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### Clinical Experience With Prolonged-Release Nicotinic Acid in Statin-Treated Patients Managed in the Usual-Care Setting in Austria: An Analysis from the Niaspan<sup>®</sup>-Induced HDL-Elevation for Optimizing Risk Control (NEMO) Study

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Low HDL cholesterol is an independent risk factor for adverse cardiovascular outcomes and is prevalent in statin-treated patients in Europe. The Niaspan<sup>®</sup>-induced HDL-Elevation for Optimizing Risk Control (NEMO) study was an open, uncontrolled, observational evaluation of the effects of 6 months of prolonged-release nicotinic acid (target dose 2000 mg/day) in 1053 statin-treated patients with low HDL cholesterol and/ or hypertriglyceridaemia and additional cardiometabolic risk factors in four European countries. This analysis focuses on the effects observed in 220 patients recruited in Austria. Tolerability and safety were principal study endpoints (particularly treatment-related adverse drug reactions [ADRs]). The prevalence of coronary heart disease and hypertension was higher in Austria versus the overall NEMO population. Flushing (mostly of mild severity) was the most common side effect of prolonged-release nicotinic acid: 35 % of the patients flushed in the first month, declining to 14 % in the sixth month. Other ADRs occurred mainly in the gastrointestinal (9 %) and nervous systems (5 %). There were no treatment-related serious ADRs. Tolerability was assessed in 152 patients and was rated as 'acceptable', 'good' or 'very good' for 75 % of patients. Treatment with prolonged-release nicotinic acid increased HDL cholesterol by 24 % and decreased triglycerides by 11 % at 6 months, with modest decreases in total (-4 %) and LDL cholesterol (-8.2 %). Overall, the incidence of side effects and efficacy outcomes were comparable for prolonged-release nicotinic acid in the Austrian and overall NEMO populations. Correction of low HDL cholesterol with prolonged-release nicotinic acid may represent a rational therapeutic strategy for managing the residual cardiometabolic risk after statin treatment in Austria, as else-where. **J Clin Basic Cardiol 2007; 10 (online): 7–10.** 

Key words: prolonged-release nicotinic acid, dyslipidaemia, cardiovascular risk, tolerability, safety, HDL cholesterol

ow HDL cholesterol is prevalent within Europe [1] and is an independent risk factor for cardiovascular disease, and confers an increased risk of adverse cardiovascular outcomes irrespective of the level of LDL cholesterol [2–7], or of the presence or absence of statin treatment [8]. Correction of low HDL cholesterol in statin-treated patients may therefore represent a rational strategy to ameliorate the considerable burden of residual cardiovascular risk in this population. In Austria, a factor encompassing low HDL cholesterol, high triglycerides and small LDL was an important predictor of disease progression in patients with coronary artery disease [9]. This held true particularly for patients with impaired fasting glucose and in patients with manifest diabetes mellitus.

Nicotinic acid (niacin in some countries) is the most potent treatment currently available for increasing circulating levels of HDL cholesterol [10]. However, the use of nicotinic acid has been hindered by concerns relating to its tolerability profile (particularly with regard to cutaneous flushing) and concerns over safety (a perception that nicotinic acid may induce dysglycaemia or hepatic dysfunction) [11, 12]. Many physicians are cautious regarding statin-based combinations following the serious muscle side effects observed in patients receiving cerivastatin-gemfibrozil combinations [13, 14]. Niaspan<sup>®</sup> is a prolonged-release formulation of nicotinic acid with a pharmacokinetic profile designed to reduce the incidence of flushing relative to immediate-release nicotinic acid, and to minimize the risk of hepatic side effects relative to sustained-release formulations [15].

The Niaspan<sup>®</sup>-induced HDL-Elevation for Optimizing Risk Control (NEMO) study was an international, multicentre, observational study designed to evaluate the tolerability and safety of prolonged-release nicotinic acid under usual-care conditions in Austria, the Netherlands, Sweden and Ireland [16]. Epidemiological studies demonstrate that important differences in cardiometabolic risk factor status may occur between regions within Europe [1, 17], and it is important to understand the effects of cardiovascular medications in defined geographical populations wherever possible. Accordingly, we present an analysis of the effects of prolonged-release nicotinic acid in Austrian patients within the NEMO study.

#### Methods

#### Design

NEMO was a prospective, multi-centre, open-label, observational, uncontrolled trial. The design of the study has been described in detail elsewhere [16]. Briefly, prolonged-release nicotinic acid was administered according to its prescribing information [18] as part of the usual care provided by the physicians of patients within the trial. The maximum permitted daily dose of prolonged-release nicotinic acid is 2000 mg. Tolerability and safety were the main endpoints, measured as treatment-related (possible, probable, not assessable or missing relationship to treatment) adverse drug reactions (ADRs). Standard definitions (MedRA terms) were used to define ADRs and serious ADRs. Data on lipid parameters and a global cardiovascular risk score (based on the algorithm derived from the Prospective Cardiovascular Münster [PROCAM] study [17]) were also collected.

#### Patients

Principal recruitment criteria included: age at least 18 years; addition of prolonged-release nicotinic acid to a statin within the previous 2 months; HDL cholesterol < 1.3 mmol/L and/ or triglycerides > 1.7 mmol/L before treatment; one or more of: coronary artery disease (indicated by at least one previous myocardial infarction or revascularization of a coronary ste-

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nosis of at least 70 % on angiography, or stroke); diabetes mellitus type 2; 10-year PROCAM risk of myocardial infarction > 20 %. The study was conducted in a manner consistent with all relevant national and European Union legislation and the Declaration of Helsinki. Neither ethical approval nor informed consent by patients was required for this non-interventional study.

#### Statistics

Data were analysed using descriptive statistics. No significance testing was performed. All percentages are based on the total number of patients who received treatment.

#### Results

#### Patients

Two hundred and twenty of the 1053 patients in the NEMO study were recruited in Austria (21 %). The Austrian population contained slightly more male subjects than the overall population (Tab. 1). The Austrian population also contained a markedly higher proportion of patients with hypertension (80 % vs 57 %) or coronary heart disease (71 % vs 53 %), with slightly higher prevalence of other forms of cardiovascular disease, such as myocardial infarction, coronary revascularization or cerebrovascular disease (see Tab. 1). Other demo-

#### Table 1. Patients

	Patients in Austria (n = 220)	All patients (n = 1053)
Males (%)	86.8	79.3
Mean age (years)	60.4 (10.6)	58.4 (10.9)
Mean weight (kg)	86.3 (13.5)	88.0 (16.0)
Ethnicity (%) White/Caucasian Asian Black Other/not recorded	96.8 1.4 0.0 1.8	94.5 2.6 0.8 2.2
Total cholesterol (mmol/L)	4.6 (1.2)	4.7 (1.4)
Triglycerides (mmol/L)	2.5 (1.7)	3.2 (2.5)
LDL cholesterol (mmol/L)	3.0 (1.1)	2.6 (1.1)
HDL cholesterol (mmol/L)	1.0 (0.2)	0.9 (0.3)
Fasting plasma glucose (mmol/	L) 6.4 (2.1)	6.8 (2.4)
HbA <sub>1C</sub> (%)	6.5 (1.3)	6.6 (1.4)
Systolic blood pressure (mmHg)	) 133 (19)	136 (19)
Diastolic blood pressure (mmHg	g)        80 (11)	80 (10)
Hypertension (%)	79.5	56.7
Coronary heart disease	70.9	53.0
Prior myocardial infarction	35.5	30.3
PTCA or stent	36.4	23.8
CABG	17.7	14.2
Cerebrovascular disease (%)	19.5	10.3
Peripheral vascular disease (%)	11.8	12.9
Diabetes (%)	39.1	42.1
Metabolic syndrome (%)*	59.1	53.1
Family history for CVD (%)	36.4	42.1
Smoking (%) Current smoker Ex smoker	19.5 36.8	21.7 38.8

\* National Cholesterol Education Program/Adult Treatment Panel III criteria. Figures in parentheses are SD.

 
 Table 2. Principal reasons for treatment discontinuation after end of the observation period (% patients)

	Patients in Austria (n = 220)	All patients (n = 1053)
Flushing	9.1	11.1
ADR unrelated to flushing	11.8	8.4
Insufficient efficacy	6.4	10.5
Lost to follow-up	9.5	6.2
Patient declined further treatme	nt 10.9	14.1
Further treatment not required	2.3	0.8

ADR: treatment-related adverse drug reactions. Patients could have discontinued for an ADR in more than one category.

graphic and disease characteristics differed little between the populations. About one patient in five was a current smoker. All patients received a statin, according to the recruitment criteria for the study, with 42 % receiving simvastatin, 31 % receiving atorvastatin, 11 % receiving fluvastatin, 9 % receiving pravastatin, 4 % receiving rosuvastatin and 0.5 % receiving lovastatin.

Details of treatment discontinuations after the end of the observation period are shown in Table 2. Information on the proportion of patients continuing treatment with prolonged-release nicotinic acid was available for 164 patients (75 %): 79 patients continued treatment (36 % of all Austrian patients) while 85 patients (39 %) did not. ADRs (related to or unrelated to flushing) and patient request were the most common reasons for treatment discontinuation.

#### **Tolerability and Safety**

As flushing is an ADR of special interest with nicotinic acidbased therapy, this and other ADRs are discussed separately. Almost all ADRs unrelated to flushing were treatmentrelated (36 patients [16 %] reported ADRs, and in 34 patients [15 %], these ADRs were considered drug-related). The most common treatment-related ADRs other than flushing occurred in the gastrointestinal and nervous systems (Tab. 3).

Table 3. Clinical ADRs unrelated to flushing (% patients)

Adverse drug reaction	Patients in Austria (n = 220)	All patients (n = 1053)
Skin and subcutaneous disorders (any)	3.2	4.1
Pruritus	1.8	2.7
Gastrointestinal disorders (any)	8.6	3.8
Upper abdominal pain	5.5	1.1
Constipation	1.4	0.3
Nausea	0.9	1.0
Diarrhoea	1.4	0.6
Nervous system disorders (any)	4.5	3.8
Headache	1.8	0.9
Vertigo	1.8	0.4
Musculoskeletal/connective tissue disorders (ar	ıy) 0.5	1.2

ADRs (treatment-related adverse drug reactions) relating to any MedDRA system organ class that occurred in more than 1 % of patients in either population are shown, with specific clinical ADRs within each body system that occurred in more than 1 % of patients for either population (this approach lists ADRs that occurred in 3 or more patients in the population in Austria). Treatment-related ADRs were those for which investigators did not rule out a causal relationship with prolonged-release nicotinic acid (see methods).



**Figure 1.** Incidences of flushing during the NEMO study. Percentages refer to overall populations (n = 220 for the Austrian population and n = 1053 for the overall population). The severity of flushes was rated by study investigators.

One patient reported two serious ADRs (pneumonia and haemoptysis), which were considered unrelated to treatment. No patient died. Overall, the tolerability and safety profiles of prolonged-release nicotinic acid for ADRs other than flushing were similar in Austria to those seen in the general population.

Flushing was commonly observed during the study (Fig. 1). The frequency of flushing tended to decrease over time, with 35 % reporting flushing in the first month and 14 % reporting flushing in the final month of treatment. Most flushes were mild or moderate in severity. No flushing episode constituted a serious ADR according to standard clinical trial definitions (MeDRA). The frequency of flushing appeared to be lower in Austria than in the overall population during the early months of the study. Between 23 % and 30 % of patients took a non-steroidal anti-inflammatory agent as prophylaxis for flushing in any given month.

There were no clinically significant changes in laboratory parameters. With regard to liver function parameters, the mean change in glutamyl oxaloacetic transaminase (GOT [aspartate aminotransferase/AST]) was -8 U/L from a baseline value of 30 U/L, with a corresponding change in glutamyl pyruvic transaminase (GPT [alanine aminotransferase/ ALT]) of -2 U/L from a baseline value of 32 U/L. Mean plasma glucose and mean glycated haemoglobin (HbA<sub>1C</sub>) decreased slightly on average. Mean blood pressure was unaffected. Mean creatinine kinase increased slightly at 6 months, by 16 U/L from a baseline value of 112 U/L. Serum creatinine was essentially unchanged at study end (mean increase of 2 mmol/L from a baseline value of 88 mmol/L).

An overall rating of tolerability was provided by investigators. Tolerability was assessed in 152 patients and was judged to be 'poor' in 25 %, 'acceptable' in 14 %, 'good' in 24 %, and 'very good' in 37 %.

#### Lipid Parameters

Mean HDL cholesterol was relatively low at baseline, consistent with the recruitment criteria for the study (Tab. 1). Marked increases in HDL cholesterol were observed, with a mean increase from baseline of 18 % after 2–3 months and 24 % after 6 months (Fig. 2). Mean triglycerides were decreased by –14 % at 2–3 months, with little change thereafter (final mean change –11 %). Modest reductions in total cholesterol (mean change of up to –4 %) and LDL cholesterol (mean change up to –8 %) were also observed. These changes were similar to those observed in the overall population (mean changes in HDL cholesterol, triglycerides, total cho-



Figure 2. Effects on lipid profiles (means ± SE)

lesterol and LDL cholesterol were 23 %, -15 %, -4 % and -4 %, respectively).

An overall treatment response in 127 patients was judged by investigators to be 'poor' in 20 % of patients, 'acceptable' in 23 %, 'good' in 32 % and 'very good' in 25 %. The mean PROCAM score (10-year risk of myocardial infarction) was also measured. This parameter (mean  $\pm$  SEM) was reduced from 45.7  $\pm$  0.7 at baseline to 39.0  $\pm$  0.9 at study end (mean values for the overall population were 45.6  $\pm$  0.4 and 41.3  $\pm$ 0.4, respectively).

#### Discussion

The NEMO study recruited a population of statin-treated patients with atherogenic dyslipidaemia (low HDL cholesterol and/or hypertriglyceridaemia) and other cardiometabolic risk factors. The prevalence of coronary heart disease in Austria was higher in this population than in the overall NEMO population, despite the use of identical recruitment criteria in the four countries which recruited patients with broadly similar lipid profiles, on average. A markedly higher prevalence of hypertension in the Austrian population relative to the overall population may have contributed to this difference in the prevalence of coronary heart disease between the populations. A slightly higher proportion of males, a slightly higher level of LDL cholesterol and a slightly higher prevalence of the metabolic syndrome may have contributed to this difference in coronary heart disease prevalence in Austria, although differences were not observed between populations in other potentially important risk factors such as diabetes, family cardiovascular disease history or smoking. This is an intriguing, although preliminary, finding which warrants further study.

The incidence of flushing, the main side effect associated with nicotinic acid, was not higher in Austria relative to the NEMO population and was consistent with that observed in other clinical evaluations of this prolonged-release nicotinic acid formulation [15]. The tendency for the incidence of flushing to decrease over time was also consistent with previous clinical experience (although withdrawals from treatment were likely to have contributed to this decrease, and the lack of placebo control represents a general limitation of the NEMO study). The incidence of other ADRs was low, and also consistent with previous clinical experience. In particular, there was no evidence of a clinically significant incidence of muscle or hepatic toxicity. It should be noted that these data were gathered under usual-care conditions, which are directly relevant to the routine management of dyslipidaemia.

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The improvement in the lipid profile in Austrian patients was similar to that observed elsewhere, with an increase in HDL cholesterol of > 20 %, a marked decrease in triglycerides and a decrease in the global cardiovascular risk score (PROCAM). The addition of nicotinic acid to a statin has been shown previously to delay or reverse the progression of atherosclerosis [19, 20]. Moreover, a nicotinic acid-statin combination has also been shown to induce a marked reduction in cardiovascular event rates of up to 90 % compared with placebo [21]. Thus, correction of low HDL cholesterol with nicotinic acid is consistent with a reduced risk of adverse cardiovascular events, although increasing levels of HDL cholesterol by other mechanisms may not provide such a benefit [22–24].

In conclusion, this analysis from the NEMO study describes the therapeutic profile of prolonged-release nicotinic acid in an Austrian population of statin-treated patients with atherogenic dyslipidaemia and other cardiometabolic risk factors. Prolonged-release nicotinic acid was generally well tolerated in this population, with the expected incidence of flushing, and produced marked improvements in HDL cholesterol and triglycerides. Correction of low HDL cholesterol with prolonged-release nicotinic acid may represent a rational therapeutic strategy for managing the residual cardiometabolic risk after statin treatment in Austria, as in other populations. Of note, the increase in HDL cholesterol was larger after 6 months (24 %) than after 2-3 months (18 %). Long-term administration of prolonged-release nicotinic acid is therefore required to achieve the maximum effects on HDL cholesterol.

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