Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Low-dose Colchicine

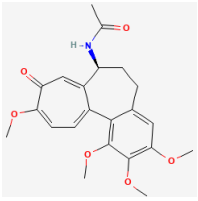
Evidence Summary

It is an anti-inflammatory agent and can reduce the risk of adverse cardiovascular events related to vascular inflammation in combination with other cardioprotective agents. Low doses have a good safety profile.

Neuroprotective Benefit: Through its anti-inflammatory activity and potential capacity to reduce the risk of stroke in those with cardiovascular risk factors, it may help protect against vascular dementia, though this has yet to be assessed.

Aging and related health concerns: Low dose colchicine protects against major adverse cardiovascular events as a secondary prevention strategy, likely through its anti-inflammatory activity. It may also reduce the risk of liver cancer.

Safety: Low dose colchicine is generally well tolerated. Gastrointestinal events are the most common side effects, and more prevalent at higher doses. The toxicology profile is dose dependent, as high doses can be lethal.

Availability: Rx	**Dose**: 0.5 mg per day orally for secondary prevention for cardiovascular disease. 0.6 mg/day for gout prevention (1.2 mg plus 0.6 mg for acute gout attacks)	**Chemical formula:** $C_{22}H_{25}NO_6$ **MW**: 399.4 g/mol  Source: PubChem
Half-life: 20-40 hours from plasma/serum with multiple dosing	**BBB**: Negligible penetrance (P-gp substrate)	
Clinical trials: Low-dose colchicine has been tested in numerous clinical trials for cardiovascular disease, including the Phase 3 COLCOT (n= 4,745), LoCoDo2 (n= 5,522), COP-AF (n=3,209), and CONVINCE (n=3,154) trials.	**Observational studies**: Colchicine use has been associated with lower risk for liver cancer in one study. Studies regarding colchicine use and risk for cognitive impairment have been mixed.	

What is it?

Colchicine is derived from the corms (underground stems) of the *Colchicum autumnale* plant, also called the autumn crocus. It is an ancient herbal remedy for joint pain [1]. Colchicine was first purified from the plant in the 1800's and has long been used for the treatment of gout. Colchicine, under the brand name Colcrys, became an FDA approved drug in 2009 for the prevention of gout flares and treatment of familial Mediterranean fever. Colchicine has also been used off-label in a variety of other conditions for its anti-inflammatory properties. It acts by binding tubulin and disrupting microtubule dynamics, which impacts cell division, transport, and migration. At therapeutic doses, it preferentially accumulates in neutrophils, preventing their activation and migration. It can also reduce the activation and secretion of pro-inflammatory mediators in other inflammatory leukocyte populations, such as macrophages. Based on its anti-inflammatory properties, colchicine has been tested in the context of cardiovascular disease to mitigate the risk of major adverse cardiovascular events. Based on the results of several large studies, particularly the COLCOT and LoCoDo2 trials, low dose colchicine was approved in 2023 as the first anti-inflammatory agent for secondary prevention in cardiovascular disease [2]. The dose of colchicine used for cardiovascular disease is lower than is typically used for gout, and as a result has a stronger safety profile. Efforts are ongoing to determine the populations with cardiovascular risk factors who are most likely to benefit from the addition of low dose colchicine.

Neuroprotective Benefit: Through its anti-inflammatory activity and potential capacity to reduce the risk of stroke in those with cardiovascular risk factors, it may help protect against vascular dementia, though this has yet to be assessed.

Types of evidence:

- 1 Phase 2 trial of low dose colchicine in ALS
- 2 pilot clinical trials of colchicine in probable AD patients
- 1 retrospective cohort study of colchicine use and dementia risk
- I observational study of colchicine use in familial Mediterranean fever and cognition
- Several laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

Colchicine could potentially mitigate cerebrovascular damage associated with vascular dementia, or increase the risk for dementia, depending on the dose and the population.
At therapeutic doses, colchicine may benefit the cerebrovasculature through its anti-inflammatory properties. While the results of individual studies vary, the totality of evidence suggests that colchicine may reduce the risk for stroke, at least in certain high-risk populations [3]. However, direct administration of colchicine to the brain is used to impair learning and memory in rodents model systems [4; 5]. Therefore, if colchicine reaches the brain in high doses, it may have a negative impact on cognition. Colchicine is a substrate for the P-glycoprotein (P-gp) transporter, and typically does not reach the brain in appreciable quantities with standard short-term dosing. Individuals with a compromised BBB may be at higher risk for potential impacts to the brain in the context of prolonged use at moderate to high doses within the therapeutic range.

A retrospective cohort study in Taiwan compared rates of dementia in patients ≥40 years old with gout prescribed colchicine (n=6147) relative to those prescribed urate lowering therapy (n=6,147) [6]. Daily doses for gout prevention typically range from 0.6 mg to 1.2 mg. During the 14-year follow-up, the incidence of dementia was higher in those taking colchicine, with an adjusted hazard ratio (HR) of 1.45 (95% Confidence Interval [CI] 1.05 to 1.99). A higher cumulative dose was associated with higher risk, such that incidence rates were highest in those that used colchicine for greater than 30 days (adjusted HR: 1.53, 95% CI 1.01 to 2.32). A potential caveat of this study is that a prior cohort study in Taiwan found that the gout patients on urate lowering therapy had a lower incidence of dementia relative to

those without gout (HR: 0.71, 95% CI 0.65 to 0.78), In which case, the findings of this study might suggest that, unlike urate lowering therapy, standard dose colchicine is not associated with reduced risk of dementia. Observational studies in other populations would support the notion that colchicine use does not increase the risk for cognitive decline. In addition to gout, colchicine is approved for use in familial Mediterranean fever, at a relatively high dose of 1.2 to 2.4 mg per day. A study including 55 patients with familial Mediterranean fever with an average age of 74 years, taking colchicine for 25.1 ± 8.9 years did not show evidence of cognitive impairment, as their cognitive status, based on Mini-Mental State Examination (MMSE) scores, was higher than the population-based norm (27.2 ± 2.2 vs. 25.5 ± 2.4) [7].

Human research to suggest benefits to patients with dementia:

Colchicine was tested in pilot trials in the late 1990s in patients with probable Alzheimer's disease at a dose of 1.2 mg per day (0.6 mg twice per day) as an anti-inflammatory approach [8; 9]. One study tested colchicine in 11 patients for four weeks, while the other study tested colchicine in combination with hydroxychloroquine (200 mg twice daily) in nine patients for 11 weeks. The studies were primarily designed to test safety and tolerability, and significant effects on cognitive measures were generally not observed.

Low-dose colchicine (i.e. 0.5 mg/day) has not been specifically tested in dementia patients, but trials to date have not shown evidence of cognitive worsening in populations with cardiovascular risk factors, suggesting that low doses likely do not exacerbate disease pathology [10]. It has not been tested whether, aside from potentially mitigating cerebrovascular inflammation, low-dose colchicine could also potentially offer clinical benefits in the context of vascular dementia.
The risk for colchicine poisoning would be a major concern in a dementia population, since the therapeutic index is so narrow, and an accidental overdose could be fatal.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Colchicine is used to induce learning and memory impairments in rodents for dementia models [5]. This typically involves intracerebroventricular injections of colchicine directly into the CNS of the animals, which impairs neuronal function by disrupting microtubule dynamics. At standard therapeutic doses, colchicine typically does not accumulate in the CNS, and exerts its impacts peripherally [11]. It primarily accumulates within peripheral immune cells, resulting in anti-inflammatory activity. Preclinical studies

also suggest that colchicine can impact autophagy pathways [12; 13]. By modulating autophagy, colchicine could potentially block the accumulation of toxic protein aggregates, such as TDP-43 [12]. Based on its purported modulation of inflammation and autophagy pathways, colchicine was tested in a pilot clinical trial in patients with amyotrophic lateral sclerosis (ALS) [12].

Colchicine was tested in a placebo-controlled Phase 2 RCT in 54 ALS patients taking riluzole (Co-ALS) (NCT03693781). Participants were treated with colchicine at a dose of 0.01 mg/kg or 0.005 mg/kg per day (in a 70 kg adult, this translates to 0.7 mg and 0.35 mg, respectively) for 30 weeks, and followed for 54 weeks. The trial did not achieve its primary outcome of a significant slowing of disease progression based on no more than a 4-point decline on the ALS Functional Rating Scale - Revised (ALSFRS-R) scores at the end of 30 weeks, though there was a trend in favor of colchicine [14]. At the 0.005 mg/kg dose, the endpoint was achieved by approximately one-third (33.3%) of participants, in comparison to 13.3% in the placebo group (95% CI 0.39 to 40.42, p=0.416). A similar trend was not observed with the 0.01 mg/kg dose, in which only 7.1% of participants achieved a positive response. A greater percentage of patients experienced disease slowing at the 0.005mg/kg dose during treatment (mean difference: 0.53, 95% CI 0.07 to 0.99, p=0.022) and after treatment (mean difference 0.46, 95% CI 0.07 to 0.84, p=0.020), relative to placebo. There were also non-significant trends toward better survival and preserved respiratory function at the 0.005 mg/kg dose. Levels of neurotoxic insoluble TDP-43 increased in placebo patients, but remained stable or decreased in colchicine-treated patients. There were no significant differences on biomarkers related to neurodegeneration, inflammation, or autophagy.

APOE4 interactions: Not established

Aging and related health concerns: Low dose colchicine protects against major adverse cardiovascular events as a secondary prevention strategy, likely through its anti-inflammatory activity. It may also reduce the risk of liver cancer.

Types of evidence:

- 3 meta-analyses of RCTs assessing colchicine for major adverse cardiovascular events
- 2 meta-analyses of RCTs assessing colchicine for stroke prevention
- 2 Phase 3 RCTs for low-dose colchicine in cardiovascular disease
- 1 Phase 3 RCT for low-dose colchicine in prevention of atrial fibrillation
- 1 Phase 3 RCT for low-dose colchicine in prevention of recurrent stroke

- 3 benefits analyses of low dose colchicine in cardiovascular disease
- 2 subset analyses of low-dose colchicine in patients with Type 2 diabetes
- 3 trials assessing lower dose colchicine regimens for gouty arthritis
- 1 retrospective study assessing the relationship between colchicine and liver cancer risk
- Numerous laboratory studies

Cardiovascular disease: BENEFIT FOR SECONDARY PREVENTION
Based on the results of the COLCOT and LoCoDo2 trials, European and American guidelines were updated to recommend the use of low-dose colchicine, at a dose of 0.5 mg per day, for secondary prevention of cardiovascular disease. The 2021 European Society of Cardiology (ESC) guidelines recommend low-dose colchicine (0.5 mg/day) as a Class 11b intervention for secondary prevention in patients with cardiovascular disease with inadequately controlled risk factors [15]. The FDA approved low-dose colchicine (0.5 mg/day) in 2023 for secondary prevention in patients with coronary artery disease [10]. It is the first anti-inflammatory agent approved for cardiovascular disease.

The COLCOT trial (NCT02551094) tested the ability of low-dose colchicine (0.5 mg/day) to protect against adverse cardiovascular events when administered within 30 days of a prior myocardial infarction in a cohort of 4,745 patients [16]. This study assessed the ability of colchicine to offer benefit on a background of medications used to manage cardiovascular risk, such that 98 to 99% of participants were taking aspirin, a different antiplatelet agent, and/or a statin. The primary end point of the trial was a composite of death from cardiovascular causes, resuscitated cardiac arrest, myocardial infarction, stroke, or urgent hospitalization for angina leading to coronary revascularization. The trial was designed based on a 7% event rate in the placebo group at 24 months, which was close to the observed event rate of 7.1% at a median follow-up of 22.6 months. In comparison, the event rate was only 5.5% in the colchicine group, such that there was a 23% reduction in these cardiovascular events with colchicine (HR: 0.77; 95% CI 0.61 to 0.96; P=0.02). In terms of the individual components, trends toward reductions were observed for death from cardiovascular causes, (HR: 0.84, 95% CI 0.46 to 1.52), resuscitated cardiac arrest (HR: 0.83, 95% CI 0.25 to 2.73), and myocardial infarction (HR: 0.91, 95% CI 0.68 to 1.21), while significant reductions were observed for stroke (HR: 0.26, 95% CI 0.10 to 0.70), and urgent hospitalization for angina leading to coronary revascularization (HR: 0.50, 95% CI 0.31 to 0.81).

The LoCoDo2 trial (ACTRN12614000093684) tested the ability of low-dose colchicine (0.5 mg/day) to prevent adverse cardiovascular events in a cohort of 5,522 patients with chronic stable coronary disease [17]. Similar to the COLCOT trial, colchicine was tested on the background of other medication, with

99.7% taking an antiplatelet agent or an anticoagulant, 96.6% taking a lipid-lowering agent, 62.1% taking a beta-blocker, and 71.7% taking an inhibitor of the renin–angiotensin system. The trial was designed based on a primary event rate, the composite of cardiovascular death, nonprocedural myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization, of 2.6% per year. The trial achieved its primary endpoint, with an event occurring in 9.6% of participants in the placebo group, but in only 6.8% of participants in the colchicine group with a median follow-up of 28.6 months (HR: 0.69, 95% CI 0.57 to 0.83; P<0.001). A similar benefit was observed on the secondary composite endpoint of cardiovascular death, spontaneous myocardial infarction, or ischemic stroke, with an event rate of 5.7% in the placebo group and 4.2% in the colchicine group (HR: 0.72, 95% CI 0.57 to 0.92; P = 0.007).

While these have been the largest and most compelling trials to date, cardiovascular benefits have been observed with colchicine in a variety of studies in participants with cardiovascular risk factors. Although benefits have been observed at several different doses, low-dose colchicine offers the best therapeutic profile. A network meta-analysis of 15 RCTs testing colchicine at one of three different dosing levels including a total of 13,539 patients with coronary artery disease found that the low dose regimen was most consistently associated with clinical cardiovascular benefit [18]. Network meta-analysis indicated that low-dose colchicine was associated with a significant reduction in major adverse cardiovascular events (MACE) (Risk Ratio [RR]: 0.51, 95% CI 0.32 to 0.83), recurrent myocardial infarction (RR: 0.56, 95% CI 0.35 to 0.89), recurrent stroke RR: 0.48, 95% CI 0.23 to 1.00), and hospitalization (RR 0.44, 95% CI 0.22 to 0.85). A meta-analysis of eight RCTs including 5,872 patients treated with different doses of colchicine after acute myocardial infarction also found that colchicine was associated with a reduced risk of MACE (RR: 0.56, 95% CI 0.48 to 0.67; P < 0.00001) [19]. Subgroup analysis indicated that the reduction in MACE was most prominent in studies using low-dose colchicine (0.5 mg/day), when the follow-up period was over one year, and when it was administered within three days after myocardial infarction. Within the subcategories of MACE, colchicine appears to offer greater protection against acute vascular events than against mortality. A meta-analysis of seven RCTs including 12,114 patients with coronary vessel disease found that colchicine was associated with significant reductions in the risk of urgent coronary revascularization (RR: 0.58, 95% CI 0.37 to 0.92), myocardial infarction, (RR: 0.75, 95% CI 0.62 to 0.90), and stroke (RR: 0.46, 95% CI 0.28 to 0.74), but was not with cardiovascular-related mortality (RR: 0.85, 95% CI 0.57 to 1.27), or all-cause mortality (RR: 1.14, 95% CI 0.76 to 1.69) [20].

One analysis examined the range of individual absolute benefits from low-dose colchicine according to patient risk profiles based on 10-year absolute risk reductions for MACE and MACE-free life-years gained [21]. Low-dose colchicine was compared to other secondary prevention interventions, including LDL-

cholesterol reduction to 1.4 mmol/L and systolic blood pressure lowering to 130 mmHg. The lifetime benefit for low-dose colchicine was estimated to be 2.0 (interquartile range [IQR] 1.6 to 2.5) MACE-free years, and 3.4 (IQR 2.6 to 4.2) MACE plus coronary revascularization (MACE+)-free life-years gained. The lifetime benefit for LDL-c lowering and systolic blood pressure lowering were calculated as 1.2 (IQR 0.6 to 2.1) and 0.7 (IQR 0.0 to 2.3) MACE-free life-years gained, respectively. Low-dose colchicine was estimated to be the most effective treatment for reducing MACE in 49% of patients, while intensive blood pressure–lowering therapy is likely to be the most effective in 28%, and intensive lipid-lowering therapy is likely to be most effective for 23% of patients. Low-dose colchicine was estimated to be the best, second best, and least effective strategy in 48.7%, 40.9%, and 10.4% of patients, respectively, based on the estimated gain in MACE-free life expectancy. Low-dose colchicine may be particularly useful in patients unable to reach or maintain the recommended LDL-c and blood pressure targets. The addition of low-dose colchicine is estimated to exceed the benefits observed with lipid and blood pressuring lowering therapies alone. The median estimated gains in life expectancy for the combination of low-dose colchicine, LDL-c reduction to 1.4 mmol/L, and systolic blood pressure reduction to 130 mmHg were 4.0 (IQR 2.9 to 5.5) MACE-free years, and 6.6 (IQR 4.6 to 9.5) MACE+-free years. A time to benefit analysis based on pooled data from four RCTS including 11,594 participants with cardiovascular disease estimated that it took 11 months (95 % CI 0.59 to 21.3) of colchicine treatment to prevent on incidence of MACE in 100-colchicine-treated patients [22].

A cost effectiveness study of low-dose colchicine for patients with chronic coronary disease in the Netherlands estimated that low-dose colchicine would add 0.04 quality adjusted life-years (QALY) compared with standard of care [23]. There was a 96% and 94% chance of being cost effective, from a societal and healthcare perspective, respectively, when using a willingness to pay of €50,000/QALY, as long as annual costs for low-dose colchicine do not exceed €221 per patient.

Mechanism: The cardiovascular benefits of colchicine are expected to stem from its anti-inflammatory properties [24]. Colchicine preferentially accumulates in neutrophils and inflammatory leukocytes. By interfering with microtubule dynamics, it blocks the cytoskeletal reorganization required for leukocyte activation and migration in response to inflammatory stimuli. Colchicine has also been shown to inhibit activation of the NLRP3 inflammasome, and downstream production of IL-1β, in preclinical models of atherosclerosis [25]. In particular, colchicine inhibited the uptake of cholesterol crystals by macrophages, thereby preventing cholesterol crystal-induced activation of the NLRP3 in macrophages as well as the formation of foam cells. This may be related to the colchicine-mediated downregulation of the oxidized LDL receptor, CD63, on macrophages. Low dose

colchicine was also found to protect against chemotherapy-related cardiotoxicity in a hamster model by facilitating autolysosome degradation, leading to the clearance of damaged mitochondria and reduction of reactive oxygen species [13].

There are efforts underway to determine the population of patients that are most likely to benefit from low-dose colchicine therapy. As an anti-inflammatory agent, it is expected that individuals with an elevated inflammatory profile would be most likely to achieve cardiovascular benefit.
Several trials have assessed the potential impact of colchicine to systemic inflammation by measuring blood levels of C-reactive peptide (CRP), however, the results have been inconsistent across trials, which may be related to differences in the baseline characteristics of the study populations. A combined analysis using individual patient paired pre and post samples (n=429) from the COLCOT and LoDoCo-MI trials testing low-dose colchicine (0.5 mg/day) in following acute myocardial infarction found that levels of high-sensitivity CRP (hs-CRP) were not significantly different when considered as a continuous variable, but colchicine use was associated with higher odds of having hs-CRP values ≤1.0 mg/L compared to placebo (OR: 1.64, 95% CI 1.07 to 2.51) [26]. The role of low-dose colchicine in reducing hs-CRP levels will be examined more extensively in the COLOR-ACS trial (NCT05250596), which is evaluating the effects of low-dose colchicine in combination with high-dose atorvastatin on inflammatory markers in patients with non-ST-elevation acute coronary syndrome [27].

***Type 2 diabetes**:* Patients with T2D and coronary artery disease have an increased risk of MACE, which is thought to be related to higher levels of vascular inflammation [28]. Analyses from the COLCOT and LoCoDo2 trials have examined whether the presence of T2D affects the cardiovascular benefit profile from low-dose colchicine. The analysis from the COLCOT study included 959 patients with T2D, with 462 assigned to colchicine and 497 assigned to placebo [28]. The intention-to-treat analysis found that similar to the overall cohort, the colchicine treatment was associated with fewer adverse cardiovascular events (HR: 0.65; 95% CI 0.44 to 0.96; P = 0.03), such that the effect of colchicine on the primary outcome was not significantly affected by the presence or absence of diabetes. The analysis from the LoCoDo2 trial included 1,007 patients with coronary artery disease and T2D at baseline [29]. This group tended to have a greater burden of cardiovascular risk factors relative to the overall study population. Consistent with this, T2D patients in the placebo group experienced a higher rate of adverse cardiovascular events (MACE+) relative to those without diabetes (13% vs 8.8%). Similar to what was seen with the COLCOT trial, there was no significant interaction between diabetes status and treatment effect. Additionally, there was a trend toward a reduction in cases of newly onset T2D with colchicine (1.5% vs 2.2%).

The impact of low-dose colchicine on inflammatory markers (hs-CRP) in patients with coronary artery disease and T2D and a heighted inflammatory response based on baseline white blood cell counts will be further explored in a Phase 2 trial (UMIN000029170) [24].

Atrial fibrillation: POTENTIAL BENEFIT FOR PREVENTION

The development of atrial fibrillation, which is a common form of irregular heartbeat, is associated with inflammation [30]. Atrial remodeling, fibrosis, and coagulation in response to cardiac damage are thought to be the primary drivers of atrial fibrillation, and inflammation can exacerbate these processes. Evidence suggests that colchicine may be able to reduce the risk of atrial fibrillation, at least in some contexts, likely through its anti-inflammatory properties [31]. It may also impact coagulation by reducing the formation of neutrophil-platelet aggregates through its inhibition of NETosis, the formation of neutrophil extracellular traps [32].

A meta-analysis of 17 RCTs including 16,238 participants examined the efficacy of colchicine for the prevention of atrial fibrillation [31]. The included trials tested a dose range from 0.5 mg to 1.2 mg, and treatment duration from five days to three months. In the combined analysis, there were fewer incidences of atrial fibrillation in colchicine treated patients (6.6%) relative to placebo treated patients (9.0%) (RR: 0.75, 95%CI 0.68 to 0.83, P < 0.001). Benefits were observed for short-term, medium term, and long-term outcomes. In subgroup analyses, benefits were observed for all tested age groups, for the prevention of first onset atrial fibrillation, as well as for recurrent atrial fibrillation. Benefits were observed across the tested dose range and duration. Colchicine use was associated with a lower risk of atrial fibrillation in the context of pulmonary vein isolation/ablation (RR: 0.66, 95% CI 0.54 to 0.81) or cardiac surgery (RR: 0.63, 95% CI 0.52 to 0.75), but not for non-cardiac thoracic surgery (RR:0.85, 95% CI 0.66 to 1.10). The latter finding is driven by the outcome of the Phase 3 COP-AF trial (NCT03310125) which tested the ability of colchicine at a dose of 0.5 mg twice per day for ten days starting within four hours prior to major non-cardiac thoracic surgery in 3,209 participants aged 55 and over [33]. Colchicine was not associated with a lower incidence of clinically important perioperative atrial fibrillation (6.4% vs 7.5%) (HR: 0.85, 95% CI 0.65 to 1.10; absolute risk reduction: 1.1%, 95% CI -0.7 to 2.8; P=0.22) or myocardial injury after noncardiac surgery (18.3% v 20.3%) (HR: 0.89, 0.76 to 1.05; absolute risk reduction: 2.0%, -0.8 to 4.7; P=0.16), the co-primary efficacy endpoints, relative to placebo. However, it did show a small, but statistically significant, reduction on the composite of the two endpoints (22.4% vs. 25.9%) (HR: 0.84, 95% CI 0.73 to 0.97). The overall event rate of the study was lower than anticipated, which suggests that it may have been underpowered to detect a small, but clinically meaningful effect. This trial also highlights that the ability of colchicine to reduce the risk of perioperative atrial fibrillation may depend on the type of surgery, such as whether inflammation is the

primary driver of risk, as well as the ability of colchicine to adequately dampen the inflammatory response and associated atrial remodeling in that surgery setting.

Stroke: POTENTIAL BENEFIT FOR PREVENTION IN SOME HIGH-RISK POPULATIONS

Clinical trials have found that low-dose colchicine reduces rates of MACE in populations with cardiovascular disease. Stroke is included within the MACE composite, and when the individual components were assessed, most studies also found significant reductions in recurrent stroke rates [18]. A meta-analysis of four RCTs including 5,553 patients with a history of cardiovascular disease found that colchicine was associated with a reduced risk for incident stroke during the follow-up period (RR: 0.31, 95% CI 0.13 to 0.71) [34]. Similarly, another meta-analysis of six RCTs with a mean follow-up period of two years including 11,870 participants assessing stroke prevention with colchicine in patients with coronary artery disease also found that colchicine was associated with a lower risk of stroke (RR: 0.49, 95% CI 0.31 to 0.80; P = 0.004) [3].

The Phase 3 CONVINCE trial tested the ability of low dose colchicine (0.5 mg/day) to reduce rates of recurrent ischemic stroke and cardiovascular events in patients with non-severe, non-cardioembolic stroke and transient ischemic attack [35]. The primary analysis included 3,144 patients, 88% of which had a stroke as their qualifying event, with a median NIHSS score of 1. During the median follow-up of 34 months, there was no significant difference in rates of recurrent ischemic stroke, myocardial infarction, cardiac arrest, or hospitalization with unstable angina, with the primary endpoint occurring in 9.8% of colchicine-treated participants compared with 11.8% of those receiving standard care alone (adjusted HR: 0.84, 95% CI 0.68 to 1.05, P=0.12) [36] (tctMD). Secondary analyses trended toward benefits with colchicine, and those with established coronary disease showed the greatest benefit. CRP levels were reduced with colchicine treatment, indicative of its anti-inflammatory effects. It is thought that colchicine may be most relevant for patients with atherosclerosis due to the role of vascular inflammation, and future studies may need to distinguish patients by stroke subtype. The lack of significant benefit on the primary endpoint may have been related to underpowering, as 8% fewer outcomes occurred than anticipated in the trial design. Additionally, there was a high degree of non-compliance with colchicine, and significant differences favoring colchicine were observed on some endpoints using an on-treatment analysis. While the CONVINCE trial alone did not show benefit, a meta-analysis combining the results of this trial with four prior trials in which CONVINCE provides 80% of the weight, found colchicine to be associated with a significantly lower risk of ischemic stroke (RR: 0.73, 95% CI 0.58 to 0.90).

Together these studies suggest that low-dose colchicine is likely to offer preferential benefit on cardiovascular and cerebrovascular outcomes in distinct subpopulations of patients, which have yet to be clearly defined.
Colchicine was tested in a pilot open-label trial for its ability to reduce inflammation following an acute minor ischemic stroke or transient ischemic attack [37]. Participants (n=39) were randomized within 24 h after symptom onset to one of four dosing groups for 14 days ranging from 0.5 mg/day to those containing a higher loading dose (from 1-3 mg) followed by a maintenance dose (0.5-1 mg). Blood levels of hs-CRP were reduced from baseline with colchicine, with no clear dose effect. No significant effect was observed on IL-6 levels.

Cancer: POTENTIAL PROTECTION AGAINST LIVER CANCER IN HIGH-RISK PATIENTS
Colchicine exerts anti-cancer properties in a variety of cancer lines in cell culture stemming from its microtubule modulating properties [38]. Cell division requires microtubule reorganization, thus actively dividing cells, such as rapidly proliferating cancer cells, are sensitive to cell arrest upon exposure to colchicine.
A retrospective study in Taiwan assessed the association between colchicine use and liver cancer (hepatocellular carcinoma) in patients at high risk for liver cancer based on a diagnosis with chronic hepatitis, stemming from Hepatitis B and C, or fatty liver disease [38]. The study compared 10,353 colchicine users with 10,353 non-users and assessed two decades of medical data. The study found a 19% reduction in liver cancer risk (Odds Ratio [OR]: 0.81, 95% CI 0.69 to 0.96) with colchicine use, with a potential dose-response relationship of greater protection with more prolonged use.

Gout: BENEFIT
Colchicine is FDA approved for the prevention and treatment of acute gout attacks (gouty arthritis). Inflammation from the buildup of uric acid is the main driver of gout attacks, thus colchicine mitigates these attacks through its anti-inflammatory properties [39]. Unlike urate lowering therapy, colchicine does not impact the formation of the uric acid crystals or other disease etiology. There has been an evidence-based shift in recent years from the original high dose regimen to a lower dose regimen stemming from the results of the AGREE trial (NCT00506883) in which patients receiving an oral 1.2 mg loading dose followed by a 0.6 mg dose within one hour achieved a similar degree of pain reduction during an acute gout flare as patients receiving the high-dose regimen (4.8 mg total over 6 hours) [40]. An RCT in 80 patients with acute crystal-associated arthritis tested the requirement for a loading dose [41]. Participants receiving a non-loading regimen of 0.6 mg followed by another 0.6 mg after 12 hours showed a similar degree of pain reduction compared to those receiving a loading regimen of 1.2 mg

followed by 0.6 mg after one hour and another 0.6 mg after 12 hours. Colchicine is most effective when administered close to the onset of the gout flare. The open label COLCHICORT trial (NCT03128905) compared the efficacy of colchicine (1.5 mg on day 1 followed by 1 mg on day 2) with oral prednisone (30 mg on days 1 and 2) on joint pain in 111 patients aged 65 and older admitted to the hospital with acute calcium pyrophosphate crystal arthritis [42]. Short-term efficacy on joint pain was similar between the two treatments, though prednisone appeared to offer preferential benefit in the context of knee joint pain relative to other joints.

Safety: Low dose colchicine is generally well tolerated. Gastrointestinal events are the most common side effects, and more prevalent at higher doses. The toxicology profile is dose dependent, as high doses can be lethal.

Types of evidence:

- 2 meta-analyses of RCTs of colchicine for cardiovascular disease
- 1 systematic review of long-term safety with low dose colchicine
- 1 meta-analysis of RCTs assessing safety of colchicine
- 1 systematic review of case reports for myopathy
- 3 reviews of colchicine safety and drug interaction concerns
- 2 safety analyses from LoCoDo2 trial
- 1 pharmacokinetic study of low-dose colchicine in healthy males
- Numerous laboratory studies

Colchicine has a dose dependent safety profile [11]. There is a narrow therapeutic dose window in which colchicine shows clinical efficacy in the context of inflammatory conditions, but aside from gastrointestinal side effects, is generally well-tolerated. Doses in excess of the therapeutic range are associated with a variety of toxicities, and can be fatal. Current dosing guidelines range from 0.5 to 2.4 mg per day, though prior guidelines used even higher doses of 3 to 4.8 mg for acute indications. Lethal doses are those > 7 mg, however, due to pharmacokinetic variance, particularly in terms of bioavailability, the threshold for toxicity may be lower in some individuals [2].
The efficacy and toxicity of colchicine both stem from its effects on microtubule dynamics. Colchicine disrupts tubulin polymerization, which impacts cell structure, transport, and motility [2]. At high enough levels, colchicine will lead to cell arrest, as cell division is dependent on intact microtubule dynamics, ultimately resulting in multi-organ failure and death [43]. The cellular toxicity of colchicine at

therapeutic doses is limited because it is subject to efflux by the P-gp transporter. As a result, it preferentially accumulates in leukocytes, namely neutrophils, which lack this efflux pump. At therapeutic doses, colchicine is largely restricted to leukocytes, where it interacts with tubulin, which dampens the activity of these inflammatory cells [2]. The remaining low levels of uncomplexed colchicine in the serum are rapidly cleared. As a result, serum levels are not reflective of pharmacodynamic responses related to efficacy. They are, however, an important measure for safety. As doses increase, the leukocytes become saturated, resulting in much higher levels in the serum.

A pharmacokinetic study in 21 healthy Japanese male volunteers confirmed that low doses of 0.25 mg or 0.5 mg exhibited a similar profile as had been characterized for higher doses, in that plasma levels peaked by 1-2 hours, with a terminal half-life around 24 hours, while leukocyte levels peaked at 8-24 hours, and remained detectable for at least 168 hours [44].

The safe upper limit of colchicine in the serum is typically considered to be 3 mg/L [2]. Conditions that could lead to colchicine exceeding this limit include high cumulative dosing, renal or hepatic impairment, or through drug interactions [10].

Colchicine is generally not recommended in individuals with renal or hepatic impairment because colchicine is metabolized by the liver and cleared by the kidney [10]. Reduced metabolism/clearance results in elevated levels which could potentially lead to toxicity with cumulative dosing. Continuous low-dose colchicine should not be used in individuals with greater than stage 3a renal impairment, as rare cases of bone marrow suppression and myotoxicity have been reported with colchicine use in this population [10]. The concerns with colchicine toxicity are most prominent at higher doses. Doses of 0.6 mg/day could exceed safe levels in those with renal impairment, but serum colchicine levels remain below the 3 mg/L limit at doses of 0.5 mg/day even in those with moderate renal impairment (eGFR ≥ 45mL/min/1.73 m^2) [2; 10].
Long-term safety from studies assessing low-dose colchicine (0.5 mg/day) in patients with cardiovascular disease suggest that with this dosing regimen, colchicine does not impair kidney or liver function [10]. A study of 1,776 participants from the LoCoDo2 trial taking low-dose colchicine for 2 to 4 years found that colchicine was not associated with significant changes in creatinine and BUN levels, but there were mild elevations in creatine kinase [45]. This was not associated with any change in renal function, and no differences were observed in the proportion of participants with renal impairment at baseline transitioning to a more severe stage. Similarly, mild elevations in alanine aminotransferase (ALT) (30 U/L vs. 26 U/L) were observed, but there were no significant differences in median levels of gamma-glutamyl

transpeptidase (GGT) or bilirubin [45]. Aside from not inducing harm, there is some evidence to suggest that colchicine may be renoprotective. A nested case–control study from Korea in in 3,085 patients exposed to colchicine compared with 11,715 age-matched controls found that colchicine exposure >90 days was associated with a reduced risk of progressive chronic kidney disease (adjusted OR: 0.77, 95% CI 0.61 to 0.96) [10].

Muscle toxicity has also been reported with colchicine, though cases are uncommon and typically occur in the context of renal impairment and drug interactions [11]. A systematic review of case reports including 143 cases of neuromyopathy, or myopathy associated with colchicine use at therapeutic doses found that 82% of cases were associated with either a significant comorbidity or a drug-interaction, with 40% of cases associated with both factors [46]. Renal disease was the most common comorbidity, while macrolide antibiotics were the most common strongly interacting drugs. The mean daily dose was 1.25±0.60, typically for gout, and 70% of cases resolved completely upon drug cessation. The risk for myotoxicity is thought to stem primarily from interactions with other drugs that contain a risk for myotoxicity rather than from colchicine itself. Muscular toxicity is a side effect of statins, and some statins, such as simvastatin, lovastatin, and atorvastatin, interact with colchicine, because they are CYP34A/P-gp substrates. Thus, high doses of both drugs could increase the risk for myotoxicity. Other classes of statins, such as pravastatin, fluvastatin, and rosuvastatin do not have this interaction, thus their use with colchicine would not be expected to increase the risk for myotoxicity or other side effects.

Colchicine has not been associated with increased risk for bleeding, deep vein thrombosis, or pulmonary embolism[10]. Although it interferes with neutrophil-platelet aggregation as part of its mechanism of action, it does not interfere with platelet-platelet aggregation, and thus does not impact clotting. Consistent with this, colchicine (0.6 mg/day) was safely used in combination with P2Y12 inhibitors (ticagrelor or prasugrel) in a trial of 200 patients with acute coronary syndrome undergoing percutaneous coronary intervention [47].

Across studies, the primary adverse effects associated with colchicine are gastrointestinal events, particularly diarrhea and nausea. These effects are dose-related and tend to subside in time. A meta-analysis of eight RCTs including 5,872 participants testing colchicine following acute myocardial infarction found that colchicine was associated with an increased risk of gastrointestinal events (RR: 2.99, 95% CI 1.14 to 7.82) [19]. However, this was driven by short-term use (≤5 days) (RR: 5.89, 95% CI 1.14 to 30.52) such that events occur shortly after drug initiation, but generally do not persist, as the risk was no longer significantly elevated with longer term (> 1 month) use (RR: 4.47, 95% CI 0.46 to 43.64).

The risk also increases with dose, as this analysis found that gastrointestinal events were significantly increased with a 1 mg dose (RR: 4.88, 95% CI 1.07 to 22.22), but not with a 0.5 mg dose (RR: 1.21, 95% CI 0.64 to 2.28). Similarly, a network meta-analysis including 15 RCTs testing colchicine at three different dosing levels found that high dose and loading dose regimens were associated with an increased risk for gastrointestinal events (RR: 2.84; 95% CI 1.26 to 6.24), while low doses (0.5 mg/day) did not elevate risk [18]. A systematic review of 35 RCTs, primarily testing colchicine for gout, liver cirrhosis, or pericarditis, including 8,659 participants found that gastrointestinal events were more prevalent with colchicine (17.6% vs 13.1%) (RR: 1.7, 95% CI 1.3 to 2.3), with diarrhea as the most common (RR: 2.4, 95% CI 1.6 to 3.7), but rates of liver toxicity, myotoxicity, hematological toxicity, and infections were not significantly elevated with colchicine relative to comparators [48].

In the COLCOT trial testing low dose (0.5 mg/day) colchicine in patients with acute myocardial infarction, overall rates of adverse events were similar between study arms [16]. Diarrhea was the most common adverse event with colchicine, but rates (9.7% vs 8.9%) were not significantly different from placebo. Pneumonia was a serious adverse event that occurred more frequently with colchicine (0.9% vs 0.4%). This is suggestive of an increased risk for infection, but a similar trend has not been observed in other studies.

In the LoCoDo2 trial testing low dose (0.5 mg/day) colchicine in patients with chronic coronary artery disease, gastrointestinal events were the most common reason for discontinuation during the run-in period prior to randomization [17]. No clinically relevant interactions were observed between low dose colchicine and statins. There was a higher rate of non-cardiovascular deaths in the colchicine group (HR:1.51, 95% CI 0.99 to 2.31), however, there was no specific cause associated with colchicine [49]. Rates of cancer and infection were similar across groups, and an age >65 was the only significant predictor associated with non-cardiovascular mortality in this cohort, suggesting the deaths may have been driven by age-related co-morbidities.

Drug interactions: Colchicine is a substrate for CYP34A and P-glycoprotein, thus it interacts with drugs that act as CYP34A/P-gp inhibitors or inducers [50]. It appears that inhibition of both CYP34A and P-gp is needed to substantially increase colchicine levels to a potentially toxic level, however, most CYP34A inhibitors also inhibit P-gp. CYP34A/P-gp inducers would be expected to reduce colchicine levels, and case reports with rifampin and carbamazepine suggest that this reduction occurs in patients. Patients with renal or hepatic impairment are most vulnerable to toxicity stemming from drug interactions with CYP34A/P-gp modulators. The risks are also related to dose, as higher doses are more likely to veer into the toxic range, such that these risks can be mitigated through dose reductions.

According to Drugs.com, there are 286 drug interactions, including 108 major interactions. Some major drug classes that can raise levels of colchicine include imidazole antifungals, HIV antiretroviral protease inhibitors, macrolide antibiotics, calcium channel blockers, and the antidepressant nefazodone (WebMD, GoodRx). The use of colchicine with some classes of drugs with a risk of muscle damage can further increase that risk, including the heart medication digoxin, and anti-cholesterol medication, including some statins (including simvastatin, lovastatin, and atorvastatin) and fibrates. Grapefruits and grapefruit juice should be avoided when taking colchicine because grapefruit contains furanocoumarins, which act as CYP34A inhibitors, which could interfere with the metabolism of colchicine, leading to elevated levels (Drugs.com).

Sources and dosing:

In 2023, the FDA approved the use of low-dose colchicine for cardiovascular inflammation in the form of a 0.5 mg oral tablet taken once daily, marketed as Locodo from Agepha Pharma. The brand name of colchicine used for gout and familial Mediterranean fever is Colcrys®, which is distributed by Takeda. Generic versions are also available. There are slight variations in the expert recommendations regarding the dosing scheme for acute gout flares. The European League Against Rheumatism (EULAR) recommends a loading dose of 1 mg followed by 0.5 mg on day one of the gout flare [51]. The American guidelines recommend 1.2 mg as a loading dose followed by 0.6 mg one hour later (FDA Label)[43]. Dosing for the prevention of flares is 0.5 or 0.6 mg once or twice per day. The dosing for familial Mediterranean fever depends on age. For adults, the recommended dose is 1.2 to 2.4 mg per day taken as a single dose or divided into two doses.

Research underway:

There are several trials testing low dose colchicine primarily for cardiovascular indications (Clinicaltrials.gov). Trials will assess the impact of low dose colchicine for improving exercise capacity in patients with heart failure, the inhibition of abdominal aortic aneurysm growth, reduction of residual vascular risk in patients with peripheral artery disease, treatment of acute coronary syndromes, prevention of acute atherothrombotic ischemic stroke, effects on platelet reactivity, reduction of inflammation in acute coronary syndrome, prevention of vascular inflammation in non-cardio embolic stroke, reducing inflammation after STEMI, reducing recurrent in-stent restenosis, preventing ischemic stroke due to atherosclerosis in combination with ticagrelor, and the reduction of MACE and ischemic stroke in combination with rivaroxaban. Colchicine is also being tested for cancer-related indications

including, the prevention of chemotherapy-induced cardiotoxicity, the prevention of radiation-induced dermatitis, and for the suppression of pro-tumorigenic inflammation in patients with urothelial cancer and other solid tumors.

Search terms:

Pubmed, Google: Low dose colchicine

- cerebrovascular, brain, cardiovascular, stroke, clinical trial, meta-analysis, safety

Websites visited for Low-dose colchicine:

- Clinicaltrials.gov
- Drugs.com (Colchicine, Locodo)
- WebMD.com
- PubChem
- DrugBank.ca

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