NCCHTA

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Technology Assessment Report commissioned by the NIHR HTA Programme - Protocol

1. Title of the project:
Aldosterone antagonists for post-myocardial infarction heart failure

2. Name of TAR team and ‘lead’
CRD/CHE Technology Assessment Group (Centre for Reviews and Dissemination/Centre for Health Economics), University of York.

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3. Plain English Summary
Changes in the heart muscle following a myocardial infarction (MI) can lead to the development of heart failure, characterised by symptoms such as breathlessness, fluid retention and fatigue. Approximately 40% of people who experience an acute MI go on to develop heart failure. The hormone aldosterone is thought to play a crucial role in the changes in the heart muscle, leading to the progression of heart failure and its symptoms. Aldosterone antagonists, spironolactone and eplerenone, can be used in combination with other drugs for the treatment of heart failure. One clinical trial has demonstrated the beneficial effects of eplerenone in heart failure following MI but spironolactone has only been studied in more general heart failure patients. Although spironolactone is less expensive than eplerenone, eplerenone is thought to cause fewer side effects. The aims of this project are to determine how precisely the relative clinical and cost-effectiveness of spironolactone and eplerenone in patients with heart failure following MI can be determined from the available evidence, to identify whether an RCT comparing spironolactone with eplerenone would be worthwhile, and to inform the design of a future trial.
4. Decision problem
Background

Post-MI HF
Cardiac necrosis following an MI, along with ventricular remodelling, causes a healthy ventricle to become severely dysfunctional, with impaired pumping ability of the heart, leading to heart failure (HF). Ventricular remodelling occurs rapidly immediately post-MI, and more slowly thereafter. The initial stage of ventricular remodelling is the thinning of the wall of the ventricle in the area of the infarct, and the dilation of the ventricular chamber. This is followed by compensatory hypertrophy and fibrosis including lengthening of the non-infarcted part of the myocardium. Initially ventricular remodelling preserves stroke volume and pump function of the left ventricle, however these changes become maladaptive over time. LVSD is the most common cause of post-MI HF. Other causes of HF after MI are papillary muscle dysfunction and mitral regurgitation or arrhythmias (e.g. atrial fibrillation). HF may also develop after an MI in the absence of any of these problems. Aldosterone facilitates ventricular remodelling by promoting the development of myocardial fibrosis, leading to the progression of HF and its symptoms. Heart failure reduces life expectancy, and is associated with symptoms such as breathlessness, fluid retention and fatigue.

The incidence of post-MI HF is increasing in the UK due to the shifting age distribution of the population and increased survival after acute MI. Approximately 707,000 people in the UK aged 45 years and older are thought to have HF (393,000 men; 314,000 women), with prevalence increasing steeply with age (1% under 65 years; 6-7% 75 to 84 years; 12-22% 85 years and older). Approximately 40% of patients that experience an acute MI suffer HF. The number of people with post-MI HF in the UK for the year 2000 was estimated to be 130,000 to 202,000 and estimated costs to the NHS to be £125 to 181 million. Studies suggest that women and individuals with a history of cardiac disease or diabetes mellitus are at higher risk of post-MI HF.

The main drugs used to treat patients with HF and systolic dysfunction are ACE inhibitors, angiotensin receptor blockers, beta-blockers and aldosterone antagonists (mineralocorticoid receptor antagonists). Aldosterone antagonists include spironolactone, eplerenone, the active metabolite of spironolactone, canrenone, and its salt, potassium canrenoate.

Spironolactone
Spironolactone (Aldactone, Pharmacia Ltd; alternative names include Novo-Spiroton, Spiractin, Spirotone, Vero Spiron and Ber lactone) is a potassium-sparing diuretic licensed for use for HF in the UK. It inhibits the effect of aldosterone by competing for intracellular aldosterone receptors in the collecting duct, increasing water and sodium excretion and decreasing the excretion of potassium. Spironolactone is available combined with hydroflumethiazide (Aldactide, Pharmacia Ltd), hydrochlorothiazide (Aldactazide, Pfizer Ltd) or furosemide (Lasilactone, Sanofi- Aventis). Spironolactone is indicated in patients with moderate to severe HF (New York Heart Association Class III and IV) due to LVSD.

According to the Summary of Product Characteristics (SPC), the advised dose of spironolactone (Aldactone) in adults with congested cardiac failure is 100 mg daily,
gradually increased up to 400 mg daily if required, with a maintenance dose of 25 to 200 mg daily once oedema is controlled. However, high doses of spironolactone are rarely used, with most patients receiving between 12.5 and 50 mg daily. The SPC state that adverse drug reactions associated with spironolactone include electrolyte disturbances, hyperkalaemia, leukopenia, thrombocytopenia, malaise, gastrointestinal disturbances, and drowsiness, rashes, and abnormal hepatic and renal function. Due to the effect on androgen receptors and other steroid receptors, gynaecomastia, testicular atrophy, sexual dysfunction, and menstrual irregularities may occur. Being a mineralocorticoid antagonist, spironolactone may reduce the effectiveness of antidepressant drugs in the treatment of major depression, presumably by interfering with normalization of the hypothalamic-pituitary-adrenal axis in patients receiving antidepressant therapy.

There is evidence that spironolactone administered with an ACE inhibitor can prevent post-MI remodelling more effectively than ACE inhibitor alone. The Randomised Aldactone Evaluation Study (RALES) is a multicentre, randomised, double-blind, parallel group comparison, administering 25 to 50 mg daily of spironolactone to patients with heart failure and a LVEF 35% or less; 54% had ischemic HF. The trial found that the addition of spironolactone to an ACE inhibitor and loop diuretic significantly reduced mortality in patients with severe HF, RR 0.70 (95% CI: 0.60, 0.82, p<0.001).

**Eplerenone**

Eplerenone (Ispra; Pfizer Ltd) is a selective aldosterone antagonist used as an adjunct in the management of chronic HF. It is specifically indicated for the reduction of risk of cardiovascular death in patients with HF and left ventricular dysfunction within 3–14 days of an acute MI, in combination with standard therapies and as treatment against hypertension.

Eplerenone is similar to spironolactone, but has a greater affinity for the mineralocorticoid receptor and as a result is thought to have fewer side effects. According to the SPC, the usual starting dose of eplerenone is 25 mg once daily, increasing to 50 mg daily after approximately 4 weeks. The SPC state that common adverse drug reactions associated with eplerenone include hyperkalaemia, hypotension, dizziness, altered renal function, and increased creatinine concentration.

The Eplerenone Post myocardial infarction Heart Failure Efficacy and Survival Study (EPHESUS) is a multicentre, randomised, double-blind, parallel group comparison, administering 25 to 50 mg daily of eplerenone to patients with ischemic HF and a LVEF 40% or less. The trial showed a significant reduction in mortality in patients with acute MI complicated by left ventricular dysfunction and HF, RR 0.85 (95% CI: 0.75, 0.96, p=0.008). Based on the results of EPHESUS, the SIGN guidelines for acute coronary syndromes indicate that patients with clinical MI complicated by left ventricular dysfunction (ejection fraction <0.40) where there are clinical signs of HF should take eplerenone therapy in addition to standard therapy. Eplerenone was approved by FDA for treatment of hypertension in 2002, and for patients who have congested cardiac failure after a myocardial infarction in 2004. The most recent NICE guidelines for HF state that eplerenone is not licensed for use in the treatment of HF in the UK.
Canrenone
Canrenone is the active metabolite of both spironolactone and potassium canrenoate. Neither canrenone or potassium canrenoate are licensed as human medicines in either Europe or the USA and therefore will not be considered in this assessment. Available data on canrenone and potassium canrenoate may be used where appropriate to complement the evidence base for spironolactone.

Canrenone has been studied: the AntiRemodeling Effect of Aldosterone receptors blockade with canrenone IN mild Chronic Heart Failure (AREA IN-CHF) trial is a multicentre, randomised, double-blind, parallel group comparison, administering 25 to 50 mg daily of canrenone to patients with NYHA class II heart failure and a LVEF <45%. Of the 467 patients recruited into the trial, 52% had ischaemic HF. There was no difference between canrenone and placebo in terms of cardiovascular death, however, there was a significant reduction in the composite outcome of cardiac death or hospitalisation for cardiac causes; 7.9% with canrenone and 15.1% with placebo (p=0.02).

Project outline
This topic has been referred to the HTA by the NICE Clinical Guideline 48 (MI: Secondary prevention in primary and secondary care for patients following a myocardial infarction. May 2007). The guideline development group (GDG) identified two RCTs of aldosterone antagonists in patients with heart failure and LV dysfunction (EPHESUS and RALES). Only one trial (EPHESUS) specifically examined the effectiveness in patients with LV dysfunction following an MI. Eplerenone treatment, in addition to ACE inhibitors and beta blockers, was associated with a reduced risk of the two primary endpoints: death from any cause (RR 0.85, 95% CI 0.75 to 0.96) and the combination of death from cardiovascular causes or hospitalisation for cardiovascular events (RR 0.87, 95% CI 0.79 to 0.95). In addition, evidence from two studies were identified which examined the cost-effectiveness of eplerenone based on the effectiveness data from the EPHESUS study. Both studies demonstrated that eplerenone appears to be cost effective in patients early after MI with LV dysfunction.

The use of spironolactone, in addition to standard therapy, has been demonstrated in the RALES study to significantly reduce the risk of both morbidity and death among patients with severe heart failure. Approximately 54% of patients in the study had an ischaemic cause for heart failure. Several studies have also evaluated the cost-effectiveness of spironolactone in the overall population, demonstrating that spironolactone appears to be highly cost-effective or may even dominate standard care (i.e. it is potentially both cheaper and more effective).

A recent pharmacoeconomic review of eplerenone concluded that future clinical and economic comparison of eplerenone and spironolactone would be of particular interest, particularly in view of the lower drug acquisition costs for spironolactone than for eplerenone. However, this review reached similar conclusions to the GDG that a comparison of these two drugs in patients who have had an acute MI and who have symptoms and/or signs of heart failure and LV dysfunction is not currently feasible due to the limited data on spironolactone specifically in patients after an MI and the lack of clinical data directly comparing the two drugs.
From an economic perspective, the GDG recognised that the correct comparison should be between eplerenone and spironolactone. Although spironolactone was reported to be widely used in post MI patients, the GDG considered that there was no direct effectiveness evidence in this patient group. In the absence of direct evidence, the GDG subsequently recommend treatment with eplerenone for patients who have had an acute MI and who have symptoms and/or signs of heart failure and LV dysfunction.

**Objectives**
The primary objective is to evaluate the relative clinical effectiveness and cost-effectiveness of spironolactone and eplerenone in patients with heart failure (HF) following myocardial infarction (MI), and to explore the possibility of conducting an indirect comparison of spironolactone and eplerenone in post-MI HF. A range of alternative approaches will be considered and will be used as the basis for considering issues related to the relative cost-effectiveness of spironolactone and eplerenone. A second objective is to use Expected Value of Information analyses to determine the need for further research, to identify the research questions critical to decision making, and to help inform the design of future studies and to consider implementation issues.

5. **Outline of work**
The review will be undertaken in a series of related phases:

- **Phase 1: Update review of clinical-effectiveness evidence.**
The existing clinical-effectiveness evidence identified within NICE Clinical Guideline 48 related to the use of eplerenone and spironolactone will be updated. The update review will be undertaken systematically following the general principles recommended in CRD Report 418 and the QUOROM statement. A draft search strategy devised for MEDLINE using the Ovid interface is detailed in Appendix 1; this will be developed further and converted to run appropriately on other databases.

Scoping searches will be carried out to identify systematic reviews, guidelines or major clinical trials (both completed and ongoing) using the following resources: Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment Database (HTA), National Library for Health Guidelines Finder, National Guidelines Clearing House, Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov and the metaRegister of Controlled Trials (mRCT). The bibliographies of all relevant reviews and guidelines and all included studies will be checked for further potentially relevant studies.

Clinical trials will be identified by searching major healthcare information databases including MEDLINE, EMBASE and CENTRAL. In addition, information on studies in progress will be sought by searching ClinicalTrials.gov and the metaRegister of Controlled Trials (mRCT).
Adverse effects information will be identified through searches of Meylers, Dynamed, AHFS Drug Information, US Food and Drug Administration (FDA) website and the TOXLINE database.

Manufacturers and trial authors will be approached in an attempt to obtain patient level data, or summary statistics for ischemic subgroups from trials of general heart failure patients.

- **Inclusion and exclusion criteria**
  Two reviewers will independently screen all titles and abstracts. Full paper manuscripts that may be relevant will be obtained where possible and the relevance of each study assessed independently by two reviewers according to the criteria below. Discrepancies will be resolved by discussion, or by referral to a third reviewer when necessary.

- Population: Studies including adults with clinical signs of heart failure and left ventricular systolic dysfunction (LVSD) (left ventricular ejection fraction (LVEF) \(\leq 45\%\)) following a myocardial infarction. Subgroup of interest is those with severe LVSD (LVEF <30%).

- Interventions: Treatment with spironolactone or eplerenone, used in addition to optimal medical management for heart failure. Studies evaluating the effectiveness of the metabolites of spironolactone, canrenone and potassium canrenoate, will also be sought to provide supplementary information on efficacy.

- Comparators: Placebo plus optimal medical management, or optimal medical management.

- Outcomes: All cause/cardiac mortality; all cause/cardiac hospitalisation rates; composite outcomes of mortality and hospitalisation rates; improvement in NYHA classification; cardiovascular events; adverse effects of treatment (specifically gynaecomastia and hyperkalaemia or clinical events resulting from hyperkalaemia); health-related quality of life.

- Study designs: Randomised controlled trials (RCTs) will be used to evaluate clinical efficacy, with additional large observational studies included for the evaluation of adverse effects.

- **Quality assessment**
  The quality of the individual studies will be assessed by one reviewer, and independently checked by a second reviewer. Any disagreements will be resolved by consensus and if necessary a third reviewer will be consulted. The quality of included studies will be assessed using standard checklists adapted as necessary to incorporate topic-specific quality issues.

- **Methods of analysis/synthesis**
  Data relating to both study design and quality will be extracted by one reviewer using a standardised data extraction form and checked by a second reviewer. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary. Key study characteristics, patient outcomes and study quality will be summarised in
narrative and tables. Where appropriate, meta-analysis will be employed to estimate a summary measure of effect on relevant outcomes based on intention to treat analyses, and potential sources of heterogeneity will explored. Subgroup analyses will be performed for those with severe LVSD if sufficient data is available.

**Phase 2: Exploration of ‘exchangeability’ of trial evidence and indirect comparisons**

We do not anticipate any evidence which directly compares the effectiveness or cost-effectiveness of eplerenone and spironolactone (or its metabolites) in patients with post-MI-HF. In the absence of direct evidence, formal approaches to making indirect comparisons based on quantitative methods will be explored. The validity of the assumptions required to make such comparisons will depend on the degree of exchangeability of evidence which can be assumed across the existing trial populations and subgroups.

One approach will be to consider the post-MI subgroups of controlled trials of aldosterone antagonists in more detail. This will require close examination of the patient characteristics of the populations of the available trials (RALES, EPHESUS and possibly AREA) and other possible sources of heterogeneity (e.g. concomitant medication, length of follow-up, definition of endpoints etc). If possible we will try to obtain individual patient data for the post-MI HF subgroups recruited in the included studies or summary statistics for the relevant sub-group. If this is not possible we will analyse the available data using quantitative or narrative synthesis as appropriate for the degree of ‘exchangeability’ between the trials.

Depending upon the limitations of the available data, it may be necessary to consider expert elicitation with a sample of cardiologists (n=5) to quantify their beliefs about the relative effectiveness of these two drugs in the specific population considered by the decision problem. Mathematical approaches to elicitation will be applied to quantify the uncertainty using a histogram approach. Linear opinion pooling will be applied to combine the separate experts’ responses.

These alternative approaches considered within Phase 2 will be used as the basis for informing an indirect comparison of the relative effectiveness of eplerenone and spironolactone (or its metabolites) for the purposes of informing the subsequent phases of work.

**Phase 3: Development of a new decision-analytic model to evaluate the cost-effectiveness of aldosterone antagonists from an NHS perspective**

The existing cost-effectiveness evidence identified within NICE Clinical Guideline 48 related to the use of eplerenone and spironolactone will be updated. The update searches will be undertaken systematically using the databases MEDLINE, EMBASE and CENTRAL. In addition, searches of NHS EED and HEED will be carried out, along with a search of the Economics Working Papers archive (IDEAS).

These sources will be used to identify studies of the cost-effectiveness of epleronone and spironolactone for the management of heart failure. A broad range of studies will be considered in the assessment of cost-effectiveness including economic evaluations conducted alongside trials, modeling studies and analyses of administrative databases. Only full economic evaluations that compare two or more options and consider both
costs and consequences (including cost-effectiveness, cost-utility and cost-benefit analyses) will be included in the review of economic literature.

The review will examine existing decision-analytic models in detail, with the aim of identifying important structural assumptions, highlighting key areas of uncertainty and outlining the potential issues of generalising from the results of existing models. This review will be used to identify the central issues associated with adapting existing decision models to address the specific research question posed and to assist in the development of a new decision model drawing on the issues identified in the clinical and cost-effectiveness review. The presence of any data gaps (e.g. resource use data) that may need to be filled during the development of the model will be identified and additional searches may be required.

Subject to the availability of suitable data, a new decision-analytic model will be developed to estimate the cost-effectiveness of aldosterone antagonists in post MI HF. The results of Phase 2 will be used as the basis for informing the model assumptions related to the relative effectiveness of the drugs. The model will have a lifetime horizon and consider costs from the perspective of the NHS. The model will be used to relate intermediate outcomes to final health outcomes, expressed in terms of quality-adjusted life years (QALYs).

Data on costs will be sought from the literature and through relevant national databases (e.g. reference costs). Information on quality of life and decrements in utility values associated with events will be obtained from the literature. Discounting will be undertaken at an annual rate of 3.5% on costs and benefits

A probabilistic model will be developed which requires that each input in the model is entered as an uncertain, rather than a fixed, parameter. Using Monte Carlo simulation, this parameter uncertainty, is translated into uncertainty in the overall results. This ultimately helps decision makers understand the probability that, in choosing to fund an intervention, they are making the wrong decision – that is, decision uncertainty. This is presented using cost-effectiveness acceptability curves which show the probability that each intervention is cost-effective conditional of a range of possible threshold values which NHS decision makers attach to an additional QALY.

**Phase 4: Assessment of the value of information and implementation issues**

To consider future research priorities in the NHS, the model will be used to undertake analyses of the expected value of information. The expected value of perfect information (EVPI) will be estimated for the overall decision problem and for key parameters. EVPI represents the expected costs of decision uncertainty since perfect information would eliminate the possibility of making the wrong decision. Hence, EVPI for the overall decision problem represents the value of eliminating all uncertainty and EVPI for key parameters (termed partial EVPI) represents the value of eliminating uncertainties in particular subsets of parameters. Separate analyses will be undertaken to reflect the variability considered in the decision model itself. Per patient EVPI estimates will be scaled up to reflect the relevant UK population size and will adopt an appropriate time-horizon.
EVPI also represents the maximum amount that a decision-maker should be willing to pay for additional evidence to inform this decision in the future. EVPI provides an upper bound on the value of additional research. This valuation provides an initial hurdle, acting as a necessary requirement for determining the potential efficiency of further primary research. Applying this decision rule, additional research should only be considered if the EVPI exceeds the expected cost of the research. In addition to providing a global estimate of the total cost of uncertainty related to all inputs in the model, EVPI can also be estimated for individual parameters (and groups of parameters) contained in the model. The objective of this analysis (termed partial EVPI) is to identify the model parameters where it would be most worthwhile obtaining more precise estimates. Given the exploratory nature of this work, the results will provide an indication of the potential value of a trial which directly compares the drugs.

We will also consider issues relating to the potential value of implementation strategies. Current use of aldosterone antagonists will be informed from published sources and relevant databases. The results of this will then be used to establish the potential value of implementation strategies which could be used to alter existing practice to the most cost-effective strategy outlined in Phase 3.

Phase 4 will therefore provide the basis for identifying research priorities regarding future research as well as related implementation issues.

6. Clinical expertise
Dr Ameet Bakhai (Consultant Cardiologist, Barnet General Hospital, London) and Dr Klaus Witte (Senior Lecturer and Honorary Consultant Cardiologist, University of Leeds and Leeds General Infirmary, UK) have agreed to act as clinical advisors during the course of the project. Three additional clinicians will be approached separately to participate in an external advisory group should elicitation be undertaken.

7. Competing interests of authors
None of the authors have any conflicts of interest.

8. Timetable/milestones

<table>
<thead>
<tr>
<th>Submission of</th>
<th>Date</th>
</tr>
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<tbody>
<tr>
<td>Team submit draft protocol</td>
<td>23 December 2008</td>
</tr>
<tr>
<td>Expected date for HTA to send comments on draft protocol</td>
<td>12 January 2009</td>
</tr>
<tr>
<td>Team submit final protocol to HTA</td>
<td>16 January 2009</td>
</tr>
<tr>
<td>Team submit assessment report to HTA</td>
<td>31 March 2009</td>
</tr>
</tbody>
</table>
9. References


16. Lewis BS, Mehta SR, Fox KA, Halon DA, Zhao F, Peters RJ, et al. Benefit of clopidogrel according to timing of percutaneous coronary intervention in patients with...
acute coronary syndromes: further results from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study. *Am Heart J* 2005;150:1177-84.
Appendix 1: Example MEDLINE search strategy

1   exp Heart Failure/
2   "heart failure$".ti,ab.
3   "HF".ti,ab.
4   "CHF".ti,ab.
5   "cardiac failure$".ti,ab.
6   "coronary failure$".ti,ab.
7   "myocardial failure$".ti,ab.
8   "heart decompensation".ti,ab.
9   "cardia$ decompensation".ti,ab.
10  1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11  exp Myocardial Infarction/
12  "heart attack$".ti,ab.
13  "heart infarct$".ti,ab.
14  "cardiac infarct$".ti,ab.
15  "cardial infarct$".ti,ab.
16  "myocardial infarct$".ti,ab.
17  "myocardium infarct$".ti,ab.
18  "MI".ti,ab.
19  "AMI".ti,ab.
20  11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21  10 and 20
22  "post AMI HF".ti,ab.
23  "postmyocardial infarct$".ti,ab.
24  "postmyocardium infarct$".ti,ab.
25  "post MI".ti,ab.
26  21 or 22 or 23 or 24 or 25
27  exp Aldosterone Antagonists/
28  "aldosterone antagonist$".ti,ab.
29  27 or 28
30  Spironolactone/
31  spironolactone.ti,ab,rn.
32  52-01-7.rn.
33  aldactone.ti,ab,rn.
34  (novo-spiroton or novospiroton or "novo spiroton").ti,ab,rn.
35  spiractin.ti,ab,rn.
36  spirotone.ti,ab,rn.
37  verospiron.ti,ab,rn.
38  berlactone.ti,ab,rn.
39  30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38
40  eplerenone.ti,ab,rn.
41  inspra.ti,ab,rn.
42  40 or 41
43  Canrenone/
44  canrenone.ti,ab,rn.
45  976-71-6.rn.
46  contaren.ti,ab,rn.
47  luvion.ti,ab,rn.
48  aldadiene.ti,ab,rn.
49  phanurane.ti,ab,rn.
50  43 or 44 or 45 or 46 or 47 or 48 or 49
51  Canrenoate Potassium/
52  (canrenoate adj potassium).ti,ab,rm.
53  2181-04-6.rn.
54  canrenol.ti,ab,rm.
55  soldactone.ti,ab,rm.
56  "Kalium-Can".ti,ab,rm.
57  diurek.ti,ab,rm.
58  Kanrenol.ti,ab,rm.
59  luvion.ti,ab,rm.
60  venactone.ti,ab,rm.
61  spiroctan.ti,ab,rm.
62  51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61
63  29 or 39 or 42 or 50 or 62
64  randomized controlled trial.pt.
65  controlled clinical trial.pt.
66  randomized.ab.
67  placebo.ab.
68  drug therapy.fs.
69  randomly.ab.
70  trial.ab.
71  groups.ab.
72  64 or 65 or 66 or 67 or 68 or 69 or 70 or 71
73  (animals not (humans and animals)).sh.
74  72 not 73
75  26 and 63 and 74
76  RALES.ti,ab.
77  EPHESUS.ti,ab.
78  "AREA IN CHF".ti,ab.
79  77 or 76 or 78
80  63 or 79
81  26 and 74 and 80