Low-dose colchicine for the prevention of cardiovascular events after percutaneous coronary intervention: rationale and design of the COL BE PCI trial

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ABSTRACT

Introduction Patients with coronary artery disease (CAD) remain vulnerable to future major atherosclerotic events after revascularization, despite effective secondary prevention strategies. Inflammation plays a central role in the pathogenesis of CAD and recurrent events. To date, there is no specific anti-inflammatory medicine available with proven effective, cost-efficient, and favorable benefit-risk profile, except for colchicine. Initial studies with colchicine have sparked major interest in targeting atherosclerotic events with anti-inflammatory agents, but further studies are warranted to enforce the role of colchicine role as a major treatment pillar in CAD. Given colchicine's low cost and established acceptable long-term safety profile, confirming its efficacy through a pragmatic trial holds the potential to significantly impact the global burden of cardiovascular disease.

Methods The COL BE PCI trial is an investigator-initiated, multicenter, double-blind, event-driven trial. It will enroll 2,770 patients with chronic or acute CAD treated with percutaneous coronary intervention (PCI) at 19 sites in Belgium, applying lenient in- and exclusion criteria and including at least 30% female participants. Patients will be randomized between 2 hours and 5 days post-PCI to receive either colchicine 0.5 mg daily or placebo on top of contemporary optimal medical therapy and without run-in period. All patients will have baseline hsCRP measurements and a Second Manifestations of Arterial Disease (SMART) risk score calculation. The primary endpoint is the time from randomization to the first occurrence of a composite endpoint consisting of all-cause death, spontaneous non-fatal myocardial infarction, non-fatal stroke, or coronary revascularization. The trial is event-driven and will continue until 566 events have been reached, providing 80% power to

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Abbreviations: ACS, Acute coronary syndrome; CCS, Chronic coronary syndrome; EQ-5D-5L, EuroQol 5 dimensions 5-level; hsCRP, high-sensitivity C-reactive protein; PHQ-2, Patient Health Questionnaire-2; PCI, Percutaneous coronary intervention; OD, once daily; SAQ-7, Seattle Angina Questionnaire 7; SMART, Second Manifestations of Arterial Disease.

Classifications Coronary artery disease.

Short abstract rationale and design of the COL BE PCI trial, investigating low-dose colchicine for secondary prevention after PCI.

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detect a 21 % reduction in the primary endpoint taking a premature discontinuation of 15% into account. We expect a trial duration of approximately 44 months.

Conclusion The COL BE PCI Trial aims to assess the effectiveness and safety of administering low-dose colchicine for the secondary prevention in patients with both chronic and acute coronary artery disease undergoing PCI. Trial registration: ClinicalTrials.gov: NCT06095765. (Am Heart J 2024;278:61–71.)

Background

Coronary artery disease (CAD) remains a major global health concern.[1] Despite advancements in pharmacological treatment and revascularization with percutaneous coronary intervention (PCI), recurrent cardiovascular events remain frequent. In the largest and most recent study of all-comer PCI patients (the Global Leaders trial), the annual rate of recurrent cardiovascular events (the composite of death, acute coronary syndrome, stroke, or revascularization) was up to 8.6%.[2] Hence, there is an unmet clinical need to reduce recurrent events in this high-risk population.

Inflammation plays a central role in the pathogenesis of atherosclerosis and therefore in CAD.[3,4] High-sensitivity C-reactive protein (hsCRP), as a marker of inflammation, has been well-validated as an independent risk factor for future cardiovascular events.[5-8] The central role of inflammation was recently underscored in a meta-analysis in 31,245 statin-treated patients with -or at high risk of- atherosclerotic disease.[9] This meta-analysis demonstrated that the residual inflammatory risk, as measured by hsCRP, was a much stronger predictor of future cardiovascular events and death than the residual risk attributed to LDL-c levels. This implies that further risk reduction could be expected from adjunctive anti-inflammatory therapies rather than from even more potent lipid-lowering therapy. However, as of today, no specific anti-inflammatory agent has thus far been proven to be both effective[10] and cost-beneficial,[11] except for colchicine. This ancient anti-inflammatory, ubiquitously available and inexpensive drug has shown to reduce risk by 23 to 31% in patients following an acute myocardial infarction[12] as well as in patients with chronic coronary artery disease.[13] In addition to its anti-inflammatory properties, colchicine harbors pleiotropic effects by reducing the formation of prothrombotic neutrophil extracellular traps (NETS), which might be of additional benefit in the prevention of stent thrombosis.[14]

Despite 2 large positive trials, the uptake of colchicine in cardiovascular prevention has been rather limited, while the recent 2023 European Society of Cardiology (ESC) Guidelines for the Management of Acute Coronary Syndromes and the 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease provided a class IIb recommendation for this indication, in contrast to a class I indication for statins.[15,16] Additional trials are therefore warranted to reinforce the external validity of the landmark trials of colchicine in CAD. In fact, around 19% of the patients in the COLCOT trial[12] stopped their trial regimen prematurely and 2.5% were lost to follow-up. In addition, women were underrepresented in the LoDoCo2 trial[13] (only 15 % of participants). The most remarkable finding in the LoDoCo2 trial was that the efficacy in the primary endpoint was mainly driven by the Australian population (1,904 patients, hazard ratio [HR] 0.51; 95% confidence interval [CI] [0.39-0.67]), in contrast to a neutral effect in the larger Dutch population (3,618 patients, HR 0.92; 95% CI [0.71-1.20]). Whether this is related to the play of chance, the ineffectiveness of colchicine depending on local practices, different colchicine formulations, or different patient selection remains unknown. Finally, none of the largest 2 previous trials systematically assessed baseline hsCRP, which is the key marker of inflammation (see Table 1 for a comparison of the major trials).[5-9]

Taken together, additional data appears to be necessary to assess the effectiveness of colchicine and to convince the cardiovascular community to adopt this drug in secondary prevention strategies. We therefore believe there is a need for a pragmatic trial of low-dose colchicine post-PCI, without a run-in period, and including at least 30% of women. For this aim, we designed the COLchicine in BElgium in patients with coronary artery disease after Percutaneous Coronary Intervention (COL BE PCI) trial.

Methods

Study design and oversight

The COL BE PCI trial is an investigator-initiated, multicenter, event-driven, randomized, double-blinded placebo-controlled trial investigating the efficacy of colchicine 0.5 mg once daily versus placebo as an adjunctive to the optimal standard of care after PCI. Participants with CAD treated with percutaneous PCI will be included in 19 participating Belgian sites. A list of the COL BE PCI investigators and contributors is provided in Supplementary Appendix 1. The trial is preregistered on ClinicalTrials.gov (NCT06095765) and approved by the Federal Agency for Medicines and Health Products (FAMHP) and Ethical Committee according to the EU

Table 1. Adequately powered randomized double-blind placebo-controlled trials of colchicine in secondary cardiovascular prevention

Trial	COL BE PCI	COLCOT[12]	LoDoCo2[13]	CLEAR SYNERGY[25]	COLCARDIO-ACS[26]	TACTIC[27]
Identifier	NCT06095765	NCT02551094	ACTRN12614000093684	NCT03048825	ACTRN12616000400460	NCT06215989
Status	Ongoing	Completed	Completed	Ongoing	Ongoing	Not yet recruiting
Number of patients	Target 2770	4745	5522	Target 7063	Target 3000	Target 6574
Study cohort	ACS and CCS Post-PCI	MI 93.0% post-PCI	CCS and clinically stable for at least 6 months Post-PCI	MI* Post-PCI	ACS, with hsCRP ≥2 mg/L measured 4-52 weeks post-ACS	ACS
Percentage Women	At least 831 (30%)	909 (19.2%)	846 (15.3%)	NA	NA	NA
Time from index PCI to randomization	2 hours up to 5 days post PCI	Within 30 days post-MI; mean 13.4 days	NA	Within 72 hours post PCI for MI	4-52 weeks post-ACS	Within 48 hours after diagnosis of ACS
Run-in period	No	No	Yes; 1 month, 15.4% drop-out	No	Yes; 28 days	No
hsCRP measurement at baseline	Yes, in all patients	Only in 207 (4.4%)	No	NA	Yes, in all patients	NA
Exclusion criterium for kidney dysfunction	Creatinine clearance <30 mL/min/1.73 m^2	Creatinine level >2x upper limit of normal	Creatine level >1.7 mg/dL or Creatinine clearance <50 mL/min/1.73 m^2	Creatinine clearance <30 mL/min/1.73 m^2	Creatinine clearance <45 mL/min/1.73 m^2	Creatinine clearance <30 mL/min/1.73 m^2
Randomization versus placebo	1:1	1:1	1:1	1:1, 2 × 2 factorial design with spironolactone vs placebo	1:1	1:1
Colchicine dose	0.5 mg OD	0.5 mg OD	0.5 mg OD	0.5 mg OD	0.5 mg OD	0.5 mg OD
Follow up	Shortest follow up at least 2 y	Median 22.6 mo	Median 28.6 mo	Estimated average follow-up of 2 y	Target median follow-up of 3 y	1 y
Primary endpoint	All-cause death, spontaneous (nonprocedural) myocardial infarction, stroke, coronary revascularization	Cardiovascular death, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina leading to coronary revascularization.	Cardiovascular death, spontaneous (nonprocedural) myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization	All-cause death, recurrent target vessel MI, stroke, ischemia-driven target vessel revascularization	Myocardial infarction, urgent unscheduled revascularization, cardiovascular death, and nonfatal stroke	Cardiovascular death, nonfatal ischemic stroke, nonfatal spontaneous myocardial infarction, readmission for ACS, and ischemia driven (unplanned) revascularization

(continued on next page)

Table 1. (*continued*)

Trial	COL BE PCI	COLCOT[12]	LoDoCo2[13]	CLEAR SYNERGY[25]	COLCARDIO-ACS[26]	TACTIC[27]
Results on primary endpoint	NA	5.5 vs 7.1 %, HR 0.77; (95% CI 0.61-0.96; $P = .02$)	6.8 vs 9.6 %, HR 0.69; (95% CI 0.57-0.83; $P < .001$)	NA	NA	NA
Countries	Belgium (Multicentric)	Canada, Argentina, Chile, Colombia, France, Germany, Italy, Lebanon, Portugal, Spain, Tunisia, United Kingdom	Australia, The Netherlands	Canada, Colombia, Switzerland, North Macedonia, Australia, Serbia, United Kingdom, United States, Czechia, France, Hungary, Poland, The Netherlands	Australia, Chile	China (Monocentric)
Funding	Belgian Health Care Knowledge Center (KCE)	Government of Quebec, the Canadian Institutes of Health Research, and philanthropic foundations	The National Health Medical Research Council of Australia, the Sir Charles Gairdner Research Advisory Committee, the Withering Foundation the Netherlands, the Netherlands Heart Foundation, the Netherlands Organization for Health Research and Development, and a consortium of Teva, Disphar, and Tiofarma in the Netherlands.	Canadian Institutes of Health Research (CIHR), Boston Scientific Corporation	National Health and Medical Research Council (NHMRC), National Heart Foundation of Australia	NA

Abbreviations: ACS, acute coronary syndrome; CCS, chronic coronary syndrome; PCI, percutaneous coronary intervention; MI, myocardial infarction; OD, once daily; NA, not available; HR, hazard ratio; CI, confidence interval; hsCRP, high-sensitivity C-reactive protein; FU, follow up

* MI in the CLEAR SYNERGY trial: ST-segment-elevation myocardial infarction or very large non-ST-segment elevation myocardial infarction

Table 2. Inclusion and exclusion criteria of the COL BE PCI trial

Inclusion criteria.
1. Age ≥45 y.
2. Coronary artery disease (acute or chronic) treated with PCI and optimal medical therapy, with at least 1 additional risk factor:
a. Age ≥60 y
b. Diabetes mellitus, on treatment or new diagnosis with HbA1c ≥6.5%
c. Current smoking
d. Treated hypertension or blood pressure systolic ≥140 mmHg or diastolic ≥90 mmHg
e. Total cholesterol >240 mg/dL untreated, or treated LDL >70 mg/dL
f. HDL <40 mg/dL
g. hsCRP >2 mg/L AND chronic coronary syndrome
h. eGFR <60 mL/min (MDRD)
i. History of vascular disease:
• CAD (PCI prior to index, CABG, MI)
• stroke (ischemic or hemorrhagic)
• carotid artery revascularization
• PAD (revascularization, ABI <0.85 at rest, amputation due to atherosclerotic disease)
• AAA (repair, distal aortic anteroposterior diameter >3.0cm)
3. Able to be enrolled/randomized between 2 h and 5 d post PCI
4. Able to provide written informed consent.
Exclusion criteria
1. Women who are pregnant, breastfeeding, or of childbearing potential who are not using an effective method of contraception. Or women who intend to donate oocytes.
2. Men who plan to father children during the study period or who are unwilling to use effective forms of contraception. Or men who intend to donate sperm.
3. Any contraindication or known intolerance to colchicine.
4. Chronic use of -or need for- colchicine.
5. Auto-immune disease or other disease requiring current or planned chronic systemic steroids, immunosuppressant or biologic drug targeting the immune system (for example, TNF blockers, anakinra, rituximab, abatacept, tocilizumab etc.).
6. Creatinine clearance <30 mL/min/1.73 m2.
7. Cirrhosis Child-Pugh stadium B and C, or acute severe liver disease.
8. Neuromuscular disease or nontransient CK levels > 5 x ULN (unless due to MI).
9. History of cancer or lymphoproliferative disease within the last 3 y, other than successfully treated nonmetastatic cutaneous squamous cell or basal cell carcinoma, or localized cervix carcinoma in situ.
10. Current or planned use of any strong inhibitor of CYP3A4 or p-glycoprotein: macrolide antibiotics (clarithromycin, telithromycin), azole antifungal agents (ketoconazole, voriconazole, fluconazole, itraconazole), cyclosporine, HIV medication (ritonavir, lopinavir, tipranavir, atazanavir, darunavir, indinavir, saquinavir).
11. Chronic diarrhea, or inflammatory bowel disease (Crohn's disease or ulcerative colitis).
12. Drug or alcohol abuse.
13. Planned cardiovascular interventions known on the day of screening.
14. Currently enrolled in another investigational trial.
15. Considered to be an unsuitable candidate by the investigator.

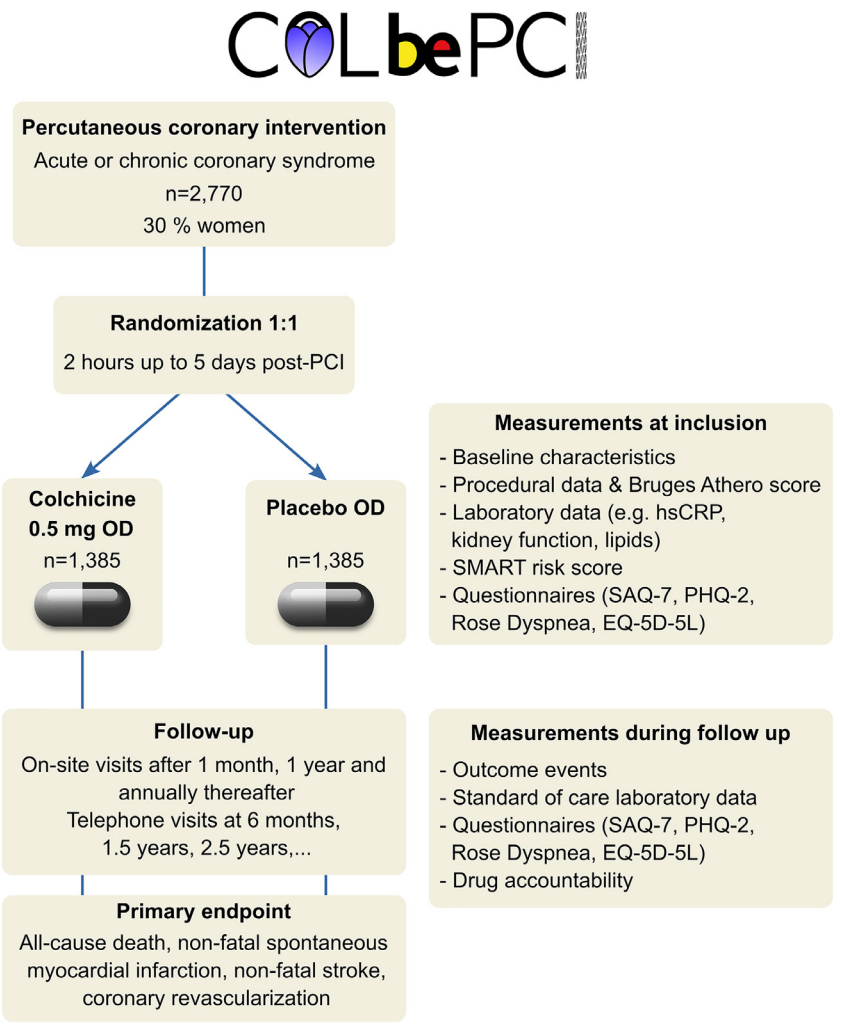
AAA, aneurysm of the abdominal aorta; ABI, ankle-branch index; CABG, coronary artery bypass graft;
CAD, coronary artery disease; CK, creatine kinase; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein cholesterol; MDRD, Modification of Diet in Renal Disease; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; ULN, upper limit of normal.

Clinical Trials Regulation (CTR, No 536/2014) with EU CT number 2023-505028-74-00. The study will follow the updated ICH guidelines for good clinical practice E6 (R2) in compliance with the Declaration of Helsinki and applicable regulatory requirements. A Steering Committee and Patient Advisory Board revised and approved the trial protocol, informed consent form, patient card, medication intake calendar and questionnaires.

Study population and randomization

Patients with CAD presenting as acute or chronic coronary syndromes and treated with PCI will be enrolled when meeting all inclusion and considering all exclusion criteria (see Table 2), and after written informed consent was obtained. Randomization will be done between 2 hours and 5 days after the index PCI through an interactive web-based randomization/treatment allocation system (IWRS) using permuted-block randomization with varying block sizes and stratified by participating site and birth sex. To assure that at least 30% of the patients will be female, at most 1939 (70%) men will be included by closing the male stratum and restricting the inclusion to female patients only until the required sample size is obtained.

Figure 1. Trial flow chart Legend: Flowchart illustrating the patient population, randomization process, schedule of follow-up assessments, and the primary endpoint of the trial. The end of the study will occur after 566 first outcome events. Abbreviations: EQ-5D-5L, EuroQol 5 dimensions 5-level; hsCRP, high-sensitivity C-reactive protein; OD, once daily; PCI, Percutaneous coronary intervention; PHQ-2, Patient Health Questionnaire-2; SAQ-7, Seattle Angina Questionnaire 7; SMART, Second Manifestations of Arterial Disease.



Study treatment and follow-up

Colchicine 0.5 mg and a matching placebo (investigational medicinal product or IMP) were manufactured by Tiofarma (The Netherlands), are visually identical and have a blinded packaging. Study medication is to be taken once daily on top of guideline-directed optimal medical treatment and local clinical practices. Compliance will be assessed using a patient calendar and by drug accountability at each on-site trial visit.

On-site follow-up visits are scheduled at 1-3 months post-PCI and yearly thereafter with telephone visits every 6 months between the annual on-site visits until the targeted number of first outcome events has been reached (see Figure 1 for trial flow chart).

Study measurements

Clinical data

Baseline demographics, health status, prior cardiovascular diseases and treatments, index PCI data (including the Bruges Athero Score, see Supplementary Appendix 2) as well as cardiovascular medication at discharge will be collected. Patient-reported outcomes based on the ICHOM Standard Set for CAD (Seattle Angina Questionnaire 7 Angina Frequency [SAQ7-AF], Rose Dyspnea Scale, and Patient Health Questionnaire–2 [PHQ-2]) and the EuroQol 5 dimensions 5-level (EQ-5D-5L) will be collected at every on-site visit.

Blood tests

A mandatory blood sample at inclusion will be performed and analyzed by the local laboratories for the variables comprised in the SMART risk score (cholesterol, creatinine, and hsCRP).[17] In addition, at every on-site visit, standard-of-care laboratory data taken at the discretion of the treating physician will be collected by the participating sites.

Outcome data

The following data will be collected and actively asked for at every visit: mortality, myocardial infarction, stroke or transient ischemic attack, coronary revascularization, stent thrombosis, peripheral revascularization, and carotid revascularization.

Study endpoints

The primary endpoint is the time from randomization to the first occurrence of a composite endpoint consisting of all-cause death, spontaneous (nonprocedural) nonfatal myocardial infarction (MI; type 1, 4B & C), nonfatal stroke, or coronary revascularization (see Supplementary Appendix 3 for definitions). All-cause death was chosen instead of cardiovascular death as part of the primary endpoint from a pragmatic point of view and based on a recent meta-analysis showing, besides a nonsignificant trend toward reduced cardiovascular death, a nonsignificant trend toward increased noncardiovascular death.[18] All-cause death will therefore serve as a net clinical benefit for both cardiovascular and noncardiovascular deaths. The other components of the primary endpoint are the major cardiovascular events (MACE), reflecting the possible effect of colchicine on stabilizing the coronary and other arterial territories.

Secondary and tertiary endpoints are listed in Supplementary Appendix 4. All primary and secondary endpoint events will be adjudicated by an independent Event Adjudication Committee (EAC) whose members are unaware of treatment assignments, relying on original source data and according to predefined definitions documented in the endpoint adjudication charter. The EAC members are experienced clinicians with a track record in cardiovascular research.

Safety

As colchicine is widely used and is generally regarded as safe at a low dosage of 0.5 mg daily, only limited safety data will be collected (see Supplementary Appendix 5).[19] In analogy to previous colchicine studies, noncardiovascular serious adverse events (SAEs) not possibly related to the IMP that are expected to occur with high frequency in the population under study (eg, depression, trauma, chronic obstructive pulmonary disease, etc.) will not be collected.

An independent Data Safety Monitoring Board (DSMB) will review unblinded patient-level data for safety on an ongoing basis during the trial and will advise the sponsor regarding the continuing safety of trial subjects and those yet to be recruited, as well as the continuing validity and scientific merit of the trial. The DSMB may not suggest early trial termination for efficacy and no formal interim analysis for efficacy will be performed.

Data monitoring

The COL BE PCI trial will be monitored to achieve high protocol compliance and data quality, as well as to ensure the subjects' safety and rights. A Clinical Trial Monitoring Plan has been created following the national regulations and the ICH-GCP guidelines.

Sample size calculation

A conventional power calculation considered an annual rate of the primary endpoint of 8.5% in the placebo arm according to the incidence from previous trials.[2] Based on LoDoCo2[13] with HR = 0.69 (95% CI: 0.57-0.83), COLCOT[12] with HR = 0.77 (95% CI: 0.61-0.96), and the meta-analysis of Fiolet et al.[18] with relative risk (RR) = 0.67 (95% CI: 0.55-0.82), we assumed a hazard ratio of 0.75 in favor of the colchicine treatment group. Under the assumption that 15% of the participants will prematurely discontinue the drug (10.5% and 18.4% premature discontinuation of the drug was observed in LoDoCo2 and COLCOT, respectively), the hazard ratio will increase to 0.79 (H1, alternative hypothesis). Assuming exponential survival curves with the above event rate, a hazard ratio of 0.79, a 1:1 randomization, and using a log-rank test at a 2-sided significance level of 0.05, 566 events will have 80% power to show superiority of the colchicine treatment group. We plan to randomize 2,770 participants into the trial (1385 per treatment group). We anticipated to recruit 1,662 participants per year. In addition, we assumed a uniform dropout rate of 2% up to 6 months and a low constant dropout rate corresponding to a cumulative dropout rate of 3% at 2 years later on. The last randomized patient will be followed for about 24 months until the target of 566 first events has been reached. Given the above recruitment, event and dropout rate, the recruitment period will last about 20 months and the anticipated duration of the trial under H1 will be 44 months (3.67 years). In 10,000 simulations, the study duration ranged from 39.0 to 49.2 months with an average of 44 months. Sample size calculation was performed using EAST 6.4.

The trial will ensure to enroll at least 30% of female participants by including at most 1,939 men (70%).

Statistical analysis

A full statistical analysis plan (SAP), in which all the details of the planned analyses are described, will be finalized before database lock. The key items of this plan are described below.

Definition of analysis populations

The primary analysis will be the full analysis set (FAS) which will include all randomized participants. Participants will be analyzed according to the intention-to-treat principle, that is in the group to which they were randomized, irrespectively which treatment was received, if any. In addition, a per-protocol analysis set (PPS) will be used for sensitivity analyses. These will exclude participants from the FAS with major protocol violations like e.g. stop taking the study medication. All major protocol deviations that lead to exclusion from the PPS will be fully documented in the Analysis Sets Specification Document which will be dated and signed before database lock.

Summary of baseline data and flow of participants

Continuous variables will be summarized by treatment group by the number of nonmissing data points, mean, standard deviation, median, and interquartile range. Categorical and ordinal variables will be summarized by treatment group by observed frequencies and percentages relative to the total number of nonmissing items. A CONSORT flow diagram will be produced to describe the flow of participants.

Primary outcome analysis

The primary endpoint will be analyzed using a stratified (on birth sex) log-rank test on the FAS at a significance level of 0.05. The randomized study treatment will be used to assign participants and events to treatment groups; all adjudicated events that occur until the study end will be taken into account (i.e., independent of whether or not a participant was still on study medication). The time to the primary endpoint will start from the date of randomization. In addition, the hazard ratio with a 95% CI will be reported from a stratified (on birth sex) Cox proportional hazards model in which only a treatment indicator will be present. The PH assumption will be explored by plotting the log(-log(survival function)) against the log of time by treatment group and checked for parallelism. Efron's method will be used for dealing with ties. A Kaplan-Meier curve by treatment groups will be constructed.

A similar analysis of the PPS will serve as a sensitivity analysis. In addition, other sensitivity analyses will be planned. These will include an analysis that considers study drug compliance among others. Full details on the sensitivity analyses will be specified in the SAP.

Procedures to account for missing or spurious data

Real-time data checks will be built into the data collection tool (or electronic case report form) and further data management queries including missing data and out-of-range values will be issued to the sites regularly, in accordance with the data management plan. Outstanding data queries will be reviewed regularly by the trial coordinating and data management teams. Feedback will be provided to all sites regularly.

Protocol deviations will be classified (major/minor) based on the Protocol Deviation Criteria List. The Data Management plan will describe how Protocol Deviations will be identified, handled, and recorded. Major deviations will be flagged to the trial statistician and the trial Sponsor. The handling of missing data will be described in the SAP.

Prespecified subgroup analysis

The foreseen subgroup analyses for the primary endpoint are provided in Supplementary Appendix 6. In addition to an analysis of each subgroup, a test for interaction between the treatment group and subgroup will be reported.

Timeline

The first patient was included in January 2024. Enrolment of all 2,770 patients is expected to be completed in October 2025 with the last patient coming for the end-of-study visit in November 2027. As of the date of manuscript submission (May 2024), 477 patients have already been included in the trial.

Discussion

The COL BE PCI trial aims at providing novel insights and advancements in probing colchicine's potential benefits post-PCI by introducing elements not seen in previous studies. Most previous and ongoing trials have either used a run-in period of 4 weeks or started to include patients only 2 to 6 weeks post-ACS or PCI instead of immediately. A run-in period in clinical trials is known to overestimate the treatment effects and minimize the risks, thereby reducing the external validity of the results to daily practice.[20] In addition, the first days post-ACS and post-PCI are the most vulnerable periods with the highest rate of recurrent events.[2] It is therefore important to reduce risk immediately following an ACS and/or PCI.[2] A role for colchicine in this high-risk period seems to be supported by mechanistic studies where colchicine was administered before or immediately after PCI, which showed a blunted increase of circulating IL-6 and hsCRP levels at 22-24 hours[21], an attenuated neutrophil extracellular trap formation (an important mediator for plaque destabilization and thrombus formation)[14] and a reduced myocardial infarction size[22]. These data suggest that colchicine should be initiated at an early stage post-PCI and without a run-in period, hence supporting our study design to randomize from 2 hours up to 5 days post-PCI. In addition, we plan to include all PCI patients, irrespective of their clinical presentation (acute or chronic), comparable to universal statin therapy.

Another feature of our trial design is the deliberate inclusion of at least 30% of women. Clinical trials in CAD have historically enrolled predominantly male participants, which potentially limits its generalizability. Notably, only 15% of the included patients in the LoDoCo2

trial were women.[13] However, cardiovascular disease is the leading cause of death in women and the disease remains understudied, under-recognized, underdiagnosed, and undertreated.[23] This trial aims to be representative of the gender prevalence of CAD in Europe.[24]

A third point of interest is the measurement of hsCRP at baseline for all patients to assess their baseline inflammatory risk. Whether colchicine is effective irrespective of the hsCRP level or, on the contrary, only when it is elevated, remains to be demonstrated.

Furthermore, there are additional risk factors beyond hsCRP that aid in predicting future cardiovascular risk. This is the reason why the SMART risk score will be considered in our trial, as a validated holistic marker of the residual cardiovascular risk (including not only hsCRP, but also lipid levels, blood pressure, smoking status, diabetes, and previous medical history).[17] In the era of personalized medicine, the general assumption that all patients with cardiovascular disease are at the same risk of recurrent events needs to be reconsidered. There is substantial variation in the estimated future risk of recurrent major vascular events, as demonstrated in 6,904 patients with vascular disease by the SMART study group: 18% of the patients had a <10% risk at 10-year, while 22% have >30% 10-year risk.[17] It is therefore of major interest to determine this residual risk for all CAD patients and to confirm the efficacy of colchicine in those patients with the highest residual risk, hereby defining a specific subgroup with possibly the highest treatment benefit.

A fifth notable aspect of the trial design is the incorporation of patient-reported outcomes (PROs) to assess the impact of colchicine therapy on the quality of life and symptom burden post-PCI. While clinical endpoints such as recurrent myocardial infarction or (cardiovascular) mortality are crucial measures of efficacy, understanding the patient's perspective is equally important. By including PROs such as the assessment of angina frequency and functional capacity, the trial aims to provide a comprehensive evaluation of colchicine's effects beyond traditional clinical endpoints. This patient-centered approach not only enriches the trial's findings but also ensures that the therapy aligns with patient preferences and priorities, ultimately enhancing its real-world applicability and patient care.

Some limitations should be acknowledged. This study is only recruiting patients in Belgium for budgetary reasons, which may impact the generalizability of the data. Secondly, procedural characteristics and PCI indications will not be reviewed by a core lab.

Conclusion

The COL BE PCI trial is an investigator-initiated, multicenter, randomized, double-blinded placebo-controlled trial investigating the efficacy of low-dose colchicine as an adjunctive to optimal standard of care in 2,770 patients immediately after PCI for both acute and chronic coronary syndromes. The trial aims to reinforce the external validity of low-dose colchicine in the secondary prevention of CAD in general and post-PCI in particular, in a pragmatic way with no run-in period, including at least 30% of women and not excluding patients with moderate kidney dysfunction. We also attempt to bring novel perspectives by integrating baseline hsCRP and SMART risk score assessments to improve our understanding of colchicine's role in the management of CAD.

Conflict of Interest

The authors have no conflict of interest related to the content of this paper.

CRediT authorship contribution statement

Emmanuel De Cock: Conceptualization, Investigation, Methodology, Project administration, Visualization, Writing – original draft. **Shakeel Kautbally:** Conceptualization, Investigation, Methodology, Writing – review & editing. **Frank Timmermans:** Conceptualization, Investigation, Methodology, Writing – review & editing. **Kris Bogaerts:** Methodology, Writing – review & editing. **Claude Hanet:** Investigation, Writing – review & editing. **Walter Desmet:** Investigation, Writing – review & editing. **Olivier Gurné:** Investigation, Writing – review & editing. **Pascal Vranckx:** Investigation, Writing – review & editing. **Nick Hiltrop:** Investigation, Writing – review & editing. **Karl Dujardin:** Investigation, Writing – review & editing. **Philippe Vanduynhoven:** Investigation, Writing – review & editing. **Paul Vermeersch:** Investigation, Writing – review & editing. **Charles Pirlet:** Investigation, Writing – review & editing. **Kurt Hermans:** Investigation, Writing – review & editing. **Bert Van Reet:** Investigation, Writing – review & editing. **Bert Ferdinande:** Investigation, Writing – review & editing. **Adel Aminian:** Investigation, Writing – review & editing. **Willem Dewilde:** Investigation, Writing – review & editing. **Antoine Guédès:** Investigation, Writing – review & editing. **François Simon:** Investigation, Writing – review & editing. **Frederic De Roeck:** Investigation, Writing – review & editing. **Frédéric De Vroey:** Investigation, Writing – review & editing. **J. Wouter Jukema:** Investigation, Writing – review & editing. **Peter Sinnaeve:** Conceptualization, Investigation, Methodology, Writing – review & editing. **Ian Buysschaert:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing – original draft.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2024.08.022.

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