Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

longest exposure and follow up of individuals treated with inclisiran. In both arms, inclisiran administration was associated with a reduction in LDL cholesterol from baseline over the course of the study (47·5% [95% CI 50·7–44·3] in the inclisiran-only arm) and associated with good tolerability.

ORION-3 provides a number of important insights with regard to the clinical use of inclisiran. The findings represent the longest clinical experience of administration, with some patients treated for up to 4 years. Given that the durability of the lipid-lowering effects provides the opportunity for infrequent administration, establishing the longer term efficacy and safety profile is essential. This study extends previous experience of a small number of injections to establish the clinical effects of administration of inclisiran for 4 years. An intriguing element of the study design involved the switch from placebo to inclisiran via a period of administration of evolocumab. Given that integration of inclisiran in health-care systems can permit changing existing therapy with a PCSK9 monoclonal antibody to RNA interference, it is also important to understand the lipid efficacy and safety effects of this transition.

The ultimate validation of inclisiran therapy will be established via the results of long-term cardiovascular outcomes trials. There are currently three such studies that are in progress, evaluating the cardiovascular efficacy and long-term safety of inclisiran in both primary and secondary prevention settings. Along with the expected degree of LDL cholesterol lowering producing a reduction in cardiovascular events, these studies will also provide important information regarding longer term safety and tolerability in a much larger cohort of patients than early studies have the power to comprehensively investigate. This presents a new opportunity for cardiovascular prevention that involves twice yearly administration of an agent with the potential to substantially reduce LDL cholesterol in patients treated with maximally tolerated statin therapy. As many patients will ultimately require a combination of lipid-lowering agents to achieve the increasingly aggressive LDL cholesterol goals advocated by guidelines, the ability to introduce further choice in clinical practice is an important step forward for patients. As a result, the ORION studies could help pave the way for more effective lipid-lowering treatment for patients with high cardiovascular risk.

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Blood lipids after COVID-19 infection

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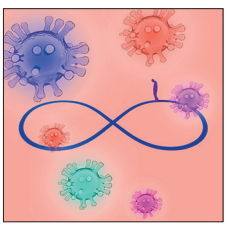
Atherosclerotic cardiovascular disease incidence is increased both during acute COVID-19 infection and for an indefinite period afterwards.[1,2] For this reason it has been recommended that lipid-lowering medication is generally continued throughout the period of active infection and subsequently.[2] In this issue of *The Lancet Diabetes & Endocrinology*, Evan Xu and colleagues[3] provide evidence that this advice should go further. From a large observational study using participants from the US Department of Veterans Affairs database, they assessed the risks and burdens of incident dyslipidaemia in the post-acute phase of SARS-CoV-2 infection using 51 919 COVID-positive participants compared with two COVID-negative control groups. The authors found increased LDL cholesterol, triglycerides, total cholesterol, and decreased HDL cholesterol in survivors of COVID-19 compared with controls who had never had a positive COVID test. The degree of

dyslipidaemia was greatest in those in whom the infection had been most severe and had required admission to intensive care. The authors adjusted the data to allow for confounding factors. Nevertheless, questions remain about whether the adverse post-COVID effect on dyslipidaemia is directly caused by the infection itself or indirectly by behavioural factors operating during the recovery period, such as reduced physical activity due to post-viral lethargy and persistent loss of exercise capacity, or dietary indulgence following the return of taste or the jubilation of survival. Greater certainty about their conclusions could be provided by a longitudinal study, which might, for example, be possible if lipids were measured in participants in a controlled vaccine trial. However, whatever the reason for the post-COVID dyslipidaemia, the immediate clinical message is the same: blood lipids should be checked as part of cardiovascular risk evaluation after recovery and, if necessary, lipid-lowering medication initiated or intensified.

The report by Xu and colleagues[3] raises fundamental questions about the origins of dyslipidaemia in general. We know that the acute effect of infection or serious illnesses from other causes is to lower LDL cholesterol, sometimes profoundly.[4,5] At the same time there is a tendency for triglycerides to rise and for HDL cholesterol to decrease. LDL cholesterol is usually restored to premorbid concentrations as the acute illness abates, but in chronic inflammation the increase in triglyceride and decreased HDL persists probably due to the effect of inflammatory cytokines.[4,5] Although the aetiology of long COVID remains speculative, clear evidence that a state of chronic inflammation can persist even in asymptomatic survivors is accruing.[6,7] During such inflammation, the composition and functional capacity of HDL also changes and it has thus been called pro-inflammatory or pro-atherogenic HDL. Serum amyloid A, released during inflammation, interferes with the ability of HDL to protect LDL from pro-atherogenic modifications such as oxidation and glycation. Furthermore, decreases in apolipoprotein A1 in HDL reduce its capacity to receive excess tissue cholesterol, which is believed to occur through the ATP binding cassette A1 and to be an important early phase of reverse cholesterol transport.[5]

The effects of chronic inflammation on lipoprotein metabolism have been extensively investigated in obesity. Adipose tissue, particularly when it is centrally located (metabolic syndrome), contains inflammatory cells that release cytokines causing dyslipidaemia. Reversal by bariatric surgery restores triglyceride and HDL metabolism towards normality, but has little effect on LDL cholesterol.[8] Persisting effects on LDL after the apparent resolution of inflammation are unexplained and remind us just how imperfect our knowledge is of what determines LDL cholesterol concentrations in adulthood. Recently, because of their potential to lower LDL cholesterol by pharmacological inhibition, interest has sparked in two factors that influence the balance between LDL catabolism and production. These are proprotein convertase subtilisin or kexin type 9 (PCSK9), which has a major effect on hepatic receptor-mediated LDL catabolism[9] and angiopoietin-like protein 3 (ANGPTL3), which regulates the production of LDL from its precursor very low density lipoprotein.[10] It has been hypothesised that both can increase during inflammation.[9–11]

We clearly need to learn more about how cholesterol metabolism is permanently imprinted by nutrition and infection or inflammation.



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I declare no competing interests.

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