REVIEW

OPEN

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

David M. Diamond[a], *Benjamin T. Bikman*[b] *and Paul Mason*[c]

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-

[a]Department of Psychology, University of South Florida, Tampa, Florida, [b]Department of Cell Biology and Physiology, Brigham Young University, Provo, Utah, USA and [c]Concord Orthosports, Concord, New South Wales, Australia

Correspondence to David M. Diamond, PhD, Dept. of Psychology (PCD 4118G), 4202 E., Fowler Ave., University of South Florida, Tampa, FL, USA. Tel: +1 813 974 0480; fax: +1 813 974 4617;
e-mail: ddiamond@usf.edu

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

DOI:10.1097/MED.0000000000000764

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 [7–17,18▪▪,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 [24▪,25–28,29▪,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 [35–37,38▪]. 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 '*threefold 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, Jeppesen *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

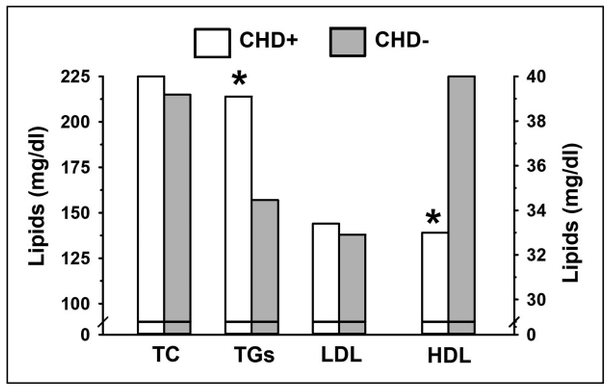

FIGURE 1. Data from Austin *et al.* [148] which illustrate the association of high triglycerides (TGs) and low HDL with coronary heart disease (CHD+). Total cholesterol (TC) and LDL levels were unrelated to CHD status. * = $P < 0.05$ in lipid levels between those with (CHD+) compared to those without (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.* [18▪▪], 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 lbLDL 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 [48▪,226▪].

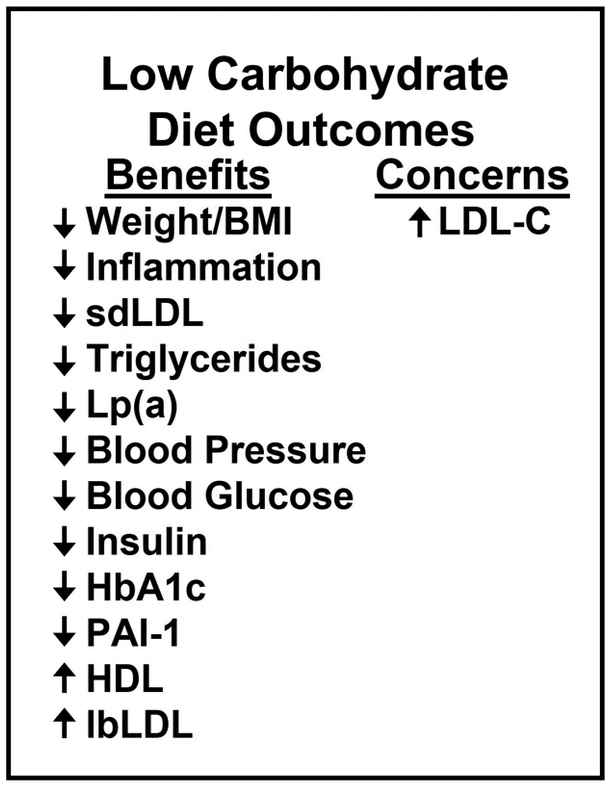

FIGURE 2. Summary of effects of LCD on CVD risk biomarkers (from [226▪] with permission). CVD, cardiovascular disease; LCD, low carbohydrate diet.

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 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.

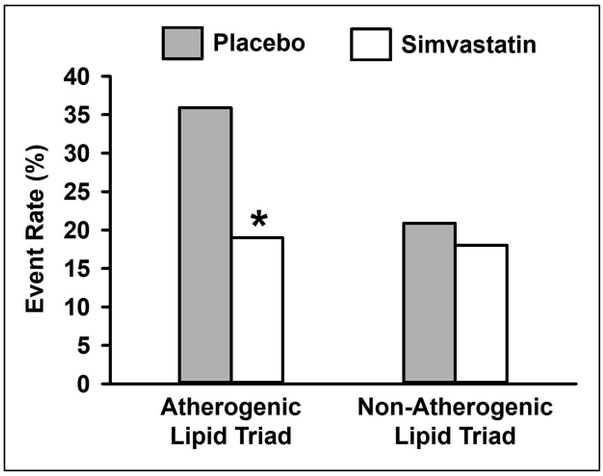

FIGURE 3. Posthoc analysis of data from the 4S study [35,227] in which patients were treated with Simvastatin (open) or placebo (grey). The analysis distinguished patients with the atherogenic lipid triad (high LDL, high TGs, low HDL) versus patients with the nonatherogenic lipid triad (high LDL, low 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.

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.

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

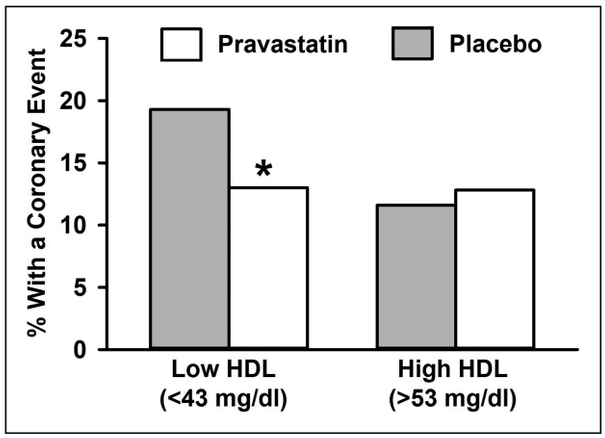

FIGURE 4. Data from the PROSPER study [228]. Patients were treated with Pravastatin (open) or placebo (grey). There was a significant reduction of coronary events only in the patients with low HDL (<43 mg/dl) but not in patients with high HDL (>53 mg/dl). HDL, high-density lipoprotein.

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.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Part 1 - Obesity and Fad Diets. In: *Select Committee on Nutrition and Human Needs of the United States Senate* Washington, D.C.: United States; 1973. p. 110. https://books.google.com/books?id=VoB1yAEACAAJ&printsec=frontcover&source=gbs_ge_summary_r&hl=en#v=onepage&q&f=false
2. A critique of low-carbohydrate ketogenic weight reduction regimens. A review of Dr Atkins' diet revolution. JAMA 1973; 224:1415–1419.
3. Kirkpatrick CF, Bolick JP, Kris-Etherton PM, *et al.* Review of current evidence and clinical recommendations on the effects of low-carbohydrate and very-low-carbohydrate (including ketogenic) diets for the management of body weight and other cardiometabolic risk factors: a scientific statement from the National Lipid Association Nutrition and Lifestyle Task Force. J Clin Lipidol 2019; 13:689–711.
4. Lichtenstein AH, Appel LJ, Vadiveloo M, *et al.* 2021 dietary guidance to improve cardiovascular health: a scientific statement from the American heart association. Circulation 2021; 144:e472–e487.
5. Keys A, Menotti A, Karvonen MJ, *et al.* The diet and 15-year death rate in the seven countries study. Am J Epidemiol 1986; 124:903–915.
6. D'Souza MS, Dong TA, Ragazzo G, *et al.* From fad to fact: evaluating the impact of emerging diets on the prevention of cardiovascular disease. Am J Med 2020; 133:1126–1134.
7. DuBroff R, de Lorgeril M. Fat or fiction: the diet-heart hypothesis. BMJ Evid Based Med 2019; 26:3–7.
8. Yudkin J. Etiology of cardiac infarction. Arch Intern Med 1959; 104:681–683.
9. Reiser R. Saturated fat in diet and serum-cholesterol concentration - critical examination of literature. Am J Clin Nutr 1973; 26:524–555.
10. Mann GV. Diet-heart: end of an era. N Engl J Med 1977; 297:644–650.
11. Malhotra A. Saturated fat is not the major issue. BMJ 2013; 347:f6855.
12. Noakes TD, Windt J. Evidence that supports the prescription of low-carbohydrate high-fat diets: a narrative review. Br J Sports Med 2017; 51:133–139.
13. Noakes TD. The women's health initiative randomized controlled dietary modification trial: An inconvenient finding and the diet-heart hypothesis. SAMJ 2013; 103:824–825.
14. Noakes TD. The 2012 University of Cape Town Faculty of Health Sciences centenary debate 'Cholesterol is not an important risk factor for heart disease, and the current dietary recommendations do more harm than good'. South Afr J Clin Nutr 2015; 28:19–33.
15. Ravnskov U. A hypothesis out-of-date. the diet-heart idea. J Clin Epidemiol 2002; 55:1057–1063.
16. Heileson JL. Dietary saturated fat and heart disease: a narrative review. Nutr Rev 2020; 78:474–485.
17. Harcombe Z. US dietary guidelines: is saturated fat a nutrient of concern? Br J Sports Med 2019; 53:1393–1396.
18. ■■ Astrup A, Magkos F, Bier DM, *et al.* Saturated fats and health: a reassessment and proposal for food-based recommendations JACC state-of-the-art review. J Am Coll Cardiol 2020; 76:844–857.

This is a comprehensive review of the literature on saturated fats (SFAs), LDL and CVD. The authors conclude there are no beneficial effects of reducing SFA intake on CVD and total mortality. The evidence does not support limiting the intake of food rich in SFAs. They also note that any increase in LDL-C from SFA consumption, per se, is due to an increase in larger (benign) LDL particles.

19. Harcombe Z, Baker JS, Cooper SM, *et al.* Evidence from randomised controlled trials did not support the introduction of dietary fat guidelines in 1977 and 1983: a systematic review and meta-analysis. Open Heart 2015; 2:e000196.
20. DiNicolantonio JJ. The cardiometabolic consequences of replacing saturated fats with carbohydrates or Omega-6 polyunsaturated fats: do the dietary guidelines have it wrong? Open Heart 2014; 1:e000032.
21. Malhotra A, Redberg RF, Meier P. Saturated fat does not clog the arteries: coronary heart disease is a chronic inflammatory condition, the risk of which can be effectively reduced from healthy lifestyle interventions. Br J Sports Med 2017; 51:1111–1112.
22. Boren J, Chapman MJ, Krauss RM, *et al.* Low-density lipoproteins cause atherosclerotic cardiovascular disease: pathophysiological, genetic, and therapeutic insights: a consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J 2020; 41:2313–2330.
23. Mach F, Baigent C, Catapano AL, *et al.* 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). Eur Heart J 2020; 41:111–188.
24. ■ O'Neill B, Raggi P. The ketogenic diet: pros and cons. Atherosclerosis 2020; 292:119–126.

This is a constructive debate between two cardiologists on the benefits of a ketogenic diet versus concerns regarding CVD risk.

25. Mindrum MR. Let's be clear about expected cardiovascular risk: a commentary on the massive rise in LDL cholesterol induced by carbohydrate restriction in the proposed 'lean mass hyper-responder' phenotype. Curr Dev Nutr 2022; 6:.
26. Buren J, Ericsson M, Damasceno NRT, Sjodin A. A ketogenic low-carbohydrate high-fat diet increases LDL cholesterol in healthy, young, normal-weight women: a randomized controlled feeding trial. Nutrients 2021; 13:.
27. Mansoor N, Vinknes KJ, Veierod MB, Retterstol K. Effects of low-carbohydrate diets v. low-fat diets on body weight and cardiovascular risk factors: a meta-analysis of randomised controlled trials. Br J Nutr 2016; 115:466–479.
28. Moore JM, Diefenbach D, Nadendla M, Hiebert N. Evidence for a lean mass hyperresponder phenotype is lacking with increases in LDL cholesterol of clinical significance in all categories of response to a carbohydrate-restricted diet. Curr Dev Nutr 2022; 6:nzac043.

29. Norwitz NG, Feldman D, Soto-Mota A, *et al.* Elevated LDL cholesterol with a ■ carbohydrate-restricted diet: evidence for a 'lean mass hyper-responder' phenotype. Curr Dev Nutr 2022; 6:nzab144.

This is a report based on survey data collected from individuals consuming an LCD. A subset of individuals developed extremely high LDL-C, with low TG and high HDL, which the authors referred to as 'lean mass hyper-responders.'

30. Gardner CD, Landry MJ, Perelman D, *et al.* Effect of a ketogenic diet versus mediterranean diet on HbA1c in individuals with prediabetes and Type 2 diabetes mellitus: the interventional keto-med randomized crossover trial. Am J Clin Nutr 2022; nqac154.
31. Reiter-Brennan C, Osei AD, Iftekhar Uddin SM, *et al.* ACC/AHA lipid guidelines: personalized care to prevent cardiovascular disease. Cleve Clin J Med 2020; 87:231–239.
32. Abramson J, Kaplan RM, Redberg RF. Questioning the benefit of statins for low-risk populations-medical misinformation or scientific evidence? JAMA Cardiol 2020; 5:233.
33. Redberg RF, Katz MH. Statins for primary prevention: the debate is intense, but the data are weak. JAMA 2016; 316:1979–1981.
34. Byrne P, Cullinan J, Smith A, Smith SM. Statins for the primary prevention of cardiovascular disease: an overview of systematic reviews. BMJ Open 2019; 9:.
35. Pedersen TR, Kjekshus J, Berg K, *et al.* Randomized trial of cholesterol-lowering in 4444 patients with coronary-heart-disease - the scandinavian simvastatin survival study (4s). Lancet 1994; 344:1383–1389.
36. Lee JD, Morrissey JR, Mikhailidis DP, Patel V. CARDS on the table: should everybody with type 2 diabetes take a statin? Curr Med Res Opin 2005; 21:357–362.
37. Colhoun HM, Betteridge DJ, Durrington PN, *et al.* Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 2004; 364:685–696.
38. Byrne P, Demasi M, Jones M, *et al.* Evaluating the association between low- ■ density lipoprotein cholesterol reduction and relative and absolute effects of statin treatment: a systematic review and meta-analysis. JAMA Intern Med 2022; 182:474–481.

This is a systematic review and meta-analysis of RCTs that assessed the absolute (AR) versus relative risk (RR) benefits of statin therapy for all-cause mortality, myocardial infarction, and stroke. The overall absolute risk benefit of statin therapy was ~1% with treatment compared to placebo.

39. Brown MS, Goldstein JL. How Ldl receptors influence cholesterol and atherosclerosis. Sci Am 1984; 251:58–66.
40. HDL (Good), LDL (Bad) Cholesterol and Triglycerides; Written by American Heart Association editorial staff and reviewed by science and medicine advisers. https://www.heart.org/en/health-topics/cholesterol/hdl-good-ldl-bad-cholesterol-and-triglycerides. Accessed July 25, 2022
41. Mundal L, Sarancic M, Ose L, *et al.* Mortality among patients with familial hypercholesterolemia: a registry-based study in Norway, 1992–2010. J Am Heart Assoc 2014; 3:e001236.
42. Robinson JG, Williams KJ, Gidding S, *et al.* Eradicating the burden of atherosclerotic cardiovascular disease by lowering apolipoprotein B lipoproteins earlier in life. J Am Heart Assoc 2018; 7:e009778.
43. Hovland A, Mundal LJ, Igland J, *et al.* Risk of ischemic stroke and total cerebrovascular disease in familial hypercholesterolemia: a register study from Norway. Stroke 2019; 50:172–174.
44. Harlan WR, Graham JB, Estes EH. Familial hypercholesterolemia - a genetic and metabolic study. Medicine 1966; 45:77–110.
45. Williams RR, Hasstedt SJ, Wilson DE, *et al.* Evidence that men with familial hypercholesterolemia can avoid early coronary death - an analysis of 77 gene carriers in 4 Utah Pedigrees. JAMA 1986; 255:219–224.
46. Sijbrands EJ, Westendorp RG, Defesche JC, *et al.* Mortality over two centuries in large pedigree with familial hypercholesterolaemia: family tree mortality study. BMJ 2001; 322:1019–1023.
47. Neil A, Cooper J, Betteridge J, *et al.* Reductions in all-cause, cancer, and coronary mortality in statin-treated patients with heterozygous familial hypercholesterolaemia: a prospective registry study. Eur Heart J 2008; 29:2625–2633.
48. Diamond DM, Alabdulgader AA, de Lorgeril M, *et al.* Dietary recommenda- ■ tions for familial hypercholesterolaemia: an evidence-free zone. BMJ Evid Based Med 2021; 26:295–301.

This is a review/commentary that challenged the prevailing view that people with FH should be on a low cholesterol/low fat diet. The review also addressed IR and susceptibility to coagulopathy as primary causal factors for CVD in FH people. The authors suggested that patients with FH and atherogenic dyslipidemia should consider an LCD.

49. Ravnskov U, de Lorgeril M, Kendrick M, Diamond DM. Inborn coagulation factors are more important cardiovascular risk factors than high LDL-cholesterol in familial hypercholesterolemia. Med Hypoth 2018; 121:60–63.
50. Huijgen R, Kastelein JJ, Meijers JC. Increased coagulation factor VIII activity in patients with familial hypercholesterolemia. Blood 2011; 118:6990–6991.
51. Jansen ACM, van Aalst-Cohen ES, Tanck MWT, *et al.* Genetic determinants of cardiovascular disease risk in familial hypercholesterolemia. Arterioscler Thromb Vasc Biol 2005; 25:1475–1481.
52. Cavaillon JM, Fitting C, Haeffnercavaillon N, *et al.* Cytokine response by monocytes and macrophages to free and lipoprotein-bound lipopolysaccharide. Infect Immun 1990; 58:2375–2382.
53. Ravnskov U. High cholesterol may protect against infections and atherosclerosis. QJM 2003; 96:927–934.
54. Superti F, Seganti L, Marchetti M, *et al.* Sa-11 rotavirus binding to human serum-lipoproteins. Med Microbiol Immunol 1992; 181:77–86.
55. Karbasi-Afshar R, Khedmat H, Izadi M. Helicobacter pylori Infection and atherosclerosis: a systematic review. Acta Med Iran 2015; 53:78–88.
56. Khoshbayan A, Taheri F, Moghadam MT, *et al.* The association of Chlamydia pneumoniae infection with atherosclerosis: review and update of in vitro and animal studies. Microb Pathog 2021; 154:104803.
57. Ravnskov U, McCully KS. Infections may be causal in the pathogenesis of atherosclerosis. Am J Med Sci 2012; 344:391–394.
58. Shi H, Li Y, Dong C, *et al.* Helicobacter pylori infection and the progression of atherosclerosis: a systematic review and meta-analysis. Helicobacter 2022; 27:e12865.
59. Wang X, He Q, Jin D, *et al.* Association between helicobacter pylori infection and subclinical atherosclerosis: a systematic review and meta-analysis. Medicine (Baltimore) 2021; 100:e27840.
60. Khan S, Rahman HN, Okamoto T, *et al.* Promotion of atherosclerosis by Helicobacter cinaedi infection that involves macrophage-driven proinflammatory responses. Sci Rep 2014; 4:4680.
61. Besseling J, Kastelein JJP, Defesche JC, *et al.* Association between familial hypercholesterolemia and prevalence of type 2 diabetes mellitus. JAMA 2015; 313:1029–1036.
62. Parhofer KG. Lower diabetes rate in patients with familial hypercholesterolaemia: what is the link? Eur J Prev Cardiol 2020; 27:1647–1648.
63. Perez-Calahorra S, Civeira F, Guallar-Castillon P, *et al.* Behavioural cardiovascular risk factors and prevalence of diabetes in subjects with familial hypercholesterolaemia. Eur J Prev Cardiol 2020; 27:1649–1660.
64. Skoumas I, Ioakeimidis N, Vlachopoulos C, *et al.* Statin therapy and risk of diabetes mellitus in aging patients with heterozygous familial hypercholesterolemia or familial combined hyperlipidemia: a 10-year follow-up. Angiology 2018; 69:242–248.
65. Parhofer KG. Interaction between glucose and lipid metabolism: more than diabetic dyslipidemia. Diabetes Metab J 2015; 39:353–362.
66. Ravnskov U, Diamond DM, Hama R, *et al.* Lack of an association or an inverse association between low-density-lipoprotein cholesterol and mortality in the elderly: a systematic review. BMJ Open 2016; 6:.
67. Ravnskov U, de Lorgeril M, Diamond DM, *et al.* LDL-C does not cause cardiovascular disease: a comprehensive review of the current literature. Expert Rev Clin Pharmacol 2018; 11:959–970.
68. Okuyama H, Hamazaki T, Hama R, *et al.* A critical review of the consensus statement from the european atherosclerosis society consensus panel 2017. Pharmacology 2018; 101:184–218.
69. Cromwell WC, Otvos JD, Keyes MJ, *et al.* LDL particle number and risk of future cardiovascular disease in the Framingham Offspring Study-Implications for LDL management. J Clin Lipidol 2007; 1:583–592.
70. Noakes TD. Hiding unhealthy heart outcomes in a low-fat diet trial: the ■■ Women's Health Initiative Randomized Controlled Dietary Modification Trial finds that postmenopausal women with established coronary heart disease were at increased risk of an adverse outcome if they consumed a low-fat 'heart-healthy' diet. Open Heart 2021; 8:.

This landmark paper is an analysis of The Women's Health Initiative Randomized Controlled Dietary Modification Trial (WHIRCDMT). The author pointed out that the only significant finding in the WHIRCDMT study was that postmenopausal women with CHD randomised to a low-fat 'heart-healthy' diet were at greater risk of developing additional CHD events compared with women with CHD on the control diet. The increased risk of CHD was far greater in women with metabolic syndrome and IR, while LDL-C was a poor predictor of CHD risk.

71. Steffen BT, Guan WH, Remaley AT, *et al.* Apolipoprotein B is associated with carotid atherosclerosis progression independent of individual cholesterol measures in a 9-year prospective study of Multi-Ethnic Study of Atherosclerosis participants. J Clin Lipidol 2017; 11:1181–1191.
72. Polonsky TS, McClelland RL, Jorgensen NW, *et al.* Coronary artery calcium score and risk classification for coronary heart disease prediction. JAMA 2010; 303:1610–1616.
73. Mohlenkamp S, Lehmann N, Moebus S, *et al.* Quantification of coronary atherosclerosis and inflammation to predict coronary events and all-cause mortality. J Am Coll Cardiol 2011; 57:E886–E1886.
74. Yeboah J, Young R, McClelland RL, *et al.* Utility of nontraditional risk markers in atherosclerotic cardiovascular disease risk assessment. J Am Coll Cardiol 2016; 67:139–147.
75. Kavousi M, Elias-Smale S, Rutten JH, *et al.* Evaluation of newer risk markers for coronary heart disease risk classification: a cohort study. Ann Intern Med 2012; 156:438–444.
76. Shaikh K, Li D, Nakanishi R, *et al.* Low short-term and long-term cardiovascular and all-cause mortality in absence of coronary artery calcium: A 22-year follow-up observational study from large cohort. J Diab Compl 2019; 33:616–622.
77. Kramer CK, Zinman B, Gross JL, *et al.* Coronary artery calcium score prediction of all cause mortality and cardiovascular events in people with type 2 diabetes: systematic review and meta-analysis. BMJ 2013; 346:.

78. Blaha M, Budoff MJ, Shaw LJ, *et al.* Absence of coronary artery calcification and all-cause mortality. JACC Cardiovasc Imaging 2009; 2:692–700.

79. Nakanishi R, Li D, Blaha MJ, *et al.* All-cause mortality by age and gender based on coronary artery calcium scores. Eur Heart J Cardiovasc Imaging 2016; 17:1305–1314.

80. Valenti V, Hartaigh BO, Heo R, *et al.* A 15-year warranty period for asymptomatic individuals without coronary artery calcium a prospective follow-up of 9,715 individuals. JACC-Cardiovasc Imaging 2015; 8:900–909.

81. Miname MH, Bittencourt MS, Moraes SR, *et al.* Coronary artery calcium and cardiovascular events in patients with familial hypercholesterolemia receiving standard lipid-lowering therapy. JACC Cardiovasc Imaging 2019; 12:1797–1804.

82. ■■ Mortensen MB, Cainzos-Achirica M, Steffensen FH, *et al.* Association of coronary plaque with low-density lipoprotein cholesterol levels and rates of cardiovascular disease events among symptomatic adults. JAMA Netw Open 2022; 5:.

This study assessed CAC in symptomatic patients in relation to their LDL-C levels. The authors reported that in patients with severely elevated LDL-C levels of at least 190 mg/dL who were universally considered to be at high risk by guidelines, absence of calcified and noncalcified plaque on coronary computed tomographic angiography was associated with low risk for CVD events. Their findings suggest that CAC scoring is superior to LDL-C in assessing future CVD risk.

83. ■■ Sandesara PB, Mehta A, O'Neal WT, *et al.* Clinical significance of zero coronary artery calcium in individuals with LDL cholesterol >/=190 mg/dL: The Multi-Ethnic Study of Atherosclerosis. Atherosclerosis 2020; 292:224–229.

This study demonstrated that among people with LDL-C >190 mg/dL, younger age, female sex, and the absence of diabetes were associated with CAC=0. CAC=0 was associated with a low risk of cardiovascular events, even in individuals with very high LDL-C.

84. ■■ Bittencourt MS, Nasir K, Santos RD, Al-Mallah MH. Very high LDL cholesterol: the power of zero passes another test. Atherosclerosis 2020; 292:207–208.

This editorial addressed the findings that the prevalence and progression of CAC was dependent on well known risk factors, such as older age, male sex, presence of diabetes and smoking, but not on LDL-C levels. The author suggested that CAC may be a superior measure to determine CVD treatment strategies than is LDL-C reduction.

85. Yu Y, Zhou ZW, Su K, *et al.* Association between coronary artery atherosclerosis and plasma glucose levels assessed by dual-source computed tomography. J Thor Dis 2018; 10:6050–6059.

86. Jenkins PV, O'Donnell JS. ABO blood group determines plasma von Willebrand factor levels: a biologic function after all? Transfusion 2006; 46:1836–1844.

87. Paquette M, Dufour R, Baass A. ABO blood group is a cardiovascular risk factor in patients with familial hypercholesterolemia. J Clin Lipidol 2018; 12:383–389.

88. Reyes-Soffer G, Westerterp M. Beyond Lipoprotein(a) plasma measurements: Lipoprotein(a) and inflammation. Pharmacol Res 2021; 169:105689.

89. Libby P. The changing landscape of atherosclerosis. Nature 2021; 592:524–533.

90. Boffa MB, Koschinsky ML. Oxidized phospholipids as a unifying theory for lipoprotein(a) and cardiovascular disease. Nat Rev Cardiol 2019; 16:305–318.

91. Alonso R, Argueso R, Alvarez-Banos P, *et al.* Familial hypercholesterolemia and lipoprotein(a): two partners in crime? Curr Atheroscler Rep 2022; 24:427–434.

92. Vuorio A, Watts GF, Kovanen PT. Lipoprotein(a) as a risk factor for calcific aortic valvulopathy in heterozygous familial hypercholesterolemia. Atherosclerosis 2019; 281:25–30.

93. Jansen AC, van Aalst-Cohen ES, Tanck MW, *et al.* The contribution of classical risk factors to cardiovascular disease in familial hypercholesterolaemia: data in 2400 patients. J Intern Med 2004; 256:482–490.

94. Wilson DP, Jacobson TA, Jones PH, *et al.* Use of Lipoprotein(a) in clinical practice: a biomarker whose time has come. A scientific statement from the National Lipid Association. J Clin Lipidol 2019; 13:374–392.

95. ■■ Willeit P, Yeang C, Moriarty PM, *et al.* Low-density lipoprotein cholesterol corrected for lipoprotein(a) cholesterol, risk thresholds, and cardiovascular events. J Am Heart Assoc 2020; 9:.

These investigators noted that conventional 'LDL-C' assays measure cholesterol content in both LDL and Lp(a) particles. They reported that 'LDL-C' was associated with CVD only when the Lp(a) cholesterol content was included in its measurement. When correcting for Lp(a), LDL-C was not associated with CVD events.

96. DuBroff R. A reappraisal of the lipid hypothesis. Am J Med 2018; 131:993–997.

97. Ravnskov U. The fallacies of the lipid hypothesis. Scand Cardiovasc J 2008; 42:236–239.

98. Ware WR. The mainstream hypothesis that LDL cholesterol drives atherosclerosis may have been falsified by noninvasive imaging of coronary artery plaque burden and progression. Med Hypoth 2009; 73:596–600.

99. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 1988; 37:1595–1607.

100. Kraft J. Diabetes epidemic & you. Bloomington: Trafford Publishing; 2008.

101. Haffner SM, Stern MP, Hazuda HP, *et al.* Cardiovascular risk factors in confirmed prediabetic individuals. Does the clock for coronary heart disease start ticking before the onset of clinical diabetes? JAMA 1990; 263:2893–2898.

102. Lu MC, Fang WC, Li WC, *et al.* The Association between insulin resistance and cardiovascular disease risk: a community-based cross-sectional study among Taiwanese people aged over 50 years. Int J Environ Res Public Health 2020; 17:.

103. Hill MA, Yang Y, Zhang L, *et al.* Insulin resistance, cardiovascular stiffening and cardiovascular disease. Metabolism 2021; 119:154766.

104. Adeva-Andany MM, Fernandez-Fernandez C, Carneiro-Freire N, *et al.* Insulin resistance underlies the elevated cardiovascular risk associated with kidney disease and glomerular hyperfiltration. Rev Cardiovasc Med 2020; 21:41–56.

105. Pyorala M, Miettinen H, Laakso M, Pyorala K. Hyperinsulinemia predicts coronary heart disease risk in healthy middle-aged men: the 22-year follow-up results of the Helsinki Policemen Study. Circulation 1998; 98:398–404.

106. Wang Y, Wan EYF, Mak IL, *et al.* The association between trajectories of risk factors and risk of cardiovascular disease or mortality among patients with diabetes or hypertension: a systematic review. Plos One 2022; 17:.

107. Slivnick J, Lampert BC. Hypertension and heart failure. Heart Fail Clin 2019; 15:531–541.

108. Nieuwdorp M, van Haeften TW, Gouverneur MCLG, *et al.* Loss of endothelial glycocalyx during acute hyperglycemia coincides with endothelial dysfunction and coagulation activation in vivo. Diabetes 2006; 55:480–486.

109. Ghosh K. Diabetes as a prothrombotic state. In: Kartha CC, Ramachandran S., Pillai RM, editors. Mechanisms of vascular defects in diabetes mellitus. Springer International Publishing; 2017. pp. 361–376.

110. Tan KCB, Chow WS, Ai VHG, *et al.* Advanced glycation end products and endothelial dysfunction in type 2 diabetes. Diab Care 2002; 25:1055–1059.

111. Tessari P, Cecchet D, Cosma A, *et al.* Nitric oxide synthesis is reduced in subjects with type 2 diabetes and nephropathy. Diabetes 2010; 59:2152–2159.

112. Domingues N. Insulin resistance as a predictor of cardiovascular diseases. Revista Portuguesa De Cardiologia 2021; 40:545–546.

113. Reaven GM. Insulin resistance/compensatory hyperinsulinemia, essential hypertension, and cardiovascular disease. J Clin Endocrinol Metab 2003; 88:2399–2403.

114. Reaven G. Insulin resistance, hypertension, and coronary heart disease. J Clin Hypertens (Greenwich) 2003; 5:269–274.

115. Soleimani M. Insulin resistance and hypertension: new insights. Kidney Int 2015; 87:497–499.

116. Esler M, Rumantir M, Wiesner G, *et al.* Sympathetic nervous system and insulin resistance: from obesity to diabetes. Am J Hypertens 2001; 14:304S–309S.

117. Egan BM. Insulin resistance and the sympathetic nervous system. Curr Hypertens Rep 2003; 5:247–254.

118. Facchini FS, Stoohs RA, Reaven GM. Enhanced sympathetic nervous system activity. The linchpin between insulin resistance, hyperinsulinemia, and heart rate. Am J Hypertens 1996; 9:1013–1017.

119. Tack CJ, Lenders JW, Willemsen JJ, *et al.* Insulin stimulates epinephrine release under euglycemic conditions in humans. Metabolism 1998; 47:243–249.

120. Reaven GM, Lithell H, Landsberg L. Hypertension and associated metabolic abnormalities–the role of insulin resistance and the sympathoadrenal system. N Engl J Med 1996; 334:374–381.

121. Henning RJ. Obesity and obesity-induced inflammatory disease contribute to atherosclerosis: a review of the pathophysiology and treatment of obesity. Am J Cardiovasc Dis 2021; 11:504–529.

122. Yu XH, Fu YC, Zhang DW, *et al.* Foam cells in atherosclerosis. Clin Chim Acta 2013; 424:245–252.

123. Park YM, Kashyap SR, Major JA, Silverstein RL. Insulin promotes macrophage foam cell formation: potential implications in diabetes-related atherosclerosis. Lab Invest 2012; 92:1171–1180.

124. Musunuru K. Atherogenic dyslipidemia: cardiovascular risk and dietary intervention. Lipids 2010; 45:907–914.

125. Toth PP. Insulin resistance, small LDL particles, and risk for atherosclerotic disease. Current Vasc Pharmacol 2014; 12:653–657.

126. Siri-Tarino PW, Krauss RM. Diet, lipids, and cardiovascular disease. Curr Opin Lipidol 2016; 27:323–328.

127. Ivanova EA, Myasoedova VA, Melnichenko AA, *et al.* Small dense low-density lipoprotein as biomarker for atherosclerotic diseases. Oxid Med Cell Longev 2017; 2017:1273042.

128. Dev K, Sharma SB, Garg S, *et al.* Glycated apolipoprotein B-A surrogate marker of subclinical atherosclerosis. Diabetes Metab Synd 2016; 10:78–81.

129. Soran H, Durrington PN. Susceptibility of LDL and its subfractions to glycation. Curr Opin Lipidol 2011; 22:254–261.

130. Younis NN, Soran H, Pemberton P, *et al.* Small dense LDL is more susceptible to glycation than more buoyant LDL in Type 2 diabetes. Clin Sci 2013; 124:343–349.

131. Hopkins PN, Stephenson S, Wu LL, *et al.* Evaluation of coronary risk factors in patients with heterozygous familial hypercholesterolemia. Am J Cardiol 2001; 87:547–553.

132. Kolovou GD, Kostakou PM, Anagnostopoulou KK. Familial hypercholesterolemia and triglyceride metabolism. Int J Cardiol 2011; 147:349–358.
133. Sarwar N, Danesh J, Eiriksdottir G, *et al.* Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. Circulation 2007; 115:450–458.
134. Zhang B, Menzin J, Friedman M, *et al.* Predicted coronary risk for adults with coronary heart disease and low HDL-C: an analysis from the US National Health and Nutrition Examination Survey. Curr Med Res Opin 2008; 24:2711–2717.
135. Haffner SM, Mykkanen L, Robbins D, *et al.* A preponderance of small dense LDL is associated with specific insulin, proinsulin and the components of the insulin resistance syndrome in nondiabetic subjects. Diabetologia 1995; 38:1328–1336.
136. Austin MA, Mykkanen L, Kuusisto J, *et al.* Prospective study of small LDLs as a risk factor for noninsulin dependent diabetes mellitus in elderly men and women. Circulation 1995; 92:1770–1778.
137. Shi HL, Guo JW, Xu K, *et al.* Study on the value of small dense low-density lipoprotein in predicting cardiovascular and cerebrovascular events in the high-risk stroke population. J Clin Lab Anal 2022; 36:e24278.
138. Zhao CX, Cui YH, Fan QA, *et al.* Small dense low-density lipoproteins and associated risk factors in patients with stroke. Cerebrovasc Dis 2009; 27:99–104.
139. Zhou PY, Liu JC, Wang LY, *et al.* Association of small dense low-density lipoprotein cholesterol with stroke risk, severity and prognosis. J Atheroscler Thromb 2020; 27:1310–1324.
140. Gerber PA, Thalhammer C, Schmied C, *et al.* Small, dense LDL particles predict changes in intima media thickness and insulin resistance in men with type 2 diabetes and prediabetes–a prospective cohort study. PLoS One 2013; 8:e72763.
141. Bokemark L, Wikstrand J, Attvall S, *et al.* Insulin resistance and intima-media thickness in the carotid and femoral arteries of clinically healthy 58-year-old men. The Atherosclerosis and Insulin Resistance Study (AZR). J Internal Med 2001; 249:59–67.
142. Lee CK, Liao CW, Meng SW, *et al.* Lipids and lipoproteins in health and disease: focus on targeting atherosclerosis. Biomedicines 2021; 9:.
143. Hoogeveen RC, Gaubatz JW, Sun W, *et al.* Small dense low-density lipoprotein-cholesterol concentrations predict risk for coronary heart disease: the Atherosclerosis Risk In Communities (ARIC) study. Arterioscler Thromb Vasc Biol 2014; 34:1069–1077.
144. St-Pierre AC, Cantin B, Dagenais GR, *et al.* Low-density lipoprotein subfractions and the long-term risk of ischemic heart disease in men: 13-year follow-up data from the Quebec Cardiovascular Study. Arterioscler Thromb Vasc Biol 2005; 25:553–559.
145. Tsai MY, Steffen BT, Guan W, *et al.* New automated assay of small dense low-density lipoprotein cholesterol identifies risk of coronary heart disease: the Multiethnic Study of Atherosclerosis. Arterioscler Thromb Vasc Biol 2014; 34:196–201.
146. Ai M, Otokozawa S, Asztalos BF, *et al.* Small dense LDL cholesterol and coronary heart disease: results from the Framingham offspring study. Clin Chem 2010; 56:967–976.
147. Berneis KK, Krauss RM. Metabolic origins and clinical significance of LDL heterogeneity. J Lipid Res 2002; 43:1363–1379.
148. Austin MA, Breslow JL, Hennekens CH, *et al.* Low-density lipoprotein subclass patterns and risk of myocardial infarction. JAMA 1988; 260:1917–1921.
149. Campos H, Blijlevens E, McNamara JR, *et al.* LDL particle size distribution. Results from the Framingham offspring study. Arterioscler Thromb 1992; 12:1410–1419.
150. Jeppesen J, Hein HO, Suadicani P, Gyntelberg F. Low triglycerides-high high-density lipoprotein cholesterol and risk of ischemic heart disease. Arch Intern Med 2001; 161:361–366.
151. Quispe R, Martin SS, Jones SR. Triglycerides to high-density lipoprotein-cholesterol ratio, glycemic control and cardiovascular risk in obese patients with type 2 diabetes. Curr Opin Endocrinol Diabetes Obes 2016; 23:150–156.
152. Caselli C, De Caterina R, Smit JM, *et al.* Triglycerides and low HDL cholesterol predict coronary heart disease risk in patients with stable angina. Sci Rep 2021; 11:20714.
153. Sniderman AD. ApoB vs non-HDL-C vs LDL-C as markers of cardiovascular disease. Clin Chem 2021; 67:1440–1442.
154. Sniderman AD, Thanassoulis G, Glavinovic T, *et al.* Apolipoprotein B particles and cardiovascular disease: a narrative review. JAMA Cardiol 2019; 4:1287–1295.
155. Castillo-Nunez Y, Morales-Villegas E, Aguilar-Salinas CA. Triglyceride-rich lipoproteins: their role in atherosclerosis. Rev Invest Clin 2021; 74:061–070.
156. Lawler PR, Akinkuolie AO, Ridker PM, *et al.* Discordance between circulating atherogenic cholesterol mass and lipoprotein particle concentration in relation to future coronary events in women. Clin Chem 2017; 63:870–879.
157. Otvos JD, Mora S, Shalaurova I, *et al.* Clinical implications of discordance between low-density lipoprotein cholesterol and particle number. J Clin Lipidol 2011; 5:105–113.
158. Pencina MJ, D'Agostino RB, Zdrojewski T, *et al.* Apolipoprotein B improves risk assessment of future coronary heart disease in the Framingham Heart Study beyond LDL-C and non-HDL-C. Eur J Prev Cardiol 2015; 22:1321–1327.
159. Gjuladin-Hellon T, Davies IG, Penson P, Amiri Baghbadorani R. Effects of carbohydrate-restricted diets on low-density lipoprotein cholesterol levels in overweight and obese adults: a systematic review and meta-analysis. Nutr Rev 2019; 77:161–180.
160. Menke A, Casagrande S, Cowie CC. Contributions of A1c, fasting plasma glucose, and 2-h plasma glucose to prediabetes prevalence: NHANES 2011–2014. Ann Epidemiol 2018; 28:681-685.
161. Gast KB, Tjeerdema N, Stijnen T, *et al.* Insulin resistance and risk of incident cardiovascular events in adults without diabetes: meta-analysis. PLoS One 2012; 7:e52036.
162. Zhang X, Li J, Zheng S, *et al.* Fasting insulin, insulin resistance, and risk of cardiovascular or all-cause mortality in nondiabetic adults: a meta-analysis. Biosci Rep 2017; 37:.
163. Diabetes Prevention Program Research Group. Knowler WC, Fowler SE, *et al.* 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. Lancet 2009; 374: 1677–1686.
164. Volek JS, Feinman RD. Carbohydrate restriction improves the features of Metabolic Syndrome. Metabolic Syndrome may be defined by the response to carbohydrate restriction. Nutr Metab (Lond) 2005; 2:31.
165. Volek JS, Fernandez ML, Feinman RD, Phinney SD. Dietary carbohydrate restriction induces a unique metabolic state positively affecting atherogenic dyslipidemia, fatty acid partitioning, and metabolic syndrome. Prog Lipid Res 2008; 47:307–318.
166. Dashti HM, Mathew TC, Khadada M, *et al.* Beneficial effects of ketogenic diet in obese diabetic subjects. Mol Cell Biochem 2007; 302:249–256.
167. Karam JG, McFarlane SI, Feinman RD. Carbohydrate restriction and cardiovascular risk. Curr Cardiovasc Risk Rep 2008; 2:88–94.
168. ■ Kelly T, Unwin D, Finucane F. Low-carbohydrate diets in the management of obesity and type 2 diabetes: a review from clinicians using the approach in practice. Int J Environ Res Public Health 2020; 17:.

This is an overview of the evidence for carbohydrate excess as a contributor to diabetes and obesity by practicing clinicians. The authors address the importance of de-prescription of diabetes medications with LCD, and that patients should eat ad libitum to satiety. They also do not consider an increase in LDL-C with LCD a concern as the diet increases large LDL particles, which are not associated with increased cardiovascular risk.

169. ■ Norwitz NG, Loh V. A standard lipid panel is insufficient for the care of a patient on a high-fat, low-carbohydrate ketogenic diet. Front Med (Lausanne) 2020; 7:97.

This is a case study of a 24-year-old white Caucasian male with biopsy-confirmed ulcerative colitis, diagnosed at age 21. The subject adopted a ketogenic diet (75-80% fat, 15-20% protein, 4-5% carbohydrates). Within 1 week of adopting this diet, his gastrointestinal symptoms improved. His LDL-C increased from 90 to 321, which is considered 'high risk' in a standard panel. However, the increase in LDL-C was driven exclusively by an increase in large LDL, which is not associated with CVD risk.

170. ■ Barrea L, Caprio M, Watanabe M, *et al.* Could very low-calorie ketogenic diets turn off low grade inflammation in obesity? Emerging evidence. Crit Rev Food Sci Nutr 2022; 1–17.

This is a comprehensive review that addresses the underlying anti-inflammatory and antioxidant mechanisms of ketogenic diets and their possible recruitment in the treatment of obesity and obesity-related disorders.

171. Gram-Kampmann EM, Hansen CD, Hugger MB, *et al.* Effects of a 6-month, low-carbohydrate diet on glycaemic control, body composition, and cardiovascular risk factors in patients with type 2 diabetes: an open-label randomized controlled trial. Diab Obes Metab 2022; 24:693–703.
172. ■■ Volek JS, Phinney SD, Krauss RM, *et al.* Alternative dietary patterns for Americans: low-carbohydrate diets. Nutrients 2021; 13:.

A state-of-the-art review by scholars in the field of nutrition. These authors conclude that obesity, metabolic syndrome and T2D are all strongly associated with IR, which is exacerbated by increased dietary carbohydrate and improved by restricting carbohydrate. They argue that the focus of the Dietary Guidelines for Americans (DGA) on limiting fat, especially saturated fat, is out of touch with contemporary research. They assert that the LCD is a safe, effective and sustainable approach to addressing the nutritional needs of Americans.

173. Bailey WA, Westman EC, Marquart ML, Guyton JR. Low glycemic diet for weight loss in hypertriglyceridemic patients attending a lipid clinic. J Clin Lipidol 2010; 4:508–514.
174. Foley PJ. Effect of low carbohydrate diets on insulin resistance and the metabolic syndrome. Curr Opin Endocrinol Diabetes Obes 2021; 28:463–468.
175. Harvey C, Schofield GM, Zinn C, *et al.* Low-carbohydrate diets differing in carbohydrate restriction improve cardiometabolic and anthropometric markers in healthy adults: a randomised clinical trial. PeerJ 2019; 7:e6273.
176. Feinman RD, Pogozelski WK, Astrup A, *et al.* Dietary carbohydrate restriction as the first approach in diabetes management: critical review and evidence base. Nutrition 2015; 31:1–13.
177. Boden G, Sargrad K, Homko C, *et al.* Effect of a low-carbohydrate diet on appetite, blood glucose levels, and insulin resistance in obese patients with type 2 diabetes. Ann Intern Med 2005; 142:403–411.

178. ■■ Danan A, Westman EC, Saslow LR, Ede G. The ketogenic diet for refractory mental illness: a retrospective analysis of 31 inpatients. Front Psychiatry 2022; 13:951376.

This is a novel approach toward the clinical utility of the ketogenic diet. The investigators demonstrated improved metabolic markers in their patients on a ketogenic diet. More importantly, they showed that the diet was effective in improving measures of mental illness, including significant and substantial improvements in depression and psychosis in patients which had been refractory to pharmacological treatments.

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.

180. O'Neill BJ. Effect of low-carbohydrate diets on cardiometabolic risk, insulin resistance, and metabolic syndrome. Curr Opin Endocrinol Diabetes Obes 2020; 27:301–307.

181. ■ Cipryan L, Litschmannova M, Maffetone PB, *et al.* Very low-carbohydrate high-fat diet improves risk markers for cardiometabolic health more than exercise in men and women with overfat constitution: secondary analysis of a randomized controlled clinical trial. Front Nutr 2022; 9:.

This 12-week very low carb diet intervention in individuals with overfat constitution was effective for favorable changes in HOMA-IR (compared to HIIT), Adpn/Lep ratio, and diastolic BP.

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.

183. Pinto A, Bonucci A, Maggi E, *et al.* Anti-oxidant and anti-inflammatory activity of ketogenic diet: new perspectives for neuroprotection in Alzheimer's Disease. Antioxidants (Basel) 2018; 7:63.

184. Dupuis N, Curatolo N, Benoist JF, Auvin S. Ketogenic diet exhibits anti-inflammatory properties. Epilepsia 2015; 56:e95–e98.

185. Wood RJ, Volek JS, Davis SR, *et al.* Effects of a carbohydrate-restricted diet on emerging plasma markers for cardiovascular disease. Nutr Metab (Lond) 2006; 3:19.

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.

187. Westman EC, Yancy WS Jr, Olsen MK, *et al.* Effect of a low-carbohydrate, ketogenic diet program compared to a low-fat diet on fasting lipoprotein subclasses. Int J Cardiol 2006; 110:212–216.

188. Fernandez ML, Wood RJ, Dell'Ova C, *et al.* Weight loss induced by a carbohydrate restricted diet favorably affects markers of inflammation and heart disease without increasing plasma homocysteine concentrations. Faseb J 2006; 20:A426–A1426.

189. Volek JS, Phinney SD, Forsythe CE, *et al.* Carbohydrate restriction has a more favorable impact on the metabolic syndrome than a low fat diet. Lipids 2009; 44:297–309.

190. Krebs JD, Bell D, Hall R, *et al.* Improvements in glucose metabolism and insulin sensitivity with a low-carbohydrate diet in obese patients with type 2 diabetes. J Am Coll Nutr 2013; 32:11–17.

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 deprescribe 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 clincal 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.

199. ■ Gavidia K, Kalayjian T. Treating diabetes utilizing a low carbohydrate ketogenic diet and intermittent fasting without significant weight loss: a case report. Front Nutr 2021; 8:687081.

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. ■■ Athinarayanan 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 preponderence 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. Athinarayanan 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 DIETFITS 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, Cevval 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, Kruip 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.

238. Siudut J, Zabczyk M, Wolkow P, *et al.* Intensive low-density lipoprotein cholesterol lowering improves fibrin clot properties: association with lipoproteins and C-reactive protein. Vascul Pharmacol 2022; 144:106977.

239. Diamond DM, de Lorgeril M, Kendrick M, *et al.* Formal comment on 'Systematic review of the predictors of statin adherence for the primary prevention of cardiovascular disease'. Plos One 2019; 14:.

240. Diamond DM, Ravnskov U. How statistical deception created the appearance that statins are safe and effective in primary and secondary prevention of cardiovascular disease. Expert Rev Clin Pharmacol 2015; 8:201–210.

241. Golomb BA, Dimsdale JE, Koslik HJ, *et al.* Statin effects on aggression: results from the UCSD statin study, a randomized control trial. Plos One 2015; 10:.

242. Golomb BA, Evans MA. Statin adverse effects a review of the literature and evidence for a mitochondrial mechanism. Am J Cardiovasc Drugs 2008; 8:373–418.

243. Golomb BA, Evans MA, Dimsdale JE, White HL. Effects of statins on energy and fatigue with exertion: results from a randomized controlled trial. Arch Internal Med 2012; 172:1180–1182.

244. Golomb BA, Kwon EK, Koperski S, Evans MA. Amyotrophic lateral sclerosis-like conditions in possible association with cholesterol-lowering drugs an analysis of patient reports to the University of California, San Diego (UCSD) statin effects study. Drug Saf 2009; 32:649–661.

245. Golomb BA, Verden A, Messner AK, *et al.* Amyotrophic lateral sclerosis associated with statin use: a disproportionality analysis of the FDA's adverse event reporting system. Drug Saf 2018; 41:403–413.

246. Cederberg H, Stancakova A, Yaluri N, *et al.* Increased risk of diabetes with statin treatment is associated with impaired insulin sensitivity and insulin secretion: a 6 year follow-up study of the METSIM cohort. Diabetologia 2015; 58:1109–1117.

247. Padala KP, Padala PR, McNeilly DP, *et al.* The effect of HMG-CoA reductase inhibitors on cognition in patients with Alzheimer's dementia: a prospective withdrawal and rechallenge pilot study. Am J Geriatr Pharmacother 2012; 10:296–302.

248. Allen SC, Mamotte CDS. Pleiotropic and adverse effects of statins-do epigenetics play a role? J Pharmacol Exp Ther 2017; 362:319–326.

249. Izadpanah R, Schachtele DJ, Pfnur AB, *et al.* The impact of statins on biological characteristics of stem cells provides a novel explanation for their pleiotropic beneficial and adverse clinical effects. Am J Physiol Cell Physiol 2015; 309:C522–531.

250. Kitzmiller JP, Mikulik EB, Dauki AM, *et al.* Pharmacogenomics of statins: understanding susceptibility to adverse effects. Pharmgenomics Pers Med 2016; 9:97–106.

251. Abramson JD, Rosenberg HG, Jewell N, Wright JM. Should people at low risk of cardiovascular disease take a statin? BMJ 2013; 347:.

252. Yusuf S, Bosch J, Dagenais G, *et al.* Cholesterol lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med 2016; 374:2021–2031.

253. Goodarzi MO, Li X, Krauss RM, *et al.* Relationship of sex to diabetes risk in statin trials. Diabetes Care 2013; 36:e100–e101.

254. Ridker PM, Danielson E, Fonseca FA, *et al.* Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008; 359:2195–2207.

255. Aiman U, Najmi A, Khan RA. Statin induced diabetes and its clinical implications. J Pharmacol Pharmacother 2014; 5:181–185.

256. Abbasi F, Lamendola C, Harris CS, *et al.* Statins are associated with increased insulin resistance and secretion. Arterioscler Thromb Vasc Biol 2021; 41:2786–2797.

257. Sanvee GM, Panajatovic MV, Bouitbir J, Krahenbuhl S. Mechanisms of insulin resistance by simvastatin in C2C12 myotubes and in mouse skeletal muscle. Biochem Pharmacol 2019; 164:23–33.

258. Rees-Milton KJ, Norman P, Babiolakis C, *et al.* Statin use is associated with insulin resistance in participants of the Canadian multicentre osteoporosis study. J Endocr Soc 2020; 4:.

259. Sukhija R, Prayaga S, Marashdeh M, *et al.* Effect of statins on fasting plasma glucose in diabetic and nondiabetic patients. J Investig Med 2009; 57:495–499.

260. Sadighara M, Amirsheardost Z, Minaiyan M, *et al.* Toxicity of atorvastatin on pancreas mitochondria: a justification for increased risk of diabetes mellitus. Basic Clin Pharmacol Toxicol 2017; 120:131–137.

261. Dai YL, Luk TH, Siu CW, *et al.* Mitochondrial dysfunction induced by statin contributes to endothelial dysfunction in patients with coronary artery disease. Cardiovasc Toxicol 2010; 10:130–138.

262. Zhang Q, Qu H, Chen YH, *et al.* Atorvastatin induces mitochondria-dependent ferroptosis via the modulation of Nrf2-xCT/GPx4 axis. Front Cell Dev Biol 2022; 10:.

263. Eliasson P, Dietrich-Zagonel F, Lundin AC, *et al.* Statin treatment increases the clinical risk of tendinopathy through matrix metalloproteinase release - a cohort study design combined with an experimental study. Sci Rep 2019; 9:17958.

264. Barrons R. Statin-associated autoimmune myopathy: review of the literature. J Pharm Pract 2022; 8971900211040291.

265. Bruckert E, Hayem G, Dejager S, *et al.* Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients–the PRIMO study. Cardiovasc Drugs Ther 2005; 19:403–414.

266. Chung YH, Lee YC, Chang CH, *et al.* Statins of high versus low cholesterol-lowering efficacy and the development of severe renal failure. Pharmacoepidemiol Drug Saf 2013; 22:583–592.

267. Dormuth CR, Hemmelgarn BR, Paterson JM, *et al.* Use of high potency statins and rates of admission for acute kidney injury: multicenter, retrospective observational analysis of administrative databases. BMJ 2013; 346:f880.
268. Corrao G, Soranna D, Casula M, *et al.* High-potency statins increase the risk of acute kidney injury: evidence from a large population-based study. Atherosclerosis 2014; 234:224–229.
269. Muldoon MF, Barger SD, Ryan CM, *et al.* Effects of lovastatin on cognitive function and psychological well being. Am J Med 2000; 108:538–546.
270. Jurcau A, Simion A. Cognition, statins, and cholesterol in elderly ischemic stroke patients: a neurologist's perspective. Medicina-Lithuania 2021; 57:.
271. Roy S, Weinstock JL, Ishino AS, *et al.* Association of cognitive impairment in patients on 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors. J Clin Med Res 2017; 9:638–649.
272. Sahebzamani FM, Munro CL, Marroquin OC, *et al.* Examination of the food and drug administration black box warning for statins and cognitive dysfunction. J Pharmacovigil 2014; 2:1000141.
273. Kobalava ZD, Villevalde SV, Vorobyeva SV. Effects of high-dose statin therapy on cognitive functions and quality of life in very high cardiovascular risk patients. Kardiologiia 2018; 57:34–41.
274. Roy S, Hyman D, Ayyala S, *et al.* Cognitive function assessment in patients on moderate- or high-intensity statin therapy. J Clin Med Res 2020; 12:255–265.
275. Tan B, Rosenfeldt F, Ou R, Stough C. Evidence and mechanisms for statin-induced cognitive decline. Expert Rev Clin Pharmacol 2019; 12:397–406.
276. Guo Y, Zou G, Qi K, *et al.* Simvastatin impairs hippocampal synaptic plasticity and cognitive function in mice. Mol Brain 2021; 14:41.

