Primary aldosteronism in general practice: organ damage, epidemiology and treatment

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Objectives: Part 1) To assess the prevalence of PA in general practice (part 1 of this study);Part 2) To describe differences of cardiorenovascular damage in newly diagnosed hypertensive patients with versus without PA (part 2 of this study);Part 3...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Cardiac disorders, signs and symptoms NEC
Study type	Observational non invasive

Summary

ID

NL-OMON37681

Source
ToetsingOnline

Brief title
PAGODE

Condition

- Cardiac disorders, signs and symptoms NEC
- Adrenal gland disorders
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
high blood pressure, primary aldosteronism

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: mineralocorticoid receptor antagonists (MRA), organ damage, prevalence, primary aldosteronism

Outcome measures

Primary outcome

Part 1: Prevalence of primary aldosteronism in newly diagnosed hypertensive

patients in Dutch general practice

Part 2: Difference in cardiorenovascular damage in patients with versus without

PA, based on a composite of the following parameters:

- Left ventricular mass index in g/m2

- Intima-media thickness of carotid artery in mm

- Pulse wave velocity in m/s

- Central aortic blood pressure in mmHg

- Flow-mediated dilation in %

- Albuminuria in mg albumin per mmol creatinin

Part 3: Difference in reduction of daytime systolic ABPM in patients with

normokalemic PA versus patients with essential hypertension in a

standardized treatment regimen during conventional antihypertensive therapy

Secondary outcome

Part 2: to observe differences in

• Serum potassium

• Low density lipoprotein

• Total cholesterol to high density lipoprotein ratio

Part 3: to observe differences in

• Reduction of daytime systolic ABPM in patients with PA versus patients with essential hypertension in a standardized treatment regimen during spironolactone (or eplerenone)

• Serum potassium response using conventional antihypertensive medication

• Adverse effects using conventional antihypertensive medication

• Serum potassium response using spironolactone (or eplerenone)

• Adverse effects using spironolactone (or eplerenone)

Study description

Background summary

Rationale: primary aldosteronism (PA) is the most frequent form of secondary hypertension. It is caused by autonomous secretion of aldosterone, encompassing a group of disorders predominated by a unilateral aldosterone-producing adenoma (APA) and bilateral adrenal hyperplasia (BAH). Diagnosis of PA is relevant for two reasons: 1) independent of the level of blood pressure, hypertension due to autonomous aldosterone secretion causes more cardiovascular damage than essential hypertension; 2) PA requires specific treatment: adrenalectomy in case of APA and mineralocorticoid receptor antagonists (MRA) in case of BAH. Although previously presumed a rare condition (prevalence <1%), PA is now estimated to affect 6 to 20% of the hypertensive population. Given this high prevalence of PA, as well as the amount of cardiovascular damage and the available specific treatment, the question is raised whether screening of PA should be introduced in Dutch general practice. To answer this important question, several issues with regard to PA need to be elucidated:
1) International studies report a prevalence of PA in general practice of 6-13%. Prevalence in the Dutch population is still unknown;
2) Because of underdiagnosis of PA and long delay in diagnosis of PA after recognition of hypertension (mean eight years), data on characteristics of

early diagnosed PA are lacking. Proof of early cardiovascular damage would strengthen the case of screening for PA and needs to be studied;
3) Consequently, the diagnostic delay has lead to lack of data on optimal treatment in early PA. In the current guideline (NHG-guideline Cardiovascular risk management) a regimen of antihypertensive drugs is advised, and only if hypertension is refractory for >6 months patients are referred. It is unknown if hypertension is resistant to therapy in the initial phase of PA. If not, this would also argue for early biochemical screening for PA, because even if blood pressure is controlled, the detrimental effect of aldosterone itself will go on unopposed. It is therefore required to study the response to antihypertensive drugs (not MRA) in these patients.

Study objective

Objectives:
Part 1) To assess the prevalence of PA in general practice (part 1 of this study);
Part 2) To describe differences of cardiorenovascular damage in newly diagnosed hypertensive patients with versus without PA (part 2 of this study);
Part 3) To compare the difference in blood pressure reduction to hypertensive treatment (conventionial and with mineralocorticoid receptor antagonists) in newly diagnosed hypertensive patients with versus without PA (part 3 of this study).
These three objectives are essential to answer the question of whether general practitioners should screen for PA.

Study design

Study design:
Part 1) Prospective cross-sectional study;
Part 2) Descriptive cross-sectional study;
Part 3) Clincal observational study with intervention.

Study burden and risks

• In part 1 of the study all newly diagnosed hypertensive patients will extend their standard diagnostic blood examination with an additional blood sample to determine the aldosterone-renin ratio (ARR), this causes no extra burden nor risk. In order to obtain a reliable estimate of the prevalence of PA, it is important to collect an ARR from every patient with newly diagnosed hypertension;
• In part 2, patients with an increased ARR will be referred to our hospital for a sodium loading test to confirm or exclude PA. A cardiac ultrasound will be made as part of the standard diagnostic workup. Patients will be asked to participate in additional examinations, which includes four non-invasive vascular measurements and testing for albuminuria. This enhanced diagnostic

workup will take 90 minutes (see next bullet for examinations and their risks);
• In part 2 a sample of patients with normal ARR (matched controls) will be invited to participate in the following non-invasive measurements, which encompass the following risks and burden:
a. Left ventricular mass index by cardiac ultrasound: negligible risk, no pain;
b. Intima-media thickness of carotid artery by ultrasound: negligible risk, no pain;
c. Pulse wave velocity by Sphygmocor: negligible risk, no pain;
d. Central aortic blood pressure by Sphygmocor: negligible risk, no pain;
e. Endothelial function by flow-mediated dilation of the brachial artery: negligible risk, uncomfortable feeling in arm during examination;
f. Albuminuria by urine sample: negligible risk, no pain.
This extended diagnostic workup will take 120 minutes.
• Patients with an increased ARR may directly benefit to a large extend from participation, because if PA is diagnosed, they will not have the usual diagnostic delay of PA of eight years;
• Patients with normal ARR (matched controls) will benefit from participation at an individual level. The results of the diagnostic workup can be used as contributing factors in the assessment of their cardiovascular risk profile (NHG-guideline *Cardiovascular risk management*);
• In part 3 all patients will be treated with the same antihypertensive medication they would have received if they hadn*t been included, but due to the inclusion of the study, medication will be stopped after eight weeks. After a 'wash-out' period of four weeks, treatment with MRA will follow. This can be justified for three reasons:
- In non-study circumstances patients with newly diagnosed PA will receive a diagnostic workup for subtyping PA, followed by appropriate therapy (adrenalectomy or MRA). Because of the interruption of the standard diagnostic workup by participation in our study, direct treatment with MRA would seem more appropriate. However, no data exists on the effect of conventional antihypertensive treatment in the early phase of PA, nor data that suggest harm;
- A wash-out period of four weeks is too short cause harm. In case of complaints due to hypertension, medication will be restarted;
- Patients without PA will be exposed for four weeks to possible adverse effects of spironolactone (especially reversible gynaecomastia and libido loss in men). In case of adverse effects spironolactone will be stopped and replaced by equipotent dose of eplerenone.

Contacts

Public
Universitair Medisch Centrum Sint Radboud

Geert Grooteplein-Zuid 16
Nijmegen 6525 GA
NL
Scientific
Universitair Medisch Centrum Sint Radboud

Geert Grooteplein-Zuid 16
Nijmegen 6525 GA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Newly diagnosed hypertensive patients in general practice

Exclusion criteria

Use of antihypertensive medication
Heart failure class II, III or IV (according to the New York Heart Association)
Pregnancy or breastfeeding

Study design

Design

Study type: Observational non invasive

Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	13-08-2013
Enrollment:	1100
Type:	Actual

Ethics review

Approved WMO Date:	21-06-2013
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-07-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-12-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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
ClinicalTrials.gov	NCTnummervolgt
CCMO	NL40133.091.12