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Clinical and Scientific Debates on Atherosclerosis

ApoB in clinical care: Pro and Con

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HIGHLIGHTS

Highlights - Pro

- ApoB is a more accurate measure of cardiovascular risk than LDL C or non HDL C.
- ApoB is a more accurate measure of the adequacy of lipid therapy than LDLC or non HDL C.
- ApoB is essential to diagnose Type III hyperlipidemia.
- ApoB should replace LDL C/non-HDL C in routine clinical care.

Highlights – Con

- Apo B lipoprotein measurement needed for research.
- Apo B levels - Too much information for clinic.
- Apo B - Not needed for risk prediction in primary prevention.
- Apo B - Not needed for determining treatment thresholds/goals.
- Apo B - Not needed for guiding treatment.

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ABSTRACT

Whether apoB adds significantly to the assessment of the risk and therapy of the atherogenic dyslipoproteinemias has been vigorously contested over many years. That trapping of apoB lipoprotein particles within the arterial wall is fundamental to the initiation and maturation of atherosclerotic lesions within the arterial wall is now widely accepted. At the same time, the concept that primary prevention should be based on the risk of a cardiovascular event, a measure that integrates the effects of age, sex, blood pressure, lipids and other factors, has also become widely accepted. Within the risk framework, the issue becomes whether apoB adds significantly to the assessment of risk. On the other hand, it can be argued that the risk model undervalues how important a role that LDL and blood pressure play as causes of atherosclerosis and that when considered as causes, the importance of apoB emerges. These are the two sides of the debate that will be presented in the article that follows: one will highlight the pros of measuring apoB, the second the cons. The reader can make up his or her mind which side of the issue they favour.

1. Pro: in defense of ApoB - Dr. Allan D. Sniderman

> 'There are two young fish swimming along and they happen to meet an older fish swimming the other way, who nods at them and says. "Morning boys, how's the water?' And the two young fish swim on for a bit, and then eventually one looks over at the other and goes. "What the hell is water?"
>
> David Foster Wallace: This Is Water

1.1. Introduction

Dr. Robinson and I differ on the value of apoB in clinical care. In this era of evidence-based medicine, how can that be? Surely all that counts is the evidence and surely the evidence speaks for itself. Not so. The evidence does not speak. The evidence is mute. Our conclusions are not the evidence but our interpretations of the evidence. The validity of our interpretations is determined by many factors including the quality of the design of the studies, the quality of the methods used to obtain the results, and the quality of the analysis of the results. In addition- and

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this is the main point of this essay-our interpretations of the results of any study are inevitably based on the overall framework of thought within which we reason about the problem in general-the waters in which we swim.

The conclusions I draw about the value of apoB differ from the conclusions Dr. Robinson draws about apoB because we reason from different waters. Dr. Robinson reasons principally from a risk and group perspective whereas I reason principally from a causal and individual perspective. We may use the same words but we use them differently. To illustrate, I will begin with three clinical examples that provide direct evidence of the value of apoB in clinical care. To the best of my knowledge, no guideline or expert consensus group has considered the use of apoB in any of these circumstances.

Example 1: Diagnosis of type III hyperlipoproteinemia

Dr. Robinson and I, and all the guidelines, and virtually everyone else agree that patients with familial hypercholesterolemia (FH) should be treated based on diagnosis even though most younger FH patients would not qualify based on the calculated 10-year risk of a cardiovascular events. The natural history is so malign and the risk to the individual so clear, that doubt disappears. As opposed to FH, which is characterized by marked elevation of cholesterol-rich LDL lipoprotein particles, type III hyperlipoproteinemia is characterized by marked elevation of abnormal cholesterol-enriched VLDL and chylomicron remnant particles. Much less is known about the pathogenesis of type III than FH but all the available literature, starting from the description of type III by Donald Fredrickson his colleagues [1,2] and as well as others [3,4], indicates that the cardiovascular risk associated with type III is extremely high, indeed close to, if not equal to, that posed by heterozygotic FH and that, just as with heterozygotic FH, therapy is justified on diagnosis. So far, so good.

The problem is that type III cannot be diagnosed using a conventional lipid panel. Originally, the diagnosis of type III depended on paper electrophoresis and ultracentrifugation, methodologies that are not available now even in the majority of the most specialized lipid clinics. Happily, type III can be diagnosed, simply and accurately, by measuring total cholesterol, triglycerides and apoB by methods that should be readily available in any standard clinical chemistry laboratory [5]. Estimates of the prevalence of type III in the general population vary [4], but a number approach and even exceed the frequency of FH, particularly when diagnosis is based on the apoB algorithm since it is now evident that type III may be expressed in milder as well as more extreme forms [6].

So here is where we are: no one disputes that type III is dangerous and should be diagnosed and treated. But type III can be diagnosed in regular clinical care only if apoB can be measured. However, not only has no guideline recommended using apoB so that type III can be diagnosed, no guideline or expert consensus group has even considered the issue. If making the diagnosis of FH is worthwhile, why is making the diagnosis of type III not worthwhile? How different is the water in which we think about FH and the water in which we think about type III?

Example 2: Not all patients with elevated LDL C have on elevated LDL

A 45 year old American male is found to have an LDL C of 135 mg/dl, a non-HDL C of 160 mg/dl, an HDL C of 40 mg/dl. His levels of LDL C and HDL C levels are equivalent to the 75th percentile of the population. His 10-year CVD risk is 2.4% based on the 2013 ACC/AHA guidelines [7]. Accordingly, based on present guideline recommendations, statin therapy for his hypercholesterolemia would not be recommended. What should the patient be told? If this is all the information available, then the patient must be informed he has an elevated cholesterol and that dietary and lifestyle interventions are appropriate because an elevated cholesterol is an important risk factor for cardiovascular disease. Moreover, while his risk over 10-years may be low, it is high over 15 years and beyond [8].

But what if that conclusion is not correct in this individual? Let us say, his apoB is 90 mg/dl. This would demonstrate he had a normal number of cholesterol-enriched particles. Multiple discordance analyses have demonstrated that cardiovascular risk is not significantly increased in those with normal numbers of cholesterol-enriched apoB particles compared to those with normal numbers of apoB particles containing an average mass of cholesterol [9–17]. Simply put, the normal apoB in this case would demonstrate that the adverse conclusions based on LDL C and non-HDL C are not correct and that the patient need not be concerned on this basis about his cardiovascular health. On the other hand, were his apoB to have been elevated, the concern about increased cardiovascular risk due to apoB lipoproteins would have been established unequivocally. The chances of the first outcome-the benign outcome-would be about 25% whereas the chances of the second outcome-the more concerning outcome-would be about 75% [14]. For information this consequential, we should not accept an error rate of one in four in the assessment of an individual patient. The guidelines have also been silent on this clinical challenge.

Example 3: How bad is bad?

A 59 year old male presents with atypical chest pain but a positive family history of heart disease-his father died at age 50- and a 10 year history of treated hypertension and known hypercholesterolemia. His triglycerides were 6.73 mmol/L (554 mg/dl), his LDL C, measured directly, was 3.59 mmol/L (138 mg/dl) and his apoB was 155 mg/dl. How high was his LDL? How deviant were his apoB lipoproteins from normal? His LDL C was high-the 75th percentile of the American population. However, his apoB was greater than the 98th percentile of the population. The issue is not whether he should be treated with statins. The issue is just how great a threat did his plasma apoB lipoproteins pose to his arteries and therefore to his life? The answer-a great deal, not meaningfully less than heterozygotic FH. Not only was the level of apoB more informative than LDL C, it made the need for family study to potentially identify familial combined hyperlipidemia even more relevant [18]. While the precise pathophysiology of familial combined hyperlipidemia remains obscure, it is an undisputed cause of premature coronary artery disease, it is generally easily treatable, and diagnosis of the phenotype identifies families that should be screened for other affected members. This is yet another argument for apoB that has not been considered by guidelines or expert consensus groups.

1.2. Moving from patients to concepts

These patients represent concrete examples of issues that have not been recognized by those who have made decisions about the utility of apoB, perhaps because of the way the problem was framed. It is the framework we will now examine.

1.2.1. Causes of CVD versus the risk of CVD

Dr. Robinson will argue that apoB adds little to the prediction of risk in primary prevention; that is, adding apoB to a standard 10-year risk prediction model will not meaningfully change the c-statistic. And she is right. But what does this mean? The c-statistic represents an integrated estimate of the predictive powers of all the variables included in the risk algorithm. It has been an accepted epidemiological truism that if a marker did not significantly increase the c-statistic, it did not add importantly to the clinical information available. I disagree with this interpretation and I will demonstrate beneath just why. Indeed, I disagree with much of the framework of the conventional risk approach. On this, Dr. Robinson and I do not just swim in different lakes. We swim in different oceans on different planets. To understand why I think apoB is so important, it is essential for the reader to appreciate

just how differently we think about risk. Accordingly, I will set it out the concerns I have about the conventional risk approach.

Concern 1: All 10-year risk algorithms underestimate the importance of the causes of CVD as determinants of CVD risk

LDL, blood pressure, smoking cause CVD disease. Prospective observational studies have demonstrated unequivocally that the risk of CVD increases exponentially as LDL and blood pressure increase. Randomized clinical trials of LDL and blood pressure lowering have demonstrated unequivocally that if LDL or blood pressure are lowered significantly, the risk of CVD is lowered substantially. But blood pressure and LDL contribute only marginally to the risk as calculated by the risk algorithm. For example, in the Framingham study, the c statistic for the risk of death was 0.750 based on age and sex alone. Taking all the major conventional risk factors into account increased, the c-statistic to only 0.800 [19,20]. This means that knowing all the conventional risk factors and taking into account all the information they convey increases the accuracy in prediction by only one in 20 pairs. Improving by one in twenty is a trivial gain.

Clearly, the estimate of risk is dominated by age and sex. Clearly, these algorithms do not properly assess the risk due to LDL and blood pressure, smoking, and diabetes. If these algorithms are insensitive to the effect of LDL itself on risk, why should we expect them to be sensitive to the differences in concentration in highly correlated markers of LDL? [21].

Accordingly, the conclusion that apoB should not be measured if it does not change the c-statistic should be rejected.

Concern 2: Should primary prevention be based just on risk?

With a few limited exceptions, ACC/AHA determined that eligibility for primary prevention with statin therapy should be based on the 10-year estimate of risk [7]. CVD risk is low until age 40, increases gradually until age 60, and then increases exponentially [19]. A 10-year risk threshold of 7.5% means that almost all men and half of women over 60 will be eligible for prevention with medical therapy whereas only a small minority of those under 60 will be eligible [22,23]. But risk is a fraction: the numerator is the number of cases over a specified period of time whereas the denominator is a constant number of the population. This makes the rates of events comparable at different ages. However, there are many more people under 60 than over 60. The fact is that almost half of all cardiovascular events occur in those under the age of 60 [19]. This means that most of those who have events before age 60 would not have been eligible for therapy before their clinical event. Just as catastrophically, much of the arterial disease that will cause clinical events after 60 developed within the arterial wall before age 60. What comes after is the bitter fruit of what was allowed to happen before. Surely, this should call the risk model of CVD prevention, which is so age dependent, into question.

Age is not a simple variable [22]. The damage to the arterial wall caused by apoB lipoprotein particles occurs over time, not independently of time. Age represents the time over which the arterial wall is exposed to the malign effects of LDL or blood pressure. Small differences in levels of LDL over a lifetime are associated with large differences in cardiovascular risk over a lifetime [24]. However, age could also be associated with adverse biological changes that could increase the adverse effects of LDL and blood pressure on the arterial wall. Sorting out how much is attributable to each should be an important goal of ongoing research. In the meantime, we should recognize the distorting effect of treating age as an independent variable in the risk algorithm when it comes to determining if apoB should be introduced into clinical care.

1.3. The causes of atherosclerosis and the benefit of treating the causes of atherosclerosis

My fundamental thesis is that Dr. Robinson and I disagree because she swims in the waters of Risk whereas I swim in the waters of Causality. One advantage I claim is that I can be sure that my estimates of the causes of cardiovascular disease apply to the individual in whom they were measured whereas she cannot be sure that her estimates of risk do. The apoB I measure in a patient is their apoB. The risk she estimates for a patient may or may not be their risk [25]. This does not mean estimating risk is meaningless. But it does mean there is an inescapable element of uncertainty when applied to the individual and therefore, the wise clinician and the wise patient should not base the whole decision on whether to treat or not to treat just on an arbitrary dividing line in the level of CVD risk.

Trapping of apoB particles within the arterial wall initiates and drives the atherosclerotic process from beginning to end [26]. The likelihood of an apoB particle entering and being trapped within the arterial wall is directly related to the concentration of apoB particles within the lumen of the arterial wall. Each apoB lipoprotein particles contains one molecule of apoB but the mass of cholesterol within an apoB particle can vary substantially with some containing more than the average while others contain less. Multiple discordance analyses have demonstrated that risk relates primarily to the number of apoB particles rather than to the mass of cholesterol within them [9–17]. Cholesterol is not the only poison within the apoB particle. Oxidized phospholipids promote inflammation and atherosclerosis [27], fragments of apoB can promote inflammation and vasogenesis [28,29] and immune responses to apoB can drive destructive processes within the arterial wall [30]. At a practical level, this means that apoB adds to the information currently available from LDL C and/or non-HDL C. At a logical level, this means that apoB should be the primary measure of the atherogenic risk attributable to the apoB lipoproteins. At a clinical level, this means there is no reason any more to measure LDL C or non-HDL C.

These conclusions do not contradict the literature that CVD risk rises as the levels of LDL C and non-HDL C increase and that CVD risk decreases as the levels of LDL C and non-HDL C decrease. On the contrary, they simply sharpen these relations and make them more precise. It is not that LDL C or non-HDL C are ‘wrong’. They are merely less precise than apoB and precision should matter in clinical care.

Dr. Robinson can only disregard or dismiss all these findings if she claims that only risk matters, causes do not. But we have already shown the illusory nature of that view. The apoB lipoproteins do matter. Simply look at the results of the RCTs of statin therapy. No one doubts that if LDL C is reduced by 38.5 mg/dl, CVD risk is reduced by approximately 20% [31]. Moreover, the benefits of statin therapy are more directly related to the lowering of apoB than to LDL C or non-HDL C [32].

But there is more proof now available. CETP inhibitors when added to statin therapy have either failed or only marginally improved clinical outcomes, notwithstanding that the combination results in a robust lowering of LDL C [17]. Brian Ference and his colleagues, developed genetic analogues of statin and CETP inhibitors and using Mendelian randomization demonstrated that the decrease in apoB induced by the combination was substantially less than the decrease in LDL C and that the clinical outcome in the clinical trials corresponded exactly to that predicted by the decrease in apoB rather than to the decrease in LDL C. This was the specific conclusion of their paper [17]. But this conclusion applies more broadly.

They also did a genome-association study, which identified 21 independently inherited variants that were associated with discordant changes in LDL-C and apoB similar to those with combined CETP-statin therapy and, to a lesser degree, to those associated with statin therapy [33]. In analyses of just over 180,000 subjects a genetic score of these variants was associated with a significantly less than expected risk of

CHD per 10-mg dl lowering of LDL C. By contrast, a genetic score associated with concordant changes in LDL-C and apoB showed the expected lower risk of CHD per 10-mg dl lowering of LDL C. Benefit was always the same per 10-mg lowering of apoB. This demonstrates that the reduction of cardiovascular risk is more closely associated with lowering of apoB than with lowering of LDL C. Taken together, therefore, the body of evidence supporting apoB as the preferred marker of the adequacy of therapy is broad and deep.

This has practical consequence in assessing the adequacy of therapy. The 2013 ACC/AHA guidelines did not endorse target levels for statin therapy [7]. I did not agree with their view. I also do not agree with the target levels for apoB that have been listed by guideline groups that have endorsed apoB as a secondary target for LDL lowering therapy [34,35]. For high-risk patients, their goal for apoB has been 80 mg/dl but without any rationale stated as to why this level was selected. My view is that the target for apoB should be the population equivalent level for LDL C, just as the target levels for non-HDL C are the population equivalent level for LDL C. However, a target level for LDL C of 70 mg/dl corresponds to approximately the 10th percentile of the American population whereas a target level for apoB of 80 mg/dl corresponds to approximately the 35th percentile of the American population [36]. Martin and his colleagues have demonstrated that approximately one third of those who reach their LDL C or non-HDL C targets would not reach the population equivalent level of apoB of 60 mg/dl [36]. In this era of PCSK9 therapy, it makes more sense to me to measure apoB and select those with higher levels rather than to lower the LDL C target for everyone even further. To benefit from LDL lowering therapy, the level of LDL must be high enough to lower meaningfully. Martin et al. have shown that apoB is demonstrably a better tool for this purpose than LDL C or non-HDL C [36]. Indeed, as we will now discuss, the demonstrable limitations of the estimation of LDL C should eliminate it for this purpose.

1.4. Measurement

Not widely appreciated is that LDL C, which remains the centrepiece of the conventional lipid system, can be calculated by multiple equations [37–39] or measured directly by multiple methods [38,40] with different results possible for each method and each approach. Which one is the true LDL-C? Furthermore, the direct assays of LDL C perform reasonably well in normolipidemic samples but have not been validated in dyslipidemic samples and are associated with considerable error [41]. Strikingly, there is no evidence that directly measured LDL C is a more accurate marker of CVD risk than calculated LDL C. There is, therefore, no evidence justifying the additional costs of directly measured LDL-C since either non-HDL-C or apoB could be used in hypertriglyceridemic samples.

Non-HDL C is the primary alternative to apoB. Non-HDL C is derived as total cholesterol-HDL C. Total cholesterol can be measured precisely with little bias. However, directly measured HDL C has not been validated in dyslipidemic samples and is not standardized [38–42]. This could produce significant error in the calculation of non-HDL C, particularly at low concentrations of total cholesterol. Moreover, non-HDL C requires two measurements, the errors of which sum. The final nail in the coffin of non-HDL C is that, as noted above, discordance analyses have shown apoB to be superior to non-HDL C as a marker of cardiovascular risk. Programmes to harmonize the lipid assays do exist and need to be supported. The assay of apoB is standardized [43] and laboratories using assays from manufactures that participate in quality assurance programmes can achieve good to excellent results [41,42]. However, when this does not occur, significant variance in values that are reported for apoB will occur [44].

Nevertheless, further efforts to improve standardization and precision of the measurement of apoB are reasonable. Particularly important is to improve manufacturers' compliance with standardization programmes. Fasting is not required to measure apoB. The assay of apoB is not costly at present and if use increased, cost would be reduced. Moreover, not measuring plasma TC, TG, d-LDL-C and d-HDL-C routinely would reduce the present costs of care. The European Atherosclerosis Society and the European Federation of Clinical Chemistry and Laboratory Medicine (EAS/EFCC and LM) concluded that "Non-HDL-C is not a clinically adequate surrogate of apoB …" [42]. as did the American Association for Clinical Chemistry [41].

1.5. Conclusions

Dr. Robinson has many more companions in the waters in which she swims than I do in the waters in which I swim. The guidelines have been, and remain, the cholesterol guidelines. LDL C has been, and remains, the gold standard for the assessment of cardiovascular risk and the adequacy of LDL lowering therapy even though multiple head to head comparisons show that apoB is a more precise marker of risk than LDL C or non-HDL C and that apoB is also a more precise marker of the benefit of therapy and the adequacy of therapy than LDL C or non-HDL C. The reason for the superiority of apoB is not mysterious. Trapping of apoB particles within the arterial wall is the fundamental step in the pathophysiology of atherosclerosis. Because the cholesterol content of apoB particles is variable, neither LDL C nor non-HDL C is always a precise marker of apoB particle number in plasma and apoB particle number is the critical determinant of the number of apoB particles entering and being trapped within the arterial wall. ApoB can be measured accurately and inexpensively in any clinical laboratory. By contrast, there is not even an agreed-on method to estimate or measure LDL C.

Dr. Robinson and I may think about the world in different ways but there is only one world. Well-designed and well-executed experiments are the only acceptable method to choose between competing images of the world. Otherwise evidence-based medicine becomes opinion-based medicine. Given the evidence I have reviewed, I submit that apoB should be the primary marker of the cardiovascular risk and the adequacy of lipid lowering therapy and patients should be benefitting from its routine application in clinical care.

2. Con: Apo B for CVD risk stratification: too much information – Dr. Jennifer G. Robinson

2.1. Apo B lipoprotein measurement needed for research

Retention of apolipoprotein B-containing (Apo B) lipoproteins in the arterial subendothelium is the root cause of atherosclerotic cardiovascular disease (ASCVD) [45]. Retained low density lipoprotein (LDL) and triglyceride-rich remnant apo B lipoproteins potently provoke maladaptive immune activation [46,47], which then promotes cell recruitment, further plaque development, and ultimately acute ASCVD events [48,49]. Reducing the inflow of toxic apo B lipoproteins into the arterial intima allows normal scavenger and phagocytic clearance mechanisms to clear the apo B lipoprotein overload [50]. Epidemiologic studies show that the rate of plaque progression and occurrence of ASCVD events is associated with the level of and duration of exposure to apo B lipoproteins [8,51,52]. A causal role for LDL and other apo B lipoproteins is supported by genetic Mendelian randomization studies, where individuals with loss of function mutations have lower lifetime risks of coronary heart disease, despite the presence of other risk factors [24,47,53]. Given the fundamental causal role of apo B in ASCVD, why not routinely measure apo B levels in clinical practice?

2.2. Apo B levels: too much information for clinic

Current guidelines recommend the measurement of LDL cholesterol (LDL-C) levels, and some additionally recommend measuring non-high density lipoprotein cholesterol (non-HDL-C) levels as a more accurate assessment of the burden of atherogenic lipoproteins [54–58]. None of

the major guidelines recommend the routine use of apo B level for risk stratification or as treatment thresholds or goals.

There are several reasons that adding apo B levels to clinical treatment guidelines is not needed. Indeed, a more complicated message may be confusing to the non-lipidologist, and result impede appropriate LDL-C lowering drug therapy.

2.2.1. Apo B - not needed for risk prediction in primary prevention

Current guideline recommend the use of risk prediction equations derived from population-based cohorts to identify individuals for drug therapy [54,59]. For most individuals, LDL-C and apo B levels are largely concordant, and apo B level adds little to risk prediction based on LDL-C level [13,15]. However, in a subset with discordance between apo B and LDL-C level, there is an excess risk of coronary events with higher apo B levels. This is not surprising since LDL-C is only one of the circulating apo B lipoproteins. Patients with overnutrition, dysglycemia, or genetic predisposition that place them at increased ASCVD risk are likely to have very low density lipoprotein (VLDL) and downstream intermediate density lipoproteins (IDL) constitute a larger proportion of circulating apo B lipoproteins. Thus, there is less likely to be a discordance between apo B and non-HDL-C level, which includes VLDL cholesterol and IDL cholesterol [15].

Another limitation of the analyses demonstrating excess risk from discordance is that they have evaluated coronary heart disease rather than the broader outcomes of ASCVD events, which also includes stroke [13,15]. Notably, the US risk calculators already incorporate non-HDL by using both total cholesterol and HDL-C in the ASCVD risk prediction equations, so there is no reason to add non-HDL-C levels [60]. The SCORE charts for predicting 10-year risk of fatal CVD that are recommended by the European guideline include total cholesterol but not HDL-C [55].

Analyses have not yet been published that evaluate the ability of apo B levels to correctly reclassify patient risk. While many biomarkers are independently associated with increased CVD risk after adjusting for traditional risk factors, few have been shown to correctly increase or decrease the risk estimate to reclassify risk enough to alter treatment decisions [60]. It is unlikely that adding apo B level, which is collinear with LDL-C and non-HDL-C, would provide enough new information to reclassify significant number of individuals for treatment. Moreover, advancing age, sex, presence of other cardiovascular risk factors, insulin resistance or diabetes, chronic over-nutrition, and genetic predisposition more strongly influence the rate of atherosclerotic cardiovascular disease progression and development of cardiovascular events than any measurement of lipoproteins alone [52,61]. Indeed, subclinical atherosclerosis (carotid or peripheral plaque or coronary artery calcification) begins to occurs once when LDL-C levels are > 60 mg/dl, so apo B measurement would be unlikely to provide more discrimination [52]. Indeed, only coronary artery calcification, a direct measure of plaque burden, has been shown to meaningfully reclassify patients for statin therapy based on 10-year ASCVD risk [62].

2.2.2. Apo B - not needed for determining treatment thresholds/goals

In statin-treated patients, both non-HDL-C and apo B levels better predict subsequent ASCVD events than LDL-C levels, and do so with similar accuracy [63]. The Friedewald equation has been widely used to calculate LDL-C levels from measured total cholesterol, triglyceride, and HDL-C levels (LDL-C = total cholesterol minus triglycerides/5 minus HDLC) [37]. More recently, a method for more accurately calculating LDL-C based on triglyceride level has been developed [39]. When the more accurate LDL calculation method is used, guideline-recommended management based on treatment goals would be altered in only a small fraction of individuals by adding either non-HDL-C (2%) or apo B (1%) goals, including those in high risk groups [36].

2.2.3. Apo B - not needed for guiding treatment

Apo B levels are unlikely to influence choice of therapy. Meta-analyses of randomized trials of drug therapy clearly show that the magnitudes of LDL-C or non-HDL-C reduction are driving the magnitude of the relative reduction in ASCVD risk [64–66]. Reduction in apo B levels does not consistently improve risk prediction over the reduction in LDL-C or non-HDL-C levels [67]. For statins, although apo B reduction did add information for coronary heart disease events, it worsened prediction for stroke risk reduction.

The 2013 American College of Cardiology/American Heart Association (ACC/AHA) cholesterol guideline recommended high intensity statin therapy for high risk patients based on the consistent ASCVD reduction benefits of high intensity statins in randomized trials [54]. Subsequent trials of nonstatins added to background statin therapy have shown incremental ASCVD risk reduction from adding ezetimibe or a PCSK9 inhibiting monoclonal antibody (mAb) [68–72]. In none of these trials was a treatment-to-goal approach utilized, so it is difficult to directly determine the potential for an ASCVD risk reduction from titrating to an apo B target. However, adding a drug to achieve an apo B target after achieving an LDL-C < 1.8 mmol/L (< 70 mg/dL) would likely result in marginal further ASCVD risk reduction (in the case of ezetimibe) or result in low value care (in the case of PCSK9 mAbs even with discounting) [73]. For example, ezetimibe lowers LDL-C an about 20% when added to background statin therapy. So in a patient with an LDL-C = 1.78 mmol/L (69 mg/dL), an adding ezetimibe would lower LDL-C about 0.39 9 mmol/L (15 mg/dL), for about an 8% further reduction in ASCVD risk (using Cholesterol Treatment Trialists association of 22% reduction in major CVD events per 1 mmol/L (39 mg/dL) reduction in LDL-C [74]). If this were a very high risk patient, such as a patient with ASCVD and diabetes on a moderate intensity statin (e.g., > 30% 10-year ASCVD risk), the 5-year absolute ASCVD risk reduction would be about 1.2%, or a 83 patients would need to be treated for 5 years to prevent one ASCVD event (NNT) [73]. The NNT for adding a PCSK9 mAb is lower (about 33 with a 65% LDL-C reduction), but unlikely to be considered a good value (< $100,000 US dollars per quality adjusted life year) unless PCSK9 mAb is discounted to well below $5500 US dollars per year.

In addition, treatment goals can result in inappropriate treatment responses. For example, choosing a low intensity statin (< 30% LDL-C reduction on average) to “get to goal”, when high intensity statins (≥50% LDL-C reduction on average) have been shown in multiple randomized trials to reduce ASCVD events more than moderate intensity statins [54].

3. Conclusions

Apo B lipoproteins initiate and accelerate atherosclerosis. However, knowledge of apo B levels is not needed to inform clinical practice. Indeed, adding apo B targets or thresholds is unnecessary, and could lead to undue confusion and treatment inertia by clinicians.

Conflicts of interest

A. D. Sniderman: nothing to declare.

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References

[1] D.S. Fredrickson, R.I. Levy, R.S. Lees, Fat transport in lipoproteins–an integrated approach to mechanisms and disorders, N. Engl. J. Med. 276 (1967) 34–42, https://doi.org/10.1056/NEJM196701052760107 contd.

[2] J. Morganroth, R.I. Levy, D.S. Fredrickson, The biochemical, clinical, and genetic features of type III hyperlipoproteinemia, Ann. Intern. Med. 82 (1975) 158–174.

[3] W.R. Hazzard, J.L. Goldstein, M.G. Schrott, A.G. Motulsky, E.L. Bierman, Hyperlipidemia in coronary heart disease. 3. Evaluation of lipoprotein phenotypes

of 156 genetically defined survivors of myocardial infarction, J. Clin. Invest. 52 (1973) 1569–1577, https://doi.org/10.1172/JCI107333.
[4] P.N. Hopkins, E.A. Brinton, M.N. Nanjee, Hyperlipoproteinemia type 3: the forgotten phenotype, Curr. Atherosclerosis Rep. 16 (2014), https://doi.org/10.1007/s11883-014-0440-2 440–19.
[5] J. De Graaf, P. Couture, A. Sniderman, A diagnostic algorithm for the atherogenic apolipoprotein B dyslipoproteinemias, 4 (2008) 608–618, https://doi.org/10.1038/ncpendmet0982.
[6] A.D. Sniderman, J. De Graaf, G. Thanassoulis, A.J. Tremblay, S.S. Martin, P. Couture, The spectrum of type III hyperlipoproteinemia, J. Clin. Lipidol. (2018), https://doi.org/10.1016/j.jacl.2018.09.006.
[7] N.J. Stone, J.G. Robinson, A.H. Lichtenstein, C.N. Bairey Merz, C.B. Blum, R.H. Eckel, et al., ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, Circulation 129 (2014) (2013) S1–S45, https://doi.org/10.1161/01.cir.0000437738.63853.7a.
[8] A.M. Navar-Boggan, E.D. Peterson, R.B. D'Agostino, B. Neely, A.D. Sniderman, M.J. Pencina, Hyperlipidemia in early adulthood increases long-term risk of coronary heart disease, Circulation 131 (2015) 451–458, https://doi.org/10.1161/CIRCULATIONAHA.114.012477.
[9] A.D. Sniderman, A.C. St-Pierre, B. Cantin, G.R. Dagenais, J.-P. Després, B. Lamarche, Concordance/discordance between plasma apolipoprotein B levels and the cholesterol indexes of atherosclerotic risk, Am. J. Cardiol. 91 (2003) 1173–1177.
[10] W.C. Cromwell, J.D. Otvos, M.J. Keyes, M.J. Pencina, L. Sullivan, R.S. Vasan, et al., LDL particle number and risk of future cardiovascular disease in the Framingham offspring study - implications for LDL management, J. Clin. Lipidol. 1 (2007) 583–592, https://doi.org/10.1016/j.jacl.2007.10.001.
[11] J.D. Otvos, S. Mora, I. Shalaurova, P. Greenland, R.H. Mackey, D.C. Goff, Clinical implications of discordance between low-density lipoprotein cholesterol and particle number, J. Clin. Lipidol. 5 (2011) 105–113, https://doi.org/10.1016/j.jacl.2011.02.001.
[12] A.D. Sniderman, S. Islam, S. Yusuf, M.J. McQueen, Discordance analysis of apolipoprotein B and non-high density lipoprotein cholesterol as markers of cardiovascular risk in the INTERHEART study, Atherosclerosis 225 (2012) 444–449, https://doi.org/10.1016/j.atherosclerosis.2012.08.039.
[13] S. Mora, J.E. Buring, P.M. Ridker, Discordance of low-density lipoprotein (LDL) cholesterol with alternative LDL-related measures and future coronary events, Circulation 129 (2014) 553–561, https://doi.org/10.1161/CIRCULATIONAHA.113.005873.
[14] M.J. Pencina, R.B. D'Agostino, T. Zdrojewski, K. Williams, G. Thanassoulis, C.D. Furberg, et al., Apolipoprotein B improves risk assessment of future coronary heart disease in the Framingham Heart Study beyond LDL-C and non-HDL-C, Eur. J. Prev. Cardiol. 22 (2015) 1321–1327, https://doi.org/10.1177/2047487315569411.
[15] J.T. Wilkins, R.C. Li, A. Sniderman, C. Chan, D.M. Lloyd-Jones, Discordance between apolipoprotein B and LDL-cholesterol in young adults predicts coronary artery calcification: the CARDIA study, J. Am. Coll. Cardiol. 67 (2016) 193–201, https://doi.org/10.1016/j.jacc.2015.10.055.
[16] P.R. Lawler, A.O. Akinkuolie, P.M. Ridker, A.D. Sniderman, J.E. Buring, R.J. Glynn, et al., Discordance between circulating atherogenic cholesterol mass and lipoprotein particle concentration in relation to future coronary events in women, Clin. Chem. 63 (2017) 870–879, https://doi.org/10.1373/clinchem.2016.264515.
[17] B.A. Ference, J.J.P. Kastelein, H.N. Ginsberg, M.J. Chapman, S.J. Nicholls, K.K. Ray, et al., Association of genetic variants related to CETP inhibitors and statins with lipoprotein levels and cardiovascular risk, Jama 318 (2017) 947–956, https://doi.org/10.1001/jama.2017.11467.
[18] J.L. Goldstein, H.G. Schrott, W.R. Hazzard, E.L. Bierman, A.G. Motulsky, Hyperlipidemia in coronary heart disease II. Genetic analysis OF lipid levels IN 176 families and delineation OF a new inherited disorder, combined hyperlipidemia, J. Clin. Invest. 52 (1973) 1544–1568, https://doi.org/10.1172/JCI107332.
[19] A.D. Sniderman, G. Thanassoulis, K. Williams, M. Pencina, Risk of premature cardiovascular disease vs the number of premature cardiovascular events, JAMA Cardiol. 1 (2016) 492–494, https://doi.org/10.1001/jamacardio.2016.0991.
[20] T.J. Wang, P. Gona, M.G. Larson, G.H. Tofler, D. Levy, C. Newton-Cheh, et al., Multiple biomarkers for the prediction of first major cardiovascular events and death, N. Engl. J. Med. 355 (2006) 2631–2639, https://doi.org/10.1056/NEJMoa055373.
[21] A.D. Sniderman, M. Pencina, G. Thanassoulis, Limitations in the conventional assessment of the incremental value of predictors of cardiovascular risk, Curr. Opin. Lipidol. 26 (2015) 210–214, https://doi.org/10.1097/MOL.0000000000000181.
[22] A.D. Sniderman, C.D. Furberg, Age as a modifiable risk factor for cardiovascular disease, Lancet 371 (2008) 1547–1549, https://doi.org/10.1016/S0140-6736(08)60313-X.
[23] M.J. Pencina, A.M. Navar-Boggan, R.B. D'Agostino, K. Williams, B. Neely, A.D. Sniderman, et al., Application of new cholesterol guidelines to a population-based sample, N. Engl. J. Med. 370 (2014) 1422–1431, https://doi.org/10.1056/NEJMoa1315665.
[24] B.A. Ference, H.N. Ginsberg, I. Graham, K.K. Ray, C.J. Packard, E. Bruckert, et al., Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel, Eur. Heart J. 38 (2017) 2459–2472, https://doi.org/10.1093/eurheartj/ehx144.
[25] A.D. Sniderman, R.B. D'Agostino, M.J. Pencina, The role of physicians in the era of predictive analytics, Jama 314 (2015) 25–26, https://doi.org/10.1001/jama.2015.6177.
[26] J. Borén, K.J. Williams, The central role of arterial retention of cholesterol-rich apolipoprotein-B-containing lipoproteins in the pathogenesis of atherosclerosis: a triumph of simplicity, Curr. Opin. Lipidol. 27 (2016) 473–483, https://doi.org/10.1097/MOL.0000000000000330.
[27] X. Que, M.-Y. Hung, C. Yeang, A. Gonen, T.A. Prohaska, X. Sun, et al., Oxidized phospholipids are proinflammatory and proatherogenic in hypercholesterolaemic mice, Nature 558 (2018) 301–306, https://doi.org/10.1038/s41586-018-0198-8.
[28] D.F.J. Ketelhuth, F.J.O. Rios, Y. Wang, H. Liu, M.E. Johansson, G.N. Fredrikson, et al., Identification of a danger-associated peptide from apolipoprotein B100 (ApoBDS-1) that triggers innate proatherogenic responses, Circulation 124 (2011), https://doi.org/10.1161/CIRCULATIONAHA.111.051599 2433–43– 1–7.
[29] I. Avraham-Davidi, Y. Ely, V.N. Pham, D. Castranova, M. Grunspan, G. Malkinson, et al., ApoB-containing lipoproteins regulate angiogenesis by modulating expression of VEGF receptor 1, Nat. Med. 18 (2012) 967–973, https://doi.org/10.1038/nm.2759.
[30] A. Gisterå, D.F.J. Ketelhuth, Lipid-driven immunometabolic responses in atherosclerosis, Curr. Opin. Lipidol. 29 (2018) 375–380, https://doi.org/10.1097/MOL.0000000000000540.
[31] R. Collins, C. Reith, J. Emberson, J. Armitage, C. Baigent, L. Blackwell, et al., Interpretation of the evidence for the efficacy and safety of statin therapy, Lancet 388 (2016) 2532–2561, https://doi.org/10.1016/S0140-6736(16)31357-5.
[32] G. Thanassoulis, K. Williams, K. Ye, R. Brook, P. Couture, P.R. Lawler, et al., Relations of change in plasma levels of LDL-C, non-HDL-C and apoB with risk reduction from statin therapy: a meta-analysis of randomized trials, J. Am. Heart Assoc. 3 (2014) e000759, , https://doi.org/10.1161/JAHA.113.000759.
[33] A.D. Sniderman, Differential response of cholesterol and particle measures of atherogenic lipoproteins to LDL-lowering therapy: implications for clinical practice, J. Clin. Lipidol. 2 (2008) 36–42, https://doi.org/10.1016/j.jacl.2007.12.006.
[34] European Association for Cardiovascular Prevention & Rehabilitation, Z. Reiner, A.L. Catapano, G. De Backer, I. Graham, M.-R. Taskinen, et al., ESC/EAS guidelines for the management of dyslipidaemias: the task force for the management of dyslipidaemias of the European society of Cardiology (ESC) and the European atherosclerosis society (EAS), Eur. Heart J. 32 (2011) 1769–1818, https://doi.org/10.1093/eurheartj/ehr158.
[35] T.J. Anderson, J. Grégoire, R.A. Hegele, P. Couture, G.B.J. Mancini, R. McPherson, et al., Update of the Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult, Can. J. Cardiol. 29 (2013) (2012) 151–167, https://doi.org/10.1016/j.cjca.2012.11.032.
[36] V. Sathiyakumar, J. Park, R. Quispe, M.B. Elshazly, E.D. Michos, M. Banach, et al., Impact of novel LDL-C assessment on the utility of secondary non-HDL-C and ApoB targets in selected worldwide dyslipidemia guidelines, Circulation 117 (2018) 032463, https://doi.org/10.1161/CIRCULATIONAHA.117.032463 CIRCULATIONAHA.
[37] W.T. Friedewald, R.I. Levy, D.S. Fredrickson, Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge, Clin. Chem. 18 (1972) 499–502.
[38] M.J.A. Oliveira, H.E. van Deventer, L.M. Bachmann, G.R. Warnick, K. Nakajima, M. Nakamura, et al., Evaluation of four different equations for calculating LDL-C with eight different direct HDL-C assays, Clin. Chim. Acta 423 (2013) 135–140, https://doi.org/10.1016/j.cca.2013.04.009.
[39] S.S. Martin, M.J. Blaha, M.B. Elshazly, P.P. Toth, P.O. Kwiterovich, R.S. Blumenthal, et al., Comparison of a novel method vs the Friedewald equation for estimating low-density lipoprotein cholesterol levels from the standard lipid profile, Jama 310 (2013) 2061–2068, https://doi.org/10.1001/jama.2013.280532.
[40] W.G. Miller, G.L. Myers, I. Sakurabayashi, L.M. Bachmann, S.P. Caudill, A. Dziekonski, et al., Seven direct methods for measuring HDL and LDL cholesterol compared with ultracentrifugation reference measurement procedures, Clin. Chem. 56 (2010) 977–986, https://doi.org/10.1373/clinchem.2009.142810.
[41] AACC Lipoproteins and Vascular Diseases Division Working Group on Best Practices, T.G. Cole, J.H. Contois, G. Csako, J.P. McConnell, A.T. Remaley, et al., Association of apolipoprotein B and nuclear magnetic resonance spectroscopy-derived LDL particle number with outcomes in 25 clinical studies: assessment by the AACC Lipoprotein and Vascular Diseases Division Working Group on Best Practices, Clin. Chem. 59 (2013) 752–770, https://doi.org/10.1373/clinchem.2012.196733.
[42] M.R. Langlois, M.J. Chapman, C. Cobbaert, S. Mora, A.T. Remaley, E. Ros, et al., Quantifying atherogenic lipoproteins: current and future challenges in the era of personalized medicine and very low concentrations of LDL cholesterol. A consensus statement from EAS and EFLM, Clin. Chem. 64 (2018) 1006–1033, https://doi.org/10.1373/clinchem.2018.287037.
[43] S.M. Marcovina, J.J. Albers, H. Kennedy, J.V. Mei, L.O. Henderson, W.H. Hannon, International federation of clinical chemistry standardization project for measurements of apolipoproteins A-I and B. IV. Comparability of apolipoprotein B values by use of international reference material, Clin. Chem. 40 (1994) 586–592.
[44] J. Cao, B.T. Steffen, W. Guan, A.T. Remaley, J.P. McConnell, V. Palamalai, et al., A comparison of three apolipoprotein B methods and their associations with incident coronary heart disease risk over a 12-year follow-up period: the Multi-Ethnic Study of Atherosclerosis, J. Clin. Lipidol. 12 (2018) 300–304, https://doi.org/10.1016/j.jacl.2017.12.013.
[45] J.G. Robinson, K.J. Williams, S. Gidding, J. Borén, I. Tabas, E.A. Fisher, et al., Eradicating the burden of atherosclerotic cardiovascular disease by lowering apolipoprotein B lipoproteins Earlier in life, J. Am. Heart Assoc. 7 (2018), https://doi.org/10.1161/JAHA.118.009778.
[46] A. Varbo, M. Benn, A. Tybjaerg-Hansen, B.G. Nordestgaard, Elevated remnant cholesterol causes both low-grade inflammation and ischemic heart disease,

whereas elevated low-density lipoprotein cholesterol causes ischemic heart disease without inflammation, Circulation 128 (2013) 1298–1309, https://doi.org/10.1161/CIRCULATIONAHA.113.003008.
[47] A.B. Wulff, B.G. Nordestgaard, A. Tybjaerg-Hansen, APOC3 loss-of-function mutations, remnant cholesterol, low-density lipoprotein cholesterol, and cardiovascular risk: mediation- and meta-analyses of 137 895 individuals, Arterioscler. Thromb. Vasc. Biol. 38 (2018) 660–668, https://doi.org/10.1161/ATVBAHA.117.310473.
[48] K.J. Williams, I. Tabas, E.A. Fisher, How an artery heals, Circ. Res. 117 (2015) 909–913, https://doi.org/10.1161/CIRCRESAHA.115.307609.
[49] K.J. Moore, F.J. Sheedy, E.A. Fisher, Macrophages in atherosclerosis: a dynamic balance, Nat. Rev. Immunol. 13 (2013) 709–721, https://doi.org/10.1038/nri3520.
[50] I. Tabas, Russell ross memorial lecture in vascular biology: molecular-cellular mechanisms in the progression of atherosclerosis, arterioscler. Thromb. Vasc. Biol. 37 (2017) (2016) 183–189, https://doi.org/10.1161/ATVBAHA.116.308036.
[51] E. Salfati, S. Nandkeolyar, S.P. Fortmann, S. Sidney, M.A. Hlatky, T. Quertermous, et al., Susceptibility loci for clinical coronary artery disease and subclinical coronary atherosclerosis throughout the life-course, Circ. Cardiovasc. Genet. 8 (2015) 803–811, https://doi.org/10.1161/CIRCGENETICS.114.001071.
[52] L. Fernández-Friera, V. Fuster, B. López-Melgar, B. Oliva, J.M. García-Ruiz, J. Mendiguren, et al., Normal LDL-cholesterol levels are associated with subclinical atherosclerosis in the absence of risk factors, J. Am. Coll. Cardiol. 70 (2017) 2979–2991, https://doi.org/10.1016/j.jacc.2017.10.024.
[53] J.C. Cohen, E. Boerwinkle, T.H. Mosley, H.H. Hobbs, Sequence variations in PCSK9, low LDL, and protection against coronary heart disease, N. Engl. J. Med. 354 (2006) 1264–1272, https://doi.org/10.1056/NEJMoa054013.
[54] N.J. Stone, J.G. Robinson, A.H. Lichtenstein, C.N. Bairey Merz, C.B. Blum, R.H. Eckel, et al., ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, J. Am. Coll. Cardiol. 63 (2014) (2013) 2889–2934, https://doi.org/10.1016/j.jacc.2013.11.002.
[55] Authors/Task Force Members, A.L. Catapano, I. Graham, G. De Backer, O. Wiklund, M.J. Chapman, et al., ESC/EAS guidelines for the management of dyslipidaemias: the task force for the management of dyslipidaemias of the European society of Cardiology (ESC) and European atherosclerosis society (EAS) developed with the special contribution of the European assocciation for cardiovascular prevention & rehabilitation (EACPR), Atherosclerosis 253 (2016) (2016) 281–344, https://doi.org/10.1016/j.atherosclerosis.2016.08.018.
[56] C.E. Orringer, T.A. Jacobson, J.J. Saseen, A.S. Brown, A.M. Gotto, J.L. Ross, et al., Update on the use of PCSK9 inhibitors in adults: recommendations from an expert panel of the national lipid association, J. Clin. Lipidol. 11 (2017) 880–890, https://doi.org/10.1016/j.jacl.2017.05.001.
[57] T.A. Jacobson, M.K. Ito, K.C. Maki, C.E. Orringer, H.E. Bays, P.H. Jones, et al., National lipid association recommendations for patient-centered management of dyslipidemia: part 1–full report, J. Clin. Lipidol. 9 (2015) 129–169, https://doi.org/10.1016/j.jacl.2015.02.003.
[58] T.A. Jacobson, K.C. Maki, C.E. Orringer, P.H. Jones, P. Kris-Etherton, G. Sikand, et al., National lipid association recommendations for patient-centered management of dyslipidemia: Part 2, J. Clin. Lipidol. 9 (2015), https://doi.org/10.1016/j.jacl.2015.09.002 S1–122.e1.
[59] A.L. Catapano, I. Graham, G. De Backer, O. Wiklund, M.J. Chapman, H. Drexel, et al., ESC/EAS guidelines for the management of dyslipidaemias: the task force for the management of dyslipidaemias of the European society of Cardiology (ESC) and European atherosclerosis society (EAS)developed with the special contribution of the European assocciation for cardiovascular prevention & rehabilitation (EACPR), Eur. Heart J. 37 (2016) (2016) 2999–3058, https://doi.org/10.1093/eurheartj/ehw272.
[60] D.C. Goff, D.M. Lloyd-Jones, G. Bennett, S. Coady, R.B. D'Agostino, R. Gibbons, et al., ACC/AHA guideline on the assessment of cardiovascular risk: a report of the american College of cardiology/american heart association task force on practice guidelines, J. Am. Coll. Cardiol. 63 (2014) (2013) 2935–2959, https://doi.org/10.1016/j.jacc.2013.11.005.
[61] S.S. Gidding, J.S. Rana, C. Prendergast, H. McGill, J.J. Carr, K. Liu, et al., Pathobiological determinants of atherosclerosis in youth (PDAY) risk score in young adults predicts coronary artery and abdominal aorta calcium in middle age: the CARDIA study, Circulation 133 (2016) 139–146, https://doi.org/10.1161/CIRCULATIONAHA.115.018042.
[62] J. Yeboah, T.S. Polonsky, R. Young, R.L. McClelland, J.C. Delaney, F. Dawood, et al., Utility of nontraditional risk markers in individuals ineligible for statin therapy according to the 2013 american College of cardiology/american heart association cholesterol guidelines, Circulation 132 (2015) 916–922, https://doi.org/10.1161/CIRCULATIONAHA.115.016846.
[63] S.M. Boekholdt, B.J. Arsenault, S. Mora, T.R. Pedersen, J.C. LaRosa, P.J. Nestel, et al., Association of LDL cholesterol, non-HDL cholesterol, and apolipoprotein B levels with risk of cardiovascular events among patients treated with statins: a meta-analysis, Jama 307 (2012) 1302–1309, https://doi.org/10.1001/jama.2012.366.
[64] J.G. Robinson, B. Smith, N. Maheshwari, H. Schrott, Pleiotropic effects of statins: benefit beyond cholesterol reduction? A meta-regression analysis, J. Am. Coll. Cardiol. 46 (2005) 1855–1862, https://doi.org/10.1016/j.jacc.2005.05.085.
[65] J.G. Robinson, S. Wang, B.J. Smith, T.A. Jacobson, Meta-analysis of the relationship between non-high-density lipoprotein cholesterol reduction and coronary heart disease risk, J. Am. Coll. Cardiol. 53 (2009) 316–322, https://doi.org/10.1016/j.jacc.2008.10.024.
[66] M.G. Silverman, B.A. Ference, K. Im, S.D. Wiviott, R.P. Giugliano, S.M. Grundy, et al., Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis, Jama 316 (2016) 1289–1297, https://doi.org/10.1001/jama.2016.13985.
[67] J.G. Robinson, S. Wang, T.A. Jacobson, Meta-analysis of comparison of effectiveness of lowering apolipoprotein B versus low-density lipoprotein cholesterol and nonhigh-density lipoprotein cholesterol for cardiovascular risk reduction in randomized trials, Am. J. Cardiol. 110 (2012) 1468–1476, https://doi.org/10.1016/j.amjcard.2012.07.007.
[68] C.P. Cannon, M.A. Blazing, R.P. Giugliano, A. McCagg, J.A. White, P. Theroux, et al., Ezetimibe added to statin therapy after acute coronary syndromes, N. Engl. J. Med. 372 (2015) 2387–2397, https://doi.org/10.1056/NEJMoa1410489.
[69] M.S. Sabatine, R.P. Giugliano, A.C. Keech, N. Honarpour, S.D. Wiviott, S.A. Murphy, et al., Evolocumab and clinical outcomes in patients with cardiovascular disease, N. Engl. J. Med. 376 (2017) 1713–1722, https://doi.org/10.1056/NEJMoa1615664.
[70] G. Schwartz, M. Szarek, D. Bhatt, V. Bittner, R. Diaz, J. Edelberg, et al., The ODYSSEY OUTCOMES trial: topline results alirocumab in patients after acute coornary syndrome, in: American College of Cardiology - 7th Scientific Sessions, n.d.
[71] J.G. Robinson, M. Farnier, M. Krempf, J. Bergeron, G. Luc, M. Averna, et al., Efficacy and safety of alirocumab in reducing lipids and cardiovascular events, N. Engl. J. Med. 372 (2015) 1489–1499, https://doi.org/10.1056/NEJMoa1501031.
[72] M.S. Sabatine, R.P. Giugliano, S.D. Wiviott, F.J. Raal, D.J. Blom, J. Robinson, et al., Efficacy and safety of evolocumab in reducing lipids and cardiovascular events, N. Engl. J. Med. 372 (2015) 1500–1509, https://doi.org/10.1056/NEJMoa1500858.
[73] J.G. Robinson, R. Huijgen, K. Ray, J. Persons, J.J.P. Kastelein, M.J. Pencina, Determining when to add nonstatin therapy: a quantitative approach, J. Am. Coll. Cardiol. 68 (2016) 2412–2421, https://doi.org/10.1016/j.jacc.2016.09.928.
[74] Cholesterol Treatment Trialists' (CTT) Collaborators, P.M. Kearney, L. Blackwell, R. Collins, A. Keech, J. Simes, et al., Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis, Lancet 371 (2008) 117–125, https://doi.org/10.1016/S0140-6736(08)60104-X.