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# The Role of Niacin in the Management of Dyslipidemia

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## Abstract

Niacin or nicotinic acid has been used for the management of dyslipidemia for over 50 years, and it is the first medication that has been shown to reduce both coronary disease events and mortality. It is unique among the various lipid therapies in that it can not only reduce all of atherogenic lipid fractions (total cholesterol, low-density lipoprotein, very low-density lipoprotein, non-HDL lipoproteins, and triglycerides), but is also the most effective agent for raising high-density lipoprotein (specifically Apolipoprotein A-1). It is also the only lipid therapy that can lower lipoprotein (a). Niacin also has non-lipid benefits that improve vascular health and reduce atherogenesis. Niacin therapy was initially hampered by a high incidence of side effects, especially flushing, but this has largely been overcome by extended-release formulations and dosing and administering properly. Despite the failure of two recent clinical trials to show benefit of combining niacin with statins, there are many trials that support using niacin as monotherapy or in combination with other lipid agents including statins. Niacin is also the cheapest lipid agent available, and with the epidemic of cardiovascular disease in the world, it offers great value in the population-wide management of this health problem.

**Keywords:** niacin, nicotinic acid, HDL-C, Lp(a), niacin formulations

## 1. Background: early niacin trials

Niacin or vitamin B3 comes in two forms, nicotinamide and nicotinic acid (NA), but only NA has lipid management benefits. The recommended daily allowance of vitamin B3 for nutritional benefit is only 20–30 mg/day, but the dose needed for lipid benefits is much higher and depends on whether one is using immediate-release (IRNA) 3000–6000 mg/day or extended-release (ERNA) 1000–2000 mg/day formulations [1, 2]. The lipid benefits of NA were discovered serendipitously in the 1940–1950s when mega-doses of vitamins were being used in the management of mental health disorders. It was noted that high doses of NA lowered total cholesterol significantly. It was at that same time that elevated cholesterol was found to be associated with increased risk of cardiovascular disease (CVD) that led to the early trials of NA for management of dyslipidemia. Investigators in those early studies did not know what the mechanism of action of NA was but they were impressed that not only did NA lower total cholesterol by 20+%, but also specifically lowered beta lipoprotein cholesterol (LDL-C), raised alpha lipoprotein cholesterol (HDL-C), and lowered triglycerides (TG) [3, 4].

It became evident at that time that high cholesterol was not only associated with increased risk of CVD, but also diet and lifestyle interventions were usually not adequate to reduce cholesterol levels. This led to a large clinical trial, The Coronary Drug Project, that was a head to head trial of the cholesterol lowering agents available then (Thyroxine, Estrogen-two forms, Clofibrate and IRNA). The study was conducted from 1969 to 1975 and had five treatment arms and a large placebo arm totaling 8341 subjects [5]. The thyroxine and both estrogen treatment arms were terminated early due to lack of benefit and the clofibrate arm had some lipid improvements that failed to show reduction in coronary events. The IRNA arm not only demonstrated significant improvements in clinically important lipid fractions (total cholesterol, LDL-C, HDL-C, and TG) but, more importantly, it had a significant decrease in coronary events compared to placebo group. In addition, long-term (15 years) follow-up showed 11% decrease in mortality in the IRNA group compared to the placebo [6]. The only negative aspect of the Coronary Drug Project was the high incidence of flushing (>60%) in the IRNA treatment group. The immediate-release formulation of NA was used in that study, and, even though the majority of subjects were able to develop some level of tolerance, 8% had to drop out due to flushing.

2. NA mechanism of action

Nicotinic acid offers multiple clinical benefits to the lipid profile but the most unique and important is its ability to raise HDL-C. The 2017 Guidelines on the Management of Dyslipidemia list low HDL-C and a major risk factor for coronary disease because of important role of HDL-C in reverse cholesterol transport [7]. No agent is more potent at raising HDL-C than NA. NA not only NA raises HDL-C but also selectively prevents liver catabolism of apolipoprotein A-1, which is the key HDL lipoprotein needed for reverse cholesterol transport [8]. Thus NA increases both the capacity and the efficiency of HDL-C cholesterol transport. The liver is the site of synthesis of TG, very low-density lipoprotein (VLDL), lipoprotein (a) (Lp(a)), and LDL-C, and NA attaches to and antagonizes the hydroxycarboxylic acid-2 receptor of hepatocytes. This inhibits a hepatic microsomal enzyme (diacylglycerol acyltransferase-2) that is necessary for the final step in the production of those lipids [8]. Not only does NA reduce the beta lipoproteins that make up LDL-C,

<b>Lipid benefits</b>
-Lowers total cholesterol
-Lowers LDL-C cholesterol (specifically low-density LDL-C)
-Lowers triglycerides
-Lowers Lp(a)
-Raises HDL-C (specifically apolipoprotein A-1)
<b>Non-lipid benefits</b>
-Inhibits vascular inflammation/reduces reactive oxygen species
-Reduces oxygenation of LDL-C
-Reduces intravascular adhesion molecules and monocyte chemo-attractant protein-1 (atherogenesis initiators)
-May reduce the size and functional recovery time of acute stroke
Ref. [7–9].

**Table 1.**  
*Summary of niacin lipid and non-lipid cardiovascular benefits.*

but also more specifically NA reduces the small dense LDL-C particles that are most atherogenic. Furthermore, NA is one of the best agents to lower TG and is the only medication that significantly lowers Lp(a), which is also a significant independent risk factor for coronary disease [7].

In addition, in vitro research using human aortic endothelial cells has demonstrated impressive non-lipid benefits of NA in reducing risk of coronary disease. Researchers found that: (1) NA inhibits vascular inflammation by reducing reactive oxygen species, (2) NA reduces LDL-C oxidation making it less atherogenic, and (3) NA reduces vascular adhesion molecules and monocyte chemo-attractant protein-1, which decreases the attachment of monocytes and macrophages to the vascular wall, a key element in early atherogenesis [8]. An animal study demonstrated an additional non-lipid effect of NA, which is a neuroprotective benefit following stroke. The study involved inducing a stroke by middle cerebral artery occlusion in rats. Rats induced with NA within 2 hours of occlusion had a reduced volume of brain tissue damage and improved the functional recovery compared with controls [9] (**Table 1**).

### 3. Side effects of NA

Despite its many benefits, NA utilization can be hampered by a number of adverse side effects. The good news is virtually all NA side effects are reversible, and most can be minimized or eliminated by appropriate dosing and administration. The most common side effect is flushing and that is more common with IRNA and the initial doses of ERNA. Flushing is caused by release of prostaglandin D2 and prostaglandin E2 from Langerhans cells in the skin and macrophages [8]. In most persons, this flushing response can be minimized by proper dosing and administration (discussed later). William Parsons Jr., a co-investigator in the Coronary Drug Project and an early proponent of NA, was quite disappointed that many clinicians never learned “how to do” niacin resulting in higher dropout rates in NA therapy than that was warranted. This led him to writing a book, “Cholesterol Control Without a Diet! The Niacin Solution” for both lay and professional persons in an effort to educate all on proper NA administration [10].

Another side effect that is sometimes seen with ERNA therapy (but almost never with IRNA) is impaired liver function. This is due to methyl group depletion in the hepatocytes, secondary to the metabolic amidization in the liver of NA to nicotinamide [8]. This problem was shown to be preventable or reversible in most cases without loss of lipid benefit in studies using wax-matrix ERNA (WM-ERNA; Endur-Acin by Endurance Products Inc.) by either dose reduction or methyl group supplementation with methionine [11, 12]. Hepatic transaminase levels should be monitored during NA therapy. Modest transaminase level increases are acceptable, but NA dose reduction should be implemented if levels approach 2–3 times normal limits.

Increased blood glucose levels with NA therapy had raised concerns about its use in persons with diabetes or impaired glucose tolerance (metabolic syndrome). Blood glucose should be monitored in patients on NA treatment but that concern has been largely dismissed by the results from clinical trials. A controlled trial using WM-ERNA in non-diabetics showed only a 1% rise in baseline glucose levels at 6 weeks that returned to baseline by 6 months [13]. The AIM-HIGH trial that used polygel ERNA (PG-ERNA; Niaspan, AbbVie Inc.) specifically recruited persons with low HDL-C and high TG (metabolic syndrome or MS) found a 5% rise initially from baseline glucose levels that returned to baseline over 2 years, and there was no difference in the development of diabetes in the two treatment groups [14]. A post-hoc analysis of the Coronary Drug Project (that used IRNA) found that the subgroup of



subjects with MS had comparable reduction in coronary events and long-term mortality to the other subjects in the IRNA treatment group [15]. The consensus is that the benefits of treating lipid risk factors in persons with MS or diabetes outweighs any modest increase that NA treatment may cause to insulin resistance.

There are a number of less common side effects with NA treatment most of which are manageable without discontinuing therapy. Gastrointestinal upset can occur in some individuals and may be due to increased acid production on NA treatment. This is usually managed by splitting the daily dose and taking it with meals. Acid blocking agents may also help. Hyperuricemia may also occur with NA treatment and uric acid levels should be monitored routinely along with blood glucose levels and liver function tests. Nicotinuric acid is a by-product of liver metabolism of NA and can compete with renal excretion of uric acid causing levels to rise. The clinician must decide whether the continued use of NA would require additional management of uric acid levels is worth the lipid benefits. Increased homocysteine levels can occur with NA treatment and these should also be monitored routinely during NA therapy. Hyper-homocysteinemia is also a risk factor for cardiovascular disease that can be managed by folic acid supplementation. Some persons may experience a rash with flushing that usually clears with the development of tolerance, and in a rare instance, a darkened patch of skin may occur (acanthosis nigricans). All of these side effects are completely resolvable/reversible by discontinuing NA if other management of the side effect is unsuccessful.

#### **4. Selecting appropriate patients for NA therapy**

As described above, the pleiotropic benefits of NA treatment make it an excellent choice for mixed dyslipidemias. One of the most prevalent forms of mixed dyslipidemia that is uniquely suited to NA treatment is MS (low HDL-C, high TG). A study of prevalence of MS in the United States showed 34% of all adults and 55% of persons over the age of 60 has MS [16]. An 8 year prospective study of cardiovascular risk (Framingham) in 3323 middle-aged adults in the United States found the risk of developing CVD over that 8 year period for persons with MS was 34% for men and 16% for women [17]. An epidemiology study of the prevalence of MS in European countries found it as high as 71.7% of adults in some countries and MS-associated CVD prevalence as high as 52% [18]. Thus, the prevalence and the high risk of CVD with MS make this a very large population of persons who would benefit from NA therapy, especially those persons with normal or modest elevations of LDL-C.

The problem of treating MS with NA as monotherapy is achieving the LDL-C goal for that person. Since cardiovascular risk assessment views MS as the equivalent of having a prior coronary event the LDL-C goal is usually more aggressive (e.g. 70 mg/dl) and that can be difficult to achieve on NA alone. A meta-analysis in 2010 of NA studies using NA alone or in combination with other agents showed a 26% reduction in coronary events. In addition, they showed a decrease in coronary atherosclerosis in 92% of persons treated with NA, as well as a reduction in carotid intimal thickness of 17 mm per year of NA treatment [2]. Most of these studies were conducted prior to the introduction of statins for lipid management. The compliment of the lipid benefits of NA and the effective LDL-C lowering benefit of statin drugs led to clinical trials using PG-ERNA with statins which did demonstrate broad improvement of lipid profiles (decreased LDL-C, TG, Lp(a), and increased HDL-C) [19, 20]. Modeling of lipid therapy from these studies indicated that an ERNA with a statin would produce optimal lipid values for reducing coronary disease [21].

The early success in lipid profile improvement of combination trials of PG-ERNA/statin led to the development of two very large clinical trials of combination PG-ERNA/statin therapy that were intended to demonstrate conclusively the benefit of combined treatment on the reduction of cardiovascular events and mortality (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes [AIM-HIGH] and Second Heart Protection Study—Treatment of HDL to Reduce the Incidence of Vascular Events [HPS-2 THRIVE]) [22, 23]. The much-anticipated results of those trials were very disappointing and not only failed to demonstrate reduction in vascular events but also appeared to show increased adverse events and side effects with that combination. Critics of these two trials pointed out major design flaws in both studies that raise serious questions about the validity of any conclusions drawn from study results. The AIM-HIGH trial was terminated early because of what was thought to be an increase in cerebrovascular accidents in the PG-ERNA/statin treatment group, which in later analysis was found to be an artifact [22]. The main conclusion of the AIM-HIGH trial was that the combined PG-ERNA/statin treatment group did not show a decrease in cardiovascular events. This, in fact, was not true for the subgroup who were in the highest tertile of baseline TG and the lowest tertile of baseline HDL-C, both lipid fractions that benefitted from the NA addition to treatment [24]. Another AIM-HIGH post-hoc analysis of remnant lipoproteins and HDL-C2 showed that the PG-ERNA/statin treatment group did demonstrate improvements that could confer benefit in prevention of cardiovascular events, but perhaps this was not able to be demonstrated because of early termination [25]. Others also point out that the Coronary Drug Project took 6 years to demonstrate a reduction in coronary events with NA therapy, so the failure of AIM-HIGH and HPS-2 THRIVE to demonstrate the same may have been due to early termination of these studies [26]. Also, one of the lipid benefits of adding NA to a statin is the additional lowering of LDL-C which did occur in the AIM-HIGH trial. However, this benefit was muted since the control group had a second LDL-C lowering drug (ezetimibe) added to their treatment to match any LDL-C lowering by NA in the treatment group [22].

The HPS-2 THRIVE trial was actually PG-ERNA in combination with Laropiprant, a prostaglandin DP1 receptor inhibitor that reduces the NA flushing side effect, and together this combination was added to statin therapy. The investigators had no idea when designing the study that the PG-ERNA/Laropiprant combination would cause such an increase in myopathies especially in Chinese subjects. Of the 25,673 study subjects over 11,000 were Chinese, and their annual incidence of myopathy was 800% greater than that European subjects on the same treatment [27]. Critics of the HPS-2 THRIVE trial felt the addition of Laropiprant to the NA treatment group confounded the outcomes and thus they do not accept it as a legitimate study of the combination of NA and statin therapy [26]. The main conclusion of the HPS-2 THRIVE study was similar to the AIM-HIGH study; that is, the addition of NA to statin therapy did not improve cardiovascular outcomes, and, in fact, resulted in an increase in serious adverse effects [23]. Despite the design flaws in these large trials, the consensus is that adding NA to statin therapy in persons who are already at their LDL-C goal does not improve clinical outcomes. These two large studies raised serious questions about what is the appropriate combination therapy with statins in persons who have not reached their LDL-C goal. While this controversy still lingers, many feel the effectiveness of NA in reducing LDL-C (especially small dense LDL-C 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 [26].

Recent changes in recommendations of national cholesterol treatment guidelines in the United States have increased the number who are considered eligible to start

statin therapy (absolute risk of cardiac event >7.5% over 10 years) to over 50 million persons [28]. The rate of statin intolerance (stopping therapy) in general population cholesterol intervention is 18–20% or about 10 million persons (statin intolerant) in the United States who are candidates for other lipid therapy interventions [29]. This represents another large target group that is appropriate for NA therapy since none of the other agents available have a broad range of lipid and non-lipid benefits for prevention of CVD [8, 26]. Some have suggested that proprotein-convertase subtilisin/kexin type 9 (PCSK-9) inhibitors be used when statin intolerance is encountered. At a cost of \$15,000/year for PCSK-9 inhibitors and an estimated incremental cost of \$330,000 per quality-adjusted life-years (QALYs), this option is very limited [30].

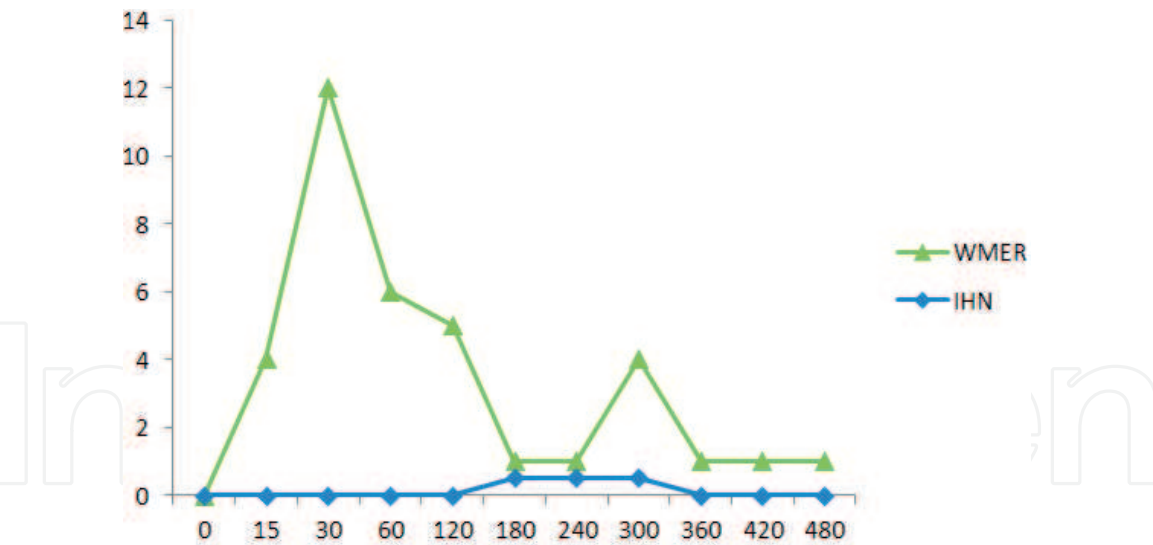
Perhaps the largest group of persons who would be logical candidates for NA lipid therapy globally are those whose risk scores indicate need to initiate lipid treatment but either they, individually, or their health system cannot afford statin treatment. Cardiovascular disease has grown at epidemic rates in developing countries and those countries account for over 80% of all cardiovascular deaths annually [31]. Using microsimulation modeling, analysts recently demonstrated that initiating statin therapy at the recommended 7.5% risk threshold would be an incremental cost-effectiveness ratio of \$37,000 per QALYs gained [32]. This may be considered cost-effective in a developed country, but in a developing country this is prohibitive. Not only does NA have the broadest profile of lipid and non-lipid benefits for coronary disease/mortality reduction, it is also the cheapest available lipid lowering agent. Thus, it makes sense as a public health strategy for developing countries to initiate population level of lipid therapy intervention with NA monotherapy adding other agents as needed, and reserve initiation with statin therapy to the subset of persons with high/very high risk status.

Persons with isolated dyslipidemic fractions such as low HDL-C, or high TG are also reasonable candidates for NA therapy and NA is the only agent at present that can significantly lower Lp(a). A meta-analysis of clinical trials specifically targeting hypertriglyceridemia (two trials were NA monotherapy, one NA with fibrates) showed significant reduction in coronary events especially if high TG was associated with low HDL-C [33]. A meta-analysis of clinical trials of NA to lower Lp(a) showed significant reductions of 22–24%, and a case report of NA with a statin showed a dramatic 88% reduction [34, 35].

## 5. Choosing an NA formulation

The early clinical trials of NA used immediate-release formulations with good lipid results but many of those trials had unacceptably high drop-out rates due to flushing [36]. In an effort to reduce the flushing side effects, sustained-release NA formulations were developed. These did reduce flushing but continuous/sustained exposure of the liver to NA resulted in a high incidence of impaired liver function [36]. Researchers found that an intermediate (between immediate and sustained) or ERNA provided the best reduction in flushing side effects and also reduced the liver issues encountered with the more sustained-release formulations [36]. Another formulation that was made popular by its “no flush” claim is inositol hexanicotinate (six molecules of niacin attached to inositol). There are many NA products available on-line and over-the-counter that claim to be extended-release preparations but most of them have not been studied for safety, efficacy, and side effects in controlled clinical trials. Poon conducted an *in vitro* dissolution study of 19 non-prescription NA products comparing them to 1 prescription PG-ERNA product (Niaspan) [37]. He found wide variation in dissolution rates suggesting the *in vivo* NA release from these products would be difficult to predict.





**Figure 1.**  
Mean blood levels (ng/ml) over 8 hours of NA after single dose of 500 mg of wax-matrix nicotinic acid (WMER) and 500 mg dose of inositol hexanicotinate (IHN).

In selecting an NA product for clinical use, it is best to stay with products that have demonstrated safety and efficacy in clinical trials. The PG-ERNA, Niaspan, is the only NA formulation that has been approved by the US Food and Drug Administration for lipid therapy and is the standard by which other NA products are measured. It is by far the most extensively tested NA formulation having been used in both monotherapy and combined therapy with other agents including the AIM-HIGH and HPS-2 THRIVE studies. It has consistently demonstrated the desired lipid benefits and has typically had a total drop-out rate of 18–19% (9–10% due to flushing intolerance and 8–9% due to other adverse effects) [38]. Another polygel extended-release NA product, Slo-Niacin (Upsher-Smith Inc.) has also been extensively tested in clinical trials and was used in a large Veteran’s Administration NA interchange study. Veterans who were on Niaspan (5321 subjects) were switched to Slo-Niacin and followed for 2 years. The results showed comparable safety/side effects and lipid benefits and Slo-Niacin had even greater lowering of TG [39]. A third NA product that uses a wax-matrix for its extended-release formulation is Endur-Acin (Endurance Products Inc). Endur-Acin has demonstrated comparable if not better lipid results compared the PG-ERNAs and it has exceptional safety and side effect rates with an average total drop-out rate of only 3–8% for 4 clinical trials totaling more than 400 subjects [11, 13, 40, 41]. Since age is one of the strongest non-lipid risk factors for CVD, it is worth noting that a post-hoc analysis of one of the Endur-Acin trials showed that older persons enjoyed even better lipid results than younger persons with no increase in side effects or drop-out rates [42]. The only clinical trial testing inositol NA as monotherapy showed its claim of “no flush” is a scam. In a head to head comparison trial with wax-matrix NA (Endur-Acin) that included pharmacokinetics of both agents, wax-matrix NA demonstrated an optimal extended-release and absorption curve over 8 hours and inositol NA had a flat line absorption curve demonstrating no bioavailability at all [41] (See **Figure 1**).

## 6. NA dosing and administration: “How to do” niacin

Guidelines recommend determining the patients risk score for likelihood of a coronary event in the next 10 years and discussing treatment options and goals before initiating treatment. Initiation of NA therapy also should be preceded by



baseline check of lipids, blood glucose, hemoglobin A1C, uric acid, homocysteine, and liver transaminases to be sure the patient is an appropriate candidate. If you are primarily targeting low HDL-C with NA therapy, the most effective formulation is IRNA. Even though that form of NA has the highest rate of flushing it can be minimized in most persons by proper dosing and administration: (1) initiating therapy at a low dose (250–500 mg) and gradually increasing over 1–2 weeks to allow tolerance to develop, (2) giving aspirin with the dose of NA to block the prostaglandin response, and (3) giving the NA dose with meals to slow the rate of absorption. The Coronary Drug Project using IRNA had only an 8% drop-out rate due to flushing. Typically, IRNA dosing is advanced to at least 3000 mg/day for optimal HDL-C response but can be increased to as high as 6000 mg/day in divided doses with meals to reach goals as tolerated. Lipids and blood chemistries should be rechecked at 6 weeks and monitored at 6 week intervals until targeted dose has been reached. If chemistries remain within normal limits (liver transaminases acceptable up to three times, the upper limit of normal) then monitoring interval can be extended to 3 months once targeted dose has been reached. For most persons whose liver function tests approach/exceed three times the upper limit of normal, simply reduce dosage by half and recheck tests in 2 weeks. They are most likely sensitive to the amidization metabolism of NA in the liver and are becoming depleted of methyl groups. They will usually continue to have excellent lipid results at the lower dose and will also benefit from a diet rich in “methyl donor” foods (kale, berries, fish, nuts, etc.) or taking a methionine supplement. In the Endur-Acin versus inositol clinical trial six persons on Endur-Acin had dose reduction due to liver enzyme elevations, yet all had a good lipid response and five were able to reach their LDL-C goal [41]. If additional lipid lowering agents are needed, follow up can be adjusted to take into consideration monitoring that added agent or any possible interactions of agents.

For essentially all other NA lipid therapies (other than isolated low HDL-C), ERNA is better tolerated and more effective for the other lipid fractions. Initiating dosing for ERNA therapy is essentially the same as IRNA as listed above. Most of the PG-ERNA studies have used one time/day dosing at bedtime with a small snack for two reasons: (1) convenience (and it can be given at the time a statin is supposed to be given) and (2) to match the time of peak hepatic lipid synthesis. The PG-ERNAs (Niaspan and Slo-Niacin) also have a somewhat higher rate of flushing than the WM-ERNA (Endur-Acin) so giving it in a near fasting state may also reduce the chance of early breakdown of the polygel capsule that might happen with the increased peristaltic activity of a meal. Critics of the bedtime NA dosing used in the AIM-HIGH and HPS-2 THRIVE studies, however, 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 triggering release of epinephrine and hepatic gluconeogenesis which might have caused some of the negative results found in those studies [26]. Also, persons taking any ERNA should be cautioned to avoid consuming a hot beverage with dosing since that can accelerate NA release and risk flushing.

In targeting appropriate patients for NA lipid therapy, it is helpful to know what lipid changes to expect for typical dosing of NA. Increases in HDL-C are typically in the +12 to +22% range with an IRNA dose of 3000 mg or an ERNA (Niaspan, Slo-Niacin, Endur-Acin) dose of 1500–2000 mg with IRNA and Niaspan being toward the better response end. Decreases in LDL-C for those agents are typically in the –12 to –26% with Endur-Acin toward the better response end. Decreases in TG are typically –10 to –15% and Lp(a) about –18 to –22% [11, 43–45]. Knowing the patients baseline lipid/chemistry levels and their 10 year coronary risk score can help in choosing an NA agent and dosing strategy. A person with isolated low HDL-C would be a good candidate for IRNA or possibly Niaspan if they do not tolerate the

flushing with IRNA. A person with MS, since they are considered higher risk for a coronary event (lower LDL-C goals), might do well to start on Endur-Acin and get the extra LDL-C benefit. In a clinical trial using Endur-Acin in persons with mild to moderate dyslipidemia 78% of persons with 0–1 cardiac risk factor and 44% of persons with 2 or more risk factors were able to get to their LDL-C goal along with the additional NA benefits in other lipid fractions [41]. A person whose baseline chemistries suggest glucose intolerance might best be placed on mealtime dosing to avoid reactive hypoglycemia and epinephrine release, and, of course, anyone with pre-existing liver function issues would best be started on IRNA. Management of side effects and adverse events from NA therapy are covered above (**side effects of NA**). Despite the bad press from the AIM-HIGH and HPS-2 THRIVE studies, NA has been used successfully with virtually every class of lipid lowering agent especially statins. With the possible exception of adding NA therapy to a person who is already at their LDL-C goal on statins, providers should feel comfortable adding other agents to NA or NA to other agents to achieve lipid goals [46, 47].

Last but not least in considering NA for lipid therapy is the cost. There are many very inexpensive NAs available in pharmacies, health supplement stores, and on-line, all claiming to lower cholesterol. But the patient should be advised to stay with those products that have been proven safe and effective in clinical trials, and specifically to avoid the NAs that claim “no flush” (inositol hexanicotinate) that have been proven “no benefit”. Endur-Acin (WM-ERNA) and Slo-Niacin (PG-ERNA) are available on-line for only \$8–9.00 USD/month for treatment ([www.endur.com](http://www.endur.com); [www.slo-niacin.com](http://www.slo-niacin.com)). Niaspan is available only by prescription and is more expensive as are generic statins which are about 5–6 times more expensive. The cost may not be a big issue for persons with full drug coverage health insurance. But for others, even those with a co-pay, taking a medication that you will need for the rest of your life can be a substantial expense.

## 7. Conclusion

Nicotinic acid is the first dyslipidemia medication to reduce both CVD events and mortality. No other lipid medication has the breadth of lipid and non-lipid benefits for managing CVD risk. Specifically, NA is the best agent for raising HDL-C, one of the best agents for lowering TG and the only medication that can significantly lower Lp(a). This is in addition to ability of NA to significantly lower LDL-C, and non-HDL-C. Unique non-lipid benefits include reduction of LDL-C oxidation and other oxidative species as well as prevention of inflammatory adhesion molecules in the vascular intima all of which are associated with atherogenesis. The initial clinical experience with IRNA was hampered by fairly high rates of flushing intolerance, but this has been largely overcome by the development of ERNA and attention to proper dosing and administration. Initial clinical trials of NA as monotherapy and in combination with other agents (statins, fibrates, and bile acid sequestrants) all showed significant lipid benefits. Two very large clinical trials (AIM-HIGH, and HPS-2 THRIVE) that were intended to confirm the benefits of NA/statin combined therapy had very disappointing results. Unfortunately, despite significant design flaws in these two studies, their results have led to widespread discontinuance of NA, both in combination with statins and even NA monotherapy. The real conclusion that seems supported by the two large clinical trials is that adding NA to statin treatment when a person is already at their LCL-C goal probably does not add benefit. But to disregard all of the prior positive NA studies and the fact that these large trials had serious design flaws is unfair judgment of NA. In fact, a 2013 meta-analysis


of prior NA trials of both monotherapy and NA combined with other agents (included the Aim-High trial) showed that NA reduced risk of any CVD event by 34% and specifically major coronary event by 25% [48]. A similar meta-analysis of statin trials showed a 22 and 27% risk reduction for the same endpoints, respectively [49]. The obvious preference for statins when initialing lipid therapy is based on its effectiveness in lowering LDL-C, the prime lipid target in CVD risk reduction. But the NA trial with Endur-Acin showed that in a population with mild to moderate dyslipidemia, 50% or more of persons can reach their LDL-C goal with NA monotherapy and enjoy the additional lipid and non-lipid CVD benefits of NA therapy. Also, a recent study designed to evaluate the effects on atherogenic factors (lipid and non-lipid) when ERNA is added to statin therapy in MS patients showed an impressive array of positive benefits [50]. So, providers should continue to value its use in the many dyslipidemia patients who are appropriate for NA therapy and learn “how to do” NA for optimal results.

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