Clinical Medicine Reviews in Vascular Health

Lipid Regulation with Niacin Extended-Release (Niaspan-R™)

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Abstract: Recent clinical trial data indicates that while normalizing serum LDL levels remains an important target in reducing adverse cardiovascular outcomes, it is not the whole story. Statins are very effective drugs for reducing LDL, but they are not sufficient to prevent the majority of cardiovascular events. The focus is now shifting towards a combined approach: reducing LDL, but also increasing HDL, low levels of which often persist despite statin treatment.
Niacin is the single most effective agent for increasing HDL, but its use has been limited because of tolerability issues affecting compliance. Niaspan-R™ is an extended-release formulation designed to reduce flushing and has been shown clinically to be as effective as immediate-release preparations. There is also a significant body of clinical evidence demonstrating the particular value of Niaspan-R™ when used in combination with existing lipid-lowering therapy. This review will consider this data and discuss the role of Niaspan-R™ in future treatment of mixed dyslipidemias.

Keywords: dyslipidemia, Niaspan-R™, atherosclerosis, HM74A, PPAR
Introduction
The efficacy of niacin (nicotinic acid; vitamin B₃) as an agent for normalizing blood lipid profiles is well documented. Not only is it one of the most effective clinical treatments available, but its use is also associated with a significant improvement in associated cardiovascular outcomes.¹⁻⁹ However, its clinical usefulness has been limited because of the occurrence of side-effects sufficiently severe to influence compliance. The most problematic of these is cutaneous flushing, which has been shown to result from signalling through the DP₁ receptor, triggered by the production of PGD₂ in Langerhans cells following activation of the niacin receptor.¹⁰⁻¹⁵ In attempting to address these issues, a number of sustained- and extended-release formulations have been developed, each with markedly different pharmacokinetic properties.² Sustained-release preparations are not approved for clinical use and are only available as food supplements. Extended-release preparations offer a pharmacokinetic ‘mid-ground’ between sustained-release formulations and the short-acting immediate-release niacin, and these have proved successful clinical agents.³,⁴,⁶,⁸ Niaspan-R™, (Abbott, formerly Kos Pharmaceuticals) is one such preparation and is the only formulation currently available on prescription. This review will consider the role of Niaspan-R™ in treating dyslipidemia and its associated cardiovascular sequelae.

Abnormal lipid profiles are a major risk factor for cardiovascular disease
Although cardiovascular disease is multifactorial, abnormal blood lipids are recognised as being the major modifiable risk factor and therefore a crucial target for pharmaceutical intervention. The term ‘dyslipidemia’ is general banner that covers a wide range of lipid abnormalities, but it is considered that the profile attracting the highest risk is that consisting of elevated LDL-cholesterol (LDL-c) and triglycerides, combined with low HDL-cholesterol (HDL-c).¹,¹⁶ This combination is frequently referred to as the ‘atherogenic triad’, and is often seen in patients with insulin resistance, metabolic syndrome, diabetes or abdominal obesity.¹⁷,¹⁸ It is becoming increasingly clear that even this category can be further broken down into subsets, each with a very different risk of cardiovascular disease.¹⁹⁻²¹ This analysis is likely to become increasingly important as not all patients respond equally to current lipid-lowering therapies.

Abnormal blood lipids promote the development of atherosclerosis
Vascular disease is characterized by the development of atherosclerotic plaques, typically within the intimal layer of medium-sized muscular vessels such as the coronary and carotid arteries (for review see).²² These plaques are thought to form as a response to injury, and atherosclerosis can be considered a chronic inflammatory response. Circulating monocytes enter the intima, differentiating into macrophages, which express (among other cell surface proteins) scavenger receptors such as CD36 and SR-A.²³,²⁴ Subsequent uptake of large quantities of oxidized LDL gives rise to the classic macrophage foam cell, the major cellular component of the plaque. These cells release cytokine signals that not only trigger recruitment of more monocytes, but also of smooth muscle cells which are induced to migrate from the underlying vascular media. These smooth muscle-derived cells also ingest oxidized LDL, taking on a foamy appearance, as well as secreting connective tissue (primarily collagen) which forms a fibrous cap over the top of the plaque.²⁵,²⁶ This cap acts to stabilize the whole structure: destabilization of the plaque may lead to plaque rupture and clot formation, which is the event underlying infarction.²⁷ Plaque destabilization is thought to arise as a result of increased activity of matrix metalloproteinases, most notably MMP-1 and MMP-9²⁵,²⁸,²⁹ In addition to plaque formation, abnormal blood lipids are known to impact directly on cardiovascular function. High blood lipid levels have been shown to promote vascular smooth muscle cell proliferation, leading to an increase in coronary artery intima-media thickness, itself a marker for clinical events such as myocardial infarction (MI).⁴,³⁰ The decreased vascular compliance observed with this increased media thickness contributes to impaired ventricular function, a condition exacerbated by the directly inflammatory effects of the blood lipids themselves. Elevated lipids and atherosclerosis are also known to be associated with heightened oxidative stress, enhancing oxidation of LDL and thus further increasing the drive for plaque formation.³¹⁻³³
Size matters

LDL is thus a major driver of atherosclerosis. Indeed, it represents the major cholesterol-carrying plasma lipid fraction, responsible for delivery of cholesterol to tissues, including the intimal wall. These particles are composed of a hydrophobic core of cholesterol esters and triglycerides. This core is surrounded by a mixture of phospholipids and free cholesterol, with the glycosylated apolipoprotein B (apoB) located on the surface. The function of apoB is two fold: firstly it provides structural integrity, and secondly, it acts as the ligand allowing recognition of the particle by hepatic LDL-receptors.19–21 Binding of apoB to these receptors triggers endocytosis, essential for LDL-uptake by the liver. There is only one apoB molecule per LDL particle, which means that measurements of plasma apoB give a direct indication of the number of LDL particles within the blood. Although often discussed a discrete entity, LDL particles are in fact heterogeneous, varying in size and hydrated density, and there is increasing evidence to support the notion that different sub-particle profiles are associated with varying cardiovascular risk.19–21 Indeed, it is clear that not all individuals with elevated LDL develop premature cardiovascular disease and, furthermore, reducing LDL does not guarantee a reduction in risk.34–36 Small dense LDL particles have been shown to be particularly atherogenic, even when the plasma concentration of LDL falls within the normal range.21,37 This is exemplified by hyperapoBetalipoproteinemia, a specific dyslipidemia known to have a strong positive correlation with coronary artery disease.37 It is not entirely clear why small dense LDL particles are more atherogenic, but there are a number of possible explanations: Such particles are relatively high in triglycerides, but are cholesterol-ester depleted, and have a decreased affinity for the LDL receptor, resulting in decreased clearance.20,38 Furthermore, smaller particles have been shown to have an increased susceptibility to oxidation, which would render them suitable ligands for uptake by macrophage scavenger receptors, thus promoting atherosclerosis.20,39 It has also been suggested that smaller particles show an increased potential for interaction with arterial endothelial cell proteoglycans, which may also contribute to atherosclerosis.40 Another possible explanation is the fact that a decrease in size and density of LDL particles is associated with a reduced capacity for fibrinolysis, which may mean an increased susceptibility to thrombosis, which would make adverse outcomes such as unstable angina and MI more likely.

Some authors have suggested that it is not the small dense LDL particle per se that is responsible for the increased cardiovascular risk, but merely that this phenotype is a marker for an underlying unfavourable metabolic alteration (see).20 Such metabolic abnormalities include elevated triglycerides, VLDL and IDL: elevated triglycerides drive the reduction in particle size by acting as a substrate for cholesterol ester exchange protein (CETP), meaning that LDL particles become enriched in triglycerides whilst losing cholesteryl esters. Other metabolic abnormalities that may be associated with small dense LDL are those characterized by decreased HDL and/or apoA1, which would indicate a reduced capacity for reverse cholesterol transport and therefore an increased likelihood of atherosclerosis. Interestingly, LDL particle size appears to be a heritable trait.

Certain environmental factors have been shown to have an effect on LDL particle size. Such factors include overweight and obesity, (especially abdominal fat distribution),41 diet,42 exercise,41 alcohol intake43 and use of oral contraceptives.44

Classically, high fat diets have been thought to be problematic, but there is increasing evidence to suggest that it is a high carbohydrate intake that is particularly detrimental with regard to cardiovascular risk.42 High carbohydrate diets lead to hypertriglyceridemia and a decreased clearance of apoB containing particles, ultimately resulting in an increase in the number of small, dense LDL particles. While total carbohydrate intake is important, the type is also significant: foods with a high glycemic index are more likely to result in a small dense LDL particle profile than those carbohydrates which do not provoke big changes in blood glucose. Similarly, the type of fat contained within the diet has a significant effect in the LDL profile. Both mono-and polyunsaturated fats have potent triglyceride lowering effects, leading to an increase in larger, more buoyant LDL.42

Exercise promotes an increase in larger, more buoyant LDL particles, a profile known to be associated with a lower cardiovascular risk.20 The benefits of exercise on plasma lipids are due to an increase in lipoprotein lipase activity, resulting in a lowering
of plasma triglycerides and ultimately not only a
decrease in overall LDL levels, but a shift towards
the larger, less dense particles. This effect is further
enhanced by a reduction in CETP activity.41,45

Overweight and obesity, especially abdominal fat
distribution, are also known to be associated with an
unfavourable LDL profile,20,46 an effect that appears
to be due to increased hepatic lipase activity.47,48
Certainly weight loss is associated with a return to a
more favourable LDL profile.42

The importance of LDL profile is further under-
lined by observations that modification affects clinical
outcomes. Clinical studies investigating LDL profile
modification are reviewed by Rizzo and Berneis,44
leading the authors to conclude that ‘therapeutic
modulation of distinct LDL subspecies is also of great
benefit in reducing risk of cardiovascular outcomes’.

LDL subclasses are not the only lipid variants
that have significant implications for cardiovascular
risk. Low HDL has long been recognized as a risk
factor for adverse cardiovascular outcomes since the
Framingham Heart Study,49 a finding that was con-
firmed by a number of other trials, including the Pro-
spective Cardiovascular Munster (PROCAM) study34
and the Coronary Primary Prevention Trial.50 Despite
these findings, until recently, LDL has generally been
viewed as the most important factor. Statin treatment
has been shown to be very effective in reducing LDL
levels, but it is estimated that some 70% of cardiovas-
cular events cannot be prevented by such treatment.51–56
Not only are patients with overt coronary artery dis-
ease commonly seen to have persistently low levels
of HDL even after statin therapy, but there have
also been a number of clinical studies that convinc-
ingly demonstrate the benefits of interventions that
target HDL. These trials are reviewed elsewhere57,58
but include the Veterans Affairs HDL Intervention
Trial (VA-HIT), the Helsinki Heart Study (HHS), the
Bezafibrate Infarction Prevention Study (BIP) and
the HDL Atherosclerosis Treatment Study (HATS).
Consequently the importance of HDL as a thera-
pic target is increasingly reflected in risk man-
geriment guidelines, especially those concerning
treatment of diabetes, which is particularly likely to
be associated with an atherogenic lipid profile includ-
ing low HDL and high triglycerides.59 In fact, evi-
dence from the above trials supported the findings of
both the Framingham and PROCAM studies that
not only is low HDL an independent risk factor for
cardiovascular disease, but that this risk is larger than
that resulting from elevated LDL. Like LDL, HDL
represents a heterogeneous population of lipoprotein
particles and, similarly, certain subclasses appear to
have particular risk associations. The presence of
large, buoyant (less dense) HDL particles has been
shown to be cardioprotective, and therefore absence
would be associated with an increased risk of cardio-
vascular disease. As Bays and McGovern37 suggest,
it is likely that ‘recognition of these heterogeneities
may have diagnostic and therapeutic implications’.

One of the problems in moving towards such
subparticle analysis as a means of risk assessment
is the fact that there are a number of different ways
of analyzing lipid particle size and density,60–62 and
each identifies a different number of sub-fractions,
which can make comparison between different stud-
ies difficult. Using gradient gel electrophoresis, seven
subclasses of LDL (I, IIa, IIb, IIIa, IIIb, IVa and IVb)
have been identified, with subclasses IIIa and IIIb rec-
ognized as being the most pro-atherogenic (these are
the small dense particles described above). Similarly,
five subclasses of HDL particles can be identified
(2a, 2b, 3a, 3b, 3c) and it is appears that the 2b (large
buoyant) subclass is particularly cardioprotective.37
Patients can be divided into two groups, based on
their individual particle profile. ‘Phenotype A’ is used
to describe patients whose LDL is made up primarily
of large, less dense particles. ‘Phenotype B’ represents
those at the other end of the spectrum whose LDL is
composed largely of the small, dense, proatherogenic
particles. Patients whose LDL particles are of an
intermediate size and density are referred to as ‘AB’.
Phenotype B is associated with an increased risk of
adverse cardiovascular outcomes.21 Interestingly, this
division also explains why not all patients with high
LDL develop cardiovascular disease—particle size
is independent of plasma cholesterol levels—similar
levels of LDL could represent large numbers of small
dense particles or fewer large buoyant particles. The
risk associated with these profiles appears to hold
true for both men and women, but it is less clear with
regard to ethnicity.20

Given this understanding, it may be reasonable
to articulate as a treatment goal a shift in phenotype
from B to A. Low fat diets do not appear to be partic-
ularly effective in mediating this shift, but endurance
exercise does, a factor thought to be related to increasing expression of skeletal muscle PPARs (discussed later). Current recommended treatments for dyslipidemia vary with regard to their effects on particle profile: statins appear simply to lower the overall level of LDL. Fibrates, on the other hand, do increase particle size, and this is most likely because of their potency at reducing plasma triglyceride levels. However, niacin appears to be the superior agent in this regard, as it not only restores a favorable particle profile, but also is able to shift the phenotype from B to A.

The realization that reduction of LDL alone is not sufficient has led to the search for treatment options which, unlike statins, both reduce LDL and increase HDL. Niacin is the single most effective clinical agent currently available for tackling both these aspects, and the development of Niaspan-R™, with its increased tolerability, has made it a more reasonable prospect for the prevention of cardiovascular disease. Furthermore, clinical data indicates that combinations of niacin and statins offer a real advance on previous treatments in that they are well-tolerated and offer the combined benefits of increasing HDL while dramatically reducing levels of LDL. Recent increases in understanding of the molecular mechanism of action of niacin preparations have also made possible the development of novel therapeutic agents that harness the benefits but avoid the side-effects that affect compliance.

Mechanism of Action, Metabolism and Pharmacokinetic Profile

Niacin receptors

Many of the effects of niacin are known to be mediated by signalling through specific receptors. In humans, two such receptors have been identified: HM74A and HM74 (GPR109a and b), which represent distinct gene products. HM74A is the orthologue of the murine PUMA-G and evidence suggests that its activation is responsible for many of the clinical effects, including the changes in plasma lipids. Both receptors are Gi-coupled: activation thus leads to a downregulation in intracellular cAMP, and this action is thought to account for the major effects on lipid-lowering. cAMP, via activation of PKA, is the major activator of hormone sensitive lipase, which catalyses adipocyte lipolysis. Inhibition of cAMP therefore results in reduced FFA release, directly reducing plasma concentrations. It is hypothesised that this drop results in a reduced substrate supply for synthesis of TGs and VLDLs by the liver, and that the reduction of VLDL limits CETP-mediated exchange of cholesterol from HDL to VLDL and of TG from VLDL to HDL. The overall effect is a reduced catabolism of HDL and a decreased production of LDL. Furthermore, niacin may directly inhibit the uptake and catabolism of ApoA1-containing HDL particles. HM74A shows a specific spatiotemporal distribution. It is highly expressed in adipocytes, and many immune cells, including the epidermal Langerhans cells. In most cell types, activation of Gi-coupled receptors does not lead to the release of large amounts of arachidonic acid from the cell membrane, and therefore prostanoïd production is unlikely to be significantly increased. However, in certain cell types, there appears to be a synergism between Gi and other G-protein subunits leading to the activation of phospholipase C and the subsequent generation of IP3 and DAG. The resulting increase in intracellular calcium concentration activates PKC, which in turn phosphorylates and activates phospholipase A2, catalysing the release of arachidonic acid. The precise molecular mechanism of this synergism is unclear, but it seems to be a feature of the epidermal Langerhans cells, which also express abundant amounts of PGD2 synthase, and thus one of the effects of niacin signalling in these cells is the production of vasoactive PGD2, responsible for the observed hyperemia. There is little or no detectable expression in hepatocytes, skeletal muscle and pancreatic β-cells, all tissues involved in glucose handling, which is perhaps surprising, given the fact that signalling through HM74A has profound effects on glucose metabolism.

Niacin is unlikely to be the endogenous ligand for HM74A as the concentrations required to elicit clinical effects are orders of magnitude greater than those ever achieved physiologically. β-hydroxybutyrate is the most likely candidate: this small water-soluble carboxylic acid is one of three ketone bodies released by the liver as a bi-product of fatty acid oxidation, and plasma concentrations thus rise in during conditions when glucose cannot be used as the primary energy source. Such conditions include fasting, as well as insulin-deficient states such as diabetes. β-hydroxybutyrate appears to act as part of a negative feedback response...
that, by inhibiting adipocyte lipolysis, limits ketogenesis, protecting against ketoacidosis. Interestingly, β-hydroxybutyrate appears to enhance insulin sensitivity, unlike niacin.77–80

Peroxisome proliferator-activated receptors
Not all of the beneficial effects of niacin are likely to be due to its direct lipid lowering effects. There is increasing evidence to suggest that prostaglandin production mediated by HM74A signalling provides ligands for the peroxisome-proliferator activated receptors (for review see).81 These nuclear hormone receptors are transcription factors that mediate lipid trafficking at the cellular level. Prostaglandin D₂ is rapidly broken down to yield 15-deoxy Δ¹₂,1₄-prostaglandin J₂ (15d-PGJ₂), the endogenous ligand for PPARγ. PPARγ is a major regulator of adipocyte differentiation and fat storage. It thus transcriptionally regulates genes promoting fat storage and inhibiting lipolysis,82,83 enhancing the effects of niacin on blood lipids. Furthermore, PPARγ activation is associated with enhanced insulin sensitivity (the glitazones are agonists of this receptor),84–86 an effect thought to be mediated by the inhibition of TNF-α and resistin release from adipocytes. PPARγ signalling is also known to inhibit expression of the matrix metalloproteinase MMP-9, enhancing plaque stability.86,87

Niacin treatment not only provides ligands for PPARγ, but it also upregulates expression of all three PPAR isoforms (α, γ and δ).63,88 PPARα is abundantly expressed in the heart, liver and skeletal muscle, where it controls a subset of genes involved in fatty acid oxidation, and thus is important in lipid clearance. Its activation also inhibits NF-κB signalling, having a direct anti-inflammatory effect, further enhanced by the fact that β-oxidation is the main route for eicosanoid clearance.89 The fibrate class of drugs are agonists of this receptor.

The role of PPARδ is less clear: there is some evidence to suggest that PPARδ agonism is both pro-inflammatory and induces lipid accumulation in a foam cell model.90 However, PPARδ agonists have been shown to have a favourable effect on plasma lipid profiles.91 Certainly, upregulation of PPARδ by skeletal muscle appears to be at least part of the reason why endurance exercise has such a beneficial effect on plasma lipid profiles, although in these circumstances, the increase in PPARδ expression is accompanied by an upregulation of PPARα expression.63 PPARα appears to control genes involved in fatty acid uptake, as well as those involved in fatty acid transport to the mitochondrion. The concomitant expression of PPARα enhances β-oxidation and clearance of these fats. This effect may well explain why both niacin treatment and endurance exercise are able to elicit a shift in phenotype from B to A.

Niacin Metabolism
Niacin is administered orally, after which it undergoes extensive first-pass metabolism in a dose rate-specific manner. In humans, niacin can be metabolized by one of two pathways: the first is a low-affinity, high capacity pathway resulting in conjugation products such as nicotinuric acid that are active at the niacin receptor (HM74A). In contrast, the second pathway is high-affinity, low capacity, leading to the generation of nicotinamide and nicotinamide adenine dinucleotide (NAD⁺) as well as pyrimidine metabolites.13 Breakdown through this pathway thus leads to an increase in cellular NAD⁺ pools.

Immediate-release preparations rapidly saturate the low-capacity pathway, meaning that the vast majority is metabolized to yield species active at the niacin receptor, thus having the beneficial effects with regard to the inhibition of adipocyte lipolysis, but that also produce a high incidence of flushing.13 Sustained-release preparations (which are not licensed for clinical use, but can be bought as food supplements) undergo a much greater part of their metabolism through the low capacity pathway, and it is thought that this is responsible for the hepatotoxicity observed with such preparations.2 Products of the low-capacity pathway (nicotinamide, NAD⁺ and pyrimidine metabolites) are likely to be beneficial with regard to cardiovascular disease, not least because the increase in intracellular pools of NAD⁺ acts to inhibit production of reactive oxygen species (ROS). This is accompanied by a downregulation in NF-κB signalling, leading to a decreased expression of a number of pro-inflammatory genes, including adhesion molecules and cytokines known to be important in atherosclerotic plaque formation, as well as enzymes involved in oxidation of LDL.92 There is also evidence to suggest that increasing intracellular pools of NAD⁺
may confer protection against ischemia-reperfusion injury following MI, by increasing cellular capacity to withstand oxidative stress. Nicotinamide has also been shown to have effects on insulin secretion, which may be beneficial in diabetes. Co-administration with intensive insulin therapy has been shown to preserve β-cell function and increase insulin (and C-peptide) secretion. These effects appear to be related to the increase in intracellular NAD⁺, as well as the inhibition of cytokines, notably IL-1β. Nicotinamide undergoes further metabolism to yield 1-methylnicotinamide, which has been shown to have an antithrombotic effect. Extended-release preparations, such as Niaspan-R™, undergo significant metabolism through both pathways, with the result that the lipid-lowering (and PPAR-activating) benefits are similar to those seen with immediate-release niacin, but with the additional advantage of reduced flushing, plus the benefits mediated by the actions of nicotinamide and NAD⁺. Niaspan-R™ is a niacin preparation, contained within a superporous hydrogel matrix, described by the manufacturers as the ‘hydrogel programmed release formulation’, designed to deliver the active ingredient at ‘an intermediate rate’. Approximately 60%–70% of the niacin is absorbed and peak plasma concentration is achieved within 4–5 hours, compared with 1–2 hours for immediate-release preparations.

Side effects

The major side effect of niacin is flushing: certainly this is the side effect most commonly cited as the reason for discontinuation of therapy. In addition to this, an elevation in liver enzymes (including alanine aminotransferase and aspartate aminotransferase) is sometimes observed, and it is thought that this is due to the hepatotoxic effects of metabolites produced through the nicotinamide/NAD⁺ pathway. Certainly, sustained-release preparations which are much more extensively metabolized through this pathway are associated with liver damage. It might seem reasonable to assume that Niaspan-R™, as an intermediate-acting agent may be more likely than immediate-release formulations to cause liver problems. While there is some indication that Niaspan-R™ treatment may be associated with elevated liver enzymes, this not significantly more so than for immediate-release preparations and certainly it does not appear to be any more hepatotoxic than a statin.

With regard to the flushing, Niaspan-R™ has been shown to have a 50% reduction in both the incidence and severity of flushing, compared with immediate-release preparations.

Given that Niaspan-R™/statin combinations appear to be of particular benefit in treating high risk patients, it is also reassuring to see that Niaspan-R™ does not appear to potentiate the adverse effects associated with statin treatment. In combination, there is no higher incidence of liver toxicity and there does not appear to be any increase in the risk of rhabdomyolysis. Furthermore, immediate-release preparations of niacin are known to be associated with adverse effects on glucose tolerance, potentially limiting the usefulness of this agent in treating a group of patients known to be at a much increased risk of cardiovascular disease. Niaspan-R™, in contrast, appears to have only a minimal effect on glycemic control, and even this can be corrected by appropriate adjustment of the anti-diabetic therapy. Not only this, but the efficacy of Niaspan-R™ in correcting abnormal blood lipids is not blunted in patients with insulin resistance. This has led to the observation that ‘concerns over hyperglycemia should not deter the administration of Niaspan-R™ for the correction of low HDL-cholesterol in a type 2 diabetic patient’. It is also of interest to note that any adverse effects of niacin on glycaemic control can be attenuated by concomitant endurance exercise. Both niacin and exercise are known to reduce plasma triglycerides through different mechanisms (as discussed above), and it may seem reasonable to hypothesise that they may have a synergistic effect. This would appear not to be the case. Niacin reduces fasting triglycerides, while exercise tends to reduce post-prandial triglycerides, and it appears that niacin, in fact, attenuates the triglyceride-lowering effects of exercise. However, the combination of niacin and exercise also reduces blood insulin levels, and this may well offset the reduction in insulin sensitivity associated with niacin treatments, regardless of formulation.

Clinical Studies

There have been a number of clinical trials that demonstrate the efficacy of niacin as a treatment for adjusting blood lipid levels, and also that these effects translate...
into a significant reduction in adverse cardiovascular outcomes. These studies include the Coronary Drug Project, which looked at a number of different drug interventions, and showed that niacin had a beneficial effect with regard to survival that persisted long after treatment had been discontinued. Other trials such as the Familial Atherosclerosis Treatment Study (FATS) and the HDL-Atherosclerosis Trial Study provided additional data revealing the particular effectiveness of combining niacin with other lipid-lowering agents to reduce clinical outcomes.

### Efficacy of Niaspan-R™

Niaspan-R™ first gained FDA approval in 1997. Interestingly, this initial approval was to market the drug specifically for ‘lowering LDL, triglycerides and ApoB in patients with hypercholesterolemia and mixed dyslipidemia’. It was a year later when the manufacturers, Kos Pharmaceuticals (now acquired by Abbott), obtained supplementary approval to market the drug as an agent for increasing HDL levels.

There have been a number of clinical trials that indicate that Niaspan-R™ is equally effective as immediate-release preparations both in terms of its effects on lipids and on cardiovascular outcomes, and these are discussed below.

Knopp and colleagues (1998) describe a double-blind, randomized placebo-controlled clinical trial which demonstrated that the effect on HDL of a single bedtime dose of Niaspan-R™ is similar to that observed with immediate-release niacin administered in divided daily dose. Two other clinical trials confirm this, and also show that the effects of Niaspan-R™ are dose-dependent up to 2500–3000 mg. These studies (reviewed in) also demonstrate that Niaspan-R™ causes significant reductions in plasma levels of lipoprotein(a), itself a significant risk factor for adverse cardiovascular outcomes and known to be unaffected by any other currently-available lipid modifying agent. Furthermore, in all studies Niaspan-R™ treatment within the therapeutic range also yielded dose-related decreases in total cholesterol and LDL, as well as lipoprotein(a). These studies indicate that Niaspan-R™ is at least as effective as immediate-release niacin in normalizing lipid profiles, and that these changes translate into a similar reduction in clinical events.

Niaspan-R™ not only increases HDL while reducing LDL, but the profile of the particle subclass is also favorably affected. Treatment with Niaspan-R™ (either 1000 or 2000 mg doses) was shown to increase the pool of the larger, buoyant HDL particles, whilst decreasing the number of small, dense LDL particles that are a particular risk factor with regard to adverse cardiovascular outcomes.

### Niaspan-R™ in combination with statins

Combinations of Niaspan-R™ and statins have proved particularly effective at normalizing lipid profiles and improving clinical outcomes, a finding which has been clearly documented through the ARBITER (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol) trial series. The initial trial set out to compare the efficacy of high-dose (80 mg/day) atorvastatin with 40 mg/day pravastatin in 161 patients who were receiving treatment for either primary or secondary prevention of cardiovascular disease. The endpoints of this study included blinded, serial measurements of the intima-media thickness of the distal carotid artery. Over a period of 12 months, this measurement remained unchanged in patients receiving pravastatin, but a significant reduction was observed in patients receiving atorvastatin. This end-point was taken to be indicative of a regression in atherosclerosis, and it is likely that this was related to the relative effects of the different statins on LDL: atorvastatin produced significantly greater reductions of this lipoprotein that did pravastatin. Although measuring a surrogate end-point, this study was taken as evidence that clinically significant gains may result from the additional LDL

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**Figure 1.** Niaspan-R™ has pleiotropic effects which are beneficial to the cardiovascular system.
lowering gained by using higher doses of statins. While this is indeed true, increasing the statin dose is associated with a significant increase in the occurrence of adverse effects.115,116 This, combined with the increasing pool of evidence to support the notion that raising HDL should also be a therapeutic aim, led to the ARBITER 2 trial, which was the first study aiming to investigate the effect of adding Niaspan-R™ to a statin.3,4,117

Niaspan-R™ was the chosen niacin formulation because of its reduced side effect profile compared with immediate-release preparations. ARBITER 2 was a randomized, double-blind placebo controlled trial, involving 167 patients undergoing treatment for secondary prevention of cardiovascular disease. Other inclusion criteria included established statin treatment and an LDL measurement below 3.4 mmol/L. Once again, intima-media thickness of the carotid artery was the primary endpoint, while secondary endpoints included cardiovascular events. The results showed that while Niaspan-R™ had no further effect on LDL levels, there was a significant increase in HDL levels (mean 21%). With regard to the primary endpoint, over the 12 months of the study, patients not receiving Niaspan-R™ experienced a significant increase in mean carotid intima-media thickness, something which was not observed in the Niaspan-R™ group. Patients receiving Niaspan-R™ also had a reduced incidence of cardiovascular events, although the study was not sufficiently powered to measure the significance of this.3,4,117

ARBITER 3 was an extension of the ARBITER 2 study. It involved the same patient group: those already on Niaspan-R™ continued their therapy, and the patients given placebo in the original study were switched to Niaspan-R™. The change in therapy not only increased levels of HDL, but also brought about a significant regression of carotid intima-medial thickness.35,99,105,118

The results of a number of other trials support these findings. Wolfe and colleagues119 describe a retrospective analysis evaluating the effects on lipid profiles of adding Niaspan-R™ to the treatment regimen of patients who were already receiving a statin. The patients in this study had been prescribed Niaspan-R™ because they either had persistently high LDL, despite the statin treatment, or had low HDL regardless of LDL concentration. Patients from both groups saw a marked improvement in HDL levels, and this was accompanied by a dose-dependent decrease in both total cholesterol and LDL. A marked reduction in triglyceride levels was also observed, although this was maximal at the 1000 mg dose. Perhaps the most significant finding was the observation that

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**Table 1. Summary of main prospective trials investigating Niaspan-R™/statin combinations.**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>Duration</th>
<th>1° endpoint</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARBITER 2</td>
<td>Placebo or Niaspan-R™ added to patient’s existing statin therapy. Most patients on simvastatin.</td>
<td>12 months</td>
<td>Coronary artery intima-media thickness (CiMT).</td>
<td>No increase in CiMT for treatment group, compared with an increase of 0.044 for control ($P &lt; 0.001$), 21% increase in HDL.</td>
</tr>
<tr>
<td>ARBITER 3</td>
<td>Extension of ARBITER 2: placebo group now receiving Niaspan-R™.</td>
<td>A further 12 months</td>
<td>Coronary artery intima-media thickness (CiMT).</td>
<td>Patients converting from placebo show significant CiMT regression ($−0.095 \pm 0.019$; $P &lt; 0.001$). Regression inversely correlated with HDL change.</td>
</tr>
<tr>
<td>ADVOCATE</td>
<td>Niaspan-R™/lovastatin cf atorvastatin or simvastatin monotherapy.</td>
<td>16 weeks</td>
<td>Full lipid profile, including LDL/HDL subgroup analysis, A/B phenotype.</td>
<td>Mean inc. in HDL of 33 mg/dL for combination, cf 6 and 7 for atorv and simv respectively. 35 B to A conversions of 11 and 13 for atorv and simv ($P &lt; 0.005$).</td>
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the biggest improvements were observed in patients who had both the lowest HDL and the highest LDL. This suggests that Niaspan-R™ is particularly effective in targeting patients at the highest risk and who do not respond to statin therapy. Interestingly, this study also suggests that the choice of statin is important when considering combination therapy with Niaspan-R™. At 2000 mg doses, Niaspan-R™, in combination with lovastatin, raised the HDL by 29%, compared to 9.5% with the statin alone. This combination was much more effective than Niaspan-R™ administered with either simvastatin or atorvastatin, which gives further evidence to support the use of particular statins in the treatment of cardiovascular disease.

Niaspan-R™/statin combinations have also been shown to improve the lipoprotein particle subclass profile. In fact, treatment with such combinations is associated with a shift from the atherogenic B phenotype to the lower risk A profile although, as before, lovastatin appears to be superior to other statins in this regard. These studies included ADVOCATE (ADvicor Vs Other Cholesterol-modulating Agents Trial Evaluation) in which the end-points included LDL, HDL and TG levels, but also looked at the percentage change of LDL within the IIIa/IIIb subgroups, and percentage change of HDL within the 2b class. Patients were also defined in respect of their A/B phenotype before the study, and this was later reassessed. The majority of patients began the study with a type B phenotype. The Niaspan-R™/lovastatin combination proved to be particularly effective in increasing particle size and density, reducing the total percentage of LDL within the III/IIIb subclasses. Similarly, it proved effective in increasing the proportion of HDL within the cardioprotective 2b class. Overall, this combination was seen to be 3–4 times more effective than combinations of either atorvastatin or simvastatin at converting phenotype B to A.

This finding that lovastatin is more effective than other statins in combination with Niaspan-R™ is perhaps unexpected: atorvastatin treatment in patients with CHD has been shown to increase HDL particle size in a dose-dependent manner and redistributes HDL towards large cholesterol-rich particles. The reason for these differences may be due to the comparative efficacy of different statins at reducing triglyceride levels, or alternatively that certain statins may inhibit CETP activity.

Longer-term studies indicate that the beneficial effects observed with Niaspan-R™ drug combinations persist over much longer periods of time, certainly up to at least 2 years. These studies indicate that the effects of Niaspan-R™ in combination with a statin on HDL similar to that observed with Niaspan-R™ alone, but that addition of the statin induces clinically significant reductions in LDL and triglycerides when compared with Niaspan-R™ alone (reviewed in). More information regarding the value of Niaspan-R™ and simvastatin combinations will be forthcoming from the AIM-HIGH (Atherothrombosis Intervention in Metabolic syndrome with low HDL-C/high triglyceride and Impact on Global Health outcomes) study. This multicentre trial has recruited over 3000 people with existing cardiovascular disease whose LDL levels are currently controlled using simvastatin, and will report in 2011. These patients have elevated triglycerides and low HDL. In addition to their statin treatment, participants are randomly assigned either placebo or Niaspan-R™, the primary endpoint will be significant cardiovascular events including death, MI and ischaemic stroke.

Niaspan-R™ in diabetes

ADVENT (Assessment of Diabetes control and eValuate the Efficacy of Niaspan-R™ Trial) was a short-term (16 week), double-blind, placebo-controlled trial, assessing safety and efficacy (as well as tolerability) of Niaspan-R™ for the treatment of dyslipidemia associated with type 2 diabetes. 149 patients were randomized to receive either placebo or Niaspan-R™, the primary endpoint was significant cardiovascular events including death, MI and ischaemic stroke.

One drawback with niacin treatment is its effect on glucose disposal: this is a potentially serious problem with regard to the usefulness of niacin as a clinical agent, as many patients who present with cardiovascular disease have a background of insulin resistance and type 2 diabetes. ADVENT investigated the effect of Niaspan-R™ on blood glucose levels and whether or not glucose control could be restored by concomitant adjustment of the anti-diabetic therapy. Most patients were receiving some kind of anti-diabetic medication, usually either metformin or a sulphonylurea, although some were on insulin. Approximately half of the patients were also on statin.
therapy, most commonly atorvastatin. At the higher dose, Niaspan-R™ was seen to significantly elevate HDL whilst reducing plasma triglycerides. A non-significant decrease in plasma lipoprotein(a) was also observed. Fasting blood glucose was seen to be elevated in both groups receiving Niaspan-R™ treatment, although this was apparently controlled satisfactorily by adjusting the anti-diabetic medication. HbA1c was used as a measurement of longer term glycemic control, and this was not affected by the lower dose of Niaspan-R™. Patients receiving the 1500 mg dose were seen to have elevated HbA1c, although this only just reached significance. The authors consider that this slight reduction in glucose control is unlikely to be problematic: it is recognised that tight control of glucose is important in reducing the microvascular complications observed with diabetes, but that control of plasma lipids is important in the prevention of the macrovascular events that underlie the cardiovascular events. It is likely that the lipid-related benefits of Niaspan-R™ treatment outweigh the potential risks of a small increase in HbA1c. It may also be that adding a glitazone to the treatment regimen may offset this problem, although there is evidence to suggest that some glitazones (notably rosiglitazone) may themselves have adverse effects with regard to clinical cardiovascular outcomes. It is worthy of note that the ADVENT trial also showed that Niaspan-R™ was also effective in patients with the metabolic syndrome.

Another study by Grundy and colleagues compared the benefits of a Niaspan-R™/lovastatin combination with fenofibrate, specifically in patients with type 2 diabetes. Two doses of Niaspan-R™ were compared: 1000 or 1500 mg/d. This was a 20 week, double-blind, randomized trial, with the end point being a full lipid profile, including measurement of the atherogenic lipoprotein(a). The Niaspan-R™/lovastatin combination (regardless of the Niaspan-R™ dose) was significantly more effective in both increasing HDL and decreasing total cholesterol, non-HDL cholesterol and lipoprotein(a) than fenofibrate.

These prospective studies are supported by a retrospective analysis of a group of 53 type 2 diabetics. Niaspan-R™, either as monotherapy or in combination with atorvastatin, was effective not only at increasing HDL and decreasing total cholesterol, non-HDL cholesterol and lipoprotein(a) than fenofibrate. This effect was also seen in the ADVENT trial, where Niaspan-R™ was shown to be effective in patients with the metabolic syndrome.
assessing vasodilatory response to both ischemia and to sublingual glyceryl trinitrate. A total of 71 patients were included in the study and were randomized to receive either placebo or 2000 mg/d Niaspan-R™. After 12 months, there was a significant reduction in the plaque area of the carotid arteries (as measured by plaque index—wall area involved normalized to total artery area) in patients receiving Niaspan-R™, compared with placebo. After six months of treatment, Niaspan-R™ treated patients showed a significantly greater reduction in aortic plaque area when compared with controls. Although not significant, there was also a trend that suggested that endothelial dysfunction was improving in patients receiving Niaspan-R™.

All patients in this study were also receiving statins, once again supporting the particular value of adding Niaspan-R™ to existing anti-lipid therapies. All patients in the study had low-HDL, with either evidence of carotid atherosclerosis, peripheral arterial disease, or type 2 diabetes with coronary artery disease, indicating that Niaspan-R™ is as effective in reducing atherosclerotic plaque size in diabetic patients as in non-diabetics.

Some of the more recent studies investigating the potential value of Niaspan-R™ in the treatment of diabetes have given further insight into the molecular mechanism through which HDL exerts its cardioprotective effects. Sorrentino and colleagues126 used sequential ultracentrifugation to isolate HDL, both from healthy controls and from patients suffering from type 2 diabetes. The effects of this HDL on a number of vascular processes was examined, including endothelial nitric oxide and superoxide production, endothelial-dependent vasodilation and endothelial repair. HDL from healthy controls was shown to elicit significant endothelial nitric oxide production, reducing oxidative stress and enhancing both vasodilation and endothelial repair. These effects were not seen with the HDL derived from the type 2 diabetics. Patients in the diabetic group (33 patients) were randomized to receive a three month intervention with either placebo or a once-daily dose (1500 mg) of Niaspan-R™. Treatment with Niaspan-R™ increased the ability of the ‘diabetic’ HDL to induce the vasoactive effects elicited by the control HDL. Furthermore, the results suggested that the HDL extracted from the plasma of the diabetic patients showed increased lipid oxidation, and that

the beneficial effects of Niaspan-R™ resulted from inhibition of this oxidation. These results also indicate that it is not simply the quantity of plasma HDL that is important, but its quality, with regard to its ability to protect the endothelium and thus protect against the development of atherosclerosis. This study in patients with type 2 diabetes extends the results of a previous study by Warnholtz and colleagues,127 which looked at the effect of Niaspan-R™ on endothelial dysfunction in a group of 107 patients, who were selected on the basis of having coronary artery disease, regardless of their baseline lipid measurements. The measurements taken during the study included measurement of plasma lipids, as well as flow-mediated vasodilation of the brachial artery and nitroglycerin-mediated endothelium–independent vasodilation. This was a double-blind 12-week trial, with patients randomly assigned to receive either placebo or 1000 mg/d dose of Niaspan-R™. Initial analysis of the results suggested that treatment had no effect on flow parameters. However, post-hoc subgroup analysis revealed that flow was significantly improved in patients who had begun the study with low HDL. The combined results of these studies would suggest that Niaspan-R™ is effective in improving endothelial function in patients with low HDL, a common presenting feature of type 2 diabetes.

In addition to the clinical trial data, there is a growing body of evidence to support the value of Niaspan-R™ beyond its role in primary and secondary prevention, as a potential treatment to minimize the damage caused by adverse cardiovascular outcomes. A number of experimental studies have addressed the role of Niaspan-R™ in improving functional outcomes after experimental stroke. The results of these experiments are very promising: Niaspan-R™ treatment has been shown to improve cerebral blood flow and to promote both angiogenesis and arteriogenesis following stroke,128–130 with a measurable improvement in functional outcomes, both as monotherapy and in combination with a statin. These effects are thought to be the result of a Niaspan-R™-induced reduction in TNF-α activity, with a concomitant increase in expression of the pro-angiogenic growth factor VEGF. While it remains to be seen if this translates into the clinical setting, it seems likely that the benefits of Niaspan-R™ therapy extend far beyond its effects on blood lipids.
Safety and Tolerability

The principal issues with regard to safety and tolerability of niacin preparations are flushing and elevation of liver enzymes reflecting possible hepatotoxicity. Both of these are still potential problems with extended-release preparations. Theoretically, because of reduced metabolism through the low-affinity, high capacity pathway, there should be less PGD₂ produced in response to Niaspan-R™ therapy, and this does indeed appear to be the case. A number of studies have compared Niaspan-R™ with immediate-release niacin⁶⁷,¹³¹,¹³² and both frequency and intensity of flushing are significantly lower with Niaspan-R™. However, in all Niaspan-R™ trials so far there has still been a significant dropout as a result of flushing,¹³³ and considerable work has gone into attempting to alleviate this problem. As the flushing results from prostaglandin production, it is known that low-dose aspirin can be effective and, of course, this may have additional cardiovascular benefit because of its antiplatelet effects. Aspirin treatment has not proved to be completely effective, however, and other approaches for reducing flushing have been pursued, including the use of Niaspan-R™ combined with antagonists of the DP₁ receptor.

A recent study by Maccubin et al¹³⁴ compared Niaspan-R™ monotherapy with a combination of Niaspan-R™ and the DP₁ antagonist laropiprant, measuring the severity of side effects, especially flushing. Patients included those with evidence of existing ischemic heart disease (these patients were required to be on a statin), those with diabetes (but no evidence of ischemic heart disease) and non-diabetic patients with two or more cardiovascular risk factors and no evidence of ischemic heart disease. Approximately half of the patients were on statin therapy. Patients were excluded from the trial if there was any evidence of elevated liver enzymes, and poorly controlled (or newly diagnosed) diabetics were also not included.

Laropiprant was shown to decrease both the incidence and intensity of NiaspanR™-induced flushing. In addition, there was no significant increase in other adverse effects when compared with Niaspan-R™ monotherapy. There was no evidence of any hepatitis-related adverse effects, but there was a significantly greater increase in alanine aminotransferase/aspartate aminotransferase levels in the group that received laropiprant. It is also important to note that this was a very short term study (lasting 12 weeks), and while the effects on lipid profiles appear to be similar to those observed with Niaspan-R™ monotherapy, it is not yet clear whether the combination drug will have the same benefits in the long term, especially with regard to clinical outcomes. It may well be possible that there will be longer-term issues with taking DP₁ receptor antagonists. While DP₁ mediated signalling is known to have pro-inflammatory effects, there is also a considerable amount of evidence to suggest that it may also have anti-inflammatory effects, especially at the level of the vessel wall. DP₁ signalling is known to result in the production of anti-inflammatory cytokines while concomitantly reducing production of pro-inflammatory mediators. Signalling events mediated through this receptor may act to stabilize the plaque and prevent increases in artery intima-media thickness (discussed in).⁸¹ It is long-term safety concerns such as these mean that the combination has failed to gain FDA approval as yet. HPS2-THRIVE (Heart Protection Study—Treatment of HDL to Reduce the Incidence of Vascular Events) is an ongoing longer-term study that will further assess the effects of combined Niaspan-R™ and laropiprant, but this time in combination with simvastatin and ezetimibe. This study is expected to report in 2012.¹³⁵

The other significant adverse effect of Niaspan-R™ is the potential for liver damage. Levels of the liver enzymes aspartate aminotransferase and/or alanine aminotransferase are generally taken as being early evidence of problems, with levels in excess of three times the upper limit of normal being taken as a cause for concern. There is no evidence to suggest that such occurrences are any more likely in patients on Niaspan-R™ compared with immediate-release niacin, even in patients who are receiving concomitant statin treatment.⁹,⁶⁷–⁶⁹,⁹⁸,¹³⁶,¹³⁷ With regard to statins, a rare (but serious) side effect is rhabdomyolysis, a problem known to be potentiated when statins are combined with fibrates. There is no evidence to suggest any such potentiation when statins are combined with Niaspan-R™, which further underlines the value of this combination in treating dyslipidemia.

Other Forms of Extended Release Niacin

While Niaspan-R™ may be the only extended release form of niacin available on prescription, there are
other formulations available over the counter. Issues with the cost of Niaspan-R™ have promoted interest in alternatives, and there are two such preparations that are used clinically: Slo-Niacin™ and Endur-acin™. Compared to the huge amount of clinical data for Niaspan-R™, these other formulations have not been extensively studied, but there is clinical evidence to suggest they may be equally effective. The Slo-niacin™ and atorvastatin treatment of Lipoprotein and Inflammatory Markers in combined hyperlipidemia (SLIM) study was a prospective, open-label study that measured the effect of Slo-niacin™ treatment (alone or in combination with atorvastatin) on a number of lipid and inflammatory markers, and found that improvements in both were similar to those observed with other niacin formulations used in combinations with statins. Of particular interest in this study was the observation that ALT levels were in fact reduced, suggesting that this formulation is less likely to cause hepatotoxicity. These results are backed up by the findings of a retrospective study that looked at patients who had switched from Niaspan-R™ to Slo-niacin™ because of the cost issue. The change over appeared to well-tolerated and there was a small but significant increase in HDL levels. There was no significant change in ALT or AST levels. Both of these studies were relatively small (42 and 142 patients respectively), but suggest that this formulation is likely to have a valuable role in the treatment of mixed dyslipidemias.

The second formulation, Endur-acin, contains niacin within a wax-based matrix. Kinetic data indicate that this preparation gives a peak plasma niacin concentration at about 6 hours, confirming that it is indeed an extended release preparation. The clinical data are very limited, but suggest that Endur-acin is effective in favourably altering blood lipid profiles but is associated with elevations in liver enzymes.

Conclusion: The Place of Niaspan-R™ in Therapy
Increasingly, clinical data underscores the importance of treating all aspects of dyslipidemia. While it is undoubtedly true that high LDL correlates very strongly with an increased risk of adverse cardiovascular outcomes, it is clear that this is not the only problem. Low levels of HDL and high levels of triglycerides are also significant, independent risk factors, and currently favoured treatments for dyslipidemias have a much less dramatic effect on these than on LDL. It is important to realize that low HDL/high triglyceride dyslipidemias are a frequent feature of type 2 diabetes, a condition associated with a significantly elevated risk of cardiovascular disease. Consequently, there is a need to pursue alternative treatments that are effective in increasing HDL, and Niaspan-R™ is particularly effective in this regard. Not only this, it would appear that Niaspan-R™ can be prescribed along side LDL-reducing medication without any potentiation of adverse effects. Indeed, when administered with statins, there appears to be a synergistic enhancement with regard to effects on lipid profiles, an effect that translates to an improvement in clinical outcomes. Previous concerns that have limited the clinical use of niacin are the occurrence of adverse effects (notably flushing and liver toxicity) and the potential effects on glucose disposal in diabetic and pre-diabetic patients. Recent evidence indicates that these problems are not serious, and that Niaspan-R™, especially when used in conjunction with statin therapy is likely to offer significant clinical benefits.

Disclosure
This manuscript has been read and approved by the author. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The author and peer reviewers of this paper report no conflicts of interest. The author confirms that they have permission to reproduce any copyrighted material.

References


10. Morrow JD, Parsons WG, Roberts LJ. Release of markedly increased quan-


22. Kepler M, Bivona G, Bellia C. Therapeutical approach to plasma homo


27. Badimon L, Vilahur G, Sanchez S, Duran X. Atherosclerosis plaque forma


31. Alexander RW. Hypertension and the pathogenesis of atherosclerosis. Oxid

32. Ciaccio M, Bivona G, Bellia C. Therapeutical approach to plasma homo


38. Nigon F, Lesnik P, Rouis M, Chapman MJ. Discrete subspecies of human low density lipoproteins are heterogeneous in their interaction with the cel

39. Tribble DL, Holl IG, Wood PD, Krauss RM. Variation in oxidation suscep

40. Galeano NF, Al-Haideri M, Keyserman F, Rumsey SC, Deckelbaum RJ. Small dense low density lipoprotein has increased affinity for LDL receptor

41. Koh Y, Ben-Ezra V, Biggerstaff KD, Nichols DL. Responses of blood lipids and lipoproteins to extended-release niacin and exercise in sedentary post


cance exercise training raises high-density lipoprotein cholesterol and lowers small low-density lipoprotein and very low-density lipoprotein indepen


