

---

Kelly PJ, Murphy S, Coveney S, Purroy P, Lemmens R, Tsivgoulis G, Price C.  
[Anti-inflammatory approaches to ischaemic stroke prevention](#). *Journal of  
Neurology, Neurosurgery & Psychiatry* 2017

**Copyright:**

This is the authors' accepted manuscript of an article that has been published in its final definitive form by BMJ, 2017

**DOI link to article:**

<https://doi.org/10.1136/jnnp-2016-314817>

**Date deposited:**

12/01/2018



This work is licensed under a [Creative Commons Attribution-NonCommercial 3.0 Unported License](#)

**TITLE:**

Anti-inflammatory approaches to ischaemic stroke prevention

**AUTHORS:**

Peter J Kelly<sup>1</sup> MD, Sean Murphy<sup>2</sup> MD, Sarah Coveney<sup>1</sup> MB, Francisco Purroy<sup>3</sup> MD, Robin Lemmens<sup>4-6</sup> MD, Georgios Tsivgoulis<sup>7</sup> MD, Chris Price<sup>8</sup> MD,

**AFFILIATION:**

1. Health Research Board Irish Stroke Clinical Trials Network and Mater University Hospital/University College Dublin
2. Health Research Board Irish Stroke Clinical Trials Network and Mater University Hospital/University College Dublin/Royal College of Surgeons Ireland
3. Stroke Unit, Department of Neurology, Hospital Universitari Arnau de Vilanova de Lleida. and Universitat de Lleida, Biomedical research institute of Lleida, Universitat de Lleida, Spain.
4. KU Leuven - University of Leuven, Department of Neurosciences, Experimental Neurology and Leuven Research Institute for Neuroscience and Disease (LIND), B-3000 Leuven, Belgium
5. VIB, Vesalius Research Center, Laboratory of Neurobiology, B-3000 Leuven, Belgium
6. University Hospitals Leuven, Department of Neurology, B-3000 Leuven, Belgium
7. Second Department of Neurology, National & Kapodistrian University of Athens, School of Medicine, Athens, Greece
8. Institute of Neuroscience, Newcastle University, UK

### ***Introduction:***

The World Health Organisation (WHO) estimates that cardiovascular diseases are the leading cause of death globally, causing 17.5 million deaths in 2012. Of these, stroke was the second leading cause of global death[1]. Cerebrovascular disease is the most common cause of neurological disability in older adults, and contributes substantially to dementia. Stroke incidence rates are increasing rapidly in low-income and middle-income countries, and absolute numbers are rising in high-income countries due to increasing life-expectancy[2]. The American Heart Association estimates that annual total (direct and indirect) costs of stroke were \$34 Billion in 2011[3].

Primary and secondary prevention of early and late recurrent events is a major strategy to reduce the overall burden of stroke. Anti-thrombotic, lipid-lowering, anti-hypertensive therapy and lifestyle modification are proven approaches for stroke prevention[4]. Recent data indicate that atherosclerotic plaque inflammation may be an important contributor to plaque destabilisation and thrombo-embolic events. In patients with coronary artery disease, clinical trials of anti-inflammatory therapies to prevent subsequent vascular events are under way. We aimed to review the medical literature relating to plaque inflammation in cerebrovascular disease, with a specific focus on clinical trials targeting atherosclerotic inflammation for secondary stroke prevention.

### ***Importance of atherosclerosis in cerebrovascular disease:***

Atherosclerosis of the aorta, cervical, or intracranial large or small arteries is a major pathophysiological finding causally related to or associated with a large proportion of ischemic stroke. This view is supported by four main lines of evidence.

First, direct imaging evidence of atherosclerotic narrowing of the aorta or cranio-cervical arterial system is common in patients with ischaemic stroke or transient ischaemic attack (TIA). Population-based and hospital studies have reported ipsilateral carotid stenosis ( $\geq 50\%$  arterial lumen narrowing) in 12-20% of ischaemic stroke patients[5-10], with intracranial atherosclerosis (ICAS) in a further 8-10% of North American/European and 30-50% of Asian patients[11,12]. Symptomatic ICAS is associated with pathological features of plaque instability (rupture, inflammation) and inflammatory markers such as CRP and leucocyte count predict recurrent vascular events in patients with ICAS[13-17]. Recent data also suggest that arterial stenosis of less than 50% may play an aetiological role in acute ischaemic stroke. A cross sectional study of 85 Embolic Stroke Unknown Source (ESUS) cases imaged by CT angiography showed that plaque 3-5 mm in thickness was present ipsilateral to the stroke in 11-35% of cases versus 1-15% on the contralateral side. There was a poor correlation between plaque volume and degree of stenosis[18].

Second, indirect evidence suggests that atherogenic embolism originating from the arterial system is likely to contribute to a substantial proportion of patients with stroke in whom no direct mechanism is identified, which account for 18-35% of all stroke in registries and clinical trials[19]. In the EMBRACE trial, paroxysmal atrial fibrillation (AF) was detected in only 16% at 90 days of patients with cryptogenic stroke or transient ischaemic attack (TIA) who underwent prolonged cardiac monitoring[20]. In the CRYSTAL-AF, trial AF was detected in 9% of cryptogenic stroke/TIA patients at 6 months and 30% by 36 months[21]. However, it is unclear whether late detection of AF in CRYSTAL-AF was causally related to the initial event. Taken together, these data suggest that a substantial proportion of cryptogenic stroke/TIA cases were unrelated to cardiac embolism.

In the North Dublin Population Stroke Study, 73% of patients with TOAST-classified stroke

of unidentified etiology had evidence of aortic or cranio-cervical atherosclerosis defined by the ASCO classification[22]. Thick (>4mm) plaque of the aortic arch is also frequent in patients with cryptogenic stroke, with a prevalence of 28% reported in one prospective study[23]. In this study, plaque >4mm was almost 5 times more frequent in patients with cryptogenic stroke compared with those with stroke of identified cause (adjusted odds ratio 4.7, CI 2.2-10.1), supporting the hypothesis that aortogenic embolism may have accounted for symptoms. Further indirect evidence supporting a role of aortogenic embolism may emerge from ongoing trials currently evaluating rivaroxaban and dabigatran for secondary prevention in patients with embolic stroke of undetermined source (ESUS).

Third, micro-atheroma is an important contributor to ischaemic disease of cerebral small vessels (arteries and arterioles), which accounts for up to 20% of stroke and is a major contributor to dementia[24]. Although the pathophysiology of cerebral ischaemic small vessel disease is varied and not fully understood, existing data suggest two common mechanisms[24]: (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.

Fourth, randomised clinical trials in patients with non-cardioembolic stroke and TIA have demonstrated benefit of targeting plaque-related lipid accumulation with high-dose atorvastatin and platelet activation to prevent recurrent stroke and coronary events[25-27].

### **High residual vascular risk in stroke survivors:**

Although sub-optimal secondary prevention is common among survivors of stroke and

TIA[28, 29], the residual risk of recurrent stroke, coronary events and vascular death is substantial even among those treated with high rates of established secondary preventive medications. Data from recent clinical trials and stroke registries indicate a recurrent stroke risk of 2.5-4% per year in patients treated with high rates of statin and antiplatelet therapies after stroke and TIA[30-33]. A systematic review reported a cumulative pooled recurrent stroke risk of 11.1% at one year and 26.4% at 5 years[34]. 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[35]. Early stroke recurrence risk after first stroke and TIA is highest in patients with large-artery atherosclerosis of the cervical carotid arteries, intracranial vessels, or posterior circulation, compared with other stroke mechanisms[33, 36-39]. The mechanisms explaining this residual risk are unclear. However, evidence from multiple sources support the hypothesis that inflammation-related plaque instability may be an important contributing factor[40].

### **Inflammation and pathophysiology of atherosclerotic plaque:**

Accumulating evidence supports the view that inflammation is of key importance in the pathophysiology of atherosclerotic plaque destabilisation and thrombo-embolism[41-43]. A large body of experimental data indicates that inflammatory cells are involved in all stages of atherosclerosis development. Trans-endothelial migration of circulating monocytes is a key event in the initiation of atherosclerotic plaque, mediated by surface adhesion molecule expression in response to endothelial stimuli such as arterial tension, non-laminar flow, cigarette smoke constituents, and angiotensin 2. Retention of low-density lipoprotein (LDL) lipids in the extracellular matrix of the arterial wall is accompanied by

differentiation of monocytes and lipid uptake to lipid-laden 'foamy' macrophages. Differentiation of macrophages into pro-inflammatory subsets (M1 macrophages) results in local expression of pro-inflammatory cytokines, particularly interleukin 1-beta (IL 1 $\beta$ ) and tumour necrosis factor-alpha (TNF- $\alpha$ ). Cytokines such as platelet-derived growth factor (PDGF) promote recruitment and proliferation of smooth muscle cells into the endothelial cell layer, which express matrix proteins such as collagen and elastin. As plaque progression continues, a fibrous cap of endothelial cells mainly smooth muscle cells and collagen develops, overlying a plaque matrix comprising monocyte-macrophages, connective tissue proteins, extracellular lipids, smooth muscle cells, and neo-vascularisation. Local ingress of T-helper (T-H1) cells produce pro-inflammatory cytokines, particularly interferon-gamma (IFN- $\gamma$ ), while T-regulatory cells produce inhibitory cytokines such as IL-10 and TGF- $\beta$ . Apoptosis of macrophages and SMCs releases lipid and cellular debris within the extracellular matrix, to form a lipid-rich necrotic core containing pro-coagulant tissue factor. Expression of cytokines and collagenolytic enzymes such as metalloproteinases from macrophages and other cells contributes to erosion and rupture of the fibrous cap, exposure of circulating platelets and coagulation factors to the pro-thrombotic core, and subsequent thrombo-embolism.

***Association of stroke with inflammation from clinical studies:***

Clinical and epidemiological data supporting the association of plaque inflammation with stroke are derived from six main sources: (1) Epidemiological studies of inflammatory biomarkers (2) Epidemiological studies of the association of infection with stroke risk (3) Genetic epidemiological studies of gene polymorphisms in inflammation-pathway proteins (4) Clinical-pathological studies (5) Plaque imaging studies (6) Randomised clinical trials

of anti-inflammatory agents in vascular disease.

### **(1) Epidemiological studies of inflammatory biomarkers:**

The central inflammatory pathway is characterised by the key cytokines interleukin-1, interleukin-6 [IL-6], and tumor-necrosis factor  $\alpha$  [TNF- $\alpha$ ]. Epidemiological studies have consistently described dose-dependent associations between circulating blood biomarkers of this pathway and vascular disease, including stroke. Such biomarkers can be considered as ‘downstream’ (eg. C-reactive protein [CRP]) and ‘up-stream’ markers (eg. IL-6, TNF- $\alpha$ )[43].

The Emerging Risk Factors Collaboration have described the relationship between circulating CRP and incident stroke in 160,309 individuals without vascular disease in prospective studies[44]. After adjusting for age, sex, and study, a linear relationship was observed between circulating CRP and risk of ischaemic stroke, which remained (although attenuated) after further adjustment for existing vascular risk factors (Figure 1). The adjusted relative risk per 3-fold increase in CRP was 1.27 (95% CI 1.15-1.40). A similar relationship was observed for coronary disease.

CRP is increased following acute stroke in response to tissue injury and infection, proportionate to the severity of the acute event[45]. In the post-acute phase, CRP remains elevated compared with control subjects, with greatest elevation in patients with large-artery stroke mechanisms. CRP has been reported to independently predict recurrent stroke risk in patients with stroke or TIA due to carotid or intracranial atherosclerosis[46,47]. Recently, CRP measured at baseline was reported to independently predict the risk of recurrent stroke and vascular events in the SPS3 and CHANCE trials. In 1244 patients with lacunar stroke in SPS3, baseline CRP was associated with a 2.32-fold increase in the adjusted hazard of recurrent stroke and

vascular events (highest versus lowest quartile)[48]. In 3044 patients with non-severe non-cardioembolic stroke in the Chinese CHANCE trial, patients in the highest CRP quartile measured at baseline had a 1.46-fold increase in the adjusted risk of early recurrent stroke at 90 days, and increased risk of stroke at 1 year[49]. In 1,232 patients with recent stroke/TIA in the Oxford Vascular Study, CRP measured in the acute phase was an independent predictor of 90-day stroke recurrence (adjusted hazard ratio 1.15, CI 1.02-1.30)[50]. Broadly consistent findings have been observed with other inflammatory biomarkers, including fibrinogen and IL-6[50,51].

## (2) Studies of association between infection and stroke risk:

Inflammation of the cerebral arterial wall in response to direct infection by varicella zoster virus has long been recognized as a cause of ischaemic stroke. Other viruses (CMV, hepatitis B, hepatitis C, Epstein-Barr virus), fungal (aspergillus, histoplasma), and bacterial (syphilis, mycobacterium tuberculosis, H influenzae) may also trigger cerebral vasculitis and stroke, via direct arterial wall invasion, immune-complex deposition, or secondary cryoglobulinaemia[52-54]. These occur typically, although not exclusively, in immune-suppressed patients. HIV has recently been associated with extensive remodeling of the cerebral arterial wall, although the role of inflammation in this process is unclear[55].

Epidemiological studies have reported associations between chronic infection and stroke risk. Infective agents have been diverse, including Chlamydia pneumoniae, H influenzae, H pylori, Herpes simplex 1 and 2, CMV, and Epstein Barr virus[56]. The Northern Manhattan Study reported an association (adjusted hazard ratio 1.39) between overall infectious burden, defined as cumulative exposure to several pre-specified infective agents, and first-ever stroke risk[57]. However, this finding requires further confirmation, as other studies

have not demonstrated an association between chronic infectious burden and stroke risk[58,59]. Recent data suggests that acute infection may be associated with higher stroke risk. In an analysis from the Cardiovascular Health Study, Elkind and colleagues reported increased risk of first-ever stroke associated with hospital admission for treatment of infection, with greatest risk observed at earliest time-points[60]. The adjusted hazard ratio for stroke within 90 days of admission was 2.4 (CI 1.6-3.4). Further studies are required to definitively confirm this finding.

### (3) Genetic epidemiology studies:

Despite sophisticated analytical methods, the interpretation of epidemiological studies investigating blood biomarkers may be limited by residual confounding and ‘reverse causality’ (where sub-clinical disease may influence the biomarker levels).

Epidemiological studies of gene variants affecting protein function in key pathways overcome these limitations, as by definition exposure is determined prior to the onset of disease.

One such functional polymorphism exists in the IL-6 receptor gene, causing an alanine -to - aspartate substitution at position 358 of the expressed protein, resulting in reduced membrane-bound IL-6 receptor, impaired IL-6 signalling, and reduced expression of downstream CRP and fibrinogen. Two ‘Mendelian randomisation studies’ have reported associations of this polymorphism with reduced risk of coronary heart disease after adjusting for conventional risk factors, in a dose-dependent fashion depending on number of 358Ala alleles inherited, with consistent effect sizes (per allele, 3.4%, CI 1.8-5 and 5%, CI 3-7)[61,62]. Similar reductions in CRP and fibrinogen were observed, supporting the biological plausibility of the findings. However, stroke was not reported as an outcome in these studies. Genome wide association studies in ischemic stroke patients with sufficiently

large sample sizes may elucidate the role of these variants in stroke.

(4) Clinical-pathological studies:

Pathological studies also support an association between plaque inflammation and clinical events. For example, an analysis of resected carotid plaque from 526 patients with symptomatic carotid stenosis in the Oxford Plaque Study found that 66% of patients had evidence of marked inflammation in resected plaque from the ipsilateral internal carotid artery, while 64% had other features of plaque instability (thin fibrous cap, large lipid core, cap rupture, or superficial thrombus)[63]. Extensive macrophage infiltration was independently associated with plaque rupture (adjusted odds ratio 3.52,  $p < 0.001$ ), as were cap thickness  $< 200\mu\text{m}$  (OR 2.64), intraplaque haemorrhage (OR 2.65), and large lipid core (OR 4.03) (all ORs adjusted,  $p < 0.001$  for all).

Similar findings were observed in a smaller study investigating the relationship of plaque inflammation with early recurrent stroke[64]. In 44 consecutive patients with ipsilateral carotid stenosis and TIA/ischaemic stroke who had endarterectomy within 10 days (interquartile range 7-17 days), early stroke recurrence pre-endarterectomy was associated with extensive macrophage and lymphocyte infiltration (Oxford Plaque Score  $\geq 3$ ), low fibrous content,  $\geq 25\%$  cap disruption, and plaque neovascularization. After adjustment for age and degree of stenosis, high macrophage density was the only independent predictor of early stroke recurrence (adjusted HR 9.0,  $p = 0.04$ ).

Matrix metalloproteinases (MMPs) are proteolytic enzymes for which sub-endothelial matrix collagen and elastin are known substrates. In patients with small artery disease, increased inflammatory cells (macrophages, activated microglia) expressing MMPs are present around affected arterioles and areas of ischemic demyelination and MMP-9 is increased in cerebrospinal fluid[65,66].

(5) Plaque imaging studies:

Positron emission tomography using 18-fluorodeoxyglucose (FDG-PET) is a validated technique for imaging plaque metabolic activity, mainly related to inflammatory monocyte-macrophage activity. Tawakol reported high FDG uptake in symptomatic carotid plaque, with high ( $r=0.89$ ) correlation with plaque macrophage density[67]. Cross-sectional studies have established that plaque FDG uptake is correlated with other markers of plaque instability, such as micro-embolic signals on transcranial Doppler ultrasound, unstable plaque morphology, and expression of inflammatory cytokines and proteases[68-70]. Longitudinal studies in patients who underwent whole-body PET for cancer screening have reported that aortic FDG uptake independently predicts late vascular events, including stroke. In 60 patients with recent stroke/TIA and ipsilateral carotid stenosis, we found that carotid plaque FDG uptake was an independent predictor of early pre-endarterectomy stroke recurrence, after adjusting for age and degree of stenosis (adjusted HR 6.1, CI 1.3-28.8,  $p=0.02$ ) (Figure 2)[71]. The 90-day stroke recurrence rate for patients in the highest FDG uptake tertile was 59% compared with 19% and 13% in the lowest tertiles (log-rank  $p=0.03$ ) (Figure 3). Other groups have reported similar findings[72,73]. An international multi-centre study (BIOVASC) is under way to test the validity of these findings in an independent cohort.

(6) Randomised trials in patients without cerebrovascular disease:

In patients without clinical cerebrovascular disease, several randomised clinical trials testing the hypothesis that inhibiting inflammation may prevent cardiovascular events have been completed or are under way (Table 1). In addition to their lipid-lowering effects, statins are known to influence other biological pathways (pleiotropic effects) including anti-

inflammatory effects. Small studies have demonstrated reduction in blood biomarkers and plaque FDG uptake in a dose-dependent manner by statins[74,75]. In the JUPITER trial, 17,802 patients without a history of vascular disease, low-normal LDL cholesterol, and  $CRP \geq 2\text{mg/L}$  were randomly allocated to receive either rosuvastatin 20mg or placebo[76]. Rosuvastatin treatment reduced LDL by 50% and CRP by 37%. The trial was halted early due to benefit, with a relative risk reduction in major vascular events of 46% in rosuvastatin-treated patients. In a pre-specified secondary analysis, the relative risk reduction for stroke was 48% ( $p=0.002$ ). However, the interpretation of these findings was unclear due to the non-specific effects of rosuvastatin on both inflammation and LDL metabolism.

Other trials which targeted secretory lipoprotein-associated phospholipase A2 (LpPLA2), which has been hypothesized to be implicated in atherosclerosis development using specific antagonists (darapladib, varespladib) did not show benefit in patients with recent or stable coronary disease[77-79]. However, as LpPLA-2 is not centrally involved in the classical IL1-IL6-TNF $\alpha$  inflammatory pathway, these results should be interpreted with caution.

Clinical trials using specific and direct anti-inflammatory interventions are under way in non-stroke populations (Table)[40,43]. In CANTOS, canakinumab (an interleukin-1 $\beta$  antagonist) is under evaluation in 10,000 patients with stable coronary disease selected on the basis of  $CRP \geq 2\text{mg/L}$ . The National Institutes of Health-funded Cardiovascular Inflammation Reduction Trial (CIRT) is comparing low-dose weekly methotrexate (15 or 20mg per week) with placebo plus recommended care in 7,000 patients with stable coronary disease and diabetes or metabolic syndrome. In Australia, the LoDoCo2 trial is examining the efficacy of low-dose colchicine compared with placebo in addition to usual care in patients with stable coronary disease (see below). An ongoing trial is comparing the IL-6 antagonist tocilizumab with entanercept for prevention of major

cardiovascular events in patients with rheumatoid arthritis and cardiovascular risk factors.

**Randomised trials of anti-inflammatory treatments for secondary stroke prevention:**

To assess the literature of trials of anti-inflammatory agents for stroke prevention, we conducted a systematic review of published data. We searched MEDLINE for completed published trials and the Clinicaltrials.gov registry for ongoing trials. Pre-specified inclusion criteria were: (1) randomised controlled trials testing the addition of anti-inflammatory agents to standard care in patients with clinical cerebrovascular disease (study size 100 patients or more with at least 80% of included patients with stroke/TIA); (2) inclusion of stroke as a primary or secondary outcome measure; (3) inclusion of adults only (age  $\geq 18$  years); (4) English language publication; (5) publication year 1966-July 2016. The initial search strategy (Web-appendix) revealed 453 studies. However, after review of abstracts, only a single ongoing trial (CONVINCE) testing low-dose colchicine for secondary prevention in patients with clinical cerebrovascular disease was identified.

***Crystal-induced inflammation and atherosclerosis:***

Crystallised extracellular cholesterol has long been recognized as a common feature of atherosclerotic plaque, but was often considered as a bystander phenomenon in plaque development. Recent experimental and clinical-pathological studies have shown that microscopic cholesterol crystals form very early in atherosclerotic plaque development, and may be a potent inflammatory stimulus for neutrophils and macrophages. Studies in ApoE-deficient mice have demonstrated that cholesterol crystals activate monocytes-

macrophages via the intracellular nucleotide-binding leucine-rich repeat-containing pyrin receptor (NLRP) inflammasome protein complex. This causes increased IL-1 $\beta$  expression, which is known as a key event in the initiation of local and systemic inflammatory cascades, evidenced by elevated IL-6 and CRP[80-82]. These important observations provide direct evidence linking plaque lipid metabolism and inflammation. Indirect support for these findings in humans is provided by a PET study in patients with symptomatic carotid stenosis, where 18-FDG uptake in symptomatic plaque was associated with total and LDL cholesterol, and inversely associated with HDL cholesterol, after adjustment for confounding variables[83].

Uric acid is a product of purine metabolism which undergoes hepatic and renal elimination in vivo. Uric acid is a potent antioxidant with neuroprotective effects in animal models, and established safety in humans[84]. However, hyperuricaemia is strongly associated with atherosclerosis risk factors, such as hypertension, renal impairment, obesity, metabolic syndrome and ethanol excess[85]. In epidemiological studies, serum urate has been associated with inflammatory blood biomarkers, suggesting that hyperuricaemia may predispose to a pro-inflammatory state[86,87]. Some studies have described associations between hyperuricaemia and subclinical markers of atherosclerosis, such as carotid intima-media thickness and coronary artery calcification burden[88]. However, these associations have not persisted after adjustment for vascular risk factors, raising the possibility that uric acid may be a risk marker rather than a causal factor. Data are conflicting regarding the association between uric acid and cardiovascular events, including stroke. Several studies have also reported positive associations. For example, in the Rotterdam study, the hazard ratio of ischaemic stroke was 1.77 (CI 1.1-2.83) in the fifth compared with the first quintile of uric acid, with only minimal attenuation after adjustment for vascular risk factors[89].

However other studies, including the Framingham and ARIC studies, have not replicated these findings[90,91].

In gout, monosodium urate crystals are deposited in joints and bursae, causing activation of the NLRP inflammasome, IL-1 $\beta$  generation, and both local and systemic inflammation.

Crystal-induced inflammation, via either cholesterol and/or monosodium urate crystals, may be a common mechanism underlying the associations between inflammation, lipid metabolism, and hyperuricaemia.

#### **Potential of colchicine for prevention of atherosclerotic events:**

Colchicine has been a mainstay of treatment for gout for centuries[92,93]. Although traditionally high-dose colchicine was associated with gastro-intestinal problems when used for acute gout flares, recent guidelines have recommended that similar efficacy may be achieved with major improvements in tolerability when lower doses are used[92].

Long-term low-dose colchicine is safe and effective for gout prevention, and has been a corner-stone of treatment of Bechet's Disease and Familial Mediterranean Fever for decades[93].

Via binding to  $\alpha$ - and  $\beta$ -tubulin proteins, colchicine has multiple anti-inflammatory properties including inhibition of microtubule polymerization, with inhibition of leucocyte rolling and endothelial adhesion, impaired leucocyte motility, phagocytosis, and cytokine secretion. It inhibits crystal-induced activation of the NLRP inflammasome, thus inhibiting caspase-1 proteolysis and interleukin-1 $\beta$  secretion in monocyte-macrophages.

Observational data report lower rates of coronary disease in gout and FMF associated with

colchicine therapy[94]. In patients with stable coronary atherosclerosis treated with low-dose colchicine, statins, and antiplatelet agents, CRP was reduced by 60%, but was unchanged in controls ( $p=0.002$ )[95]. In the LoDoCo randomised trial, 532 patients with chronic stable coronary disease were randomised to the lowest-available dose of colchicine (0.5mg/day) or usual care[96]. Almost all were taking antiplatelet agents and high-dose statins at baseline, and anti-hypertensive therapy as-indicated. Over a median follow-up of 36 months, the risk of major cardiovascular events was reduced by 67% in patients treated with low-dose colchicine (HR 0.33, CI 0.18-0.59,  $p<0.001$ ) (Figure 4). Only 5 stroke events occurred (as expected in this patient sample), but the direction of benefit for stroke was similar to that for coronary events (4 strokes in controls versus 1 in colchicine group,  $p=0.18$ ). Colchicine had an excellent safety profile. The commonest adverse effect was intestinal upset (2.5%) with myalgia in 2 patients (0.9%) and myositis, rash, itch, alopecia, or peripheral neuropathy reported in 1 patient each ( $<0.5\%$ ) and no excess of death observed. Recent trials have also demonstrated benefit of low-dose colchicine (0.5-1mg/day) for prevention of recurrent pericarditis and reduced infarct size when used acutely in patients with ST-elevation myocardial infarction[97,98].

A 2016 Cochrane systematic review has investigated the safety and benefits of long term colchicine use with particular emphasis on cardiovascular disease[99]. It included 39 trials overall of 4992 patients, and 4 trials of 1230 patients with heart disease. The risk of myocardial infarction was reduced by 80% (relative risk 0.2, CI 0.07-0.57, 2 trials, 652 patients, moderate quality evidence). No increased risk of serious adverse events was observed. Colchicine was associated with increased GI intolerance, generally mild and short-lived.

## **CONVINCE: Can anti-inflammatory therapy with colchicine prevent recurrent stroke?**

The underlying pathophysiology of recurrent vascular events in patients with non-cardioembolic stroke is likely to resemble that in patients with coronary artery disease. Informed by the growing body of experimental and clinical data supporting a rationale for treatment with colchicine in vascular disease, the CONVINCE trial will test the hypothesis that daily low-dose colchicine (0.5mg/day) combined with usual care (lifestyle advice plus antiplatelet, antihypertensive, and lipid-lowering therapy) will have benefit for prevention of recurrent stroke and major vascular events compared with usual care alone[100]. Similar to other stroke secondary prevention trials of antiplatelet and lipid-lowering therapy, CONVINCE will include patients with non-severe (modified Rankin score 3 or less) stroke or TIA, randomised between 72 hours and 28 days of symptom onset and followed for a median of 36 months. Patients with cardioembolic stroke/TIA, those with other identified non-atherosclerotic stroke mechanisms (eg. arterial dissection), or contra-indication to colchicine therapy will be excluded. The tolerability and safety of colchicine will be closely monitored, with a pre-specified review after completion of randomization of the initial 10% of the trial sample (internal pilot 'Vanguard' stage).

### **Conclusion:**

Atherosclerosis of different vessels has been associated with a large proportion of ischemic stroke. Growing evidence has emerged, based on experimental, epidemiological, and clinical data in recent years to support the hypothesis that inflammatory pathways are key mediators in the development of atherosclerosis, leading to stroke and other vascular events. This 'inflammation hypothesis' has been the basis of several clinical trials using

different agents in patients with coronary disease and colchicine has shown promising therapeutic potential to date. These findings require further study in ischemic stroke, and will be tested in the CONVINCE trial. Further trials are needed to improve our understanding of the role of atherosclerotic inflammation in stroke pathogenesis.

#### **REFERENCES:**

1. World Health Organisation. Cardiovascular Diseases Fact Sheet.  
<http://www.who.int/mediacentre/factsheets/fs317/en/> (Accessed December 14th, 2016)
2. Feigin V, Lawes CM, Bennett D. Worldwide stroke incidence and early case-fatality reported in 56 population-based studies: a systematic review. *Lancet Neurol* 2009;8:355-69
3. American Heart Association. Heart and Stroke Statistics 2013 update. *Circulation* 2013;127:e6-e245
4. Hankey GJ. Secondary stroke prevention. *Lancet Neurol* 2014;13:178 – 194
5. Kelly PJ, Crispino G, Sheehan O, et al. Incidence, event rates, and early outcome of stroke in Dublin, Ireland: the North Dublin population stroke study. *Stroke* 2012;43:2042–7
6. Lovett JK, Coull AJ, Rothwell PM. Early risk of recurrence by subtype of ischaemic stroke in population-based incidence studies. *Neurology* 2004;62:569-73
7. Petty GW, Brown RD, Whisnant JP et al. Ischemic stroke subtypes. A population-based study of functional outcome, survival, and recurrence. *Stroke* 2000;31:1062-68
8. Kolominsky-Rabas PL, Weber M, Gefeller O, et al. Epidemiology of ischaemic stroke subtypes according to TOAST criteria. *Stroke* 2001;32:2735-40

9. Grau AJ, Weimar C, Buggle F, et al. Risk factors, outcome and treatment in subtypes of ischaemic stroke. The German Stroke Data Bank. *Stroke* 2001;32:2559-66
10. Bejot Y, Caillier M, Ben Salem D, et al. Ischaemic stroke subtypes and associated risk factors: a French population based study. *J Neurol Neurosurg Psych* 2008;79:1344-48
11. Meseguer E, Lavallee PC, Mazighi M, et al. Yield of systematic transcranial Doppler in patients with transient ischaemic attack. *Ann Neurol* 2010;68:9-17
12. Bang OY. Intracranial atherosclerosis: current understanding and perspectives. *J Stroke* 2014;16:27-35
13. Arenillas JF. Intracranial atherosclerosis and inflammation: Lessons from the East and the West. *Brain Circ* 2015;1:47-52
14. Ogata J, Masuda J, Yutani C, et al. Mechanisms of cerebral artery thrombosis: a histopathological analysis on eight necropsy cases. *J Neurol Neurosurg Psychiatry* 1994;57:17-21
15. Chen XY, Wong KS, Lam WW, et al. Middle cerebral artery atherosclerosis: histological comparison between plaques associated with and not associated with infarct in a postmortem study. *Cerebrovasc Dis.* 2008;25:74-80.
16. Ovbiagele B, Lynn MJ, Saver JL, et al. Leukocyte count and vascular risk in symptomatic intracranial atherosclerosis. *Cerebrovasc Dis.* 2007;24:283-8.
17. Qureshi, AI, Caplan, LR. Intracranial atherosclerosis. *Lancet* 2014;383:984-998
18. Coutinho JM, Derkatch S, Potvin ARJ, et al. Nonstenotic carotid plaque on CT angiography in patients with cryptogenic stroke. *Neurology* 2016;87:665-72
- 19. Hart RG, Diener HC, Coutts S, et al. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol* 2014;13:429-438**
20. Gladstone D, Spring M, Dorian P et al. Atrial fibrillation in patients with cryptogenic stroke. *N Engl J Med* 2014;370:2467-77

21. Sanna T, Diener HC, Rod S, et al. Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med* 2014;370:2478-2486
22. Marnane M, Duggan CA, Sheehan OC, et al. Stroke subtype classification to mechanism-specific and undetermined categories by TOAST, A-S-C-O and Causative Classification System - Direct comparison in the North Dublin Population Stroke Study. *Stroke* 2010;41:1579-1586
23. Amarenco P, Cohen A, Tzourio C, et al. Atherosclerotic disease of the aortic arch and the risk of ischemic stroke. *N Engl J Med* 1994;331:1474-9
24. Wardlaw JM, Smith C, Dichgans M. Mechanisms of sporadic cerebral small vessel disease: insights from neuroimaging. *Lancet Neurol* 2013;32:483-97
25. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. High-Dose Atorvastatin after Stroke or Transient Ischemic Attack. *N Engl J Med* 2006;355:549-559
26. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71-86
27. Diener HC, Cunha L, Forbes C, et al. European Stroke Prevention Study 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci* 1996;143:1-13.
28. Bushnell CD, Zimmer LO, Pan WQ, et al. Persistence With Stroke Prevention Medications 3 Months After Hospitalization. *Arch Neurol* 2010;67:1456-63
29. Kumbhani DJ, Steg PG, Cannon CP, et al. Adherence to secondary prevention medications and four-year outcomes in outpatients with atherosclerosis. *Am J Med* 2013;126:693-700

30. Callaly E, Ni Chroinin D, Hannon N, et al. Rates, Predictors and Outcomes of early and late Recurrence after Stroke: The North Dublin Population Stroke Study. *Stroke* 2016;47:244-46
31. Park JH, Ovbiagele B. Optimal combination secondary prevention drug treatment and stroke outcomes. *Neurology* 2015;84:50-6
32. The SPS3 Study Group; Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial. *Lancet* 2013;382; 507–515
33. Amarenco P, Lavallée P, Labreuche J, et al. One-Year Risk of Stroke after Transient Ischemic Attack or Minor Stroke. *N Engl J Med* 2016;374:1533-1542
34. Mohan KM, Wolfe CDA, Rudd AG, et al. Risk and cumulative risk of stroke recurrence: A systematic review and meta-analysis. *Stroke* 2011;42:1489-1494
35. Touzé E, Varenne O, Chatellier G, et al. Risk of myocardial infarction and vascular death after transient ischaemic attack and ischaemic stroke. A systematic review and meta-analysis. *Stroke* 2005;36:2748-55
36. Sheehan OC, Kyne L, Kelly LA, et al. A population-based study of ABCD2 score, carotid stenosis, and atrial fibrillation for early stroke prediction after TIA: the North Dublin TIA Study. *Stroke* 2010; 41: 844-845
37. Marquardt L, Kuker W, Chandratheva A, et al. Incidence and prognosis of >50% vertebral or basilar stenosis. Prospective population based study. *Brain* 2009;132:982-88
38. Mazighi M, Tanasescu R, Ducrocq X, et al. Prospective study of symptomatic atherothrombotic intracranial stenosis; the GESICA study. *Neurology* 2006;66:1187-91
39. Merwick A, Albers GW, Amarenco P, et al. Addition of brain and carotid imaging to the ABCD2 score to improve identification of patients at high early stroke risk after transient ischaemic attack. *Lancet Neurol* 2010;9:1060-9

40. Ridker PM. Residual inflammatory risk: addressing the obverse side of the atherosclerosis prevention coin. *Eur Heart J* 2016;37:1720-2
41. Falk E, Shah PK, Fuster V. Coronary plaque disruption. *Circulation* 1995;92:657-671
42. Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. *Nature* 2011;473:317-25
43. Ridker PM, Luscher TF. Anti-inflammatory therapies for cardiovascular disease. *Eur Heart J* 2014;35:1782-1791
44. Emerging Risk Factors Collaboration. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. *Lancet* 2010;375:132-140
45. Di Napoli M, Schwaninger M, Cappelli R, et al. Evaluation of C-reactive protein measurement for assessing the risk and prognosis in ischemic stroke: a statement for health care professionals from the CRP Pooling Project members. *Stroke* 2005;36:1316-29
46. Arenillas JF, Alvarez-Sabin J, Molina CA, et al. C-reactive protein predicts further ischaemic events in transient ischaemic attack or stroke and intracranial large-artery occlusive disease. *Stroke* 2003;34:2463-70
47. Schlager O, Exner M, Mlekusch W, et al. C reactive protein predicts future cardiovascular events in patients with carotid stenosis. *Stroke* 2007;38:1263-68
48. Elkind M, Luna JM, McClure LA, et al. C-Reactive Protein as a Prognostic Marker After Lacunar Stroke; Levels of Inflammatory Markers in the Treatment of Stroke Study *Stroke* 2014;45:707-16

49. Li, J, Zhao X, Meng X, et al. High-Sensitive C-Reactive Protein Predicts Recurrent Stroke and Poor Functional Outcome. Subanalysis of the Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events Trial. *Stroke* 2016;47:2025-2030
50. Segal HC, Burgess A, Poole DL, et al. Population based study of blood biomarkers in prediction of subacute recurrent stroke. *Stroke* 2014;45:2912-17
51. The Emerging Risk Factors Collaboration. C-reactive protein, fibrinogen, and cardiovascular risk. *N Engl J Med* 2012;367:1310-20
52. Koeppen AH, Lansing LS, Peng SK, et al. Central nervous system vasculitis in cytomegalovirus infection. *J Neurol Sci* 1981;51:395-410
53. Rosales D, Garcia-Gracia C, Salgado E, et al. Primary Central Nervous System Vasculitis Triggered by Cytomegalovirus Encephalitis. *Neurology* 2013;80:Supplement P01.231
54. Scolding NJ. Central nervous system vasculitis. *Semin Immunopathol* 2009;31:527-36
55. Gutierrez J, Goldman J, Dwork AJ, et al. Brain arterial remodelling contribution to nonembolic brain infarcts in patients with HIV. *Neurology* 2015;85:1139-45
56. Esenwa CC, Elkind MS. Inflammatory risk factors, biomarkers and associated therapy in ischaemic stroke. *Nat Rev Neurol* 2016;12:594-604
57. Elkind MS, Ramakrishnan P, Moon YP, et al. Infectious burden and risk of stroke: the Northern Manhattan study. *Arch Neurol* 2010;67:33-8
58. Smieja M, Gnarpe J, Lonn E, et al. Multiple infections and subsequent cardiovascular events in the Heart Outcomes Prevention Evaluation (HOPE) Study. *Circulation* 2003;107:251-7
59. Haider AW, Wilson PW, Larson MG, et al. The association of seropositivity to Helicobacter pylori, Chlamydia pneumoniae, and cytomegalovirus with risk of cardiovascular disease: a prospective study. *J Am Coll*

*Cardiol* 2002;40:1408-13

60. Elkind MS, Carty CL, O'Meara ES, et al. Hospitalization for infection and risk of acute ischemic stroke: the Cardiovascular Health Study. *Stroke* 2011;42:1851-6

61. IL6R Genetics Consortium and Emerging Risk Factors Collaboration. Interleukin-6 receptor pathways in coronary heart disease: a collaborative meta-analysis of 82 studies. *Lancet* 2012;379:1205-1213

62. Interleukin-6 Receptor Mendelian Randomisation Analysis (IL6R MR) Consortium. The interleukin-6 receptor as a target for prevention of coronary heart disease: a mendelian randomisation analysis. *Lancet* 2012;379:1214-24

63. Redgrave JN, Gallagher PJ, Lovett JK, et al. Critical cap thickness and rupture in symptomatic carotid plaques. *Stroke* 2008; 39 (6):1722-9.

64. Marnane M, Prendeville S, McDonnell C, et al. Plaque Inflammation and Unstable Morphology Are Associated With Early Stroke Recurrence in Symptomatic Carotid Stenosis. *Stroke* 2014;45:801-806

65. Rosenberg GA. Inflammation and white matter damage in vascular cognitive impairment. *Stroke* 2009;40[suppl 1];S20-S23

66. Esiri MM, Wilcock GK, Morris JH. Neuropathological assessment of the lesions of significance in vascular dementia. *J Neurol Neurosurg Psychiatry* 1997;63;749-753

67. Tawakol A, Migrino RQ, Bashian GG, et al. In vivo 18F-fluorodeoxyglucose positron emission tomography imaging provides a noninvasive measure of carotid plaque inflammation in patients. *J Am Coll Cardiol* 2006;48:1818-1824

68. Pedersen SF, Graebe M, Fisker Hag AM, et al. Gene expression and 18FDG uptake in atherosclerotic carotid plaques. *Nucl Med Commun* 2010;31:423-29.

69. Rudd JH, Myers KS, Bansilal S, et al. Relationships among regional arterial inflammation, calcification, risk factors, and biomarkers: a prospective fluorodeoxyglucose positron-emission tomography/computed tomography imaging study. *Circ Cardiovasc Imaging* 2009;2:107–15.
70. Moustafa RR, Izquierdo-Garcia D, Fryer TD, et al. Carotid plaque inflammation is associated with cerebral microembolism in patients with recent transient ischemic attack or stroke: a pilot study. *Circ Cardiovasc Imaging* 2010;3:536–41.
71. Marnane M, Merwick A, Sheehan OC, et al. Carotid plaque inflammation on (18) F-fluorodeoxyglucose positron emission tomography predicts early stroke recurrence. *Ann Neurol* 2012;71:709-718
72. Skagen K, Johnsrud K, Evensen K, et al. Carotid plaque inflammation assessed with 18-FDG PET/CT is higher in symptomatic compared with asymptomatic patients. *Int J Stroke* 2015;10:730-736
73. Noh SM, Choi WJ, Kang BT, et al. Complementarity between (18)F-FDG PET/CT and Ultrasonography or Angiography in Carotid Plaque Characterization. *J Clin Neurol* 2013;9:176-85
74. Tahara N, Kai H, Ishibashi M, et al. Simvastatin attenuates plaque inflammation: evaluation by fluorodeoxyglucose positron emission tomography. *J Am Coll Cardiol* 2006;48:1825–31
75. Tawakol A, Fayad Z, Mogg R, et al. Intensification of Statin Therapy Results in a Rapid Reduction in Atherosclerotic Inflammation; Results of a Multicenter Fluorodeoxyglucose-Positron Emission Tomography/Computed Tomography Feasibility Study. *J Am Coll Cardiol* 2013;62:909–17

76. Ridker PM, Danielson E, Fonseca FAH, et al. Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein. *N Engl J Med* 2008;359:2195-2207
77. The STABILITY Investigators. Darapladib for Preventing Ischemic Events in Stable Coronary Heart Disease. *N Engl J Med* 2014; 370:1702-1711
78. O'Donoghue ML, Braunwald E, White HD. Effect of Darapladib on Major Coronary Events After an Acute Coronary Syndrome. The SOLID-TIMI 52 Randomized Clinical Trial. *JAMA* 2014;312:1006-1015
79. Nicholls SJ, Kastelein JJ, Schwartz GG et al. Varespladib and cardiovascular events in patients with an acute coronary syndrome: the VISTA-16 randomized clinical trial. *JAMA* 2014;311:252-62
80. Abela GS. Cholesterol crystals piercing the arterial plaque and intima trigger local and systemic inflammation. *J Clin Lipid* 2010;4:156-164
81. Duewell P, Kono H, Rayner KJ, et al. NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals. *Nature* 2010;464:1357-1362
82. Rajamäki K, Lappalainen J, Oorni K, et al. Cholesterol Crystals Activate the NLRP3 Inflammasome in Human Macrophages: A Novel Link between Cholesterol Metabolism and Inflammation. *PLoS ONE* 2010 5(7):e11765
83. Ni Chronin D, Marnane M, Akijian L, et al. Serum lipids associated with inflammation-related PET-FDG uptake in symptomatic carotid plaque. *Neurology* 2014;82:1-7
84. Chamorro A, Amaro S, Castellanos M, et al. Safety and efficacy of uric acid in patients with acute stroke (URICO-ICTUS): a randomised, double-blind phase 2b/3 trial. *Lancet*

*Neurol* 2014;13:453-60

85. Gagliardi AC, Miname MH, Santos RD. Uric acid: A marker of increased cardiovascular risk. *Atherosclerosis* 2009;202:11-7.

86. Ruggiero C, Cherubini A, Ble A et al. Uric acid and inflammatory markers. *Eur Heart J* 2006;27:1174-81.

87. Ruggiero C, Cherubini A, Miller E 3rd, et al. Usefulness of uric acid to predict changes in C-reactive protein and interleukin-6 in 3-year period in Italians aged 21 to 98 years. *Am J Cardiol* 2007;100:115-21

88. Coutinho Tde A, Turner ST, Peyser PA, et al. Associations of serum uric acid with markers of inflammation, metabolic syndrome, and subclinical coronary atherosclerosis. *Am J Hypertens* 2007;20:83-9.

89. Bos MJ, Koudstaal PJ, Hofman A, et al. Uric acid is a risk factor for myocardial infarction and stroke: the Rotterdam study. *Stroke* 2006;37:1503-7

90. Moriarity JT, Folsom AR, Iribarren C, et al. Serum uric acid and risk of coronary heart disease: Atherosclerosis Risk in Communities (ARIC) Study. *Ann Epidemiol* 2000;10:136-43

91. Culleton BF, Larson MG, Kannel WB, et al. Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study. *Ann Intern Med* 1999;131:7-13

92. Stack J, Ryan J, McCarthy G. Colchicine: New insights to an old drug. *Am J Therapeutics* 2015;22:e151-157;

93. Cocco G, Chu DC, Pandolfi S. Colchicine in clinical medicine. A guide for internists. *Eur J Intern Med* 2010;21:503-8

94. Crittenden DB, Lehmann RA, Schneck L, et al. Colchicine use is associated with decreased prevalence of myocardial infarction in patients with gout. *J Rheumatol* 2012;39:1458-64

95. Nidorf M, Thompson PL. Effect of colchicine (0.5mg twice daily) on high-sensitivity C-reactive protein independent of aspirin and atorvastatin in patients with stable coronary artery disease. *Am J Cardiol* 2007;99:805-807
96. Nidorf SM, Eikelboom JW, Budgeon CA, et al. Low-dose colchicine for secondary prevention of cardiovascular disease. *J Am Coll Cardiol* 2013;61:404-410
97. Imazio M, Bobbio M, Cecchi E, et al. Colchicine as first-choice therapy for recurrent pericarditis. Results of the CORE (colchicine for recurrent pericarditis) trial. *Arch Int Med* 2005;165:1987-1991
98. Deftereos S, Giannopoulos G, Angelidis C, et al. Anti-Inflammatory Treatment With Colchicine in Acute Myocardial Infarction: A Pilot Study. *Circulation* 2015;132:1395-1403
99. Hemkens LG, Ewald H, Gloy VL, et al. Colchicine for prevention of cardiovascular events. *Cochrane Database Syst Rev* 2016;DOI:10.1002/14651858.
100. Colchicine for prevention of Vascular Inflammation in Non-CardioEmbolic stroke (CONVINCE) – a randomised clinical trial of low-dose colchicine for secondary prevention after stroke. EudraCT:2015-004505-16

<b>Trial</b>	<b>Agent</b>	<b>Target</b>	<b>Included</b>	<b>Result</b>
JUPITER	Rosuvastatin	Multiple	No cardiovascular disease, no indication for statins, CRP $\geq$ 2mg/L	Completed. Relative risk reduction (RRR) 46% in MACE (p<0.00001)
LoDoCo	Colchicine	Multiple	Stable CAD	Completed. Relative risk reduction (RRR) 67% in MACE (p<0.001)
CIRT	Low-dose methotrexate (15 or 20mg/wk) plus standard treatment	Multiple	Stable CAD (MI<5 yr), T2DM, met syndrome	Ongoing
CANTOS	Canakinumab	IL-1B	Stable CAD (MI>30d), CRP $\geq$ 2 mg/L	Ongoing
ENTRACTE	Tocilizumab	IL-6	Rheumatoid arthritis with cardiovascular risk factors	Ongoing
LoDoCo2	Colchicine	Multiple	Stable CAD	Ongoing
CONVINCE	Colchicine	Multiple	Non-cardioembolic stroke	Ongoing

Table: Large prevention trials targeting atherosclerotic inflammation in cardiovascular disease

## Figure Legends:

### Figure 1:

Linear association of CRP with new coronary disease (top) and stroke (bottom) in 160,309 individuals without vascular disease, adjusted for age, sex, and study (left, graphs A), and additionally for vascular risk factors (right, graphs B). Adjusted relative risk (RR) per 3-fold increase in CRP was 1.37 (CI 1.27-1.48) for coronary heart disease and 1.27 (CI 1.15-1.4) for ischaemic stroke

### Figure 2:

2a (left image): Axial CT angiogram of patient with left hemisphere TIA and internal carotid artery origin stenosis (arrow)

2b (right image): Fused 18-FDG PET/CT image demonstrating focus of increased FDG uptake reflecting inflammatory hyper-metabolism at site of carotid mural plaque (arrow)

### Figure 3:

Early recurrent stroke in patients with non-severe stroke or TIA and ipsilateral carotid stenosis, stratified by tertile of 18-FDG uptake in symptomatic plaque on PET/CT. Stroke recurrence rates were 59% in highest FDG uptake tertile vs 19% and 13% in the lowest and middle tertiles (log-rank  $p=0.03$ ). In a Cox regression model adjusted for age and degree of stenosis the HR for stroke recurrence was 6.1 per 1 standard uptake value of plaque FDG activity (CI 1.3-28.8,  $p=0.02$ )

### Figure 4:

Relative risk of major cardiovascular events in LoDoCo trial in patients with stable coronary disease treated with low-dose colchicine plus usual care compared with usual care alone

