A lipid profile (LP) is used in clinical practice to assess risk of cardiovascular disease (CVD) and to guide therapy. The standard LP includes a direct measurement of plasma total cholesterol, triglyceride, and HDL cholesterol concentrations, and derived estimates of LDL cholesterol, non–HDL cholesterol, and lipid ratios. Expert guidelines recommend that accurate assessment of the LP requires a fast of 9 to 12 h. The principal reason is to diminish the biological variation in the plasma triglyceride concentration after ingestion of a fatty meal. Another reason is to compare plasma lipid levels with fasting data from healthy individuals. A fasting triglyceride concentration is also required for accurate estimation by the Friedewald formula of the cholesterol in LDL, the principal atherogenic lipoprotein.

The established practice of fasting has been challenged by population studies that have shown that components of the LP, including triglycerides, do not change greatly when measured at different times during the day in nonfasting individuals. Compelling epidemiology data also show that nonfasting concentrations of triglycerides, LDL cholesterol, non–HDL cholesterol, and HDL cholesterol, as well as the lipid ratios, are significant predictors of cardiovascular (CV) events, possibly more than in the fasting state. Can these findings be extended to patients with type 2 diabetes, a group with a high prevalence of hypertriglyceridemia and perturbed cholesterol-rich lipoprotein metabolism?

Investigators from the Copenhagen General Population Study have assessed the plasma concentrations of lipids, lipoproteins, apolipoproteins, and albumin in 58,434 individuals, 2270 of whom had diabetes. Participants were asked the time since their last meal, and nonfasting blood samples were categorized according to that information. In individuals with and without diabetes, the plasma triglyceride concentration remained increased for up to 7 h after the last meal. A mean postprandial increase of 0.6 mmol/L (23 mg/dL) in the plasma LDL cholesterol was observed, along with a proportionate change in the albumin concentration. Adjustment for albumin, and hence hemodilution, nullified the reductions in LDL cholesterol. The apolipoprotein B concentration did not change significantly in either group in the postprandial period. The mean maximal postprandial increase in triglyceride concentration was 0.2 mmol/L (17.7 mg/dL) in both diabetics and nondiabetics. The authors inferred that assessment of the LP (including triglycerides) is appropriate in nonfasting blood samples from diabetic patients.

When interpreting these findings, one should note the limitations of the study. First, only a small proportion of the total population was diabetic (<4%), limiting the statistical power to detect true changes in the LP. Second, the LP was not measured in the same individual at different time points after the last meal, again limiting the statistical power. Third, half of the diabetics were on statins, dampening the biological variation in the LP compared with nontreated patients. Fourth, the investigators were not able to report whether nonfasting lipids, lipoproteins, and apolipoprotein concentrations were predictive of CVD in the diabetics.

This last deficiency is bridged by a study of 1337 type 2 diabetics who were followed for 8 years. van Dieren et al. confirmed that components of the LP, with the exception of triglycerides, did not change significantly over the postprandial period. More importantly, nonfasting lipid concentrations, including triglycerides, were highly predictive of CV events, independently of postprandial time. These studies together provide supportive evidence for using a nonfasting blood sample to assess dyslipidemia and risk of CVD in type 2 diabetes.

These data provide an opportunity to discuss the significance of hypertriglyceridemia in type 2 diabetes and other potential limitations of a standard LP. Assessing plasma lipids in the fasted state overlooks the fact that individuals eat regularly and thus spend most of the day in a postprandial state. Postprandial lipoproteins of both intestinal and hepatic origin contribute to atherogenesis, particularly owing to the ac-
cumulation in plasma of cholesterol-rich remnant lipoproteins. Delayed remnant lipoprotein clearance is a feature of diabetic dyslipidemia (7). Hypertriglyceridemia, being associated with hepatic steatosis and oversecretion of large triglyceride-rich VLDL, is central to the pathophysiology of dyslipoproteinemia in type 2 diabetes (7). Hypertriglyceridemia causes qualitative changes in LDL and HDL, which are facilitated by cholesteryl ester transfer protein and hepatic lipase, with the accumulation of small dense particles in the plasma. Hypertriglyceridemia, arbitrarily defined as a triglyceride concentration $>2.0$ mmol/L ($>177$ mg/dL) in a nonfasting sample, is hence an integrative indicator of atherogenic dyslipoproteinemia. The non–HDL cholesterol concentration, however, is a better marker of remnant lipoproteins than triglycerides (1, 2, 11), but includes a large component of LDL cholesterol. A perceived deficiency of a standard LP is that it does not include a direct measurement of the total number of atherogenic lipoprotein particles, such as serum apolipoprotein B concentration, or LDL, as assessed by nuclear magnetic resonance spectroscopy. Recent data suggest, however, that measuring apolipoprotein concentrations has no advantage over the lipid ratios in predicting CV events in diabetic patients (12). These additional direct estimates of atherogenic particles are theoretically appealing and independent of prandial status; however, they increase costs, require physician and public education on their use, and generally have not been incorporated into treatment guidelines.

A nonfasting LP has unquestionable practical value, particularly in view of the increasing use of point-of-care analyzers. These devices give physicians instant lipid results and can be used at any time during the day, regardless of whether the patient has fasted. Their use can also encourage screening for dyslipidemias and enhance physician adherence to guidelines and patient compliance with treatment.

But are there potential drawbacks to the use of LPs obtained from nonfasting blood samples? Epidemiologic studies of women have shown that the nonfasting state is associated with lower plasma concentrations of LDL cholesterol, non–HDL cholesterol, and apolipoprotein B than the fasting state, and with a reduced ability to predict CV events (13). Although this notion has been contested (6), the issue remains controversial, and the nonfasting state could lead to misclassification of CV risk and false reassurance of therapeutic efficacy, particularly with respect to LDL cholesterol (14). Lund et al. (15) also recently reported that a fast meal depresses LDL cholesterol in diabetics by 0.2–0.4 mmol/L (7.7–15.4 mg/dL) (as assessed by direct and indirect methods), with the Friedewald formula misclassifying 38% of patients and two-thirds of statin users into a lower CV risk.

Although a nonfasting triglyceride concentration $>4$ mmol/L ($>354$ mg/dL) signifies an increased susceptibility to pancreatitis and hepatic steatosis, in practice these patients will need to be reassessed in the nonfasting state, incurring additional inconvenience and costs. Although Langsted and Nordestgaard (8) recognized this requirement, they did not provide an estimate of the frequency with which a repeat fasting LP was required. A major hurdle for nonfasting samples is that the overwhelming majority of expert guidelines and all clinical interventional trials with both diabetic and non diabetic individuals are based on fasting samples (1, 2, 11). In the management of diabetic dyslipidemia, patients on a statin and having good glycemic control with nonfasting plasma triglycerides $>2.2$ mmol/L ($>195$ mg/dL) and HDL cholesterol $<1.0$ mmol/L ($<38.7$ mg/dL) should be considered candidates for adding a fibrate or nicotinic acid to their treatment to prevent CV events (11). Evidently, measurement of the nonfasting plasma triglyceride concentration has the potential to overestimate the number of patients requiring combination therapy with a statin, with increased risks of drug side effects and costs. The relative benefits of using a nonfasting LP to guide lipid-regulating treatment decisions remains unresolved.

What are our recommendations regarding lipid testing in the fed and fasting state? The guiding principle is to use common sense and judgment that is both practical and cost-effective. Clear distinctions between screening, assessment, and treatment are required. As initial screening for dyslipidemia, a nonfasting sample is sufficient. Familial hypercholesterolemia can readily be identified when a plasma cholesterol concentration $>7$ mmol/L ($>271$ mg/dL) (fasting or nonfasting) is associated with xanthomas and/or a family/ personal history of premature CVD. Diabetes-related dyslipidemia can be readily ascertained by an increased triglyceride concentration and a depressed HDL cholesterol concentration. A nonfasting blood sample is particularly convenient when screening children, although the large biological variation in plasma lipids in this age group requires that abnormal results be confirmed with a fasting sample. Individuals with a “normal” nonfasting LP should be reassured about their lipid-mediated risk of CVD. A repeat LP in the fasted state is recommended for all individuals having an initial nonfasting triglyceride value $>2$ mmol/L ($>177$ mg/dL), for such results point to atherogenic dyslipidemia and signify metabolic syndrome, type 2 diabetes, or familial combined hyperlipidemia (2, 11). Whether based on a fasting or nonfasting blood sample, an increased plasma triglyceride concentration should act as a
trigger for estimating atherogenic lipoproteins via assessment of either non–HDL cholesterol or, resources permitting, the apolipoprotein B concentration (2, 11). When drug therapy is initiated or altered in patients, with or without diabetes, fasting samples should be used. Patients with isolated hypercholesterolemia on stable drug therapy can be evaluated in the nonfasting state. Lipid ratios may perform well in epidemiologic studies (12), but “treating a ratio” is another matter. Expert guidelines accordingly specify therapeutic targets for LDL cholesterol, non–HDL cholesterol, and, increasingly, apolipoprotein B (2, 11).

We submit that a standard LP measured in the fasted state should continue as the benchmark for risk assessment, diagnosis, and therapy of lipid disorders, with consideration given to nonfasting samples in specific clinical circumstances and in the initial screening for dyslipidemias.

References