

STATE-OF-THE-ART PAPER

Non-High-Density Lipoprotein Cholesterol Versus Apolipoprotein B in Cardiovascular Risk Stratification

Do the Math

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With the emergence of new lipid risk markers and a growing cardiometabolic risk burden in the United States, there is a need to better integrate residual risk into cardiovascular disease (CVD) risk stratification. In anticipation of the Adult Treatment Panel IV (ATP IV) guidelines from the National Cholesterol Education Program (NCEP), there exists controversy regarding the comparative performance of the 2 foremost markers, apolipoprotein B (apoB) and non-high-density lipoprotein cholesterol (non-HDL-C), as they relate to the current standard of risk assessment and treatment: low-density lipoprotein cholesterol (LDL-C). Although some emerging markers may demonstrate better performance compared with LDL-C, certain fundamental characteristics intrinsic to a beneficial biomarker must be met prior to routine use. Collectively, studies have found that non-HDL-C and apoB perform better than LDL-C in CVD risk prediction, both on- and off-treatment, as well as in subclinical CVD risk prediction. The performance of non-HDL-C compared with apoB, however, has been a point of ongoing debate. Although both offer the practical benefits of accuracy independent of triglyceride level and prandial state, non-HDL-C proves to be the better marker of choice at this time, given established cutpoints with safe and achievable goals, no additional cost, and quick time to result with an easy mathematical calculation. The purpose of this review is to assess the performance of these parameters in this context and to discuss the considerations of implementation into clinical practice. (J Am Coll Cardiol 2011;58:457–63) © 2011 by the American College of Cardiology Foundation

Less is more.

—Ludwig Mies van der Rohe (1)

Current guidelines from the National Cholesterol Education Program (NCEP) rely on low-density lipoprotein cholesterol (LDL-C) as the primary therapeutic target in the prevention of cardiovascular disease (CVD) (2). Although LDL-C is well established as an important prognostic marker of coronary heart disease (CHD), population trends suggest the need for better risk stratification. Epidemiological considerations include the recurrence of acute coronary syndromes in up to one-half of patients with “normal” cholesterol levels, and the occurrence of coronary events despite the aggressive use of statins (3). Although statin therapy provides a significant relative risk reduction of 30%, many CHD patients are still having events with LDL-C at goal (2,4,5). In the United States, more than 50% of acute coronary syndromes are recurrent in nature

despite a 6-fold increase in the control of LDL-C among hypercholesterolemic patients (3). Taken together, these findings suggest opportunities for further risk reduction of this population. Emerging research has identified potential surrogate lipid markers for assessing cardiovascular risk, including apolipoprotein B (apoB), small dense LDL, LDL particle number, and non-high-density lipoprotein cholesterol (non-HDL-C). The aim of this review is to compare the current standard-of-care lipid marker—LDL-C—to the 2 foremost emerging markers in CVD risk stratification, non-HDL-C and apoB.

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The Conventional Marker of Risk: LDL-C

A conventional lipid panel reports several parameters, including total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG). Of these, the NCEP (2) and the American Heart Association (3) recommend using LDL-C as a primary target of therapy in conjunction with assessing cardiovascular risk factors. Guidelines over the past 3 decades have maintained that LDL-C should be the main target of treatment based on several large trials (6–9), with the corollary that intensifi-

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Abbreviations and Acronyms

AACC = American Association of Clinical Chemistry
ACC = American College of Cardiology
ADA = American Diabetes Association
apoB = apolipoprotein B
CHD = coronary heart disease
CI = confidence interval
CVD = cardiovascular disease
HDL-C = high-density lipoprotein cholesterol
HR = hazard ratio
LDL-C = low-density lipoprotein cholesterol
NCEP = National Cholesterol Education Program
NRI = net reclassification index
TC = total cholesterol
TG = triglycerides
VLDL-C = very low-density lipoprotein cholesterol

cation of therapy to further lower LDL-C in secondary prevention patients is now warranted (10).

Although LDL-C is a well-founded target, emerging findings suggest that it has become a suboptimal marker of risk for a number of reasons (11,12). Population trends in the United States by the National Health and Nutrition Examination Survey (NHANES) and the American Heart Association report that the prevalence of each individual characteristic of the metabolic syndrome has increased over the past decade and is projected to continue increasing at a rapid rate (Table 1) (3,13–15). These characteristics lead to a larger free fatty acid burden on hepatocytes, as well as down-regulation of lipoprotein lipase (LPL) through relative insulin inefficiency (16). Such changes result in a preponderance of very low-density lipoprotein cholesterol (VLDL) and other lipoproteins, which are better accounted for by non-HDL-C and apoB

compared with LDL-C. Importantly, the value routinely reported as LDL-C by laboratories is calculated using the Friedewald equation, which is known to lose accuracy with elevated triglycerides or with an LDL-C <100 mg/dl (17,18). Given the growing cardiometabolic burden in the United States, targets of therapy other than LDL-C need to be considered.

Emerging Markers of Risk: ApoB and Non-HDL-C

With the intent of assessing complete lipid atherogenic risk burden—rather than a partial one, such as LDL-C—the ideal parameter is one that accounts for all atherogenic cholesterol particles, including LDL-C, Lp(a), intermediate-density lipoprotein cholesterol, chylomicron remnants, and VLDL-C (19,20). The dynamic flux of lipoproteins between subtypes under direction of LPL and cholesterol ester transfer protein (CETP) makes direct assessment of total atherogenic burden a challenge, which is significantly improved by apoB and non-HDL-C (19,21). Apolipoprotein B is able to directly measure the aggregate number of all atherogenic lipoproteins because each atherogenic particle contains 1 apoB₁₀₀ molecule.

Non-HDL-C is an established secondary target of therapy per the NCEP ATP III guidelines that remains underutilized in the clinical setting (22). With conventional analysis, non-HDL-C is able to quantify total atherogenic

burden by measuring the aggregate amount of “cholesterol” in all contributive particles. Non-HDL-C is a quick and simple calculation of TC minus HDL-C (TC – HDL-C), and can be obtained in the non-fasting state without affecting results.

Moving beyond LDL-centric management. Although LDL-C has been the primary measure used to estimate CVD risk by guidelines for over 3 decades, there are now many studies demonstrating consistent outperformance by non-HDL-C (23–29). In the Lipid Research Clinics Program Follow-Up study (11), 4,462 primary prevention individuals (age: 40 to 64 years) were followed over an average of 19 years. In this study, Cui et al. (11) found that non-HDL-C was a stronger predictor of all-cause mortality, as well as CVD mortality compared with LDL-C (chi-square for non-HDL-C: 24.3, and chi-square for LDL-C: 5.0). The BARI (Bypass Angioplasty Revascularization Investigation) study (25) followed 1,514 secondary prevention patients with multivessel disease for 5 years and found that non-HDL-C was a significant, independent predictor of nonfatal myocardial infarction (MI) (relative risk [RR]: 1.049, $p < 0.05$, per 10 mg/dl increase) with dose-dependent effects on multivariate analysis. Furthermore, LDL-C was not a significant predictor of either of these endpoints or all-cause mortality (25).

Although current recommendations are limited to therapeutic targeting of non-HDL-C in patients who have a TG level ≥ 200 mg/dl (or ≥ 2.26 mmol/l), non-HDL-C has been proven to perform better than LDL-C at all TG levels. In the SHEP (Systolic Hypertension in the Elderly Program) (26), for example, 4,736 primary and secondary prevention patients (mean age 72 years) were assessed for CHD risk. In this study, non-HDL-C was found to be an independent predictor of CHD regardless of TG level, whereas LDL-C lost predictive value with TG > 400 mg/dl (26). Similarly, in the EPIC-Norfolk study (30), non-HDL-C was the strongest predictor of future CHD (men and women, age 45 to 79 years) across all other lipid-stratified levels, including patients with a TG < 200 mg/dl. The ERFC (Emerging Risk Factors Collaboration) (31)

Table 1 United States: A Growing Cardiometabolic Phenotype

	1994–2002	2003–2010	Δ (%)
MetS	23.7%	34.0%	+10.3
High TG	27.0%	33.0%	+6.0
High TG and low HDL-C	2.1%	4.8%	+2.7
Type II diabetes mellitus	7.9%	10.7%	+2.8
Impaired fasting glucose	6.1%	25.9%	+19.8
Obesity	19.8%	33.7%	+13.9

Boldface values highlight the percent change in each individual characteristic of the metabolic syndrome. Percentage prevalence of cardiometabolic profile characteristics in adults ≥ 20 years of age in the United States. Individual characteristics include those of metabolic syndrome (MetS): high triglycerides (TG) (≥ 150 mg/dl), low high-density lipoprotein cholesterol (HDL-C) (< 40 mg/dl in men, < 50 mg/dl in women), impaired fasting glucose (fasting plasma glucose: 100 mg/dl to 125 mg/dl), type 2 diabetes mellitus, and obesity (body mass index ≥ 30 kg/m²). Table is based on data from Lloyd-Jones et al. (3), Flegal et al. (13), Gardner et al. (14), and Mokdad et al. (15).

found that TG levels were not independently associated with CHD risk once adjusted for non-HDL-C in 302,430 individuals. These findings support the expanded use of non-HDL-C as a primary therapeutic target. By using non-HDL-C as a primary therapeutic target, management of patients will become less fragmented through allowance of single-parameter risk stratification independent of TG level.

Non-HDL-C and the cardiometabolic profile. Approximately 34% of adults in the United States have the metabolic syndrome with characteristically high TG, low HDL-C, and LDL-C often within normal limits. Given this predisposition, in the setting of an increasingly obese, insulin-resistant, and diabetic population in the United States (Table 1), LDL-C has become less of an important marker of CVD risk (3). Pertaining to these epidemiologic trends, a pooled post-hoc analysis of outcomes using data from 4 large studies—FCS (Framingham Cohort Study), FOS (Framingham Offspring Study), LRCF (Lipid Research Clinics Prevalence Follow-Up) study, and the MRFIT (Multiple Risk Factors Intervention Trials)—demonstrated significantly higher values of non-HDL-C in diabetic patients compared with nondiabetic patients (194.1 and 176.7 mg/dl, respectively, $p < 0.001$), but nearly identical LDL-C levels (148.6 and 148.0 mg/dl, respectively, $p = 0.68$) (11,32). These findings underscore the limited ability of LDL-C to account for the well-established cardiometabolic lipid burden in this population (11,32).

Non-HDL-C is a better therapeutic target than LDL-C for several well-based reasons. In population studies, non-HDL-C correlates better with the characteristics of the metabolic syndrome (14,23,32). Non-HDL-C is twice as good as LDL-C in predicting risk reduction, and has demonstrated dose-dependent effects in predictive models of CVD more consistently than LDL-C (20,23,27–29,32). Cutpoints for non-HDL-C goals are based on well-established goals for LDL-C used in the current NCEP guidelines (Table 2).

Non-HDL-C or ApoB: the ongoing debate. There exists continuing controversy as to the comparative performance of non-HDL-C and apoB. Epidemiological studies and ran-

domized controlled trials, including AFCAPS/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study) (33), AMORIS (Apolipoprotein Mortality Risk Study) (34), and INTERHEART (35), have played an integral role in introducing apoB and apolipoprotein ratios as parameters that may offer more than conventional lipid measures in CVD risk prediction (36).

CVD risk prediction in epidemiological studies. The AMORIS (34) study found that apoB was a more accurate predictor of CVD risk compared with LDL-C among 175,553 healthy individuals (mean age 47 years) (RR for MI: 1.33 and 1.53 in men and women, respectively) (36). These findings, however, have questionable utility given significant design limitations including lipid measurement through nonconventional methodology and minimal adjustment for confounding variables (34). The INTERHEART study demonstrated a graded association of the apoB/apoA-I ratio to risk of MI in 29,972 individuals. This study, however, did not directly assess apoB compared with LDL-C (35).

Multiple studies report that apoB has the strongest association with CHD risk compared with conventional measures (37–40). The Health Professionals Follow-Up study (40), for instance, compared lipid measures in the prediction of CHD among 18,225 men (age 40 to 75 years) and found that although non-HDL-C outperformed LDL-C in CHD risk prediction (non-HDL-C RR: 2.99, $p_{\text{trend}} = 0.006$; LDL-C RR: 0.86, $p_{\text{trend}} = 0.75$), apoB outperformed non-HDL-C (apoB RR: 3.99, $p_{\text{trend}} = 0.02$; non-HDL-C RR: 0.73, $p_{\text{trend}} = 0.76$) in multivariate-adjusted models. The high age-adjusted Spearman correlation coefficient between non-HDL-C and apoB ($r = 0.93$, $p < 0.0001$)—a common finding in several studies (27,41–43)—underscores the significant degree of colinearity between these 2 parameters, which renders logistic regression analyses less reliable (5). Furthermore, implicit to the relationship of high correlation in the setting of moderate concordance is the inability of apoB as an individual measure to substitute for a conventional lipid parameter such as non-HDL-C, but rather to be used adjunctively with it (19,36,40).

In the Women's Heart Study (27), 15,632 healthy women ≥ 45 years of age were followed prospectively over 10 years. Future major cardiovascular events were found to be equally associated with apoB (hazard ratio [HR]: 2.50, 95% confidence interval [CI]: 1.68 to 3.72) and non-HDL-C (HR: 2.51, 95% CI: 1.69 to 3.72), both of which performed better than all other individual lipid and apolipoprotein parameters (27).

The most compelling and largest epidemiological study to date was completed by the Emerging Risk Factors Collaboration (31). In this analysis of 22 studies with 91,307 individuals, non-HDL-C and apoB were the most predictive parameters in fully adjusted analyses (non-HDL-C HR: 1.59, 95% CI: 1.36 to 1.85; apoB HR: 1.58, 95% CI: 1.39 to 1.79) (31). However, others have criticized the

Table 2 Current NCEP Guidelines for LDL-C and Non-HDL-C

Risk Level	LDL-C Goal (mg/dl)	Non-HDL-C Goal (mg/dl)
Highest risk (CHD, CHD equivalent, or 10-yr risk score $>20\%$)	<100 ($<70^*$)	<130 ($<100^*$)
Moderately high risk (≥ 2 risk factors, or 10-yr risk score = 10%–20%)	<130 ($<100^{*\dagger}$)	<160 ($<130^\dagger$)
Moderate risk (≥ 2 risk factors, or 10-yr risk score $<10\%$)	<130	<160
Low risk (<2 risk factors, or 10-yr risk score $<10\%$)	<160	<190

*Optional goal for very-high risk patients; † optional goal for higher-risk patients. Table is based on data from NCEP Expert Panel (2).

apoB = apolipoprotein B; CHD = coronary heart disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; NCEP = National Cholesterol Education Program.

analysis since it excluded 2 large favorable apolipoprotein studies (34,35).

On-treatment CVD risk prediction. In AFCAPS/ TexCAPS, on-treatment apoB was a better predictor than LDL-C for developing an acute coronary event in 6,605 primary prevention individuals (apoB, $p < 0.0001$; LDL-C, $p = 0.062$) (33). This study, however, did not assess the comparative performance of apoB and non-HDL-C in CVD risk prediction.

Recently, the TNT (Treating to New Targets) (29) and IDEAL (Incremental Decrease in Endpoints through Aggressive Lipid Lowering) (28) trials prospectively assessed cardiovascular outcomes in 18,018 secondary prevention individuals (mean age: 61.3 years) randomized to low-versus high-dose statin therapy. In these predominantly normotriglyceridemic individuals, non-HDL-C better predicted cardiovascular risk when prospectively compared with LDL-C (23,28,29).

A combined analysis of both trials assessed comparative on-treatment performance of apoB, LDL-C, and non-HDL-C (23). In this analysis, non-HDL-C was found to have a higher association with future major cardiovascular events (HR: 1.31, 95% CI: 1.19 to 1.44, $p < 0.001$) compared with LDL-C (HR: 0.90, 95% CI: 0.82 to 0.99, $p = 0.04$), and was equally as associated (HR: 1.19, $p < 0.001$) with future major cardiovascular events as apoB (HR: 1.19, $p < 0.001$) (23,28,29). Direct pair-wise comparison of apoB and non-HDL-C, however, showed that non-HDL-C was more strongly associated with major cardiovascular events (HR: 1.14, $p = 0.06$) than apoB (HR: 1.05, $p = 0.47$) (23).

Risk reclassification. With clinical prognostic models, the impact that a given marker may have on outcomes can be accurately assessed by calculating the percentage of reclassified individuals expressed as the net reclassification index (NRI) (44). Although the Framingham Study found that apoB (men, RR: 1.37, $p < 0.001$; women, RR: 1.38, $p < 0.001$) was better than non-HDL-C (men, RR: 1.22, $p = 0.005$; women, RR: 1.28, $p = 0.01$) in CHD risk prediction, reclassification of individuals with the respective ratio parameters in sex-pooled analyses was minimally affected (0.1%) and not statistically significant (41).

These findings were further supported in the Women's Health Study (45), in which apoB only reclassified 2.6% of all individuals when compared with a conventional lipid

ratio reference model (TC/HDL-C). Notably, the reclassification percentage reported included both correctly and incorrectly reclassified individuals, thereby making the exceptionally low NRI even lower for correctly reclassified individuals. These findings indicate the negligible benefit of using apoB or the apoB/apoA-I ratio in cardiovascular risk prediction when considering their effect on outcomes from a practical standpoint.

Subclinical atherosclerosis: non-HDL or apoB? Non-HDL-C and apoB as predictors of subclinical atherosclerosis have been assessed in multiple studies with conflicting findings (42,46,47). Although developed imaging modalities allow for indirect assessment of subclinical vascular disease, postmortem examination from the PDAY (Pathological Determinants of Atherosclerosis in Youth) study (48,49) may offer a more definitive assessment (49). In this study, individuals from 15 to 34 years of age who died of external causes were autopsied. Extent of fatty streaks and raised lesions in the thoracic aorta, abdominal aorta, and right coronary artery for each individual were graded by independent pathologists (48). A multiple linear regression analysis was completed assessing the association of lipid and apolipoprotein parameters to vascular lesion grading. Non-HDL-C was significantly associated with fatty streaks in all 3 sites assessed ($p = 0.0001$), as well as with raised lesions in the abdominal ($p = 0.0465$) and thoracic aorta ($p = 0.0103$). ApoB was not significantly associated with any raised lesions, and was at best, 16 times less associated with fatty streaks compared with non-HDL-C (48,49). Collectively, these findings favor non-HDL-C over apoB as a better measure of subclinical atherosclerosis and global prognostic risk.

Treatment targets. Although treatment goals for LDL-C and non-HDL-C are delineated in the NCEP guidelines, apoB goals to date have been controversial and unclear (17,36). While treatment targets for apoB—like those for LDL-C and non-HDL-C—can be derived from certain population studies, there exists a large discrepancy in the proposed apoB cutpoints by different national organizations (Table 3) (17,36,50).

The American Diabetes Association (ADA)/American College of Cardiology (ACC) (15) position statement recommends an apoB goal of <80 mg/dl in highest-risk patients and <90 mg/dl in high-risk patients. In contrast, the American Association of Clinical Chemistry (AACC)

Table 3 Discrepant ApoB Cutpoints

	NCEP LDL-C Goals	ApoB Goals		
		ADA/ACC	AACC	CCS
Highest-risk patients, mg/dl	<70	<80	NS	NS
High-risk patients, mg/dl	<100	<90	<80	<80
Moderate-risk patients, mg/dl	<130	NS	<100	<80

Table is based on data from Brunzell et al. (17), Contois et al. (36), and Genest et al. (50).

AACC = American Association of Clinical Chemistry; ADA/ACC = American Diabetes Association/American College of Cardiology; CCS = Canadian Cardiovascular Society; NS = not specified; other abbreviations as in Table 2.

(36) recommends an apoB goal of <80 mg/dl in high-risk patients. The Canadian Cardiovascular Society is in disagreement with the ADA/ACC and the AACC, as they recommend an apoB <80 mg/dl as the primary therapeutic target in high- and moderate-risk patients (50).

The NCEP LDL-C goals of 70 mg/dl, 100 mg/dl, and 130 mg/dl correspond to different apoB cutpoints depending on whether Framingham (55 mg/dl, 80 mg/dl, and 100 mg/dl, respectively) or NHANES III (70 mg/dl, 90 mg/dl, and 110 mg/dl, respectively) population percentiles are applied (51). These discrepant percentile equivalents may contribute to the varying cutpoints proposed by different national organizations (Table 3) (17,36,50). Additionally, percentiles for cutpoints based on certain populations—particularly with Framingham—are somewhat outdated in corresponding lipid parameters, given interval gain over the past 2 decades in characteristics of the metabolic syndrome (Table 1) (3,13,52). With apoB cutpoints arbitrarily set on different population percentiles and only intermittently on LDL-C goals (17,36,50,51), current proposed therapeutic targets need to be re-evaluated.

Although studies with lower goal attainment rates of apoB compared with non-HDL-C suggest that non-HDL-C is a less useful target, it is important not to equate more challenging goal attainment with better outcomes. Stein *et al.* (19) found that although a majority of patients achieved LDL-C or non-HDL-C goal ($\approx 60\%$), only a minority achieved an apoB <90 mg/dl ($\approx 30\%$) in >22,000 specimens. The poor apoB goal attainment rate across all groups studied, normotriglyceridemic and hypertriglyceridemic individuals, and at all risk levels, highlights the likelihood of miscalibrated cutpoints for apoB, as well as the limited availability of efficacious interventions for apoB goal-directed therapy. With statins as the current mainstay of treatment, 1 study assessed the differential effects of the most commonly used statins at a full spectrum of approved doses in lowering major lipid parameters for 17,035 predominantly high-risk individuals (53). Despite the wide array of interventions applied, the substantially higher population percentile that apoB was lowered to (55th, $p < 0.001$) compared with non-HDL-C (29th, $p < 0.001$) or LDL-C (22nd, $p < 0.001$) suggests a need for better apoB-directed medications (Table 3). Furthermore, the

inability to achieve a mean apoB level below the 55th percentile in the setting of recommended goals for apoB ranging from the 10th to 50th percentile by national organizations (17,36,50,51,53), underscores a concerning treatment–goal gap that necessitates identification of effective treatment strategies and appropriate cutpoints for apoB prior to implementation. To reach the current proposed apoB goals, therapies in addition to high-dose statins would inevitably be needed, yet the evidence base for this approach is still incomplete.

Practical barriers to ApoB implementation. There are significant barriers to making apoB a primary therapeutic target in the management of individuals at risk for CVD. Briefly considering the immediate test costs puts into perspective the financial concern of such a paradigm shift in lipid management. Current mean values from national reference laboratories indicate a unit cost of checking 1 routine apoB level is \$79.15, whereas the unit cost of checking an entire conventional lipid panel including TC, TG, LDL-C, HDL-C, and non-HDL-C is only \$59.20 (Table 4). Since apoB cannot act as a stand-alone target, the projected cost of this test is one that becomes compounded.

Although apoB testing methods have been standardized to a greater degree over the past several years, there still remains a significant lag time in test result reporting. The mean time to report for national reference labs for apoB is on average up to 4 times longer than that of non-HDL-C (Table 4). The discrepancy in test turnaround time despite fairly equivalent run-time is due to lack of routine in-house apoB testing in most U.S. hospitals and clinics (Table 4). Furthermore, introducing a new conceptual framework of apolipoproteins will likely require a long timeframe for physician's acceptance, given that it took several decades for LDL-C to be routinely incorporated into clinical practice. In contrast, non-HDL-C exists within the current conceptual framework of lipids and enables physicians to assess patients at the same time as that of a conventional lipid panel. This allows for a patient–physician interaction that may enable faster initiation of lipid-lowering therapies, a greater number of effective interventions, better targeting with goal-directed therapy, and less likelihood of patients being lost to follow-up.

Table 4 National Reference Laboratory Indices of ApoB Versus Non-HDL-C Cost and Time to Report

National Reference Lab	ApoB Methodology	ApoB		Non-HDL-C	
		Unit Cost (\$)	Time to Report	Unit Cost (\$)	Time to Report
ARUP Lab	Immunonephelometry	50.00	1–4 days	30.00	<1 day
Mayo Medical Lab	Turbidimetry	108.30	1–4 days	88.40	<1 day
Mean values		79.15	1–4 days	59.20	<1 day
Unit cost Δ , %		$\uparrow$ 33.7% with apoB			
Time-to-report Δ , %		$\uparrow$ up to 300% for apoB			

Boldface values highlight the mean values relevant to cost and time to report for each marker. Table is based on 2010 data from National Reference Laboratories: ARUP and Mayo Medical Laboratories. Abbreviations as in Table 2.

Table 5 Comparative Performance of Emerging CVD Risk Markers: LDL-C, Non-HDL-C, and ApoB

	LDL-C	Non-HDL-C	ApoB
Performance			
Relevance to emerging population		X	X
Assesses residual cardiometabolic risk		X	X
Off-treatment CVD risk prediction	X	XX	XX
On-treatment CVD risk prediction		XX	XX
Subclinical CVD prediction		XX	X
Treatment reduces risk	X	XX	XX
Additional risk reclassification		X	X
Ease of use			
Independent of prandial state		X	X
Independent of triglyceride level		X	X
Familiar conceptual framework	X	X	
Well-defined treatment targets	X	X	
Well-defined intervention effects	X	X	
Can safely meet recommended goals	X	X	
Practical limitations			
Routine in-hospital testing	X	X	
Additional direct cost			XX
Delayed time-to-result			XX

CVD = cardiovascular disease; other abbreviations as in Table 2.

Conclusions

Both apoB and non-HDL-C are valuable parameters available to physicians for CVD risk stratification, with benefits beyond that of LDL-C (Table 5). Although available evidence suggests slightly better performance of apoB when compared with non-HDL-C, significant practical limitations of such a paradigm shift make apoB more of an “additional” lipid test rather than an “advanced” lipid test. Notable limitations of apoB include: 1) controversial findings of better performance compared with non-HDL-C; 2) arbitrary treatment cutpoints, with ongoing disagreement between national organizations; 3) insignificant population benefit by NRIs; 4) potential increases in estimated direct healthcare costs; 5) lag time in test-result reporting up to 4 times that of conventional parameters, with likely delays in appropriate intervention; 6) lag time of conceptual understanding by the majority of practicing physicians; and 7) poor goal attainment rates on standard therapies, including high-dose statins, with limited evidence for other available interventions and therapeutic effects. Although apoB looks very promising and may be of benefit in select patients, more definitive evidence is needed on establishing appropriate cutpoints and further delineating its benefits prior to implementation.

Non-HDL-C, in contrast, demonstrates competitive performance compared with apoB and offers several benefits that apoB does not, including: 1) established cutpoints based on LDL-C levels, which remain valid and independent of increasingly discrepant population percentiles; 2) no additional cost; 3) quick calculation of TC minus HDL-C; 4) well-documented intervention effects; and 5) existence within our current “cholesterol-oriented” conceptual frame-

work, lending itself to minimal physician–education lag time, and easy transition with implementation. These benefits may lead to a cost savings with use of non-HDL-C as a primary target by improving overall management of CVD risk, and minimizing immediate test repetition by physicians for confounded specimen samples. Although both non-HDL-C and apoB perform better than LDL-C, non-HDL-C is currently a more realistic primary target of therapy, given its ease of use and implementation.

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