Can Measurement of Serum Apolipoprotein B Replace the Lipid Profile Monitoring of Patients with Lipoprotein Disorders?

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Background: Current clinical guidelines require that five indices (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and the total/HDL cholesterol ratio) be measured or calculated to assess the lipid-related risk of vascular disease. All five are also targets of therapy and therefore all must be measured initially and at follow-up. Considerable evidence indicates that apolipoprotein B (apo B) is a better index of reaching or not reaching treatment targets than total or LDL cholesterol.

Methods: The objective of this study was to examine whether measurement of a single marker (apo B) led to the same categorization of risk as the traditional five indices (lipid profile). If both apo B and lipid profile indicated that the patient was either within or outside their respective treatment targets, the indices were considered concordant. If not, the indices were considered discordant. Concordance/discordance was examined in 215 patients at their first and last clinic visit.

Results: Concordance was high in both higher (88% at the first and 92% at the last clinic visit) and lower (76% at the first and 78% at the last clinic visit) risk groups at both the initial and final visits. Discordance was virtually restricted to the group with hypertriglyceridemia with normal concentrations of apo B, a group in which little independent evidence points to any substantially increased risk of vascular disease.

Conclusions: These data raise the possibility that at least for high risk patients treated with statins, follow-up could be simplified and expenses reduced if only apo B were measured. They also raise the possibility that outcome might be improved if the therapeutic algorithm were simplified.

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Current Canadian guidelines to estimate the risk of vascular disease attributable to serum lipid concentrations require measurement of total cholesterol, triglycerides, and HDL cholesterol, as well as calculation of LDL cholesterol and the total cholesterol/HDL cholesterol ratio (1). The actual decision of whether therapy is necessary is determined on the basis of these values, as well as the presence of other risk factors such as age, sex, increased blood pressure, and whether there is evidence of coronary disease or diabetes. Necessarily, a considerable amount of information must be integrated to reach an appropriate decision. If treatment is decided, current practice is to measure or calculate all five lipid indices on each of the return visits. Again this information must be integrated to determine whether the therapy used has achieved the desired targets.

Unfortunately, most patients do not reach their designated target lipid concentrations, although all the reasons for this fact have not been determined. One hypothesis that might partially explain this failure could be the complexity inherent in the present algorithm because both the patient and the doctor have to assimilate a considerable amount of information. If it were possible to reduce the number of indicators examined at follow-up after therapy had begun, the process might be more effectively executed.

Not only is the present approach complex, but other indices have been suggested that may be better predictors of cardiovascular risk, both on initial diagnosis and at follow-up. The best studied and established of these is the measurement of plasma apolipoprotein B (apo B). Each of the atherogenic particles in plasma (VLDL, LDL, intermediate-density lipoprotein, and lipoprotein(a)) contains one molecule of apo B and, therefore, plasma apo B measures

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the total number of atherogenic particles (2). This is important because one of the most common dyslipidemias associated with premature vascular disease (hypertriglyceridemic hyper-apo B) is characterized by increased numbers of LDL particles, which are smaller and denser because they contain less cholesterol (3). Because these LDL particles are cholesterol depleted, measurement of the total and LDL cholesterol does not accurately reflect their number in plasma. The fact that this difference is clinically important has been demonstrated in prospective epidemiologic studies and in primary and secondary prevention trials of the effect of LDL-lowering therapy on coronary risk (4–13).

Accordingly, the present study was designed to examine the concordance of serum apo B with the conventional lipid indices (lipid profile) in patients being assessed and treated at a Lipid Clinic (St. Paul’s Hospital, Vancouver, Canada). Our question was whether changes in apo B would accurately mirror the changes in the lipid profile; were this to be the case, we could consider, during follow-up at least, simplifying the process considerably.

Materials and Methods

Data from 215 consecutive patients coming for a follow-up visit to the clinic were examined at their initial (visit 1) and current (visit n) visit. For each patient, the fasting lipid profile and apo B were determined. The coronary artery disease risk of each patient was calculated according to the new Framingham tables (14).

The lipid concentrations for the four different levels of risk were chosen according to the recent Canadian Recommendations for management and treatment of dyslipidemias (1). Corresponding values of apo B were selected as follows: a value of apo B <1.20 g/L was selected as the cutoff value for the highest risk group. This corresponded to the 75th percentile for the Canadian adult population and was, therefore, similar to that chosen for the lipid concentrations (15). Similarly, the value of 0.9 g/L for apo B in the lowest risk group corresponds to approximately the 25th percentile of the population (15), a concentration that also corresponded to the percentile value chosen for the lipids. By the same reasoning, values of apo B of 1.0 g/L and 1.10 g/L were chosen as the cutoff values for the moderate and high risk groups, respectively. On the basis of the level of risk, target therapeutic concentrations for each risk group for both lipids and apo B were chosen and are shown in Table 1. Thus the target apo B in the very high risk group was <900 mg/L, a target concentration that has been endorsed by the Canadian Cardiovascular Society (16).

Lipoprotein lipids and apo B were measured by a nephelometric method with a WHO-IFCC calibrator and an external quality-control “Sequel” from the Canadian Reference Laboratory (Beckman Array 360 system) on fasting samples in the clinical laboratory of St. Paul’s Hospital. The CV for the measurement of apo B was 2.6%, for total cholesterol 0.9%, for HDL cholesterol 2.4%, and for triglycerides 1.2%.

Concordance/Discordance

Risk was calculated for each patient on the basis of the Framingham tables. Each patient was assigned to a target concentration on the basis of either lipids and/or apo B. If lipids and apo B yielded the same result (i.e., the same relative target concentration for the given risk calculated from the Framingham tables), they were deemed concordant; if they did not, they were deemed discordant. Our objective was to determine whether one measurement (apo B) yielded the same information as the other five (the lipoprotein lipids and ratio).

Results

Patients (n = 215) seen at visit n were also assessed by all relevant indices at visit 1. Not surprisingly, given the fact that all had been referred to a lipid clinic, 151 patients (70%) had lipid and/or apo B values outside the target concentrations. Of the total group, the lipid and apo B results from 174 patients (81%) were concordant. However, 41 patients (19%) were discordant principally because triglyceride concentrations were outside the target range in 26 (12%; Fig. 1). If the patients were divided into only two groups according to the Framingham tables, namely higher risk (>20% risk of coronary artery disease in 10 years) and lower risk (<20% risk of coronary artery disease in 10 years), concordance was even higher at 88% in the higher risk group. This difference was statistically significant (P = 0.02) by Pearson χ² test. The residual discordance was again primarily attributable to hypertriglyceridemia. In the lower risk group, discordance was slightly lower at 76% and, again, discordance was mainly

<table>
<thead>
<tr>
<th>Table 1. Canadian guidelines with apo B added.</th>
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<tbody>
<tr>
<td><strong>Degree of risk</strong></td>
</tr>
<tr>
<td>Very high (&gt;30% or CAD or DM)</td>
</tr>
<tr>
<td>High (20–30%)</td>
</tr>
<tr>
<td>Moderate (10–20%)</td>
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<tr>
<td>Low (&lt;10%)</td>
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LDL-C, LDL cholesterol; TC, total cholesterol; TG, triglycerides.

Figure 1

Illustration of target concordance, either within or outside the target, in patients at visit 1. W, within target concentration; O, outside target concentration; trg, triglyceride.
attribute to patients with hypertriglyceridemia with normal apo B.

The same analyses were performed at the last visit \(n\), on average 5 years later; however, the concordance or discordance of the data was independent of the interval between visit 1 and visit \(n\). At 92%, concordance was slightly greater at visit \(n\) than visit 1 in the higher risk group. In the lower risk group concordance was the same as at visit 1 (Table 2). There was an 83% concordance between lipids and apo B at visit \(n\), a result that was slightly better than at visit 1 \(P > 0.1\); McNemar \(\chi^2\) test). Concordance was also high in a subgroup of 19 patients with diabetes (79%), discordance was, again, caused by very high triglyceride concentrations (2% of patients had triglycerides >10 mmol/L).

**Discussion**

This study demonstrated that patients could be categorized according to their degree of risk in terms of those who did and did not reach the treatment targets, virtually as accurately, by one index (apo B) as by five others (lipid profile). This was true for both higher and lower risk patients at both the first and last visits.

Discordance was low and virtually restricted to a single group (hypertriglyceridemia) with a normal apo B. In this specific group, several cross-sectional studies have shown that the likelihood of vascular disease is substantially less than in patients with hypertriglyceridemic hyper-apo B (16–22). Even more importantly, the Quebec Cardiovascular Study demonstrated prospectively that hypertriglyceridemic hyper-apo B was associated with a threefold increase in the risk of vascular events, whereas hypertriglyceridemia with a normal apo B was not (23).

Several studies have now demonstrated that apo B and apo A1 remain predictive of outcome in patients on therapy, whereas lipoprotein lipids do not. For example, Moss et al (11) observed that in 1045 treated post-myocardial infraction patients, clinical events during follow-up were not predicted by lipoprotein lipids, but were

<table>
<thead>
<tr>
<th>Group</th>
<th>Concordance</th>
<th>Discordance</th>
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<tbody>
<tr>
<td></td>
<td>Overall, %</td>
<td>W, n</td>
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<tr>
<td>Higher risk</td>
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<tr>
<td>Visit 1</td>
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<td>Visit (n)</td>
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<td>Lower risk</td>
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<td></td>
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<tr>
<td>Visit 1</td>
<td>76</td>
<td>23</td>
</tr>
<tr>
<td>Visit (n)</td>
<td>78</td>
<td>44</td>
</tr>
</tbody>
</table>

\(^a\) W, within target; \(O\), outside target; Lipids+/apo B−, met lipid but not apo B targets; Lipids−/apo B+, met apo B but not lipid targets.

\(^b\) 7% (6) met apo B but not triglyceride targets.

\(^c\) 5% (5) met apo B but not triglyceride targets.

\(^d\) 15% (20) met apo B but not triglyceride targets.

\(^e\) 9% (12) met apo B but not lipid targets.
used widely (25). Availability of these materials and appropriate external quality controls both in the United States and Canada should change the current perception. Similarly, reference intervals for apo B have been established in various populations. Our cutoff values (25th and 75th percentile) are derived from these studies and are consistent with those chosen for lipids. Another potential issue is a selection bias of patients included in this study. This patient cohort represents that seen at a lipid clinic. It includes, therefore, a wide variety of lipid disorders that occur within the general population. Nevertheless, the results of this pilot study must be confirmed in a larger group that directly represents the general population, such as the Quebec Cardiovascular Study. It is possible, of course, that some of the hypertriglyceridemic patients may not have been fasting or used alcohol, but this would tend to reduce not increase discordance. Furthermore, it can be argued that follow-up for only apo B will be most useful in patients on statins; however, in the other individuals, it may still be necessary to repeat full lipid profiles, particularly in those with fluctuating triglyceride concentrations. Another issue was whether the individuals with low HDL and normal apo B are at risk, but this does not appear to be the case as pointed out in recent reviews (26–27).

In conclusion, our study suggests that use of a single index, namely serum apo B, is as efficient for categorization and follow-up of most patients with dyslipidemia as the currently used lipid profile. Thus, although the lipid profile will remain essential for the initial diagnosis, the follow-up of many dyslipidemic patients could be simplified. Our results also raise the possibility that outcome might be improved if the algorithm to assess response were simplified.

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