Safety and tolerability of prolonged-release nicotinic acid in patients aged ≥ 65 years enrolled in NAUTILUS

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Abstract

Older patients are often at high risk for cardiovascular disease. Low high-density lipoprotein (HDL) cholesterol is an independent risk factor for cardiovascular disease. Prolonged-release nicotinic acid (Niaspan®) is a once-daily formulation of nicotinic acid with improved tolerability compared with the immediate-release formulation. It may be used to correct low levels of HDL cholesterol. NAUTILUS (the multiceNtre, open, uncontrolled sAfety and tolerability stUdy of a modified release nicoTinic acId formuLation in sUbjects with dySlipidaemia and low HDL cholesterol) evaluated prolonged-release nicotinic acid at doses of up to 2,000 mg/day once daily in 566 patients, of whom 33.6% were aged ≥ 65 years.

A similar incidence of adverse events (AE) was observed following 15 weeks of prolonged-release nicotinic acid treatment in older *vs.* younger patients for all-cause AE (55.3% *vs.* 63.3%) and for treatment-related AE (46.3% *vs.* 52.1%). Most AE were related to flushing, which also occurred at similar frequency in older and younger patients (39.5% *vs.* 43.4%).

Gastrointestinal AE were the most common AE apart from flushing, and occurred in 12.1% of older patients and 14.4% of younger patients. Serious AE were uncommon. There was no hepatotoxicity or serious muscle toxicity. Marked improvements in indices of atherogenic dyslipidaemia were observed (increases from baseline in HDL cholesterol of 26% in older and 21% in younger patients and decreases in triglycerides of 16% and 9%, respectively).

Prolonged-release nicotinic acid is well tolerated and effective in older patients, and is suitable for correction of low HDL cholesterol in this population.

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Introduction

Cardiovascular disease is still the leading cause of death in Western populations. This is particularly true among older patients, in whom death rates from cardiovascular causes outstrip those from other leading causes of mortality, such as cancer or respiratory disease.[1,2] Age itself is a cardiovascular risk factor, and the prevalence of other cardiovascular risk factors and the associated overall risk of an adverse cardiovascular event increase steeply with age.[3-5] Moreover, the prevalence of cardiovascular risk factors associated with the metabolic syndrome has increased sharply within the last decade.[6] Controlling cardiovascular risk in the older patient is therefore important and intervention trials in older populations have shown that addressing individual cardiovascular risk factors within this population has the potential to deliver marked and clinically significant improvements in cardiovascular prognosis.[7-11]

Observational studies conducted during the last three decades have identified low levels of high-density lipoprotein (HDL) cholesterol as an independent cardiovascular risk factor.[12-17] Intervention studies using agents that raise levels of HDL cholesterol, such as nicotinic acid, have confirmed the important influence of low HDL cholesterol on cardiovascular prognosis.[18-20] Indeed, nicotinic acid is the most effective agent currently available for increasing levels of HDL cholesterol.[3] A prolonged-release formulation of nicotinic acid (Niaspan®), with once-daily administration and improved tolerability compared with the immediate-release formulation,[21,22] has been shown to inhibit the progression of atherosclerosis in patients with low HDL-cholesterol.[23] The administration of nicotinic acid-based therapy to older patients with low HDL cholesterol may therefore make an important contribution to the reduction of cardiovascular risk,

Table 1. Overview of adverse events (AE)

		Any AE (%)	Flushing (%)	Unrelated to flushing (%)
All-cause AE	≥ 65 years	55.3	39.5	32.6
	< 65 years	63.3	43.4	40.2
Treatment-related AE	≥ 65 years	46.3	39.5	15.8
	< 65 years	52.1	42.8	19.9
All-cause serious AE	≥ 65 years	5.3	0.0	5.3
	< 65 years	2.9	0.3	2.9
Treatment-related serious AE	≥ 65 years	0.5	0.0	0.5
	< 65 years	0.5	0.0	0.5
Withdrawal for AE	≥ 65 years	25.3	15.3	11.1
	< 65 years	13.6	6.9	7.4

Treatment-related AE were defined as AE with a possible or unassessable relationship to study treatment

Table 2. Most common all-cause adverse events (AE) excluding flushing

	Age < 65 years (n=376)	Age ≥ 65 years (n=190)
Gastrointestinal system	14.4%	12.1%
Abdominal pain	2.1%	1.6%
Diarrhoea	4.8%	2.1%
Nausea	2.4%	3.7%
Laboratory parameters	3.5%	2.1%
Musculoskeletal/connective tissue	4.5%	4.2%
Skin/subcutaneous	6.9%	6.8%
Pruritus	2.4%	3.7%

AE by body system or individual AE are shown where they occurred in > 2% of either subgroup. Patients could have an AE both related to and unrelated to flushing

when administered in combination with treatments that address other risk factors common in this population, such as statins, antithrombotic agents and antihypertensive agents.

Since the tolerability and safety profiles of treatments may differ between older and younger patients, treatments should be evaluated carefully in older patients. Accordingly, we present an analysis of the tolerability and safety of prolonged-release nicotinic acid in older patients with dyslipidaemia and low HDL cholesterol enrolled in the NAUTILUS study.

Patients and methods

The NAUTILUS study was an open-label, uncontrolled phase IIIb study conducted in Germany. Patients eligible for the study had dyslipidaemia, including low HDL cholesterol (< 1.0 mmol/L [< 40 mg/dL] in men and < 1.2 mmol/L [< 46 mg/dL] in women), despite four weeks of treatment with diet. Triglycerides were required to be < 9.0 mmol/L (< 800 mg/dL). Exclusion criteria included uncontrolled diabetes, significant hepatic or renal disease, stroke within the previous six months, peripheral artery disease, unstable angina, and a history of myocardial infarction or uncontrolled arrhythmia.

Patients received once-daily treatment with prolonged-release nicotinic acid for 15 weeks. The dose of prolonged-release nicotinic acid was titrated, depending on tolerability, from 375 mg during week 1; to 500 mg during week 2; 750 mg during week 3; 1,000 mg during weeks 4–7; 1,500 mg during weeks 8–11; and 2,000 mg during weeks 12–15. Patients continued the study only if they received at least one dose of prolonged-release nicotinic acid 1,000 mg, although a dose reduction to 750 mg/day was permitted if required. The safety population was defined as all patients who received study medication. The main purpose of the study was to evaluate the safety and tolerability of prolonged-release nicotinic acid, and only limited efficacy analyses were undertaken in an intention-to-treat population comprising patients who received study medication and provided data (n=563). Laboratory parameters were measured in a central laboratory. Younger and older patients are defined as those aged < 65 years and ≥ 65 years, respectively, throughout.

Results

Patients

The safety population included 566 patients recruited at 112 centres. The majority of premature discontinuations (25.6%) were due to adverse events (AE; 16%). The study population was mostly Caucasian (99.3%) and male (67.5%) and 190 patients (33.6%) were aged ≥ 65 years. Mean body mass index (BMI) was 30.7 kg/m^2. Cardiometabolic risk factors at baseline included diabetes (58.1%), hypertension (63%) and coronary heart disease (39%).

Safety and tolerability

Overview of tolerability and safety

Most AE were related to flushing, and these are discussed separately below. Apart from flushing, the frequency of all-cause AE and treatment-related AE (defined as those AE with a possible or unassessable relationship to treatment) was similar in the two age groups (table 1). The most commonly observed all-cause AE occurred in the gastrointestinal system, with no difference in incidence according to age (table 2). There were no elevations of aspartate transaminase (AST) (glutamic oxaloacetic transaminase; GOT) or alanine transaminase (ALT) (glutamate pyruvate transaminase; GPT) to more than three times the upper limit of normal (ULN), and no elevations of creatine phosphokinase (CPK) to more than five times the ULN. Older patients were more likely to withdraw from treatment because of an AE (table 1). Three patients reported serious adverse events that were defined as treatment-related (all categorised by investigators as having a 'possible' relationship to treatment), of whom one was ≥ 65 years. No patient died during the study.

Increases in blood glucose levels were common. There were no clear or consistent differences in the proportions of older or

Figure 1. Numbers of flushes per patient in NAUTILUS

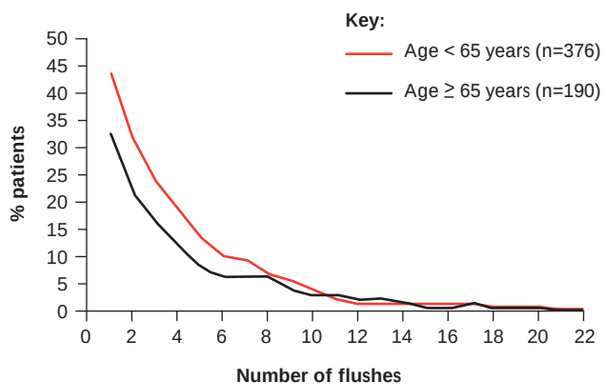
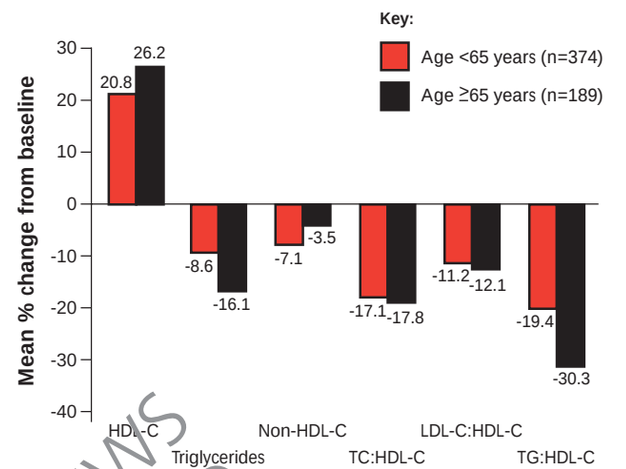


Figure 2. Effects on lipid parameters in NAUTILUS



Key: HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides

younger patients with an increase in glycosylated haemoglobin (HbA_{1C}) from baseline of > 0.2% units (46.5% and 44.8% of patients, respectively), > 0.5% units (21.8% and 20.1% of patients, respectively) or > 1.0 % units (8.5% and 8.3% of patients, respectively). Changes to antidiabetic treatment were also common: in the overall population, the dose was decreased in 14 patients and stopped altogether in 93 patients.

Flushing

Almost all instances of flushing were considered related to treatment (according to the definition given above). There was no marked difference in the incidence of flushing between older and younger patients (table 1). In addition, the incidence of flushing declined over time in a similar manner in older and younger patients (figure 1). Indeed, fewer than 5% of patients in either age group were still reporting flushes from week 10 onwards, and fewer than 10% of patients reported more than five flush events. Older patients were more likely to withdraw from treatment because of flushing (table 1).

The median time to onset of flushing from ingestion of study medication was 60 minutes in both age groups. Older patients tended to flush for slightly longer (median duration 60 *vs.* 45 minutes) but less often (mean number of flushes per week 1.8 [SEM 0.2] for younger patients and 1.4 [SEM 0.2] for older patients).

Effects on the lipid profile

The mean HDL cholesterol level in the overall population at baseline was 0.86 mmol/L (33 mg/dL) in men and 0.99 mmol/L (38 mg/dL) in women, and the mean triglyceride level was 2.9 mmol/L (257 mg/dL). Mean total cholesterol was 4.8 mmol/L (184 mg/dL), and mean low-density lipoprotein (LDL) cholesterol was 2.9 mmol/L (114 mg/dL) at baseline. A marked increase in HDL cholesterol and marked decreases in triglycerides were observed for both age groups with prolonged-release nicotinic acid treatment (figure 2). Larger average changes in HDL cholesterol and triglycerides were observed in the older patient group.

Discussion

The tolerability of prolonged-release nicotinic acid, as indicated by the incidence of AE or serious AE, was similar in older and younger patients in this study. This was true both for events related and unrelated to flushing, which is the principal side effect associated with nicotinic acid-based therapy.[20-22] There was no indication of a higher incidence of individual AE or adverse laboratory findings in older patients. There was an increased rate of premature treatment discontinuation in the older subgroup, but older patients are well known to be more likely than their younger counterparts to discontinue clinical trials for AE. Overall, the tolerability of prolonged-release nicotinic acid was not influenced by patients' age to a clinically significant extent.

The safety and tolerability profiles of nicotinic acid are strongly influenced by its formulation.[24-26] Two metabolic pathways metabolise nicotinic acid: a high affinity/low capacity pathway, which is responsible for nicotinic acid-mediated hepatotoxicity, and a low affinity/high-capacity pathway, which mediates flushing. An earlier sustained-release formulation of nicotinic acid released the drug at a low rate that did not saturate the first pathway, increasing the proportion of nicotinic acid metabolised by it and leading to hepatotoxicity. Conversely, a dose of immediate-release nicotinic acid easily saturates this pathway, directing nicotinic acid towards the higher-capacity/lower-affinity pathway and causing flushing. A prolonged-release formulation of nicotinic acid (Niaspan®) was developed with an intermediate rate of delivery of nicotinic acid between these immediate-release and sustained-release formulations. Prolonged-release nicotinic acid

Key messages

- Older patients with low levels of HDL cholesterol are at markedly elevated cardiovascular risk
- Niaspan® was well tolerated, irrespective of age, in the NAUTILUS study
- These results support the use of prolonged-release nicotinic acid to correct low HDL cholesterol levels in older patients

is not associated with clinically significant hepatotoxicity (as observed in the present study), and induces a lower incidence of flushing compared with immediate-release nicotinic acid, (as observed in head-to-head comparisons of these agents).[27]

Rises in blood glucose have also been associated with the administration of nicotinic acid. Changes in blood glucose were common in the present study, but were difficult to interpret in light of the frequent and unexplained changes of antidiabetic medicines administered as concomitant therapy during the study. In general, the changes made to antidiabetic medication were consistent with less intensive glycaemic management, so it is unsurprising that increases in HbA_{1C} were observed. Previous randomised evaluations of prolonged-release nicotinic acid, whether given as monotherapy or combined with a statin, found that changes in glycaemia in patients with diabetes were minor and easily accommodated by adjustments of antidiabetic therapies.[28,29]

The measurement of lipid parameters was a secondary objective of this study. Treatment with prolonged-release nicotinic acid was equally effective in increasing levels of HDL cholesterol, and in decreasing levels of triglycerides, in both age groups. The magnitude of the effects on these parameters were consistent with effects on these parameters as determined in previous randomised trials.[30,31]

Conclusions

Older patients with low levels of HDL cholesterol are likely to be at substantially elevated global cardiovascular risk, and require intervention to improve their overall cardiovascular risk profile. Prolonged-release nicotinic acid was well tolerated in older (≥ 65 years) and younger patients at once-daily doses of up to 2,000 mg/day in the NAUTILUS study. These doses were sufficient to induce marked improvements in levels of HDL cholesterol and triglycerides. The results of the NAUTILUS study support the use of prolonged-release nicotinic acid to correct low HDL cholesterol in older patients.

Conflict of interest

The NAUTILUS study was supported by an unrestricted grant from Merck KGaA, Darmstadt, Germany.

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Book reviews

Valvular heart disease

Authors: Andrus BW, Baldwin JC
Publisher: Manson Publishing Ltd, London, 2006
ISBN: 1840760583 Price: £60

This is a clearly written summary of heart valve disease with excellent illustrations. The invasive pressure tracings are very good indeed. A special and attractive feature is the insertion of an illustrative case history at the end of each chapter. In addition to the material that one might expect to see, there are chapters on drug-induced heart disease, quality improvement in valvular disease, and future developments, including percutaneous techniques for repair and replacement. Some of the chapters are outstanding, such as the management of asymptomatic mitral valve prolapse.

The contemporary trend in cardiology is for physical signs to be overlooked in favour of some form of high resolution, preferably 3-D imaging modality. It is therefore refreshing to find a chapter devoted to physical signs. Unfortunately, the authors have confined themselves exclusively to murmurs, with no discussion of the jugular venous pulse or the character of the carotid pulse. It is strange to find only a minimal mention of aortic valve repair in the chapter on aortic regurgitation. In the chapter on tricuspid regurgitation there is a figure which has escaped the proof-reader's scrutiny, as it depicts the insertion of an annuloplasty ring into a mitral orifice.

These criticisms apart, it is a very useful handbook and would be a good guide for physicians with an interest in cardiology, or as an introductory text at the postgraduate level.

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Transcatheter valve repair

Editors: Hijazi ZM, Bonhoeffer P, Feldman T, Ruiz CE
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ISBN: 1841844721 Price £95

As the mortality for most cardiac surgical procedures is now in low single figures, the spotlight has fallen on morbidity. Simultaneously, the technological and technical experience gained with coronary stenting has enabled gifted interventional cardiologists to explore transcatheter valve repair and replacement. This timely book is edited and contributed to by four of the leaders in this rapidly advancing field.

There are some distinguishing features of this new approach. Unlike any other cardiological development, this one requires serious multidisciplinary engagement of cardiologists, surgeons, cardiac imaging specialists and engineers. A further feature of this emerging sub-speciality is the biotechnology revolution in both medical devices and in tissue engineering. The creative use of new biomaterials, nanotechnology and catheter-based delivery systems will be required, and the first shoots of this development are described in this text.

The percutaneous replacement of the pulmonary valve is already well advanced in patients and this is clearly and honestly described. The pattern of the text is a division into four sections for each heart valve and, within each section, chapters on the pathophysiology, the haemodynamic evaluation, and the standard current surgical treatment are set beside the possibilities of percutaneous intervention. At the end of the book are separate chapters on tissue engineering and valve testing. The illustrations are of high quality throughout.

This inaugural text should serve as an inspiration to cardiologists, forward-thinking surgeons and young interventionists of all stripes in training.

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