Despite the extensive literature on the relationship of lipid and lipoprotein particles to coronary heart disease (CHD) incidence, the specific association of triglycerides with incident CHD has arguably generated more disagreement than any other measure. The most parsimonious explanations for this controversy are that contradictory results abound and that positive studies typically show a modest effect size. Two published meta-analyses concurred that triglycerides were independent risk factors for CHD, even after adjustment for high-density lipoprotein (HDL) cholesterol, which is strongly and inversely correlated with triglycerides (1, 2). In the first meta-analysis, published in 1996 (1), the overall relative risk for CHD was 1.12 for men and 1.37 for women per 1 mmol/L (88.6 mg/dL) of triglycerides. The second meta-analysis, published in 2007 and updated with recent studies (2), showed a relative risk of about 1.4 comparing the top triglyceride tertile with the bottom triglyceride tertile. The relative risk increased to about 1.7 with correction for regression dilution bias (due to within-individual triglyceride variation) (2). Against this background, many studies have reported effect modification—differing relative risks for CHD in specific subgroups. The most consistent findings have been higher relative risks in women (1), those with lower total cholesterol or low-density lipoprotein (LDL) cholesterol levels (3–5), those with lower HDL cholesterol levels (3, 5), those with diabetes (6, 7), and younger persons (3, 8). The effect in younger persons is of particular interest because aging has complex effects on cardiovascular risk factor associations.

In this issue, Tirosh and colleagues (9) examine a specific subset: young men. They report the association between the first of 2 triglyceride measurements obtained 5 years apart with incident CHD in 13,953 younger (age 26 to 45 years) men (9). The results are striking; triglycerides were strongly associated with CHD risk. After an average follow-up of 10.5 years, men in the fifth quintile of triglycerides compared with men in the lowest quintile, had a multivariable hazard ratio for CHD of 4.1.

Even more strikingly, the authors found that change in triglyceride levels between the initial and the second measurement 5 years later was associated with change in CHD risk. They placed men into tertiles of first and second measurements of triglycerides, excluded CHD events in the 5 years between the triglyceride measurements, and measured CHD incidence in the 5.5 years after the second triglyceride measurement. They found that increases in triglyceride levels were associated with increased CHD risk and decreases in triglyceride levels were associated with decreased CHD risk. For men starting in the first tertile, the relative risk was 6.8 for those whose second measurement placed them in the highest tertile (compared with those remaining in the first tertile). Further analyses showed statistically significant correlations between reduced triglyceride levels and adoption of favorable lifestyle behaviors, such as eating breakfast (yes, it helps!), losing weight, increasing physical activity, and stopping smoking. Adoption of unhealthy behaviors was associated with increases in triglyceride levels. Other investigators had observed these relationships in cross-sectional observations in population studies (10). The evidence described by Tirosh and colleagues is stronger because they measured behavior and triglyceride levels at 2 time points, between which some men altered their lifestyle.

Tirosh and colleagues’ work was carefully performed in a large cohort, with thoughtful and extensive analyses that included the effects of behavioral change. It is a major contribution to the literature on triglycerides and CHD risk. Nevertheless, some findings seem anomalous at first reading. Previous studies (cited in the first paragraph) showed hazard ratios less than 2.0. Tirosh and colleagues observed hazard ratios of 3.8 to 9.1. These hazard ratios seem high, especially for men, in whom the relationship between triglycerides and incident CHD is weaker than that in women. Are they a clue to a flaw in the research? The answer is no—the results are quite consistent with previous research.

The answer lies in the youth of the cohort. The cohort was so young that not a single man died of myocardial infarction in 10.5 years of follow-up and only 7 had non-fatal myocardial infarctions. The remaining 163 incident CHD cases were diagnosed by angiography. Research has consistently shown that the excess risk attributable to most cardiovascular risk factors varies very little with advancing age. In this young cohort, the excess risk for CHD due to high triglyceride levels combined with the low CHD risk in the group with low triglyceride levels to produce high hazard ratios. The identical excess risk added to the higher CHD risk in older cohorts with low triglyceride levels would result in a hazard ratio similar to that typically observed in studies of older groups (1, 2). Total cholesterol levels early in life also have much stronger associations with CHD than those later in life (11, 12).

Have we learned something new (and dynamic) in the demonstration that increasing triglyceride levels are associated with increasing risk and decreasing triglyceride levels with decreasing risk? The authors comment that the changes in CHD risk associated with changes in triglyceride levels seemed to reflect cumulative exposure to triglycerides over the entire study. I think this assessment is fair. Another way to think about these findings is that performing 2 separate triglyceride measurements on each man corrects for regression dilution bias (which is due to variation among several measurements in the same person). Indeed, the hazard ratios for change in triglyceride levels in Tirosh and colleagues’ Figure 2 seem to represent a simple average
of the hazard ratios associated with the average of the 2 triglyceride measurements. Regression dilution bias can be especially misleading in studies of triglycerides because several triglyceride measurements in the same person tend to vary so much (3).

The study’s most important limitation, the lack of data on persons with triglyceride levels greater than 3.39 mmol/L (>300 mg/dL), may not be remeulative, because this group apparently routinely received treatment to lower triglyceride levels. However, the results in these men, perhaps adjusted for intervention, would be valuable. The authors missed one opportunity, which they can easily remedy: They can use these data to test for the often-reported modification of the CHD risk associated with triglycerides by HDL cholesterol, LDL cholesterol, and fasting plasma glucose levels.

The data here complement the growing body of evidence that triglycerides have an independent effect on the incidence of CHD. Elevated triglyceride levels are not simply an innocent epiphenomenon of insulin resistance in the metabolic syndrome. For example, the authors of a study in a nationally representative sample correlated the individual components of the metabolic syndrome with cardiovascular disease. Although all components except waist circumference had statistically significantly elevated relative risks, triglycerides had the strongest correlation with prevalent cardiovascular disease, followed by low HDL cholesterol level, insulin resistance, and hypertension (13). At a cellular level, triglycerides per se may not be responsible for atherogenesis, because very high triglyceride levels may not predict CHD (3, 8, 14). Instead, the villain may be the atherogenic lipoprotein remnants that accompany more typical triglyceride elevations. A recent publication suggests that nonfasting triglyceride levels are strongly correlated with levels of remnant lipoprotein cholesterol (8). Moreover, in 2 recent publications (8, 15), nonfasting triglyceride levels predicted incident CHD events better than fasting triglyceride levels. These papers suggest that a standardized postmeal triglyceride level may be the best way to measure the atherogenic potential of triglycerides.

Does treatment for high triglyceride levels reduce CHD events? This question is difficult to answer, because all behavioral and pharmacologic therapies for elevated triglyceride levels also influence other lipid and lipoprotein fractions. However, clinical trials consistently show that patients with elevated triglyceride levels receive the most benefit from lipid therapy, regardless of the primary target of the specific therapy (LDL cholesterol, HDL cholesterol, or triglyceride level) (16–19). For example, in the Scandianavian Simvastatin Survival Study, persons with high LDL cholesterol levels accompanied by low HDL cholesterol and high triglyceride levels had significant benefit from simvastatin therapy, whereas those with isolated LDL cholesterol levels did not, despite identical LDL cholesterol reductions in both groups (19). In addition, a growing body of evidence suggests that dual dyslipidemic therapy using a statin and niacin—the latter affecting primarily HDL cholesterol and triglyceride levels—provides particularly strong cardiovascular risk reduction (20, 21).

For the clinician, the data reviewed here emphasize the importance of “rediscovering” triglycerides as a cardiovascular risk factor. As highlighted by Tirosh and colleagues, behavioral therapies—most important, weight loss and exercise—are a crucial part of any treatment directed at high triglyceride levels. For the public at large, the greatest concern is the obesity epidemic, which fuels triglyceride levels and other metabolic syndrome components that increase CHD risk. The public health sector and the medical care sector must join forces to address this pressing public health problem.

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