Trends in the characteristics, treatment and prognosis of people with symptomatic heart failure and the use of aldosterone antagonists: Analysis Plan

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Introduction
The purpose of our study is to describe the prevalence/incidence, characteristics and prognosis of people with moderate to severe symptomatic heart failure requiring diuretics for symptoms, describe their medication use, replicate the RALES trial using propensity scores and investigate whether there was a change in prescribing patterns for spironolactone following RALES trial publication in 1999, and subsequent NICE guidelines for treatment of symptomatic heart failure in 2003 and 2010.

Objectives
1. Describe the characteristics of those people receiving high dose loop diuretics or intravenous loop diuretics at any strength with symptomatic heart failure in terms of age, sex, year and social deprivation.

2. Evaluate the time trends in the number of people issued prescriptions for spironolactone and other medication for heart failure in people with symptomatic heart failure, following the RALES trial and NICE guidelines.

3. Describe variation in duration and dose of spironolactone in people with symptomatic heart failure.

4. Describe the characteristics of people with symptomatic heart failure receiving, or not receiving, spironolactone in a – the overall population and b – after applying exclusion criteria.

5. Contrast the survival in otherwise similar people with symptomatic heart failure, treated or not treated with spironolactone.

Study population
The study population is men and women aged 30 to 99 years who are permanently registered with a general practice (patflags A or C) that is part of THIN (The Health Improvement Network) that have 80% or more of Postcode Variable Information (PVI) data available on Townsend scores. Patients must have been registered some time between the years 1995 and 2010 and have been prescribed at least one prescription for high dose loop diuretics defined as \( \geq 80 \text{mg/day Furosemide or equivalent in bumetanide (} \geq 2 \text{mg)} \) or torasemide \( \geq 20 \text{mg} \) at some time during that period. For those that had two different loop diuretics prescribed on the same day, if the individual drug quantities do not constitute high dose, then each drug must be prescribed in at least half high dose quantities. For example, if a person is prescribed furosemide and bumetanide on the same day, then they should be receiving at least 40mg a day furosemide and 1mg bumetanide. If people are prescribed two or more prescriptions for the same drug but at different strength, dose per day will be calculated by adding doses of the two drugs to calculate mg per day and then any amount
above the thresholds listed above will be considered to be receiving high dose loop diuretics. If a person is prescribed more than one identical prescription on one day, it is assumed these are consecutive prescriptions being written in a batch. Therefore, these are considered to be separate for the purposes of working out the dose and whether it is considered high. These people are the cohort that will hereafter be referred to as those with symptomatic heart failure.

**Exclusion criteria**

For those who were prescribed spironolactone, high dose loop diuretics must have been prescribed prior to that (with any time interval).

**Exclusion criteria for objective 4**

On the palliative care register (defined using QOF codes: 1Z01, 2JE, 8BA2, 8BAP, 8BAS, 8BAT, 8BAe, 8BJ1, 8CM1.%, 8CM4, 8CME, 8H6A, 8H7L, 8H7g, 8HH7, 8IEE, 9EB5, 9Ng7, ZV57C)\(^5\)

Congenital heart disease (using "C:\THIN0902 pregnancies\drug_wordlists\100210 SHORT malformation codes IN RG.dta" (on LM computer), with the exception of the Read codes starting with a G)

Unstable angina in the three months before baseline

Liver failure

A cancer Read code in the three months before baseline

Had a heart transplant

Serum creatinine concentration of more than 2.5mg per decilitre (221\(\mu\)mol per litre) in the 12 months before baseline. In this extraction, values have been constrained to be between 20 \(\mu\)mol per litre to 1000 \(\mu\)mol per litre (after Email discussion with Kate)

Serum potassium concentration of more than 5.0mmol per litre in the 12 months before baseline. In extraction these will be limited to values between 1mmol per litre and 10mmol/litre (after Email discussion with Kate).

Addison’s disease

Cirrhosis of the liver

Hypnoatraemia

Nephrotic syndrome

Malignant ascites

Primary hyperaldosteronism

Additionally, individual people will have to conform to the following timings (which should be in a plausible order) in order to be a member of the cohort:

1. A person’s start date is the latest of the AMR date, Acceptable Computer Use (ACU) or date of registration with the General Practice date + 12 months following registration.
2. A person’s end date is the earliest of the date of transfer out of the practice, date of death, end of the study date (31/12/2011) or last data collection from the General Practice.
3. Those on high dose loop diuretics must not have been prescribed spironolactone before high dose loop diuretics.

For objective 1, it will also be necessary to extract data on all other people in THIN who are permanently registered (patflag A or C), conform to the practice characteristics, timing, gender, age but who are not taking high dose loop diuretics over the course of follow-up. All other objectives will only use data from those who have symptomatic heart failure.

**Start of follow up**

Start of follow up for those objectives 1 and 2 will be the first day of entry into the cohort (after 1995). In those not receiving spironolactone, the start of follow up (for objectives 3 and 5) will be deduced using regression where the outcome is the number of days between
first high dose loop diuretic prescription and spironolactone and possible explanatory factors will be the same as for propensity score analysis (see later in this analysis plan). Follow up will be informed from objectives 1 and 2 and survival analysis. Survival analysis will be used to see whether people in this cohort die and how long after the start of follow up until they die.

Data extraction
Therapy records (TherRecs), Patient records (PatRecs), Medical records (MedRecs), AHD records (AhdRecs) and Townsend deprivation quintile (PVIRecs) of the study population (those with symptomatic heart failure) will be extracted.

Data on age, sex and Townsend deprivation quintile will be extracted from those not prescribed high dose loop diuretics (for Objective 1).

Other variables
Drug code lists for loop diuretics (Furosemide, bumetanide, torasemide; BNF chapter 2.2.2), ACE inhibitors (BNF chapter 2.5.5.1), amiodarone (BNF chapter 2.3.2), angiotensin receptor blockers (ARB; BNF chapter 2.5.5.2), antiarrhythmic drugs (other than the ones extracted separately, BNF chapter 2.3), antiplatelet drugs (except aspirin, BNF chapter 2.9), beta blockers (BNF chapter 2.4), calcium channel blockers (BNF chapter 2.6.2), diuretics (other than the high dose loop diuretics of interest and spironolactone, BNF chapter 2.2), hydralazine with nitrate (BNF chapter 2.5.1), hypertension and heart failure drugs (apart from the ones extracted separately, BNF chapter 2.5), digoxin (BNF chapter 2.1.1), spironolactone (BNF chapter 2.2.3), nitrates (BNF chapter 2.6.1), hydralazine (BNF chapter 2.5.1), lipid regulating drugs (BNF chapter 2.12), oral anticoagulants (BNF subchapter 2.8.2), other antianginal drugs and peripheral vasodilators and related drugs (BNF subchapters 2.6.3 and 2.6.4), potassium supplements (BNF chapter 9.2.1.1) and low dose aspirin (BNF chapter 2.9), insulin (BNF chapter 6.1.1), Sulfonylureas (BNF chapter 6.1.2.1) and Metformin (BNF chapter 6.1.2.2) will be created. We have identified Read codes for symptomatic heart failure including codes that indicate conditions such as acute pulmonary oedema, cardiac failure and the severity of symptoms, for example, the New York Heart classification using the guidelines provided by Davé and Petersen. All code lists will be reviewed by a general practitioner. In addition we will identify records for smoking, alcohol, blood pressure, weight, height and comorbid conditions including hypertension, diabetes, chronic kidney disease (CKD), liver disease, stroke, dementia referrals and admissions for heart failure, cardiology, general/geriatric (six variables) and comorbidity index based on medication prescribed (excluding BNF chapters 14 and 15; vaccines and anaesthesia). Referrals and admissions will be recorded as the number of times they have a relevant referral/admission code in the year before baseline. However, there are only likely to be sufficient events to use these are continuous (or categorical with more than two categories) for the general/geriatric admissions and referrals. Socio-demographic variables to be extracted are: age, sex, deprivation (Townsend quintiles) and ethnicity.

For the health indicators (alcohol consumption, smoking status, weight, blood pressure), data will be taken from up to five years before baseline, with the value nearest to baseline utilised. Height will be extracted from any time, and the last one recorded utilised. For other conditions (asthma, atrial fibrillation, cardiovascular disease, chronic kidney disease, COPD, death (all cause), dementia, diabetes, home oxygen, housebound, hypertension, hypothyroidism, learning disabilities), data will be taken from any time before baseline and recorded as a dichotomous variable (condition present versus condition not present). Breathlessness and depression will be recorded as dichotomous variables using data from the year before baseline. Breathlessness will also be recorded in five categories to try to get a handle on the severity of breathlessness experienced (none, unspecified breathlessness, mild breathlessness, moderate breathlessness, severe breathlessness). Drug prescriptions will be taken in the year before baseline; these will be dichotomous variables; has been
prescribed the given drug versus has not been prescribed the drug. Smoking status will be recorded in three categories (current smoker, ex-smoker and non-smoker (plus missing)); alcohol consumption status will be recorded as heavy or dependent drinkers (36+ units per week for women and 51+ units per week for men) versus people who drink less or have missing data. Ethnicity will be recorded as white, black, south Asian and other (+missing).

**Dealing with missing loop diuretic dose data**

There is substantial missing data relating to doses of medications received. This will be investigated and where possible the dose for that given person used. Some stated doses will be unrealistic (more than six tablets a day for loop diuretics from preliminary work); these will be set to missing. Where the dose is unknown (or unrealistic and therefore set to missing), dose will be imputed using a hotdeck technique\(^2\). This process will have to be undertaken soon after extraction of potentially relevant therapy records so that dose can be used as an inclusion criterion. The exact process used is documented in the study population section of this document.

**Dealing with missing spironolactone dose data**

**Other missing data**

There will be missing data in Townsend quintile, smoking status, and ethnicity. Missing data will be recorded in separate categories for these variables when deriving propensity scores. For propensity score matching height, weight, systolic and diastolic blood pressures will be categorised into quintiles (+missing).

**Statistical analysis**

Analysis will be performed using R, SAS and Stata

1. **Describe the characteristics of those people receiving high dose loop diuretics or intravenous loop diuretics at any strength with symptomatic heart failure in terms of age, sex, year and social deprivation.**

   Data will be analysed using Poisson regression accounting for clustering by general practice (using xtpoisson in Stata) to determine the rates of symptomatic heart failure, overall, by sex, age and Townsend deprivation quintile univariately. Following that, multivariable models will be constructed including age group, sex and Townsend deprivation quintile. Interactions between age group and Townsend deprivation quintile, age group and gender will also be explored. Incidence rate ratios and 95% confidence intervals (CI) will be presented.

2. **Evaluate the time trends in the number of people issued prescriptions for spironolactone and other medication for heart failure in people with symptomatic heart failure, following the RALES trial and NICE guidelines.**

   Initially incidence rates of spironolactone prescriptions per quarter of a year (January to March, April to June, July to September and October to December) will be calculated. Time trend analysis will be performed using segmented regression\(^3\) to show the extent of a change in prescription patterns after the publication of RALES trial\(^4\) in 1999 and the NICE guidelines in 2003 [http://www.nice.org.uk/CG108](http://www.nice.org.uk/CG108). The quarters of change will be taken to be the quarters after the publication of the RALES trial and NICE 2003 guidelines; however, we will carry out sensitivity analyses with the timing of change.

3. **Describe the characteristics of people with symptomatic heart failure receiving, or not receiving, spironolactone.**

   Initially univariate analyses will be carried out to compare those who are and are not prescribed spironolactone from 2007. Statistical tests will be t-tests or non-parametric equivalents (continuous data) or chi square tests (categorical data). These will be tabulated,
and as the data are likely to show many statistically significant differences, clinically significant differences will be noted.

Following that, the comparability of the population that is prescribed spironolactone with those who do not receive spironolactone will be described using propensity scores. Possible variables included in the construction of the propensity score will be:

**Sociodemographic**
- Age
- Ethnicity
- Sex
- Townsend deprivation quintile

**Health indicators**
- Admission for cardiac
- Admission for general/geriatric
- Admission for heart failure
- Alcohol consumption status
- Blood pressure
- Body weight
- Comorbidity index
- Height
- Referral for cardiac
- Referral for general/geriatric
- Referral for heart failure
- Smoking status

**Diseases/ symptoms**
- Asthma
- Atrial fibrillation
- Breathlessness
- Cardiovascular disease
- Chronic kidney disease
- COPD
- Dementia
- Depression
- Diabetes
- Heart failure (Read code)
- Home oxygen
- Housebound
- Hypertension
- Hypothyroidism (QOF codes C03, C04)
- Learning disabilities

**Drugs**
- ACE inhibitors
- Amiodarone
- ARB
- Low dose aspirin
- Beta blockers
- BNF 2.2
- BNF 2.3
- BNF 2.5
- BNF 2.6.3, 2.6.4
- BNF 2.8.2
BNF 2.9
BNF 2.12
Calcium channel blockers
Digoxin
Hydralazine
Insulin
Metformin
Nitrates
Potassium supplements
Sulphonylureas
Year of first dose of high dose loop diuretic

Variables will be omitted from the propensity score if they affect less than 1% of this cohort (home oxygen, housebound, learning disability, antiarrhythmic drugs (BNF chapter 2.3) and hydralazine).

Propensity scores will only be calculated for those in the cohort who are taking either ACE inhibitors or ARB to align the cohort to RALES as far as possible. Univariate comparisons will then be repeated on the cohort who were propensity score matched (between those who did and did not take spironolactone).

4 Describe variation in duration and dose of spironolactone in people with symptomatic heart failure.
This objective will only be calculated for those who receive spironolactone at any point during the study period. This can be through any number of prescriptions but they must be receiving at least 25mg per day to replicate the level of dosing in the RALES trial. Those who take spironolactone long term will be identified.

The dose will be calculated. As with dosing of loop diuretics, some of the dose values are likely to be missing. These missing data will be handled.

Information on length of prescription will also be required, to work out exposure, where this information is missing, information from preceding and following prescriptions will be used along with usual doses from the BNF. Discontinuation will be considered to have occurred if there is a gap of more than 90 days between prescriptions. The cumulative length of exposure will be calculated and account taken for the length of time that covers. The amount of time taking these drugs uninterrupted and the patterns of intermittent use will be examined. Following this analysis, we will determine the categorisation for objective 5.

The dose will be calculated and then presented in a histogram to discover the usual dose.

5 Contrast the survival in otherwise similar people with symptomatic heart failure, treated or not treated with spironolactone.
Using the propensity scores generated in objective 3, those with similar characteristics in the two groups (those who do and do not take spironolactone), will be matched using a very precise optimal matching algorithm in SAS. The difference between the linear predictor between those who receive spironolactone and those who do not will be no more than 0.001 and will be subject to sensitivity analysis (at 0.01).

Once the matching has taken place and the study population for this objective achieved, then the descriptive analyses used in objective 3 will be repeated and results placed in the same table. Following this, data will be analysed using Kaplan Meier survival curves and a log rank test to compare survival functions. Hazard ratio and 95%CI for difference in mortality will be calculated using Cox regression, exploring practice as a group frailty.
Additional supportive analysis will be performed to assess whether practice should be added into the propensity score criteria, also to assess the propensity score by practice. Finally we will describe the characteristics of those who cannot be matched.

We will investigate the survival of people with symptomatic heart failure treated or not treated with spironolactone using the prescribing patterns of general practices as an instrumental variable. If there is a tendency for some practices to prescribe and others not to prescribe (influenced by local prescribing policies), practice will be associated with the outcome through the exposure (spironolactone) and will act as an instrumental variable.

Supportive analysis to validate objectives 1-5
Supportive analysis will be performed in a subgroup with a prescription for spironolactone AND a Read code for symptomatic heart failure. As high dose loop diuretics are also given to people with acute renal disease, the analyses will be also performed in those people without acute renal disease (defined using Read codes).

References


