Is apolipoprotein B a strong indicator of future heart disease in a patient, and what are the typical reference ranges? Above what range is considered high/high risk?

Background

Lipoproteins are complexes responsible for the transport of plasma lipids.[1,2] Lipid constituents include free cholesterol, esterified cholesterol, triglycerides, and phospholipids. The protein components are known as apolipoproteins or apoproteins; they provide structural stability and may also function as ligands or cofactors in the regulation of lipoprotein metabolism. There are several different types of apolipoproteins; specific apolipoproteins and details including their functions and sites of synthesis are listed in Table 1.

Table 1. Selected characteristics of apolipoproteins; adapted from *Goodman and Gilman*'s *The Pharmacological Basis of Therapeutics*, 13th ed.[1]

Apolipoprotein	Average concentration (mg/dL)	Sites of synthesis	Functions
A-I	130	Liver, intestine	Structural in HDL; LCAT cofactor; ligand of ABCA1 receptor; reverse cholesterol transport
A-II	40	Liver	Forms –S-S- complex with apo E-2 and E-3, inhibiting their binding to lipoprotein receptors
A-V	<1	Liver	Modulates triglyceride incorporation into hepatic VLDL; activates LPL
B-100	**85**	**Liver**	**Structural protein of VLDL, IDL, LDL; LDL receptor ligand**
B-48	**Fluctuates according to dietary fat intake**	**Intestine**	**Structural protein of chylomicrons**
C-I	6	Liver	LCAT activator; modulates receptor binding of remnants
C-II	3	Liver	Lipoprotein lipase cofactor
C-III	12	Liver	Modulates receptor binding of remnants
E	5	Liver, brain, skin, gonads, spleen	Ligand for LDL receptor and receptors binding remnants; reverse cholesterol transport (HDL with apo E)
(a)	Variable (under genetic control)	Liver	Modulator of fibrinolysis

apo=apolipoprotein; HDL=high-density lipoprotein; IDL=intermediate-density lipoprotein; LCAT=lecithin:cholesterol acyltransferase; LDL=low-density lipoprotein; LPL=lipoprotein lipase; VLDL=very low-density lipoprotein

Apolipoprotein B (apoB) exists in 2 forms: B-48 and B-100.[2] B-48 is formed in the intestine and is found in chylomicrons and their remnants; B-100 is synthesized in the liver and is found in very low-density lipoprotein (VLDL), VLDL remnants (i.e., intermediate-density lipoprotein [IDL]), low-density lipoprotein (LDL), and lipoprotein (a) (Lp(a)). The sum of LDL, IDL, Lp(a), VLDL, and chylomicron particles and remnants may be referred to as non-high-density lipoprotein (non-HDL)-cholesterol.

Atherosclerosis is the key underlying process contributing to most clinical atherosclerotic cardiovascular disease (ASCVD) events and is the leading cause of death in the United States and other Western countries.[2,3] Lipoproteins containing apoB-100 convey lipids (including LDL- and non-HDL-cholesterol) into the artery wall. The National Lipid

Association (NLA) asserts that an elevated level of cholesterol carried by apoB-containing lipoproteins (namely, LDL- and non-HDL-cholesterol) is a root cause of atherosclerosis. Remnant lipoproteins that contain apoB-48 can also enter the artery wall, contributing to atherosclerosis.

Among the 5 major classes of lipoproteins (HDL, LDL, IDL, VLDL, and chylomicrons), LDL is the predominant carrier of cholesterol, accounting for ~75% of the cholesterol carried by non-HDL particles.[3] The remaining 25% is carried by triglyceride-rich particles (VLDL, IDL, chylomicrons, and their remnants). Notably, 1 molecule of apoB is present in all atherogenic lipoproteins, including LDL, VLDL, IDL, and Lp(a).[4] Thus, it has been stated that apoB concentration is a direct indicator of the number of circulating particles with atherogenic potential.[3]

Guideline recommendations

There are several guidelines for the management of dyslipidemia that address monitoring of apoB, including those of the NLA, the European Society of Cardiology/European Atherosclerosis Society (ESC/EAS), the Canadian Cardiovascular Society (CCS), and the American Association of Clinical Endocrinologists (AACE).[3-6] Descriptions of the recommendations regarding apoB may be found in Table 2. Of note, the 2013 American College of Cardiology/American Heart Association (ACC/AHA) guideline on treatment of blood cholesterol does not contain recommendations regarding the monitoring of apoB and, therefore, was not included in Table 2.[7]

Table 2. Selected guideline recommendations regarding measurement of apoB in patients with dyslipidemia.

Organization, year of publication	ApoB as a target	Recommended target levels for apoB	Other comments
AACE 2018[a,6]	ApoB should be targeted, along with LDL-C and non-HDL-C, in patients with type 2 diabetes at risk for CVD	Targets dependent on risk category for CVD:[b] • Extreme risk: <70 mg/dL • Very high risk: <80 mg/dL • High risk: <90 mg/dL • Moderate or low risk: apoB targets not recommended	Data from several studies have shown that apoB, non-HDL-C, and LDL-P levels can remain suboptimal even when LDL-C reaches an optimal level. Consider other lipid-modifying agents in combination with maximally tolerated statins when therapeutic levels of LDL-C, non-HDL-C, apoB, or LDL-P have not been reached. To lower apoB or LDL-P: intensify statin and/or add ezetimibe, PCSK9 inhibitor, colesevelam, and/or niacin.
CCS 2016[4]	Consider apoB and non-HDL-C as alternate targets to LDL-C to evaluate risk of CVD events	Primary prevention of CVD: <0.8 g/L (80 mg/dL) Consider initiating statin therapy for primary prevention of CVD if apoB ≥1.2 g/L (120 mg/dL)	Multiple observational studies and RCTs have shown that non-HDL-C and apoB predict CVD risk similarly or better than LDL-C. ApoB, as well as TC, HDL-C, and non-HDL-C, does not vary appreciably after eating; thus, non-fasting lipid testing of these markers is acceptable.

Organization, year of publication	ApoB as a target	Recommended target levels for apoB	Other comments
ESC/EAS 2016[5]	Primary parameters for baseline lipid evaluation should include TC, triglycerides, HDL-C, and LDL-C. ApoB:ApoA1 ratio, Lp(a), and non-HDL-C are additional analyses that may be considered. In general, apoB (as well as non-HDL-C) can be considered a secondary target when analysis is available. LDL-C should be considered the primary target.	Targets dependent on risk category for CVD:[c] • Very high CV risk: <80 mg/dL • High CV risk: <100 mg/dL	ApoB is a metabolic factor that can affect one's risk for CVD. The ESC/EAS advocates use of SCORE to estimate total CVD risk.[c] Several prospective studies have shown that apoB is equal to LDL-C and non-HDL-C in risk prediction; however, apoB has not been evaluated as a primary treatment target in clinical trials. A major disadvantage is that apoB is not included in algorithms for calculation of global risk for CVD.
NLA 2015[3]	ApoB is an optional, secondary target for treatment	Measurement of apoB not necessary until patient has been treated to his/her goal levels for atherogenic cholesterol (LDL-C and non-HDL-C) ApoB targets depend on risk category for CVD:[d] • Very high risk: <80 mg/dL • Low, moderate, or high risk: <90 mg/dL	Both apoB and non-HDL-C have been shown to be better predictors of ASCVD risk than LDL-C in epidemiologic studies. Measurement of apoB and non-HDL-cholesterol does not require fasting; however, non-HDL-C is favored over apoB because it is universally available and requires no additional expense compared to a standard lipid profile.

[a]These guidelines are focused on the management of patients with type 2 diabetes but address prevention of CVD in these patients.
[b]Risk factors by category are as follows: **extreme risk**=progressive ASCVD in patients after achieving LDL-C <70 mg/dL, established clinical CVD in patients with diabetes, chronic kidney disease stage 3 or 4, or heterozygous familial hypercholesterolemia, or history of ASCVD before age 55 years in males or 65 years in females; **very high risk**=established or recent hospitalization for acute coronary syndrome, coronary, carotid, or peripheral vascular disease, diabetes or chronic kidney disease stage 3 or 4 with 1 or more risk factors, or heterozygous familial hypercholesterolemia; **high risk**=2 or more risk factors and 10-year risk >10% or coronary heart disease risk equivalent including diabetes or chronic kidney disease stage 3 or 4 with no other risk factors; **moderate risk**=2 or more risk factors and 10-year risk <10%; **low risk**=≤1 risk factor
[c]Risk category based on SCORE system, which estimates 10-year cumulative risk of a first fatal atherosclerotic event. Criteria for high or very high CVD risk include documented CVD, type 1 or type 2 diabetes, very high levels of individual risk factors, and chronic kidney disease
[d]Criteria for very high risk: presence of ASCVD or diabetes (type 1 or 2) with ≥2 other major ASCVD risk factors or evidence of end-organ damage

AACE=American Association of Clinical Endocrinologists; apoB=apolipoprotein B; ASCVD=atherosclerotic cardiovascular disease; CCS=Canadian Cardiovascular Society; CVD=cardiovascular disease; ESC/EAS=European Society of Cardiology/European Atherosclerosis Society; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; LDL-P=low-density lipoprotein particle number; NLA=National Lipid Association; non-HDL-C=non-high-density lipoprotein cholesterol; PCSK9=proprotein convertase subtilisin/kexin type 9; RCTs=randomized controlled trials; SCORE=Systemic Coronary Risk Estimation; TC=total cholesterol

Most of the organizations listed in Table 2 recommend apoB as an optional target to monitor in patients at risk for cardiovascular disease.[3-5] In contrast, the AACE recommends targeting apoB along with LDL-cholesterol and non-HDL-cholesterol in patients with type 2 diabetes at risk for cardiovascular disease.[6] All of the organizations recommend specific levels of apoB to target.[3-6] There is variability in the recommended target levels, with goals ranging from <70 to <100 mg/dL; most of the organizations recommend different goals based on the patient's level of risk for cardiovascular disease, which is defined differently across the guidelines. None of the guidelines include baseline apoB levels in their stratification of risk for cardiovascular disease.

In addition to the aforementioned guidelines, the American Association for Clinical Chemistry (AACC) issued a statement about apoB as an indicator of cardiovascular events.[8] They sought to evaluate the utility of apoB and LDL-particle number (LDL-P, determined by nuclear magnetic resonance [NMR]) and reviewed 25 clinical studies containing 85 outcomes for which both biomarkers were determined. The AACC found significant associations between these biomarkers and cardiovascular outcomes in 21 of the 25 studies (84%). Associations were generally equivalent, but some discordance was observed (i.e., disagreement in their association with different clinical outcomes – 1 biomarker was statistically significant but the other was not in 18 comparisons). The AACC concluded that apoB and/or LDL-P should be adopted into cardiovascular disease risk screening and treatment guidelines as indicators of atherogenic particle numbers and further stated that apoB may be preferable to LDL-P due to its availability, scalability, standardization, and relatively low cost.

There may be several advantages to monitoring apoB. The NLA, CCS, and ESC/EAS all state that apoB has been shown to be equal or superior to LDL-cholesterol in predicting the risk of cardiovascular disease. Accurate measurement of apoB also does not require fasting. However, apoB may not be universally available. Additionally, the ESC/EAS notes that apoB has not been evaluated as a predefined treatment target in clinical trials, and it is not included in algorithms for calculation of global risk of cardiovascular disease.

Literature review

From a search of the literature, several studies were identified in which apoB was investigated as a marker of cardiovascular risk. Multiple meta-analyses were retrieved. Selected aspects of their methodology and results are described in Table 3. Though the methodologies of the meta-analyses differ in their inclusion criteria as well as their statistical analyses, all meta-analyses found significant associations between apoB levels and risk of cardiovascular events. However, the findings were not uniformly in agreement. For example, findings from the meta-analyses by Thanassoulis et al and Sniderman et al suggest that apoB may be more strongly associated with cardiovascular risk reduction compared to other markers. In contrast, the findings of Robinson et al and Boekholdt et al suggest that apoB does not consistently predict cardiovascular risk and that non-HDL-cholesterol and LDL-cholesterol may be stronger predictors.

Summary

In summary, apolipoproteins are specialized proteins that complex with lipid constituents to form lipoproteins.[1,2] Apolipoproteins not only support the formation of lipoproteins, but they also mediate binding to receptors and activate enzymes in lipoprotein metabolism. The NLA asserts that an elevated level of cholesterol carried by apoB-containing lipoproteins is a root cause of atherosclerosis.[3] All atherogenic lipoproteins, including LDL, VLDL, IDL, and Lp(a), contain a single molecule of apoB;[4] thus, apoB concentration has been deemed a direct indicator of the number of circulating particles with atherogenic potential.[3] Monitoring of apoB is addressed by several guidelines, including those of the NLA, ESC/EAS, CCS, and AACE.[3-6] The NLA, ESC/EAS, and CCS recommend consideration of apoB as a secondary or alternate target to LDL-cholesterol and suggest target levels ranging from <70 to <100 mg/dL depending on the patient's risk for cardiovascular disease.[3-5] The AACE recommends monitoring apoB in addition to LDL-C and non-

HDL-C in patients with type 2 diabetes at risk for cardiovascular disease.[6] Importantly, none of the guidelines include apoB levels in their stratification of risk for cardiovascular disease.[3-6] The CCS does recommend initiating pharmacotherapy for primary prevention of cardiovascular disease in patients with apoB ≥120 mg/dL.[4]

From a search of the literature, it appears that the role of apoB as a marker of cardiovascular risk has been investigated; however, as per the referenced guidelines, it has not been investigated as a primary treatment target in clinical trials.[3-6] Several meta-analyses have been published addressing the potential utility of apoB as a predictor of cardiovascular risk with mixed findings.[9-13] Significant associations have been observed between apoB and CV events, but the extent and comparative strength of association to other markers, including LDL-C and non-HDL-C, are debatable. It is also important to note the lack of universal availability of apoB measurement and the fact that apoB levels are not currently included in risk estimates of cardiovascular disease. Thus, routine measurement of apoB may not be recommended at this time.

Table 3. Selected characteristics of meta-analyses investigating apoB as a marker of cardiovascular risk.

Reference	Objective	Included studies	MA design/models	Primary outcome(s)	Results[a]	Conclusions
Thanassoulis 2014[9]	To determine the relations between statin-induced changes in LDL-C, non-HDL-C, and apoB to reduction in risk of future CV events	7 PC, RCTs of statin therapy reporting 1-year changes from baseline in LDL-C, non-HDL-C, and apoB during statin therapy	Frequentist MA; Bayesian MA also used but results reported in supplementary appendix	CV event risk reduction with 95% CIs from statins per change in each lipid marker	Frequentist analysis: Mean relative risk reductions per SD change in lipid marker (95% CI): • LDL-C: **20.1%** (15.6, 24.3) • Non-HDL-C: **20.0%** (15.2, 24.7) • apoB: **24.4%** (19.2, 29.2) LDL-C vs. non-HDL-C: overall within-trial difference with respect to risk reduction was not statistically significant (2.4%, [-3.6, 8.4]) apoB vs. LDL-C: **21.6% greater risk reduction** (12.0, 31.2) apoB vs. non-HDL-C: **24.3% greater risk reduction** (22.4, 26.2)	Relative risk reduction of CV events across these studies was more closely related to reductions in apoB than to reductions in either non-HDL-C or LDL-C.
Robinson 2012[10]	To determine if reductions in apoB provide additional CVD risk information after considering LDL-C and non-HDL-C reductions	25 RCTs of ≥2 years' duration, designed to evaluate the effect of diet, statins, niacin, fibrates, bile acid sequestrants, or surgery, and involving ≥1 measurement of apoB, TC, LDL-C, and HDL-C after baseline	Bayesian MA	Association of mean absolute apoB decrease with relative risk of CHD, stroke, or CVD	Combined analysis: 10 mg/dL decrease in apoB associated with: • **6.3% decrease in overall CVD risk** (95% CI 1.8, 10.6; 25 RCTs) • **9.4% decrease in CHD risk** (95% CI 4.6, 13.8; 24 RCTs) • 3.9% decrease in stroke risk (95% CI -4.3, 11.9; 19 RCTs) ApoB was the same as LDL-C for predicting CVD risk decrease, but non-HDL-C decrease outperformed apoB decrease Analysis of statin trials (12 RCTs): 10 mg/dL decrease in apoB associated with:	Across drug classes, reductions in apoB did not consistently improve risk prediction over LDL-C and non-HDL-C decreases. Across statins, reductions in apoB added information to LDL-C and non-HDL-C reductions for prediction of CHD, but not for predicting stroke or overall CVD risk.

Reference	Objective	Included studies	MA design/models	Primary outcome(s)	Results[a]	Conclusions
					• **11.6% decrease in overall CVD risk** (95% CI 3.5, 20.5) • **15.9% decrease in CHD risk** (95% CI 8.6, 23.7) • 9.1% decrease in stroke risk (95% CI -6.8, 27.7) Non-HDL-C decrease and LDL-C decrease were better predictors of CVD risk decrease than apoB decrease	
Boekholdt 2012[11]	To evaluate the relative strength of association of LDL-C, non-HDL-C, and apoB with CV risk among patients treated with statins	8 RCTs with mean follow-up duration ≥2 years, investigating treatment with a statin, and in which TC, LDL-C, HDL-C, TG, and apolipoproteins were measured at baseline and at 1 year	NS	Time to first major CV event (fatal or nonfatal MI, fatal other CAD, hospitalization for UA, and fatal or nonfatal stroke), represented as HRs with 95% CIs	Adjusted HRs (95% CI) for major CV events per 1-SD increase: • LDL-C: **1.13** (1.10, 1.17) • Non-HDL-C: **1.16** (1.12, 1.19) • ApoB: **1.14** (1.11, 1.18) **HRs were significantly higher for non-HDL-C than LDL-C** (p=0.002) **and apoB** (p=0.02); no significant difference between apoB and LDL-C (p=0.21) Proportion of treatment effect explained by lipid/apolipoprotein levels in terms of HR (95% CI) • Standard risk factors: **0.80** (0.76, 0.83) • LDL-C: **0.89** (0.85, 0.94) • Non-HDL-C: **0.92** (0.87, 0.97) • ApoB: **0.90** (0.86, 0.95) Proportion of treatment effect in terms of percentages (95% CI) • Standard risk factors: -- • LDL-C: **50%** (33, 69) • Non-HDL-C: **64%** (45, 84) • ApoB: **54%** (38, 70)	On-treatment levels of LDL-C, non-HDL-C, and apoB were each associated with risk of future major CV events, but the strength of this association was greater for non-HDL-C than for LDL-C and apoB.

Reference	Objective	Included studies	MA design/models	Primary outcome(s)	Results[a]	Conclusions
Sniderman 2011[12]	To determine the overall balance of evidence comparing standardized RRRs for CVD of apoB, non-HDL-C, and LDL-C	12 studies reporting risk estimates of non-HDL-C and apoB	Random-effects model	RRRs per 1-SD increment for apoB, non-HDL-C, and LDL-C	Overall geometric mean RRRs (95% CIs): • ApoB: **1.43** (1.35, 1.51) • Non-HDL-C: **1.34** (1.24, 1.44) • LDL-C: **1.25** (1.18, 1.33) Comparisons of RRRs: • **ApoB RRR was 5.7% higher than the non-HDL-C RRR** (95% CI 2.4, 9.1) • **Non-HDL-C RRR was 5.0% higher than the LDL-C RRR** (95% CI 0.9, 9.1) • **ApoB RRR was 12.0% higher than the LDL-C RRR** (95% CI 8.5, 15.4) Based on the RRRs, the authors ranked the markers in this order: apoB>non-HDL-C>LDL-C Over a 10-year period, a non-HDL-C strategy would prevent 300,000 more events than an LDL-C strategy, and an apoB strategy would prevent 500,000 more events than a non-HDL-C strategy	ApoB was the most potent marker of CV risk; LDL-C was the least potent, and non-HDL-C was intermediate.
Emerging Risk Factors Collaboration 2009[13]	To produce reliable estimates of the associations of major lipids and apolipoproteins in relation to CV risk	68 prospective cohort studies of CV risk factors involving patients without any known history of CHD at baseline and with complete information on TC,	Random-effects model	CHD (first-ever MI or fatal CHD); adjusted HRs calculated	Adjusted HRs (95% CIs) for CHD: Among 68 studies: • TG: 0.99 (0.94, 1.05) • HDL-C: **0.78** (0.74, 0.82) • Non-HDL-C: **1.50** (1.39, 1.61) Among subset of 22 studies:	Lipid assessment can be simplified by measurement of either cholesterol levels or apolipoproteins (as opposed to triglycerides), as evidenced by the similar HRs seen with

Reference	Objective	Included studies	MA design/models	Primary outcome(s)	Results[a]	Conclusions
		HDL-C, TG, and several conventional risk factors; subset of 22 studies had additional information on apoB and apoA1			• Non-HDL-C/HDL-C: **1.50** (1.38, 1.62) • ApoB/apoA1: **1.49** (1.39, 1.60) • Non-HDL-C: **1.42** (1.06, 1.91) • LDL-C: **1.38** (1.09, 1.73)	non-HDL-C/HDL-C as with apoB/apoA1.

[a]Statistically significant results are in bold print

apoB=apolipoprotein B; CAD=coronary artery disease; CHD=coronary heart disease; CI=confidence interval; CV=cardiovascular; CVD=cardiovascular disease; HDL-C=high-density lipoprotein cholesterol; HR=hazard ratio; LDL-C=low-density lipoprotein cholesterol; MA=meta-analysis; MI=myocardial infarction; non-HDL-C=non-high-density lipoprotein cholesterol; NS=not specified; PC=placebo-controlled; RCTs=randomized controlled trials; RRRs=relative risk reductions; SD=standard deviation; TC=total cholesterol; TG=triglycerides; UA=unstable angina

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