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Drivers of mortality in patients with chronic coronary disease in the low-dose colchicine 2 trial☆

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ABSTRACT

Background: Low-dose colchicine significantly reduces the risk of cardiovascular events in patients with chronic coronary disease. An increase of non-cardiovascular death raised concerns about its safety. This study reports cause-specific mortality and baseline predictors of mortality in the *Low-Dose Colchicine 2 (LoDoCo2)* trial.

Methods: Patients with chronic coronary disease were randomly allocated to colchicine 0.5 mg once daily or placebo on a background of optimal medical therapy. Cause-specific mortality data were analysed, stratified by treatment status. Multivariate analyses were performed to examine the predictors of mortality as well as cardiovascular and non-cardiovascular death.

Results: After a median 28.6 months follow-up, 133 out of 5522 participants (2.4%) died. Forty-five deaths were cardiovascular (colchicine versus placebo: 20 [0.7%] versus 25 [0.9%], HR, 0.80; 95% CI, 0.44–1.44), while eighty-eight deaths were non-cardiovascular (53 [1.9%] versus 35 [1.3%]; HR, 1.51; 95% CI, 0.99–2.31). Forty-eight deaths were due to cancer (26 [0.9%] versus 22 [0.8%]), thirteen end-stage pulmonary disease (9 [0.3%] versus 4 [0.1%]), eight infection (4 [0.1%] versus 4 [0.1%]), five dementia (4 [0.1%] versus 1 [0.0%]) and five related multiple organ failure (3 [0.1%] versus 2 [0.1%]). Multivariable analysis demonstrated age > 65 years was the only independent baseline characteristic associated with non-cardiovascular death (HR, 3.65; 95% CI, 2.06–6.47).

Conclusions: During the *LoDoCo2* trial, assignment to colchicine was not associated with an adverse effect on any specific causes of death. Most deaths were related to non-cardiovascular causes, underscoring the importance of comorbidities as drivers of all-cause mortality in patients with chronic coronary disease.

Abbreviations: CANTOS, Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease; COLCOT, Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction; eGFR, estimated glomerular filtration rate; HR, hazard ratio; CI, confidence interval; IL, interleukin; LoDoCo2, Low-Dose Colchicine 2.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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1. Introduction

Anti-inflammatory therapy reduces the risk of cardiovascular events in patients with coronary disease. [1–3] However, there are concerns that suppressing the immune response may expose patients to an increased risk of serious infections. This concern was first raised in the *Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease (CANTOS)* trial, which demonstrated that inhibiting interleukin (IL)-1β with canakinumab reduced the risk of cardiovascular events. Despite these benefits, canakinumab did not reduce all-cause mortality and was associated with an increase in neutropenia and a small increase in the number of fatal infections, raising concerns about the safety of targeting IL-1β in patients with coronary disease. [1]

Recently, strong evidence has emerged to support cardiovascular benefits of low-dose colchicine in coronary artery disease. [2,3] Colchicine has broad anti-inflammatory effects. It is avidly taken up by leucocytes and endothelium and affects the expression of a range of interleukins including IL-1β, IL-6 and IL-18. These immunomodulating actions are believed to explain its effectiveness in the prevention of inflammatory flares in patients with gout, pericarditis, and Familial Mediterranean fever. [4,5]

The *Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction* (*COLCOT)* and *Low-Dose Colchicine 2* (*LoDoCo2)* trials together randomized >10,000 participants with coronary disease, with follow-up extending out to five years, demonstrating that low-dose colchicine on top of usual medical therapy reduced the composite of cardiovascular death, myocardial infarction, stroke, and coronary revascularization. [2,3] In both trials, colchicine did not affect all-cause mortality. While non-cardiovascular mortality was not a pre-specified endpoint, on post hoc analysis of the *LoDoCo2* trial colchicine was associated with a numeric increase in non-cardiovascular deaths. [3] To adequately judge the benefit/safety ratio with the possible widespread use of colchicine for coronary disease, this observation warrants detailed examination. [6] Here we report cause-specific mortality and baseline predictors of mortality.

2. Methods

2.1. Study population

The *LoDoCo2* trial (Australian New Zealand Clinical Trials Registry; ACTRN12614000093684) was a randomized, parallel, double-blind trial that evaluated the effect of adding colchicine 0.5 mg once daily or placebo in patients with chronic coronary disease on a background of optimal medical therapy. Randomization was performed in a 1:1 ratio with the use of a computerized algorithm, with stratification according to country. Details of the trial design are described elsewhere. [7] In brief, patients aged 35 to 82 years with proven coronary artery disease were recruited. In Australia, participants were recruited from private practices across metropolitan Perth and regional centers in Western Australia. In the Netherlands, participants were recruited from the outpatient clinics of 30 hospitals. The study excluded patients with cardiovascular events within the prior six months and those with advanced renal impairment (serum creatinine <150 mmol/l or estimated glomerular filtration rate (eGFR) <50 mL/min/1.73m^2), severe heart failure, known intolerance to colchicine, and dependency, frailty, or a predicted life expectancy <5 years. All participants had proven tolerant to a 30-day trial of open label colchicine. The full list of the in- and exclusion criteria is published in the trial design paper. [7]

The study was conducted according to the guidelines of the 1975 Declaration of Helsinki. The trial protocol was approved by a centralized institutional review board in each participating country: Sir Charles Gairdner Group HREC, Perth, Australia (HREC No. 2013–236) and MEC-U, Nieuwegein, the Netherlands (MEC-U No. R16.027). All trial participants provided written informed consent to participate in the trial. The trial was overseen by an independent data and safety monitoring board. The trial was ended due to completion, and the primary results of the trial have previously been published. [3]

2.2. Outcomes

Every six months participants presented in person to provide feedback about the status of their health. Outcomes were recorded, including admission to hospital for myocardial infarction, coronary intervention, or stroke. All correspondence related to clinical visits, hospital admissions, investigations and reports were obtained to determine and verify the occurrence of potential outcomes.

The primary efficacy outcome of the trial was the composite of cardiovascular death, myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization. Secondary outcomes included death from any cause, and cardiovascular death. Non-cardiovascular death was reported as a safety outcome. All deaths were adjudicated by a by a local member of the clinical events committee, blinded to treatment allocation, by assessment of a discharge summary or clinical notes, information by treating physician or a death certificate, and, if available, an autopsy report. If the adjudicator agreed with the site investigator, the event was confirmed. If the adjudicator did not agree a second adjudicator reviewed the clinical information, and consensus was reached after deliberation.

2.3. Statistical analysis

Cause-specific mortality data were tabulated according to treatment assignment. Baseline characteristics for the randomized population, comparing participants who died with those did not, were summarized using mean ± standard deviation for quantitative data and as proportions for categorical data. A univariate analysis was used to examine predictors of all-cause death, and multivariate analyses were used to examine the predictors of all-cause, cardiovascular and non-cardiovascular death by Cox proportional hazard models.

3. Results

Between August 2014 and December 2018, the LoDoCo2 trial enrolled 5522 patients with chronic coronary artery disease, with a median follow-up of 29 months (interquartile range, 21–44), and a maximum of 63 months. Vital status was confirmed in all patients. In each trial group, 10.5% of the patients permanently discontinued trial medication. Over the course of the trial, out of 5522 randomized patients, 133 (2.4%) died during. Forty-five deaths were due to cardiovascular causes (colchicine versus placebo: 20 [0.7%] versus 25 [0.9%], hazard ratio [HR], 0.80; 95% confidence interval [CI], 0.44–1.44), while eighty-eight deaths were due to non-cardiovascular causes (53 [1.9%] versus 35 [1.3%]; HR, 1.51; 95% CI, 0.99–2.31). Non-cardiovascular deaths were more frequent than cardiovascular deaths in both treatment groups. The majority of deaths were due to cancer (26 [0.9%] versus 22 [0.8%]), end-stage pulmonary disease (9 [0.3%] versus 4 [0.1%]), or infection (4 [0.1%] versus 4 [0.1%]). Categories of cause-specific mortality including non-cardiovascular death are listed in Table 1. Although there were more non-cardiovascular deaths in those assigned to colchicine compared with placebo, there was no significant difference in any specific cause of non-cardiovascular deaths between treatment groups**.** Of particular note was the finding that deaths due to the two conditions most likely to be affected by an adverse effect of colchicine on the immune system, i.e., cancer and infection, were largely identical.

In a univariate analysis, baseline characteristics associated with an increased risk of all-cause mortality included age > 65 years, diabetes, atrial fibrillation, and prior coronary artery bypass grafting. In contrast, statin use and anti-platelet therapies were associated with a reduced risk of all-cause mortality (Table 2). Multivariable analyses demonstrated that the baseline characteristics independently associated with all-cause

Table 1
Causes of death.

	Total, n = 5522		Colchicine, n = 2762		Placebo, n = 2760	
	n	(%)	n	(%)	n	(%)
All Deaths	133	(2.41)	73	(2.64)	60	(2.17)
Cardiovascular causes of deaths						
Sudden death	28	(0.51)	11	(0.40)	17	(0.62)
Major bleeding	6	(0.11)	2	(0.07)	4	(0.14)
Myocardial infarction	4	(0.07)	2	(0.07)	2	(0.07)
Heart failure	2	(0.04)	2	(0.07)	0	(0.00)
Stroke	2	(0.04)	1	(0.04)	1	(0.04)
Other	3	(0.05)	2	(0.07)	1	(0.04)
Non-cardiovascular causes of deaths						
Cancer	48	(0.87)	26	(0.94)	22	(0.80)
End stage pulmonary disease	13	(0.24)	9	(0.33)	4	(0.14)
Infection	8	(0.14)	4	(0.14)	4	(0.14)
Dementia	5	(0.09)	4	(0.14)	1	(0.04)
Multiple organ failure	5	(0.09)	3	(0.11)	2	(0.07)
Accidental	5	(0.09)	3	(0.11)	2	(0.07)
Other[a]	3	(0.07)	3	(0.11)	0	(0.00)
Unknown cause	1	(0.02)	1	(0.04)	0	(0.00)

[a] Cerebral arteritis, myeloma, post-operative aspiration pneumonitis.

mortality were: age > 65 years, current smoking, prior coronary artery bypass grafting, lipid lowering therapy and anti-platelet therapy. Baseline characteristics associated with cardiovascular death were diabetes, prior coronary bypass surgery, lipid lowering therapy and anticoagulant therapy. The only baseline characteristic independently associated with a non-cardiovascular death was age > 65 years (HR, 3.65; 95% CI, 2.06–6.47; Table 3).

4. Discussion

During the *LoDoCo2* trial, all-cause mortality was low, mostly related to non-cardiovascular causes in both treatment arms, and was unaffected by treatment with colchicine. Although the number of non-cardiovascular deaths was numerically higher in those assigned to colchicine, the incidence of specific causes of death, including cancer and infection, was no different in those assigned to colchicine or placebo. The proportion of cardiovascular to non-cardiovascular deaths was consistent with the number reported in the general population of non-hospitalized patients, [8] and consistent with recent reports in patients with chronic coronary disease treated with statins. [9] Together, these data underscore the importance of comorbidities as major drivers of all-cause mortality in well-managed patients with chronic coronary disease. [10–12]

Clinical experience over the last 70 years has confirmed the safety of long-term use of colchicine at doses >0.5 mg daily in a wide range of patients with a variety of conditions. Aside from intentional overdose, colchicine has not been associated with the development of any specific disease or cause of death. [5] Tabular meta-analyses of the contemporary placebo controlled trials of long-term low-dose colchicine in patients with and without cardiovascular disease in >15,000 patients have

Table 2
Univariate analyses.

	Alive, n = 5389		All Deaths, n = 133		Univariate analysis		
Characteristic	n	(%)	n	(%)	HR	(95% CI)	p-value
Age (mean ± SD)	65.7	± 8.6	70.9	± 7.1			
≤ 65 years	2394	(44)	30	(23)	1		
> 65 years	2995	(56)	103	(77)	2.44	(1.62–3.66)	<0.01
Female	834	(15)	12	(9)	0.58	(0.32–1.06)	0.08
Country							
Australia	1825	(34)	79	(59)	1		
The Netherlands	3564	(66)	54	(41)	1.01	(0.67–1.54)	0.95
Current smoker	632	(12)	16	(12)	1.44	(0.84–2.47)	0.18
Hypertension	2732	(51)	76	(57)	1.24	(0.88–1.76)	0.21
Diabetes	973	(18)	34	(26)	1.56	(1.05–2.3)	0.03
Renal function							
Stage 1,2	5092	(94)	124	(93)	1		
Stage 3	297	(6)	9	(7)	1.85	(0.92–3.72)	0.08
Prior ACS	4547	(84)	111	(83)	1.05	(0.67–1.67)	0.82
Prior coronary revascularization	4518	(84)	103	(77)	0.85	(0.56–1.29)	0.45
Prior CABG	677	(13)	33	(25)	2.17	(1.47–3.22)	<0.01
Prior PCI	4094	(76)	83	(62)	0.65	(0.45–0.92)	0.02
Atrial Fibrillation	623	(12)	26	(20)	1.88	(1.22–2.89)	<0.01
Gout	430	(8)	16	(12)	1.55	(0.92–2.62)	0.10
Antiplatelet therapy	4919	(91)	112	(84)	0.40	(0.25–0.65)	<0.01
Dual antiplatelet therapy	1252	(23)	28	(21)	0.81	(0.53–1.23)	0.32
Anti-coagulant	645	(12)	27	(20)	2.10	(1.37–3.22)	<0.01
Statin	5067	(94)	121	(91)	0.52	(0.29–0.95)	0.03
High dose statins	3329	(62)	84	(63)	0.76	(0.53–1.1)	0.15
Ezetimibe	1051	(20)	22	(17)	1.04	(0.65–1.65)	0.88
Lipid lowering agent	5212	(97)	123	(92)	0.35	(0.18–0.67)	<0.01
ACE or ARB	3862	(72)	98	(74)	1.08	(0.74–1.6)	0.68
Beta-blocker	3342	(62)	85	(64)	1.26	(0.88–1.8)	0.21
Calcium channel blocker	1210	(22)	34	(26)	1.13	(0.76–1.66)	0.55
Treatment							
Placebo	2700	(50)	60	(45)	1		
Colchicine	2689	(50)	73	(55)	1.21	(0.86–1.71)	0.26

ACE = angiotensin converting enzyme, ACS = acute coronary syndrome, ARB = angiotensin receptor blocker, CABG = coronary artery bypass grafting, CI = confidence interval, HR = hazard ratio, PCI = percutaneous coronary intervention, SD = standard deviation.

Table 3
Multivariate analyses.

	All-cause death			CV death			Non-CV death		
Characteristic	HR	(95% CI)	p-value	HR	(95% CI)	p-value	HR	(95% CI)	p-value
Age									
>65 years	2.18	(1.43–3.32)	0.0003				3.65	(2.06–6.47)	<0.0001
<65 years	1						1		
Female									
Current smoker	1.83	(1.06–3.17)							
Hypertension									
Diabetes				2.96	(1.63–5.37)	0.0004			
Renal function									
Stage 1,2									
Stage 3									
Prior ACS									
Prior CABG	1.84	(1.24–2.75)		3.09	(1.67–5.74)	0.0003			
Prior PCI									
Antiplatelet therapy	0.51	(0.31–0.82)							
Anti-coagulant				3.27	(1.74–6.12)	0.0002			
High dose statins									
Ezetimibe									
Lipid lowering agent	0.38	(0.20–0.74)		0.19	(0.08–0.45)	0.0002			
ACE or ARB									
Beta-blocker									
Calcium channel blocker									
Treatment									
Placebo									
Colchicine									

ACE = angiotensin converting enzyme, ACS = acute coronary syndrome, ARB = angiotensin receptor blocker, CABG = coronary artery bypass grafting, CI = confidence interval, CV = cardiovascular, HR = hazard ratio, PCI = percutaneous coronary intervention.

not linked colchicine with the composite of non-cardiovascular death or any specific disease or cause of death. [13–16] In ongoing future studies, it will be important to ensure that safety meta-analyses consider disease-specific causes of death rather than the composite of non-cardiovascular mortality. [17]

4.1. Limitations

The number of non-cardiovascular deaths in the trial was low, and the number of deaths attributed to a specific cause other than cardiovascular disease and cancer was very low, which limits power. For this reason, these data are insufficient to definitively exclude a causal link between long-term colchicine and any specific cause of death. As we did not prospectively collect an exhaustive list of comorbidities at randomization, we cannot exclude the possibility that a baseline imbalance in comorbidities in the treatment groups accounted for some of the differences in non-CV deaths.

5. Conclusions

During the *LoDoCo2* trial, assignment to colchicine was not associated with an adverse effect on total deaths, nor with any specific causes of death. In particular, deaths due to cancer and infection were equivalent. Most deaths were related to non-cardiovascular causes, underscoring the importance of comorbidities as drivers of all-cause mortality in patients with chronic coronary disease.

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CRediT authorship contribution statement

Tjerk S.J. Opstal: Investigation, Visualization, Writing – original draft. **Stefan M. Nidorf:** Conceptualization, Investigation, Writing – original draft. **Aernoud T.L. Fiolet:** Investigation, Writing – review & editing. **John W. Eikelboom:** Conceptualization, Supervision, Writing – review & editing. **Arend Mosterd:** Investigation, Writing – review & editing. **Willem A. Bax:** Investigation, Validation, Writing – review & editing. **Charley A. Budgeon:** Data curation, Formal analysis, Visualization. **Eelko Ronner:** Resources, Investigation, Writing – review & editing. **Fransisco J. Prins:** Resources, Investigation, Writing – review & editing. **Jan G.P. Tijssen:** Methodology, Data curation, Formal analysis. **Astrid Schut:** Resources, Funding acquisition, Writing – review & editing. **Peter L. Thompson:** Supervision, Writing – review & editing. **Saloua El Messaoudi:** Supervision, Writing – review & editing. **Jan H. Cornel:** Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

Declaration of Competing Interest

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

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