Low Dose Colchicine in Coronary Disease

Colchicine is a generic medication for the treatment of gout. It also inhibits several inflammatory pathways known to be associated with atherosclerosis. Colchicine holds promise as a widely available medication that could be repurposed for the secondary

prevention of atherosclerotic cardiovascular disease (ASCVD), based on the results of large clinical trials such as LoDoCo2, presented at the virtual ESC Congress 2020 and published simultaneously.**(Ref:1)**

It had already been shown in 4,745 patients with a recent MI that a colchicine dose of 0.5 mg daily led to a significantly lower risk of ischemic

cardiovascular events than placebo. **(Ref:2)**

In an earlier trial of low-dose colchicine in patients with ASCVD (LoDoCo), Nidorf et al. demonstrated that the rate of acute cardiovascular events was lower among those who received 0.5 mg of colchicine once daily than among those who did not receive colchicine. LoDoCo, however, was an open-label

trial involving only 532 participants. **(Ref:3)** Clearly, there needed to be a much larger, randomized trial to confirm those results – and that was LoDoCo2.

Nidorf and colleagues randomized patients with stable, established ASCVD – based on angiography or coronary computed tomography – who were tolerant to colchicine during a 30-day open-label run-in phase. Of 6,528

enrolled in the trial, 91.3% of patients tolerated open-label therapy, and of those who were intolerant, most reported transient gastrointestinal symptoms. (Early intolerance was markedly reduced after patients were begun at a daily half-dose for 1 week and then placed on the full 0.5 mg/day dose.) Once patients were on therapy, they tolerated it very well over time.

After the run-in period, 5,552 patients were randomized to colchicine 0.5 mg daily or placebo on a background of lipid-lowering and antithrombotic therapy.**(Ref:1)** The primary endpoint was a composite of cardiovascular death, MI, ischemic stroke, or ischemia-driven coronary revascularization.

During a median follow-up of almost 30 months, the primary endpoint occurred

in 187 (6.8%) patients in the colchicine group, compared with 264 (9.6%) in the placebo group (hazard ratio [HR]: 0.69; 95% confidence interval [CI]: 0.57 to 0.83; $p < 0.001$). When the components of the primary endpoint were analyzed separately, a consistent trend was seen in the colchicine arm for all endpoints, including significantly

lower rates of MI and ischemia-driven coronary revascularization (**Table**).

LoCoDo2: Colchicine in Patients with Chronic Coronary Disease

	Colchicine (n = 2,762)	Placebo (n = 2,760)	HR (95% CI)	p Value
Primary endpoint*	6.8%	9.6%	0.69 (0.57-0.83)	<0.001
Select secondary endpoints				
CV death	0.7%	0.9%	0.80 (0.44-1.44)	
Myocardial infarction	3.0%	4.2%	0.70 (0.53-0.93)	0.01
Ischemic stroke	0.6%	0.9%	0.66 ((0.35-1.25)	0.20
Ischemia-driven coronary revascular-ization	1.8%	2.4%	0.75 (0.60-0.94)	0.01
Death from any cause	2.6%	2.2%	1.21 (0.86-1.71)	
Adverse events†				
Noncardio-vascular death	1.9%	1.3%	1.51 (0.99-2.31)	

*Cardiovascular death, myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization

†Intention-to-treat population

Safety Signal?

The crude rates of both all-cause mortality and noncardiovascular death were higher with colchicine than with placebo, but the difference was not significant, based on the 95% CI. The authors acknowledged that while the trend might have been due to chance, "the hazard ratio of 1.51 (for noncardiovascular death) is of potential

concern." They added that the individual causes of death did not permit a clear interpretation of this finding.

In the earlier COLCOT trial, noncardiovascular mortality occurred in 23 patients who received colchicine and 20 patients who received placebo. When results were combined for COLCOT, LoDoCo, and LoDoCo2, there

was no significant effect of active therapy on noncardiovascular death.
Significant bone marrow toxicity or death related to colchicine use have been reported only in the setting of intentional overdose or coadministration with clarithromycin.
Low-dose colchicine was well tolerated over the longer term: the rate of permanent discontinuation was low

(<10%) and was similar among those taking placebo.
During a maximum follow-up of 5 years, low-dose colchicine was not associated with any serious adverse effects. Neutropenia and myotoxicity were rare and no more frequent with the drug than with placebo.
No unfavorable effects were found when active therapy was combined with

statin therapy, even at high doses of statins, which were used by 68.1% of the entire study group. The risk of infection leading to hospitalization or death, or new or fatal cancer, was also no different compared with placebo.

According to Nidorf, MD the first author of the LoDoCo2 paper, and Peter Lindsay Thompson, MD : “Colchicine is a unique, sophisticated agent that has

the potential to be successfully repurposed beyond its existing widespread role in the secondary prevention of acute inflammatory flares in gout and FMF (familial Mediterranean fever)."**(Ref:4)**

As for who should not be considered candidates for a trial of low-dose colchicine, Dr. Nidorf included patients with advanced renal disease, patients

with known hematologic conditions (neutropenia in particular), and those already on clarithromycin, as well as some antifungal and antirejection therapies.

Take-home Messages:

- Among patients with coronary artery disease, most of whom were already receiving proven secondary prevention therapies, once-daily

colchicine resulted in a 31% lower relative risk of cardiovascular death, spontaneous myocardial infarction (MI), ischemic stroke, or ischemia-driven coronary revascularization (the composite primary endpoint) compared to placebo.

- In the large LoDoCo2 trial, the effects of colchicine appeared to be consistent across each component of

the primary endpoint and all secondary composite endpoints.

- Numerically, there were more all-cause deaths and more noncardiovascular deaths in the colchicine arm. While this could have been due to chance, the individual causes of death did not permit a clear interpretation of these two findings.

References:

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2. **Tardif JC, Kouz S, Waters DD, et al.** Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction. *N Engl J Med* 2019;381:2497-505.
3. **Nidorf SM, Eikelboom JW, Budgeon CA, Thompson PL.** Low-dose colchicine for secondary prevention of cardiovascular

disease. *J Am Coll Cardiol* 2013;61:404-10.

4. **Nidorf SM, Thompson PL.** Why Colchicine Should Be Considered for Secondary Prevention of Atherosclerosis: An Overview. *Clin Ther* 2019;41:41-8.