For decades, cardiovascular risk attributed to lipids beyond low-density lipoprotein (LDL) has focused appropriately on high-density lipoprotein (HDL). Indubitable observational data show a consistent inverse relationship between baseline HDL-C concentrations and cardiovascular risk. Yet, fidelity as a prospective risk marker does not guaranty that an analyte either lies in a causal pathway for disease, or that its therapeutic manipulation will yield clinical benefits. Indeed, multiple strategies to raise HDL levels therapeutically have thus far failed to forestall events in clinical trials [e.g. currently available fibrates, niacin, and the investigated cholesteryl ester transfer protein (CETP) inhibitors]. We await eagerly with an open mind, however, results from the ongoing outcome trials with two additional CETP inhibitors. We also recognize that steady-state concentrations of HDL-C in plasma likely do not reflect the flux of HDL particles, their potential for mediating reverse cholesterol transport, and other putative functions of HDL subclasses. For example, a large body of in vitro and experimental animal studies indicates that HDL particles may have many beneficial actions beyond reverse cholesterol transport. These putative properties of HDL particles include anti-oxidant and anti-inflammatory effects, attributes not assessed by the simple laboratory measurement of HDL-C. These functional facets of HDL may provide novel targets for therapeutic manipulation in a more subtle fashion in the future. Yet, concordant with the data from clinical intervention trials showing lack of benefit (or even harm) with current approaches to pharmacological boosting of HDL-C, recent genetic studies have also cast doubt on HDL-C as a causal risk factor.1

While HDL-C has stood in the spotlight, centre stage, triglycerides have tarried in the wings as a causal cardiovascular risk factor. Adjustment for HDL-C and for other potential confounders tends to attenuate or nullify the association between triglyceride concentration and prospective cardiovascular risk.2,3 HDL-C and triglyceride concentration in plasma tend to vary inversely, such that high levels of triglycerides associate with low levels of HDL, until recently the presumed causal partner in the pair (Figure 1). Curiously, we generally measure fasting triglycerides, although many spend most of their time in post-prandial in the state, bathing our arteries with triglyceride-rich lipoproteins.4 Yet, current data show that either fasting or fed triglyceride concentrations associate with cardiovascular events.5,6

Fasting or fed, perhaps adjusting triglycerides for HDL-C, instead of the other way around, has misled us. Have we have collectively chosen a seat on the wrong side of the HDL/triglyceride seesaw? (Figure 1). Recent genetic studies have occasioned a re-examination of triglycerides as a causal cardiovascular risk factor. Contemporary
genetic analyses indicate that higher concentrations of triglyceride and remnant lipoproteins contribute directly to the pathogenesis of ischaemic heart disease. The cholesterol content of remnant particles rather than triglycerides themselves likely comprise the causal moiety contained in this lipoprotein class. The actual gene or genes responsible for this association have remained conjectural. One protein associated with triglyceride-rich lipoproteins, apolipoprotein C3 (APOC3), associates with cardiovascular risk. The study of the Amish population in Pennsylvania suggested that carriers of an inactive APOC3 gene have lower triglycerides and lower coronary artery calcium scores than unaffected individuals. Two independent large studies recently published in New England Journal of Medicine provide strong evidence for the causal role of APOC3 and triglycerides in atherosclerotic vascular disease. Exxon sequencing of large cohorts in the USA tracked four loss-of-function variants in APOC3. The individuals with such variants had lower triglyceride concentrations, and correspondingly lower risk of coronary heart disease in validation studies. A parallel study performed in Danish populations that screened for certain known mutations in APOC3 yielded a similar result, and showed that those with lifelong low levels of triglycerides due to these gene variants have fewer stroke as well as ischaemic heart disease events.

These results make sense mechanistically (Figure 2), as APOC3 can inhibit lipoprotein lipase (LPL), limiting the clearance of triglycerides from plasma (in part by interfering with LPL activation by APOCII) and impeding the clearance of atherogenic lipoproteins by the liver. APOC3 may also have direct proinflammatory effects, and/or impair some of the putative beneficial properties attributed to HDL particles. Indeed, HDL particles that bear APOC3 associate with increased rather than decreased risk for coronary heart disease. APOC3 can augment apoptosis of endothelial cells as well. The risk contribution determined from genetic analysis of APOC3 exceeds that estimated by observational studies, supporting the effects of lifelong alteration in this exposure and/or adverse effects of these apolipoprotein on vascular pathobiology not captured in the lipid values per se. The finding that remnant cholesterol, but not LDL cholesterol, associates with inflammation, as measured by C-reactive protein, also provides mechanistic support for triglyceride-rich lipoproteins as a trigger for atherothrombotic events.

As individuals with the APOC3 loss-of-function mutations also had higher concentrations of plasma HDL, one cannot formally exclude that higher HDL contributed to the risk reduction observed in these two studies. Indeed, case reports of combined deficiency of
apolipoprotein AI (the major protein constituent of HDL particles) and APOC3 associated with premature atherosclerosis. Yet the preponderance of the current genetic evidence sways the seesaw surely to the triglyceride side.

These results have important implications for clinical practice. They should renew interest in triglycerides and APOC3 as therapeutic targets for cardiovascular risk reduction. These recent genetic studies show that a lifetime of lower exposure to APOC3 reduced cardiovascular risk. Whether therapeutic intervention on these targets might mitigate cardiovascular risk of patients with well-controlled LDL levels over a shorter time span will require rigorous clinical evaluation. These new, exciting, and concordant genetic studies in humans should stimulate this quest.

In the meantime, what should clinicians do to manage patients who present with hypertriglyceridemia? These new data regarding a causal role for triglycerides in increasing cardiovascular risk should prompt us today to redouble our efforts to reduce hypertriglyceridemia in our patients using non-pharmacological approaches. We should examine the medication list for agents that might raise triglyceride levels such as estrogens and retinoid acid products. We should consider whether alcohol consumption or thyroid disease contributes to dyslipidemia in individual patients. We should strive to achieve optimum control in diabetic patients. We can discourage excessive carbohydrate consumption in those with hypertriglyceridemia.

The tension twixt triglycerides and HDL told above provides one example of how modern genetic tools have begun to yield practical dividends for preventive and cardiovascular specialists. In another recent instance of note, the identification of proprotein convertase subtilisin kexin 9 (PCSK9) as a cause of autosomal-dominant hypercholesterolemia has led to the development of novel therapeutic agents in warp speed, and spawned a series of global trials currently evaluating their effectiveness in improving cardiovascular outcomes. In the case of triglycerides in general, and specifically APOC3, studies currently underway with omega-3 fatty acids and development of anti-sense oligonucleotides or siRNA that target APOC3 may yield practical applications of the inversion in emphasis described here. We stand on the threshold of an exciting era in cardiovascular disease when genetic insights can guide our practice, challenge our preconceptions, point to new mechanisms, and promise ultimately to usher in novel therapies to help our patients at risk.

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