CONVINCE (COlchicine for preventioN of Vascular Inflammation in Non-CardioEmbolic stroke) - a randomised clinical trial of low-dose colchicine for secondary prevention after stroke.

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Primary objectiveTo investigate the efficacy of low dose colchicine (0.5mg/day) plus usual care (antiplatelet, lipid-lowering, antihypertensive treatment, and appropriate lifestyle advice) compared with usual care alone to prevent non-fatal...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Central nervous system vascular disorders
Study type	Interventional

Summary

ID

NL-OMON49701

Source
ToetsingOnline

Brief title
CONVINCE

Condition

- Central nervous system vascular disorders

Synonym
Cerbrovascular Events. Stroke.

Research involving
Human

Sponsors and support

Primary sponsor: University College Dublin
Source(s) of monetary or material Support: Ministerie van OC&W,The Health Research Board;Ireland

Intervention

Keyword: Efficacy, Prophylaxis, Safety, Therapy

Outcome measures

Primary outcome

Primary outcome measures:

The primary efficacy outcome measure will be time to the first occurrence of non-fatal recurrent ischaemic stroke, non-fatal myocardial infarction, non-fatal cardiac arrest, hospitalization for unstable angina or vascular death.

Events confirmed through centralised adjudication to meet protocol-defined primary outcome criteria, will be included in the analyses of the number of occurrences of the composite primary outcome for the respective treatment group.

The components of the primary composite efficacy outcome measure are defined below:

1. Non-fatal ischaemic stroke: defined as one of the following:

(a) A new focal neurological deficit, presumed due to cerebrovascular disease, persisting beyond 24 hours, without intracerebral haemorrhage or

other mimic condition (eg. abcess, tumour, subdural haematoma) on brain CT or MRI.

(b) Brain imaging is strongly recommended for evaluation of recurrent stroke events. If brain imaging is not performed, but the focal neurological deficit is acute in onset, persists beyond 24 hours, and is consistent with stroke in the opinion of the Site Investigator/Outcomes Committee, it will be classified as non-fatal ischaemic stroke

(c) If acute new focal symptoms/signs last less than 24 hours but If brain CT or MRI demonstrates acute ischaemic change, (i.e. consistent with the *tissue definition* of TIA).

Note: In patients with symptom duration less than 24 hours, in whom brain CT/MRI are normal or not performed, they will be categorised as *TIA* and not counted as stroke.

(d) Retinal infarction, confirmed by an ophthalmologist.

(e) Spinal cord infarction, with mimic conditions excluded by spinal MRI.

2. Non-fatal myocardial infarction: defined according to the 3rd Universal Definition of MI criteria.

3. Non-fatal cardiac arrest: defined as recovery from sudden collapse, with ECG rhythm-strip verified cardiac asystole, ventricular tachycardia, or ventricular fibrillation

4. Hospitalization for Unstable Angina: TIMI definition (Appendix 6 of research protocol)

5. Vascular death: Defined as death caused by recurrent ischaemic stroke within the previous 30 days or sudden death due to verified cardiac causes (cardiac arrest, myocardial infarction (as defined above or on autopsy), without other identified cause. Ischaemic stroke will be defined as detailed above.

Secondary outcome

Secondary Outcomes:

1. Safety

The following safety outcomes will be compared between colchicine-treated and usual care groups:

i. Adverse events (non-serious and serious)

ii. Gastrointestinal (vomiting, nausea, diarrhoea)

iii. Myalgia requiring discontinuation of study medication

iv. Myopathy (defined as muscle pain or weakness associated with creatine kinase 2 or more times greater than the upper limit of normal (ULN))

v. Hepatic impairment (transaminases (AST or ALT) >=2 ULN)

vi. Myelosuppression (defined per NIH Common Toxicity Criteria as at least Grade 2 suppression of circulating blood counts; ie. haemoglobin less than 10 and greater than 8 g/dL in the absence of major bleeding;absolute neutrophil count <1.5 - 1.0 x 109/L;platelet count <75.0 - 50.0 x 109/L)

vii. Moderate or severe renal impairment, defined as glomerular filtration rate (GFR) less than 50 ml/min/1.73m2 on two measures at least 3 months apart

viii. Peripheral neuropathy, defined as new or worsened symptoms of numbness, parasthesiae, burning or weakness in the extremities, with confirmation on nerve conduction studies

ix. Rash, itch, or alopecia

x. Major haemorrhage, per International Society on Thrombosis and Haemostasis classification. This includes fatal and non-fatal intracranial haemorrhage. (Although colchicine has not been associated with adverse effects on platelet function or coagulation, we will record major haemorrhage rates)

xi. All cause-fatality

2. Components of composite primary outcome measure

The effect of colchicine on each of the components of the primary composite outcome measure will be analysed separately.

3. Recurrent fatal or non-fatal ischaemic stroke

Comparison of fatal plus non-fatal ischaemic stroke between colchicine and usual care arms will be performed. Fatal and non-fatal ischaemic stroke will be defined as in primary outcomes section above.

4. Recurrent disabling/non-disabling ischaemic stroke

Comparison of rates of recurrent disabling ischaemic stroke (modified Rankin score 3-5) and recurrent non-disabling ischaemic stroke (modified Rankin score

0-2) between colchicine and usual care arms will be performed.

5. Disability

Comparison of disability in colchicine-treated and usual care groups will be assessed by modified Rankin score (shift analysis and proportion with no, mild, or moderate disability, defined as Rankin score of 0-2).

6. Treatment effect interaction

The effect of colchicine treatment on the primary outcome stratified by categories of key baseline variables (eg. age, gender, large artery stenosis) will be assessed.

7. Health economic outcomes

The effect of colchicine treatment on direct cumulative costs of health resource utilisation related to Quality Adjusted Life Years (QALYs) during the trial will be assessed.

Exploratory outcome measures:

1. Cognition

Cognition at baseline and end of study will be measured using the Montreal Cognitive Assessment, [MOCA, Appendix 3] and compared between colchicine and usual care groups.

2. Quality of life

Health-related quality of life (self-reported) will be measured and compared using EuroQoL (EQ5D-5L) (Appendix 5 of the research protocol).

3. CRP

Associations between colchicine treatment effect and baseline CRP will be analysed.

4. Cumulative number of ischaemic events

The relationship between colchicine therapy and the cumulative total number of component events in the primary outcome cluster detected over the duration of the trial will be investigated.

Study description

Background summary

Importance of stroke:

The World Health Organisation (WHO) estimates that cardiovascular diseases are the leading cause of death globally, causing 17.3 million deaths in 2008. Of these, stroke was the second leading cause of global death and a major cause of healthcare costs.

Importance of atherosclerosis in cerebrovascular disease:

Population-based studies by our group and others have reported ipsilateral carotid atherosclerosis (>=50% arterial lumen narrowing) in up to 20% of ischaemic stroke patients, with intracranial atherosclerosis in a further 8-12%. Athero-thrombosis in the arterial tree is also likely to account for a substantial proportion of the 30-40% of patients with stroke in whom no direct mechanism is identified. For example, 73% of patients in the North Dublin Population Stroke Study with TOAST-classified stroke of unidentified etiology

had evidence of aortic or cranio-cervical atherosclerosis defined by the ASCO classification.

In addition, disease of cerebral small vessels (arteries and arterioles) accounts for up to 20% of stroke and is a major contributor to dementia. Although the pathophysiology of cerebral ischaemic small vessel disease is varied and not fully understood, existing data suggest two common mechanisms: (1) micro-atheroma of larger penetrating arterioles, causing single, frequently-symptomatic acute lacunar infarcts, and (2) lipohyalinosis (*arteriolosclerosis*), more frequently associated with diffuse white matter hyperintensity on neuroimaging and neuropathological evidence of cerebral demyelination.

After exclusion of stroke due to a defined cardio-embolic source (eg. atrial fibrillation) or other identified mechanism (eg. carotid dissection), atherosclerosis of the aorta, cervical, or intracranial large or small arteries is a major pathophysiological mechanism underlying most ischemic stroke. Randomised trials of statins and antiplatelet agents (eg. SPARCL, CHANCE) have demonstrated benefit of targeting plaque-related lipid accumulation and platelet activation in non-cardioembolic stroke to prevent recurrent vascular events.

High risk of recurrent vascular events in stroke survivors:

Despite high rates of optimal medical and surgical treatment, we and others have demonstrated high risk of recurrent stroke associated with atherosclerosis of the internal carotid and intracranial arteries. A recent systematic review reported a cumulative pooled recurrent stroke risk of 11.1% at one year and 26.4% at 5 years. The risk of myocardial infarction and vascular death is also substantial in long-term stroke/TIA survivors. In a systematic review (39 studies, 65,996 patients), Touze found a 2.1%/year rate of non-stroke vascular death and 0.9%/year risk of non-fatal Myocardial Infarction (MI) in stroke survivors.

Importance of inflammation:

Accumulating evidence indicates that inflammation is of key importance in the pathophysiology of atherosclerotic plaque destabilisation and thrombo-embolism. The central inflammatory pathway is characterised by the key cytokines interleukin-1, interleukin-6 [IL-6], and tumor-necrosis factor α [TNF-α]. Epidemiological studies have consistently described dose-dependent associations between *downstream* markers of this pathway (eg. C- reactive protein [CRP]) and *up-stream* markers (eg. IL-6, TNF-α]) and vascular disease, including stroke.
Mendelian randomisation studies have shown that polymorphisms in the IL-6 receptor are associated with lower CRP and reduced vascular risk. In the JUPITER trial, rosuvastatin reduced the rate of vascular events in patients

with low LDL but high CRP at entry, with benefit proportionate to the degree of CRP reduction.

In large-artery atherosclerosis, plaque inflammatory cells (mainly monocyte-macrophages), are increasingly recognised as key mediators of lipid oxidation, plaque remodelling, smooth muscle cell apoptosis, loss of extracellular matrix integrity via release of collagenolytic matrix metalloproteinases and other proteolytic enzymes, leading to fibrous cap rupture and thrombo-embolism. Tawakol reported high FDG uptake on positron emission tomography (PET) in symptomatic carotid plaque, with high (r=0.89) correlation with plaque macrophage density. We have shown that carotid plaque inflammation-related FDG uptake predicts stroke recurrence independently of stenosis.

In cerebral small artery disease, available data indicate that inflammation may be an important mediator of lacunar stroke and arteriolar pathology. In patients with small artery disease, increased inflammatory cells (macrophages, activated microglia) expressing matrix metalloproteinases (MMPs) are present around affected arterioles and ischemic demyelination, and MMP-9 is increased in cerebrospinal fluid. In SPARCL, patients with lacunar stroke randomised to atorvastatin lipid-lowering therapy had similar reduction in stroke and coronary events as those with large-artery atherosclerosis. In lacunar stroke patients enrolled in the SPS3 trial, baseline CRP independently predicted recurrent stroke and vascular events.

Recent laboratory and clinical-pathological studies have shown that cholesterol crystals form in atherosclerotic plaques, and may activate the nucleotide-binding leucine-rich repeat-containing pyrin receptor (NLRP) inflammasome, an intracellular protein complex which promotes IL-1β expression in response to crystal stimulation, leading to elevated IL-6 and CRP These important observations provide direct evidence linking plaque lipid metabolism and inflammation.

Why is this trial needed now?

Few completed trials have directly tested the benefit of anti-inflammatory agents for vascular risk reduction. Small studies have demonstrated reduction in inflammatory blood and imaging surrogate-markers such as plaque FDG uptake in a dose-dependent manner by statins, possibly mediated by an anti-inflammatory effect. The LoDoCo1 trial demonstrated a 66% relative risk reduction in cardiovascular events in patients with stable coronary disease treated with low-dose colchicine, plus anti-platelet agents and statins, compared with usual care.
However, several trials are currently under way. In CANTOS, canukinumab (an interleukin-1β antagonist) is under evaluation in 10,000 patients with stable coronary disease. The National Institutes of Health (NIH) funded Cardiovascular Inflammation Reduction Trial (CIRT) is comparing low-dose weekly methotrexate

with placebo plus recommended care in 7,000 patients with coronary disease and diabetes or metabolic syndrome. In Australia, the LoDoCo2 trial is testing low-dose colchicine for prevention of vascular events in 3,000 patients with stable coronary syndromes. Other trials have recently targeted inflammatory pathways (eg. LpPLA2) unrelated to the IL1-IL6-TNFα pathway (STABILITY, VISTA, SOLID-TIMI52).
Description of Colchicine and Rationale for the study

Overview:
The investigational product to be studied is low-dose colchicine, 0.5mg daily, taken by mouth for a median duration of approximately 36 months (range 12-60 months). In Europe, colchicine is registered and marketed in a number of countries by several pharmaceutical companies in generic forms (usually 0.5mg and 1mg tablets, 0.6mg tablets in some countries). The US FDA also approved single ingredient oral colchicine (0.6mg tablet) in 2009.

Pharmacokinetics - absorption, distribution, metabolism, excretion:
Colchicine has been used for many years for the treatment of acute gout and other inflammatory and arthritic conditions. Derived originally from the Autumn Crocus (Colchicium autumnale), colchicine is readily-absorbed after oral administration in the jejunum and ileum, by a P-glycoprotein (ABCB1-transporter) dependent process. It undergoes significant 1st-pass hepatic metabolism, resulting in oral bioavailability averaging 45% (range 24-88%) in healthy volunteers. It is excreted primarily (80-90%) via biliary secretion (via the cytochrome P450 CYPA34 system), and also partly by the renal route (10-20%), and via intestinal epithelium.

Mechanism:
Its primary cellular action is binding to α- and β-tubulin proteins, which are highly-expressed in neutrophils and monocyte-macrophage inflammatory cells. It has multiple anti-inflammatory properties including inhibition of microtubule polymerization, with inhibition of E-selectin mediated leucocyte rolling and endothelial adhesion, and leucocyte motility, phagocytosis, and cytokine secretion. In vitro, colchicine inhibits crystal-induced activation of the NLRP inflammasome, possibly via inhibition of microtubule polymerisation, which is a pre-requisite for inflammasome assembly. This leads to inhibition of proteolytic cleavage of pro-IL1β by caspase-1, leading to reduced secretion of active interleukin-1β from monocytes and macrophages.

Rationale for use in atherosclerotic vascular disease:
As described above, accumulating evidence indicates that inflammation is a key process in the pathophysiology of atherosclerosis, coronary disease, and stroke. Non-randomised data report lower rates of coronary disease in gout and Familial Mediterranean Fever (FMF) patients treated with long-term low-dose colchicine therapy compared to colchicine-untreated patients.
In stable coronary patients treated with statins and antiplatelet agents with elevated CRP, a 4-week treatment with low-dose colchicine was associated with

significant reduction in CRP compared with controls, providing proof-of-concept that colchicine could impair inflammation in patients with atherosclerotic vascular disease.

Following this study, one of our collaborators (SM Nidorf) demonstrated 66% reduced risk of recurrent vascular events in 532 patients with stable coronary disease randomised to low-dose colchicine (0.5mg/day) compared with usual care. This large benefit was observed despite high (>90%) rates of statin and antiplatelet treatment in colchicine and control arms. At present, a large (3,000 patients) placebo-controlled randomised trial of low-dose (0.5mg/day) colchicine (LoDoCo2) is under way in Australia to independently validate these findings in stable coronary patients.

Recent trials have also demonstrated benefit of colchicine at a dose of 0.5-1mg/day for prevention of recurrent pericarditis. More recently, in a trial of patients with acute ST-elevation myocardial infarction, colchicine (loading dose 2mg, followed by 0.5-1mg/day for 5 days) caused lower creatine kinase ($p<0.001$), lower MRI infarct size ($p=0.019$) and lower relative infarct size ($p=0.034$) compared with placebo.
While no systematic Cochrane reviews of colchicine for vascular prevention exist, in a recent review Ridker and Luscher stated *large-scale*.trials of colchicine in secondary prevention are warranted*.

The underlying pathophysiology of recurrent vascular events in patients with non-cardioembolic stroke is likely to resemble that in patients with coronary artery disease. Therefore, we have selected the same low colchicine dose (0.5mg/day) taken by mouth, as has already shown efficacy and safety in the LoDoCo1 trial.

Safety:
The safety profile of colchicine is highly dose-dependent. According to the UK SPC and FDA SPC, the most commonly reported adverse reaction in clinical trials of colchicine for gout prophylaxis and acute treatment was diarrhoea. Less common gastrointestinal adverse events were nausea, abdominal pain, and vomiting. These effects were far more common at high colchicine doses (up to 4.8mg daily) compared with intermediate doses (1.8mg daily). Other adverse events reported at a frequency of 2% or greater in studies of patients taking high and intermediate doses (1.8mg and 4.8mg) of colchicine included nervous system disorders, headache, and pharygolaryngeal pain.

Per the FDA SPC, excessive accumulation or overdose of colchicine has been associated with a range of other adverse events, which are *generally reversible upon temporarily interrupting treatment or lowering the dose*. These include: neuropathy, alopecia, rash, myelosuppression, elevated transaminases (ALT and/or AST), myopathy, muscle pain, rhabdomyolysis, azoospermia, oligospermia. Serious toxic reactions associated with overdosage include myelosuppression, disseminated intravascular coagulopathy, cardiac toxicity,

central nervous system toxicity, and death.

Low-dose colchicine has been used safely for many years for prevention of inflammatory complications of FMF and Bechet*s disease. In contrast to the higher doses of colchicine frequently used for treatment of acute gout, low-dose (0.5mg/day) colchicine has been used in recent cardiovascular trials with excellent safety profiles. In 42 patients assigned to 0.5-1.0mg daily in the CORE trial (mean follow up 20 months), no serious adverse events occurred. Mild diarrhoea developed in 3 patients, which quickly resolved on stopping or lowering the dose. In the LoDoCo1 trial, among 282 patients assigned 0.5mg colchicine daily (mean age 66.5 years, mean follow up 36 months), the overall withdrawal rate was 16%, similar to recent trials of statins and dabigatran for stroke prevention. Diarrhoea and other GI adverse effects occurred in 13%, myalgia/myositis in 1%, with rash, itch, alopecia, and *peripheral neuritis* each in 1 patient.

Adverse effects are more likely in patients with moderate-to-severe renal failure (creatinine clearance <50mL/min), hepatic failure/cirrhosis, or those taking CYP3A4 inhibitors (macrolide antibiotics, HIV protease inhibitors, itraconazole, ketoconazole, diltiazem, verapamil, grapefruit juice) or P-Glycoprotein (PGP) inhibitors (macrolide antibiotics, cyclosporine). Such patients will be excluded from the trial. If a short course of one of these agents (eg. clarithromycin) is required, a dose interruption of colchicine will be allowed during treatment. Five cases of myopathy have been reported in the literature in patients co-administered statins with colchicine. Careful monitoring will be performed for myopathic symptoms in such patients, and they will be instructed to report significant myalgias to study personnel.

Colchicine crosses the placenta and is secreted into breast milk of nursing mothers, with unknown effects upon the developing foetus and infant. Pre-menopausal women will be excluded from entry into the trial.

Study objective

Primary objective

To investigate the efficacy of low dose colchicine (0.5mg/day) plus usual care (antiplatelet, lipid-lowering, antihypertensive treatment, and appropriate lifestyle advice) compared with usual care alone to prevent non-fatal recurrent ischaemic stroke, myocardial infarction, cardiac arrest, hospitalization for unstable angina and vascular death after ischaemic stroke or transient ischaemic attack (TIA) not caused by cardiac embolism or other defined causes unrelated to atherosclerosis.

Secondary objectives

1. To investigate the safety of low dose colchicine (0.5mg/day) plus usual care

(antiplatelet, lipid-lowering, antihypertensive treatment, and appropriate lifestyle advice) compared with usual care alone.
2. To investigate the effect of colchicine on each component of the composite primary outcome measure.
3. To investigate the effect of colchicine on fatal and non-fatal ischaemic stroke combined.
4. To investigate the effect of colchicine on recurrent disabling and non-disabling ischaemic stroke.
5. To investigate the effect of colchicine on late disability compared with usual care.
6. To assess whether the effect of treatment on the primary outcome is materially different among different categories of patient defined at baseline.
7. To investigate the effect of colchicine on direct health care costs, adjusted for quality-adjusted life years.

Study design

CONVINCE is a randomised, open-label, blinded endpoint-assessed, parallel group Phase 3 clinical trial, comparing low-dose colchicine plus usual care to usual care alone for prevention of recurrent non-fatal ischaemic stroke, myocardial infarction and cardiac arrest, hospitalization for unstable angina and vascular death after ischaemic stroke or TIA, not caused by cardiac embolism or other defined mechanisms unrelated to atherosclerosis.

Randomisation:

Randomisation will be conducted using a minimisation algorithm, to ensure groups are balanced for key prognostic variables affecting recurrent stroke risk. The following mandatory variables will be included in the algorithm for randomisation:
(1) age (less than 70, 70 or greater)
(2) time since qualifying stroke/TIA (7 days or less, greater than 7 days)
(3) type of qualifying event (stroke or TIA).

Imaging of cervical and intracranial arteries is not mandatory prior to randomisation, but is strongly encouraged. If information on large artery stenosis (ie. verified carotid, vertebral, or intracranial artery stenosis 50% or greater) is available at the time of randomisation, the algorithm will include this data to achieve balance for this variable. Baseline data will be entered at the same visit as treatment allocation, although non-mandatory data fields may be entered later.

Randomisation will take place via an Interactive Web Response System (IWRS),. Before randomisation occurs, informed consent and verification of trial eligibility of key inclusion/exclusion criteria must be performed by the site study staff.

In practice, when a patient is randomised, the patient will be allocated to active treatment, or, usual care. If randomised to study medication, the patient will be given one dose from the next available package of study medication at the study site. This package (minus the first dose) and a second package will be given to the patient to take home. The patient will be advised to take the medication once daily and in the morning. If the dose is forgotten in the morning it can be taken at a later time in the day. The patient will also be instructed never to take more than one tablet per day even if a previous day/days dosage has been missed

Blinding:

This is a Prospective Randomised Open-Label Blinded-Endpoint (PROBE) trial, similar to other recent trials of stroke prevention (eg. RE-LY) and acute treatment (eg. ESCAPE). Participants and treating physicians will be aware of treatment allocation to colchicine or usual care. Therefore, to control for bias, assessment of outcome events will be achieved by assessment of defined *hard* endpoints with pre-specified objective evidence to support identification (see Section 8.1, Primary Outcome Measure). The assessment will be conducted by an Outcomes Adjudication Committee blinded to treatment allocation. The OAC will meet or teleconference regularly during the conduct of the trial.

SCREENING - RANDOMISATION - Investigational Arm - FOLLOW UP
Low-dose Colchicine
(0.5mg/d) plus Usual Care (antiplatelet, lipid-
lowering,
antihypertensive, lifestyle advice).

Control Arm - FOLLOW
UP
Usual Care alone
(antiplatelet, lipid-lowering, antihypertensive, lifestyle
advice).

Intervention

Low dose colchicine (0.5mg/day)

Study burden and risks

The risks of low-dose colchicine in the intended sample group for study are judged to be low, as outlined in previous sections and the SPC. The benefits may be as high as a 66% reduction in the risk of recurrent stroke, coronary events, or vascular death, as reported in the LoDoCo trial. The anticipated benefit risk to the patient population will be evaluated on an ongoing basis by

the sponsor.

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 Written informed consent consistent with ICH-GCP guidelines and local laws signed prior to all
trial-related procedures. 2 Age 40 years or greater3 A brain CT or MRI has excluded primary intracranial haemorrhage4a. Patient diagnosed with - An ischaemic stroke without major disability (modified Rankin score 3 or less)
Or
4b. A high-risk - defined as (one or more of the following)

TIA with DWI hyperintensity on acute MRI
TIA with ABCD2 >= 4
TIA with >= 50% Stenosis of the artery territory consistent with symptoms. 5 Qualifying stroke/TIA probably caused by large artery stenosis, small artery occlusion (lacunar
stroke), or cryptogenic embolism, with cardiac embolism or other defined stroke mechanism
deemed unlikely in the opinion of the treating physician.6 The stroke/TIA has occurred more than 72 hours before randomisation AND no more than 28
days prior to randomisation.7 eGFR greater than or equal to 50 ml/min.8. In the opinion of the treating physician, patient is medically-stable, capable of participating in a
randomised trial, and willing to attend follow-up.

Exclusion criteria

1. Stroke/TIA, probably caused by identified atrial fibrillation (permanent or paroxysmal), in the
opinion of the treating physician.2. Stroke/TIA probably caused by other identified cardiac source (intra-cardiac thrombus,
endocarditis, metallic heart valve, low ejection fraction <30%), 3. Stroke/TIA caused by dissection, endocarditis, paradoxical embolism, drug use, venous
thrombosis, carotid or cardiac surgery, hypercoagulability states, migraine, or inherited
cerebrovascular disorders .4. History of myopathy or myalgias with raised creatine kinase (CK) on statin therapy.5. Blood dyscrasia (haemoglobin <10g/dLplatelet count <150 x109/L,white cell count <4 x109/L) 6. Impaired hepatic function (transaminsases ALT and/or AST greater than twice upper limit of
normal) 7. Concurrent treatment with colchicine contraindicated drugs:- CYP3A4 inhibitors (clarithromycin,
erythromycin, telithromycin, other macrolide antibiotics, ketoconazole, itraconazole, voriconazole,
ritonavir, atazanavir, indinavir, other HIV protease inhibitors, verapamil, diltiazem, quinidine,
digoxin, disulfiram) or P-gp inhibitors (cyclosporine) at randomisation. 8. Symptomatic peripheral neuropathy and pre-existing progressive neuromuscular disease9. Inflammatory bowel disease (Crohn*s or ulcerative colitis) or chronic diarrhoea.10. Dementia, sufficient to impair independence in basic activities of daily living.11. Active malignancy, known hepatitis B or C, or HIV infection.12. Impaired swallow preventing oral administration of Colchicine13. History of poor medication compliance.14. Unlikely to comply with study procedures due to severe or fatal comorbid illness or other factor

(eg. inability to travel for follow up visits), in opinion of randomising physician.15. Pregnancy, breast-feeding, or pre-menopausal woman 16. Patient concurrently participating in another clinical trial with an investigational drug or device, or
use of investigational drug within 30 days of the Screening visit or 5 half lives before the
screening visit (whichever is longer) 17. Known allergy or sensitivity to colchicine.18. Requirement for colchicine therapy for treatment of acute gout, gout prevention, or other rheumatological disorder19. Requirement for chronic daily immunosuppressants,
oral steroids, or non-steroidal anti-inflammatory drugs (NSAIDs)
-term stroke/TIA survivors. In a systema

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	18-03-2021
Enrollment:	100
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Tiofarma B.V/Wockhardt UK Ltd/Morningside Healthcare Ltd
Generic name:	Colchicine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	24-07-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-03-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-04-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-09-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-09-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-11-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-11-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-08-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-09-2021

Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2015-004505-16-NL
ClinicalTrials.gov	NCT02898610
CCMO	NL69808.018.19