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Colchicine in Acute Myocardial Infarction - the CLEAR Trial

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Abstract

Background: Inflammation is associated with cardiovascular events. Colchicine appears to be a promising agent in reducing events based on recent trials.

Methods: Using a 2-by-2 factorial design at 104 centers in 14 countries, we randomly assigned 7,062 patients post myocardial infarction to receive either colchicine or placebo and spironolactone or placebo. The results of the colchicine trial are reported here. The primary outcome was the composite of cardiovascular death, myocardial infarction, stroke or unplanned ischemia-driven coronary revascularization.

Results: Out of 7,062 participants, only 45 (0.6%) had an unknown vital status, which is likely missing at random. The primary outcome occurred in 322 of 3528 patients (9.1%) in the colchicine group and 327 of 3534 patients (9.3%) in the placebo group over a median follow-up of three years (hazard ratio 0.99; 95% confidence interval (CI) 0.85-1.16, p=0.93). The individual components of the primary outcome were similar between the two arms. As expected, colchicine reduced C reactive protein levels significantly. Regarding adverse events, diarrhea was increased with colchicine versus placebo (10.2% vs. 6.6%, p<0.001) but serious infections were not.

Conclusion: In patients post myocardial infarction, colchicine, when started early and continued for a median of 3 years, did not reduce the composite of CV death, MI, stroke or unplanned ischemia-driven coronary revascularization.

Trial registration: ClinicalTrials.gov number NCT03048825

Inflammation is thought to be an important mechanism for atherosclerosis in both the acute and chronic phases. Increased inflammatory markers are associated with a worse prognosis in acute coronary syndromes.[1] Canakinumab, an interleukin 1β inhibitor, showed a reduction in ischemic events in patients with previous myocardial infarction but increased fatal infections.[2] Therefore, more data about the effect of anti-inflammatory agents on cardiovascular events is needed.

Colchicine inhibits neutrophils and the release of inflammatory chemokines, including interleukin 1 and 6.[3] A trial of 4745 patients where colchicine was initiated within 30 days of a myocardial infarction and a trial of 5522 patients with stable coronary artery disease reported beneficial cardiovascular effects of colchicine, whereas 2 recent trials in patients with ischemic stroke (n=8343, n=3154) reported no reductions in cardiovascular events with colchicine with the caveat that one trial was a short term treatment trial (3 months).[4-7]

The European Society of Cardiology has recently provided a class IIa recommendation for colchicine in patients with atherosclerotic coronary artery disease.[8] However, colchicine's use in such patients is low. Given the biological rationale and encouraging evidence, we conducted the CLEAR trial to provide examine the effect of colchicine in post-myocardial infarction patients.

Methods

Study Design

The CLEAR trial was an international, investigator-initiated, multicenter, prospective randomized placebo-controlled 2x2 factorial design trial of colchicine versus placebo and spironolactone versus placebo in patients with acute myocardial infarction. We previously published information on the trial design.[9] All participants, investigators, healthcare providers, data collectors and outcome adjudicators were blinded to treatment allocation. A stent registry for SYNERGY stents in ST-elevation myocardial infarction (STEMI) was embedded within the trial (N=733) and has been published.[10]

Initially, patients were only eligible if they had STEMI and underwent percutaneous coronary intervention (PCI). To increase recruitment rates, the steering committee modified the protocol on April 5, 2020, to enroll patients with large non-ST-elevation myocardial infarction (NSTEMI) who had PCI plus one or more of the following risk criteria: (1) left ventricular ejection fraction ≤45%, (2) diabetes mellitus, (3) multivessel coronary artery disease defined as a ≥50% stenosis in a second major epicardial vessel, (4) prior myocardial infarction, or (5) age >60 years. The detailed eligibility criteria are provided in Table S1.

Ethics committees of participating centers and national regulatory authorities approved the trial. All patients provided written informed consent. The Population Health Research Institute at McMaster University and Hamilton Health Sciences in Hamilton, Canada, coordinated the trial, collected and held all trial

data, and RM and SFL conducted all analyses. The steering committee designed the trial protocol and vouched for the integrity and completeness of data and analyses. SJ wrote the paper with input of co-authors and the steering committee decided to publish paper. The trial funders had no role in the design and conduct of the trial. An independent Data and Safety Monitoring Committee monitored the accumulating safety and efficacy data.

Randomization

Patients were randomized in a factorial 1:1:1:1 allocation to receive colchicine/spironolactone, colchicine/spironolactone placebo, colchicine placebo/spironolactone or colchicine placebo/spironolactone placebo, as soon as possible after the index PCI. Randomization was performed using permuted blocks within a 24-hour computerized central system at the Population Health Research Institute. Randomization was stratified by study center and whether the patient had a STEMI or NSTEMI.

Outcomes

The primary efficacy outcome was the time-to-first occurrence of cardiovascular death, myocardial infarction, stroke or ischemia-driven revascularization. Key secondary outcomes were 1) time-to-first occurrence of cardiovascular death, myocardial infarction, or stroke, and 2) total events for cardiovascular death, myocardial infarction, stroke, or ischemia-driven

revascularization. Please see table S2 for detailed outcome definitions and table S3 for a full list of outcomes.

A committee of clinicians blinded to the treatment allocation adjudicated all the primary outcome events, major bleeding, and stent thromboses. A blinded angiographic core laboratory at the Population Health Research Institute reviewed all ischemia-driven revascularizations and stent thromboses. The detailed definitions of outcomes are available in the supplementary appendix (Table S2).

Trial interventions

Study drugs were colchicine tablets of 0.5 mg and spironolactone tablets of 25 mg or matching placebos. Tiofarma, Netherlands, provided both study drugs with raw materials produced by Indena S.p.A., Milan, Italy. At the beginning of the trial, colchicine dosage was weight-based for the first 90 days, with patients weighing ≥70 kg receiving twice-a-day dosing and patients <70 kg receiving once-a-day dosing. Subsequently, everyone received once-daily dosing. However, after blinded interim analyses showing higher than expected discontinuation rates and the COLCOT trial showing efficacy with the once-daily colchicine, the steering committee adopted the once-daily colchicine 0.5 mg throughout the treatment period starting in September 2020.[4]

Statistical Considerations

The initial sample size calculation for cardiovascular death, recurrent myocardial infarction or stroke was based on a time-to-event analysis with an anticipated control event rate of 15% at three years, 80% power, a 2-sided type 1 error level of 5%, a 2% loss to follow-up in both arms, study drug discontinuation of 12.5%, and the assumption of no interaction with spironolactone. Based on the above assumptions, it was estimated that 4,000 participants (an expected 512 events) were needed to detect a 25% relative risk reduction using a log-rank test. In April 2020, an interim analysis of blinded event rates demonstrated a 3% per year event rate and so estimated an event rate of 9% at years which was consistent with several recent trials.[4] As a result, the sample size was increased from 4,000 to 7,000 patients to maintain study power of 80%, with an estimated 546 events needed to detect a 25% relative risk reduction. The sample size was increased without knowledge of any treatment effects.

For the primary analysis, patients were evaluated according to the groups in which they were randomized. A two-sided, log-rank test was used to compare the two randomized groups. A p-value of less than 0.05 was considered significant. The hazard ratio and 95% confidence interval were estimated using a Cox proportional hazards regression model with the treatment group as the independent variable stratifying by spironolactone or placebo and STEMI or NSTEMI. The Fine-Gray subdistribution hazard model was used to account for competing risks of non cardiovascular death in the composite outcome and cardiovascular death, cardiovascular death for non cardiovascular death and all

cause mortality for other outcomes. The total event was analyzed using Prentice, William, Peterson (PWP model with the gap time and the Lin Wei Yang Ying (LWYY) model. Secondary outcomes were analyzed using the same approach. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals may not be used in place of hypothesis testing. An interaction between factorial treatment groups is not expected but will be tested at 5% significance level.

Subgroup Analyses

The pre-specified subgroups were analyzed using the Cox regression model with an interaction term for the subgroup. The pre-specified subgroups were i) age ≥65 versus <65 years (consistent effect), ii) female versus male (consistent effect), iii) diabetes versus no diabetes (greater benefit in diabetes), iv) multivessel versus single vessel disease (greater benefit in multivessel disease), v) STEMI versus NSTEMI (consistent effect), vi) estimated glomerular filtration (GFR) rate ≥60 versus <60 mL/min/1.73m^2 (consistent effect), vii) weight-based dosing initially used in the trial with three groups: a) once daily colchicine <70 kg, b) twice daily colchicine ≥70 kg, and c) once daily colchicine ≥70 kg (greater benefit with higher dose) and viii) Pre, during and post Covid pandemic phases (reduced effect during Covid pandemic). Geographic region (North America versus Europe versus Other) was added as a post hoc subgroup to demonstrate consistency.

Sensitivity analyses

We undertook on-treatment analyses excluding patients who discontinued the study drug on the same day of randomization and censored patients seven days after permanent study drug discontinuation.

C reactive protein was not mandated but measurements as a part of clinical care were collected on case report forms. The C reactive protein values were analyzed using a linear mixed model with repeated measures, adjusted for the baseline value, and the mean difference (MD) was reported.

Results

Between February 1, 2018, and November 8, 2022, 7062 participants were enrolled from 104 centers in 14 countries. Of these, 3528 were randomized to colchicine and 3534 to placebo. Out of 7,062 participants, only 45 (0.6%) had an unknown vital status, with two having experienced the primary outcome. The remaining 43 participants had no recorded outcome or final visit, and their vital status was unknown (missing). Given that the missing data was rare and evenly distributed between the colchicine and placebo groups (table S4), the missingness is likely to be at random.

Baseline characteristics were well balanced between the groups, with the overall mean age being 61 years and 20.4% of patients being female (Table 1). Approximately 9% had prior myocardial infarction, 10% had prior PCI, and 19%

had diabetes mellitus. Most patients randomized had STEMI (95%), and 5% of patients had NSTEMI.

The median time from symptom onset to randomization was 26.8 hours (interquartile range [IQR], 15.9 – 42.4), and the median time from randomization to the first dose of study drug was 1.6 hours (IQR, 0.6 – 7.4). The discharge medications were similar in both groups (Table 1).

The median duration of therapy was three years (IQR, 2.14 – 3.71), and the drug was discontinued in 25.9% of patients allocated to colchicine and 25.5% to placebo.

C Reactive Protein

The least square mean (standard error) of CRP at 3 months, adjusted for baseline, was 2.98 (0.19) mg/L in 1,384 patients randomized to Colchicine and 4.27 (0.19) mg/L in 1,419 patients randomized to Placebo, with a MD of -1.28 (-1.81, -0.75) mg/L.

Efficacy

The primary outcome occurred in 322 of 3528 patients (9.1%) in the colchicine group compared with 327 of 3524 patients (9.3%) in the placebo group (hazard ratio [HR], 0.99; 95% CI 0.85-1.16; P=0.93) (Table 2, Figure 2) with median treatment durations of 1089 days (2.98 years) for colchicine and 1090 days (2.98 years) for placebo. The spironolactone factorial had no significant effect on the results of the comparison of colchicine versus placebo for the primary outcome (P=0.96 for interaction). The composite of cardiovascular death,

myocardial infarction, or stroke occurred in 241 patients (6.8%) in the colchicine group and 250 patients (7.1%) in the placebo group (HR, 0.98; 95% CI 0.82-1.17). The total event analysis (including recurrent events) for the primary outcome was 376 events (3.53% per year) in the colchicine group vs. 389 events (3.67% per year) in the placebo group (HR, 0.98; 95% CI 0.85-1.13) for both PWP and LWYY models with median treatment durations of 1078 days (2.95 years) for colchicine and 1092 days (2.99 years) for placebo.

Cardiovascular mortality was similar (3.3% colchicine versus 3.2% placebo; HR, 1.03; 95% CI 0.80-1.34) as were the other components of the primary and secondary outcomes (Table 2). Non-cardiovascular death occurred in 45 (1.3%) of the colchicine group compared to 66 (1.9%) in the placebo group (HR, 0.68; 95% CI 0.46-0.99).

The on-treatment analyses were consistent with the primary analysis and are presented in the supplementary online appendix (Table S5). The primary outcome was consistent across all pre-specified subgroups except for lower events in patients ≥70 kg who received twice-daily colchicine for the first three months (figure 3). The results were similar during the different COVID-19 pandemic phases.

Safety

The rate of serious adverse events and adverse events were not different between groups (Table 3). More colchicine patients (n=361; 10.2%) had diarrhea compared to placebo patients (n=233; 6.6%), p<0.001. There was no difference in serious infection with colchicine vs. placebo.

DISCUSSION

Despite lowering C reactive protein levels, colchicine, given for a median of 3 years, did not reduce the primary outcome of cardiovascular death, myocardial infarction, stroke, or unplanned ischemia-driven coronary revascularization or any of its individual components in patients after myocardial infarction. As expected, colchicine increased the rate of diarrhea compared to placebo.

The most comparable trial to CLEAR is the COLCOT trial (N=4,745), which randomized patients within 30 days of an acute myocardial infarction to colchicine 0.5 mg daily or placebo, and with 301 primary events reported colchicine had a 23% relative reduction in cardiovascular death, myocardial infarction, resuscitated cardiac arrest, stroke, or urgent hospitalization for angina requiring revascularization.[4] The LODOCO 2 trial randomized patients with stable coronary artery disease to colchicine 0.5 mg daily or placebo and with 451 primary events reported colchicine had a 31% relative reduction in the primary outcome of cardiovascular death, myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization.[5] The largest trial with colchicine, CHANCE 3

(N=8,345), randomized patients with minor-to-moderate stroke or transient ischemic attack to colchicine 0.5 mg twice daily on days 1-3 and 0.5 mg daily on days 4 to 90 or placebo, and with 534 primary events demonstrated colchicine had no effect on stroke (HR, 0.98; 95% CI, 0.83-1.16) or the secondary outcome (n=607 events) of cardiovascular death, myocardial infarction, transient ischemic attack, or stroke (HR 0.96; 95% CI 0.82-1.13).[7] The caveat is that this trial was a short term treatment trial and so colchicine may not have enough time to have a treatment effect. The CONVINCE trial randomized 3154 patients with an ischemic stroke to colchicine 0.5 mg daily or usual care for a median of 34 months, and with 338 primary events reported no effect of colchicine on the primary outcome of ischemic stroke, myocardial infarction, cardiac arrest, hospitalization for unstable angina, or vascular death (HR 0.84; 95% CI, 0.68-1.05).[6]

The CLEAR trial is the largest trial in patients with coronary artery disease, with 649 primary outcome events, which is significantly more outcome events than prior trials in those with coronary artery disease. An analysis of trials showed that those with more than 600 outcome events rarely showed spurious results disproven by subsequent trials.[11] Our on-treatment analysis was consistent with our intention-to-treat analysis, suggesting our findings are robust. Furthermore, we did not find significant interaction by our subgroup analyses related to the COVID-19 pandemic, making it unlikely that we missed a treatment effect due to the pandemic. Lastly, the effects estimates were consistent throughout all the individual components and on-treatment analysis. Finally, the increase in diarrhea

and reduction in C reactive protein were as expected and support the biologic effects of colchicine in this trial.

While the reasons for the divergent results with the older data are not immediately evident, the three latest trials, CLEAR, CHANCE and CONVINCE, involve more than twice the number of events (approximately 1500 events) and likely provide the most robust evidence to date of the effects of colchicine in patients with vascular disease.

Recent meta-analyses have reported a nominal excess in non-cardiovascular death with colchicine.[12] We found the exact opposite, with a lower rate of non-cardiovascular death with colchicine versus placebo, suggesting there is likely no effect on non-cardiovascular death.

The COLCOT trial showed an excess of pneumonia, while LODOCO 2 did not show any increased infection[4,5]. We found no excess in serious infection with colchicine compared to placebo.

In 2024, The European Society of Cardiology upgraded its recommendation for colchicine from class IIb to class IIa for patients with atherosclerotic coronary artery disease; however, this change was made before the current data were available.[8] Similarly, the United States Food and Drug Administration had approved colchicine to treat coronary artery disease prior to the current data.

Canakinumab, an IL-1β inhibitor, showed a 15% reduction in ischemic events in patients post-MI in the CANTOS trial (N=10 061).[2] Whereas a trial of

4786 patients who had a myocardial infarction or multivessel coronary artery disease demonstrated no benefit of methotrexate on the primary outcome (n=408 events), a composite of cardiovascular death and nonfatal myocardial infarction, stroke, and hospitalization for unstable angina that led to urgent revascularization; HR 0.96; 95% CI, 0.79-1.16 with the caveat that methotrexate did not reduce inflammatory markers. The ongoing ARTEMIS trial of 10,000 patients is evaluating the effects of ziltivekimab versus placebo in patients with acute myocardial infarction on the primary outcome of cardiovascular death, myocardial infarction, or stroke. The divergent results of the trials of canakinumab, methotrexate and colchicine highlight the need for large trials that target different parts of the inflammatory pathways.

Limitations

First, based on the 95% CI of the primary outcome results, we cannot exclude a benefit of 15% or smaller, that could be clinically important. Second, women and visible minorities were underrepresented in the trial compared to the incidence of disease worldwide. Third, our 25% discontinuation rate was higher than anticipated; however, our on-treatment sensitivity analyses demonstrated consistent results to our primary analyses. Fourth, we do not have sufficient power to rule out a treatment effect for twice-daily colchicine, and this hypothesis would need to be tested in future clinical trials. Fifth, only patient reported compliance

was used as pill counts were not possible during the pandemic. Sixth, gout was not collected as an outcome in the trial.

In conclusion, in patients post myocardial infarction, colchicine started early and continued for a median of 3 years, did not reduce cardiovascular death, myocardial infarction, stroke or unplanned ischemia-driven revascularization but was associated with an increase in diarrhea.

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Table 1. Baseline and procedural characteristics

	Colchicine N=3528		Placebo N=3534	
Demographics				
Age, years (mean ±SD)	60.6	±10.3	60.7	±10.3
Age > 75 yr (%)	301	(8.5)	270	(7.6)
Female (%)	725	(20.5)	713	(20.2)
Race or ethnic group (%)				
American Indian or Alaskan Native	7	(0.2)	3	(0.1)
Asian	95	(2.7)	89	(2.5)
Black or African American	24	(0.7)	23	(0.7)
Native Hawaiian or Other Pacific Islander	9	(0.3)	9	(0.3)
White	3233	(91.6)	3249	(91.9)
Other	153	(4.3)	159	(4.5)
Geographic Region				
North America	1010	(28.6)	1012	(28.6)
Europe	2356	(66.8)	2359	(66.8)
Other	162	(4.6)	163	(4.6)
Killip ≥2 Heart failure at randomization (%)	25	(0.7)	24	(0.7)
NSTEMI at presentation	165	(4.7)	184	(5.2)
STEMI at presentation	3363	(95.3)	3350	(94.8)
Location of STEMI				
Anterior (%)	1304	(38.8)	1326	(39.6)
Inferior (%)	1940	(57.7)	1892	(56.5)

Lateral (%)	423	(12.6)	434	(13.0)
Posterior (%)	341	(10.1)	319	(9.5)
History				
Current smoker (%)	1461	(41.4)	1423	(40.3)
Hypertension (%)	1620	(45.9)	1613	(45.6)
Diabetes Mellitus (%)	658	(18.7)	645	(18.3)
Prior myocardial infarction (%)	309	(8.8)	324	(9.2)
Prior percutaneous coronary intervention (%)	345	(9.8)	364	(10.3)
Medications at discharge				
Aspirin	3428	(97.2)	3405	(96.3)
Clopidogrel	1478	(41.9)	1497	(42.4)
Ticagrelor	1611	(45.7)	1571	(44.5)
Prasugrel	381	(10.8)	413	(11.7)
ACE or ARB	2750	(77.9)	2768	(78.3)
Statin	3408	(96.6)	3416	(96.7)
SGLT2 inhibitor	110	(3.1)	101	(2.9)
Initial PCI procedure				
Bare-metal stent*	12	(0.3)	8	(0.2)
≥1 drug-eluting stent*	4619	(96.3)	4694	(95.8)
Angioplasty only*	146	(3.0)	165	(3.4)
Number of stents* Median (IQR)	1.0	(1.0-2.0)	1.0	(1.0-2.0)
Total stent length* mm Mean (SD)	23.8	(8.6)	23.8	(8.8)
Stent diameter* mm Mean (SD)	3.2	(0.5)	3.1	(0.5)
Multivessel coronary disease	1735	(49.2)	1742	(49.3)

Coronary artery bypass grafting (%)	137	(2.7)	139	(2.8)
Intra-aortic balloon pump (%)	45	(1.3)	49	(1.4)

***Total number of stents 9695 with 4797 for Colchicine vs. 4898 for Placebo.**

Table 2: Primary and Secondary Outcomes

	Colchicine (n=3528) (%)	**Placebo (n=3534) (%)**	**Hazard Ratio**	**95% CI**	**P Value**
Primary outcome					
CV death, MI, stroke or ischemia driven coronary revascularization	322 (9.1%)	327 (9.3%)	0.99	0.85-1.16	0.93
Components of primary outcome					
CV death	117 (3.3%)	113 (3.2%)	1.03	0.80-1.34	
Recurrent MI	102 (2.9%)	111 (3.1%)	0.88	0.66-1.17	
Stroke	50 (1.4%)	43 (1.2%)	1.15	0.72-1.84	
Ischemia driven coronary revascularization	164 (4.6%)	166 (4.7%)	1.01	0.81-1.17	
Other outcomes					
CV death, MI or stroke	241 (6.8)	250 (7.1)	0.98	0.82-1.17	
All cause death	162 (4.6%)	179 (5.1%)	0.90	0.73-1.12	
Non CV death	45 (1.3%)	66 (1.9%)	0.68	0.46-0.99	
Pericarditis	33 (0.9%)	22 (0.6%)	1.53	0.88-2.65	

Atrial Fibrillation	91 (2.6%)	89 (2.5%)	0.98	0.72-1.33	

* widths of the intervals have not been adjusted for multiplicity and that the intervals may not be used in place of hypothesis testing

Table 3: Adverse Events

	Colchicine (n=3528) (%)	Placebo (n=3534) (%)	P value
Serious Adverse Events	235 (6.7)	261 (7.4)	0.22
Gastrointestinal serious adverse event	35 (1.0)	33 (0.9)	0.81
Hematologic* serious adverse event	0(0)	8(0.2)	0.005
Serious infection	87 (2.5%)	101 (2.9%)	0.85
Adverse Events	1124 (31.9)	1119 (31.7)	0.86
Diarrhea	361 (10.2)	233 (6.6)	<0.001

*3 anemia, 2 Febrile neutropenia, 3 pancytopenia and 2 thrombocytopenia

Figure Legends

Figure 1: Flow chart of the CLEAR trial

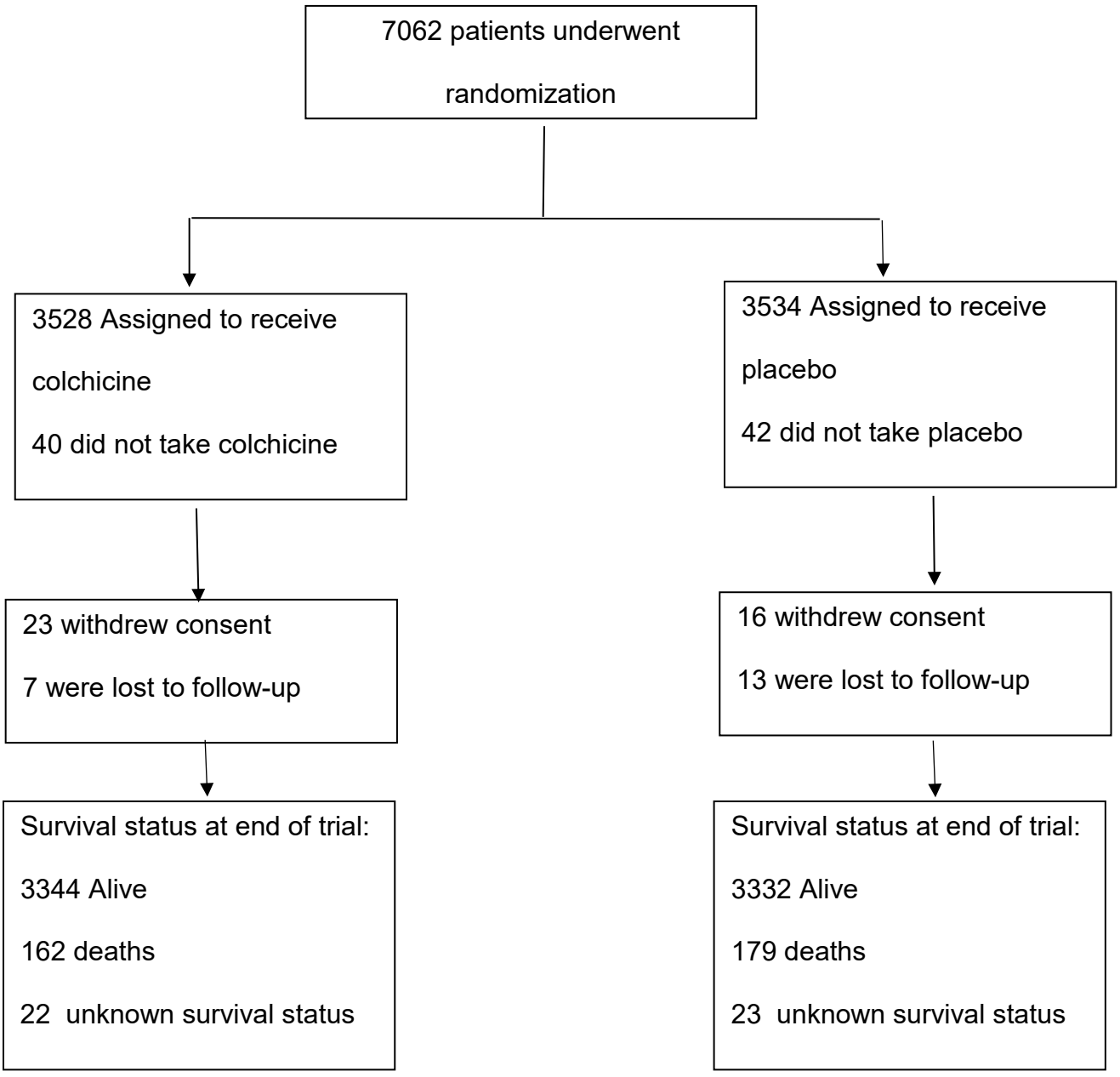
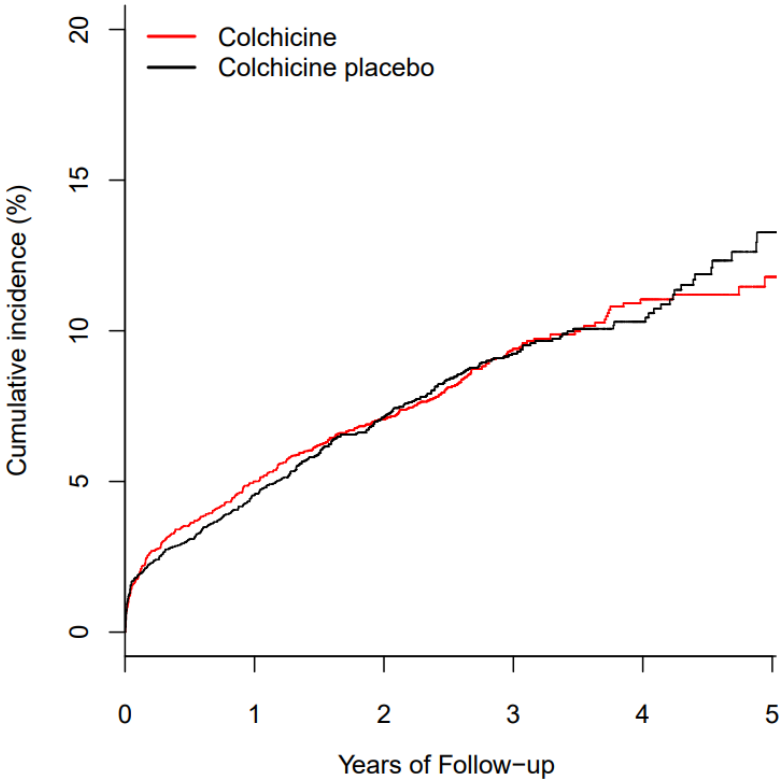
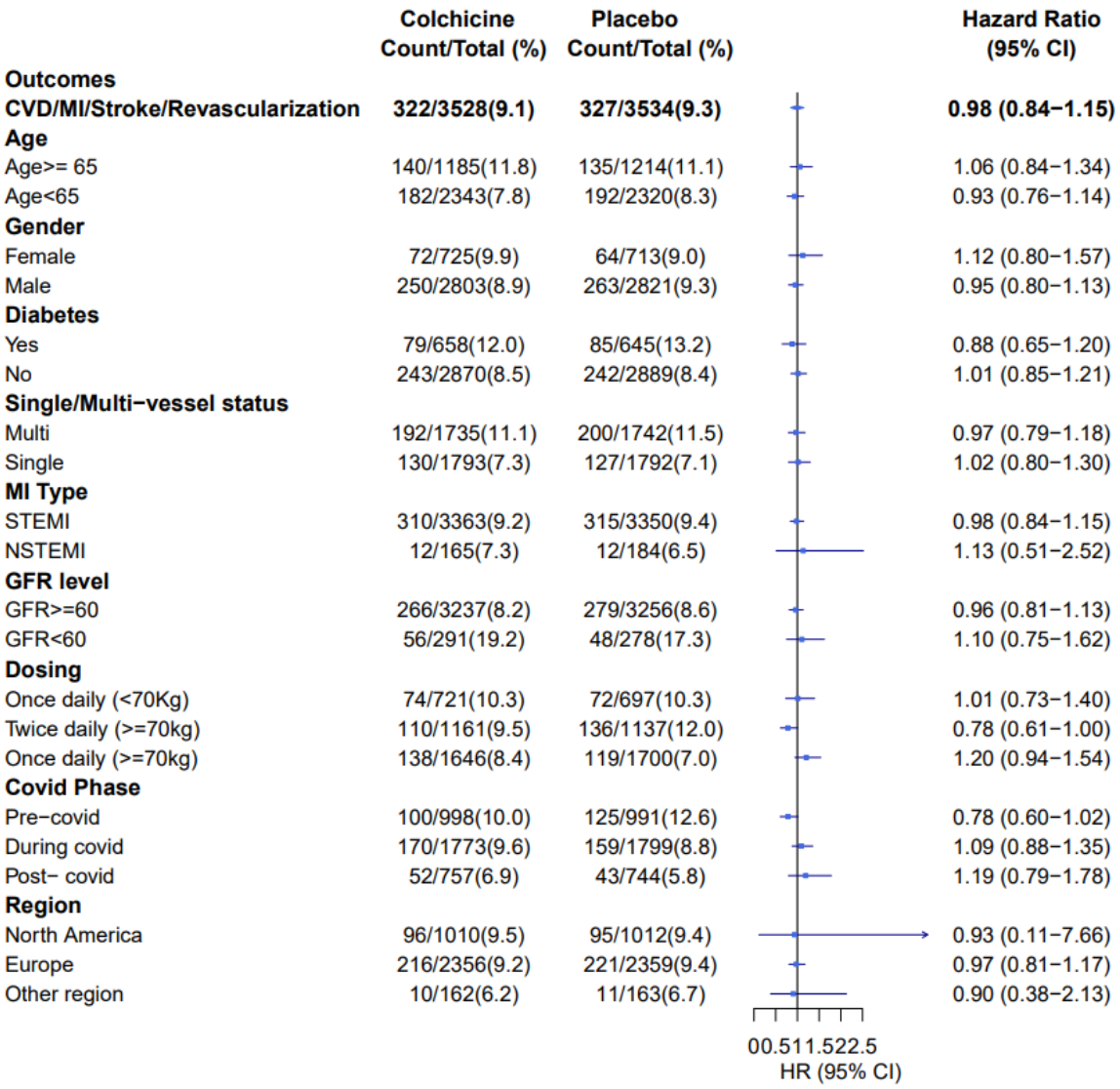


Figure 2: Kaplan Meier event curves for CV death, MI, stroke or ischemia-driven revascularization



No. at Risk						
Colchicine	3528	3329	2688	1686	697	183
Placebo	3534	3349	2683	1674	659	163

Figure 3: Forest plot of Primary Outcome in pre-specified subgroups



References

1. Barrett TD, Hennan JK, Marks RM, Lucchesi BR. C-reactive-protein-associated increase in myocardial infarct size after ischemia/reperfusion. The Journal of pharmacology and experimental therapeutics 2002;303(3):1007-13. (In eng). DOI: 10.1124/jpet.102.040600.
2. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. The New England journal of medicine 2017;377(12):1119-1131. (In eng). DOI: 10.1056/NEJMoa1707914.
3. Leung YY, Yao Hui LL, Kraus VB. Colchicine-Update on mechanisms of action and therapeutic uses. Seminars in arthritis and rheumatism 2015;45(3):341-50. (In eng). DOI: 10.1016/j.semarthrit.2015.06.013.
4. Tardif JC, Kouz S, Waters DD, et al. Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction. The New England journal of medicine 2019;381(26):2497-2505. (In eng). DOI: 10.1056/NEJMoa1912388.
5. Nidorf SM, Fiolet ATL, Mosterd A, et al. Colchicine in Patients with Chronic Coronary Disease. New England Journal of Medicine 2020. DOI: 10.1056/NEJMoa2021372.
6. Kelly P, Lemmens R, Weimar C, et al. Long-term colchicine for the prevention of vascular recurrent events in non-cardioembolic stroke (CONVINCE): a randomised controlled trial. The Lancet 2024;404(10448):125-133. DOI: 10.1016/S0140-6736(24)00968-1.
7. Li J, Meng X, Shi F-D, et al. Colchicine in patients with acute ischaemic stroke or transient ischaemic attack (CHANCE-3): multicentre, double blind, randomised, placebo controlled trial. BMJ 2024;385:e079061. DOI: 10.1136/bmj-2023-079061.
8. Vrints C, Andreotti F, Koskinas KC, et al. 2024 ESC Guidelines for the management of chronic coronary syndromes: Developed by the task force for the management of chronic coronary syndromes of the European Society of Cardiology (ESC) Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS). European heart journal 2024. DOI: 10.1093/eurheartj/ehae177.
9. d'Entremont MA, Lee SF, Mian R, et al. Design and rationale of the CLEAR SYNERGY (OASIS 9) trial: A 2x2 factorial randomized controlled trial of colchicine versus placebo and spironolactone vs placebo in patients with myocardial infarction. American heart journal 2024;275:173-182. (In eng). DOI: 10.1016/j.ahj.2024.06.007.
10. Jolly SS, Lee SF, Mian R, et al. SYNERGY-Everolimus-Eluting Stent With a Bioabsorbable Polymer in ST-Elevation Myocardial Infarction: CLEAR SYNERGY OASIS-9 Registry. The American journal of cardiology 2024;220:111-117. (In eng). DOI: 10.1016/j.amjcard.2024.02.021.

11. Montori VM, Devereaux PJ, Adhikari NKJ, et al. Randomized Trials Stopped Early for BenefitA Systematic Review. JAMA 2005;294(17):2203-2209. DOI: 10.1001/jama.294.17.2203.
12. Fiolet ATL, Opstal TSJ, Mosterd A, et al. Efficacy and safety of low-dose colchicine in patients with coronary disease: a systematic review and meta-analysis of randomized trials. European heart journal 2021;42(28):2765-2775. (In eng). DOI: 10.1093/eurheartj/ehab115.