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Review

Critical review of 2016 ACC guidelines on therapies for cholesterol lowering with reference to laboratory testing

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ABSTRACT

Introduction: This review discusses new guidelines that were released in 2016 and 2017 for assessing risk of coronary disease (ASCVD) and treatments and that appear to have replaced the 2013 guidelines which superseded the National Cholesterol Education Program Adult Treatment Panel Guidelines (ATP). To put the new guidelines in prospective, I briefly review the history of prior guidelines. The newest guidelines seem to support the idea that elevated LDL cholesterol (C) is a cause of ASCVD. The Review also discusses issues related to these guidelines, especially measurement of LDLC, the importance of nonHDLC and puzzling results that do not seem to support the cause and effect idea.
Methods: Literature review and critical discussion.
Conclusions: The 2016 guidelines appear to eliminate most of the flaws in the prior 2013 guidelines that replaced the ATP. They do not seem to rely on randomized control studies alone but the totality of all of the evidence. The new guidelines still fail to identify some persons with characteristics of metabolic syndrome that may be of increased risk for ASCVD although they address some of the problems in treating this group. The guidelines identify LDL cholesterol and nonHDL cholesterol target concentrations that are important for laboratory professionals since they should be defined on reports and are important for consultation.

1. Introduction

In 1988, the National Cholesterol Education Program (NCEP) released its first adult treatment panel (ATP) for assessing levels of cholesterol [1]. This was followed in 1994 by ATP II [2]. ATP I outlined a strategy for primary prevention of coronary heart disease in persons with elevated (≥ 160 mg/dL) low density lipoprotein (LDL) cholesterol (C), and borderline elevated (130–159 mg/dL) LDLC. They also defined multiple other risk factors. ATP II was released in 1994, It affirmed the approach of ATP I and set a new LDLC goal of < 100 mg/dL [3]. It raised persons with diabetes to the highest risk group, identified persons with multiple risk factors for more intense treatment and introduced the idea that persons with metabolic syndrome should be considered for intensified therapeutic lifestyle changes. It also defined LDLC < 100 mg/dL as optimal.

In 2002, the NCEP released ATP III [3] which was endorsed by the American Heart Association (AHA) and the American Diabetes Association [4]. It indicated that for patients with triglycerides between 200 mg/dL and 500 mg/dL, nonHDLC could be a secondary target while for patients with triglycerides > 500 mg/dL, first triglyceride should be lowered, then, LDLC should be treated to goal with nonHDLC as a secondary target. These guidelines were reaffirmed by the American College of Cardiology (ACC)/AHA in 2006 and a lower target level of < 70 mg/dL LDLC was suggested for secondary prevention in highest risk patients [5].

In 2013, the American College of Cardiology ACC/AHA released new guidelines from an expert group [6] that replace the ATP. Members of the ATP IV expert group, that were working on, but had not yet completed, ATP IV, transitioned to the new group. Thus, the ACC/AHA expert group replaced the ATP IV expert group. The term coronary heart disease used in the ATP guidelines was also replaced with the term arteriosclerotic coronary vascular disease (ASCVD). The guidelines, outlined in Table 1, were based largely on evidence obtained from randomized control trials (RCT). The guidelines did not speculate on

Abbreviations: NCEP, National Cholesterol Education Program; ATP, adult treatment panel; LDL, low density lipoprotein; C, cholesterol; AHA, American Heart Association; ACC, American College of Cardiology; HDL, High density lipoprotein; total C – HDLC, nonHDLC; RCT, randomized control trials; ASCVD, arteriosclerotic coronary vascular disease; BMI, body mass index; VLDL, very low density lipoproteins; IDL, intermediate density lipoproteins; apo B, apolipoprotein B-100; dLDLC, direct LDLC; Lp(a), lipoprotein (a); BQ, beta-quantification; CRMLN, Control Reference Method Laboratory network; ELP, electrophoresis; PCSK9, proprotein convertase subtilisin/kexin type 9

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Table 1
Intensity of treatment for four groups.

Group	Treatment intensity
1. Adults ≥ 21 years of age with clinical ASCVD	≤ 75 years, high intensity, moderate if intolerable > 75 years moderate to intense
2. Adults ≥ 21 years with LDLC ≥ 190 mg/dL (familial hypercholesterolemia)	High intensity statin to achieve > 50% reduction in LDLC May consider non-statin for further reduction Screening of close relatives
3. Adults 40–75 without ASCVD with diabetes LDLC 70–190 mg/dL	Moderate intensity High intensity if ≥ 7.5% 10 y risk
4. Adults WO ASCVD or diabetes > 7.5% 10 y risk	Estimate with Pooled Cohort Equation Moderate to high intensity statin

evidence from other types of trials. The Expert Panel was unable to find evidence from RCT to support the concept that lowering LDLC or nonHDLC concentrations to targets reduces risk of ASCVD as had been suggested in the ATP reports [6]. Nor did the panel find sufficient evidence from RCT that drugs other than statins should be used to reduce risk. The panel did find RCT evidence that suggested that the intensity of statin therapy should be used to reduce ASCVD risk in those groups that would benefit the most. As shown in Table 1, the panel defined 4 major benefit groups as a target but did not define end point cholesterol concentration targets. It was assumed that high dose statin would lower LDLC to ≥ 50% and moderate dose to 30 - < 50%, although, in group 2, familial hypercholesterolemia, they did mention high intensity statin should be used to lower LDLC < 50% and that nonstatin therapy could be used, if needed, to reach this < 50% target.

Global risk is the absolute risk of an ASCVD-related event over a specific period, usually 10 years. The risk estimate is based on major risk factors and is calculated using an empiric equation in contrast to the conventional clinical approach to primary prevention of cardiovascular disease that relies on identification and treatment of individual risk factors, such as hypertension and hyperlipidemia and that does not account for the fact that major cardiovascular risk factors contribute multiplicatively to overall risk [7]. Global risk assessment has become increasingly important with the advent of the obesity epidemic leading to an increase in persons with metabolic syndrome and multiple risk factors. The 2013 panel introduced the Omnibus Pooled Cohort equation risk calculator to assess risk. This is an Excel Program that can be downloaded from a Google search at "2013 ACC/AHA Cardiovascular Risk Calculator - Static on AWS". Although the ATP Panels relied largely on the Framingham Study 10-year risk scores, the Omnibus calculator is based on multivariate equations that were developed from 9 long standing population based cohort studies funded by National Heart Lung and Blood Institute. Apparently healthy, aged 40–79. 9 year old, white women and men, African American women and men, along with Hispanic men and women were included by the risk assessment working group. The percentages used to develop the equations refer to hard ASCVD events, and not necessarily mortality. The details of this evidence based methodological approach are available as an Evidence report [8].

The characteristics entered into the calculator are: sex, age, race, total cholesterol, HDLC, systolic blood pressure, on treatment for high blood pressure, diabetes, and smoking. The Expert Panel defined a 10 year risk of ≥ 7.5% as grounds for primary prevention treatment. It is important to notice that the calculator provides both 10-year risk and lifetime risk (30 year) as well as 10-year and lifetime optimal risk for a person of the same age. As will be discussed below, both 10-year and lifetime risk should be considered when determining treatment, since lifetime risk adds additional risk burden information [9], especially in younger persons [10].

It is of interest that neither weight circumference nor body mass index (BMI) are used in the calculator, nor did the 2016 Expert Panel include much about obesity. The ATP III discussed abdominal obesity as a coronary risk factor at length, but ATP III concluded that much of the risk associated with overweight appears to be mediated through other factors such as dyslipidemia, hypertension and diabetes. These factors are included in the Omnibus Risk calculator and, therefore, may indirectly assess risk appropriately in many obese patients.

The 2013 guideline were very controversial and ignited a flurry of descent, ranging from overestimation of risk by the Omnibus Risk calculator to failure to treat to appropriate cholesterol concentration [11,12]. Due to perceived flaws, the guidelines lead to only a modest change in practice by cardiologists [13].

In my view, these guidelines showed four flaws: 1. although the defined doses of statin drop LDLC > 50% or 30–50% on the average, this may not be true in every case, so without targeting cholesterol concentrations, some patients may not reach appropriate cutoffs. 2. Some patients with familial hypercholesterolemia may exhibit such high LDLC levels that a 50% drop may still leave the LDLC well above optimal. 3. The guideline recommended management for patients with high triglycerides as defined in other papers but the guidelines in these other papers used LDLC and nonHDLC concentrations as targets [3,4,14] and since the 2013 guidelines did not define targets, the renderings were inconsistent. 4. The most common dyslipidemia is familial combined hyperlipidemia [15]. This is a condition where high density lipoprotein (HDL) cholesterol (HDLC) is moderately decreased and triglycerides in very low density lipoproteins (VLDL) and intermediate density lipoproteins (IDL) moderately elevated. This condition was shown to be a familiarly defined phenotype that increased the risk of ASCVD by 3-fold [16,17]. Persons with this condition exhibit a predominance of small dense LDL that was first separated on polyacrylamide gel electrophoresis as subclass B [16,18]. Although electrophoresis was first used to identify subclass B, other methods including ultracentrifugation, nuclear magnetic resonance spectroscopy and more recently simpler precipitation methods have been developed to measure small dense LDL [19]. These small dense atherogenic particles contain more protein and less cholesterol so that, although such serum contain more than the normal amount of particles, LDLC concentrations are often minimally elevated, in the range of 100–130 mg/dL. More recently it has become apparent that many overweight persons develop this phenotype which is among the characteristics of the metabolic syndrome [20]. The guidelines did not focus well on persons with this condition.

2. Metabolic syndrome

A cluster of metabolic characteristic that may accompany insulin resistance was first called Syndrome X [21,22] and later termed, the metabolic syndrome [20,23]. Table 2 provides the NCEP definition of these characteristics which is the most widely utilized definition [20]. The world Health Organization defines metabolic syndrome similarly,

Table 2
Criteria for metabolic syndrome.

Triglyceride		≥ 150 mg/dL
HDLC	Men	< 40 mg/dL
	Women	< 50 mg/dL
Small dense LDL (more apo B particles)		
Abdominal obesity (waist circumference)	Men	> 102 cm (> 40 in)
	Women	> 88 cm (> 35 in)
Blood pressure		≥ 130/≥ 85 mm Hg
Fasting glucose (insulin resistance)		≥ 100 mg/dL

except insulin resistance is required [20]. By the NCEP definition, a person exhibiting any three of these characteristics may be considered to have metabolic syndrome. Two of these characteristics are a part of the combined hyperlipidemia dyslipidemia - elevated triglyceride and decreased HDLC. Although small dense LDL is also a common characteristic of combined hyperlipidemia, it loses most of its predictive power when HDLC and triglyceride are concomitantly measured [16,24].

3. Measurement of LDLC

LDLC is measured by homogeneous methods directly (d) LDLC or calculated from total C, HDLC and triglyceride. DLDLC does not require fasting while an overnight fast is required for calculated LDLC since elevated triglyceride causes calculated LDLC to be altered. This is because triglyceride rich VLDL and chylomicrons contain less cholesterol per particle than LDL. Generally, calculated LDLC is considered inaccurate above a triglyceride level of 400 mg/dL.

The most common calculation is by the Friedewald equation [25]. The Friedewald equation was developed about 1969 or 1970 in the Laboratory of Levy to roughly estimate the concentration of LDLC without the need for sequential ultracentrifugation. William Friedewald was a fellow in the Laboratory. Much later, in an interview with Henry Blackburn Friedewald said: "Bob Levy had this idea that there was a stoichiometry, an actual necessary relationship, between triglycerides and cholesterol in the VLDL portion. . in a constant 5 to 1 ratio. Bob gave (the project) to me and said, 'I think there's really something here.' I said, 'We're really trying to measure LDL; we don't really care about VLDL cholesterol, so let's look at that. Although there was a fair amount of error in the estimate of VLDL, because VLDL cholesterol is such a small percentage of the total [cholesterol] it didn't make a big difference. When, in fact, we used [total plasma] triglycerides divided by 5 (or multiplied by 0.2) we got a really strong correlation between LDL [cholesterol] estimated by the equation and that measured [by ultracentrifuge]." The equation has stood the test of time.

Many of the original clinical LDLC lowering studies used an ultracentrifuge method that is simpler than the sequential ultracentrifugation method. This simpler method is called beta-quantification (BQ). It is interesting that the calculation of LDLC by equation includes lipoprotein (a) [Lp(a)] and IDL and so does the BQ reference method so that theoretically the two approaches give similar information while generally dLDLC methods may measure Lp(a) to varying extents [26] or may not measure Lp(a) [27,28].

The Cholesterol Reference Method Laboratory Network (CRMLN) is a network of highly specialized laboratories that work directly with manufacturers and laboratories to assess the analytical accuracy and precision of tests. Calculated LDLC is not certified by CRMLN that certifies the various manufacturers for total cholesterol, triglyceride, dLDLC and direct HDLC. Nevertheless, the components of the equation are certified. Also, the variability of the equation is dependent on three variables, but, VLDLC is a small percentage of the total so it does not add much variability. Direct HDLC adds much less variability than the older precipitation methods [29]. We estimated the accuracy of the Friedewald equation and another equation where the multiplying factor is 0.16 rather than 0.2. We used the Helena electrophoresis (ELP) method to measure about 246 samples with triglyceride < 400 mg/dL after standardizing the electrophoretic method against BQ. We included LDLC and Lp(a). We found that the original Friedewald equation was more accurate with an LDLC of 160 mg/dL by ELP = 161 and 70 by ELP = 69, with an $r^2 = 0.95$. Both equations showed < 5% bias from BQ [29]. There are also more complicated formula approaches for calculating LDLC that adjust for variations in triglycerides and nonHDLC that one may consider [30].

Although dLDLC is certified by CRMLN, it remains unclear how accurate various methods are since different methods use different combinations of antibodies and chemicals to inhibit or precipitate HDL, chylomicrons and beta-lipoprotein fractions other than LDL [26]. Moreover apo B containing lipoproteins are extremely heterogeneous [26], containing IDL, LDL and three subclasses of VLDL. The heterogeneity of LDL extends beyond that of IDL and LDL contains several different subclasses [26]. Some VLDL does not contain apolipoprotein E and may behave like LDL [31]. Because of the heterogeneity, homogeneous separation of chylomicrons, VLDL, IDL, from one another is much more difficult than homogeneous separation of all apo B containing proteins from HDL [26]. Thus, it is not surprising that concerns regarding the performance of homogeneous dLDL methods still exist while direct HDLC has become the mainstay for measuring HDLC.

In general, homogeneous LDLC methods perform better in Type III patients and in patients when triglyceride is > 400 mg/dL but it is still unclear that these are consistently accurate and specific for LDLC or show significantly better concordance than the Friedewald equation in classification of most patients for risk [26]. Nor is it clear in practice how well they agree with one another, while it is clear, that when lipoprotein lipid profiles are desired, they add about double to the total cost [26]. Considering the difficulty in separating beta lipoproteins fractions from one another, one might expect substantial variations over time from lot to-lot.

An assessment by the Canadian External Quality Control Laboratory that is a part of CRMLN seemed to confirm this method variation. This assessment showed that homogeneous dLDLC methods showed an average of 18.4% total error, while calculated LDLC showed 12.5% error in samples from 18 laboratories [32]. The larger total error is most likely due to disagreement between the methods because the bias for calculated LDLC and dLDLC was similar at 4.9% and 5.3% respectively, while the coefficient of variation was 3.9% for calculated LDLC and almost twice as high (6.7%) for dLDLC that theoretically should be lower than calculated LDLC if the methods agreed well.

Thus, the advantages of assessing calculated LDLC over dLDLC seem to be lower cost, because calculated LDLC comes with the standard lipid profile, at least as good accuracy, and consistently better agreement with BQ. Since calculated LDLC includes Lp(a), samples with very high Lp(a) usually will appear to have an elevated LDLC. Lp(a) is not lowered by treatment with a statin. Thus, a further advantage of looking at calculated LDLC is that some patients with elevated Lp(a) will appear to have an elevated calculated LDLC that will respond poorly to statins. In such a case, it is appropriate to measure Lp(a). Since Lp(a) has been shown to have an association with coronary heart disease [33], especially when premature. This feature of calculated LDLC may help identify higher risk individuals that may or may not be available with dLDLC.

Moreover, in a study of 27,331 healthy women with triglyceride < 400 mg/dL, a dLDLC method was compared with LDLC calculated by the Friedewald equation and although the association of LDLC with ASCVD was nearly identical in fasting specimens, nonfasting specimens showed an LDLC of 11.5 mg/dL lower by the dLDLC method [34]. This would have classified most of 20.7% of the patients into a lower risk category than the fasting specimens [34]. As a result, it would be best to collect fasting specimens for both calculated LDLC and dLDLC.

Based on the above reasons (evidence), It is my opinion that calculated LDLC, obtained from the routine lipid profile is the preferred method except when triglyceride concentrations are above about 400 mg/dL where calculated LDLC is known to be increasingly inaccurate. Here dLDLC methods are recommended. Triglyceride rich VLDL are metabolized to IDL and then LDL [35,36]. Very high triglyceride is generally caused by an obstruction in the reaction where lipoprotein lipase converts VLDL to IDL. As a result, most patients with very elevated triglyceride exhibit very low LDLC - usually < 70 mg/dL. In type III hyperlipidemia, IDL cannot be converted to LDL, similarly LDLC is usually very low. As a result, in both cases, even if dLDLC methods are less accurate, it would make little clinical difference if the dLDLC was 70 ± 20 mg/dL - it would be clear it was low, as expected.

Table 3
Patient populations, targets and therapies.

Categories of patient condition	Target	Additional drug treatment to target if reduction is < target
Age 40–75 without clinical ASCVD and without diabetes, baseline LDLC 70–189 mg/dL and 10 year risk > 7.5% for primary prevention	30–49% reduction on statin (may consider LDLC < 100 mg/dL or non-HDLC < 130 mg/dL)	Consider Ezetemibe or bile acid sequestrant (second)
Stable clinical ASCVD with no comorbidities on statins for secondary prevention	≥ 50% reduction on statin (may consider LDLC < 70 mg/dL or non-HDLC < 100)	First consider Ezetemibe Second consider PCSK9 inhibitor
Clinical ASCVD with comorbidities on statins For secondary prevention	≥ 50% reduction on statin (may consider LDLC < 70 mg/dL or non-HDLC < 100 mg/dL)	First consider Ezetemibe Second consider PCSK9 inhibitor
Clinical ASCVD with LDLC ≥ 190 mg/dL due to familial hypercholesterolemia for secondary prevention	≥ 50% reduction on statin (may consider LDLC < 70 mg/dL or non-HDLC < 100 mg/dL)	Consider Ezetemibe or bile acid sequestrant (second line) or PCSK9 inhibition
Without ASCVD with LDLC ≥ 190 mg/dL due to familial hypercholesterolemia	≥ 50% reduction on statin (may consider LDLC < 100 mg/dL or non-HDLC < 130 mg/dL)	Consider Ezetemibe first or bile acid sequestrant (second line) or PCSK9 inhibitor
Age 40–75 without clinical ASCVD with diabetes, baseline LDLC 70–189 mg/dL for primary prevention	≥ 50% reduction on statin (may consider LDLC < 100 mg/dL or may consider non-HDLC < 130 mg/dL)	Consider Ezetemibe first or bile acid sequestrant (second line) or PCSK9 inhibitor

non-HDLC = non-high density lipoprotein cholesterol.

4. Measurement of NonHDLC, and apo B

Apolipoprotein B-100 (apo B) has been shown to be a better predictor of coronary risk than LDLC [37] which was affirmed in ATP III [3]. A major reason for its predictive power is because, apo B is a component of all of the beta-lipoproteins (LDL/VLDL/IDL) and is, therefore, a measure of the major protein in all of the atherogenic prone lipoproteins, including small dense LDL. NonHDLC is a measure of cholesterol in all atherogenic prone beta-lipoproteins. It is calculated by subtracting the HDLC from the total cholesterol. NonHDLC agrees very closely with apo B [38,39] and both are a better coronary risk predictors than LDLC [3,40,41]. Importantly, neither requires fasting since they are relatively unchanged after eating. A major advantage of nonHDLC over apo B is that nonHDLC is calculated from the routine lipid screen, while apo B requires additional testing.

Since nonHDLC is a better risk factor for ASCVD than LDLC, It is likely that eventually, it will become the preferred target. But most clinical outcome studies have targeted LDLC which means if the studies are reexamined and, nonHDLC substituted for LDLC, the result would be statistically suspect since it would become a retrospective study. Nevertheless, the newest guidelines [42] shown in Table 3 indicate that nonHDLC is equivalent to LDLC in all categories.

5. The 2016 ACC expert consensus guidelines and more recent RCT

In 2016, the ACC Expert Task Force released new guidelines [43] for managing non-statin therapies and treating serum cholesterol. These guidelines appear to cover more than treatment with non-statin therapies as the title implies, but the newest guidelines in the NCEP/AHA/ACC series since they cover reference ranges as well as treatment. They reintroduce and extend which LDLC concentrations should be targeted, they defined the use of nonHDLC concentration targets in certain groups and they define which drugs should be used to reach these targets. The information should be of interest to laboratory practitioners since they define the reference ranges [43] for cholesterol as well as treatment protocols. In my opinion, some weaknesses, remain, although these newest guideline mend many of the holes found in the 2013 guidelines.

These guidelines were modified in 2017 [42] by the same ACC expert panel that released the 2016 guidelines and the 2017 guidelines are outlined in Table 3. The populations that would be treated have not changed from the recommendations of the 2013 guidelines shown in Table 1 [6] and the treatment cutoff for persons 40–75 years without apparent disease remains 7.5% risk. The Omnibus risk calculator is still used to assess the 10 year, lifetime and optimal risk.

The 2016 expert group seemed to base some of the guidelines on RCT published since 2013. One of these studies was the *IMProved* Reduction of Outcomes: Vytorin Efficacy Internationaltrial (IMPROVE_IT) [44], first presented at the AHA meetings in November 21, 2014, which showed that the cholesterol lower drug ezetimibe added to a moderate-intensity statin (simvastatin) demonstrated a statistically significant reduction in ASCVD events over 7 years of follow-up. This was a secondary prevention trial of about 18,000 subjects with about 5000 clinical events. The addition of ezetimibe to 40 mg simvastatin reduced ASCVD risk by 6.4% when compared with patients who received simvastatin alone ($p = 0.016$). Average baseline LDLC was 95 mg/dL. Simvastatin lowered it to 69.5 mg/dL and 10 mg ezetimibe further lowered LDLC to 53.7 mg/dL.

The other studies were clinical trials of Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. PCSK9 binds to low-density lipoprotein (LDL) receptors, promoting their degradation and thus increasing LDLC in serum. Human antibodies that are subcutaneously injected and inhibit PCSK9 were described in two different studies: AMG-145 (evolocumab) [45] for statin intolerant patients and REGN 747 (Alirocumab) for patients with heterozygous familial hypercholesterolemia [46] in 2012. These agents were shown to reduce LDLC about 50% beyond that of standard therapy. Moreover, these agents were shown to statistically significantly reduce ASCVD over 78 weeks [47] and 11.1 months [48] and approved by the Food and Drug Administration [43]. After the 2016 guidelines were released FOURIER, a secondary prevention RCT was completed [49]. In this trial 27,564 patients with LDLC levels of 70 mg/dL or higher, who were receiving statin therapy, were randomly assigned to receive evolocumab (either 140 mg every 2 weeks or 420 mg monthly). Over 2.2 years, there was a 59% decrease in LDLC from a median baseline value of 92 mg/dL to 30 mg/dL ($p < 0.001$), and evolocumab treatment significantly reduced the risk of the ASCVD by 20% with a hazard ratio of 0.85 [49]. This RCT helps confirm the causal relationship between LDLC and ASCVD such that a consensus statement from the EAS concluded that evidence from inherited disorders, prospective epidemiological studies, Mendelian randomization studies and RCT establishes that LDL is not only a biomarker but a definitive cause of ASCVD [50]. The 2017 updated guidelines by the ACC expert committee [42] focus in part on the most recent trials, mentioned above, involving ezetimibe and PSCK9 inhibitors, their use in conjunction with statins and their use with patients who appear to be statin intolerant. The conclusion of these

guidelines is the lower the LDLC the better, especially in high risk persons.

6. Critical discussion

In my opinion, the guidelines defined by the 2017 expert group (Table 3) [42] rightly reestablish LDLC therapeutic target concentrations, noting that in certain high risk groups including familial hypercholesterolemia with ASCVD, LDLC < 70 mg/dL is desirable. They suggest that for patients with co-morbidities and diabetes, who often have elevated triglyceride and are often overweight, nonHDLC is an appropriate target. This feature along with the LDLC target appropriately adapts the 2016 guideline to prior guidelines for patients with elevated triglyceride [3,4,14]. Also, the guideline suggest that a ≥ 50% LDLC reduction is desirable but that levels of LDLC < 70 mg/dL or < 100 mg/dL or nonHDLC < 100 mg/dL or < 130 mg/dL can also be targeted. Moreover, other therapies are recommended if statins alone do not bring the cholesterol to target.

Thus, in familial hypercholesterolemia, for primary prevention, if the level after statin treatment appeared to still be too high, it would be appropriate to add non-statin therapy cited in Table 3 (for example, if the original LDLC level was 240 mg/dL and a statin reduced it to 119 mg/dL, it would be appropriate to treat with non-statin therapy to < 100 mg/dL or nonHDLC to < 130 mg/dL). Also, in high risk patients with combined hyperlipidemia and small dense LDL where the LDLC is already close to 100 mg/dL, the guidelines state it is appropriate to treat to reduce LDLC to < 50%, which would be about 50 mg/dL. Besides, in patients with statin intolerance, the guidelines suggest, it would be appropriate to use a low dose of a statin that is better tolerated along with a higher dose of a non-statin therapy to reach the target concentration. They also indicate that PCSK9 inhibitors should be the last choice which is very reasonable because of their cost and because of adherence issues related to injections.

One area of weakness in the 2016 guidelines relates to persons with characteristics of metabolic syndrome. Since neither BMI, weight circumference, triglyceride, nor glucose level is included in the Omnibus calculation, many insulin resistance patients may not be treated even though evidence indicates they are at higher risk. Thus, patients with combined hyperlipidemia and low LDLC may not be identified as being at higher risk, especially those at a young age, since age is by far the most sensitive variable in the risk score. Nevertheless, hypertension, and HDLC that are characteristic of the metabolic syndrome are included. Besides, the calculator, uses total cholesterol, not LDLC, and since total cholesterol is largely nonHDLC, many persons with combined hyperlipidemia will have an elevated total cholesterol and this, along with a low HDLC will produce an elevated lifetime risk. Although younger persons with these characteristics will often show a ten year risk < 7.5%, they may show a very high life time risk as compared to optimal. The guideline suggest that it is not unwise to treat a person with a very high lifetime risk.

For example, a 50 year old Caucasian man with a height of 5′11″ weight of 195 lb, which translates into a Body Mass Index (BMI) of 27.2, a cholesterol of 200 mg/dL, HDLC of 35 mg/dL and a fasting blood glucose of 120 mg/dL who does not smoke and has no family history of heart disease and whose blood pressure is 140/90 mmHg, would calculate out to a 5.9% 10 year risk that is below the 7.5% cutoff for primary prevention treatment. But because of the low HDLC, and elevated total cholesterol his lifetime risk would be 46% compared to an optimal risk for a person of the same age of 5%. Although the 10 year risk is < 7.5%, clearly, this patient exhibits metabolic syndrome with 5 of 5 characteristic (blood pressure, HDLC, triglyceride, BMI and glucose indicating insulin resistance) and is of increased ASCVD risk. The very high lifetime risk might be a useful marker to encourage the patient to embrace lifestyle changes to reduce risk - loss of weight through calorie restriction, increase in exercise. If this tactic was unsuccessful, the high lifetime risk would be sufficient reason to begin lipid lowering therapy. Although many such persons may be treated on a similar basis, it is hoped that future improvements in the risk calculations will embrace BMI, triglyceride and glucose concentrations so that risk for metabolic syndrome patients will be more readily identified.

The addition of nonHDLC as a target equivalent to LDLC in the 2016 guidelines [43] for certain groups is also important. NonHDLC measurement is largely unaffected by triglyceride concentrations. For these reasons, the European Society for Cardiology/European Atherosclerosis Society guidelines [51,52] stated: nonHDLC may be substituted for LDLC in assessing risk in patients with elevated triglycerides, especially when associated with diabetes, kidney disease or metabolic syndrome. The 2016 guidelines [43] lists nonHDLC as a target for appropriate groups. This means that, in appropriate patients, if triglyceride is elevated, nonHDLC can be used as the initial screen so that suspect calculated LDLC values need not be initially evaluated, since guidelines [4,53,54], suggest triglyceride should be lowered to < 500 mg/dL after which lipid lowering therapy should be commenced to an appropriate LDLC or nonHDLC target (Table 3). As shown in Table 3, the 2017 modification [42], indicates that nonHDLC is an appropriate target in all groups. Thus, if the calculated LDLC values are suspect, they can be compared against the nonHDLC values to assess accuracy with the knowledge that there should be a 30 mg/dL difference between the two. If the LDLC and nonHDLC are in disagreement a dLDLC or apo B can be measured. Concurrently, it is important to recognize that patients with metabolic syndrome and elevated triglyceride may exhibit LDLC near 100 mg/L but their nonHDLC may be elevated. Because they often have increased numbers of small dense LDL.

The 2016 expert committee [43] mentioned new RCT for support, nevertheless, like the ATP Committees before them, the panel seemed to base the recommendations not only on RCT but on the totality of the evidence. For example, ezetimibe was shown to reduce risk when added to simvastatin only. Yet, the Committee identified it as the second choice after statin therapy. It seems reasonable to extend this concept to other statins, although it is unlikely studies with other statins and ezetimibe together will be conducted. The committee also recommended, PCSK9 inhibitors as an important therapy, although the longer term 2.2 year study was not published until after the guidelines were released [49]. It still remains uncertain that these antibodies will not have side effects over the longer term. Yet, these conclusions seem reasonable since they balance side effect risk against benefit, since persons with familial hypercholesterolemia are near certain to develop ASCVD over their lifetime while there is no good evidence that the drugs will have substantial side effects. The 2017 Committee [42] also defined nonHDLC as a primary target with good reason, although the primary prospective outcome in few RCT have evaluated nonHDLC.

7. Puzzling areas that remain

Although substantial evidence supports causality between high LDLC and ASCVD, there remains some confusing results [50] because some drugs that lower LDLC do not seem to lower ASCHD risk when added to a statin. These are CETP inhibitors and niacin.

A CETP gene mutation was first described in Japanese populations [55]. Homozygosity for this mutation resulted in very elevated levels of HDLC and those with an HDLC > 80 mg/dL showed a reduced level of ASCVD [56] that was similar to persons with very high HDLC without such a mutation. Nevertheless, subjects who were heterozygous for the mutation showed an increased risk for ASCVD [57].

Torcetrapib is a CETP inhibitor that was shown to increase HDLC concentrations by > 61% while decreasing LDLC 20% [58,59]. Although HDLC was substantially increased and LDLC decreased, as compared to statin alone, torcetrapib increased cardiovascular events in a secondary prevention RCT [relative risk (RR) = 1.21] and increased nonfatal MI (RR = 1.21), although both did not reach statistical significance. It also significantly increased death from all cause

(RR = 1.58, p = 0.006). Because of these adverse results, the study was terminated. Other studies confirmed these findings [60]. There was also progression of disease as assessed by measurement of carotid arterial wall thickness (CIMT) [61]. Anacetrapib a second CETP inhibitor increased HDLC on the average from 41 mg/dL to 101 mg/dL and reduced LDLC was by 50% [62]. It also did not appear to reduce ASCVD after one year of treatment in patients with familial heterozygous hypercholesterolemia [63]. Nevertheless, a very recent publication indicated that after a mean of 4.1 years anacetrapib treatment caused a modest 9% decrease in ASCVD beyond statin treatment alone in a secondary prevention study [64].

Niacin (nicotinic acid) is a B vitamin (vitamin B3). It has been shown that niacin is an effective medication for increasing high-density lipoprotein (HDL) cholesterol and reducing LDLC. In fact, it has a broad effect on the lipid profile, reducing all atherogenic beta-lipoproteins [65]. Thus, in the Coronary Drug Project Research Group study mean triglyceride concentrations were reduced by 19.4% and total cholesterol by 9.6% [66]. Yet two studies that showed niacin substantially lowered LDLC but did not show a reduction in ASCVD. The AIM-High was a randomized secondary prevention study of 3414 high risk patients, in which the experimental group received extended release niacin, a statin or/and ezetimibe as needed to lower LDLC below 80 mg/dL compared with a control group receiving only the statin and ezetimibe [67]. Although niacin lowered the triglyceride level from 164 mg/dL to 122 mg per deciliter (34%), and lowered the LDL cholesterol level from 74 mg/dL to 62 mg/dL (19%) There was no reduction in ASCVD.

In the second study - the HPS2 – Thrive - 26,673 high-risk patients were studied in a secondary prevention study for 3.9 years [68,69]. LDLC was significantly lowered 10 mg/dL and triglyceride by 33 mg/dL but again there was no reduction in ASCVD.

The recent results from study of anacetrapib [64], discussed above, begin to unravel the puzzle as to why CETP inhibitors reduced LDLC beyond that of a statin alone in some studies but did not appear to reduce risk for ASCVD. The CETP inhibitor Torcetrapib increased HDLC and lowered LDLC but it increased risk of cardiovascular events and death from any cause [60]. The most likely reason the drug failed is because it acted on the renin-angiotensin-aldosterone axis that produced only a moderate increase in systolic blood pressure but also a decrease in serum potassium, increases in serum sodium, bicarbonate, and aldosterone [59,60], so that the any positive effect of lowering LDLC was likely counter balanced by these negative effects. This conclusion is supported by findings that the CETP inhibitor dalcetrapib substantially increased HDLC but did not lower LDLC or effect the renin-angiotensin-aldosterone axis but had a neutral outcome on risk [70] while, as discussed above, anacetrapib substantially increased HDLC and lowered LDLC beyond the effect of a statin alone and after 4.1 years decreased ASCVD but the decrease was modest, only 9%, beyond statin treatment, a decrease that is consistent with what would have been expected from commensurate LDLC lowering [71].

Niacin significantly reduced LDLC but did not reduce ASCVD. The reason for this failure is poorly understood. The failure of niacin accompanying specific LDLC reducing drugs to reduce ASCVD risk remains a puzzle. Niacin by itself has been shown to reduce ASCVD in RCTs [72,73]. Niacin inhibits the synthesis of VLDL by directly inhibiting diacylglycerol acyltransferase 2 that causes a decrease in VLDL triglycerides, IDLC and LDLC [65]. Niacin inhibits the HDL apo AI catabolism pathway, resulting in increased HDL levels [65]. Niacin is a ubiquitous vitamin that has wide spread and complex effects. It is possible that very high levels of niacin could have effects that are unknown.

Thus, it appears that drugs that therapeutically lower LDLC beyond a statin alone, and do not have detrimental side effects, reduce ASCVD beyond a statin alone, except for niacin. These include ezetimibe, PCSK9 inhibitors [50] and now and apparently the CETP inhibitor anacetrapib [71]. It seems that additional study is needed to understand the reason for the variance with niacin.

References

[1] Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. The expert panel, Arch. Intern. Med. 148 (1988) 36–69.
[2] National Cholesterol Education Program, Second report of the expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel II), Circulation 89 (1994) 1333–1445.
[3] National Cholesterol Education Program (NCEP), Third Report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III) final report, Circulation 106 (2002) 3143–3421.
[4] J.B. Buse, H.N. Ginsberg, G.L. Bakris, et al., Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association, Circulation 115 (2007) 114–126.
[5] S.C. Smith Jr., J. Allen, S.N. Blair, et al., AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute, Circulation 113 (2006) 2363–2372.
[6] N.J. Stone, J.G. Robinson, A.H. Lichtenstein, 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 (2013) S1–45.
[7] A.J. Viera, S.L. Sheridan, Global risk of coronary heart disease: assessment and application, Am. Fam. Physician 82 (2010) 265–274.
[8] J.D.C. Goff, D.M. Lloyd-Jones, et al., Systemetic evidence review from the risk assessment working group, https://wwwnhlbinihgov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/risk-assessment/, (2013) (2013:1 -139).
[9] M.J. Pencina, R.B. D'Agostino Sr., M.G. Larson, J.M. Massaro, R.S. Vasan, Predicting the 30-year risk of cardiovascular disease: the framingham heart study, Circulation 119 (2009) 3078–3084.
[10] K. Ketlogetswe, R.S. Blumenthal, Thirty-year multivariate risk assessment is a stronger predictor of cardiovascular disease than the 10-year model, Clin. Chem. 55 (2009) 2085–2087.
[11] F. Lopez-Jimenez, V. Simha, R.J. Thomas, et al., A summary and critical assessment of the 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk in adults: filling the gaps, Mayo Clin. Proc. 89 (2014) 1257–1278.
[12] R.A. Vogel, The new cholesterol guidelines: finally more light than heat, J. Am. Coll. Cardiol. 64 (2014) 920–921.
[13] Y. Pokharel, F. Tang, P.G. Jones, et al., Adoption of the 2013 American College of Cardiology/American Heart Association Cholesterol Management Guideline in Cardiology Practices Nationwide, JAMA Cardiol. 2 (2017) 361–369.
[14] M. Miller, N.J. Stone, C. Ballantyne, et al., Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association, Circulation 123 (2011) 2292–2333.
[15] C.A. Aguilar Salinas, M. Zamora, R.A. Gomez-Diaz, R. Mehta, F.J. Gomez Perez, J.A. Rull, Familial combined hyperlipidemia: controversial aspects of its diagnosis and pathogenesis, Semin. Vasc. Med. 4 (2004) 203–209.
[16] M.A. Austin, J.L. Breslow, C.H. Hennekens, J.E. Buring, W.C. Willett, R.M. Krauss, Low-density lipoprotein subclass patterns and risk of myocardial infarction, JAMA 260 (1988) 1917–1921.
[17] M.A. Austin, B. McKnight, K.L. Edwards, et al., Cardiovascular disease mortality in familial forms of hypertriglyceridemia: a 20-year prospective study, Circulation 101 (2000) 2777–2782.
[18] R.M. Krauss, Atherogenicity of triglyceride-rich lipoproteins, Am. J. Cardiol. 81 (1998) 13B–17B.
[19] T. Hirano, Y. Ito, G. Yoshino, Measurement of small dense low-density lipoprotein particles, J. Atheroscler. Thromb. 12 (2005) 67–72.
[20] S.M. Grundy, H.B. Brewer Jr., J.I. Cleeman, S.C. Smith Jr., C. Lenfant, Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition, Circulation 109 (2004) 433–438.
[21] G.M. Reaven, Banting lecture 1988: role of insulin resistance in human disease, Diabetes 37 (1988) 1595–1607.
[22] G.M. Reaven, The role of insulin resistance and hyperinsulinemia in coronary heart disease, Metabolism 41 (1992) 16–19.
[23] S.M. Grundy, Point: the metabolic syndrome still lives, Clin. Chem. 51 (2005) 1352–1354.
[24] S. Kathiresan, J.D. Otvos, L.M. Sullivan, et al., Increased small low-density lipoprotein particle number: a prominent feature of the metabolic syndrome in the Framingham Heart Study, Circulation 113 (2006) 20–29.
[25] B.G. Nordestgaard, M. Benn, Fasting and nonfasting LDL cholesterol: to measure or calculate? Clin. Chem. 55 (2009) 845–847.
[26] M. Nauck, G.R. Warnick, N. Rifai, Methods for measurement of LDL-cholesterol: a critical assessment of direct measurement by homogeneous assays versus calculation, Clin. Chem. 48 (2002) 236–254.
[27] G. Yoshino, T. Hirano, T. Kazumi, New clinical application of direct and chemical measurement of low density lipoprotein cholesterol-estimation of compositional changes in triglyceride-rich lipoprotein fraction, Nihon Rinsho 57 (1999) 2745–2753.
[28] J. Ordonez-Llanos, A.M. Wagner, R. Bonet-Marques, J.L. Sanchez-Quesada,

F. Blanco-Vaca, F. Gonzalez-Sastre, Which cholesterol are we measuring with the Roche direct, homogeneous LDL-C Plus assay? Clin. Chem. 47 (2001) 124–126.
[29] N. Abudu, S.S. Levinson, Calculated low-density lipoprotein cholesterol remains a viable and important test for screening and targeting therapy, Clin. Chem. Lab. Med. 45 (2007) 1319–1325.
[30] S.S. Martin, M.J. Blaha, M.B. Elshazly, 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.
[31] E. Campos, S. Jackle, G. Chi Chen, R.J. Havel, Isolation and characterization of two distinct species of human very low density lipoproteins lacking apolipoprotein E, J. Lipid Res. 37 (1996) 1897–1906.
[32] D.W.J.B. Seccombe, A. Ho, Comparison of proficiency testing (PT) data from a fresh serum lipid program for the direct measurement of LDL, apoprotein A-1 and apoprotein B, Fats of Life, vol. 21, 2007, pp. 22–24.
[33] S. Erqou, S. Kaptoge, P.L. Perry, et al., Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality, JAMA 302 (2009) 412–423.
[34] S. Mora, N. Rifai, J.E. Buring, P.M. Ridker, Comparison of LDL cholesterol concentrations by Friedewald calculation and direct measurement in relation to cardiovascular events in 27,331 women, Clin. Chem. 55 (2009) 888–894.
[35] W.P. Castelli, The triglyceride issue: a view from Framingham, Am. Heart J. 112 (1986) 432–437.
[36] M.A. Austin, Plasma triglyceride as a risk factor for coronary heart disease, Am. J. Epidemiol. 129 (1989) 249–259.
[37] S.S. Levinson, S.G. Wagner, Measurement of apolipoprotein B-containing lipoproteins for routine clinical laboratory use in cardiovascular disease, Arch. Pathol. Lab. Med. 116 (1992) 1350–1354.
[38] S.S. Levinson, S.G. Wagner, Immunonephelometric/turbidimetric apolipoprotein B assays for the clinical laboratory, Clin. Chim. Acta 223 (1993) 31–42.
[39] N. Abate, G.L. Vega, S.M. Grundy, Variability in cholesterol content and physical properties of lipoproteins containing apolipoprotein B-100, Atherosclerosis 104 (1993) 159–171.
[40] S.S. Levinson, Comparison of apolipoprotein B and non-high-density lipoprotein cholesterol for identifying coronary artery disease risk based on receiver operating curve analysis, Am. J. Clin. Pathol. 127 (2007) 449–455.
[41] H.E. van Deventer, W.G. Miller, G.L. Myers, et al., Non-HDL cholesterol shows improved accuracy for cardiovascular risk score classification compared to direct or calculated LDL cholesterol in a dyslipidemic population, Clin. Chem. 57 (2011) 490–501.
[42] D.M. Lloyd-Jones, P.B. Morris, C.M. Ballantyne, et al., Focused update of the 2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology Task Force on expert consensus decision pathways, J. Am. Coll. Cardiol. 70 (2017) 1785–1822.
[43] D.M. Lloyd-Jones, P.B. Morris, C.M. Ballantyne, et al., ACC expert consensus decision pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology Task Force on clinical expert consensus documents, J. Am. Coll. Cardiol. 68 (2016) 92–125.
[44] C.P. Cannon, M.A. Blazing, R.P. Giugliano, et al., Ezetimibe added to statin therapy after acute coronary syndromes, N. Engl. J. Med. 372 (2015) 2387–2397.
[45] D. Sullivan, A.G. Olsson, R. Scott, et al., Effect of a monoclonal antibody to PCSK9 on low-density lipoprotein cholesterol levels in statin-intolerant patients: the GAUSS randomized trial, JAMA 308 (2012) 2497–2506.
[46] F. Raal, R. Scott, R. Somaratne, et al., Low-density lipoprotein cholesterol-lowering effects of AMG 145, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease in patients with heterozygous familial hypercholesterolemia: the reduction of LDL-C with PCSK9 inhibition in Heterozygous Familial Hypercholesterolemia Disorder (RUTHERFORD) randomized trial, Circulation 126 (2012) 2408–2417.
[47] J.G. Robinson, M. Farnier, M. Krempf, et al., Efficacy and safety of alirocumab in reducing lipids and cardiovascular events, N. Engl. J. Med. 372 (2015) 1489–1499.
[48] M.S. Sabatine, R.P. Giugliano, S.D. Wiviott, et al., Efficacy and safety of evolocumab in reducing lipids and cardiovascular events, N. Engl. J. Med. 372 (2015) 1500–1509.
[49] M.S. Sabatine, R.P. Giugliano, A.C. Keech, et al., Evolocumab and clinical outcomes in patients with cardiovascular disease, N. Engl. J. Med. 376 (2017) 1713–1722.
[50] B.A. Ference, H.N. Ginsberg, I. Graham, 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.
[51] A.L. Catapano, Z. Reiner, G. De Backer, 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), Atherosclerosis 217 (2011) 3–46.
[52] M.F. Piepoli, A.W. Hoes, S. Agewall, et al., European guidelines on cardiovascular disease prevention in clinical practice: the sixth joint task force of the European Society of Cardiology and Other Societies on cardiovascular disease prevention in clinical practice (constituted by representatives of 10 societies and by invited experts) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR), Eur. Heart J. 37 (2016) 2315–2381.
[53] J.D. Brunzell, M. Davidson, C.D. Furberg, et al., Lipoprotein management in patients with cardiometabolic risk: consensus conference report from the American Diabetes Association and the American College of Cardiology Foundation, J. Am. Coll. Cardiol. 51 (2008) 1512–1524.
[54] M. Miller, N.J. Stone, C. Ballantyne, et al., Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association, Circulation 123 (2011) 2292–2333.
[55] J.S. Forrester, R. Makkar, P.K. Shah, Increasing high-density lipoprotein cholesterol in dyslipidemia by cholesteryl ester transfer protein inhibition: an update for clinicians, Circulation 111 (2005) 1847–1854.
[56] Y. Moriyama, T. Okamura, A. Inazu, et al., A low prevalence of coronary heart disease among subjects with increased high-density lipoprotein cholesterol levels, including those with plasma cholesteryl ester transfer protein deficiency, Prev. Med. 27 (1998) 659–667.
[57] A.R. Tall, X. Jiang, Y. Luo, D. Silver, 1999 George Lyman Duff memorial lecture: lipid transfer proteins, HDL metabolism, and atherogenesis, Arterioscler. Thromb. Vasc. Biol. 20 (2000) 1185–1188.
[58] M.E. Brousseau, E.J. Schaefer, M.L. Wolfe, et al., Effects of an inhibitor of cholesteryl ester transfer protein on HDL cholesterol, N. Engl. J. Med. 350 (2004) 1505–1515.
[59] S.E. Nissen, J.C. Tardif, S.J. Nicholls, et al., Effect of torcetrapib on the progression of coronary atherosclerosis, N. Engl. J. Med. 356 (2007) 1304–1316.
[60] P.J. Barter, M. Caulfield, M. Eriksson, et al., Effects of torcetrapib in patients at high risk for coronary events, N. Engl. J. Med. 357 (2007) 2109–2122.
[61] J.J. Kastelein, S.I. van Leuven, L. Burgess, et al., Effect of torcetrapib on carotid atherosclerosis in familial hypercholesterolemia, N. Engl. J. Med. 356 (2007) 1620–1630.
[62] C.P. Cannon, S. Shah, H.M. Dansky, et al., Safety of anacetrapib in patients with or at high risk for coronary heart disease, N. Engl. J. Med. 363 (2010) 2406–2415.
[63] J.J. Kastelein, J. Besseling, S. Shah, et al., Anacetrapib as lipid-modifying therapy in patients with heterozygous familial hypercholesterolaemia (REALIZE): a randomised, double-blind, placebo-controlled, phase 3 study, Lancet 385 (2015) 2153–2161.
[64] L. Bowman, J.C. Hopewell, F. Chen, et al., Effects of anacetrapib in patients with atherosclerotic vascular disease, N. Engl. J. Med. 377 (2017) 1217–1227.
[65] S. Malik, M.L. Kashyap, Niacin, lipids, and heart disease, Curr. Cardiol. Rep. 5 (2003) 470–476.
[66] Clofibrate and niacin in coronary heart disease, JAMA 231 (1975) 360–381.
[67] W.E. Boden, J.L. Probstfield, T. Anderson, et al., Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy, N. Engl. J. Med. 365 (2011) 2255–2267.
[68] HPS2-THRIVE Collaborative Group, HPS2-THRIVE randomized placebo-controlled trial in 25,673 high-risk patients of ER niacin/laropiprant: trial design, pre-specified muscle and liver outcomes, and reasons for stopping study treatment, Eur. Heart J. 34 (2013) 1279–1291.
[69] M.J. Landray, R. Haynes, J.C. Hopewell, et al., Effects of extended-release niacin with laropiprant in high-risk patients, N. Engl. J. Med. 371 (2014) 203–212.
[70] G.G. Schwartz, A.G. Olsson, M. Abt, et al., Effects of dalcetrapib in patients with a recent acute coronary syndrome, N. Engl. J. Med. 367 (2012) 2089–2099.
[71] R.A. Hegele, CETP inhibitors - a new inning? N. Engl. J. Med. 377 (2017) 1284–1285.
[72] T.C. Villines, E.J. Stanek, P.J. Devine, et al., The ARBITER 6-HALTS trial (arterial biology for the investigation of the treatment effects of reducing cholesterol 6-HDL and LDL treatment strategies in atherosclerosis): final results and the impact of medication adherence, dose, and treatment duration, J. Am. Coll. Cardiol. 55 (2010) 2721–2726.
[73] P.L. Canner, K.G. Berge, N.K. Wenger, et al., Fifteen year mortality in coronary drug project patients: long-term benefit with niacin, J. Am. Coll. Cardiol. 8 (1986) 1245–1255.