension phase that immediately followed the double-blind phase, fewer than 50% of patients were using an ACEI and/or ARB, although this does not directly affect the interpretation of the findings from the double-blind phase.

Given the multinational scope of the trial and the associated diversity in economic prosperity, health care resources and clinical practice patterns, along with the relatively small proportion of North American patients represented within the trial population (< 10%), generalizability of the results to a Canadian context is challenging, particularly when the number of Canadian patients studied was just 38 (1.4%). Moreover, trial patients were mostly older, male, and white, with a baseline level of CV risk that may be in excess of the risk level that typifies NYHA class II HF patients encountered in Canadian clinical practice.

To what extent the findings regarding eplerenone from EMPHASIS-HF may compare with spironolactone therapy remains unknown, as an evidence gap persists with respect to the use of spironolactone in patients with NYHA class I-II HF. Although the decision to use a placebo as the comparator in EMPHASIS-HF could be argued as reasonable, the trial has been criticized[23] for not taking the opportunity to additionally study the comparative effectiveness and safety of eplerenone against spironolactone. Evidence from the Randomized Aldactone Evaluation Study (RALES) trial demonstrating the benefit of spironolactone on all-cause mortality,[24] published in 1999, is limited to patients with (severe) NYHA class III-IV HF. A literature search performed by CDR was unable to uncover any direct evidence comparing eplerenone with spironolactone on clinical outcomes in a population representative of the indication for eplerenone under review. A small (n=107) study by Yamaji et al.[25] of four months' duration compared the metabolic effects of the two agents, but did not look at clinical outcomes. Although a retrospective analysis[26] reported benefits of spironolactone usage in NYHA I/II patients, the retrospective design, small sample size, lack of consistent outcome collection, and the possibility of residual confounders rendered the results of this study inconclusive with respect to the efficacy of spironolactone in patients with mild HF. Likewise, systematic reviews and indirect comparisons have been published of eplerenone and spironolactone, such as one by Chatterjee et al.,[27] which concluded that eplerenone was not more effective than spironolactone. However, this analysis mixed various indications and severities of heart failure and therefore did not clarify the relative effectiveness of eplerenone versus spironolactone in mild NYHA HF. Several other meta-analyses investigating the effects of aldosterone antagonists as a class in NYHA class I/II patients were identified;[27-29] however, these studies were not sufficiently informative regarding the specific benefit-risk profile of spironolactone. Overall, the published data for spironolactone in NYHA I/II patients do not provide conclusive evidence for its clinical effectiveness, or the presence of a class effect for MRAs in this population.

In spite of the dearth of evidence, clinicians — including the expert consulted for this review — report using spironolactone in milder HF.[22] The reasons range from cost,[22] to insurance coverage issues (in the case of the clinical expert consulted for this review), and the belief that the difference between the agents resides not in efficacy but in receptor selectivity and therefore adverse effect profile.[9,22] Eplerenone, in having lower affinity for androgen and progesterone receptors, may be associated with fewer sexual adverse effects (e.g., gynecomastia) compared with spironolactone.[18] Clinical practice guidelines from the Canadian Cardiovascular Society[4] make recommendations on the use of MRAs strictly in line with the findings of RALES,[24] EPHESUS,[30] and EMPHASIS-HF, by suggesting specific MRA agents. In contrast, American[9] and European[1] guidelines are more nuanced in terms of their recommendations, citing the same evidence along with uncertainty about interchangeability, but remaining less absolute in their tone about the use of one MRA agent over another.

Concerns regarding the detrimental impact of HF on quality of life and the ability to perform activities of daily living figured prominently in the patient group input received by CDR. Unfortunately, no quality of life data were collected during the trial. Instead, the manufacturer made use of published health utilities for modelling the effect of treatment on quality of life in the pharmacoeconomic submission.[31] These

data were primarily derived from a subset of EPHESUS, a trial[30-32] that studied patients post-acute MI who developed HF or had diabetes, in association with an LVEF ≤ 40 %. There is some uncertainty as to how reflective these utilities are of patients enrolled in EMPHASIS-HF. Likewise, NYHA class data were collected during the trial, but not analyzed, and so it is unknown how patients' symptoms may have changed (i.e., improved, worsened, or stayed the same) over the course of the trial. Because improving HF-related symptomatology is a central objective of treatment in HF,[1] the lack of data on symptoms or quality of life is an important limitation of the evidence available from EMPHASIS-HF.

### 4.2.2 Harms

Because the trial was stopped early for efficacy reasons, the risk of adverse events conferred by eplerenone in the population studied may be underestimated as a consequence of the shorter period during which patients were exposed to treatment. In addition, the interpretation of adverse events data is complicated by the overlap between clinical (efficacy) event and adverse event data, where efficacy outcomes such as CV events were included in the reporting of the overall incidence of adverse events.

The overall frequency of adverse events (which included CV events) was similar between eplerenone (72.0%) and placebo (73.6%) groups. Individual adverse events — except cardiac failure (17.4% versus 21.8%) and hyperkalemia (8.0% versus 3.7%) — occurred at low frequencies between both groups without particular pattern of concentration. By way of comparison, hyperkalemia in the EPHESUS trial[30] appeared less frequent (EPL 3.4% versus PL 2.0%), possibly because of the lower disease severity or differences in background therapy in this population. In RALES,[24] only serious hyperkalemia (serum K+ ≥ 6 mEq/L) was reported (spironolactone [SPI] 2% versus PL 1%); the corresponding rates for serious hyperkalemia in EMPHASIS-HF were 2.5% (EPL) versus 1.9% (PL). Gynecomastia or other breast disorders were infrequent (0.7% versus 1.0%) in EMPHASIS-HF; in RALES,[24] gynecomastia was reported 10 times more frequently with spironolactone treatment than with placebo (10% versus 1%). Due to differences in populations and treatments between the EMPHASIS-HF and RALES trials, absolute adverse event rates for eplerenone and spironolactone cannot be reliably compared across trials. However, the large difference in the relative risks for gynecomastia between eplerenone in EMPHASIS-HF and spironolactone in RALES, combined with the reported differences in androgenic receptor affinities between the two drugs,[11] suggest that eplerenone is associated with a lower risk of gynecomastia than spironolactone.

Serious adverse events — except cardiac failure (EPL 13.8% versus PL: 17.8%) — were similarly infrequent and unremarkable in distribution, including renal impairment (EPL 1.8% versus PL 1.3%) and hyperkalemia (EPL 1.2% versus PL 0.5%). WDAEs occurred in 188 (13.8%) patients in the eplerenone group and 222 (16.2%) in the placebo group, while temporary discontinuations or dose reductions due to adverse events occurred in 229 (16.8%) and 185 (13.5%) patients, respectively. In both RALES[24] (SPI 8% versus PL 5%) and EPHESUS[30] (EPL 4.4% versus PL 4.5%), the frequency of WDAEs was less than in EMPHASIS-HF. It is unclear why the frequency of WDAEs would differ to the extent it does between EMPHASIS-HF and the other two trials.

An open-label extension trial of 12 months' duration was carried out following the early completion of the double-blind phase.[33] Although there was no comparator arm, no additional safety signals were identified from these observational data. It is unclear, however, why only fewer than half of patients were taking an ACEI (or ARB) during the open-label phase. (See APPENDIX 5: OPEN-LABEL EXTENSION STUDY SUMMARY for summary of data.)

### 4.3 Other Considerations

Based on discussion with the clinical expert consulted for this review, the following potential off-label uses of eplerenone were identified:

- HF with preserved LVEF
- Acute decompensated HF
- Asymptomatic (NYHA class I) HF with reduced LVEF
- HF patients with reduced LVEF:
  - < 55 years old
  - > 75 years old
  - with renal failure
- Treatment of hypertension
- Treatment of non-cardiac peripheral edema

# 5. CONCLUSIONS

In one, adequately designed randomized controlled trial, eplerenone was shown to reduce the risk of a composite outcome event (death from CV causes or a first hospitalization for HF) compared with placebo in patients with NYHA class II systolic chronic HF. The individual components of the composite outcome occurred at a lower rate in the eplerenone group compared with placebo, and the difference was statistically significant. The number of deaths from any cause was lower in the eplerenone group (12.5%) than the placebo group (15.5%). Quality of life data were not collected during the trial; nor was there an analysis of changes in NYHA class over time. The safety profile of eplerenone appeared similar to placebo, although hyperkalemia occurred about twice as frequently with eplerenone. Serious adverse events (other than cardiac failure) were infrequent, while WDAEs were similar between groups. Because the trial was stopped early for efficacy reasons after a median of only 21 months, the long-term risk of adverse events may be underestimated. There was no evidence to inform the comparative efficacy and safety of eplerenone and spironolactone in patients with NYHA class II systolic chronic HF.

# APPENDIX 1: PATIENT INPUT SUMMARY

*This section was summarized by CADTH staff based on the input provided by patient groups. It has not been systematically reviewed.*

**1. Brief Description of Patient Group Supplying Input**

The Heart and Stroke Foundation (HSF) is a volunteer-based national charity with more than 85 offices across the country and comprises 130,000 volunteers and more than 1,000 staff. HSF is a leader in efforts to eliminate heart disease and stroke, reduce their impact through initiatives to prevent disease, save lives, and promote recovery. In 2012, HSF invested more than $107 million into research, health promotion and community programs and has raised and invested more than $1.35 billion in heart and stroke research since 1956. HSF has received funding from pharmaceutical manufacturers, including but not limited to Abbott, Amgen, Allergan, AstraZeneca, Bayer Health Care, Boehringer Ingelheim, Bristol-Myers Squibb, Janssen, Merck, Merz, Novartis, Pfizer and Sanofi. No conflict was declared in the preparation of their submission.

**2. Condition and Current Therapy Related Information**

This information was gathered through literature searches, HSF health information, and guidelines and policies from credible organizations.

Heart failure (HF) is a common condition that develops after the heart becomes damaged or weakened by heart attacks or other medical conditions. It is estimated that there are 500,000 Canadians living with HF, and 50,000 new patients are diagnosed each year. HF is one of the leading causes of hospitalization and death for the elderly in Canada, and while survival rates have improved, the median survival is around three years from diagnosis.

Symptoms of HF include shortness of breath, persistent coughing or wheezing, swelling of the ankles, feet, sacrum, or abdomen due to fluid backup, fatigue or loss of energy, loss of or change in appetite, and increased heart rate. Fluid backup may also occur in the lungs, leading to shortness of breath and fatigue, and can accumulate to the point of acute pulmonary edema, a life-threatening condition requiring emergency treatment.

Treatment plans for HF can include lifestyle changes, medications, and surgery and ongoing care. Successful treatment relies on the patient and caregivers' commitment and ability to actively manage their condition. Self-care can be difficult for patients with HF, as early symptoms are subtle and the treatment regimen can be complex; it can be stressful or difficult to adjust to new medications, diet, and/or lifestyle changes. Physically, many people with HF find it difficult to handle common tasks they once could; for example, shopping, housekeeping, bathing, or dressing. Quality of life is often lower for individuals who are unable to care for themselves. Being employed and having improved functional capacity are areas that contribute to a higher quality of life score for HF patients.

HF is often associated with a range of comorbidities, frequent hospitalizations, and an unpredictable course of disease. Caring for a loved one with HF often presents both physical and emotional challenges. It is a long-term commitment of time and energy and requires prominent changes in daily life that can be stressful. This burden can increase in caregivers with poor mental or physical health, those who feel isolated, or those without sufficient social or professional support. As individuals with HF have deteriorating physical abilities, the support required from caregivers increases, sometimes to the point

that caregivers report an impact on their own health. Often as a result of anxiety or a patient's symptoms, caregivers can experience sleep disturbances that can negatively affect their ability to provide care. Challenges in increasing levels of needed care can also contribute to psychiatric and physical morbidities in caregivers.
In 2004 and 2005, HF was the fourth most expensive medical condition in Canada in terms of hospitalization costs. A major contributing factor to this was end-of-life care.

**3. Related Information about the Drug Being Reviewed**
No information was provided regarding experiences with or expectations for eplerenone.

# APPENDIX 2: LITERATURE SEARCH STRATEGY

| OVERVIEW | |
|---|---|
| Interface: | Ovid |
| Databases: | Embase 1974 to present<br>MEDLINE Daily and MEDLINE 1946 to present<br>MEDLINE In-Process & Other Non-Indexed Citations<br>**Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid. |
| Date of Search: | August 30, 2013 |
| Alerts: | Weekly search updates until (January 15, 2014) |
| Study Types: | Randomized controlled trials; controlled clinical trials; safety data |
| Limits: | No date or language limits were used<br>Human filter was applied<br>Conference abstracts were excluded |

| SYNTAX GUIDE | |
|---|---|
| / | At the end of a phrase, searches the phrase as a subject heading |
| .sh | At the end of a phrase, searches the phrase as a subject heading |
| MeSH | Medical Subject Heading |
| exp | Explode a subject heading |
| * | Before a word, indicates that the marked subject heading is a primary topic;<br>or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings |
| adj | Requires words are adjacent to each other (in any order) |
| adj# | Adjacency within # number of words (in any order) |
| .ti | Title |
| .ab | Abstract |
| .ot | Original title |
| .hw | Heading word; usually includes subject headings and controlled vocabulary |
| .pt | Publication type |
| .rn | CAS registry number |
| .nm | Name of substance word |
| pmez | Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present |
| oemezd | Ovid database code; Embase 1974 to present, updated daily |
| ae | Adverse effects/Adverse drug reaction |
| to | Toxicity/Drug toxicity |
| it | Drug interaction [Embase only] |
| ct | Contraindications [MEDLINE only] |
| po | Poisoning [MEDLINE only] |

| MULTI-DATABASE STRATEGY | |
|---|---|
| **Line #** | **Strategy** |
| 1 | *Eplerenone/ |
| 2 | (Inspra* or eplerenon* or Epoxymexrenon* or CGP-30083 or CGP30083 or "Cgp 30 083" or HSDB-7522 or HSDB7522 or SC-66110 or SC66110).ti,ab. |
| 3 | or/1-2 |
| 4 | 3 use oemezd |
| 5 | (Inspra* or eplerenon* or Epoxymexrenon* or CGP-30083 or CGP30083 or "Cgp 30 083" or HSDB-7522 or HSDB7522 or SC-66110 or SC66110 or 107724-20-9 or 6995V82D0B).ti,ot,ab,sh,rn,hw,nm. |
| 6 | 5 use pmez |
| 7 | 4 or 6 |
| 8 | (Randomized Controlled Trial or Controlled Clinical Trial).pt. |
| 9 | Randomized Controlled Trial/ |
| 10 | Randomized Controlled Trials as Topic/ |
| 11 | "Randomized Controlled Trial (topic)"/ |
| 12 | Controlled Clinical Trial/ |
| 13 | Controlled Clinical Trials as Topic/ |
| 14 | "Controlled Clinical Trial (topic)"/ |
| 15 | Randomization/ |
| 16 | Random Allocation/ |
| 17 | Double-Blind Method/ |
| 18 | Double Blind Procedure/ |
| 19 | Double-Blind Studies/ |
| 20 | Single-Blind Method/ |
| 21 | Single Blind Procedure/ |
| 22 | Single-Blind Studies/ |
| 23 | Placebos/ |
| 24 | Placebo/ |
| 25 | Control Groups/ |
| 26 | Control Group/ |
| 27 | (random* or sham or placebo*).ti,ab,hw. |
| 28 | ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw. |
| 29 | ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw. |
| 30 | (control* adj3 (study or studies or trial*)).ti,ab. |
| 31 | (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw. |
| 32 | allocated.ti,ab,hw. |
| 33 | ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw. |
| 34 | or/8-33 |
| 35 | 7 and 34 |
| 36 | exp animals/ |
| 37 | exp animal experimentation/ or exp animal experiment/ |
| 38 | exp models animal/ |
| 39 | nonhuman/ |
| 40 | exp vertebrate/ or exp vertebrates/ |
| 41 | or/36-40 |

| MULTI-DATABASE STRATEGY | |
|---|---|
| **Line #** | **Strategy** |
| 42 | exp humans/ |
| 43 | exp human experimentation/ or exp human experiment/ |
| 44 | or/42-43 |
| 45 | 41 not 44 |
| 46 | 35 not 45 |
| 47 | *Eplerenone/ae, it, to |
| 48 | Mineralocorticoid Receptor Antagonists/ae, ct, to, po |
| 49 | 6 and 48 |
| 50 | exp *drug toxicity/ |
| 51 | exp *drug hypersensitivity/ |
| 52 | *abnormalities, drug-induced/ |
| 53 | exp *postoperative complications/ |
| 54 | exp *intraoperative complications/ |
| 55 | exp *adverse drug reaction/ |
| 56 | exp *drug safety/ |
| 57 | exp *side effect/ |
| 58 | exp *postoperative complication/ |
| 59 | exp *peroperative complication/ |
| 60 | (safe or safety).ti. |
| 61 | side effect*.ti. |
| 62 | (adverse or undesirable or harm* or toxic or injurious or risk or risks or reaction* or toxic or toxicit* or toxologic* or complication* or noxious or tolerability or poison* or teratogen* or intoxication or warning*).ti. |
| 63 | ((drug or chemically) adj induced).ti. |
| 64 | or/50-63 |
| 65 | 7 and 64 |
| 66 | 47 or 49 or 65 |
| 67 | 66 not 45 |
| 68 | 46 or 67 |
| 69 | 68 not conference abstract.pt. |
| 70 | remove duplicates from 69 |

| OTHER DATABASES | |
|---|---|
| PubMed | Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used. |
| Trial registries (Clinicaltrials.gov and others) | Same keywords, limits used as per MEDLINE search. |

### Grey Literature

| | |
|---|---|
| Dates for Search: | August 2013 |
| Keywords: | Inspra (eplerenone); heart failure |
| Limits: | No date or language limits used |

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters), were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

# APPENDIX 3: EXCLUDED STUDIES

**TABLE 12: EXCLUDED STUDIES**

| Reference | Reason for Exclusion |
|---|---|
| Collier TJ, et al. Eur Heart J. 2013 Sep;34(36):2823-9. | Inappropriate outcomes (risk score analysis) |
| Udelson JE, et al. Circ Heart Fail. 2010 May;3(3):347-53. | Inappropriate outcomes (not clinically relevant) |
| Yamaji M, et al. Am Heart J. 2010 Nov;160(5):915-21. | Inappropriate outcomes (not clinically relevant) |
| Deswal A, et al. J Card Fail. 2011 Aug;17(8):634-42. | Inappropriate patient population (PEF) |

.

# APPENDIX 4: DETAILED OUTCOME DATA

**TABLE 13: OTHER EFFICACY OUTCOMES**

| | EMPHASIS-HF[8] | |
|---|---|---|
| **Outcome[a]** | **EPL** | **PL** |
| **Sudden Cardiac Death[7]** | | |
| N (%) | 60 (4.4) | 76 (5.5) |
| HR[b] | 0.76 | |
| 95% CI | 0.54 to 1.07 | |
| *P* value | 0.12 | |
| **Fatal/Non-fatal MI** | | |
| N (%) | 45 (3.3) | 33 (2.4) |
| HR | 1.32 | |
| 95% CI | 0.84 to 2.06 | |
| *P* value | 0.23 | |
| **Fatal/Non-fatal Stroke** | | |
| N (%) | 21 (1.5) | 26 (1.9) |
| HR | 0.79 | |
| 95% CI | 0.44 to 1.41 | |
| *P* value | 0.42 | |
| **Development of New AF or Flutter** | | |
| N (%) | 32/950 (3.4) | 52/937 (5.5) |
| HR | 0.59 | |
| 95% CI | 0.38 to 0.91 | |
| *P* value | 0.018 | |
| **ICD Insertion** | | |
| N (%) | 61 (4.5) | 59 (4.3) |
| HR | 0.99 | |
| 95% CI | 0.69 to 1.42 | |
| *P* value | 0.98 | |
| **CRT Device Insertion** | | |
| N (%) | 33 (2.4) | 41 (3.0) |
| HR | 0.77 | |
| 95% CI | 0.49 to 1.22 | |
| *P* value | 0.27 | |
| **Quality of Life** | | |
| N (%) | NR | NR |
| HR | NR | |
| 95% CI | NR | |
| *P* value | NR | |

| | EMPHASIS-HF[8] | |
|---|---|---|
| **Outcome**[a] | **EPL** | **PL** |
| **Change in NYHA Class** | | |
| N (%) | NR | NR |
| HR | NR | |
| 95% CI | NR | |
| *P* value | NR | |

AF = atrial fibrillation; CI = confidence interval; CRT = cardiac resynchronization therapy; EPL = eplerenone; EMPHASIS-HF = Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; HR = hazard ratio; ICD = implantable cardioverter-defibrillator; MI = myocardial infarction; NR = not reported; NYHA = New York Heart Association; PL = placebo.

[a]Outcomes identified as important to the review (Section 2.2.1 for review protocol).

[b]Adjusted HRs presented throughout.

Source: Study CSR[8], Zannad et al., 2011.[7]

**TABLE 14: PRIMARY COMPOSITE EFFICACY OUTCOME IN EMPHASIS-HF BY PRE-SPECIFIED SUBGROUPS**

| | Overall | | N/S America | | Age < 75 | | Age ≥ 75 | | LVEF < 30% | | LVEF ≥ 30% | | eGFR < 60 | | Hx of diabetes | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **HF HOSP + CV DEATH** | **EPL** | **PL** | **EPL** | **PL** | **EPL** | **PL** | **EPL** | **PL** | **EPL** | **PL** | **EPL** | **PL** | **EPL** | **PL** | **EPL** | **PB** |
| N (%) | **249 (18.3)** | **356 (25.9)** | 19 (11.0) | 38 (22.0) | 171 (16.5) | 249 (23.8) | 78 (23.6) | 107 (32.7) | 180 (19.3) | 267 (27.3) | 66 (15.5) | 89 (22.6) | 107 (24.4) | 163 (34.5) | 99 (21.6) | 141 (35.3) |
| HR[a] | **0.63** | | 0.45 | | 0.66 | | 0.66 | | 0.65 | | 0.67 | | 0.62 | | 0.54 | |
| 95% CI | **0.54 to 0.74** | | 0.26 to 0.79 | | 0.54 to 0.80 | | 0.49 to 0.88 | | 0.54 to 0.78 | | 0.49 to 0.92 | | 0.49 to 0.79 | | 0.42 to 0.70 | |
| $P_i$ value | --- | | 0.46 | | 1.00 | | | | 0.89 | | | | 0.50 | | 0.10 | |

CI = confidence interval; CV = cardiovascular; EMPHASIS-HF = Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; eGFR = estimated glomerular filtration rate; EPL = eplerenone; HF = heart failure; Hosp = hospitalization; HR = hazard ratio; Hx = history; LVEF = left ventricular ejection fraction; N/S America = North and South America; $P_i$ = probability of treatment-by-subgroup interaction; PL = placebo; SPI = spironolactone.

[a]Adjusted HRs presented.

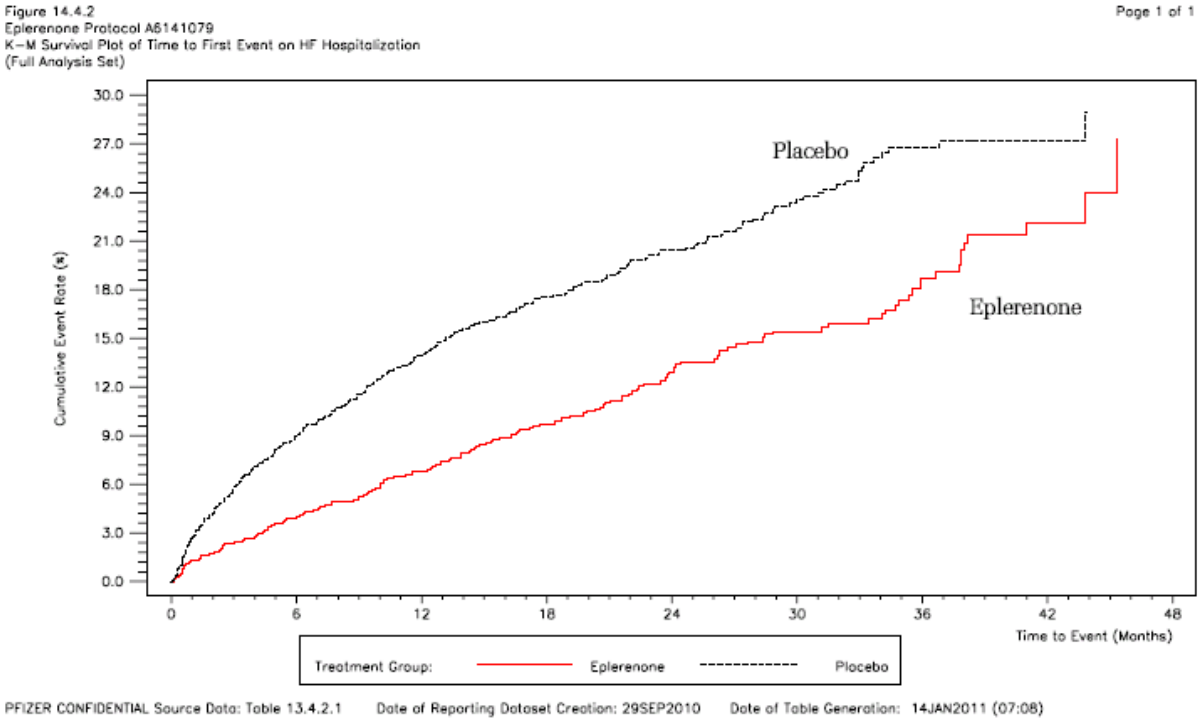
Source: Study CSR[8], Zannad et al., 2011.[7]

**TABLE 15: CARDIOVASCULAR DEATH AND HOSPITALIZATIONS IN PATIENTS AGED < 75 YEARS AND ≥ 75 YEARS**

| | Overall | | Age < 75 years | | Age ≥ 75 years | |
|---|---|---|---|---|---|---|
| **Primary: CV Death or HF Hospitalization** | **EPL** | **PL** | **EPL** | **PL** | **EPL** | **PL** |
| N (%) | **249 (18.3)** | **356 (25.9)** | 171 (16.5) | 249 (23.8) | 78 (23.6) | 107 (32.7) |
| HR | **0.63** | | 0.66 | | 0.66 | |
| 95% CI | **0.54 to 0.74** | | 0.54 to 0.80 | | 0.49 to 0.88 | |
| *P* value | **< 0.0001** | | < 0.0001 | | 0.005 | |
| **CV Mortality** | | | | | | |
| N (%) | 147 (10.8) | 185 (13.5) | 96 (9.3) | 134 (12.8) | 51 (15.5) | 51 (15.6) |
| HR | 0.76 | | 0.69 | | 0.98 | |
| 95% CI | 0.61 to 0.94 | | 0.53 to 0.90 | | 0.67 to 1.45 | |
| *P* value | 0.012 | | 0.006 | | 0.92 | |
| **All-cause Hospitalization** | | | | | | |
| N (%) | 408 (29.9) | 491 (35.8) | 296 (28.6) | 344 (32.9) | 112 (33.9) | 147 (45.0) |
| HR | 0.77 | | 0.82 | | 0.69 | |
| 95% CI | 0.67 to 0.88 | | 0.70 to 0.96 | | 0.54 to 0.88 | |
| *P* value | < 0.0001 | | 0.014 | | 0.003 | |
| **CV Hospitalizations** | | | | | | |
| N (%) | 304 (22.3) | 399 (29.1) | 219 (21.2) | 276 (26.4) | 85 (25.8) | 123 (37.6) |
| HR | 0.69 | | 0.76 | | 0.62 | |
| 95% CI | 0.60 to 0.81 | | 0.64 to 0.91 | | 0.47 to 0.82 | |
| *P* value | < 0.0001 | | 0.002 | | 0.0007 | |
| **HF Hospitalizations** | | | | | | |
| N (%) | 164 (12.0) | 253 (18.4) | 114 (11.0) | 170 (16.3) | 50 (15.2) | 83 (25.4) |
| HR | 0.58 | | 0.64 | | 0.55 | |
| 95% CI | 0.47 to 0.70 | | 0.51 to 0.82 | | 0.38 to 0.77 | |
| *P* value | < 0.0001 | | 0.0003 | | 0.0007 | |

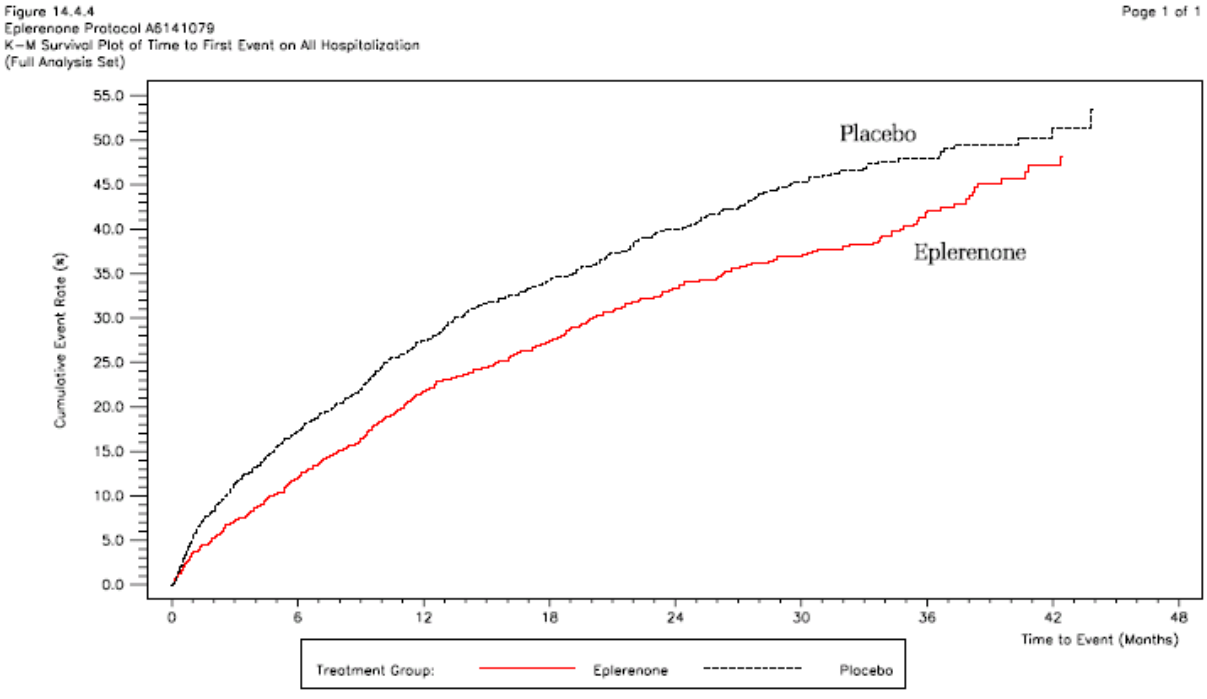
CI = confidence interval; CV = cardiovascular; EPL = eplerenone; HF = heart failure; HR = hazard ratio; PL = placebo.
Source: Study CSR.[8]

**FIGURE 3: KAPLAN–MEIER SURVIVAL PLOT OF TIME TO FIRST EVENT ON HEART FAILURE HOSPITALIZATION**



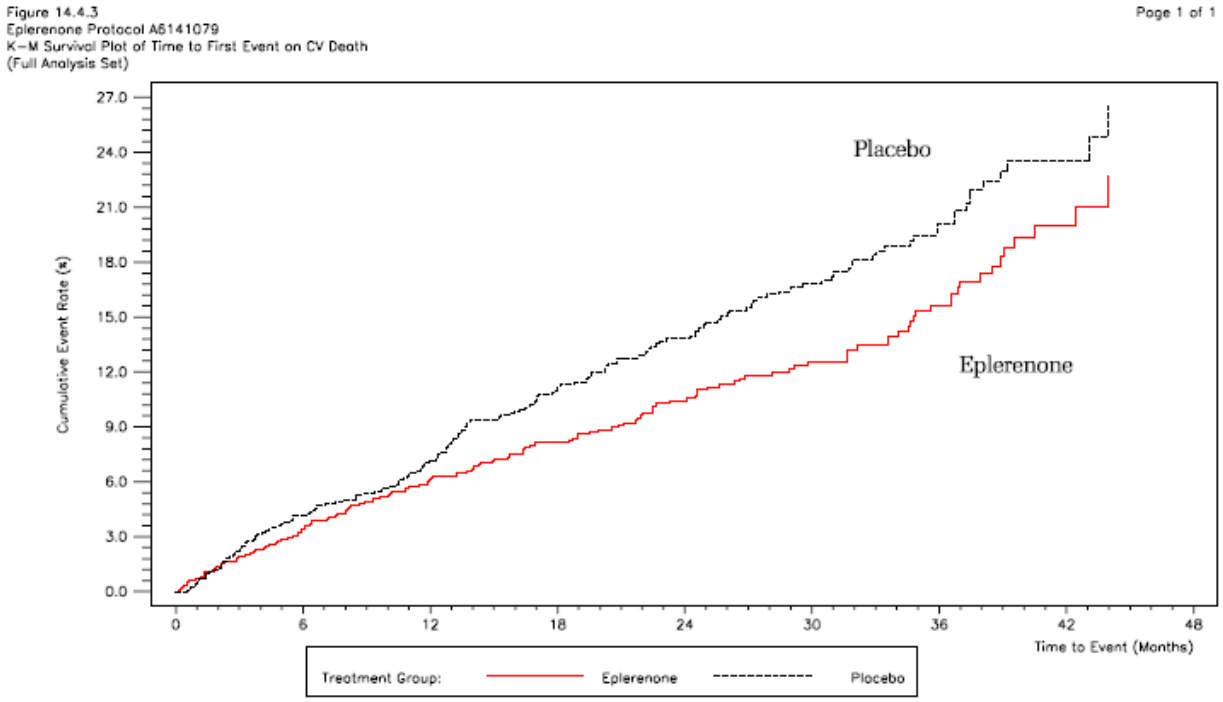

Source: Study CSR.[8]

**FIGURE 4: KAPLAN–MEIER SURVIVAL PLOT OF TIME TO FIRST EVENT ON ALL HOSPITALIZATION**



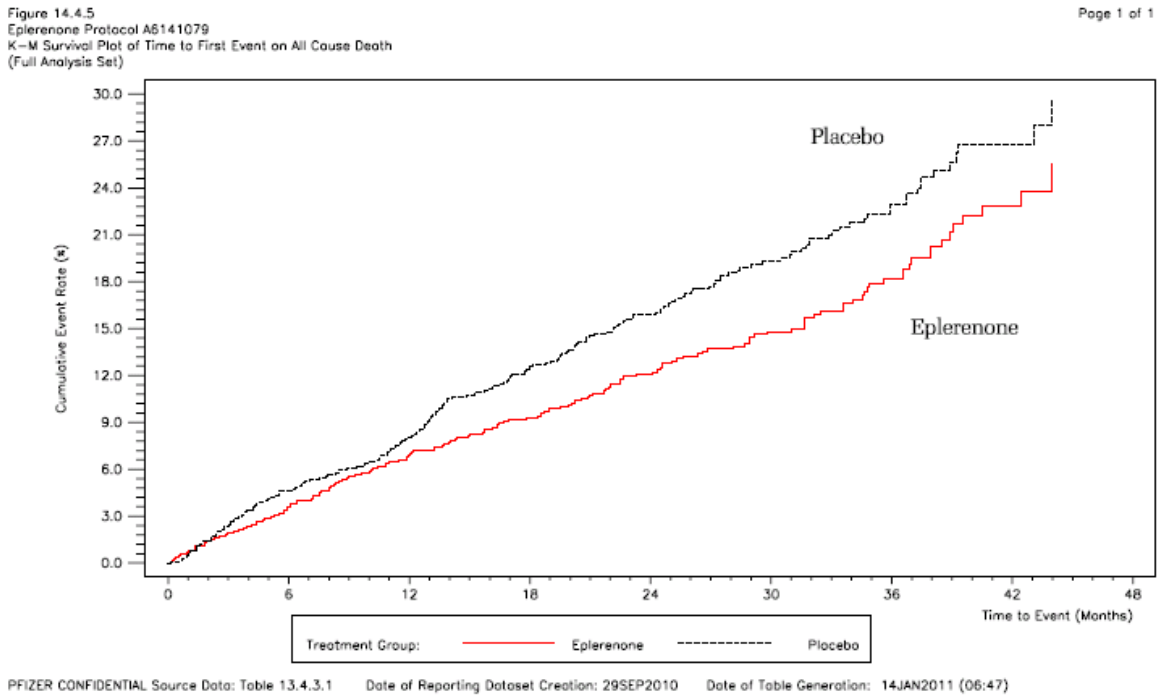

Source: Study CSR.[8]

**FIGURE 5: KAPLAN–MEIER SURVIVAL PLOT OF TIME TO FIRST EVENT ON CARDIOVASCULAR DEATH**




Source: Study CSR.[8]

**FIGURE 6: KAPLAN–MEIER SURVIVAL PLOT OF TIME TO FIRST EVENT ON ALL-CAUSE DEATH**




Source: Study CSR.[8]

# APPENDIX 5: OPEN-LABEL EXTENSION STUDY SUMMARY

## Objective

To summarize the results of the open-label extension study to Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF).[33] The following summary is based on unpublished data provided by the manufacturer on the open-label extension phase.

## Findings

### Study Design

After the interim analysis of EMPHASIS-HF on May 6, 2010, enrolment in the double-blind phase was stopped. A 12-month open-label phase was added to give all enrolled patients continuing access to eplerenone treatment. All patients who had been randomized into the double-blind phase of the trial and had not withdrawn consent were eligible to participate in the open-label phase if their estimated glomerular filtration rate (eGFR) was $\geq$30 mL/min/1.73 $m^2$ at the double-blind closeout visit. Adverse event data were collected during the open-label phase, including laboratory measurements (serum potassium), and vital signs. There were no efficacy outcomes measured.

Upon entry into the open-label extension phase, patients received 25 mg eplerenone daily. At four weeks, the dose of eplerenone could be increased to 50 mg daily.

A total of 1,246 patients were screened for the extension phase; 1,245 were enrolled and treated, and 1,098 completed treatment. This included 514 (41.3%) patients in Western Europe and Australia, 448 (36.0%) patients in Eastern Europe, 162 (13.0%) patients in South and North America, and 121 (9.7%) patients in Asia, Middle East, and Africa. A total of 147 patients (11.8%) discontinued, including 48 patients who discontinued due to death during the open-label extension phase.

The majority of patients were male (960 [77%]). The mean age of patients was 68.1 years, and the mean body mass index was 27.9 kg/$m^2$. The majority of patients were white (89.0%). Only 48% of patients were taking an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB) concomitantly. Therefore, this cohort is significantly different in this respect from the cohort originally randomized in the EMPHASIS-HF trial.

### Results

The median duration of treatment was 364 days in the open-label extension phase (range: 1 to 516). The adverse event results are presented in Table 16 below. There were 56 deaths and the most common causes of death were cardiac failure (n = 9), condition aggravated (n = 9), pneumonia (n = 5), sudden death (n = 5), sudden cardiac death (n = 5), and myocardial infarction (n = 5). The most common serious adverse event (SAE) was cardiac failure (3.5%) (Table 16).

**TABLE 16: RESULTS SUMMARY FOR OPEN-LABEL EXTENSION**

| | Any Cause | Treatment-Related |
|---|---|---|
| Patients evaluable for AEs | 1,245 | 1,245 |
| No. of AEs | 2,133 | 248 |
| Patients with AEs (%) | 767 (61.6) | 166 (13.3) |
| Patients with SAEs (%) | 251 (20.2) | 12 (1.0) |
| Patients with severe AEs(%) | 160 (12.9) | 13 (1.0) |
| Patients discontinued due to AEs (%) | 69 (5.5) | 29 (2.3) |
| Patients with dose reduction or temporary discontinuation due to AEs (%) | 99(8.0) | 40 (3.2) |
| No. of deaths | 56 (4.5%) | Not reported |
| Potassium > 6 mEq/L | 16 (1.3) | Not reported |
| Potassium > 5.5 mEq/L | 68 (5.5) | Not reported |
| Potassium < 4 mEq/L | 352 (28) | Not reported |
| Potassium < 3.5 mEq/L | 45 (3.6) | Not reported |

AE = adverse event; mEq = milliequivalent; SAE = serious adverse event.

## Summary

The goal of the study was to simply provide access to eplerenone. Design limitations (open label, no control group, cohort not treated with ARB or ACEI) limit its usefulness for providing any further information on the risk of harm for eplerenone. No new safety concerns were identified in the open-label extension phase.

# APPENDIX 6: SUMMARY OF OTHER STUDIES

## 1. Objective

To summarize the findings from a post-hoc analysis of repeat hospitalizations from the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial.[15]

## 2. Findings

### Introduction

Rogers et al.[15] published a post-hoc analysis of repeat hospitalizations in the EMPHASIS-HF trial, with a focus on hospitalizations due to heart failure (HF). The authors undertook this analysis because the original analysis was limited to eplerenone's impact on first hospitalization. Repeat hospitalization data are potentially informative because of the impact on quality of life and costs of disease management. For example, in the placebo group, 110 patients had a second or subsequent admission for HF in comparison to 167 patients who experienced only one HF hospitalization. The primary analysis of the trial data excluded the information represented by these 110 events.

### Methods

The authors calculated the cumulative incidence of HF hospitalizations and the average number of admissions per 100 patient-years, for each treatment group. A negative binomial regression model was used to obtain an estimate of the effect of eplerenone on the rate of HF hospitalizations. This model was chosen because it accounts for the likelihood that recurrent hospitalizations within individuals are not independent. The model was adjusted for similar covariates that were used in the primary outcome analysis of the study and sensitivity analysis was performed using unadjusted models.

### Results

The data and risk reductions from the analysis are presented in Table 17. In the placebo group, there were 481 HF hospitalizations during 2,831 years of follow-up, in comparison with 312 HF hospitalizations during 2,916 years of follow-up in the eplerenone group. HF hospitalizations rates, per 100 person-years, were 16.99 in the placebo group and 10.70 in the eplerenone group (rate ratio [95% confidence interval (CI)] 0.63 [0.55 to 0.73] $P < 0.0001$). The negative binomial regression model gave a rate ratio for the eplerenone group, in comparison with the placebo group, of 0.53 (95% CI [0.42 to 0.66] $P < 0.0001$).

The authors argue that the raw calculations (without incorporating follow-up time) show that if only first hospitalizations are used, the effect of eplerenone is underestimated. If only first admissions for HF are considered, the absolute risk reduction is 6 admissions per 100 patients. If all hospitalizations are considered, the absolute risk reduction is 12 admissions per 100 patients. In this study, hospitalization for HF was defined as an overnight stay, or longer, in a hospital environment (emergency room, observation unit or in-patient care, or similar facility, including admission to a day facility) with a discharge diagnosis that included a cardiovascular reason for hospitalization.[8] This was specified in the study protocol, but there appears to be some subjectivity inherent in this definition. This is a limitation to the analysis of hospitalization data because the threshold for hospitalizing the subject may have varied between (and within) the geographical regions in which the study was conducted.

**TABLE 17: SUMMARY OF EFFICACY RESULTS**

| | Placebo | Eplerenone | Relative Risk Reduction (95% CI); (Absolute Risk Reduction) |
|---|---|---|---|
| No. of patients | 1,373 | 1,364 | --- |
| No. of Deaths | 253 | 205 | 18% (NR) |
| No. of CV deaths | 215 | 178 | 17% (NR) |
| All-cause hospitalization | | | |
| Patients with ≥ 1 admission | 551 | 462 | 16% (NR) |
| Patients with ≥ 2 admissions | 256 | 195 | 23% (NR) |
| Total admissions | 1,123 | 862 | 23% (NR) |
| HF hospitalization | | | |
| Patients with ≥ 1 admission, n (%) | 277 (20%) | 186 (14%) | 32% (20% to 43%); (6 per 100 patients) |
| Patients with ≥ 2 admissions | 110 | 67 | 38.69 (NR) |
| Total admissions, n (%) | 481 (35%) | 312 (22.9%) | 35% (NR); (12 per 100 patients) |
| Patients with no. of hospitalizations for HF | | | |
| 1 | 167 | 119 | --- |
| 2 | 60 | 41 | --- |
| 3 | 24 | 13 | --- |
| 4 | 12 | 6 | --- |
| 5 | 10 | 2 | --- |
| 6 | 4 | 1 | --- |
| 7 | 0 | 2 | --- |
| 8 | 0 | 1 | --- |
| 10 | 0 | 1 | --- |

CI = confidence interval; CV = cardiovascular; HF = heart failure; NR = not reported.

## 3. Summary

Rogers et al. performed a post-hoc analysis of repeat hospitalization data from the EMPHASIS-HF study. The results of their analyses are congruent with the primary analysis of hospitalization data. They showed lower rates of all hospitalizations for eplerenone, compared with placebo, and these differences were statistically significant in favour of eplerenone.

# REFERENCES


1. The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. Eur Heart J [Internet]. 2012 [cited 2013 Oct 11];33:1787-847. Available from: http://eurheartj.oxfordjournals.org/content/33/14/1787.full.pdf
2. Heart and Stroke Foundation [Internet]. Ottawa: Heart and Stroke Foundation of Canada. Statistics; 2012 [cited 2013 Oct 18]. Available from: http://www.heartandstroke.com/site/c.ikIQLcMWJtE/b.3483991/
3. Tracking heart disease and stroke in Canada 2009 [Internet]. Ottawa: Public Health Agency of Canada; 2012 Nov 24. [cited 2013 Oct 18]. Available from: http://www.phac-aspc.gc.ca/publicat/2009/cvd-avc/pdf/cvd-avs-2009-eng.pdf
4. McKelvie RS, Moe GW, Ezekowitz JA, Heckman GA, Costigan J, Ducharme A, et al. The 2012 Canadian Cardiovascular Society heart failure management guidelines update: focus on acute and chronic heart failure. Can J Cardiol. 2013 Feb;29(2):168-81.
5. e-CPS [Internet]. Ottawa: Canadian Pharmacists Association; 2013 [cited 2013 Aug 8]. Available from: https://www.e-therapeutics.ca Subscription required.
6. CDR submission binder: Inspra (eplerenone) tablets, 25 mg and 50 mg; new indication. Company: Pfizer Canada Inc. [**CONFIDENTIAL** manufacturer's submission]. Kirkland (QC): Pfizer Canada Inc; 2013 Jul.
7. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med. 2011 Jan 6;364(1):11-21.
8. Clinical study report SC-066110: the effect of eplerenone versus placebo on cardiovascular mortality and heart failure hospitalization in subjects with NYHA class II chronic systolic heart failure (EMPHASIS-HF) [**CONFIDENTIAL** internal manufacturer's report]. New York: Pfizer; 2011.
9. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Dranzer MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol [Internet]. 2013 Oct [cited 2013 Oct 11];62(16):e147-239. Available from: http://content.onlinejacc.org/article.aspx?articleID=1695825
10. Colucci WS. Predictors of survival in heart failure due to systolic dysfunction. 2013 Jul 11 [cited 2013 Oct 29]. In: UpToDate [Internet]. Release: 21.8 - C21.149. Waltham (MA): UpToDate; 1992 - . Available from: www.uptodate.com Subscription required.
11. Struthers A, Krum H, Williams GH. A comparison of the aldosterone-blocking agents eplerenone and spironolactone. Clin Cardiol. 2008 Apr;31(4):153-8.
12. Eschalier R, McMurray JJ, Swedberg K, van Veldhuisen DJ, Krum H, Pocock SJ, et al. Safety and efficacy of eplerenone in patients at high-risk for hyperkalemia and/or worsening renal function: analyses of EMPHASIS-HF study subgroups. J Am Coll Cardiol. 2013;62(17):1585-93.
13. Krum H, Shi H, Pitt B, McMurray J, Swedberg K, van Veldhuisen DJ, et al. Clinical benefit of eplerenone in patients with mild symptoms of systolic heart failure already receiving optimal best practice background drug therapy: analysis of the EMPHASIS-HF study. Circ Heart Fail. 2013 Jul 1;6(4):711-8.

14. Preiss D, van Veldhuisen DJ, Sattar N, Krum H, Swedberg K, Shi H, et al. Eplerenone and new-onset diabetes in patients with mild heart failure: results from the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF). Eur J Heart Fail. 2012 Aug;14(8):909-15.
15. Rogers JK, McMurray JJ, Pocock SJ, Zannad F, Krum H, van Veldhuisen DJ, et al. Eplerenone in patients with systolic heart failure and mild symptoms: analysis of repeat hospitalizations. Circulation. 2012 Nov 6;126(19):2317-23.
16. Swedberg K, Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Shi H, et al. Eplerenone and atrial fibrillation in mild systolic heart failure: results from the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure) study. J Am Coll Cardiol. 2012 May 1;59(18):1598-603.
17. Zannad F, McMurray JJ, Drexler H, Krum H, van Veldhuisen DJ, Swedberg K, et al. Rationale and design of the Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure (EMPHASIS-HF). Eur J Heart Fail [Internet]. 2010 Jun [cited 2013 Sep 5];12(6):617-22. Available from: http://eurjhf.oxfordjournals.org/content/12/6/617.full.pdf+html
18. Dhillon S. Eplerenone: a review of its use in patients with chronic systolic heart failure and mild symptoms. Drugs. 2013;73(13):1451-62.
19. Sullivan EJ. Clinical trial endpoints [slides on the Internet]. Rockville (MD): U.S. Food and Drug Administration; 2013. [cited 2013 Oct 11]. Available from: http://www.fda.gov/downloads/Training/ClinicalInvestigatorTrainingCourse/UCM337268.pdf
20. Manufacturer's comments on CDR clinical and pharmacoeconomic reviewers' reports on eplerenone (Inspra) [**CONFIDENTIAL** manufacturer's report]. Kirkland (QC): Pfizer Canada; 2013 Nov 15.
21. Inspra (eplerenone): tablets 25 mg and 50 mg [product monograph]. Kirkland (QC): Pfizer Canada Inc; 2012 Aug 21.
22. Nagarajan V, Chamsi-Pasha M, Tang WH. The role of aldosterone receptor antagonists in the management of heart failure: an update. Cleve Clin J Med [Internet]. 2012 Sep [cited 2013 Sep 5];79(9):631-9. Available from: http://www.ccjm.org/content/79/9/631.full.pdf+html
23. Gupta S, Fugh-Berman AJ, Scialli A. Ethics and eplerenone. J Med Ethics. 2013 Feb;39(2):110-4.
24. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med [Internet]. 1999 Sep 2 [cited 2013 Oct 21];341(10):709-17. Available from: http://content.nejm.org/cgi/reprint/341/10/709.pdf
25. Yamaji M, Tsutamoto T, Kawahara C, Nishiyama K, Yamamoto T, Fujii M, et al. Effect of eplerenone versus spironolactone on cortisol and hemoglobin A1(c) levels in patients with chronic heart failure. Am Heart J. 2010 Nov;160(5):915-21.
26. Baliga RR, Ranganna P, Pitt B, Koelling TM. Spironolactone treatment and clinical outcomes in patients with systolic dysfunction and mild heart failure symptoms: a retrospective analysis. J Card Fail. 2006 May;12(4):250-6.
27. Chatterjee S, Moeller C, Shah N, Bolorunduro O, Lichstein E, Moskovits N, et al. Eplerenone is not superior to older and less expensive aldosterone antagonists. Am J Med. 2012 Aug;125(8):817-25.
28. Ezekowitz JA, McAlister FA. Aldosterone blockade and left ventricular dysfunction: a systematic review of randomized clinical trials. Eur Heart J [Internet]. 2009 Feb [cited 2013 Sep 6];30(4):469-77. Available from: http://eurheartj.oxfordjournals.org/content/30/4/469.full.pdf+html

29. Hu LJ, Chen YQ, Deng SB, Du JL, She Q. Additional use of an aldosterone antagonist in patients with mild to moderate chronic heart failure: a systematic review and meta-analysis. Br J Clin Pharmacol. 2013 May;75(5):1202-12.

30. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med. 2003 Apr 3;348(14):1309-21.

31. Pharmacoeconomic evaluation. In: CDR submission binder: Inspra (eplerenone) tablets, 25 mg and 50 mg; new indication. Company: Pfizer Canada Inc. [**CONFIDENTIAL** manufacturer's submission]. Kirkland (QC): Pfizer Canada Inc; 2013 Jul.

32. Common Drug Review. Eplerenone (Inspra - Pfizer Canada Inc.). Indication: heart failure post myocardial infarction. CEDAC final recommendation [Internet]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009 Nov. [cited 2013 Oct 22]. Available from: http://www.cadth.ca/media/cdr/complete/cdr_complete_Inspra_November-27-2009.pdf

33. Pfizer response to October 11, 2013 request for additional information regarding the Inspra HF CDR review. Synopsis clinical study report: eplerenone. [**CONFIDENTIAL** additional manufacturer's information]. Pointe-Claire/Dorval (QC): Pfizer Canada Inc.; 2013 Oct 23.