



Statin therapy is not warranted for a person with high LDL-cholesterol on a low-carbohydrate diet

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Purpose of review

Although there is an extensive literature on the efficacy of the low carbohydrate diet (LCD) for weight loss and in the management of type 2 diabetes, concerns have been raised that the LCD may increase cardiovascular disease (CVD) risk by increasing the level of low-density lipoprotein cholesterol (LDL-C). We have assessed the value of LDL-C as a CVD risk factor, as well as effects of the LCD on other CVD risk factors. We have also reviewed findings that provide guidance as to whether statin therapy would be beneficial for individuals with high LDL-C on an LCD.

Recent findings

Multiple longitudinal trials have demonstrated the safety and effectiveness of the LCD, while also providing evidence of improvements in the most reliable CVD risk factors. Recent findings have also confirmed how ineffective LDL-C is in predicting CVD risk.

Summary

Extensive research has demonstrated the efficacy of the LCD to improve the most robust CVD risk factors, such as hyperglycemia, hypertension, and atherogenic dyslipidemia. Our review of the literature indicates that statin therapy for both primary and secondary prevention of CVD is not warranted for individuals on an LCD with elevated LDL-C who have achieved a low triglyceride/HDL ratio.

Keywords

atherogenic dyslipidemia, carbohydrate restriction, cardiovascular disease, insulin-resistant phenotype, ketogenic diet, metabolic syndrome, obesity

'.. there are things we know we know. We also know there are known unknowns; that is to say, we know there are some things we do not know.'

Donald Rumsfeld

INTRODUCTION

In 1973, Dr Robert Atkins was called to testify before the US Senate Select Committee on Nutrition and Human Needs [1]. The committee was charged with investigating, amongst others, the eponymously named high fat 'Atkins' diet, which was considered '*nutritionally unsound and potentially dangerous*'. Nutrition experts called upon were unanimous in their testimony that this diet was potentially harmful. Dr Fred Stare, for example, Chairman of Harvard's Department of Nutrition stated '*... any diet which tends to be high in saturated fat and cholesterol tends to elevate the chance that the individual will get heart disease.*' (pg 17). This viewpoint on the potential hazards of the Atkins diet was expressed that year in an editorial in JAMA which stated, '*Perhaps the greatest danger (of the Atkins diet) is related to*

hyperlipidemia, which may be induced by such a regimen' ... which '*could be responsible for accelerating atherosclerosis*' [2]. These concerns with an Atkins, that is, low carbohydrate diet (LCD) expressed 50 years ago have persisted, as evidenced by the recent proclamation by the National Lipid Association Nutrition and Lifestyle Task Force, that long-

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Curr Opin Endocrinol Diabetes Obes 2022, 29:497–511

DOI:10.1097/MED.0000000000000764

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KEY POINTS

- Critics of the LCD have focused on its effects on LDL-C, while largely disregarding the beneficial effects of the LCD on more robust CVD risk factors.
- There is an extensive literature on measures which are superior to LDL-C as reliable markers of CVD risk, such as hypertension, insulin resistance, LDL particle subtypes, and components of the metabolic syndrome.
- Randomized controlled trial (RCTs) have demonstrated that individuals with high LDL-C and LCD-like nonatherogenic lipid markers (low TGs, high HDL-C), have a low rate of coronary events under nontreatment conditions. Most notably, subjects with high LDL-C and nonatherogenic lipid markers derived no benefit from statin treatment.
- A balanced review of the literature indicates that statin therapy is not warranted for people on a low-carbohydrate diet with elevated LDL-C and with a nonatherogenic lipid profile (low TGs, high HDL-C).

term consumption of the LCD increases the risk of all-cause and cardiovascular mortality [3].

Concerns with the safety of the LCD are based, in part, on the diet-heart hypothesis, which postulates that unrestricted consumption of saturated fat (from animal fat and tropical oils) on an LCD may raise serum cholesterol levels, thereby increasing one's risk of developing cardiovascular disease (CVD) [4–6]. This hypothesis, however, has failed to receive empirical support, with decades of scholarly critiques of its flaws [7–17,18²²,19–21]. We concur with DuBroff and de Lorgeril [7] that the diet-heart hypothesis survives only because its proponents *'selectively cite evidence that validates their own viewpoint while disregarding evidence to the contrary'*.

An extension of the diet-heart hypothesis is the view that an elevated level of low-density lipoprotein cholesterol (LDL-C), under any circumstance, *'is unequivocally recognized as the principal driving force in the development of (atherosclerotic cardiovascular disease)'* [22] and that *'the key initiating event in atherogenesis is the retention of low-density lipoprotein (LDL) cholesterol (LDL-C) . . . within the arterial wall'* [23]. This perspective on LDL-C as inherently atherogenic has been the driving force in recent concerns that an LCD-induced increase in LDL-C increases one's risk for developing CVD [24²⁵,25–28,29³⁰,30].

Regarding an increase in LDL-C on an LCD in relation to the risk of a coronary event, we shall paraphrase the quote from Donald Rumsfeld by stating there are known knowns and known unknowns about LCD, LDL-C, and CVD. It is known that the LCD improves many CVD-relevant

biomarkers, but it is not known with certainty if an increase in LDL-C on an LCD is proatherogenic, neutral or beneficial. The basis of our lack of knowledge on this issue is the absence of any published long-term clinical trials which have characterized hard coronary events, for example, myocardial infarction, stroke or coronary death, in people who develop high LDL-C on an LCD. Therefore, despite the concerns expressed repeatedly over the past 5 decades, there is no conclusive research to indicate whether an increase in LDL-C for someone on an LCD has any effect, beneficial or harmful, on CVD outcomes.

We have approached the issue of LDL-C concerns on an LCD with the following strategy. First, we have evaluated the dogmatic view held by various heart disease organizations that high LDL-C is inherently atherogenic [22,23,31]. Second, we have reviewed research on measures which are superior to LDL-C, such as insulin resistance (IR) and LDL particle subtypes, as markers of CVD risk. Third, we have reviewed findings that demonstrate the LCD improves all biomarkers which are strongly associated with CVD. Lastly, while there is active debate about the merits of statin therapy in primary prevention of CVD [32–34], statin therapy in secondary prevention trials and in high risk populations, such as those with type 2 diabetes, have reported a small coronary event and mortality absolute risk benefit [35–37,38³⁹]. We have addressed whether this modest benefit of statin treatment can be attributed to the lowering of LDL-C, per se, or through other mechanisms. More importantly, we have evaluated whether the benefit of statin treatment reported in clinical trials can be extended to people on an LCD with elevated LDL-C.

ASSESSMENT OF LOW-DENSITY LIPOPROTEIN CHOLESTEROL AS A CAUSAL FACTOR IN CARDIOVASCULAR DISEASE

In 1985, Brown and Goldstein received the Nobel Prize for their research on LDL-C in people with familial hypercholesterolemia (FH). They discovered that this genetic condition involves impaired binding of LDL to its membrane receptor, which results in dramatically elevated serum levels of LDL-C. Because people with FH exhibited premature CVD, Brown and Goldstein declared there was a *'causal relation between an elevated level of circulating LDL and atherosclerosis'* [39], thereby providing support for the lipid hypothesis, in which LDL-C is described as inherently atherogenic. Since then, this pejorative view of LDL-C as the 'bad cholesterol' has been promoted by high profile heart disease organizations, such as the

American Heart Association [40], as well as the European Atherosclerosis Society, which states 'LDL is unequivocally recognized as the principal driving force in the development of ASCVD' (atherosclerotic cardiovascular disease) [22].

Studies on the FH population, however, provide an extensive literature highlighting inconsistencies with the lipid hypothesis. For example, if LDL-C is inherently atherogenic, the burden of atherosclerosis should increase with the time of exposure to LDL-C. That is, cardiovascular mortality would be predicted to increase with age as a direct consequence of the time of exposure to LDL-C. To the contrary, CVD mortality in FH individuals declines with age [41]. Elderly individuals with FH exhibit an equivalent risk of CVD mortality to those in the non-FH population, despite a lifetime of exposure to high LDL-C. This finding directly conflicts with the dual component hypothesis that LDL-C is inherently atherogenic, and that CVD risk increases with the duration of LDL-C exposure [42]. That elderly FH individuals exposed to decades of high LDL-C demonstrate no increase in CVD mortality, as well as no increase in morbidity, for example, ischemic stroke [43], compared to the general population, undermines the lipid hypothesis, that is, that high LDL-C is inherently atherogenic.

Further challenging to the lipid hypothesis is that FH individuals have a lifetime all-cause mortality rate which is equivalent to, or even lower, than that of the general population [41,44–47]. We submit three explanations for the longevity of people with FH. First, the small subset of individuals with FH that die prematurely of CVD appear to be genetically susceptible to develop coagulopathy, independent of their LDL-C levels [48,49–51]. In one example, Jansen *et al.*, [51] reported that whereas LDL-C did not differ between CVD and non-CVD FH patients, those with a polymorphism for the prothrombin (coagulation factor II) gene exhibited over twice the incidence of CVD than those without the polymorphism. Second, LDL-C is an important component of the immune system [52–54]. Chronically elevated LDL-C levels may enhance aspects of immune functioning, thereby lowering rates of mortality from cancer and infection [41,46,47]. In related work, elevated LDL-C may protect against bacterial infection, which can promote the development of atherosclerosis [53,55–60]. Third, FH individuals, either through lifestyle choices or favorable genetics, have a relatively low rate of type 2 diabetes [61–65], which itself is a significant risk factor for CVD. These three observations help to explain why FH individuals do not face an increased risk of CVD mortality with advanced age, as well as the greater longevity of people in the general population with high LDL-C, compared to those with low LDL-C [66].

Despite several influential heart disease organizations holding the position that LDL-C is a cause of CVD, it has long been recognized that LDL-C is a poor marker of risk for CVD [67–69,70,71], as well as cardiovascular and all-cause mortality [66]. For example, calcification within the coronary arteries, in contrast to LDL-C, is a reliable measure of CVD risk. Coronary artery calcium (CAC) scoring has proven to be the single best predictor of fatal and nonfatal coronary events [72–75], including CVD risk in diabetic and nondiabetic patients [76–78], as well as in young, mid-age and elderly patients [79]. CAC scoring also excels at long-term risk prediction over periods of more than a decade [76,78,80]. Moreover, among those with genetically confirmed FH, approximately half showed no detectable CAC and had a favorable prognosis, despite significantly elevated LDL-C levels [81].

The superiority of CAC to LDL-C in relation to plaque development, as well as coronary events, in high-risk patients was demonstrated recently by Mortensen *et al.* [82]. These investigators identified CAC levels as being superior to, and independent of, LDL-C, as a biomarker of coronary event rate. In related work, Miname *et al.* [81] reported that coronary events in statin-treated patients were associated with increased CAC scores, and were unrelated to on-treatment LDL-C. Moreover, these investigators found that the ascending gradient of CAC scores was associated with increases in fasting glucose and not in on-treatment LDL-C values.

In one representative example of the value of CAC scoring, Sandesara *et al.* [83] reported that over one third of individuals with very high LDL-C (>190 mg/dl) had a zero CAC score. Hence, the zero CAC score had more predictive utility than LDL-C because these individuals had a very low risk for future coronary events. These findings, as well as related research, were discussed by Bittencourt *et al.* [84], who concluded 'treatment of individuals with very high LDL-C (>190 mg/dl) irrespective of their clinical risk... might not be the most prudent approach...'. These investigators further noted that low CAC scores, and therefore the low CVD risk, in 'individuals with very high LDL-C should make us question at least part of our understanding of the atherosclerotic process.'

In addition to CAC scoring, serological markers have demonstrated clear superiority to LDL-C levels in assessing CVD risk. For example, Yu *et al.* [85] reported that markers of the insulin-resistant phenotype, specifically elevated fasting plasma glucose, hemoglobin A1c and triglycerides (TG), were all positively correlated with the severity of coronary stenosis; LDL-C levels, in contrast, showed no correlation with coronary stenosis. In another example, FH individuals that carry an A, B or AB blood group

(which is associated with increased coagulation [86]), have a twofold increased risk of CVD, compared to those with blood type O [87].

Often overlooked in the discussion about LDL-C as a cardiovascular risk factor is the heterogeneity of different LDL particles. That is, the 'total LDL-C' reported in a conventional lipid panel represents the sum of a heterogeneous population of different low-density lipoprotein particles [71]. One unique population of LDL particles is known as lipoprotein (a) (Lp(a)). Lp(a) is a modified LDL particle in which an apolipoprotein (a) molecule is covalently attached to the ApoB100 moiety of an LDL particle. The link of Lp(a) to CVD may be driven by its pro-inflammatory effects [88]. Lipid peroxidation colocalizes with Lp(a) to contribute to the pathogenesis of CVD by promoting endothelial dysfunction, lipid deposition, inflammation, and arterial calcification [89]. This research has provided strong support for the view that an elevated plasma concentration of Lp(a) is an independent risk factor for the development of CVD in FH and non-FH individuals [90–94]. It is notable that Willeit *et al.* [95[■]] recently reported that correcting for the Lp(a) component in the total LDL-C measure eliminated isolated LDL-C as a CVD risk factor. This refined assessment of LDL-C, which takes into account the Lp(a) subfraction, provides a mechanistic basis for why LDL-C is a poor marker of CVD risk.

In summary, the pejorative view of LDL-C as the '*bad cholesterol*', which is inherently atherogenic, is not supported by a balanced review of the literature. Numerous investigators who have assessed the clinical literature have concluded that the lipid hypothesis persists today only because of the biases of its proponents [49,67,68,96,97]. Characteristic of this sentiment is the opinion that '*evidence falsifying the hypothesis that LDL drives atherosclerosis has been largely ignored*' [98], and the perspective of three cardiologists that '*LDL cholesterol risk has been exaggerated - Decades of emphasis on the primacy of lowering plasma cholesterol, as if this was an end in itself, ... has been misguided.*' [21]. Finally, the negative impact of the emphasis on LDL-C reduction in developing therapeutics has also been recognized, leading DuBroff [96] to conclude that the '*LDL-C-centric approach to cardiovascular disease prevention may have distracted us from investigating other pathophysiologic mechanisms and treatments.*'

INSULIN RESISTANCE, LIPIDS, AND CARDIOVASCULAR DISEASE

There is an extensive literature demonstrating that biomarkers other than LDL-C provide more reliable assessments of CVD risk. Furthermore, mechanisms

have been clearly described for these biomarkers, affording biological plausibility. Of these other risk factors, IR, which is related to hyperinsulinemia and hyperglycemia, is perhaps the most important. Over 3 decades ago, Gerald Reaven summarized the research on IR by stating that the physiological '*attempt to compensate for IR sets in motion a series of events that play an important role in the development of both hypertension and coronary artery disease*', and that '*variations in insulin-stimulated glucose uptake determine to an enormous degree the likelihood that an individual will develop premature atherosclerotic vascular disease*' [99]. Kraft's [100], conviction that those with CVD not known to have diabetes were '*simply undiagnosed*' revealed his insight into the core mechanisms of CVD. Contemporary research has confirmed that IR is a strong and independent predictor of CVD, with compelling evidence that IR is a major causal influence on the pathophysiology of CVD [101–105]. This is driven in no small part by the causal role of IR in the development of type 2 diabetes, itself being the greatest risk for CVD [106].

There are myriad mechanisms whereby IR contributes to the pathogenesis of atherosclerosis. IR-related measures that are well established independent risk factors for CVD include hypertension [107], glycocalyx disruption secondary to hyperglycemia [108], prothrombosis [109], advanced glycation end product associated endothelial dysfunction [110] and impaired nitric oxide synthesis [111]. These IR-related mechanisms contribute to adverse effects on blood vessel structure and function [102,103,112].

Through multiple distinct mechanisms, IR is often the primary driver for hypertension [113,114], including stimulation of sodium retaining channels within the nephron [115], as well as activation of the sympathetic nervous system [116–118]. The chronic hyperinsulinemia that occurs concurrently in IR promotes chronically elevated epinephrine, which elicits cardiovascular activation, including increased cardiac output and systemic vasoconstriction [119,120], as well as an enhancement of platelet aggregation [121].

IR-associated hyperinsulinemia is also associated with CVD risk through increased macrophage lipid accrual in blood vessels. As macrophages accrue lipids, they become 'foam cells'. Foam cells are a staple feature of atherosclerotic plaques, not only constituting a major portion of the plaque itself, but also contributing to atherosclerosis by aggressively secreting pro-inflammatory cytokines [122]. Park *et al.* [123] demonstrated that insulin increased macrophage oxidized LDL uptake by more than 80% and produced almost three times greater total lipid uptake into the macrophage in as little as 16 h.

IR, and more specifically, type 2 diabetes and obesity, are associated with serum lipid components which are well established risk factors for CVD. Specifically, LDL-C is contained in heterogeneous particles which range in size and composition from a small dense LDL (sdLDL) to a large buoyant LDL (lbLDL) (which is distinct from the inclusion of Lp (a) in the total LDL-C measure, as discussed previously). Circulating sdLDL, unlike lbLDL, readily undergoes atherogenic modifications in plasma, including glycation, which is associated with heightened inflammation, hyperglycemia, and an increased incidence of CVD in the general population [127–130], and in FH individuals [131,132].

The distinction between LDL particle subclasses based on size and density is also important because sdLDL is a component of the atherogenic dyslipidemia risk triad, composed of elevated levels of TGs and sdLDL, in concert with low HDL-C [124–126]. High TGs, elevated sdLDL and low HDL-C are each, individually, strong markers of CVD risk [71,89,133–142]. Conversely, lbLDL has not been shown to be a CVD risk factor, as demonstrated in the Atherosclerosis Risk in Communities Study [143], the Quebec Cardiovascular Study [144], the Multiethnic Study of Atherosclerosis [145] and the Framingham Offspring Study [146]. Ultimately, the assessment of sdLDL and lbLDL subpopulations provides a greater prediction of CVD risk than does LDL-C [142].

The superiority of the atherogenic dyslipidemia risk triad over total LDL-C as a reliable means of assessing CVD risk has been known for more than 3 decades [147]. In 1988, Austin *et al.* [148] reported that individuals with the atherogenic dyslipidemia risk triad, referred to as pattern B, exhibited a '*three-fold increased risk of myocardial infarction, independent of age, sex, and relative weight.*'. Even then, it was understood that total cholesterol and LDL-C were of limited value as markers of CVD risk (Fig. 1). Comparable findings were demonstrated in the Framingham Offspring Study [149], in which low HDL-C levels and elevated TGs were correlated with reduced lbLDL, increased sdLDL, and an increased incidence of coronary artery disease. Similarly, Jepsen *et al.* [150] reported a significantly greater incidence of ischemic heart disease in men with the combination of high TGs/low HDL, compared to men with low TGs/high HDL, independent of whether the men had low or high LDL-C. Related work has shown that an elevated TG to HDL-C ratio is predictive of both a pattern B LDL-C profile, dominated by sdLDL, and an overall increase in cardiovascular risk [151]. Similar findings were reported by Caselli *et al.* [152], who reported that high TG and low HDL-C levels were associated with

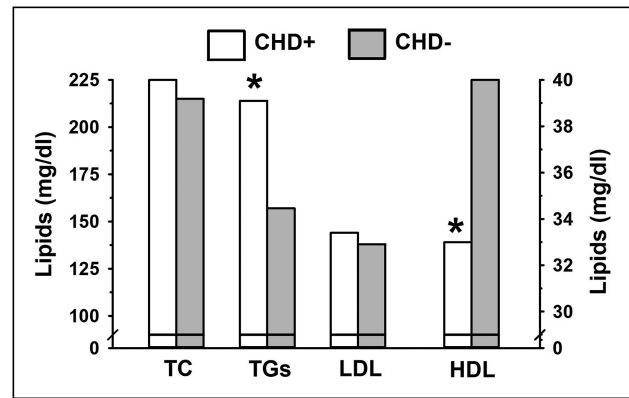


FIGURE 1. Data from Austin *et al.* [148] which illustrate the association of high triglycerides (TGs) and low HDL with coronary heart disease (CHD+). Total cholesterol (TC) and LDL levels were unrelated to CHD status. * = $P < 0.05$ in lipid levels between those with (CHD+) compared to those without (CHD-) coronary heart disease. HDL, high-density lipoprotein; LDL, low-density lipoprotein.

CVD progression, which was independent of LDL-C levels and lipid lowering treatments. In summary, the atherogenic dyslipidemia risk triad is far superior to total LDL-C as a measure of CVD risk.

In recent years, investigators have focused on LDL particle number (ApoB), rather than LDL-C, as a superior measure of CVD risk [69,153,154]. This measure, however, has significant limitations. First, it is not limited to the LDL population, with LDL particles also found on Lp(a), an independent CVD risk factor, as well as VLDL-C and IDL-C, both of which are associated with TG, another CVD risk factor [142,155]. Second, the preferential use of particle number, rather than LDL-C, does not distinguish between particle types (sdLDL, lbLDL, Lp (a)), which have been shown to be differentially associated with CVD (as described above).

The appearance of a discordance between LDL-C and total particle number, where the particle count is higher than expected, has been suggested to serve as a superior measure of CVD risk than is LDL-C [69,156]. However, the discordance correlates closely with measures of IR, for example, metabolic syndrome and diabetes [156]. In three representative trials, Otvos *et al.* [157], Pencina *et al.* [158] and Cromwell *et al.* [69] reported that the discordance between LDL-C and LDL particle number was superior to LDL-C, alone, as a CVD risk factor. However, patients presenting with the ApoB discordance had higher BMI, fasting glucose, and TGs, an increased incidence of diabetes and hypertension, as well as lower HDL-C, than those that were concordant. Hence, the discordance between particle number and LDL-C is merely a surrogate marker for

atherogenic dyslipidemia (dominance of elevated TGs, low HDL, and smaller LDL particles) and IR (see also [159] for related review and discussion).

EFFECTS OF LOW CARBOHYDRATE DIETS ON CARDIOVASCULAR DISEASE RISK FACTORS

Atherogenic dyslipidemia is prevalent in individuals with metabolic syndrome, prediabetes, and type 2 diabetes, which is currently afflicting millions of people in the US [160]. Chronic exposure to high levels of glucose and insulin are driving factors in the development of CVD [161,162]. Modest dietary changes can be more effective in the treatment of metabolic syndrome than commonly used antidiabetic drugs in improving CVD risk [163]. Specifically, improvement in the cluster of components of metabolic syndrome is intimately connected with carbohydrate restriction in adults [164–167,168[■],169[■],170[■],171,172[■],173–177,178[■],179–180,181[■]] and in adolescents [182]. LCDs have been shown to improve other CVD risk factors, as well, such as visceral fat, blood pressure, Lp(a) and inflammation [183–189]. It is therefore highly relevant that LCDs have been studied in numerous RCTs and case reports which show improvement in glucose, lipid and insulin-based CVD risk factors, including an LCD-mediated reduction in the need for hypoglycemic medication [178[■],190,191[■],192,193[■],194[■],195,196[■],197,198[■],199[■]].

LCDs are also effective at attenuating the atherogenic dyslipidemia risk triad (reducing TGs, sdLDL, increasing lbLDL) [159,169[■],172[■],200[■],201]. In a randomized, parallel trial comparing the effects of an LCD to a low-fat diet (LFD) in obese adults, the LCD resulted in greater weight loss, increased HDL-C, decreased TGs and C-reactive protein than the LFD [202]. A meta-analysis concluded that compared to LFDs, LCDs significantly lowered predicted risk of atherosclerotic cardiovascular disease [203], including reductions in plasma TGs and increased HDL-C [204,205[■]], which collectively carry a robust predictive value that dramatically outperforms LDL-C [206].

While many studies of LCDs have been relatively short-term (<6 months), there are longer-term trials and individual case reports that demonstrate the effectiveness, and sustainability of these diets [166,168[■],169[■],207–209]. For example, after 1 year, a group of participants with type 2 diabetes following a ketogenic diet demonstrated robust improvements in several cardiovascular risk markers, including decreased TGs, sdLDL particles, blood pressure, and antihypertensive medications [210,211]. These findings have been replicated and

extended to 2–3 year-long LCD trials, documenting improvements in numerous CVD risk biomarkers [212–214], including a 2 year LCD intervention which demonstrated improvements in LDL particle size and carotid intima media thickness, a commonly used marker of atherosclerosis [200[■]]. The longest assessment of LCD effects on record is by Heussinger *et al.* [215], who documented the safety and effectiveness of the ketogenic diet over a 10-year period in the treatment of patients with epilepsy, without evidence of an increase in CVD risk biomarkers.

It is notable that Unwin's group has incorporated LCD guidance in their treatment of patients with type 2 diabetes and prediabetes for over 6 years, including the de-prescribing of diabetes-related medications [168[■],213,216[■],217[■]]. These clinicians have reported the safety and efficacy of the LCD, with statistically significant improvements in their patients for weight, HbA1c, lipid profiles and blood pressure.

Although weight loss typically occurs in response to an LCD, improvements in atherogenic dyslipidemia are primarily a result of carbohydrate restriction, rather than weight or fat loss, per se [172[■],199[■],218,219]. The consistent and often dramatic improvement in these biomarkers in response to LCDs is strong support for the view that carbohydrate restriction, independent of weight loss, lowers CVD risk.

The basis of the diet-heart hypothesis is the great concern that consumption of food rich in saturated fat would increase risk for CVD. However, in an RCT by Volek *et al.* [189], subjects in the LCD group exhibited superior improvements in CVD risk factors than the LFD group, despite the LCD group having consumed more than three times as much saturated fat as the LFD group. Moreover, Volek *et al.* [204], Dreon *et al.* [220], Sharman *et al.* [201], and Hays *et al.* [221] all demonstrated that an LCD rich in saturated fat increased LDL size, leading to a dominance of lbLDL, thereby lowering CVD risk. Similar findings were reported by Ebbeling *et al.* [222], who found that a high saturated fat, LCD improved measures of insulin-resistant dyslipidemia, without affecting LDL-C, when compared to lower saturated fat diets.

In related work, Cole *et al.* [223] studied the effects of a moderately low carbohydrate (30%), high fat (55%) diet, supplemented with up to 1800 mg/day of cholesterol (from eggs), on serum lipids in FH subjects. These investigators reported that consumption of additional fat and cholesterol, in the context of an LCD, lowered TGs, and raised HDL, while not affecting LDL-C levels. Comparable findings were reported in the DIETFITS weight loss

RCT [224]. These investigators reported that LDL-C in subjects on an LCD was stable across a broad range in dietary cholesterol changes from baseline (>500 mg/day) that the participants consumed over 12 months.

These studies, as well as those reviewed by Astrup *et al.* [18²²], reinforce the perspective of the cardiologist, Bahl [225], that ‘*an overreliance in public health on saturated fat as the main dietary villain for cardiovascular disease has distracted from the risks posed by other nutrients, such as carbohydrates.*’

In summary, the LCD, independent of the amount of saturated fat in the diet and weight loss, leads to significant improvements in the most robust lipid risk markers for CVD, characterized by reductions in TGs and sdLDL, with associated increases in lLDL and HDL-C. LCDs also reduce body weight, inflammatory markers, blood pressure, and blood glucose, and increase insulin sensitivity. These findings are summarized in Fig. 2 and in our recent reviews [48²²⁶].

WOULD LOW-DENSITY LIPOPROTEIN CHOLESTEROL REDUCTION BENEFIT AN INDIVIDUAL ON A LOW CARBOHYDRATE DIET?

Given that elevated LDL-C may occur for individuals on an LCD, concerns have been raised that the diet may therefore increase CVD risk. These concerns have been expressed despite a paucity of evidence that total LDL-C is a reliable CVD risk factor. In contrast, there is extensive evidence regarding the efficacy of carbohydrate reduction to improve the most reliable CVD risk biomarkers, such as hyperglycemia, IR, inflammation, hypertension, body weight, and the atherogenic dyslipidemia risk triad. The LCD is also effective at ameliorating components of metabolic syndrome, itself a significant CVD risk factor. While the improvements in these biomarkers support the argument in favor of the CVD benefit of LCDs, it remains that they are surrogate markers only. That is, as surrogate markers they do not provide conclusive evidence that an LCD, with an associated increase in LDL-C, will result in a beneficial effect on hard coronary events, such myocardial infarction or coronary death.

The relative degree of uncertainty as to the outcomes of an LCD-induced elevation of LDL-C raises the question as to whether HMG CoA reductase inhibitor therapy (statins) is indicated for those on an LCD. This question takes on more significance in the context of increasing popularity of different LCDs, including assisting in the management of obesity and diabetes, both representing significant cardiovascular risk factors themselves. Despite the

Low Carbohydrate Diet Outcomes	
Benefits	Concerns
↓ Weight/BMI	↑ LDL-C
↓ Inflammation	
↓ sdLDL	
↓ Triglycerides	
↓ Lp(a)	
↓ Blood Pressure	
↓ Blood Glucose	
↓ Insulin	
↓ HbA1c	
↓ PAI-1	
↑ HDL	
↑ lLDL	

FIGURE 2. Summary of effects of LCD on CVD risk biomarkers (from [226²²] with permission). CVD, cardiovascular disease; LCD, low carbohydrate diet.

popularity of LCDs, we are aware of no published clinical trials involving subjects with high LDL-C on an LCD, or of trials on subjects on an LCD with statin treatment, with an assessment of hard coronary outcomes. Therefore, it cannot be stated with certainty whether a patient should be concerned about high LDL-C on an LCD, and whether a patient with high LDL-C on an LCD would benefit from statin treatment.

With the caveat of this uncertainty explicitly stated, findings from two RCTs provide guidance as to whether people with a typical LCD biomarker profile (high HDL/low TGs) with high LDL-C, are at increased risk of experiencing a coronary event, and whether they may benefit from statin therapy.

The first RCT was based on a reanalysis of the 4S trial [35], which was a secondary CVD prevention trial in men and women with a history of angina pectoris or acute myocardial infarction. The reanalysis of the 4S trial assessed hard coronary events in placebo or statin treated subjects, all of whom had elevated LDL-C, with either an atherogenic lipid profile (high TGs/low HDL) or a nonatherogenic lipid profile (low TGs/high HDL) [227]. The first finding of importance is that within the placebo group, individuals with an LCD-like (nonatherogenic) lipid profile had a lower

incidence of coronary events than placebo-treated individuals with an atherogenic lipid profile (Fig. 3). This finding indicates that the presence of an atherogenic lipid profile, independent of LDL-C, provided a reliable indication of the risk of coronary events in untreated individuals.

The second finding of the 4S reanalysis was that statin treatment produced a significant reduction of coronary events only in those subjects with the atherogenic lipid profile. By contrast, statin treatment produced no significant benefit in those subjects with an LCD-like (nonatherogenic) lipid profile (Fig. 3). That is, despite statin treatment reducing LDL-C to an equivalent level in those with an atherogenic and nonatherogenic lipid profile, only the group with a baseline atherogenic profile demonstrated a treatment-associated reduction in hard coronary events. This finding supports the view that individuals on an LCD with high LDL-C and a nonatherogenic lipid profile (low TGs/high HDL-C) would not benefit from statin therapy.

A second RCT provides findings complementary to the 4S posthoc analysis. The prospective study of Pravastatin in the elderly at risk (PROSPER) study [228] enrolled elderly men (aged 70–82 years) with preexisting vascular disease or who were at increased risk of CVD because they had hypertension,

diabetes, and/or were smokers. The men were administered pravastatin or placebo, and then assessed for fatal and nonfatal coronary events over 3 years. What is noteworthy is the apparent influence of HDL-C levels on coronary events in the placebo and statin-treated groups. Subjects on the placebo with low HDL-C (<43 mg/dl), consistent with IR, and an atherogenic lipid profile, developed a significantly greater incidence of coronary events than placebo subjects with high HDL-C (>53 mg/dl), independent of their LDL-C levels. This first observation demonstrates that the HDL-C level is a superior indicator of CVD risk than is LDL-C in untreated individuals.

The second observation from the PROSPER study is that benefits of statin treatment occurred only for those subjects with low HDL, independent of their LDL-C levels (Fig. 4). As the authors noted ‘Variation in baseline LDL concentrations did not relate to risk of a coronary event or treatment efficacy. Benefit was predominantly in the lowest tertile of HDL-cholesterol ...’. With low HDL-C being a feature of atherogenic dyslipidemia, this finding is consistent with the 4S reanalysis, and provides additional support for the notion that those with high LDL-C and a nonatherogenic lipid profile (low TGs/high HDL-C) are unlikely to benefit from statin therapy.

The absence of a relation between LDL-C and coronary event reduction with statin treatment suggests that it is their pleiotropic, for example, anti-inflammatory and anticoagulant, effects [229–238], rather than LDL-C reduction, per se, that results in a relatively small reduction in coronary events and mortality. Therefore, a person on an LCD with a nonatherogenic lipid profile (low TGs/high HDL-C) is more likely to experience the adverse effects of statins [239–252], including an increased risk of new onset type 2 diabetes [246,253–258], an increase in fasting blood glucose in patients with and without diabetes [259], mitochondrial dysfunction [260–262], tendinopathy [263], myopathy [264,265], acute kidney injury/renal failure [266–268] and cognitive deficits [247,269–276], than benefits.

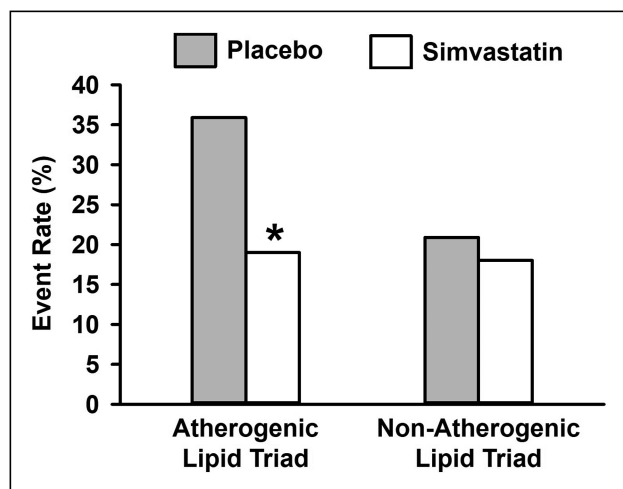


FIGURE 3. Posthoc analysis of data from the 4S study [35,227] in which patients were treated with Simvastatin (open) or placebo (grey). The analysis distinguished patients with the atherogenic lipid triad (high LDL, high TGs, low HDL) versus patients with the nonatherogenic lipid triad (high LDL, low TGs, high HDL). Coronary event rate was higher in placebo-treated groups with the atherogenic lipid triad compared to the placebo group with the nonatherogenic lipid triad. Simvastatin treatment reduced coronary event rate only in the atherogenic lipid triad. * = $P < 0.05$. HDL, high-density lipoprotein; LDL, low-density lipoprotein, TG, triglycerides.

SUMMARY AND CONCLUSION

We have addressed concerns regarding high LDL-C in individuals on an LCD, which began 5 decades ago and persist to the present day. Our review has evaluated whether these concerns are justified based on three levels of analysis. First, critics of the LCD have focused on how the diet may increase LDL-C. However, there is a substantial literature demonstrating that LDL-C is of limited utility as a CVD risk factor. Second, we reviewed the literature on LCD improvements in CVD risk factors which are

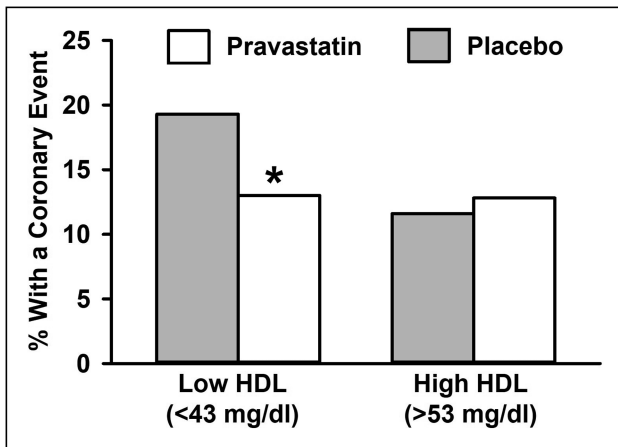


FIGURE 4. Data from the PROSPER study [228]. Patients were treated with Pravastatin (open) or placebo (grey). There was a significant reduction of coronary events only in the patients with low HDL (<43 mg/dl) but not in patients with high HDL (>53 mg/dl). HDL, high-density lipoprotein.

superior to LDL-C, such as IR, hypertension, hyperglycemia, LDL particle subtypes, and metabolic syndrome. Third, we summarized RCTs which demonstrate that individuals with high LDL-C and an LCD-like lipid profile (low TGs and high HDL-C), had a low rate of coronary events under nontreatment conditions and derived no CVD benefit from statin therapy. Therefore, our review of the literature provides support for the conclusion that LDL-C reduction with a statin would not provide any benefit in primary or secondary prevention of CVD for an individual on an LCD.

Acknowledgements

None.

Financial support and sponsorship

The open access publication cost was provided by the Duke University Research Fund.

Conflicts of interest

There are no conflicts of interest.

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- 179.** Das S, McCreary J, Shamim S, Kalayjian T. Reversal of severe hypertriglyceridemia with intermittent fasting and a very-low-carbohydrate ketogenic diet: a case series. *Curr Opin Endocrinol Diabetes Obes* 2020; 27:308–311.
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- 182.** Stoica RA, Diaconu CC, Rizzo M, *et al.* Weight loss programmes using low carbohydrate diets to control the cardiovascular risk in adolescents (Review). *Exp Ther Med* 2021; 21:90.
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- 186.** Faghihnia N, Tsimikas S, Miller ER, *et al.* Changes in lipoprotein(a), oxidized phospholipids, and LDL subclasses with a low-fat high-carbohydrate diet. *J Lipid Res* 2010; 51:3324–3330.
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- 191.** Ahmed SR, Bellamkonda S, Zilbermint M, *et al.* Effects of the low carbohydrate, high fat diet on glycemic control and body weight in patients with type 2 diabetes: experience from a community-based cohort. *BMJ Open Diabetes Res Care* 2020; 8:.

In a community-based cohort of type 2 diabetes, the LCD was associated with superior A1C reduction, greater weight loss and significantly more patients discontinuing or reducing antihyperglycemic therapies, compared to usual care, suggesting that the LCD may be a metabolically favorable option in the dietary management of type 2 diabetes.

- 192.** Westman EC, Tondt J, Maguire E, Yancy WS. Implementing a low-carbohydrate, ketogenic diet to manage type 2 diabetes mellitus. *Expert Rev Endocrinol Metab* 2018; 13:263–272.
- 193.** Westman EC, Yancy WS Jr. Using a low-carbohydrate diet to treat obesity and type 2 diabetes mellitus. *Curr Opin Endocrinol Diabetes Obes* 2020; 27:255–260.

This is a review of research on how low-carbohydrate diets have been utilized clinically for many years to treat obesity and T2DM and can be used alongside effective monitoring to safely prescribe dispensable medications for these diseases.

- 194.** Moriconi E, Camajani E, Fabbri A, *et al.* Very-low-calorie ketogenic diet as a safe and valuable tool for long-term glycemic management in patients with obesity and type 2 diabetes. *Nutrients* 2021; 13:.

This is a clinical study designed to assess LCD versus low calorie diet effects in patients with type 2 diabetes and obesity. The LCD was superior to low calorie diet in all metabolic measures. Moreover, 26.6% of LCD patients had stopped all antidiabetic medications, and 73.3% were taking only metformin, whereas 46.6% of the low calorie diet patients had to increase antidiabetic medications.

- 195.** Yancy WS Jr, Mitchell NS, Westman EC. Ketogenic diet for obesity and diabetes. *JAMA Intern Med* 2019; 179:1734–1735.
- 196.** Cucuzzella M, Riley K, Isaacs D. Adapting medication for type 2 diabetes to a low carbohydrate diet. *Front Nutr* 2021; 8:688540.

This is an important paper designed to close the gap between the clinical evidence, basic science, and pharmacology of T2D medications to the practical application and teamwork needed to facilitate safe medication reduction in the primary care setting when applied to an LCD.

- 197.** Murdoch C, Unwin D, Cavan D, *et al.* Adapting diabetes medication for low carbohydrate management of type 2 diabetes: a practical guide. *Br J Gen Pract* 2019; 69:360–361.

- 198.** Bouillet B, Rouland A, Petit JM, Verges B. A low-carbohydrate high-fat diet initiated promptly after diagnosis provides clinical remission in three patients with type 1 diabetes. *Diabetes Metab* 2020; 46:511–513.

This is a novel approach toward the use of the LCD in the treatment of patients with type 1 diabetes (T1D). This case study of three T1D patients experienced clinical remission after commencing an LCD soon after their diagnosis. The frequency of hypoglycaemia was low, and the patients experienced clinical remission, defined as the withdrawal of insulin therapy for at least 3 months. The study demonstrates that the use of LCD may preserve b-cell function in patients with residual insulin secretion at diagnosis.

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This is an important case report demonstrating a substantial reduction in A1C without clinically significant weight loss in patients that utilized LCD with intermittent fasting. These results demonstrate that metabolic improvements can occur on an LCD in the absence of weight loss.

- 200.** Athinayanan SJ, Hallberg SJ, McKenzie AL, *et al.* Impact of a 2-year trial of nutritional ketosis on indices of cardiovascular disease risk in patients with type 2 diabetes. *Cardiovasc Diabetol* 2020; 19:208.

This 2 year trial compared lipid outcomes in patients with usual care versus LCD. Consumption of an LCD in patients with type 2 diabetes lowered levels of small LDL particles that are commonly increased in diabetic dyslipidemia and are a marker for heightened CVD risk. A corresponding increase in concentrations of larger (nonatherogenic) LDL particles was responsible for higher levels of plasma LDL-C.

- 201.** Sharman MJ, Kraemer WJ, Love DM, *et al.* A ketogenic diet favorably affects serum biomarkers for cardiovascular disease in normal-weight men. *J Nutr* 2002; 132:1879–1885.

- 202.** Bazzano LA, Hu T, Reynolds K, *et al.* Effects of low-carbohydrate and low-fat diets: a randomized trial. *Ann Intern Med* 2014; 161:309–318.

- 203.** Sackner-Bernstein J, Kanter D, Kaul S. Dietary intervention for overweight and obese adults: comparison of low-carbohydrate and low-fat diets. A meta-analysis. *PLoS ONE* 2015; 10:.

- 204.** Volek JS, Sharman MJ, Forsythe CE. Modification of lipoproteins by very low-carbohydrate diets. *J Nutr* 2005; 135:1339–1342.

- 205.** Tzenios N, Lewis ED, Crowley DC, *et al.* Examining the efficacy of a very-low-carbohydrate ketogenic diet on cardiovascular health in adults with mildly elevated low-density lipoprotein cholesterol in an open-label pilot study. *Metab Syndr Relat Disord* 2022; 20:94–103.

This open-label study demonstrated that 140 days of an LCD significantly reduced body fat, weight, BMI, SBP, HbA1c and increased muscle mass and HDL-C in healthy participants with mildly elevated LDL-C levels. The authors suggest that the increase in LDL-C reflects a preponderance of nonatherogenic phenotype A in all subjects.

- 206.** Wakabayashi I, Daimon T. Comparison of discrimination for cardio-metabolic risk by different cut-off values of the ratio of triglycerides to HDL cholesterol. *Lipids Health Dis* 2019; 18:156.

- 207.** Dashti HM, Mathew TC. Prevention of obesity using low carbohydrate ketogenic diet. *Kuwait Med J* 2009; 41:3–12.

- 208.** Brown A, McArdle P, Taplin J, *et al.* Dietary strategies for remission of type 2 diabetes: a narrative review. *J Hum Nutr Diet* 2022; 35:165–178.

- 209.** Gardner CD, Kiazand A, Alhassan S, *et al.* Comparison of the Atkins, Zone, Ornish, and LEARN diets for change in weight and related risk factors among overweight premenopausal women. *JAMA* 2007; 297:969–977.

- 210.** Bhanpuri NH, Hallberg SJ, Williams PT, *et al.* Cardiovascular disease risk factor responses to a type 2 diabetes care model including nutritional ketosis induced by sustained carbohydrate restriction at 1 year: an open label, nonrandomized, controlled study. *Cardiovasc Diabetol* 2018; 17:.

- 211.** Hallberg SJ, McKenzie AL, Williams PT, *et al.* Effectiveness and safety of a novel care model for the management of type 2 diabetes at 1 year: an open-label, non-randomized, controlled study. *Diabetes Ther* 2018; 9:583–612.

- 212.** Athinayanan SJ, Adams RN, Hallberg SJ, *et al.* Long-term effects of a novel continuous remote care intervention including nutritional ketosis for the management of type 2 diabetes: a 2-year nonrandomized clinical trial. *Front Endocrinol (Lausanne)* 2019; 10:348.

- 213.** Unwin DJ, Tobin SD, Murray SW, *et al.* Substantial and sustained improvements in blood pressure, weight and lipid profiles from a carbohydrate restricted diet: an observational study of insulin resistant patients in primary care. *Int J Environ Res Public Health* 2019; 16:.

- 214.** Phelan S, Wyatt H, Nassery S, *et al.* Three-year weight change in successful weight losers who lost weight on a low-carbohydrate diet. *Obesity (Silver Spring)* 2007; 15:2470–2477.

- 215.** Heussinger N, Della Marina A, Beyerlein A, *et al.* 10 patients, 10 years - Long term follow-up of cardiovascular risk factors in Glut1 deficiency treated with ketogenic diet therapies: a prospective, multicenter case series. *Clin Nutr* 2018; 37:2246–2251.

- 216.** Unwin D, Khalid AA, Unwin J, *et al.* Insights from a general practice service evaluation supporting a lower carbohydrate diet in patients with type 2 diabetes mellitus and prediabetes: a secondary analysis of routine clinic data including HbA1c, weight and prescribing over 6 years. *BMJ Nutr Prev Health* 2020; 3:285–294.

This is a real world approach by clinicians who are treating obese and diabetic patients with LCD in routine primary care over 6 years. They report statistically significant improvements in patients for weight, HbA1c, lipid profiles and blood pressure, as well as significant drug budget savings.

- 217.** Unwin D, Unwin J, Crocombe D, *et al.* Renal function in patients following a low carbohydrate diet for type 2 diabetes: a review of the literature and analysis of routine clinical data from a primary care service over 7 years. *Curr Opin Endocrinol Diabetes Obes* 2021; 28:469–479.

There is concern that higher protein intake on LCD may promote renal damage. These clinicians reviewed research on LCD, renal and cardiovascular risk factors in relation to their observations in a real-world, primary care setting. They reported that the LCD improved renal and cardiovascular risk factors.

- 218.** Hyde PN, Sapper TN, Crabtree CD, *et al.* Dietary carbohydrate restriction improves metabolic syndrome independent of weight loss. *JCI Insight* 2019; 4:.

- 219.** Paoli A, Rubini A, Volek JS, Grimaldi KA. Beyond weight loss: a review of the therapeutic uses of very-low-carbohydrate (ketogenic) diets. *Eur J Clin Nutr* 2013; 67:789–796.

- 220.** Dreon DM, Fernstrom HA, Campos H, *et al.* Change in dietary saturated fat intake is correlated with change in mass of large low-density-lipoprotein particles in men. *Am J Clin Nutr* 1998; 67:828–836.

- 221.** Hays JH, DiSabatino A, Gorman RT, *et al.* Effect of a high saturated fat and no-starch diet on serum lipid subfractions in patients with documented atherosclerotic cardiovascular disease. *Mayo Clin Proc* 2003; 78:1331–1336.

- 222.** Ebbeling CB, Knapp A, Johnson A, *et al.* Effects of a low-carbohydrate diet on insulin-resistant dyslipoproteinemia: a randomized controlled feeding trial. *Am J Clin Nutr* 2022; 115:154–162.

- 223.** Cole TG, Pfleger B, Hitchins O, Schonfeld G. Effects of high cholesterol high fat diet on plasma lipoproteins in familial hypercholesterolemia. *Metabolism* 1985; 34:486–493.

- 224.** Vergara M, Hauser ME, Aronica L, *et al.* Associations of changes in blood lipid concentrations with changes in dietary cholesterol intake in the context of a healthy low-carbohydrate weight loss diet: a secondary analysis of the DIETITS trial. *Nutrients* 2021; 13:.

- 225.** Bahl R. The evidence base for fat guidelines: a balanced diet. *Open Heart* 2015; 2:e000229.

- 226.** Diamond DM, O'Neill BJ, Volek JS. Low carbohydrate diet: are concerns with saturated fat, lipids, and cardiovascular disease risk justified? *Curr Opin Endocrinol Diabetes Obes* 2020; 27:291–300.

This review integrates a historical perspective on the LCD with a critical assessment of the concerns that consumption of saturated fat, in the context of an LCD, will increase risk for CVD.

- 227.** Ballantyne CM, Olsson AG, Cook TJ, *et al.* Influence of low high-density lipoprotein cholesterol and elevated triglyceride on coronary heart disease events and response to simvastatin therapy in 4S. *Circulation* 2001; 104:3046–3051.

- 228.** Shepherd J, Blauw GJ, Murphy MB, *et al.* Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002; 360:1623–1630.

- 229.** Ravnskov U. Implications of 4S evidence on baseline lipid levels. *Lancet* 1995; 346:181.

- 230.** Adams NB, Lutsey PL, Folsom AR, *et al.* Statin therapy and levels of hemostatic factors in a healthy population: the Multi-Ethnic Study of Atherosclerosis. *J Thromb Haemost* 2013; 11:1078–1084.

- 231.** Park HS, Gu JY, Yoo HJ, *et al.* Thrombin generation assay detects moderate-intensity statin-induced reduction of hypercoagulability in diabetes. *Clin Appl Thromb Hemost* 2018; 24:1095–1101.

- 232.** Bordbar M, de Mutsert R, Ceval M, *et al.* Differential effect of statin use on coagulation markers: an active comparative analysis in the NEO study. *Thromb J* 2021; 19:.

- 233.** Satny M, Hubacek JA, Vrablik M. Statins and inflammation. *Curr Atheroscler Rep* 2021; 23:.

- 234.** Owens AP 3rd, Mackman N. The antithrombotic effects of statins. *Annu Rev Med* 2014; 65:433–445.

- 235.** Krysiak R, Okopien B, Herman Z. Effects of HMG-CoA reductase inhibitors on coagulation and fibrinolysis processes. *Drugs* 2003; 63:1821–1854.

- 236.** Biedermann JS, Kruij M, van der Meer FJ, *et al.* Rosuvastatin use improves measures of coagulation in patients with venous thrombosis. *Eur Heart J* 2018; 39:1740–1747.

- 237.** Sadowitz B, Maier KG, Gahtan V. Basic science review: statin therapy—Part I: the pleiotropic effects of statins in cardiovascular disease. *Vasc Endovascular Surg* 2010; 44:241–251.

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