Immediate release niacin effect at stratified lipid levels

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ABSTRACT

Background: The Coronary Drug Project demonstrated a significant decrease in non-fatal myocardial infarction, and total mortality using immediate release niacin (IRN). However, AIM-HIGH and HPS-2-THRIVE showed no additional benefit from adding niacin to statin therapy.

Objective
To evaluate the efficacy and tolerability of IRN on low-density-lipoprotein-cholesterol (LDL-C), high-density-lipoprotein-cholesterol (HDL-C), triglycerides, and lipoprotein (a) (Lpa) at stratified lipid levels in a monotherapy IRN group (MTG) and a combined therapy group (CTG) statin + IRN.

Methods: We retrospectively studied 185 patients who were prescribed IRN for elevated LDL-C, triglycerides, lipoprotein a (Lpa), or low HDL-C. All patients used the same IRN products.

Results: 157 patients had complete records. (MTG = 74 patients, CTG = 83 patients with 68 combined with statins). Mean IRN dose = 2474 mg. Mean duration = 3.05 years.

If initial LDL-C was < 130, LDL-C did not decrease significantly with IRN. If initial LDL-C = = 130, LDL-C decreased 35% in MTG vs. 32% decrease in CTG. If initial HDL-C < 40, there was a 40% increase in MTG vs. 61% increase in CTG. If initial triglycerides > 150, there was a 48% decrease in MTG vs. 54% decrease in CTG. Lpa decreased 49% for all patients with initially elevated Lpa. Data except for LDL-C < 130 were significant (p < .001).

Conclusion: Lowering LDL-C is the corner stone for decreasing cardiovascular events. IRN reduces LDL-C significantly when initial LDL-C > 130, but not significantly when LDL-C < 130. Patients in AIM-HIGH and HPS-2-THRIVE received statin therapy causing very low initial LDL-C. Our results may explain why adding niacin to statin therapy failed in AIM-HIGH and HPS-2-THRIVE since niacin did not further lower LDL-C.

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1. Introduction

The first report regarding decreasing total serum cholesterol with immediate release niacin (IRN) was published in 1955 [1]. This initial report was followed by a number of studies demonstrating similar findings [2–5], but most of these studies regarded reduction of total serum cholesterol and triglycerides since high density lipoprotein-cholesterol (HDL-C) was not frequently analyzed at that time and low density lipoprotein-cholesterol (LDL-C) was not measured or calculated. The seminal study regarding niacin was the Coronary Drug Project begun in 1966 [6] and concluded in 1974. This double blind, randomized, placebo-controlled, male only, secondary prevention study demonstrated the efficacy of niacin for decreasing definite nonfatal recurrent myocardial infarction but failed to demonstrate a significant decrease in total mortality and cause specific mortality. However, a follow-up study with nearly complete ascertainment of the original niacin and placebo groups at 15 years demonstrated a significant 11% decrease in mortality for the niacin group compared to placebo group even though the niacin group was no longer treated after conclusion of the original study [7].

Niacin has been demonstrated over the course of other studies to increase HDL-C, and decrease LDL-C, LDL particles, apoprotein B, triglycerides, and lipoprotein (a) [8,9]. Epidemiologic studies suggest that these changes in lipids would be beneficial [10]. In this regard, studies more recent than the Coronary Drug Project using longer acting niacins have demonstrated positive results in clinical trials for reductions in plaque and cardiovascular events [11,12]. Despite these salutary results, niacin has not been widely used because of side effects, which include cutaneous issues such as flushing, itching, and occasional rash. Other reported side effects include increasing fasting glucose [2], uric acid [3], increased atrial fibrillation, and gastrointestinal effects such as abdominal pain, diarrhea, and decreased appetite [6]. These side effects
led to the development and utilization of niacin preparations that were more slowly released to reduce the side effects, particularly flushing. Many of these products are nonprescription preparations sold as food additives. Approximately a decade ago an extended release form became a prescription medication that has gained favor with many physicians because of its once daily dosage and presumed decrease in flushing [13]. Further, studies using longer acting niacins with or without a statin have demonstrated positive results in clinical trials [11,12]. The IRN form is currently seldom used today. The extended release prescription product in conjunction with intensive statin and other therapy was recently used in a clinical trial, AIM-HIGH [9], which failed to demonstrate that adding this niacin preparation provided an additional benefit beyond that of statins combined with other lipid treatments. Further, the HPS-2-THRIVE [14] study demonstrated a higher incidence of adverse drug reactions in the simvastatin-lipid treatments. Further, the HPS-2-THRIVE [14] study demonstrated a higher incidence of adverse drug reactions in the simvastatin–extended release niacin–loropiprant (with or without ezetimibe) group than in the control statin arm without significant additional reduction in cardiovascular events. Thus, results for use of longer acting niacin forms have given inconsistent results. The major purpose of adding niacin in most studies has been to increase HDL-C and niacin products have been used in conjunction with statins and ezetimibe to lower LDL-C. Whether raising HDL-C pharmacologically is useful remains an unresolved issue [15], but lowering LDL-C has been demonstrated in many studies to reduce cardiovascular events [16,17]. Niacin also reduces LDL-C and the immediate release form may reduce LDL-C more than the extended release form. Immediate release niacin is very inexpensive compared to a prescription extended release form and the immediate release form has been used in our lipid clinic for many years. The purpose of the current study was 1) to determine at what lipid levels IRN causes the greatest changes in LDL-C, HDL-C, lipoprotein a, and triglycerides 2) to determine the side effects of a more modern immediate release preparation than that used in the Coronary Drug Project and 3) to evaluate the lipid results of immediate release niacin as monotherapy and as an addition to prior statin therapy.

2. Methods

This was a retrospective study of all patients recommended to take immediate release niacin (IRN) in a lipid clinic between 1980 and 2013. Study data were retrieved from paper charts or electronic records. The study was approved by the Institutional Review Boards of the University of Arizona and informed consent was deemed unnecessary since data were kept in an anonymous manner.

2.1. Patients

Treatment with IRN was recommended for patients > 18 years. Patients were prescribed niacin due to several common etiologies: statin and other LDL-C lowering medication intolerance with elevated LDL-C, considerably elevated triglyceride, very low HDL, elevated Lpa, and as an adjunct for those with familial hyperlipidemia whose LDL-C remained substantially elevated after statin therapy.

2.2. Niacin protocol

All patients used the same preparations of immediate release niacin (Rugby Pharmaceutical Company 100 mg with the product # 0536–4076-01-2 and 500 mg with the product numbers of 0-0536-4078-10-8). All patients were started on the same niacin protocol with the initial dose of 50 mg taken following meals 3 times per day. The dose was doubled every 2 weeks. Chewable 81 mg aspirin was used on alternate weeks or as necessary to prevent flushing. To stop a severe flush patients were instructed to chew three 81 mg aspirins and drink a large glass of water. Aspirin was discontinued as soon as patients no longer experienced flushing. The maximal daily dose of IRN was decided by correction of the lipid abnormality or 3000 mg daily, whichever came first.

2.3. Data collection

The reason for initiation of niacin therapy, initial pre-niacin data and last niacin data were recorded. The following parameters were identified: birthdate, date for first and most recent evaluation, comorbidities, LDL-C, HDL-C, triglyceride, lipoprotein (a) (Lpa), fasting glucose, alanine transaminase (ALT) and aspartate transaminase (AST). Patients were specifically asked about adverse reactions to niacin at each clinic visit and results were recorded except for initial, occasional, mild flushes at low doses of niacin. Co-administered lipid medications and reason for discontinuing niacin, if applicable, were also recorded.

2.3.1. Laboratory data

All blood samples were collected in the fasting condition. LDL-C was computed from the Friedewald equation if triglycerides were <400 mg/dL. If triglycerides >400 mg/dL, LDL-C was obtained via direct measurement. If a patient had normal Lpa on the initial sample, no further Lpa measurements were obtained. If Lpa was abnormal, and the patient had no recent infection, Lpa was re-measured at full niacin dosage.

2.4. Statistical analysis

To evaluate changes in different lipid panel parameters paired t test T-tests were used to compare initial and final data within each group (MTG, CTG). Values of p < 0.05 were considered significant. Changes between MTG and CTG and at stratified lipid levels were tested by unpaired T-test.

3. Results

3.1. Study cohort

Of the 185 eligible patients, 23 patients had missing records leaving 162 patients with available records. Most of those with missing records were initially evaluated between 1980 and 1995 as some of these records were purged by the hospital. Of the 162 patients who had records, 5 never started IRN or never returned for a second visit leaving 157 patients for analysis, all of whom had initial and on treatment data. However, not all data for Lpa, fasting glucose, ALT, and AST were available on the last evaluation. In that instance we included analyses for the prior to final visit.

Of the 157 patients with available records, 74 were treated with MTG and 83 were on the CTG and other lipid lowering medications such as statin, gemfibrozil, fenofibrate, or omega 3 fatty acids. 68 of the 83 patients were treated only with the combination of IRN + statins. These 68 patients will be called the CTG. The mean age for these 157 patients was 55.8 years; mean duration of niacin therapy was 3.05 years. Of the 157 patients, 53 had primary prevention and the remainder as secondary prevention. Secondary prevention was defined as patients having had a documented stroke, myocardial infarction, coronary bypass surgery, coronary intervention procedures at catheterization, coronary calcium score > 400, significant carotid atherosclerosis or significant peripheral vascular disease.

Data for lipid changes and number of patients for the following parameters are included in Tables 1-3.

3.1.1. LDL-C change

(Data are reported in mg/dL).
Table 1
Effects of IRN on stratified lipid levels.

<table>
<thead>
<tr>
<th>Monotherapy - IRN (n = 74)</th>
<th>Combined therapy group (post- statin + IRN) (n = 68)</th>
</tr>
</thead>
<tbody>
<tr>
<td># of patients</td>
<td>Mean difference</td>
</tr>
<tr>
<td>LDL-C</td>
<td>-27.16% (143.67–104.64)</td>
</tr>
<tr>
<td>LDL-C &lt; 100</td>
<td>-7.42% (85.64–92.00)</td>
</tr>
<tr>
<td>LDL-C &lt; 130</td>
<td>-6.05% (99.67–93.67)</td>
</tr>
<tr>
<td>LDL-C &gt; 130</td>
<td>-35.27% (173.00–111.98)</td>
</tr>
<tr>
<td>LDL-C &gt; 160</td>
<td>-37.67% (196.88–122.67)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>+29.84% (53.30–69.20)</td>
</tr>
<tr>
<td>HDL-C &gt; 40</td>
<td>+27.84% (60.16–76.91)</td>
</tr>
<tr>
<td>HDL-C &gt; 40</td>
<td>+40.00% (31.44–49.48)</td>
</tr>
<tr>
<td>Tri[a]</td>
<td>-36.95% (142.16–89.63)</td>
</tr>
<tr>
<td>Tri &lt; 150</td>
<td>-19.13% (85.95–69.51)</td>
</tr>
<tr>
<td>Tri &gt; 150</td>
<td>-47.60% (240.00–125.74)</td>
</tr>
<tr>
<td>Glucose[a]</td>
<td>+1.90% (98.46–100.33)</td>
</tr>
<tr>
<td>ALT[a]</td>
<td>-12.32% (27.56–24.16)</td>
</tr>
<tr>
<td>AST[a]</td>
<td>+15.32% (22.77–26.26)</td>
</tr>
</tbody>
</table>

3.2. Effect of mono-therapy IRN on LDL-C

LDL-C decreased 27.2% (p < .001) for the 74 patients regardless of the starting LDL-C. For patients with initial LDL-C < 100 (n = 17) and <130 (n = 29), LDL-C changes were not statistically significant at -7.4% (p = .38) and -6.1% (p = .26), respectively. If starting LDL-C was ≥130 mg/dl (n = 45), the mean LDL-C decreased significantly (−35.3%) (p < .001). If initial LDL-C was ≥160 mg/dl (n = 24), the mean LDL-C decrease was significant (−37.7%) (p < .001).

Table 2
IRN effects on the lipid panels of all patients in both groups (MTG + CTG).

<table>
<thead>
<tr>
<th># of pt</th>
<th>Mean difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>-24.86% (131.62–98.95)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LDL-C &lt; 130</td>
<td>-6.11% (93.18–87.48)</td>
<td>0.18</td>
</tr>
<tr>
<td>LDL-C &gt; 130</td>
<td>-34.73% (168.16–109.75)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LDL-C &gt; 160</td>
<td>-37.00% (194.92–122.89)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HDL-C</td>
<td>+32.37% (50.60–66.72)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HDL-C &gt; 40</td>
<td>+27.05% (60.16–76.43)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HDL-C &gt; 40</td>
<td>+53.75% (30.51–46.92)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Tri[a]</td>
<td>-39.46% (154.14–92.93)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Tri &lt; 150</td>
<td>-20.44% (88.36–71.00)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Tri &gt; 150</td>
<td>-50.23% (276.13–132.50)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Lp[a]-initial (elevated)[a]</td>
<td>-49.16% (301.72–152.13)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Glucose-whole group</td>
<td>+2.33% (98.75–101.06)</td>
<td>.50</td>
</tr>
<tr>
<td>Glucose-end (elevated)[a]</td>
<td>+17.19% (91.53–106.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ALT-whole group</td>
<td>-5.04% (28.12–26.70)</td>
<td>.53</td>
</tr>
<tr>
<td>ALT-end elevated[a]</td>
<td>+63.10% (26.71–43.57)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>AST-whole group</td>
<td>+8.15% (25.47–27.54)</td>
<td>.14</td>
</tr>
</tbody>
</table>

3.3. Effect of IRN combined therapy on LDL-C

For all patients already on statin therapy, addition of IRN further reduced mean LDL-C 22.4% (n = 68) (p < .001). For patients with statin LDL-C < 100 mg/dl (n = 32) and <130 (n = 37), LDL-C change was not significant at +6.3% (p = .45) and -10.6% (p = .15), respectively. However, if initial LDL-C on statin therapy was ≥130 (n = 31), addition of IRN decreased LDL-C further (−32.3%) (<.001). If LDL-C on statin therapy was >160 mg/dl (n = 12), addition of IRN caused a further LDL-C decrease of 33.5% (p < .05).

Comparison of mean IRN LDL-C induced change in MTG and CTG was not significantly different. These data show that the further mean decrease in LDL-C as the result of IRN following statin therapy was essentially identical to the mean decrease in LDL-C from monotherapy. Data further demonstrate that IRN does not change LDL-C significantly when LDL-C is <130 mg/dl. Additionally when comparing LDL-C values at <100 mg/dl and LDL-C between 100 and 130 mg/dl, no significant decrease occurred. However, the reduction in LDL-C when LDL-C < 130 compared with LDL-C ≥130 achieved statistical significance (p < .01) for both MTG and CTG. (Fig. 1).

3.3.1. HDL-C change
(Data are reported in mg/dl).

3.4. Effect of mono-therapy IRN on HDL-C

HDL-C increased 29.9% (p < .001) for the 74 patients regardless of the starting HDL-C. If initial HDL-C was ≥40 (n = 56), HDL-C increased

Table 3
Side effects of IRN.

<table>
<thead>
<tr>
<th>n = 157</th>
<th># of patients</th>
<th>Mono-therapy</th>
<th>Combined therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flush</td>
<td>36</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>Macular edema</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Chest pain</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Niacin-induced acanthosis</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Significant infection</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

[a] IRN = immediate release niacin.
[b] LDL-C = low density lipoprotein cholesterol.
[c] HDL-C = high density lipoprotein cholesterol.
[d] Tri = triglycerides.
[e] Lp(a) = lipoprotein a.
[f] Since different tests were used for Lpa measuring, we reported % change. Patients were evaluated by the same test each time. Values greater than the upper normal limits were considered to be elevated. Because statins do not alter Lpa, result for monotherapy and combined therapy was combined.
[g] Patients who started with normal glucose (<100 mg/dl) ended with elevated glucose (≥100 mg/dl).
[h] ALT = alanine transaminase.
[i] AST = aspartate transaminase.
[j] Excluded one patient who started with an HDL-C of 7 and increased to 80 with IRN.
27.8% (p < .001). If initial HDL-C was < 40 (n = 18), the mean increase in HDL-C was 40% (p < .001).

3.5. Effect of IRN combined therapy on HDL-C

When IRN was added to existing statin therapy, (n = 68) mean HDL-C increased 34.9% (p < .001). If initial HDL-C was ≥ 40 (n = 47), HDL-C increased 24.4% (p < .001). If the initial HDL-C on statin therapy was < 40 (n = 21), mean increase in HDL-C was 60.7% (p < .001).

However, there was not a statistically significant difference of mean HDL-C change between MTG and CTG which showed that the increase in HDL-C was constant irrespective of the effect of the statin therapy. (Fig. 2).

3.5.1. Triglycerides
(Data are reported in mg/dl).

3.6. Effect of mono-therapy IRN on triglycerides

Triglycerides decreased a mean of 37% for 74 patients regardless of their initial triglycerides level. If the initial triglycerides ≥ 150 (n = 27), mono-therapy with IRN decreased mean triglycerides by 47.6% (p < .001).

3.7. Effect of combined therapy on triglycerides

Mean triglycerides decreased 41.8% (p < .001) for 68 patients in the combined therapy regardless of their initial triglycerides on statin therapy. If the initial triglycerides ≥ 150 (n = 19), the mean decrease in triglycerides was 54.5% (p < .05).

There was not a statically significant difference for triglycerides change between MTG and CTG. (Fig. 2).

3.7.1. Lipoprotein a (Lpa) for patients with initially elevated Lpa

3.7.1.1. Effect of IRN on Lp(a) for both MTG and CTG (n = 48). Lpa decreased 49.2% for the group with initially elevated Lpa (p < .001). 22 of 48 patients with initially elevated Lpa had values that fell into the normal range after treatment with IRN.

3.7.1.1.1. Side effects. Table 3 shows adverse effects of INR. Among 157 patients in the study, five side effects occurred: significant flushing (n = 36), macular edema (n = 3), chest pain (n = 1), niacin induced acanthosis (n = 1), and dry mouth (n = 1). No patients were found to have encountered significant infections but infection was evaluated retrospectively. No gastrointestinal bleeding was reported. Gastrointestinal side effects were not a patient complaint despite their occurrence in prior studies.

Among these patients, many experienced occasional brief, mild flushes when taking IRN at 200–250 mg following each meal. 36 patients reported 1 or more significant flushes that required additional aspirin for relief. Three patients flushed repeatedly at 50 mg of IRN and none of these were able to tolerate high dose INR. The remainder of patients continued to high dose INR and was still taking IRN at the most recent visit.

3.7.1.1.2. Compliance. Three patients stopped niacin therapy because of uncontrolled flushing and an additional 2 stopped because of macular edema. IRN was reinstated in one macular edema patient without recurrence of the problem.

4. Discussion

The most important features of this study were 1) demonstration of a significant decrease of approximately 35% in LDL-C by IRN during mono-therapy and combined therapy with a statin when LDL-C at values greater than 130 mg/dl but IRN did not decrease LDL-C significantly when LDL-C was in a lower range (< 130 mg/dl). Thus 130 mg/dl appears to be a threshold effect for LDL-C. It is possible that the major clinically important effect of niacin is LDL-C reduction. For patients who are intensively statin treated and have LDL-C in the range below 130 mg/dl such as occurred in 2 recent studies (AIM-HIGH and HDL-C and triglycerides changes. The lines over bars represent the standard errors. "HDL-C = high density lipoprotein cholesterol.

Fig. 1. Changes in LDL-C (MTG vs. CTG). The y-axis displayed the %change in LDL-C after monotherapy and combined therapy. On the x-axis, the black bar represents the monotherapy and the gray bar represents the combined therapy. Three groups of bars represent how LDL-C changed at different initial stratified LDL-C levels. Changes in LDL-C < 130 is nonsignificant, other changes are significant. There is no significant difference between the monotherapy and the combined therapy. LDL-C = low density lipoprotein cholesterol. *NS = not significant. The lines over bars represent the standard errors.

Fig. 2. Changes in HDL-C and triglycerides (tri) (MTG vs. CTG). The y-axis displayed the %change in HDL-C and triglycerides after monotherapy and combined therapy. On the x-axis, the black bar represents the monoRx and the gray bar represents the combined therapy. Two groups of bars represent HDL-C and triglycerides changes. The lines over bars represent the standard errors. "HDL-C = high density lipoprotein cholesterol. **HDL-C = high density lipoprotein cholesterol. **LDL-C = low density lipoprotein cholesterol.
4.1. LDL-C reduction

LDL reduction with statins has been shown to decrease subsequent cardiovascular endpoints in a variety of studies [16–18]. IRN also reduced coronary death or nonfatal myocardial infarction significantly in the Coronary Drug Project [6]. However, in the Coronary Drug Project, total serum cholesterol and triglycerides were measured, but LDL-C and HDL-C were not measured or computed. However, it is very likely that non-HDL was reduced in the Coronary Drug Project and this may have accounted for decreased events. Subsequent studies have also demonstrated that LDL-C is significantly decreased by IRN [19,20]. Reduction in LDL-C in the current study was approximately 35%, and this is a generally similar reduction reported with less intensive statin therapy. Further, niacin therapy has been reported to have some of the same pleiotropic effects of statins [21–23]. However, no study is available to evaluate whether reduction in LDL-C resulting from niacin provides the same outcome result as a similar reduction in LDL-C by statins. Nonetheless, if LDL-C reduction is the main target of therapy, niacin can lower LDL-C.

4.2. IRN increases HDL-C

It remains unclear whether the increase in HDL-C resulting from use of niacin as demonstrated by this study and others [24,25] is of clinical importance. Outcome studies showed that raising HDL-C with gemfibrozil was associated with decreased events, particularly for those with initially substantially elevated triglycerides [24,25]. However, those studies also demonstrated a quite significant decrease in non-HDL-C. Further, the HATS trial [11], utilizing simvastatin and a longer release niacin (and some patients in the HATS study were treated with immediate release niacin), demonstrated a 90% decrease in the composite endpoints of cardiovascular events with respect to placebo group. This 90% event reduction far exceeds event reductions with statin monotherapy [16–18,26] but the exact reason for the remarkable event reductions in HATS is unclear. Recently, trials which featured raising HDL-C with niacin and a statin had different conclusions. In the AIM HIGH trial, results of extended release niacin with intensive statin therapy were compared to intensive simvastatin therapy plus placebo therapy. Although HDL-C increased more in the niacin group, no difference was found in outcome when the 2 groups were compared. In the HPS-2–THRIVE study, outcome results of extended release niacin with laropiprant and simvastatin were compared to outcome results with simvastatin plus placebo (the placebo included some immediate release niacin to induce flushing). The results showed no outcome benefit from the addition of extended release niacin plus laropiprant but did demonstrate increased side effects including gastrointestinal, dermal issues, and infections among other side effects. Further, raising HDL-C with CETP inhibitors added to statin therapy failed to improve cardiovascular outcomes [15]. Niacin definitely raises HDL-C, but whether this result is of clinical importance remains an open question that cannot be evaluated by the current study. Another study showed that infusing apo A1 Milano decreased plaque volume, but the objective on that study was not to merely raise HDL-C [27].

4.4. Effects of IRN on Lpa

In the current study only individuals with elevated Lpa had an analysis for percent change. Percent change for those with initially elevated Lpa was a 45% decrease. A generally similar reduction was noted in both the mono-therapy group and the combined therapy group which was expected since statins do not alter Lpa levels. Our results are somewhat similar to those in Carlson [29]. Mean Lpa decrease $= −38\%$ even though they use higher doses of niacin (4 g), but they did not exclude individuals with initially normal Lpa. A further finding in the study of Carlson et al. was the demonstration that the reduction in Lpa was essentially linear with respect to the decrease in LDL-C. Although niacin has been shown to generally decrease or reverse the deposition of atherosclerotic plaque [12], no outcome study of Lpa reduction has been performed.

The use of IRN may require more physician–patient discussion time than for extended release niacin. Best results appeared to occur with detailed explanation of the protocol which uses increasing doses of IRN and the use of the prostaglandin inhibitor, aspirin. The protocol used in this study was adopted to allow very gradual increase in IRN dosing. The slow increase allows patients to gain confidence at relatively low doses, usually with no flushes. Flushes, when they occur, usually begin within the first 20 min following ingestion of IRN and are usually quite brief lasting 5–10 min. Use of 81 mg of aspirin usually eliminates

4.3. Niacin side effects

The most common side effect of niacin in this study was significant cutaneous flushing (n = 36). Most flushes occurred at approximately 200 mg of IRN. Although few people flushed at lower doses on this protocol, 3 patients experienced severe flushing at 50 mg of IRN. Two of the 3 patients reached higher doses, but flushing was of such severity that all 3 were advised to discontinue IRN therapy. It is unknown why some patients experience severe adverse reactions to IRN and most others have minimal side effects. One common complaint was that some patients took IRN on an empty stomach or with a minimal meal and experienced a flush. This was usually alleviated by reiterating that IRN should be taken after a meal and/or take aspirin to block flushes, particularly in the beginning of therapy. Almost all patients, with the exception of the 3 patients who had flushing at minimal IRN doses reported absence or very infrequent or mild flushes as the dose was raised beyond 200 mg taken with each of the 3 daily meals. For those patients who used aspirin, some developed mild bruising but no significant hemorrhage. Almost all patients were able to discontinue aspirin without flushing within several months or less.

Some patients increased their niacin dose above 3000 mg/day presumably to achieve an enhanced effect. This practice was discouraged. Three patients who increased their daily dose > 3000 mg developed macular edema. This is a known side effect of high-dose niacin and has been reported to occur in 0.67% of patients taking niacin in doses of 3000 mg/day or more [28]. The symptom of macular edema was visual blurring. Discontinuing niacin resulted in elimination of macular edema within several days. Two of these patients never restarted niacin. The third patient who had markedly elevated Lpa and calcific carotid changes restarted niacin at 2500 mg without further difficulty and had no evidence of macular edema as evaluated periodically by an ophthalmologist. One patient with metabolic syndrome developed niacin-induced acanthosis at 1500 mg/day. This is a known but uncommon adverse reaction to niacin. One patient developed dry mouth at 3000 mg but continued taking drug. It is possible that dry mouth was underreported by patients. Although our study was not designed to evaluate infections, upon review of the patients, none suffered a significant infection. However, our study was much smaller than HPS-2–THRIVE. Additionally, our patients did not take laropiprant. Laropiprant, a drug initially studied for relieving allergic symptoms, has not been approved for use in the United States by the FDA. It has been reported to cause adverse reactions in Europe with or without niacin. HPS-2–THRIVE was a study of niacin + laropiprant and it is unclear whether non-flushing side effects in HPS-2–THRIVE resulted from niacin or laropiprant or a combination of the two drugs. Further, no patient in the currently study had a cardiovascular event while taking IRN, but our study may have been too small to have observed an event.
flushes, but not always. The type of aspirin and we utilized was the chewable variety in order to get quicker absorption. Use of coated aspirin is usually not as effective because the flush occurs before the aspirin is absorbed. Patients who did have a significant flush usually obtained relief within 5 to 10 min by chewing three 81 mg aspirin and drinking a large glass of water which improved aspirin dissolution and absorption.

4.5. Study limitations

Our retrospective study has definite limitations. The population size was relatively small with 157 patients. However, with limited indications it is difficult to have a large population in a clinical setting. Some early medical records had been purged and even though some of these patients remain in our practice, their initial values were no longer available and thus these patients were not included in the study. Our data were not collected at exactly the same time points for all patients and thus it is not possible to do any time relationships. The estimates of flushing may be underestimated since we did not keep a detailed record of individuals who experienced early treatment minor or brief flushes. The authors were surprised by the lack of complaints regarding gastrointestinal symptoms in reports of others. The significance of this lack of gastrointestinal side effects remains unclear. Finally, this study is not an outcome study.

5. Conclusion

The results of this study offer insight into a possible reason why some outcome studies did not show significant benefit with niacin combined with a statin. Niacin does not substantially decrease LDL-C and they hypothesized that patients who did take niacin in association with a statin and aspirin may have received an additive benefit. Niacin does not substantially decrease LDL-C with a long-term treatment duration, J. Am. Cardiol. 55 (2010) 2721–2726.

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