Low-dose colchicine for secondary prevention of cardiovascular disease - LoDoCo2 trial

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The primary objective is to determine the effect of low dose (0.5mg once daily) colchicine on the occurrence of the composite endpoint of acute coronary syndrome, fatal or non-fatal out of hospital cardiac arrest and atherosclerotic stroke in...

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

Summary

ID

NL-OMON50634

Source
ToetsingOnline

Brief title
LoDoCo2

Condition

- Coronary artery disorders

Synonym
stable coronary artery disease; atherosclerosis

Research involving
Human

Sponsors and support

Primary sponsor: WCN (Werkgroep Cardiologische centra Nederland)
Source(s) of monetary or material Support: ZonMw,stichting WSN;in-kind bijdrage leden WCN;generieke fabrikant betaalt IP

Intervention

Keyword: cardiovascular disease, colchicine, inflammation, secundary prevention

Outcome measures

Primary outcome

the composite outcome of sudden cardiac death, non-fatal out of hospital cardiac arrest, acute coronary syndromes or atherosclerotic ischemic stroke.

per protocol v2.6 20 August 2019 changed into

the composite outcome of cardiovascular death, myocardial infarction, ischemic stroke, or ischemia-driven revascularization.

per protocol v2.7 22 January 2020 changed into

the composite of cardiovascular death, myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization.

Secondary outcome

1. Time to the first coronary or cerebral atherosclerotic event: the composite of sudden cardiac death, non-fatal out of hospital cardiac arrest, myocardial infarction or unstable angina irrespective of revascularization, or atherosclerotic ischemic stroke (the composite endpoint of the first LoDoCo trial)
2. The composite of cardiovascular death, non-fatal myocardial infarction or non-fatal ischemic stroke
3. All-cause mortality
4. All myocardial infarction

5. All coronary revascularizations

6. Acute coronary syndromes related to stent or graft disease, irrespective of revascularization

per protocol v2.6 20 August 2019 changed into

The secondary objectives of this study are to evaluate clinical efficacy of treatment with colchicine 0.5mg once daily as compared to placebo in patients with stable coronary artery disease on the incidence of first occurrence of

1. Myocardial infarction

2. Ischemia-driven revascularization

3. Cardiovascular death or myocardial infarction

4. Cardiovascular death

5. Death from any cause

6. the composite of sudden cardiac death, non-fatal out of hospital cardiac arrest, myocardial infarction or unstable angina irrespective of revascularization, or atherosclerotic ischemic stroke (the composite endpoint of the first LoDoCo trial),

7. the composite of cardiovascular death, non-fatal myocardial infarction or non-fatal ischemic stroke,

8. Acute coronary syndromes related to stent or graft disease, irrespective of revascularization

tertiary

1. New onset or first recurrence of atrial onset fibrillation or atrial flutter

2. New onset of diabetes mellitus and

3. Deep vein thrombosis and/or pulmonary embolism.

For the Dutch cohort: to facilitate cost-effectivenes analysis:

1. emergency department visits

2. hospitalisations

3. quality of life and productivity

per protocol v2.7 22 January 2020 changed into

The secondary objectives of this study are to evaluate clinical efficacy of treatment with colchicine 0.5mg once daily as compared to placebo in patients with stable coronary artery disease on the incidence of first occurrence of

1. the composite of cardiovascular death, myocardial infarction or ischemic stroke

2. the composite of myocardial infarction or ischemia-driven coronary revascularization

3. the composite of cardiovascular death or myocardial infarction

4. Ischemia-driven coronary revascularization

5. Myocardial infarction

6. Ischemic stroke

7. Death from any cause

8. Cardiovascular Death

Study description

Background summary

Despite major advances in treatment, the burden of cardiovascular disease remains high. Worldwide, an estimated 17.5 million people died from cardiovascular diseases in 2012, of which an estimated 7.4 million due to coronary artery disease. Cardiovascular disease is the second most common cause of mortality in the Netherlands, responsible for 40.000 deaths per year with an estimated cost of 7 billion euro per year. There are approximately 600.000 people with coronary artery disease in the Netherlands, leading to 10.000 deaths per year.

Coronary artery disease and its complications are a disease of atherosclerosis. Key players in the disease process are atherosclerotic plaque growth and erosion or rupture of the fibrous cap covering the plaque. Rupture exposes the pro-coagulant material causing thrombo-embolic occlusion of the coronary artery, leading to myocardial infarction. Plaque instability is the result of injury caused by a local inflammatory response from the atheroma. Critical elements in the treatment of coronary artery disease thus are controlling lipid burden, plaque integrity and inflammatory response. For modulation of the latter several inflammatory pathways and therapeutic targets exist. Inhibiting the effect of interleukin-6 (Il-6) may be essential, as this inflammatory cytokine has proven to play a causal role in cardiovascular disease. IL-6 is mediated by interleukin-1 (IL-1) and the so called NLRP3 inflammasome, both upregulated by cholesterol crystals, forming the link between cholesterol deposition and inflammation in atherosclerosis. These inflammatory cytokines have a complex biochemical interaction. Inhibition of their action may decrease inflammatory effects and reduce athero-thrombotic complications in patients with coronary artery disease.

The elucidation of possible causative inflammatory agents in atherosclerosis and the similarities in pathophysiology in other inflammatory disorders have led to rediscovery of conventional anti-inflammatory drugs in atherosclerosis. Colchicine, used since decades as anti-inflammatory drug in the treatment of gout, pericarditis and Familiar Mediterranean Fever, is an anti-mitotic drug that inhibits multiple inflammatory pathways (IL-1, IL-6, the NLRP3-inflammasome). There is broad clinical experience with this low cost drug, serious adverse side effects are uncommon in those without renal impairment and so far it is the only anti-inflammatory drug with proven effect in patients with coronary artery disease. Using a prospective randomised open blinded end-point (PROBE) design the original low dose colchicine for prevention of cardiovascular disease (LoDoCo) trial demonstrated an impressive 67% reduction (hazard ratio: 0.33; 95% confidence interval [CI] 0.18 to 0.59) in the occurrence of the composite of acute coronary syndrome, out-of-hospital

cardiac arrest, or non-cardioembolic ischemic stroke in patients with stable coronary artery disease.

Study objective

The primary objective is to determine the effect of low dose (0.5mg once daily) colchicine on the occurrence of the composite endpoint of acute coronary syndrome, fatal or non-fatal out of hospital cardiac arrest and atherosclerotic stroke in patients with stable coronary artery disease.

per protocol v2.6 20 August 2019 changed into
The primary objective of this study is to evaluate clinical efficacy of treatment with colchicine 0.5mg once daily as compared to placebo in patients with stable coronary artery disease on the incidence of first occurrence of the composite of cardiovascular death, myocardial infarction, ischemic stroke, or ischemia-driven revascularization.

Study design

Prospective, multi-centre, randomised, double blinded, placebo controlled phase II trial that will run in Australia and the Netherlands.

Intervention

colchicine 0.5mg once daily

Study burden and risks

Burden: low, asides once daily one extra tablet no extra test (nor laboratory nor imaging) are necessary
Risks: low, due to the low dose of colchcine and exclusion of renal impairment, to reduce the risk of increased levels of colchicine. Furthermore, colchicine is used since decades as anti-inflammatory drug in the treatment of gout, pericarditis and Familiar Mediterranean Fever.

Contacts

Public
WCN (Werkgroep Cardiologische centra Nederland)

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Utrecht 3511 EP
NL
Scientific

WCN (Werkgroep Cardiologische centra Nederland)

Moreelsepark 1
Utrecht 3511 EP
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Age >35 and <82 years
2. Proven coronary artery disease; as evidenced by coronary angiography, CT coronary angiography or a Coronary Artery Calcium Score (Agatston score >400). Individuals with a history of bypass surgery are only eligible if they have undergone coronary artery bypass surgery more than 10 years before, or have angiographic evidence of graft failure or have undergone percutaneous intervention since their bypass surgery
3. Clinically stable for at least six months

Exclusion criteria

1. Women who are pregnant, breast feeding or may be considering pregnancy during the study period
2. Renal impairment as evidenced by a serum creatinine >150 µmol/l or estimated glomerular filtration rate (eGFR) <50mL/min/1.73m2
3. Severe heart failure * systolic or diastolic New York Heart Association Functional classification 3 or 4
4. Moderate or severe valvular heart disease considered likely to require intervention,
5. Dependency, frailty or a predicted life expectancy < 5 years
6. Peripheral neuritis, myositis or marked myo-sensitivity to statins

7. Requirement for long term colchicine therapy for any other reason
8. Current enrollment in another trial

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):	27-10-2016
Enrollment:	3580
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	colchicine 0.5mg
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	25-04-2016
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	01-08-2016
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-10-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-10-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-10-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	10-01-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-02-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-04-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	07-09-2017
Application type:	Amendment

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-10-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-11-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-12-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-02-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-03-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	08-05-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-06-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO

Date:	17-07-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-10-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	07-01-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-01-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-08-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	07-10-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-03-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-04-2020
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
Other	ACTRN12614000093684
EudraCT	EUCTR2015-005568-40-NL
CCMO	NL56036.100.16

Study results

Date completed: 17-02-2020

Actual enrolment: 5522

Summary results
Trial is onging in other countries