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Clinical and scientific debates on atherosclerosis

HDL cholesterol and ASCVD risk stratification: A debate

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HIGHLIGHTS

- HDL-C is a strong, graded and coherent biomarker of cardiovascular health.
- A very high HDL-C is not necessarily protective against ASCVD.
- Mendelian randomization does not support HDL-C as a causal cardiovascular risk factor.
- The clinical trial data does not support raising HDL-C pharmacologically to decrease outcomes.
- HDL function (e.g. cellular cholesterol efflux) may be the way forward.

ABSTRACT

This debate is designed to review the usefulness of the cholesterol mass within high-density lipoproteins (HDL-C) to predict the risk of atherosclerotic cardiovascular disease (ASCVD).

Pro: There is much current confusion regarding the role of high density lipoproteins (HDLs) in atherosclerotic cardiovascular disease (ASCVD). While it is an established fact that the concentration of HDL cholesterol is a robust, independent, inverse predictor of the risk of having an ASCVD event, recent studies have questioned whether HDLs actually protect against ASCVD. But this in no way challenges that fact that the concentration of HDL cholesterol is a powerful tool to be used in risk stratification of ASCVD.

Con: The measurement of HDL-C in the 1970 heralded a new area of promising and exciting research in cardiovascular disease. The measurement of HDL-C has been part of cardiovascular risk stratification for the past three decades. HDL have pleotropic beneficial effects on the arterial vasculature and promote the removal of excess cholesterol from lipid laden macrophages. These effects are only weakly correlated with HDL-C levels. While HDL-C is associated with atherosclerotic cardiovascular disease, the epidemiological relationship falters at the extremes of measurement. Mendelian randomization does not support a link of causality and to date, attempts to raise HDL-C pharmacologically have not yielded the expected outcomes. The time has come to consider abandoning HDL-C for cardiovascular risk prediction and clinical decision making and to double efforts to develop better biomarkers of HDL function.

1. Pro: Dr. Philip Barter

HDL-C should continue to be used for risk stratification of ASCVD.

1.1. Introduction

The concentration of high density lipoprotein cholesterol (HDL-C) has long been established as a robust, independent, inverse predictor of the risk of having an atherosclerotic cardiovascular disease (ASCVD) event and should continue to be used in risk stratification of ASCVD.

The reason for much current confusion about the role of HDLs in ASCVD development relates to the fact that it is still not proven that HDLs actually protect and that they should be a target of interventions designed to prevent ASCVD events in humans. But this in no way invalidates the value of HDL cholesterol concentration in risk stratification of ASCVD. As argued below, there is no doubt that the concentration of HDL cholesterol continues to be an independent, inverse predictor of the risk of having an SASCVD event, whether or not HDLs should be the target of therapeutic intervention.

The evidence that HDL cholesterol levels predict ASCVD risk will first be discussed before examining a possible role of HDLs in protecting against the disease. But to repeat what is stated above, even if HDLs do not protect against the risk of having an ASCVD event, there is no escaping the fact that the concentration of HDL cholesterol is an independent, inverse predictor of the risk of having an event.

1.2. Population studies

An inverse relationship between the concentration of cholesterol in

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HDLs and the risk of developing premature coronary heart disease (CHD) has been observed in many large-scale population studies [1–6]. In several of these studies, the concentration of HDL cholesterol has actually been the single most powerful lipid predictor of future ASCVD events. In one large study, the concentration of HDL cholesterol was also an inverse predictor of total mortality [7]. Furthermore, a low level of HDL cholesterol remains predictive of future ASCVD risk even when the concentration of cholesterol in low density lipoproteins (LDLs) has been reduced to low levels by treatment with statins [8–11].

Perhaps the most compelling evidence that the concentration of HDL cholesterol is an independent, inverse predictor of ASCVD has been provided by an analysis performed by The Emerging Risk Factors Collaboration [12].

This analysis used Individual records obtained from 68 long-term prospective studies. The analysis included 302,430 people who did not have manifest vascular disease at the time of inclusion in the study. During 2.79 million person-years of follow-up, there were 8857 non-fatal myocardial infarctions, 3928 coronary heart disease (CHD) deaths, 2534 ischemic strokes, 513 hemorrhagic strokes, and 2536 unclassified strokes.

In this analysis, levels of HDL cholesterol and non– HDL cholesterol were both strongly associated (in opposite directions) with CHD risk in an approximately log-linear manner. Triglyceride levels were not associated with CHD risk after adjusting for HDL cholesterol, non–HDL cholesterol and other standard risk factors. It was concluded that triglyceride measurement provides no additional information about vascular risk beyond that provided by HDL cholesterol and non–HDL cholesterol. HDL cholesterol and non–HDL cholesterol levels were independent from each other, as well as from triglyceride levels and other risk factors [12].

In support of these human population studies, there are numerous intervention studies in animals showing that an increase in the concentration of HDLs inhibits the development of atherosclerosis [13–16]. To date, however, interventions targeting HDLs in humans have not translated into a reduced risk of having an ASCVD event.

1.3. Genetic studies

Some of the confusion regarding HDLs and ASCVD has been generated by genetic studies [17]. Genetic variation in scavenger receptor class B type 1 (SRB1) has been shown to influence HDL cholesterol levels but has no impact on ASCVD risk [17]. Likewise, polymorphisms in endothelial lipase associated with high HDL cholesterol did not translate into reduced CVD risk [17]. While these data challenge the view that raising levels of HDL cholesterol reduces risk of ASCVD events, in reality, all they show is that the cholesterol in HDLs does not protect. They say nothing about protection that may be provided by one or more of the known HDL functions. To date, none of the genetic studies has investigated relationships between HDL function and ASCVD risk.

1.4. HDL cholesterol level and HDL function

HDLs have many functions that have the potential to protect against the development ASCVD (see below). In most circumstances these HDL functions correlate with the concentration of HDL cholesterol. In other words, in most people the concentration of HDL cholesterol is a marker of a range of potentially protective functions of HDLs. This is important since, while the cholesterol transported in HDLs is most unlikely to protect, there are several HDL functions that may well protect.

1.5. Potentially protective functions of HDL

HDLs promote efflux of cholesterol from macrophages in the artery wall [18]. HDLs also inhibit vascular inflammation [19,20] and have anti-oxidant [19] and anti-thrombotic [21] properties. They enhance endothelial function [22], promote endothelial repair, [23,24] increase angiogenesis, [25] suppress the production and mobilization of monocytes and neutrophils from bone marrow [26] and have anti-diabetic properties [27,28]. However, which (if any) of these functions of HDLs is clinically important is not known. Nor is it known which HDL component(s) or which HDL subpopulations are responsible for these potentially cardio-protective properties. This lack of insight is largely due to the fact that HDLs consist of multiple subpopulations of particles that differ in terms of particle density, size, shape, surface charge and composition [29,30]. These subpopulations are continually interconverted from one to another by a range of plasma factors [29]. It is currently not feasible to isolate specific HDL subpopulations in amounts that are sufficient to investigate their functionality in a systematic manner. And finally, if HDLs do protect against ASCVD, it is not known how long it takes for a protective HDL function to translate into a reduction in ASCVD events.

As discussed below, there are circumstances in which HDLs become dysfunctional and the concentration of HDL cholesterol no longer equates with HDL function [31] and, as a consequence, no longer predicts of the risk of having an ASCVD event. But this is the exception rather than the rule. Most people have HDLs that function normally.

There is evidence from human studies that interventions that raise the level of HDL cholesterol have varying effects on specific HDL subpopulations. Until we know which HDL components and which HDL subpopulations relate to specific, potentially cardio-protective HDL functions, and until we have much more information about the effects of HDL-raising therapies on HDL composition, HDL subpopulation distribution and HDL function, it is difficult to predict how any specific HDL-targeted therapy will impact on human cardiovascular risk.

1.6. Targeting HDLs in animal studies

There is a considerable body of evidence from animal studies that raising the concentration of HDLs inhibits the development of atherosclerosis. For example, over-expression of apoA-I in mice [15,16] and rabbits, [32] as well as intravenous infusions of HDLs into rabbits [13] inhibits the development of atherosclerosis. There is also evidence that increasing endogenous HDL cholesterol levels by inhibiting CETP in cholesterol-fed rabbits is associated with a reduction in susceptibility to the development of atherosclerosis [33–37].

1.7. Targeting HDLs in human studies

In one proof-of-concept study in humans, five infusions of reconstituted HDLs containing apoA-I_{Milano} given at weekly intervals resulted in significant regression of coronary atheroma as assessed by intravascular ultrasound [38]. But there is still no evidence that therapies targeting HDLs reduce the risk of having an ASCVD event.

1.8. Clinical outcome trials in human

Most human clinical outcome trials designed to assess the effects of therapies that target HDLs have used agents that have an impact on factors in addition to HDLs, making it difficult to assess the effects of HDL-raising on the clinical outcomes.

1.8.1. Niacin

Treatment with niacin decreases levels of plasma triglyceride and LDL cholesterol in addition to raising levels of HDL cholesterol, making it difficult to interpret the positive outcome associated with treatment with niacin in the Coronary Drug Project [39]. In two subsequent trials using niacin in statin treated patients, there was no reduction in ASCVD events [40,41].

1.8.2. CETP inhibition

Inhibition of CETP in humans increases levels of HDL cholesterol

and in most cases also reduce non-HDL cholesterol levels. However, when tested in humans in randomized clinical outcome trials, three different CETP inhibitors (torcetrapib, [42] dalcetrapib, [43] and evacetrapib [44] all failed to reduce ASCVD events. In the case or torcetrapib, the treatment caused harm, possibly because of serious off-target adverse effects of torcetrapib unrelated to inhibition of CETP [42]. The failure of dalcetrapib may have been because it was terminated too soon and was tested in patients after anb ACS event at a time when the HDL fraction is known to be dysfunctional [45]. This possibility was supported by the observation that the concentration of HDL cholesterol did not predict ASCVD events even in the placebo group in this trial [43]. The failure of evacetrapib in the ACCELERATE trial may simply have been because the trial was terminated after only two years of follow-up, at a time too short to be able to detect benefit.

The REVEAL trial using the CETP inhibitor anacetrapib included more than 30,000 high-risk, statin-treated people who were randomized to receive anacetrapib or placebo with a planned four-year follow up [46]. The participants in REVEAL were treated intensively with atorvastatin prior to randomization and had a very low mean baseline LDL cholesterol level of 61 mg/dL, a mean non-HDL cholesterol level of 92 mg/dL and a mean HDL cholesterol level of 40 mg/dL. Treatment with anacetrapib increased the level of HDL cholesterol by 104% and decreased the non-HDL cholesterol level by 18%. During the median 4.1 years of follow up, the primary outcome was reduced from 11.8% in the placebo group to 10.8% in those treated with anacetrapib (rate ratio, 0.91; 95% confidence interval, 0.85 to 0.97; P = 0.004). The magnitude of this benefit was consistent with that observed for comparable reductions in non-HDL cholesterol levels in statin trials [46]. This does not, however, prove that the benefit was due to the reduction in non- HDL cholesterol; nor does it exclude a benefit related to an increase in HDL functionality. Participants in REVEAL whose baseline LDL cholesterol level was in the upper tertile (> 66 mg/dL) had a statistically significant reduction in the primary endpoint of 13%. In those whose baseline non-HDL cholesterol level was in the upper tertile (> 101 mg/dL), the reduction in the primary endpoint was a statistically significant 17% [46]. There were no significant between group differences in the risk of death, cancer or other serious adverse events in this trial.

The reduction in coronary events in those treated with anacetrapib did not become apparent until after two years of treatment [46]. During the third year, however, the reduction in coronary events was 13%, while coronary events occurring beyond 4 years of treatment were reduced by a statistically significant 17%. This delay in benefit highlights the possibility that the failure of evacetrapib to reduce cardiovascular events in ACCELERATE may have been related to termination of the trial after only two years of follow up.

1.9. Loss of functionality of HDLs

HDL function may be compromised in some people [31]. Under such circumstances, the concentration of HDL cholesterol may no longer be a marker of HDL function and may no longer be an inverse predictor of ASCVD events. But this exception in no way invalidates the fact that in most people, especially those without clinical evidence of ASCVD, the concentration of HDL cholesterol is a robust, independent, inverse predictor of the risk of having an ASCVD event.

1.10. Is a high level of HDL cholesterol ever harmful?

There are reports of increased ASCVD events and even increased mortality associated with very high levels of HDL cholesterol [47]. The reason why such findings are in conflict with the vast number of population studies that have found an inverse relationship is not known. It is possible (but not proven) that under some circumstances HDLs not only lose their protective properties but may also become harmful and pro-atherogenic. However, these exceptions in no way invalidate the observed robust inverse relationship between the concentration of HDL cholesterol and ASCVD risk in the vast majority of people.

To put this in perspective, it is worth considering the relationship of LDL cholesterol levels with ASCVD risk. There is no question that the LDL cholesterol level contributes substantially to ASCVD risk prediction. This is not invalidated by the fact that a small percentage of people with low levels of LDL cholesterol have an ASCVD event or that some people with elevated LDL cholesterol have low risk. Similarly, the fact that a small proportion of people with very high HDL cholesterol levels do have an ASCVD event does not invalidate the importance of the HDL cholesterol level as an inverse predictor of having an ASCVD event in the vast majority of people.

So, whether or not HDLs actually protect against ASCVD, there is no escaping the evidence supporting the proposition that the concentration of HDL cholesterol should continue to be used in the risk stratification of ASCVD.

2. Con: Dr. Jacques Genest

HDL-C should no longer be used for ASCVD risk stratification

The biological plausibility that high density lipoproteins have a beneficial pleiotropic effects on the arterial vascular system is incontrovertible [48]. There is also strong evidence that altered HDL particles may have, at least in-vitro and in animal models deleterious effects and promote, rather than prevent atherosclerosis [31]. These effects, however, appear to be mediated by the complex proteome [49], lipidome [50] and likely, the RNAome [51] of HDL. The most important function of HDL appears the ability of apoA-I and lipid-poor HDL to remove cholesterol from lipid-laden macrophages within the atherosclerotic plaque and, through reverse cholesterol transport, eliminate if by re-secretion into the bile. Cellular cholesterol efflux capacity has been shown in moderately large studies, to associate with cardiovascular risk [52–54]. Yet, the correlation between cellular efflux capacity and HDL-C is not very strong. Lastly, plasma HDL-C may not reflect the pathophysiology of reverse cholesterol transport in the arterial wall. The concentration of apoA-I within atherosclerotic plaques is up to 100 fold that of plasma and is extensively modified rendering it dysfunctional [55,56].

I will base the argument that HDL cholesterol should not be used for cardiovascular risk stratification by reviewing the epidemiology of HDL-C and ASCVD, the genetic epidemiology of HDL-C and ASCVG and the clinical trial data.

2.1. Epidemiologic association does not imply causality

High density lipoprotein cholesterol (HDL-C) has been labeled as a risk factor for atherosclerotic cardiovascular disease for more than 40 years [5]. Implicit in the early understanding of this relationship was the reciprocal maxim that raising HDL-C would lead to improved cardiovascular outcomes –the “HDL Hypothesis”. The association between HDL-C levels and risk of ASCVD is strong, graded and coherent across population studied [12]. For decades, epidemiologists and clinicians have come to appreciate that HDL-C levels are markedly influenced by the company it keeps. Fit, lean, healthy subjects that drink alcohol in moderation have a higher HDL-C than those who are sedentary, are obese, smoke cigarettes, have a lower socio-economic status, have elevated plasma triglyceride and glucose levels and have chronic inflammatory conditions. It has been argued that HDL-C is really a biomarker of cardiovascular health [57].

The epidemiology of HDL-C and health starts to unravel at extremes of HDL-C levels. In patients with elevated HDL-C, Ko et al. showed a consistent inverse relationship between HDL-C and cardiovascular events, but a lack of protection at HDL-C levels > 90 mg/dL (2.3 mmol/) and an increase in non-cardiovascular outcomes in the CANHEART study of 631,762 individuals. The Authors concluded that “HDL-C is a heavily confounded factor that may be a marker of poor overall health,

rather than an independent and modifiable risk factor" [58]. Madsen et al. examined 52 268 men and 64 240 women from Copenhagen City Heart and the Copenhagen General Population prospective studies. The lowest all-cause mortality was observed at a HDL-C level of 1.9 mmol/L 73 mg/dL in men and 2.4 mmol/L (93 mg/dL). The adjusted hazard ratios for all-cause mortality were 1.36 (95% CI: 1.09–1.70) for men with HDL cholesterol of 2.5–2.99 mmol/L (97–115 mg/dL) and 2.06 (1.44–2.95) for men with HDL cholesterol ≥3.0 mmol/L (116 mg/dL). For women, corresponding hazard ratios were 1.10 (0.83–1.46) for HDL cholesterol of 3.0–3.49 mmol/L (116–134 mg/dL) and 1.68 (1.09–2.58) for HDL cholesterol ≥3.5 mmol/L (135 mg/dL) [47]. This paradoxical increase in all-cause mortality at very high HDL-C levels remains unexplained.

In a meta-analysis of 8 statin treatment trials, Boekholdt et al. showed that both HDL-C and apoA-I levels were associated with a reduction in cardiovascular risk. However, an increase in apoA-I, but not in HDL-C levels was associated with a reduced risk of major cardiovascular events [59]. These results were largely confirmed in US Veterans with decreased renal function; Bowe et al. showed an increase in total mortality at HDL-C levels > 90th percentile [60]. Conversely, Ridker et al. examined the predictive value of HDL-C in the JUPITER trial. In 17,802 subjects at high cardiovascular risk treated with rosuvastatin 20 mg or placebo, HDL-C levels did not predict of residual cardiovascular risk in patients who reach a very low LDL-C level [61]. Finally, the measurement of HDL-C does not improve risk prediction beyond the conventional European Systematic *COronary Risk* Evaluation (SCORE) risk algorithm [62].

2.2. Genetics of HDL and ASCVD risk. HDL genes do not shed much light

The identification of the major genes involved in HDL biogenesis, apoA-I and the ATP binding cassette transporter 1 (ABCA1) and HDL metabolism offered many potential novel therapeutic avenues [57]. Both *APOAI* and *ABCA1* gene defects were associated with very low HDL-C and increased cardiovascular risk. This association, however, most likely reflected referral bias. Frikke-Schmidt et al. examined participants in three cohorts from Copenhagen with mutations in *ABCA1* causing a low HDL-C. A total of 109 heterozygote carriers were identified among 41,961 subjects; there were 6666 cases of ischemic heart disease. The adjusted odds ratio for ischemic heart disease was 0.93 (95% CI, 0.53–1.62) (carriers *vs.* non-carriers). On the basis of these results, the Authors concluded that loss-of-function mutations in ABCA1 were not associated with an increased risk of ASCVD [63].

Voight et al. performed two mendelian randomization studies in 20,913 myocardial infarction cases and 95,407 controls using single nucleotide polymorphisms (SNP) in the endothelial lipase (*LIPG*) gene and in another group of 12,482 cases of MI and 41,331 controls, using 14 SNPs that exclusively associate with HDL-C. No association between genetic polymorphisms that raise or lower HDL-C and risk of myocardial infarction was observed [17]. This observation challenged the concept that raising HDL-C would translate into a decreased risk of myocardial infarction. Holmes et al. examined blood lipids in relation to myocardial infarction using Mendelian randomization. Neither the restricted allele score using 19 SNPs (OR: 0.91; 95% CI: 0.42, 1.98) nor the unrestricted HDL-C allele score, using 48 SNPs adjusted for triglycerides, LDL-C, or statin use (OR: 0.81; 95% CI: 0.44, 1.46) showed a robust association with MI [64].

Based on Mendelian randomization studies, it seems clear that a genetically determined isolated low HDL-C does not increase cardiovascular risk. It is also clear that very rare mutations that cause a complete absence of apoA-I may have a causal relationship with ASCVD [65]. The evidence of mutations at the *ABCA1* gene, even in Tangier disease (homozygous *ABCA1* mutations) is much less clear.

2.3. Clinical trial data. The proof is (not) in the pudding

Tenets of the "HDL hypothesis" have been challenged by epidemiology and genetics. The effects of a therapeutic modality that exclusively raises HDL-C (without affecting other lipoproteins of pathways) has proven elusive. To date, therefore, clinicians had to rely in inference from clinical trials to assess whether raising HDL-C decreases ASCVD outcomes. The fibric acid derivatives, or fibrates activate peroxisome proliferator-activated receptor alpha (PPARα) and enhance lipoprotein lipase activity, in part, by decreasing the expression of its inhibitor, apoCIII. In the statin era, the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) and ACCORD (Action to Control Cardiovascular Risk in Diabetes -also with fenofibrate) trials failed to reduce cardiovascular outcomes in diabetic patients, despite a significant increase in HDL-C [66]. Newer PPARα and γ, such as Aleglitazar, also failed to change outcomes in diabetic patients [67]. Niacin has been used for over 60 years to treat lipoprotein disorders and has been used in early clinical trials. The AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL Cholesterol/High Triglyceride and Impact on Global Health Outcomes) was a relatively modest trial of 3300 patients with ASCVD and residual dyslipidemia did not meet its primary outcome of reducing ASCVD risk [68]. The large HPS2-THRIVE (Heart Protection Study-2 Treatment of HDL to Reduce the Incidence of Vascular Events) randomized 25,673 high-risk patients taking simvastatin to placebo or the combination of niacin and laropiprant (an inhibitor of prostaglandin D2, thought to mediate the cutaneous flushing reaction seen with niacin. While no beneficial effects on ASCVD risk were observed, an increase in complications led to the withdrawal of the combination drug and a decrease in the use of niacin clinically [65].

2.3.1. Cholesteryl ester transfer protein (CETP) inhibitors

As discussed above, this class of drug causes a marked increase in HDL-C (also a decrease non-HDL-C in calculated LDL-C). Trials with torcetrapib, dalcetrapib and evacetrapib ended because of toxicity or futility [68]. The REVEAL trial (Heart Protection-3 Randomized EValuation of the Effects of Anacetrapib Through Lipid-modification) randomized 30,449 patients with ASCVD on atorvastatin with atherosclerotic vascular disease who were receiving intensive atorvastatin therapy to placebo or anacetrapib, 100 mg/day. The baseline mean LDL –C leves was 1.6 mmol/L (61 mg/dL) cholesterol level of 61 mg per deciliter (1.58 mmol per liter). After a median follow-up of 4 years, the primary outcome was reduced by an absolute rate of 1.0% (rate ratio, 0.91; 95% CI, 0.85 to 0.97; $p = 0.004$). HDL-C increased by 104% and non-HDL-C decreased by 18% (0,44 mmol/L or 17 mg/dL). While there were no differences in the risk of death, cancer or serious adverse events, this very modest benefit was likely explained by the modest reduction in non HDL-C. Anacetrapib is no longer pursued as a therapeutic option.

Novel agents that increase apoA-I protein or function include apoA-I mimetics, HDL mimetics and reconstituted HDL and RVX 208 a Bromodomain and Extra Terminal (BET) antagonist that raises the transcriptional regulation of apoA-I show promise in animal models and early phase clinical trials [69]. However, it main anti-atherosclerotic mechanism of action is to increase HDL function.

2.4. Three strikes and you're out

More than 40 years after Miller's seminal finding that HDL-C is associated with myocardial infarction [5], much time, toil and treasure has been spent on measuring it and treating it. The epidemiology of HDL-C and ASCVD has taught us that a low HDL-C keeps bad company. It is on these risk factors that we should concentrate and address cigarette smoking, physical inactivity, abdominal obesity, socio-economic status, the metabolic syndrome and diabetes, not HDL-C.

Being born with a low HDL-C does not predispose to an increased

risk of ASCVD (unless the genetic disorder is of a severe nature for apoA-I). Clinicians may have erred in putting healthy patients with low HDL-C on medications to prevent cardiovascular disease; conversely, the root cause of the low HDL-C may have been overlooked in patients with multiple cardiovascular risk factors.

The clinical trial shows the futility of raising HDL-C as a therapeutic target. Perhaps it is time to relinquish the historical prerogative and privilege that HDL-C has gained unchallenged. Other biomarkers of cardiovascular risk that show the same characteristics shown above, such as homocysteine, lipoprotein associated phospholipase A2 (LpPLA2), and, perhaps C-Reactive protein (CRP) have undergone rigorous epidemiological, genetic and clinical studies and, after careful consideration, are not part of most current ASCVD prevention guidelines.

2.5. Time to think outside the box and back to the drawing board. HDL function

There is agreement that modulation HDL functions for therapeutic purposes shows considerable promise. The future lies in the identification of novel biomarkers of HDL function that predict outcomes and that of new targets that act in the arterial subendothelium. Developing biomarkers of HDL biogenesis that is, the ability of apoA-I or lipid-poor HDL to remove cellular cholesterol that can be scaled up to a clinical test will be essential. Developing drugs that can harness HDL biogenesis will probably represent the path forward [70]. In this respect, the identification of novel HDL binding proteins, such as desmocollin 1 (DSC1) offers a potential novel therapeutic target [71]. But basing our clinical decision-making and targeting a HDL-C level should be a thing of the past.

3. Conclusion

In conclusion, both protagonist and antagonist agree that the “HDL Hypothesis” is not dead. We differ on the value of HDL-C for cardiovascular risk stratification.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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