Non-HDL Cholesterol: A New Endpoint in Cardio-Metabolic Health Monitoring

To the Editor: Cardiovascular disease (CVD) is estimated to be responsible for 50% of excess all-cause mortality in mentally ill persons. This high metabolic risk results in the life expectancy of individuals with mental health disorders being significantly reduced, as patients die up to 25 years earlier than the general population.[1]

Accelerated CVD risk in psychiatric patients is multifactorial and the causes are not entirely understood. Patients with mental illness are more likely to have modifiable risk factors that increase their CVD risk, including smoking, poor diet, and physical inactivity. In addition to these predisposing risk factors, mounting evidence indicates that some antipsychotic treatments can further elevate CVD risk in treated individuals via adverse effects including weight gain, alterations in lipid and glucose metabolism, and consequent insulin sensitivity. The differential cardiovascular potential of some second-generation antipsychotics has been shown, with a higher risk potential for agents such as clozapine or olanzapine compared with other equally effective agents (Table 1).[2]

Monitoring. As the cardiovascular potential of antipsychotics is a controllable risk factor, patients receiving all atypical antipsychotics should be routinely monitored for elevations in CVD risk factors.[2] However, undermonitoring and undertreatment of risk factors in patients with psychiatric disorders are common when compared with the general population. Results of a recent multistate Medicaid study estimate glucose and lipid monitoring rates at less than 20% and 10%, respectively.[3] Examination of the reasons for such low levels of monitoring, particularly of lipids, deserves greater attention. Potentially, clinicians may find it difficult to get patients to attend regular checkups or indeed may struggle to obtain fasting samples from patients with psychiatric disorders. Current methods of lipid monitoring commonly used to predict CVD risk include measurement of various circulating lipid fractions including low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, total cholesterol (TC), and triglyceride (TG) levels. As these current lipid markers are challenging to monitor comprehensively, especially in psychiatric practice, new measures have been proposed, including measurements of non-HDL cholesterol. Non-HDL cholesterol encompasses all atherogenic cholesterols and is the sum of LDL, intermediate density lipoprotein (IDL), and very low-density lipoprotein (VLDL) cholesterols, as well as lipoprotein(a) and chylomicron remnants.

Non-HDL cholesterol: a new endpoint in cardiometabolic health. With continued research, it is becoming increasingly apparent that non-HDL cholesterol is indeed a robust predictor of future CVD events, both in the general population[4] and in patients with diabetes.[5] For example, one study described the utility of non-HDL cholesterol as an initial screening tool by demonstrating that the corresponding odds ratios of a first nonfatal myocardial infarction for non-HDL cholesterol in the second, third, and fourth quartiles were 1.83 (95% confidence interval [CI], 1.07–3.14), 2.07 (95% CI, 1.23–3.49), and 2.33 (95% CI, 1.39–3.90) ($P < .01$), respectively.[4] More recently, Jiang et al[5] have shown that an increase of 29 ng/dL of non-HDL cholesterol in patients with diabetes is associated with 50% increased cardiovascular risk.

There are a number of advantages associated with measurement of non-HDL cholesterol. Calculation of non-HDL cholesterol is straightforward and can be ascertained from a routine lipid panel as TC minus HDL cholesterol.

Table 1. Variability in Weight Gain and Lipid Abnormalities Among Second-Generation Antipsychotics[a]

Drug	Weight Gain	Risk for Diabetes	Worsening Lipid Profile
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
Aripiprazole[b]	+/–	–	–
Ziprasidone[b]	+/–	–	–

[a]Adapted with permission from the American Diabetes Association.[2]
[b]Newer drug with limited long-term data.
Abbreviation: D = discrepant results.
Symbols: + = increase effect, – = no effect.

This is easier than the equation used to calculate LDL cholesterol: in mg/dL: LDL cholesterol = TC – HDL cholesterol – (0.20 × triglycerides). Non-HDL cholesterol is also highly correlated with apolipoprotein B (apo B), the major apolipoprotein of all atherogenic lipoproteins, and therefore provides an accurate measure of the cholesterol in atherogenic particles.[6] LDL (derived from an equation) does not capture all apo B components of cholesterol, leading to insulin resistance (predicted by triglycerides) and hyperinsulinemia. In addition, non-HDL cholesterol is less sensitive to postprandial influences than measurements of triglycerides or LDL and can be reliably measured even in the nonfasting state.[6] National Cholesterol Education Program (NCEP) guidelines suggested that the goal for non-HDL cholesterol should be 30 mg/dL higher than the LDL goal, as a significant fraction of non-HDL cholesterol is contained in VLDL, not LDL. Thus, high levels of non-HDL cholesterol are indicative of cardiovascular risk, even without abnormal LDL levels, and provide greater sensitivity.

Studying metabolic risk factors: the CAMP trial. Clearly, the inclusion of metabolic risk factors as a safety endpoint in clinical studies can provide clinically useful data. Population studies provide a valuable means of assessing risk, and inclusion of non-HDL cholesterol measurement can provide useful data on metabolic risk. A large population study of metabolic health was initiated among the National Institute of Mental Health (NIMH)–sponsored Schizophrenia Trials Network in 2007 called the Comparison of Antipsychotics for Metabolic Problems (CAMP).[7] This multicenter, randomized, controlled study will enroll 300 patients with schizophrenia/schizoaffective disorder who require a treatment switch due to elevated cardiovascular risk. Inclusion criteria include a body mass index (BMI) ≥ 27 kg/m^2 and a non-HDL cholesterol level ≥ 160 mg/dL. The primary outcome measure will be the mean difference in non-HDL cholesterol level changes between patients assigned to continue existing treatment compared to patients assigned to switch. Other endpoints include continued antipsychotic effectiveness following a switch from a high cardiovascular risk medication to a lower liability agent.

Conclusions. Consideration of cardiovascular risk must become standard clinical procedure when prescribing atypical antipsychotics, and close monitoring of changes in metabolic parameters is necessary. Non-HDL cholesterol provides a convenient, valuable, clinically applicable endpoint: it does not require a fasting plasma sample and reflects the sum of serum cholesterol carried by all of the potentially atherogenic lipoproteins (LDL, VLDL, IDL, and remnant lipoproteins). Data arising from studies such as CAMP should provide information on possible clinical strategies for reducing primary and secondary cardiovascular risk in patients with schizophrenia.

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