The role of the kynurenine pathway of tryptophan metabolism in cardiovascular disease

An emerging field

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Summary
Coronary heart disease and stroke, the deadliest forms of cardiovascular disease (CVD), are mainly caused by atherosclerosis, a chronic inflammatory disease of the artery wall driven by maladaptive immune responses in the vessel wall. Various risk factors for CVD influence this pathogenic process, including diabetes mellitus, hypertension, dyslipidaemia, and obesity. Indoleamine 2,3-dioxygenase (IDO), an enzyme catalyzing the rate-limiting step in the kynurenine pathway of tryptophan degradation, is strongly induced by inflammation in several tissues, including the artery wall. An increasing body of evidence indicates that IDO promotes immune tolerance, decreases inflammation, and functions as a homeostatic mechanism against excessive immune reactions. This review provides an overview of the emerging field of the kynurenine pathway of tryptophan metabolism in CVD, emphasizing the role of IDO-mediated tryptophan metabolism and its metabolites in the modulation of ‘classical’ cardiovascular risk factors, such as hypertension, obesity, lipid metabolism, diabetes mellitus, and in the development of atherosclerotic CVD.

Schlüsselwörter
Tryptophan, Kynurenin, Indolamin, Entzündung, kardiovaskulär, Atherosklerose, Adipositas, Diabetes, Lipide, Cholesterin, Hypertonie, Schlaganfall

Zusammenfassung

Cardiovascular diseases (CVDs) are the leading cause of mortality worldwide. Over 17 million individuals died due to cardiovascular causes in 2008, which accounts for one third of global deaths (1).

The overall disease burden is characterized not only by high mortality rates but also by substantial disability and socioeconomic costs. In 2010, the direct healthcare costs of CVDs in the United States were US-$ 272.5 billion (2). Although population-wide management of traditional risk factors for CVDs (e.g. hyperlipidaemia, high-blood pressure, glycaemia) has reduced the incidence of cardiovascular events in developed countries, substantial residual risk remains. Thus, translational therapeutic strategies targeting novel molecular pathways involved in the development of CVDs are needed.

The most common CVDs, coronary artery disease and cerebrovascular disease, are mainly caused by atherosclerosis, a chronic inflammatory disease of large- and medium-sized arteries. The main patho-
logical feature of atherosclerosis is the formation of a plaque – also known as atheroma – in the tunica intima, the innermost layer of the vessel wall. This process is initiated by accumulation of apolipoprotein B-containing particles in the subendothelial space, and progresses through activation of vascular cells and recruitment of circulating immune cells. Early atherosclerotic plaques – known as fatty streaks – are predominantly populated by macrophages that take up modified cholesterol and become lipid-laden foam cells.

Advanced plaques are characterized by a core rich in extracellular lipids and cellular debris, which is surrounded by a fibrous cap composed of smooth muscle cells and collagen fibers.

During all stages of atherosclerosis, immune cells, including macrophages and T cells, populate the plaque and affect disease progression through secretion of cytokines, chemokines, proteases and pro-thrombotic factors (3, 4). The role of inflammation in atherosclerosis is well recognized, and modulation of innate or adaptive immune responses has shown promising results in experimental models (5–7).

Indoleamine 2,3-dioxygenase (IDO) is an enzyme catalyzing the first and rate-limiting step of tryptophan metabolism along the kynurenine pathway (Fig. 1). There is growing evidence indicating that increased IDO activity
- induces tolerance and immune-escape,
- fine-tunes inflammation, and
- functions as a homeostatic mechanism that prevents excessive immune responses (8).

Pharmacological inhibition of IDO results in disease aggravation in several models of inflammatory disease, including
- experimental autoimmune encephalomyelitis (9),
- collagen-induced arthritis (10),
- asthma (11), and
- colitis (12).

Atherosclerosis-related inflammation is driven by Th1-type cytokines, including IFN-γ (13), which is the most potent inducer of IDO. This observation along with evidence on IDO expression by atheroma-associated cells – including macrophages, vascular smooth muscle cells and endothelial cells (14) – suggesting that the kynurenine pathway may as well be involved in atherosclerosis.

This review gives a brief overview of the kynurenine pathway, and discusses the role of IDO-mediated tryptophan metabolism and its downstream metabolites in the modulation of cardiovascular risk factors and the development of atherosclerotic CVD.

### Kynurenine pathway

The essential amino acid tryptophan (TRP) is required by all forms of life (15). Apart from being a building block for protein synthesis, TRP has two additional metabolic fates.

1. It is utilized for the biosynthesis of the neurotransmitter serotonin and the hormone melatonin.
2. The second pathway, which accounts for more than 95% of peripheral catabolism of free TRP, is known as the ‘kynurenine pathway’ and includes several biologically active metabolites, collectively called ‘kynurenines’.

Three enzymes catalyze the first and rate-limiting step of the pathway (16, 17):
- tryptophan 2,3-dioxygenase (TD0) in the liver and brain,
- indoleamine 2,3-dioxygenase-1 (IDO1; IDO), and
- the recently discovered and not well-studied IDO1 paralog, indoleamine 2,3-dioxygenase-2 (IDO2).

IDO is expressed at basal levels by antigen presenting cells (APCs), including macro-

![Image of the kynurenine pathway](image-url)

**Fig. 1** The major metabolites and enzymes involved in tryptophan metabolism: IDO, indoleamine 2,3-dioxygenase; TDO, tryptophan 2,3-dioxygenase; TPH, tryptophan hydroxylase; KAT, kynurenine aminotransferase; KYNU, kynureninase; KMO, kynurenine 3-monooxygenase; 3HAO, 3-hydroxyanthranilate 3,4-dioxygenase; QPRT, quinolinate phosphoribosyltransferase; ACMSD, 2-amino-3-carboxymuconate semialdehyde decarboxylase; NAD, nicotinamide adenine dinucleotide.
phages and dendritic cells, and is strongly induced by the proinflammatory cytokine IFN-γ and to a lesser extent by type I interferons, tumor necrosis factor (TNF), and lipopolysaccharide (LPS) (18).

Initially, the kynurenine pathway was predominantly recognized for its role in the production of nicotinic acid or vitamin B3 (19). However, in 1970s and 1980s several kynurenines were shown to exert biological functions and implicated in brain pathophysiological processes. In particular, quinolinic acid (QUIN) was shown to cause convulsions after being injected in the brain ventricles of mice, and was identified as a selective N-methyl-D-aspartate (NMDA) receptor antagonist (20). Moreover, 3-hydroxykynurenine (3-HK), an endogenous free radical generator, was associated with neurotoxicity and brain degeneration (21). Another TRP metabolite, kynurenic acid (KYNA), was shown to be an antagonist of NMDA receptor (22) and 7 nicotinic receptor in the brain (23), both of which are involved in cognition.

Remarkably, KYNA levels in the central nervous system have been associated with cognitive impairment and schizophrenia (24, 25). Of note, in contrast to TRP and L-kynurenine (KYN), the mentioned metabolites can hardly penetrate the blood-brain barrier (26).

Tryptophan metabolism along the kynurenine pathway was proposed to exert a protective function against infection, as suggested by the inhibitory effects of TRP depletion on bacterial, viral, and parasitic infections (27). Apart from being an evolutionary conserved survival strategy, TRP availability was also proposed to regulate immune responses. Munn and Mellor were the first to highlight the importance of TRP catabolism in the maintenance of immune tolerance. They showed that IDO expression in the murine placenta prevents the rejection of the allogeneic fetus by maternal T cells (28, 29).

According to the TRP depletion theory, IDO activation in antigen-presenting cells deprives T cells of this essential amino acid, thus suppressing proliferation and inducing apoptosis (29). TRP depletion in vitro results in cell cycle arrest of activated T cells rendering them susceptible to apoptosis (30). These effects were suggested to be mediated through the GCN2 kinase pathway, a stress response program that is activated in T cells in response to increased uncharged transfer RNA (tRNA) levels caused by TRP insufficiency (31). Hence, the immunosuppressive function of IDO has also been implicated in cancer development since IDO-expressing tumours are more resistant to immune rejection (32), and IDO expression within the tumour microenvironment and tumour-draining lymph nodes correlates with poor clinical prognosis (33, 34).

Apart from TRP depletion, recent studies have shown that a series of TRP metabolites have immunomodulatory properties.

In particular, KYN, 3-HK, and 3-hydroxyanthranilic acid (3-HAA) are able to suppress T cell proliferation in a synergistic fashion (35). Notably, 3-HAA and QUIN were shown to promote Th1 (but not Th2) cell apoptosis via caspase-8 activation and cytochrome c release from the mitochondria (36).

A possible mechanism mediating the function of 3-HAA is the impairment of calcium signalling that is crucial for T cell activation (37). There is also evidence suggesting that some TRP metabolites can suppress T cell responses via intracellular reactive oxygen species formation or glutathione depletion (38, 39). In addition, IDO activation and subsequent production of TRP metabolites, such as KYN, has been shown to be crucial for regulatory T cell differentiation (40). IDO activation in plasmacytoid dendritic cells (pDCs) has been shown to induce antigen-specific anergy in T cells in vitro and in vivo (31, 34).

Moreover, it has been proposed that IDO mediates signalling functions (independent of its enzymatic activity), which are required for the TGFβ-induced immunomodulatory effects in pDCs (41).

IDO-mediated tryptophan metabolism modulates CVD risk factors

Effects of kynurenines on blood pressure

Wang and colleagues showed that IDO-mediated conversion of TRP to KYN by the endothelium results in arterial relaxation and lower blood pressure. KYNA, but not TRP, 3-HK, KYNA, 3-HAA or QUIN, was shown to relax pre-constricted porcine coronary arteries and mouse or rabbit aorta in a dose-dependent manner. In vivo, intravenous administration of KYN transiently decreased the mean blood pressure in a dose-dependent manner in hypertensive rats. Additionally, it was shown that TRP induced the relaxation of IFNγ-pretreated porcine coronary arteries, a response that was endothelium-dependent and abrogated with the addition of the IDO inhibitor 1-methyltryptophan (1-MT) (42).

The effects of KYN on vasodilation were suggested to be mediated by activation of guanylate cyclase and adenylyl cyclase (42). In line with the experimental data, it was shown that TRP degradation to KYN strongly correlated with hypotension during sepsis in humans (43). Taken together, these findings identify the kynurenine pathway as potential regulator of vascular tone and a possible target for drug development against hypertension.

KYNA, an antagonist of α7 nicotinic receptor in the central nervous system, has been implicated in the autonomic regulation of blood pressure (23). Notably, nicotinic receptor agonists have been found to increase blood pressure in rats (44), whereas injection of KYNA in the rostral ventrolateral medulla – an area in the brainstem that controls autonomic functions – reduced blood pressure in spontaneously hypertensive rats (45).

Interestingly, a missense mutation in the kynurenine aminotransferase 1 (KAT-1), an enzyme that metabolizes KYN to KYNA (Fig. 1), has been identified in spontaneously hypertensive rats (46). Indeed, KYNA levels in different regions of the brain of spontaneously hypertensive rats were significantly lower than those of normotensive controls (47), suggesting that the...
mutation could lead to decreased KAT-1 activity. Apart from KAT-1, another enzyme of the kynurenine pathway, kynureninase (KYNU), has been hypothesized to regulate KYNA levels in the brain. A polymorphism of this gene in rats has been suggested to influence systolic blood pressure. Accordingly, elevated mRNA levels of KYNU were detected in the brainstem of spontaneously hypertensive rats compared to normotensive controls (48).

Kynurenine pathway, obesity and lipid metabolism

Obesity, which is a key feature of the metabolic syndrome and proposed an independent predictor of cardiovascular disease, has been associated with chronic low-grade inflammation (49). Inflammation was shown to enhance TRP degradation, as evidenced by elevated plasma KYN to TRP ratio (KYN/TRP) (50–53). In this context, it has been shown in adult Finnish individuals (50, 51) that KYN/TRP correlates

- positively with body mass index, waist circumference, low-density lipoprotein (LDL), triglycerides, and
- negatively with high-density lipoprotein (HDL).

Of note, increased TRP degradation along the kynurenine pathway, which is observed in obesity and other inflammatory states, has been suggested to decrease serotonin levels in the brain and predispose to depressive disorders (54). Despite the epidemiological links between obesity and IDO activation, experimental data on potential effects of kynurenines on obesity are limited.

Interestingly, IDO knockout (IDO−/−) mice on high-fat diet exhibited increased F4/80 and TNF mRNA levels in their white adipose tissue compared to wild-type controls (55). Further, IDO deficiency was shown to exacerbate hepatic inflammation, as evidenced by increased macrophage infiltration, and TNF, IL-6, IL-1β and IFN-γ mRNA levels.

Accumulating evidence implicates fat and liver inflammation in the regulation of lipid metabolism (56). Indeed, experimental studies indicate that the kynurenine pathway can affect plasma lipids. Administration of 3-HAA to LDL receptor knockout (LDLr−/−) mice significantly decreased total plasma cholesterol and triglyceride levels. The reduction in total cholesterol was due to decreased chylomicron/VLDL fraction. Moreover, 3-HAA significantly increased HDL cholesterol (57). In another study, LDLr−/− and IDO−/− double knockout mice showed a significant increase in serum lipids, particularly triglycerides (58). However, further studies are warranted to explore the mechanisms underlying the effects of kynurenines on lipid metabolism.

Kynurenine pathway and diabetes mellitus

Epidemiological studies have linked activation of the kynurenine pathway and subsequent production of downstream metabolites to insulin resistance and type 2 diabetes. In patients with chronic hepatitis C virus infection, serum KYN concentrations correlated with insulin resistance and pancreatic β-cell function (59). Elevated IDO expression and serum concentrations of KYN, 3-HK and KYNA were found high in diabetic retinopathy patients (60). Additionally, xanthurenic acid (XA) levels were significantly higher in the urine of patients with type 2 diabetes compared to healthy individuals (61).

In experimental studies, two TRP metabolites have been suggested to be potentially diabetogenic: XA and KYNA. Both metabolites (at millimolar levels) inhibited glucose-induced proinsulin synthesis in isolated rat pancreatic islets (62). Although high concentrations of metabolite have been used in these experiments, it was suggested that local overproduction of these metabolites could lead to decreased insulin storage in β-cells, thus predisposing to a diabetic state. KYNA was suggested to be diabetogenic due to its function as NMDA receptor antagonist affecting the brain-liver axis. Particularly, 7-chlorokynurenic acid, a pharmacologic precursor of KYNA, was shown to abrogate the inhibitory effect of NMDA receptor agonists on hepatic glucose secretion when infused into the dorsal vagal complex of rats (63).

Xanthurenic acid, resulting from transamination of 3-HK, induced the development of experimental diabetes in rats (64).

It should be mentioned that 3-HK, the precursor of XA, could alternatively be converted to 3-HAA by KYNU and lead to nicotinamide adenine dinucleotide (NAD) production as end product. KYNU requires pyridoxal-5-phosphate (P5P; pyridoxine; vitamin B6) as cofactor, and vitamin B6 deficiency results in a shift of the pathway from NAD production to increased XA formation.

Of note, chronic inflammation has been associated with low plasma vitamin B6, which could lead to increased formation of the diabetogenic metabolite XA (65, 66).

This observation led Oxenkruge et al. to hypothesize that chronic low grade inflammation and the resulting vitamin B6 deficiency could affect the formation of TRP metabolites that subsequently could predispose individuals to insulin resistance and diabetes mellitus (67).

The kynurenine pathway has also been implicated in diabetes mellitus type 1. Falzarino et al. showed that 1-MT exacerbated streptozotocin-induced diabetes in mice, while the TLR9 ligand CpG protected against diabetes in an IDO-dependent manner (68). Earlier studies had suggested that supraphysiological intracellular NAD levels could affect β-cell functions including pro-insulin synthesis (69).

Definitive treatment of type 1 diabetes mellitus may be achieved by transplantation of pancreatic islets, an outcome that has been shown to be influenced by IDO expression. Transplantation of IDO-overexpressing pancreatic islets from pre-diabetic NOD mice to immunodeficient NOD-scid mouse recipients significantly prolonged graft survival after adoptive transfer of diabetogenic NOD spleen cells (70). In another study, prolonged pancreatic islet graft survival induced by the immunosuppressive agent CTLA-4-immunoglobulin was shown to be dependent on upregulation of IDO by antigen-presenting cells (71). Furthermore, in a pancreatic islet xenotransplantation mouse model, a collagen matrix containing IDO-expressing fibroblasts significantly reduced the number of infiltrating immune cells into the islet xenografts (72). Interestingly, IFN-γ treatment of isolated human islets increased IDO mRNA expression and enzyme activity in endocrine
Biomarker versus pathophysiology

Kynurenine pathway and atherosclerosis

Chronic systemic low-grade inflammation, a proposed prognostic factor for cardiovascular outcomes, results in IDO over-expression followed by increased TRP catabolism.

Therefore, plasma KYN/TRP has been suggested as a biomarker of inflammatory states that could influence cardiovascular disease.

High KYN/TRP has been identified as a predictor of acute coronary events in patients without preexisting coronary artery disease (74). In addition, KYN/TRP is a predictor for major coronary events and all-cause mortality in patients with coronary artery disease (75). Low TRP plasma concentration and high KYN/TRP have been found in patients with coronary heart disease compared to healthy controls (76). In two other studies with young and middle-aged individuals, enhanced IDO activity was associated with intima-media thickness (IMT) and several cardiovascular risk factors – including age, BMI, plasma lipids and CRP – in a univariate analysis (50, 51). Further, the association between KYN/TRP and IMT has also been shown in a modiﬁcation of arterial diseases at high risk for CVD (77), and increased TRP degradation has been correlated with plasma concentrations of neopterin (74, 75), a biomarker of cell-mediated immune activation that has been linked with atherosclerotic CVD (78).

In addition to KYN/TRP, several metabolites along the kynurenine pathway have been identiﬁed as potential biomarkers of atherosclerosis. Particularly, 3-HK has been independently associated with the presence of CVD in chronic renal disease patients (79).

In a similar patient population, anthranilic acid (AA) and 3-HAA correlated with plasma concentrations of CCL2 and CCL4 (80). QUIN as well as the QUIN/KYN ratio were independently associated with IMT in patients with renal disease (81, 82). Although the cross-sectional nature of these studies cannot prove causality, these ﬁndings generate the hypothesis that IDO-dependent TRP catabolism can affect atherogenesis. This notion is further supported by studies showing that IDO protein is expressed in atherosclerotic plaques, and is activated in atheroma-associated cells (14, 83).

Experimental data suggest a protective role of IDO in vascular inﬂammation. In a model of graft arteriosclerosis, it was shown that IDO is necessary for the maintenance of medial immunoprivilege. In this model, human coronary arteries were transplanted into immunodeﬁcient mice followed by administration of human allogeneic peripheral blood mononuclear cells (PBMCs). Treatment with 1-MT resulted in signiﬁcantly increased inﬁltration of leucocytes (CD45RO+ cells) in the media and increased T cells in the intima (84). In another study, IDO expression in lymphoid organs of LDLr−/− mice was suggested to partially mediate the beneﬁcial effect of echosapentaenoic acid on atherosclerosis regression (85). Similarly, IDO-dependent suppression of T cell proliferation was suggested to contribute to the atheroprotective role of plasmacytoid dendritic cells (86).

Administration of the TRP metabolite 3-HAA to LDLr−/− mice (57)
- modulated inﬂammatory responses,
- lowered plasma cholesterol and triglycercides, and
- signiﬁcantly decreased atherosclerosis.

3-HAA had been previously shown to inhibit LDL oxidation by PBMC and puriﬁed monocytes in a concentration-dependent manner (87), and to inhibit TNF-induced MCP-1 secretion, VCAM-1 expression, and nuclear factor-kappaB (NF-xB) activation via HO-1 induction in human umbilical vein endothelial cells (HUVECs) (88). Thus, 3-HAA emerges as an important atheroprotective metabolite.

Kynurenine pathway and stroke

Epidemiological studies suggest that the activity of the kynurenine pathway, as reﬂected by plasma KYN/TRP, correlates with the
- stroke-induced inﬂammatory response,
- stroke severity and
- its long-term clinical outcome (89, 90).

An elevated KYN/TRP has also been associated with post-stroke cognitive impairment (91). In contrast, neurological function, infarct size and brain swelling of wild type and IDO-deﬁcient mice were comparable 24 hours after the induction of transient cerebral ischaemia (92). Despite the evidence that IDO could not inﬂuence the outcome of brain ischaemia in mice, the kynurenine pathway remains a potential therapeutic target, for example due to the neuroprotective properties of KYNA and the vasodilatory effect of KYN.

The kynurenine pathway has been suggested as a potential target for agents aiming at increasing the formation of the NMDA receptor antagonist KYNA and at decreasing the formation of QUIN, which is an agonist of the same receptor. Although KYNA penetrates the blood-brain barrier poorly, analogs and prodrugs with better bioavailability have been developed and may be of therapeutic use in stroke (93, 94). Of note, in the rat four-vessel occlusion model of ischaemia, use of a KYNA analog showed neuroprotective effects with post-ischaemic administration (95).

KYNA, the immediate precursor of KYNA, signiﬁcantly reduced neuronal damage and infarct volume, pre-ischaemic intraperitoneal administration in different rat models of brain ischaemia-hypoxia (96–98). It has been suggested that KYNA easily penetrates into the brain where it can be hydrolyzed to KYNA. In the same line of evidence, administration of kynurenine 3-monoxygenase (KMO) inhibitors signiﬁcantly reduced neuronal damage and infarct size in different models of brain ischemia (99).

Speculatively, apart from being a precursor of KYNA, KYN could improve perfusion of the ischaemic brain area through vasorelaxation (42). However, a recent study using a rat model of transient brain ischaemia suggested that post-ischaemic administration of KYN can be harmful (100).

An interesting ﬁnding in stroke patients was that plasma levels of 3-HAA in the ﬁrst two weeks after stroke were markedly de-
Increased whereas those of AA were increased compared with healthy subjects. Among stroke patients, 3-HAA to AA ratio was significantly lower in patients who died within 21 days compared to survivors, while plasma 3-HAA levels negatively correlated with infarct size (90). Thus, further investigations are needed to define whether IDO-mediated TRP metabolism can directly impact the outcome of stroke, or be used as a biomarker of stroke severity.

Therapeutic implications, conclusion

Chronic systemic low-grade inflammation associated with traditional risk factors for CVD results in enhanced TRP degradation. Hence, KYN/TRP has been proposed as a potential predictive and prognostic biomarker of atherosclerotic CVDs. Furthermore, the kynurenine pathway could be directly and/or indirectly implicated in the modulation of vascular inflammation and atherosclerosis (Fig. 2).

Released by the endothelium, KYN was shown to induce vessel relaxation and reduce systemic blood pressure. KYN in the brain rostral ventrolateral medulla has been implicated in the autonomic regulation of blood pressure. Taking into account that IDO inhibition reverses septic shock associated-hypotension and improves survival, the kynurenine pathway emerges as a promising target for the treatment of hypertension. Speculatively, the vasodilatory effects of KYN and the neuroprotective properties of KYNA could provide therapeutic alternatives for the treatment of ischaemic stroke, i.e. by improving microcirculatory reperfusion of the ischaemic areas of the brain.

Although the influence of KYNA on blood pressure could have atheroprotective effects, evidence suggests that KYNA as well as AA are diabetogenic through direct effects on the release of pro-insulin by pancreatic islets or the autonomic regulation of glucose secretion. On the other hand, control of autoimmune responses through the induction IDO may represent a valuable target in the prevention and treatment of type 1 diabetes.

Experimental data suggest that IDO and 3-HAA play an atheroprotective role regulating lipoprotein metabolism. 3-HAA has been initially referred to as a TRP metabolite carrying anti-oxidant and anti-inflammatory effects. Yet, it was demonstrated that administration of 3-HAA to LDLr−/− mice lowers plasma cholesterol and triglycerides – an effect attributed to a significant reduction in plasma levels of VLDL,
and a significant increase in HDL. In line with these results, it has been shown that lack of IDO, which leads to decreased levels of 3-HAA, substantially increase serum lipids, particularly triglycerides.

Altogether, these data indicate that targeting the kynurenine pathway may have important implications for the development of novel therapeutic approaches against atherosclerotic CVD, by simultaneously influencing inflammation and lipid metabolism.

The complete understanding of the role of the kynurenine pathway in the modulation of cardiovascular risk factors, vascular inflammation, and atherosclerosis, as well as its associated and triggered molecular mechanisms of action, warrants further investigation. Indeed, this is an emerging field of research that harbours high potential to expand the range of therapies to prevent and treat CVD.

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Conflict of interest
DFJK holds a patent application on the use of 3-hydroxyanthranilic acid for the prevention and treatment of hyperlipidaemia and its complications.

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