Evaluation of Lipid Profile and Residual Cardiovascular Risk in Patients Prior to Initiation of Niaspan Therapy

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Abstract

Background: Despite significant impact of statins, there are a number of patients with residual risk of cardiovascular disease who have optimally controlled low-density lipoprotein cholesterol (LDL-C). Niaspan (extended-release nicotinic acid or niacin-ER) is indicated for its use as monotherapy for the treatment of very high triglyceride (TG) levels and for the raising of high-density lipoprotein cholesterol (HDL-C) representing those residual risk populations. The patient characteristics and lipid profile, prior to initiation of therapy, in the real-world clinical setting has not been well documented. **Objectives:** This study evaluated lipid levels among patients initiating Niaspan in real-world clinical practice. **Methods:** Patients with a first prescription of Niaspan were identified using electronic medical record data from GE. Lipid values were categorized into optimal and nonoptimal TG or HDL-C levels. **Results:** There were 89 091 new users. Most patients had nonoptimal TG, HDL-C, TG/HDL-C ratio, LDL-C, and non-HDL-C levels. Among those with nonoptimal TG and HDL, the ratio of TG to HDL-C was higher among younger age groups (mean ratio 12.0 in males; 10.58 in females aged 18 to <40 years). TG was significantly correlated with non-HDL-C (0.41, $P < .001$) but not with LDL-C. Among those with LDL-C <100 mg/dL, 64.3% had nonoptimal TG/HDL-C ratio and approximately 70% had non-HDL-C $\geq$ 130 mg/dL. More than a third of the patients had diagnosis of coronary heart disease or coronary heart disease risk equivalent. **Conclusion:** Majority of Niaspan users had nonoptimal TG and/or HDL-C. The correlation of nonoptimal TG levels with non-HDL-C levels further support that Niaspan was targeted to population with residual risk for cardiovascular disease.

Keywords

dyslipidemia, drug utilization evaluation, cardiovascular drugs, databases, methodology

Introduction

Statins have been established as the mainstream therapy for both primary and secondary prevention of cardiovascular disease (CVD), and it is suggested that 40% of CVD-related events may be reduced by statin therapy.¹ Still there is a large residual risk of CVD that may be caused by multiple factors and persist among patients who have optimally controlled low-density lipoprotein cholesterol (LDL-C).² This “residual risk” is mainly due to low high-density lipoprotein cholesterol (HDL-C) and elevated triglyceride (TG) levels.³ The combination of high TG and low HDL-C is recognized as a lipid risk factor for the development of atherosclerotic CVD. The role of TG in the atherogenic components of lipids have been identified many years ago that showed relationship of LDL phenotypes with levels of TG.³ In clinical practice, LDL-C is measured from fasting blood using the Friedwald equation ($LDL-C = TC - HDL - TG/5$), which is inaccurate if the blood samples tested are nonfasting and/or if TG level is greater than 400

mg/dL.⁴ The importance of various types of dyslipidemia as a major contributor to CVD risk is highlighted by the INTERHEART study, a global case-control study in 52 countries, in which dyslipidemia was not defined solely by LDL-C but as the ratio of apolipoprotein B to apolipoprotein A-I (apoB/apoAI), which is representative of the ratio of concentrations of atherogenic very-low-density lipoprotein (VLDL), intermediate density lipoprotein (LDL-C), and high-density lipoprotein (HDL).⁵ Evidence for HDL-C as an independent risk factor has also been evaluated for sometimes and is still not settled as a residual risk under new guidelines.⁶ Non-HDL-C is another marker (represents Apo B, Lp(a), and TG-rich VLDL) that has been shown to

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be an even more potent risk factor for CVD than LDL-C. The INTERHEART case-control study with 15 152 cases and 14 820 controls showed that raised apoB/apoA ratio had more than 3 times the risk of having myocardial infarction and large population attributable risk (3.25 for top vs lowest quintile, PAR 49.2% for top 4 quintiles vs lowest quintile).⁶ Due to strong correlation of non-HDL-C with Apo B levels⁷ as well as correlation of TG levels with the ratio TG/HDL-C, it is likely that TG and TG/HDL-C will correlate with apoB/apoA ratio. Although HMG-CoA reductase inhibitors, also known as statins, lower LDL-C levels, its impact on triglycerides and HDL-C are limited.⁵

Niacin ER (extended-release nicotinic acid) is indicated for its use as monotherapy for the treatment of very high TG levels and for raising HDL-C levels. In patients who achieve normal LDL-C by statin treatment yet have high TG and/or low HDL-C, addition of niacin to statins lowers triglyceride levels and/or increases HDL-C levels. There is evidence that the addition of niacin to statins can reduce atherosclerosis and CVD events.⁸⁻¹¹ Niacin ER can effectively modify atherogenic dyslipidemia by lowering TG, increasing HDL-C, and transforming small LDL-C into normal-sized LDL-C.¹² However, a recent large simple trial has failed to demonstrate benefit of adding Niacin ER to statin therapy.¹³

The National Cholesterol Education Program ATPIII guidelines recommended that Niacin shall be considered as a single agent in higher risk persons with atherogenic dyslipidemia who do not have a substantial increase in LDL-C levels, and in combination therapy with other cholesterol-lowering drugs in high-risk persons with atherogenic dyslipidemia combined with the elevated LDL-C levels.¹⁴

In the real-world care setting, patient characteristics and their lipid profile prior to receiving Niacin ER have not been well studied, particularly in patients who had optimum levels of LDL-C but high TG and/or low HDL-C. Furthermore, the relationship of high TG levels with non-HDL-C in such setting have not been assessed previously. This study was undertaken to understand the patient characteristics and various lipid profiles of patients prior to starting Niacin ER.

Methods

This is a retrospective cohort study using General Electric (GE) Centricity electronic medical record (EMR) database that identified the new users of Niacin ER. The GE database contains patient-level clinical data elements obtained from Centricity Physician Office EMR (formerly Logician) for Clinical Data Services reporting. Data are collected from 40 000 clinicians and 20 000 nurse practitioner/physician assistant (12 500 MDs in the MQIC [Medical Quality Improvement Consortium] practicing in mid-large size group practices in the United States). Majority of the physicians are in primary care (85% family practice, internal

medicine, obstetrics and gynecology, pediatrics, and other specialties).

The index date of new Niacin ER prescription was from July 1, 2000, to June 30, 2013. This is the date of first prescription of Niacin ER, where first prescription is defined as the absence of any prescription of Niacin ER or Niacin ER containing combination products (Simcor or Advicor) in the previous 6 months prior to the first prescription of Niacin ER. All individuals 18 years and older at index date first Niacin ER prescription were included in this study.

New Users of Niacin ER

Patients initiating therapy of Niacin ER between July 1, 2000, and June 30, 2013, were identified using General Product Index categories, product names, or other available identifiers. The medication dimension table in the GE database does not contain the variables of drug manufacturer. However, another source, RedBook, captures such data. Using both these sources that can be linked by a common National Drug Code (NDC), we determined the manufacturer of a drug in the GE system indicating these are specific to Niacin ER manufactured by Abbott/AbbVie pharmaceuticals.

All subjects had a minimum of 6-month history of enrollment and medication information to evaluate if all Niacin ER users are true new users (Figure 1). Subjects less than 18 years of age or had less than 6 months enrollment period in the database or used Niacin ER or Niacin ER combination products within 6 months prior to the index date of new prescriptions were excluded.

A subset of patients was selected based on following additional criteria: had at least one lipid test (including TG or HDL-C) available during the 6-month observation period. Most proximal lipid values at/prior to index date indicating new user (including LDL-C, HDL-C, and TG, etc) were examined. This subgroup was further stratified into various TG, LDL-C, HDL-C, and non-HDL-C categories and TG/HDL-C ratio to have a better understanding of the lipid profiles of these subjects. The TG levels were categorized as <150 mg/dL, 150 to <200 mg/dL, 200 to <400 mg/dL, and ≥400 mg/dL. The LDL-C levels were categorized as <100 mg/dL, 100 to <130 mg/dL, 130 to <160 mg/dL, and ≥160 mg/dL. The HDL-C levels were categorized as nonoptimal if HDL-C level was <40 mg/dL in men and <50 mg/dL in women. For non-HDL-C levels, the categories were <130 mg/dL, 130 to <160 mg/dL, 160 to <190 mg/dL, and ≥190 mg/dL. Using these categories, we further characterized the joint distribution of these lipid factors. For example, we examined the subgroup where the LDL-C was optimum (<100 mg/dL), proportion of nonoptimal TG levels and/or nonoptimal HDL-C, or combination of nonoptimal TG and HDL-C levels.

Some patients did not have any lipid laboratory records within the GE database. The age, gender, and history of

Figure 1. Diagrammatic description of Niaspan new users in the GE electronic medical record database.

*Index date is defined as the date of first prescription of Niaspan looking back at least 6 months.

cardiovascular comorbidities between those who had a lipid value recorded versus those who did not have such records were compared. The presence of cardiovascular comorbidities was determined by at least one medical record observed during the 6-month observation period prior to index date, based on ICD-9-CM codes (International Classification of Diseases, 9th Revision, Clinical Modification).

Statistical Analysis

The statistical analysis was done using frequency comparisons between categories of lipid variables; age groups 18 to <40, 40 to <55, 55 to <65, 65 to <75, and 75+ years; and gender (male, female) for the new users of Niacin ER. Pearson's correlation of various lipid values (continuous variables) were done to understand the relationship of these lipid levels with each other. This was examined in each gender and age group to evaluate any difference by age and gender. Also, prevalence of selected CVD among new users of Niacin ER prior to starting therapy was analyzed. Missing data were taken into consideration and presented either in tables or in footnote as appropriate. SAS statistical software (version

9.3; SAS Institute, Cary, NC) was used in all data management and analyses.

Results

Demographics

Of the 89 091 new users, 65.0% were men and more than 90% were above 40 years old. Age distribution of new Niacin ER users did not show significant difference by gender. Approximately 77% ($n = 68\,538$) of new Niacin ER users had HDL-C or TG levels measured within 6 months prior to initiation of therapy. Proportion of patients missing lipid data (not recorded in the GE database) did not vary by age and gender.

Lipid Values Prior to Niacin ER Use

Mean ($\pm$ SD) for TG, HDL-C, TG/HDL-C ratio, LDL-C, and non-HDL-C levels for females were 221.6 ± 139.7 mg/dL, 46.4 ± 15.8 mg/dL, 5.7 ± 4.9 , 123.5 ± 46.2 mg/dL, and 164.5 ± 51.4 , respectively. Corresponding values for men were 213.3 ± 145.9 mg/dL, 36.4 ± 10.9 mg/dL, 6.6 ± 5.7 , 99.7 ± 37.9 mg/dL, and 139.7 ± 47.2 , respectively.

Table 1. Lipid Values of New Users of Niaspan 6 Months Prior to First Prescription in the GE Database Between 2000 and 2013.

	Female	Male	All
All new Niaspan users with at least one TG value	24 408	42 479	66 887
All new Niaspan users with at least one HDL-C value	24 406	42 761	67 167
Nonoptimal TG (≥ 150 mg/dL)	15 715 (64.4)	25 107(59.1)	40 822 (61.0)
Very high TG (≥ 400 mg/dL)	2367 (9.7)	4245 (9.9)	6612 (9.9)
Nonoptimal HDL-C (<40 mg/dL in men, <50 mg/dL in women)	15 805 (64.8)	30 186(70.6)	45 991(68.5)
Among those with both TG and HDL-C levels measured	23 906	41 610	65 516
Nonoptimal TG and nonoptimal HDL-C	11 687 (48.9)	19 291 (46.4)	30 978 (47.3)
Among those either TG or HDL-C levels measured	24 908	43 630	68 538
Either nonoptimal TG or nonoptimal HDL-C	20 005 (80.3)	38 972 (89.3)	58 977 (86.0)

Abbreviations: TG, triglyceride; HDL-C, high-density lipoprotein cholesterol.

Table 2. Pearson Correlation of Triglycerides With Other Lipids and Lipoproteins.

	Males			Females			Total		
	N	Coefficient ^a	P Value	N	Coefficient ^a	P Value	N	Coefficient ^a	P Value
HDL-C	41610	-0.23	<.0001	23906	-0.35	<.0001	65516	-0.24	<.0001
LDL-C	39486	-0.01	.23	22693	-0.12	<.0001	62179	-0.04	<.0001
Non-HDL-C	41018	0.48	<.0001	23549	0.32	<.0001	64567	0.41	<.0001
TG	41789	0.41	<.0001	23969	0.20	<.0001	65758	0.32	<.0001
Apo B	229	0.33	<.0001	120	0.34	.0002	349	0.34	<.0001
Apo A	89	0.14	.19	49	0.08	.5735	138	0.11	.21
Lpa	319	-0.05	.39	144	-0.08	.324	463	-0.06	.19

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.

^a“-” sign indicates negative correlation; “+” sign indicate positive correlation.

Lipid abnormalities prior to Niacin ER use

Among those who had a TG or HDL-C value recorded, 84% had nonoptimum levels of either TG or HDL-C and 47.3% had nonoptimal levels of both TG and HDL-C. The TG/HDL-C ratio was higher in patients with nonoptimal TG and HDL-C compared with patients with optimum levels of TG and HDL-C (Table 1). Among nonoptimal TG and HDL patients, the ratio of TG to HDL-C was higher among younger age group (mean ratio 12.0 in males; 10.58 in females aged 18 to <40) compared with other age groups. There was no correlation between TG and LDL-C. However, TG was positively (0.41 , $P < .001$) correlated with non-HDL-C and negatively correlated with HDL-C (-0.24 , $P < .001$) (Table 2). Among those with LDL-C <100 mg/dL, 64.3% had high TG/HDL-C ratio (>3 ; mean $\pm$ SD 7.5 ± 4.5 for females and >3.75 ; mean $\pm$ SD 8.3 ± 4.9 for males). In the same group of patients, approximately 77% had non-HDL-C ≥ 130 mg/dL (Table 3). More than a third of the patients had diagnosis of coronary heart disease (CHD) or CHD risk equivalent (Table 4).

Discussion

To date the patient characteristics and their lipid profile prior to receiving Niacin ER have not been well characterized in

Table 3. Distribution of TG, HDL-C, and Non-HDL-C Among Patients With Optimal LDL-C^a.

Patient Group	n (%) With Nonoptimal Levels
TG measured (N = 30 101)	17 310 (57.5)
HDL-C measured (N = 30 347)	23 241 (76.6)
TG and HDL-C measured (N = 29 747)	14 622 (49.2)
TG/HDL-C ratio measured (N = 29 747)	19 842 (66.7)
Non-HDL-C measured (N = 30 061)	23 107 (76.9)

Abbreviations: TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

^aOptimal LDL-C: <100 mg/dL. Nonoptimal TG: ≥ 150 mg/dL. Nonoptimal HDL-C: <40 mg/dL in males and <50 mg/dL in females. High TG/HDL-C ratio: males >3.75 and females >3 .

real-world clinical practice, particularly in patients who had optimal levels of LDL-C but nonoptimal TG and/or HDL-C. To our knowledge, no studies have specifically compared non-HDL-C levels and TG levels in new users of Niacin ER. Therefore, this study primarily focused on non-HDL-C, TG, HDL-C, and ratio of TG/HDL-C and their distribution in new users of Niacin ER.

Given the treatment indication of Niacin ER, as expected, we found almost 77% of new users of Niacin ER had either

Table 4. Prevalence of CVD^a Among Niaspan Users Prior to Start of Therapy.

Patient Group	n (%)
Users with no TG and HDL-C levels measured (N = 20 553)	6591 (32.1)
Optimal TG and HDL-C levels (N = 11 599)	3608 (31.1)
Nonoptimal TG and HDL-C levels (N = 30 978)	10 799 (34.9)
Nonoptimal TG or HDL-C levels (N = 55 835)	19 362 (34.7)

Abbreviations: CVD (cardiovascular disease)^a; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol.

^aMyocardial infarction, angina, other acute and chronic ischemic heart diseases, TIA/stroke, abdominal aortic aneurysm, peripheral vascular disease, peripheral arterial disease, diabetes, hyperlipidemia, hypertension.

nonoptimal TG or HDL-C levels. Niacin ER or nicotinic acid is known to be one of the most effective agents currently available for patients who need medication for increasing levels of HDL-C and reducing TG levels.⁷

As this study demonstrated that even among patients with optimal LDL-C <100 mg/dL, there is a large proportion of population with residual cardiovascular risk manifested by nonoptimal TG and HDL-C, which is also strongly correlated with non-HDL-C levels. Studies have shown that non-HDL-C maybe a highly useful lipid measure for assessing risk and evaluating response to lipid lowering therapy.¹⁴ Although the impact of Niacin ER on all residual risk population for CHD in real-world clinical practice is not known, the lipid profile of the population studied, particularly patients who had non-optimal TG and HDL-C correlated with non-HDL-C, suggests that a high residual risk population has been targeted by Niacin ER in real-world clinical practice setting.

Another important marker to be considered is the small, dense LDL, which is considered to be highly atherogenic, since it is more readily oxidized than larger LDL species and more likely incorporated in the matrix of plaque formation. The elevated TG, low HDL-C, and small, dense LDL are known as atherogenic lipoprotein phenotype (ALP) associated with increased risk of CHD. More than one third of our study population had a diagnosis of CHD or CHD risk equivalent prior to Niaspan use that did not vary by lipid residual risk profile indicating that therapy was based on lipid risk profile rather than prior CHD history. The most striking feature of our study was the fact that ratio of TG to HDL-C was very high among younger age group aged less than 40 years of age. Our study also found that the same age group also had undesirable non-HDL-C irrespective of CVD or CVD risk equivalent status. According to the American Heart Association, the average annual rates of first cardiovascular event rise from 3 per 1000 men at 35 to 44 years of age to 74 per 1000 men at 85 to 94 years of age. For women, comparable rates occur 10 years later in life.¹⁵⁻¹⁷ Despite lower rates of CVD in the younger population, residual risk

identification (lipid parameters affected by lifestyle and genetic predisposition) and treatment is important from a public health standpoint as demonstrated by a 12-year coronary heart disease mortality study among 40- to 59-year-old men in Moscow and St Petersburg where 40 to 59 year olds had an increased risk of cardiac death due to lifestyle characteristics.¹⁸

Strengths and Limitations of Study

This study of real-world Niaspan usage over a 13-year period (2000-2013) necessarily does not reflect the potential impact of recent CVD guidelines.¹³ However, this study does capture important aspects of the medical management of dyslipidemia using a well-established nonstatin mechanism. This may serve as a benchmark that can be compared with future real-world usage of adjuvant lipid lowering agents such as Niaspan compared with statin use alone to accurately assess the management of CVD risk based on the newer treatment guidelines.

The GE data are essentially population-based clinical practice and minimize some degree of selection bias with respect to socioeconomic status, geographic region, and race/ethnicity. The EMR database allows for the capture of data on laboratory values, demographic characteristics, comorbidity along with diagnosis, medication orders, and procedures. However, the data source is encounter driven. The data are collected for purposes other than research. So we are unable to capture medical records that were outside of the clinics contributing data to the GE system. While the ability to capture laboratory measurements prior to starting Niacin ER therapy is an important strength of this study, lipid tests performed outside the GE network could not be captured in this database even when the diagnoses or prescriptions are recorded. Therefore, although approximately 23% of new Niacin ER users had no recorded lipid values, they could have assessed elsewhere and referred to the GE system. Furthermore, the EMR reflects that a drug was prescribed but does not indicate that the prescription was filled or picked up (as claims data do). Given that NDC code is presented as a unique 11-digit numeric identifier in RedBook and a 9-digit code in the GE database, there is a possibility of not capturing all Niacin ER manufacturers in the GE database. Nevertheless, as patient demographic characteristics did not vary by availability of lipid values in GE and given the large practice database, the results presented in this study are robust and demonstrated use of Niacin ER in populations with residual risk unlikely to be addressed by conventional LDL-C lowering therapy.

Conclusion

This EMR-based study of new users of Niacin ER demonstrated that the majority of Niacin ER users had nonoptimal

TG and/or HDL-C. The relationships of nonoptimal TG with non-HDL-C further support the evidence of residual risk of CVD in a population that had optimum LDL-C levels. This study shows that in real-world practice, Niacin ER use was targeted to populations with residual risk for CVD.

Authors' Note

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Declaration of Conflicting Interests

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