Potential Effect of an Apoprotein B-based Algorithm on Management of New Patients with Hypertriglyceridemia Referred to a Specialty Lipid Clinic

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ABSTRACT

Background: In patients with hypertriglyceridemia, non-high density lipoprotein cholesterol (nonHDL-C) is a targeted goal. However, apoprotein B100 (apoB) may be superior in predicting cardiovascular risk so we assessed the utility of an apoB-based.

Methods: New patients (n=125) who had both apoB and standard lipids measured on the same day were included and we determined the concordances of having achieved goal lipid levels based upon proposed apoB versus nonHDL-C (ATP III) targets in patients with elevated TG (>150 mg·dl^{-1}) levels.

Results: Although apoB was correlated with nonHDL-C ($r = 0.47$, $p < 0.001$), the tests had only a fair level of agreement when categorizing the percentage of patients achieving lipid goals for their degree of cardiovascular risk ($\kappa = 0.22$). Among patients with an elevation in nonHDL-C above ATP III goals, between 12–42% had achieved target apoB. On the contrary, between 44–50% of patients were found to be at nonHDL-C but not apoB target. The results were not substantively altered if the analyses were confined to patients with TG values between 200–499 mg·dl^{-1}, rather than all patients with TG levels >150 mg·dl^{-1}, as specifically outlined in ATP III guidelines. In total, >50% of all subjects would have been treated either more or less aggressively following an apoB-based therapeutic algorithm.

Conclusions: Our findings confirm that the majority of patients referred with hypertriglyceridemia would be managed differently by following an apoB-based treatment algorithm compared to ATP III guidelines. Although many patients would be candidates for more intense therapy, many would be treated less aggressively.

Introduction

Plasma apoprotein B_{100} (apoB) represents the total concentration of lipoproteins that play a pathological role in atherosclerosis (eg low density lipoprotein [LDL], very low density lipoprotein remnants).[1,2] Due to variations in lipoprotein composition, substantial differences in apoB can occur among patients despite a similar LDL-cholesterol (LDL-C). Targeting only LDL-C does not adequately treat all atherogenic lipoprotein subfractions, nor does it address elevated lipoprotein particle numbers[3]. Due to these shortcomings, the National Cholesterol Education Program Adult Treatment Panel (ATP III) proposed using a secondary goal beyond LDL-C in patients with hypertriglyceridemia. The guidelines propose targeting non-high-density lipoprotein cholesterol (non-HDL-C), a better cardiovascular (CV) risk marker in patients with high triglyceride (TG) levels,[4,5] as a clinically useful surrogate marker of apoB. However, discordances between non-HDL-C and apoB have been shown to occur in population studies.[6,7,8]

The apoB concentration is more biologically linked to the genesis of atherosclerosis than is the simple level of cholesterol within any subset of particles.[1] Some epidemiological studies confirm that apoB may be superior to both LDL-C and non-HDL-C in predicting CV risk.[1,6,9,10] This possible inferiority of non-HDL-C may be due to several factors, including the fact that much of the cholesterol content within this calculated fraction often falls within larger non-atherogenic particles.[1] Several studies have also suggested that any LDL-C, non-HDL-C, or TG value may not provide additional CV risk information among patients in whom apoB is known.[1,8,9]

The prevalence of obesity is growing at a prodigious rate[11] and thus both moderate (150–500 mg·dl^{-1}) and severe (>500 mg·dl^{-1}) hypertriglyceridemia are now common findings. Therefore, the ATP III recommendation to target treatment of non-HDL-C in such patients is becoming increasingly more relevant to clinical practice.[4] This often leads to the requirement to add more medications (e.g., fibrate, niacin, fish oil) to first-line statin treatment. However, due to weaknesses of non-HDL-C, some experts have suggested targeting apoB as an alternative strategy.[12] Although unproven at this time, the epidemiological studies do provide some evidence to support the notion that it may be valid to manage patients based solely upon apoB targets, regardless of their TG or non-HDL-C values.[1,8,9] In population surveys, this approach has already been shown to identify a substantial fraction of patients who may possibly be undertreated by using conventional lipid goals.[8]

The University of Michigan Lipid Management program is a tertiary care specialty lipid disorders clinic that receives

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referrals from a large geographic area. A sizeable proportion of our patients are referred specifically for management of hypertriglyceridemia. Although apoB and non-HDL-C have been shown to be discordant in population studies,[8] we are not aware of this relationship being explicitly characterized among patients referred to a specialty lipid clinic. Given the complexity of lipid disorders, the severity of hypertriglyceridemia (e.g., many patients with TG values $>1{,}000\ mg{\cdot}dl^{-1}$) and the nature of the referral biases to our clinic, findings from other cohorts cannot be generalized to our unique patient network. Thus, the purpose of this study was to assess how an apoB-based treatment algorithm might alter our management decisions compared with ATP III guidelines, specifically among our new patient referrals prior to utilizing apoprotein values for patient care. We hypothesized that basing treatment targets upon apoB, rather than non-HDL-C (per ATP III guidelines), would result in substantial differences in subsequent management. While it has been suggested that apoB-based management would identify a large percentage of patients that are undertreated,[8] we also expressly sought to quantify the number of individuals with high TG values that would be treated less aggressively (i.e., those who have apoB at goal despite an elevated non-HDL-C). We believed that this may represent an underappreciated, sizeable group of patients with a less atherogenic form of hypertriglyceridemia who could avoid additional medications (possibly appropriately so) by targeting only apoB goals.

Methods

This study was approved by the Institutional Review Board of the University of Michigan. We performed a retrospective review of all new patient visits (ie initial evaluation) to the Preventive Cardiology and Lipid Management Clinic at the University of Michigan during the past 2 years. All subjects who had fasting traditional lipids plus apoB measured (at the same visit) at the University of Michigan Hospital Clinical Chemistry Laboratory and in whom we were able to identify their ATP III goal lipid values were identified. We then included in the subsequent analyses only subjects with elevated TG values above optimal ($>150\ mg{\cdot}dl^{-1}$). Secondarily, we also evaluated patients with TG values $>200\ mg{\cdot}dl^{-1}$, and additionally, specifically between $200–499\ mg{\cdot}dl^{-1}$, where further treatments options are based upon non-HDL-C goals (not LDL-C) as specifically recommended by ATP III. This is the scenario where apoB may be most useful,[1] and where direct comparisons with non-HDL-C are meaningful. Thus, concordances with LDL-C levels, as has been reported elsewhere,[7] are not clinically meaningful among our study patients with high TG values, as non-HDL-C is the ATP III lipid goal and in most situations more difficult to treat (i.e., LDL-C goal will be met in almost all patients at non-HDL-C target).[4]

Relationships between lipoprotein values were determined by Pearson and Spearman (if non-normal distribution) correlation coefficients. We then categorized subjects by CV risk strata per ATP III guidelines[4] and determined the discordances among patients deemed to be at target goals for non-HDL-C and for apoB (κ value). The impact of using several different hypothetical apoB goals was investigated based upon targets proposed elsewhere.[8,12]

The main study results that were evaluated are what would be our indicated next course of action among these patients seen on their first visit based upon the 2 different treatment algorithms. Outcomes following the ATP III guideline algorithm: patients would be deemed potential candidates for more aggressive treatment, per ATP III, if non-HDL-C was elevated, but apoB was at goal; and for less aggressive treatment per ATP III if non-HDL-C was at goal, but apoB was elevated. Outcomes following the apoB-based algorithm: patients would be deemed potential candidates for more aggressive treatment, per apoB, if apoB was elevated, but non-HDL-C was at goal; and for less aggressive treatment per apoB if apoB was at goal, but non-HDL-C was elevated.

Results

There were 125 subjects who had all lipid parameters measured (Table 1). As these were patients initially referred to us for complex lipid disorders, many patients had not yet met ATP III goals despite most taking medications on the first visit. For the entire population, the non-HDL-C and apoB were moderately well-correlated ($r = 0.47$; $p < 0.001$). Similar to previous reports, however, there was only a fair concordance between them when categorizing whether or not individuals have met their lipids goals based upon their CV risk status ($\kappa = 0.22$).[7] The concordance analysis was based upon standard apoB goals (bold values in Table 2),[8,12] but did not substantially vary when using different target values.

Once TG levels are elevated ($>150\ mg{\cdot}dl^{-1}$), non-HDL-C may be a more appropriate target in all patients to reduce CV risk. Our main results show that among such new patients referred to us, between 12%–42% of patients with a high non-HDL-C actually have apoB at goal for their level of CV risk (Table 2). These patients would be treated less aggressively per the apoB algorithm. The results were similar when excluding patients with very high TG values defined as $>1{,}000\ mg{\cdot}dl^{-1}$ or $>500\ mg{\cdot}dl^{-1}$, as they may require more treatment solely to reduce the risk of developing pancreatitis. However, ATP III guidelines only specifically suggest targeting non-HDL-C goals based upon the outlined risk factor categories solely in patients with TG values between 200 and $499\ mg{\cdot}dl^{-1}$. As this TG range included the majority of our patients previous analyses (excluded 8 patients), it is important to note that all results (all percentages in Tables 2 and 3) were not substantively different if the analyses were carried out only within this

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Table 1. Patient Characteristics of the Entire Cohort Stratified by Risk

	Total group	Low risk	Intermediate risk	High risk
	n = 125	n = 44 (35%)	n = 34 (27%)	n = 47 (38%)
Demographics				
Age (years)	50±13	45±13	53±12	51±12
Sex (M/F)	57 F	27 F	12 F	18 F
	68 M	17 M	22 M	29 M
BMI ($kg \cdot m^{-2}$)	30±8	27±5	28±5	36±9
Lipids ($mg \cdot dl^{-1}$)				
LDL-C	131±58	144±59	137±60	115±51
HDL-C	46±26	59±38	36±10	40±14
Triglyceride	350±421	272±323	316±387	449±506
Non-HDL-C	192±66	195±64	191±52	191±76
ApoB	119±35	126±38	119±34	111±32
ApoA	132±45	147±60	122±22	123±37
Medications (#pts)				
Statins	44	9	11	24
Ezetemibe	31	10	8	13
Niacin	16	3	5	8
Resins	30	4	7	19
Fibrates	11	3	1	7
Fish oils	19	3	5	11

All values are mean±standard deviation Low risk = <2 risk factors and no CV disease or risk equivalents[4] Intermediate risk = ≥2 risk factors and no CV disease or risk equivalents[4] High risk = CV disease, risk equivalents, and/or a Framingham risk score ≥20[4]. Abbreviations: BMI, body mass index; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; ApoB, apoprotein B_{100}; ApoA, Apoprotein A.

more limited specific population that directly accords with ATP III guidelines.

The results also confirmed the more commonly reported finding that a different subset of subjects would be treated more aggressively per the apoB algorithm.[8] Between 44%–50% of patients with non-HDL-C at goal do not have apoB at goal (Table 3). Between both subsets of patients, >50% of all subjects would have been treated either more or less aggressively following an apoB-based therapeutic algorithm compared with non-HDL-C algorithm. This is the case whether strictly following ATP III guidelines (including only patients with TG values between 200–499 $mg \cdot dl^{-1}$ in the study), or including all patients with high TG levels (more liberally defined as all patients with TG values >150 $mg \cdot dl^{-1}$, between 150–500 $mg \cdot dl^{-1}$, or between 150–1,000 $mg \cdot dl^{-1}$).

Discussion

The apoB has been shown to be a superior CV risk predictor in most scenarios by some epidemiological studies and is often discordant to both LDL-C and non-HDL-C.[1,6–10] We have shown this discordance to be present specifically within our unique cohort of patients with hypertriglyceridemia referred to a specialty care lipid clinic. The results confirmed previous reports showing that a therapeutic algorithm based upon apoB can identify a sizeable group of undertreated individuals by using non-HDL-C goals.[8] While this is true, we have further highlighted an underrecognized group of patients. Among those with hypertriglyceridemia (defined by several different thresholds and ranges) and non-HDL-C above ATP III targets (even specifically in patients with TG values only between 200–499 $mg \cdot dl^{-1}$), there also exists a sizeable portion who have already achieved

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Table 2. Patients with apoB at Goal Despite Having Elevated Triglycerides (≥ 150 mg·dl^{-1}) and Elevated Non-HDL Cholesterol

All subjects (n = 125)	Non-HDL and triglycerides elevated (#patients)	Non-HDL and triglycerides elevated AND apoB at goal	
Risk Category			
		apoB cut point	#patients
Low (n = 44)	12	≤110	4 (33%)
		≤120	5 (42%)
Intermediate (n = 34)	17	≤90	1 (6%)
		≤105	4 (24%)
		≤110	6 (35%)
High (n = 47)	31	≤80	2 (6%)
		≤90	4 (12%)

Non-HDL-C goals defined per ATP III guidelines: low (<2 risk factors), intermediate (≥2 risk factors without cardiovascular disease or any risk equivalent), and high risk (cardiovascular disease, any risk equivalent, or a Framingham risk score ≥20%) with targets <190, 160, and 130 mg·dl^{-1}, respectively. Primary outcome apoB goals derived from guidelines and the literature.[8,12] Abbreviations: HDL, high density lipoprotein; HDL-C, high density lipoprotein cholesterol; ApoB, apoprotein B$_1$00.

Table 3. Patients at each Risk Category with Non-HDL-C at Goal, but an Elevated apoB

All subjects (n = 125)	Non-HDL at goal (#patients)	Non-HDL at goal AND apoB elevated	
Risk Category			
		apoB cut point	#patients
Low (n = 44)	24	≥110	16 (67%)
		≥120	12 (50%)
Intermediate (n = 34)	11	≥90	6 (55%)
		≥105	5 (45%)
		≥110	4 (36%)
High (n = 47)	9	≥80	5 (56%)
		≥90	4 (44%)

Non-HDL-C goals defined per ATP III guidelines: low (<2 risk factors), intermediate (≥2 risk factors without cardiovascular disease or any risk equivalent), andhigh risk (cardiovascular disease, any risk equivalent, or a Framinghamrisk score ≥20%)with targets <190, 160, and 130 mg·dl$_{-1}$, respectively. Primary outcome apoB goals derived from guidelines and the literature.[8,12] Abbreviations: HDL, high density lipoprotein; HDL-C, high density lipoprotein cholesterol; ApoB, apoprotein B$_1$00.

apoB goal. Thus, if we are to propose using an apoB-based treatment algorithm in the future to guide our subsequent management of new patients with elevated TG values, the majority (>50%) would receive different recommendations from ATP III. This has important implications for us, and potentially (if corroborated) for other referral-based specialty lipid clinics.

The fact that apoB, reflecting the number of atherogenic lipid particles, often remains elevated despite the overall cholesterol content of lipoproteins being at goal (i.e., non-HDL-C) is well-recognized.[8] We have now shown this to be the case, even among patients with complex lipid disorders referred to our specialty clinic. This discordance occurred fairly homogeneously among patients at all levels of overall CV risk (Table 3). Lipoprotein particle numbers are often more difficult to reduce with medications than is the overall content of non-HDL-C in the blood.[1,4] On the contrary, there is a reciprocal group with apoB at goal, yet non-HDL-C elevated. We hypothesize that this may be comprised of individuals with a less atherogenic distribution of TG-rich lipoprotein subfractions. In our patients (Table 2), most of these individuals appeared to be of lower overall CV risk. Such cases may occur in the setting of severe hypertriglyceridemia due to chylomicronemia (e.g., types I and V hyperlipidemia) or in patients with elevations in large, less atherogenic, very low density lipoprotein particles (e.g., some patients with type IV hyperlipidemias).[1–3] In such situations, non-HDL-C will be elevated due to high cholesterol content specifically within fewer numbers of large lipid particles that are likely to be much less atherogenic. Epidemiological studies suggest that this situation carries less CV risk and that apoB is a superior predictor of future events.[9,10] These findings suggest that many patients in our clinic who would normally be construed as candidates for more medications based upon standard ATP III guidelines, may in actuality, appropriately, avoid this burden by basing management upon an apoB-based algorithm.

All studies of apoB have been epidemiological or retrospective observations within clinical trials.[10–16] The actual goals for apoB are not well determined and require more clarification by outcome studies. Thus, the thresholds selected for apoB in our study[8,12] are relatively arbitrary and minor adjustments of these values did modestly alter our results (Tables 2 and 3). Moreover, there are no clinical trial data confirming that modulating therapy based upon apoB levels (and disregarding non-HDL-C) leads to equal or superior patient CV outcomes. For example, it is rational to expect that since high TG values may not statistically convey

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excess CV risk once apoB is at goal,[9] that withholding TG-lowering medications in this setting would not produce worse outcomes. However, such a management strategy requires formal testing and validation from randomized clinical trials. Additional limitations of this study are selection biases and the small sample size. Nevertheless, the major thrust of this study was to purposely evaluate the potential differences between treatment algorithms specifically within our unique referral-based cohort prior to proposing to utilize an apoB-based algorithm in our specialty lipid clinic. Thus, the observation of outcomes within our selected patients was actually an a priori rationale for this study design. In fact, our study is novel in that we focused solely upon subjects with high TG levels (plus a high non-HDL-C) in a real world specialty lipid practice and also because we specifically highlighted the prevalence of the reciprocal discordance (high TG levels and non-HDL-C, but with apoB at goal). Our results may not be generalized to the population as whole, even though much larger studies have found similar discordances.[8] More importantly, however, these findings need to be confirmed in other specialty lipid clinics in order to demonstrate the true impact that apoB-based algorithms may have on patient management if they are ever to be more broadly recommended by national guidelines in the future.

An apoB-based algorithm would lead to substantially different treatment strategies in most patients compared to non-HDL-C targets, and even specifically ATP III guidelines, among our patients seen with high TG values in our specialty lipid clinic. Although many patients would be treated more aggressively per apoB, as has been demonstrated in larger population surveys,[8] we also identified a sizeable group that would, on the contrary, be managed less intensely. Further corroborations of these observations in specialty clinics are needed. Due to the fact that most patients in our clinic would be treated differently, it is reasonable to posit that the actual CV outcome rates of patients following the 2 treatment algorithms may substantially differ. We believe, therefore, that a randomized clinical trial basing lipid targets upon apoB versus conventional goals may be warranted.

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