CLEAR SYNERGY (OASIS 9)
A 2x2 factorial randomized controlled trial of CoLchicine and spironolactonE in patients with myocARdial infarction/SYNERGY Stent Registry - Organization to Assess Strategies for Ischemic Syndromes 9

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In patients with acute MI (STEMI or Non-STEMI) who have undergone PCI, the objectives are to determine: 1. If colchicine can reduce the incidence of cardiovascular death, recurrent MI, or stroke. 2. If routine use of spironolactone can reduce the...

Ethical review	Approved WMO
Status	Completed
Health condition type	Heart failures
Study type	Interventional

Summary

ID

NL-OMON56069

Source
ToetsingOnline

Brief title
CLEAR SYNERGY (OASIS 9)

Condition

- Heart failures

Synonym
myocardial infarction, STEMI, stroke

Research involving
Human

Sponsors and support

Primary sponsor: Population Health Research Institute of McMaster University and Hamilton Health Sciences Centre
Source(s) of monetary or material Support: Canadian Institutes of Health Research (CIHR) Boston Scientific Corporation (BSC) Investigator-Sponsored Research Grant

Intervention

Keyword: Colchicine, Spironolactone, Stent

Outcome measures

Primary outcome

SYNERGY Stent Registry:

• Major Adverse Cardiac Events (see protocol for definitions)

Colchicine and Spironolactone 2x2 Factorial RCT:

• Colchicine vs. placebo: Time to event of the composite of CV death, recurrent

MI, stroke or unplanned ischemia driven revascularization over duration of

follow-up

• Spironolactone vs. placebo: Total composite events of CV death or new or

worsening heart failure over duration of follow-up

Secondary outcome

SYNERGY Stent Registry:

- Incidence of Definite Stent Thrombosis within 1 year.

Study description

Background summary

Although first generation durable-polymer drug eluting stents (DES) were associated with lower rates of stent restenosis compared to bare-metal stents (BMS), they were associated with increased rates of late and very late stent thrombosis. This could be due to the durable polymer and prolonged exposure to the drug leading to chronic vessel inflammation, delayed hypersensitivity reactions, and chronic fibrin deposition. This prolonged drug exposure related to permanent polymer may lead to impaired stent strut endothelialization.

Bioabsorbable polymers were designed to prevent abnormal healing induced by durable-polymer drug eluting stents (DES), limiting the exposure of the drug with a bioabsorbable polymer. Randomized trials using bioabsorbable polymers were associated with superior clinical outcomes compared with bare-metal stents (BMS) and first-generation DES. Permanent Polymer Everolimus eluting stents have been shown in meta-analyses of randomized trials to be associated with lower rates of stent thrombosis compared to BMS and DES.

Colchicine binds to unpolymerized tubulin heterodimers, forming a stable complex that inhibits the formation of microtubules of neutrophils. Colchicine inhibits adhesion of neutrophils to vascular endothelium and inhibits release of IL-1β and IL-18. Colchicine has been shown to lower hs-CRP. By reducing inflammation, colchicine can reduce infarct size and the incidence of subsequent new plaque rupture and as a result prevent adverse coronary events.

By reducing aldosterone levels post STEMI by spironolactone (aldosterone-antagonist), adverse ventricular remodeling may be reduced and cardiovascular death and new or worsening heart failure events may be prevented.

Study objective

In patients with acute MI (STEMI or Non-STEMI) who have undergone PCI, the objectives are to determine:
1. If colchicine can reduce the incidence of cardiovascular death, recurrent MI, or stroke.
2. If routine use of spironolactone can reduce the incidence of cardiovascular death or new or worsening heart failure.

In patients with STEMI who have undergone PCI, the objectives of these studies are to determine:

1. The rate of Major Adverse Cardiac Events (MACE) in patients who have

received a SYNERGY everolimus eluting stent
compared to a historical performance goal.

Objective of the biomarker substudy
1. Assess the effect of colchicine on neutrophil activation in response to AMI.
2. Examine clinical and genetic factors that determine heterogeneity of treatment response and distinguish colchicine responders from nonresponders.
3. Explore the derivation of a risk score that includes markers of neutrophil activity and is associated with adjudicated MACE over 5 years after AMI, and assess the impact of colchicine on the relation between this risk score and MACE.

Study design

Multicenter, international, controlled, randomized, blinded, 2x2 factorial design with an embedded stent registry.

Intervention

- SYNERGY stent (recommended when available)
- Colchicine 0.5 mg tablet, once daily.
- Spironolactone 25 mg tablet, once daily

Study burden and risks

Burden: low-intermediate: Medical examination (weight, length, bloodpressure, bloodsampling, ECG) upon randomisation, including medical history, ethnicity.
Once or twice a day one extra tablet and 5-7 extra visits to the hospital (3,6,12, 24, 36, 48 and60 months).
Stent placement is already part of standard procedure.
Risks: low, colchicine and spironolactone are implemented in daily practice for other diseases and are extensively investigated (see section E9).

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. a) Patients with STEMI referred for PCI within 12 hours of symptom onset, have a culprit lesion amenable to
stenting, and with planned SYNERGY stent implantation for SYNERGY registry
OR
b) Patients with STEMI referred for PCI within 48 hours of symptom onset, not prospectively enrolled in SYNERGY
STENT registry.
OR
c) Patients with diagnosis of Non STEMI with ischemic symptoms and either Hs Troponin > or = 200x ULN or Troponin > or = 100x ULN who have undergone PCI with one of the following:
i. LVEF< or =45%
ii. Diabetes
iii. Multivessel CAD defined as 50% stenosis in 2nd major epicardial vessel
iv. Prior MI
v. Age >60 years

2. Able to be enrolled/randomized within 72 hours of index PCI (however patients should be

randomized as soon as possible after PCI)
3. Written informed consent

Exclusion criteria

1. Age <=18 years
2. Pregnancy, breastfeeding, or women of childbearing potential who are not using an effective method of contraception
3. Any medical, geographic, or social factor making study participation impractical or precluding required follow-up
4. Systolic blood pressure <90 mm Hg
5. Active diarrhea
6. Known allergy or contraindication to everolimus, the Synergy stent or any of its components
7. Unable to receive dual antiplatelet therapy
8. Any contraindication or known intolerance to colchicine or spironolactone
9. Requirement of colchicine or mineralocorticoid antagonist for another indication
10. History of cirrhosis or current severe hepatic disease
11. Current or planned use of any of: cyclosporine, verapamil, HIV protease inhibitors, azole antifungals, or macrolide antibiotics
12. Creatinine clearance <30 ml/min/1.73m2
13. Serum Potassium >5.0 meq/L

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Completed

Start date (anticipated):	13-07-2020
Enrollment:	550
Type:	Actual

Medical products/devices used

Generic name:	SYNERGY-Stent
Registration:	Yes - CE intended use
Product type:	Medicine
Brand name:	Aldactone
Generic name:	spironolactone
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	colchicine 0.5mg
Generic name:	colchicine 0.5mg
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	05-02-2020
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-02-2020
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-10-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-11-2020

Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-11-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-12-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-12-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	03-02-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	10-03-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-03-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-04-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	28-04-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-09-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-09-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	31-10-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-11-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-01-2024
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	30-01-2024
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-05-2024
Application type:	Amendment

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	07-06-2024
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
EudraCT	EUCTR2017-000487-15-NL
ClinicalTrials.gov	NCT03048825
CCMO	NL71984.100.19

Study results

Date completed:	28-06-2024
Results posted:	30-12-2024

First publication
01-01-1900