TO THE EDITOR: Fitzgerald et al. (Jan. 5 issue) report that inclisiran, a long-acting RNA interference (RNAi) therapeutic inhibitor of proprotein convertase subtilisin–kexin type 9 (PCSK9), is safe and effective in the lowering of low-density lipoprotein (LDL) cholesterol among healthy volunteers. The advantage of inclisiran is sustained suppression of PCSK9 and LDL cholesterol for at least 6 months, which allows for twice-yearly administration.

Although there were no serious adverse events among healthy volunteers in the phase 1 trial, if adverse events occur among future recipients of this agent, it might be necessary to administer a neutralizing drug to reverse potentially long-lasting adverse effects. For example, factor Xa inhibitors have been associated with acute major bleeding, for which neutralizing drugs have been developed. For long-acting RNAi drugs, adverse events might not be serious but could be prolonged. Perhaps a specific neutralizing (rescue) drug for RNAi inhibitors should be developed for such circumstances.

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TO THE EDITOR: Fitzgerald et al. describe a promising new strategy for the lowering of LDL cholesterol. Inclisiran may be a useful alternative to statins or monoclonal antibody therapy because of the relatively infrequent administration requirement.

Recent clinical genetic studies have shown that in patients with glucose intolerance, genetic variants in PCSK9 or HMGCR that result in reduced LDL cholesterol levels (presumably from loss of function) were associated with similar independent and additive effects to increase the risk of diabetes per unit decrease in LDL cholesterol. Since PCSK9 inhibitors and statins use distinct mechanisms to lower LDL cholesterol, it seems likely that LDL reduction is related to both protection against cardiovascular disease and promotion of diabetes. This suggests that the effect of most statins to promote diabetes is an on-target drug effect.

Given these observations, future outcome studies of PCSK9 inhibitors or oligonucleotide therapeutic agents should be designed for optimal detection of adverse metabolic effects.

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TO THE EDITOR: The study by Fitzgerald et al. poses the question as to whether inclisiran is suitable for long-term treatment of hyperlipidemia. In contrast with PCSK9 antibodies, which target plasma PCSK9, inclisiran inhibits PCSK9 synthesis intracellularly. The high prevalence of nonalcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) in obese patients with diabetes may warrant special consideration;
perhaps inclisiran should be contraindicated in these patients.1 The involvement of PCSK9 in liver-cell metabolism goes beyond regulation of the LDL receptor and facilitates liver-cell regeneration after hepatic damage.2 PCSK9 also attenuates the expression of CD81,3 which has been implicated in hepatitis C and Plasmodium falciparum infections.

Long-term hepatic silencing of PCSK9 expression by inclisiran may be worrisome in patients with hyperlipidemia in whom hepatic health is already challenged by NAFLD or NASH and in those living in regions in which the incidence of hepatitis C infection is high, such as in Central Asia and East Asia, North Africa, and the Middle East. In such settings, inclisiran may augment the risk of liver disease and could potentially lead to irreparable liver damage.

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TO THE EDITOR: Fitzgerald et al. report that subcutaneous administration of inclisiran achieves long-term LDL cholesterol reduction with no serious adverse events in the short term. Inclisiran belongs to a new class of nucleotide-based nonstatin molecules that may hold promise for reducing rates of cardiovascular events in patients who do not have a response to statins or have adverse effects.1

We noticed that the inclisiran nucleotide backbone bears stabilizing phosphorothioate modifications. Since phosphorothioate-modified nucleotides have platelet-activating and prothrombotic effects in the same dose range as effective doses of inclisiran,2 the trial should have included platelet-activation assays. Platelets may circulate in an activated state without obvious changes in measures of hemostasis, which could be missed when searching for serious adverse events. This factor is particularly relevant considering that the inclisiran target population includes thrombosis-prone patients with hypercholesterolemia.3 Thus, there is a possibility that an RNAi agent in the systemic circulation may be harmful to the patient’s health. Ongoing trials should elucidate the true clinical benefit and possible thrombotic risks of inclisiran.

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TO THE EDITORS: In response to the comments of Masuda et al. and Koh regarding the long-term safety of inclisiran: patients who are heterozygous or homozygous for loss-of-function mutations in PCSK9 have lifelong reduced or absent circulating levels of PCSK9 without apparent untoward effects.1 Therapeutic monoclonal antibodies that lower PCSK9 levels have been extensively studied across thousands of patient-years and are shown to have an acceptable side-effect profile. Although reversal agents have been developed for some new oral anticoagulants, antidotes or reversal agents were neither necessary for favorable benefit–risk assessment nor required for approval of these therapeutic agents for clinical use. Similarly, regardless of a potential association between lowering of LDL cholesterol and incident diabetes, the benefits of intensive therapy to lower LDL cholesterol levels far outweigh the potential for diabetes in patients at risk for infections.
atherosclerotic cardiovascular events.\(^2\) In the ORION-1 trial,\(^3\) no significant increases in levels of glycated hemoglobin were seen with inclisiran.

In response to the query by Lansberg and Banerjee regarding the hepatic safety of long-term PCSK9 inhibition: no adverse liver findings have been identified to date in studies of either inclisiran or PCSK9 therapeutic antibodies. Recent studies have shown that statins decrease the progression to cirrhosis in patients who have coinfection with the human immunodeficiency virus and hepatitis C virus.\(^4\) Furthermore, Ramanathan et al. have reported that blockade of PCSK9 had no effect on either CD81 levels or entry of hepatitis C virus.\(^5\) In addition, there is no accumulation of cholesterol or triglyceride in the livers of mice or humans that lack PCSK9. In the ORION-1 trial, no adverse findings with respect to liver function were seen with inclisiran.

In response to the comments of Lancellotti and Oury: single-stranded oligonucleotides with long stretches (18 or more) of phosphorothioate linkages may have platelet-activating effects. Inclisiran is a double-stranded RNA with only 6 phosphorothioate linkages, which are distributed across both strands and thus do not form a consecutive stretch. Because of their less hydrophobic nature, RNAi therapeutic agents have a much lower potential for protein binding, and no substantial effects on platelets have been found to date in either preclinical models or clinical trials of RNAi therapeutic agents; in the ORION-1 trial, there were no effects on platelet counts with inclisiran.

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