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# Colchicine for Secondary Cardiovascular Prevention in Coronary Disease

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**A** large body of evidence has demonstrated the important role of inflammation in atherosclerosis.<sup>1</sup> Inhibition of interleukin-1 $\beta$  by the injectable antibody canakinumab reduced the rate of cardiovascular events by 15% in the CANTOS study (Canakinumab Anti-inflammatory Thrombosis Outcomes Study).<sup>2</sup> However, canakinumab is extremely expensive and not approved for cardiovascular prevention, and was associated with a slight but significant increase in septic shock and reduced risk of cancer mortality. In addition, methotrexate, another agent with anti-inflammatory properties, failed to provide beneficial effects on cardiovascular outcomes or biomarkers of inflammation in a large randomized trial.<sup>3</sup> In contrast, colchicine is an orally administered, inexpensive anti-inflammatory medication that has been shown to reduce significantly nonfatal cardiovascular events in patients with coronary artery disease.<sup>4–6</sup>

The COLCOT trial (Colchicine Cardiovascular Outcomes Trial) randomly assigned 4745 patients to receive colchicine 0.5 mg once daily or placebo within 30 days after a myocardial infarction (MI).<sup>4</sup> The median duration of follow-up was 22.6 months. Low-dose colchicine reduced the risk of the primary end point of time to first cardiovascular event, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina requiring coronary revascularization by 23% compared to placebo. The risk of the total burden of these primary ischemic cardiovascular events (both first and recurrent) was also reduced by 34% with colchicine in COLCOT. The benefit was due to effects on all components of the primary end point, with hazard ratios of 0.26 (95% confidence interval [CI], 0.10–0.70) for stroke; 0.50 (95% CI, 0.31–0.81) for urgent hospitalization for angina requiring coronary revascularization (the main weight); 0.84 (95% CI, 0.46–1.52) for cardiovascular death; and 0.91 (95% CI, 0.68–1.21) for MI. Colchicine was also shown to have a more marked effect on MI when initiated within the first 3 days after the acute coronary syndrome.<sup>5</sup>

The results of the LoDoCo2 trial (Low-Dose Colchicine-2) complemented those of COLCOT. LoDoCo2 included 5522 patients with chronic coronary disease who were randomized to receive low-dose colchicine or placebo.<sup>6</sup> Patients were followed for a median duration of 28.6 months. The risk of the primary end point of cardiovascular death, MI, ischemic stroke, or ischemia-driven coronary revascularization was reduced by 31% by colchicine. As compared with placebo, colchicine reduced the risk of cardiovascular death, MI and stroke by 28% and that of MI by 30%.

It is against the backdrop of these trials that the results of the smaller Australian COPS study (Colchicine in Patients With Acute Coronary Syndrome) are reported by Tong et al in this issue of *Circulation*.<sup>7</sup> COPS was a study of 795 patients with an

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acute coronary syndrome followed for 12 months. The hazard ratio for the primary composite outcome of all-cause mortality, acute coronary syndrome, noncardio-embolic ischemic stroke, or unplanned ischemia-driven urgent revascularization was 0.65 (95% CI, 0.38–1.09) in favor of colchicine. The result was not statistically

significant because COPS was small, with a total of 62 primary end point events. In contrast, there was a total of 752 patients with primary end point events in COLCOT and LoDoCo2.

In COPS, the numbers of deaths were 8 and 1 in the colchicine and placebo groups, respectively. The

**Table. Comparison of COLCOT, COPS and LoDoCo2.**

Randomization group	COLCOT				COPS				LoDoCo2			
	N=4745		Hazard ratio (95% CI)	P value	N=795		Hazard ratio (95% CI)	P value	N=5522		Hazard ratio (95% CI)	P value
	Colchicine n=2366	Placebo n=2379			Colchicine n=396	Placebo n=399			Colchicine n=2762	Placebo n=2760		
Age, y	≥ 18				18–85				35–82			
Acute coronary syndrome	< 30 days postmyocardial infarction				yes†				Stable CAD No event in the past 6 mo			
Coronary artery disease	Myocardial infarction				≥30% luminal stenosis in epicardial vessel of >2.5 mm diameter by angiographic assessment				Invasive or CT coronary angiography Coronary artery calcium score > 400 U			
Median follow-up, mo	22.6				12				28.6			
Components of the primary end point	cardiovascular death, cardiac arrest, myocardial infarction, stroke, or urgent hospitalization for angina requiring coronary revascularization				death, acute coronary syndrome, ischemia-driven urgent revascularization, or stroke				cardiovascular death, myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization			
Primary efficacy end point, n (%)	131 (5.5)	170 (7.1)	0.77 (0.61–0.96)	0.02	24	38	0.64 (0.38–1.09)	0.09	187 (6.8)	264 (9.6)	0.69 (0.57–0.83)	<0.001
Mortality												
All-cause mortality death, n (%)	43 (1.8)	44 (1.8)	0.98 (0.64–1.49)		8	1	8.2 (1.03–65.61)	0.047	73 (2.6)	60 (2.2)	1.21 (0.86–1.71)	
CV death, n (%)	20 (0.8)	24 (1.0)	0.84 (0.46–1.52)		3	1	3.1 (0.32–29.71)		20 (0.7)	25 (0.9)	0.80 (0.44–1.44)	
Non CV death, n (%)	23 (1.0)	20 (0.8)			5	0		0.023	53 (1.9)	35 (1.3)	1.51 (0.99–2.31)	
Components of the composite primary end point, ITT population												
Deaths due to any cause	Not included among primary end point				8	1	8.2 (1.03–65.61)	0.047	Not included among primary end point			
CV death, n (%)	20 (0.8)	24 (1.0)	0.84 (0.46–1.52)		Not included among primary end point				20 (0.7)	25 (0.9)	0.80 (0.44–1.44)	
Resuscitated CA, n (%)	5 (0.2)	6 (0.3)	0.83 (0.25–2.73)		Not included among primary end point				Not included among primary end point			
MI, n (%)	89 (3.8)	98 (4.1)	0.91 (0.68–1.21)		Not included among primary end point				83 (3.0)	116 (4.2)	0.70 (0.53–0.93)	0.01
ACS	Not included among primary end point				11	20	0.56 (0.27–1.18)	0.13	Not included among primary end point			
Stroke, n (%)	5 (0.2)	19 (0.8)	0.26 (0.10–0.70)		2	5	0.41 (0.08–2.10)	0.28	16 (0.6)	24 (0.9)	0.66 (0.35–1.25)	0.20
UHARCR or unplanned revascularization, n (%)	25 (1.1)	50 (2.1)	0.50 (0.31–0.81)		3	12	0.26 (0.07–0.92)	0.037*	135 (4.9)	177 (6.4)	0.75 (0.60–0.94)	0.01
Selected secondary end points												
DVT or PE, n (%)	10 (0.4)	7 (0.3)	1.43 (0.54–3.75)		NA				17 (0.6)	16 (0.6)	1.06 (0.53–2.10)	
Atrial fibrillation (and flutter in LoDoCo2), n (%)	36 (1.5)	40 (1.7)	0.93 (0.59– 1.46)		NA				126 (4.6)	148 (5.4)	0.84 (0.66–1.07)	

ACS indicates acute coronary syndrome; CA, cardiac arrest; CAD, coronary artery disease; COLCOT, Colchicine Cardiovascular Outcomes Trial; COPS, Colchicine in Patients With Acute Coronary Syndrome; CV, cardiovascular; CVD, cardiovascular death; DVT, deep venous thrombosis; ITT, intention to treat; LoDoCo2, Low-Dose Colchicine-2; MI, myocardial infarction; NA, not available; PE, pulmonary embolism; TIA, transient ischemic attack; and UHARCR, urgent hospitalization for angina requiring coronary revascularization.

\*Urgent revascularization, to be more accurate.

†In the COPS trial, the delay between index MI and randomization is reported to be short but is not provided in detail.

value of that observation is uncertain and may reflect the play of chance (Table) and should be interpreted conservatively. Indeed, there were more than twice the number of patients with incomplete follow-up than that of deaths in COPS, and all follow-up procedures were conducted centrally by only 2 part-time research staff members for 795 patients (personal communication). This may explain the unusually low rate of deaths (0.25%) in the placebo group of COPS. In contrast, the corresponding numbers were 43 and 44 deaths in COLCOT (hazard ratio (HR), 0.98; 95% CI, 0.64–1.49) and 73 and 60 deaths (HR, 1.21; 95% CI, 0.86–1.71) in LoDoCo2. Although not powered to detect a benefit on fatal events when taken in isolation, cardiovascular deaths occurred in 20 and 24 patients HR, 0.84; 95% CI, 0.46–1.52) in COLCOT and 20 and 25 patients (HR, 0.80; 95% CI, 0.44–1.44) in LoDoCo2.

The numbers of noncardiovascular deaths in the COPS study were 5 and 0 in the two study arms. The respective numbers were 53 and 35 in LoDoCo2 (HR, 1.51; 95% CI, 0.99–2.31). This trend is inconsistent with safety results from randomized clinical trials investigating colchicine use in patients with gout, familial Mediterranean fever, and pericarditis, which have not suggested an imbalance in all-cause mortality or noncardiovascular deaths.<sup>8,9</sup> In the COPS study, the increased dose of colchicine during the first month of follow-up (0.5 mg twice daily) might have contributed to the different result observed. In addition, 3 of 5 colchicine patients who died from noncardiovascular causes in COPS had discontinued colchicine prior to date of death, which may suggest that on-treatment analyses may provide further evidence to the safety of colchicine for noncardiovascular mortality. In COLCOT,<sup>4</sup> a small but significant increase in the incidence of pneumonia was observed in the colchicine group (0.9%) compared to placebo (0.4%), but this difference was not observed in LoDoCo2.<sup>6</sup> There was also, in the latter study, no imbalance between study arms in hospitalization for infection or gastrointestinal reason and diagnosis of cancer.<sup>6</sup> More importantly, there was no significant difference in mortality of all causes between patients randomly assigned to receive colchicine or placebo in the 10,267 patients included in COLCOT and LoDoCo2. Importantly, median follow-up duration was twice as long in these much larger studies than in COPS.

The underlying mechanisms for the cardiovascular benefits of colchicine have not yet been entirely delineated. Although this knowledge is certainly not essential for the clinical use of colchicine, it would allow for the determination of the potential of various inflammatory pathways and related medications. The only known target of colchicine is binding to tubulin, which affects microtubule polymerization and ultimately inflammasome activation and interleukin-1 $\beta$ /6 release. The pleiotropic actions of colchicine include reduced

migration of white blood cells and lowering of cellular adhesion molecules and inflammatory chemokines.<sup>10</sup>

In this issue of *Circulation*, Opstal et al conducted a proteomic analysis of the LoDoCo2 trial in 174 patients who underwent blood sampling at baseline and at the end of the 30-day run-in treatment period with colchicine.<sup>11</sup> Targeted proteomic analysis included 184 proteins measured in serum with Olink cardiovascular panels. Colchicine resulted in a significant reduction of 37 serum proteins. Attenuation of the NLRP3 inflammasome pathway was supported by a reduction of interleukin-18, interleukin-1 receptor antagonist, and interleukin-6. These effects may be partially upstream of the NLRP3 inflammasome, as suggested by the reduction of NF- $\kappa$ B essential modulator, which is involved in the activation of the NLRP3 inflammasome. In addition, the largest reductions during colchicine therapy concerned proteins involved in neutrophil degranulation, such as myeloblastin, carcinoembryonic antigen-related cell adhesion molecule 8, azurocidin, and myeloperoxidase. The absence of a placebo group in this 30-day run-in study represents a limitation of the analysis.

In conclusion, colchicine at a dose of 0.5 mg once daily reduces inflammasome activation and neutrophil degranulation and lowers the risk of ischemic cardiovascular events both in patients with a recent MI and in those with stable chronic coronary artery disease. In the postMI setting, initiation of colchicine within the first 3 days after the event, before hospital discharge, appears to provide even greater benefits.<sup>5</sup> In patients with chronic coronary disease, colchicine should not be administered with strong cytochrome P450 3A4 inhibitors. The addition of colchicine to standard of care has been shown to be an economically dominant strategy that generates cost savings.<sup>12</sup> Given that it reduces nonfatal cardiovascular events without affecting all-cause mortality, low-dose colchicine could be considered for patients with coronary disease and no severe renal dysfunction to reduce the considerable related cardiovascular morbidity.

## ARTICLE INFORMATION

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