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Could colchicine reduce cardiovascular events in coronary artery disease without increasing all-cause mortality: Avoid optical illusions!

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Coronary artery disease remains the leading cause of death worldwide, despite advances in both pharmacological and interventional management. Inflammation is involved in atherosclerosis, both early in the formation and later triggering the rupture of a vulnerable plaque. Recently, cytokine-targeted treatment approaches have emerged as promising in the management of atherosclerotic disease. Inhibition of interleukin-1 β by canakinumab reduced the rate of cardiovascular events by 15% in the CANTOS study (Canakinumab Anti-inflammatory Thrombosis Outcomes Study) [1]. However, canakinumab's use may lead to significant side effects (increased risk of fatal infections, leukopenia, thrombocytopenia), while its high cost prevents from a widespread clinical translation in the setting of secondary prevention. In addition, the administration of Tocilizumab, a humanized monoclonal antibody against the IL-6 receptor, after myocardial infarction, reduced myocardial/reperfusion injuries [2]. Furthermore, colchicine, a low-cost and well-known anti-inflammatory agent widely used in pericarditis, gout, and familial Mediterranean fever, has been shown to inhibit the pathways involving IL-1 β , IL-6, and IL-18. Several large international clinical studies have shown that Colchicine is associated with a significantly lower non-fatal cardiovascular events in patients with coronary disease compared to placebo group.

In the COLCOT trial [3](Colchicine Cardiovascular Outcomes Trial), 4745 patients were randomly assigned to receive colchicine 0.5 mg once daily or placebo within 30 days after a myocardial infarction (MI). The median duration of follow-up was 22.6 months. A Low-dose colchicine led to a significantly lower risk of ischemic cardiovascular events when compared to the placebo (hazard ratio 0.77, 95% CI: 0.46–1.52), but no change in overall survival (hazard ratio 0.98, 95% CI 0.64–1.49). Moreover, earlier initiation (within 3 days) was associated with incremental clinical benefits [4].

In the LoDoCo-2 trial [5], 5522 patients with chronic coronary artery disease were randomized to placebo or colchicine 0.5 mg once daily. The primary endpoint of cardiovascular death, spontaneous myocardial infarction, ischemic stroke, or ischemia driven coronary revascularization occurred less frequently in the colchicine arm (hazard ratio 0.69, 95% CI 0.57–0.83) during a median follow-up of 28.6 months.

Finally, a meta-analysis has confirmed that Colchicine reduced by 49% the composite endpoint in the patients with chronic coronary syndrome and caused a non-significant 23% risk reduction in acute coronary syndrome [6].

However, LoDoCo-2 trial showed a slightly increased rates of death from any cause and non-cardiovascular death within the colchicine group. Nonetheless, the observed between group difference was not statistically significant (overall death, colchicine versus placebo: 73 [2.6%] versus 60[2.2%], HR, 1.21; 95% CI, 0.86–1.71, and non-cardiovascular death 53 [1.9%] versus 35 [1.3%]; HR, 1.51; 95% CI, 0.99–2.31). These findings were not reported in the COLCOT trial where the incidence rates of non-cardiovascular death was similar in the two groups (23 patients versus 20 patients).

In this new analysis, Opstal et al. [7] address this issue by a detailed analysis of causes of deaths. Most of non-cardiovascular deaths were due to cancer (Colchicine versus placebo: 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%]), hence, there was no significant difference in any specific cause of non-cardiovascular deaths between treatment groups. Death from cerebral arteritis, myeloma, post operative aspiration were only reported in the colchicine group. These data could suggest an imbalance in comorbidities between groups at baseline. On the other hand, attributing an exact cause of death is submitted to a subjective component and could be challenging, which can lead to a misclassification into cardiovascular or non-cardiovascular death. When death certificates are used for coding causes of deaths, there is evidence of overreporting of cardiovascular deaths [8].

In LoDoCo2, the median follow up is 28.6 months and most of patients had their last ACS >2 years ago at inclusion. Compared to COLCOT, a longer-term follow up could explain the increase in non-cardiovascular death, especially if there was a difference between the origin of ACS at baseline (STEMI vs UA/NSTEMI) [9], data not published in the two trials until now. Cardiovascular and non-cardiovascular deaths are indeed competing risk: if cardiovascular mortality decreases, there may be an apparent increase in non-cardiovascular mortality [10]. In the latter analyses of LoDoCo2, age > 65 years old was the only characteristic at baseline associated with an increased risk of non-cardiovascular death [7]. Thus, patients in LoDoCo2 were relatively older than in COLCOT (respectively, mean age Colchicine versus Placebo: 65.8 ± 8.4 versus 65.9 ± 8.7 ; and 60.6 ± 10.7 versus 60.5 ± 10.6).

In conclusion, Colchicine is well known since centuries, and clinical experience has demonstrated the safety of a long-term use of this molecule in a large body of pathologies. Its efficiency by reducing cardiovascular death in LoDoCo2 should not be masked by interpreting the overall mortality. In this case, the increased rate of non-cardiovascular could be due to a random chance and not directly linked to Colchicine.

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