SUPPLEMENT

Emerging Nutrition Science on Fatty Acids and Cardiovascular Disease: Nutritionists' Perspectives[1,2]

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ABSTRACT

Recent dietary guidance for heart health recommends a reduction (by ~50%) in saturated fatty acid (SFA) intake to reduce LDL cholesterol and to decrease risk of cardiovascular disease (CVD). The 2010 Dietary Guidelines for Americans recommends substituting unsaturated fat [both polyunsaturated and monounsaturated fatty acids (PUFAs and MUFAs, respectively)] for SFAs. There are many dietary options that can be implemented to replace SFAs, given the different sources of unsaturated fats in the food supply. Compelling evidence exists for the cardioprotective benefits of n–3 (ω-3) PUFAs, both marine- and plant-derived. In addition, the evidence of cardioprotective benefits of n–6 (ω-6) PUFAs is strong, whereas that for MUFAs is mixed, although there is emerging evidence of benefits. Quantitatively, lowering SFAs by 50% will require, in part, substituting food sources of n–6 and n–3 PUFAs and MUFAs for food sources of SFAs. The use of n–3 PUFAs as a replacement for SFAs will result in a shortfall in reaching the SFA goal because of the relatively low amounts that can be incorporated in the diet, even with very high n–3 PUFA substitution. SFAs also can be replaced with dietary carbohydrate and/or protein. Replacing SFAs with carbohydrate, specifically refined sources, however, has little impact on reducing CVD risk. There is evidence about the health benefits of dietary protein on CVD risk, which merits study. Dietary guidelines have advanced considerably with the "replacement of SFA with unsaturated fat message" instead of recommending decreasing SFAs alone. A key question that remains is what is the optimal mix of macronutrients to maximally reduce CVD risk. *Adv Nutr* 2015;6:326S–337S.

Keywords: saturated fatty acids, polyunsaturated fatty acids, monounsaturated fatty acids, omega-3 fatty acids, cardiovascular disease

Introduction

A reduction in SFAs is a core dietary recommendation that has been issued by many health and government organizations to reduce the risk of cardiovascular disease (CVD)[3]. The 2013 AHA/American College of Cardiology Guideline on Lifestyle Management to Reduce Cardiovascular Risk (1) recommends a dietary pattern that achieves 5–6% of calories from SFAs for LDL-cholesterol lowering. The WHO and the 2010 Dietary Guidelines for Americans recommend consuming <10% of energy from SFAs (2). Moreover, the 2010 Dietary Guidelines for Americans recommends decreasing SFAs to <7% of energy to achieve a further lowering of CVD risk (2). In 2006 and 2010, the AHA recommended <7% of calories from SFAs to reduce CVD risk. Current dietary guidance recommends a Dietary Approaches to Stop Hypertension (DASH)–like dietary pattern that emphasizes vegetables, fruit, whole grains, low-fat dairy products, poultry, fish, legumes, and nontropical vegetable oils and nuts and that limits intake of sodium, sweets, sugar-sweetened beverages, and red meats for improving cardiometabolic health (1). This dietary pattern is low in SFAs (< 7% of energy). When decreasing SFAs it is essential to know the health consequences of the replacement macronutrients (i.e., carbohydrate, protein, MUFA, and/or PUFA). The 2010 Dietary Guidelines for Americans recommends that SFA calories be replaced with unsaturated FAs (2). The impetus for this was research demonstrating that replacing dietary SFAs with carbohydrate, primarily from refined carbohydrate and added sugars, had

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[3] Abbreviations used: AF, atrial fibrillation; ALA, α-linolenic acid; CAD, coronary artery disease; CVD, cardiovascular disease; DASH, Dietary Approaches to Stop Hypertension; EE, ethyl ester; LA, linoleic acid; LCFA, long-chain fatty acid; MCFA, medium-chain fatty acid; MCT, medium-chain triglyceride; MI, myocardial infarction; RCT, randomized controlled trial; SBP, systolic blood pressure; SCD, sudden cardiac death; SDA, stearidonic acid; TC, total cholesterol.

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adverse health consequences. Consequently, there has been great interest in identifying the optimal replacement macronutrients for SFAs. Over the years, there has been some progress in reducing dietary SFAs; however, current intake in the United States is ~11% of calories, which is approximately twice the newest recommendation made by the AHA/American College of Cardiology; hence, much remains to be done to achieve this SFA goal for LDL-cholesterol lowering.

To place this in context, with a 2000-calorie diet, lowering SFAs from 11% to 5.5% of energy would require decreasing daily SFA intake from 24.4 to 12.2 g. Thus, 12.1 g of SFAs must be replaced with an equivalent amount of unsaturated fat. Current consumption of MUFAs and PUFAs in the United States is 12% of calories and 7% of calories, respectively. On a 2000-calorie diet, this represents 27 g of MUFAs and 16 g of PUFAs. Because dietary fat typically provides a mixture of FAs, when substituting one food source of fat for another to reduce SFAs (and increase unsaturated fat), it is important to appreciate that the replacement fat source will contribute not only unsaturated fat but SFAs as well.

Evidence to Support Current Dietary Recommendations

SFAs

Dietary recommendations typically focus on reducing total SFAs without any targets for the individual SFA. On the basis of meta-analyses of clinical studies, for every 1% increase in energy from SFAs, LDL-cholesterol concentrations increase by ~12.7–17.4 mg/L and HDL-cholesterol concentrations increase by 4.3–5.0 mg/L (3). Advances in research over the past decades now provide a substantial body of evidence about the health effects of individual SFAs. In an analysis by Micha and Mozaffarian (4) of randomized controlled trials (RCTs) of lipid and nonlipid risk factors, prospective cohort studies of disease endpoints, and RCTs of disease endpoints for cardiometabolic effects of SFA consumption, the responses varied depending on the chain length of the specific SFA. Among the long-chain SFAs, lauric acid (12:0) has the greatest LDL-cholesterol-increasing effect, but decreases the total cholesterol (TC):HDL-cholesterol ratio (-0.037; $P < 0.001$) because it elicits the greatest increase in HDL cholesterol. Myristic (14:0) and palmitic (16:0) acids increase LDL and HDL cholesterol comparably; however, there is little effect on the TC:HDL-cholesterol ratio: -0.003 ($P = 0.832$) and 0.005 ($P = 0.019$), respectively (4, 5). In contrast, stearic acid (18:0) has a neutral effect on LDL-cholesterol concentrations and increases HDL cholesterol the least. These findings and other recent epidemiologic studies clearly indicate that individual SFAs have differential effects on CVD risk. Translating this science to dietary recommendations for individual SFAs, however, is fraught with challenges because most food sources that provide SFAs are mixtures of individual SFAs. Currently, soybean oil is the most commonly consumed vegetable oil in the United States, and its popularity continues to grow as consumers heed the recommendations to replace SFAs with unsaturated fats. However, like most food sources of unsaturated FAs, soybean oil contains SFAs (2 g/tablespoon). Therefore, replacing 1 tablespoon (15 g) of butter, for example, with 1 tablespoon (15 g) of soybean oil would result in a reduction of 5 g of SFAs. Consequently, with any replacement strategy where food sources of SFAs are replaced with food sources of unsaturated FAs, there always is some accompanying SFA that is added back to the diet. Nonetheless, efforts need to focus on reducing major food sources of SFAs in the diet, which are provided primarily by animal fats, and to some extent tropical oils.

Medium-chain TGs

Medium-chain FAs (MCFAs) have a chain length of 6–12 carbons. MCFAs differ from long-chain FAs (LCFAs) with respect to digestion, absorption, and metabolism (6). As reviewed by Labarthe et al. (6), MCFAs are absorbed into the portal circulation, rapidly taken up by hepatocytes, and preferentially β-oxidized in the mitochondria. Importantly, there is little incorporation into TGs. Consequently, they do not appear to be deposited in adipose tissue. Because dietary MCFAs are shunted toward oxidation rather than adipose tissue deposition, they increase energy expenditure. A typical diet is low in medium-chain TGs (MCTs). Major food sources of MCTs are coconut oil and dairy fat. Because of the unique metabolic effects of MCFAs compared with LCFAs, there is ongoing research exploring whether MCFAs affect body weight (7). Some studies have evaluated the role of MCT oil as a potential fat- or weight-loss agent. Although beneficial effects on body fat mass and weight were reported (8–10), further research is needed. These studies will help clarify whether MCFAs can have a clinically meaningful role in weight loss. Moreover, other biological effects of MCT oil, and relative to this review, on CVD risk factors need to be established before recommendations can be made.

Few clinical studies have examined the effects of MCFAs on CVD risk factors (11–13). Results from these studies were inconsistent, with some reporting similar increases in TC and LDL cholesterol after MCFA and palm oil consumption (12). Hill et al. (11) reported a reduction in TC with an LCFA diet (provided by soybean oil low in SFAs and high in unsaturated FAs, particularly PUFAs) but not the MCT diet, as well as a 3-fold increase in fasting TG concentrations with the MCT but not the LCFA diet. Reductions in HDL cholesterol (13) and the absence of effects on TC, LDL cholesterol, and HDL cholesterol were also reported with MCFA consumption (11). Hu et al. (14), however, observed no increase in the risk of coronary heart disease (CAD) from short- to medium-chain SFA (4:0–10:0) consumption in the Nurses' Health Study, whereas consumption of individual longer-chain SFAs (12:0–18:0) did show an increase in the risk of CAD. In a controlled clinical study, Tremblay et al. (15) found that 20 g of MCT oil vs. 20 g of corn oil had no significant effect on the plasma lipoprotein profile and TG-rich apo B-48 and VLDL apo B-100 kinetics. It is clear that additional research is needed to comprehensively evaluate the effects of MCTs on body weight, weight loss, and CVD risk. Irrespective of any beneficial effects of MCTs,

they likely will not be a suitable substitute for SFAs because the foods rich in MCTs also are high in SFAs, and oil sources of MCTs are costly and of limited culinary application.

Unsaturated FAs

PUFAs. Replacing SFAs with PUFAs, MUFAs, carbohydrate, or protein affects CVD risk factors differently. There is clinical trial evidence that replacing SFAs with PUFAs decreases CVD events (5, 16–18). In a systematic review and meta-analysis of cohort studies and RCTs, Skeaff and Miller (19) concluded that there is considerable evidence that replacement of SFAs by PUFAs was associated with a significant reduction in CAD events. Likewise, many RCTs have provided supportive evidence of the benefits of substituting PUFAs for SFAs. In a review of RCTs by Mozaffarian et al. (5), replacing SFAs with PUFAs significantly decreased risk of CAD or associated mortality rates. Specifically, there was a 10% reduction in CAD risk for every 5% energy substitution of mainly n–6 PUFAs. Moreover, these investigators also reported that for each 5% of energy from PUFAs that replaced SFAs, LDL cholesterol decreased by 100 mg/L without a significant reduction in HDL cholesterol. This resulted in a lowering of the TC:HDL-cholesterol ratio by 0.16.

Interestingly, an analysis published in 2012 of early RCT studies reported that a combination of both n–6 and plant and marine sources of n–3 PUFAs substituted for SFAs reduced CAD events by 22%, whereas just n–6 PUFA replacement had no beneficial effect (20). However, the early n–6 PUFA-only studies reviewed in this article had substantial limitations, which precludes meaningful conclusions being made about the n–6 PUFA-only trials used in the analysis conducted by Ramsden et al. (20). A meta-analysis of observational studies by Jakobsen et al. (21) demonstrated that replacing SFAs with PUFAs reduced the risk of coronary events by 13% and the risk of coronary deaths by 26%. In contrast, replacing SFAs with either MUFAs or carbohydrate marginally increased the risk of coronary events (perhaps due to the food sources of MUFAs, i.e., from animal sources high in SFAs, and the type of carbohydrate substituted, mainly refined carbohydrate) but not coronary deaths. On the basis of the body of evidence, it is clear that replacing SFAs with PUFAs lowers the risk of CAD as well as LDL-cholesterol concentrations (and the TC:HDL-cholesterol ratio).

Linoleic acid. In 2009, an AHA Science Advisory recommended consumption of 5–10% of energy from n–6 PUFAs for CAD risk reduction. The advisory also noted that to reduce n–6 PUFAs from the current intake (~7% of energy) would likely increase CAD risk. This conclusion was based on the evidence from RCTs of morbidity/mortality outcomes, case-control and cohort observational studies of coronary disease outcomes, short-term RCTs of CAD risk factors, and long-term animal experiments. With respect to observational studies, a meta-analysis of 25 case-control studies evaluating blood/tissue n–6 PUFA content and CAD events showed that linoleic acid (LA; 18:2n−6) content was inversely associated with CAD risk (22). After publication of the AHA Science Advisory in 2009, a pooled analysis of 11 cohort studies from the United States and Europe in 344,696 subjects followed for 4–10 y reported that replacing 5% of energy from SFAs with PUFAs was associated with a decreased risk of coronary events by 13% and coronary deaths by 26% (21). Katan (23), in an accompanying editorial, reaffirmed the recommendation of the AHA Science Advisory for n–6 PUFAs on the basis of the analysis published by Jakobsen et al. (21) and the existing evidence base, which included RCTs.

In a prospective cohort study in women (n = 91,981) from the Nurses' Health Study, Chiuve et al. (24) observed an inverse and protective association of n–6 PUFAs on sudden cardiac death (SCD) risk, independent of traditional CAD risk factors. In the Cardiovascular Health Study, Wu et al. (25) recently reported that higher plasma phospholipid LA concentrations were associated with a lower total mortality that was due to CVD causes, especially nonarrhythmic CAD mortality (HR: 0.51; 95% CI: 0.32, 0.82; P-trend = 0.001). Moreover, in a systematic review and meta-analysis of prospective cohort studies, Farvid et al. (26) reported that a 5% energy increase in LA (and substituted for SFAs) was associated with a 9% lower risk of CAD events (RR: 0.91; 95% CI: 0.86, 0.96) and a 13% lower risk of CAD deaths (RR: 0.87; 95% CI: 0.82, 0.94). In contrast, Ramsden et al. (27), in a reanalysis of data from the Sydney Diet Heart Study (1966–1973), reported that replacing SFAs with LA was associated with an increased rate of mortality from all-cause death, CAD, and CVD. Importantly, the primary source of LA in the Sydney Diet Heart Study was stick margarine that contained *trans* fat, which could explain the adverse effects reported.

There is robust evidence from several RCTs that convincingly demonstrates the CAD benefits of dietary n–6 PUFAs. A meta-analysis of 6 RCTs (28) reported that replacing SFAs with n–6 PUFAs reduced the risk of CAD events by 24%, which was attributed to a significant LDL-cholesterol-lowering effect. Although some of the benefits reported in these RCTs were not due to the increase in n–6 PUFA intake but rather the removal of SFAs and cholesterol, the reduction in events with diets very high (~15% of energy) in PUFAs supports the position that there are no detrimental effects of PUFA intake. In addition, there is convincing evidence from short-term controlled feeding studies that n–6 PUFAs have independent cholesterol-lowering properties beyond the removal of SFAs (29).

α-Linolenic acid. There is a growing evidence base for a beneficial relation of α-linolenic acid (ALA; 18:3n–3; a long-chain essential n–3 PUFA derived from plants and vegetable oils) with cardiovascular health. Most prospective observational studies demonstrate that consumption of 2–3 g of ALA/d reduces risk of CAD.

In a systematic review and meta-analysis of dietary and biomarker studies of ALA and CVD risk, Pan et al. (30) concluded that, in observational studies, higher ALA exposure

was associated with a moderately lower risk of CVD. The analysis demonstrated a lower pooled RR estimate of CVD (RR: 0.90; 95% CI: 0.81, 0.99; I^2 = 49.0%) in 13 comparisons of dietary ALA. Nonsignificant, but similar, trends were observed for CVD in 17 comparisons in which biomarkers of ALA were used. The findings of Pan et al. (30) also demonstrated that each 1-g/d increase in ALA intake was associated with a 10% lower risk of CAD death. Consistent with these findings, Albert et al. (31) conducted a prospective analysis to examine the association between dietary ALA intake and the risk of SCD, other fatal CAD, and nonfatal myocardial infarction (MI) in women participating in the Nurses' Health Study. After 18 y of follow-up they found that compared with women in the lowest quintile of ALA intake (0.37% of energy), those in the highest 2 quintiles (0.60% and 0.74% of energy) had a significantly lower SCD risk (38–40%). No association was observed for fatal CAD or nonfatal MI. More recently, Fretts et al. (32) reported that higher ALA intake was associated with a lower risk of total and noncardiovascular mortality in older adults who participated in the Cardiovascular Health Study. The HRs for total mortality and noncardiovascular mortality were 0.73 (95% CI: 0.61, 0.88) and 0.64 (95% CI: 0.52, 0.80), respectively, for the highest quintile of ALA intake compared with the lowest.

In a prospective cohort analysis of 227 patients with type 2 diabetes, dos Santos et al. (33) found that dietary PUFA intake >9.0% of total energy was associated with an up to 70% risk reduction for cardiac events. The protective role of PUFAs was especially significant for ALA, with the highest intake of ALA (highest quartile: >1.25% of energy) being associated with a 42% reduction in risk of cardiac events.

Six RCTs conducted between 2008 and 2010 assessed the effects of ALA on CVD risk markers (34–39). Three studies compared ALA to EPA and DHA and 3 studies used a placebo control. Of those studies that compared ALA to EPA + DHA, 2 studies (34, 36) randomly assigned participants to groups that received 1.2, 2.0, 2.4, or 3.6 g ALA/d or 0.6, 1.2, or 2 g of EPA + DHA/d via flax or fish-oil capsules for 12 wk. There was no effect of ALA or EPA + DHA at any dose on plasma lipids or inflammatory markers. In the third study (35), participants were randomly assigned to 1 of 3 intervention groups (ALA, EPA, or DHA) and asked to consume a specified margarine daily for 6 wk. The margarines provided either 4.4 g ALA, 2.2 g EPA, or 2.3 g DHA. There was no effect of the diets on TC and LDL cholesterol; however, TGs significantly (and similarly) decreased in each of the groups. In addition, DHA significantly increased HDL cholesterol, whereas no changes were found for ALA or EPA.

Three other studies were conducted to evaluate the effects of ALA on lipids/lipoproteins and inflammatory markers (37–39). In these studies, ALA was provided as flaxseed oil, ALA-enriched margarines, or other ALA-enriched foods and compared with a placebo control. These studies showed mixed and variable results on the lipids/lipoproteins and the inflammatory markers evaluated, which could be explained in part by the marked differences in the treatment and control diets.

Compared with EPA + DHA, there is less clinical trial evidence that has evaluated the effects of ALA on CVD morbidity and mortality. Relative to the simplicity of conducting EPA + DHA supplement studies, ALA studies are more complicated because ALA is incorporated via food sources, which changes the composition of the test diet. For example, ground flaxseed is often used to provide ALA; however, it is difficult to differentiate the effects of the components in flaxseed from those of ALA as well as the other changes in the nutrient profile of the diet when this approach is implemented (39). Similarly, when provided as a spread, the inclusion of other FAs alters the composition of the test diet. Thus, when ALA is added to a test diet using different food sources, it is challenging to control the background diet for just ALA. In contrast, in EPA + DHA supplement studies, the background diet is unchanged.

There has been one study, the Alpha Omega Trial, that was designed to evaluate the effects of ALA vs. EPA + DHA vs. all 3 n–3 PUFAs on CVD endpoints (40). Patients (n = 4837) with a history of MI within 10 y of enrollment (median interval: 3.7 y) were randomly assigned to 1 of 4 margarines supplemented with the following: *1*) EPA + DHA (400 mg of EPA + DHA), *2*) ALA (2 g), *3*) EPA + DHA and ALA, or *4*) nonsupplemented margarine (placebo). The primary endpoint was major cardiovascular events defined as fatal and nonfatal cardiovascular events and cardiac interventions. All study participants received state-of-the-art antihypertensive, antithrombotic, and lipid-modifying therapy. Margarine consumption was 18.8 g/d, which provided 226 mg EPA + 150 mg DHA, and 1.9 g ALA, or both, according to the assigned treatment group. During the 40-mo follow-up period, a major cardiovascular event occurred in 13.9% of participants. None of the treatment diets had an effect on the rate of major CVD events. Relative to ALA, the 2 ALA diets (either alone or in combination with EPA + DHA) had no effect compared with placebo. However, there was a 27% reduction in major cardiovascular events among women in the ALA groups, which approached significance (HR: 0.73; P = 0.07).

In a follow-up analysis of the Alpha Omega Trial, patients were categorized into a consistent statin-user group (n = 3740) or a consistent non–statin-user group (n = 413) to evaluate how statin use modified the effects of n–3 PUFAs in patients with a history of MI (41). In statin users, there was no effect of n–3 PUFAs on major cardiovascular events (adjusted HR: 1.02; 95% CI: 0.80, 1.31; P = 0.88). In non–statin users, although not statistically significant, EPA + DHA or ALA reduced major cardiovascular events by 18% and 10%, respectively. When the EPA + DHA plus ALA groups were combined, only 9% experienced an event vs. 18% in the placebo group (adjusted HR = 0.46; 95% CI: 0.21, 1.01; P = 0.05). These findings suggest that treatment with statins modifies the effects of n–3 PUFAs on the incidence of cardiovascular events (41). In addition, although low-dose treatment with n–3 PUFAs had no effect on major cardiovascular events in statin users, the combination of EPA + DHA (400 mg) and ALA (2 g/d) had benefits on cardiovascular events in patients not taking statins.

Although not designed specifically to evaluate the effects of ALA on coronary events in post-MI patients, the Lyon Diet Heart Study evaluated the effects of a Mediterranean-type diet (consistent with AHA Diet and Lifestyle Recommendations) high in ALA on composite measures of coronary recurrence. Patients (n = 303) in the experimental group were advised to adopt a Mediterranean-type diet and consume margarine supplied by the study. A canola oil–based margarine was provided that was low in SFAs and high in ALA. After 27 mo, risk of cardiac death and nonfatal MI decreased by >60% (42), and after 46 mo there was a 50–70% lower risk of recurrent heart disease (43). The only plasma FA that was significantly associated with a lower risk of MI plus cardiovascular death was ALA (RR: 0.20; 95% CI: 0.05, 0.84). EPA and DHA were not associated with a lower risk of CAD (43). Because of the many diet differences between the treatment and control groups, it is not possible to conclude that ALA accounted for the effects reported.

In the Finnish Mental Hospital Study (44, 45), vegetable oils, mainly soybean oil that contained ALA, replaced dairy fats for 6 y after which the diets were switched. Interestingly, adipose tissue concentrations of ALA increased 3-fold in men and 5-fold in women consuming the diet with soybean oil. The soybean oil diet decreased the incidence of electrocardiographic change or death by 67% in men (P = 0.001) and by 60% in women (P = 0.10). This study is an example of the cardiovascular benefits of replacing SFAs with PUFAs that also contained ALA. Because of the study design, it is not possible to conclude that ALA accounted for these effects. Nonetheless, the results are suggestive of a benefit of ALA.

Current intake of ALA in the United States is 1.8 g/d for men and 1.4 g/d for women. Increasing consumption to 2–3 g/d, as has been recommended (46), could be a strategy for replacing some SFA calories with unsaturated FAs. Implementing this strategy comes with the realization that ~10 g SFAs/d would still need to be replaced in the diet. Food sources of ALA include flaxseed and flaxseed oil, vegetable oils (i.e., soybean oil), and some nuts (i.e., walnuts). To attain a daily intake of 2–3 g, current consumption would have to be increased by up to 2 g. This recommendation could be met with a 1-ounce (28-g) serving of walnuts (2.6 g of ALA) or 1 tablespoon (15 g) whole flaxseeds (2.3 g ALA), both of which can be incorporated in the diet (e.g., in mixed dishes or in salads) as a replacement strategy for high-fat meats or cheeses to reduce dietary SFAs. However, as noted, food sources of ALA also contain some SFAs, albeit in low amounts.

EPA and DHA. In 2012, 2 meta-analyses of marine-derived n–3 PUFA supplementation on primary prevention of CVD were reported. Kotwal et al. (47) conducted a meta-analysis of 20 RCTs and reported that n–3 PUFA supplementation protected against cardiovascular death (RR: 0.86; 95% CI: 0.75, 0.99; P = 0.03); however, there was no significant effect on composite CVD events (RR: 0.96; 95% CI: 0.90, 1.03; P = 0.24), coronary events (RR: 0.86; 95% CI: 0.67, 1.11; P = 0.24), or on total mortality (RR: 0.95; 95% CI: 0.86, 1.04; P = 0.28). Delgado-Lista et al. (48) reviewed 21 clinical trials and RCTs (mainly in individuals at high risk of CVD) of dietary and supplemental marine-derived n–3 PUFA intake on CVD risk compared with either placebo or usual diet for ≥6 mo. They reported an overall decrease of 10% in risk of having a cardiovascular event of any kind (OR: 0.90; 95% CI: 0.85, 0.96; P = 0.001), a 9% decrease in risk of cardiac death (OR: 0.91; 95% CI: 0.83, 0.99; P = 0.03), and an 18% decrease in coronary events (fatal and nonfatal; OR: 0.82; 95% CI: 0.75, 0.90; P < 0.001), and a trend toward lower total mortality (5% reduction in risk; OR: 0.95; 95% CI: 0.89, 1.02; P = 0.15) after consumption of marine-derived n–3 PUFAs.

In a meta-analysis of secondary prevention studies by Casula et al. (49), which included 11 RCTs providing ≥1 g marine-derived n–3 PUFA supplements/d for >1 y to patients with existing CVD, they observed significant risk reductions in cardiac death (−32%), sudden death (−33%), and MI (−25%); no significant effect was reported for all-cause mortality and stroke. Likewise, in a report from the Agency for Healthcare Research and Quality, EPA + DHA supplementation (0.27–6.0 g/d) decreased the RR of cardiac mortality by 11% (50). Other meta-analyses reported no protective benefit of EPA + DHA intake on CVD risk (51–53). These variable findings could be explained by differences in study design, subject populations, dose, duration, and absence or presence of pre-existing vascular diseases at entry (53).

Both epidemiologic and clinical studies have shown that fish and fish oil consistently reduce CAD death (~35%), CAD sudden death (~50%), and ischemic stroke (~30%). Arrhythmias are the major cause of SCD, which is the leading cause of cardiac death in the United States (54). However, 3 recent systematic reviews failed to show any antiarrhythmic effect of marine-derived n–3 PUFAs on atrial fibrillation (AF). A review of 9 RCTs by Khoueiry et al. (55) that compared dietary marine-derived n–3 PUFA supplementation with placebo found no significant risk reduction in SCD or ventricular arrhythmias. Likewise, in a meta-analysis of 16 RCTs, Mariani et al. (56) reported no evidence that use of n–3 PUFAs prevented either postoperative or recurrent AF. Moreover, Mozaffarian et al. (57) reported in a meta-analysis of 8 short-term RCTs that fish oil use did not "appreciably" reduce postoperative AF.

The studies conducted to date have used different forms of n–3 PUFAs, including seafood and supplements that provide marine n–3 PUFAs in different forms. n–3 PUFA capsules are available as over-the-counter supplements or as prescription formulations. There are 3 types of fish-oil products commercially available: TGs, ethyl esters (EEs), and phospholipids. The most common product contains 180 mg EPA and 120 mg DHA per 1000 mg fish oil (i.e., 30% EPA + DHA). Many fish-oil supplements are in the EE form. EPA and DHA EE are formed during the distillation process that is required to purify the oil. Specifically, EEs are highly refined n–3 PUFAs that are created by reacting FFAs with ethanol in a process called trans-esterification. This process involves removing the glycerol backbone of fish-oil TGs, resulting in FFAs and a free glycerol molecule. An ethanol

molecule is then attached to each of the FFAs, which creates the EE. The synthesis of EEs results in a concentration of EPA and DHA that is greater than that in fish. Supplements that provide >30% EPA + DHA and do not indicate their chemical structure are most likely EEs. Because of evidence suggesting an increased bioavailability of supplements in the TG form, some manufacturers convert EE concentrates back to the TG form in a process called glycerolysis. Food-grade enzymes cleave the ethanol molecule from the FA, creating an FFA and a free ethanol molecule. Glycerol is then added back to the solution where the enzymes re-esterify the FAs onto the glycerol, recreating a TG. These oils are commonly referred to as re-esterfied (or reformed) TGs, which have an identical structure to natural TGs but with higher concentrations of EPA and DHA. Because these products are re-esterified TGs they cost more to produce than EEs. Some supplements, such as salmon oils, may contain TGs only or a blend with EEs to achieve higher EPA + DHA concentrations; however, this information does not have to be listed on the label. In general, cod liver oil products are rarely blended with EEs so they are almost always in the TG form. The phospholipid form is currently only found in krill oil supplements and is the least concentrated source of EPA + DHA. EPA and DHA from krill oil, which is largely phospholipid bound, may be absorbed more efficiently than n–3 PUFA from fish oils (58, 59); however, further evidence is needed to confirm this.

Another commercially available EPA + DHA product is the free (nonesterified) FA form. The free acids of EPA and DHA are considered to be the most bioavailable because they do not require lipolytic release by intestinal lipases for absorption. This has been confirmed recently in the ECLIPSE (Epanova Compared to Lovaza in a Pharmacokinetic Single-dose Evaluation) I (60) and II (61) studies. The ECLIPSE study showed a 4-fold greater increase in plasma concentrations of EPA + DHA for a 4-g dose of the FFAs vs. the EE forms in response to a low-fat 1-d menu (little fat for breakfast and lunch and 9 g of fat/900 kcal at dinner before the dose was administered). In response to a higher fat 1-d menu (20 g of fat for breakfast and 30 g of fat for both lunch and dinner), plasma concentrations of EPA + DHA were 1.3-fold greater with the FFA vs. the ester forms. Key questions remain about what the clinical importance is of greater bioavailability of EPA + DHA. It could be that saturation of RBC membranes could occur faster at a similar dose vs. other forms of the FAs or that lower doses are needed to achieve maximal membrane incorporation. To date, research has demonstrated a reduction in cardiovascular events with EE formulations and fatty fish, as well as fish-oil supplements (62). On the basis of the available evidence, it would appear that all forms of EPA + DHA can confer cardiovascular benefits; however, it likely may be that this is achieved with different doses of very-long-chain n–3 PUFAs, which reflects bioavailability.

Recommendations have been made for EPA + DHA for healthy individuals and coronary patients. For healthy individuals, 250 mg of EPA + DHA/d is recommended by the 2010 Dietary Guidelines for Americans (2). The most recent guidance for coronary patients issued in 2012 by the American College of Cardiology Foundation, AHA, American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons (Guideline for the Diagnosis and Management of Patients with Stable Ischemic Heart Disease) (63) recommends that fish and/or fish-oil supplementation is indicated only for the control of a patient's lipid profile (class IIB; level of evidence, B).

Current consumption of EPA + DHA in the United States is ~90 mg/d (30 mg EPA + 60 mg DHA). Increasing consumption to current recommendations (250 mg/d) would require a 2-fold increase in seafood intake—from 1 serving (3 ounces or 84 g) of seafood per week to 2 servings (6 ounces or 168 g) per week (with an emphasis on oily fish for at least one meal). As is apparent, 250 mg EPA + DHA/d does not suffice as a strategy for markedly lowering dietary SFAs. However, if oily fish were substituted for fatty meat or cheese, this would be an effective strategy to decrease dietary SFAs. For example, replacing two 3-ounce (84-g) servings of high-fat meat/wk with two 3-ounce (84-g) servings of salmon would lower SFA intake by 9 g and increase PUFAs by 8 g, and concurrently achieve current recommendations for EPA + DHA intake.

MUFAs. Compared with PUFAs, the clinical trial evidence evaluating the effects of MUFAs on CAD events is lacking. Although not designed to specifically evaluate the effects of MUFAs, the PREDIMED (Prevención con Dieta Mediterránea) trial reported beneficial effects of experimental diets high in MUFAs (from either extra-virgin olive oil, 50 g/d, or mixed nuts, 30 g/d) on major CVD events (a composite of MI, stroke, or death from cardiovascular causes) in individuals at high cardiovascular risk (64). Clinical studies have shown that when MUFAs replace carbohydrate in the diet, TGs, VLDL cholesterol, C-reactive protein (CRP), and blood pressure decrease, whereas HDL cholesterol and apo A-I increase (3, 65, 66). In the most recent review of RCTs and observational studies, Micha and Mozaffarian (4) evaluated the effects of isocaloric replacement of different FA classes for dietary carbohydrate on lipids and lipoproteins, and assessed the associations of replacing MUFAs for SFAs on risk of CAD. Consumption of MUFAs as a substitute for carbohydrate resulted in a lowering of TC, LDL cholesterol, apoB, and the TC:HDL-cholesterol ratio with little effect on TGs. These effects were comparable to those observed for PUFAs when substituted for carbohydrate, with the exception that PUFAs slightly decreased HDL cholesterol and apo A-I, whereas MUFAs did not. Similar results were recently reported in a large multicenter controlled feeding study for 2 high-MUFA oils and a high-PUFA oil blend on TC and LDL cholesterol (67). In contrast, in a pooled analysis of 11 cohort studies, there was a trend for an increased CAD risk when MUFAs replaced SFAs (HR: 1.19; 95% CI: 1.00,1.42) for reasons that may pertain to the food source

or sources of MUFAs (i.e., animal products) and/or the lack of control for *trans* fat in the analyses (21). The authors concluded that replacing SFAs with MUFAs resulted in uncertain effects on CAD risk.

A comprehensive review by Gillingham et al. (68) reported beneficial effects of a high-MUFA diet (>15% of total calories) on cardiometabolic risk factors including decreased waist circumference, blood pressure, TGs, and glucose and increased HDL cholesterol (68). Similarly, Schwingshackl et al. (69) in a meta-analysis that investigated the long-term (≥6 mo) effects of high-MUFA (>12% MUFAs) vs. low-MUFA (≤12% MUFAs) diets on cardiovascular risk factors reported significant differences between high- and low-MUFA diets for fat mass (−1.94 kg; 95% CI: −3.72, −0.17 kg; $P = 0.03$), systolic blood pressure (SBP; −2.26 mm Hg; 95% CI = −4.28, −0.25 mm Hg; $P = 0.03$), and diastolic blood pressure (−1.15 mm Hg; 95% CI: −1.96, −0.34 mm Hg; $P = 0.005$) favoring the high-MUFA diets.

Meta-analyses of cohort studies, including those by Skeaff and Miller (19) and Jakobsen et al. (21), did not show benefits of MUFA-rich diets on relative CAD events and death. In contrast, a meta-analysis by Mente et al. (70) reported a significant inverse correlation between MUFA (but not PUFAs)-rich diets and risk of coronary events. Most recently, Schwingshackl and Hoffmann (71) summarized the available evidence regarding MUFAs and CVD risk. They concluded that the evidence from long-term prospective cohort studies provides unclear results about associations of MUFAs with risk of CAD. They also pointed out that there are considerably fewer meta-analyses evaluating the associations of MUFAs with CVD/CAD compared with the number of systematic reviews and meta-analyses for PUFAs.

Hooper et al. (72) updated the Cochrane meta-analysis on the benefits of low-fat vs. modified-fat diets on CVD in individuals at risk of CVD as well as low-risk population groups. The results reaffirmed the importance of reducing dietary SFAs with replacement/partial replacement with unsaturated fat. However, what remains to be resolved is what is the ideal mix of MUFAs and PUFAs (both n–3 and n–6) for maximal CVD risk reduction?

Other dietary FAs

Stearidonic acid. As concern over the sustainability of fish populations increases, alternative dietary sources of n–3 PUFAs are being developed to achieve EPA and DHA recommendations. Although there are many nonfish food sources of plant-derived ALA, conversion to longer-chain EPA and especially to DHA is very low. Stearidonic acid (18:4, SDA) is an intermediate FA in the biosynthetic pathway from ALA to very-long-chain n–3 PUFAs (principally EPA), and the conversion from SDA is more efficient than from ALA (73). However, there are few food sources of SDA, and those that exist are not commonly consumed (i.e., hemp oil, some fish, and certain seeds).

A genetically modified soybean has been developed by the introduction of genes for enzymes (Δ6 and Δ15 desaturases) that decreased LA with a consequent increased conversion of ALA to SDA (74). The resulting oil is SDA-enriched (18–28% of the total FA content). Clinical studies of the effect of SDA on the EPA content of RBCs showed a significant increase in EPA when SDA is consumed. Studies of the biological effects of SDA in humans demonstrate little effect on blood lipids and inflammatory outcomes, perhaps because the intakes of SDA evaluated have been too low to sufficiently enrich target cells and tissues with EPA (75). It is expected that further studies of SDA will be conducted, likely with novel natural or genetically modified seed oil crops to evaluate health outcomes. Because SDA is less prone to oxidation than EPA + DHA, it has been added to different foods. Consumer acceptance is comparable to conventional soybean oil (75). SDA-fortified foods such as salad dressings, margarine, and sausage are designed to help consumers increase intakes of n–3 PUFAs. As noted above for EPA and DHA, the relatively small amounts of SDA in foods (when substituted for SFAs) will have little impact on decreasing total SFAs unless higher-SFA foods are replaced.

trans-Palmitoleate. Palmitoleic acid (*cis*-16:1n–7) is produced by endogenous fat synthesis and has been linked to both beneficial and deleterious metabolic effects. Animal studies suggest that endogenous palmitoleic acid may protect against insulin resistance and metabolic dysregulation; however, results from human studies are mixed. Findings from human studies are difficult to interpret due to the confounding effects of lifestyle factors (i.e., dietary intake, smoking status, physical activity level, etc.) and tissue sources (liver vs. adipose tissue) of palmitoleate synthesis. In contrast, *trans*-palmitoleate (*trans*-16:1n–7) is an exogenous source of 16:1n–7 (76).

Although consumption of *trans* fats from partially hydrogenated oils adversely affects CVD risk, *trans*-palmitoleate, derived mainly from naturally occurring dairy and other ruminant *trans* fats, has not been associated with higher CVD risk (77). On the contrary, some studies demonstrated inverse associations between dairy consumption and risk of insulin resistance, diabetes, and metabolic syndrome. To evaluate the relation between *trans*-palmitoleate and metabolic risk, Mozaffarian et al. (76) analyzed data from >5000 adults, aged ≥65 y in the Cardiovascular Health Study, and found that *trans*-palmitoleate concentrations correlated strongly with dairy fat consumption. They reported that higher *trans*-palmitoleate concentrations were associated with slightly lower adiposity (i.e., BMI and waist circumference) and with higher HDL-cholesterol concentrations (1.9% across quintiles; $P = 0.040$), lower TG concentrations (−19.0%; $P < 0.001$), a lower TC:HDL-cholesterol ratio (−4.7%; $P < 0.001$), lower CRP concentrations (−13.8%; $P = 0.05$), and lower insulin resistance (HOMA; −16.7%; $P < 0.001$). *trans*-Palmitoleate also was associated with a substantially lower risk of new-onset diabetes, including a 56% lower risk in quintile 4 (HR: 0.44; 95% CI: 0.30, 0.66) and a 64% lower risk in quintile 5 (HR: 0.36; 95% CI: 0.23, 0.57) vs. quintile 1 (P-trend < 0.001). For *trans*-palmitoleate that is found in red meat (in contrast to dairy), there are no

epidemiologic data to support a protective role for red meat and incident diabetes. Thus, these findings may help explain the previously reported benefits of dairy consumption, suggesting that there may be compounds in dairy products that reduce risk of cardiometabolic disease. Until further studies are conducted, caution is warranted about recommending full-fat dairy products as a source of *trans*-palmitoleate because of the accompanying SFA content.

Carbohydrate

The effect of carbohydrate as a replacement for SFAs likely depends on the type (simple vs. complex) consumed. In a large prospective cohort study (53,644 men and women), investigators reported that after a median of 12 y, substitution of SFAs with carbohydrate (5% of energy) was associated with a modest increase (7%) in coronary event risk; however, there was no difference in mortality (21). In a subsequent observational analysis, Jakobsen et al. (78) further showed that replacement of 5% of energy from SFAs by carbohydrate with a low glycemic index was associated with a nonsignificant reduction in CVD risk, whereas replacing SFAs by carbohydrate with a high glycemic index was associated with a 33% increased risk of MI (78).

Likewise, in a cohort of >75,000 women participating in the Nurses' Health Study, dietary glycemic load was positively associated with risk of CAD. Glycemic load was calculated as a function of glycemic index, carbohydrate content, and frequency of intake of individual foods reported on a validated FFQ at baseline. The RRs from the lowest to highest quintiles of glycemic load were 1.00, 1.01, 1.25, 1.51, and 1.98 (95% CI: 1.41, 2.77 for the highest quintile; *P*-trend < 0.0001). This relation remained after adjusting for age, smoking status, total energy intake, and other CAD risk factors. Furthermore, the association was most evident among women with body weights that were above average (i.e., BMI >23 kg/m^2) (79).

In a review of RCTs and large prospective cohort trials, Micha and Mozaffarian (4) concluded that replacement of SFAs with carbohydrate provides no benefit. When compared with carbohydrate, SFAs increase TC, LDL-cholesterol and apoB concentrations but also lower TG concentrations and increase HDL-cholesterol and apo A-I concentrations. Because of the increase in TC and LDL cholesterol and increase in HDL cholesterol, there is no significant effect on the TC:HDL-cholesterol ratio (4).

In the Women's Health Initiative, the largest RCT conducted to date, postmenopausal women were randomly assigned to either a low-fat (<20% of calories; <7% SFAs) intervention or to a control group. After 8.1 y of follow-up, there were no significant differences in the risk of CAD, stroke, or CVD, which demonstrated no benefit of a reduced-fat diet (80). However, in this study, dietary targets were not met; although SFA amounts were lower in the intervention group than in the control group (9.5% and 12.4% of calories, respectively), fat intake for the intervention group was 28.8%. There was a trend toward a greater reduction in CAD risk among women in the intervention group who reached the lowest intakes of SFAs (<6%) or the highest intakes of vegetables and fruit (≥6.5 servings/d). Taken together, this suggests that the effects of substitution of carbohydrate may vary depending on dietary carbohydrate quality (i.e., fruit and vegetables vs. refined-carbohydrate foods).

In the PREDIMED trial, the control group consumed 37.0% of calories from fat vs. 41.2% and 41.5% of calories in the 2 Mediterranean-style treatment groups, and more carbohydrate (43.7% vs. 41.7% and 41.4% of calories in the 2 treatment groups). In all groups, SFAs represented 9% of calories. The control group had a 30% higher incidence of major CVD events compared with the Mediterranean-style diet treatment groups (64). The DASH dietary pattern, which is low in SFAs (7%) and high in fiber-rich, complex carbohydrate decreased LDL cholesterol by 9% and HDL cholesterol by 7.5% without any effect on TGs (81). In a meta-analysis of 60 trials (3), replacing SFAs with refined carbohydrate typically decreases LDL and HDL cholesterol and increases TGs. Research is needed to evaluate the effects of different food sources of carbohydrate, as well as types of carbohydrate, on cardiometabolic risk. This is an important question because the current US diet provides ~33% of calories from total fat, and the recommended DASH diet contains ~27–30% of calories from total fat. Thus, to achieve the recommended target for total fat, some calories, preferably from SFAs will have to be replaced with dietary carbohydrate or protein. If carbohydrate is the replacement (or partial replacement) of choice, it will be important to identify ideal carbohydrate sources for substitution.

Protein

When protein (either lean animal protein or vegetable protein) replaces SFAs and/or carbohydrate, there are many benefits on CVD risk factors (82, 83). Importantly, however, there is no clinical trial evidence that has evaluated the effects of replacing SFAs with protein on CVD events.

Epidemiologic evidence reported an inverse association between protein intake and risk of CVD. Larsson et al. (82), in a prospective cohort study in Swedish women, reported an inverse association between total and animal protein intake and risk of stroke (RR: 0.74; $P = 0.006$). Replacing 5% of calories from SFAs with protein was associated with a 13% lower risk of total stroke (82). In the Nurses' Health Study, vegetable protein and fat were associated with a 30% decrease in CAD risk (83). In the Women's Health Initiative Dietary Modification Trial, protein consumption was inversely associated with CAD risk (HR: 0.85; 95% CI: 0.75, 0.97) (84). In this trial, however, comparisons between animal and vegetable protein were not evaluated.

The OMNI (Optimal Macronutrient Intake) Heart Trial evaluated a modified DASH diet in which some carbohydrate replaced either protein or unsaturated fat (65). Participants ($n = 164$ adults) with prehypertension or hypertension were randomly assigned to 1 of 3 heart-healthy, low-SFA (6%) diets that emphasized a different macronutrient. The carbohydrate

diet was similar to the DASH diet [58% carbohydrate, 27% fat (6% SFAs, 13% MUFAs, 8% PUFAs), 15% protein]; the protein diet replaced 10% of carbohydrate calories with protein (approximately one-half from plant protein) and the unsaturated-fat diet substituted 10% of carbohydrate calories with unsaturated fat, both MUFAs and PUFAs. All diets improved CVD risk compared with baseline. However, the protein diet (vs. the carbohydrate diet) reduced SBP further by 1.4 mm Hg ($P = 0.002$) among all participants and by 3.5 mm Hg ($P = 0.006$) in participants with hypertension, LDL cholesterol by 33 mg/L ($P = 0.01$), TGs by 157 mg/L ($P < 0.001$), and HDL cholesterol by 13 mg/L ($P = 0.02$). In addition, the unsaturated-fat diet lowered SBP by 1.3 mm Hg ($P = 0.005$) and diastolic blood pressure by 2.9 mm Hg ($P = 0.02$) in participants with hypertension, as well as TGs by 96 mg/L ($P = 0.02$), and increased HDL cholesterol by 11 mg/L ($P = 0.03$); there was no additional effect on LDL cholesterol compared with the carbohydrate diet (65). This study demonstrates that substituting carbohydrate with either protein or unsaturated fat may enhance the effectiveness of the DASH diet on CVD risk reduction. Thus, partial substitution of carbohydrate with either protein or unsaturated fat for SFAs lowers SBP further, improves lipids/lipoproteins, and thereby reduces the risk of CVD (65).

There is evidence that replacing dietary SFAs and carbohydrate with plant protein or lean animal protein foods benefits CVD risk factors. This could reflect the amino acid profile of the protein consumed. For example, L-arginine in foods such as nuts, beans, and tuna may improve endothelial function. L-Arginine is the amino acid precursor for the endogenous vasodilator NO. NO plays a role in maintaining vascular health and function (85). In many vascular disease states, NO production is impaired as a result of endothelial dysfunction, which may in part be caused by a decrease in L-arginine availability. In a meta-analysis of 12 studies, Bai et al. (86) evaluated the effects of L-arginine supplementation (3–24 g/d) on vascular function and observed a significant improvement in endothelial function (assessed by flow-mediated dilatation) in individuals with impaired baseline flow-mediated dilatation (<7%). Further studies are needed that evaluate food sources rich in arginine (as well as other amino acids) and how they affect cardiovascular health.

Implementing Current Dietary Recommendations

Current dietary guidance recommends substituting unsaturated FAs for SFAs (2). However, individuals require additional guidance to implement these recommendations. On the basis of the research reviewed herein, there is convincing evidence that replacing SFAs with PUFAs decreases CVD risk, whereas there is less evidence for the cardioprotective effects of MUFAs. Interestingly, there has been a marked increase in high-MUFA liquid vegetable oils now in the marketplace that are replacing higher PUFA counterparts. Examples include high-oleic sunflower and canola oils.

As such, previous recommendations to replace solid fats with oils may result in a decrease in PUFAs. Thus, high-PUFA food sources should be included in the diet. For example, fatty fish such as salmon, trout, and herring, especially farm raised, have high concentrations of PUFAs, and n–6 PUFAs in particular. Nuts, seeds, and some liquid vegetable oils are rich sources of n–6 PUFAs. Replacing one 3-ounce (84-g) serving of high-fat meat with a 3-ounce (84-g) serving of salmon would reduce SFAs by 8 g while increasing total PUFAs by 3 g, of which 2.1 g are EPA + DHA. With the increasing prevalence of high-MUFA oils (including olive oil) to replace solid fats, it is important to ensure that foods that replace high-SFA foods provide all unsaturated FAs.

Conclusions

In summary, it is important to consider which nutrient or nutrients should replace SFAs when implementing current dietary recommendations to lower SFAs. It is clear that substituting PUFAs (both n–6 and n–3) for SFAs decreases CVD morbidity and mortality. Replacing SFAs primarily with refined carbohydrate does little, if anything, to lower CVD risk and major risk factors. The evidence for MUFAs and protein (and possibly complex carbohydrate) as replacements for SFAs shows some promise for decreasing CVD risk status; however, further evidence is needed from long-term controlled clinical studies. There is abundant evidence for the benefits of plant- and marine-derived n–3 PUFAs that supports current dietary recommendations. However, as a replacement for SFAs, especially for marine-derived n–3 PUFAs, there is little (<500 mg/d) quantitative displacement. Further research is needed to define the ideal "mix" of macronutrients to replace SFAs in the diet to maximally benefit CVD risk.

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