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# The Niacin Rebirth: Revisiting the Potential of Nicotinic Acid Therapy for Cardiovascular Disease and Niacin Supplementation for Healthy Aging

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## ABSTRACT

The aging of the global population and the associated increase in chronic disease burden requires a paradigm shift in how we care for older adults, one that could benefit from exploring a return to nicotinic acid (NA) therapy for dyslipidemia management and niacin supplementation to support healthy aging. Despite the exceptional benefits NA demonstrated in the Coronary Drug Project for improving dyslipidemia, reducing cardiovascular disease (CVD), and enhancing longevity, it has since experienced a significant decline in usage. Several factors have contributed to this decline, including poor dosing and side effect management by providers; poor outcomes of subsequent trials that combined NA with statin drugs that, in retrospect, have been attributed to poor study design; and, a faulty meta-analysis that concluded NA did not significantly reduce CVD. In addition, recent research reveals statins increase the risk of dementia in older persons, and providers are urged to look for alternative ways to manage dyslipidemia. One alternative is NA. This review explains the factors that led to the decline in NA use, provides an overview of the lipid and non-lipid effects of niacin (as NA or nicotinamide) for treating dyslipidemia and other age-related diseases, describes clinical protocols that promote efficacy and patient compliance, and identifies other factors that may contribute to a revival of niacin usage, or a "Niacin Rebirth."

**Keywords:** niacin formulations, nicotinic acid, niacinamide, cardiovascular disease, glaucoma, chronic kidney disease, stroke, dyslipidemia, healthy aging.

## Introduction

Despite efforts to raise awareness, promote healthier habits, and leverage advances in medicine, cardiovascular disease (CVD) continues to be the leading cause of mortality and a major contributor to disability. Globally, the number of people with CVD has almost doubled from 271 million in 1990 to 523 million in 2019. Moreover, the estimated number of people dying prematurely as a result of CVD has dramatically increased from 12.1 million in 1990 to 18.6 million in 2019. During the same period, the number of years people live with CVD-related disabilities has almost doubled from 17.7 million to 34.4 million.[1]

Moreover, with the aging of the global population, the prevalence of age-related chronic conditions is expected to rise, increasing the demand for healthcare services and exerting financial pressure on individuals and healthcare systems alike.[2] This intersection of global aging and increasing disease burden requires a paradigm shift in how we care for older adults, one that could benefit from exploring a return to nicotinic acid (NA) therapy for dyslipidemia management and niacin to support healthy aging.

This review examines the reasons behind the decrease in the use of NA, provides an overview of the lipid and non-lipid effects of niacin (either as NA or nicotinamide) in the treatment of dyslipidemia and other age-related disease, describes clinical protocols that promote efficacy and patient compliance, and discusses potential factors that could lead to a resurgence in the utilization of niacin.

Niacin, or vitamin B3, comes in two forms: NA and nicotinamide (or niacinamide). NA is important for dyslipidemia management in individuals of all ages, with particular significance for older adults. NA is the best agent for raising high density lipoprotein (HDL) cholesterol,[3] and optimal levels have been shown to improve longevity.[4] NA is one of the best agents to reduce triglycerides. NA is not only effective at lowering low-density lipoprotein (LDL) cholesterol by 15% to 25%, but it also reduces LDL oxidation, which is necessary for the development of atherogenesis, and selectively lowers levels of small dense LDL particles which are the most atherogenic form.[5] NA is the only oral agent that can reduce high levels of lipoprotein (a) (Lp[a]), one of the most pathogenic forms of dyslipidemia.[6] In short, NA is the only agent that can improve every form of dyslipidemia, making it the best agent with which to initiate treatment of dyslipidemia in all persons, especially older persons. Moreover, preliminary results of a recent case series indicate NA may be a useful alternative to statin drugs in older individuals for lipid management, potentially reducing the risk of statin-induced dementia.[7]

Oral nicotinamide (and NA when metabolized by the liver to nicotinamide) are the precursors for the metabolic nutrient nicotinamide adenine dinucleotide (NAD+). NAD+ is an intracellular chemical that is essential for virtually every cell in the body for energy production and optimal cellular health and function. NAD+ is especially important to produce stem cells, the cells that are required for the replacement of damaged or worn-out cells in the body. Stem cell production and replacement are crucial for older adults because they require more of these cells, yet their ability to produce them decreases with age.

## Lipid Benefits of NA

The Coronary Drug Project, conducted from 1966 to 1975, was a nationwide clinical trial of 5 agents (d-thyroxine, high-dose estrogen, low-dose estrogen, clofibrate, and NA vs. placebo). At the time, each agent was thought to have a benefit for prevention of CVD. The d-thyroxine and both dosages of estrogen were eliminated from the study early because of serious side effects and lack of benefit. While both clofibrate and NA demonstrated lipid benefits (NA more than clofibrate), NA was the first agent to demonstrate a reduction in the risk of CVD. The study participants included 8,340 men, 30-64 years of age, who had a prior history of at least one heart attack. The treatment was 3,000-6,000 mg of regular (immediate release) NA taken for an average of 6 years. This NA treatment improved key lipid fractions, including total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides. Most importantly, NA treatment significantly reduced heart attacks by 27%, strokes by 24%, and cardiovascular surgery by 46% compared to placebo. A 15-year follow-up study revealed another benefit. Not only did NA treatment reduce the risk of death by 11% compared to placebo, but it also provided a long-term survival benefit, adding 1.6 years of life expectancy, on average.[8,9]

The results of the Coronary Drug Project focused new attention on clinical trials of NA for the management of dyslipidemia and prevention of CVD. Unfortunately, many of the early follow-up studies using immediate-release NA failed to instruct study participants in proper management of dosing to prevent flushing and other side effects. The Coronary Drug Project had a dropout rate of 9% due to flushing, whereas several of the follow up studies had up to 6 times that dropout rate due to flushing and other side effects. This inability to effectively manage the side effects of immediate-release NA tarnished the impressive results of the Coronary Drug Project, and refocused NA research for the next 2 decades (1980s and 1990s) on controlled-release formulations of NA to minimize side effects yet maintain benefits. In addition, this was the period when statin drugs were discovered, and their impressive management of LDL cholesterol further decreased enthusiasm for the use of NA for the management of dyslipidemia and prevention of CVD.

Nonetheless, an impressive amount of research in the 1980s and 1990s identified 2 controlled-release NA formulations that significantly reduced flushing side effects while improving dyslipidemia: polygel NA (Niaspan®, AbbVie, Inc.; Slo-Niacin®, MainPointe Pharmaceuticals, LLC) and wax-matrix NA (Endur-Acin®, Endurance Product Company, Inc.). Polygel NA studies with a controlled-release NA over 6-7 hours showed a moderate flushing dropout rate similar to the 9% dropout rate seen in the Coronary Drug Project. In addition, polygel NA was found to be particularly

effective in increasing HDL cholesterol levels. Since bowel peristalsis can accelerate polygel NA release, which can then increase flushing side effects, it is recommended to avoid taking polygel NA with meals.[10,11] By contrast, wax-matrix NA has a more reliable controlled-release rate over 6-8 hours and has been shown to be more effective than polygel NA at reducing LDL cholesterol with a dropout rate of only 3% to 8% . Unlike polygel NA, taking wax-matrix NA with meals promotes optimal tablet dissolution and NA release. Although, it is prudent to avoid particularly hot foods or drinks that could result in premature NA release and flushing.[12,13]

Metabolic syndrome is a condition characterized by a form of dyslipidemia associated with impaired insulin sensitivity, also known as prediabetes. It affects more than one third of adults in the United States. Its prevalence is even higher among older U.S. adults and in certain European countries, with close to 60% being affected. The dyslipidemia associated with metabolic syndrome is characterized by elevated triglycerides and low HDL cholesterol and is a significant risk for CVD. NA is the best agent with which to manage this specific type of dyslipidemia.[14,15] There is always concern that a medication may not work as well or have increased negative side effects in older persons. However, post hoc analysis of a wax-matrix NA dosing study showed that older participants had better lipid benefits with fewer side effects than younger participants on similar dosing.[16]

## Non-Lipid Benefits of NA and Nicotinamide

In addition to the lipid benefits of NA, additional studies reveal a wide range of significant non-lipid benefits. One benefit is the reduction of vascular inflammation/reactive oxygen species and prevention of oxidation of LDL cholesterol, thereby reducing its atherogenic potential.[17] Another important non-lipid benefit is the ability of NA to reduce intravascular adhesion molecules and monocyte chemo-attractant protein-1, both atherogenesis initiators.[18] This benefit has become increasingly significant with the discovery of 5 oral flora pathogens (Bale-Doneen research) that can cause a heart attack if they get into the bloodstream.[19] Oral hygiene problems like gingivitis, cavities, dental abscess, among others that are more common in older people increase the risk of this dangerous bacteremia. However, NA reduces this risk by reducing the intravascular adhesion molecules needed for the pathogens to attach to vascular intima and trigger inflammation and clotting. Interestingly, the Coronary Drug Project showed NA can reduce the incidence of stroke, and subsequent animal studies suggest that NA may also reduce the size and functional recovery time of acute stroke.[20] Even relatively low dosages of NA (100-500 mg, 1-3 times per day) have been shown to help improve renal function in persons with kidney failure and can be critical in helping such patients (mostly older persons) avoid progression of renal failure to needing dialysis.[21] Ultrasound monitoring of vascular intimal thickness of coronary and carotid arteries during an NA study showed progressive decrease in intimal thickness of 17 microm/year.[22] NA is literally "cleaning the pipes." Part of liver metabolism of NA includes adding a methyl group to NA to convert it to nicotinamide, which is the precursor of NAD+. NAD+, as mentioned earlier, is critical for intracellular energy and stem cell production. This is so important for older people that it is appropriate to add the nicotinamide form of niacin (1,500-3,000 mg/day) to the daily regimen of persons 65 years and older. Nicotinamide has also been shown to help prevent/improve glaucoma, the most common cause of blindness in older persons.[23] Moreover, aging cells and tissues may require more NAD+ to meet metabolic demands, lose their ability to adequately synthesize NAD+, or both.[24]

## NA Use Plummets Due to Two Large "Flawed" Clinical Trials

At the beginning of the 21st century, the increasing global incidence of mortality from CVD and the prevalence of metabolic syndrome as one of the main risk factors stimulated interest in finding other agents that could complement statins in managing dyslipidemia. The Coronary Drug Project had already shown benefits of immediate-release NA in managing the dyslipidemia of metabolic syndrome. The improvement of controlled-release formulations over immediate-release NA in both lipid benefits (e.g., increase in HDL cholesterol and reduction of triglycerides) and management of flushing and other side effects made controlled-release NA a logical choice. However, two large studies with serious design flaws would soon cast doubt on the effectiveness of NA.

The first flawed study was a large controlled clinical trial started in 2006 called the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH) trial.[25] After screening for suitable study participants, the researchers ultimately assigned over 3,400 patients, aged 45 years and older, who had vascular disease and abnormal blood lipid profiles, to one of two treatment groups. All participants were on statin therapy and, if needed, a second drug (ezetimibe) to keep the blood level of LDL cholesterol in an optimal range between 1.03 mmol/L (40 mg/dl) and 2.07 mmol/L (80 mg/dl). Those assigned to the control group took only the statins (with ezetimibe, as needed). Those assigned to the treatment group added controlled-release NA (2,000 mg/day) in the form of the prescription drug Niaspan to their statin/ezetimibe therapy. Follow up was supposed to last for up to about 7 years, similar to the length of the Coronary Drug Project. But the AIM-HIGH trial was stopped prematurely after only 3 years because of a suspected increase in the incidence of strokes in the statin/NA combination group. The differences in blood lipid levels observed between the groups were relatively modest, so researchers concluded the addition of NA to statins does not improve cardiovascular outcomes. Unfortunately, the disappointing conclusions published after the AIM-HIGH trial seriously damaged the reputation of NA even though a post hoc analysis of the AIM HIGH study showed the concern for increased strokes in the statin/NA combination group was a statistical error.[26] Further analysis of the participants on the statin/NA combination with the highest levels of

triglycerides and lowest levels of HDL cholesterol also showed that they did have a significant reduction in death and cardiovascular events.[27] In addition, further post hoc analysis of the lipids revealed a trend in lipid improvements that likely would have produced positive results that would support the use of NA with statins if the study had been continued for 7 years.[28] Unfortunately, the post hoc studies of AIM-HIGH were not widely shared. As a result, the general perception that NA does not help statins in managing metabolic syndrome and may even cause harm has persisted.

The second flawed clinical trial started in 2007. It was significantly larger than the AIM-HIGH trial with over 7 times the number of participants. It was called the Heart Protection Study 2: Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trial.[29] For this global trial, researchers enrolled more than 25,670 adults, between the ages of 50 to 80 years, who had vascular disease and were already taking a statin drug to control LDL cholesterol. The researchers randomly assigned the participants to one of two groups: Niaspan prescription drug (2,000 mg/day) with laropiprant, a non-steroidal anti-inflammatory drug to help reduce flushing side effects, or a matching placebo. For most participants, follow up lasted about 4 years that, like the AIM HIGH trial, was significantly shorter than the Coronary Drug Project. The initial enthusiasm for this study was even greater than that for the AIM-HIGH trial since it included a much larger, global study group and included laropiprant to reduce NA flushing side effects. The investigators had no idea when designing the study that the NA/laropiprant combination would cause a dramatic increase in myopathies, especially in the Chinese participants. Of the 25,673 study participants, over 11,000 were Chinese, and their annual incidence of myopathy was 800% greater than that for the European participants on the same treatment.[30] The main conclusion of the HPS2-THRIVE study was similar to that of the AIM-HIGH study: The addition of NA to statin therapy not only failed to improve cardiovascular outcomes, it may increase serious adverse effects.[31]

The NA "death sentence" that resulted from these large trials was further reinforced by the publication of an NA meta-analysis in 2019 that concluded that NA therapy does not improve clinical outcomes in dyslipidemia.[32] Remarkably, over 83% of the data used in this meta-analysis came from the AIM HIGH and HPS2-THRIVE trials with no mention of the trial design flaws. Moreover, almost all of the studies (13/15) included in the meta-analysis had a relatively short duration of 3-4 years. The only 2 studies that showed significant improvement in CVD lasted at least 6 years. Interestingly, the meta-analysis failed to conclude that the appropriate length of NA treatment should be at least 6 years to demonstrate benefits, but it did report that virtually all the NA studies showed improvement in lipoproteins.

With the global increase in mortality from CVD and the significant rate of statin drug intolerance (18% to 20%), the search for effective complementary or replacement drugs for statins continues.[33] The one drug that appears to meet these criteria for managing high risk dyslipidemia is proprotein-convertase subtilisin/kexin type 9 (PCSK-9) inhibitors.[34] Unfortunately, the drug costs over $15,000 per year, making it unaffordable for most developing countries and financially dependent populations in developed countries, who make up 80% of the high-risk individuals.[35] The fact that many clinical trials of both NA monotherapy and combined NA/statin treatment of dyslipidemia have demonstrated positive lipid benefits and that wax-matrix NA is only about $170 per year indicates that a "rebirth" of NA is needed.

## A Niacin Rebirth

Clinicians who were aware of the post hoc evaluation of the AIM-HIGH study have remained interested in the use of NA with statins and were looking forward to the results of the HPS2-THRIVE study. Like the AIM-HIGH study, the disappointing results of the HPS2-THRIVE study were also felt to be due to a poor study design. Critics of the HPS2-THRIVE trial felt the addition of laropiprant to the NA treatment group confounded the outcomes and, as a result, they do not accept it as a legitimate study of the combination of NA and statin therapy.[31] While this controversy still lingers, many feel the effectiveness of NA in reducing LDL cholesterol (especially small dense LDL cholesterol particles) as well as the other lipid benefits as shown in earlier studies continues to make NA an appropriate combination with statins to achieve lipid goals and desired clinical endpoints.[31]

Critics of the bedtime NA dosing used in the AIM-HIGH and HPS2-THRIVE studies point out that dosing NA in a fasting or near fasting state causes a drop in non-esterified fatty acids. This, in turn, can inadvertently cause a transient drop in blood glucose that triggers release of epinephrine and hepatic gluconeogenesis. This may have caused some of the negative results found in those studies. Most of the polygel NA studies also used once daily dosing at bedtime with a small snack for convenience (it could be taken at the time when a statin is supposed to be given) and to match the time of peak hepatic lipid synthesis. The polygel NA formulations also have a somewhat higher rate of flushing than the wax-matrix NA formulations, so giving it in a near fasting state may also reduce the chance of early breakdown of the polygel delivery that can happen with the increased peristaltic activity of a meal. By contrast, wax-matrix NA is taken with meals, so it does not cause this potential problem, and its reliable release of NA over 6-8 hours is more effective than the polygel formulations at reducing LDL cholesterol.

The continued interest in the potential lipid benefits of wax-matrix NA and the benefits of both NA and nicotinamide and other supplements for healthy aging such as berberine,[36,37,38,39,40] taxifolin,[41,42,43,44,45] and mixed tocotrienols[46,47,48,49,50,51,52,53,54] led our research group to develop a case series that addresses several issues related to aging, including the reduction or elimination of statin drug use. The study has been completed and full results are expected to be published soon. However, given chronic statin therapy in older persons can increase the risk of dementia and may increase muscle and joint pain, it is worth noting here

that all 7 of the study completers who were on statin drugs at study entry were able to eliminate use of the drug while maintaining blood lipid levels that are as good and often better than their baseline entry levels on statins.

Findings from this case series also support the lessons learned from prior wax-matrix NA studies, including the importance of a "start low and go slow" approach when initiating NA treatment. Even though the average maintenance dosage of wax-matrix NA for most patients is 750-1,000 mg twice daily with meals (or 1,500-2,000 mg/day), it will dramatically increase flushing and other adverse side effects if treatment is initiated at that level.

Before initial NA dosing, baseline blood lipids, including Lp(a), should be obtained. Baseline values for the liver enzymes aspartate transferase (AST) and alanine transaminase (ALT), uric acid, and homocysteine should also be measured and, if in the normal range, treatment can be initiated with 250 mg of wax-matrix NA given twice daily with meals. To reduce the risk of flushing, meals should avoid excessively hot foods and drinks. To reduce the risk of liver toxicity, meals should also include methyl donor foods. If the patient tolerates the initial dosing for the first 1-2 weeks and has normal baseline blood tests, the dosage may be advanced to 500 mg twice daily with meals/methyl donor foods and maintained at that level for 6 weeks. It is then appropriate to retest lipid levels, liver function, uric acid and homocysteine to assess lipid response and detect any risk of toxicity early. One NA metabolite, nicotinuric acid, can compete with renal excretion of uric acid and increase the risk of a gout attack, but that can be avoided if it is detected early and preventive measures taken. Problems with elevated homocysteine levels can be eliminated if detected early by simply adding a vitamin B12/folate supplement.

Perhaps the most important aspect of the "start low and go slow" dose-initiating practice is the monitoring of liver function (i.e., AST and ALT tests). Our prior wax-matrix NA dosing studies have shown that approximately 10% of individuals experience liver hypersensitivity to NA. As a result, they develop liver toxicity with elevated liver enzymes and severe dysphoria, along with gastroenteritis symptoms, when taking the typical maintenance level dosage of NA. Previously, it was believed that these patients were unable to tolerate NA and would be removed from NA therapy. However, our research has shown that they can do very well and have even better lipid results if the sensitivity is detected early, and they are maintained on the lower dosage (e.g., 500 mg wax-matrix NA twice daily). Two of the participants in our case series were found to have NA hypersensitivity. Although their elevated lipid levels were improving with NA therapy, they had to temporarily pause NA treatment to allow for remission of side effects before resuming NA therapy at a lower dosage.

## Conclusion

The 2023 World Health Report reveals alarming statistics of rising mortality rates from CVD. This trend is particularly pronounced in eastern Europe, Asia, India, and Africa where there are limited resources available for managing healthcare. Additionally, in the United States and Europe, the prevalence of metabolic syndrome is increasing among older individuals.[55] Furthermore, managing CVD with only lifestyle interventions (e.g., diet, exercise) continues to lack any meaningful impact, especially in developing countries. The result is a worldwide need for affordable and effective interventions that can help reverse this trend. Moreover, while statins remain the preferred pharmaceutical option for most providers for managing dyslipidemia, their affordability in developing countries can be a challenge. In addition, statins have been shown to deplete intracellular levels of CoQ10,[56] an important molecule for muscular health and function. This statin-induced CoQ10 depletion contributes to a high rate of statin intolerance, reaching approximately 18% to 20%.[57] Statins have also been shown to cause dementia in older people, which can further limit their utility in this population. PCSK9 inhibitors have been shown to be an effective pharmaceutical option for managing dyslipidemia and quite helpful for persons with statin intolerance; however, the high cost makes this option unaffordable for much of the population at risk of CVD.[58] These factors—the alarming global rise in mortality from CVD, the failure of lifestyle intervention, and the adverse effects and cost burden of drugs—is likely to contribute to a resurgence in the use of niacin, a "Niacin Rebirth."

It's time to revisit the early impressive NA research, understand the flaws in subsequent studies, and invest in well-designed clinical trials to help practitioners understand the therapeutic value of niacin as an affordable, effective option to manage all types of dyslipidemia and support healthy aging.

In summary:

1. NA is the best agent to raise HDL cholesterol levels, which improves reverse cholesterol transport and helps "clean the pipes." Higher levels of HDL have been linked to increased longevity.
2. NA is one of the best agents to reduce triglycerides, part of the dyslipidemia of metabolic syndrome that is increasing in our older population.
3. NA is quite good at reducing LDL cholesterol (15% to 20%), and specifically reduces the most pathogenic small dense LDL particles and prevents oxidation of LDL, which makes LDL pathogenic.
4. NA is the only oral agent that can reduce Lp(a), a pathogenic lipoprotein associated with CVD, especially stroke in older men.
5. Beyond lipid benefits, nicotinamide (a NA metabolite) as well as the nicotinamide form of niacin (vitamin B3) are essential for intracellular energy metabolism of every cell in the body. Nicotinamide also provides critical precursors to produce stem cells, which are necessary for replacing damaged cells in the body. This function is particularly important for older individuals.
6. NA, even in low dosages (100-500 mg, 1-3 times per day) can improve renal failure and help older

people avoid progression to dialysis or transplant.

7. NA and its unique ability to reduce the monocyte chemo-attractant protein A-1 helps prevent intravascular plaque formation and reduce heart attack risk of pathogenic oral flora bacteria.
8. Last, but not least, our research has shown that the wax-matrix form of controlled-release NA is not only the best NA formulation to reduce LDL cholesterol without excess flushing or other side effects, it is also one of the least expensive therapeutic options currently available.

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## References


1. Roth GA, Mensah GA, Johnson CO, et al. Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 study [published correction appears in *J Am Coll Cardiol*. 2021 Apr 20;77(15):1958-1959. Doi: 10.1016/j.jacc.2021.02.039]. *J Am Coll Cardiol*. 2020;76(25):2982-3021. Doi:10.1016/j.jacc.2020.11.010

2. Chang AY, Skirbekk VF, Tyrovolas S, Kassebaum NJ, Dieleman JL. Measuring population ageing: an analysis of the Global Burden of Disease Study 2017. *Lancet Public Health*. 2019;4(3):e159-e167. Doi:10.1016/S2468-2667(19)30019-2

3. Lukasova M, Hanson J, Tunaru S, Offermanns S. Nicotinic acid (niacin): new lipid-independent mechanisms of action and therapeutic potentials. *Trends Pharmacol Sci*. 2011;32(12):700-707. Doi:10.1016/j.tips.2011.08.002

4. Rahilly-Tierney CR, Spiro A, 3rd, Vokonas P, Gaziano J.M. Relation between high-density lipoprotein cholesterol and survival to age 85 years in men (from the VA Normative Aging Study). *Am J Cardiol*. 2011;107:1173–1177. Doi: 10.1016/j.amjcard.2010.12.015.

5. Jellinger PS. American Association of Clinical Endocrinologists/American College of Endocrinology management of dyslipidemia and prevention of cardiovascular disease clinical practice guidelines. *Diabetes Spectr*. 2018;31(3):234-245. Doi:10.2337/ds18-0009

6. Sahebkar A, Reiner Ž, Simental-Mendía LE, Ferretti G, Cicero AF. Effect of extended-release niacin on plasma lipoprotein(a) levels: a systematic review and meta-analysis of randomized placebo-controlled trials. *Metabolism*. 2016;65(11):1664-1678. Doi:10.1016/j.metabol.2016.08.007

7. Prasanna P, Liu S, Silverman D. Lipophilic statins in subjects with early mild cognitive impairment: associations with conversion to dementia and decline in posterior cingulate brain metabolism in a long-term prospective longitudinal multi-center study. *J Nucl Med*. 2021;62(supp 1). Abstract 102.

8. Berge KG, Canner PL. Coronary drug project: experience with niacin. Coronary Drug Project Research Group. *Eur J Clin Pharmacol*. 1991;40 Suppl 1:S49-S51. Doi.org/10.1007/BF03216290.

9. Canner PL, Berge KG, Wenger NK, et al. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. *J Am Coll Cardiol*. 1986;8(6):1245-1255. Doi:10.1016/s0735-1097(86)80293-5.

10. Morgan JM, Capuzzi DM, Guyton JR, et al. Treatment effect of Niaspan, a controlled-release niacin, in patients with hypercholesterolemia: a placebo-controlled trial. *J Cardiovasc Pharmacol Ther*. 1996;1(3):195-202. Doi:10.1177/107424849600100302.

11. Knopp RH, Alagona P, Davidson M, et al. Equivalent efficacy of a time-release form of niacin (Niaspan) given once-a-night versus plain niacin in the management of hyperlipidemia. *Metabolism*. 1998;47:1097-1104. Doi:10.1016/s0026-0495(98)90284-0.

12. Keenan JM, Fontaine PL, Wenz JB, Myers S, Huang ZQ. Niacin revisited: a randomized, controlled trial of wax-matrix sustained-release niacin in hypercholesterolemia. *Arch Intern Med*. 1991;151(7):1424-1432. Doi:10.1001/archinte.151.7.1424.

13. Keenan JM. Wax-matrix extended-release niacin vs inositol hexanicotinate: a comparison of wax-matrix, extended-release niacin to inositol hexanicotinate "no-flush" niacin in persons with mild to moderate dyslipidemia. *J Clin Lipidol*. 2013;7(1):14-23. Doi:10.1016/j.jacl.2012.10.004.

14. Shin D, Kongpakpaisarn K, Bohra C. Trends in the prevalence of metabolic syndrome and its components in the United States 2007-2014. *Int J Cardiol*. 2018;259:216-219. Doi:10.1016/j.ijcard.2018.01.139.

15. Canner PL, Furberg CD, McGovern ME. Benefits of niacin in patients with versus without the metabolic syndrome and healed myocardial infarction (from the Coronary Drug Project). *Am J Cardiol*. 2006;97(4):477-479. Doi:10.1016/j.amjcard.2005.08.070.

16. Keenan JM, Bae CY, Fontaine PL, et al. Treatment of hypercholesterolemia: comparison of younger versus older patients using wax-matrix sustained-release niacin. *J Am Geriatr Soc*. 1992;40(1):12-18. Doi:10.1111/j.1532-5415.1992.tb01822.x.

17. Li Y, Yang G, Yang X, et al. Nicotinic acid inhibits vascular inflammation via the SIRT1-dependent signaling pathway. *J Nutr Biochem*. 2015;26(11):1338-1347. Doi:10.1016/j.jnutbio.2015.07.006.

18. Kamanna VS, Kashyap ML. Mechanism of action of niacin. *Am J Cardiol*. 2008;101(8A):20B-26B. Doi:10.1016/j.amjcard.2008.02.029.

19. Bale BF, Doneen AL, Vigerust DJ. High-risk periodontal pathogens contribute to the pathogenesis of atherosclerosis. *Postgrad Med J*. 2017;93(1098):215-220. Doi:10.1136/postgradmedj-2016-134279.

20. Shehadah A, Chen J, Zacharek A, et al. Niaspan treatment induces neuroprotection after stroke. *Neurobiol Dis*. 2010;40(1):277-283. Doi:10.1016/j.nbd.2010.05.034.

21. McConnell S, Penberthy WT. Reversing chronic kidney disease with niacin and sodium bicarbonate [press release]. Wichita, KS: Orthomolecular Medicine News Service; October 14, 2021. http://orthomolecular.org/resources/omns/v17n22.shtml. Accessed May 29, 2024.

22. Bruckert E, Labreuche J, Amarenco P. Meta-analysis of the effect of nicotinic acid alone or in combination on cardiovascular events and atherosclerosis. *Atherosclerosis*. 2010;210(2):353-361. Doi:10.1016/j.atherosclerosis.2009.12.023.

23. Tribble JR, Otmani A, Sun S, et al. Nicotinamide provides neuroprotection in glaucoma by protecting against mitochondrial and metabolic dysfunction. *Redox Biol*. 2021;43:101988. Doi:10.1016/j.redox.2021.101988.

24. McReynolds MR, Chellappa K, Baur JA. Age-related NAD+ decline. *Exp Gerontol*. 2020;134:110888. Doi: 10.1016/j.exger.2020.110888.

25. AIM-HIGH Investigators. The role of niacin in raising high-density lipoprotein cholesterol to reduce cardiovascular events in patients with atherosclerotic cardiovascular disease and optimally treated low-

density lipoprotein cholesterol: rationale and study design. The Atherothrombosis Intervention in Metabolic syndrome with low HDL/high triglycerides: Impact on Global Health outcomes (AIM-HIGH). *Am Heart J*. 2011;161(3):471-477.e2. Doi:10.1016/j.ahj.2010.11.017.

26. Teo KK, Goldstein LB, Chaitman BR, et al. Extended-release niacin therapy and risk of ischemic stroke in patients with cardiovascular disease: the Atherothrombosis Intervention in Metabolic syndrome with low HDL/High Triglycerides: Impact on Global Health outcome (AIM-HIGH) trial. *Stroke*. 2013;44(10):2688-2693. Doi:10.1161/STROKEAHA.113.001529.

27. Guyton JR, Slee AE, Anderson T, et al. Relationship of lipoproteins to cardiovascular events: the AIM-HIGH Trial (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes). *J Am Coll Cardiol*. 2013;62(17):1580-1584. Doi:10.1016/j.jacc.2013.07.023.

28. Toth PP, Jones SR, Slee A, et al. Relationship between lipoprotein subfraction cholesterol and residual risk for cardiovascular outcomes: a post hoc analysis of the AIM-HIGH trial. *J Clin Lipidol*. 2018;12(3):741-747.e11. Doi:10.1016/j.jacl.2018.03.077.

29. HPS2-THRIVE Collaborative Group, Landray MJ, Haynes R, et al. Effects of extended-release niacin with laropiprant in high-risk patients. *N Engl J Med*. 2014;371(3):203-212. Doi:10.1056/NEJMoa1300955.

30. HPS2-THRIVE Collaborative Group. HPS2-THRIVE randomized placebo-controlled trial in 25 673 high-risk patients of ER niacin/laropiprant: trial design, pre-specified muscle and liver outcomes, and reasons for stopping study treatment. *Eur Heart J*. 2013;34(17):1279-1291. Doi:10.1093/eurheartj/eht055.

31. Superko HR, Zhao XQ, Hodis HN, Guyton JR. Niacin and heart disease prevention: engraving its tombstone is a mistake. *J Clin Lipidol*. 2017;11(6):1309-1317. Doi:10.1016/j.jacl.2017.08.005.

32. D'Andrea E, Hey SP, Ramirez CL, Kesselheim AS. Assessment of the role of niacin in managing cardiovascular disease outcomes: a systematic review and meta-analysis. *JAMA Netw Open*. 2019;2(4):e192224. Doi:10.1001/jamanetworkopen.2019.2224.

33. Saxon DR, Eckel RH. Statin Intolerance: a literature review and management strategies. *Prog Cardiovasc Dis*. 2016;59(2):153-164. Doi:10.1016/j.pcad.2016.07.009.

34. Arrieta A, Page TF, Veledar E, Nasir K Economic evaluation of PCSK9 inhibitors in reducing cardiovascular risk from health system and private payer perspectives. *PLoS One*. 2017;12(1):e0169761. Doi:10.1371/journal.pone.0169761.

35. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet*. 2006;367(9524):1747-1757. Doi:10.1016/S0140-6736(06)68770-9.

36. Lan J, Zhao Y, Dong F, et al. Meta-analysis of the effect and safety of berberine in the treatment of type 2 diabetes mellitus, hyperlipemia and hypertension. *J Ethnopharmacol*. 2015;161:69-81. Doi:10.1016/j.jep.2014.09.049

37. Zhang P, Ma D, Wang Y, et al. Berberine protects liver from ethanol-induced oxidative stress and steatosis in mice. *Food Chem Toxicol*. 2014;74:225-232. Doi:10.1016/j.fct.2014.10.005

38. Warowicka A, Nawrot R, Goździcka-Józefiak A. Antiviral activity of berberine. *Arch Virol*. 2020;165(9):1935-1945. Doi:10.1007/s00705-020-04706-3

39. Imenshahidi M, Hosseinzadeh H. Berberine and barberry (Berberis vulgaris): A clinical review. *Phytother Res*. 2019;33(3):504-523. Doi:10.1002/ptr.6252

40. Feng R, Shou JW, Zhao ZX, et al. Transforming berberine into its intestine-absorbable form by the gut microbiota. *Sci Rep*. 2015;5:12155. Doi:10.1038/srep12155

41. Sunil C, Xu B. An insight into the health-promoting effects of taxifolin (dihydroquercetin). *Phytochemistry*. 2019;166:112066. Doi:10.1016/j.phytochem.2019.112066

42. Joo SJ, Park HJ, Park JH, et al. Flavonoids from Machilus japonica stems and their inhibitory effects on LDL oxidation. *Int J Mol Sci*. 2014;15(9):16418-16429. Doi:10.3390/ijms150916418

43. Kolhir VK, Bykov VA, Teselkin YO, et al. Use of a new antioxidant diquertin as an adjuvant in the therapy of patients with acute pneumonia. *Phytother Res*. 1998;12:606-608. Doi.org/10.1002/(SICI)1099-1573(199812)12:8<606::AID-PTR367>3.0.CO;2-U

44. Gogoi N, Chowdhury P, Goswami AK, Das A, Chetia D, Gogoi B. Computational guided identification of a citrus flavonoid as potential inhibitor of SARS-CoV-2 main protease. *Mol Divers*. 2021;25(3):1745-1759. Doi:10.1007/s11030-020-10150-x

45. Fischer A, Sellner M, Neranjan S, Smieško M, Lill MA. Potential inhibitors for novel coronavirus protease identified by virtual screening of 606 million compounds. *Int J Mol Sci*. 2020;21(10):3626. Doi:10.3390/ijms21103626

46. Naomi R, Shafie NH, Kaniappan P, Bahari H. An interactive review on the role of tocotrienols in the neurodegenerative disorders. *Front Nutr*. 2021;8:754086. Doi:10.3389/fnut.2021.754086

47. Gopalan Y, Shuaib IL, Magosso E, et al. Clinical investigation of the protective effects of palm vitamin E tocotrienols on brain white matter. *Stroke*. 2014;45(5):1422-1428. Doi:10.1161/STROKEAHA.113.004449

48. Yuen KH, et al. Effect of mixed-tocotrienols in hypercholesterolemic subjects. *Funct Foods Health Dis*. 2011;3:106-117. Doi.org/10.31989/ffhd.v1i3.136

49. Anstey KJ, Ashby-Mitchell K, Peters R. Updating the evidence on the association between serum cholesterol and risk of late-life dementia: review and meta-analysis. *J Alzheimers Dis*. 2017;56(1):215-228. Doi:10.3233/JAD-160826

50. O'Byrne D, Grundy S, Packer L, et al. Studies of LDL oxidation following alpha-, gamma-, or delta-tocotrienyl acetate supplementation of hypercholesterolemic humans. *Free Radic Biol Med*. 2000;29(9):834-845. Doi:10.1016/s0891-5849(00)00371-3

51. Radhakrishnan A, Tudawe D, Chakravarthi S, Chiew GS, Haleagrahara N. Effect of γ-tocotrienol in

counteracting oxidative stress and joint damage in collagen-induced arthritis in rats. *Exp Ther Med*. 2014;7(5):1408-1414. Doi:10.3892/etm.2014.1592
52. Lewis ED, Meydani SN, Wu D. Regulatory role of vitamin E in the immune system and inflammation. *IUBMB Life*. 2019;71(4):487-494. Doi:10.1002/iub.1976
53. Lu Y, Zhang Y, Pan Z, et al. Potential "therapeutic" effects of tocotrienol-rich fraction (TRF) and carotene "against" bleomycin-induced pulmonary fibrosis in rats via TGF-β/Smad, PI3K/Akt/mTOR and NF-κB signaling pathways. *Nutrients*. 2022;14(5):1094. Doi:10.3390/nu14051094
54. Sailo BL, Banik K, Padmavathi G, Javadi M, Bordoloi D, Kunnumakkara AB. Tocotrienols: The promising analogues of vitamin E for cancer therapeutics. *Pharmacol Res*. 2018;130:259-272. Doi:10.1016/j.phrs.2018.02.017
55. World Heart Federation. World Heart Report 2023: Confronting the World's Number One Killer. Geneva, Switzerland. https://world-heart-federation.org/wp-content/uploads/World-Heart-Report-2023.pdf. Published 2023. Accessed May 29, 2024.
56. Qu H, Guo M, Chai H, Wang WT, Gao ZY, Shi DZ. Effects of coenzyme q10 on statin-induced myopathy: an updated meta-analysis of randomized controlled trials. *J Am Heart Assoc*. 2018;7(19):e009835. Doi:10.1161/JAHA.118.009835
57. Saxon DR, Eckel RH. Statin intolerance: a literature review and management strategies. *Prog Cardiovasc Dis*. 2016;59(2):153-164. Doi:10.1016/j.pcad.2016.07.009
58. Arrieta A, Page TF, Veledar E, Nasir K. Economic evaluation of PCSK9 inhibitors in reducing cardiovascular risk from health system and private payer perspectives. *PLoS One*. 2017;12(1):e0169761. Doi:10.1371/journal.pone.0169761