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Non-HDL-C or Apolipoprotein-B versus LDL-C Screening for Evaluation and Treatment of Atherosclerotic Cardiovascular Disease

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Abstract

- Lowering low-density lipoprotein cholesterol (LDL-C) concentration in the population has been a goal of researchers and clinicians to prevent atherosclerotic cardiovascular disease (ASCVD).
- Controversy surrounds using [LDL-C] as the primary lipid biomarker to evaluate the risk of cardiovascular events. An article search dating back to 2005 of PubMed and The Cochran Library was conducted.
- The purpose of this investigation was to determine if LDL-C should be the primary lipid biomarker used to determine ASCVD treatment and prevention. This investigation researched other lipid biomarkers and targets to determine clinical relevance and if the level of those markers more accurately represents ASCVD in adults 21-75 years of age not afflicted by other chronic diseases.
- It was found that both non-high-density lipoprotein cholesterol (non-HDL-C) and apolipoprotein B (apoB) both better represent ASCVD risk than LDL-C, with apoB being superior to non-HDL-C.

Introduction

- ASCVD is the most common cause of death worldwide. In 2010, ASCVD accounted for approximately 16 million deaths, 40% of deaths in the developed world (Kasper et al., 2015).
- Researchers and clinicians divide their treatment strategies in to 2 categories; primary prevention and secondary prevention. Primary prevention seeks to prevent new-onset ASCVD, while secondary prevention extends to all other patients with already established ASCVD.
- Lowering LDL-C levels to set target goals using statin drugs is the standard treatment regime.
- Early in the 21st century researchers started to question if LDL-C was actually the biomarker that best predicted ASCVD. ApoB and non-HDL-C were lipid biomarker that received much attention and research.
- One ApoB molecule is attached to each VLDL, IDL, and LDL. Measuring apoB directly measures the number of all 3 atherogenic lipid particles. Its measurement requires fasting, a high cost, and is not standardized.
- Non-HDL-C is calculated by subtracting HDL-C from total cholesterol. Like apoB, non-HDL-C measurement is a way to determine combined levels of VLDL, IDL, and LDL

Statement of the Problem

- With so many different lipid biomarkers used to evaluate ASCVD risk, and multiple treatment and prevention guidelines available, it is challenging for a primary care provider to select the most efficacious and cost-effective treatment plan.

Research Questions

- What are the current guidelines for ASCVD treatment and prevention in adults 21-75 years of age?
- In the rural primary care setting, where state-of-the-art laboratory equipment is unavailable, the use of which lipid biomarker is most efficacious in assessing ASCVD risk in male and female adults 21-75 years of age?

Literature Review

Lipid Guidelines

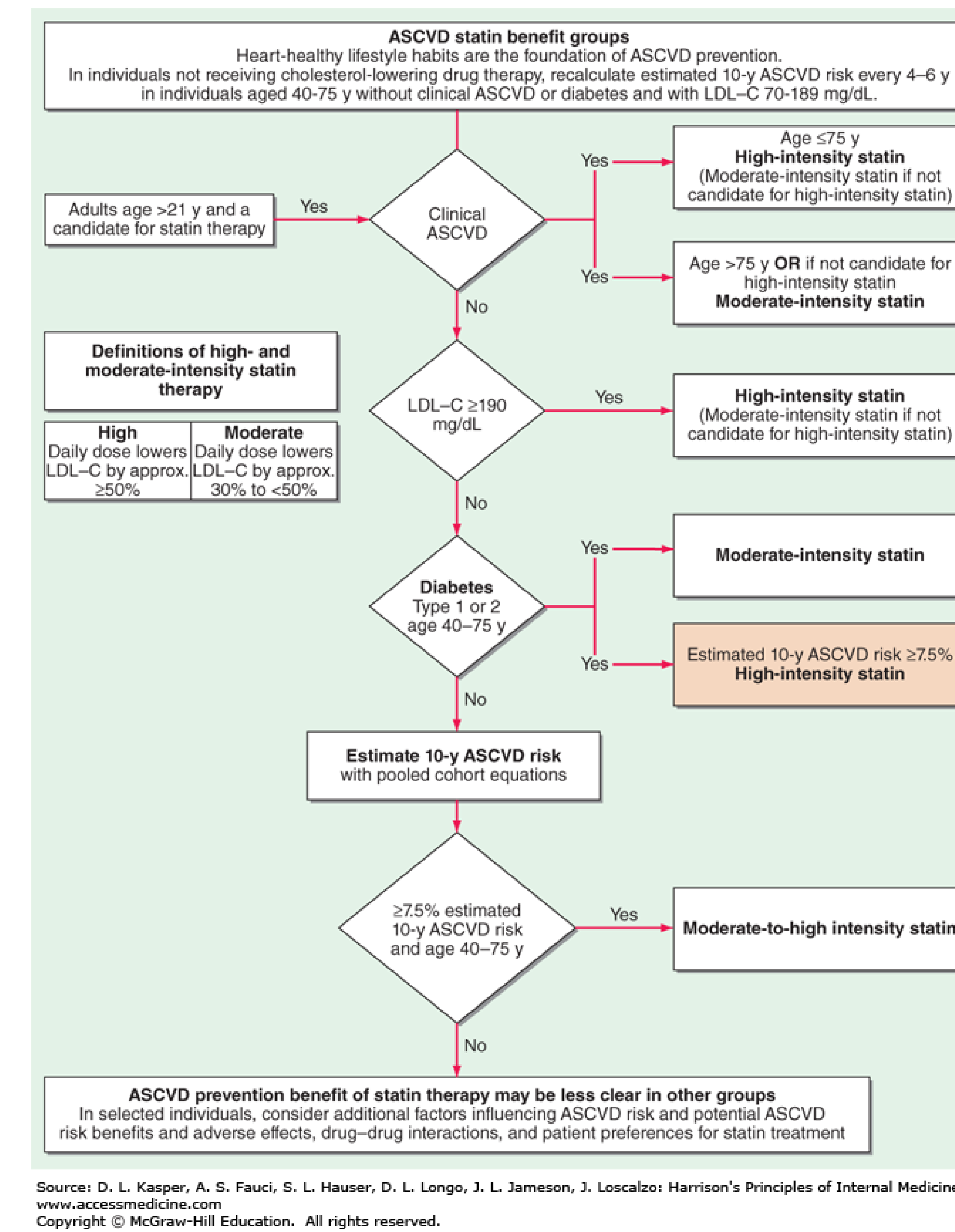
- In 2013 guidelines by the American College of Cardiology and American Heart Association, by Stone et al. (2013) were released. These guidelines brought about a departure from the previous guidelines, eliminating goals for LDL-C. Instead of LDL-C therapeutic goals, on the basis of a large consistent body of evidence, 4 major statin benefit groups were identified for whom the ASCVD risk reduction clearly outweighs the risk of adverse events.
 - Secondary prevention in individuals with clinical ASCVD
 - Primary prevention in individuals with primary elevations of LDL-C ≥ 190 mg/dL
 - Primary prevention in individuals with diabetes 40-75 years of age who have LDL-C 70-189 mg/dL,
 - Primary prevention in individuals without diabetes and with estimated 10-year ASCVD risk $\geq 7.5\%$, 40 to 75 years of age with LDL-C 70-189 mg/dL (Stone et al., 2013).
- Two other prominent guidelines, from the International Atherosclerosis Society (IAS) and the National Lipid Association (NLA), each use LDL-C concentration levels to determine successful pharmacological prevention of ASCVD. However, because evidence shows that VLDL is atherogenic like LDL, both guidelines also contain an additionally recommended goal for Non-HDL-C.

Lipoprotein Physiology

- Plasma lipoproteins are divided into five major classes based on their relative density: chylomicrons, very-low-density lipoproteins (VLDLs), intermediate-density lipoproteins (IDLs), low-density lipoproteins (LDLs), and high-density lipoproteins (HDLs).

Lipid Biomarkers

- LDL-C has been the mainstay biomarker and pharmacologic target to prevent ASCVD. However, new research has provided evidence that other lipid biomarkers better represent the risk of developing ASCVD.
- A meta-analysis conducted by Boekholdt et al. (2012) compared lipid biomarker levels in patients treated with statin medications with risk of cardiovascular events. The adjusted hazard ratios (HRs) for major CV events per 1-SD increase were 1.13 (95% CI 1.10-1.17) for LDL-C, 1.16 (95% CI 1.12-1.19) for non-HDL-C, and 1.14 (95% CI 1.11-1.18) for apoB. These HRs were significantly higher for non-HDL-C than LDL-C ($P=0.002$) and apoB ($P=0.02$). This data led the authors to conclude "that among statin treated patients, non-HDL-C had a stronger association with risk of major cardiovascular events than LDL-C and apolipoprotein B" (Boekholdt et al., 2012, p. 1307).
- A case-control study by Pischon et al. (2005), compared apoB, non-HDL-C, LDL-C, and other lipid markers as predictors of coronary heart disease. After adjustment for matching factors, the relative risk of CHD in the highest quintile compared with the lowest quintile was 2.76 (95% confidence interval [CI], 1.66 to 4.58) for non-HDL-C, 3.01 (95% CI, 1.81 to 5.00) for apoB, 1.81 (95% CI, 1.12 to 2.93) for LDL-C, 0.31 (95% CI, 0.18 to 0.52) for HDL-C, 2.41 (95% CI, 1.43 to 4.07). The authors concluded "that non-HDL-C was more strongly correlated with CHD than LDL-C", but that "apoB showed the strongest association with risk of CHD" and "apoB was associated with increased risk of CHD even after adjustment for LDL-C or non-HDL-C" (Pischon et al., 2005).
- Sniderman et al. (2011) attempted to identify all "published epidemiological studies that contained estimates of the relative risks of non-HDL-C and apoB of fatal or nonfatal ischemic cardiovascular events" (p. 338). The authors reported that apoB was the most potent marker of cardiovascular risk (RRR, 1.43; 95% CI, 1.35 to 1.51), LDL-C was the least (RRR, 1.25; 95% CI, 1.18 to 1.33), and non-HDL-C was intermediate (RRR, 1.34; 95% CI, 1.24 to 1.44).



Discussion

Treatment Goals

- The ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, by Stone et al. (2013), is one of the most widely used guideline by clinicians in the U.S. The most recent report published in 2013 brought about departure from past reports and a different approach than guidelines from other cardiovascular associations. These guidelines were the first to exclude treatment goals for LDL-C. Rather than using the concentration of lipids in the blood as a treatment goal, the ACC/AHA guidelines use the intensity of statin therapy as the goal of treatment.
- These new guidelines, and the absence of cholesterol targets, started a debate amongst clinicians and researchers. Guidelines by the International Atherosclerosis Society (Expert Dyslipidemia Panel of the International Atherosclerosis Society Panel members, 2014), the National Lipid Association (Jacobson et al., 2015), and previous ATP guidelines all included LDL-C treatment goals.

Lipid Biomarkers

- Up until recently all the attention has been paid to LDL-C, so-called 'bad cholesterol'. All previous guidelines used the concentration of LDL-C in the blood to determine the type of intervention and assess for successful treatment. LDL-C is now firmly entrenched in the minds of patients and clinicians alike as the primary marker for cardiovascular health.
- Boekholdt et al. (2012) found that non-HDL-C is more strongly associated with cardiovascular events than LDL-C and apoB.
- Research by Pischon et al. (2005) and Sniderman et al. (2011) found that apoB was the superior lipid biomarker, but that non-HDL-C was also more strongly correlated with CHD than LDL-C.

Applicability to Clinical Practice

Lipid Guidelines

- Treatment goals suggested by the NLA and IAS facilitate effective communication between the patient and clinician
- Treatment goals provide an easily understandable means to discuss progress towards effective therapy. This will maximize long-term adherence by the patient to the treatment strategy.

Lipid Biomarkers

- Non-HDL-C is the most efficacious lipid biomarker to assess risk of ASCVD and to evaluate successful treatment in rural primary care medicine.
- Non-HDL-C simplifies results for both the clinician and the patient, is universally available, has low cost, does not require fasting, and has been proven by research to be efficacious.
- Non-HDL-C does not require addition laboratory equipment or studies besides the already standardized lipid panel. Non-HDL-C testing is simpler, calculated as the difference of 2 stable and easily measured parameters, total cholesterol and HDL-C.

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