A Randomized Controlled Trial of Aliskiren in the Prevention of Major Cardiovascular Events in Elderly People Aliskiren Prevention Of Later Life Outcomes (APOLLO, CSPP100G2301)

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Primary1. To determine whether treatment with an aliskiren-based regimen (in part combined with amlodipine or hydrochlorothiazide) compared to a non-aliskiren based regimen, both on top of non-study BP lowering agents where applicable, reduces the...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cardiac disorders, signs and symptoms NEC
Study type	Interventional

Summary

ID

NL-OMON34220

Source
ToetsingOnline

Brief title
APOLLO

Condition

- Cardiac disorders, signs and symptoms NEC
- Vascular hypertensive disorders

Synonym
cardiovascular events

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma BV

Intervention

Keyword: Aliskiren, APOLLO, Cardiovascular Events

Outcome measures

Primary outcome

Composite of CV death, non-fatal MI, non-fatal stroke and significant heart

failure.

Secondary outcome

Effect on daily activities, renal function, total death.

Study description

Background summary

Cardiovascular disease (CVD) remains the leading cause of death and is expected to remain so in the foreseeable future. It is estimated that globally in 2005, 17.5 million people died from CVD (30% of all deaths), this is projected to increase to 20 million by 2015. CVD and its risk factors, especially hypertension, are important determinants of physical and cognitive disability and dependence in the elderly, with resultant high mortality and morbidity. Hypertension is highly prevalent and is a dominant cardiovascular (CV) risk factor. It is especially common, and reaches epidemic proportions in the elderly, contributing to high rates of major vascular events, including stroke, myocardial infarction, heart failure and renal dysfunction. In elderly individuals who have underlying coronary heart, cerebrovascular and/or peripheral arterial diseases (PAD), hypertension increases their risk by three fold or more. Effective treatment of hypertension, in primary and secondary prevention, would be expected to substantially reduce this risk.
While hypertension is defined as a SBP > 140 mmHg or diastolic of > 90 mmHg, most studies of blood pressure lowering in elderly people have enrolled those with SBP > 160 mmHg and diastolic blood pressure (DBP) > 90 mmHg. In those placebo-controlled studies, with entry BP > 160/90 mmHg and in which SBP was reduced by at least 10 mmHg by active therapy compared to placebo, significant

reductions in CVD risk were clearly shown. In most studies of individuals with lower levels of entry BP, BP lowering with active treatments vs. controls, there were no clear reductions in major vascular events, although promising differences were observed in some studies with the exception of special drugs in special populations where specific BP reduction and non-hypertensive effects of the drugs were being evaluated e.g. the HOPE or the EUROPA studies. At present there are little convincing data as to whether BP lowering per se in elderly individuals with SBP 159 mmHg or below is beneficial. Indeed this lack of information has been highlighted in the most recent revision of the European Society of Hypertension reappraisal of guidelines on hypertension management. Despite the lack of data from clinical studies, some guidelines recommend lowering BP in individuals with BP between 140 and 159 mmHg (SBP 130 mmHg in diabetes), based on extrapolations from the epidemiologic data in people without preexisting CVD. By contrast, in those with preexisting CVD, the relationship between BP and events is not linear. Therefore, clarifying whether BP lowering in elderly individuals with BP between 130 and 159 mmHg, especially those with preexisting CVD, will lead to worthwhile reductions in major clinical outcomes is important from three perspectives First, a clinical perspective (as clear evidence will remove uncertainty and provide the evidence to treat or not); second, a public health perspective (the population burden from hypertension is greater from Stage 1 hypertension, than at higher levels), and third, from an economic perspective (the largest expenditure for antihypertensive medications and related visits is likely to be in stage 1 hypertension). If studies demonstrate a lack of a clinically important effect of BP lowering in such populations, then prevention efforts can be redirected to other measures. If clear benefit is demonstrated, then this should lead to more widespread use of antihypertensive therapy. Often such therapy requires the combination of multiple medications to reach target levels, with the attendant increases in costs, greater complexity associated with drug interactions leading to intolerance and poor adherence, particularly in the elderly. Therefore it is important that the data justify the decision to treat this level of BP.
The purpose of the APOLLO study is to evaluate the effects of a regimen that uses as a foundation the direct renin inhibitor, aliskiren, in addition to standard medical therapy, in individuals * 65 years of age, with SBP 130 to 159 mmHg, in a placebo-controlled clinical trial. No single BP lowering drug is likely to produce the 10 mmHg or more reduction of SBP needed in order to see clinical effect, in those with Stage 1 hypertension, and so combined therapy will be necessary. The renin angiotensin aldosterone system (RAAS) modulating effects of the direct renin inhibitor, aliskiren, would be expected to lead to incremental clinical benefits in addition to its blood pressure lowering effect.

Study objective

Primary
1. To determine whether treatment with an aliskiren-based regimen (in part

combined with amlodipine or hydrochlorothiazide) compared to a non-aliskiren based regimen, both on top of non-study BP lowering agents where applicable, reduces the risks of major CV events (composite of CV death, non-fatal MI, non-fatal stroke and significant heart failure)
2. To determine whether intensified therapy with aliskiren plus an additional BP lowering drug (amlodipine or hydrochlorothiazide) compared to placebo, both on top of non-study BP lowering agents where applicable, reduces the risk of major CV events.
Secondary
To determine whether treatment with an aliskiren-based regimen compared to non-aliskiren based regimen:
1. Prevents decline in the ability to perform everyday activities independently (key secondary objective).
2. Prevents decline in renal function
3. Reduces total mortality.
Tertiary (exploratory)
To assess the effects of an aliskiren-based regimen on specific cardiovascular outcomes (including components of the composite primary outcome; resuscitated cardiac arrest, heart failure, coronary artery revascularization, atrial fibrillation, unstable angina, worsening angina or new angina), diagnosis of new diabetes, the components of health-related successful ageing, depression, all cause hospitalizations, surgical procedures, non-CV death, development of LVH by ECG criteria, microvascular complications of diabetes, malignancy, and biomarkers.

Study design

Multicenter randomized double-blind phase IIIB study with 2x2 factorial design and 2 strata.
3 study phases:
* Pre-run-in (1-4 weeks): Without study medication. Assessment of BP stability.
* Run-in (4-5 weeks): allocation to 1 of 2 treatments, base don existing thiazide (HCT)/calciumantagonist (CA) treatment:
a. CA: HCT 12,5/25 mg plus alsikiren 150/300 mg per day (titration).
b. HCT: amlodipine 5 mg plus aliskiren 150/300 mg per day (titration).
c. No CA or HCT: Randomized allocation to group a or b.
* Double-blind treatment phase (estimated approx. 5 years): randomization to
a. Aliskiren 300 mg plus amlodipine 5 mg of HCT 25 mg per day (combination arm).
b. Aliskiren 300 mg (aliskiren monotherapy arm).
c. Amlodipine 5 mg or HCT 25 mg per day (amlodipine or HCT monotherapy arm).
d. Placebo.
Additional open-label blood lowering drugs if necessary.
Stratification for centre and background therapy.
There are 3 optional substudies: pharmacogetic research (blood), ambulatory BP recording, MRI scans of the brain.
Annual follow-up of patients health after end of study (at least 5 years).
Ca 11.000 randomized patients.

Operations committee, steering committee, independent DSMB, event adjudication committee.

Intervention

Treatment with aliskiren plus amlodipine or HCT or aliskiren alone or amlodipine or HCT alone or placebo.

Study burden and risks

Risk: Adverse events of study medication.
Burden:
Visits: 4 visits and 2 telephone calls in 1st 4,5 months. Thereafter 2 visits and 1 telephone call with an interval of 3 months, thereafter visit every 6 months. Final visit 1 months after end of treatment phase. Therafter yearly contact about health (may be by telephone) during at least 5 years.
Blood tests (safety, blood sugar, lipids, biomarkers): every visit, 400-500 ml with study duration of 5 year.
In addition periodically: Physical examination and ECG.
Questionnaires and test, approx. yearly:
* Standard Assessment of Global-Activities in the Elderly (SAGE) with components of 5-item Barthel Scale for BADL and the Lawton Scale for IADL
* Montreal Cognitive Assessment (MoCA)
* Timed Up and Go (TUG)
* Digit Symbol Substitution Test (DSS)
* Geriatric Depression Scale (short form)
* European Quality of Life-5 Dimensions (EQ-5D)
* Mini Mental State Examination (MMSE) in a subset of participants.
Optional: pharmacogenetic blood test (1x 10 ml). Results will not be communicated, ambulatory 24h blood pressure recording (2x), MRI scan brain (2x).

Contacts

Public
Novartis

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

* Patients with an SBP of 130-159 mmHg with and without additional CV riskfactors, with and without cardiovascular disease (see protocol for details).
* 65 years and above (secondary prevention) or 70 years and above (primary prevention).

Exclusion criteria

* Current treatment with aliskiren, an ACE-inhibitor, an ARB or an aldosterone antagonist and unable to discontinue this therapy in those without clinical vascular disease. Individuals with CVD or type 2 diabetes and/or renal dysfunction may receive an ACE-inhibitor or an ARB, but not both.
* Contraindications to study drugs.
* Use of both thiazide diuretic and amlodipine or another calcium channel blocker. Patients on only one of these two classes of drugs are eligible.
* Uncontrolled hypertension (systolic blood pressure * 160 mmHg and/or diastolic blood pressure 100 mmHg and above)
* Symptomatic heart failure, requiring the use of loop diuretics.
* Hemodynamically significant primary valvular or outflow tract obstruction.
* Acute stroke < 3 months or TIA * 7 days before study start.
* Acute coronary syndrome < 1 months before study start.
* Cardiac procedure < 3 months before study start.
* eGFR * 30 ml/min/1.73m2.
* Serum potassium 5.3 mmol/L and above.
* Concurrent treatment with cyclosporine or quinidine.

* Chronic use of NSAIDs or COX 2 inhibitors in patients with eGFR < 60 ml/min/1.73m2 .

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-03-2011
Enrollment:	200
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Hydrocloorthizide
Generic name:	Hydrocloorthizide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Norvasc
Generic name:	amlodipine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Rasilez
Generic name:	Aliskiren
Registration:	Yes - NL intended use

Ethics review

Approved WMO
Date: 17-12-2010

Application type: First submission

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 02-03-2011

Application type: First submission

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 21-03-2011

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 23-03-2011

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 18-05-2011

Application type: Amendment

Review commission: METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO
Date: 31-05-2011

Application type: Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	12-09-2011
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	29-09-2011
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	13-12-2011
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	21-12-2011
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	08-03-2012
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	21-03-2012
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	29-03-2012
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	12-04-2012
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	16-05-2012
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	11-06-2012
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Not approved Date:	24-02-2014
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Not approved Date:	09-04-2014
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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
Other	clinicaltrials.gov; registratienummer nnb.
EudraCT	EUCTR2009-010170-38-NL
CCMO	NL33444.098.10