Cardiovascular disease (CVD) remains a significant cause of morbidity and mortality worldwide. Although significant progress has been made in reducing the prevalence of CVD in the developed world, countries adopting the Westernized high-fat, high-sugar, low-exercise lifestyle have shown an increasing prevalence (1). It is also important to recognize the paradigm shift in understanding the underlying pathophysiology of CVD. The previous model was of a progressive increase in size over time of an atheromatous plaque encroaching on the lumen of a vessel producing, initially, angina due to partial blockage and then, subsequently, complete occlusion (hence ischemic injury). The demonstration that acute plaque rupture/destabilization affecting a nonocclusive and often non–flow-limiting lesion was the mechanism of acute coronary injury (2) has resulted in evidence-based interventions. These evidence-based interventions, derived from the results of large-scale multicenter clinical trials, have significantly reduced the morbidity and mortality for acute myocardial infarction. There has also been significant progress in primary prevention (where there is no known underlying CVD) and secondary prevention (where the individual is known to have CVD such as a previous myocardial infarction). The recognition of the role of cardiovascular risk factors including cholesterol as one of the key modifiable risks has been accompanied by the development of cardioprotective medication, specifically cholesterol-lowering drugs. Currently, the most commonly used, and most clinically effective, class of cholesterol-lowering drugs is the hydroxymethylglutaryl-CoA reductase (HMGCoA) inhibitors, generally referred to as “statins.”

The landmark Scandinavian Simvastatin Survival Study provided definitive evidence of the benefit of statin therapy in secondary prevention (3) and has been followed by a series of other studies, all of which conclusively support the role of statins in primary and secondary prevention (4). However, statin therapy continues to attract negative publicity, which has led to a public perception of adverse health effects (5). Much of the concerns arise from the use of statin therapy in primary prevention. There is no doubt that statin therapy confers benefit for secondary coronary prevention, but the utility in primary prevention is controversial. Current CVD risk stratification scoring systems show typical areas under the ROC curve in the range 0.65–0.85. They are good at identifying high-risk and low-risk individuals. The challenge is identifying patients within the intermediate-risk group who are at high risk of future CVD events and would likely benefit from early treatment (6).

Laboratory testing is central to the primary and secondary prevention of CVD and management.
of CVD risk. Cholesterol measurement is a crucial part of the process because even the most astute clinician is unable to say what a patient’s lipid profile is by physical examination. The measurement of total cholesterol has been the mainstay of the initial epidemiological and then clinical studies. Total cholesterol measurement is well characterized; the methods are well developed and standardized. However, measurement of total cholesterol has clinical limitations. Lipoprotein fractionation is required to define the atherogenic phenotype of any one individual. People with high total cholesterol due to an elevation of HDL are frequently encountered in clinical practice. A raised HDL is cardioprotective, but such individuals may inappropriately receive statin therapy for a perceived atherogenic total cholesterol elevation. Although measurement of total cholesterol, triglyceride, HDL, and measured or calculated LDL are now routinely provided (or should be) as part of the standard lipid profile, there are methodological concerns. HDL methodology has improved from the original precipitation methods, but true standardization remains problematic. LDL is often calculated rather than measured, and the calculation methodology is significantly affected by the HDL method used and triglyceride values, while direct LDL measurement is also imperfect (7, 8). In addition, when cholesterol levels are low, there is a significant inaccuracy in LDL measurement (9). Currently, perception in clinical practice is that “lower is better” for aggressive cholesterol-lowering in secondary prevention. If clinicians are routinely using LDL, the measurement with which they are most familiar, inaccurate values when total cholesterol is low may result in inappropriate or insufficient treatment. There is also the problem of lipoprotein size (10). Small, dense LDLS are considered more atherogenic. Finally, there are other types of lipoproteins that can contribute significantly to the lipoprotein phenotype, namely intermediate-density lipoprotein (IDL) and VLDL. IDL and VLDL are known to be atherogenic, but are not routinely measured. IDL and VLDL are increased in dyslipidemia states, most notably in diabetes, the epidemic of modern times. The routine provision of the non-HDL fraction in laboratory reports goes some way to address the problem of failure to measure IDL and VLDL directly. Non-HDL reporting is simple and cost-effective because it is a mathematical equation based on values quantified in a general lipid screen that can be easily programmed into the LIS. It has only 2 measurement errors (total cholesterol and HDL), unlike the 3 of calculated LDL (total cholesterol, HDL, and triglyceride), but it fails to address the fundamental problem: measuring the number of atherogenic particles (11). Accurate characterization of the lipid phenotype is required to assist in risk stratification of the patient, especially in patients at intermediate risk. Direct measurement of apolipoproteins, specifically apolipoprotein (apo) A1 and apo B 100 (apo B) addresses this problem. In a large-scale epidemiological study, the apo B/A1 ratio was found to be one of the most powerful risk predictors for CVD (12). Methodologically, measurement of apo B is superior to measurement or calculation of LDL (13). Why then are apo A and apo B not recommended for routine measurement? The current guidelines are equivocal. American and European guidelines do not routinely recommend first-line measurement of apo A1 and apo B, although they suggest optimal concentrations for apo B reduction. The only guidelines clearly recommending apo B measurement are those of the Canadian Cardiac Society (14, 15). There are 2 potential reasons for not routinely measuring apo A1 and apo B: cost and lack of evidence. In this respect, the review article, “Lipoprotein Biomarkers and Risk of Cardiovascular Disease: A Laboratory Medicine Best Practices (LMBP) Systematic Review,” by Sandhu et al. (16), published in this issue, is a welcome addition to the literature. This
review systematically covers the literature, is contemporary (covering the period until July 2015), and addresses some of the weaknesses of previous studies by controlling for other risk factors. It therefore fills an evidence gap and shows, quite clearly, the scientific basis for apo A1 and apo B measurement. However, the problem of cost, or more properly, cost-effectiveness, remains. The high cost of CVD to the individual and society means that the cost benefit of lipoprotein measurement is likely to be favorable, but formal economic modeling is needed. Acceptance of the cost benefit will then leave only one, regrettably nontrivial, problem: educating clinicians in how to use apo A1 and apo B measurement in clinical practice. Luckily, many specialist practitioners already use apolipoprotein measurements, and the cardiology community as a whole is currently much more receptive to innovation in the area of cardiovascular risk management. They have enthusiastically adopted statin treatment, and there is no reason why they cannot embrace up-to-date measurement technology.

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