Abstract: Scientific interest in triglyceride-rich lipoproteins has fluctuated over the past many years, ranging from beliefs that these lipoproteins cause atherosclerotic cardiovascular disease (ASCVD) to being innocent bystanders. Correspondingly, clinical recommendations have fluctuated from a need to reduce levels to no advice on treatment. New insight in epidemiology now suggests that these lipoproteins, marked by high triglycerides, are strong and independent predictors of ASCVD and all-cause mortality, and that their cholesterol content or remnant cholesterol likewise are strong predictors of ASCVD. Of all adults, 27% have triglycerides >2 mmol/L (176 mg/dL), and 21% have remnant cholesterol >1 mmol/L (39 mg/dL). For individuals in the general population with nonfasting triglycerides of 6.6 mmol/L (580 mg/dL) compared with individuals with levels of 0.8 mmol/L (70 mg/dL), the risks were 5.1-fold for myocardial infarction, 3.2-fold for ischemic heart disease, 3.2-fold for ischemic stroke, and 2.2-fold for all-cause mortality. Also, genetic studies using the Mendelian randomization design, an approach that minimizes problems with confounding and reverse causation, now demonstrate that triglyceride-rich lipoproteins are causally associated with ASCVD and all-cause mortality. Finally, genetic evidence also demonstrates that high concentrations of triglyceride-rich lipoproteins are causally associated with low-grade inflammation. This suggests that an important part of inflammation in atherosclerosis and ASCVD is because of...
Clinical focus on whether to treat elevated triglyceride-rich lipoproteins has fluctuated over the past many years (Figure 1, illustrating my personal view; Table). This fluctuation was driven by changes in the evidence base, suggesting that these lipoproteins either cause atherosclerotic cardiovascular disease (ASCVD) or simply represent innocent by-standers to low high-density lipoprotein (HDL) cholesterol and possibly more important has been the lack in development in the evidence base suggesting a treatment benefit or not by lowering triglyceride-rich lipoproteins. In other words, there has not been a single, large, randomized trial aimed at reducing ASCVD by reducing triglyceride-rich lipoproteins selectively in individuals with elevated levels.

For mild-to-moderately elevated triglycerides (2–10 mmol/L; 176–880 mg/dL), in the 1980s, advice was given in parallel to treat elevated triglycerides and cholesterol,1–3 but from then on until 2011, most recommendations mainly focused on elevated low-density lipoprotein (LDL) cholesterol and largely ignored mild-to-moderately elevated triglycerides4–10 (Table). From 2011, some,11,12,14,17 but not all,13,15,16 publications now advised on treating mild-to-moderately elevated triglycerides in high-risk individuals. These latter differences in recommendations were largely driven by whether only randomized, double-blind trial evidence for a benefit of triglyceride-lowering was evaluated, or whether the totality of evidence including randomized trials, epidemiology, genetics, and biology was evaluated. Many scientists and clinicians view the majority of fibrate trials as failed clinical trials for the triglyceride hypothesis; however, these trials did not examine the effect of reducing triglyceride-rich lipoproteins on ASCVD and all-cause mortality risk in individuals with elevated triglycerides.

For elevated total and LDL cholesterol, agreement has largely existed from the 1980s to 2014 and all publications recommend treating elevated levels in high-risk individuals (Table), the definition of which has changed over time with more and more people being considered at high risk as time went by.1–12,15–17 For reduced HDL cholesterol, the majority of publications advise against treatment caused by the lack of randomized trial evidence. Finally, for severely elevated triglycerides (>10 mmol/L; >880 mg/dL), all publications from the 1980s to 2014 unanimously advise to reduce levels with the aim of reducing the risk of pancreatitis,1,4,6,11–14,17 even in the lack of randomized trial evidence.

The early interest in mild-to-moderately elevated triglycerides was driven by several factors, including epidemiological evidence, clinical understanding that patients with hypertriglyceridemia including remnant hyperlipidemia have high ASCVD risk, early randomized trials suggesting benefit of triglyceride-lowering, and the Zilversmit hypothesis that atherogenesis is a postprandial phenomenon caused by high levels of triglyceride-rich lipoproteins1–5,8 (Figure 1, illustrating my personal view). Then clinical interest focused (rightfully so) on LDL cholesterol, caused by several factors of which the most important were demonstration of mutations in the LDL receptor as the cause of familial hypercholesterolemia with high LDL levels and premature ASCVD,19 leading to the Nobel Prize award to Brown and Goldstein in 1985, the development of statins,20 and the consequent demonstration in large, randomized, double-blind statin trials that LDL reduction lead to reduced ASCVD and all-cause mortality.21

High interest in low HDL cholesterol also indirectly led to a long period with reduced interest in triglyceride-rich lipoproteins (Figure 1, illustrating my personal view); this came from epidemiological recognition that low HDL cholesterol is a better predictor of ASCVD risk than high triglycerides, and that when the association between high triglycerides and high ASCVD risk is adjusted for HDL cholesterol levels, the association is attenuated.22 However, on a population level, high concentrations of triglyceride-rich lipoproteins are associated with low concentrations of HDL cholesterol, and vice versa,23 and until recently, it remained unclear which of

<table>
<thead>
<tr>
<th>Nonstandard Abbreviations and Acronyms</th>
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<tr>
<td>ASCVD</td>
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<tr>
<td>CETP</td>
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<td>HDL</td>
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<td>IHD</td>
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<td>LDL</td>
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<tr>
<td>MI</td>
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<td>VLDL</td>
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Figure 1. My personal view of changes among most clinicians in clinical focus on different lipoprotein classes for reduction of atherosclerotic cardiovascular disease over time. ASCVD indicates atherosclerotic cardiovascular disease; FH, familial hypercholesterolemia; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and TG, triglycerides.
### Table. Early and Recent US and European Guidelines, Recommendations, and Consensus Statements on How to Treat Elevated Triglycerides and Other Lipid Fractions

<table>
<thead>
<tr>
<th>Publication</th>
<th>Organization</th>
<th>Region</th>
<th>Recommendation to Treat With Lifestyle Modification and Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1984, Grundy et al&lt;sup&gt;1&lt;/sup&gt;</td>
<td>AHA recommendation</td>
<td>US</td>
<td>Mild-to-Moderately Elevated Triglycerides* (or Elevated Non-HDL Cholesterol)</td>
</tr>
<tr>
<td>1987, Lewis et al&lt;sup&gt;2&lt;/sup&gt;</td>
<td>EAS strategies</td>
<td>Europe</td>
<td>Yes</td>
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<tr>
<td>1988, Lewis et al&lt;sup&gt;3&lt;/sup&gt;</td>
<td>EAS policy statement</td>
<td>Europe</td>
<td>Yes</td>
</tr>
<tr>
<td>1988, Goodman et al&lt;sup&gt;4&lt;/sup&gt;</td>
<td>ATP-I-NCEP</td>
<td>US</td>
<td>No</td>
</tr>
<tr>
<td>1993, Grundy et al&lt;sup&gt;5&lt;/sup&gt;</td>
<td>ATP-II-NCEP</td>
<td>US</td>
<td>Yes</td>
</tr>
<tr>
<td>1994, Pyörälä et al&lt;sup&gt;6&lt;/sup&gt;</td>
<td>ESC, EAS, and ESH recommendation</td>
<td>Europe</td>
<td>No</td>
</tr>
<tr>
<td>1998, Wood et al&lt;sup&gt;7&lt;/sup&gt;</td>
<td>ESC, EAS, and ESH recommendation</td>
<td>Europe</td>
<td>No</td>
</tr>
<tr>
<td>2001, Grundy et al&lt;sup&gt;8&lt;/sup&gt;</td>
<td>ATP-III-NCEP</td>
<td>US</td>
<td>Yes</td>
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<tr>
<td>2003, De Backer et al&lt;sup&gt;9&lt;/sup&gt;</td>
<td>ESC, EAS, ESH, and others guidelines</td>
<td>Europe</td>
<td>No</td>
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<tr>
<td>2007, Graham et al&lt;sup&gt;10&lt;/sup&gt;</td>
<td>ESC, EAS, ESH, and others guidelines</td>
<td>Europe</td>
<td>No</td>
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<tr>
<td>2011, Chapman et al&lt;sup&gt;11&lt;/sup&gt;</td>
<td>EAS consensus</td>
<td>Europe</td>
<td>Yes</td>
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<tr>
<td>2011, Reiner et al&lt;sup&gt;12&lt;/sup&gt;</td>
<td>ESC/EAS guidelines</td>
<td>Europe</td>
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<td>2011, Miller et al&lt;sup&gt;13&lt;/sup&gt;</td>
<td>AHA scientific statement</td>
<td>US</td>
<td>No</td>
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<tr>
<td>2012, Berglund et al&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Endocrine Society guidelines</td>
<td>US</td>
<td>Yes</td>
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<tr>
<td>2012, Perk et al&lt;sup&gt;15&lt;/sup&gt;</td>
<td>ESC, EAS, ESH, and others guidelines</td>
<td>Europe</td>
<td>No</td>
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<tr>
<td>2014, Stone et al&lt;sup&gt;16&lt;/sup&gt;</td>
<td>ACC/AHA guidelines</td>
<td>US</td>
<td>No</td>
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<tr>
<td>2014, Hegele et al&lt;sup&gt;17&lt;/sup&gt;</td>
<td>EAS consensus</td>
<td>Europe</td>
<td>Yes</td>
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</table>

Among early and recent recommendations from Europe and the United States on how to treat elevated triglycerides and other lipid fractions with the aim of preventing cardiovascular disease and pancreatitis, some publications are clear in their advice, but unfortunately this is not the case for all. To help readers, the information in this table has tried to simplify the advice given in the various publications: Should the lipid fraction be treated or not? AHA indicates American Heart Association; ATP-NCEP, Adult Treatment Panel National Cholesterol Education Program; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; ESH, European Society of Hypertension; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Yes, in high-risk individuals; (Yes), in some cases in high-risk individuals, and after 2001 often associated or estimated at no additional cost.

*In this article, mild-to-moderately elevated triglycerides is defined according to a recent EAS redefinition of hypertriglyceridemia to 2–10 mmol/L (176–880 mg/dL) and severely elevated triglycerides to >10 mmol/L (880 mg/dL).<sup>22</sup> However, in the various articles, listed the lower limit for mild-to-moderately elevated triglycerides range from 1.7 to 2.3 mmol/L (150–200 mg/dL), driven by limits set in mg/dL rather than in mmol/L on a continuous risk scale. Correspondingly, the lower limit for severely elevated triglycerides varies from 5.7 mmol/L (500 mg/dL) to 11.4 mmol/L (1000 mg/dL).

†Not mentioned in this article.

Measurement and Population Distribution

Triglyceride-rich lipoproteins contain both triglycerides and cholesterol, besides phospholipids and various proteins. For clinical purposes, 2 simple and straightforward measurements can be used to evaluate plasma concentrations of these lipoproteins, that is, plasma triglycerides and remnant cholesterol (Figure 2). These 2 measurements come with a standard lipid profile consisting of plasma concentrations of triglycerides, total cholesterol, LDL cholesterol, and HDL cholesterol, as remnant cholesterol like non-HDL cholesterol can be calculated or estimated at no additional cost.

The population distribution of plasma triglycerides is skewed with a tail toward higher levels (Figure 2, top). In the Copenhagen white population, the Copenhagen General Population Study, 27% of adults have mild-to-moderately elevated triglycerides of 2 to 10 mmol/L (176–880 mg/dL), whereas only 0.1% of adults have severely elevated triglycerides >10 mmol/L (880 mg/dL). Mild-to-moderately elevated concentrations are largely caused by overweight-obesity and diabetes mellitus, at the same time genetic variation and alcohol intake also contribute; severely elevated triglycerides are often caused by severely dysregulated diabetes mellitus, alcoholism, and in rare cases by homozygosity for mutations...
Mild-to-moderately elevated triglycerides increase the risk of ASCVD, whereas severely elevated triglycerides increase the risk of acute pancreatitis and possibly that of ASCVD.

Triglyceride measurement has the advantage that it is a direct, precise, and accurate measurement of all triglycerides in plasma. A drawback is that it is unlikely that triglycerides per se is the cause of atherosclerosis, as triglycerides, unlike cholesterol, can be degraded by most cells in the body. Therefore, intuitively and rightfully many scientists and clinicians view high triglycerides with skepticism as a cause of atherosclerosis and ASCVD.

Triglyceride measurement has the advantage that it is a direct, precise, and accurate measurement of all triglycerides in plasma. A drawback is that it is unlikely that triglycerides per se is the cause of atherosclerosis, as triglycerides, unlike cholesterol, can be degraded by most cells in the body. Therefore, intuitively and rightfully many scientists and clinicians view high triglycerides with skepticism as a cause of atherosclerosis and ASCVD. Also, unlike cholesterol, triglycerides do not accumulate in the atherosclerotic plaque. High triglycerides should thus merely be viewed as a marker of high levels of cholesterol in triglyceride-rich lipoproteins. A limitation of solely evaluating high triglycerides is that the cholesterol to triglyceride content in triglyceride-rich lipoproteins varies. Therefore, clinically, it seems more appropriate to estimate/calculate or measure the cholesterol content of triglyceride-rich lipoproteins, that is, remnant cholesterol.

Remnant cholesterol can be estimated as total cholesterol minus LDL cholesterol minus HDL cholesterol, as done previously, such estimation or calculation of remnant cholesterol in hypertriglyceridemic individuals requires a direct LDL cholesterol assay at triglyceride levels >4.5 mmol/L (400 mg/dL). This means that remnant cholesterol is all plasma cholesterol not found in LDL and HDL, that is, in all triglyceride-rich lipoproteins. In the fasting state, this constitutes cholesterol in very low-density lipoprotein (VLDL) and intermediate-density lipoprotein, whereas in the nonfasting state, cholesterol in chylomicron remnants is also included. Importantly, even in the nonfasting state, calculated remnant cholesterol is mainly cholesterol in VLDL and intermediate-density lipoprotein. As triglycerides in all chylomicrons secreted from the intestine and in all VLDL particles secreted from the liver are partially degraded by lipoprotein lipase as soon as these lipoproteins enter into the bloodstream,
practically all triglyceride-rich lipoproteins represent some form of remnants—with the sole exception of triglyceride-rich lipoproteins in individuals with complete lipoprotein lipase deficiency found in one in a million. Although the use of the word remnants differs among lipid experts; for simplicity, the term remnant cholesterol can be used to describe the cholesterol content of all triglyceride-rich lipoproteins.

Remnant cholesterol can be measured with labor-intensive and relatively expensive ultracentrifugation and with nuclear magnetic resonance spectroscopy, whether of which is broadly applied for routine clinical use. Also, a direct, automated assay exists that measures ≈13% of the calculated remnant cholesterol; however, at present, there is no fully automated, commercial assay available that measures cholesterol in all triglyceride-rich lipoproteins combined, corresponding to calculated remnant cholesterol. Such an assay likely will find future clinical use, as calculated remnant cholesterol is a strong causal risk factor for ASCVD.

The population distribution of calculated remnant cholesterol is also skewed with a tail toward higher levels (Figure 2, bottom). In the Copenhagen General Population Study, 21% of adults have elevated remnant cholesterol >1 mmol/L (39 mg/dL). Elevated remnant cholesterol is largely caused by overweight-obesity and diabetes mellitus, at the same time genetic variation also contributes.

Non-HDL cholesterol is calculated or estimated as total cholesterol minus HDL cholesterol and is equivalent to LDL and remnant cholesterol combined. The use of non-HDL cholesterol for cardiovascular disease risk prediction has been emphasized in several recent guidelines and consensus papers.

Epidemiology

For plasma triglycerides, early meta-analyses demonstrated that high levels were associated with high risk of ASCVD, even when HDL cholesterol was adjusted for. This was confirmed in later meta-analyses.

In 2007 to 2008, studies from the Copenhagen City Heart Study and the Women’s Health Study showed that particularly elevated nonfasting triglycerides were associated with high risk of ASCVD, that is, for myocardial infarction (MI), ischemic heart disease (IHD), and ischemic stroke, as well as for all-cause mortality. For individuals in the general population without lipid-lowering therapy, nonfasting triglycerides >5 mmol/L (440 mg/dL) versus <1 mmol (88 mg/dL) were associated with 17- and 5-fold risk of MI in women and men during 27 years of follow-up. Corresponding values for IHD were 6- and 3-fold, for ischemic stroke 5- and 3-fold, and for all-cause mortality 4- and 2-fold in women and men. Such higher risks in women than in men have also been observed previously and were in the Copenhagen City Heart Study partly explained by confounding from higher alcohol intake in men than in women. In other words, in men with low alcohol intake, the risks of ASCVD and all-cause mortality were similar to those in women. Interestingly, in the Women’s Health Study, elevated triglycerides were associated with high risk of IHD in the nonfasting state, but not in the fasting state.

In 2009, the Emerging Risk Factors Collaboration published combined analyses including 302430 individuals from 68 long-term prospective studies and 12785 coronary events and observed that increasing nonfasting and fasting triglycerides were associated with increasing risk of IHD. This association was attenuated after adjustment for HDL cholesterol and abrogated after additional adjustment for non-HDL cholesterol (=remnant cholesterol and LDL cholesterol combined), suggesting that it may be not only elevated triglycerides per se that is the cause of IHD but also the cholesterol content in remnant particles. In support of this idea, it is cholesterol, and not triglycerides, that accumulates in the atherosclerotic plaque. Nevertheless, this does not exclude that the process of triglyceride hydrolysis within the plaque could contribute to plaque inflammation (see Biology section of this article). Also, the Emerging Risk Factors Collaboration including 173312 individuals from 32 long-term prospective studies and 2534 stroke events found that elevated triglycerides were associated with increased risk of ischemic stroke. The Emerging Risk Factors Collaboration only documented increased risk of IHD up to mean elevated triglycerides of ≈2.8 mmol/L (246 mg/dL) and increased risk of ischemic stroke up to ≈2.2 mmol/L (194 mg/dL), simply because that study only examined risks in 10 or 5 equally sized groups, despite the fact that triglycerides are highly skewed toward extremely high levels.

In 2014, in studies combining the Copenhagen City Heart Study and the Copenhagen General Population Study with ≈100000 individuals, and with similar statistical power as for the Emerging Risk Factors Collaboration, extreme high concentrations of nonfasting triglycerides were associated with high risk of ASCVD and with all-cause mortality (Figure 3). Indeed, for individuals in the general population with nonfasting triglycerides of 6.6 mmol/L (580 mg/dL) versus 0.8 mmol/L (70 mg/dL), the risks were 5.1-fold for MI, 3.2-fold for IHD, 3.2-fold for ischemic stroke, and 2.2-fold for all-cause mortality.

For calculated nonfasting remnant cholesterol in studies including 56657 individuals, we first reported that those in the top versus bottom quintile (>1.1 versus <0.4 mmol/L; >43 versus <15 mg/dL) had 2.3-fold risk of IHD. Furthermore, as examined in 82890 individuals from the Copenhagen City Heart Study and Copenhagen General Population Study combined, the risk of MI increased continuously with increasing remnant cholesterol similarly to that for increasing LDL cholesterol (Figure 4, top), even when the analysis for remnant cholesterol was adjusted for LDL cholesterol, and vice versa. When compared with individuals with nonfasting remnant cholesterol levels <0.5 mmol/L (19 mg/dL), the risks for MI were 1.8-fold for a remnant cholesterol level of 0.5 to 0.99 mmol/L (19–38 mg/dL), 2.2-fold for 1.0 to 1.49 mmol/L (39–58 mg/dL), and 3.0-fold for remnant cholesterol ≥1.5 mmol/L (58 mg/dL).

Surprisingly, as examined in the same 82890 individuals from the Copenhagen City Heart Study and Copenhagen General Population Study combined, the risk of all-cause mortality increased continuously with increasing remnant cholesterol concentrations, but not with increasing LDL cholesterol (Figure 4, bottom). When compared with individuals with nonfasting remnant cholesterol levels <0.5 mmol/L (19 mg/dL), the risk for all-cause mortality was...
1.4-fold in individuals with remnant cholesterol level of ≥1.5 mmol/L (58 mg/dL). These results agreed with previous observations in the Copenhagen City Heart Study that increasing plasma triglycerides (as a marker of remnant cholesterol) were associated with increasing all-cause mortality in individuals in the general population, whereas this was not the case for increasing levels of total cholesterol (as a marker of LDL cholesterol). This difference likely is explained by the fact that elevated total cholesterol was associated with increased death from cardiovascular disease, but not with increased death from cancer or other causes, whereas elevated triglycerides were associated with increased mortality from cardiovascular disease and from cancer and other causes.

Finally, as much of the epidemiological data were collected when statins were only beginning to emerge as standard of care, it is important to consider what the evidence is, if any, that elevated triglyceride-rich lipoproteins matters in the statin-treated patient. Certainly, in several trials, including patients on statins, elevated triglyceride-rich lipoproteins also seem to be associated with residual risk of ASCVD.

Genetics to Examine Causality
Epidemiology alone cannot determine causality, and several different types of evidence are necessary to understand whether a risk factor is in fact a causal factor, that is, whether elevated triglyceride-rich lipoproteins is a cause of ASCVD. Besides epidemiology, this includes other evidence from...
human studies in the form of randomized trial evidence and evidence from genetics. Finally, biological insight on potential mechanisms from elevated triglyceride-rich lipoproteins to atherosclerosis and ASCVD is likewise important, as described below.

Each of the 3 types of human evidence has advantages and limitations that are important to understand and compare (Figure 5), that is, before any attempt of causal inference are made. Common to all 3 approaches is the potential limitation of statistical power, one that can only be solved by conducting huge and costly studies. As randomized trials usually are the most expensive of the 3 types of human studies, it is important to understand the value of the evidence coming from epidemiology and Mendelian randomization studies, particularly in cases where randomized trials cannot be conducted for economical, ethical, or other reasons.

In epidemiology as described above, observational studies examine association between elevated triglycerides or remnant cholesterol and risk of ASCVD and take advantage of the natural nonrandom distribution of these risk factors in human

**Figure 4.** Nonfasting remnant and low-density lipoprotein (LDL) cholesterol on a continuous scale and risk of myocardial infarction and all-cause mortality in the general population. Examined in 82 890 individuals from the Copenhagen City Heart Study and Copenhagen General Population Study combined using cubic spines with 4 knots. Hazard ratios (full line) with 95% confidence intervals (dotted lines) were adjusted for age, sex, smoking, hypertension, physical activity, alcohol consumption, lipid-lowering therapy, time since last meal, time of day for blood sampling, and for women also for oral contraceptive use, hormone-replacement therapy, and menopausal status. Adapted from Varbo et al44 with permission of the publisher. Copyright ©2015, the American Association for Clinical Chemistry.

**Figure 5.** Comparison of observational studies, randomized trials, and Mendelian randomization studies to help understand causality from high triglycerides and remnant cholesterol to atherosclerotic cardiovascular disease. TG indicates triglycerides.
populations (Figure 5, left). However, this study design has 2 major limitations in the form of potential confounding and reverse causation. Confounding means that a third factor could be associated with both elevated triglyceride-rich lipoproteins and ASCVD, and thus be the real cause of ASCVD rather than elevated triglyceride-rich lipoproteins per se. Reverse causation means that ASCVD or the underlying and clinically often asymptomatic disease atherosclerosis may cause elevated triglyceride-rich lipoproteins rather than vice versa. Another limitation of observational studies is that risk factors typically are only measured once and therefore the association observed will only represent a single point estimate and will entail the problem of regression dilution bias. The latter means that the effect size of the risk estimate is underestimated. However, if repeated measurements of the risk factor exist, then regression dilution bias can be adjusted for, as done for the data presented in Figures 3 and 4.

Randomized, double-blind trials overcome the problem of confounding simply by the randomization method that secures equal distribution of potential confounders between active drug and placebo groups (Figure 5, middle). Also, reverse causation is not an issue as ASCVD even in its preclinical form of atherosclerosis cannot influence the randomization process. Besides huge cost and often too little statistical power, a major limitation of randomized trials in the understanding of causality is pleiotropic effects. This means that the drug of interest not only lowers triglyceride-rich lipoproteins but also, for example, lowers LDL cholesterol and lipoprotein(a), and raises HDL cholesterol. Then, in case of a positive or negative effect on ASCVD incidence, it becomes nearly impossible to deduce whether it was the drug-induced changes in triglyceride-rich lipoproteins, LDL, lipoprotein(a), or HDL that caused the change in ASCVD incidence. In randomized trials, pleiotropic effects are sometimes referred to as off-target effects, that is, whether the pleiotropic effect is thought to be an unwanted and potentially harmful side effect.

Mendelian randomization studies of human genetics have many similarities with randomized, double-blind trials, and thus advantages over observational studies in conventional epidemiology (Figure 5, right). Like randomized trials, Mendelian randomization studies are double-blind and confounding and reserve causation are not issues because of nature’s own randomization method during distribution of alleles to sperm and egg cells during meiosis. These studies have the additional advantage over both epidemiology and randomized trials that genetics typically capture a life-long effect, whereas randomized trials only run for 2 to 10 years, and whereas observational studies are limited to the time between risk factor assessment and end of follow-up. Another advantage of Mendelian randomization studies over observational studies is that regression dilution bias is not a problem, as genotypes will not change on repeated measurement. Like a drug in randomized trials, genetics can have the problem of pleiotropic or off-target effects, effects that may complicate interpretation of the results with respect to causality of a single lipoprotein class. Another potential problem of Mendelian randomization studies includes linkage disequilibrium with other causative genetic variants close by; however, this is not a problem for understanding causality as long as the other genetic variant exerts its effect through the same lipoprotein class. Furthermore, population admixture can be a major problem if both genotype and the disease studied are found preferentially in certain subpopulations; however, this potential problem can be largely circumvented by either only studying ethnically homogeneous populations or by adjusting for different ethnicity using genetic information. Finally, it is essential to use genetic variation with sufficiently large effect sizes on the lipoprotein class of interest, as variants with small effect sizes may still be affected by confounding.

Figure 5 suggests that randomized trials and Mendelian randomization studies should give similar results, which seems generally to be the case for studies of LDL and HDL cholesterol. However, it would seem like a puzzle that some CETP genetic variations are associated with both elevated HDL cholesterol and reduced ASCVD (especially in the Copenhagen City Heart Study) and yet HDL cholesterol increasing cholesteryl ester transfer protein (CETP) inhibitors to date have failed in clinical trials to reduce ASCVD. However, genetic CETP inhibition led not only to elevation in HDL cholesterol but also to decreases in triglycerides and LDL cholesterol and unlike the CETP inhibitor torcetrapib did not seem to be associated with any off-target effects, effects that possibly explain the negative effect in the torcetrapib trial. Alternatively, it is also theoretically possible that the large HDL particles generated during pharmacological inhibition of CETP promotes rather than inhibits the development of atherosclerosis and ASCVD. In support of such a possibility, genetic variants in CETP that through protein alteration led to elevated HDL cholesterol led to increased ASCVD, and vice versa, in our studies. Taken together, the CETP example illustrates that careful thinking is essential when results from epidemiology, randomized trials, and Mendelian randomization studies are compared.

Genetics
The most difficult problem to solve in understanding potential causality between elevated triglyceride-rich lipoproteins and ASCVD is to deal with pleiotropy, that is, most specifically that high triglycerides are associated with low HDL cholesterol on a population level. In other words, what is the chicken and what is the egg in the causal association with ASCVD. This puzzle was addressed in 2 different ways in 2013, and each approach came to the same conclusion: elevated triglyceride-rich lipoproteins are causally associated with ASCVD, whereas low HDL cholesterol is not. Supporting the latter, several previous studies have used genetics to show that HDL cholesterol levels are not causally associated with ASCVD. Varbo et al selected genetic variants robustly associated with a single lipoprotein, without effects on other lipoproteins, to test the causal effect of life-long exposure on risk of IHD. After a prespecified plan and based on current evidence from the literature, we therefore carefully selected 15 genetic variants affecting levels of (1) nonfasting remnant cholesterol alone (explained 1.5% of variation), (2) nonfasting remnant cholesterol and HDL cholesterol combined (explained 0.8% of variation), (3) HDL cholesterol alone (explained 0.7% of
variation), or (4) LDL cholesterol alone as a positive control (explained 1.7% of variation; Figure 6, top); thus, the statistical power only differed by a factor of 2 between the 4 groups. Importantly, several other genotypes were considered for inclusion but were a priori not included, exemplified by apoE genotypes that affect levels of all the lipoproteins studied, and therefore would be difficult to use in an attempt to infer causality to a single lipoprotein class.

We genotyped 73,513 white individuals of Danish descent from Copenhagen, of whom 11,984 had IHD, and we directly compared causal odds ratios from instrumental variable analyses with hazard ratios from observational analyses. The causal risk increase for a 1-mmol/L (39 mg/dL) genetic increase of nonfasting remnant cholesterol was 2.8-fold, with a corresponding observational estimate of 1.4-fold (Figure 6, top). Importantly, when the effect size for the causal estimate is much larger than the observational for the same increase in a lipoprotein, then this represents additional strong evidence for a causal life-long exposure, exactly as observed for high lipoprotein(a) levels and increased risk of MI. For nonfasting remnant cholesterol to HDL cholesterol ratio, corresponding values were 2.9-fold causal and 1.2-fold observational for a 1 U increase in the ratio (Figure 6, top). However, for HDL cholesterol, corresponding values were 0.7-fold causal and 1.6-fold observational for a 1-mmol/L (39 mg/dL) decrease. Finally, for LDL cholesterol, corresponding values were 1.5-fold causal and 1.1-fold observational for a 1-mmol/L (39 mg/dL) increase. Taken together, these data demonstrate that elevated remnant cholesterol is causally associated with ASCVD, that is, independent of low HDL cholesterol levels, whereas low HDL cholesterol is not a cause of ASCVD.

Do et al approached the same puzzle differently: they included 185 single nucleotide polymorphisms found in genome-wide association studies to be associated with levels of plasma triglycerides, HDL cholesterol, and LDL cholesterol, irrespective of whether these single nucleotide polymorphisms had known pleiotropic effects. Across the 185 single nucleotide polymorphisms, genetically determined elevated triglyceride levels were strongly associated with IHD, even after adjusting for both LDL cholesterol and HDL cholesterol levels (Figure 6, bottom). Likewise, genetically determined elevated LDL cholesterol levels were strongly associated with
IHD, even after adjusting for both triglyceride and HDL cholesterol levels. The pattern for HDL cholesterol was, however, different. Across the 185 single nucleotide polymorphisms, although genetically determined lower HDL cholesterol levels were associated with IHD, this association was rendered nonsignificant after accounting for both triglyceride and LDL cholesterol levels. Taken together, these data also demonstrate that triglyceride-rich lipoproteins are causally associated with ASCVD, independent of HDL cholesterol levels, whereas low HDL cholesterol levels per se are not.

Several early studies likewise provided evidence that genetically elevated triglycerides are causally associated with increased risk of ASCVD. Most importantly, mutations in LPL, the gene coding for the triglyceride-degrading plasma enzyme lipoprotein lipase, lead to life-long high triglycerides and increased risk of ASCVD.66-68 Individuals heterozygous for lipoprotein lipase deficiency were 4.9-fold more common among patients with IHD than among individuals from the general population.66 Also, for LPL 4 versus 0 triglyceride-reducing alleles, a reduction in nonfasting triglycerides of 36% caused an ASCVD reduction of 46%.35 Furthermore, early on it was recognized that genetic variation in the apoA1-C3-A4 gene complex, where apoc3 is an inhibitor of lipoprotein lipase, was associated with hypertriglyceridemia and possibly could have an impact on longevity and predisposition to atherosclerosis.49

Further new insights from genetics involving various proteins influencing lipoprotein lipase function, in the APOA5, APOC3, and ANGPTL3 genes, have likewise strongly supported the idea that elevated triglyceride-rich lipoproteins are causally related to ASCVD.35,37 Lipoprotein lipase is the key enzyme in plasma-degrading triglycerides, whereas apoC3, apoA5, and ANGPTL3 modulate lipoprotein lipase function and influence liver uptake of remnants.

For APOA5 genetic variation, a doubling in genetically elevated remnant cholesterol levels was causally associated with a 2.2-fold risk of MI, with a corresponding observational estimate of 1.7-fold;46 for a genetic doubling in nonfasting triglycerides, corresponding risk increases were 1.9-fold causally and 1.6-fold observationally. Similar findings were observed in another large Mendelian randomization study using a single APOA5 genetic variant.70 Finally, for APOA5 2 versus 0 triglyceride-reducing alleles, a reduction in nonfasting triglycerides of 35% caused an ASCVD reduction of 24%.35

For APOC3 loss-of-function heterozygosity, Pollin et al71 in 2008 observed reduced triglycerides and remnant cholesterol, and a parallel association with reduced coronary artery calcification, a biomarker of subclinical atherosclerosis and a predictor of ASCVD. In 2014, we further observed that heterozygotes of APOC3 loss-of-function mutations had a reduction in nonfasting triglycerides of 44% and a 41% reduced risk of ASCVD in individuals from the Copenhagen general population.72 In a parallel study published back-to-back and including 18 different cohorts combined, APOC3 loss-of-function heterozygosity caused a 39% reduction in triglycerides and a 40% reduced risk of ASCVD.73 Although it has been suggested that these reduction in ASCVD risk might be explained by reduction in LDL cholesterol rather than by reduction in triglyceride-rich lipoproteins,74 in the largest samples from the studies of Pollin et al,71 Jørgensen et al,72 and Crosby et al,73 the LDL cholesterol reductions by APOC3 loss-of-function heterozygosity were only 3%, 9%, and 3%, reductions that are unlikely to explain a 40% reduced ASCVD risk.

For all-cause mortality, only a single study has examined a potential causal relationship with triglyceride-rich lipoproteins using genetics and the Mendelian randomization design:75 during a median 24 and 17 years of 100% complete follow-up, 9991 and 4005 individuals died in observational and genetic analyses, respectively, in the Copenhagen City Heart Study. In observational analyses when compared with individuals with nonfasting plasma triglycerides of 3.00 to 4.99 mmol/L (266–442 mg/dL), the risks of all-cause mortality were reduced by 11% for 2.00 to 2.99 mmol/L (177–265 mg/dL), by 26% for 1.00 to 1.99 mmol/L (89–176 mg/dL), and by 41% for individuals with nonfasting triglycerides of <1.00 mmol/L (89 mg/dL). Importantly, for a genetically derived 1-mmol/L (89 mg/dL) lower concentration in nonfasting triglycerides because of LPL genetic variation, the risk of all-cause mortality was reduced by 50%, with a corresponding observational estimate of 13%. In essence, these data illustrate that a reduction in triglyceride-rich lipoproteins will not only likely lead to reduced incidence of ASCVD but also likely lead to a substantial reduction in all-cause mortality.

**Randomized Trials**

Results from most published randomized trials unfortunately cannot inform as to whether reducing triglycerides and remnant cholesterol reduce the risk of ASCVD and all-cause mortality. This is because not a single, large, randomized trial has examined the effect of reducing triglyceride-rich lipoproteins on ASCVD and all-cause mortality risk in individuals with elevated triglycerides. Rather, many trials have excluded individuals with triglycerides >4.5 mmol/L (396 mg/dL), including the majority of statin trials. Therefore, only studies with a mix of individuals with low and mild-to-moderately elevated triglycerides can be examined, and in these studies, those with low triglycerides represent the majority. Nevertheless, such randomized trials still suggest a treatment benefit by reducing triglycerides in those with high triglycerides at study entry,15

Importantly, an often forgotten controlled trial of 555 consecutive post-MI patients from Sweden, as the only one of all fibrate trials, recruited particularly patients with high triglycerides and compared triglyceride- and cholesterol-lowering treatment with fibrate and niacin in combination versus no treatment: all-cause mortality was reduced by 26% and IHD mortality by 36%.76 All other fibrate trials did not select individuals based on high triglycerides, and as several such trials failed their primary end points, we look forward to a fibrate trial designed to test the hypothesis that reduction in high triglycerides and high remnant cholesterol will lead to reduced ASCVD. Nevertheless, among fibrate trials including subgroup analyses for participants with baseline triglycerides ≥2 mmol/L,76-81 a 1-mmol/L (88 mg/dL) reduction in triglycerides caused a reduction in IHD events of 54% overall and of 43% in those with high triglycerides.35 The risk reduction in those with high triglycerides was observed in all individual
studies,76–80 and even when fibrate was used as add-on to statin treatment.81 Although these effect sizes caused by triglyceride-lowering are indeed larger than the corresponding reduction of 22% in ASCVD events and 10% in all-cause mortality per 1-mmol/L (39 mg/dL) reduction in LDL cholesterol in statin trials,21 the strength of the scientific evidence favoring triglyceride reduction is much weaker than the combined evidence favoring LDL reduction.

Therefore, for now, randomized trial evidence alone seems too weak to convince scientists and clinicians that triglyceride-rich lipoproteins cause ASCVD, whereas in combination with new insights from epidemiology, genetics, and biology for understanding disease mechanism, as reviewed in the present article, this argument for causality seems much stronger.

Biology

Over the years, biological insights into a potential mechanism from elevated triglyceride-rich lipoproteins to atherosclerosis and ASCVD have come from animal, in vitro, and human studies. Many mechanisms have been proposed involving both atherosclerosis and thrombogenesis, but the present review will not cover them all. Rather, it will try to delineate what to me appears to be the simplest chain of events from elevated plasma levels of triglyceride-rich lipoproteins through development of atherosclerosis and ultimately ASCVD and early death. Recent novel insights from human studies using genetics and the Mendelian randomization approach will be incorporated in this simplified chain of event story.

A necessity for triglyceride-rich lipoproteins to cause atherosclerosis and ASCVD is their ability to enter into the arterial intima, the location of the atherosclerotic plaque, leading ultimately to ASCVD. Studies aimed at understanding such transport come from a combination of human and animal in vivo kinetic studies, using labeled lipoproteins injected intravenously. This is followed by plasma sampling and ultimately removal of arterial intimal tissue for assessment of the amount of labeled lipoproteins in plasma and intima, that is, to calculate the extent of transport of lipoproteins between plasma and intima. Needless to say, such studies are difficult to conduct in humans and are only possible when labeled lipoproteins are injected a few hours before an elective operation aimed at removing arterial intima, for example, through carotid endarterectomy or through operations on the heart or aorta. Therefore, part of this evidence comes from animal studies that allow termination of the animal at the end of the experiment for removal of arterial intimal tissue.

Using such approaches, one of the early puzzles that haunted the hypothesis that triglyceride-rich lipoproteins are causally associated with atherosclerosis and ASCVD was solved. The puzzle was as follows: for higher and higher LDL cholesterol levels including both heterozygous and homozygous familial hypercholesterolemia, the higher was the risk of ASCVD;62,82,85 however, this was not the case for higher and higher triglycerides. Indeed, individuals with the chylomicronemia syndrome caused by lipoprotein lipase deficiency, and thus no triglyceride degradation in plasma, were largely protected against ASCVD despite severe hypertriglyceridemia often >100 mmol/L (88,000 mg/dL).47 In an animal model of severe hypertriglyceridemia, the alloxan-diabetic, cholesterol-fed rabbit, exactly the same was observed in 1949 by 2 sets of investigators: despite plasma triglycerides often >100 mmol/L (88,000 mg/dL) atherosclerosis did not develop.62,83 In the 1980s, we then hypothesized that this peculiar phenomenon could be explained by the fact that at such high triglycerides, the triglyceride-rich chylomicrons were simply too large to cross the endothelial barrier and therefore could not enter intima and cause atherosclerosis: in 2 independent studies, we then went on to show that this was in fact the explanation,64,85 as also depicted in Figure 7.

About LDL, human and animal studies showed that this lipoprotein indeed can enter the arterial intima (Figure 7), and that this process most likely represents passive molecular sieving that increases with increasing plasma LDL concentration, decreasing lipoprotein size, increasing blood pressure, and with arterial injury.66–91 LDL can also leave the intima again,88,92–94 but only through the lumen against the pressure gradient generated from blood pressure, whereas LDL particles are too large to penetrate the elastic lamina of the media.94,95 In other words, LDL gets trapped in the arterial intima and attachment to proteoglycans, or other components of the arterial intima may further facilitate LDL trapping within the intima.

But then what happens to triglyceride-rich lipoproteins present in plasma at mild-to-moderate hypertriglyceridemia as found in 27% of adults in a typical Western country? (ie, lipoproteins of a size intermediate to that of LDL and the huge chylomicrons; Figure 2). A combination of human and animal studies has demonstrated that these medium-sized triglyceride-rich lipoproteins can in fact enter into the intima (Figure 7) although at a slightly slower speed than the smaller LDL particles.88,90 However, once these triglyceride-rich lipoproteins have entered into the intima, they may get trapped preferentially to LDL—possibly simply because of the larger molecular size, making reentry into the arterial lumen against a blood pressure gradient even more difficult than for LDL particles or because of entrapment by components of the arterial intima.98,99–108

On entrance and possible trapping within the arterial intima, it seems likely that lipoprotein lipase either at the endothelial surface or within the arterial intima degrades triglycerides leading to liberation of free fatty acids and monoacylglycerols, both of which are toxic to tissues and thus likely will generate local inflammation (Figure 7)18,37,98–100; however, evidence that liberated free fatty acids and monoacylglycerols induce intimal inflammation in vivo in humans is not so strong. Nevertheless, lipoprotein lipase is expressed in macrophages and foam cells in human atherosclerotic plaques,101–103 and lipoprotein lipase may have a stimulatory role in human foam cell formation from triglyceride-rich lipoproteins.104 Furthermore, animal models suggest in the absence of elevated plasma lipoproteins that in vivo human or mice lipoprotein lipase overexpression by macrophages in the artery wall promotes foam cell formation and atherosclerosis.105–108 It can be speculated that what happens in the arterial intima after penetration of triglyceride-rich lipoproteins from plasma, with triglyceride hydrolysis and liberation of free fatty acids and monoacylglycerols, may
be a miniature of what happens in the pancreas at extremely high plasma triglycerides, with liberation of toxic amounts of free fatty acids, severe inflammation including lipid-filled macrophages, necrosis, and pancreatitis.\textsuperscript{109,110}

Also, triglyceride-rich lipoproteins, unlike LDL particles, can be taken up directly by macrophages turning these cells into the hallmark cells of the atherosclerotic plaque, that is, macrophage foam cells rich in indigestible cholesterol droplets, whereas triglycerides, proteins, and phospholipids are degraded. Whereas LDL particles need to be modified, for example, through oxidation, to be taken up by macrophages,\textsuperscript{111} triglyceride-rich lipoproteins can be taken up by peripheral macrophages via the VLDL receptor without modification, without downregulation by intracellular lipoproteins, and likely in concert with lipoprotein lipase\textsuperscript{112}; however, other receptors such as the apoB48 receptor and the LDL receptor–related protein can also facilitate uptake of triglyceride-rich lipoproteins by macrophages.\textsuperscript{113,114} Although the VLDL receptor is expressed in human atherosclerotic lesions,\textsuperscript{115} no human data exist to document exactly which receptor(s) might facilitate uptake of triglyceride-rich lipoproteins into macrophage foam cells in vivo within the human arterial intima. The presence of these cells in the intima likewise is a source of local intimal inflammation (Figure 7).

But do elevated levels of triglyceride-rich lipoproteins then lead to low-grade inflammation at a whole-body level, as detected by slightly elevated levels of C-reactive protein in plasma? To examine this question using genetics to imply causality, we studied 60,608 individuals from Copenhagen using a Mendelian randomization design\textsuperscript{43}: a 1-mmol/L (39 mg/dL) higher level of remnant cholesterol was associated observationally with a 37% higher C-reactive protein level (Figure 7, lower right) and causally with a 28% higher level. For LDL cholesterol, a 1-mmol/L (39 mg/dL) higher level was associated observationally with only a 7% higher C-reactive protein level (Figure 7, upper right), and we found no causal association. These data thus demonstrate that elevated remnant cholesterol and triglyceride-rich lipoproteins are causally associated with low-grade inflammation, whereas elevated LDL cholesterol is not.

Supporting the finding of no strong relationship between C-reactive protein and LDL cholesterol, patients with heterozygous familial hypercholesterolemia and genetically high levels of LDL cholesterol as a result of a defect in the LDL receptor found either no difference in C-reactive protein levels between patients and controls\textsuperscript{116–119} or only slightly higher levels of C-reactive protein in patients when compared with controls.\textsuperscript{120–122} Furthermore, patients with homozygous familial hypercholesterolemia, who have extremely high levels of LDL cholesterol and therefore have a high risk of early atherosclerosis, only had slightly increased levels of C-reactive protein when compared with controls.\textsuperscript{123} Therefore, the
simplest explanation would be that elevated LDL cholesterol does not cause low-grade inflammation, whereas elevated triglyceride-rich lipoproteins do, as discussed above. However, it is only possible to infer that triglyceride-rich lipoproteins cause low-grade inflammation at a whole-body level, and not specifically arterial intimal inflammation, as there is no convincing evidence from humans in vivo that a more inflammatory atherosclerosis is produced by elevated triglyceride-rich lipoproteins. Finally, it can be speculated that because overweight-obesity genetically is a direct cause of elevated levels of C-reactive protein, then the strong genetic, causal association of elevated remnant cholesterol with high C-reactive protein is rather caused by overweight-obesity and the associated metabolic syndrome and insulin resistance directly. However, because overweight-obesity genetically is a direct cause of elevated remnant cholesterol, and the opposite seems unlikely, the most likely chain of events seems to be that overweight-obesity causes elevated levels of triglyceride-rich lipoproteins that then lead to whole-body low-grade inflammation and also likely to intimal inflammation.

Finally, because overweight-obesity is an important driver of high plasma levels of triglyceride-rich lipoproteins and thus of elevated remnant cholesterol (Figure 2 and Figure 7, upper left part), and because overweight-obesity in Mendelian randomization studies is causally associated with increased risk of IHD, it seems important to understand whether elevated remnant cholesterol can explain part of the increased IHD risk in overweight-obese individuals. To examine this question, we included ∼900,000 individuals from Copenhagen in a Mendelian randomization design with mediation analyses; the 3 intermediate variables that explained the highest excess risk of IHD from genetically determined obesity were LDL cholesterol with 8%, systolic blood pressure with 7%, and remnant cholesterol with 7% excess risk of IHD. Corresponding observational excess risks using conventional body mass index were 21%, 11%, and 20%, respectively. Taken together, these data suggest that elevated remnant cholesterol, LDL cholesterol, and blood pressure in overweight-obese individuals each partly explains the increased ASCVD risk seen in these individuals.

In summary, a simple chain of events from elevated triglyceride-rich lipoproteins to increased ASCVD risk could be as follows: a main cause of elevated triglyceride-rich lipoproteins in plasma is overweight-obesity, which leads to increased penetration into and entrapment within the arterial intima of triglyceride-rich lipoproteins, leading to local and whole-body low-grade inflammation caused by triglyceride hydrolysis and macrophage foam cell formation, the hallmark cell of atherosclerosis ultimately causing increased risk of ASCVD and premature death.

Conclusion and Perspectives

New insights from epidemiology, genetics, and biology on potential mechanisms now strongly suggest that elevated triglyceride-rich lipoproteins represent causal risk factors for inflammation, ASCVD, and all-cause mortality. However, we need evidence from randomized intervention trials showing that lowering of triglyceride-rich lipoproteins and remnant cholesterol reduces inflammation, ASCVD, and all-cause mortality in those with elevated levels. Fortunately, the first of such studies have already started in individuals already receiving a statin, add-on placebo-controlled, triglyceride-lowering n-3 fatty acids therapy to reduce residual risk is currently being tested in 2 ongoing trials (Reduction of Cardiovascular Events Outcomes trial [REDUCE-IT; ClinicalTrials number NCT01492361] and Outcomes Study to Assess Statin Residual Risk Reduction With Epanova in High CV Risk Patients With Hypertriglyceridemia [STRENGTH; NCT02104817]). Furthermore, yet another trial has just been announced to evaluate triglyceride reduction using a selective peroxisome proliferator activator receptor-α modulator in high-risk diabetic patients with high triglyceride and low HDL cholesterol levels who are already taking statins. Finally, there is a need for randomized intervention trial evidence showing that lowering of triglycerides and remnant cholesterol in primary prevention reduces ASCVD in those with elevated triglyceride-rich lipoproteins. Most needed is a placebo-controlled primary prevention trial in individuals with mild-to-moderately elevated triglycerides without elevated LDL cholesterol, using a potent statin versus placebo possibly in a 2-by-2 design with addition of another triglyceride-lowering agent versus placebo; a potent statin is preferred as such drugs have already been shown to reduce ASCVD and all-cause mortality with minimal side effects. Although it could be argued that it is unethical not to treat individuals with mild-to-moderately elevated triglycerides without elevated LDL cholesterol, the reality is that most such patients today are not offered lipid-lowering therapy.

Disclosures

Børge G. Nordestgaard has received lecture and consultancy honoraria from AstraZeneca, Merck, Omthera, Sanofi, Regeneron, IONIS Pharmaceuticals, Aegerion, Dezima, Fresenius, B Braun, Kaneka, Amgen, Lilly, Denka-Seiken.

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Triglyceride-Rich Lipoproteins and Atherosclerotic Cardiovascular Disease: New Insights From Epidemiology, Genetics, and Biology
Børge G. Nordestgaard

Circ Res. 2016;118:547-563
doi: 10.1161/CIRCRESAHA.115.306249

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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