The Effect of Years-Long Exposure to Low-Dose Colchicine on Renal and Liver Function and Blood Creatine Kinase Levels: Safety Insights from the Low-Dose Colchicine 2 (LoDoCo2) Trial

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Abstract

Background and Objective The Low-Dose Colchicine-2 (LoDoCo2) trial showed that 2–4 years exposure to colchicine 0.5 mg once daily reduced the risk of cardiovascular events in patients with chronic coronary artery disease. The potential effect of years-long exposure to colchicine on renal or liver function and creatine kinase (CK) has not been systematically evaluated and was investigated in this LoDoCo2 substudy.

Methods Blood samples drawn from 1776 participants at the close-out visit of the LoDoCo2 trial were used to measure markers of renal function (creatinine, blood urea nitrogen [BUN]), liver function (alanine aminotransferase [ALT], γ-glutamyl transferase [GGT], bilirubin and albumin), and CK. Renal and liver function as well as hyperCKemia (elevated CK) were categorized to the degree of elevation biomarkers as mild, mild/moderate, moderate/severe, and marked elevations.

Results In total, 1776 participants (mean age 66.5 years, 72% male) contributed to this analysis, with a median exposure to trial medication of 32.7 months. Compared with placebo, colchicine was not associated with changes in creatinine and BUN but was associated with elevations in ALT (30 U/L vs. 26 U/L; \( p < 0.01 \)) and CK (123 U/L vs. 110 U/L; \( p < 0.01 \)). Most elevations in ALT and CK were mild in both treatment groups. There were no moderate to marked ALT elevations (> 5–10 × upper limit of normal [ULN]) in both treatment groups, and 6 (0.7%) colchicine-treated vs. 2 (0.2%) placebo-treated participants had moderate to marked CK elevations (> 5–10 × ULN).

Conclusion In chronic coronary artery disease, 2–4 years of exposure to colchicine 0.5 mg once daily was associated with small elevations in ALT and CK, but was not associated with changes in renal function.

Triale Registration https://www.anzctr.org.au; ACTRN12614000093684, 24 January 2014.

1 Introduction

Large, randomized trials have demonstrated that long-term treatment with colchicine 0.5 mg once daily reduced the risk of cardiovascular death, myocardial infarction, stroke or ischemia-driven revascularization in patients with chronic coronary artery disease (CAD) [1–4]. Based on these results, several international guidelines have incorporated colchicine in recommendations for secondary prevention of CAD [5–7]. Despite this, medical professionals are often hesitant to prescribe colchicine due to concerns about its long-term safety, especially when used in combination with statins.

Supporting the safety of long-term colchicine, randomized trials demonstrating its efficacy for cardiovascular prevention have not reported clinical episodes of renal, hepatic, or muscle toxicity; however, none of the trials have systematically documented the effects of colchicine on renal or liver function or on blood levels of creatine kinase (CK). These data are needed to give confidence to potential prescribers and are expected to become increasingly important with the progressive uptake of colchicine for the long-term management of patients with chronic CAD.
In chronic coronary artery disease (CAD), 2–4 years of exposure to colchicine 0.5 mg once daily compared with placebo was associated with small elevations in alanine aminotransferase (ALT), albumin, and creatine kinase (CK) levels, but was not associated with changes in renal function.

The majority of elevations in ALT, albumin and CK were mild. More marked elevations in these biomarkers were uncommon and not significantly different by treatment group.

These data suggest that despite modest elevations in liver enzymes and CK, 2–4 years of exposure to colchicine 0.5 mg once daily appears to be well tolerated in patients with chronic CAD.

In this study, we report the effect of 2–4 years of exposure to colchicine 0.5 mg once daily on renal and liver function and blood levels of CK at the end of treatment in a large subset of participants in the Low-Dose Colchicine-2 (LoDoCo2) trial.

2 Methods

2.1 Study Design

The LoDoCo2 trial was a randomized, double-blind, placebo-controlled trial that examined the effect of adding colchicine 0.5 mg daily on top of usual care in patients with chronic CAD. Details of the trial design have been described elsewhere [2, 8]. In brief, 5522 patients aged 35–82 years with proven CAD were recruited in Australia (n = 1904) and The Netherlands (n = 3618). All participants had proven tolerance to a 30-day trial of open-label colchicine. The trial excluded patients with cardiovascular events within the prior 6 months and those with moderate to marked renal impairment (serum creatinine > 150 mmol/L or estimated glomerular filtration rate [eGFR] < 50 mL/min/1.73 m²), severe heart failure, known intolerance to colchicine, and dependency. The primary efficacy outcome of the trial was the composite of cardiovascular death, myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization. Secondary endpoints included major adverse cardiovascular events (MACE) and the individual components of the primary outcome. All cardiovascular events were adjudicated by a clinical events committee, blinded to treatment allocation.

2.2 Close-Out Blood Samples

Towards the end of the trial, participants were invited to have blood samples collected at the time of their close-out visit for later testing. At the time of blood collection, participants were still taking trial medication and both the participants and investigators remained blinded to treatment assignment.

2.3 Laboratory Assessment

Blood was collected into a 4.5 mL citrate tube, a 10 mL serum tube, and a 10 mL ethylene diamine tetra acetic acid (EDTA) tube. Within 4 h of collection, samples were centrifuged (2000 times gravity at room temperature for 10 min), and serum or plasma was removed and stored at − 80°C. Samples were stored for approximately 2.5 years before analysis.

Biomarkers of renal function included creatinine and blood urea nitrogen (BUN). The eGFR was calculated using the Chronic Kidney Disease Epidemiology (CKD-EPI) formula. An eGFR of > 90 mL/min/1.73 m² was considered normal. Renal function was categorized as mildly decreased (60–89 mL/min/1.73 m²); mildly to moderately decreased (45–59 mL/min/1.73 m²); moderately to severely decreased (30–44 mL/min/1.73 m²); severely decreased (15–29 mL/min/1.73 m²), and kidney failure (< 15 mL/min/1.73 m²) [9].

Biomarkers of liver function included alanine aminotransferase (ALT), γ-glutamyl transferase (GGT), bilirubin and albumin. Albumin is a protein exclusively synthesized by the liver and as such is a marker of liver synthetic function and liver health [10–12].

Liver damage and function were categorized according to the degree of elevation of biomarkers, as mildly elevated (< 5 × upper limit of normal [ULN]), moderately elevated (5–10 × ULN), and markedly elevated (> 10 × ULN) [11, 13]. Serum albumin levels were categorized as low (< 35 g/L) and clinically significant hypoalbuminemia (< 25 g/L) [14]. HyperCKemia (elevated CK) was categorized according to the degree of elevation of CK levels: very mildly elevated (1.1–1.5 × ULN), mildly elevated (1.51–5 × ULN), moderately elevated (5.1–10 × ULN), and markedly elevated (> 10 × ULN) [15, 16].

All biomarkers were measured using Abbott Architect c Systems (Abbott Laboratories, Abbott Park, IL, USA).

2.4 Statistical Analysis

Continuous data were presented as means and standard deviation when normally distributed, or median and interquartile range (25th–75th percentile) when non-normally distributed. The significance of any differences in baseline characteristics between participants included in the subanalysis and
those in the complete LoDoCo2 cohort was assessed using an independent samples t test for continuous variables and a Chi-square test for categorical variables.

The significance of any differences in biomarker levels between treatment groups were tested using an independent samples t test when normally distributed or Mann–Whitney U test when non-normally distributed. Differences in proportions between colchicine and placebo treatment were compared using a Chi-square test with a p value for trend. Statistical analysis was performed using IBM SPSS version 25.0 (IBM Corporation, Armonk, NY, USA). Figures were made using R (The R Foundation for Statistical Computing, version 3.6.2).

3 Results

3.1 Baseline Characteristics

A total of 1776/5522 participants agreed to have blood samples taken, of whom an equal proportion were randomized in Australia and The Netherlands. The clinical characteristics of the 1776 participants who contributed to this analysis are shown in Table 1. The median duration of exposure to the trial medication was 32.7 months (24.0–48.6 months). Overall, baseline characteristics of the included participants were similar to the complete LoDoCo2 population and well-balanced between treatment groups, as described previously (electronic supplementary Table 2) [2]. The mean age was 66.5 years and most participants were taking statins (94%).

3.2 Renal Function

Median levels of creatinine were 82.7 µmol/L (74.0–94.4 µmol/L) in the colchicine group versus 82.6 µmol/L (73.5–94.0 µmol/L) in the placebo group (p = 0.99) [Table 2]. Median levels of BUN were 6.3 mmol/L (5.3–7.5 mmol/L) in the colchicine group versus 6.3 mmol/L (5.3–7.5 mmol/L) in the placebo group (p = 0.96) [Table 2]. The mean eGFR was 79.3 ± 15.3 mL/min/1.73 m² in the colchicine group and 79.6 ± 15.4 mL/min/1.73 m² in the placebo group (p = 0.76) [Table 2].

After categorizing participants according to the severity of renal impairment, the proportion of participants with mildly to markedly decreased renal function was not significantly different between treatment groups (p value for trend > 0.92) [Table 3]. The number of participants with normal renal function was 783 (88.5%) in those assigned to colchicine and 780 (88.6%) in those assigned to placebo, while the number of participants with mildly to severely reduced renal function at the end of treatment was 103 (11.3%) in those assigned to colchicine versus 101 (11.4%) in those assigned to placebo. Two participants assigned to colchicine had markedly reduced eGFR levels versus one participant assigned to placebo. In participants with a moderately decreased renal function at baseline (stage 3a based on the Kidney Disease: Improving Global Outcomes [KDIGO] guidelines), the proportion of participants with mild, mild/moderate, or moderate/severe decreased renal function at the end of the trial was similar between treatment groups (p value for trend 0.62).

3.3 Liver Function

Median ALT levels at the end of treatment were higher on colchicine compared with placebo. The absolute difference was 4.0 U/L (30.0 U/L [22.0–40.0 U/L] vs. 26.0 U/L [19.0–34.0]; p < 0.01) [Table 2; Fig. 1]. After categorizing ALT levels according to mild, moderate, or marked elevations, differences were seen in the mildly elevated range of ALT levels in 246 participants (27.5%) in the colchicine group and 153 participants (17.4%) in the placebo group.

The number of participants at the end of treatment with ALT levels in the normal range was 658 (73.5%) in the colchicine group versus 730 (82.9%) in the placebo group. One participant in the colchicine group had ALT levels in the moderately elevated range, whereas no participants had ALT levels in the markedly elevated range (p value for trend < 0.01) [Table 2].

Median levels of GGT and bilirubin were not significantly different between the colchicine and placebo treatment groups (p = 0.31 and p = 0.73) [Table 2]. After categorizing participants according to mild, moderate, or marked elevations, the proportion of participants in different categories was similar by treatment group (p value for trend = 0.37 and p = 0.67, respectively) [Table 2]. 143 participants (16.0%) in the colchicine group, compared with 132 participants (15.0%) in the placebo group, had mildly elevated GGT levels. Six participants (0.7%) in the colchicine group, compared with three participants (0.3%) in the placebo group, had moderately elevated GGT levels. No participant in either treatment group had markedly elevated GGT levels. Of the 284 participants with elevated GGT levels, 136 also had an elevated ALT level and one who was being treated with colchicine had an ALT > 200 U/L. No participants with elevation of both markers had ALT levels > 400 U/L. There were no participants with moderately or severely elevated bilirubin levels in both treatment groups.

Mean albumin levels were higher on colchicine compared with placebo. The absolute difference was 0.4 g/L (43.0 g/L ± 2.4 vs. 42.6 g/L ± 2.5; p < 0.01) [Table 2]. After categorizing participants according to albumin levels, from clinically significant hypoalbuminemia to hyperalbuminemia, there was no difference between colchicine and placebo treatment (p value for trend = 0.18) [Table 3]. The number of participants with normal albumin levels was 892 (99.7%)
in those assigned to colchicine and 880 (99.9%) in those assigned to placebo.

### 3.4 HyperCKemia

Median CK levels were higher on colchicine compared with placebo. The absolute difference was 13 U/L (123.0 U/L [84.0–184.0 U/L] vs. 110.0 U/L [77.0–164.0 U/L]); \( p < 0.01 \) [Table 2; Fig. 2]. The overall distribution of participants with mild, moderate, or marked elevations of CK was different between treatment groups (\( p \) value for trend = 0.03), driven by differences in the proportion of patients with very mildly or mildly elevated levels. The number of participants with normal CK levels was 689 (77.0%) in the colchicine group and 724 (82.2%) in the placebo group (Table 3). The number of participants with very mildly elevated CK levels was 130 (14.5%) in the colchicine group and 99 (11.2%) in the placebo group. Sixty-four (7.2%) participants in the colchicine group and 54 (6.1%) participants in the placebo group had mildly elevated CK.
levels. Five (0.6%) participants in the colchicine group and two (0.2%) participants in the placebo group had moderately elevated CK levels. Only one (0.1%) participant in this cohort, who was taking colchicine, had markedly elevated CK levels (Table 3).

Information about symptoms of myalgia was available in four participants with moderately elevated CK levels and one participant with a markedly elevated CK level. Of the three participants with moderately elevated CK levels who were taking colchicine, two complained of myalgia; however, the one participant taking placebo did not complain of myalgia. The only participant with markedly elevated CK levels on colchicine complained of myalgia. None of these participants ceased their trial medication.

### 4 Discussion

In this cohort of 1776 participants who were still taking colchicine or placebo at the time blood was taken at the close-out of the LoDoCo2 trial, we found that median levels of ALT, albumin, and CK were slightly higher after colchicine treatment. However, the majority of elevations in ALT, albumin, and CK were mild. More marked elevations in these biomarkers were uncommon and were not significantly different by treatment group. These data suggest that despite modest elevations in liver enzymes and CK, 2–4 years of exposure to colchicine 0.5 mg once daily appears to be well tolerated in patients with chronic CAD treated with the full range of therapies for secondary prevention, including angiotensin-converting enzyme inhibitors, β-blockers, calcium channel blockers, and (high-dose) statins.

Experience in patients with chronic gout or familial Mediterranean fever suggests that long-term use of low-dose colchicine has no direct toxic effects on the kidneys and may be reno-protective [17, 18]. Our results demonstrate that 2–4 years of exposure to colchicine 0.5 mg once daily in patients with CAD was not associated with renal dysfunction and is consistent with these findings. Nonetheless, patients with moderate or severe renal impairment have a reduced ability to clear colchicine, which might predispose to systemic adverse effects [19]. Accordingly, guidelines recommend dose reduction to 0.5 mg once daily in these patients when colchicine is used for the treatment of acute gout. Similar dose reductions are recommended when colchicine is used concomitantly with specific medications [19, 20]. In the LoDoCo2 trial, patients with eGFR < 50 mL/min/1.73 m² were excluded from enrolment in order to reduce the risks of adverse effects and potential drug–drug interactions. The safety of long-term use of low-dose colchicine in patients with CAD and eGFR < 50 mL/min/1.73 m² is being evaluated as part of the ongoing CLEAR SYNERGY trial (Colchicine and Spironolactone in Patients With MI/SYNERGY Stent Registry; NCT03048825).

In our study, the observation of mild elevations in ALT and albumin is in line with that seen in patients with pericarditis treated with months-long therapy [21]. No differences in GGT and bilirubin levels were observed between those taking either colchicine or placebo. The number of participants with markedly elevated ALT levels was very low. Moreover, the ALT levels were well below levels commonly seen in patients taking long-term statin therapy [22, 23]. We do not have an explanation for the mild albumin elevations but can confirm that most participants had albumin levels in the normal range. Furthermore, it is reassuring

### Table 2  End-of-study levels of different biomarkers in the LoDoCo2 subpopulation

| Biomarker                          | Colchicine [n = 895] | Placebo [n = 881] | p value | ULN |
|-----------------------------------|----------------------|-------------------|---------|-----|
| **Renal function**                |                      |                   |         |     |
| Creatinine [µmol/L]               | 82.7 (74.0–94.4)     | 82.6 (73.5–94.0)  | 0.99    | 110 |
| Blood urea nitrogen [mmol/L]      | 6.3 (5.3–7.5)        | 6.3 (5.3–7.5)     | 0.96    | 30  |
| Estimated glomerular filtration rate [mL/min/1.73 m²] | 79.3 (15.3)          | 79.6 (15.4)       | 0.76    | 120 |
| **Liver function**                |                      |                   |         |     |
| Alanine aminotransferase [U/L]    | 30.0 (22.0–40.0)     | 26.0 (19.0–34.0)  | < 0.01 | 40  |
| γ-Glutamyl transferase [U/L]      | 30.0 (21.0–48.0)     | 30.0 (21.0–44.0)  | 0.31    | 60  |
| Bilirubin [µmol/L]                | 9.5 (7.0–12.2)       | 9.2 (7.2–12.0)    | 0.73    | 20  |
| Albumin [g/L]                     | 43.0 (2.4)           | 42.6 (2.5)        | < 0.01 | 50  |
| Creatine kinase [U/L]             | 123.0 (84.0–184.0)   | 110.0 (77.0–164.0)| < 0.01 | 190 |

Data are expressed as mean (SD) or median (25th–75th percentile). p values were calculated using an independent samples t test or Mann–Whitney U test where applicable.

SD standard deviation, ULN upper limit of normal, U unit, LoDoCo2 Low-Dose Colchicine-2 trial
that compared with placebo, colchicine was not associated with clinically important hypoalbuminemia. In line with previous studies, no participants with severe hepatic toxicity were observed, even when used in combination with long-term statin therapy [24, 25]. Lastly, in the main LoDoCo2 trial, no participants stopped colchicine use because of liver adverse effects.

CK levels are often routinely measured in patients treated with statins. Since colchicine and some statins are both substrates of the CYP3A4 enzyme, combined use can result in competitive inhibition with an increased risk for muscle-related toxicity [26]. In Dutch patients enrolled in the LoDoCo2 study, myalgia was more commonly reported in participants taking colchicine compared with placebo [2], but in most cases was mild and did not lead to permanent discontinuation. Mild drug-induced CK elevations (up to 1.5 × ULN) are generally considered benign and not a reason for permanent withdrawal of therapy [16, 27, 28]. Our results demonstrating only (very) mild to moderate CK elevations are consistent with the conclusion of the American Heart Association expert group that the concomitant use of statins and (low-dose) colchicine in patients with coronary disease is well tolerated [26]. At the same time, it is important to note that there have been isolated case reports of rhabdomyolysis shortly after the introduction of statins in patients taking colchicine in the setting of advanced renal dysfunction [29]. Similarly, isolated cases of myotoxicity presenting with fatigue and progressive muscle weakness have been associated with the chronic use of colchicine [30]; thus, in case these symptoms appear in patients using

| Laboratory value | Category | Range | Colchicine [n = 895] | Placebo [n = 881] | p value for trend |
|------------------|---------|-------|----------------------|------------------|-----------------|
| eGFR (mL/min/1.73 m²) | Normal | > 90 | 238 (26.6) | 235 (26.7) | 0.92 |
| Mildly decreased | 60–89 | 554 (61.9) | 545 (61.9) | |
| Mildly to moderately decreased | 45–59 | 87 (9.7) | 86 (9.8) | |
| Moderately to severely decreased | 30–44 | 14 (1.6) | 14 (1.6) | |
| Markedly decreased | 15–29 | 2 (0.2) | 1 (0.1) | |
| Kidney failure | < 15 | 0 (0.0) | 0 (0.0) | |
| ALT (U/L) | Normal (< ULN) | < 40 | 658 (73.5) | 730 (82.9) | < 0.01 |
| Mildly elevated (1–5 × ULN) | 40–200 | 236 (26.4) | 151 (17.1) | |
| Moderately elevated (5–10 × ULN) | 200–400 | 1 (0.1) | 0 (0.0) | |
| Markedly elevated (> 10 × ULN) | >400 | 0 (0.0) | 0 (0.0) | |
| GGT (U/L) | Normal (< ULN) | < 60 | 745 (83.2) | 746 (84.7) | 0.37 |
| Mildly elevated (1–5 × ULN) | 60–300 | 143 (16.0) | 132 (15.0) | |
| Moderately elevated (5–10 × ULN) | 300–600 | 6 (0.7) | 3 (0.3) | |
| Markedly elevated (> 10 × ULN) | >600 | 0 (0.0) | 0 (0.0) | |
| Bilirubin (µmol/L) | Normal (< ULN) | < 20 | 842 (94.1) | 833 (94.6) | 0.67 |
| Mildly elevated (1–5 × ULN) | 20–100 | 53 (5.9) | 48 (5.4) | |
| Moderately elevated (5–10 × ULN) | 101–200 | 0 (0.0) | 0 (0.0) | |
| Markedly elevated (> 10 × ULN) | >200 | 0 (0.0) | 0 (0.0) | |
| Albumin (g/L) | Normal | 35–50 | 892 (99.7) | 880 (99.9) | 0.18 |
| Clinically significant hypoalbuminemia | < 25 | 0 (0.0) | 0 (0.0) | |
| Hypoalbuminemia | 25–35 | 1 (0.1) | 1 (0.1) | |
| Hyperalbuminemia | > 50 | 2 (0.2) | 0 (0.0) | |
| Creatine kinase (U/L) | Reduced (< LLN) | < 30 | 6 (0.7) | 2 (0.2) | 0.03 |
| Normal (LLN–ULN) | 30–190 | 689 (77.0) | 724 (82.2) | |
| Very mildly elevated (1.1–1.5 × ULN) | 191–285 | 130 (14.5) | 99 (11.2) | |
| Mildly elevated (1.5–5 × ULN) | 286–950 | 64 (7.2) | 54 (6.1) | |
| Moderately elevated (5–10 × ULN) | 951–1900 | 5 (0.6) | 2 (0.2) | |
| Markedly elevated (> 10 × ULN) | >1900 | 1 (0.1) | 0 (0.0) | |

Data are shown as count (%). To identify differences in the several categories of laboratory values between colchicine and placebo, p values for trend were calculated using a Chi-squared test. The range column depicts the normal laboratory values in males, but for the analysis the appropriate normal laboratory values for males and females were used. No adjustment for multiple testing was applied

eGFR estimated glomerular filtration, ALT alanine aminotransferase, GGT γ-glutamyltransferase, U unit, LLN lower limit of normal, ULN upper limit of normal, LoDoCo2 Low-Dose Colchicine-2 trial

△ Adis
The Effect of Colchicine on Safety Biomarkers

The effect of colchicine on safety biomarkers is an important consideration, especially when considering long-term colchicine and/or statin therapy. The concomitant use of colchicine and statins should be re-evaluated [15].

4.1 Limitations

Since blood samples were only drawn at the close-out visit of the trial, it is not known whether the variances in biomarker levels truly developed during the trial and were thus related to colchicine. Furthermore, as data regarding alcohol consumption, exercise routines, or concomitant use of off-label medications were not collected, it is also not known whether the variances and isolated aberrant results were affected by these or other unknown factors. Furthermore, because blood samples were not available from all participants at close-out, including the equal number of participants who died in each group (2.5%) or prematurely ceased their trial medication during the trial (~10%), these results only reflect the laboratory findings in the large proportion of participants who remained tolerant and continued with therapy up until their close-out visit. Finally, we do not know whether a longer duration of treatment may influence the observed elevations in biomarkers.

Fig. 1 Distribution of ALT levels in the treatment groups. The figure shows the distribution of ALT levels for all substudy participants taking colchicine and placebo. Horizontal grey lines indicate the ULN, 5 × ULN, and 10 × ULN. ALT alanine aminotransferase, ULN upper limit of normal.

Fig. 2 Distribution of CK levels in the treatment groups. The figure shows the distribution of CK levels for all substudy participants taking colchicine and placebo. Horizontal grey lines indicate the LLN, ULN, 1.5 × ULN, 5 × ULN, and 10 × ULN (myotoxicity). One outlier in the colchicine group was removed with a CK level of 4123 U/L. CK creatine kinase, LLN lower limit of normal, ULN upper limit of normal, U unit
5 Conclusion

In chronic CAD, 2–4 years of exposure to colchicine 0.5 mg once daily compared with placebo was associated with small elevations in ALT, albumin, and CK levels but was not associated with changes in renal function. These data suggest that despite modest elevations in liver enzymes and CK, 2–4 years of exposure to colchicine 0.5 mg once daily appears to be well tolerated in patients with chronic CAD.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40261-022-01209-8.

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Declarations

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Ethics statement The trial protocol was approved by a centralized Institutional Review Board in each participating country.

Consent to participate All participants gave their informed consent to have blood drawn at the close-out visit at the end of the LoDoCo2 trial.

Consent for publication Not applicable.

Availability of data and material The data underlying this article will be shared upon reasonable request to the Steering Committee via the following e-mail address: A.Mosterd@meandermc.nl.

Code availability Not applicable.

Author contributions All authors contributed to the conception of the strategy. The first draft of the manuscript was written by AB and NM, and all authors edited and commented on previous versions. All authors have read and approved the final manuscript.

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