A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED TRIAL EVALUATING THE SAFETY AND EFFICACY OF EARLY TREATMENT WITH EPLERENONE IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

Published: 17-09-2010
Last updated: 04-05-2024

To assess the impact of eplerenone on cardiovascularmortality and morbidity in patients with acutemyocardial infarction (STEMI) when initiated withinthe first 24 hours of onset of symptoms (preferablyduring the first 12 hours)To investigate the...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Myocardial disorders
Study type	Interventional

Summary

ID

NL-OMON36477

Source
ToetsingOnline

Brief title
REMINDER

Condition

- Myocardial disorders

Synonym
Heart attack

Research involving

Human

Sponsors and support

Primary sponsor: Pfizer
Source(s) of monetary or material Support: pharmaceutical industry (Pfizer)

Intervention

Keyword: Acute Myocardial Infarction, Early Treatment, Eplerenone (Inspra), Placebo

Outcome measures

Primary outcome

The primary endpoint:

Time to first event of :

- Cardiovascular mortality

- Re-hospitalization or extended initial hospital stay due to diagnosis of

heart failure

- Sustained ventricular tachycardia or fibrillation

- Ejection fraction <= 40% after 1 month or BNP >200 pg/ml or NT-proBNP >450

pg/ml (age<50 years); >900 pg/ml (age 50-75 years) or >1800 pg/ml (age>75

years) after 1 month.

Secondary outcome

1. Time to cardiovascular mortality.

2. Time to diagnosis of heart failure.

3. Time to first and each subsequent episode (after an event free interval of >=

48 hours) of

sustained ventricular tachycardia or ventricular fibrillation.

4. Time to first recorded ejection fraction of <= 40% (recorded 1 month or later

postrandomization).

5. Time to BNP >200 pg/ml or NT-proBNP >450, >900 or >1800 pg/ml for ages <50

years,

50-75 years and >75 years, respectively (recorded 1 month or later

post-randomization).

6. Time to decision to provide an implantable cardioverter defibrillator (ICD)

or cardiac

resynchronization therapy (CRT).

7. Time to second or subsequent non-fatal myocardial infarction.

8. QRS duration at 6 months post-randomization.

9. Left atrial diameter (recorded on each occasion an echocardiogram is

conducted).

10. Change in serum levels of biomarkers at 6 months post-randomization. Blood

samples

for biomarkers will be stored and analyzed post completion of the study.

Study description

Background summary

Eplerenone, an antagonist at the mineralocorticoid receptor, has wide-ranging effects on the
heart at a cellular and tissue level. The EPHESUS trial demonstrated a significant
improvement in survival when eplerenone is initiated three to fourteen days following acute
myocardial infarction complicated by left ventricular systolic dysfunction and signs and
symptoms of congestive heart failure. Although evidence exists that cardiac remodeling

begins almost immediately after a heart attack, the average delay between myocardial
infarction and the initiation of eplerenone was seven days, which may miss an early window
of opportunity to influence the myocardium favourably.
In addition, based on the current practice patterns, many patients have already been
discharged from hospital by the time eplerenone would be started.
This study will test the hypothesis that starting eplerenone promptly after infarction will be
safe and efficacious in reducing adverse outcomes with potential long term benefits.

Study objective

To assess the impact of eplerenone on cardiovascular mortality and morbidity in patients with acute myocardial infarction (STEMI) when initiated within the first 24 hours of onset of symptoms (preferably during the first 12 hours)
To investigate the effect of eplerenone on serum biomarkers of collagen metabolism / myocardial fibrosis (eg, ICTP, PINP, PIIINP) and cardiovascular risk (eg, ADMA and adiponectin) and to potentially relate these measures to clinical outcomes.

Study design

A multicentre, randomized, double-blind, placebocontrolled, 2-arm, parallel group trial comparing eplerenone plus standard of care to placebo plus standard of care in patients post-myocardial infarction.

Intervention

Treatment will be administered daily for a minimum period of 6 months and a maximum period of approximately 17 months. Predetermined study visits will take place at day 1, week 1, week 4, 6 months and 6 monthly thereafter until the study is completed.

Study burden and risks

ADVERSE EVENTS:
Most commonly seen: High potassium in the blood, dizziness, low blood pressure, diarrhea, nausea and kidney problems (such as increased urination).

Less commonly seen (less than 1 in 100 patients): Dehydration, high cholesterol. high triglycerides, low sodium in the blood, insomnia, headache, abnormal heart beat, dizziness when sitting or standing up too quickly, blood clot in the leg, irritation of the throat, flatulence, vomiting, skin itching, increased sweating, back pain, leg cramps, malaise, increase in BUN, increase in creatinine level in the blood, infection of the kidney and increase in white blood cells in the blood.

Contacts

Public
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Scientific
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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Evidence of a personally signed and dated informed consent document obtained prior to the initiation of any study procedures and indicating that the subject (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

2. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
3. Subjects must be male or non-pregnant female aged >=18 years of age at the time informed consent is obtained.
4. If the subject is female, she must be post-menopausal,or is surgically sterile, and is not lactating.
5. Subjects must have experienced a myocardial infarction (STEMI) within the previous 24 hours confirmed by symptoms and ECG.

Exclusion criteria

1. The subject has received any investigational medication or used any investigational device within 30 days prior to the first dose of study medication or is actively participating in any investigational drug or device study, or is scheduled to receive an investigational drug other than eplerenone or to use an investigational device during the course of the study.
2. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study. Subjects who have experienced a previous myocardial infarction may be included provided all other inclusion / exclusion criteria are met.
3. Subjects with inability to follow protocol procedures according to the investigation.
4. The subject has any condition which, in the opinion of the Investigator, makes participation in this study not in the best interest of the subject.
5. The subject has a severe organic disorder or has had surgery or disease of the gastrointestinal tract which, in the opinion of the Investigator, may interfere with the absorption, pharmacokinetics, or elimination of the study drug.
6. The subject has a co-morbid condition that would be expected to result in death during the next year (eg, terminal cancer, AIDS, etc) including subjects receiving immunosuppressive or antineoplastic therapy.
7. The subject has current evidence of alcohol or drug abuse problems, which in the Investigator's opinion, precludes study participation.
8. Subjects treated with eplerenone or other aldosterone antagonists within the past 1 month.
9. The subject has an implanted cardiac defibrillator (ICD).
10. The subject is awaiting cardiac transplant.
11. The subject has uncontrolled hypotension (SBP<90mmHg).
12. Subjects with eGFR <=30ml/min (based on admission serum creatinine and the MDRD formula) or serum creatinine >=220µmol/L.
13. Subjects with a known low ejection fraction of less than 40% or any previous history of heart failure.
14. Patients who have haemodynamically relevant aortic or mitral valve stenosis as judged by the investigator.
15. Subjects with a diagnosis of hypertrophic cardiomyopathy.
16. Subjects who have had cardiac surgery within 30 days prior to randomization.

17. Concomitant use of potassium sparing diuretics (eg, spironolactone, triamterene or amiloride) or subjects who in the opinion of the investigator require treatment with potassium sparing diuretics. Use of potassium preparations or supplements will be allowed on a case by case basis at the discretion of the Investigator.
18. Concomitant use of potent cytochrome p450 3A4 (CYP3A4) inhibitors, such as but not limited to: ketoconazole; itraconazole; nefazodone; troleandomycin; clarithromycin; ritonavir; nelfinavir.
19. Concomitant use of cytochrome p450 3A4 (CYP3A4) inducers, such as but not limited to: St. John*s wort; rifampin; carbamazepine; phenytoin; phenobarbitol.
20. Subjects who are likely to require treatment during the trial period with drugs not permitted by this protocol.
21. Subjects with preexisting significant hepatic disease (for example, known positive serology for viral hepatitis) or aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) >3 times the upper limits of normal.
22. Subjects with a known sensitivity or intolerance to eplerenone, spironolactone or tablet excipients.
23. Donation of blood or blood products for transfusion at any time during the trial or until 30 days after completion of treatment.
24. Prisoners or subjects who are compulsorily detained (involuntary incarcerated) for treatment of either a psychiatric or physical illness must not be enrolled into this study.
25. The subject has been previously admitted to the study.

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-06-2011
Enrollment:	10

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Inspra
Generic name:	Eplerenone
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	17-09-2010
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	29-03-2011
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-06-2011
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-07-2011
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-01-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	27-02-2012

Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-04-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-07-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-07-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2010-019844-38-NL
ClinicalTrials.gov	NCT01176968
CCMO	NL33120.100.10