Role of Arginase 2 as a potential pharmacological target for the creation of new drugs to correct cardiovascular diseases

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Introduction: The review provides relevant information about arginase 2, the role of this enzyme in the formation of endothelial dysfunction and, as a consequence, the development of cardiovascular diseases.

History of the discovery of arginase and its functions: The discovery of arginase took place long before its active study as a substance that affects the formation of endothelial dysfunction.

Role of arginase 2 in the development of a number of cardiovascular diseases: The role of NO synthase and arginase 2 in the formation of oxidative stress is determined. The pathophysiological mechanisms of the development of a number of cardiovascular diseases, such as coronary heart disease, atherosclerosis, and aortic aneurysm, are described. The modern possibilities of treatment of endothelial dysfunction in the pathology of the cardiovascular system and the possibility of creation of new drugs are considered. An increase in the activity of arginase 2 was proven to occur in the case of the development of coronary heart disease (CHD), hypertension, type II diabetes mellitus, hypercholesterolemia, as well as in the process of aging. According to the WHO, coronary heart disease and apoplectic attack have topped the list of causes of death worldwide over the past 15 years.

Arginase 2 as a potential pharmacological target: The purpose of this literature review is to determine the possibilities of use of arginase 2 as a new target for the pharmacological correction of cardiovascular diseases.

Keywords
arginase 2, cardiovascular diseases, endothelial dysfunction.

Introduction
Cardiovascular and metabolic diseases are at the moment recognized by the WHO as the most important global health problem. The leading role in the pathogenesis of these pathologies is played by endothelial dysfunction, which is manifested in a decrease in the bioavailability of nitric oxide (Durante et al. 2007). This causes research interest in the pathophysiological mechanisms of the occurrence and development of the endothelial component of these diseases (Korokin et al. 2011; Pokrovskii et al. 2012; Danilenko et al. 2017).
Speaking about the bioavailability of nitric oxide, one cannot disregard the role of the essential arginine amino acid, which is a substrate for NO synthase and arginase. These are the metabolic enzymes that support the homeostasis of the NO-synthase-arginine-arginase system and provide a stable level of nitric oxide. Two fundamental mechanisms for reducing the amount of NO have been described: a decrease in its synthesis and excessive deactivation of reactive oxygen species (ROS) (Durante et al. 2007).

Mammalian arginase, a manganese-metalloenzyme that hydrolyzes L-arginine to L-ornithine and urea, participates in the regulation of nitric oxide synthesis, while competing for the substrate with nitric oxide synthase. Three isoforms of NO synthase are currently known: neuronal NOS (nNOS, or NOS-1), neuronal NOS (iNOS, or NOS-2) and endothelial NOS (eNOS, or NOS-3) (Berkowitz et al. 2003). An increased expression of arginase leads to an increase in the consumption of arginine and the synthesis of urea and ornithine; at the same time the availability of arginine for NO synthase decreases and, as a result, the production of nitric oxide decreases. A number of studies have shown the critical contribution of arginase to the development of cardiovascular and metabolic diseases: an increase in arginase activity has been revealed in the case of hypertension, type II diabetes mellitus, hypercholesterolemia, atherosclerosis, and as the aging process progresses (Gerstein et al. 2008).

For now, two isoforms of arginase are known that catalyze the same reaction. Arginase 1 is a protein that consists of 322 amino acids and is conventionally considered to be a liver isoform. Although arginase 1 was originally detected only in the liver, it has now been proven that it can be found in endothelial cells and vascular myocytes, being a cytosolic enzyme. Arginase 2, in turn, is distributed in many organs and tissues and is a mitochondrial enzyme, which is by 58% identical in structure to arginase 1 (Ash et al. 2000). Due to the active involvement of arginase in the synthesis of ornithine and urea, competitive to NO synthase, arginase causes excessive formation of reactive oxygen species, which, in turn, contributes to oxidative stress. In addition, this enzyme is an inducer of the synthesis of polyamines and proline (Li et al. 2001), and also contributes to the processes of proliferation and remodeling of smooth muscle fibres of a vessel wall.

There are studies suggesting the anti-inflammatory effect of superexpression of arginase 1 by its interaction with endothelial NO synthase in rabbits. Pro-inflammatory mediators, reactive oxygen and nitrogen species (RONS), glucose, and oxidized low-density lipoprotein (ox-LDL) are endogenous stimulators of arginase expression. Reducing the level of L-arginine, the above factors are predictors of the formation of endothelial dysfunction. After oxidation, low-density lipoproteins bind to the lectin-like receptors of LDL-1 and stimulate the activation of arginase. Oxidized LDL also block the production of NO through increased synthesis of caveolin I, which interferes with the activity of NO synthase (John and Schneider 2003).

The development of an inflammatory reaction is accompanied by macrophages producing lipopolysaccharides, interleukins (IL-4, IL-6) and interferons-gamma, which are inducers of arginase activity (Eelen et al. 2018). In addition, inflammation disrupts the function of carriers of cationic amino acids that are involved in the transport of arginine, which also leads to a decrease in NO synthesis. The discovery of such an endogenous vasodilator as nitric oxide fundamentally changed the understanding of endothelial functions.

Furchgott and Zawadzki (1980) demonstrated the involvement of endothelial cells in support of hemovascular homeostasis. These authors showed that the endothelium performs not only a barrier function, but also participates in the most complicated scheme of regulation of vascular tone, producing a number of vasodilating and vasoconstrictor factors. The imbalance of these factors leads to the development of endothelial dysfunction, which underlies the formation of atherosclerotic vascular disease, as well as the development of cardiovascular, renal and metabolic diseases (Pokrovsky et al. 2008).

Taking into account the importance of NO metabolism in the formation of cardiovascular pathology and the fact that arginase causes a decrease in the bioavailability of nitric oxide, the reason why the relationship between NO and arginase is currently recognized as a key regulatory pathway of the vascular system becomes clear. There is only one substrate for arginase – L-arginine, the active use of which can provoke not only a deficiency of NO, but also a decrease in its protective effects on endothelium: prevention of abnormal vasoconstriction, inhibition of platelet aggregation and a decrease in the expression of adhesion molecules on the surface of endothelial cells (Verdegem et al. 2014).

Recent studies have shown that an increased arginase activity accompanies the development of cardiometabolic diseases, such as hypertension, ischemic reperfusion lesions, diabetes mellitus and the aging process (Mapanga and Essop 2016). These data have become the prerequisite for a more active study of the possibility of inhibiting arginase in order to correct endothelial dysfunction.

History of the Discovery of Arginase and Its Functions

In 1904, Kossel and Dakin, when administrating the studied enzyme which would later be known as “arginase” into the liver of mammals, noted a decrease in arginine levels and a hydrolysis process linked to it, resulting in the formation of ornithine and urea. After that event, other researchers began to report the presence of arginase in various organs and tissues of animals. So Clementi discovered this enzyme in the liver of amphibians, fish, turtles and kidneys of birds. The obtained data were further supplemented by Edlbacher and Rottler, who in their turn revealed arginase in the liver, kidneys, thymus, testicles and placenta of mammals, and also showed that the amount of enzyme in males was higher (Kossel and Dakin 1904).

In 1927, Chaudhuri carried out studies on 32 birds and showed the presence of arginase in their kidneys and testicles, and also confirmed the previously expressed as-
sumption about the gender difference in the distribution of this enzyme: arginase was present in the genitals of only males (Chaudhuri 1927). In the future, the sexual difference in the metabolism of arginase and the role of steroid hormones in the realization of its effects were actively discussed; this enzyme was also assumed to participate in some pathological processes (Tousoulis et al. 2002).

Subsequent studies proved not only the presence of arginase in organs and tissues in various animal species, but also an active participation of this enzyme in the formation of cardiovascular disorders. For example, Buga et al. (1996) for the first time described the process of arginase expression in rat aortic endothelial cells and noted that endogenous inhibition of this enzyme by NG-hydroxy-L-arginine (an intermediate compound in the synthesis of NO from L-arginine) could provide a sufficient amount of arginine for NO synthesis.

The relationship between the arginase activity and endothelial dysfunction due to the aging process was shown by Berkowitz et al. (2016), who performed a comparative analysis of old and young Wistar rats (Steppan et al. 2016). The dependence of atherosclerotic vascular changes on the arginase activity was actively studied by a team of researchers under the supervision of Ryoo. They were the first to describe a high potential of pharmacological inhibition of arginase in order to protect a vessel wall from atherosclerotic changes (Aldemir et al. 2003).

Role of arginase 2 in the development of a number of cardiovascular diseases

The direct connection between the development of endothelial dysfunction and the formation of cardiovascular pathology is the fact proved by many experimental and clinical studies (Demougeot et al. 2005; Morris et al. 2005; Yakushev et al. 2015; Koklin and Danilenko 2019). Ludmer et al. (1988) in their unique work described the vasoconstrictive effect of acetylcholine in patients with atherosclerosis. Using angiography of the coronary arteries, they found that intracoronary administration of this drug causes a vascular spasm, which provokes the formation of endothelial dysfunction.

Coronary heart disease (CHD), hypertensive disease, advanced atherosclerosis, vascular disorders in type II diabetes mellitus, in pulmonary hypertension, and in hypoestrogenic conditions, as well as a number of other processes are accompanied by hypoxia and, consequently, the transition of endothelium to hypoxic metabolism (Hein et al. 2003; Demougeot et al. 2005). Under conditions of oxygen deficiency, mitochondrial respiration is impaired and the ability of cytochrome to bind oxygen is reduced, due to which a large number of electrons are formed, which cause the synthesis of ROS, rather than NO, from arginine. It is these metabolic changes that are fundamental in the formation of endothelial dysfunction. Hypoxia is a cause of the excessive activity of the transcription factor 1, which contributes to neovascularization in the area of ischemia. Reperfusion tissue injuries are also accompanied by activation of oxidative stress and a decrease in the activity of NO synthase (Hein et al. 2003; Villalba et al. 2016). There is evidence of increased glycolysis processes in endothelial cells under the conditions of hypoxia.

As soon as the relationship between endothelial dysfunction and an early development of atherosclerosis was described (Drexler et al. 1991), the connection between impaired metabolism of endothelial cells and elementary changes in a vessel wall became apparent. Dhawan et al. (2005) created an experimental model on monkeys fed a high-cholesterol diet in order to demonstrate the independence of NO and endothelial dysfunction. In the animals that were at the same time injected with L-arginine, an expressed decrease in formation of ateromas was observed, due to an adequate endothelial function and an increased NO level (Chicoine et al. 2004). In a similar vein, several other experimental studies were carried out, and all of them showed the relationship between a low level of arginase, accompanied by the formation of endothelial dysfunction, and the development of the atherosclerotic process, as well as a more serious cardiovascular pathology in the future.

Atherosclerosis is a chronic progressive condition, in which atherosclerotic plaques are deposited on the endothelial surface of the major arteries, which causes narrowing of the vessel lumens and damage to the subendothelial layers. This is a multifactorial lesion of a vessel wall, but cholesterol and inflammatory mediators make the largest contribution to the formation of atheromas. At the initial stage of an atherosclerotic plaque formation, functional or structural damage to the vessel wall occurs. This contributes to the accumulation of adhesion molecules with subsequent fixation of monocytes on endothelial cells, after which they migrate to the subendothelial space and turn into macrophages. Along with this process, there is an active accumulation of LDL in the intima. Activation of oxidative stress and an increase in the number of reactive oxygen species, which include superoxide anion, leads to the oxidation of these lipoproteins to oxidized LDL (Kovamees et al. 2015).

As mentioned above, a decrease in the bioavailability of nitric oxide is a key link in the pathogenesis of cardiovascular diseases. However, the development of endothelial dysfunction against the background of deficiency of NO, is not always accompanied by atherosclerotic changes in blood vessels (Lefer and Lefer 1996). A complex cascade of reactions and interactions between circulating substances, cellular receptors and intracellular signaling mechanisms always leads to a disrupted hemovascular homeostasis. The main mechanism to support the bioavailability of nitric oxide is to maintain a constant balance between the activity of endothelial NO synthase and arginase isoforms. The first signs of atherosclerosis are recorded when an imbalance occurs, which involves excessive production of ROS, a decrease in the availability of NO, or both of these processes (Pokrovskaya 2008). Ar-
arginase is involved in the process of atherogenesis mainly due to the creation of deficiency of nitric oxide, which causes vasoconstriction, inhibition of platelet aggregation and adhesion of leukocytes to a blood vessel wall and the formation of atheromas.

Another scenario for the development of atherosclerosis is through the oxidation of low density lipoproteins, which facilitate the conversion of phagocytes into foam cells. This process leads to the synthesis of reactive oxygen species catalyzed by NADPH oxidase. In the experimental models with monkeys, the data were also obtained demonstrating that hypercholesterinemia stimulated the synthesis of asymmetric dimethyl-L-arginine (ADMA), which is an endogenous inhibitor of NO synthase.

Ryoo et al. (2013), studying the role of arginase 2 in the development of atherosclerosis, found that oxidized LDL stimulated the release of this enzyme and reduced the production of NO. In that study, mice with the deletion of the arginase 2 gene were used, which received a diet rich in cholesterol. As a result, in such animals a decreased arginase function improved the functional state of endothelial cells, compared with the intact mice. Thus, the study showed that genetic inhibition of arginase had a protective effect on endothelium (Loscalzo 2001).

The hypothesis of oxidative modification as a critical stage in the development of atherosclerosis is also worth mentioning. According to this theory, for atherosclerotic changes to happen, it is not enough just to increase the amount of LDL; these lipoproteins have to undergo oxidative changes: oxidized LDL are recognized by specific macrophage receptors, absorbed by phagocytes and accumulate in them.

The special role of arginase 2 is confirmed by the study on mice with artificial inhibition of arginase gene expression. The activity of arginase 2 in the endotheliocytes of such animals was significantly reduced, which suggested the primacy of this isoform of this enzyme (Topal et al. 2006). In other studies, inhibition of this very arginase 2, including in the animals fed a high cholesterol diet, led to the restoration of endothelial function, increased NO level and vasodilation (Ignarro et al. 2001).

One of the known mechanisms of activation of atherosclerotic changes is apoptosis of endothelial cells. Confirming this, Sushek et al. (2003) demonstrated that the expression of interleukin-1, tumor necrosis factor α and interferon gamma in rats with the blocked arginase 2 gene led to apoptosis of endothelial cells at the administration of hydrogen peroxide. At the same time, at high levels of nitric oxide, no cell death was observed, which suggested a protective effect of arginine on endothelium.

An increase in the amount of ROS caused by a high activity of arginase 2 is one of the reasons for the formation of endothelial cell dysfunction in animals with atherosclerosis. The same direct relationship is observed in the development of coronary heart disease and vascular disorders in patients with type 2 diabetes mellitus. However, the effect of arginase on endothelial cells in vivo has not been fully studied yet. Nevertheless, many researchers agree that the formation of ROS is stimulated by pro-inflammatory factors and leads to an impaired endothelial function.

Pro-inflammatory conditions in blood vessels have a direct relationship with impaired endothelial function and the development of atherosclerosis. The production of cytokines stimulates the activity of arginase and reduces the expression of the NO synthase gene, ultimately leading to an increase in the production of reactive oxygen species. In this vein, Spillmann et al. (2014) studied the relationship between liver X-receptors (LXR, a hormone receptor involved in cholesterol reverse transport) and an increased activity of tumor necrosis factor. The results obtained by these researchers suggest that LXR agonists decrease mRNA expression and arginase 2 activity, and therefore, restore the bioavailability of NO.

Cai et al. (2020) focused on the study of inflammatory factors responsible for the formation of endothelial dysfunction. They showed an increase in the arginase activity in the aorta of rats when exposed to serum amyloid A- lipoprotein produced by the liver.

Aneurysms are local balloon-like expansions in an arterial wall, which are mainly caused by an impaired endothelial function, a destroyed extracellular matrix and a decreased number of smooth muscle cells. The formation of an aneurysm is based on the development of an inflammatory process, accompanied by the activation of oxidative stress and, as a result, by an increase in ROS originating from macrophages, smooth muscle cells, fibroblasts, and endothelial cells. A recent study provides the data confirming the crucial role of endothelial ROS in aortic dissection in transgenic mice with endothelium specific increased expression of NADPH oxidase 2. In the studied cases, an increase in the reactive oxygen species in blood was connected with an increase in episodes of aortic dissection in response to stimulation by angiotensin 2 (Vandekeere et al. 2015; Rafii et al. 2016) ROS induce endothelial cells to secrete cyclophilin A, which, in turn, causes the activation of the inflammatory process of a vessel wall, the production of matrix metalloproteinases and remodelling of a vessel wall, which ultimately leads to its dissection. Thus, in the prevention of aneurysm and aortic dissection, the most important step is the correction of metabolic disorders of endothelial cells.

Another mechanism contributing to the development of endothelial dysfunction is shear stress, which is a predisposing moment in the atheroma formation process (Sonin et al. 2002). It is the stress acting along the surface area (a vessel wall) and is part of the total stress. Teupser et al. (2006), when studying pig carotid endothelial cells, demonstrated an increased expression of arginase 2 after induction of shear stress by an oscillatory change compared to the level of this stress over the previous three days. To confirm the role of this enzyme in the described changes, a control group of animals was introduced into the study, to which the arginase inhibitor – hydroxy-nor-L-arginine (Nor-NOHA) was administered, which led to a decrease in ROS production and an increase
in the proliferation of smooth muscle cells of the vessel wall. Regarding this effect, Xiong et al. (2017) studied the role of arginase 2 in the proliferation of smooth muscle fibres of a vessel wall using human umbilical veins as an example and demonstrated that activation of this enzyme potentiated proliferative processes in vascular cells. Xiong et al. (2017) also observed the progression of aging and activation of apoptosis in the absence of arginine 2, emphasizing the progression of atherosclerosis due to the resulting weakness of the vascular layers. The administration of thrombin into cells of a human umbilical vein increased the expression of arginase 18 hours later, and a peak effect was reached 24 hours later. In that study, an HMG-CoA inhibitor fluvastatin, which distorts the RhoA-ROCK pathway and leads to a decrease in arginase expression under the influence of thrombin, was also administered. The similar effects were observed in that study with the administration of other ROCK inhibitors.

Studying the role of arginase 2 in inflammatory reactions, Ming et al. (2012) found its protective effect in the development of insulin resistance, type 2 diabetes and atherosclerosis in mice with a deficiency of this isoform. The group of researchers supervised by Weissman, when comparing a vascular function between transgenic C57Bl/6 mice with enhanced expression of the arginase 2 gene and control groups of animals, revealed an endothelium-mediated vasodilation disorder induced by ACh in the transgenic group. Those authors also proved that an increased activity of arginase 2, regardless of the level of lipids in plasma, was a sufficient reason for the development of inflammatory changes and the formation of atherosclerosis (Zhang et al. 2015).

There is evidence in the literature that arginase has not only a harmful effect on the functional state of endothelium, but this enzyme can also have a beneficial effect on the vessel wall. This ability, as the case may be, to play either a protective or damaging role puts arginase in an even more interesting perspective. For example, Teupser et al. (2006), studying genes for predisposition to atherosclerosis, showed that an increased expression of the arginase 1 gene in macrophages promotes resistance to atherosclerotic changes, presumably by implementation of anti-inflammatory mechanisms. The atheroprotective role of this isoform of arginases is realized in several ways, such as differential activation of macrophages, modulation of an inflammatory response in smooth muscle cells of a vessel wall, and an impaired stability of an atherosclerotic plaque.

**Arginase 2 as a potential pharmacological target**

As it follows from all the above data, an increase in the arginase gene expression and/or a direct increase in its activity undoubtedly leads to the formation of endothelial dysfunction and the development of atherosclerotic vascular changes. The main pathway for the action of this enzyme is realized through a competitive effect on NO synthase and a decrease in NO production (Iyer et al. 2002; Boger 2014).

In the early 1990s, arginase inhibitors were developed, initially, to study the effects that occur when the activity of this enzyme decreases. However, the observed effects brought promising results in terms of correcting the endothelial function, decreasing a cholesterol level, stabilizing blood pressure and normalizing metabolic disorders (Morris et al. 1997).

Arginase inhibitors are classified into selective and non-selective, as well as into specific, directly blocking the enzyme itself, and non-specific, acting indirectly. In order to inhibit arginase, there was an attempt made to use an intermediate compound of NO synthesis – N-hydroxy-L-arginine (NOHA). But the attempt failed due to the fact that this substance was also a coenzyme of the P450 cytochrome, and No-hydroxy-nor-L-arginine (nor-NOHA) was synthesized to substitute it. Difluoromethylornithine, which blocks ornithine decarboxylase and, accordingly, increases the amount of arginine via uric acid metabolism, was studied in vitro and in vivo as an arginase inhibitor. A side effect of this substance was the development of independent vascular reactions and the accumulation of ornithine (Shi et al. 2001). Such substances as S-(2-boronethyl)-L-cysteine, 2(S)-amino-6-hexanoic acid and L-norvaline are also interesting in terms of blocking the effects of arginase. The currently known arginase inhibitors are low-selective or non-selective and affect both arginase 2 and arginase 1. In the experiment, hyperammonemia was observed in the mice with an arginase 1 knockout gene and all the animals died on the 10–14th days of postnatal development (Kasten et al. 2013). The identification of such side effects of a decreased activity of arginase 1 indicates the relevance of searching for a highly selective arginase 2 inhibitor with the expressed cardioprotective and endothelioprotective properties. Moreover, at the moment there are no drugs from the group of selective arginase 2 inhibitors at the global pharmaceutical market (Jung et al. 2005; Salmite et al. 2015).

One of the recent clinical studies showed that arginase inhibitors had a positive effect on endothelium in patients with familial hypercholesterolemia. In patients with atherosclerosis, endothelial dysfunction correlates with the plasma content of natural arginine analogues, competitive endogenous inhibitors of NO synthase. There are two such substances: asymmetric dimethylarginine (ADMA) and monomethylarginine (L-NMMA). A number of previously mentioned studies suggested a possible productive use of L-arginine, both in monotherapy and in combination with antihypertensive drugs in cases of endothelial dysfunction caused by ADMA and/or L-NMMA. In (Loya-Rendon et al. 2005), it was shown that such a therapy (latter) clearly increased the activity of endothelial NO synthase and, as a result, increased NO synthesis, which was expressed in correcting endothelial dysfunction.

The data of the studies already completed as of todate directly or indirectly confirm a high potential of even
non-specific inhibition of arginase. For example, in rats with metabolic syndrome treated with citrulline, norvaline or ornithine, normalization of blood pressure levels was observed compared with the control group. Such an effect was achieved directly by the increase in the bioavailability of nitric oxide and indirectly by reversing hypertriglyceridemia and insulin resistance (Durante et al. 2007; Xu et al. 2014). Holowatz and Kenney (2007) proved the connection of essential arterial hypertension with the reduced reflex vasodilation of skin vessels and found that acute nonspecific inhibition of arginase restored this reflex. Atorvastatin has a similar effect, its administration for months resulted in the restoration of the function of skin microcirculation vessels in patients with hypercholesterolemia, and the observed effect was mediated by a decrease arginase activity. The analysis of all the studies whose results are available at the moment shows that there are a number of metabolic processes catalyzed by this enzyme, which can be potentially influenced in order to correct cardiometabolic disorders.

**Conclusion**

At the moment, there are a large number of studies confirming the participation of arginase in the regulation of the bioavailability of nitric oxide, the formation of endothelial dysfunction, the development of atherosclerosis, and a number of other cardiovascular and metabolic disorders. However, the pathophysiological mechanisms of the arginase in various conditions are not completely clear, which makes it imperative to describe in detail the molecular pathways of the metabolism of this enzyme.

The main obstacle to a more accurate understanding of the difference in the effects of the two isoforms of arginases seems to be the difficulty in creating a specific inhibitor for each of them. This difficulty is due to the great similarity of the chemical structure of these enzymes (58%), which have almost identical metal clusters and active site configurations in their compositions. Nonspecific inhibition of the activity of both arginases is a problem of current studies, since it does not make it possible to determine which isoform the observed effects belong to.

Clinical trials are strictly limited, so few researchers have evaluated the role of arginase in humans. The study of reactions catalyzed by isoforms of this enzyme is a vast area for the development of new methods of treatment and prevention of many clinical conditions. A large number of effective studies which have been carried out in recent decades indicate the participation of arginase in the formation of endothelial dysfunction, and, consequently, of cardiovascular and metabolic diseases. The introduction of a pharmacological agent selectively inhibiting the activity of arginase 2 into a therapy of such conditions will significantly expand the prospects for the correction of these pathological processes.

Thus, to identify the details of the mechanisms of transcription, transduction, as well as the action of arginase itself and to develop pharmacological methods of affecting these processes in the treatment and prevention of cardiovascular and metabolic diseases are a very promising area for further research.

**Conflict of interest**

The authors have no conflict of interest to declare.

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