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Ischemic Heart Disease

Time-to-treatment initiation of colchicine and cardiovascular outcomes after myocardial infarction in the Colchicine Cardiovascular Outcomes Trial (COLCOT)

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Aims The COLchicine Cardiovascular Outcomes Trial (COLCOT) demonstrated the benefits of targeting inflammation after myocardial infarction (MI). We aimed to determine whether time-to-treatment initiation (TTI) influences the beneficial impact of colchicine.

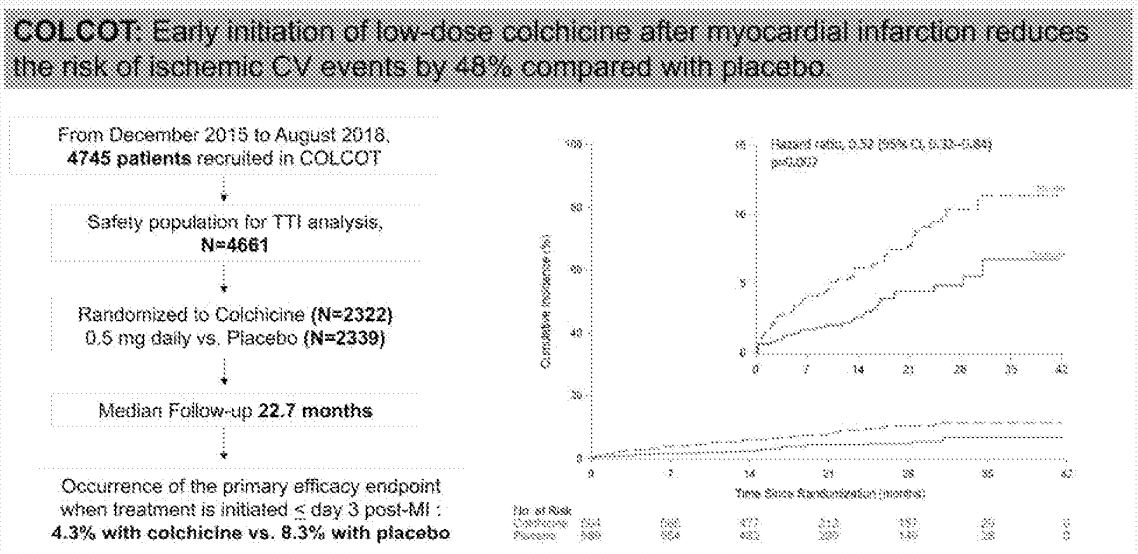
Methods and results In COLCOT, patients were randomly assigned to receive colchicine or placebo within 30 days post-MI. Time-to-treatment initiation was defined as the length of time between the index MI and the initiation of study medication. The primary efficacy endpoint was a composite of cardiovascular death, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina requiring coronary revascularization. The relationship between endpoints and various TTI (<3, 4–7 and >8 days) was examined using multivariable Cox regression models. Amongst the 4661 patients included in this analysis, there were 1193, 720, and 2748 patients, respectively, in the three TTI strata. After a median follow-up of 22.7 months, there was a significant reduction in the incidence of the primary endpoint for patients in whom colchicine was initiated < Day 3 compared with placebo [hazard ratios (HR) = 0.52, 95% confidence intervals (CI) 0.32–0.84], in contrast to patients in whom colchicine was initiated between Days 4 and 7 (HR = 0.96, 95% CI 0.53–1.75) or > Day 8 (HR = 0.82, 95% CI 0.61–1.11). The beneficial effects of early initiation of colchicine were also demonstrated for urgent hospitalization for angina requiring revascularization (HR = 0.35),

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	all coronary revascularization (HR = 0.63), and the composite of cardiovascular death, resuscitated cardiac arrest, MI, or stroke (HR = 0.55, all $P < 0.05$).
Conclusion	Patients benefit from early, in-hospital initiation of colchicine after MI.
Trial Registration	COLCOT ClinicalTrials.gov number, NCT02551094.

Graphical Abstract



Keywords Cardiovascular inflammation • Time-to-treatment initiation • Colchicine • COLCOT • Inflammasome

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Introduction

Myocardial infarction (MI) is associated with an acute exacerbation of cardiovascular (CV) inflammation superimposed on the chronic atherosclerosis-related inflammatory process.[1] Intense inflammation observed at the time of an acute MI has been shown to be involved in the pathogenesis of post-infarction remodelling, with NLRP3 inflammasome activation playing a particularly important and deleterious role in this setting.[2–5] Colchicine is an inexpensive, orally administered, potent anti-inflammatory medication that was initially extracted from the plant autumn crocus. Its mechanism of action is through the inhibition of tubulin polymerization leading to effects on cellular adhesion molecules, inflammatory chemokines, and the inflammasome.[6–8] Colchicine at the low dose of 0.5 mg daily was shown to significantly reduce the risk of ischaemic CV events by 23% compared with placebo when initiated within the first 30 days after MI in the COLchicine Cardiovascular Outcomes Trial (COLCOT).[9]

Whether the timing of inflammation reduction after MI has a clinical impact is not known. Specifically, the importance of initiating colchicine immediately during the hospitalization for MI remains to be determined. We hypothesized that early initiation of inflammation reduction with colchicine is associated with greater clinical benefits after MI. Therefore, we aimed to determine whether TTI of colchicine influenced its beneficial impact on CV outcomes in COLCOT.

Methods

Study design and patient population

COLCOT was an international multicentre, randomized, double-blinded trial that randomly assigned patients to receive either low-dose colchicine

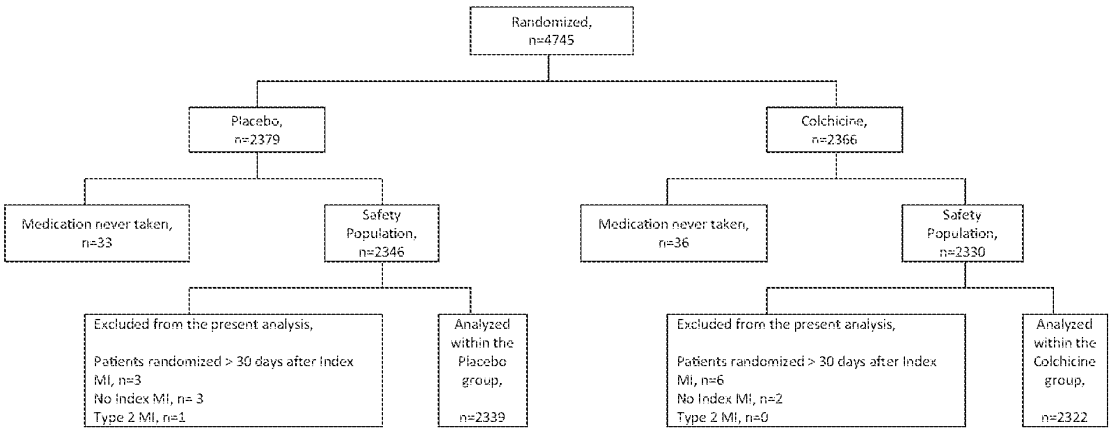


Figure 1 Subject disposition, flow chart diagram.

(0.5 mg once daily) or placebo. The study protocol and main results have been published.[9] Patients were considered eligible if they had a recent MI (<30 days). Main exclusion criteria were severe heart failure, reduced left ventricular ejection fraction (<35%), recent stroke (<3 months), type 2 MI, recent (<3 years), or planned coronary artery bypass graft (CABG), history of cancer (<3 years), and inflammatory bowel disease or chronic diarrhoea. All patients enrolled in the trial benefitted from percutaneous coronary intervention whenever indicated and guidelines-directed management of CV disease prior to randomization.[9] Clinical follow-up consisted of evaluations at 1 and 3 months after randomization and every 3 months thereafter. An independent clinical endpoint committee, blinded to trial-group assignment, adjudicated clinical endpoints. The trial was locally approved by the various institutional review boards, and all patients signed a written informed consent before enrolment.[9]

Efficacy endpoints

The primary efficacy endpoint was a composite of CV death, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina requiring coronary revascularization. The secondary endpoints consisted of the components of the primary efficacy endpoint, all-cause death, and a composite of CV death, resuscitated cardiac arrest, MI, or stroke.[9] Exploratory endpoints included all coronary revascularizations, including both elective and urgent coronary revascularizations.[9]

Cut-offs for time-to-treatment initiation of colchicine

Three different cut-offs for TTI were used in order to determine the association between early initiation of therapy and clinical outcomes. These cut-offs were determined based on the usual journey of patients with MI.[10,11] The first 30-day post-MI timeline was divided into three independent periods of time and analysed as such: from Day 0 to 3, referring to in-hospital management; from Day 4 to 7, referring to early post-discharge period, and from Day 8 to 30, referring to late post-discharge period.

Statistical analysis

Data were centrally analysed by an independent academic biostatistics centre at the Montreal Health Innovations Coordinating Center.[9] The present analysis was conducted amongst patients who received at least one dose of the study medication (referred to as the safety population in the main protocol,[9] *Figure 1*). Time-to-treatment initiation was defined as the length of time in days between the index MI and the initiation of the study medication, and three specific cut-offs were analysed (≤ Day 3, Days 4 to 7, and ≥ Day 8). Early initiation of therapy was defined as TTI ≤3 days. Baseline characteristics were summarized using counts and percentages for categorical variables and mean ± standard deviation (SD) for continuous variables. For each baseline characteristic, comparisons were made using ANOVA for continuous variables and Chi-Square test for categorical variables according to TTI strata. Analyses of the efficacy endpoints, expressed as time to event, were conducted according to TTI. Adjusted hazard ratios (HR) along with 95% confidence intervals (CI) were calculated from stepwise multivariable Cox regression models adjusted for the same covariates that were used in the main analysis of the COLCOT trial.[9] All statistical tests were two-sided and conducted at the 0.05 significance level. Statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

Results

Baseline characteristics

Of the 4745 patients randomized in COLCOT, 4661 were included in the present analysis (colchicine, $N = 2322$; placebo, $N = 2339$) (*Figure 1*). Overall, patients were randomized at 13.5 ± 10.1 days following the index MI, 25.6% between Days 0 and 3, 15.4% between Days 4 and 7 and 59.0% at Day 8 or after. Baseline characteristics were similar between the colchicine and placebo groups (*Table 1*). Patients were mostly men (81.0%) with a mean age of 60.5 years, 20.2% had diabetes, 51.0% had a history of hypertension, 29.7% were active smokers, and 16.8% had had a prior percutaneous coronary intervention (PCI). Background therapy included aspirin, a second

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Table 1 Baseline characteristics according to treatment allocation

Characteristics	All patients (*N* = 4661)	Colchicine group (*N* = 2322)	Placebo group (*N* = 2339)
Age (years), mean ± SD	60.5 ± 10.6	60.6 ± 10.6	60.5 ± 10.6
Male sex, no. (%)	3774 (81.0%)	1861 (80.1%)	1913 (81.8%)
BMI (kg/m^2), mean ± SD	28.3 ± 4.7	28.2 ± 4.8	28.4 ± 4.7
Current smoking, no./total no. (%)	1382/4659 (29.7)	694/2322 (29.9%)	688/2337 (29.4%)
History of hypertension, no. (%)	2377 (51.0)	1160 (50.0)	1217 (52.0)
History of diabetes, no. (%)	942 (20.2)	451 (19.4)	491 (21.0)
Prior MI, no. (%)	751 (16.1)	360 (15.5)	391 (16.7)
Prior PCI, no. (%)	783 (16.8)	382 (16.5)	401 (17.1)
Prior CABG, no. (%)	146 (3.1)	66 (2.8)	80 (3.4)
Prior HF, no. (%)	90 (1.9)	48 (2.1)	42 (1.8)
Prior stroke or TIA, no. (%)	119 (2.6)	53 (2.3)	66 (2.8)
PCI associated with the index event, no. (%)	4336 (93.0)	2154 (92.8)	2182 (93.3)
Medication use, no. (%):			
Aspirin	4605 (98.8)	2291 (98.7)	2314 (98.9)
Other anti-platelet agent	4567 (98.0)	2267 (97.6)	2300 (98.3)
Statin	4615 (99.0)	2297 (98.9)	2318 (99.1)
Beta-blocker	4143 (88.9)	2077 (89.4)	2066 (88.3)
TTI 0–3 days, no. (%)	1193 (25.6)	604 (26.0)	589 (25.2)
TTI 4–7 days, no. (%)	720 (15.4)	364 (15.7)	356 (15.2)
TTT ≥8 days, no. (%)	2748 (59.0)	1354 (58.3)	1394 (59.6)
Time from index MI to randomization (days), mean ± SD	13.5 ± 10.1	13.5 ± 10.1	13.5 ± 10.0
Time from Index MI to PCI (days), mean ± SD	1.4 ± 2.9	1.4 ± 2.9	1.4 ± 2.9
Time from PCI to randomization (days), mean ± SD	11.9 ± 9.9	11.9 ± 9.9	11.9 ± 9.9

Data were missing on the following characteristics: age (assessed according to date of birth; see below) for 431 patients (213 in the colchicine group and 218 in the placebo group) and body-mass index (the weight in kilograms divided by the square of the height in meters) for 5 (1 and 4 patients, respectively).
Date of birth was not required field because it was considered in some countries to be sensitive data that could allow for the identification of patients.
For statistical reporting, missing information regarding the day of birth was replaced by 15, and missing information regarding the month and day of birth was replaced by 1 July.
CABG, coronary artery bypass graft surgery; HF, heart failure; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack.

anti-platelet agent and a statin in 98.8%, 98.0%, and 99.0% of patients, respectively. The vast majority of patients (93.0%) underwent PCI during the index hospitalization, with no difference in terms of time to PCI between the two groups.

Baseline characteristics according to TTI strata are shown in *Table 2*. Patients in whom therapy was initiated between Days 0 and 3, when compared with those at Days 8–30, were younger (59.1 ± 10.8 vs. 61.3 ± 10.4 years) and more often active smokers (43.8% vs. 20.2%), had less commonly hypertension (41.1% vs. 56.2%), and diabetes (17.4% vs. 22.0%) but underwent more often PCI associated with the index MI (95.8% vs. 91.3%), all $P < 0.05$.

Effects of time-to-treatment initiation on the primary efficacy endpoint

The effects of colchicine on the primary endpoint according to TTI are shown in *Table 3* and *Figure 2*. A primary endpoint event occurred in 4.3% of patients in the colchicine group, as compared with 8.3% of those in the placebo group when TTI was between Days 0 and 3 (*N* = 1193, HR = 0.52, 95% CI 0.32–0.84, *P* = 0.007, *Figure 3A*). Corresponding rates were 6.0% and 5.9% when TTI was between Days 4 and 7 (*N* = 720) and 5.7% and 7.1% when TTI was on Day 8 or after (*N* = 2748), but these differences between groups did not reach statistical significance. *Table 3* also shows the percentages of patients with events and the hazard ratios for the components of the primary endpoint, including CV death (HR = 1.04, 95% CI 0.15–7.37), resuscitated cardiac arrest (HR = 0.33, 95% CI 0.03–3.20), MI (HR = 0.58, 95% CI 0.32–1.05), stroke (HR = 0.21, 95% CI 0.02–1.81), and urgent hospitalization for angina requiring coronary revascularization (HR = 0.35, 95% CI 0.14–0.88).

Effects of time-to-treatment initiation on the secondary and exploratory efficacy endpoints

The effects of colchicine on the secondary and exploratory endpoints are shown in *Table 3*. The secondary efficacy endpoint consisting of a composite of CV death, cardiac arrest, MI, or stroke occurred in 3.3% of the patients in the colchicine group and in 6.1% of those in the placebo group when TTI was between Days 0 and 3 (HR = 0.55; 95% CI, 0.32–0.95, *Figure 3B*). The exploratory endpoint of all coronary revascularizations occurred in 5.5% of patients in the colchicine

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Table 2 Baseline characteristics according to time-to-treatment initiation

Characteristics	TTI 0–3 days (*N* = 1193)	TTI 4–7 days (*N* = 720)	TTT ≥ 8 days (*N* = 2748)	*P*[a]	*P*[b]
Age (years), mean ± SD	59.1 ± 10.8	60.1 ± 11.0	61.3 ± 10.4	<0.0001	<0.0001
Male sex, no. (%)	980 (82.2)	605 (84.0)	2189 (80.0)	0.014	0.071
BMI (kg/m^2), mean ± SD	28.1 ± 4.6	27.7 ± 4.6	28.6 ± 4.8	<0.0001	0.004
Current smoking, no. (%)	522 (43.8)	306 (42.6)	554 (20.2)	<0.0001	<0.0001
History of hypertension, no. (%)	490 (41.1)	343 (47.6)	1544 (56.2)	<0.0001	<0.0001
History of diabetes, no. (%)	208 (17.4)	130 (18.1)	604 (22.0)	0.001	0.001
Prior MI, no. (%)	170 (14.3)	111 (15.4)	470 (17.1)	0.070	—
Prior PCI, no. (%)	182 (15.3)	107 (14.9)	494 (18.0)	0.035	0.037
Prior CABG, no. (%)	34 (2.9)	30 (4.2)	82 (3.0)	0.218	—
Prior HF, no. (%)	14 (1.2)	12 (1.7)	64 (2.3)	0.046	0.017
Prior stroke or TIA, no. (%)	20 (1.7)	21 (2.9)	78 (2.8)	0.084	—
PCI associated with the index event, no. (%)	1143 (95.8)	685 (95.1)	2508 (91.3)	<0.0001	<0.0001
Medication use, no. (%)					
Aspirin	1181 (99.0)	715 (99.3)	2709 (98.6)	0.219	—
Other anti-platelet agent	1177 (98.7)	708 (98.3)	2682 (97.6)	0.072	—
Statin	1188 (99.6)	708 (98.3)	2719 (98.9)	0.024	0.047
Beta-blocker	1093 (91.6)	642 (89.2)	2408 (87.6)	0.001	0.0003
Time from index MI to randomization (days), mean ± SD	2.1 ± 0.8	5.1 ± 1.1	20.8 ± 6.6	—	
Time from index MI to PCI (days), mean ± SD	0.4 ± 0.7	1.4 ± 1.8	1.8 ± 3.6	<0.0001	<0.0001
Time from PCI to randomization (days), mean ± SD	1.6 ± 0.9	3.7 ± 1.9	18.8 ± 7.3	<0.0001	<0.001

Data were missing on the following characteristics: age (assessed according to date of birth; see below) for 431 patients (213 in the colchicine group and 218 in the placebo group) and body-mass index (the weight in kilograms divided by the square of the height in meters) for 5 (1 and 4 patients, respectively).
Date of birth was not a required field because it was considered in some countries to be sensitive data that could allow for the identification of patients. For statistical reporting, missing information regarding the day of birth was replaced by 15, and missing information regarding the month and day of birth was replaced by 1 July.
CABG, coronary artery bypass graft surgery; HF, heart failure; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack.
[a]Group comparison TTI 0–3 vs. TTI 4–7 vs. TTI ≥ 8 days.
[b]Group comparison TTI 0–3 vs. TTI ≥ 8 days.

group, as compared with 8.7% of those in the placebo group when TTI was between Days 0 and 3 (HR = 0.63, 95% CI 0.40–0.97). There were six deaths in both study groups when TTI was between Days 0 and 3 (HR = 1.03, 95% 0.33–3.19).

Discussion

This analysis of COLCOT shows that early initiation of low-dose colchicine within the first 3 days after MI is associated with a reduction of 48% in the risk of the primary endpoint consisting of a composite of CV death, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina requiring coronary revascularization, in comparison with placebo. This result was due to a lower incidence of MIs, strokes, and urgent hospitalizations for angina leading to coronary revascularization. The secondary efficacy endpoint consisting of a composite of CV death, resuscitated cardiac arrest, MI, or stroke was also significantly reduced by 45% with early initiation of low-dose colchicine. The benefits were more marked when treatment was initiated within the first 3 days after MI, as compared with between Days 4 and 30, supporting the strategy of in-hospital initiation of colchicine in order to improve CV outcomes post-MI.

Acute inflammatory response following myocardial infarction

Convincing evidence converge towards inflammation as a key factor in CV disease progression and exacerbation.[12] In the acute phase of MI, cardiomyocyte necrosis generates damage-associated molecular patterns, which in turn activate the complement cascade and stimulate toll-like receptor and interleukin-1 signalling.[13,14] These factors trigger an intense inflammatory response that may lead to adverse myocardial remodelling[3] and in which activated inflammasomes within myocardial fibroblasts play a crucial role.[2,3,5] Furthermore, an acute systemic inflammation response has been demonstrated in patients with recent MI[15,16] and associated with infarct size.[17] Colchicine binds to tubulin and prevents microtubule polymerization, consequently reducing inflammasome activation and pro-inflammatory cytokine release. Colchicine concentrates preferentially in white blood cells, thus exerting its anti-inflammatory effects even at low doses.[18] The importance of early initiation of colchicine on CV outcomes after MI in COLCOT is compatible with an effect on innate immune cells.[17] Short-term anti-inflammatory therapy with colchicine was also associated with smaller infarct size and reduced inflammatory response in a pilot study of patients with STEMI undergoing primary PCI.[19]

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Table 3 Efficacy endpoints according to time-to-treatment initiation (*N* = 4661, colchicine vs. placebo)

Endpoints	TTI 0–3 days, *N* = 1193 Colchicine vs. placebo, no. (%) HR (95% CI); *P*	TTI 4–7 days, *N* = 720 Colchicine vs. placebo, no. (%) HR (95% CI); *P*	TTI ≥ 8 days, *N* = 2748 Colchicine vs. placebo, no. (%) HR (95% CI); *P*
Primary composite endpoint	26 (4.3%) vs. 49 (8.3%) 0.52 (0.32–0.84); *P* = 0.007	22 (6.0%) vs. 21 (5.9%) 0.96 (0.53–1.75); *P* = 0.896	77 (5.7%) vs. 99 (7.1%) 0.82 (0.61–1.11); *P* = 0.200
CV death	2 (0.3%) vs. 2 (0.3%) 1.04 (0.15–7.37); *P* = 0.970	2 (0.5%) vs. 4 (1.1%) 0.45 (0.08–2.46); *P* = 0.356	15 (1.1%) vs. 18 (1.3%) 0.89 (0.45–1.76); *P* = 0.734
Resuscitated cardiac arrest	1 (0.2%) vs. 3 (0.5%) 0.33 (0.03–3.20); *P* = 0.340	2 (0.5%) vs. 1 (0.3%) 1.90 (0.17–20.95); *P* = 0.600	2 (0.1%) vs. 2 (0.1%) 1.02 (0.14–7.22); *P* = 0.986
MI	17 (2.8%) vs. 29 (4.9%) 0.58 (0.32–1.05); *P* = 0.071	16 (4.4%) vs. 9 (2.5%) 1.67 (0.74–3.78); *P* = 0.218	52 (3.8%) vs. 59 (4.2%) 0.93 (0.64–1.35); *P* = 0.710
Stroke	1 (0.2%) vs. 5 (0.8%) 0.21 (0.02–1.81); *P* = 0.156	1 (0.3%) vs. 3 (0.8%) 0.28 (0.03–2.71); *P* = 0.272	2 (0.1%) vs. 11 (0.8%) 0.19 (0.04–0.84); *P* = 0.029
Urgent hospitalization for angina requiring coronary revascularization	6 (1.0%) vs. 17 (2.9%) 0.35 (0.14–0.88); *P* = 0.026	4 (1.1%) vs. 6 (1.7%) 0.63 (0.18–2.24); *P* = 0.476	15 (1.1%) vs. 26 (1.9%) 0.61 (0.32–1.16); *P* = 0.131
Secondary composite endpoint	20 (3.3%) vs. 36 (6.1%) 0.55 (0.32–0.95); *P* = 0.031	18 (4.9%) vs. 16 (4.5%) 1.04 (0.53–2.03); *P* = 0.919	67 (4.9%) vs. 77 (5.5%) 0.92 (0.66–1.28); *P* = 0.629
All-cause death	6 (1.0%) vs. 6 (1.0%) 1.03 (0.33–3.19); *P* = 0.962	8 (2.2%) vs. 7 (2.0%) 1.03 (0.37–2.84); *P* = 0.957	26 (1.9%) vs. 31 (2.2%) 0.90 (0.53–1.51); *P* = 0.684
All coronary revascularizations	33 (5.5%) vs. 51 (8.7%) 0.63 (0.40–0.97); *P* = 0.037	25 (6.9%) vs. 18 (5.1%) 1.41 (0.76–2.61); *P* = 0.275	72 (5.3%) vs. 94 (6.7%) 0.81 (0.59–1.10); *P* = 0.172

The primary composite endpoint included CV death, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina requiring coronary revascularization. The secondary composite endpoint included CV death, resuscitated cardiac arrest, MI, and stroke. Only the initial event was counted in the analyses of time to first event for the primary composite endpoint and for the secondary composite endpoint.
Covariates included in the stepwise multivariable Cox regression models are: age; sex; BMI; smoking status; history of diabetes; history of hypertension; history of dyslipidaemia; prior MI; prior coronary revascularization (prior PCI or prior CABG); prior heart failure. All models also included TTI, group and the interaction between group and TTI.
CI, confidence interval; CV, cardiovascular; MI, myocardial infarction; HR, hazard ratio; PCI, percutaneous coronary intervention; TTI, time-to-treatment initiation.

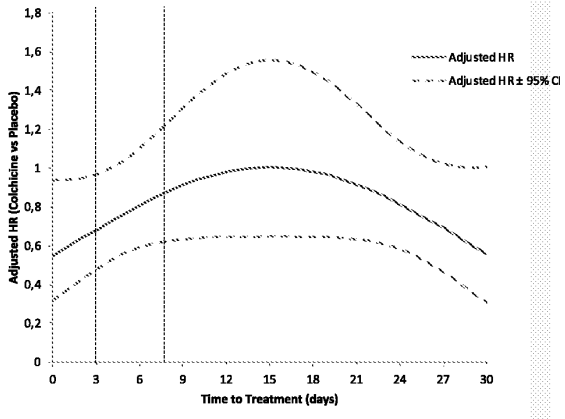


Figure 2 Associations between time-to-treatment initiation and the risk of occurrence of the primary composite endpoint. The adjusted hazard ratio and 95% confidence intervals come from a quadratic multivariable Cox regression model.

The benefit of colchicine in reducing the risk of stroke was large in COLCOT, which supports the favourable vascular effects of inflammation reduction with this medication. Whether there is a particular effect of colchicine on the cerebral vascular bed is unknown. In contrast, there was no significant impact of colchicine on the incidence of atrial fibrillation in COLCOT.

Targeting residual cardiovascular risk with anti-inflammatory therapy

Inflammation contributes to all phases of atherosclerotic disease, and recent data from randomized trials have provided novels insights into the role of inflammation modulation for CV risk reduction.[20] The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS) of patients with stable coronary disease demonstrated that the selective IL-1 β inhibitor canakinumab yielded a reduction of 15% in the risk of a CV event,[21] which was correlated with the lowering of inflammation biomarker levels.[22] The main COLCOT results revealed that colchicine reduced the risk of ischaemic CV events by 23% in the post-MI setting.[9] Results from the present COLCOT analysis suggest that early suppression of inflammation after MI provides

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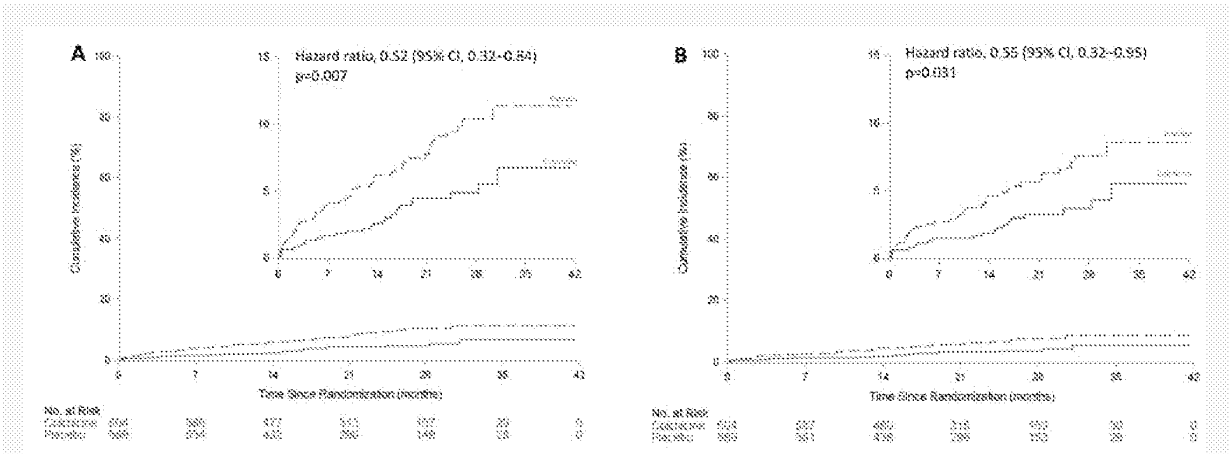


Figure 3 Kaplan–Meier event curves for the primary and secondary efficacy composite endpoints in the colchicine group and the placebo group according to time-to-treatment initiation. The inset shows the same data on an enlarged *y*-axis. (*A*) Cumulative incidence of the primary composite endpoint in patients with time-to-treatment initiation ≤ 3 days; (*B*) Cumulative incidence of the secondary composite endpoint in patients with time-to-treatment initiation ≤ 3 days.

even greater benefits, with a reduction of 48% in the risk of the composite primary endpoint when colchicine was initiated between Days 0 and 3. The demonstrated cost-effectiveness of low-dose colchicine also supports its large-scale use after MI.[23] Results of the LoDoCo2[24] study of patients with stable coronary artery disease will complement those of COLCOT in the post-MI setting.

Limitations

This analysis has limitations. Time-to-treatment initiation was analysed using three strata chosen according to the usual journey of patients with uncomplicated MI. A larger trial might have allowed a better assessment of individual endpoints and subgroups.

Conclusions

Early initiation of low-dose colchicine after MI greatly reduced the risk of ischaemic CV events compared with placebo. These results support in-hospital initiation of adjunctive anti-inflammatory therapy with colchicine for post-MI prevention.

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Conflict of interest: N.B. reports personal fees from AstraZeneca, outside the submitted work; J.-C.T. reports grants from Government of Quebec, Canadian Institutes of Health Research, Montreal Heart Institute Foundation, during the conduct of the study; grants from Amarin, grants and personal fees from Astra Zeneca, grants, personal fees and other from Dalcor, grants from Esperion, Ionis, grants and personal fees from Sanofi, Servier, grants from RegenXBio, outside the submitted work; In addition, J.-C.T. has a patent Genetic markers for predicting responsiveness to therapy with HDL-raising or HDL mimicking agent pending, a patent Methods for using low-dose colchicine after MI pending to Invention assigned to the Montreal Heart Institute, and a patent Methods of treating a coronavirus infection using Colchicine pending; D.D.W. reports personal fees from Pharmascience, outside the submitted work; F.J.P. has nothing to disclose; A.P.M. reports personal fees from Bayer, Fresenius, and Novartis, outside the submitted work; R.D. reports grants from MHIRC, during the conduct of the study; grants from DALCOR, outside the submitted work; C.B. has nothing to disclose; W.K. reports personal fees from AstraZeneca, Novartis, Pfizer, The Medicines Company, DalCor, Kowa, Amgen, Corvidia, Daiichi-Sankyo, Berlin-Chemie, Sanofi, and Bristol-Myers Squibb, grants and non-financial support from Singulex, Abbott, Roche Diagnostics, and Beckmann, outside the submitted work; J.L.-S. reports grants from Montreal Heart Institute, during the conduct of the study; grants from Bayer, Pfizer, Sanofi, and Boheringer Ingleheim, outside the submitted work; H.G. has nothing to disclose; G.S.K. receiving lecture fees from Bayer, Servier, Novartis, AstraZeneca, Bristol-Myers Squibb, Roche, and Pfizer; L.B., A.O., R.I., and J.C.G. have nothing to

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Interest of colchicine in the treatment of acute myocardial infarct responsible for heart failure in a mouse model

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ABSTRACT

Background: Inflammation is deeply involved in the pathophysiology of ischemia-reperfusion (I/R) lesions and ventricular remodeling due to an acute myocardial infarction (AMI). Colchicine as a pleiotropic anti-inflammatory molecule may exert cardioprotective effects under acute ischemia. Here, we aimed to evaluate the impact of colchicine on reperfusion injury in a mouse model.

Method: Myocardial ischemia/reperfusion (I/R) injury was induced in C57BL/6 male mice, after 45 min ligation of the left coronary artery followed by reperfusion. 400 μg/kg of colchicine or the vehicle was administrated intraperitoneally (i.p.) 25 min before the reperfusion (blinded administration). Mice were sacrificed at 24 h after the acute myocardial ischemia (AMI) and the infarct size was determined. Circulating level of troponin and cytokines profile were assessed 4 h after the AMI. An echocardiography was performed in a follow-up group mice, 48 h and 8 weeks after the AMI.

Results: The infarct size was reduced in colchicine treated mice (39.8 ± 3.5% *versus* 52.9 ± 3.2%, $p < 0.05$). Troponin was significantly lower in the colchicine treated mice (7015.7 ± 1423.7 pg/mL, $n = 5$ *vs* 30,723.7 ± 7959.9 pg/mL in the placebo group, $n = 6$; $p < 0.0001$).

Fibrosis was decreased in the Colchicine group (24.51 ± 3.13% *vs* 11.38 ± 2.46%, $p = 0.03$). In the follow-up group mice ($n = 8$), there were no differences between mice treated with placebo ($n = 9$) and mice treated with colchicine ($n = 9$) regarding to cardiac remodeling parameters but outflow approximated by the ITV was higher in the colchicine group.

Conclusion: In conclusion, colchicine allowed a significant reduction of infarct size in mice, improves hemodynamic parameters and decrease cardiac fibrosis.

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1. Introduction

Ischemic heart failure (HF) is a progressive disorder characterized by poor quality of life, a poor prognosis (5-year survival <50%, worse than most of common types of cancers), and a tremendous burden on health care costs [1]. In Europe and the United States ~1–2% of the entire health care budget is spent on HF. The prevalence of HF is expected to rise due to the aging population and better treatment of cardiovascular disease that precedes HF [2]. Therefore, it is mandatory to explore innovative approaches. Over the last decade, among the pathophysiological mechanisms associated with ischemic HF progression, inflammatory processes appear appealling to define new therapeutic strategies [3–5]. Indeed, after an acute myocardial infarction, inflammation could be involved at least at two levels, by worsening the infarct size at the very onset of the reperfusion, or at later stages by worsening the cardiac remodeling [4, 5].

Cardiac remodeling is a crucial determinant of the clinical outcome of HF and is linked to disease progression and poor prognosis. The remodeling process is characterized by activation of "compensatory" systems, including the renin-angiotensin system (RAS) and the sympathetic nervous system (SNS). Although initially aimed at maintaining adequate circulation, over time the sustained activation of compensatory neurohormonal systems actually contributes to the adverse remodeling process leading to HF. In parallel, cardiac remodeling is

Abbreviations: AAR, area at risk; AMI, acute myocardial infarction; CAD, coronary artery disease; HF, Heart failure; IA, infarcted area; IR, ischemia-reperfusion; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; RAS, renin-angiotensin system; SNS, sympathetic nervous system; STEMI, ST elevation myocardial infarction; TTC, Triphenyl-tetrazolium chloride.

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accompanied by a progressive inflammatory response characterized by inflammatory cells infiltration and pro-inflammatory cytokines, which favors fibrosis expansion [6]. As such, the severity of ischemic HF is positively correlated to the inflammatory profile [7]. Despite current treatment regimens for HF that effectively target known neurohormonal system activation, clinical outcomes remain poor. Other targets, such as cardiac fibrosis, are currently left untreated [8].

Colchicine is a mitotic spindle poison used for centuries for the treatment and prevention of gouty attacks and rheumatic complaints and is one of the oldest drugs still currently available [9]. It could exert pleiotropic anti-inflammatory effects. Especially, colchicine has direct anti-inflammatory effects [10] by inhibiting key inflammatory signaling networks as the inflammasome, pro-inflammatory cytokines and expression of adhesion molecules, preventing both local chemoattraction of inflammatory cells such as neutrophils [11] and systemic inflammation including the decrease of release of IL-1β by the neutrophils [12–14]. At the cellular level, colchicine could also exert antiarrhythmic effects [15]. In *in vivo* models, colchicine has been demonstrated to inhibit apoptosis in rats [16] and to exert indirect antifibrotic effects, by inhibiting the release of profibrotic factors [17]. Although, in a dog model subjected to a 120-min coronary artery occlusion followed by 6-h reperfusion [18], IV injection of colchicine reduce post-ischemic myocardial neutrophil accumulation, no myocardial protection could be detected in terms of infarct size. More recently colchicine has been proposed to reduce infarct size in patients [19] suggesting that colchicine could be a potential therapeutic strategy for treatment of heart failure induced by acute myocardial infarct. However, the cardioprotective impact of colchicine remains under debate.

Thus, the objective of this study was to evaluate the impact of colchicine on infarct size and cardiac remodeling in a mice model of acute myocardial infarction. We demonstrated that colchicine reduced myocardial infarct size and left ventricular remodeling was accompanied by a profound anti-inflammatory effects.

2. Method

2.1. Experimental model

Eight to ten weeks C57BL/6 male mice, were randomized into 2 groups: colchicine or placebo. Myocardial ischemia-reperfusion (IR) injuries were induced in all mice under general anesthesia with intramuscular injection of ketamine (50 mg/kg) and xylazine (10 mg/kg) and after orotracheal intubation with a 22G venous catheter for controlled ventilation (Minivent, Harvard Apparatus) with controlled stroke (10 μL/g) and frequency (150/min). After left thoracotomy and muscular dissection, ligation of the left coronary artery was performed with a 8–0 silk and a smooth catheter was applied on the artery to obtain an ischemia for 45 min. The ischemia was visually confirmed by the change in myocardial color turning into white and was followed by reperfusion obtained by the catheter removal. 400 μg/kg, 1 mg/kg and 2 mg/kg of colchicine or placebo was administrated intraperitoneally (i.p.) 25 min before the reperfusion (blinded administration). The determination of the dose is described elsewhere [20]. Muscle and cutaneous plans were sutured with silk 6–0. Mice were extubated and placed at 32 °C (RT) for 1 h. Sham-operated animals were subjected to the same surgical procedure, but the ligation remained untied. This study was approved by the local ethic committee for animal experimentation and registered by the national committee under the number CEEA-LR-12079.

Sham-operated mice underwent the same procedure without the LAD occlusion/reperfusion and treated with saline (n = 5) or colchicine (400 μg/kg, i.p.; n = 5).

2.2. Infarct size

Twenty-four hours after IR, intracardiac Evans blue injection was performed (500 μL) with a 30 G1/2 needle. Euthanasia was induced by intracardiac injection of 10% potassium chlorate.

The heart was then removed and the left ventricle (LV) was cut in 1 mm thick transverse slices, stained with Triphenyl-tetrazolium chloride 1.5% (TTC) and incubated at 37° for 2 h. The slices where then transferred in 0.9% saline serum at 4 °C and double blind analyzed with a binocular microscope (×10). The area at risk (AAR) and infarcted area (IA) were determined by computerized planimetry with ImageJ® software. The viable perfused myocardium was colored in blue, the IA in white and the ischemic viable myocardium in red. 5 slices were double blind analyzed on both side. The AAR was compounded by the IA and the ischemic but viable myocardium. The AAR/total area and IA/AAR ratios were calculated. Results are expressed in average of percentage of AAR on total area and percentage of IA on AAR, on the 5 slices.

2.3. Blood analysis

Twenty-four hours after reperfusion, a subgroup of mice was dedicated for blood analysis after intracardiac puncture under Isoflurane anesthesia. The blood was centrifuged 10 min at 5000 rpm and the serum obtained was stored at −20 °C. The myocardium injury biomarker T troponin and the major cytokines implicated in inflammatory process (IL1β, IL6, IL10, CCL2-MCP1) were measured by Multiplex (Milliplex® MAP Millipore, Billerica, MA) following the manufacture indications. Briefly, 2 plates of 96 wells were used, one for the T troponin and one for the other cytokines assay. 125 μL of serum was necessary per well, without dilution for T troponin dosage and with a 1:2 ratio dilution for the cytokines. The magnetic balls were prepared and incubated with serums overnight. The assays were triplicated for each serum with 2 negative controls by plate. The data were revealed by Luminex Multiplex assay.

2.4. Transthoracic echocardiography

A group of mice, after the same ischemia-reperfusion protocol was followed during 10 weeks.

An echocardiographic follow-up was performed 48 h, 14 days and 8 weeks after the infarction, under Isoflurane anesthesia with a maintained 36 °C body temperature and 450–500/min heart rate. The transthoracic echocardiography (Vevo2100; VisualSonics) were double blind realized, with a 40 MHz probe, TM and 2D modes were used with long and short axis parasternal views. Left ventricular ejection fraction (LVEF), left ventricular end-systolic and end-diastolic diameter, E/A profile reflecting diastolic function and aortic ITV reflecting the cardiac output were assessed.

2.5. Fibrosis study

All the mice dedicated to the long-term follow-up were sacrificed 10 weeks after ischemia-reperfusion for fibrosis study. Briefly, the heart was removed and the left ventricle was separated. The left ventricle was embedded into paraffin and 8 μm thick slices were obtained. The fibrotic area, in blue, was determined by Masson Trichrome (HT15 kit, Sigma Aldrich, France) and quantified using ImageJ. The percentage of total fibrosis area was calculated as the sum of blue-stained areas divided by total ventricular area.

2.6. Clinical sub study

A clinical trial [21] was conducted in parallel by our team and aimed to assess the impact of colchicine in post-myocardial infarction on inflammation, particularly on the peak of CRP. A sub-study was performed to investigate the impact of colchicine treatment on ventricular remodeling and to identify its predictive imaging parameters. A transthoracic echocardiography was performed in all patients included in this study. Treatment with colchicine was administered on the first day of the STEMI, for a period of 1 month at 1 mg dose per day. The left ventricular remodeling was defined as the increase in left ventricular end-diastolic volume (LVEDV) >20% at 1 month.

2.7. Statistical analysis

Statistical analyses were realized with GraphPad Prism (version 5, GraphPad software, La Jolla, CA). A Mann-Whitney test was used to compare the 2 groups of mice treated with colchicine or placebo for each analysis. The significance was fixed at $p < 0.05$. All data are expressed as percentage, mean and standard error of mean.

3. Results

3.1. Toxicity and effect of colchicine on infarct size

A preliminary phase aimed to identify the toxicity and the optimal dose of colchicine according to literature [18,20,22–24]. The ischemia-reperfusion protocol was performed with a 2 mg/kg dose of colchicine in 2 animals, 3 received 1 mg/kg of colchicine and 9 mice 400 μg/kg of colchicine. The placebo (saline serum) was administrated in 10 mice. Higher dose (≥1 mg/kg) of colchicine were toxic for 3 mice (60%) with early unexpected death (<24 h). The 400 μg/kg dose was then considered as optimal as none of them died prematurely. The two left mice treated with the higher dosage were excluded.

Twenty-six mice were sacrificed 24 h after ischemia for histological analysis, 13 in the placebo group and 13 in the colchicine group. Mean AAR/total area ratio were 52.6 ± 1.1% in the colchicine group *vs* 50.6 ± 0.8% in the placebo group ($p = 0.9$). Mean IA/AAR ratio were 39.8 ± 3.5% in the colchicine group *vs* 52.9 ± 3.2% in the placebo group ($p < 0.05$), with a significant reduction of the infarct size in the colchicine group (Fig. 1, A, B, C). After 24 h after reperfusion, the T troponin level was significantly reduced in mice treated with colchicine (7015.7 ± 1423.7 pg/mL, n = 5 *vs* 30,723.7 ± 7959.9 pg/mL in the placebo

group, n = 6; p < 0.0001) (Fig. 1, D). Consequently, these results suggest that a low-dose of colchicine prior to reperfusion decreases myocardial injury and infarct size 24 h after an acute myocardial ischemia.

3.2. Colchicine and inflammation

To determine if the potential benefits of colchicine on myocardial injury was associated with an anti-inflammatory effect of the drug, the main inflammatory cytokines were measured 24 h after reperfusion (see Fig. 2). The IL6 level was 197.8 ± 48.4 pg/mL in the colchicine group (n = 5) *vs* 2303.0 ± 1007.6 pg/mL in the placebo group (n = 6), p = 0.0001. The IL10 level was 20.2 ± 18.2 pg/mL in the colchicine group (n = 5) *vs* 183 ± 50.4 pg/mL in the placebo group (n = 6), p < 0.0001. MCP-1 level was also significantly lower in the group treated with colchicine (n = 5), 185.4 ± 75.4 pg/mL *vs* 640 ± 121 pg/mL in the placebo group (n = 6), p < 0.0001. The level of IL1β was not significant different between the 2 groups (p = 0.3, Fig. 2). Importantly, there was no significant differences in the Sham-groups. In conclusion, 24 h after ischemia-reperfusion, colchicine decreases the systemic pro-inflammatory cytokines.

3.3. Colchicine and post-infarction cardiac remodeling

To evaluate long-term effects of colchicine and the potential anti-fibrotic effect of the drug, a group of mice was followed during 10 weeks post-reperfusion. On 22 mice (11 in each group), 2 died before the 24th hour and 2 were excluded (1 in each group) for thoracotomy scar infection. The follow-up was realized for 9 mice in the colchicine group and 9 in the placebo group. All mice were sacrificed after 10 weeks to perform histological analyses. The initial body weight was similar between the two groups, 25.0 ± 1.0 g in the colchicine group *vs* 26.3 ± 2.0 g in the placebo group, p = 0.5 and there was no difference in terms of weight gain during the follow-up, p = 0.6.

Under echocardiography, the heart rate was comparable in both groups (531 ± 10 in the colchicine group *vs* 515 ± 11 in the placebo group, p = 0.9) and no significant difference was found for the LVEF (p = 0.2), E/A ratio (p = 0.08), (Fig. 3 A and B). The aortic ITV was significantly higher in mice treated with colchicine (p = 0.015) (Fig. 3 C) at 48 h and 14 days post reperfusion. After 8 weeks, aortic ITV remained significantly higher in the colchicine group, compared to the placebo group, p = 0.014 (Fig. 3 D). However, end-diastolic diameter (p = 0.7), end-systolic diameter (p = 0.2), LVEF (p = 0.09), and E/A ratio (p = 0.9) (Fig. 3C) were unchanged. Altogether this data indicates that colchicine improves cardiac hemodynamic parameters at long term with an improvement of cardiac output.

In the clinical sub-study, 44 patients were included, 23 received colchicine and 21 the optimal treatment alone. All the patients got complete and successful revascularization. Remodeling was observed in 12 patients, 4 patients of colchicine group *vs* 8 of the optimal treatment group alone. The percentage of necrosis was similar (independently of the remodeling). The percentage of variation in LVEDV was 6.8% (95% CI:[−3.1–16.6]; p = 0.3) for the colchicine group and 28.9% (95% CI:[9.3–48.5]; p = 0.4) for the control group. The LVEDV was correlated

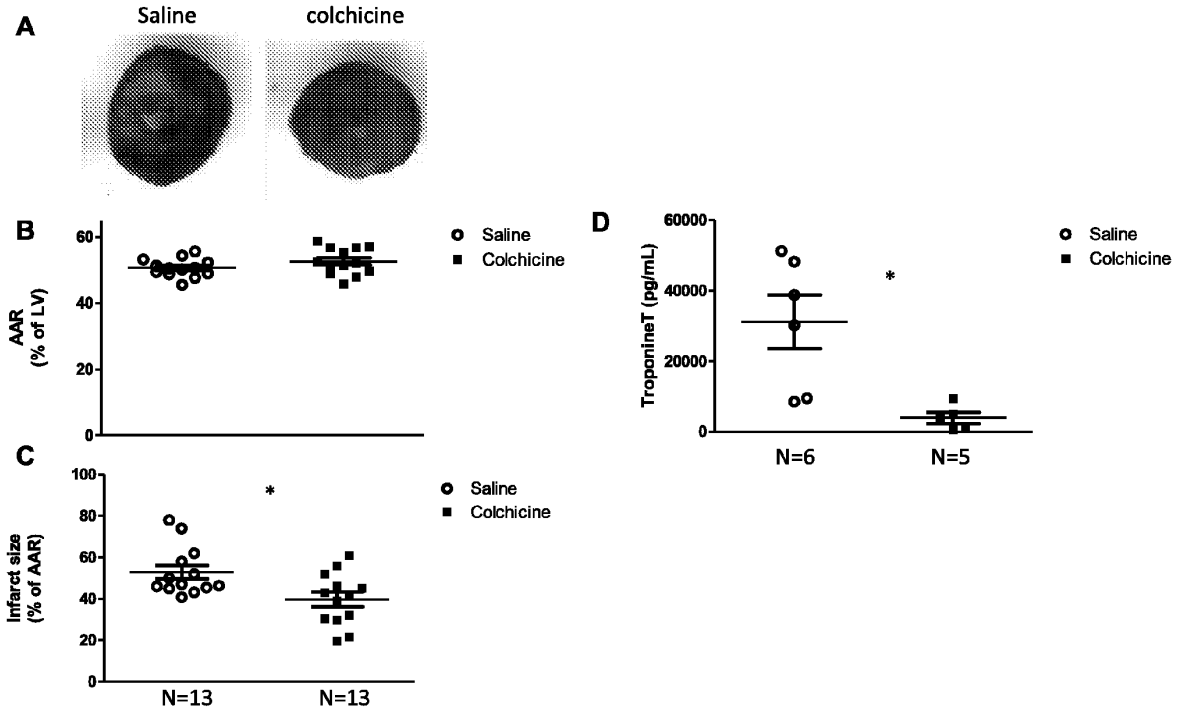


Fig. 1. Infarct size in mice treated with placebo (saline) or colchicine, 24 h after ischemia-reperfusion. A: Placebo and colchicine treated mice left ventricular slices after blue Evans injection and incubation in 2,3,5-triphenyltetrazolium (TTC), normal myocardium appears in deep blue, necrotic area in white and viable ischemic area in red. B: Area at risk (AAR)/total area of ventricular slice ratio in placebo and colchicine treated mice after blue Evans intracardiac injection and incubation in TTC. C. Infarct size/area at risk ratio in placebo and colchicine treated mice after blue Evans intracardiac injection and incubation in TTC. D: serum troponin T level (pg/mL) after intracardiac puncture in placebo and colchicine treated mice *p < 0.05.

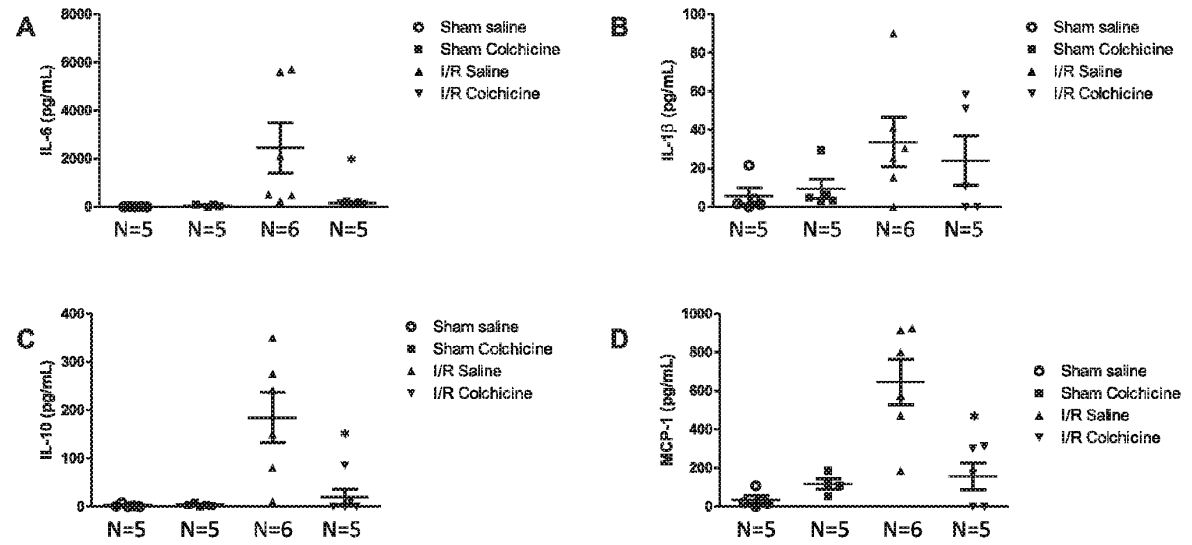


Fig. 2. Comparison of arterial inflammatory cytokines level, IL6 (A), IL1β (B) IL10 (C) and MCP-1 (D) between the four groups, Sham-operated mice treated with saline (placebo) or colchicine and mice subjected to ischemia-reperfusion and treated with saline (placebo) or colchicine, respectively, after 24 h after Sham-surgery or ischemia-reperfusion and multiplex analysis. *$p < 0.05$.

to the remodeling, negatively at baseline (coefficient −0.43; $p < 0.05$), and positively at 1 month (coefficient 0.43; $p < 0.05$). This data suggests that remodeling should be more present in the control group, corroborating the anti-remodeling impact of Colchicine in patients.

3.4. Colchicine and cardiac fibrosis

Fibrosis was evaluated in 5 mice from the placebo group and 5 mice from the colchicine group.

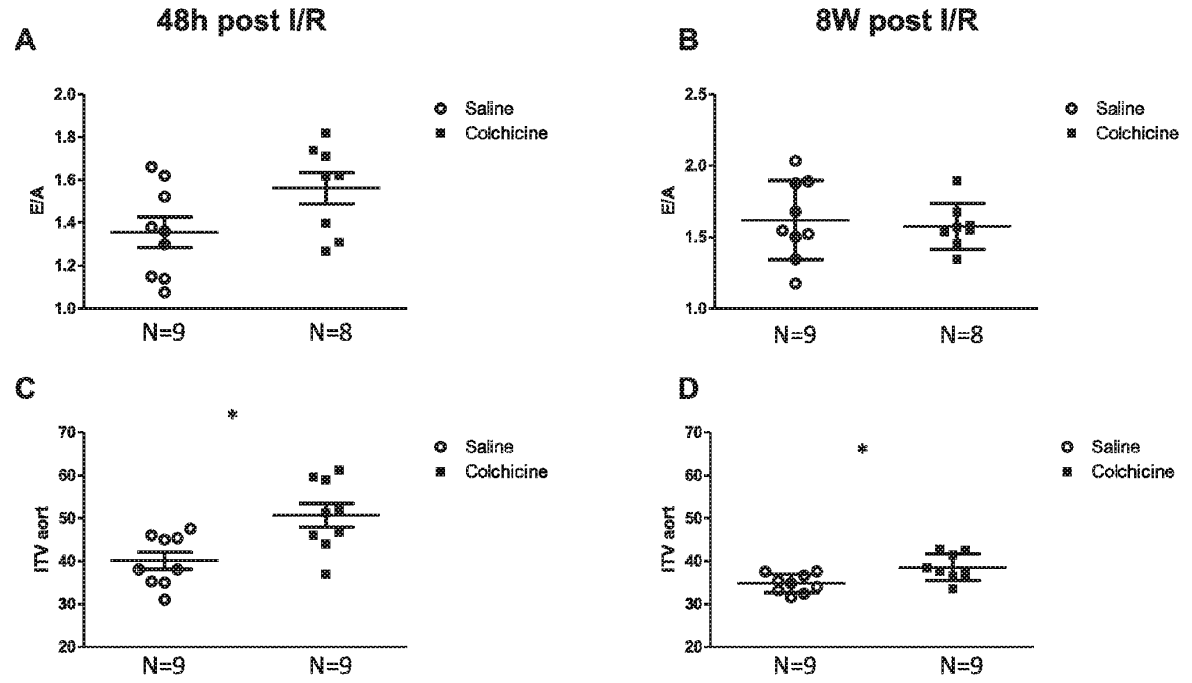


Fig. 3. Comparison of echocardiographic parameters between placebo and colchicine group mice. A: Comparison of E/A ratio between the two study groups 48 h after ischemia-reperfusion. B: Comparison of aortic ITV between the two study groups 48 h after ischemia-reperfusion. C: Comparison of E/A ratio between the two study groups 8 weeks after ischemia-reperfusion. D: Comparison of aortic ITV between the two study groups 8 weeks after ischemia-reperfusion. *$p < 0.05$.

Area of myocardial fibrosis was significantly more important in the placebo group, 24.51 ± 3.13% *vs* 11.38 ± 2.46% in the colchicine group, p = 0.03, (Fig. 4).

4. Discussion

This study aimed to evaluate, the cardioprotective effect of colchicine in a mouse model of myocardial ischemia-reperfusion. Our data demonstrate that a treatment with colchicine is associated with 1) a decrease in infarct size, 2) a decrease in systemic inflammatory response and 3) an improvement in long term cardiac output and myocardial fibrosis.

A unique i.p. injection of colchicine (0.4 mg/kg), during ischemia, reduces infarct size (IA/AAR), and circulating T troponin level 24 h after ischemia-reperfusion, reflecting a reduction in myocardial injury. These data are in accordance with those obtained in a recent human study. Indeed, this clinical study realized in acute myocardial injury showed a reduction in infarct size with lower level of serum creatine kinase, troponin as well as infarct size assessed by MRI, in patients treated with colchicine 5 days [19]. Similarly, our recent clinical trial [21], showed a significant reduction in left ventricular remodeling in the group of patients treated with colchicine. This cardioprotective effect on infarct size was accompanied by a systemic anti-inflammatory effect characterized by a decrease in cytokines implicated in post-ischemic inflammatory response such as IL 6 and MCP-1. Inflammation is known to exert deleterious effects during acute phase of myocardial infarction with an increase in pro-thrombotic phenomenon [25], in endothelial dysfunction [26] and is associated with adverse outcomes [27,28]. Some inflammatory cytokines, as MCP-1, play an important role in inflammatory cells recruitment [29,30]. Indeed, MCP-1 level is known to increase in several experimental myocardial infarction models [31] and to play a major role in leukocyte recruitment, angiogenesis, inflammation activation and resolution. In a rat model of MI, an anti-MCP-1 therapy decreased infarct size presumably through a decrease in adhesion molecule expression and myocardial infiltration by macrophages [32]. Similarly, in a gene therapy study targeting MCP-1, the authors showed an attenuation of left ventricular dilatation in a murine model of myocardial infarction, suggesting an important role of this cytokine in the post-infarction cardiac remodeling [33].

Other interleukins increase after myocardial infarction. IL-10 plays a major role in post-infarction inflammation resolution by inhibiting IL-6 secretion, a pro-inflammatory cytokine involved in myocardial ischemia [34,35]. Here we demonstrated that colchicine significantly decreases serum levels of the main cytokines implicated in post-infarction inflammation (IL-10, IL-6 et MCP-1) 24 h after reperfusion, suggesting a positive effect on inflammatory cells recruitment in the acute phase of MI. However, several pro-inflammatory cytokines frequently involved in the acute phase of myocardial infarction (TNF-α, IL1-β, TGF-β…) were not detected, probably due to the unique dosage realized at 24 h after the reperfusion [36].

In addition to acute cardioprotective effect, colchicine also exerted a long-term potential positive effects on cardiac hemodynamic with an

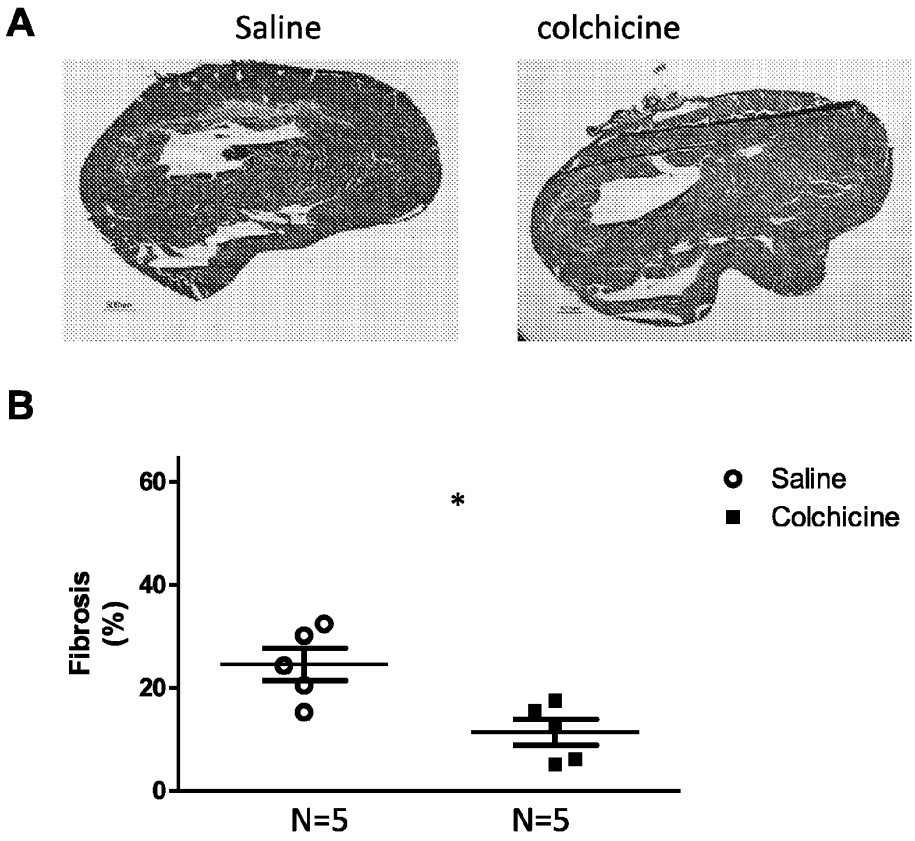


Fig. 4. Fibrosis evaluation with Masson' trichrome coloration A: Heart slices from placebo and colchicine group mice on bifocal microscope after Masson' Trichrome coloration. Fibrosis appears in blue. B: Percentage of fibrosis in heart slices from placebo and colchicine mice. *p < 0.05.

increase in aortic ITV reflecting cardiac output, on echocardiography realized 8 weeks after AMI. However, usual parameters evaluating the left ventricular diameters (LVEF) were not modified by the treatment with colchicine in the mouse model but were improved in the clinical study. Similar data were found in a clinical study with a reduction in left ventricular remodeling and an improvement in LVEF [19].

Moreover, the histological assessment of fibrosis demonstrates a decrease in post-ischemic myocardial development of fibrosis. Accordingly, this anti-fibrotic effect of colchicine was also demonstrated in a rabbit model of heart failure, reducing fibrosis in left atrium, exerting thus an anti-arrhythmic effect by decreasing the new onset of atrial fibrillation [37]. Although the exact mechanisms remain unclear and might be linked to its anti-inflammatory effect, the anti-fibrotic effect is also largely proven in pericarditis [38] models as well as in several organs, particularly in the liver [39].

4.1. Study limitation

The relatively small number of mice dedicated to each exploration is one of the main limitation. However, the adjudication, surgery and analyses were blinded and the main result on infarct size was obtained in 13 animals by group.

Yet, this study aimed to have a first approach on the effect of the colchicine in the acute phase of acute myocardial infarction and at long term, on the evolution toward chronic heart failure. The second limit is the absence of multimodality imaging as cardiac MRI to evaluate differently parameters as infarct size, ventricle remodeling and fibrosis quantification.

The third limitation is the determination of the dose of colchicines in this model. Indeed, preliminary experiments were performed to determine the dose of colchicine used in the animal model (data not shown). A higher dose could indeed exert deleterious effects (narrow therapeutic window in clinical use) but lower dose could be not efficient. A longer or one-shot administration could of course be valuable options. Importantly, the basic and clinical approach cannot be strictly the same route or doses of administrations, hence discrepancing and limiting extrapolation to each other.

Finally, molecular and cellular mechanisms were not extensively explored in this study.

5. Conclusion

In this study, a unique dose of colchicine at the early stage of myocardial infarction decreases myocardial injuries with a reduction in infarct size and T troponin level at 24 h, similarly to recent clinical data. These cardioprotective effects are probably linked to the limitation of the systemic inflammation *via* the inhibition of the main inflammatory cytokines implicated in the acute phase of myocardial infarction. More importantly, colchicine improves long term cardiac remodeling with improved hemodynamic parameters and reduced myocardial fibrosis. Thus colchicine appears as a promising new therapeutic strategy for chronic ischemic heart failure.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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Anti-Inflammatory Treatment With Colchicine in Acute Myocardial Infarction

A Pilot Study

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Background—Inflammatory processes have been identified as key mediators of the deleterious effects of ischemia/reperfusion in ST-segment–elevation myocardial infarction. Colchicine is a substance with potent anti-inflammatory properties, suitable for safe use in patients with cardiovascular disease. The purpose of this study was to test the hypothesis that a short course of colchicine treatment could lead to reduced infarct size.

Methods and Results—Patients presenting with ST-segment–elevation myocardial infarction ≤12 hours from pain onset (treated with primary percutaneous coronary intervention) were randomly assigned to colchicine or placebo for 5 days. The primary outcome parameter was the area under the curve of creatine kinase-myocardial brain fraction concentration. A subset of patients underwent cardiac MRI with late gadolinium enhancement 6 to 9 days after the index ST-segment–elevation myocardial infarction. One hundred fifty-one patients were included (60 in the MRI substudy). The area under the creatine kinase-myocardial brain fraction curve was 3144 (interquartile range [IQR], 1754–6940) $ng \cdot h^{-1} \cdot mL^{-1}$ in the colchicine group in comparison with 6184 (IQR, 4456–6980) $ng \cdot h^{-1} \cdot mL^{-1}$ in controls ($P<0.001$). Indexed MRI-late gadolinium enhancement–defined infarct size was 18.3 (IQR, 7.6–29.9) mL/1.73 m^2 in the colchicine group versus 23.2 (18.5–33.4) mL/1.73 m^2 in controls ($P=0.019$). The relative infarct size (as a proportion to left ventricular myocardial volume) was 13.0 (IQR, 8.0–25.3) % and 19.8 (IQR, 13.7–29.8) %, respectively ($P=0.034$).

Conclusions—These results suggest a potential benefit of colchicine in ST-segment–elevation myocardial infarction, but further clinical trials are necessary to draw secure conclusions, especially considering the fact that the present study was not powered to assess clinical end points.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01936285.

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Key Words: area under curve ■ creatine kinase, MB form ■ gadolinium ■ magnetic resonance imaging ■ neutrophil ■ troponin T

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Over the past years, a substantial volume of evidence has accumulated identifying inflammatory processes as key mediators of the deleterious effects of ischemia/reperfusion-related phenomena in patients presenting with ST-segment–elevation myocardial infarction (STEMI).[1–4] Nevertheless, equally impressive is the lack of clinically applicable therapeutic strategies that could mitigate these processes, thus providing significant cardioprotection.

Clinical Perspective on p 1403

Despite the well-known fact that inflammation plays an important role in coronary artery disease development and progression,[5,6] there have been few attempts to systematically examine the potential role of anti-inflammatory treatment in this setting, possibly because of a lack in anti-inflammatory agents without the adverse cardiovascular safety profile of corticosteroids and nonsteroidal anti-inflammatory drugs.[7–9]

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Colchicine is a substance with potent anti-inflammatory properties, having a unique mechanism of action, which allows for safe use in patients with cardiovascular disease.[10]

The purpose of the present clinical study was to test the hypothesis that a short course of treatment with colchicine could lead to reduced infarct size in patients presenting with STEMI and treated with primary percutaneous coronary intervention.

Methods

This was a prospective, double-blinded, placebo-controlled study, performed in 2 primary percutaneous coronary intervention referral hospitals in the greater Athens area, whereas MRI studies were all performed in a third (separate) center. Patients presenting with STEMI, ≤12 hours from the onset of chest pain, from July 2013 until March 2015, were included. Main exclusion criteria were: age ≤18 or ≥80 years, active inflammatory or infectious disease or known malignancy, current treatment with corticosteroids or other anti-inflammatory agents, known hypersensitivity to colchicine or current chronic treatment with colchicine, severe renal failure (estimated glomerular filtration rate <30 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$), hepatic failure (Child-Pugh class B or C), cardiac arrest, ventricular fibrillation or cardiogenic shock as presenting symptom, stent thrombosis, angina within 48 hours before infarction, previous myocardial infarction, occlusion of the left main or left circumflex coronary artery or with evidence of coronary collaterals to the region at risk on initial coronary angiography, presence of metallic implants (ferromagnetic material), and inability or unwillingness to provide informed consent. The protocol was approved by the institutional review boards and was implemented in accordance with the provisions of the Declaration of Helsinki. All patients provided informed consent.

After completion of the diagnostic coronary angiography, patients were randomly assigned (using a 1:1 allocation scheme based on a computer-generated randomization algorithm – an R language script was used for this purpose) to receive colchicine, starting with a loading dose of 2 mg (1.5 mg initially followed by 0.5 mg 1 hour later) and continuing with 0.5 mg twice daily, or placebo, for 5 days (Figure 1). Patients with <60 kg body weight received 0.5 mg once daily. Monitoring of adverse events focused on gastrointestinal manifestations, hepatotoxicity, myelotoxicity, and myotoxicity. Operators and personnel involved in patient follow-up and management were blinded as to patient allocation (patient treatment was identified by a serial number; assignment records were kept in a digital file that was unlocked after conclusion of the last patient follow-up procedures and database locking).

All patients received standard-of-care treatment for STEMI. During primary percutaneous coronary intervention, bivalirudin, heparin, and glycoprotein IIb/IIIa inhibitors were used at the discretion of the treating interventionalist. Standard medical therapy was administered, including β-blockers, statins, acetyl-salicylic acid, and ticagrelor or prasugrel at recommended daily dosages.

The primary outcome parameter was the area under the curve of creatine kinase-myocardial brain fraction (CK-MB) concentration over 72 hours after admission (calculated using the Simpson summing rule[11]). CK-MB was measured on admission and every 4 hours thereafter. Maximal high-sensitivity troponin T was a secondary outcome measure during the same time period. A subset of patients from the total cohort underwent cardiac MRI with late gadolinium enhancement (LGE) 6 to 9 days after the index STEMI (MRI subgroup). In this subgroup, absolute myocardial infarct volume, determined by LGE, was the primary outcome measure. Myocardial infarct volume indexed to body surface area and relative infarct size (proportion of absolute infarct volume to left ventricular myocardial volume) were secondary outcome measures.

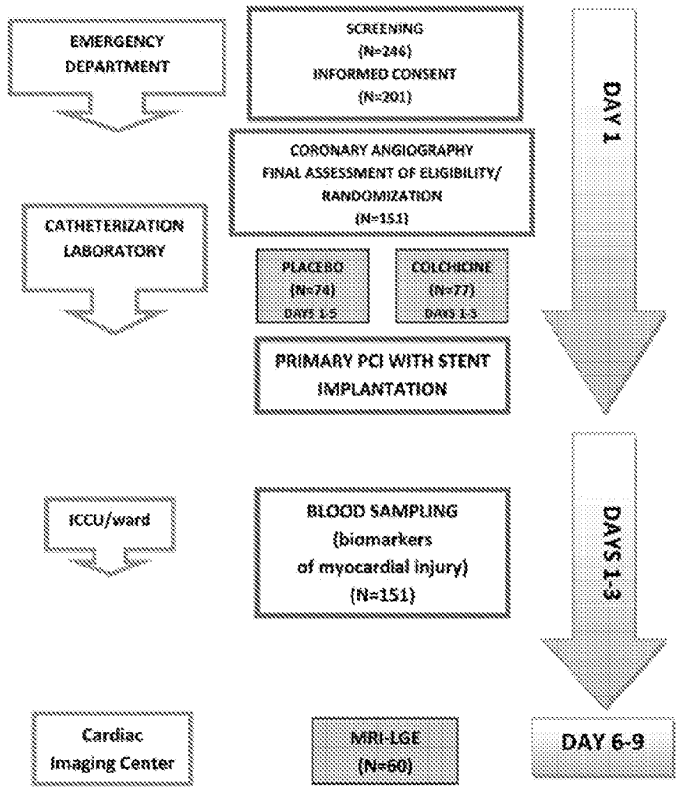


Figure 1. Study flow chart. All patients were screened at the emergency department and consent was sought. Final eligibility was determined in the catheterization department, as per protocol requirements. All exclusions at this stage were the result of protocol provisions. ICCU indicates intensive coronary care unit; LGE, late gadolinium enhancement; and PCI, percutaneous coronary intervention.

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Blood samples for high-sensitivity troponin T (Elecsys Troponin T hs assay, Roche Diagnostics; lower detection limit 5 pg/mL) and CK-MB (Elecsys CK-MB assay, Roche Diagnostics; lower detection limit <0.1 ng/mL) measurement, and other analyses (complete blood count, biochemistries, including high-sensitivity C-reactive protein, etc), as well, were obtained at baseline (on admission), every 4 hours for the first 72 hours postpresentation, and every 12 hours thereafter. All patients had a standard transthoracic echocardiographic study performed before discharge, whereupon left ventricular ejection fraction was calculated with the modified Simpson rule.

Cardiac MRI

The cardiac MRI protocol was performed on a 1.5T Siemens Symphony system (Erlangen, Germany). Approximately 8 to 9 minutes after administration of 0.015 to 0.02 mmol/kg of gadobutrol (Gadovist, Bayer Hellas AG), a multiphase inversion-recovery steady-state free precession scan ("TI-scout") was acquired in the mid short-axis plane to determine the optimal inversion time (TI) to null normal myocardium for delayed enhancement imaging. The time that corresponded to the image with sufficiently nulled myocardium was input as the TI into the subsequent inversion recovery segmented turbo flash sequence used for delayed enhancement imaging. Typically, the TI spanned 230 to 330 ms over the course of the study. Other imaging parameters were: repetition time/echo time/flip = 700 ms/4.18 ms/25 deg, 8 mm thickness, field of view = 255×340 mm, 192×256, and 25 segments. Acquisition was performed in the short axis, covering the left ventricle from base to apex. In addition, single slices were acquired in the long axis, 4-chamber and 3-chamber views. The TI was increased as needed as time passed (10–20 minutes after gadobutrol administration). To quantify the myocardial scar, short-axis delayed enhancement images were analyzed by using the freely available for research purposes software Segment, version 1.9 R2354 (http://segment.heiberg.se; Figure 2).

Sample Size Estimation and Statistical Analysis

Preliminary measurements in patients presenting with STEMI at our institution had an area under the CK-MB concentration curve in the first 72 hours of ≈6000 U [(ng/mL)×h] with a standard deviation of ≈3000 U. It was calculated that, to detect a 25% reduction in the primary outcome measure with 85% probability (type II error probability 0.15), at an α-level (type I error probability) of 0.05, 150 subjects would have to be included. Analysis was performed on an intention-to-treat basis (all randomly assigned patients). Continuous variables were expressed as median (25th–75th percentile). Comparisons of central tendencies and correlations were tested using nonparametric tests (Mann-Whitney U and Spearman, respectively). Categorical variables were expressed as counts and percentages and compared by using the χ^2 test (or Fisher exact test, if the generated 2×2 contingency tables contained cells with expected counts ≤5). SPSS 17 software package (SPSS Inc, Chicago, IL) and R language were used for all analyses. P values <0.05 (2-sided) were considered as indicative of statistical significance.

Results

One hundred fifty-one patients (104 male) were included in the final analysis (77 in the colchicine group and 74 controls). Sixty (41 male) of these patients were included in the MRI substudy. The epidemiological and clinical characteristics of the 2 cohorts (as a whole and divided in the 2 treatment arms) are summarized in the Table. The 2 treatment arms were similar in respect to important baseline parameters, both in the whole cohort (the only notable trend was a nonsignificantly higher thrombus burden in the colchicine arm) and the MRI subgroup. The MRI subgroup characteristics did not differ in any significant way from those of the total cohort.

Total Cohort

The median number of CK-MB measurements per patient was 16 (15–16; without any significant difference between treatment groups; P=0.226). The area under the curve of CK-MB concentration was 3144 (1754–6940) ng·h·mL^{-1} in the colchicine group in comparison with 6184 (4456–6980) ng·h·mL^{-1} in patients who took placebo (P<0.001; Figure 3). A similar difference was observed in maximum troponin values: median maximum high-sensitivity troponin T was 19 763 (6692–51 922) pg/mL and 45 550 (19 706–75 556) pg/mL in the colchicine and control arms, respectively (P=0.001), although one cannot fail to note the marked dispersion of values in the colchicine group, also obvious in the area-under-the-CK-MB-curve boxplot graph (Figure 3). The predischarge

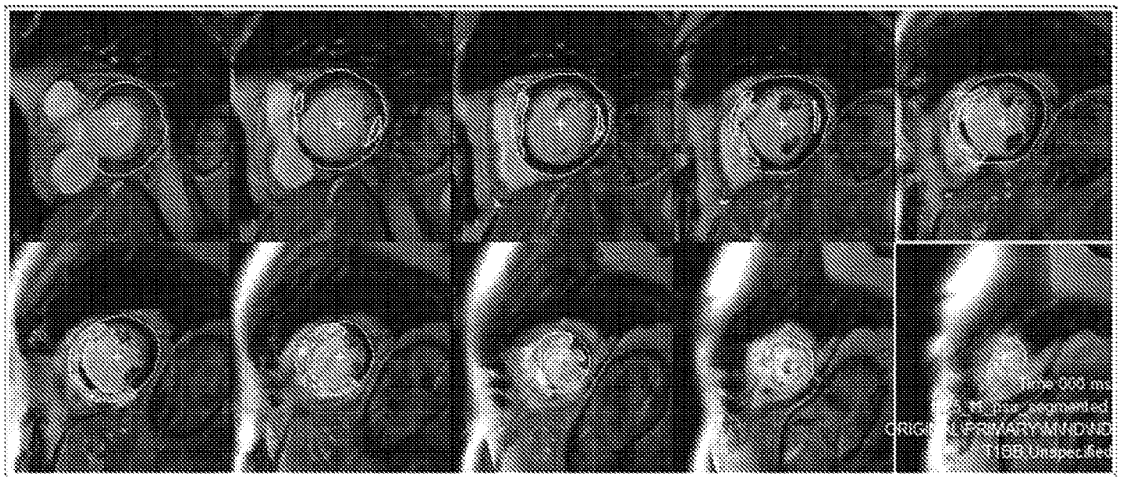


Figure 2. MRI-LGE images. Example of scar delineation using the Segment software with the weighted area method (infarcted pixels are weighted with their signal intensity). The yellow line denotes the complete affected area (scar), and the pink line is a graphical representation of the corresponding weighted area. Microvascular obstruction is indicated in red. For further information, read Heiberg et al.[12] LGE indicates late gadolinium enhancement.

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Table. Demographic, Clinical, and Procedural Patient Characteristics per Randomization Group

	Total (N=151)			MRI Subset (n=60)		
	Control	Colchicine		Control	Colchicine	
Variable	(n=74)	(n=77)	*P* Value	(n=29)	(n=31)	*P* Value
Age, y	58 (51–68)	58 (52–64)	0.800	57 (50–66)	59 (54–66)	0.277
Male sex	52 (70)	52 (68)	0.716	20 (69)	21 (68)	0.919
Body mass index, kg/m^2	27.1 (24.6–30.8)	27.1 (25.3–30.7)	0.611	27.4 (24.4–30.5)	28.1 (26–31.4)	0.420
Body surface area, m^2	1.89 (1.79–1.98)	1.90 (1.79–1.98)	0.855	1.92 (1.78–1.99)	1.91 (1.79–2.02)	0.865
eGFR, mL·min^{-1}·1.73 m^{-2}	84 (56–99)	75 (55–100)	0.836	86 (57–100)	81 (60–101)	0.982
Smoking	36 (49)	43 (56)	0.376	15 (52)	15 (48)	0.796
Diabetes mellitus	19 (26)	13 (17)	0.186	8 (28)	6 (19)	0.451
Dyslipidemia	35 (47)	44 (57)	0.226	13 (45)	16 (52)	0.599
Hypertension	29 (39)	31 (40)	0.893	7 (24)	12 (39)	0.225
Ischemia time, min	180 (146–237)	173 (141–223)	0.609	183 (148–231)	172 (146–227)	0.673
Baseline hs-TnT, pg/mL	34 (8–304)	37 (9–361)	0.786	22 (7–462)	35 (8–403)	0.982
Baseline CK-MB, ng/mL	44 (35–71)	59 (33–74)	0.984	44 (37–76)	43 (34–73)	0.923
Baseline neutrophil count, /μL	7131 (5913–7950)	6947 (5929–8935)	0.587	6800 (5761–7997)	6643 (5577–9230)	0.559
Baseline CRP, mg/L	2.46 (1.02–5.22)	2.39 (1.18–4.60)	0.553	2.81 (1.11–4.97)	2.31 (1.16–3.58)	0.847
Culprit vessel						
LAD	40 (54)	44 (57)	0.703	17 (59)	16 (52)	0.586
RCA	34 (46)	33 (43)		12 (41)	15 (48)	
TIMI thrombus burden	4 (3–5)	5 (4–5)	0.068	4 (3–5)	5 (3–5)	0.241
TIMI flow 3 post-pPCI	57 (77)	53 (69)	0.258	24 (83)	21 (68)	0.179

Continuous variables are summarized as median (interquartile range). Categorical variables are presented as count (percentage). CRP indicates C-reactive protein; eGFR, estimated glomerular filtration rate (Cockroft-Gault); hs-TnT, high-sensitivity troponin T; LAD, left anterior descending; pPCI, primary percutaneous coronary intervention; RCA, right coronary artery; and TIMI, thrombolysis in myocardial infarction.

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echocardiographic left ventricular ejection fraction was 53 (44–59) % in the colchicine group versus 46 (38–51) % in controls (P=0.003).

MRI Subgroup

MRI-LGE–defined infarct size, both in terms of absolute infarct volume and relative infarct size (proportion of infarct to left ventricular myocardial volume) was smaller in colchicine-treated individuals (Figure 4). Absolute infarct volume was 25.1 (20.0–35.9) mL in controls as opposed to 18.8 (8.1–28.5) mL in the colchicine group (P=0.019). After normalization for body surface area, the corresponding indexed infarct sizes were 23.2 (18.5–33.4) mL/1.73 m^2 versus 18.3 (7.6–29.9) mL/1.73 m^2 (P=0.019). The relative infarct size was 19.8 (13.7–29.8) % and 13.0 (8.0–25.3) %, respectively (Figure 4). Biomarker-defined infarct size was also lower in colchicine-treated patients of the MRI subset, similarly to the total cohort (Figure 4). As expected, there was a significant correlation between MRI- and biomarker-defined infarct size, which suggests good internal consistency of the data (Figure 5A).

Study Treatment Discontinuation and Adverse Effects

Overall, 23 of 151 patients discontinued treatment before taking all study drug doses. The discontinuation rate was 26% in the colchicine group (20 of 77 patients), as opposed to 4% in the control group (3 of 74 patients; P<0.001). The reason for discontinuing the study drug was reported as diarrhea in 16 of 23 cases (15 belonged to the colchicine group and 1 to the control group) and nausea/vomiting in 3 cases (all in the colchicine group). In 1 case, marked elevation in serum alanine aminotransferase was reported as the reason for study drug discontinuation (up to ≈5 times the upper reference limit, without any sequelae). No cases of myelotoxicity were reported. In-hospital death occurred in 1 patient of the colchicine group and 1 of the control group (on days 4 and 5 of hospitalization, respectively).

The area under the curve of CK-MB concentration was 2312 (1201–5743) ng·h·mL^{-1} in patients of the colchicine group who completed treatment (n=57) versus 5920 (2998–8858) ng·h·mL^{-1} in those who stopped treatment (n=20; P=0.003). The corresponding values for absolute infarct size in the MRI subgroup were 12.4 (6.8–25.9) mL in patients who completed colchicine treatment (n=24) versus 29.1 (26.1–36.6) mL in those who discontinued (n=7; P=0.008).

Inflammatory Markers

Maximal neutrophil count (the highest neutrophil count measured during hospitalization) was 7543 (6549–10 118) /μL in the colchicine group in comparison with 8922 (7880–10 307)/μL in controls (P=0.008). It was significantly associated with relative and absolute MRI-LGE infarct size (Figure 5B), and with the area under the CK-MB curve (Spearman ρ 0.79; P<0.001). These correlations were significant independently of study treatment (colchicine or placebo).

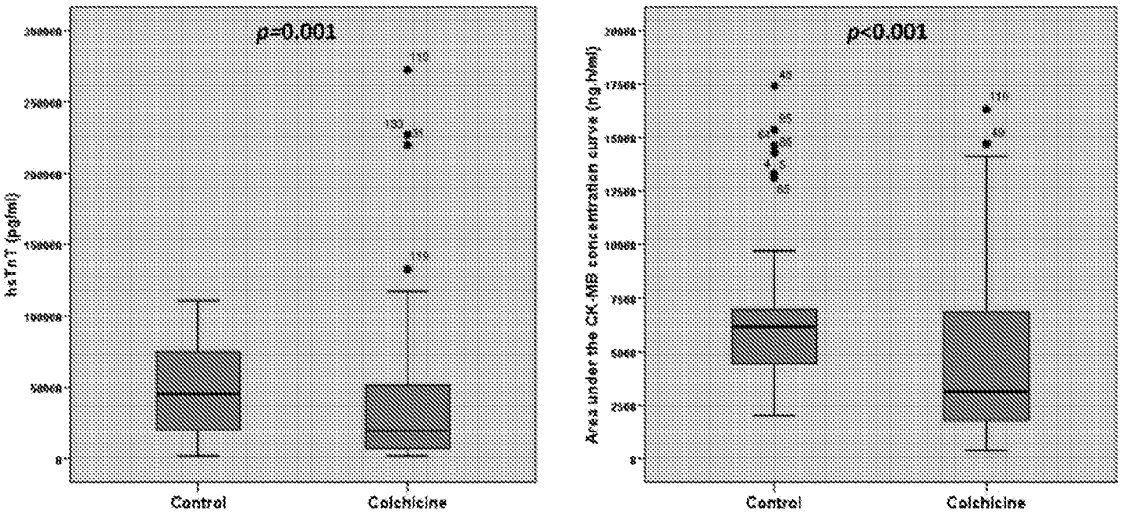


Figure 3. Myocardial injury biomarkers in the total cohort. Boxplot graphs illustrating the distribution of highest post-MI hs-TnT (**left**) and area under the curve of CK-MB concentration (**right**) in the total of 151 patients (the thick horizontal black line corresponds to the median, the box to the interquartile range, and the whiskers to the range bar extreme values, which are represented by dots and are defined as data points found outside 1.5 times the interquartile range, below or above the 25th and 75th percentiles, respectively). CK-MB indicates creatine kinase-myocardial brain fraction; hs-TnT, high-sensitivity troponin T; and MI, myocardial infarction.

Maximal C-reactive protein levels were also higher in the control group than in the colchicine-treated patients (63.8 [34.7–103.4] mg/L versus 42.9 [16.3–71.4] mg/L; P=0.019). Maximal C-reactive protein was correlated (although less strongly than neutrophil count) with relative MRI-LGE infarct size (Spearman ρ 0.42; P=0.001), indexed absolute infarct size (Spearman ρ 0.43; P=0.001), and the area under the CK-MB curve (Spearman ρ 0.38; P<0.001).

Discussion

The results of this prospective randomized study indicate that treatment with colchicine in patients with STEMI undergoing primary percutaneous coronary intervention is associated with smaller infarct size, as defined by both biomarker release and MRI-LGE. This effect was accompanied by a substantial treatment-related difference in markers of post–myocardial infarction inflammatory response, namely neutrophil count and C-reactive protein. These latter parameters were quite strongly associated with infarct size.

Inflammation has been shown to be implicated in several processes involved in the sequence of events that follow the obstruction of an epicardial coronary artery in the context of STEMI, including thrombus composition,[13] endothelial function,[14,15] postinfarction myocardial function,[16,17] clinical events,[18–22] and, even, peri-infarct kidney injury.[23] There is also evidence that timelier reperfusion leads to a blunted inflammatory response,[24] whereas C-reactive protein levels following STEMI are predictive of left ventricular remodeling,[25] and inflammatory mediators are correlated with biomarkers of cardiac dysfunction.[26] Most importantly, specific components of the cellular inflammatory response have been shown to be strongly correlated with STEMI-related myocardial damage: monocyte response has been associated with severe myocardial injury and poor functional outcome after STEMI,[27] and neutrophil peaks have been found to predict MRI-defined infarct size.[28] In view of this evidence, the significant inverse correlation of colchicine treatment with post-STEMI neutrophil rise, which was observed in the present study, suggests a potential mechanism of the observed beneficial effect of colchicine (along with the observed association of neutrophil count with infarct size, which was strong for all patients independently of treatment allocation).

Colchicine is a drug with well-known anti-inflammatory properties, shown to be safe in various settings of cardiovascular disease.[29–31] Its unique effects stem from its ability to interfere with microtubule polymerization. At a structural level, each hollow microtubule is assembled from 13 parallel protofilaments, which in turn comprise alternating, very tightly linked, α- and β-tubulin subunit pairs organized along a longitudinal axis.[32] Colchicine binds to the intradimeric α-β interface, in the center of the tubulin heterodimer.[33–35] By interfering with microtubule polymerization, colchicine affects virtually every process that requires cytoskeletal changes, including cell mitosis, exocytosis, and motility, and, mainly owing to its pharmacokinetics, these effects are particularly potent on inflammatory cells.[36] Inhibition of interleukin-1 production by activated neutrophils, downregulation of tumor necrosis factor-α receptors in macrophages and endothelial cells, and impairment of the adhesion of neutrophils to the vascular endothelium, probably through modulation of endothelial E-selectin and neutrophil L-selectin surface expression, are some of the ways colchicine affects inflammatory responses.[36,37]

Experimental or clinical data regarding the role of colchicine in STEMI are sparse. In 1 study, in an open-chest canine model of reperfusion injury, the number of circulating neutrophils, neutrophil cytotoxicity, and neutrophil myocardial accumulation after 6 hours of reperfusion were reduced in

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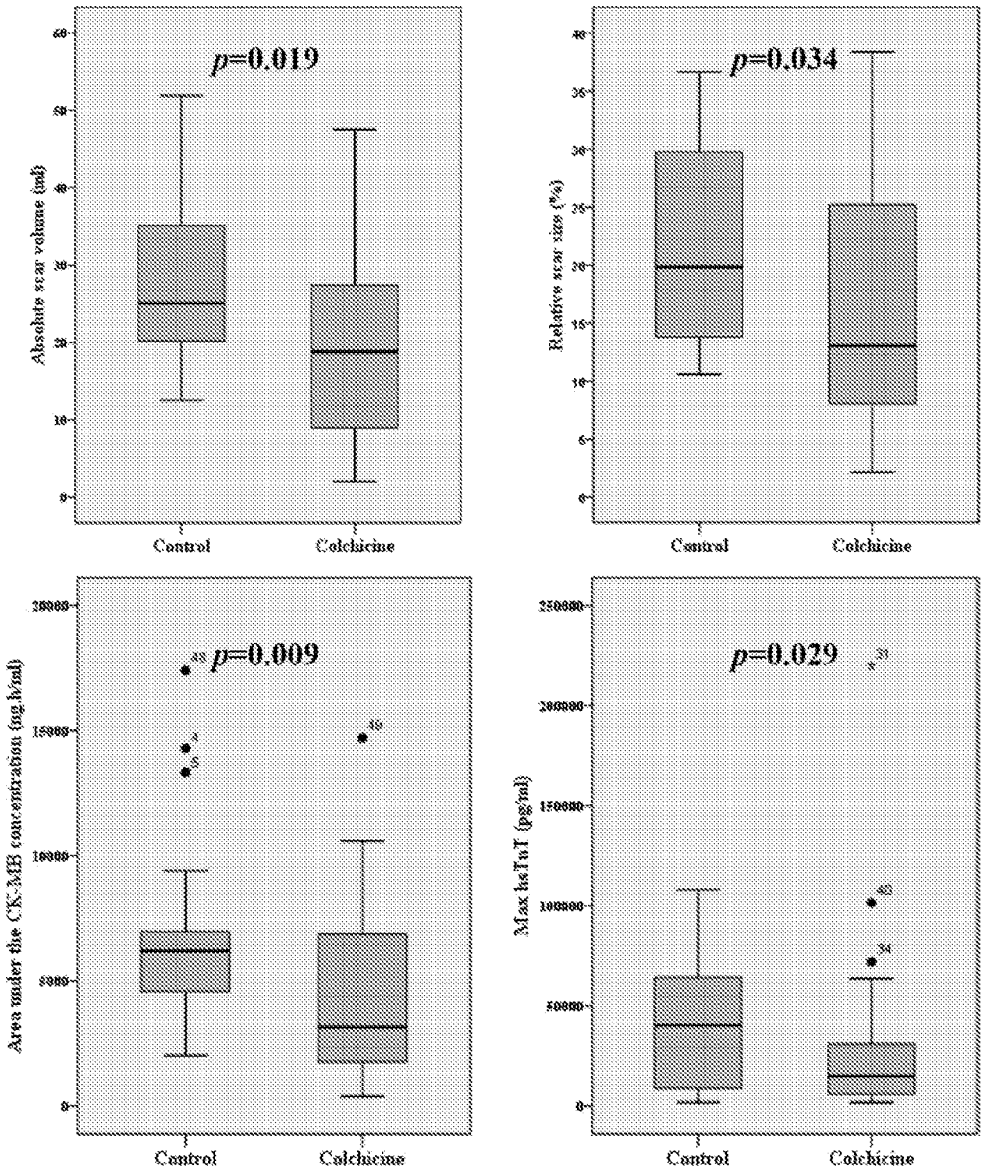


Figure 4. MRI- and biomarker-defined infarct size in the MRI subgroup. Boxplot graphs illustrating the distribution of infarct size descriptors in the 2 treatment arms in patients who underwent cardiac MRI (see Figure 3 for explanation of boxplot elements). CK-MB indicates creatine kinase-myocardial brain fraction; and hs-TnT, high-sensitivity troponin T.

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colchicine-treated dogs, although there was no difference in infarct size.[38] To our knowledge, no study has assessed the effect of colchicine on infarct size in humans. Raju et al[39] studied a mixed population of 80 patients with STEMI, non–ST-segment–elevation acute coronary syndrome, and ischemic stroke and found no difference in C-reactive protein between patients on colchicine and controls 30 days after the index event (a time point at which one would expect acute inflammatory processes to have subsided even in patients not taking any anti-inflammatory treatment, which renders this finding difficult to interpret in a clinically meaningful way). On the other hand, colchicine has already been shown to be associated with reduced myocardial damage in another setting of ischemia/reperfusion myocardial insult, namely that of cardiac surgery.[40]

Studies of other agents with anti-inflammatory action have given varying results in improving outcomes following STEMI. In 2 small studies, an interleukin-1 inhibitor was associated with a lower incidence of heart failure after the index myocardial infarction.[41,42] However, in another study in patients with non–ST-segment–elevation acute coronary syndrome, the same agent, despite a significant reduction

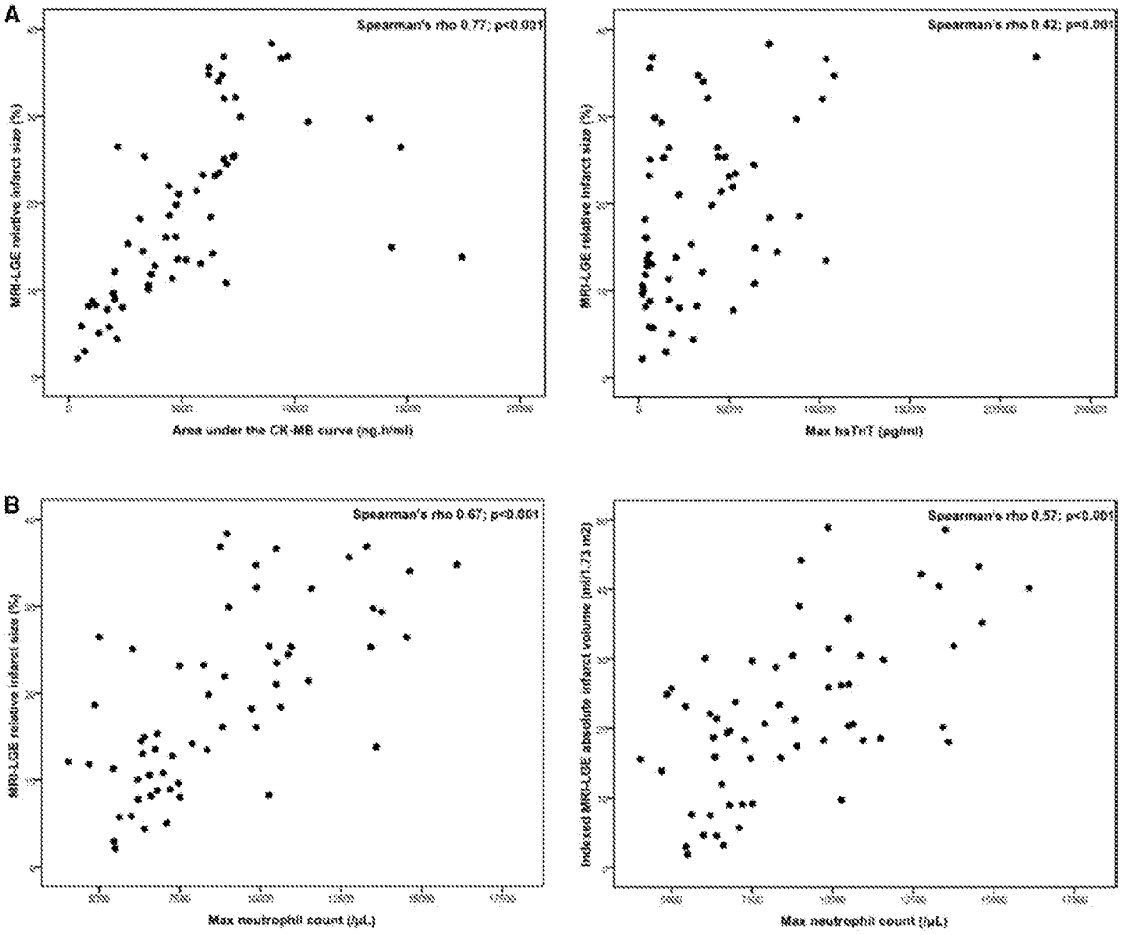


Figure 5. **A**, Correlations between biomarkers and MRI-defined infarct size. Scatterplots of biochemical vs imaging descriptors of infarct size illustrating an expected relationship between these 2 measures of infarct size. **B**, Correlations between neutrophil count and MRI-defined infarct size. Scatterplots of maximal postinfarction neutrophil absolute count vs relative (as a proportion of the left ventricular mass) and body surface area–indexed absolute infarct size. CK-MB indicates creatine kinase-myocardial brain fraction; hs-TnT, high-sensitivity troponin T; and LGE, late gadolinium enhancement.

in biomarkers of inflammation, was associated with more recurrent events at 1 year (although it should be noted that this study was not designed to evaluate clinical end points and, in any case, non–ST-segment–elevation acute coronary syndrome pathophysiology differs substantially from that of STEMI).[43] Of note, the immunosuppressive agent cyclosporine has been shown to have a beneficial effect on infarct size in STEMI[44]; although the authors suggest that cyclosporine had a cardioprotective effect as a result of inhibition of the opening of mitochondrial permeability-transition pores, the possibility that its immunosuppressive action may also have played a role in the observed effect cannot be discounted. In any case, interest in this area of research remains unabated, with large clinical trials of novel anti-inflammatory agents underway.[45]

In this context, the findings of the present study are quite remarkable, given that a favorite effect of treatment was found in all studied parameters (biomarkers and cardiac MRI). It is possible that the broadness of colchicine effects (affecting various pathways of the inflammatory processes) is an advantage in the complex pathophysiological interplay between inflammation, ischemia, and reperfusion in reperfused STEMI. However, one should probably go beyond statistical significance and note, by observing the distribution of evaluated infarct sizes in colchicine-treated patients (eg, in Figure 3), that there was a marked dispersion of values, possibly indicating considerable heterogeneity in the drug effect (or, even more probably, a result of the considerable proportion of premature discontinuation of the study drug). This observation, along with the fact that the study was not powered to demonstrate differences in hard clinical end points, must define the boundaries in generalizing these results: they are certainly compelling, pointing toward potential usefulness of colchicine in this setting, but further studies are definitely necessary to draw secure clinical conclusions.

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Study Limitations

The studied measures of infarct size (CK-MB output and MRI-LGE infarct size) are well validated in this setting, with good correlation with prognosis[46,47] – although limitations can arise both in the case of CK-MB (eg, when different sampling intervals are used in the concentration versus time plot and when comparing patients with altered enzyme kinetics) and in the case of MRI (probably the most important factor is the timing of the measurement relative to the index event). These potential sources of error were carefully kept to a minimum in the present study.

Sources of Funding

This was an investigator-initiated and -funded study.

Disclosures

None.

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CLINICAL PERSPECTIVE

In this study, a short course of colchicine treatment or placebo was administered to 151 patients with ST-segment–elevation acute myocardial infarction treated with primary percutaneous coronary intervention. Colchicine was started in the catheterization laboratory and was continued for 5 days. The primary end point was the area under the creatine kinase-myocardial brain fraction curve over the first 72 hours of hospitalization and, in a subset of 60 patients, infarct size was also assessed with cardiac MRI with late gadolinium enhancement 6 to 9 days after the index myocardial infarction. Both biomarker- and MRI-late gadolinium enhancement–defined infarct size was smaller in patients of the active treatment group. Infarct size was positively associated with markers of inflammation (neutrophil count and C-reactive protein), and colchicine treatment was correlated with lower levels of these markers. The findings suggest a role for anti-inflammatory treatment in the peri-infarct period. Although the study was not powered to assess clinical outcomes, the surrogate outcome measures that were used are well-established correlates of prognosis and clinical events. Still, for any firm recommendations for colchicine treatment in patients with acute myocardial infarction to be made, a larger study with clinical end points would be needed.

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The Low Dose Colchicine after Myocardial Infarction (LoDoCo-MI) study: A pilot randomized placebo controlled trial of colchicine following acute myocardial infarction

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Background Following an acute myocardial infarction (MI), patients with persistently elevated biomarkers of inflammation, in particular C-reactive protein (CRP), are at significantly increased risk of further cardiovascular events. Colchicine is a unique anti-inflammatory medication that has shown promise in reducing such events in patients with stable coronary heart disease. The current study tested the ability of low dose colchicine to reduce CRP levels at 30 days after an acute MI, a key marker of future outcome, and its safety and tolerability in this setting.

Methods We conducted a randomized, double-blind, trial of low-dose colchicine (0.5 mg daily) or matching placebo in 237 patients admitted with an acute MI. The primary end-point was the proportion of patients with a residual high sensitivity CRP level ≥2 mg/L after 30 days of treatment, a threshold associated with a worse prognosis.

Results At 30-day follow-up, 44% of patients treated with colchicine had a CRP level ≥2 mg/L compared to 50% of those randomized to placebo ($P = .35$) and the median CRP in patients randomized to colchicine was 1.6 mg/L (interquartile range [IQR] 0.7–3.5) compared to 2.0 mg/L (IQR 0.9–4.0) in patients randomized to placebo ($P = .11$). The median absolute reduction in CRP levels was −4.3 mg/L (IQR −1.1 to −14.1) among colchicine treated patients and −3.3 mg/L (IQR −0.9 to −14.4, $P = .44$) in placebo treated patients. The relative reduction was a fall of 78% compared to a fall of 64% ($P = .09$). Low dose colchicine was well tolerated and did not reduce compliance with other secondary preventative medications at 30-days.

Conclusion Treatment with low dose colchicine was safe and well tolerated, but was not associated with a significantly increased likelihood of achieving a CRP level <2 mg/L or lower absolute levels of CRP 30 days after an acute MI. (Am Heart J 2019;215:62-9.)

Inflammation is central to the pathogenesis of atherosclerosis and its acute manifestations.[1-3] Likewise, patients with higher levels of the inflammatory biomarker C-reactive protein (CRP) 30 days following an acute myocardial infarction (MI) are at increased risk of recurrent infarction and death due to coronary heart disease (CHD).[4] It has been hypothesized, therefore, that therapies that specifically target inflammatory pathways might reduce recurrent vascular events in this setting. One such approach is to target specific pro-inflammatory cytokines.[5] This strategy was recently tested in the Canakinumab Anti-Inflammatory Thrombosis Outcome Study (CANTOS) which demonstrated that treatment with a therapeutic monoclonal antibody targeting interleukin-1β significantly reduced major adverse cardiovascular events in survivors of an acute MI with persistently elevated CRP levels (≥2 mg/L).[6] Canakinumab is, however, a very costly treatment and was associated with a significant increase in sepsis and fatal infection.[6] There is, therefore, a clear need for cheaper and safe alternatives.

Colchicine, is one of the oldest anti-inflammatory agents available and has been used for decades to treat

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gout, familial Mediterranean fever and pericarditis. Its mechanisms of action are complex and not fully understood but include a reduced responsiveness of neutrophils to inflammatory signals[7,8] and suppressed activation of the NOD-like receptor protein 3 (NLRP3) inflammasome, a similar pathway to that inhibited by canakinumab.

Initial studies of colchicine in patients with CHD have been promising[9-13] but its ability to reduce inflammation in patients following an acute MI has not been adequately tested. Likewise, before embarking on a large and expensive end-point trial, it is essential that the safety and tolerability of colchicine is established in the post infarct setting. This is particularly important as the commonest side effect of colchicine is gastrointestinal upset, which has led to drug withdrawal in 10% to 15% of patients in prior clinical trials,[9,14] and might result in reduced adherence to other important secondary prevention medications. In addition, the combination of colchicine and high-dose statins has been rarely associated with myotoxicity[14] and there is a theoretical interaction between ticagrelor, a weak p glycoprotein and CYP3A4 inhibitor, and colchicine.

The primary objective of the current study was to test the hypothesis that patients who are commenced on low dose colchicine early after acute MI would have significantly lower levels of CRP at 30 days, suggesting a lower risk of recurrent vascular events. The secondary aims were to test a) the effects of low dose colchicine on interleukin 6 (IL-6), a key regulator of inflammation and hepatic CRP production,[15] and b) the safety and tolerability of colchicine when initiated in patients early after an acute MI.

Methods

Study design and participants

This was an investigator initiated randomized, double-blind placebo controlled clinical trial. Patients were randomized in a 1:1 ratio to receive either colchicine 0.5 mg once daily or matched placebo for 30 days. Adult (>18 years old) patients were eligible for enrolment if they had sustained a type 1 acute MI (by the 3rd universal definition[16]) within the prior 7 days. All patients were recruited at Royal Perth Hospital, Perth, Western Australia.

Exclusion criteria included a) a history of myopathy, leukopenia or thrombocytopenia; b) an estimated glomerular filtration rate <45 mL/min per 1.73m^2; c) severe hepatic dysfunction (alanine aminotransferase >3 upper limit of normal [ULN]); d) therapy with a P-glycoprotein inhibitor (eg, cyclosporin, verapamil or quinidine) or a strong CYP3A4 inhibitor (eg, ritonavir, clarithromycin or ketaconazole); e) pregnancy, lactation or women of childbearing age not using contraception; f) an indication for colchicine therapy or g) any active inflammatory or infective disease process.

The study was registered prospectively with the Australian and New Zealand Clinical Trials Registry (ACTRN12615001194550) and approved by the local human research ethics committee. All participants provided written informed consent. Funding for this research was provided by the National Heart Foundation of Australia (grant number 100616) and the Royal Perth Hospital Medical Research Foundation. Colchicine and placebo were provided free of charge by Aspen Pharmaceuticals.

Trial procedures

Patients were recruited during their index admission following acute MI. Baseline clinical data, medications, biochemistry, full blood count and creatine kinase (CK) levels were recorded and blood tests were be repeated at 30 days. Troponin I levels at presentation and the peak levels during hospitalization were recorded using a high sensitivity assay (Abbott Laboratories, Abbott Park, IL). Left ventricular ejection fraction was assessed using standard methods (wherever possible a biplane Simpsons assessment) and determined by a consultant cardiologist blinded to treatment allocation. Levels of CRP were measured using a high sensitivity assay (Architect c16000 Analyzer, Abbott Laboratories, Abbott Park, IL) at baseline (immediately prior to commencing study treatment) and at 30 days. In addition, EDTA-plasma samples taken at baseline and 30 days were aliquoted and stored at −80 °C. IL-6 levels were subsequently measured by highly sensitive ELISA (R&D Systems, Minneapolis, MN). The sensitivity of this assay is 0.7 pg/mL with inter- and intra-assay coefficients of variation <7% and <5% respectively.

At 30 days patients underwent a standardized questionnaire to document the acceptability of the study procedures and any adverse events. These were graded by the patients as mild, moderate or severe. Patients were also asked to report their compliance with study medication (number of days when this was not taken). In addition, they were asked to return their study medication bottles with any remaining tablets and a pill count was performed.

Outcomes

The primary end-point was the proportion of patients with a residual CRP level ≥2 mg/L at 30 days. Pre-specified secondary end-points included the actual levels of CRP at 30 days and the relative and absolute change in CRP levels from baseline to 30 days. Other important pre-specified outcomes included a) the proportion of recruited patients completing the study; b) adverse events; c) participant-reported compliance with study medications; and d) death and major cardiovascular events (further MI or stroke) at 30 days.

Statistical analyses

Based on prior data[3] we estimated that 30 days after an acute MI approximately 42% of patients receiving a potent statin and aspirin will have a CRP level ≥2 mg/L. On this

basis, a study of 210 patients has 90% power (2 sided α = 0.05) to detect a 50% reduction in the prevalence of CRP levels above this threshold (i.e. to 21% with CRP ≥2 mg/L), allowing for 7% data loss. This reduction in levels of CRP is less than previously reported in patients with stable CHD treated with colchicine.[17]

Data are presented as numbers (%), mean (standard deviation) and median (interquartile range), as appropriate. The normality of the distribution of variables was assessed using the Shapiro–Wilk test. Continuous variables with skewed distributions are compared using the Kruskal-Wallis test and categorical variable using the χ^2 test or Fisher's exact test, as appropriate. All analyses were performed according to the intention to treat principle using SPPS v24. All p-values are 2-sided. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

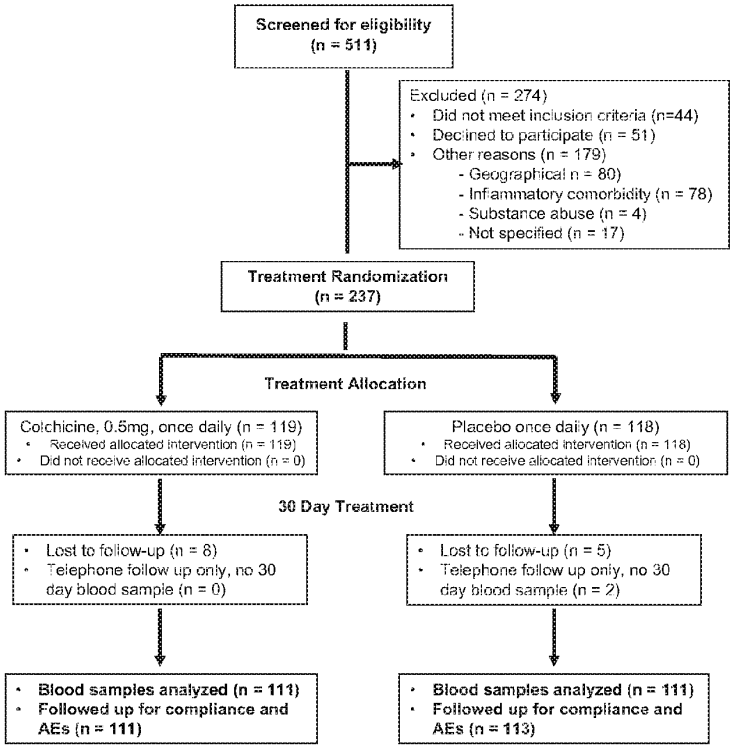
Results

Two hundred thirty seven patients were recruited between February 2016 and July 2017 and 224 patients (95%) completed the study (figure 1). Two patients, both of whom were randomized to placebo, were only able to undergo telephone follow up and did not have a follow up blood sample taken. The baseline demographic and clinical characteristics of both study groups were similar (table 1). The mean age of participants was 61 years and 182 (77%) were men. Baseline blood samples were taken a mean of 1.5 (SD 1.1) days and follow-up samples a mean of 33.3 (SD 5.6) days following the index MI.

Levels of high sensitivity C-reactive protein, interleukin 6 and other blood tests at 30 days

The median level of CRP at baseline was 7.4 mg/L (interquartile range 3.0–16.9) and was similar in both groups (P = .77, table 1 and figure 2a). At 30-day follow up, 44% (49 out of 111 participants) treated with colchicine had a CRP level ≥2 mg/L compared to 50% (56 out of 111 participants) of those randomized to placebo (P = .35, table 2) and the median CRP in patients randomized to colchicine was 1.6 mg/L (interquartile range 0.7–3.5) compared to 2.0 mg/L

Figure 1



CONSORT diagram.

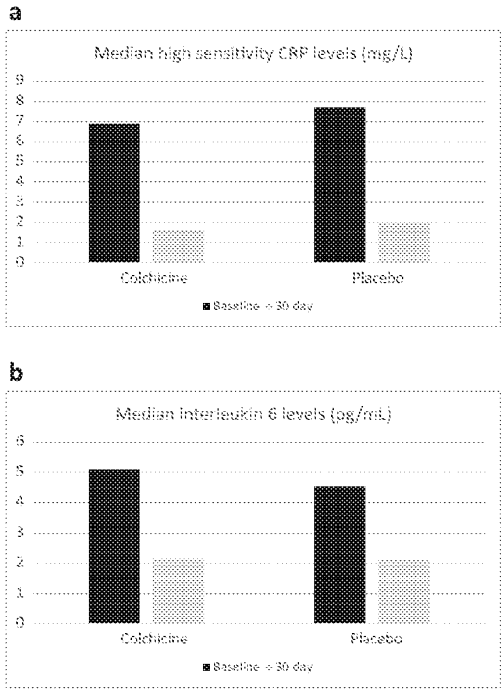
Table 1. Patient characteristics according treatment group

Characteristic	Total (n = 237)	Colchicine (n = 119)	Placebo (n = 118)	P
Age in years, mean (standard deviation)	61 (13.0)	61 (13.6)	61 (12.5)	.77
Male	182 (77%)	89 (75%)	93 (79%)	.46
Diabetes	52 (22%)	27 (23%)	25 (21%)	.78
Hypertension	112 (47%)	64 (54%)	48 (41%)	.04
Prior or current smoking	143 (60%)	77 (65%)	67 (57%)	.21
ST-elevation myocardial infarction	134 (56.5%)	63 (53%)	71 (60%)	.26
Previous myocardial infarction	36 (15%)	18 (15%)	18 (15%)	.98
Prior myocardial revascularization	27 (11%)	13 (11%)	14 (12%)	.60
Coronary angiogram during index admission	236 (99.6%)	118 (99%)	118 (100%)	.32
PCI during index admission	213 (90%)	105 (88%)	108 (91.5%)	.40
Left ventricular ejection fraction	52 (42–60)	55 (42–60)	50 (44–60)	.90
Aspirin	237 (99.6%)	118 (99%)	118 (100%)	.32
Second anti-platelet agent	233 (98%)	115 (97%)	117 (99%)	.18
Beta blocker	220 (93%)	111 (93%)	109 (92%)	.79
ACE inhibitor / Angiotensin receptor blocker	223 (94%)	114 (96%)	109 (92%)	.26
Statin	233 (98%)	115 (97%)	118 (100%)	.05
Body mass index,	28 (26–30)	28 (25–30)	28 (26–30)	.98
Admission high sensitivity troponin I (ng/L)	1345 (221–15,525)	885 (521–14,125)	2220 (298–16,425)	.19
Peak high sensitivity troponin I (ng/L)	5920 (611–30,450)	3250 (358–32,450)	9360 (975–28,875)	.18
Baseline hemoglobin, g/L	141 (15)	141 (15)	141 (16)	.94
Baseline white cell count, $x10^9$/L	9.0 (7.4–10.7)	9.0 (7.4–10.7)	9.2 (7.4–10.6)	.88
Baseline neutrophil count, $x10^9$/L	6.0 (4.7–7.7)	5.7 (4.7–7.5)	6.2 (4.7–7.8)	.39
Baseline lymphocyte count, $x10^9$/L	1.9 (1.5–2.4)	1.8 (1.5–2.4)	1.9 (1.5–2.3)	.46
Baseline creatinine, μmol/L	76 (68–87)	75 (68–87)	77 (69–87)	.38
Baseline high sensitivity C-reactive protein, mg/L	7.4 (3.0–16.9)	6.9 (3.1–14.8)	7.7 (3.0–18.9)	.77
Baseline interleukin-6, pg/mL	4.84 (3.10–9.50)	5.09 (3.42–9.99)	4.55 (3.05–8.33)	.15

Categorical data presented as n (%) and continuous data as median (interquartile range), unless otherwise stated.
PCI, percutaneous coronary intervention; ACE, angiotensin converting enzyme.

(interquartile range 0.9–4.0) in patients randomized to placebo ($P = .11$, figure 2a). The median absolute reduction in CRP levels at 30 days among colchicine treated patients was −4.3 mg/L (interquartile range −1.1 to −14.1) and in placebo treated patients it was −3.3 mg/L (interquartile range −0.9 to −14.4, $P = .44$). The relative reduction was a fall of 78% compared to a fall of 64% ($P = .09$).

Figure 2



Median levels of high sensitivity C-reactive protein and interleukin 6 at baseline and 30-days.

Levels of IL-6 at 30 days were similar in both groups both at baseline and follow-up and there were similar absolute and relative decreases in levels between baseline and 30 days (tables 1 and 2 and figure 2b). White cell counts, liver and muscle enzymes and other blood tests were also similar (tables 1 and 2).

Clinical outcomes, tolerability, and safety

There were no recorded deaths during the 30 day follow up period, though the vital status of 2 patients who were lost to trial follow-up was uncertain. Two patients suffered a major cardiac event (myocardial infarction) within 30 days; both of these participants had been randomized to placebo. Overall 38 patients (17% of the 224 who completed the study protocol) experienced any adverse event during 30 day follow up. Of these patients, 18 (of 111 who completed the study, 16%) had received colchicine and 20 (of the 113 who completed the study, 18%) placebo ($P = .859$). Fifteen patients were readmitted to hospital within 30 days of their index MI (1 due to recurrent non-ST-elevation myocardial infarction, 1 due to stent thrombosis, 7 due to non-cardiac chest pain, 2 due to pericarditic symptoms, 1 due to breathlessness, 1 due to vasovagal syncope, 1 for insertion of an implantable defibrillator and 1 due to hematuria). Of these 3 were in the colchicine treated group (out of 111, 3%) and 12 were in the placebo group (out 113, 11%; $P = .029$).

Gastrointestinal symptoms occurred in 18 patients (8%), 12 who received colchicine (11% of the 111 patients in this group who completed the study) and 6 who received placebo (5% of the 113 patients in this group who completed the study; $P = .147$). Nine patients rated these to be moderate or severe (4 who received colchicine and 5 who received placebo).

Adherence with study and other secondary prevention medications was generally good (table 3).

Discussion

The main findings of this study are that treatment with low dose colchicine (0.5 mg daily) is not associated with a significantly increased likelihood of achieving a CRP level <2 mg/L or lower absolute levels of CRP 30 days after an acute MI. Nevertheless, a trend in this direction was observed and, importantly, treatment with colchicine in

Table 2. Blood results at 30-day follow-up

	Colchicine group (n = 111)	Placebo group (n = 111)	P
High sensitivity C-reactive protein ≥2 mg/L	49 (44%)	56 (50%)	.35
High sensitivity C-reactive protein, mg/L	1.6 (0.7–3.5)	2.0 (0.9–4.0)	.11
Absolute change in C-reactive protein, mg/L	−4.3 (−1.1 to −14.1)	−3.3 (−0.90 to −14.4)	.44
Relative change in C-reactive protein (%)	−78 (−44 to −92)	−64 (−30 to −88)	.09
White cell count, $x10^9$/L	6.7 (5.8–8.7)	7.2 (6.1–8.8)	.22
Neutrophil count, $x10^9$/L	4.3 (3.4–5.4)	4.3 (3.7–5.8)	.25
Lymphocyte count, $x10^9$/L	1.9 (1.4–2.3)	1.8 (1.5–2.1)	.64
Hemoglobin, g/L	140 (133–151)	142 (132–152)	.36
Creatine kinase, U/L	116 (81–165)	101 (70–138)	.14
Alanine aminotransferase, U/L	33 (25–54)	33 (26–49)	.84
Gamma glutamyl transferase, U/L	30 (20–56)	31 (25–49)	.68
Interleukin-6, pg/mL	2.16 (1.72–2.76)	2.12 (1.66–2.77)	.95
Absolute change in interleukin-6, pg/mL	−2.44 (−0.94 to −7.56)	−2.33 (−0.56 to −5.15)	.21
Relative change in interleukin-6 (%)	−58 (−32 to −79)	−52 (−19 to −66)	.16

Categorical data presented as n (%) and continuous data as median (interquartile range).

this setting was safe and well tolerated. Readmission rates were significantly lower in the colchicine treated patients but the numbers are small, the events were diverse and the majority were for relatively benign reasons and/or events that seem unlikely related to the trial medication. Thus, the observed differences seem likely to be due to chance.

Prior studies

There is great interest in using therapies that specifically target inflammatory mechanisms in order to reduce the risk of atherosclerosis and its acute complications.[18] Potential treatments include monoclonal antibodies that target specific pro-inflammatory cytokines, such as canakinumab directed against IL-1β which has recently

Table 3. Adverse events and adherence to study and concomitant medications at 30-day follow up

	Colchicine group (n = 111)	Placebo group (n = 113)	P
Any adverse event	18 (16%)	20 (18%)	.859
Re-admission to hospital	3 (3%)	12 (11%)	.029
Adverse event not requiring hospitalisation[1]	16 (14%)[1]	8 (7%)	.087
Gastrointestinal	12 (11%)	6 (5%)	.147
Other[2]	4 (4%)	2 (2%)	.440
Discontinued study treatment due to adverse event	2 (2%)	4 (4%)	.439
Took ≥25 days of study treatment[3]	102 (92%)	103 (93%)[3]	1.000
Other medications being taken at follow up[3]			
Aspirin	110 (99%)	111 (100%)[3]	1.000
Second anti-platelet agent	106 (95%)	110 (99%)[3]	.212
Statin	107 (96%)	109 (98%)[3]	.683
Beta-blocker	105 (95%)	109 (98%)[3]	.280
ACE inhibitor or angiotensin receptor blocker	104 (94%)	106 (95%)[3]	.768

ACE, angiotensin converting enzyme.
1 One patient had readmission to hospital with chest pain (non-cardiac) and also independently experienced an adverse event not requiring hospitalization (gastrointestinal symptoms); [2] other adverse events consisted of cough (x2), rash, palpitation, breathlessness and bruising; [3] in 2 patients (both in the placebo group) these data were not recorded.

been shown to significantly reduce major adverse cardiovascular events in patients with a previous MI and residual CRP levels ≥2 mg/L, already receiving high quality conventional secondary prevention. Recently, however, the Cardiovascular Inflammation Reduction Trial investigators, reported disappointing results from a trial of 4786 patients with a prior history of myocardial infarction or multi-vessel coronary artery disease plus diabetes or metabolic syndrome randomized to low-dose methotrexate or placebo.[19] This trial was stopped prematurely after a median of 2.3 years follow up, due to crossing the pre-specified futility boundary. Despite well documented anti-inflammatory actions and supportive observational data, low dose methotrexate (15–20 mg weekly) failed to significantly reduce circulating levels of CRP, IL-1β or IL-6 when compared to placebo.[19] Likewise, there was no significant reduction in either the original primary outcome (cardiovascular death, non-fatal MI or non-fatal stroke) or an expanded outcome that also included hospitalization for unstable angina that required urgent revascularisation.[19]

Colchicine is a cheap, once daily, oral treatment that targets similar inflammatory mechanisms to canakinumab, seems safe and well tolerated by patients receiving long term therapy and has shown considerable promise in early studies of patients with CHD.

In the Low Dose Colchicine (LoDoCo) study, treatment with 0.5 mg colchicine per day in addition to standard treatment in patients with stable CHD significantly reduced the risk of developing an acute coronary syndrome, an out of hospital cardiac arrest or non-cardioembolic stroke.[9] This study was not, however, placebo controlled, though end-points were adjudicated by clinicians blinded to what treatment the patients had received. A further double-blind randomized controlled trial in a similar population is currently underway.

In patients with an acute coronary syndrome colchicine reduces the local production of IL-1β, IL-18 and IL-6, as measured in coronary sinus blood samples.[10] These reductions in all 3 inflammatory cytokines were marked (with a reduction in IL-6 of 88%) and occurred after only 24 hours of colchicine therapy. In addition, short term (24 hours) treatment with colchicine also reduces inflammasome-dependent inflammation in patients following an acute coronary syndrome, as measured by the in vitro production of IL-1β and caspase-1 protein by monocytes.[11] Thus, there are plausible biological mechanisms supporting the hypothesis that prompt treatment after acute MI would result in an early reduction in pro-inflammatory pathways and potentially a lower risk of clinical events.

Short term (5 days) treatment with colchicine appears to reduce the extent of myocardial necrosis after ST-elevation MI[12] and long term treatment has been associated with reduced features of plaque instability on coronary artery CT angiography, in particular low intensity plaque volume.[13] In this latter study treatment with colchicine 0.5 mg daily was also associated with a significantly lower level of CRP at 1 year, mean value in colchicine treated patients (n = 40) 1.85 mg/L (SD 0.9) versus 2.26 mg/L (SD 1.05) in controls (n = 40), with a 37% reduction observed in colchicine treated patients compared to a 15% reduction in untreated patients. Although this study was not randomized or placebo controlled the assessment of CT scans was undertaken by observers blinded to whether the subject had received colchicine or not. Likewise, the impact of colchicine on CRP levels was broadly similar to the current double-blinded placebo controlled trial.

Another small study has also assessed the impact of colchicine on CRP levels after an acute coronary syndrome or stroke.[20] This randomized 80 patients (73 out of 80, 91% following an acute coronary syndrome) to colchicine 1 mg daily or placebo for 30 days. At follow-up patients allocated to colchicine had a median CRP level of 1 mg/L compared to a median level of 1.5 mg/L in placebo treated patients ($P = .22$). Likewise, the percentage of patients with a CRP level <2 mg/l was higher in the colchicine treated group (77%) compared to placebo (62%). Though this did not attain statistical significance ($P = .18$) this study was very underpowered (CRP levels at 30 days were only available in 68 patients, 31 who had received colchicine and 37 who had received placebo). The results are, however, consistent with the findings from the current study and suggest that colchicine might have a modest, but potentially clinically beneficial, effect in this setting and that further work in this area is required.

Strengths and limitations

This study is the largest to date assessing the tolerability of colchicine following acute MI and its effects on markers of inflammation in patients receiving contemporary treatment, including a range of evidence based secondary preventative medications. Nonetheless, it has several limitations. It is a small, single center study which was not powered to demonstrate any impact of colchicine on adverse cardiovascular events. Likewise, it was powered to demonstrate a large reduction in levels of CRP, which was not observed in the current study, though larger reductions in CRP levels have been reported in patients with stable CHD treated with colchicine (albeit at a slightly higher dose of 0.5 mg twice daily).[17] It is possible that a larger study would have shown a significant reduction in such levels assuming a smaller, but still clinically relevant, effect size.

The other main limitation of the current trial is that it only tested the tolerability of low dose colchicine over 30 days. Other studies have, however, suggested that it is well tolerated at a dosage of 0.5 mg daily in patients with stable CHD. Thus, the main until now unresolved issue was its tolerability in patients receiving many other

medications, some of which have theoretical or known interactions with colchicine, often for the first time after an acute MI: a setting where the adverse effects of one medication may have implications for compliance with other treatments that are known to have important benefits. The current study provides reassurance in this respect.

In conclusion, we found no significant reduction in the median level of CRP, the absolute or relative reduction in levels or the percentage of patients who had levels of CRP below 2 mg/L after 30-days. All were, however, lower in colchicine treated patients which is consistent with prior data. We believe, therefore, that the totality of evidence supports the need for a large scale outcome trial in patients with recent MI. Importantly in this regard the current study demonstrates the safety and tolerability of low dose colchicine after acute MI.

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Declarations of interest

The authors have no conflicts of interest related to this work.

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Colchicine Therapy and Plaque Stabilization in Patients With Acute Coronary Syndrome

A CT Coronary Angiography Study

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ABSTRACT

OBJECTIVES The authors sought to evaluate the plaque-modifying effects of low-dose colchicine therapy plus optimal medical therapy (OMT) in patients post-acute coronary syndrome (ACS), as assessed by coronary computed tomography angiography (coronary CTA).

BACKGROUND Colchicine therapy has been postulated to have beneficial anti-inflammatory effects in patients with ACS, translating into reduction in future adverse cardiovascular events. However, whether favorable plaque modification underpins this is yet unproven.

METHODS In this prospective nonrandomized observational study of 80 patients with recent ACS (<1 month), patients received either 0.5 mg/day colchicine plus OMT or OMT alone and were followed for 1 year. Our primary outcome was change in low attenuation plaque volume (LAPV), a marker of plaque instability on coronary CTA and robust predictor of adverse cardiovascular events. Secondary outcomes were changes in other coronary CTA measures and in high-sensitivity C-reactive protein (hsCRP).

RESULTS Mean duration of follow-up was 12.6 months; mean age was 57.4 years. Colchicine therapy significantly reduced LAPV (mean 15.9 mm^3 [−40.9%] vs. 6.6 mm^3 [−17.0%]; $p = 0.008$) and hsCRP (mean 1.10 mg/l [−37.3%] vs. 0.38 mg/l [−14.6%]; $p < 0.001$) versus controls. Reductions in total atheroma volume (mean 42.3 mm^3 vs. 26.4 mm^3; $p = 0.28$) and low-density lipoprotein levels (mean 0.44 mmol/l vs. 0.49 mmol/l; $p = 0.21$) were comparable in both groups. With multivariate linear regression, colchicine therapy remained significantly associated with greater reduction in LAPV ($p = 0.039$) and hsCRP ($p = 0.004$). There was also a significant linear association ($p < 0.001$) and strong positive correlation ($r = 0.578$) between change in LAPV and hsCRP.

CONCLUSIONS Our findings suggest, for the first time, that low-dose colchicine therapy favorably modifies coronary plaque, independent of high-dose statin intensification therapy and substantial low-density lipoprotein reduction. The improvements in plaque morphology are likely driven by the anti-inflammatory properties of colchicine, as demonstrated by reductions in hsCRP, rather than changes in lipoproteins. Colchicine may be beneficial as an additional secondary prevention agent in patients post-ACS if validated in future studies. (J Am Coll Cardiol Img 2018;11:305–16)
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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

CAD = coronary artery disease

CV = cardiovascular

CVD = cardiovascular disease

CTA = computed tomography angiography

DCPV = dense calcified plaque volume

hsCRP = high-sensitivity C-reactive protein

HU = Hounsfield units

IL = interleukin

LAP = low attenuation plaque

LAPV = low attenuation plaque volume

LDL = low-density lipoprotein

MACE = major adverse cardiovascular events

NCPV = noncalcified plaque volume

OMT = optimal medical therapy

TAV = total atheroma volume

TC = total cholesterol

Inflammation plays a pivotal role in all stages of atherosclerotic plaque development, including promotion of plaque instability and acute coronary syndrome (ACS) presentation. In the coronary vasculature, inflammation is not localized to the culprit stenosis; persistent inflammatory cell activation has been demonstrated at sites remote from an index plaque rupture. This may lead to recurrent plaque rupture and cardiovascular (CV) events, despite optimal medical therapy (1,2).

Colchicine is a commonly used anti-inflammatory medication that prevents mitosis via inhibition of microtubule polymerization (3–5). Low-dose colchicine has been proven to be safe, well tolerated, inexpensive, and readily available. There is increasing evidence supporting a potentially beneficial role for colchicine therapy in prevention of cardiovascular disease (CVD). Our group has recently shown that short-term colchicine administration in patients with ACS significantly reduces systemic and local transcoronary production of inflammatory cytokines implicated in atherosclerosis (3). However, it is unknown whether these cytokine changes translate into favorable plaque modification.

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Coronary computed tomography angiography (coronary CTA) is a noninvasive imaging modality that not only detects significant coronary artery anatomic stenoses, but also allows detailed examination of coronary plaque composition. Specific plaque morphologies on coronary CTA are suggestive of vulnerability to rupture and are associated with future ACS events, such as low attenuation plaque (LAP), positive remodeling, spotty calcification, and the "napkin ring" sign. Of these, LAP has been consistently shown to be the best marker of instability and strongest prognostic predictor of a future adverse CV event (6,7). Although a number of studies have used serial coronary CTAs to assess plaque progression and changes in morphology after a specific intervention, such as statin therapy, this has never been performed with colchicine. We therefore undertook this prospectively designed pilot study to investigate whether colchicine therapy could reduce certain adverse plaque characteristics, as assessed by coronary CTA.

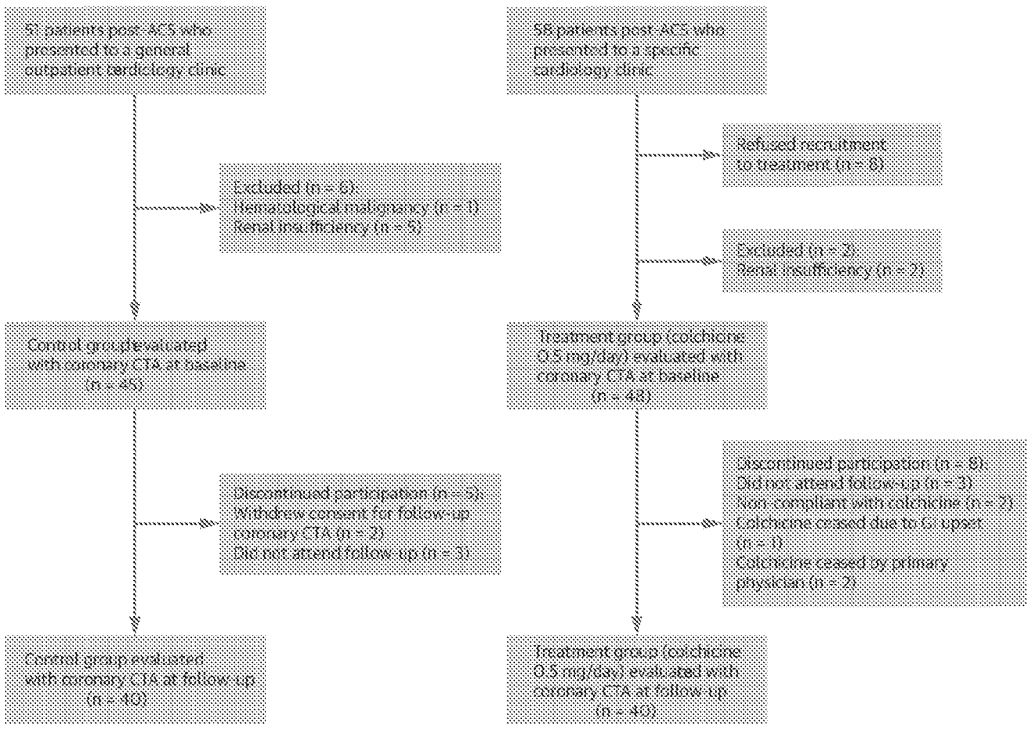
METHODS

STUDY DESIGN AND RECRUITMENT. This was a prospective, open-label, single center study at Royal Prince Alfred Hospital examining the effect of 12 months of colchicine therapy on coronary plaque morphology in patients who had recently presented (<1 month) to the hospital with an ACS (8) (Figure 1). All patients underwent invasive coronary angiography at the time of presentation and were revascularized if clinically indicated. Between January 2015 and March 2016, 48 patients were recruited from a specific cardiology clinic at our institution. These patients underwent coronary CTA and were routinely started on colchicine (0.5 mg/day). Forty patients in this treatment arm completed the study. The control arm initially consisted of 45 patients, recruited between December 2014 and October 2015 from a general cardiology outpatient clinic at the same institution; 40 patients from this arm completed the study. In both groups, all patients underwent statin and risk factor optimization at the discretion of their treating cardiologist. Because the presence of LAP on coronary CTA has been shown to be a robust predictor of future major adverse cardiovascular events (MACE), we chose change in LAP volume (LAPV) at follow-up in colchicine-treated versus nontreated patients as the primary study endpoint. The secondary endpoints were changes in other coronary CTA measures: total atheroma volume (TAV), noncalcified plaque volume (NCPV), dense calcified plaque volume (DCPV), remodeling index, and high-sensitivity C-reactive protein (hsCRP). The local Ethics Review Committee approved the study protocol and all patients gave written informed consent before participating.

EXCLUSION CRITERIA. We excluded patients with previous coronary artery bypass grafts, a hypersensitivity/allergy to colchicine, colchicine treatment for another cause, severe liver disease, renal insufficiency with creatinine clearance <45 ml/min, calcineurin or strong CYP3A4 inhibitor treatment, hematological malignancy, thrombocytopenia, leucopenia, chronic inflammatory bowel disease, pregnancy or at risk of pregnancy, and lactating women.

CLINICAL DATA AND LABORATORY MEASUREMENTS. Upon recruitment of patients, initial contact with investigators involved a comprehensive medical history, physical examination, medication evaluation, and anthropometric measurements. Blood samples were collected after an overnight 8 to 12 h fast. Samples were stored and subsequently analyzed for hsCRP, urea and creatinine, hepatic enzymes,

FIGURE 1 The Enrollment, Exclusion, and Follow-Up of Patients Post-ACS Recruited to the Control or Treatment Group



ACS = acute coronary syndrome; CTA = computed tomography angiography; GI = gastrointestinal.

low-density lipoprotein (LDL), total cholesterol (TC), high-density lipoprotein, and triglyceride levels with the use of automated diagnostic equipment.

FOLLOW-UP AND MONITORING. All patients were reviewed clinically at 3 and 12 months after enrollment for drug reactions, self-reported medication compliance (both statin and colchicine), and MACE. A follow-up period of 12 months for serial coronary CTA was chosen on the basis of prior studies (9,10) that assessed changes in plaque morphology after statin therapy.

CORONARY CTA DATA ACQUISITION. Coronary CTA was performed using a Discovery CT750 HD (GE Healthcare, Milwaukee, Wisconsin). The same protocol, image setting, and dose of contrast medium was used at both baseline and follow-up. Sublingual nitroglycerin and oral beta-blockers were administered pre-scan. The following imaging and reconstruction variables were applied: collimation 64.000 × 0.625 mm, tube voltage 100 to 120 kV, and tube current 350 to 780 milliamperes. Prospective studies were performed if the heart rate was sufficiently controlled (<60 beats/min) with images acquired from 65% to 75% of the R-R interval. An iodinated contrast material (350 g/l) (Omnipaque, GE Healthcare) was injected intravenously.

CORONARY CTA CORONARY PLAQUE ASSESSMENT. All coronary images were transferred to the workstation with the use of semiautomated plaque-based analysis software (GE Advantage workstation v4.5 cardiq express). Operators and observers were blinded for colchicine treatment or control group allocation, and experienced reporters assessed the coronary arteries. The protocol for quantitative plaque assessment has been published in previous studies (11), with 3-dimensional image reconstruction including volume rendering and curved multiplanar reformation. Vessel diameters ≥1.5 mm were evaluated and assessed based on a Society of Cardiovascular Computed Tomography 17-segment coronary artery model (12). Stented segments were excluded. A software-derived color-coded map overlay differentiated plaque categories by Hounsfield unit (HU) values. Parameters assessed included LAP (<30 HU), intermediate

TABLE 1 Baseline Characteristics of Control and Treatment Groups

	Control (n = 40)	Treatment (n = 40)	p Value
Age, yrs	58.4 ± 14.2	56.3 ± 8.9	0.42
Male	30 (75.0)	32 (80.0)	0.59
Diabetes mellitus	16 (40.0)	9 (22.5)	0.09
Hypertension	23 (57.5)	20 (50.0)	0.50
Tobacco smoking	21 (52.5)	20 (50.0)	0.82
Dyslipidemia	34 (85.0)	34 (85.0)	1.00
Previous MI	22 (55.0)	19 (47.5)	0.50
Previous PCI	23 (57.5)	28 (70.0)	0.25
Aspirin	40 (100.0)	38 (95.0)	0.15
Thienopyridine	29 (72.5)	33 (82.5)	0.28
Statin	38 (95.0)	32 (80.0)	0.04
BMI, kg/m^2	27.4 ± 3.3	26.6 ± 3.2	0.28
Follow-up period, months	12.9 ⊥ 0.6	12.2 ⊥ 3.9	0.27
Type of ACS	-	-	0.42
STEMI	6 (15.0)	3 (7.5)	-
NSTEMI	16 (40.0)	14 (35.0)	-
UAP	18 (45.0)	23 (57.5)	-
hs-Troponin T, ng/l	433.4 ± 958.1	318.3 ± 862.2	0.10
Type of treatment post-ACS	-	-	0.28
Medical only	7 (17.5)	11 (27.5)	-
PCI	33 (82.5)	29 (72.5)	-

Values are mean ± SD or n (%).

ACS = acute coronary syndrome; BMI = body mass index; hs = high-sensitivity; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; UAP = unstable angina pectoris.

attenuation noncalcified plaques (30 to 150 HU), dense calcified plaques (DCP) (351 to 1,000 HU), total atheroma volume (TAV) (TAV = LAPV + NCPV + DCPV), and total lumen volume (TLV) (151 to 350 HU) (11). The volume of each component was measured. Percent LAP, NCP, dense calcified plaques, and TAV were defined as the volume of each parameter divided by total vessel volume (TVV) (TVV = TAV + TLV). Another measure of plaque instability was remodeling index, with a plaque remodeling index >1.1 considered to be within a positive remodeled artery (5). To assess interobserver variability, LAP, NCP, dense calcified plaques, and lumen volumes on 15 randomly selected patients were independently assessed by 2 reporters. Excellent interobserver agreement was observed (κ = 0.83).

TABLE 2 Baseline Coronary CTA Plaque Parameters Between Treatment and Control Groups

	Control (n = 40)		Treatment (n = 40)		
	Baseline (mm^3)	Baseline TVV* (%)	Baseline (mm^3)	Baseline TVV† (%)	p Value‡
LAPV	39.0 ± 10.9	7.3 ± 2.0	38.8 ± 13.6	7.7 ± 2.7	0.37
DCPV	21.5 ± 11.8	4.0 ± 2.2	18.6 ± 10.1	3.7 ± 2.0	0.26
NCPV	185.0 ± 41.3	34.7 ± 7.7	181.6 ± 70.5	36.1 ± 14.0	0.79
TAV	245.5 + 42.3	46.0 + 7.9	239.0 + 76.0	47.5 + 15.1	0.64
TLV	287.9 ± 29.6	54.0 ± 5.5	264.2 ± 78.7	52.5 ± 15.6	-
RI	1.18 ± 0.16	-	1.20 ± 0.17	-	0.58

Values are mean ± SD. *Mean TVV = 533.4 mm^3. †Mean TVV = 503.2 mm^3. ‡p value comparing raw baseline values (mm^3) between the 2 groups.

CTA = computed tomography angiography; DCPV = dense calcified plaque volume; LAPV = low attenuation plaque volume; NCPV = noncalcified plaque volume; RI = remodeling index; TAV = total atheroma volume; TLV = total lumen volume; TVV = total vessel volume.

STATISTICAL ANALYSIS. Continuous variables are expressed as the mean ± SD; categorical variables are described as n (%). For univariate analysis, we used the Student *t* test to compare means between treatment and control groups for the normally distributed continuous variables: age, body mass index, follow-up period, baseline LDL, baseline TC, baseline TAV, and baseline NCPV. We used the Mann-Whitney *U* test for the remaining non-normally distributed (including outcome) variables. Comparison between groups for qualitative variables was performed using the chi-square or Fisher exact test as appropriate. We also performed a repeated measures 2-way mixed analysis of variance to determine if an interaction effect exists between treatment group (controls vs. colchicine) and time (baseline vs. follow-up) for the outcome variables. Spearman's rank order correlation coefficient (*r*) was used to evaluate the relationship between continuous outcome variables. To correct for differences between groups and to account for factors that may have influenced outcomes (particularly plaque morphology) during the follow-up period, we performed multivariate linear regression analysis. We adjusted for age, sex, body mass index, follow-up period, baseline LDL, comorbidities (diabetes mellitus, hypertension, dyslipidemia, tobacco smoking), and medication use (statin, aspirin, thienopyridines). We excluded 1 outlier (standardized residual 6.3 SDs from mean) for the change in hsCRP outcome only. A 2-tailed p value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS software version 20.0 (SPSS Inc., Chicago, Illinois).

RESULTS

BASELINE CHARACTERISTICS. From December 2014 to March 2016, we enrolled 40 patients who were assigned to colchicine 0.5 mg/day plus optimal medical therapy (OMT) and 40 patients to OMT alone. All regular medications were continued, and high-dose statin intensification therapy (aiming for LDL <1.8 mmol/l) was initiated for 70 (87.5%) patients. Before enrollment, 39 (48.75%) patients were taking statin therapy (control: n = 18; treatment: n = 21). Mean duration of follow-up was 12.6 ± 2.8 months; the mean age of patients was 57.4 ± 11.8 years. We recruited 62 men (77.5%) and 18 women (22.5%).

TABLE 3 Baseline, Follow-Up, and Changes in Lipid and Biochemical Parameters in the Control and Treatment Groups

	Baseline			Control			Treatment		
	Control (mmol/l) (n = 40)	Treatment (mmol/l) (n = 40)	p Value*	Follow-Up (mmol/l) (n = 40)	Change (%) From Baseline (mmol/l)	p Value†	Follow-Up (mmol/l) (n = 40)	Change (%) From Baseline (mmol/l)	p Value‡
LDL	2.42 ± 0.49	2.33 ± 0.71	0.52	1.93 ± 0.50	−0.49 (20.2) ± 0.49	<0.001	1.89 ± 0.52	−0.44 (19.0) ± 0.60	<0.001
TC	4.83 ± 1.10	4.49 ± 1.27	0.20	3.90 ± 0.71	−0.93 (19.3) ± 0.87	<0.001	3.80 ± 1.12	−0.68 (15.2) ± 1.23	0.001
HDL	1.21 ± 0.17	1.20 ± 0.28	0.37	1.29 ± 0.23	+ 0.07 (5.8) ± 0.25	0.08	1.20 ± 0.24	−0.01 (0.6) ± 0.27	0.93
TG	1.75 ± 0.59	1.55 ± 0.71	0.09	1.66 ± 0.46	−0.10 (5.4) ± 0.47	0.24	1.39 ± 0.64	−0.16 (10.5) ± 0.47	0.04
	Control (mg/l) (n = 40)	Treatment (mg/l) (n = 39)		Follow-Up (mg/l) (n = 40)	Change (%) From Baseline (mg/l)		Follow-Up (mg/l) (n = 39)	Change (%) From Baseline (mg/l)	
hsCRP	2.64 ± 2.06	2.95 ± 1.56	0.26	2.26 ± 1.05	−0.38 (14.6) ± 1.21	0.02	1.85 ± 0.90	−1.10 (37.3) ± 1.15	<0.001

Values are mean ± SD or mean (%) ± SD. *p Value comparing baseline values between the 2 groups. p Values comparing baseline and follow-up values in the †control group and the ‡treatment group. HDL = high-density lipoprotein; hsCRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; TC = total cholesterol; TG = triglycerides.

Baseline characteristics (Tables 1 to 3) and comorbidities of the study population in the treatment and control cohorts were similar and well matched. The 2 groups differed only in use of a statin (p = 0.04). Complete data were available except for baseline hsCRP (control: n = 40; treatment: n = 39).

CHANGES AT FOLLOW-UP. Follow-up mean ± SD and changes in coronary CTA plaque parameters for treatment and control cohorts are summarized in Table 4. During the study period, there was a reduction in all coronary CTA plaque parameters of interest (LAPV, DCPV, NCPV, TAV), with statistically significant reductions in LAPV (treatment: p < 0.001; control: p = 0.003), NCPV (treatment: p = 0.005; control: p = 0.01), and TAV (treatment: p = 0.001; control: p < 0.001) in both groups. There was also a reduction in LAPV, NCPV, and TAV as a proportion of TVV in both groups; however, there was a small increase (+0.5%) in DCPV as a proportion of TVV in the treatment group, but not in the control group (−0.1%). There was a net reduction in LAPV at follow-up in 29 (72.5%) and 33 (82.5%) patients in the control and treatment groups, respectively. Figures 2 and 3 demonstrate how semiautomated coronary CTA quantitative plaque analysis was performed in a treated patient at baseline and at 12-month follow-up.

During the study period, there was also a significant reduction (Table 3) in LDL (treatment: p < 0.001; control: p < 0.001), TC (treatment: p = 0.001; control: p < 0.001), and hsCRP (treatment: p < 0.001; control: p = 0.02) across both cohorts, and in triglycerides for the treatment group alone (p = 0.04). An increase in high-density lipoprotein was seen only in the control group; however, this change was not significant.

PRIMARY AND SECONDARY OUTCOMES. On univariate analysis (Tables 3 to 5), colchicine therapy was associated with a significant reduction in LAPV (treatment: mean 15.9 [−40.9%] ± 17.3 mm^3; control: mean 6.6 [−17.0%] ± 12.8 mm^3; p = 0.008) (Figure 4A) and hsCRP (treatment: mean 1.10 [−37.3%] ± 1.15 mg/l; control: mean 0.38 [−14.6%] ± 1.21 mg/l; p < 0.001) (Figure 4B) compared with the control group. Colchicine therapy (Tables 2 and 4) was associated with a mean 2.5% reduction in LAPV as a proportion of TVV versus a 1.0% reduction in the control group (p = 0.03).

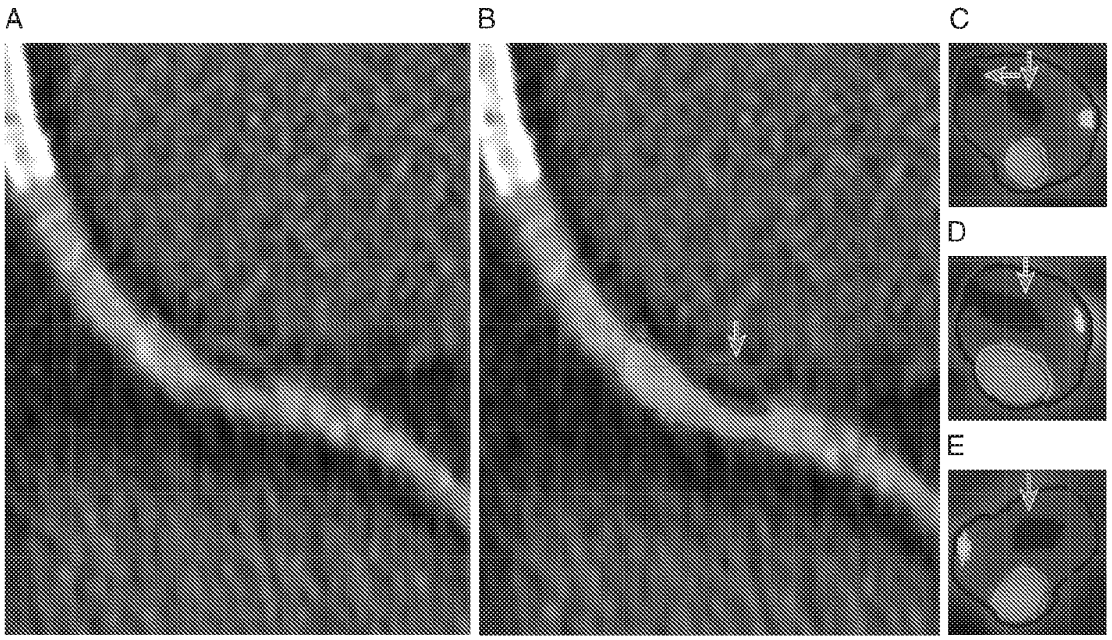
Although there was a greater reduction in TAV at follow-up coronary CTA in the treatment group, this

TABLE 4 Mean ± SD Coronary CTA Plaque Parameters at Follow-Up and Changes Compared With Baseline in the Control and Treatment Groups

	Control (n = 40)				Treatment (n = 40)			
	Follow-Up (mm^3)	Follow-Up TVV* (%)	Change (%) From Baseline (mm^3)	p Value†	Follow-Up (mm^3)	Follow-Up TVV‡ (%)	Change (%) From Baseline (mm^3)	p Value§
LAPV	32.3 ± 6.2	6.3 ± 1.2	−6.6 (17.0) ± 12.8	0.003	23.0 ± 21.4	5.2 ± 4.8	−15.9 (40.9) ± 17.3	<0.001
DCPV	19.9 ± 9.4	3.9 ± 1.8	1.6 (7.3) ± 8.3	0.32	18.5 ± 8.4	4.2 ± 1.9	0.1 (0.5) ± 8.3	0.85
NCPV	166.8 ± 48.2	32.6 ± 9.4	−18.2 (9.8) ± 43.9	0.01	155.3 ± 49.4	34.9 ± 11.1	−26.3 (14.5) ± 55.8	0.005
TAV	219.1 ± 42.3	42.8 ± 8.3	−26.4 (10.8) ± 42.1	<0.001	196.8 ± 41.6	44.2 ± 9.3	−42.3 (17.7) ± 66.6	0.001
TLV	292.5 ± 35.3	57.2 ± 6.9	-	-	248.8 ± 43.8	55.8 ± 9.8	-	-
RI	1.17 ± 0.15	-	−0.01 (0.8) ± 0.11	0.40	1.17 ± 0.13	-	−0.04 (3.2) ± 0.14	0.14

Values are mean ± SD or mean (%) ± SD. *Mean TVV = 511.6 mm^3. ‡Mean TVV = 445.6 mm^3. p Values comparing baseline and follow-up values in the †control group and the §treatment group. Abbreviations as in Table 2.

FIGURE 3 Distal Right Coronary Artery Plaque Identified at Baseline



(A) Curved planar reformat; **(B)** curved planar reformat with color overlay coded image map to identify plaque components; **(C to E)** representative cross-sectional views with color overlay. **Light blue arrows** indicate low attenuation plaque **(dark blue)**; noncalcified plaque, **purple**; dense calcified plaque, **yellow**; lumen **green**. LAP volume = 4.2 mm^3, NCP volume = 46.5 mm^3, DCP volume = 2.2 mm^3, lumen volume = 41.4 mm^3. DCP = dense calcified plaque; LAP = low attenuation plaque; NCP = noncalcified plaque.

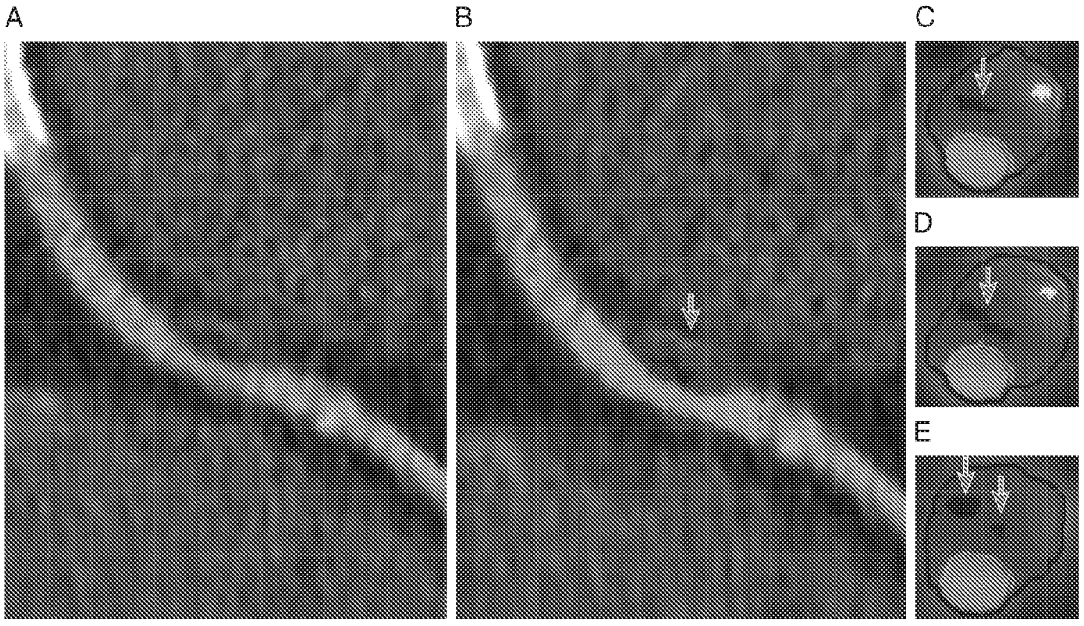
difference was not statistically significant (treatment: mean 42.3 [−17.7%] ± 66.6 mm^3; control: mean 26.4 [−10.8%] ± 42.1 mm^3; p = 0.28). Similarly, there was no significant difference between cohorts when comparing change in DCPV (p = 0.66), NCPV (p = 0.62), or remodeling index (p = 0.36). Changes in TAV, DCPV, and NCPV as a proportion of TVV (Table 4) also did not differ significantly between treatment and control groups. Finally, there was appropriate and comparable LDL reduction in both groups (treatment: mean 0.44 [−19.0%] ± 0.60 mmol/l; control: mean 0.49 [−20.2%] ± 0.49 mmol/l; p = 0.21) (Figure 4C).

Table 5 shows the multivariate linear regression analysis after adjusting for differences between cohorts and factors that may have influenced outcomes during the follow-up period (see the Methods section). In this multivariate model, colchicine therapy remained significantly associated with reduction in LAPV (p = 0.039) and hsCRP (p = 0.004) compared with controls, but there was no significant difference between groups for the other outcomes. The partial R^2 of colchicine therapy was 4.3% and 9.1% for change in LAPV (overall R^2 = 36.0%) and hsCRP (overall R^2 = 34.6%), respectively, indicating that colchicine therapy accounted for a significant proportion of the variance in these outcomes during the follow-up period.

These findings were supported by the statistically significant 2-way interaction effect between treatment group (controls vs. colchicine) and time (baseline vs. follow-up) on LAPV (p = 0.002) and hsCRP (p < 0.001) (Table 6) alone, with no effect seen for the other outcome variables.

Finally, we examined the linear relationship and strength of correlation between the 2 significant outcome variables (Figure 5A). There was evidence of a highly significant linear relationship (R^2 = 0.158; p < 0.001) and strong positive correlation (r = 0.578) between change in LAPV and change in hsCRP. Similarly, there was a highly significant linear relationship (R^2 = 0.123; p = 0.001) and moderate positive correlation (r = 0.417) between change in LAPV and change in LDL (Figure 5B); however, there was no

FIGURE 3 Distal Right Coronary Artery Plaque Reimaged After 12 Months of Oral Colchicine (0.5 mg/day)



(A) Curved planar reformat; **(B)** curved planar reformat with color overlay coded image map to identify plaque components; **(C to E)** representative cross-sectional views with color overlay. See Figure 1 legend for color descriptions. LAPV = 3.2 mm^3 (−23.8%), NCPV = 65.8 mm^3 (+41.5%), DCPV = 0.3 mm^3 (−86.4%), lumen volume = 47.2 mm^3 (+14.0%). DCPV = dense calcified plaque volume; LAPV = low attenuation plaque volume; NCPV = noncalcified plaque volume.

relationship between change in hsCRP and change in LDL ($R^2 = 0.047$; $p = 0.06$).

ADVERSE EVENTS. Only 1 patient developed an adverse event resulting from colchicine therapy (gastrointestinal intolerance, particularly diarrhea); colchicine treatment was subsequently ceased by investigators. Two patients had colchicine therapy ceased by their primary physician for unspecified reasons, and 2 were noncompliant with therapy (Figure 3).

There were no deaths or myocardial infarction in either group during the follow-up period. Two patients in the treated cohort underwent cardiac catheterization for investigation of recurrent chest pain but did not undergo percutaneous coronary intervention. One patient in the untreated cohort presented with enzyme-negative unstable angina and underwent percutaneous coronary intervention to a new culprit stenosis.

DISCUSSION

This study demonstrates, for the first time, that regular low-dose colchicine therapy has significantly greater coronary plaque-stabilizing effects than OMT alone, as evidenced by a significant reduction in both LAPV and hsCRP. These changes were seen in the context of a substantial and similar reduction in LDL in both treatment and control groups, indicative of successful statin intensification therapy post-ACS. Although there was a moderate positive correlation between change in LDL and change in LAP volume suggesting that LDL reduction may have contributed to plaque stabilization, the comparable LDL reduction in both groups suggests that improvements in plaque morphology are not driven solely by changes in LDL, but also by the anti-inflammatory properties of colchicine. This is supported by the substantially larger reduction in hsCRP in the treatment group compared with controls. Furthermore, the significant linear association and strong positive correlation between change in LAPV and change in hsCRP suggests that these 2 processes are related, and that reduction in hsCRP, mediated by colchicine's anti-inflammatory effects, is manifested simultaneously by reduction in the burden of potentially vulnerable coronary plaque.

TABLE 3 Primary and Secondary Outcomes

		Univariate Analysis		Multivariate Analysis			
	n	Change	p Value	B	Model R^2	Partial R^2	p Value
LAPV, mm^3							
Control	40	−6.6 ± 12.8	0.008	0 (Ref)	0.360	-	0.039
Treatment	40	−15.9 ± 17.3		0.232		0.043	
DCPV, mm^3							
Control	40	−1.6 ± 8.3	0.66	0 (Ref)	0.372	-	0.47
Treatment	40	−0.1 ± 8.3		−0.080		0.005	
NCPV, mm^3							
Control	40	−18.2 ± 43.9	0.62	0 (Ref)	0.229	-	0.21
Treatment	40	−26.3 ± 55.8		0.153		0.019	
TAV, mm^3							
Control	40	−26.4 ± 42.1	0.28	0 (Ref)	0.332	-	0.10
Treatment	40	−42.3 ± 66.6		0.190		0.029	
RI							
Control	40	−0.01 ± 0.11	0.36	0 (Ref)	0.133	-	0.16
Treatment	40	−0.04 ± 0.14		0.184		0.027	
hsCRP, mg/l							
Control	40	−0.38 ± 1.21	<0.001	0 (Ref)	0.346	-	0.004
Treatment	39	−1.10 ± 1.15		0.344		0.091	
LDL, mmol/l							
Control	40	−0.49 ± 0.49	0.21	0 (Ref)	0.539	-	0.48
Treatment	40	−0.44 ± 0.60		−0.067		0.003	

Values are mean ± SD.
β = standardized regression coefficients; other abbreviations as in Tables 2 and 3.

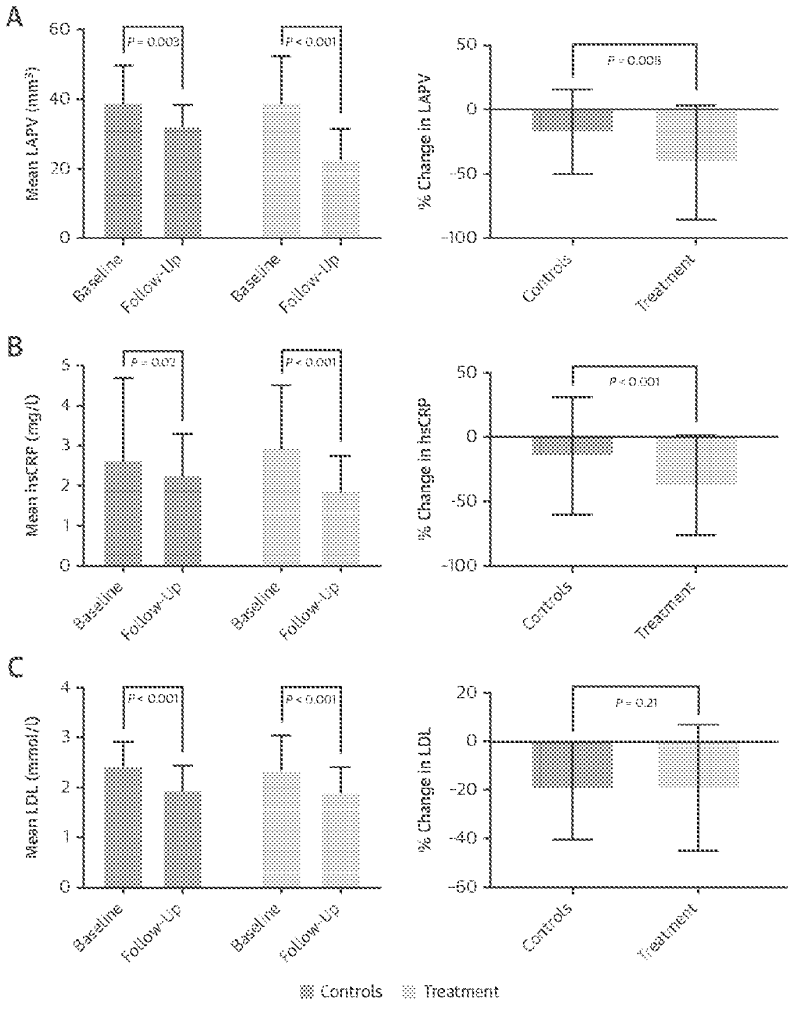
Vulnerable plaques that are prone to rupture are commonly lipid-rich, with a large necrotic core and thin fibrous cap (2,7). These can be identified on coronary CTA based on high-risk features including outward vessel positive remodeling (index >1.1), low attenuation plaque (<30 HU), spotty calcification, and the "napkin ring" sign (a ring of high attenuation around plaque) (6,7). Of these, LAP has consistently been shown to be the strongest marker of instability, which we replicated in our study.

Across 2 large studies (6,13) of more than 1,000 patients each, the presence of LAP on coronary CTA was a powerful independent predictor of ACS and MACE at follow-up, along with positive remodeling and the napkin ring sign. The strong predictive value of LAP as an adverse prognostic indicator has also been demonstrated in an ex vivo study (14) demonstrating an association between the relative area of LAP by quantitative histogram analysis and lipid-rich plaque core. Coronary CTA has also been evaluated against other high-resolution intracoronary imaging modalities, in particular intravascular ultrasound and optical coherence tomography (15). In 2 comparative studies (16,17), vulnerable thin-cap fibroatheroma plaque as assessed by optical coherence tomography were significantly associated with the presence of LAP on coronary CTA, as well as positive remodeling and napkin ring sign. Two similar comparative studies with intravascular ultrasound (15,18) showed that low-density plaque on coronary CTA correlated significantly with vulnerable plaque with a larger necrotic core plus fibrofatty tissue. One other study (19) has also demonstrated a strong correlation between CT and intravascular ultrasound for positive remodeling indices.

The plaque-stabilizing properties of statins have been evaluated by coronary CTA in several studies to date. Two prospective studies (9,10) have shown that in patients treated with a statin, there was reduced progression or a greater reduction in LAPV and TAV at follow-up compared with controls. Statins are not only highly effective for the treatment of dyslipidemias, but also exert a range of cardioprotective "pleiotropic" effects with anti-inflammatory and antioxidant properties (20). As a result, they have been universally incorporated into clinical guidelines as part of secondary prevention post-ACS. A Cochrane systematic review (20) of 18 randomized control trials (n = 14,303) comparing statin therapy (initiated within 14 days of ACS) with placebo or usual care, found that statin therapy reduced the incidence of unstable angina at 4 months post-ACS (4.8% vs. 6.3%). However, despite a trend toward risk reduction, there was no statistically significant reduction in incidence of mortality (2.5% vs. 2.8%), myocardial infarction (5.9% vs. 6.5%), total stroke, or revascularization procedures at 4 months of follow-up. These findings support the need for further agents for secondary prevention post-ACS, and colchicine may be an attractive option to serve this need via further plaque stabilization.

Indirect support for a beneficial effect of colchicine comes from 2 retrospective studies that showed reduced CVD incidence in patients with continuous colchicine use for the treatment of gout (21) and familial Mediterranean fever (22). A 2013 randomized controlled trial (LoDoCo [Low-Dose Colchicine for Secondary Prevention of Cardiovascular Disease]) of 532 patients (23) with stable coronary artery disease (CAD) followed over a median of 3 years showed that colchicine 0.5 mg/day administered in addition to high-dose statin therapy and OMT was highly effective in the prevention of nonstent-related ACS compared with placebo. This trial hypothesized these beneficial effects of colchicine were due to its ability to suppress levels of inflammatory mediators and prevent cholesterol crystal-induced neutrophil-mediated inflammation implicated in atherosclerosis. Finally, a 2015

FIGURE 4 Primary and Secondary Outcomes



(A) Mean LAPV at baseline and follow-up, and % change in LAPV, in control and treatment groups. **(B)** Mean hsCRP at baseline and follow-up, and % change in hsCRP, in control and treatment groups. **(C)** Mean LDL at baseline and follow-up, and % change in LDL, in control and treatment groups. hsCRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; other abbreviation as in Figure 3.

meta-analysis (5) of 1,301 patients in 5 randomized controlled trials showed that colchicine was associated with a >50% reduction in the composite CV outcome that included CAD, ACS, stroke, revascularization, and stable congestive cardiac failure.

Our group has explored several pathophysiological mechanisms potentially explaining the atheroprotective properties of colchicine (3,4). Exposure of neutrophils and monocytes/macrophages to various stimuli (including cholesterol crystals) in atherosclerotic plaque triggers NLRP3 inflammasome activation, which is a cytosolic multiprotein complex that promotes caspase-1-dependent interleukin (IL)-1β and IL-18 secretion (24). Caspase-1 levels strongly correlate with CV events in CAD patients, and IL-1β and IL-18 are both key inflammatory cytokines that, like

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TABLE 3 2-Way Mixed ANOVA Repeated Measures Testing for Interaction Between Treatment Group (Controls vs. Colchicine) and Time (Baseline vs. Follow-Up) on Primary and Secondary Outcome Variables

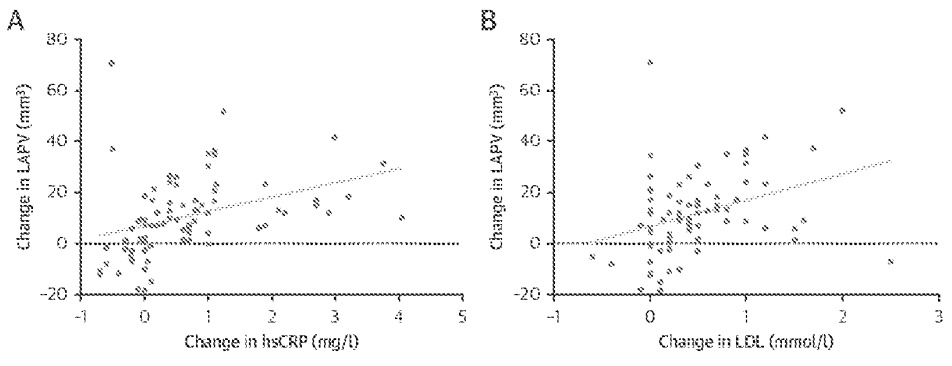
	n	F	p Value
LAPV	80	11.608	0.002
DCPV	80	0.659	0.42
NCPV	80	0.415	0.52
TAV	80	1.583	0.22
RI	80	0.881	0.35
hsCRP	79	18.398	<0.001
LDL	80	0.184	0.67

ANOVA = analysis of variance; other abbreviations as in Tables 2 and 3.

downstream IL-6, are implicated in plaque development, progression, and destabilization. We have demonstrated that in patients with ACS, there is evidence of monocyte inflammasome activation (4) with higher transcoronary gradients of IL-1β, IL-18, and IL-6 compared with controls (3) and that short-term oral colchicine suppresses monocyte secretion of IL-1β, via caspase-1 inhibition, as well as reducing transcoronary inflammasome-related cytokine gradients (3). Similar to previous studies (25), colchicine also resulted in a significant reduction in hsCRP, a cytokine synthesized in response to IL-6 release from activated monocytes. hsCRP is an inflammatory biomarker that has been credited as a potential predictive tool for screening, risk classification, and assessment of response to therapy in CVD. A hsCRP level >3 mg/l is independently associated with a 60% excess risk of incident CAD compared with levels <1 mg/l after adjusting for other risk factors (26). Furthermore, the landmark JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) trial (27) showed that statin therapy as primary prevention in patients with a low LDL but high hsCRP yielded a robust 44% reduction in risk of MACE compared with placebo. This reduction was substantially higher than expected from previous statin trials evaluating the effect of LDL reduction on MACE, suggesting that hsCRP reduction is more predictive of better outcomes than LDL reduction alone. Our study has reaffirmed the observation that reduction in hsCRP translates into favorable plaque modification independent of LDL change.

STUDY LIMITATIONS. The present study has some limitations, including a relatively small sample size and short-term follow-up (12 months) for repeat coronary CTA and serum biomarkers. Coronary CTA plaque assessment was performed by multiple experienced reporters, and although this semiautomated process was prone to the possibility of individual errors in plaque evaluation, we found very little interobserver variability (see the Methods section). However, intraobserver variability and scan-rescan repeatability were not assessed. Furthermore, in this prospective nonrandomized observational study, we were unable to perform an intention-to-treat analysis on any patients in the treatment arm who discontinued participation during the study period because they did not present for or consent to a follow-up coronary CTA. Despite the lack of randomized data, the 2 groups (treatment vs. controls) were quite well matched, with differences at baseline seen in only 1 clinical variable (statin use). There were

FIGURE 3 Simple Linear Regression Between Outcome Variables



(A) Change in LAPV and hsCRP and **(B)** change in LAPV and LDL. Abbreviations as in Figures 3 and 4.

no differences between groups in baseline coronary CTA parameters or biochemical variables. We operated a multivariate linear regression analysis to account for differences between groups, with no substantial change in p value of significance. Interestingly, statin use was lower in the treatment group, and the improved plaque morphology in this group (compared with controls) despite this implies that this effect was not mediated by differences in statin therapy. Finally, this study was not adequately powered to evaluate clinically significant endpoints such as adverse CV events and mortality.

CONCLUSIONS

This present study demonstrates, for the first time, that low-dose colchicine favorably modifies potentially vulnerable coronary plaque. The knowledge that atherosclerosis is an inflammatory disease offers new opportunities for the prevention and treatment of coronary artery disease. Accordingly, a synergistic strategy of colchicine plus statin could fundamentally shift approaches to atherosclerosis modulation.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Low-dose colchicine plus optimal medical therapy favorably modifies potentially vulnerable coronary plaque compared with optimal medical therapy alone, as assessed by coronary CTA. These improvements in plaque morphology are likely driven by the anti-inflammatory properties of colchicine.

TRANSLATIONAL OUTLOOK: Colchicine may represent a valuable therapeutic tool to add to the armament of currently available secondary prevention options. Additional large, randomized clinical trials are required to evaluate whether low-dose colchicine therapy results in lower rates of future adverse cardiovascular events.

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KEY WORDS acute coronary syndrome, atherosclerosis, colchicine, coronary artery disease, CT coronary angiography, inflammation

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First Named Inventor/Applicant Name:	Jean-Claude TARDIF
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3	Non Patent Literature	50761-021001_-_Nidorf.pdf	578588 30293e2459d898ed3c3509a529c019572b9caeeb	no	7
Warnings:					
Information:					
4	Non Patent Literature	50761-029001_-_doc_09_Nidorf_et_al_XP_85581423A.PDF	442214 32d30c941ec4208366c01f98b2912b334db1da99	no	8
Warnings:					
Information:					
5	Non Patent Literature	50761-029001_-_Tardif.pdf	185486 938c8a8a2659d54dad280294efe312e117cef75d	no	9
Warnings:					
Information:					
6	Non Patent Literature	50761-029001_-_doc_05_Tucker_et_al_XP_85888693A.PDF	596086 e0ad759dc61bac981efa30d3273e66fbd7632c52	no	10
Warnings:					
Information:					
7	Non Patent Literature	50761-029001_-_doc_04_Vaidya_XP_85581388A.PDF	534304 7b8b0d97ebbb1ba44e76fa79a33c4c28c76f867f	no	10
Warnings:					
Information:					
8	Non Patent Literature	50761-029001_-_Bouabdallaoui2.pdf	409046 c11f6b8ad0426b4e4cc589f9d927c97411d437c4	no	8
Warnings:					
Information:					

9	Non Patent Literature	Akodad.pdf	1160730 6917c928f1a42aaec05b7f0beff5fb325335bca1	no	7
Warnings:					
Information:					
10	Non Patent Literature	Deftereos.pdf	1737636 80155b8ab64f62940e660fc861cac3117e0a5b96	no	9
Warnings:					
Information:					
11	Non Patent Literature	Hennessy.pdf	1212454 5d078833db0d51aea401869 1f2d19129f6f817e8	no	8
Warnings:					
Information:					
12	Non Patent Literature	Vaidya.pdf	1495326 b58414e2a10d227374c4a7ddf0fbc4b103c5943f	no	12
Warnings:					
Information:					
		Total Files Size (in bytes):	9415903		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

CD Submission Review Results

Internal Worksheet Only - Do Not Scan

Application Number	17097285	Receipt Date	Nov 13, 2020

X	New Application		Response To Notice	Date Of Response

☐ Jumbo – Large tables are included on the CD

☒ **There are no problems with the CDs in the submission.**

Items checked below are to be selected in the PALM Pre-Exam CD problem list.

Omitted Items

	Files on compact disc are unreadable:
	Disc(s) of either set not readable:
	Disc(s) do not contain file names listed:
	Amended CD missing unamended files
	Missing compact discs

Missing Parts

	Disc(s) do not contain file names listed
	Discs contains files that are non-ASCII files:
	Only one copy of the CD, no duplicate:
	Wrong media type, e.g., CD-RW:
	The transmittal letter and specification do not list information:
	Both disc(s) contain unreadable files:
	One disc(s) contain unreadable files:
	Compact disc(s) contain viruses, but are still readable:
	EFS/Paper Submission:
	Table does not maintain data in proper alignment:
	Not proper subject matter for CD's:

Informality

	No statement in transmittal letter that CD's are the same:
	No incorporation by reference statement for the CD's:
	CD's not labeled "Copy 1" and "Copy 2":
	Deficient CD packaging:
	Deficient Labeling on CD's:
	The transmittal letter does not list information:
	The specification does not list information:
	Table less than 51 pages submitted on CD:

File Directory Attachment

	Copy of file directory listing is attached and should be mailed to applicant
	Copy of file directory listing is not attached
	Copy of file directory listing is not attached because it is over one page long

Additional Comments

Internal Worksheet Only - Do Not Scan

DocCode – SCORE

SCORE Placeholder Sheet for IFW Content

Application Number: 17097285 Document Date: 11/13/2020

The presence of this form in the IFW record indicates that the following document type was received in electronic format on the date identified above. This content is stored in the SCORE database.

Since this was an electronic submission, there is no physical artifact folder, no artifact folder is recorded in PALM, and no paper documents or physical media exist. The TIFF images in the IFW record were created from the original documents that are stored in SCORE.

- Drawing

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Form Revision Date: March 1, 2019

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
17/097,285	11/13/2020	Jean-Claude TARDIF	50761-029001

CONFIRMATION NO. 3015

21559
CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

FORMALITIES LETTER

OC000000121592036

Date Mailed: 11/27/2020

NOTICE TO FILE CORRECTED APPLICATION PAPERS

Filing Date Granted

An application number and filing date have been accorded to this application. The application is informal since it does not comply with the regulations for the reason(s) indicated below. Applicant is given **TWO MONTHS** from the date of this Notice within which to correct the informalities indicated below. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

The required item(s) identified below must be timely submitted to avoid abandonment:

- A substitute specification in compliance with 37 CFR 1.52, 1.121(b)(3), and 1.125, is required. The substitute specification must be submitted with markings and be accompanied by a clean version (without markings) as set forth in 37 CFR 1.125(c) and a statement that the substitute specification contains no new matter (see 37 CFR 1.125(b)). The specification, claims, and/or abstract page(s) submitted is not acceptable and cannot be scanned or properly stored because:
  - The application papers (including any electronically submitted papers) are not in compliance with 37 CFR 1.52 because pages 33, 36, and 43 contain text that is unreadable or of insufficient clarity. Application papers (including any electronically submitted papers) must be presented in a form having sufficient clarity and contrast between the background of the paper and the writing thereon to permit the Office to electronically reproduce the papers by use of digital imaging and optical character recognition. See 37 CFR 1.52(a)(1)(v).

Applicant is cautioned that correction of the above items may cause the specification and drawings page count to exceed 100 pages. If the specification and drawings exceed 100 pages, applicant will need to submit the required application size fee.

Items Required To Avoid Processing Delays:

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):
  Jean-Claude TARDIF

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be mailed to:

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Commissioner for Patents
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Alexandria VA 22313-1450

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Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/tlo/

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 17/097,285

APPLICATION AS FILED - PART I

	(Column 1)	(Column 2)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE($)	FEE($)		RATE($)	FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	320
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	700
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	800
TOTAL CLAIMS (37 CFR 1.16(i))	30 minus 20 =	* 10			OR	x 100 =	1000
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*				x 480 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	2820

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)	OR	RATE($)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
17/097,285	11/13/2020	1629	2980	50761-029001	30	2

CONFIRMATION NO. 3015

21559
CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

FILING RECEIPT

OC000000121592035

Date Mailed: 11/27/2020

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

Jean-Claude TARDIF, Montreal, CANADA;

Applicant(s)

INSTITUT DE CARDIOLOGIE DE MONTREAL, Montreal, CANADA;

Power of Attorney: None

Domestic Priority data as claimed by applicant

This appln claims benefit of 63/093,988 10/20/2020
and claims benefit of 62/935,865 11/15/2019

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 11/24/2020

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 17/097,285**

Projected Publication Date: To Be Determined - pending completion of Corrected Papers

Non-Publication Request: No

Early Publication Request: No

Title

EARLY ADMINISTRATION OF LOW-DOSE COLCHICINE AFTER MYOCARDIAL INFARCTION

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

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Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

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To: patentadministrator@clarkelbing.com,smmichaud@clarkelbing.com,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 21559

Nov 27, 2020 04:06:46 AM

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CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110
UNITED STATES

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Application	Document	Mailroom Date	Attorney Docket No.
17097285	NT.CR.APP.PA	11/27/2020	50761-029001
	APP.FILE.REC	11/27/2020	50761-029001

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PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

Docket No.: 50761-029001
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Utility Application of:
Jean-Claude TARDIF

Application No.: 17/097,285 Confirmation No.: 3015

Filed: November 13, 2020 Art Unit: 1629

For: EARLY ADMINISTRATION OF LOW-DOSE COLCHICINE AFTER MYOCARDIAL INFARCTION Examiner: Not Yet Assigned

PRELIMINARY AMENDMENT UNDER 37 C.F.R. § 1.115

Prior to examination on the merits, please amend the application as provided below.

Electronic Acknowledgement Receipt	
EFS ID:	41287754
Application Number:	17097285
International Application Number:	
Confirmation Number:	3015
Title of Invention:	EARLY ADMINISTRATION OF LOW-DOSE COLCHICINE AFTER MYOCARDIAL INFARCTION
First Named Inventor/Applicant Name:	Jean-Claude TARDIF
Customer Number:	21559
Filer:	Jan Tittel/James Moran
Filer Authorized By:	Jan Tittel
Attorney Docket Number:	50761-029001
Receipt Date:	04-DEC-2020
Filing Date:	13-NOV-2020
Time Stamp:	12:34:03
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Specification	50761-029001_-_Substitute_Specification.pdf	2717927 2b22650c74ace30cf7fb8f25b2e886e31989b6b0	no	46

Warnings:

Information:					
2	Applicant Response to Pre-Exam Formalities Notice	Reply.pdf	76935 e113be8034f86d3900f5ff8ce59c18d51c15ab22	no	1
Warnings:					
Information:					
3		Amendment.pdf	79397 56d0150ccf3ebb707400407540465b953773313a	yes	3

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Applicant Arguments/Remarks Made in an Amendment	3	3
	Specification	2	2
	Preliminary Amendment	1	1

Warnings:	
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Total Files Size (in bytes):	2874259

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National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

EARLY ADMINISTRATION OF LOW-DOSE COLCHICINE AFTER MYOCARDIAL INFARCTION

Background of the Invention

The invention relates to a treatment regimen for patients after suffering a myocardial infarction.

Inflammation appears to play an important role in atherosclerosis (Hansson GK, Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med* 2005;352:1685-95). Inhibition of interleukin-1β by the injectable monoclonal antibody canakinumab led to a 15% lower risk of cardiovascular events than was observed with placebo in the Canakinumab Antiinflammatory Thrombosis Outcomes Study (CANTOS) but also led to a slightly higher incidence of fatal infections (Ridker PM et al., Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med* 2017;377:1119-31). In contrast, methotrexate did not affect cardiovascular outcomes or plasma markers of inflammation in the Cardiovascular Inflammation Reduction Trial (CIRT) (Ridker PM et al., Low-dose methotrexate for the prevention of atherosclerotic events. *N Engl J Med* 2019;380:752-62). Considering these differing results and given that canakinumab is not clinically available for cardiovascular prevention, the search for a widely used alternative antiinflammatory treatment that may reduce the risk of atherosclerotic events among patients with coronary artery disease continues.

Colchicine is an inexpensive, orally administered, potent anti-inflammatory medication that was initially extracted from the autumn crocus and has been used for centuries. Its mechanism of action is through the inhibition of tubulin polymerization and microtubule generation and, possibly, effects on cellular adhesion molecules, inflammatory chemokines, and the inflammasome (Ravelli RB et al., Insight into tubulin regulation from a complex with colchicine and a stathmin-like domain. *Nature* 2004;428:198-202; Perico N et al., Colchicine interferes with L-selectin and leukocyte function-associated antigen-1 expression on human T lymphocytes and inhibits T cell activation. *J Am Soc Nephrol* 1996; 7:594-601; Pope RM and Tschopp J, The role of interleukin-1 and the inflammasome in gout: implications for therapy. *Arthritis Rheum* 2007; 56:3183-8). Colchicine is currently indicated for the treatment of gout, familial Mediterranean fever, and pericarditis (Cerquaglia C et al., Pharmacological and clinical basis of treatment of Familial Mediterranean Fever (FMF) with colchicine or analogues: an update. *Curr Drug Targets Inflamm Allergy* 2005;4:117-24; and Imazio M et al., Colchicine in addition to conventional therapy for acute pericarditis: results of the COlchicine for acute PEricarditis (COPE) trial. *Circulation* 2005;112:2012-6).

In the Low-Dose Colchicine (LoDoCo) trial, patients with stable coronary disease treated with colchicine at a dose of 0.5 mg once daily had fewer cardiovascular events than those not receiving colchicine (Nidorf SM et al., Low-dose colchicine for secondary prevention of cardiovascular disease. *J Am Coll*

Cardiol 2013;61:404-10). However, that trial enrolled only 532 patients and was not placebo-controlled.

Because acute coronary syndromes are associated with higher risks of recurrent events and exacerbated inflammation a need exists in the art for new treatment regimens.

Summary of the Invention

A clinical trial referred to as the Colchicine Cardiovascular Outcomes Trial (COLCOT) was conducted to evaluate the effects of colchicine on cardiovascular outcomes as well as its long-term safety profile in patients who had recently had a myocardial infarction.

The results of the COLCOT trial support that the use of colchicine in patients who have recently had a myocardial infarction significantly improved their quality of life in several ways. Colchicine at a daily low dose of 0.5 mg led to a statistically significant lower risk of ischemic cardiovascular events than placebo. Death from cardiovascular causes, resuscitated cardiac arrest, myocardial infarction, stroke, and urgent hospitalization for angina leading to coronary revascularization was also significantly lower among the patients who received 0.5 mg of colchicine than those who received placebo. Patients receiving low dose colchicine had reduced morbidity relative to placebo, as is demonstrated by the rates of the respective primary composite end points for the two patient populations (P = 0.02). This reduction in morbidity was particularly prominent among colchicine-receiving patients in the reduction of severe conditions, such as stroke and urgent hospitalization for angina leading to revascularization: hazard ratios are 0.26 (95% confidence interval is 0.10-0.70) and 0.50 (95% confidence interval is 0.31-0.81), respectively. Still further, unlike the use of the anti-inflammatory canakinumab for atherosclerotic events, colchicine did not increase the incidence of septic shock. Moreover, no serious adverse event of myopathy linked to colchicine occurred despite the use of statins in 99% of trial participants.

The results of the COLCOT trial have been further analyzed to determine if time to treatment initiation (TTI) had any effect on the outcome of the treatment. Three different cutoffs for TTI were used in order to determine the association between early initiation of therapy and clinical outcomes. These cutoffs were determined based on the usual journey of patients with MI. The first 30-day post-MI timeline was divided into three independent periods of time, and analyzed as such: from day 0 to 3, referring to in-hospital management; from day 4 to 7, referring to early post-discharge period and from day 8 to 30, referring to late post-discharge period.

The main COLCOT results revealed that colchicine reduced the risk of ischemic CV events by 23% in the post-MI setting. Results from the present TTI analysis support that early suppression of inflammation after MI provides even greater benefits, with a reduction of 48% in the risk of the composite primary endpoint

when colchicine was initiated between days 0 and 3. The demonstrated cost-effectiveness of low-dose colchicine also supports its large-scale use after MI. Results of the LoDoCo2 study of patients with stable coronary artery disease complement those of COLCOT in the post-MI setting.

In view of the aforementioned, the invention, in one aspect, relates to colchicine for use in a method of treating a patient after having a myocardial infarction (MI), the method comprising initiating the administration of colchicine at a daily low dose to the patient within about 3 days of the MI.

In another aspect, the invention relates to a colchicine for use in a method of treating a patient after having a MI, the method comprising initiating the administration of colchicine at a daily low dose to the patient within about 4 days of the MI.

In another aspect, the invention relates to a colchicine for use in a method of treating a patient after having a MI, the method comprising initiating the administration of colchicine at a daily low dose to the patient within about 5 days of the MI.

In another aspect, the invention relates to a colchicine for use in a method of treating a patient after having a MI, the method comprising initiating the administration of colchicine at a daily low dose to the patient within about 30 days of the MI.

In another aspect, the invention relates to a method of treating a patient after having a MI, the method comprising initiating the administration of colchicine at a daily low dose to the patient within about 3 days of the MI.

In another aspect, the invention relates to a method of treating a patient after having a MI, the method comprising initiating the administration of colchicine at a daily low dose to the patient within about 4 days of the MI.

In another aspect, the invention relates to a method of treating a patient after having a MI, the method comprising initiating the administration of colchicine at a daily low dose to the patient within about 5 days of the MI.

In another aspect, the invention relates to a method of treating a patient after having a MI, the method comprising initiating the administration of colchicine at a daily low dose to the patient within about 30 days of the MI.

In another aspect, the invention relates to the use of a daily low dose of colchicine for treating a patient

after having a MI, wherein the use is initiated within about 3 days of the MI.

In another aspect, the invention relates to the use of a daily low dose of colchicine for treating a patient after having a MI, wherein the use is initiated within about 4 days of the MI.

In another aspect, the invention relates to the use of a daily low dose of colchicine for treating a patient after having a MI, wherein the use is initiated within about 5 days of the MI.

In another aspect, the invention relates to the use of a daily low dose of colchicine for treating a patient after having a MI, wherein the use is initiated within about 30 days of the MI.

In a further aspect, the invention relates to the use of colchicine for the manufacture of a medicament for treating a patient after having a MI, wherein the colchicine is a low dose colchicine for daily administration initiated within about 3 days of the MI.

In a further aspect, the invention relates to the use of colchicine for the manufacture of a medicament for treating a patient after having a MI, wherein the colchicine is a low dose colchicine for daily administration initiated within about 4 days of the MI.

In a further aspect, the invention relates to the use of colchicine for the manufacture of a medicament for treating a patient after having a MI, wherein the colchicine is a low dose colchicine for daily administration initiated within about 5 days of the MI.

In a further aspect, the invention relates to the use of colchicine for the manufacture of a medicament for treating a patient after having a MI, wherein the colchicine is a low dose colchicine for daily administration initiated within about 30 days of the MI.

In another aspect, the present invention relates to low-dose colchicine for use in treating a patient having a MI, wherein the colchicine is for daily administration initiated within about 3 days of the MI.

In another aspect, the present invention relates to low-dose colchicine for use in treating a patient having a MI, wherein the colchicine is for daily administration initiated within about 4 days of the MI.

In another aspect, the present invention relates to low-dose colchicine for use in treating a patient having a MI, wherein the colchicine is for daily administration initiated within about 5 days of the MI.

In another aspect, the present invention relates to low-dose colchicine for use in treating a patient having

a MI, wherein the colchicine is for daily administration initiated within about 30 days of the MI.

In some embodiments, the method involves administering colchicine within 5 days of the MI (for example, at 1 day, 2 days, 3 days, or 4 days). In some embodiments, the method includes administering colchicine within 4 days of the myocardial infarction (for example, at 1 day, 2 days, or 3 days). In still other embodiments, the method includes administering colchicine within 3 days of the myocardial infarction (for example, at 1 day or 2 days).

In some embodiments, the patient administered colchicine received percutaneous coronary intervention for treating the patient's myocardial infarction.

In some embodiments, the myocardial infarction is acute MI (AMI). In some embodiments, the MI is not type 2 MI.

In some embodiments, the patient administered was previously prescribed a medication (for example, an antiplatelet agent, a statin, aspirin or a combination thereof).

In some embodiments, the patient administered is concurrently being treated with a medication (for example, an antiplatelet agent, a statin, aspirin, or a combination thereof).

In some embodiments, the patient is at a lower risk of a cardiovascular event, relative to a patient not being administered colchicine. For example, the cardiovascular event is an ischemic cardiovascular event. In some embodiments, the cardiovascular event is cardiovascular death, resuscitated cardiac arrest, myocardial infarction, stroke, or urgent hospitalization for angina requiring coronary revascularization.

In some embodiments, the patient has atherosclerotic coronary artery disease.

In some embodiments the patient does not have severe heart failure, reduced left ventricular fraction, recent stroke, type 2 MI, planned coronary artery bypass by graft (CABG), inflammatory bowel disease or chronic diarrhea.

In another aspect, the invention relates to a method of reducing the risk of or preventing a stroke in a patient after having an MI, the method comprising initiating the administration of colchicine at a daily low dose to the patient within about 30 days of an MI.

In some embodiments, the method involves administering colchicine within 4-7 days (for example, 5 days,

6 days, or 7 days) of the MI.

In some embodiments, the method involves administering colchicine within 3 days of the MI.

In another aspect, the invention relates to the use of a daily low dose of colchicine for reducing the risk of or preventing a stroke in a patient after having a MI, wherein the use is initiated within 30 days of the MI.

In another aspect, the invention relates to the use of a daily low dose of colchicine for reducing the risk of or preventing a stroke in a patient after having a MI, wherein the use is initiated between 4-7 days after the MI.

In some embodiments, the invention relates to the use of a daily low does of colchicine for reducing the risk of or preventing a stroke in a patient after having a MI, wherein the use is initiated within 3 days of the MI.

In a further aspect, the invention relates to the use of colchicine for the manufacture of a medicament for reducing the risk of or preventing a stroke in a patient after having a MI, wherein the colchicine is a low dose colchicine for daily administration initiated within 30 days of the MI.

In a further aspect, the invention relates to the use of colchicine for the manufacture of a medicament for reducing the risk of or preventing a stroke in a patient after having a MI, wherein the colchicine is a low dose colchicine for daily administration initiated between 4 and 7 days of the MI.

In another aspect, the present invention relates to the use of colchicine for the manufacture of a medicament for reducing the risk of or preventing stroke in a subject after having a MI, wherein the colchicine is for daily administration initiated within about 3 days of the MI.

In some embodiments, the administration of colchicine is initiated upon assessment in (a) an emergency department (ED), (b) the hospital, or (c) a medical office setting.

In some embodiments, colchicine is administered in the form of a tablet or a capsule (e.g., a coated tablet or capsule). In some embodiment, colchicine is administered in the form of a film-coated tablet.

In some embodiments, colchicine is administered at 0.3 to 0.7 mg. For example, colchicine is administered at 0.4 to 0.6 mg, and is preferably administered at about 0.5 mg. In some embodiments, colchicine is administered in a 0.5 mg tablet or a 0.6 mg tablet. In other embodiments, colchicine is administered in a 0.25 mg tablet.

In some embodiments, colchicine is administrated once, twice, or three times daily.

In some embodiments, colchicine is administered once per day.

In some embodiments, the colchicine is administered without pre-loading the patient with colchicine (e.g., administering a higher dose, such as 1.0 mg per day or higher (1.5 mg or 2.0 mg) in a single or multiple doses, at the onset of the treatment for one, two, or three days before switching to a lower dose of, e.g., 0.5 mg per day, for the remainder of the duration of treatment).

In some embodiments, the patient is an adult human (i.e., the patient is 18 years old or older).

In another aspect, the invention relates to colchicine for use in a method of treating a patient after having a myocardial infarction (MI), the method including the administration of colchicine at a daily low dose to the patient within about 3 days (e.g., 1 day, 2 days, and 3 days) of the MI.

Use of colchicine for treating a patient after having a myocardial infarction typically continues, as needed, throughout the life of a patient. For example, in some embodiments, the duration of treatment is for 6 months, 12 months, 18 months, 24 months, 30 months, 36 months, or even longer as is needed. In some embodiments, the duration of the treatment is for at least about 23 months.

Various colchicine formulations, including film-coated tablets, are readily available and well known in the art.

Other features and advantages of the invention will be apparent from the following Detailed Description, the Drawings, and the Claims.

Definitions

As used herein, the term “cardiovascular death” refers to death resulting from a cardiovascular disease, including coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis, or a pulmonary embolism, or sudden cardiac event, including cardiac arrest and myocardial infarction.

As used herein, the term “myocardial infarction” refers to a cardiovascular disorder characterized by localized necrosis resulting from obstruction of the blood supply. MI may be classified as an ST elevation myocardial infarction (STEMI) or Non-ST elevation myocardial infarction (NSTEMI) based on the results of an ECG. A more explicit classification system, based on international consensus in 2012, also exists. This

classifies myocardial infarctions into five types including types 1 and 2. Type-1 AMI is caused by an acute atherothrombotic coronary event; type-2 AMI is a more heterogeneous entity, where a condition other than coronary artery disease (CAD) contributes to an acute imbalance between oxygen supply (e.g., hypoxemia, anemia, hypotension) and demand (e.g., tachycardia, hypertension).

As used herein, the term "resuscitated cardiac arrest" refers an abrupt loss of heart function resulting in a loss of blood flow to the body which requires the subject be resuscitated using any method known to one of skill in the art, including cardiopulmonary resuscitation or a defibrillator.

As used herein, the term "urgent hospitalization for angina requiring coronary revascularization" refers to an immediate need for a patient to be hospitalized due to severe chest discomfort felt due to ischemic heart disease which requires surgical intervention grafting and/or stenting approaches to improving blood flow to the heart and relieve angina.

As used herein, the term "stroke" refers to a condition which occurs when the blood supply to a part of the brain is suddenly interrupted (i.e., ischemic stroke) or when a blood vessel in the brain bursts and releases blood into the spaces surrounding the brain cells (i.e., hemorrhagic stroke). The symptoms of a stroke include numbness or weakness, especially on one side of the body corresponding to the contralateral side of the stroke, confusion, trouble understanding or producing speech, impaired vision in both eyes, impaired mobility, dizziness, or loss of balance or coordination. Stroke may be diagnosed using several techniques, such as, e.g., neurological examination, blood testing, computed tomography (CT) scan, magnetic resonance imaging (MRI) scan, Doppler ultrasound, and arteriography. Although stroke is a disease of the brain, it can affect the entire body by causing, e.g., paralysis, cognitive impairment, speech impairment, emotional dysregulation, and pain.

Brief Description of the Drawings

FIG. 1 is a schematic of a flow chart of the randomization and subject disposition of the patients in the Time-to-Treatment study.

FIG. 2 is a graph of the association between the time-to-treatment initiation and the adjusted hazard ratio (solid line) with the 95% confidence intervals of the adjusted hazard ratio (dashed line) calculated using a quadratic multivariable Cox regression model.

FIG. 3A is a graph of the cumulative incidence of cardiovascular events (time-to-treatment population). Shown are the Kaplan–Meier event curves for the primary efficacy composite end point (a composite of cardiovascular death, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina requiring

coronary revascularization) in the colchicine group and the placebo group for patients with a time-to-treatment initiation of ≤ 3 days. The inset shows the same data on an enlarged y-axis.

FIG. 3B is a graph of the cumulative incidence of cardiovascular events (time-to-treatment population). Shown are the Kaplan–Meier event curves for the secondary efficacy composite end point (a composite of cardiovascular death, resuscitated cardiac arrest, myocardial infarction, or stroke) in the colchicine group and the placebo group for patients with a time-to-treatment initiation of ≤3 days. The inset shows the same data on an enlarged y-axis.

Detailed Description of the Invention

We performed a randomized, double-blind trial involving patients recruited within 30 days after a myocardial infarction. The patients were randomly assigned to receive either low-dose colchicine (0.5 mg once daily) or placebo. A total of 4745 patients were enrolled; 2366 patients were assigned to the colchicine group, and 2379 to the placebo group. Patients were followed for a median of 22.6 months.

The primary efficacy end point was a composite of death from cardiovascular causes, resuscitated cardiac arrest, myocardial infarction (e.g., acute myocardial infraction or type II myocardial infarction), stroke, or urgent hospitalization for angina leading to coronary revascularization. The components of the primary end point and safety were also assessed.

Study design and patient population

COLCOT was an international multicenter, randomized, double-blinded trial that randomly assigned patients to receive either low-dose colchicine (0.5 mg once daily) or placebo. The study protocol and main results have been published (see, Tardif et al., *N Engl J Med* 2019). Patients were considered eligible if they had a recent MI (< 30 days). Main exclusion criteria were severe heart failure, reduced left ventricular ejection fraction (< 35%), recent stroke (< 3 months), type 2 MI, recent (< 3 years) or planned coronary artery bypass graft (CABG), history of cancer (< 3 years), and inflammatory bowel disease or chronic diarrhea. All patients enrolled in the trial benefited from percutaneous coronary intervention whenever indicated and guidelines-directed management of CV disease prior to randomization (see. Tardif et al., *N Engl J Med* 2019).

Clinical follow-up consisted of evaluations at 1 and 3 months after randomization and every 3 months thereafter. An independent clinical endpoint committee, blinded to trial-group assignment, adjudicated clinical endpoints. The trial was locally approved by the various institutional review boards, and all patients signed a written informed consent before enrollment.

Efficacy Endpoints

The primary efficacy endpoint was a composite of CV death, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina requiring coronary revascularization. The secondary endpoints consisted of the components of the primary efficacy endpoint, all-cause death, and a composite of CV death, resuscitated cardiac arrest, MI, or stroke. Exploratory endpoints included all coronary revascularizations, including both elective and urgent coronary revascularizations.

Cutoffs for Time-to-Treatment Initiation (TTI) of Colchicine

Three different cutoffs for TTI were used in order to determine the association between early initiation of therapy and clinical outcomes. These cutoffs were determined based on the usual journey of patients with MI. The first 30-day post-MI timeline was divided into three independent periods of time, and analyzed as such: from day 0 to 3, referring to in-hospital management; from day 4 to 7, referring to early post-discharge period and from day 8 to 30, referring to late post-discharge period.

Results

Baseline characteristics for patients in TTI analysis

Of the 4745 patients randomized in COLCOT, 4661 were included in the TTI analysis (colchicine, N=2322; placebo, N=2339) (Figure 1). Overall, patients were randomized at 13.5±10.1 days following the index MI, 25.6% between days 0 and 3, 15.4% between days 4 and 7 and 59.0% at day 8 or after. Baseline characteristics were similar between the colchicine and placebo groups (Table 1). Patients were mostly men (81.0%) with a mean age of 60.5 years, 20.2% had diabetes, 51.0% had a history of hypertension, 29.7% were active smokers, and 16.8% had had a prior PCI. Background therapy included aspirin, a second anti-platelet agent and a statin in 98.8%, 98.0% and 99.0% of patients, respectively. The vast majority of patients (93.0%) underwent percutaneous coronary intervention (PCI) during the index hospitalization, with no difference in terms of time to PCI between the two groups.

Table 1: Baseline Characteristics according to treatment allocation for Time-to-Treatment Initiation (TTI)

Characteristics	All patients N=4661	Colchicine group N=2322	Placebo group N=2339
Age (years) – mean ± SD	60.5 ± 10.6	60.6 ± 10.6	60.5 ± 10.6
Male sex - no. (%)	3774 (81.0%)	1861 (80.1%)	1913 (81.8%)
BMI (kg/m^2) – mean ± SD	28.3 ± 4.7	28.2 ± 4.8	28.4 ± 4.7
Current Smoking - no./total no. (%)	1382/4659 (29.7)	694/2322 (29.9%)	688/2337 (29.4%)
History of Hypertension - no. (%)	2377 (51.0%)	1160 (50.0%)	1217 (52.0%)
History of Diabetes - no. (%)	942 (20.2%)	451 (19.4%)	491 (21.0%)
Prior MI - no. (%)	751 (16.1%)	360 (15.5%)	391 (16.7%)
Prior PCI - no. (%)	783 (16.8%)	382 (16.5%)	401 (17.1%)
Prior CABG - no. (%)	146 (3.1%)	66 (2.8%)	80 (3.4%)
Prior HF - no. (%)	90 (1.9%)	48 (2.1%)	42 (1.8%)
Prior Stroke or TIA - no. (%)	119 (2.6%)	53 (2.3%)	66 (2.8%)
PCI associated with the index event - no. (%)	4336 (93.0%)	2154 (92.8%)	2182 (93.3%)
Medication use - no. (%):			
Aspirin	4605 (98.8%)	2291 (98.7%)	2314 (98.9%)
Other antiplatelet agent	4567 (98.0%)	2267 (97.6%)	2300 (98.3%)
Statin	4615 (99.0%)	2297 (98.9%)	2318 (99.1%)
Beta-blocker	4143 (88.9%)	2077 (89.4%)	2066 (88.3%)

TTI 0-3 days - no. (%)	1193 (25.6%)	604 (26.0%)	589 (25.2%)
TTI 4-7 days - no. (%)	720 (15.4%)	364 (15.7%)	356 (15.2%)
TTT ≥ 8 days - no. (%)	2748 (59.0%)	1354 (58.3%)	1394 (59.6%)
Time from index MI to randomization (days) – mean ± SD	13.5 ± 10.1	13.5 ± 10.1	13.5 ± 10.0
Time from Index MI to PCI (days) – mean ± SD	1.4 ± 2.9	1.4 ± 2.9	1.4 ± 2.9
Time from PCI to randomization (days) – mean ± SD	11.9 ± 9.9	11.9 ± 9.9	11.9 ± 9.9

Abbreviations: CABG, coronary-artery bypass graft surgery; HF, heart failure; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

Data were missing on the following characteristics: age (assessed according to date of birth; see below) for 431 patients (213 in the colchicine group and 218 in the placebo group) and body-mass index (the weight in kilograms divided by the square of the height in meters) for 5 (1 and 4 patients, respectively). Date of birth was not required field because it was considered in some countries to be sensitive data that could allow for the identification of patients.

For statistical reporting, missing information regarding the day of birth was replaced by 15, and missing information regarding the month and day of birth was replaced by July 1.

Baseline characteristics according to TTI strata are shown in Table 2. Patients in whom therapy was initiated between days 0 and 3, when compared to those at days 8 to 30, were younger (59.1±10.8 vs. 61.3±10.4 years) and more often active smokers (43.8 vs. 20.2%), had less commonly hypertension (41.1 vs. 56.2%) and diabetes (17.4 vs. 22.0%) but underwent more often PCI associated with the index MI (95.8 vs. 91.3%), all $p < 0.05$.

Table 2: Baseline characteristics according to TTI

Characteristics	TTI 0-3 days N=1193	TTI 4-7 days N=720	TTT ≥ 8 days N=2748	p*	p**
Age (years) – mean ± SD	59.1 ± 10.8	60.1 ± 11.0	61.3 ± 10.4	<0.0001	<0.0001
Male sex - no. (%)	980 (82.2%)	605 (84.0%)	2189 (80.0%)	0.014	0.071
BMI (kg/m^2) - mean ± SD	28.1 ± 4.6	27.7 ± 4.6	28.6 ± 4.8	<0.0001	0.004
Current Smoking - no. (%)	522 (43.8%)	306 (42.6%)	554 (20.2%)	<0.0001	<0.0001
History of Hypertension - no. (%)	490 (41.1%)	343 (47.6%)	1544 (56.2%)	<0.0001	<0.0001
History of Diabetes - no. (%)	208 (17.4%)	130 (18.1%)	604 (22.0%)	0.001	0.001
Prior MI - no. (%)	170 (14.3%)	111 (15.4%)	470 (17.1%)	0.070	---
Prior PCI - no. (%)	182 (15.3%)	107 (14.9%)	494 (18.0%)	0.035	0.037
Prior CABG - no. (%)	34 (2.9%)	30 (4.2%)	82 (3.0%)	0.218	---
Prior HF - no. (%)	14 (1.2%)	12 (1.7%)	64 (2.3%)	0.046	0.017
Prior Stroke or TIA - no. (%)	20 (1.7%)	21 (2.9%)	78 (2.8%)	0.084	---
PCI associated with the index event - no. (%)	1143 (95.8%)	685 (95.1%)	2508 (91.3%)	<0.0001	<0.0001
Medication use - no. (%):					
Aspirin	1181 (99.0%)	715 (99.3%)	2709 (98.6%)	0.219	---
Other antiplatelet agent	1177 (98.7%)	708 (98.3%)	2682 (97.6%)	0.072	---
Statin	1188 (99.6%)	708 (98.3%)	2719 (98.9%)	0.024	0.047
Beta-blocker	1093 (91.6%)	642 (89.2%)	2408 (87.6%)	0.001	0.0003
Time from index MI to randomization (days) – mean ± SD	2.1 ± 0.8	5.1 ± 1.1	20.8 ± 6.6	<0.0001	<0.0001

Time from Index MI to PCI (days) – mean ± SD	0.4 ± 0.7	1.4 ± 1.8	1.8 ± 3.6	<0.0001	<0.0001
Time from PCI to randomization (days) – mean ± SD	1.6 ± 0.9	3.7 ± 1.9	18.8 ± 7.3	<0.0001	<0.001

Abbreviations: CABG, coronary-artery bypass graft surgery; HF, heart failure; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

Data were missing on the following characteristics: age (assessed according to date of birth; see below) for 431 patients (213 in the colchicine group and 218 in the placebo group) and body-mass index (the weight in kilograms divided by the square of the height in meters) for 5 (1 and 4 patients, respectively).

Date of birth was not a required field because it was considered in some countries to be sensitive data that could allow for the identification of patients. For statistical reporting, missing information regarding the day of birth was replaced by 15, and missing information regarding the month and day of birth was replaced by July 1.

*: Group comparison TTI 0-3 vs. TTI 4-7 vs. TTI $\geq$ 8days

**: Group comparison TTI <3 vs. TTI $\geq$ 8 days

Effects of time-to-treatment initiation on the primary efficacy endpoint

The effects of colchicine on the primary endpoint according to TTI are shown in Table 3 and Figure 2. A primary endpoint event occurred in 4.3% of patients in the colchicine group, as compared to 8.3% of those in the placebo group when TTI was between days 0 and 3 (N=1193, HR=0.52, 95% CI 0.32-0.84, p=0.007, Figure 3A). Corresponding rates were 6.0 and 5.9% when TTI was between days 4 and 7 (N=720) and 5.7 and 7.1% when TTI was on day 8 or after (N=2748), but these differences between groups did not reach statistical significance. Table 3 also shows the percentages of patients with events and the hazard ratios for the components of the primary endpoint, including CV death (HR=1.04, 95% CI 0.15-7.37), resuscitated cardiac arrest (HR=0.33, 95% CI 0.03-3.20), MI (HR=0.58, 95% CI 0.32-1.05), stroke (HR=0.21, 95% CI 0.02-1.81) and urgent hospitalization for angina requiring coronary revascularization (HR=0.35, 95% CI 0.14-0.88).

Table 3: Efficacy endpoints according to TTI (N=4661, colchicine vs. placebo)

Endpoints	TTI 0-3 days, N=1193 Colchicine vs. placebo no. (%)	TTI 4-7 days, N=720 Colchicine vs. placebo no. (%)	TTI ≥ 8 days, N=2748 Colchicine vs. placebo no. (%)
	HR (95% CI); p	HR (95% CI); p	HR (95% CI); p
Primary composite endpoint	26 (4.3%) vs. 49 (8.3%)	22 (6.0%) vs. 21 (5.9%)	77 (5.7%) vs. 99 (7.1%)
	0.52 (0.32-0.84); p=0.007	0.96 (0.53-1.75); p=0.896	0.82 (0.61-1.11); p=0.200
CV death	2 (0.3%) vs. 2 (0.3%)	2 (0.5%) vs. 4 (1.1%)	15 (1.1%) vs. 18 (1.3%)
	1.04 (0.15-7.37); p=0.970	0.45 (0.08-2.46); p=0.356	0.89 (0.45-1.76); p=0.734
Resuscitated cardiac arrest	1 (0.2%) vs. 3 (0.5%)	2 (0.5%) vs. 1 (0.3%)	2 (0.1%) vs. 2 (0.1%)
	0.33 (0.03-3.20); p=0.340	1.90 (0.17-20.95); p=0.600	1.02 (0.14-7.22); p=0.986
MI	17 (2.8%) vs. 29 (4.9%)	16 (4.4%) vs. 9 (2.5%)	52 (3.8%) vs. 59 (4.2%)
	0.58 (0.32-1.05); p=0.071	1.67 (0.74-3.78); p=0.218	0.93 (0.64-1.35); p=0.710
Stroke	1 (0.2%) vs. 5 (0.8%)	1 (0.3%) vs. 3 (0.8%)	2 (0.1%) vs. 11 (0.8%)
	0.21 (0.02-1.81); p=0.156	0.28 (0.03-2.71); p=0.272	0.19 (0.04-0.84); p=0.029
Urgent hospitalization for angina requiring coronary revascularization	6 (1%) vs. 17 (2.9%)	4 (1.1%) vs. 6 (1.7%)	15 (1.1%) vs. 26 (1.9%)
	0.35 (0.14-0.88); p=0.026	0.63 (0.18-2.24); p= 0.476	0.61 (0.32-1.16); p=0.131
Secondary Composite Endpoint	20 (3.3%) vs. 36 (6.1%)	18 (4.9%) vs. 16 (4.5%)	67 (4.9%) vs. 77 (5.5%)
	0.55 (0.32-0.95); p=0.031	1.04 (0.53-2.03); p=0.919	0.92 (0.66-1.28); p=0.629
All-cause death	6 (1.0%) vs. 6 (1.0%)	8 (2.2%) vs. 7 (2.0%)	26 (1.9%) vs. 31 (2.2%)
	1.03 (0.33-3.19); p=0.962	1.03 (0.37-2.84); p=0.957	0.90 (0.53-1.51); p=0.684
All Coronary Revascularizations	33 (5.5%) vs. 51 (8.7%)	25 (6.9%) vs. 18 (5.1%)	72 (5.3%) vs. 94 (6.7%)
	0.63 (0.40-0.97); p=0.037	1.41 (0.76-2.61); p=0.275	0.81 (0.59-1.10); p=0.172

The effects of colchicine on the primary endpoint for a TTI of less than 4 days is shown in Table 4 and Table 5. The effects of colchicine on the primary endpoint for a TTI of less than 5 days is shown in Table 6 and Table 7. Both the TTI of less than 4 days and the TTI of less than 5 days was were calculated using a basic model (Table 4 and Table 6) as well as an adjusted model (Table 5 and Table 7) which is described below in the statistical analysis section. In all cases, the interaction p-value was not significant ($p>0.05$), meaning that the conclusion over Placebo vs. Colchicine group can be obtained directly from the respective p-values for HR. In other words, relationships within the placebo and colchicine groups with TTI are both linear/parallel and the interpretation is straightforward. For a TTI of 4 days or less, colchicine was shown to offer additional protection over the placebo in both the basic (Table 4 and Table

6) and the adjusted models (Table 5 and Table 7). The adjusted models resulted in a hazard ratio (HR) of 0.58 and a p value of 0.0126.

Table 4. Effect of Colchicine with TTI of <4 days calculated using basic model

Delay between randomization and index MI	Positively adjudicated primary endpoint	Placebo N=2132	Colchicine N=2132	All N=4264
[0-4] days	n	917	908	1825
	Yes	84 (9.16%)	38 (4.19%)	88 (6.09%)
	No	833 (90.84%)	724 (95.81%)	1557 (93.91%)
[5-30] days	n	1187	1224	2411
	Yes	115 (9.69%)	93 (7.60%)	208 (8.63%)
	No	1072 (90.31%)	1131 (92.40%)	2203 (91.37%)

Cox Regression Model for Time to First Positively Adjudicated Primary Endpoint Including Treatment Group, Delay between randomization and index MI and Delay between randomization and Index MI x Randomized treatment group interaction

Interaction Effect	P-value
Delay between randomization and Index MI x Randomized treatment group	0.1191

Delay between randomization and index MI	Effect	HR (95% CI)	P-value
[0-4] days	Colchicine vs. Placebo	0.57 (0.37; 0.87)	0.0098
[5-30] days	Colchicine vs. Placebo	0.83 (0.63; 1.09)	0.1795

Notes: Model based on 0 / 4264 observations.
Counts of undetermined cause were classified as MI deaths.

Table 5. Effect of Colchicine with TTI of <4 days calculated using adjusted model

Delay between randomization and index MI	Positively adjudicated primary endpoint	Placebo N=2132	Colchicine N=2132	All N=4264
[0-4] days	n	917	908	1825
	Yes	84 (9.16%)	38 (4.19%)	88 (6.09%)
	No	833 (90.84%)	724 (95.81%)	1557 (93.91%)
[5-30] days	n	1187	1224	2411
	Yes	115 (9.69%)	93 (7.60%)	208 (8.63%)
	No	1072 (90.31%)	1131 (92.40%)	2203 (91.37%)

Cox Regression Model for Time to First Positively Adjudicated Primary Endpoint Including Treatment Group, Delay between randomization and Index MI, Delay between randomization and Index MI x Randomized treatment group Interaction, Age at randomization (years), History of diabetes, Prior coronary revascularization (prior PCI or prior CABG) and Index Heart Failure

Interaction Effect	P-value
Delay between randomization and Index MI x Randomized treatment group	0.1513

Delay between randomization and index MI	Effect	HR (95% CI)	P-value
[0-4] days	Colchicine vs. Placebo	0.58 (0.38; 0.89)	0.0126
[5-30] days	Colchicine vs. Placebo	0.88 (0.66; 1.17)	0.3729

Notes: Model based on 0 / 4264 observations.
Counts of undetermined cause were classified as MI deaths.

Table 6. Effect of Colchicine with TTI of <5 days calculated using basic model

Delay between randomization and index MI	Positively adjudicated primary endpoint	Placebo N=1736	Colchicine N=1720	All N=3456
[0-2] days	n	821	899	1720
	Yes	56 (6.8%)	43 (4.8%)	99 (5.8%)
	No	765 (93.2%)	856 (95.2%)	1621 (94.2%)
[3-29] days	n	1018	1063	2081
	Yes	113 (11.1%)	85 (8.0%)	198 (9.5%)
	No	905 (88.9%)	978 (92.0%)	1883 (90.5%)

Cox Regression Model for Time to First Positively Adjudicated Primary Endpoint Including Treatment Group, Delay between randomization and Index MI and Delay between randomization and Index MI x Randomized treatment group Interaction

Interaction Effect	P-value
Delay between randomization and Index MI x Randomized treatment group	0.0807

Delay between randomization and Index MI	Effect	HR (95% CI)	P-value
[0-2] days	Colchicine vs. Placebo	0.67 (0.46, 0.98)	0.0365
[3-29] days	Colchicine vs. Placebo	0.76 (0.58, 0.98)	0.0364

Notes: Model based on N = 3441 censored case.
Counts of colchicine group with discontinued as IN deaths.

Table 7. Effect of Colchicine with TTI of <5 days calculated using adjusted model

Delay between randomization and Index MI	Positively Adjudicated Primary Endpoint	Placebo N=1717	Colchicine N=1712	All N=3429
[0-2] days	n	819	898	1717
	Yes	56 (6.8%)	43 (4.8%)	99 (5.8%)
	No	763 (93.2%)	855 (95.2%)	1618 (94.2%)
[3-29] days	n	1018	1063	2081
	Yes	113 (11.1%)	85 (8.0%)	198 (9.5%)
	No	905 (88.9%)	978 (92.0%)	1883 (90.5%)

Cox Regression Model for Time to First Positively Adjudicated Primary Endpoint Including Treatment Group, Delay between randomization and Index MI, Delay between randomization and Index MI x Randomized treatment group interaction, Age at randomization (years), History of diabetes, Prior coronary revascularization (prior PCI or prior CABG) and Prior Heart Failure

Interaction Effect	P-value
Delay between randomization and Index MI x Randomized treatment group	0.1575

Delay between randomization and Index MI	Effect	HR (95% CI)	P-value
[0-2] days	Colchicine vs. Placebo	0.68 (0.45, 1.02)	0.0631
[3-29] days	Colchicine vs. Placebo	0.79 (0.61, 1.05)	0.1013

Notes: Model based on N = 3421 observations.
Counts of colchicine group with discontinued as IN deaths.

For a TTI of 5 days or less, colchicine showed borderline significance with respect to the benefits of administering colchicine within 5 days of an MI. This data suggests that some benefit is still possible administering colchicine 5 days after an MI, having HR 0.68 (0.45 – 1.02) and p=0.063 using the adjusted model.

Effects of time-to-treatment initiation on the secondary and exploratory efficacy endpoints

The effects of colchicine on the secondary and exploratory endpoints are shown in Table 3. The secondary efficacy endpoint consisting of a composite of CV death, cardiac arrest, myocardial infarction or stroke occurred in 3.3% of the patients in the colchicine group and in 6.1% of those in the placebo group when TTI was between days 0 and 3 (HR=0.55; 95% CI, 0.32-0.95, Figure 3B). The exploratory endpoint of all coronary revascularizations, not coronary revascularizations limited to those observed as the primary composite endpoint, including urgent revascularization following unstable angina and hospitalization, occurred in 5.5% of patients in the colchicine group, as compared to 8.7% of those in the

placebo group when TTI was between days 0 and 3 (HR=0.63, 95% CI 0.40-0.97). There were 6 deaths in both study groups when TTI was between days 0 and 3 (HR=1.03, 95% 0.33-3.19).

This TTI analysis of COLCOT shows that early initiation of low-dose colchicine within the first 3 days after MI is associated with a reduction of 48% in the risk of the primary endpoint consisting of a composite of CV death, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina requiring coronary revascularization, in comparison with placebo. This result was due to a lower incidence of MIs, strokes and urgent hospitalizations for angina leading to coronary revascularization. The secondary efficacy endpoint consisting of a composite of CV death, resuscitated cardiac arrest, MI or stroke was also significantly reduced by 45% with early initiation of low-dose colchicine. The benefits were more marked when treatment was initiated within the first 3 days after MI, as compared to between days 4 and 30, supporting the strategy of in-hospital initiation of colchicine in order to improve CV outcomes post-MI.

The main COLCOT results revealed that colchicine reduced the risk of ischemic CV events by 23% in the post-MI setting. Results from the present COLCOT analysis suggest that early suppression of inflammation after MI provides even greater benefits, with a reduction of 48% in the risk of the composite primary endpoint when colchicine was initiated between days 0 and 3. The demonstrated cost-effectiveness of low-dose colchicine also supports its large-scale use after MI. Results of the LoDoCo2 study of patients with stable coronary artery disease complement and further support those of COLCOT in the post-MI setting (see *Nidorf et al. N Engl Med, 2020. and Tong et al. Circulation, 2020)*.

Early initiation of low-dose colchicine after MI greatly reduced the risk of ischemic CV events compared with placebo. These results support in-hospital initiation of adjunctive anti-inflammatory therapy with colchicine for post-MI prevention.

Statistical Analysis

For the COLCOT trial, it was estimated that a sample of approximately 4500 patients undergoing randomization (with 2250 patients in each group) or, in terms of events, a total number of 301 patients with a first positively adjudicated primary end-point event would yield adequate power. The sample-size calculation was based on the primary efficacy end point and assumed a 27% lower risk with colchicine than with placebo, indicated by a hazard ratio of 0.724. With the use of a two-sided test at the 0.05 significance level, the trial would have 80% power if it continued until 301 positively adjudicated primary events occurred in the combined trial groups. The trial design assumed an event rate of 7% in the placebo group at 24 months, an 18-month recruitment period during which patients would be uniformly recruited, a 24-month minimum follow-up period, and a 1% annual rate of loss to follow-up or withdrawal of consent.

The efficacy analyses were conducted with the use of positively adjudicated data and according to the intention-to-treat principle. The primary end point was compared between the two trial groups with the use of a log-rank test, and the hazard ratio from a Cox proportional-hazards model, with a 95% confidence interval, was calculated. A Cox proportional-hazards model with adjustment for important baseline characteristics was also used as prespecified in the protocol.

For the present TTI analysis, the data were centrally analyzed by an independent academic biostatistics center at the Montreal Health Innovations Coordinating Center. The analysis was conducted amongst patients who received at least one dose of the study medication (referred to as the safety population in the main protocol, Figure 1). TTI was defined as the length of time in days between the index MI and the initiation of the study medication, and three specific cutoffs were analyzed (≤ day 3, days 4 to 7, and ≥ day 8). Early initiation of therapy was defined as TTI ≤ 3 days. Baseline characteristics were summarized using counts and percentages for categorical variables and mean ± standard deviation (SD) for continuous variables. For each baseline characteristic, comparisons were made using ANOVA for continuous variables and Chi-Square test for categorical variables according to TTI strata. Analyses of the efficacy endpoints, expressed as time to event, were conducted according to time to treatment initiation. Adjusted hazard ratios (HR) along with 95% confidence intervals (CI) were calculated from stepwise multivariable Cox regression models adjusted for the same covariates that were used in the main analysis of the COLCOT trial (FIG. 2). All statistical tests were two-sided and conducted at the 0.05 significance level. Statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

Examples

The following examples are provided to further illustrate some embodiments of the present invention, but are not intended to limit the scope of the invention; it will be understood by their exemplary nature that other procedures, methodologies, or techniques known to those skilled in the art may alternatively be used.

Example 1: Meta-Analysis of Randomized Controlled Trials (RCTs) of Colchicine for Secondary Prevention of Cardiovascular Disease

Data sources

Medline (PUBMED), EMBASE, and Cochrane central were searched to identify RCTs comparing colchicine to placebo or no colchicine for secondary cardiovascular prevention (inception to September 1, 2020). To maximized sensitivity, citation chasing was performed in Google Scholar, Scopus, and Web of Science. Secondary prevention was defined as patients with clinically manifest or established CAD. Query terms included “colchicine”, “coronary artery disease”, “acute coronary syndrome”, “myocardial

infarction", "cardiovascular disease", "atherosclerosis", and "secondary prevention", either separately or in combination.

Study selection, data extraction, and bias assessment

RCTs that met the following criteria were included in the meta-analysis: 1) compared daily use of low-dose (0.5 mg) colchicine to placebo or no colchicine for secondary cardiovascular prevention; 2) the study reported at least one of the following outcomes: cardiovascular death, MI, stroke, cardiac arrest, or urgent coronary revascularization; 3) other than the trial medication, patients in both arms were treated in accordance to guideline directed medical therapy; 4) the minimum follow-up was at least 1 year; and 5) trials were published in a peer-reviewed scientific journal. Review articles, editorials, meta-analyses, observational studies, and published abstracts were excluded from the present meta-analysis.

Study selection was performed by two independent reviewers, using two levels of screening. At the first level, titles and abstracts of searched studies were screened, followed by review of full texts. The reviewers were not blinded to the title of the journals, authors, or affiliated institutions. Reasons for exclusion were recorded and any discrepancies were discussed until a consensus was achieved.

Using standardized forms, data on study characteristics, patient characteristics, and outcomes were extracted on the intent-to-treat population independently by two reviewers from each eligible study. The Cochrane Collaboration risk-of-bias tool for randomized trials was used to evaluate study quality. The meta-analysis was conducted in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Outcomes

The primary efficacy endpoint was a composite of cardiovascular death, MI, ischemic stroke, and urgent coronary revascularization. Secondary efficacy endpoints consisted of the components of the primary endpoint, composite of cardiovascular death, MI, and ischemic stroke, as well as deep vein thrombosis or pulmonary embolus, and atrial fibrillation (AF). To maximize consistency in pooling efficacy endpoints among trials, the primary and secondary composite efficacy and stroke endpoints in COLCOT were modified to meet the definition of primary and stroke endpoints of the LoDoCo2 trial. Therefore, adjudicated events of resuscitated cardiac arrest and non-ischemic stroke in COLCOT were excluded from the pooled primary endpoint. The component endpoint of stroke was also restricted to include only ischemic strokes. Incidence rates and hazards ratios (HRs) were calculated for the new primary composite endpoint and ischemic stroke endpoint using individual patient data from COLCOT.

Safety outcomes were limited to serious adverse events (SAEs) and included all-cause and non-cardiovascular mortality, hospitalization for gastrointestinal event, infection, and pneumonia, as well as

diagnosis of cancer. Incidence of SAEs were recalculated for COLCOT using the intent-to-treat population.

Data synthesis and statistical analyses

The DerSimonian and Laird random-effects model was used to calculate the pooled HR and corresponding 95% confidence intervals (CI) for primary and secondary endpoints in the overall trial and in subgroup analyses of the primary endpoint. For safety outcomes, the DerSimonian and Laird random-effects model was used to compute risk ratios (RR) and corresponding 95% CIs. Heterogeneity was evaluated with the Higgins I^2 statistic. I^2 values of <25%, 25-75%, and >75% were considered to indicate low, moderate, and high degrees of heterogeneity, respectively. In subgroup analyses, the Q_b statistic was calculated to determine inconsistency and variability in the treatment effect between strata. Publication and small study bias were assessed with the Egger's regression test and visually by asymmetry in funnel plots. Sensitivity analyses were performed for the primary composite and component outcomes for 1) RCTs in patients with acute coronary syndrome (COLCOT and COPS), and 2) RCTs in patients with stable CAD (LoDoCo and LoDoCo2); and after exclusion of 3) the LoDoCo trial [open-label trial and control group was not randomized to placebo] and 4) the LoDoCo and COPS [increased dose (0.5 mg twice daily) of colchicine prescribed during first month] trials. Statistical analyses were performed using SAS software version 9.4 (*SAS Institute, Cary, North Carolina*) and Stata (Version 16, StataCorp, College Station, Texas).

RESULTS

Literature search results and risk of bias

The search strategy identified 79 studies. After the first- and second-level screening processes, four RCTs were retained in the present meta-analysis. The characteristics of included RCTs are listed in Table 8. The Low-Dose Colchicine (LoDoCo) and Low-Dose Colchicine 2 (LoDoCo2) trials assessed the efficacy of colchicine in patients with stable CAD (defined as clinically stable for ≥6 months) (see, Nidorf et al. *N Engl Med,* 2020. and Tong et al. *Circulation*, 2020). In comparison, the Colchicine Cardiovascular Outcomes Trial (COLCOT) was conducted in patients who had a recent MI (≤30 days) and the Colchicine in Patients with acute coronary Syndrome (COPS) trial enrolled patients with acute coronary syndromes (ACS) (see, Tardif et al. *N Engl J Med.*)

The pooled sample size of enrolled patients was 11,594, of which 5774 patients were randomized to colchicine and 5820 patients were randomized to placebo (or no colchicine, in the LoDoCo trial only). Three trials were designated as "low risk" for overall bias (see, Tardif et al. *N Engl J Med.*, Nidorf et al., *N Engl J Med,* 2020, and Tong et al, *Circulation,* 2020) and 1 trial was marked as being of "some concern" (see, Nirdorf et al., *J Am Coll Cardiol.* 2013; 61: 404-10) in the Cochrane Collaboration risk-of-bias assessment.

Table 8. Study characteristics

	LoDoCo	COLCOT	COPS	LoDoCo2
Year	2013	2019	2020	2020
Study design	Single-blind RCT	Double-blind, placebo controlled RCT	Double-blind, placebo controlled RCT	Double-blind, placebo controlled RCT
Study population	Stable CAD	Recent MI (<30 days)	ACS	Stable CAD
N	532	4,745	795	5,522
Key inclusion criteria	Angiographically proven CAD; clinically stable for <=6 months	MI within 30 days prior; completed planned percutaneous revascularization procedures; treated according to national guidelines that included intensive use of statins	ACS (STEMI/NSTEMI/UA); Evidenced CAD on coronary angiography, managed with either PCI or medical therapy	Evidence of CAD on invasive angiography or computed tomography angiography or a coronary calcium score of ≥400 Agaston units on a coronary-artery calcium scan; clinically stable condition for ≥6 months
Key exclusion criteria	Bypass surgery within 10 years prior	Severe heart failure; left ventricular ejection fraction <35%; stroke within the previous 3 months; type 2 index MI; coronary-bypass surgery either within previous 3 years or planned; severe renal or	CAD requiring surgical revascularization pre-existing long-term colchicine use or immunosuppressant therapy; severe hepatic or renal insufficiency; known active malignancy	Moderate-to-severe renal impairment; severe heart failure; severe valvular disease

		hepatic disease; known cancer		
Median follow-up	24 months	22.6 months	12 months	28.6 months
Primary endpoint	Composite: ACS, out-of-hospital cardiac arrest, or non-cardioembolic ischemic stroke	Composite: CV mortality, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina requiring revascularization	Composite: All-cause mortality, ACS (STEMI/NSTEMI/UA), ischemia-driven revascularization, or non-cardioembolic ischemic stroke	Composite: CV death, MI, ischemic stroke, or ischemia-driven coronary revascularization

*ACS, acute coronary syndrome; CAD, coronary artery disease; CV, cardiovascular; MI, myocardial infarction; RCT, randomized controlled trial; STEMI, ST elevation myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; UA, unstable angina

Patient Characteristics

Baseline patient characteristics for each RCT are summarized in Table 9. The mean age of patients ranged from 60 to 67 years. In all trials, <20% of enrolled patients were women and more than 90% of patients were on concomitant statin therapy. LoDoCo and LoDoCo2 trials had a higher proportion of patients who underwent prior coronary revascularization [percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) surgery]. The distribution of all other patient characteristics was relatively similar between trials.

Table 9. Patient characteristics at baseline

	LoDoCo		**COLCOT**		**COPS**		**LoDoCo2**	
	Colchicine N=250	Control N=282	Colchicine N=2366	Placebo N=2379	Colchicine N=396	Placebo N=399	Colchicine N=2762	Placebo N=2760
Age, years (mean ± SD)	67 ± 9.2	66 ± 9.6	60.6 ± 10.7	60.5 ± 10.6	59.7 ±10.2	60.0 ± 10.4	65.8 ± 8.4	65.9 ± 8.7
Women (%)	11.2%	11.0%	19.9%	18.4%	18.7%	22.3%	16.5%	14.1%
Hypertension (%)	Not reported	Not reported	50.1%	52.0%	50.8%	49.9%	51.4%	50.3%
Diabetes (%)	27.6%	32.6%	19.5%	20.9%	18.9%	19.0%	17.8%	18.7%
History of PCI (%)	55.2%	59.9%	16.6%	17.1%	12.9%	12.5%	76.0%	75.3%
History of CABG (%)	15.6%	22.0%	2.9%	3.4%	3.8%	4.8%	11.5%	14.2%
Statin use (%)	94.0%*	96.1%*	98.9%	99.1%	98.2%	99.5%	93.9%	94.0%

*The LoDoCo trial only reported use of high dose statins, not any statin use.

Clinical efficacy endpoints

Clinical efficacy results from each trial are presented in Table 10. In patients with CAD, the addition of colchicine to standard medical therapy was associated with a statistically significant reduction in the primary composite endpoint of cardiovascular mortality, MI, ischemic stroke, and urgent coronary revascularization, compared to patients on placebo or no colchicine [pooled HR 0.68 (95% CI 0.54-0.81); I^2=37.7%;]. The reduction in cardiovascular events in patients randomized to colchicine was driven by statistically significant reductions in the incidence of MIs [pooled HR 0.62 (95% CI 0.36-0.88); I^2=68.76%], ischemic strokes [pooled HR 0.38 (95% CI 0.13-0.63); I^2=0.0%], and urgent coronary revascularization [pooled HR 0.56 (95% CI 0.30-0.82); I^2=65.1%]. However, there was no statistically significant difference detected for cardiovascular mortality. Sensitivity analyses that pooled the results of COLCOT and LoDoCo2 trials demonstrated similar effect estimates for the primary composite and component outcomes, although magnitude of effect and heterogeneity (I^2) between studies decreased.

Table 10. Study efficacy outcomes

	LoDoCo[11]		**COLCOT[10]**		**COPS[13]**		**LoDoCo2[12]**	
	Colchicine N=250	Control N=282	Colchicine N=2366	Placebo N=2379	Colchicine N=396	Placebo N=399	Colchicine N=2762	Placebo N=2760
Primary composite outcome: Cardiovascular mortality, myocardial infarction, ischemic stroke, urgent revascularization								
Events, N (%)	NA	NA	130 (5.5%)	168 (7.1%)	19 (4.8%)	41 (10.3%)	187 (6.8%)	264 (9.6%)
HR (95% CI)	NA		0.77 (0.61-0.97)		0.47 (0.27-0.82)		0.69 (0.57-0.83)	
Cardiovascular mortality								
Events, N (%)	NA	NA	20 (0.8%)	24 (1.0%)	3 (0.8%)	1 (0.3%)	20 (0.7%)	25 (0.9%)
HR (95% CI)	NA		0.84 (0.46-1.52)		3.09 (0.32-29.71)		0.80 (0.44-1.44)	
Myocardial infarction								
Events, N (%)	4 (1.6%)	14 (5.6%)	89 (3.8%)	98 (4.1%)	11 (3.7%)	22 (5.5%)	83 (3.0%)	116 (4.2%)
HR (95% CI)	0.25 (0.08-0.76)		0.91 (0.68-1.21)		0.52 (0.25-1.07)		0.70 (0.53-0.93)	
Ischemic stroke								

Events, N (%)	1 (0.4%)	4 (1.6%)	4 (0.2%)	16 (0.7%)	2 (0.5%)	6 (1.5%)	16 (0.6%)	24 (0.9%)
HR (95% CI)	0.23 (0.03-2.03)		0.25 (0.08-0.75)		0.34 (0.07-1.70)		0.66 (0.35-1.25)	
Urgent coronary revascularization								
Events, N (%)	NA	NA	25 (1.1%)	50 (2.1%)	3 (0.8%)	12 (3.0%)	135 (4.9%)	177 (6.4%)
HR (95% CI)	NA		0.50 (0.31-0.81)		0.26 (0.07-0.92)		0.75 (0.60-0.94)	

*NA= not applicable. A study result was designed NA when the outcome in the study did not closely match the outcome in the present meta-analysis.

In sensitivity analyses of ACS trials (COLCOT and COPS; N=5540), the primary composite endpoint, MI, and urgent coronary revascularizations were statistically significantly reduced in patients randomized to colchicine compared to placebo. Among patients with stable CAD (LoDoCo and LoDoCo 2; N=6054), the only comparable outcome between trials was MI which was statistically significantly decreased with colchicine compared to placebo.

Although there was no statistically significant difference in the incidence of key secondary endpoints, there was a trend towards reduced AF diagnoses and AF episodes among patients randomized to colchicine [pooled HR 0.86 (95% CI 0.67-1.04); I^2=0.0%].

Visual inspection of funnel plots and the results of the Eggers test indicated there was no significant risk of publication bias for all outcomes (p>0.05 for all) except urgent coronary revascularization (p=0.02).

Subgroup analyses

The statistically significant reduction in the incidence of the primary composite cardiovascular endpoint among patients randomized to colchicine was consistent for most subgroup analyses. There was no significant heterogeneity of the effect of colchicine in the different subgroups studied. Overall, the Q_b statistic suggests that there is minimal variability and inconsistency in the treatment effect between strata in subgroup analyses (p>0.05 for all).

Major adverse events

There was no statistically significant difference between treatment arms for the risk of all-cause [pooled RR 1.04 (95% CI 0.61-1.78); I^2=62.01%] and non-cardiovascular mortality [pooled RR 1.38 (95% CI 0.99-

1.93); I^2=0.0%] (Figure 3). The rates of infections, pneumonias, hospitalizations for gastrointestinal events, and diagnoses of cancer were also not significantly different. For pneumonia, there was a high degree of heterogeneity between trials with opposite directions for the treatment effect (I^2=81.5%;).

In this contemporary meta-analysis of RCTs comparing colchicine to placebo (or no colchicine) for secondary cardiovascular prevention, we found that: 1) treatment with colchicine was associated with a 32% reduction in the incidence of major cardiovascular events; 2) significantly fewer MIs, ischemic strokes, and urgent coronary revascularizations were the primary drivers for the overall decrease in cardiovascular events; 3) the protective treatment effect of colchicine was relatively consistent among most subgroups studied, and 4) colchicine had a favorable safety profile. This is the first comprehensive meta-analysis of RCTs evaluating efficacy and safety of colchicine for secondary cardiovascular prevention in which the endpoints were harmonized across trials. Overall, the synthesis of current evidence in the present meta-analysis indicates that treatment with colchicine for secondary cardiovascular prevention confers beneficial clinical effects.

Secondary prevention of cardiovascular diseases

Although the 4 RCTs investigated the efficacy of colchicine in different segments of the CAD population, including stable CAD, recent MI, and ACS, the results of all trials consistently demonstrated that colchicine was protective against a composite endpoint of cardiovascular mortality, MI, ischemic stroke, and urgent coronary revascularization. The individual trials were not powered to detect statistically significant differences in the components of the primary endpoint. Whereas all trials showed a decrease in urgent coronary revascularizations among patients randomized to colchicine, only COLCOT detected a reduction in ischemic strokes [HR 0.25 (95% CI 0.08-0.75)] and LoDoCo2 a decrease in MIs [HR 0.70 (95% CI 0.53-0.93)]. Pooling HRs from the RCTs revealed that the attenuated risk of major cardiovascular events was attributed to risk reductions of 38%, 62%, and 44% for MIs, ischemic strokes, and urgent coronary revascularization, respectively. Although the 2 largest trials, COLCOT and LoDoCo2, contributed the most weight to analyses, the inclusion of LoDoCo and COPS tended to increase the magnitude of the risk reduction by 4-5%.

Individual trials and pooled results suggest that there is no difference in the incidence of cardiovascular or all-cause mortality with colchicine. These pooled analyses provide reassurance about the safety of colchicine for the outcome of all-cause mortality. Results from both the LoDoCo2 and COPs trials showed a trend towards increased all-cause mortality with colchicine, although neither reached statistical significance [LoDoCo2 HR 1.21 (95% CI 0.86-1.71) and COPS HR 8.20 (95% 1.02-65.61)]. The increased power from pooled analyses demonstrated that the effect of colchicine on all-cause mortality was closer to null or no effect than suggested by individual trials [pooled RR 1.04 (95% CI 0.61-1.78)].

The anti-inflammatory properties of colchicine work through various mechanisms to inhibit the pathogenesis of CAD, and subsequently reduce the incidence of ischemic cardiovascular events. In addition to targeting the NLRP3 inflammasome leading to the reduction of circulating levels of IL-1β and IL-6, colchicine also inhibits cholesterol crystals that promote inflammation and plaque instability in atherosclerosis.

Treatment effects across subgroups

The treatment effect of colchicine was similar with overlapping confidence intervals across age categories (≤65 or >65 years), presence or absence of diabetes and hypertension, and among patients with or without prior coronary revascularization. Although the risk reduction appeared less marked in women compared to men, less than 20% of trial populations were women (1977 women compared to 9617 men). It is, therefore, possible that the lack of a statistically significant reduction in cardiovascular events with colchicine in the subgroup analysis of women reflects limited power. There was no significant heterogeneity between the effects in subgroups and that in the overall population.

Safety

Colchicine has an established safety profile from its centuries of use to treat gout. There was a numerical imbalance in the number of non-cardiovascular deaths between study arms, which did not reach statistical significance. Importantly, there was no effect of colchicine on all-cause mortality. In the COPS study, the increased dose of colchicine during the first month of follow-up might have contributed to higher non-cardiovascular deaths. In addition, 3 of 5 colchicine patients who died from non-cardiovascular causes in COPS had also discontinued colchicine prior to date of death, which may suggest that on-treatment analyses may provide further evidence to the safety of colchicine for non-cardiovascular mortality. Furthermore, the quality of follow-up in COPS was poor, with more than twice the number of patients with incomplete vital status than that of deaths due to inadequate resources (2 part-time healthcare workers following 795 patients). In contrast, the quality of follow-up and rate of vital status ascertainment of the 10,267 patients included in COLCOT and LoDoCo2 were excellent and did not reveal a significant difference in non-cardiovascular mortality between study arms. Finally, the meta-analysis showed no difference in all-cause mortality between groups.

Only the COLCOT trial detected a difference in the rate of pneumonia between patients randomized to colchicine (0.9%) or placebo (0.4%). Pooled analyses of COLCOT and LoDoCo2 did not show an increased risk of pneumonia with colchicine, suggesting this result in the former may have been due to chance. The lack of a difference between groups for infections, hospitalizations, and diagnoses of cancer further validates that colchicine is safe to use in patients with CAD.

As we did not have access to patient-level data from 3 of 4 trials, only modified study-level data was used

for the present meta-analysis. Although meta-analyses based on aggregate patient data continue to be the mainstay of systematic reviews that inform clinical practice, meta-analyses based on individual patient data have several advantages including the ability to verify data, address new questions, and adjust for the same variables across studies. Finally, the small number of eligible studies precluded meta-regression analyses to determine the influence of specific variables or effect modifiers on the association between colchicine and cardiovascular events. Nevertheless, the potential for effect modification was addressed in part by subgroup analyses.

In patients with CAD, the addition of low-dose colchicine to standard medical therapy consistently and significantly reduces the incidence of major cardiovascular events compared to standard medical therapy alone. With the exception of cardiovascular mortality, significant reductions were observed for components of the primary outcome, including MIs, ischemic strokes, and urgent coronary revascularizations.

Example 2: Administration of low-dose colchicine after myocardial infarction

The results of the main COLCOT trial support that the use of colchicine in patients who have had a myocardial infarction in the past 30 days significantly improved their quality of life in several ways. The COLCOT trial was performed as follows. A randomized, double-blind trial involving patients recruited within 30 days after a myocardial infarction was performed. The patients were randomly assigned to receive either low-dose colchicine (0.5 mg once daily) or placebo. A total of 4745 patients were enrolled; 2366 patients were assigned to the colchicine group, and 2379 to the placebo group. Patients were followed for a median of 22.6 months to observe the occurrence of the primary efficacy end point which was a composite of death from cardiovascular causes, resuscitated cardiac arrest, myocardial infarction, stroke, or urgent hospitalization for angina leading to coronary revascularization. The components of the primary end point and safety were also assessed in this study.

In this randomized, double-blind, placebo-controlled, investigator-initiated trial, we assigned patients in a 1:1 ratio to receive either colchicine (at a dose of 0.5 mg once daily) or placebo. The trial protocol, available at NEJM.org, was designed by a trial steering committee.

Trial Population

Adult patients were eligible if they had had a myocardial infarction within 30 days before enrollment, had completed any planned percutaneous revascularization procedures, and were treated according to national guidelines that included the intensive use of statins.

Patients were excluded if they had severe heart failure, a left ventricular ejection fraction of less than

35%, stroke within the previous 3 months, a type 2 index myocardial infarction, coronary-bypass surgery either within the previous 3 years or planned, a history of noncutaneous cancer within the previous 3 years, inflammatory bowel disease or chronic diarrhea, neuromuscular disease or a nontransient creatine kinase level that was greater than three times the upper limit of the normal range (unless due to infarction), clinically significant nontransient hematologic abnormalities, severe renal disease with a serum creatinine level that was greater than two times the upper limit of the normal range; severe hepatic disease, drug or alcohol abuse, current or planned long-term systemic glucocorticoid therapy, or a history of clinically significant sensitivity to colchicine.

Written informed consent was obtained from all the patients before enrollment. Clinical evaluations occurred at 1 month and 3 months after randomization and every 3 months thereafter.

End Points

The primary efficacy end point was a composite of death from cardiovascular causes, resuscitated cardiac arrest, myocardial infarction, stroke, or urgent hospitalization for angina leading to coronary revascularization in a time-to-event analysis.

The secondary end points consisted of the components of the primary efficacy end point; a composite of death from cardiovascular causes, resuscitated cardiac arrest, myocardial infarction, or stroke; and total mortality in time-to-event analyses. Coronary revascularization, hospitalization for heart failure, atrial fibrillation, and deep venous thrombosis or pulmonary embolus were prespecified as exploratory end points in the protocol.

Additional prespecified exploratory end points included the change from baseline to 6 months in the high-sensitivity C-reactive protein level and the change from baseline to 12 months in the white-cell count. The C-reactive protein biomarker substudy was implemented after a protocol amendment and was optional for sites and for patients; 34 sites chose to participate in this substudy.

All serious adverse events were recorded. The only other adverse events recorded were those that were considered to be related to the gastrointestinal system, events that were judged by the investigator to be related to colchicine or placebo, or laboratory abnormalities that had been judged by the investigator to be clinically significant.

Statistical Analysis

In this event-driven trial, it was estimated that a sample of approximately 4500 patients undergoing randomization (with 2250 patients in each group) or, in terms of events, a total number of 301 patients with a first positively adjudicated primary end-point event would yield adequate power. The sample-size calculation

was based on the primary efficacy end point and assumed a 27% lower risk with colchicine than with placebo, indicated by a hazard ratio of 0.724. With the use of a two-sided test at the 0.05 significance level, the trial would have 80% power if it continued until 301 positively adjudicated primary events occurred in the combined trial groups. The trial design assumed an event rate of 7% in the placebo group at 24 months, an 18-month recruitment period during which patients would be uniformly recruited, a 24-month minimum follow-up period, and a 1% annual rate of loss to follow-up or withdrawal of consent.

The efficacy analyses were conducted with the use of positively adjudicated data and according to the intention-to-treat principle. The primary end point was compared between the two trial groups with the use of a log-rank test, and the hazard ratio from a Cox proportional-hazards model, with a 95% confidence interval, was calculated. A Cox proportional-hazards model with adjustment for important baseline characteristics was also used as prespecified in the protocol.

The analysis of the primary end point was repeated in the per-protocol population (i.e., patients without major protocol deviations). Secondary and exploratory end points expressed as time to event were analyzed similarly. The changes from baseline to follow-up were analyzed with the use of an analysis of covariance model with adjustment for baseline value, and estimates of treatment effect are presented with 95% confidence intervals.

The efficacy end points expressed as time to event could be assessed in all patients because the event dates and censoring dates were complete, with the exception of one incomplete event date for atrial fibrillation; therefore, imputation for missing data was not done.

In the analysis of time to event, the following censoring rules were used. For death from any cause and death from cardiovascular causes, data from event-free patients who completed the trial were censored at the date of trial completion, and data from patients who did not complete the trial, such as those who were lost to follow-up or who withdrew consent, were censored at the date of last contact or the date of the assessment of survival status, whichever was later.

For the analysis of death from cardiovascular causes, patients who died from a noncardiovascular cause had their data censored at the time of death.

For all other end points, including the primary end point, the same censoring rules applied, but the survival status was not used because no formal assessment of end points was done at the assessment of survival status.

An analysis of the components of the primary end point with death from noncardiovascular causes as a competing event for death from cardiovascular causes, and with death from any cause as a competing event for the other components, was conducted with the use of the Fine and Gray subdistribution hazard model (Fine JP and Gray RJ, A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;94:496-509). No missing data were imputed except for age

To account for the occurrence of multiple primary end-point events within patients, recurrent-event analyses were undertaken with the use of negative binomial regression, Andersen–Gill, and Wei–Lin–Weissfeld models (Rogers JK et al., Analysing recurrent hospitalizations in heart failure: a review of statistical methodology, with application to CHARM-Preserved. *Eur J Heart Fail* 2014;16:33-40; Andersen PK and Gill RD, Cox's regression model for counting processes: a large sample study. *Ann Stat* 1982;10:1100-20; Lin DY and Wei LJ, The robust inference for the proportional hazards model. *J Am Stat Assoc* 1989;84:1074-8; Lin DY et al. Semiparametric regression for the mean and rate functions of recurrent events. *J R Stat Soc* 2000;62:711-30; Wei LJ and Glidden DV, An overview of statistical methods for multiple failure time data in clinical trials. *Stat Med* 1997;16:833-9; Ghosh D, Methods for analysis of multiple events in the presence of death. *Control Clin Trials* 2000;21:115-26; Li QH and Lagakos SW, Use of the Wei-Lin-Weissfeld method for the analysis of a recurring and a terminating event. *Stat Med* 1997;16:925-40; Metcalfe C and Thompson SG, The importance of varying the event generation process in simulation studies of statistical methods for recurrent events. *Stat Med* 2006;25:165-79; Jahn-Eimermacher A, Comparison of the Andersen–Gill model with Poisson and negative binomial regression on recurrent event data. *Comput Stat Data Anal* 2008;52:4989-97).

An interim analysis was performed after 50% of the primary end-point events had been positively adjudicated. The prespecified stopping rule for efficacy was based on the Lan–DeMets procedure with the O'Brien–Fleming alpha-spending function. After review of the interim results, the data and safety monitoring board recommended that the trial should continue as planned.

To account for this interim analysis, the statistical significance level was set to 0.0490 for the final analysis of the primary end point. All other statistical tests were two-sided and conducted at the 0.05 significance level. Statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute). There was no prespecified plan to adjust for multiple comparisons across the multiple methods that were used to analyze the primary and secondary end points; results of these analyses are reported with point estimates and 95% confidence intervals, without P values. The 95% confidence intervals were not adjusted for multiple comparisons, and inferences drawn from them may not be reproducible. The final amendment to the statistical analysis plan was approved on August 28, 2019, before unblinding of the trial-group assignments occurred.

RESULTS

Patients

Trial enrollment began in December 2015 and was completed in August 2018; the last trial visit was in July 2019. A total of 4745 patients underwent randomization (with 2366 being assigned to the colchicine group and 2379 to the placebo group) and were followed for a median of 22.6 months. At the time of the database lock on August 28, 2019, and unblinding on August 29, 2019, vital status was available for all except 23 patients (99.5%); 89 patients (1.9%) were lost to follow-up, and 30 patients (0.6%) withdrew consent.

The characteristics of the patients at baseline are shown in Table 10.

Table 10. Characteristics of the Patients

Characteristic	Colchicine (N=2366)	Placebo (N=2379)
Age — yr	60.6±10.7	60.5±10.6
Female sex — no. (%)	472 (19.9)	437 (18.4)
White race — no./total no. (%)†	1350/1850 (73.0)	1329/1844 (72.1)
Body-mass index	28.2±4.8	28.4±4.7
Current smoking — no./total no. (%)	708/2366 (29.9)	708/2377 (29.8)
Hypertension — no. (%)	1185 (50.1)	1236 (52.0)
Diabetes — no. (%)	462 (19.5)	497 (20.9)
History of myocardial infarction — no. (%)	370 (15.6)	397 (16.7)
History of PCI — no. (%)	392 (16.6)	406 (17.1)
History of CABG — no. (%)	69 (2.9)	81 (3.4)
History of heart failure — no. (%)	48 (2.0)	42 (1.8)
History of stroke or TIA — no. (%)	55 (2.3)	67 (2.8)
Time from index myocardial infarction to randomization — days	13.4±10.2	13.5±10.1
PCI for index myocardial infarction — no./total no. (%)	2192/2364 (92.7)	2216/2375(93.3)
Medication use — no. (%)		
Aspirin	2334 (98.6)	2352 (98.9)
Other antiplatelet agent	2310 (97.6)	2337 (98.2)
Statin	2339 (98.9)	2357 (99.1)
Beta-blocker	2116 (89.4)	2101 (88.3)

* Plus–minus values are means ±SD. Data were missing on the following characteristics: age (assessed according to date of birth; see below), for 435 patients; body-mass index (the weight in kilograms divided by the square of the height in meters), for 5; and information about the index myocardial infarction, for 6. Date of birth and race were not required fields because both were considered in some countries to be sensitive data that could allow for the identification of patients. For statistical reporting, missing information regarding the day of birth was replaced by 15, and missing information regarding the month and day of birth was replaced by July 1. CABG denotes coronary-artery bypass graft surgery, PCI percutaneous coronary intervention, and TIA transient ischemic attack.

† Race was reported by the patient.

Patients were enrolled a mean of 13.5 days after myocardial infarction. The mean age of the patients was 60.6 years, 19.2% of the patients were women, and 20.2% had diabetes. Most patients (93.0%) underwent percutaneous coronary intervention for their index myocardial infarction. Aspirin, a different antiplatelet agent, and a statin were taken by 98.8%, 97.9% and 99.0% of the patients, respectively.

At the end of the trial, the trial regimen had been discontinued in 18.4% of the patients in the colchicine group and in 18.7% of those in the placebo group. Among the patients who discontinued the trial regimen, the median time of taking the trial drug was 7.1 months (interquartile range, 1.9 to 14.6) in the colchicine group, as compared with 6.1 months (interquartile range, 1.6 to 14.4) in the placebo group. Overall, the median duration of receipt of the trial drug was 19.6 months in the colchicine group and 19.5 months in the placebo group.

Clinical Efficacy End Points

A primary end-point event occurred in 5.5% of the patients in the colchicine group, as compared with 7.1% of those in the placebo group (hazard ratio, 0.77; 95% confidence interval [CI], 0.61 to 0.96; P = 0.02 by the log-rank test). A multivariable Cox regression model with adjustment for baseline covariates yielded a similar result (Table 11).

Table 11. Multivariable Cox Regression Model for Time to First Primary Endpoint.

Effect		Adjusted Hazard Ratio (95% CI)	P Value
Randomized treatment group	Colchicine vs. Placebo	0.78 (0.62-0.98)	0.03
Age at randomization (years)		1.02 (1.01-1.03)	<0.001
History of diabetes	Yes vs. No	1.86 (1.46-2.37)	<0.001
Prior coronary revascularization (PCI or CABG)	Yes vs. No	2.02 (1.58-2.58)	<0.001
Prior heart failure	Yes vs. No	1.81 (1.08-3.04)	0.03

CABG denotes coronary artery bypass graft, and PCI percutaneous coronary intervention. The model

was based on 4745 observations. All baseline characteristics that showed an association (P<0.20) with the occurrence of a first positively adjudicated primary endpoint were included in the stepwise multivariable Cox regression. For age at randomization, the hazard ratio is for an increase of one year of age.

In the prespecified per-protocol analysis involving patients who adhered to the protocol, the primary end point occurred in 5.1% of the patients in the colchicine group and in 7.1% of those in the placebo group (hazard ratio, 0.71; 95% CI, 0.56 to 0.90) (Table 12).

Table 12. Rates and Hazard Ratios for the Primary Endpoint and its Components in the Per-Protocol Population†.

Clinical Outcome	Colchicine	Placebo	Hazard Ratio (95% CI)
Per-protocol population	N=2260	N=2270	
Primary endpoint - no. (%)	115 (5.1%)	162 (7.1%)	0.71 (0.56-0.90)
CV death - no. (%)	19 (0.8%)	23 (1.0%)	0.83 (0.45-1.53)
Resuscitated cardiac arrest - no. (%)	5 (0.2%)	5 (0.2%)	1.00 (0.29-3.46)
MI - no. (%)	77 (3.4%)	92 (4.1%)	0.84 (0.62-1.14)
Stroke - no. (%)	5 (0.2%)	19 (0.8%)	0.26 (0.10-0.71)
Urgent hospitalization for angina requiring revascularization - no. (%)	22 (1.0%)	47 (2.1%)	0.47 (0.28-0.78)

CV denotes cardiovascular, and MI myocardial infarction.

†The per-protocol population consisted of patients without major protocol deviations.

Table 13 shows the percentages of patients with events and the hazard ratios for the components of the primary end point, including death from cardiovascular causes (hazard ratio, 0.84; 95% CI, 0.46 to 1.52), resuscitated cardiac arrest (hazard ratio, 0.83; 95% CI, 0.25 to 2.73), myocardial infarction (hazard ratio, 0.91; 95% CI, 0.68 to 1.21), stroke (hazard ratio, 0.26; 95% CI, 0.10 to 0.70), and urgent hospitalization for angina leading to coronary revascularization (hazard ratio, 0.50; 95% CI, 0.31 to 0.81). The hazard ratios remained unchanged in the analysis that took competing events into account.

Table 13. Major Clinical End-points (Intention-to-Treat Population)

End Point	Colchicine (N=2366)	Placebo (N=2379)	Hazard Ratio (95% CI)	P Value
	number (percent)			
Primary composite end point	131 (5.5)	170 (7.1)	0.77 (0.61–0.96)	0.02†
Components of primary end point				
Death from cardiovascular causes	20 (0.8)	24 (1.0)	0.84 (0.46–1.52)	
Resuscitated cardiac arrest	5 (0.2)	6 (0.3)	0.83 (0.25–2.73)	
Myocardial infarction	89 (3.8)	98 (4.1)	0.91 (0.68–1.21)	
Stroke	5 (0.2)	19 (0.8)	0.26 (0.10–0.70)	
Urgent hospitalization for angina leading to revascularization	25 (1.1)	50 (2.1)	0.50 (0.31–0.81)	
Secondary composite end point†	111 (4.7)	130 (5.5)	0.85 (0.66–1.10)	
Death	43 (1.8)	44 (1.8)	0.98 (0.64–1.49)	
Deep venous thrombosis or pulmonary embolus	10 (0.4)	7 (0.3)	1.43 (0.54–3.75)	
Atrial fibrillation	36 (1.5)	40 (1.7)	0.93 (0.59–1.46)	

* Only the initial event was counted in the analyses of time to first event for the primary composite end point and for the secondary composite end point. In the component analysis, all events (first and subsequent) were counted separately.

† The log-rank test and the multivariable Cox proportional-hazards model (including age, history of diabetes, previous coronary revascularization, and previous heart failure yielded similar P values.

‡The secondary composite end point included death from cardiovascular causes, resuscitated cardiac arrest, myocardial infarction, and stroke.

The secondary efficacy end point consisting of a composite of death from cardiovascular causes, cardiac arrest, myocardial infarction, or stroke occurred in 4.7% of the patients in the colchicine group and in 5.5% of those in the placebo group (hazard ratio, 0.85; 95% CI, 0.66 to 1.10). Data on the primary, secondary, and exploratory efficacy end points are provided in Table 13. Two patients had a first positively adjudicated event of urgent hospitalization for angina leading to coronary revascularization within 14 days after randomization. The median time to this clinical end point was 258 days.

Efficacy results in prespecified subgroups are shown in Table 14. The total number of primary end-point events (first and recurrent) was 154 in the colchicine group and 223 in the placebo group, over periods of 52,949 and 53,060 patient-months of follow-up, respectively. Thus, the primary end-point event rates per 100 patient-months were 0.29 in the colchicine group and 0.42 in the placebo group (rate ratio, 0.66; 95% CI, 0.51 to 0.86) (Table 15).

Table 14. Primary Efficacy Composite Endpoint in Prespecified Subgroups†.

Subgroup	Colchicine	Placebo	Hazard ratio (95% CI)
	no. of patients with event/total no. of patients (%)		
All patients	131/2366 (5.5%)	170/2379 (7.1%)	0.77 (0.61-0.96)
Smoking			
Non-smoker	47/787 (6.0%)	52/797 (6.5%)	0.90 (0.61; 1.34)
Previous smoker	46/871 (5.3%)	77/872 (8.8%)	0.59 (0.41; 0.85)
Active smoker	38/708 (5.4%)	41/708 (5.8%)	0.93 (0.60; 1.44)
History of diabetes			
Yes	40/462 (8.7%)	65/497 (13.1%)	0.65 (0.44; 0.96)
No	91/1904 (4.8%)	105/1882 (5.6%)	0.85 (0.64; 1.13)
History of hypertension			
Yes	83/1185 (7.0%)	112/1236 (9.1%)	0.76 (0.57; 1.01)
No	48/1181 (4.1%)	58/1143 (5.1%)	0.80 (0.54; 1.17)
Prior MI			
Yes	46/370 (12.4%)	47/397 (11.8%)	1.05 (0.70; 1.58)
No	85/1996 (4.3%)	123/1982 (6.2%)	0.68 (0.51; 0.89)
Prior PCI or CABG			
Yes	48/419 (11.5%)	57/447 (12.8%)	0.91 (0.62; 1.34)
No	83/1947 (4.3%)	113/1932 (5.8%)	0.72 (0.54; 0.95)
Prior stroke or TIA			
Yes	8/55 (14.5%)	9/67 (13.4%)	1.09 (0.42; 2.82)
No	123/2311 (5.3%)	161/2312 (7.0%)	0.76 (0.60; 0.96)
Sex‡			
Male	94/1894 (5.0%)	135/1942 (7.0%)	0.70 (0.54; 0.91)
Female	37/472 (7.8%)	35/437 (8.0%)	0.99 (0.63; 1.58)
White blood cell count¶			
Below median	41/660 (6.2%)	46/637 (7.2%)	0.85 (0.56; 1.29)
Above median	34/637 (5.3%)	44/664 (6.6%)	0.80 (0.51; 1.25)

CABG denotes coronary artery bypass graft, MI myocardial infarction, PCI percutaneous coronary intervention, and TIA transient ischemic attack.

†The final amendment to the statistical analysis plan, which listed the subgroups of interest, was approved on August 28, 2019 and unblinding occurred on August 29, 2019.

‡The hazard ratio for the primary endpoint was 0.70 (0.52; 0.93) in men and 0.81 (0.47; 1.41) in women in the per-protocol population.

The median value for total white blood cell count was 8.64 X 10^3/μL.

Table 15. Total (First and Recurrent) Primary Endpoint Events.

Total Primary Endpoint Events		**Colchicine (N=2366)**	**Placebo (N=2379)**	
Number of primary endpoint events per patient	0	2235	2209	
	1	111	132	
	2	18	26	
	3	1	9	
	4	1	3	
Total number of primary endpoint events		154	223	
Total follow-up months		52949	53060	
Rate of primary endpoint events per 100 patient-months		0.29	0.42	
				Hazard Ratio or Rate Ratio (95% CI)
Negative binomial model†				0.66 (0.51; 0.86)
Andersen-Gill model‡				0.69 (0.54; 0.88)
WLW model¶	1st Event			0.77 (0.61; 0.96)
	2nd Event			0.73 (0.48; 1.11)
	3rd Event			0.64 (0.37; 1.10)
	Average			0.77 (0.61; 0.96)

WLW denotes Wei-Lin-Weissfeld method.

†The negative binomial regression model was used to calculate marginal rate ratio.

‡The Andersen-Gill model was used with a robust variance estimator (sandwich estimator) to calculate hazard ratio.

Regarding Table 15, the Wei-Lin-Weissfeld marginal model was used to calculate hazard ratios for the time to the first, second and third event as well as the weighted average of these hazard ratios.

To account for the occurrence of multiple primary endpoint events within patients, recurrent event analyses were undertaken using three statistical approaches as there is no strong consensus as to which method is preferable. First, a negative binomial regression model was used with the number of events as

the outcome and the length of follow-up time in months as an offset term (Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med* 2005;352:1685-95). Marginal rate ratio was provided, along with 95% confidence interval. The Andersen and Gill model (Ridker PM, et al., Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med* 2017;377:1119-31) with a robust variance estimator (Ridker PM et al., Low-dose methotrexate for the prevention of atherosclerotic events. *N Engl J Med* 2019;380:752-62; and Ravelli RB et al., Insight into tubulin regulation from a complex with colchicine and a stathmin-like domain. *Nature* 2004;428:198-202) was utilized to account for the dependency of within-patient events based on a gap-time approach considering the time since a previous event. The Andersen-Gill model is a simple extension of the Cox model based on all events of all patients and estimates a hazard ratio assuming that the instantaneous risk of experiencing an event is the same irrespective of whether previous events occurred. Results from these two models are often similar (Perico N et al., Colchicine interferes with L-selectin and leukocyte function-associated antigen-1 expression on human T lymphocytes and inhibits T cell activation. *J Am Soc Nephrol* 1996;7:594-601; and Pope RM and Tschopp J, The role of interleukin-1 and the inflammasome in gout: implications for therapy. *Arthritis Rheum* 2007;56:3183-8). Finally, an approach based on the Wei, Lin and Weissfeld marginal model was conducted whereby times from randomization to first, second and subsequent event were modeled with a Cox proportional hazards model that used a covariance matrix estimate for the regression coefficients that accounted for the possible intra-patient correlation (Cerquaglia C et al., Pharmacological and clinical basis of treatment of Familial Mediterranean Fever (FMF) with colchicine or analogues: an update. *Curr Drug Targets Inflamm Allergy* 2005;4:117-24; Imazio M et al., Colchicine in addition to conventional therapy for acute pericarditis: results of the COlchicine for acute PEricarditis (COPE) trial. *Circulation* 2005;112:2012-6; and Nidorf SM et al., Low-dose colchicine for secondary prevention of cardiovascular disease. *J Am Coll Cardiol* 2013;61:404-10).This approach assumes that all patients are at risk for any event since randomization. Marginal hazard ratios for a k^{th} event (i.e. based on time from randomization to k^{th} event), as well as a weighted average of these hazard ratios, were provided along with 95% confidence intervals. It has been argued that this approach preserves the randomization and permits valid treatment effect estimation (Fine JP and Gray RJ, A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;94:496-509).

Biomarkers of Inflammation

High-sensitivity C-reactive protein was measured in a subgroup of only 207 patients at the time of randomization and 6 months later, and the median concentration at trial entry was 4.28 mg per liter. The baseline characteristics of these patients were similar to those of the overall population (Table 16), but the small and selected subgroup with these data limits the interpretation of these analyses. The adjusted geometric mean percent changes in the high-sensitivity C-reactive protein level at 6 months after myocardial infarction were −70.0% in the colchicine group and −66.6% in the placebo group, and the

placebo-adjusted geometric mean percent change was −10.1% percentage points in the colchicine group (95% CI, −28.6 to 13.4) (Table 17).

Table 16. Characteristics of the Trial Patients with hs-CRP data values.

Characteristic	Colchicine (N=99)	Placebo (N=108)
Age - years	62.1±9.7	61.2±10.2
Female sex - no. (%)	18 (18.2%)	14 (13.0%)
Caucasian - no. (%)	91 (93.8%)	89 (89.0%)
Body-mass index (kg/m^2)	28.8±4.5	29.1±4.2
Smoking - no. (%)	20 (20.2%)	20 (18.5%)
Hypertension - no. (%)	44 (44.4%)	62 (57.4%)
Diabetes - no. (%)	12 (12.1%)	15 (13.9%)
Prior MI - no. (%)	14 (14.1%)	16 (14.8%)
Prior PCI - no. (%)	24 (24.2%)	21 (19.4%)
Prior CABG - no. (%)	4 (4.0%)	6 (5.6%)
Prior heart failure - no. (%)	4 (4.0%)	1 (0.9%)
Prior stroke/TIA - no. (%)	1 (1.0%)	2 (1.9%)
Index MI to randomization - days	17.0±9.2	15.8±9.8
PCI for index MI - no. (%)	93 (93.9%)	104 (96.3%)
Aspirin use - no. (%)	98 (99.0%)	106 (98.1%)
Other anti-platelet agent - no. (%)	98 (99.0%)	108 (100%)
Statin use - no. (%)	99 (100%)	107 (99.1%)
Beta-blocker - no. (%)	83 (83.8%)	86 (79.6%)

CABG denotes coronary artery bypass graft surgery, MI myocardial infarction, PCI percutaneous coronary intervention, and TIA transient ischemic attack.

Table 17. Biomarkers of Inflammation.

Biomarker	Colchicine	Placebo
Hs-C reactive protein (mg/L)	N=99	N=108
Randomization, geometric mean (IQR)†	4.27 (2.12, 7.22)	5.09 (2.45, 11.96)
6 months, geometric mean (IQR)	1.37 (0.75, 2.13)	1.60 (0.90, 2.65)
Adjusted GM percent change (95% CI)‡	-70.0 (-74.6, -64.5)	-66.6 (-71.5, -60.8)
Placebo-adjusted GM percent change (95% CI)¶	-10.1 (-28.6, 13.4)	- -
Total white blood cell count ($10^3/\mu L$)	N=992	N=980
Randomization, geometric mean (IQR)†	8.54 (7.10, 10.40)	8.63 (7.20, 10.70)
12 months, geometric mean (IQR)	6.95 (5.99, 8.30)	7.03 (5.96, 8.48)
Adjusted GM percent change (95% CI)‡	-18.81 (-20.12, -17.47)	-19.02 (-20.46, -17.55)
Placebo-adjusted GM percent change (95% CI)¶	0.26 (-2.15, 2.72)	- -
Circulating lymphocytes ($10^3/\mu L$)		
Randomization, geometric mean (IQR)†	1.79 (1.40, 2.40)	1.79 (1.42, 2.46)
12 months, geometric mean (IQR)	1.83 (1.50, 2.44)	1.82 (1.50, 2.44)
Adjusted GM percent change (95% CI)‡	1.80 (-0.46, 4.11)	0.69 (-1.54, 2.98)
Placebo-adjusted GM percent change (95% CI)¶	1.10 (-2.06, 4.36)	- -
Circulating neutrophils ($10^3/\mu L$)		
Randomization, geometric mean (IQR)†	5.45 (4.36, 7.15)	5.47 (4.30, 7.46)
12 months, geometric mean (IQR)	3.95 (3.27, 5.08)	3.99 (3.34, 5.20)
Adjusted GM percent change (95% CI)‡	-27.63 (-29.48, -25.73)	-27.95 (-29.91, -25.93)
Placebo-adjusted GM percent change (95% CI)¶	0.45 (-3.28, 4.32)	- -

GM denotes geometric mean, HS high-sensitivity, and IQR inter-quartile range.

†The geometric mean was obtained by exponentiating the mean of log-transformed data.

‡ The adjusted geometric mean percent change was obtained by exponentiating the adjusted mean from the analysis of covariance model (based on log-transformed data), then subtracting 1 and multiplying by 100. The bounds of the 95% confidence intervals were obtained similarly.

In Table 17, the placebo-adjusted geometric mean percent change was obtained by exponentiating the adjusted mean difference between groups from the analysis of covariance model (based on log-transformed data), then subtracting 1 and multiplying by 100.

In addition, the C-reactive protein biomarker sub-study was implemented following a protocol amendment and was optional for sites and for patients; 34 sites accepted to participate in this substudy. There were

213 and 208 patients who provided blood samples at baseline and 6 months, respectively. Paired baseline and 6-month hs-CRP values were available in 207 patients. Clinically available white blood cell counts were obtained from 2598 patients at baseline and 1998 patients at 12 months, and paired baseline and 12-month values were available in 1972 patients. Statistical analysis was conducted on the patients who provided both baseline and follow-up data and as these were exploratory analyses, no missing data was imputed.

Information about white-cell counts at baseline and at the 12-month follow-up were also available for a relatively small subgroup of 1972 patients. The adjusted geometric mean percent changes from baseline to 1 year in the total white-cell count were −18.8% in the colchicine group and −19.0% in the placebo group, with no significant difference between groups (0.3% percentage points; 95% CI, −2.2 to 2.7).

Safety and Adverse Events

The incidence of adverse events that were considered to be related to trial drug was 16.0% in the colchicine group and 15.8% in the placebo group, and the overall incidence of serious adverse events was 16.4% and 17.2%, respectively (Table 18).

Table 18. Adverse Events (Safety Population)

Event	Colchicine (N=2330)	Placebo (N=2346)	P Value
	number of patients (percent)		
Any related adverse event†	372 (16.0)	371 (15.8)	0.89
Any serious adverse event‡	383 (16.4)	404 (17.2)	0.47
Gastrointestinal adverse event	408 (17.5)	414 (17.6)	0.90
Gastrointestinal serious adverse event	46 (2.0)	36 (1.5)	0.25
Diarrhea adverse event	225 (9.7)	208 (8.9)	0.35
Nausea adverse event	43 (1.8)	24 (1.0)	0.02
Flatulence adverse event	15 (0.6)	5 (0.2)	0.02
Gastrointestinal hemorrhage	7 (0.3)	5 (0.2)	0.56
Infection serious adverse event	51 (2.2)	38 (1.6)	0.15
Pneumonia serious adverse event	21 (0.9)	9 (0.4)	0.03
Septic shock serious adverse event	2 (0.1)	2 (0.1)	0.99
Hospitalization for heart failure	25 (1.1)	17 (0.7)	0.21
Cancer§	43 (1.8)	46 (2.0)	0.77
Anemia	14 (0.6)	10 (0.4)	0.40
Leukopenia	2 (0.1)	3 (0.1)	0.66
Thrombocytopenia	3 (0.1)	7 (0.3)	0.21

* The safety population was defined as patients who took at least one dose of colchicine or placebo. All serious adverse events

were recorded, and the only other adverse events recorded were those that were related to the gastrointestinal system, events that were judged by the investigator to be related to colchicine or placebo, or laboratory abnormalities that were judged by the investigator to be clinically significant. This table lists serious adverse events that were present in more than 2% of the patients in either trial group, adverse events that were considered to be related to colchicine or placebo in more than 5% of the patients in either trial group, and any other safety events of special interest. Chi-square tests were conducted to compare the incidence of adverse events between the trial groups.
† These adverse events were considered to be related to colchicine or placebo by the physician in charge of the participant.
‡ There was one serious adverse event of myopathy, which was attributed to high-dose statin therapy (rosuvastatin at a dose of 40 mg daily) by the local investigator and academic sponsor, in a man of short stature (165 cm, 68 kg) with normal renal function in the colchicine group who had received colchicine for 8 days 3 months before the adverse event.
§ Cancers, excluding nonmelanoma skin cancers, occurred in 42 patients (1.8%) in the colchicine group and in 44 (1.9%) in the placebo group.

At least one gastrointestinal adverse event during the double-blind period occurred in 17.5% of the patients in the colchicine group, as compared with 17.6% of those in the placebo group. Diarrhea was reported in 9.7% of the patients in the colchicine group and in 8.9% of those in the placebo group (P = 0.35), and nausea was more common in the colchicine group than in the placebo group (1.8% vs. 1.0%, P = 0.02). Pneumonia was reported as a serious adverse event in 0.9% of the patients in the colchicine group, as compared with 0.4% of those in the placebo group (P = 0.03).

In COLCOT, the risk of the primary composite efficacy end point of death from cardiovascular causes, resuscitated cardiac arrest, myocardial infarction, stroke, or urgent hospitalization for angina leading to coronary revascularization, as assessed in a time-to-event analysis, was significantly lower among the patients who were randomly assigned to receive 0.5 mg of colchicine once daily than among those who received placebo. This result was due predominantly to a lower incidence of strokes and urgent hospitalizations for angina leading to coronary revascularization.

These results were observed against a background of appropriate medications, which included aspirin, a different antiplatelet agent, and a statin in 98 to 99% of the patients. In addition, percutaneous coronary intervention was performed in 93% of the patients for their index myocardial infarction. The benefits of colchicine with regard to cardiovascular end points in COLCOT were at least as large as those of canakinumab in CANTOS (Ridker PM et al., Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med* 2017;377:1119-31). In the small subgroup of patients with available data, a large (>65%) reduction in the C-reactive protein level occurred over the first 6 months after myocardial infarction in both trial groups in COLCOT, but the difference between the changes in the groups was not significant. These findings must be interpreted cautiously given that this was a small subgroup that was not randomly selected from the full trial sample. A similar observation was made with white-cell counts. The different patient populations involved in the two trials — early after myocardial infarction in COLCOT and stable coronary disease in CANTOS — may also have affected the relationship between biomarkers of inflammation and the effects of treatments on ischemic end points.

The known benefits of colchicine in the treatment of pericarditis were not at play in COLCOT.

Postinfarction pericarditis typically occurs within the first few days after the injury, whereas the mean time from the index myocardial infarction to randomization was 13.5 days. There were only two patients with a first positively adjudicated event of urgent hospitalization for angina leading to coronary revascularization within 14 days after randomization, and the median time to this clinical end point was 258 days.

The most common adverse events observed were gastrointestinal. Diarrhea was reported in 9.7% of the patients in the colchicine group and in 8.9% of those in the placebo group, and nausea occurred in 1.8% and 1.0%, respectively. Infection as a serious adverse event was more frequent in the colchicine group than in the placebo group (in 2.2% vs. 1.6% of the patients), and pneumonia as a serious adverse event was also more frequent in the colchicine group (0.9% vs. 0.4%). These differences in the incidence of infections could be due to the play of chance or could reflect altered immunologic responses.

In contrast to canakinumab (Ridker PM et al., Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med* 2017;377:1119-31), colchicine did not increase the incidence of septic shock in our trial. Infections have previously been described in patients who have attempted suicide by taking an overdose of colchicine (Kocak Z et al., Colchicine intoxication and infection risk: a case report. *J Clin Pharm Ther* 2008;33:451-2). There was no serious adverse event of myopathy linked to colchicine despite the use of statins in 99% of the patients in the trial.

In conclusion, among patients with a recent myocardial infarction, colchicine at a dose of 0.5 mg daily led to a significantly lower percentage of patients with ischemic cardiovascular events than placebo.

Other Embodiments

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure that come within known or customary practice within the art to which the invention pertains and may be applied to the essential features hereinbefore set forth, and follows in the scope of the claims.

Some embodiments of the invention are within the following numbered paragraphs.

1. A method of treating a patient after having a myocardial infarction (MI), the method comprising initiating the administration of colchicine at a daily low dose to the patient within about 3 days of the MI.

2. A method of treating a patient after having a myocardial infarction (MI), the method comprising initiating the administration of colchicine at a daily low dose to the patient within about 4 days of the MI.

3. The method paragraph 1 or 2, wherein percutaneous coronary intervention was performed for treating the patient's MI.

4. The method of any one of paragraphs 1-3, wherein the patient was prescribed a medication.

5. The method according to paragraph 4, wherein the medication is an antiplatelet agent.

6. The method according to paragraph 4, wherein the medication is aspirin.

7. The method according to paragraph 4, wherein the medication is a statin.

8. The method according to any one of paragraphs 1-7, wherein the patient is at a lower risk of a cardiovascular event, relative to a patient not being administered colchicine.

9. The method according to paragraph 8, wherein the cardiovascular event is an ischemic cardiovascular event.

10. The method according to paragraph 8, wherein the cardiovascular event is cardiovascular death, resuscitated cardiac arrest, myocardial infarction, stroke, or urgent hospitalization for angina requiring coronary revascularization.

11. The method according to any one of paragraphs 1-10, wherein the patient has atherosclerotic coronary artery disease.

12. A method of reducing the risk of a stroke in a patient after having an MI, the method comprising initiating the administration of colchicine at a daily low dose to the patient within about 30 days of the MI.

13. The method according to paragraph 12, wherein the method comprises administering colchicine within 4-7 days of the MI.

14. The method according to paragraph 12, wherein the method comprises administering colchicine within 3 days of the MI.

16. The method according to any one of paragraphs 1-15, wherein the administration of colchicine is initiated upon assessment in (a) an emergency department (ED), (b) the hospital, or (c) a medical office

setting.

17. The method according to any one of paragraphs 1-16, wherein the colchicine is in the form of a tablet.

18. The method of paragraph 17, wherein the tablet is coated.

19. The method of paragraph 18, wherein the tablet is film-coated.

20. The method according to any one of paragraphs 1-19, wherein the colchicine is administered at 0.3 to 0.7 mg.

21. The method according to any one of paragraphs 1-20, wherein the colchicine is administered at 0.4 to 0.6 mg

22. The method according to paragraph 21, wherein the colchicine is administered at about 0.5 mg.

23. The method according to any one of paragraph 1-22, wherein the colchicine is administered once, twice or three times a day.

24. The method according to paragraph 23, wherein the colchicine is administered once per day.

25. The method of any one of paragraphs 1-24, wherein the colchicine is administered without pre-loading the patient with colchicine.

26. The method of any one of paragraphs 1-25, wherein the patient is an adult human.

Other embodiments are within the claims.

What is claimed is:

#

Docket No.: 50761-029001
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Utility Application of:
Jean-Claude TARDIF

Application No.: 17/097,285 | Confirmation No.: 3015

Filed: November 13, 2020 | Art Unit: 1629

For: EARLY ADMINISTRATION OF LOW-DOSE COLCHICINE AFTER MYOCARDIAL INFARCTION | Examiner: Not Yet Assigned

RESPONSE TO NOTICE TO FILE CORRECTED APPLICATION PAPERS

In response to the Notice to File Corrected Application Papers mailed November 27, 2020, Applicant respectfully submits the following:

1) Substitute Specification; and

2) Preliminary Amendment.

A marked-up copy of the specification is not submitted because the amendment provides clearer text, and removes shading, for the tables formerly found on pages 33, 36, and 43 of the specification. No other changes have been made to the specification.

Please apply any charges or credits to Deposit Account No. 03-2095.

Dated: December 4, 2020

Respectfully submitted,

/Jan N. Tittel/
Jan N. Tittel, Ph.D.
Registration No.: 52,290
CLARK & ELBING LLP
101 Federal Street
15th Floor
Boston, MA 02110
(617) 428-0200

REMARKS

The substitute specification provides clearer text, and removes shading, for the tables formerly found on pages 33, 36, and 43. No new matter is added by the amendments.

Please apply any charges or credits to Deposit Account No. 03-2095.

Dated: December 4, 2020

Respectfully submitted,

/Jan N. Tittel/
Jan N. Tittel, Ph.D.
Registration No.: 52,290
CLARK & ELBING LLP
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Boston, MA 02110
(617) 428-0200

AMENDMENTS TO THE SPECIFICATION

Kindly replace the specification as filed with the clean version of the substitute specification submitted herewith. No new matter is added by the amendments.

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
17/097,285	11/13/2020	1629	2980	50761-029001	30	2

CONFIRMATION NO. 3015

UPDATED FILING RECEIPT

21559
CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

OC000000121834581

Date Mailed: 12/08/2020

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

Jean-Claude TARDIF, Montreal, CANADA;

Applicant(s)

INSTITUT DE CARDIOLOGIE DE MONTREAL, Montreal, CANADA;

Power of Attorney: None

Domestic Priority data as claimed by applicant

This appln claims benefit of 63/093,988 10/20/2020
and claims benefit of 62/935,865 11/15/2019

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 11/24/2020

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 17/097,285**

Projected Publication Date: 05/20/2021

Non-Publication Request: No

Early Publication Request: No
Title

EARLY ADMINISTRATION OF LOW-DOSE COLCHICINE AFTER MYOCARDIAL INFARCTION

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 17/097,285

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	320
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	700
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	800
TOTAL CLAIMS (37 CFR 1.16(i))	30 minus 20 =	* 10			OR	x 100 =	1000
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*				x 480 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	2820

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)	OR	RATE($)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
17/097,285	11/13/2020	Jean-Claude TARDIF	50761-029001

CONFIRMATION NO. 3015

21559
CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

INFORMAL NOTICE

OC000000121834562

Date Mailed: 12/08/2020

INFORMATIONAL NOTICE TO APPLICANT

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

The item(s) indicated below are also required and should be submitted with any reply to this notice to avoid further processing delays.

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):
  Jean-Claude TARDIF

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/nton/

To: patentadministrator@clarkelbing.com,smmichaud@clarkelbing.com,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 21559

Dec 08, 2020 04:07:30 AM

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Application	Document	Mailroom Date	Attorney Docket No.
17097285	APP.FILE.REC	12/08/2020	50761-029001
	M327	12/08/2020	50761-029001

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/097,285	11/13/2020	Jean-Claude TARDIF	50761-029001	3015

21559 7590 12/22/2020

CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER	
ART UNIT	PAPER NUMBER
1615	

NOTIFICATION DATE	DELIVERY MODE
12/22/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

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Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com
smmichaud@clarkelbing.com

Decision Granting Request for Prioritized Examination (Track I)	**Application No.** 17/097,285	**Applicant(s)** TARDIF, Jean-Claude	
	Examiner JoAnne L Burke	**Art Unit** OPET	**AIA (FITF) Status** Yes

1. THE REQUEST FILED 13 November 2020 IS **GRANTED** .

The above-identified application has met the requirements for prioritized examination

A. ☑ for an original nonprovisional application (Track I).
B. ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination**. The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;

B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims** , or a multiple dependent claim;

C. filing a **request for continued examination** ;

D. filing a notice of appeal;

E. filing a request for suspension of action;

F. mailing of a notice of allowance;

G. mailing of a final Office action;

H. completion of examination as defined in 37 CFR 41.102; or

I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to JoAnne Burke at (571)272-4584. In his/her absence, calls may be directed to Petition Help Desk at (571) 272-3282.

/JOANNE L BURKE/ Lead Paralegal Specialist, OPET	

U.S. Patent and Trademark Office
PTO-2298 (Rev. 02-2012)

To: patentadministrator@clarkelbing.com,smmichaud@clarkelbing.com,
From: PAIR_eOfficeAction@uspto.gov
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Subject: Private PAIR Correspondence Notification for Customer Number 21559

Dec 24, 2020 04:10:43 AM

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UNITED STATES

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Application	Document	Mailroom Date	Attorney Docket No.
17097285	TRACK1.GRANT	12/22/2020	50761-029001

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/097,285	11/13/2020	Jean-Claude TARDIF	50761-029001	3015

21559 7590 01/13/2021

CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER	
DAVIS, BRIAN J	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
01/13/2021	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

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patentadministrator@clarkelbing.com
smmichaud@clarkelbing.com

Office Action Summary	Application No. 17/097,285	Applicant(s) TARDIF, Jean-Claude	
	Examiner BRIAN J DAVIS	Art Unit 1612	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1-30 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1,3-8,10,13-20,22 and 25-28 is/are rejected.

8) ☑ Claim(s) 2,9,11-12,21,23-24 and 29-30 is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☑ The drawing(s) filed on 13 November 2020 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 11/19/2020.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Claim Rejections - 35 USC § 102

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a)(1) the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention.

Claims 1, 3-8, 10, 14, 18, 19, 22 and 25-28 are rejected under 35 U.S.C. 102(a)(1) as being clearly anticipated by *American Heart Journal* (September 2019), Vol. 215, pp. 62-69, cited in the IDS.

The reference teaches a method of treating adult human patients (>18 years old) after a myocardial infarction (MI) comprising administering low dose (0.5 mg once daily) colchicine within 7 days of the (MI) (abstract; page 63, column 1, **Methods**). The

examiner notes for clarity of the record that the prior art teaching of administration within 7 days fully encompasses the instant teaching of within about 3 days of the MI.

The reference is drawn to a pilot, randomized, double blind, placebo-controlled trial whose patients were recruited at Royal Perth Hospital, Perth Australia (abstract; page 63, column 1, **Methods**).

The patients, in some cases, had been prescribed medications such as antiplatelet agents, aspirin, or a statin (page 65, Table 1).

Patients administered colchicine were at a lower risk of a cardiovascular event, such as MI, relative to a patient not being administered colchicine (page 66, column 1, **Clinical outcomes, tolerability and safety**).

Claim Rejections - 35 USC § 103

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 13, 15-17 and 20 are rejected under 35 U.S.C. 103 as being unpatentable over *American Heart Journal* (September 2019), Vol. 215, pp. 62-69, cited in the IDS.

Inventor teaches a method of treating a patient after having a myocardial infarction (MI) by administering daily low dose colchicine within about 3 days of the MI and wherein the patient has atherosclerotic coronary artery disease (claim 13).

Inventor further teaches that the colchicine is in the form of a tablet (claim 15), a coated tablet (claim 16), a film-coated tablet (claim 17). Claim 20 teaches a dosage of 0.5 mg.

American Heart Journal (September 2019), Vol. 215, pp. 62-69 has been substantially outlined above (102 rejection).

With respect to claim 13, inventor distinguishes over the prior art in that a patient with atherosclerotic coronary artery disease is explicitly taught. However, as is well-known in the art, most myocardial infarctions are due to atherosclerotic coronary artery disease. That being the case, one of ordinary skill in the art, before the effective filing

date of the instant invention, would have found it obvious that most, if not all, patients of the cited prior art would likely have suffered from atherosclerotic coronary artery disease. That is, the patient population taught in instant claim 13 is encompassed by the patient population of the cited prior art.

With respect to claims 15-17 and 20 inventor principally distinguishes over the prior art in that a particular delivery vehicle for the colchicine is taught. However, the cited reference is a general teaching and one of ordinary skill - absent unexpected results - would have found it obvious, before the effective filing date of the instant invention, to administer the appropriate dosage (i.e. 0.5 mg) of colchicine by any appropriate means, such a tablet, a coated tablet or a film-coated tablet, motivated by ordinary clinical considerations.

Allowable Subject Matter

Claims 2, 9, 11, 12, 21, 23, 24, 29 and 30 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRIAN J DAVIS whose telephone number is (571)272-0638. The examiner can normally be reached on M-F 8:30-5:00 PM EST.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an

interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fred Krass, can be reached at 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see https://ppair-my.uspto.gov/pair/PrivatePair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/BRIAN J DAVIS/
Primary Examiner, Art Unit 1612
1/11/2021

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/097,285	TARDIF, Jean-Claude
	Examiner	Art Unit
	BRIAN J DAVIS	1612

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
Structure/Research Topic search in CAS SciFinder (see search history printout)	01/10/2021	/BJD/
Inventor name search in PE2E	01/10/2021	/BJD/

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

/BRIAN J DAVIS/ Primary Examiner, Art Unit 1612	01/11/2021

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/097,285	TARDIF, Jean-Claude
	Examiner	Art Unit
	BRIAN J DAVIS	1612

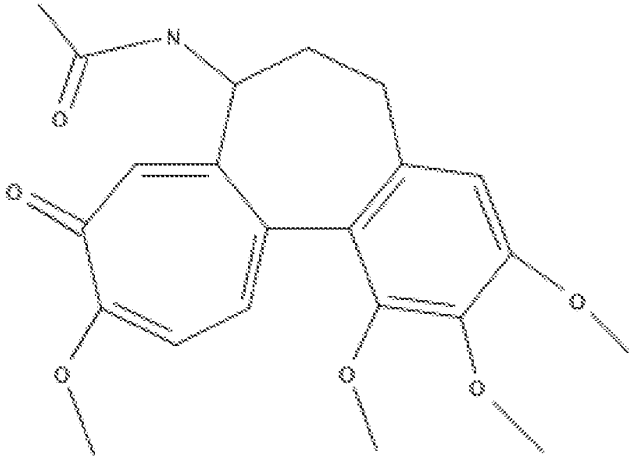
✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

CLAIMS										
☐ Claims renumbered in the same order as presented by applicant						☐ CPA		☐ T.D.		☐ R.1.47
CLAIM		DATE								
Final	Original	01/11/2021								
	1	✓								
	2	O								
	3	✓								
	4	✓								
	5	✓								
	6	✓								
	7	✓								
	8	✓								
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	24	O								
	25	✓								
	26	✓								
	27	✓								
	28	✓								
	29	O								
	30	O								

Session Began January 10, 2021 at 04:29 AM

Task Began January 10, 2021 04:32 AM

Explore substances by SUBSTRUCTURE ID(1)



Answer Type: *Substances*

Result Count: *1823*

Retrieve reference information in 1 substance (ID 2)

From ID: 1

Answer Type: *References*

Result Count: *27560*

Refine by research topic (ID 3)

Research Topic: myocardial infarction
From ID: 2

Answer Type: *References*

Result Count: *389*

Refine by research topic (ID 4)

Research Topic: low dose
From ID: 3

Answer Type: *References*

Result Count: *36*

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(Based on PTO 07-09 version)

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 3

Complete if Known	
Application Number	17/097,285
Filing Date	November 13, 2020
First Named Inventor	Jean-Claude TARDIF
Art Unit	1629
Examiner Name	Not Yet Assigned
Attorney Docket Number	50761-029001

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	A*	US-10,265,281	04-23-2019	Nidorf	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	A	WO-2014/066944-A1	05-08-2014	Heart Care Western Australia Pty Ltd		

Examiner Signature	/BRIAN J DAVIS/	Date Considered	01/10/2021

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. * CITE NO.: Those application(s) which are marked with an single asterisk (*) next to the Cite No. are not supplied (under 37 CFR 1.98(a)(2)(iii)) because that application was filed after June 30, 2003 or is available in the IFW. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

IDS Filed November 19, 2020

3024497

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /B.J.D/

PTO/SB/08b (07-09)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet	2	of	3

Complete if Known	
Application Number	17/097,285
Filing Date	November 13, 2020
First Named Inventor	Jean-Claude TARDIF
Art Unit	1629
Examiner Name	Not Yet Assigned
Attorney Docket Number	50761-029001

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	A	Akodad et al., "Interest of colchicine in the treatment of acute myocardial infarct responsible for heart failure in a mouse model," Int J Cardiol. 240:347-353 (2017).	
	B	Bouabdallaoui et al., "Time-to-treatment initiation of colchicine and cardiovascular outcomes after myocardial infarction in the Colchicine Cardiovascular Outcomes Trial (COLCOT)," Eur Heart J. 00:1-8 (2020).	
	C	Deftereos et al., "Anti-Inflammatory Treatment with Colchicine in Acute Myocardial Infarction: A Pilot Study," Circulation 132(15):1395-403 (2015).	
	D	Hennessy et al., "The Low Dose Colchicine after Myocardial Infarction (LoDoCo-MI) study: A pilot randomized placebo controlled trial of colchicine following acute myocardial infarction," Am Heart J. 215:62-69 (2019).	
	E	Newby et al., "Inflammation as a Treatment Target after Acute Myocardial Infarction," N Engl J Med. 381(26):2562-2563 (2019).	
	F	Nidorf et al., "Low-dose colchicine for secondary prevention of cardiovascular disease," J Am Coll Cardiol. 61(4):404-410 (2013).	
	G	Nidorf et al., "Why Colchicine Should Be Considered for Secondary Prevention of Atherosclerosis: An Overview," Clin Ther. 41(1):41-48 (2019).	
	H	Tardif et al., "Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction," N Engl J Med. 381(26):2497-2505 (2019).	
	I	Tucker et al., "Colchicine as a Novel Therapy for Suppressing Chemokine Production in Patients with an Acute Coronary Syndrome: A Pilot Study," Clin Ther. 41(10):2172-2181 (2019).	
	J	Vaidya et al., "Colchicine Therapy and Plaque Stabilization in Patients with Acute Coronary Syndrome: A CT Coronary Angiography Study," JACC Cardiovasc Imaging. 11(2 PT 2):305-316 (2018).	

Examiner Signature	/BRIAN J DAVIS/	Date Considered	01/10/2021

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /B.J.D/

PTO/SB/08b (07-09)
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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet	3	of	3

Complete if Known	
Application Number	17/097,285
Filing Date	November 13, 2020
First Named Inventor	Jean-Claude TARDIF
Art Unit	1629
Examiner Name	Not Yet Assigned
Attorney Docket Number	50761-029001

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	K	Vaidya et al., "The Role of Colchicine in Acute Coronary Syndromes," Clin Ther. 41(1):11-20 (2018).	

Examiner Signature	/BRIAN J DAVIS/	Date Considered	01/10/2021

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /B.J.D/

To: patentadministrator@clarkelbing.com,smmichaud@clarkelbing.com,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 21559

Jan 13, 2021 03:37:58 AM

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Application	Document	Mailroom Date	Attorney Docket No.
17097285	CTNF	01/13/2021	50761-029001
	1449	01/13/2021	50761-029001

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PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

5 March 2021 (05-03-2021)

BORDEN LADNER GERVAIS LLP
ipcipomail@blg.com

Application No.	:	**3,099,143**
Owner	:	INSTITUT DE CARDIOLOGIE DE MONTREAL
Title	:	**EARLY ADMINISTRATION OF LOW-DOSE COLCHICINE AFTER MYOCARDIAL INFARCTION**
Classification	:	A61K 31/165 (2006.01)
Your File No.	:	**PAT 109772-1**
Examiner	:	Cristina Belyea, PhD

YOU ARE HEREBY NOTIFIED OF A REQUISITION BY THE EXAMINER IN ACCORDANCE WITH SUBSECTION 86(2) OF THE *PATENT RULES*. IN ORDER TO AVOID ABANDONMENT UNDER PARAGRAPH 73(1)(*a*) OF THE *PATENT ACT*, A WRITTEN REPLY MUST BE RECEIVED WITHIN **FOUR (4)** MONTHS AFTER THE ABOVE DATE.

This application has been examined as originally filed.

The number of claims in this application is 35.

Documents Cited:

D1: Hennessy, Thomas; et al., "The Low Dose Colchicine after Myocardial Infarction (LoDoCo-MI) study: A pilot randomized placebo controlled trial of colchicine following acute myocardial infarction", *American Heart Journal*, 215, Pages 62-69, 9 January 2019 (09-01-2019)

D1 discloses the use of colchicine in a low dose of 0.5 g for treating a patient that had acute myocardial infarction (MI) within the prior 7 days (see “Study design and participants” on p.63), patients that had percutaneous coronary intervention (PCI). Some of the treated patients were prescribed a second medication, such as aspirin, anti-platelet agent, beta-blocker, statin, etc. (see Table 1). The levels of C-creative protein (CRP) were reduced in these patients.

D2: Montreal Heart Institute, "Colchicine Cardiovascular Outcomes Trial (COLCOT) (COLCOT)", *U.S. National Library of Medicine*, NCT02551094, 16 September 2015 (16-09-2015)

D2 discloses a study that evaluates the effects of long-term treatment with colchicine on the rates of cardiovascular events in patients after myocardial infarction. Patients who have suffered a documented acute myocardial infarction within the last 30 days, were treated colchicine (0.5 mg per day) after having completed any planned percutaneous revascularization procedures associated with their initial infarction.

D3: Nidorf, S.; et al., "Low-Dose Colchicine for Secondary Prevention of Cardiovascular Disease", *Journal of the American College of Cardiology*, Vol. 61, No. 4, Pages 404-410, 29 January 2013 (29-01-2013)

D3 discloses colchicine 0.5 mg/day given in addition to high-dose statins, aspirin and other standard secondary prevention therapies appear to be effective for the prevention of cardiovascular events, including stroke, in patients with stable coronary disease. Participants in the study had past myocardial infarction (see Table 1 with study population).

D4: Deftereos, S.; et al., "Anti-Inflammatory Treatment With Colchicine", *Circulation*, 132/15, P.1395-1403, 13 October 2015 (13-10-2015) https://www.ahajournals.org/doi/epub/10.1161/CIRCULATIONAHA.115.017611,

D4 discloses the treatment of patients presenting with ST-segment–elevation myocardial infarction ≤12 hours from pain onset (treated with primary percutaneous coronary intervention). The loading dose of 2 mg (1.5 mg initially followed by 0.5 mg 1 hour later) and continuing with 0.5 mg twice daily for 5 days (Figure 1). Patients with <60 kg body weight received 0.5 mg once daily. A positive effect of treatment was found in all studied parameters (biomarkers and cardiac MRI).

D5: CA2894417 MURRAY & POOLE ENTERPRISES, LTD., AU 8 May 2014 (08-05-2014)

D5 discloses the use of a medicament comprising about 0.5 mg to about 0.6 mg of colchicine and/or a salt thereof for preventing a cardiovascular event in a subject with stable coronary disease (having a history of myocardial infarction)- see claim 59. The patient may receive concurrently an anti-platelet agent or a statin. Low dose colchicine significantly reduces the risk of a cardiovascular event, including an ACS, out of hospital cardiac arrest and non-cardio-embolic ischemic stroke.

The examiner has identified the following defects in the application:

The claims of the present application appear to be directed to a treatment regimen. However, treatment regimens are not patentable subject matter in Canada as they interfere with a physician's skills or judgment which are expected to be exercised when administering the drug relying on the advice of the patentee and thus it is considered a method of medical treatment (see Axcan Pharma Inc. v. Pharmascience Inc., [2006] FC 527 [(2006), 50 C.P.R. (4th), 321 (F.C.)] and MOPOP. chapter 17).

Claims 1-15, 25-35 encompass subject-matter that was disclosed in D1 before the claim date and do not comply with paragraph 28.2(1)(*b*) of the *Patent Act*.

Claims 1-35 encompass subject-matter that was disclosed in D2 before the one-year period immediately preceding the filing date or, if the claim date is before that period, before the claim date and do not comply with paragraph 28.2(1)(*a*) of the *Patent Act*.

Claims 1-35 encompass subject-matter that was disclosed in D4 before the claim date and do not comply with paragraph 28.2(1)(*b*) of the *Patent Act*.

Claims 1-35 do not comply with section 28.3 of the *Patent Act*. These claims are directed to subject-matter that would have been obvious at the claim date to a person skilled in the art or science to which it pertains having regard to in view of D3 or D5 and the common general knowledge. Both D3 and D5 show the prevention of cardiovascular events in patients with stable coronary disease (having a history of myocardial infarction) by administering low doses of colchicine. Although these documents do not disclose the timeline of administration of these low doses, it would have been obvious to a person skilled in the art or science to study and determine the efficiency of these low doses of colchicine at different point in times after the initial cardiovascular event. Therefore, claims 1-35 are considered to lack an inventive step and contravene with section 28.3 of the *Patent Act*.

Claims 16-18 encompass subject-matter that lies outside the definition of "invention" and do not comply with section 2 of the *Patent Act*. The defined method is a method of medical treatment and is consequently not a statutory "art" or "process" (see section 23.03.01 of the *Manual of Patent Office Practice*). Even though these claims are directed to a use, the expression "initiating the administration" defines a medical step making the aforementioned claims methods of medical treatment.

Claims 29-34 encompass subject-matter that lies outside the definition of "invention" and do not comply with section 2 of the *Patent Act*. The defined method is a method of medical treatment and is consequently not a statutory "art" or "process" (see section 23.03.01 of the *Manual of Patent Office Practice*). Even though these claims are directed to a use, the expression "is administered" defines a medical step making the aforementioned claims methods of medical treatment.

Claims 1-3, 16-23 are indefinite and do not comply with subsection 27(4) of the *Patent Act*. The term "low dose" is indefinite. This terminology does not define the limits of the given dose. In the description this low dose is defined as having a range of 0.4-0.7 mg (see page 15, lines 35-37) and therefore these limits should be included in the claims.

Claims 1-3, 16-21, 23, 24 are indefinite and do not comply with subsection 27(4) of the *Patent Act*. The terminology "within about" within said claims results in the claims not clearly delineating the boundaries of the claimed subject matter. The use of the term "within" in conjunction with the qualifier "about" obscures the explicit higher limit expressed, thereby rendering the subject matter in claim 9 indefinite. The otherwise specific higher value is rendered ambiguous by the term about which contradictorily affords a degree of uncertainty to those same values.

Claim 18 is indefinite and does not comply with subsection 27(4) of the *Patent Act*. This claim does not end with a period, thereby causing a lack of clarity.

In accordance with subsection 84(2) of the *Patent Rules*, this application will no longer qualify for advanced examination requested by the applicant if the application is deemed to be abandoned or if an extension of time under subsection 3(1) of the *Patent Rules* is granted.

In view of the foregoing defects, the applicant is requisitioned, under subsection 86(2) of the

Patent Rules, to amend the application in order to comply with the *Patent Act* and the *Patent Rules* or to provide arguments as to why the application does comply.

Under section 102 of the *Patent Rules*, any amendment made in response to this requisition must be accompanied by a statement explaining the purpose of the amendment and identifying the differences between the new page and the replaced page.

Cristina Belyea, PhD
Patent Examiner
819-639-6987

As per CIPO Client Service Standards, a response to a telephone enquiry or voice mail should be provided by the end of the next business day. In the event that attempts to reach the examiner are unsuccessful, the examiner's Section Head, Shirley Arpin, can be reached at 819-639-6948.

For general inquiries: 1-866-997-1936 or for more options see http://www.ic.gc.ca/eic/site/cipointernet-internetopic.nsf/eng/wr00006.html.

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3099143A_cvb.docm

The Examination Search Report is provided for reference only and is not part of any requisition made by the examiner in accordance with the *Patent Act* or *Rules*. The applicant is not required to respond to the information contained in the Examination Search Report.

Examination Search Report

Box I: General Information			
Application No.	3,099,143	Search Report Date	2021-03-02
Title	EARLY ADMINISTRATION OF LOW-DOSE COLCHICINE AFTER MYOCARDIAL INFARCTION		
Examiner	Cristina Belyea	Search Conducted?	Yes

Box II: Family Prosecution		
Family Member	File Wrapper Reviewed	Status of Prosecution

Box III: Search History			
Claims Searched	1-35	Date of Search	2021-02-26
Type of Search Conducted (select all that apply):			
Canadian first to file search	■	Supplemental/top up search	□
Inventor/applicant search	■	Non laid open search	□
Comprehensive search	■	In-house searcher	□

Search History from Databases Consulted:

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##### CANADIAN PATENT DATABASE/INTELLECT ##########
Query
Number of Hits

1 ipc:(A61K\ 31/165 OR A61P\ 9/00 OR A61P\ 9/10) 7,471
2 ipc:(A61K\ 31/165 OR A61P\ 9/00 OR A61P\ 9/10) AND colchicine 212
3 ipc:(A61K\ 31/165 OR A61P\ 9/00 OR A61P\ 9/10) AND colchicine AND myocard* 120
4 ipc:(A61K\ 31/165 OR A61P\ 9/00 OR A61P\ 9/10) AND (claims:colchicine) AND myocard*
13
5 ipc:(A61K\ 31/165 OR A61P\ 9/00 OR A61P\ 9/10) AND colchicine AND stroke 110
6 ipc:(A61K\ 31/165 OR A61P\ 9/00 OR A61P\ 9/10) AND claims:colchicine AND stroke  13
7  ipc:(A61K\  31/165  OR  A61P\  9/00  OR  A61P\  9/10)  AND  applicant:("INSTITUT  DE
CARDIOLOGIE DE MONTREAL"~3) 10
8 ipc:(A61K\ 31/165 OR A61P\ 9/00 OR A61P\ 9/10) AND inventor:("TARDIF JEAN-CLAUDE"~3)

##### QUESTEL-ORBIT ##########
Base :  FAMPAT
SEARCH STRATEGY
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SS Results

6 34 ((COLCHICINE)/CLMS AND (PREVENT+ AND STROKE)/CLMS) AND (A61K-031/165 OR A61P-009/00 OR A61P-009/10)/IPC

5 51 ((COLCHICINE)/CLMS AND (MYOCARD+)/CLMS) AND (A61K-031/165 OR A61P-009/00 OR A61P-009/10)/IPC

4 430 (COLCHICINE)/CLMS AND (A61K-031/165 OR A61P-009/00 OR A61P-009/10)/IPC

3 28 ((COLCHICINE)/CLMS AND (STROKE)/CLMS AND (MYOCARDIAL INFARCTION)/CLMS)

2 28 ((COLCHICINE OR LODOCO)/CLMS AND (STROKE)/CLMS AND (MYOCARDIAL INFARCTION)/CLMS)

1 80 ((COLCHICINE)/CLMS AND (STROKE)/CLMS)

Version 9

COVID-19 is an emerging, rapidly evolving situation.

Public health information (CDC)

Research information (NIH)

SARS-CoV-2 data (NCBI)

Prevention and treatment information (HHS)

U.S. National Library of Medicine

ClinicalTrials.gov

Colchicine Cardiovascular Outcomes Trial (COLCOT) (COLCOT)

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT02551094

Recruitment Status : Completed
First Posted : September 16, 2015
Results First Posted : October 19, 2020
Last Update Posted : October 19, 2020

Sponsor:
Montreal Heart Institute

Information provided by (Responsible Party):
Montreal Heart Institute

Study Details | Tabular View | Study Results | Disclaimer | How to Read a Study Record

Study Description

Go to

Brief Summary:

The study evaluates whether long-term treatment with colchicine reduces rates of cardiovascular events in patients after myocardial infarction. Patients who have suffered a documented acute myocardial infarction within the last 30 days, are treated according to the national guidelines and after having completed any planned percutaneous revascularization procedures associated with their initial infarction will receive either colchicine (0.5 mg per day) or matching placebo (1:1 allocation ratio) for an estimated 2 years period or until the target of 301 primary endpoints has been reached.

Condition or disease	Intervention/treatment	Phase
Coronary Artery Disease Myocardial Infarction	Drug: colchicine Drug: colchicine placebo	Phase 3

Detailed Description:

Atherosclerosis is the most common cause of myocardial infarction, stroke and peripheral arterial disease. Research has clearly demonstrated that inflammation plays a key role in the initiation, progression and manifestations of atherosclerosis. Atherosclerotic lesions begin as an accumulation of lipid-laden cells (primarily macrophages) beneath the endothelium, and progress with the further accumulation of cells, connective-tissue elements, lipids and debris through immunological and inflammatory activation. Neutrophils and other inflammatory cells have been shown to invade culprit atherosclerotic lesions in acute coronary syndromes. It is likely that the inflammatory process is responsible for the high rate of cardiovascular events despite significant advances in the treatment of risk factors such as hypercholesterolemia and hypertension. It is vital to improve our understanding of the inflammatory nature of atherosclerotic disease and modify the inflammatory process with targeted therapies. Prospective cohort studies have consistently shown that high sensitivity C-reactive protein (hs-CRP) and several other biomarkers of inflammation are independently associated with increasing risk of future cardiovascular events in different populations. This together with animal models showing that reduced inflammation has anti-atherosclerotic effects, create the impetus to test the hypothesis that treatment of the underlying inflammatory process will contribute to improved cardiovascular clinical outcomes. Colchicine is an inexpensive, yet potent, anti-inflammatory drug approved for acute use in patients with gout and chronic use in patients with Familial Mediterranean Fever. The mechanism of action is through the inhibition of tubulin polymerization and potentially also through effects on cellular adhesion molecules and inflammatory chemokines. Colchicine may also have direct anti-inflammatory effects by inhibiting key inflammatory signaling networks known as the inflammasome and pro-inflammatory cytokines. Through the disruption of the cytoskeleton, colchicine is believed to suppress secretion of cytokines and chemokines as well as in vitro platelet aggregation. Considerable work has highlighted the potential of colchicine in the treatment of cardiovascular diseases mediated by pro-inflammatory processes. More recently colchicine has been evaluated for its effect on cardiovascular events in patients with coronary artery disease (CAD).

Study Design

Go to

Study Type :

Interventional (Clinical Trial)

Actual Enrollment :

4745 participants

Allocation:

Randomized

Intervention Model:

Parallel Assignment

Masking:

Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)

Primary Purpose:

Prevention

Official Title:

Colchicine Cardiovascular Outcomes Trial (COLCOT)

Actual Study Start Date :

December 4, 2015

Actual Primary Completion Date :

July 17, 2019

Actual Study Completion Date :

July 17, 2019

Resource links provided by the National Library of Medicine

MedlinePlus related topics: Heart Attack

Drug Information available for: Colchicine

U.S. FDA Resources

Arms and Interventions

Go to

Arm	Intervention/treatment
Active Comparator: colchicine 0.5 mg tablet of colchicine taken once a day	Drug: colchicine 0.5 mg tablet taken once a day Other Name: no other name

Arm	Intervention/treatment
Placebo Comparator: colchicine placebo 0.5 mg tablet of placebo taken once a day	Drug: colchicine placebo sugar pill manufactured to mimic colchicine 0.5 mg tablet Other Name: no other name

Outcome Measures

Go to

Primary Outcome Measures :

1. First Event of Cardiovascular Death, Resuscitated Cardiac Arrest, Acute Myocardial Infarction, Stroke, or Urgent Hospitalization for Angina Requiring Coronary Revascularization [Time Frame: From randomization to occurence of first event, assessed up to 3.5 years]

   The descriptive statistics are the number of participants having at least one of the composites of the primary endpoint.

Secondary Outcome Measures :

1. Death (Total Mortality) [Time Frame: From randomization to death, assessed up to 3.5 years]

   The descriptive statistics are the number of participants having deceased.

2. Cardiovascular Death [Time Frame: From randomization to death, assessed up to 3.5 years]

   The descriptive statistics are presented as the number of participants having had a cardiovascular death.

3. Resuscitated Cardiac Arrest [Time Frame: From randomization to event, assessed up to 3.5 years]

   The descriptive statistics are presented as the number of participants having had resuscitated cardiac arrest

4. Myocardial Infarction [Time Frame: From randomization to event, assessed up to 3.5 years]

   The descriptive statistics are presented as the number of participants having had myocardial infarction.

5. Stroke [Time Frame: From randomization to event, assessed up to 3.5 years]

   The descriptive statistics are presented as the number of participants having had a stroke.

6. Urgent Hospitalization for Angina Requiring Coronary Revascularization [Time Frame: From randomization to event, assessed up to 3.5 years]

   The descriptive statistics are presented as the number of participants having had urgent hospitalization for angina requiring coronary revascularization.

7. First Event of Cardiovascular Death, Resuscitated Cardiac Arrest, Acute MI or Stroke. [Time Frame: From randomization to occurence of first event, assessed up to 3.5 years]

   The descriptive statistics are presented as the number of participants having had a first event of cardiovascular death, resuscitated cardiac arrest, acute MI or stroke.

Other Outcome Measures:

1. First Event of Deep Venous Thrombosis or Pulmonary Embolus [Time Frame: From randomization to occurence of first event, assessed up to 3.5 years]

   The descriptive statistics are presented as the number of participants having had a first event of deep venous thrombosis or pulmonary embolus.

2. Atrial Fibrillation [Time Frame: From randomization to event, assessed up to 3.5 years]

   The descriptive statistics are presented as the number of participants having had atrial fibrillation.

3. Heart Failure Hospitalization [Time Frame: From randomization to event, assessed up to 3.5 years]

   The descriptive statistics are presented as the number of participants having had heart failure hospitalization.

4. Coronary Revascularization [Time Frame: From randomization to event, assessed up to 3.5 years]

   The descriptive statistics are presented as the number of participants having had coronary revascularization.

Eligibility Criteria

Go to

Information from the National Library of Medicine

NIH NLM

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the contacts provided below. For general information, Learn About Clinical Studies.

Ages Eligible for Study:

18 Years and older (Adult, Older Adult)

Sexes Eligible for Study:

All

Accepts Healthy Volunteers:

No

Criteria

Inclusion Criteria:

- Males and females of at least 18 years of age capable and willing to provide informed consent
- Patient must have suffered a documented acute myocardial infarction within the last 30 days
- Patient must be treated according to national guidelines (including anti-platelet therapy, statin, renin-angiotensin-aldosterone system inhibitor (preferably angiotensin-converting enzyme) and beta-blocker when indicated)
- Patient must have completed any planned percutaneous revascularization procedures associated with his or her qualifying myocardial infarction
- Female patient is either not of childbearing potential, defined as postmenopausal for at least one year or surgically sterile, or is of childbearing potential and practicing at least one method of contraception and preferably two complementary forms of contraception
- Patient is judged to be in good general health as determined by the principal investigator
- Patient must be able and willing to comply with the requirements of this study protocol

Exclusion Criteria:

- Patient with a poorly controlled medical condition, such as New York Heart Association Class III-IV heart failure, a left ventricular ejection fraction of less than 35%, recent stroke (within the past 3 months), or any other condition which in the opinion of the investigator, would put the patient at risk if participating in this study
- Patient with a Type 2 index MI (secondary to ischemic imbalance)
- Patient with a prior coronary artery bypass graft within the past 3 years, or planned
- Patient currently in cardiogenic shock or with hemodynamic instability

- Patient with a history of cancer or lymphoproliferative disease within the last 3 years other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma and or localized carcinoma in situ of the cervix
- Patient with inflammatory bowel disease (Crohn's disease or ulcerative colitis) or patient with chronic diarrhea
- Patient with pre-existent progressive neuromuscular disease or patient with creatine phosphokinase level greater than 3 times the upper limit of normal (unless due to myocardial infarction which is allowed) as measured within the past 30 days and determined to be non-transient through repeat testing
- Patient with any of the following as measured within the past 30 days, and determined to be non-transient through repeat testing: hemoglobin less than 115 grams/L, white blood cell count less than 3.0 X 10(9)/L,platelet count less than 110 X 10(9)/L, alanine aminotransferase greater than 3 times the upper limit of normal, total bilirubin greater than 2 times the upper limit of normal (unless due to Gilbert syndrome, which is allowed), creatinine greater than 2 times the upper limit of normal
- Patient with a history of cirrhosis, chronic active hepatitis or sever hepatic disease
- Female patient who is pregnant, or breast-feeding or is considering becoming pregnant during the study or for 6 months after the last dose of study medication
- Patient with a history of clinically significant drug or alcohol abuse in the last year
- Patient is currently using or plan to begin chronic systemic steroid therapy (oral or intravenous) during the study (topical or inhaled steroids are allowed)
- Patient currently taking colchicine for other indications (mainly chronic indications represented by Familial Mediterranean Fever or gout); there is no wash-out period required for patients who have been treated with colchicine and stopped treatment prior to enrollment
- Patient with history of an allergic reaction or significant sensitivity to colchicine
- Patient who has used an investigational chemical agent less than 30 days or 5 half-lives prior to the screening visit (whichever is longer)
- Patient is considered by he investigator, for any reason, to be an unsuitable candidate for the study

Contacts and Locations

Go to

Information from the National Library of Medicine

To learn more about this study, you or your doctor may contact the study research staff using the contact information provided by the sponsor.

Please refer to this study by its ClinicalTrials.gov identifier (NCT number): ***NCT02551094***

Locations

Canada, Quebec

Montreal Heart Institute
Montreal, Quebec, Canada, H1T1C8

Sponsors and Collaborators

Montreal Heart Institute

Investigators

Principal Investigator:	Jean-Claude Tardif, MD	Montreal Heart Institute
Study Director:	Andreas Orfanos, MD	Montreal Health Innovations Coordinating Centre

Study Documents (Full-Text)

Documents provided by Montreal Heart Institute:

Statistical Analysis Plan [PDF] August 28, 2019

Study Protocol [PDF] November 15, 2018

More Information

Go to

Publications automatically indexed to this study by ClinicalTrials.gov Identifier (NCT Number):

Bouabdallaoui N, Tardif JC, Waters DD, Pinto FJ, Maggioni AP, Diaz R, Berry C, Koenig W, Lopez-Sendon J, Gamra H, Kiwan GS, Blondeau L, Orfanos A, Ibrahim R, Grégoire JC, Dubé MP, Samuel M, Morel O, Lim P, Bertrand OF, Kouz S, Guertin MC, L'Allier PL, Roubille F. Time-to-treatment initiation of colchicine and cardiovascular outcomes after myocardial infarction in the Colchicine Cardiovascular Outcomes Trial (COLCOT). Eur Heart J. 2020 Nov 7;41(42):4092-4099. doi: 10.1093/eurheartj/ehaa659.

Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, Pinto FJ, Ibrahim R, Gamra H, Kiwan GS, Berry C, López-Sendón J, Ostadal P, Koenig W, Angoulvant D, Grégoire JC, Lavoie MA, Dubé MP, Rhainds D, Provencher M, Blondeau L, Orfanos A, L'Allier PL, Guertin MC, Roubille F. Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction. N Engl J Med. 2019 Dec 26;381(26):2497-2505. doi: 10.1056/NEJMoa1912388. Epub 2019 Nov 16.

Responsible Party:

Montreal Heart Institute

ClinicalTrials.gov Identifier:

NCT02551094 History of Changes

Other Study ID Numbers:

MHIPS-003

First Posted:

September 16, 2015 Key Record Dates

Results First Posted:

October 19, 2020

Last Update Posted:

October 19, 2020

Last Verified:

September 2020

Additional relevant MeSH terms:

Coronary Artery Disease
Myocardial Infarction
Infarction
Ischemia
Pathologic Processes
Necrosis
Coronary Disease
Myocardial Ischemia
Heart Diseases
Cardiovascular Diseases
Arteriosclerosis
Arterial Occlusive Diseases
Vascular Diseases
Colchicine
Gout Suppressants
Antirheumatic Agents
Tubulin Modulators
Antimitotic Agents
Mitosis Modulators
Molecular Mechanisms of Pharmacological Action
Antineoplastic Agents

Electronic Acknowledgement Receipt

EFS ID:	42397117
Application Number:	17097285
International Application Number:	
Confirmation Number:	3015
Title of Invention:	EARLY ADMINISTRATION OF LOW-DOSE COLCHICINE AFTER MYOCARDIAL INFARCTION
First Named Inventor/Applicant Name:	Jean-Claude TARDIF
Customer Number:	21559
Filer:	Jan Tittel/James Moran
Filer Authorized By:	Jan Tittel
Attorney Docket Number:	50761-029001
Receipt Date:	13-APR-2021
Filing Date:	13-NOV-2020
Time Stamp:	11:33:53
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Non Patent Literature	50761-029001_-_Office_Action.pdf	320880 b67190842caa8e1fbaa17a78eefc3f0c5ac56514	no	6

Warnings:

Information:					
2	Non Patent Literature	50761-029001_-_D2_-_MHI_NCT02551094.pdf	153089 ae4169c600f1eb5d76aebc9ca5951fd86d4871ae	no	9
Warnings:					
Information:					
			Total Files Size (in bytes):	473969	

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

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PTO/SB/08b (07-09)
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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet	1	of	1

Complete if Known	
Application Number	17/097,285
Filing Date	November 13, 2020
First Named Inventor	Jean-Claude TARDIF
Art Unit	1612
Examiner Name	B. J. Davis
Attorney Docket Number	50761-029001

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	A	Office Action for Canadian Patent Application No. 3,099,143 mailed March 5, 2021 (6 pages).	
	B	Montreal Heart Institute, "Colchicine Cardiovascular Outcomes Trial (COLCOT) (COLCOT)", U.S. National Library of Medicine, NCT02551094, dated September 16, 2015 (9 pages).	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

IDS Filed April 13, 2021

Docket No.: 50761-029001
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Utility Application of:
Jean-Claude TARDIF

Application No.: 17/097,285 | Confirmation No.: 3015

Filed: November 13, 2020 | Art Unit: 1612

For: EARLY ADMINISTRATION OF LOW-DOSE COLCHICINE AFTER MYOCARDIAL INFARCTION | Examiner: B. J. Davis

RESPONSE TO NON-FINAL OFFICE ACTION UNDER 37 C.F.R. § 1.111

In response to the Office Action dated January 13, 2021, Applicant provides the following remarks.

AMENDMENTS TO THE CLAIMS

1. (Currently Amended) A method of treating a patient after having a myocardial infarction (MI), the method comprising initiating the administration of colchicine at a daily low dose to the patient within about 3 days of the MI, wherein the colchicine is administered without pre-loading the patient with a higher dose of colchicine before the administration at the daily low dose.

2. (Original) The method according to claim 1, wherein percutaneous coronary intervention was performed for treating the patient's MI.

3. (Original) The method according to claim 1, wherein the patient was prescribed a medication.

4. (Original) The method according to claim 3, wherein the medication is an antiplatelet agent.

5. (Original) The method according to claim 3, wherein the medication is aspirin.

6. (Original) The method according to claim 3, wherein the medication is a statin.

7. (Original) The method according to claim 1, wherein the patient is at a lower risk of a cardiovascular event, relative to a patient not being administered colchicine.

8. (Original) The method according to claim 7, wherein the cardiovascular event is an ischemic cardiovascular event.

9. (Original) The method according to claim 7, wherein the cardiovascular event is resuscitated cardiac arrest.

10. (Original) The method according to claim 7, wherein the cardiovascular event is myocardial infarction.

11. (Original) The method according to claim 7, wherein the cardiovascular event is stroke.

12. (Original) The method according to claim 7, wherein the cardiovascular event is urgent hospitalization for angina requiring coronary revascularization.

13. (Original) The method according to claim 1, wherein the patient has atherosclerotic coronary artery disease.

14. (Original) The method according to claim 1, wherein the administration of colchicine is initiated upon assessment in (a) an emergency department (ED), (b) the hospital, or (c) a medical office setting.

15. (Original) The method according to claim 1, wherein the colchicine is in the form of a tablet.

16. (Original) The method of claim 15, wherein the tablet is coated.

17. (Original) The method of claim 16, wherein the tablet is film-coated.

18. (Original) The method according to claim 1, wherein the colchicine is administered at 0.3 to 0.7 mg.

19. (Original) The method according to claim 18, wherein the colchicine is administered at 0.4 to 0.6 mg

20. (Currently Amended) The method according to claim ~~16~~ 19, wherein the colchicine is administered at 0.5 mg.

21. (Original) The method according to claim 9, wherein the colchicine is administered at 0.5 mg.

22. (Original) The method according to claim 10, wherein the colchicine is administered at 0.5 mg.

23. (Original) The method according to claim 11, wherein the colchicine is administered at 0.5 mg.

24. (Original) The method according to claim 12, wherein the colchicine is administered at 0.5 mg.

25. (Original) The method according to claim 1, wherein the colchicine is administered once, twice or three times a day.

26. (Original) The method according to claim 25, wherein the colchicine is administered once per day.

27. (Cancelled)

28. (Original) The method according to claim 1, wherein the patient is an adult human.

29. (Original) A method of reducing the risk of a stroke in a patient after having an MI, the method comprising initiating the administration of colchicine at a daily low dose to the patient within about 30 days of an MI.

30. (Original) The method according to claim 29, wherein the method comprises administering colchicine within 4 to 7 days of the MI.

REMARKS

Prior to the present amendment, claims 1-30 are pending. Claims 1, 3-8, 10, 14, 18, 19, 22, and 25-28 are rejected under 35 U.S.C. § 102(a)(1). Claims 13, 15-17, and 20 are rejected under 35 U.S.C. § 103. Claims 2, 9, 11, 12, 21, 23, 24, 29, and 30 are objected to. Applicant addresses each basis for rejection and objection as follows.

Claim amendments

Claim 1 has been amended to recite that the colchicine is administered without pre-loading the patient with a higher dose of colchicine before administration of the daily low dose. Support for this amendment is found, for example, in original claim 27 and at page 7, lines 6-9 of the application as filed.

In view of the amendment to claim 1, claim 27 has been cancelled.

The dependency of claim 20 has been amended.

No new matter has been added by the present amendments. Applicant reserves the right to pursue any cancelled subject matter in this or a continuing application.

Rejection under 35 U.S.C. § 102(a)(1)

Claims 1, 3-8, 10, 14, 18, 19, 22, and 25-28 are rejected under 35 U.S.C. § 102(a)(1) as being anticipated by Hennessy et al. (American Heart Journal 215:62-69, 2019: "Hennessy"). With regard to Hennessy, the Office states (pages 2 and 3; emphasis original):

> The reference teaches a method of treating adult human patients (>18 years old) after myocardial infarction (MI) comprising administering low dose (0.5 mg dose daily) colchicine within 7 days of the (MI) (abstract; page 63, column 1, **Methods**). The examiner notes for clarity of the record that the prior art teaching of administration within 7 days fully encompasses the instant teaching of within about 3 days of the MI.

Applicant respectfully traverses this basis for rejection.

Claim 1 is directed to a method of treating a patient after having a MI, where the method includes initiating the administration of colchicine at a daily low dose to the patient within about 3 days of the MI.

Hennessy does not describe administering colchicine to a patient within about 3 days of an MI. Hennessy describes administration within 7 days of an MI. Hence, Hennessy does not describe the claimed method. On this basis alone, the anticipation rejection of claim 1, and its dependent claims, over Hennessy should be withdrawn.

Moreover, as discussed in detail below, administration of colchicine within 3 days of an MI has significant benefits relative to administration within 4 to 7 days of an MI.

Rejection under 35 U.S.C. § 103

Claims 13, 15-17, and 20 are rejected under 35 U.S.C. § 103 as being unpatentable over Hennessy. The Office states (pages 4 and 5):

> With respect to claim 13, inventor distinguishes over the prior art in that a patient with atherosclerotic coronary artery disease is [not] explicitly taught. However, as is well-known in the art, most myocardial infarctions are due to atherosclerotic coronary artery disease.
>
> * * *
>
> With respect to claims 15-17 and 20 inventor principally distinguishes over the prior art in that a particular delivery vehicle for the colchicine is taught. However, the cited reference is a general teaching and one of ordinary skill – absent unexpected results – would have found it obvious, before the effective filing date of the instant invention, to administer the appropriate dosage (i.e. 0.5 mg) of colchicine by any appropriate means, such as a tablet, a coated tablet or a film-coated tablet, motivated by ordinary clinical observations.

Claims 13, 15-17, and 20 depend from claim 1. As explained below, the features of claim 1 are nonobvious over Hennessy.

The method of claim 1 is based on the inventor's finding that administration of colchicine within about 3 days of an MI leads to patient outcomes that are significantly better when compared to a placebo. This statistically significant effect is not seen when colchicine is administered between 4 and 7 days after an MI. In particular, as is shown in Table 3 of the specification (reproduced below for reference with highlighting added), administration of colchicine within about 3 days of an MI yields a statistically significant reduction in the composite of primary endpoints (cardiovascular death, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina requiring coronary revascularization) in comparison to a placebo, whereas administration of colchicine between days 4 to 7 and on or after day 8 do not. Here, 4.3% of patients receiving colchicine within 3 days of an MI reached a primary endpoint, whereas 8.3% receiving a placebo within 3 days of an MI reached a primary endpoint. These results show a statistically significant benefit for a patient receiving colchicine within about 3 days of an MI. Patients receiving colchicine within about 4 to 7 days of an MI do not show a statistically significant benefit. Applicant submits that this result is nonobvious over the teachings by Hennessy where patients received colchicine within 7 days of an MI.

Applicant respectfully submits that the obviousness rejection of claims 13, 15-17, and 20 should be withdrawn.

Table 3: Efficacy endpoints according to TTI (N=4661, colchicine vs. placebo)

Endpoints	**TTI 0-3 days, N=1193** **Colchicine vs. placebo** **no. (%)**	**TTI 4-7 days, N=720** **Colchicine vs. placebo** **no. (%)**	**TTI ≥ 8 days, N=2748** **Colchicine vs. placebo** **no. (%)**
	HR (95% CI); p	**HR (95% CI); p**	**HR (95% CI); p**

Primary composite endpoint	26 (4.3%) vs. 49 (8.3%)	22 (6.0%) vs. 21 (5.9%)	77 (5.7%) vs. 99 (7.1%)
	0.52 (0.32-0.84); p=0.007	0.96 (0.53-1.75); p=0.896	0.82 (0.61-1.11); p=0.200
CV death	2 (0.3%) vs. 2 (0.3%)	2 (0.5%) vs. 4 (1.1%)	15 (1.1%) vs. 18 (1.3%)
	1.04 (0.15-7.37); p=0.970	0.45 (0.08-2.46); p=0.356	0.89 (0.45-1.76); p=0.734
Resuscitated cardiac arrest	1 (0.2%) vs. 3 (0.5%)	2 (0.5%) vs. 1 (0.3%)	2 (0.1%) vs. 2 (0.1%)
	0.33 (0.03-3.20); p=0.340	1.90 (0.17-20.95); p=0.600	1.02 (0.14-7.22); p=0.986
MI	17 (2.8%) vs. 29 (4.9%)	16 (4.4%) vs. 9 (2.5%)	52 (3.8%) vs. 59 (4.2%)
	0.58 (0.32-1.05); p=0.071	1.67 (0.74-3.78); p=0.218	0.93 (0.64-1.35); p=0.710
Stroke	1 (0.2%) vs. 5 (0.8%)	1 (0.3%) vs. 3 (0.8%)	2 (0.1%) vs. 11 (0.8%)
	0.21 (0.02-1.81); p=0.156	0.28 (0.03-2.71); p=0.272	0.19 (0.04-0.84); p=0.029
Urgent hospitalization for angina requiring coronary revascularization	6 (1%) vs. 17 (2.9%)	4 (1.1%) vs. 6 (1.7%)	15 (1.1%) vs. 26 (1.9%)
	0.35 (0.14-0.88); p=0.026	0.63 (0.18-2.24); p= 0.476	0.61 (0.32-1.16); p=0.131
Secondary Composite Endpoint	20 (3.3%) vs. 36 (6.1%)	18 (4.9%) vs. 16 (4.5%)	67 (4.9%) vs. 77 (5.5%)
	0.55 (0.32-0.95); p=0.031	1.04 (0.53-2.03); p=0.919	0.92 (0.66-1.28); p=0.629
All-cause death	6 (1.0%) vs. 6 (1.0%)	8 (2.2%) vs. 7 (2.0%)	26 (1.9%) vs. 31 (2.2%)
	1.03 (0.33-3.19); p=0.962	1.03 (0.37-2.84); p=0.957	0.90 (0.53-1.51); p=0.684
All Coronary Revascularizations	33 (5.5%) vs. 51 (8.7%)	25 (6.9%) vs. 18 (5.1%)	72 (5.3%) vs. 94 (6.7%)
	0.63 (0.40-0.97); p=0.037	1.41 (0.76-2.61); p=0.275	0.81 (0.59-1.10); p=0.172

Claim objection

Claims 2, 9, 11, 12, 21, 23, 24, 29, and 30 are objected to as being dependent upon a rejected base claim. The Office indicates that these claims "would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims" (Office Action at page 5). For the reasons provided above, Applicant submits that claim 1 is free of the bases for rejection raised in the present Office Action. Claims 2, 9, 11, 12, 21, 23, 24, which depend from claim 1, therefore are also in condition for allowance.

Claim 29 is an independent claim and claim 30 depends from claim 29. These claims are also free of this basis for objection.

CONCLUSION

Applicant submits that the claims are in condition for allowance, and such action is respectfully requested.

Please apply any charges or credits to Deposit Account No. 03-2095.

Dated: April 13, 2021

Respectfully submitted,

/Jan N. Tittel/
Jan N. Tittel, Ph.D.
Registration No.: 52,290
CLARK & ELBING LLP
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Docket No.: 50761-029001
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Utility Application of:
Jean-Claude TARDIF

Application No.: 17/097,285 | Confirmation No.: 3015

Filed: November 13, 2020 | Art Unit: 1612

For: EARLY ADMINISTRATION OF LOW-DOSE COLCHICINE AFTER MYOCARDIAL INFARCTION | Examiner: B. J. Davis

INFORMATION DISCLOSURE STATEMENT (IDS)

Pursuant to 37 C.F.R. §§ 1.56, 1.97, and 1.98, the attention of the United States Patent and Trademark Office is hereby directed to the references listed on the attached PTO/SB/08. It is respectfully requested that the information be expressly considered during the prosecution of the above-identified application.

This Information Disclosure Statement is filed more than three months after the filing date of this application, OR more than three months after the date of entry of the national stage in the international application, AND after the mailing date of a first Office Action on the merits, but before the mailing date of any of a Final Action under 37 C.F.R. § 1.113, a Notice of Allowance under 37 C.F.R. § 1.311 or an action that otherwise closes prosecution in this application (37 C.F.R. § 1.97(c)).

Pursuant to 37 C.F.R. § 1.97(e)(1), each item of information contained in this Information Disclosure Statement was first cited in or is a communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Information Disclosure Statement.

Submitted herewith are copies of non-patent literature in accordance with 37 C.F.R. § 1.98(a)(2).

In accordance with 37 C.F.R. § 1.97(g), the filing of this Information Disclosure Statement shall not be construed as a representation that a search has been made. In accordance with 37 C.F.R. § 1.97(h), the filing of this Information Disclosure Statement shall not be construed to be an admission that the information cited in this Information Disclosure Statement is, or is considered to be, material to the patentability as defined in 37 C.F.R. § 1.56(b).

It is submitted that the Information Disclosure Statement is in compliance with 37 C.F.R. § 1.98, and the Examiner is respectfully requested to consider the listed references.

Please apply any charges or credits to Deposit Account No. 03-2095.

Dated: April 13, 2021

Respectfully submitted,

/Jan N. Tittel/
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Doc Code: PA..
Document Description: Power of Attorney

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POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date
17/097,285	November 13, 2020

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

[x] I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above: 21559

OR

[ ] I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

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OR

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Address					
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I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

INSTITUT DE CARDIOLOGIE DE MONTREAL

[ ] Inventor or Joint Inventor (title not required below)

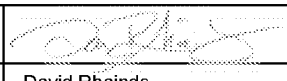
[ ] Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

[x] Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

[ ] Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature		Date (Optional)	2020-11-18
Name	David Rhainds		
Title	Deputy Director, Research Center		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

[ ] Total of 1 forms are submitted.

PTO/AIA/01 (06-12)
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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	EARLY ADMINISTRATION OF LOW-DOSE COLCHICINE AFTER MYOCARDIAL INFARCTION

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number 17/097,285 filed on 11/13/2020 .

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

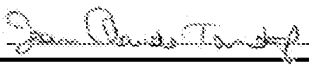
I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Jean-Claude TARDIF Date (Optional) : 2021/01/15

Signature: 

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

Electronic Acknowledgement Receipt	
EFS ID:	42436658
Application Number:	17097285
International Application Number:	
Confirmation Number:	3015
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Time Stamp:	11:31:09
Application Type:	Utility under 35 USC 111(a)

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Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		50761-029001_-_Amendment2.pdf	42952 051a54c9f7a0baadf69742bdc49bcb71c9d7ff98	yes	8

	Multipart Description/PDF files in .zip description				
	Document Description	**Start**	**End**		
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1		
	Claims	2	4		
	Applicant Arguments/Remarks Made in an Amendment	5	8		
Warnings:					
Information:					
2	Transmittal Letter	50761-029001_-_Information_Disclosure_Statement_IDS.pdf	20553 1db2de5e3d178affd6fccaec5645a9b5665d1d28	no	2
Warnings:					
Information:					
3	Information Disclosure Statement (IDS) Form (SB08)	50761-029001_-_Information_Disclosure_Statement_By_Applicant_PTO_SB-08.pdf	24063 71f840764233c6fc9d2a0e8e933ab893a8716483	no	1
Warnings:					
Information:					
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4	Power of Attorney	50761-029001_Signed_POA.PDF	229096 d9bce6b63a41892b39bd18c1b36ba940343c27c6	no	1
Warnings:					
Information:					
5	Oath or Declaration filed	50761-029001_Signed_Declaration.PDF	149540 01504d8d1366515fb95289f832d1b51a4e52557e	no	1
Warnings:					
Information:					
		Total Files Size (in bytes):	466204		

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
17/097,285	11/13/2020	Jean-Claude TARDIF	50761-029001

CONFIRMATION NO. 3015

21559
CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

POA ACCEPTANCE LETTER

OC000000124894715

Date Mailed: 04/15/2021

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 04/13/2021.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/cnguyen/

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 17/097,285	Filing Date 11/13/2020	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $100 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $480 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	04/13/2021	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 29	Minus	** 30	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	= 0		x $480 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/CAROLYN E THOMAS/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

To: patentadministrator@clarkelbing.com,smmichaud@clarkelbing.com,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 21559

Apr 15, 2021 05:19:15 AM

Dear PAIR Customer:

CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110
UNITED STATES

The following USPTO patent application(s) associated with your Customer Number, 21559 , have new outgoing correspondence. This correspondence is now available for viewing in Private PAIR.

The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

Disclaimer:
The list of documents shown below is provided as a courtesy and is not part of the official file wrapper. The content of the images shown in PAIR is the official record.

Application	Document	Mailroom Date	Attorney Docket No.
17097285	N570	04/15/2021	50761-029001

To view your correspondence online or update your email addresses, please visit us anytime at https://sportal.uspto.gov/secure/myportal/privatepair.

If you have any questions, please email the Electronic Business Center (EBC) at EBC@uspto.gov with 'e-Office Action' on the subject line or call 1-866-217-9197 during the following hours:

Monday - Friday 6:00 a.m. to 12:00 a.m.

Thank you for prompt attention to this notice,

UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/097,285	11/13/2020	Jean-Claude TARDIF	50761-029001	3015

21559 7590 04/21/2021

CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER	
DAVIS, BRIAN J	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
04/21/2021	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com
smmichaud@clarkelbing.com

Office Action Summary	Application No. 17/097,285	Applicant(s) TARDIF, Jean-Claude	
	Examiner BRIAN J DAVIS	Art Unit 1612	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 4/13/2021.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☑ This action is **FINAL.** 2b) ☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1-26 and 28-30 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☑ Claim(s) 29-30 is/are allowed.

7) ☑ Claim(s) 1,3-8,10,13-20,22,25-26 and 28 is/are rejected.

8) ☑ Claim(s) 2,9,11-12,21 and 23-24 is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☑ The drawing(s) filed on 13 November 2020 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 4/13/2021.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

102 Rejections Withdrawn

The rejection of claim 27 under 35 USC 102(a)(1), outlined in the previous Office Action, has been overcome by inventor's amendment. The amendment cancels the claim.

Claim Rejections - 35 USC § 102, MAINTAINED

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a)(1) the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention.

Claims 1, 3-8, 10, 14, 18, 19, 22, 25, 26 and 28 remain rejected under 35 U.S.C. 102(a)(1) as being clearly anticipated by *American Heart Journal* (September 2019), Vol. 215, pp. 62-69, cited in the IDS. Inventor's amendment and arguments have been carefully considered but are not persuasive.

As stated in the previous Office Action, the reference teaches a method of treating adult human patients (>18 years old) after a myocardial infarction (MI) comprising administering low dose (0.5 mg once daily) colchicine within 7 days of the (MI) (abstract; page 63, column 1, **Methods**). The examiner notes for clarity of the record that the prior art teaching of administration within 7 days fully encompasses the instant teaching of within about 3 days of the MI.

The reference is drawn to a pilot, randomized, double blind, placebo-controlled trial whose patients were recruited at Royal Perth Hospital, Perth Australia (abstract; page 63, column 1, **Methods**).

The patients, in some cases, had been prescribed medications such as antiplatelet agents, aspirin, or a statin (page 65, Table 1).

Patients administered colchicine were at a lower risk of a cardiovascular event, such as MI, relative to a patient not being administered colchicine (page 66, column 1, **Clinical outcomes, tolerability and safety**).

Inventor argues that the cited art does not describe administering colchicine to a patient within about 3 days of the myocardial infarction, but rather within 7 days of the myocardial infarction. Inventor then concludes that the cited art does not describe the instant method. The examiner respectfully disagrees.

The prior art teaches a time frame within which to administer colchicine: within 7 days of a myocardial infarction. The instant claims teach a time frame wholly encompassed by this prior art time frame: within about 3 days of a myocardial infarction. That is, on day zero after a myocardial infarction, *both* the prior art and the instant claims teach administration of colchicine. On day one after a myocardial infarction, *both* the prior art and the instant claims teach administration of colchicine. On day two after a myocardial infarction, *both* the prior art and the instant claims teach administration of colchicine. And, arguably, *both* the prior art and the instant claims ("…within *about* [emphasis added] 3 days…") teach administration of colchicine on day 3 after a myocardial infarction.

In short, inventor's argument is predicated upon the absence of an identical repetition of a set of words pertinent to a limitation in both the prior art and the instant claim set - rather than the clear teaching and meaning of those words. The prior art teaches a range. The instant claim set teaches a range within that range. Thus, with respect to days 0-3, the cited art does, indeed, as outlined above, clearly anticipate the instant invention. (Note also that where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). MPEP 2144.05.)

The examiner notes that inventor has also added a limitation to independent claim 1 that no preloading of colchicine takes place. But, since the cited art is silent with respect to any preloading, this newly added limitation is inherently encompassed and does not distinguish over the cited art.

Inventor further argues that administration of colchicine within 3 days of a myocardial infarction has significant benefits relative to administration within 4 to 7 days of a myocardial infarction. The examiner respectfully points out that an argument predicated upon unexpected results cannot overcome an anticipation rejection.

Claim Rejections - 35 USC § 103, MAINTAINED

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 13, 15-17 and 20 remain rejected under 35 U.S.C. 103 as being unpatentable over *American Heart Journal* (September 2019), Vol. 215, pp. 62-69, cited in the IDS. Inventor's amendment and arguments have been carefully considered but are not persuasive.

As stated in the previous Office Action, inventor teaches a method of treating a patient after having a myocardial infarction (MI) by administering daily low dose colchicine within about 3 days of the MI and wherein the patient has atherosclerotic coronary artery disease (claim 13).

Inventor further teaches that the colchicine is in the form of a tablet (claim 15), a coated tablet (claim 16), a film-coated tablet (claim 17). Claim 20 teaches a dosage of 0.5 mg.

American Heart Journal (September 2019), Vol. 215, pp. 62-69 has been substantially outlined above (102 rejection).

With respect to claim 13, inventor distinguishes over the prior art in that a patient with atherosclerotic coronary artery disease is explicitly taught. However, as is well-known in the art, most myocardial infarctions are due to atherosclerotic coronary artery disease. That being the case, one of ordinary skill in the art, before the effective filing date of the instant invention, would have found it obvious that most, if not all, patients of the cited prior art would likely have suffered from atherosclerotic coronary artery disease. That is, the patient population taught in instant claim 13 is encompassed by the patient population of the cited prior art.

With respect to claims 15-17 and 20 inventor principally distinguishes over the prior art in that a particular delivery vehicle for the colchicine is taught. However, the cited reference is a general teaching and one of ordinary skill - absent unexpected results - would have found it obvious, before the effective filing date of the instant invention, to administer the appropriate dosage (i.e. 0.5 mg) of colchicine by any appropriate means, such a tablet, a coated tablet or a film-coated tablet, motivated by ordinary clinical considerations.

Inventor argues that the instant method is based upon the finding that the administration of colchicine within about 3 days of a myocardial infarction leads to patient outcomes which are significantly better when compared to a placebo. Inventor references Table 3 of the specification (page 15). However, as outlined above in the 102 rejection, the 3-day range of the instant invention is fully encompassed by 7-day range of the cited art. Note that where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). MPEP 2144.05. Further, it is well established that consideration of a reference is not limited to the preferred embodiments or working examples, but extends to the entire disclosure for what it fairly teaches to a person of ordinary skill in the art. *In re Boe*, 355 F2d 961, 148 USPQ 507, 510 (CCPA 1966); *In re Chapman*, 357 F2d 418, 148 USPQ 711 (CCPA 1966): *In re Meinhardt*, 392 F2d 273, 157 USPQ 270, 272 (CCPA 1968); *In re Lamberti*, 545 F2d 747, 750, 192 USPQ 279, 280 (CCPA 1976); *In re Fracalossi*, 681 F2d 792, 794, 215 USPQ 569, 570 (CCPA 1982); *In re Kaslow*, 707 F2d 1366, 1374, 217 USPQ 1089, 1095 (Fed. Cir. 1983).

Claim Objections Withdrawn

The objection to claims 29 and 30 is withdrawn.

It was stated in the previous Office Action that claims 29 and 30 were objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. This was incorrect and the examiner regrets the error. The subject matter of these claims is allowable.

Allowable Subject Matter

Claims 2, 9, 11, 12, 21, 23 and 24 remain objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRIAN J DAVIS whose telephone number is (571)272-0638. The examiner can normally be reached on M-F 8:30-5:00 PM EDT.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fred Krass, can be reached at 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see https://ppair-my.uspto.gov/pair/PrivatePair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/BRIAN J DAVIS/
Primary Examiner, Art Unit 1612
4/19/2021

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/097,285	TARDIF, Jean-Claude
	Examiner	Art Unit
	BRIAN J DAVIS	1612

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

CLAIMS

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	01/11/2021	04/19/2021							
	1	✓	✓							
	2	O	O							
	3	✓	✓							
	4	✓	✓							
	5	✓	✓							
	6	✓	✓							
	7	✓	✓							
	8	✓	✓							
	9	O	O							
	10	✓	✓							
	11	O	O							
	12	O	O							
	13	✓	✓							
	14	✓	✓							
	15	✓	✓							
	16	✓	✓							
	17	✓	✓							
	18	✓	✓							
	19	✓	✓							
	20	✓	✓							
	21	O	O							
	22	✓	✓							
	23	O	O							
	24	O	O							
	25	✓	✓							
	26	✓	✓							
	27	✓	-							
	28	✓	✓							
	29	O	=							
	30	O	=							

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/097,285	TARDIF, Jean-Claude
	Examiner	Art Unit
	BRIAN J DAVIS	1612

CPC - Searched*		
Symbol	Date	Examiner
A61K 31/165 (cursory, 1/2021 to date)	04/15/2021	/BJD/

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
Global Dossier	04/15/2021	/BJD/
Inventor name search in PE2E	04/15/2021	/BJD/

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

/BRIAN J DAVIS/ Primary Examiner, Art Unit 1612	04/19/2021

PTO/SB/08b (07-09)
Approved for use through 07/31/2016. OMB 0651-0031
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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	17/097,285
Filing Date	November 13, 2020
First Named Inventor	Jean-Claude TARDIF
Art Unit	1612
Examiner Name	B. J. Davis
Attorney Docket Number	50761-029001

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	A	Office Action for Canadian Patent Application No. 3,099,143 mailed March 5, 2021 (6 pages).	
	B	Montreal Heart Institute, "Colchicine Cardiovascular Outcomes Trial (COLCOT) (COLCOT)", U.S. National Library of Medicine, NCT02551094, dated September 16, 2015 (9 pages).	

Examiner Signature	/BRIAN J DAVIS/	Date Considered	04/15/2021

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

IDS Filed April 13, 2021

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /B.J.D/

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	2,704	A61K31/165.cpc.	USPAT	OR	ON	2021/04/15 21:16
L2	3,425	A61K31/165.cpc.	US-PGPUB	OR	ON	2021/04/15 21:16

4/15/2021 9:17:21 PM
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To: patentadministrator@clarkelbing.com,smmichaud@clarkelbing.com,
From: PAIR_eOfficeAction@uspto.gov
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Subject: Private PAIR Correspondence Notification for Customer Number 21559

Apr 21, 2021 04:02:48 AM

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Application	Document	Mailroom Date	Attorney Docket No.
17097285	CTFR	04/21/2021	50761-029001
	1449	04/21/2021	50761-029001

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
17/097,285	11/13/2020	Jean-Claude TARDIF	50761-029001

CONFIRMATION NO. 3015

21559
CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

PUBLICATION NOTICE

OC000000125738489

Title:EARLY ADMINISTRATION OF LOW-DOSE COLCHICINE AFTER MYOCARDIAL INFARCTION

Publication No.US-2021-0145773-A1
Publication Date:05/20/2021

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Public Records Division. The Public Records Division can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Public Records Division, Alexandria, VA 22313-1450 or via the Internet.

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Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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May 21, 2021 03:57:46 AM

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Application	Document	Mailroom Date	Attorney Docket No.
17097285	NTC.PUB	05/20/2021	50761-029001

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NOTICE OF APPEAL FROM THE EXAMINER TO THE PATENT TRIAL AND APPEAL BOARD	Docket Number (Optional) 50761-029001

I hereby certify that this correspondence is being facsimile transmitted to the USPTO, EFS-Web transmitted to the USPTO, or deposited with the United States Postal Service with sufficient postage in an envelope addressed to "Commissioner for Patents, P.O. Box 1450, Alexandria, on Alexandria, VA 22313-1450" [37 CFR 1.8(a)] on _____.

Signature _____

Typed or printed name _____

In re Application of

Jean-Claude TARDIF

Application Number	Filed
17/097,285	November 13, 2020

For EARLY ADMINISTRATION OF LOW-DOSE COLCHICINE AFTER MYOCARDIAL INFARCTION

Art Unit	Examiner
1612	B. J. Davis

Applicant hereby **appeals** to the Patent Trial and Appeal Board from the last decision of the examiner.

The fee for this Notice of Appeal is (37 CFR 41.20(b)(1)) $ 840.00

☐ Applicant asserts small entity status. See 37 CFR 1.27. Therefore, the fee shown above is reduced by 50%, and the resulting fee is: $ _____

☐ Applicant certifies micro entity status. See 37 CFR 1.29. Therefore, the fee shown above is reduced by 75%, and the resulting fee is: $ _____

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☒ Payment made via EFS-Web.

☒ A petition for an extension of time under 37 CFR 1.136(a) (PTO/AIA/22 or equivalent) is enclosed. For extensions of time in reexamination proceedings, see 37 CFR 1.550.

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I am the

☐ applicant ☒ attorney or agent of record Registration number 52,290 ☐ attorney or agent acting under 37 CFR 1.34 Registration number _____

Signature /Jan N. Tittel/

Typed or printed name Jan N. Tittel, Ph.D.

Telephone Number (617) 428-0200

Date October 21, 2021

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☐ * Total of 1 forms are submitted.

Electronic Patent Application Fee Transmittal					
Application Number:	17097285				
Filing Date:	13-Nov-2020				
Title of Invention:	EARLY ADMINISTRATION OF LOW-DOSE COLCHICINE AFTER MYOCARDIAL INFARCTION				
First Named Inventor/Applicant Name:	Jean-Claude TARDIF				
Filer:	Jan Tittel/Ashley Lombardi				
Attorney Docket Number:	50761-029001				
Filed as Large Entity					
Filing Fees for Utility under 35 USC 111(a)					
Description		**Fee Code**	**Quantity**	**Amount**	**Sub-Total in USD($)**
Basic Filing:					
Pages:					
Claims:					
Miscellaneous-Filing:					
Petition:					
Patent-Appeals-and-Interference:					
NOTICE OF APPEAL		1401	1	840	840
Post-Allowance-and-Post-Issuance:					

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Extension - 3 months with $0 paid	1253	1	1480	1480
Miscellaneous:				
		Total in USD ($)		**2320**

Electronic Acknowledgement Receipt	
EFS ID:	44084979
Application Number:	17097285
International Application Number:	
Confirmation Number:	3015
Title of Invention:	EARLY ADMINISTRATION OF LOW-DOSE COLCHICINE AFTER MYOCARDIAL INFARCTION
First Named Inventor/Applicant Name:	Jean-Claude TARDIF
Customer Number:	21559
Filer:	Jan Tittel/Madeleine O'Neill
Filer Authorized By:	Jan Tittel
Attorney Docket Number:	50761-029001
Receipt Date:	21-OCT-2021
Filing Date:	13-NOV-2020
Time Stamp:	11:03:01
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$2320
RAM confirmation Number	E20210KB03400836
Deposit Account	032095
Authorized User	Madeleine O'Neill
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: 37 CFR 1.21 (Miscellaneous fees and charges) 37 CFR 1.20 (Post Issuance fees)	

37 CFR 1.19 (Document supply fees)

37 CFR 1.17 (Patent application and reexamination processing fees)

37 CFR 1.16 (National application filing, search, and examination fees)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Extension of Time	50761-029001_-_Petition_for_Extension_of_Time_Under_37_CFR_1136a_PTO_AIA-22.pdf	22605 ef190132505246242a1a162ca0742dd54283fb0f	no	1
Warnings:					
Information:					
2	Notice of Appeal Filed	50761-029001_-_Notice_of_Appeal_PTO_AIA-31.pdf	41667 aba5bf7f53dd566bf048e560d37202bf502cec91	no	1
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	40600 ae1606d3252173ec9f806c5bf50fd50d9a10333e	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	104872		

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/AIA/22 (10-20)
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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)	Docket Number (Optional) 50761-029001
Application Number 17/097,285	Filed November 13, 2020
For EARLY ADMINISTRATION OF LOW-DOSE COLCHICINE AFTER MYOCARDIAL INFARCTION	
Art Unit 1612	Examiner B. J. Davis

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

	Fee	Small Entity Fee	Micro Entity Fee	
☐ One month (37 CFR 1.17(a)(1))	$220	$110	$55	$
☐ Two months (37 CFR 1.17(a)(2))	$640	$320	$160	$
☒ Three months (37 CFR 1.17(a)(3))	$1,480	$740	$370	$ 1,480.00
☐ Four months (37 CFR 1.17(a)(4))	$2,320	$1,160	$580	$
☐ Five months (37 CFR 1.17(a)(5))	$3,160	$1,580	$790	$

☐ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 03-2095 .

☒ Payment made via EFS-Web.

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I am the

☐ applicant.

☒ attorney or agent of record. Registration number 52,290 .

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____.

/Jan N. Tittel/	October 21, 2021
Signature	Date
Jan N. Tittel, Ph.D.	(617) 428-0200
Typed or printed name	Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

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3263699

PTO/SB/30 (11-17)
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Request for Continued Examination (RCE) Transmittal

Address to:
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P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	17/097,285
Filing Date	November 13, 2020
First Named Inventor	Jean-Claude TARDIF
Art Unit	1612
Examiner Name	B. J. Davis
Attorney Docket Number	50761-029001

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. Submission required under 37 CFR 1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

   a. [ ] Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.
      i. [ ] Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
      ii. [ ] Other _____
   b. [X] Enclosed
      i. [X] Amendment/Reply
      ii. [ ] Affidavit(s)/ Declaration(s)
      iii. [X] Information Disclosure Statement (IDS)
      iv. [ ] Other _____

2. Miscellaneous

   a. [ ] Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)
   b. [ ] Other _____

3. Fees The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

   a. [X] The Director is hereby authorized to charge the following fees, any underpayment of fees, or credit any overpayments, to Deposit Account No. 03-2095 .
      i. [X] RCE fee required under 37 CFR 1.17(e)
      ii. [X] Extension of time fee (37 CFR 1.136 and 1.17)
      iii. [ ] Other _____
   b. [ ] Check in the amount of $ _____ enclosed
   c. [ ] Payment by credit card (Form PTO-2038 enclosed)
   d. [X] Payment by EFS-Web

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SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature	/Jan N. Tittel/	Date	March 21, 2022
Name (Print/Type)	Jan N. Tittel, Ph.D.	Registration No.	52,290

3288625

Docket No.: 50761-029001
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Utility Application of:
Jean-Claude TARDIF

Application No.: 17/097,285 | Confirmation No.: 3015

Filed: November 13, 2020 | Art Unit: 1612

For: EARLY ADMINISTRATION OF LOW-DOSE COLCHICINE AFTER MYOCARDIAL INFARCTION | Examiner: B. J. Davis

INFORMATION DISCLOSURE STATEMENT (IDS)

Pursuant to 37 C.F.R. §§ 1.56, 1.97, and 1.98, the attention of the United States Patent and Trademark Office is hereby directed to the references listed on the attached PTO/SB/08. It is respectfully requested that the information be expressly considered during the prosecution of the above-identified application.

This Information Disclosure Statement, pursuant to 37 C.F.R. § 1.114(c), accompanies the Request for Continued Examination (37 C.F.R. § 1.114) submitted herewith.

Submitted herewith is a copy of non-patent literature in accordance with 37 C.F.R. § 1.98(a)(2).

In accordance with 37 C.F.R. § 1.97(g), the filing of this Information Disclosure Statement shall not be construed as a representation that a search has been made. In accordance with 37 C.F.R. § 1.97(h), the filing of this Information Disclosure Statement shall not be construed to be an admission that the information cited in this Information Disclosure Statement is, or is considered to be, material to the patentability as defined in 37 C.F.R. § 1.56(b).

It is submitted that the Information Disclosure Statement is in compliance with 37 C.F.R. § 1.98, and the Examiner is respectfully requested to consider the listed references.

Please apply any charges or credits to Deposit Account No. 03-2095.

Dated: March 21, 2022

Respectfully submitted,

/Jan N. Tittel/
Jan N. Tittel, Ph.D.
Registration No.: 52,290
CLARK & ELBING LLP
101 Federal Street
15th Floor
Boston, MA 02110
(617) 428-0200

3442810

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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet	1	of	1

Complete if Known	
Application Number	17/097,285
Filing Date	November 13, 2020
First Named Inventor	Jean-Claude TARDIF
Art Unit	1612
Examiner Name	B. J. Davis
Attorney Docket Number	50761-029001

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	A	Office Action for Canadian Patent Application No. 3,099,143 mailed September 16, 2021 (4 pages).	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

IDS Filed March 21, 2022

16 September 2021 (16-09-2021)

BORDEN LADNER GERVAIS LLP
ipcipomail@blg.com

Application No.	:	**3,099,143**
Owner	:	INSTITUT DE CARDIOLOGIE DE MONTREAL
Title	:	**EARLY ADMINISTRATION OF LOW-DOSE COLCHICINE AFTER MYOCARDIAL INFARCTION**
Classification	:	A61K 31/165 (2006.01)
Your File No.	:	**PAT 109772-1**
Examiner	:	Cristina Belyea, PhD

YOU ARE HEREBY NOTIFIED OF A REQUISITION BY THE EXAMINER IN ACCORDANCE WITH SUBSECTION 86(2) OF THE *PATENT RULES*. IN ORDER TO AVOID ABANDONMENT UNDER PARAGRAPH 73(1)(*a*) OF THE *PATENT ACT*, A WRITTEN REPLY MUST BE RECEIVED WITHIN **FOUR (4)** MONTHS AFTER THE ABOVE DATE.

This application has been examined taking into account the applicant's correspondence received in this office on 5 July 2021 (05-07-2021).

The number of claims in this application is 35.

As the application is apparently directed to a plurality of inventions, as detailed below, the examiner has proceeded on the presumption that the applicant will elect the claims of **Group A**. This presumption does not affect the applicant's right to elect, one time, a different invention for prosecution. The scope of the search and examination of the claims was therefore restricted to the subject-matter of the claims of **Group A**.

Documents Cited:

D1: Hennessy, Thomas; et al., "The Low Dose Colchicine after Myocardial Infarction (LoDoCo-MI) study: A pilot randomized placebo controlled trial of colchicine following acute myocardial infarction", *American Heart Journal*, 215, Pages 62-69, 9 January 2019 (09-01-2019)

D1 discloses the use of colchicine in a low dose of 0.5 g for treating a patient that had acute myocardial infarction (MI) within the prior 7 days (see “Study design and participants” on p.63), patients that had percutaneous coronary intervention (PCI). Some of the treated patients were prescribed a second medication, such as aspirin, anti-platelet agent, beta-blocker, statin, etc. (see Table 1). The levels of C-creative protein (CRP) were reduced in these patients.

The examiner has identified the following defects in the application:

The application does not comply with subsection 36(1) of the *Patent Act*. The claims are directed to a plurality of alleged inventions as follows:

> **Group A** - Claims 1-15 are directed to the use of a daily low dose of colchicine for treating a patient after having a MI, wherein the use is initiated within 3 days or about 3 days of the MI, wherein the colchicine is for administration without pre-loading the patient with a higher dose of colchicine before administration at the daily low dose; and
> **Group B** - Claims 16-35 are directed to the use of colchicine in reducing the risk of or preventing a stroke in a patient after having a MI, the use comprising colchicine for administration at a daily low dose to the patient within 30 days or about 30 days of the MI.

The common technical feature for the claim on file is the use of low dose colchicine for treating a patient after having MI. This technical feature is not new nor inventive (see for example D1 or D4 cited in the previous office action) and therefore cannot constitute the unifying features for the claims on file.

Amended claim 1, includes the new limitation "without pre-loading the patient with a higher dose of colchicine before administration at the daily low dose", limitation not found in claim 16-35, which implies that such initial loading is encompassed by the claims of group B, differentiating the alleged inventions of the two groups.

According to subsection 36(2) of the *Patent Act*, after limiting the claims of the present application to one invention only, the applicant may make any other invention disclosed the subject of a divisional application. The applicant is advised that once an election has been made, further prosecution of the present application will be limited to the invention so elected.

Claims 1-15 encompass subject-matter that was disclosed in D1 before the claim date and do not comply with paragraph 28.2(1)(*b*) of the *Patent Act*.
The examiner has carefully considered the amendment and the applicant's reply to the lack of novelty in view of the newly amended claims, however it was not found to be persuasive.

D1 the use of colchicine in a low dose of 0.5 g for treating a patient that had acute myocardial infarction (MI) within the prior 7 days (see "Study design and participants" on p.63). The limitation of "within 3 days or about 3 days of MI" as currently claimed is encompassed by the prior art teaching of administration within 7 days of the MI.
The new amendment to the claims: "without preloading the patient with a higher does of colchicine before administration at the daily low dose" also does not distinguish over the cited document, as D1 is silent with respect to any preloading of the patient with higher doses of colchicine.

As a result, claims 1-15 are considered anticipated and fail to comply with paragraph 28.2(1)(*b*) of the *Patent Act*.

Claims 1-3 are indefinite and do not comply with subsection 27(4) of the *Patent Act*. The use if the terms "low dose" and "higher dose" are indefinite, as it is not clear what amounts are encompassed by these low and higher doses of colchicine. According to the description, at page 6, line 35-37 a low dose is defined as varying from 0.3-0.7 mg/day and the higher dose is

defined on page 7, lines 7-10 as having values of 1.0, 1.5, or 2.0 mg/day. These values clearly define said doses and should be included in the claims.

Claim 4 is indefinite and does not comply with subsection 27(4) of the *Patent Act*. This claim improperly depends on claims 2 and 3. Claims 2 and 3 are claims directed to the "Use of a daily low dose of colchicine for treating a patient after having a MI," and "Use of colchicine for the manufacture of a medicament for treating a patient after having a MI", respectively and not to “Colchicine for use”.

In accordance with subsection 84(2) of the *Patent Rules*, this application will no longer qualify for advanced examination requested by the applicant if the application is deemed to be abandoned or if an extension of time under subsection 3(1) of the *Patent Rules* is granted.

In view of the foregoing defects, the applicant is requisitioned, under subsection 86(2) of the *Patent Rules*, to amend the application in order to comply with the *Patent Act* and the *Patent Rules* or to provide arguments as to why the application does comply.

Under section 102 of the *Patent Rules*, any amendment made in response to this requisition must be accompanied by a statement explaining the purpose of the amendment and identifying the differences between the new page and the replaced page.

Cristina Belyea, PhD
Patent Examiner
819-639-6987

As per CIPO Client Service Standards, a response to a telephone enquiry or voice mail should be provided by the end of the next business day. In the event that attempts to reach the examiner are unsuccessful, the examiner's Section Head, Shirley Arpin, can be reached at 819-639-6948.

For general inquiries: 1-866-997-1936 or for more options see http://www.ic.gc.ca/eic/site/cipointernet-internetopic.nsf/eng/wr00006.html.

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3099143B_cvb.docm

The Examination Search Report is provided for reference only and is not part of any requisition made by the examiner in accordance with the *Patent Act* or *Rules*. The applicant is not required to respond to the information contained in the Examination Search Report.

Examination Search Report

Box I: General Information			
Application No.	3,099,143	Search Report Date	2021-09-16
Title	EARLY ADMINISTRATION OF LOW-DOSE COLCHICINE AFTER MYOCARDIAL INFARCTION		
Examiner	Cristina Belyea	Search Conducted?	No
No search was conducted for the following reasons :			
- Search deferred - see report for reasoning (lack of unity, excluded subject matter etc.)			N/A
- Relied on previous search results (CIPO and/or by Foreign Office)			Yes

Box II: Family Prosecution		
Family Member	File Wrapper Reviewed	Status of Prosecution
US2021145773A1	2021-09-15	In Progress
EP3821889A1	2021-09-15	In Progress
EP3821909A1	2021-09-15	In Progress

Box IV: Search History
No Search Conducted

Version 9

PTO/AIA/22 (10-20)
Approved for use through 11/30/2020. OMB 0651-0031
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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)	Docket Number (Optional) 50761-029001
Application Number 17/097,285	Filed November 13, 2020
For EARLY ADMINISTRATION OF LOW-DOSE COLCHICINE AFTER MYOCARDIAL INFARCTION	
Art Unit 1612	Examiner B. J. Davis

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

	Fee	Small Entity Fee	Micro Entity Fee	
☐ One month (37 CFR 1.17(a)(1))	$220	$110	$55	$
☐ Two months (37 CFR 1.17(a)(2))	$640	$320	$160	$
☒ Three months (37 CFR 1.17(a)(3))	$1,480	$740	$370	$ 1,480.00
☐ Four months (37 CFR 1.17(a)(4))	$2,320	$1,160	$580	$
☐ Five months (37 CFR 1.17(a)(5))	$3,160	$1,580	$790	$

☐ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 03-2095 .

☒ Payment made via EFS-Web.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant.

☒ attorney or agent of record. Registration number 52,290 .

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____.

/Jan N. Tittel/ — Signature
March 21, 2022 — Date

Jan N. Tittel, Ph.D. — Typed or printed name
(617) 428-0200 — Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☐ * Total of 1 forms are submitted.

3263699

Electronic Patent Application Fee Transmittal					
Application Number:	17097285				
Filing Date:	13-Nov-2020				
Title of Invention:	EARLY ADMINISTRATION OF LOW-DOSE COLCHICINE AFTER MYOCARDIAL INFARCTION				
First Named Inventor/Applicant Name:	Jean-Claude TARDIF				
Filer:	Jan Tittel/Ashley Lombardi				
Attorney Docket Number:	50761-029001				
Filed as Large Entity					
Filing Fees for Utility under 35 USC 111(a)					
Description		**Fee Code**	**Quantity**	**Amount**	**Sub-Total in USD($)**
Basic Filing:					
Pages:					
Claims:					
CLAIMS IN EXCESS OF 20		1202	21	100	2100
Miscellaneous-Filing:					
Petition:					
Patent-Appeals-and-Interference:					
Post-Allowance-and-Post-Issuance:					

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Extension - 3 months with $0 paid	1253	1	1480	1480
Miscellaneous:				
RCE- 1ST REQUEST	1801	1	1360	1360
		Total in USD ($)		**4940**

Electronic Acknowledgement Receipt	
EFS ID:	45274601
Application Number:	17097285
International Application Number:	
Confirmation Number:	3015
Title of Invention:	EARLY ADMINISTRATION OF LOW-DOSE COLCHICINE AFTER MYOCARDIAL INFARCTION
First Named Inventor/Applicant Name:	Jean-Claude TARDIF
Customer Number:	21559
Filer:	Jan Tittel/James Moran
Filer Authorized By:	Jan Tittel
Attorney Docket Number:	50761-029001
Receipt Date:	21-MAR-2022
Filing Date:	13-NOV-2020
Time Stamp:	16:09:29
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$4940
RAM confirmation Number	E20223KG09464955
Deposit Account	032095
Authorized User	James Moran
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: 37 CFR 1.16 (National application filing, search, and examination fees) 37 CFR 1.17 (Patent application and reexamination processing fees)	

37 CFR 1.19 (Document supply fees)

37 CFR 1.20 (Post Issuance fees)

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		50761-029001_-_Amendment2.pdf	31879 1dbf1dd41ff71f15c2f7683c61624dceb279e503	yes	7

Multipart Description/PDF files in .zip description

Document Description	Start	End
Amendment Submitted/Entered with Filing of Continued Prosecution Application (CPA)/Request for Continued Examination(RCE)	1	1
Claims	2	5
Applicant Arguments/Remarks Made in an Amendment	6	7

Warnings:

Information:

2	Request for Continued Examination (RCE)	50761-029001_-_Transmittal_--_Request_for_Continued_Examination_RCE_PTO_SB-30.pdf	25639 24305e5b389f7479d9e29ab181134c5a48f4fa82	no	1

Warnings:

This is not a USPTO supplied RCE SB30 form.

Information:

3	Transmittal Letter	50761-029001_-_Information_Disclosure_Statement_IDS.pdf	15005 e04a32361805532f42e94741e1a0bef05af0d697	no	1

Warnings:

Information:

4	Information Disclosure Statement (IDS) Form (SB08)	50761-029001_-_Information_Disclosure_Statement_By_Applicant_PTO_SB-08.pdf	23654 f8f71c92ad67e9ad0cc6189715be8bdc801a7b88	no	1

Warnings:

Information:

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5	Non Patent Literature	50761-029001_-_CA_Office_Action.pdf	281252 25db2828ecfee82875347c3e9a5c9fb678d0a723	no	4
Warnings:					
Information:					
6	Extension of Time	EOT.pdf	22499 dfd4a6c080023c94d862fbd587ee92af45367cfe	no	1
Warnings:					
Information:					
7	Fee Worksheet (SB06)	fee-info.pdf	43036 7b904f0fd9c46f1de7328e6677bb8276e9a36203	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	442964		

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Docket No.: 50761-029001
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Utility Application of:
Jean-Claude TARDIF

Application No.: 17/097,285 | Confirmation No.: 3015

Filed: November 13, 2020 | Art Unit: 1612

For: EARLY ADMINISTRATION OF LOW-DOSE COLCHICINE AFTER MYOCARDIAL INFARCTION | Examiner: B. J. Davis

RESPONSE AFTER FINAL ACTION UNDER 37 C.F.R. § 1.116

In response to the final Office Action dated April 21, 2021, further to the Notice of Appeal filed October 21, 2021, and in connection with the concurrently filed request for continued examination, Applicant provides the following remarks.

AMENDMENTS TO THE CLAIMS

1. (Currently Amended) A method of treating a patient after having a myocardial infarction (MI), the method comprising initiating the administration of colchicine at a daily low dose to the patient within about 3 days of the MI, wherein the colchicine is administered without pre-loading the patient with a higher dose of colchicine before the administration at the daily low dose, wherein percutaneous coronary intervention was performed for treating the patient's MI.

2. (Cancelled)

3. (Original) The method according to claim 1, wherein the patient was prescribed a medication.

4. (Original) The method according to claim 3, wherein the medication is an antiplatelet agent.

5. (Original) The method according to claim 3, wherein the medication is aspirin.

6. (Original) The method according to claim 3, wherein the medication is a statin.

7. (Original) The method according to claim 1, wherein the patient is at a lower risk of a cardiovascular event, relative to a patient not being administered colchicine.

8. (Original) The method according to claim 7, wherein the cardiovascular event is an ischemic cardiovascular event.

9. (Currently Amended) A method of treating a patient after having a myocardial infarction (MI), the method comprising initiating the administration of colchicine at a daily low dose to the patient within about 3 days of the MI, wherein the colchicine is administered without pre-loading the patient with a higher dose of colchicine before the administration at the daily low dose, wherein the patient is at a lower risk of a cardiovascular event, relative to a patient not being administered colchicine, and ~~The method according to claim 7,~~ wherein the cardiovascular event is resuscitated cardiac arrest, stroke, or urgent hospitalization for angina requiring coronary revascularization.

10. (Original) The method according to claim 7, wherein the cardiovascular event is myocardial infarction.

11. (Currently Amended) The method according to ~~claim 7~~ claim 9, wherein the cardiovascular event is stroke.

12. (Currently Amended) The method according to ~~claim 7~~ claim 9, wherein the cardiovascular event is urgent hospitalization for angina requiring coronary revascularization.

13. (Original) The method according to claim 1, wherein the patient has atherosclerotic coronary artery disease.

14. (Original) The method according to claim 1, wherein the administration of colchicine is initiated upon assessment in (a) an emergency department (ED), (b) the hospital, or (c) a medical office setting.

15. (Original) The method according to claim 1, wherein the colchicine is in the form of a tablet.

16. (Original) The method of claim 15, wherein the tablet is coated.

17. (Original) The method of claim 16, wherein the tablet is film-coated.

18. (Original) The method according to claim 1, wherein the colchicine is administered at 0.3 to 0.7 mg.

19. (Original) The method according to claim 18, wherein the colchicine is administered at 0.4 to 0.6 mg

20. (Previously Presented) The method according to claim 19, wherein the colchicine is administered at 0.5 mg.

21. (Original) The method according to claim 9, wherein the colchicine is administered at 0.5 mg.

22. (Original) The method according to claim 10, wherein the colchicine is administered at 0.5 mg.

23. (Original) The method according to claim 11, wherein the colchicine is administered at 0.5 mg.

24. (Original) The method according to claim 12, wherein the colchicine is administered at 0.5 mg.

25. (Original) The method according to claim 1, wherein the colchicine is administered once, twice or three times a day.

26. (Original) The method according to claim 25, wherein the colchicine is administered once per day.

27. (Cancelled)

28. (Original) The method according to claim 1, wherein the patient is an adult human.

29. (Original) A method of reducing the risk of a stroke in a patient after having an MI, the method comprising initiating the administration of colchicine at a daily low dose to the patient within about 30 days of an MI.

30. (Original) The method according to claim 29, wherein the method comprises administering colchicine within 4 to 7 days of the MI.

31. (New) The method according to claim 29, wherein the patient was prescribed a medication.

32. (New) The method according to claim 31, wherein the medication is an antiplatelet agent.

33. (New) The method according to claim 31, wherein the medication is aspirin.

34. (New) The method according to claim 31, wherein the medication is a statin.

35. (New) The method according to claim 29, wherein the patient has atherosclerotic coronary artery disease.

36. (New) The method according to claim 29, wherein the colchicine is administered at 0.5 mg.

37. (New) The method according to claim 29, wherein the colchicine is administered once per day.

38. (New) The method according to claim 29, wherein the administration of colchicine is initiated upon assessment in (a) an emergency department (ED), (b) the hospital, or (c) a medical office setting.

39. (New) The method according to claim 29, wherein the colchicine is in the form of a coated tablet.

40. (New) The method of claim 39, wherein the tablet is film-coated.

41. (New) The method of claim 29, wherein the patient is an adult human.

42. (New) The method according to claim 9, wherein the patient was prescribed a medication.

43. (New) The method according to claim 42, wherein the medication is an antiplatelet agent.

44. (New) The method according to claim 42, wherein the medication is aspirin.

45. (New) The method according to claim 42, wherein the medication is a statin.

46. (New) The method according to claim 9, wherein the patient has atherosclerotic coronary artery disease.

47. (New) The method according to claim 9, wherein the colchicine is administered once per day.

48. (New) The method according to claim 9, wherein the administration of colchicine is initiated upon assessment in (a) an emergency department (ED), (b) the hospital, or (c) a medical office setting.

49. (New) The method according to claim 9, wherein the colchicine is in the form of a coated tablet.

50. (New) The method of claim 49, wherein the tablet is film-coated.

51. (New) The method of claim 9, wherein the patient is an adult human.

52. (New) The method of claim 9, wherein the cardiovascular event is resuscitated cardiac arrest.

REMARKS

Prior to entry of the present amendment, claims 1-26 and 28-30 are pending. Claims 29 and 30 are allowed. Claims 2, 9, 11, 12, 21, 23, and 24 are objected to. Claims 1, 3-8, 10, 14, 18, 19, 22, 25, 26 and 28 are rejected under 35 U.S.C. § 102(a)(1). Claims 13, 15-17, and 20 are rejected under 35 U.S.C. § 103. Applicant addresses each basis for rejection as follows.

Amendments to the claims

Claim 1 has been amended to incorporate the features of previously pending claim 2. In view of the amendment to claim 1, claim 2 has been cancelled.

Claim 9 has been rewritten in independent form and now recites the features of amended claim 1 and of claims 11 and 12. In view of this amendment, the dependencies of claims 11 and 12 have been amended.

New claims 31-52 have been added. These new claims find support, for example, in original claims 3-6, 9, 13-17, 26, and 28.

No new matter has been added by the present amendments. Applicant reserves the right to pursue any cancelled subject matter in this or a continuing application.

Allowable subject matter

The Office indicates that claim 29 and 30 are allowable. Claims 2, 9, 11, 12, 21, 23, and 24 are "objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims" (Office Action at page 8).

Claim 1 has been amended to incorporate the features of claim 2. As such, amended claim 1 corresponds to claim 2 rewritten in independent form.

Claim 9 has been rewritten in independent form and has been amended to include the features of claims 11 and 12. Claim 21 depends from claim 9, and claims 23 and 24 depend from claims 11 and 12, respectively.

Applicant submits that the claims, as amended, are directed to subject matter that the Office has indicated to be allowable.

Rejections under 35 U.S.C. § 102(a)(1) and 35 U.S.C. § 103

1, 3-8, 10, 14, 18, 19, 22, 25, 26 and 28 stand rejected under 35 U.S.C. § 102(a)(1) as being anticipated by Hennessy et al. (American Heart Journal 215:62-69, 2019; "Hennessy"). Claims 13, 15-17, and 20 stand rejected under 35 U.S.C. § 103 as being unpatentable over Hennessy. As indicated above, the

claims have been amended to be directed to subject matter that the Office has indicated to be free of the cited art. These bases for rejection may be withdrawn.

CONCLUSION

Applicant submits that the claims are in condition for allowance, and such action is respectfully requested.

Please apply any charges or credits to Deposit Account No. 03-2095.

Dated: March 21, 2022

Respectfully submitted,

/Jan N. Tittel/
Jan N. Tittel, Ph.D.
Registration No.: 52,290
CLARK & ELBING LLP
101 Federal Street
15th Floor
Boston, MA 02110
(617) 428-0200

PTO/SB/06 (09-11)
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 17/097,285	Filing Date 11/13/2020	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $100 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $480 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	03/21/2022	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 50	Minus	** 30	= 20		x $100 =	2000
	Independent (37 CFR 1.16(h))	* 3	Minus	*** 3	= 0		x $480 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	2000

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/TINA J BARDEN/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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NOTICE OF ALLOWANCE AND FEE(S) DUE

21559 7590 04/05/2022

CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER
DAVIS, BRIAN J

ART UNIT	PAPER NUMBER
1612	

DATE MAILED: 04/05/2022

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/097,285	11/13/2020	Jean-Claude TARDIF	50761-029001	3015

TITLE OF INVENTION: EARLY ADMINISTRATION OF LOW-DOSE COLCHICINE AFTER MYOCARDIAL INFARCTION

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	07/05/2022

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

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P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

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CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

21559 7590 04/05/2022
CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/097,285	11/13/2020	Jean-Claude TARDIF	50761-029001	3015

TITLE OF INVENTION: EARLY ADMINISTRATION OF LOW-DOSE COLCHICINE AFTER MYOCARDIAL INFARCTION

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	07/05/2022

EXAMINER	ART UNIT	CLASS-SUBCLASS
DAVIS, BRIAN J	1612	424-474000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑Issue Fee ❑Publication Fee (if required) ❑Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

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21559 7590 04/05/2022

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BOSTON, MA 02110

EXAMINER	
DAVIS, BRIAN J	

ART UNIT	PAPER NUMBER
1612	

DATE MAILED: 04/05/2022

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.