Colchicine in Patients with Chronic Coronary Disease

TO THE EDITOR: In their report on a trial of low-dose colchicine (LoDoCo2) in patients with chronic coronary disease, Nidorf et al. (Nov. 5 issue)[1] found that those who received colchicine had a 31% lower risk of adverse cardiovascular events than those who received placebo (hazard ratio, 0.69; 95% confidence interval [CI], 0.57 to 0.83). This finding supports the role of inflammation as a key mediator in the development of cardiovascular disease.

In one prespecified subgroup analysis, we noticed an interesting interaction showing a greater treatment effect among the patients in Australia than among those in the Netherlands (hazard ratios of 0.51 and 0.92, respectively). According to the baseline characteristics of these groups as stratified by location, some key differences in the Netherlands population include a higher incidence of smoking (15.7% vs. 4.2%), a higher incidence of stage 3a chronic kidney disease (7.9% vs. 1.1%), and a greater use of anticoagulants (14.3% vs. 8.1%) (Table S4 in the Supplementary Appendix of the article, available at NEJM.org). Further investigation may be warranted to determine whether these differing characteristics between trial populations had any effect on outcomes. If so, the presence of such factors could influence the decision to administer colchicine for reducing cardiovascular events in patients with chronic coronary disease.

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No potential conflict of interest relevant to this letter was reported.

1. Nidorf SM, Fiolet ATL, Mosterd A, et al. Colchicine in patients with chronic coronary disease. N Engl J Med 2020;383:1838-47.

DOI: 10.1056/NEJMc2034992

TO THE EDITOR: The results of the LoDoCo2 trial confirm the efficacy and safety of low-dose colchicine that was observed in the Colchicine Cardiovascular Outcomes Trial (COLCOT)[1] and in the LoDoCo pilot study. However, the LoDoCo2 trial was limited by the low number of female patients, who accounted for only 15.3% of the trial population, a proportion that was even lower than that in COLCOT (19.2%) and in the LoDoCo pilot study (23%).

In COLCOT and LoDoCo2 trials, the investigators provided sex-specific hazard ratios for the primary efficacy end points in the Supplementary Appendix (available with the full text of the article at NEJM.org) without further discussion in the text. The between-group difference in adverse cardiovascular events between colchicine and placebo was significant in men, but not in women. In addition, adverse effects were not broken down according to sex. The inadequate inclusion of women and the underreporting of sex-specific adverse effects, which would hamper later meta-analyses, is problematic, given the similar prevalence of chronic coronary disease in the target population,[2] the pathophysiologic differences between men and women, and worse outcomes among women with cardiovascular disease. Guidelines and policies of the National Institutes of Health,[3] the Food and Drug Administration,[4] the European Commission, and the International Committee of Medical Journal Editors[5] should be followed in order to report the real effectiveness and safety of colchicine in patients with chronic coronary disease.

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DOI: 10.1056/NEJMc2034992

TO THE EDITOR: In the LoDoCo2 trial, Nidorf et al. report a lower incidence of cardiovascular events with colchicine than with placebo in chronic coronary disease. A subgroup effect suggests that the benefit applies to patients in Australia but may not apply to patients in the Netherlands. Although subgroup differences may be misleading, we have ways of judging the credibility of an observed effect.[1-3] The current analysis has several strengths, including a priori specification, the use of a relative outcome measure, a clinically important effect size, and low probability of observing a difference of at least this magnitude if false, which can be inferred from the nonoverlapping 95% confidence intervals. To quantify this last criterion, it would be useful for the authors to report the P value for the heterogeneity test they performed, according to the trial protocol.

Other important questions cannot be answered on the basis of the data that are provided. Were similar subgroup effects seen in secondary outcomes? Did race, ethnic group, medication adherence, or mode of coronary-disease diagnosis differ between the countries? And would regression analysis show independence of the effect? On the basis of the currently available information, additional trials are warranted before the use of colchicine in patients with chronic coronary disease is implemented worldwide.

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DOI: 10.1056/NEJMc2034992

TO THE EDITOR: In the LoDoCo2 trial, patients with chronic coronary disease who received colchicine had a lower risk of cardiovascular events than those who received placebo but did not have a corresponding lower risk of death. Clonal hematopoiesis of indeterminate potential (CHIP; the presence of leukemia-associated gene mutations in patients without detectable hematologic cancer) increases in incidence with age, and clones that consist of at least 10% of circulating nucleated cells are found in 10 to 15% of adults who are older than 70 years of age.[1] CHIP is associated with increased cardiovascular morbidity and mortality owing to accelerated atherosclerosis caused by proinflammatory interactions between endothelium and clonal monocytes (mediated by the NLRP3 inflammasome).[2,3] Since colchicine has been shown to suppress the activation of the NLRP3 inflammasome and the production of interleukin-1β in circulating monocytes in patients with acute coronary syndrome,[4] it may be especially beneficial in patients with CHIP. Thus, it would be of great interest if the authors could test for the presence of the CHIP mutations in at least a subgroup of patients and analyze whether an interaction exists among the receipt of colchicine, the presence of CHIP, and clinical outcomes.

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Dr. Lucijanic reports receiving consulting and lecture fees from AbbVie, Roche, Amgen, Takeda, Novartis, Janssen Pharmaceutica, Sandoz, and Alvogen. No other potential conflict of interest relevant to this letter was reported.

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DOI: 10.1056/NEJMc2034992

TO THE EDITOR: Nidorf et al. hypothesize that the protective effect of colchicine was attributable to its antiinflammatory activity. However, it should be taken into consideration that colchicine also has antiplatelet effects, which suggests that its beneficial cardiovascular properties may be due, at least in part, to an inhibitory effect on platelet activity.[1,2] The two mechanisms are not at variance with one another, since treatments targeting inflammation may also beneficially modulate platelet activation, whereas antiplatelet drugs could ameliorate the risk of thrombosis once the trigger (plaque rupture or erosion) has occurred.[3] Unfortunately, the LoDoCo2 trial does not afford the opportunity to probe directly the possibility that colchicine-mediated platelet inhibition is a clinically relevant phenomenon, since platelet activity was not tested and bleeding events were not reported.

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No potential conflict of interest relevant to this letter was reported.

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DOI: 10.1056/NEJMc2034992

THE AUTHORS REPLY: The first three correspondents raise questions about apparent quantitative differences in treatment effect among subgroups. In general, we think that the results for the overall trial provide the most reliable estimate of treatment effect. We urge caution in interpreting the primary outcome in subgroups, since such comparisons are almost always underpowered and come with increasing statistical likelihood of false positive results.[1,2] Subgroup differences are common, and the regional differences found in our trial are unexplained by known biologic mechanisms. We are currently further exploring possible reasons for these hypothesis-generating results.

We share the concern of Gebhard and Regitz-Zagrosek regarding sex-related differences in pathophysiologic features and sociocultural behavior (i.e., "gender") among patients with coronary disease. The enrollment of women in our trial was not proportional to the prevalence of cardiovascular disease among women in the general population. This reality is in line with other trials and remains a matter of concern to funders and regulatory authorities.[3,4] Various explanations, including sex-based differences in the perception of risk in participating in a trial, have been suggested in the literature.[5] We were not able to identify reasons for the underrepresentation of women in our trial. We note that our results were directionally consistent according to region and sex and in line with the findings from the earlier COLCOT, which should give health care providers the confidence to administer the treatment in various populations.

Lucijanic et al. suggest that proinflammatory effects of CHIP as mediated by the NLRP3 inflammasome could modify the treatment effects observed in our trial. The correlation of this genetic marker with clinical outcomes may identify a high-response subpopulation, but we are unable to explore this hypothesis because we currently do not have access to the required blood samples.

Finally, we agree with D'Amario et al. regarding the relevance of the colchicine–platelet interaction as possibly contributing to the benefits of the drug in preventing major adverse cardiovascular events. As the correspondents note, we were unable to address this issue in our trial because we did not perform platelet-function testing.

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Since publication of their article, the authors report no further potential conflict of interest.

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DOI: 10.1056/NEJMc2034992

Percutaneous Tracheostomy

TO THE EDITOR: In the Video in Clinical Medicine by Hashimoto et al. (Nov. 12 issue),[1] the authors describe a technique for percutaneous tracheostomy that can reduce risks to health care workers when performing aerosol-generating procedures during the Covid-19 pandemic. However, some pandemic-related modifications to practice may imperil patients. Therefore, provisions are necessary to ensure patient safety. For example, pausing ventilation during tracheostomy reduces the risk of viral transmission to clinicians but may result in life-threatening derecruitment in critically ill patients.[2] For this reason, we believe that an apnea test[2] is advisable before pausing ventilation to ensure that the patient can safely withstand the transient loss of positive end-expiratory pressure.

Another consideration is monitoring. The video by Hashimoto et al. depicts a nurse exiting the procedure room to minimize exposure; however, having a dedicated person present to monitor vital signs and sedation improves patient safety. Task-focused proceduralists cannot reliably provide this surveillance.

Finally, the video discourages the practice of suturing tracheostomy tubes to minimize the risk of skin erosion; however, there are reliable strategies for protecting skin integrity, and the use of outer flange security sutures to anchor the tracheostomy tube reduces the risk of adverse events, including bleeding[3] — a critical consideration for patients with Covid-19.[4] Dislodgment of the tracheostomy tube remains distressingly common after tracheostomy, which underscores the importance of assessing precautionary measures that may reduce the risk of airway-related adverse events.[5]

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No potential conflict of interest relevant to this letter was reported.

This letter was published on February 3, 2021, at NEJM.org.

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DOI: 10.1056/NEJMc2035339