Minireviews

New Insight into the Dietary Cause of Atherosclerosis: Implications for Pharmacology

Reynold Spector

Department of Medicine, Robert Wood Johnson Medical School, Piscataway, New Jersey

Received March 2, 2016; accepted April 21, 2016

ABSTRACT

At present, the guideline approach to the medical treatment and prevention of atherosclerotic cardiovascular disease (ASCVD) is to classify patients by risk and treat the known risk factors (contributory causes), e.g., hypertension, diabetes, obesity, smoking, and poor diet, as appropriate. All high-risk patients should receive statins. This approach has had substantial success but ASCVD still remains the number one cause of death in the United States. Until recently, the underlying cause of ASCVD remained unknown, although a potential dietary cause was suggested by the fact that vegetarians, especially vegans, have a much lower incidence of ASCVD than animal flesh eaters. Recently, consistent with the vegetarian data, substantial evidence for a cause of ASCVD in animals and humans has been discovered. Trimethylamine (TMA)-containing dietary compounds in meat, milk, and other animal foods (e.g., lecithin, choline, and carnitine) are converted by closely related gut bacterial TMA lyases to TMA, which is absorbed and converted predominantly by flavin mono-oxygenase 3 to the toxic trimethylamine N-oxide (TMAO). TMAO causes atherosclerosis in animals and is elevated in patients with coronary heart disease. Inhibition of bacterial lyases in mice prevents TMA and secondarily TMAO formation and atherosclerosis, strong evidence for the TMAO hypothesis. At present, the challenge for the pharmaceutical industry is to discover and develop a potent “broad spectrum” bacterial lyase inhibitor that, along with diet and exercise, could, if the TMAO hypothesis is correct, revolutionize the preventive treatment of ASCVD.

Introduction

In the United States, atherosclerosis in the coronary and cerebral arteries is generally a causal factor in over 600,000 cardiac and 130,000 stroke deaths per year (Mozaffarian et al., 2016). In most cases, the critical event (the “coup de grace”) is a clot that forms over a rough or cracked, nonobstructive atheromatous lesion, acutely obstructing blood flow and causing distal tissue necrosis, although, less commonly, emboli can also obstruct blood flow (Blumenthal and Kapur, 2006). Depending on where this occurs, the result may be a fatal or nonfatal myocardial infarction (MI), ischemic stroke, bowel infarction, or other less common syndromes. On the basis of careful clinical research, seven prominent contributory causes (risk factors) for atherosclerosis have been identified: increased serum cholesterol and blood pressure, diabetes, obesity, a positive family history, smoking, and an atherogenic diet (Mozaffarian et al., 2016). However, the pathophysiology in each case is complex; for example, increased blood pressure not only accelerates atherosclerosis in the large arteries but also causes arteriosclerosis with arteriolar hyaline change or even medial necrosis in malignant hypertension (Mozaffarian et al., 2016).

However, none of these “contributory causes” fully explains the underlying cause and pathophysiology of the atherosclerotic process in most cases. Yet, a somewhat successful approach has been to control these risk factors when present: lowering blood pressure with safe and effective drugs and blood cholesterol with statins; controlling type II diabetes and obesity with drugs, diet, and weight loss; stopping smoking and improving diets, e.g., with a vegetarian-type diet (Mozaffarian et al., 2016). All these measures are useful and have lowered age-adjusted mortality resulting from atherosclerotic cardiovascular disease (ASCVD) by ∼30% from 2003 to 2013 (Mozaffarian et al., 2016). As a consequence, in 2016 for the first time cancer (with more than 600,000 projected deaths) may overtake heart disease as the leading cause of death in the United States. Stroke, which used to be the second leading cause of death, has now descended to fifth place after cancer, heart disease, respiratory ailments, and accidents, thus attest- ing to the success of pharmacologic control of risk factors, primarily hypertension in this case. (Mozaffarian et al., 2016).

Notwithstanding these successes, myocardial and cerebral infarctions (ASCVD) together remain the leading cause of

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CAD, coronary artery disease; DMB, 3, 3-dimethyl-1-butanol; FMO3, flavin mono-oxygenase 3; HDL, high-density lipoprotein; HRT, hormone replacement therapy; LDL, low-density lipoprotein; MI, myocardial infarction; RCT, reverse cholesterol transport; TMA, trimethylamine; TMAO, trimethylamine N-oxide.
death in the United States and developed world (Mozaffarian et al., 2016). On the basis of convincing epidemiology work, there has been a strong suspicion that a dietary factor(s) might be an underlying cause, i.e., a necessary and sufficient cause exacerbated by the risk factors (contributory causes) enumerated above. This hypothesis, described in detail below, has recently been supported by substantial evidence in animals and humans (Wang, et al., 2011; Koeth et al., 2013; Tang et. al., 2013; Jonsson and Bäckhed; Shih, et al., 2015; Troseid, et al., 2015; Wang et al., 2015; Warrier, et al., 2015). Briefly, trimethylamine (TMA)–containing dietary compounds, found mainly in meat, milk, some fish, and other animal foods (e.g., lecithin, choline, betaine, carnitine) are converted by TMA lyases (lyases) in gut bacteria to TMA, which is absorbed and then oxidized by hepatic flavin mono-oxygenase 3 (FMO3) to the toxic trimethylamine N-oxide (TMAO). TMAO causes atherosclerosis in animals and probably humans, and is elevated in patients with atherosclerotic coronary artery disease (CAD). Before reviewing the TMAO evidence, I will review the cholesterol hypothesis, which for decades has been widely accepted as the principal cause of atherosclerosis. I will also briefly comment on the management of diabetes and hypertension, since this is relevant to prevention of atherosclerosis, and finally the epidemiology work on dietary causes of atherosclerosis.

The Cholesterol Hypothesis

Initially, the cholesterol hypothesis as a cause of atherosclerosis had three components: elevated high-density lipoprotein (HDL) was protective and elevated low-density lipoprotein (LDL) and triglycerides in blood were harmful. The HDL and triglyceride components of the hypothesis are not well supported and will not be discussed further (Spector, 2013; Medical Letter, 2013). In favor of the LDL component of the cholesterol hypothesis are: 1) the higher the LDL cholesterol, the greater the risk of CAD; 2) certain patients with rare genetic disorders and very high serum cholesterol have accelerated ASCVD; 3) feeding large quantities of cholesterol to rabbits and other animals causes atherosclerosis; and 4) statins, which lower cholesterol, are unequivocally beneficial (Scandinavian Simvastatin Survival Study Group, 1994; Spector 2013; Mozaffarian et al., 2016).

There is, however, persuasive evidence that the LDL cholesterol is not the underlying causal factor in most patients with ASCVD:

1) More than one-third of MI patients have normal or even low serum cholesterol, and many patients with elevated LDL never manifest ASCVD, thus showing that increased serum LDL is not a necessary or sufficient cause of ASCVD (Spector 2013).

2) In fact, although statins lower serum cholesterol and LDL cholesterol, they do not work primarily by slowing or regressing the atherosclerotic process (Blumenthal and Kapur, 2006). In a large 2-year placebo-controlled randomized study in patients with CAD treated with high-dose lovastatin (80 mg) or placebo, there was no difference in changes in coronary anatomy as measured by quantitative coronary angiography between drug and placebo groups, both at baseline and after 2 years of treatment (Blankenhorn et al., 1993). With maximal dose rosuvastatin (40 mg) and atorvastatin (80 mg), in two studies employing ultrasound, there was approximately a 1% decrease in coronary atheroma volume compared with baseline over 2 years (Nissen et al., 2006; Nicholls et al., 2011); however, there were no controls in the these atheroma studies and no luminal measurements, so these data are difficult to interpret, unlike the Blankenhorn et al. (1993) study referred to above with lovastatin (Blumenthal and Kapur, 2006). But what can be said from these studies is that statins do not alter the atheroma process much if at all. Yet, in a carefully done double-blind, randomized clinical trial of secondary prevention, there was approximately a 30% decrease in all-cause mortality, as well as similar decreases in MI and stroke, in patients randomized to moderate-dose simvastatin compared with placebo patients (Scandinavian Simvastatin Survival Study Group, 1994; Spector 2013, Mozaffarian et al., 2016). This trial included 100% follow up for mortality, so there is absolutely no ambiguity about the results. The mechanism of this effect we now know is not attributable to decreasing atherosclerosis per se but to stabilizing nonobstructing atheromatous plaques and preventing clot formation on them when these plaques are rough or rupture (Blumenthal and Kapur, 2006). Antiplatelet agents (e.g., aspirin) also help prevent clots on such lesions (Mora, 2012).

3) Statin efficacy is independent of baseline serum cholesterol. This has been shown in studies of both simvastatin (Heart Protection Study Collaborative Group, 2002) and pravastatin (Sacks et al., 2000).

4) Feeding huge amounts of cholesterol to rabbits is not a good model of human ASCVD, unlike the TMAO data discussed below.

5) Many drugs that lower serum LDL cholesterol and raise HDL [e.g., hormone replacement therapy (HRT) and niacin] either have no effect on ASCVD or are actually harmful (Hulley et al., 1998; Boden et al., 2011; Spector, 2013). For example, in the first large placebo-controlled trial of HRT in women who had CAD, there was no cardiovascular benefit but significantly more gall bladder and thromboembolic disease in the HRT arm (Hulley et al., 1998). Subsequent controlled trials of HRT confirmed no cardiovascular benefit or actual harm (Spector and Vesell, 2002).

6) On February 15, 2016, the FDA made its decision about the utility of Vytorin, a drug that combines 40 mg of simvastatin with 10 mg of ezetimibe, a drug which blocks cholesterol absorption. As expected, Vytorin lowers serum total and LDL cholesterol more than simvastatin (40 mg) alone. However, after a careful review of a 7-year, approximately 18,000-patient randomized controlled trial of Vytorin versus simvastatin (40 mg) alone (Cannon, et al., 2015) and other data, the FDA and its advisory committee concluded that Vytorin (40/10) was no better than simvastatin (40 mg) in preventing cardiovascular death, stroke, and MI. In short, Vytorin, which lowers total and LDL serum cholesterol more than simvastatin alone, is not more effective clinically. This result is consistent with a recent analysis of the statin data from extant randomized clinical trials (Takagi and Umemoto, 2013). This analysis does not make unjustified linear assumptions, suggests that the clinical benefit of statins is achieved with doses of 40 mg of atorvastatin or simvastatin, and that further lowering of blood cholesterol achieves very little (Spector and Snapinn, 2011; Takagi and Umemoto, 2013). For all the above reasons, serum cholesterol must be considered a contributory cause of ASCVD in some cases only.
It is worth noting that the new national guidelines (by the Veterans Administration, US Department of Defense, American Heart Association, American College of Cardiology) for the treatment and prevention of ASCVD have finally recognized these facts about statins (Downs and O’Malley, 2015). On the basis of the current treatments available, the guidelines now correctly focus on risk: BP and weight control; cessation of smoking; exercise; and statins and aspirin (Mora, 2012) for high-risk patients, with the use of moderate-dose inexpensive generic statins (e.g., 20 mg or preferably 40 mg of atorvastatin or simvastatin) for almost all high-risk patients irrespective of serum cholesterol. The guidelines have eschewed hypothetical unproven schemes like treatment to arbitrary LDL goals (Downs and O’Malley, 2015). In other words, the guidelines implicitly recognize that statins do not appreciably alter atherosclerosis but do prevent MI, stroke, and death by the mechanism noted above, and thereby reduce risk (Krumbholz and Hayward, 2010; Spector 2013; Downs and O’Malley, 2015).

Hypertension and Diabetes

Hypertension and diabetes have in common the ability to accelerate the development of atherosclerosis in large arteries and, in their more severe forms, to cause arteriolosclerosis, a separate problem. Arteriolosclerosis can manifest itself as lacunar infarcts in brain, kidney damage, retinal destruction, and, in diabetes, neuropathy owing to decreased blood flow to peripheral nerves. Current treatment of hypertension with inexpensive safe drugs (ACE inhibitors, angiotensin-receptor blockers, β-blockers, calcium channel blockers, and diuretics) is effective in lowering blood pressure; in many patients these drugs drastically reduce the risks of arteriolosclerosis and stroke (Mozaffarian, et al., 2016). Treatment of hypertension also slows the atheromatous process in large arteries. However, good control of diabetes slows the arteriolar damage but, for unclear reasons, does not have much effect on large artery atherosclerosis. In diabetes, statins and other drugs are needed to combat the risks of atherosclerosis (Downs and O’Malley, 2015; Mozaffarian, et al., 2016).

The Role of Diet

A tremendous number of epidemiology/observation studies and a few controlled trials have been published on the relationship between diet and ASCVD. The vast majority of these epidemiologic/observation studies suffer from multiple methodological deficiencies and the results are often ambiguous, misleading, or actually quantitatively incorrect, as pointed out by ourselves, and many others (Spector and Vesell, 2000; 2002, 2006a; Campbell and Campbell, 2006). These methodological deficiencies include poor validation of food questionnaires, infrequent or no assessment of change in diet, inattention to the Hill criteria for proving causality, improper use of statistics in nonrandomized studies, futile attempts to focus on one variable, “data dredging” (also termed data mining, i.e., looking for correlations in large data sets without a predetermined hypothesis, a procedure that leads to many false positive correlations), and many other errors (Spector and Vesell, 2000; 2002, 2006a; Campbell and Campbell, 2006). Two important examples of false positives studies include those that concluded that HRT and mega-vitamin E prevented ASCVD (Spector and Vesell, 2002). However, subsequent controlled trials show they were ineffective or harmful (Spector and Vesell, 2002). Another example is the advice some decades ago to switch from butter (saturated fat) to margarine on the basis of incorrect epidemiology/observation studies suggesting that saturated fat was harmful (Siri-Tarino et al., 2010); this was terrible advice since most margarine contains trans-fats, now known to be atherogenic. In recent years it has been recognized that eating saturated fat is in fact not harmful per se and the original studies were incorrect. Stampfer, the head of epidemiology at the Harvard School of Public Health, which carried out many of these earlier epidemiology/observation studies admitted, “This has been our greatest failure and disappointment—that we have not learned what people can do to lower their risk” [quoted in Campbell and Campbell (2006), who provided a detailed critique of such studies].

Because of the tremendous variability in such studies, several authors have published meta-analyses of nonrandomized epidemiology/observation studies in an attempt to answer certain questions. For example: Does red meat increase the risk of ASCVD? A recent meta-analysis of 20 epidemiology/observation studies with over one million individuals suggests it does not (Micha et al., 2010). Is this correct? See below.

However, there have been several, I believe, more revealing epidemiology studies. During and after the Second World War in England, there was more than a 50% decline in the incidence of diabetes and deaths from heart disease (Trowell, 1974). This was ascribed to the meager diets during and after the war. Consistent with the dietary hypothesis were studies of CAD and diabetes in Japanese men in Japan, Hawaii, and California (Kagan et al., 1974; Marmot et al., 1975; Worth et al., 1975; Tsunehara et al., 1990). At the time of these studies in Japanese men, there was a gradient by location, with CAD and diabetes being lowest in Japan, next Hawaii, and highest in California. The investigators in these studies suggested that the diet in Japan at the time was mainly a vegetarian-type diet and not the animal protein/fat diet of California. However, from these studies of Japanese men in Japan, Hawaii, and California, only qualitative conclusions can be drawn. Third the “China Study” showed that a mainly plant-based diet in China was associated with much less ASCVD than a nonvegetarian animal-based Western diet (Campbell and Campbell, 2006). Moreover, there have been several small controlled trials that have also suggested a vegetarian-type diet is better with respect to morbidity and mortality than a standard Western diet in patients with CAD (Campbell and Campbell, 2006).

A recent analysis of other studies in homogenous populations provides further powerful evidence for the efficacy of vegetarian diets in minimizing ASCVD mortality and morbidity. Unlike many of the negative or ambiguous studies that compared subjects who ate lesser or greater quantities of animal products noted above, e.g., the Nurses Study, these vegetarian studies compared vegetarians versus animal-product eaters (Fraser 2009). The results are clear and consistent: Vegetarians enjoy lower overall mortality and 32% lower incidence of coronary heart disease mortality than nonvegetarians. Moreover, there is a clear gradient in morbidity from vegans (no animal products permitted), to lacto-ovo vegetarians (eggs and milk permitted), to pesco-vegetarians (eggs, milk, and fish permitted), to semivegetarians, to nonvegetarians (Fraser, 2009).
However, causal interpretations are complex; between vegans and nonvegetarians there is also a gradient favoring vegans in body mass index (BMI), diabetes, and hypertension. Vegans in one study had a BMI 18% lower than nonvegetarians and a prevalence of diabetes and hypertension 22% and 25%, respectively, of nonvegetarians. Therefore, these results only allow one to conclude that a vegetarian (especially a vegan diet) is helpful in preventing ASCVD, but not to conclude exactly why. Is it the diet, the decreased BMI, blood pressure, diabetes, or a combination?

New Information

Thus, in 2010, by lowering risk factors we could effectively treat some patients with established ASCVD or prevent clinical ASCVD in those with risk factors. However, the underlying cause of atherosclerosis in the larger arteries remained unknown, although as noted above, there was convincing evidence that a vegetarian diet (especially a vegan diet) was healthier than the Western (animal-based) diet. By 2010, the best advice was Aristotle’s: “a sound mind in a sound body” and “moderation in all things.” This was translated into: Keep one’s weight at a level that maintained BMI between 20 and 25, be sure the diet contains the known essential nutrients (ions, vitamins, and essential fatty and amino acids), enjoy a balanced diet even including an occasional egg or two (Virtanen, et al., 2016), and tend toward a vegetarian diet; finally, do not forget to exercise.

However, beginning in 2011, investigators in the Cleveland Clinic and other venues published a series of groundbreaking papers suggesting TMAO formed from dietary TMA-containing nutrients, especially animal products, might, in fact, be the “toxic” metabolite, a prime cause of atherosclerosis (Wang et al., 2011; Koeth et al., 2013; Tang et al., 2013; Jonsson and Bäckhed, 2015; Shih et al., 2015; Troseid et al., 2015; Wang et al., 2015; Warrier et al., 2015). Basically, what these investigators have shown is that the TMA covalently incorporated in lecithin, choline, betaine, or carnitine can be metabolized in gut by bacterial lyases to release TMA, a gas. TMA is readily absorbed by mice and humans and converted to TMAO by liver FMO3; TMAO can cause atherosclerosis in mice (Wang et al., 2011). This process however is variable and complex. First, different gut bacteria have different abilities to form TMA from TMA-containing nutrients. This is in part because there are two distinct bacterial lyases; one consists of the cut C and cut D gene products and is termed cut C/D choline TMA lyase. The other consists of the Yea W/X gene products (Yea W/X TMA lyase). This promiscuous lyase can convert lecithin, choline, betaine, carnitine, and butyrobetaine to TMA (Falony et al., 2015; Wang et al., 2015). Both of these lyases are inhibitable to a greater or lesser extent by 3, 3 dimethyl-1-butanol (DMB) (Wang et al., 2015). There is also a third enzyme in human gut bacteria consisting of the gene products Cnt A and Cnt B termed carnitine Cnt A/B oxygenase/reductase that converts carnitine to TMA and malic semialdehyde (Falony et al., 2015; Wang et al., 2015). The quantitative importance of this enzyme remains uncertain. It is not inhibited by DNB (Wang et al., 2015). Some gut bacteria contain no TMA-forming enzymes; others contain one or two or all three of these enzymes (Falony et al., 2015). Further complicating matters, different individuals contain different levels of gut bacteria that can form TMA in vivo.

When TMA formation in mice is blocked with either DMB or antibiotics, TMAO is not formed, and in mice atherosclerosis is greatly diminished especially on a high-choline diet (Wang et al., 2015). Moreover, especially interesting is the finding that DNB blockade of lyase activity leads to gut bacteria with less lyase activity (Wang et al., 2015). It is worth noting the nontoxic DMB is found in balsamic vinegars, red wines and extra-virgin olive, and grapeseed oils (Wang et al., 2015).

After absorption, TMA is N-oxidized mainly by FMO3 (Wang et al., 2015; Warrier et al., 2015). Congenital absence of FMO3 leads to “fish odor syndrome,” a result of the inability to metabolize TMA; TMA smells like rotting fish (Wang et al., 2015). To avoid the odor, such patients avoid TMA-containing foods. In normal humans, TMA is almost completely N-oxidized to TMAO after a 600-mg TMA base “load” (Zhang et al., 1995). However, obligate heterozygotes (parents of fish odor–affected children) on a normal diet oxidize more than 90% of the TMA to TMAO, but after a 600-mg TMA base load they N-oxidize only 76 ± 3% to TMAO, clearly different than normal (96 ± 2%). (Zhang et al., 1995). Furthermore in a study of one-hundred volunteers challenged with a 600-mg base TMA, only one was within the range found among obligate heterozygotes (Zhang et al., 1995). Interestingly, in three normal Japanese women during menstruation, the ratio of TMA to TMAO in the urine increased to levels seen in obligate heterozygotes, suggesting a hormonal effect (Shimizu et al., 2007). If this observation can be confirmed and extended, it might explain why menstruating women are protected from ASCVD, i.e., lower production of the toxic TMAO.

In mice, there are large effects on FMO3 activity, with cholic acid causing upregulation and testosterone downregulation; inhibition of FMO3 has effects on reverse cholesterol transport (RCT), hepatic inflammation, and bile formation (Bennett et al., 2013; Warrier et al., 2015). Thus, inhibition of FMO3 to block formation of TMAO would not only cause fish odor syndrome but also might have effects on RCT, exacerbate hepatic inflammation, and have other complex effects. However, humans lacking FMO3, beside fish odor, are said to be healthy. Moreover, as noted above, normal humans (with the possible exception of menstruating women) efficiently convert TMA to TMAO, and the relevance of the mouse studies dealing with regulation of FMO3 (Bennett et al., 2013; Warrier et al., 2015) remains to be determined. In any case, it may be more acceptable to reduce dietary precursors of TMA than to reduce FMO3 activity.

In human studies, consistent with animal studies, TMAO was elevated in patients with ASCVD and could be suppressed with antibiotics, presumably by killing gut bacteria (Wang et al., 2015). Especially revealing was a 3-year prospective cohort study of 4007 patients with CAD in which an elevated TMAO was 2.5 times the lowest quintile; 95% confidence interval, 2–3.3; p>.001 (Tang et al., 2013). Likewise, TMAO was increased in heart-failure patients with ischemic heart disease (Troseeid et al., 2015).

This work has important implications for understanding much previous data. Assuming TMAO is the principal “culprit agent” (cause) of atherosclerosis, then it is clear why patients with normal cholesterol, weight, blood pressure, and blood sugar (i.e., without diabetes) and who don’t smoke could have severe ASCVD. They may produce excess TMAO because of...
Implications for Pharmacology

One of the most important decisions in drug discovery and development is the selection of the correct target (Spector and Vesell, 2006b). When this is done, the pharmaceutical industry has made remarkably safe and effective drugs and vaccines. In the current case, we have very strong preclinical and clinical data that TMAO lyases in gut bacteria are a worthy target, although there are different forms of this lyase in different bacterial species as noted above (Wang et al., 2015). DMB, which has an IC50 of ~10 μM in lysates of bacterial cells, is a weak competitive inhibitor but has been able to provide proof of principle (Wang et al., 2015; Jonsson and Bäckhed, 2015). The IC50 is probably much higher in intact bacterial cells. Extrapolating from the mouse work, probably 10–20 g a day of DMB in divided doses would be required in humans to inhibit intestinal bacterial lyase activity. What is needed is a full-throttle approach by the pharmaceutical companies to make a potent “broad-spectrum” bacterial lyase inhibitor, an inhibitor with an IC50 of more than 10 nM, preferably one not absorbed, so it “worked” only on bacteria in the gut or, if ultimately absorbed, rapidly metabolized. If such a compound was discovered, phase I and II trials in humans could be performed to test the compound’s ability to block TMAO production in vivo. Further development in large long-term phase III clinical trials versus placebo could be done to test (on top of statins and aspirin) whether such a compound could decrease MI, strokes, and cardiovascular deaths. If the TMAO hypothesis is correct, there should be a major effect. What is not known is exactly how TMAO might “cause” ASCVD in humans. With a potent lyase inhibitor as a tool, these hypotheses (RCT inhibition, platelet hyper-reactivity, and others) could be tested to help uncover the mechanism of TMAO toxicity if, in fact, TMAO is a causative factor in ASCVD.

In summary, in the past five years, several investigative groups have brought forward an exciting hypothesis for the actual cause of atherosclerosis. These investigators have also potentially explained the benefits of vegetarian-type diets. Moreover, they have provided strong evidence for a pharmacological target for the treatment and prevention of ASCVD (Wang et al., 2015; Zhu et al., 2016). If an effective broad-spectrum bacterial lyase inhibitor (or blocker of TMAO toxicity) can be discovered and developed that can prevent ASCVD, especially when coupled with a prudent vegetarian-type diet and exercise, we may at long last have effective tools to decrease substantially the morbidity and mortality currently associated with ASCVD.

Acknowledgments

The author thanks Michiko Spector for preparation of the manuscript.

Authorship Contributions

Wrote or contributed to the writing of the manuscript: Spector.

References


