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Review Article

Unveiling Cadmium-Induced Cardiotoxicity: Mechanisms, Challenges, and Future Perspectives: A Narrative Review

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Abstract

We investigated the mechanisms of cadmium-induced cardiotoxicity, focusing on its pathophysiological effects, potential preventive strategies, and therapeutic interventions. We further explored approaches to mitigate long-term cardiovascular risks associated with cadmium exposure. This research analyzed the molecular and cellular pathways involved in cadmium toxicity, emphasizing oxidative stress, inflammation, endothelial dysfunction, platelet-leukocyte interactions, and cardiomyocyte damage. Experimental findings and existing literature were examined to uncover the mechanisms driving cadmium-induced cardiotoxicity and to identify potential therapeutic targets. Cadmium exposure leads to oxidative stress and inflammation, resulting in endothelial dysfunction, platelet-leukocyte activation, and thromboinflammation. It disrupts calcium signaling, elevates reactive oxygen species (ROS) production, and causes cardiomyocyte loss, ultimately impairing cardiac function. Cadmium also remodels ion channels and suppresses cardiomyocyte proliferation, intensifying its cardiotoxic effects. While current therapies focus on removing circulating cadmium, they do not address the residual cardiovascular damage caused by prior exposure. Cadmium exerts significant cardiotoxic effects through oxidative stress, inflammation, and cellular activation. Future therapeutic strategies should target these pathways, particularly the activation of platelets, leukocytes, and endothelial cells, to reduce cadmium-induced cardiovascular damage and improve long-term outcomes.

Keywords: Cadmium; Cardiotoxicity; Heavy metal exposure; Pathogenesis; Thrombosis; Thromboinflammation

Introduction

A pervasive environmental contaminant, cadmium poses significant risks to human health due to its widespread presence in industrial emissions, polluted air, and contaminated food and water

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(1). Exposure to cadmium, whether through inhalation, ingestion, or environmental contact, is associated with extensive damage across multiple organ systems, including the lungs, kidneys, skeletal structure, and cardiovascular system (1, 2). Even at low levels, cadmium exerts profound disruptions on key physiological processes, particularly affecting the immune, reproductive, and cardiovascular systems (3).

Emerging evidence highlights the critical role of cadmium in the onset and progression of cardiovascular diseases (4). Cadmium tends to accumulate in cardiac and vascular tissues, where it induces structural damage, histopathological changes, and the development of cardiac fibrosis. These pathological alterations compromise the structural integrity and functional capacity of the cardiovascular system, making cadmium a significant contributor to cardiotoxicity and associated health risks (5-7).

In this study, we delve into the underlying mechanisms of cadmium-mediated cardiotoxicity, examining its molecular and cellular impacts on cardiovascular health. Furthermore, we explore both preventive strategies and therapeutic interventions aimed at mitigating cadmium-induced damage. By addressing the gaps in current understanding and highlighting potential targets for intervention, this research aimed to pave the way for innovative approaches to reduce the long-term cardiovascular risks associated with cadmium exposure.

Application of cadmium in medicine

Cadmium is generally utilized in the manufacturing of nickel-cadmium batteries (8), coatings and platings for pigments, stabilizers for plastic manufacturing, electroplating steel, and in nuclear reactors (5). Cadmium compounds were conventionally employed in black and white television phosphors, photoconductive surfaces in photocopier drums, and paint pigments (9). These qualities make it a suitable option for applications like fluorescent materials in medical devices such as fluorescent microscopes and fluorophore probes (10). Cadmium and its derivatives are also utilized in the manufacturing of radiation protection items. Recently, there has been a shift in attentions towards utilizing cadmium for the development of effective nano particles that are commonly employed in anti-cancer strategies (11, 12). Collectively, cadmium is a significant heavy metal that finds extensive use in both industrial and medical applications. However, prolonged exposure to even small amounts of cadmium can lead to serious negative consequences like cardiotoxicity.

Mechanism related cardiotoxicity

A growing body of evidence suggests that cadmium leads to notable harmful effects on the heart, such as alterations in cardiac tissue morphology, cardiac arrhythmia, remodeling of ion channels in cardiomyocytes, and cardiomyocytes apoptosis (13, 14). Additionally, some evidence also suggested that cadmium accelerate the atherosclerosis through various mechanisms (15, 16). Cadmium has the ability to promote the conversion of macrophages into M1 macrophages, resulting in the production of IL6 and TNF-α (Fig. 1) (17, 18). This, in turn, worsens the inflammatory state, which not only aids in the advancement of atherosclerosis but also promotes the development of various harmful occurrences like cardiomyocyte apoptosis, endothelial dysfunction, platelet activation, and thrombus formation, resulting in tissue ischemia such as heart ischemia (19). Cadmium induces NLRP3 inflammasome activation, resulting in the production of IL1b and IL-18 as well as the activation of caspase 1 (Fig. 1) (20). These deleterious events contribute to increased inflammation. Moreover, caspase 1 activation causes pyroptosis in vascular endothelial cells (21). Altogether, the activation of NLRP3 in vascular endothelial cells plays a crucial role in the progression of cardiovascular disease (22). The important part of deleterious cadmium mediated cardiotoxicity regulated by the activation or suppression of crucial signaling pathways like phosphatidylinositol 3-kinase (PI3K)/AKT and P38 MAPK pathways in cardiomyocytes (13, 14, 23). The atypical electrophysiological characteristics caused by cadmium can be

reversed by blocking either the PI3K-Akt or P38 MAPK signaling pathway (24). Further investigation revealed that CdCl2 treatment of H9-CMs resulted in a unique expression pattern of ion channel genes, along with decreased sodium and calcium currents. The cells underwent remodeling of cardiac ion channels in response to cadmium exposure (14). Furthermore, cadmium has the ability to directly trigger the activation of matrix metalloproteinases (MMPs) and indirectly induce MMPs activation by amplifying inflammation (25). This activation of MMPs is crucial in various extracellular matrix processes, including inflammation and fibrosis (26, 27). A study demonstrated that cadmium triggers cardiac fibrosis by activating MMP-2 and MMP-9 (25). Cadmium also induces vascular endothelial and cardiomyocyte injury by promoting the generation of reactive oxygen species (ROS) (28). In summary, exposure to cadmium is associated with the occurrence several deleterious cascades of events that contribute to the progression of cardiovascular damage.

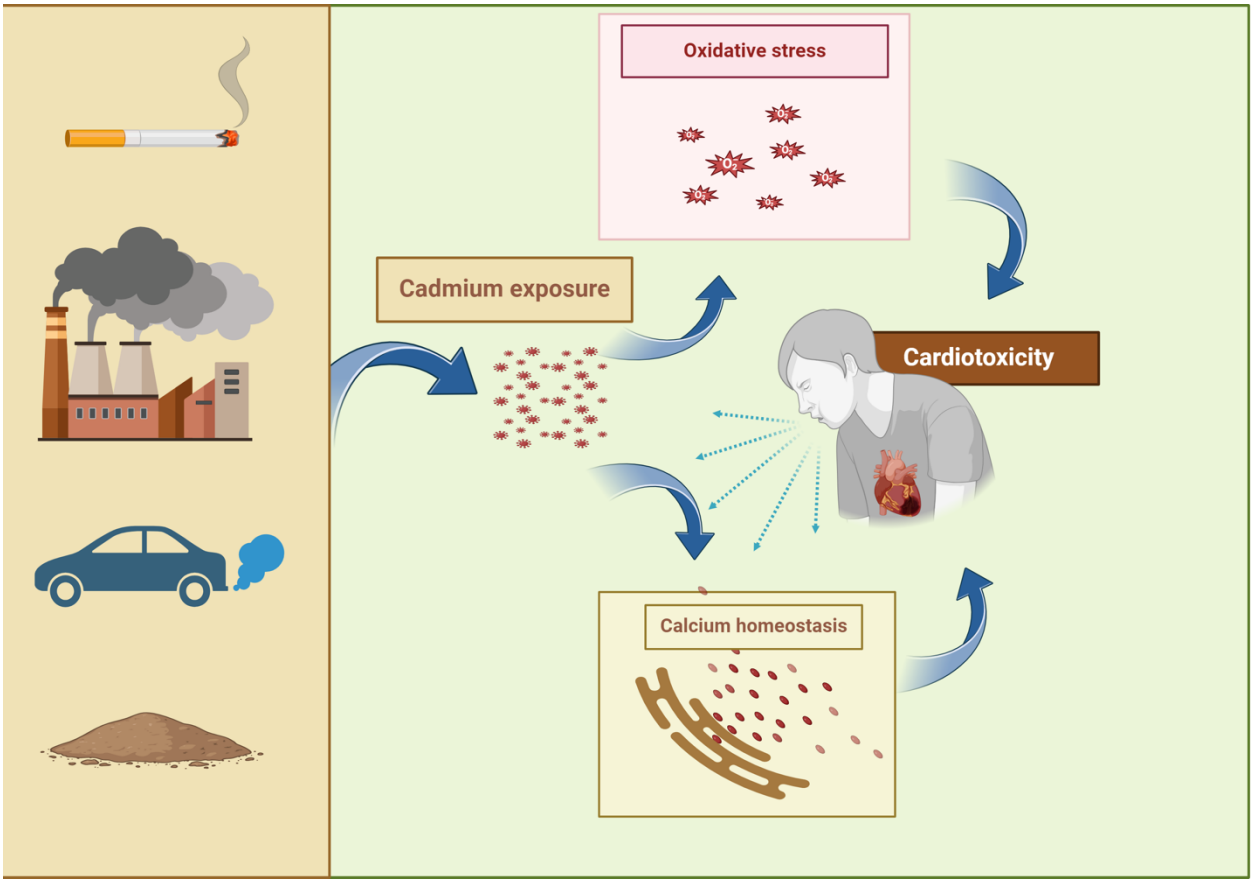

Fig. 1: Cadmium-induced inflammation: Cadmium triggers inflammatory responses via three distinct mechanisms. Firstly, it prompts the conversion of macrophages into M1 macrophages that release pro-inflammatory cytokines like TNF-α and IL1, 6. Secondly, it activates NLRP 3, leading to the formation of an inflammasome that amplifies inflammation. Lastly, it triggers the activation of the p38-MAPK pathway, further exacerbating inflammation

Oxidative stress

The activation of various cellular signaling pathways is typically linked to the oxidative stress resulting from the disparity between the production and neutralization of ROS (29). Elevation level of ROS can arise from either endogenous or exogenous sources (30). Typically, the accumulation of ROS is identified by an increase in various molecules such as hydrogen peroxide, hydroxyl ions, singlet oxygen, superoxide anions, lipid hydrop-

eroxides, and phospholipid hydroperoxides (31). The ROS accumulation often leads to the initiation of double strand DNA breaks and damage to membranes, proteins, and lipids (32). Several lines of evidence suggest that ROS generation is linked to the inhibition of the electron transfer chain in mitochondria (33). This, in turn, induces exaggerated ROS production, leading to the activation of the apoptotic process. Ultimately, this process initiates apoptosis, especially in cardiomyocytes that possess a significant number of mitochondria (34). ROS generation is often accompanied by activation of important transcription factors comprising NF-κβ, AP-1, and Nrf-2 (35). These crucial transcription factors govern the process of cardiac remodeling, distinguished by alterations in the cardiomyocytes, fibroblasts, vascular smooth muscle cells, vascular endothelial cells, and inflammatory cells, as well as modifications in the size, shape, geometry, and functionality of the heart (36). Additionally, ROS generation typically associated with disruption of cellular Calcium ions (Ca2+) homeostasis which serves as a crucial second messenger (37). Cadmium-induced oxidative stress collectively endangers patients by increasing the risk of cardiotoxicity.

Dysregulation of calcium homeostasis

Ca2+ play a crucial role in regulating a wide range of cellular functions in different types of cells, such as cardiomyocytes (38). Ca2+ plays a crucial role in regulating cardiac electrical signals and the contraction of cardiomyocytes in order to enhance blood circulation (39). Additionally, Ca2+ is involved in governing diverse activities within cardiomyocytes, such as gene transcription (40). A limited number of crucial molecular components, namely ryanodine receptors, voltage-operated calcium channels, and calcium pumps/transporters regulate cardiac calcium homeostasis (41). Any alteration in the elements participating in the regulation of cardiac calcium balance, whether caused by genetic mutation, illness, or long-term changes in blood flow, can have a substantial effect on both the functionality and characteristics of cardiomyocytes (42, 43). In this context, a piece of evidence indicated that cadmium can disrupt cellular Ca2+ homeostasis is through stimulation of intracellular Ca2+ storage release and/or extracellular Ca2+ entrance (44). Mechanistically, Cadmium has the ability to hinder the plasma membrane Ca2+-ATPase, leading to the obstruction of Ca2+ efflux (45). Additionally, it can also impede the entry of calcium into the endoplasmic reticulum and Golgi apparatus by inhibiting the activities of sarcoplasmic/endoplasmic reticulum Ca2+-ATPase or secretory pathway Ca2+-ATPase (46). Another significant mechanism through which cadmium induces calcium flux is by interacting with G-protein coupled receptors, which triggers the activation of Phospholipase C (PLC) (47, 48). This activation leads to the breakdown of phosphatidyl inositol into inositol triphosphate (IP3) and diacylglycerol (DAG). The generated IP3 subsequently binds to IP3R on the endoplasmic reticulum, resulting in calcium influx (49). The cadmium-mediated Ca2+ flux not only disrupts normal cardiomyocyte functions, potentially leading to cardiac arrhythmia, but also triggers an exaggerated level of Ca2+ that activates the apoptosis pathway (50). Elevated Ca2+ levels activate calmodulin, which in turn induces cardiomyocyte apoptosis through the mTOR and MAPK pathways (Fig. 2) (51). Additionally, calmodulin induces mitochondrial collapse, facilitating the release of cytochrome c and activation of intracellular apoptosis pathways (52). Therefore, the overload of calcium mediated by cadmium plays a critical role in cardiotoxicity.

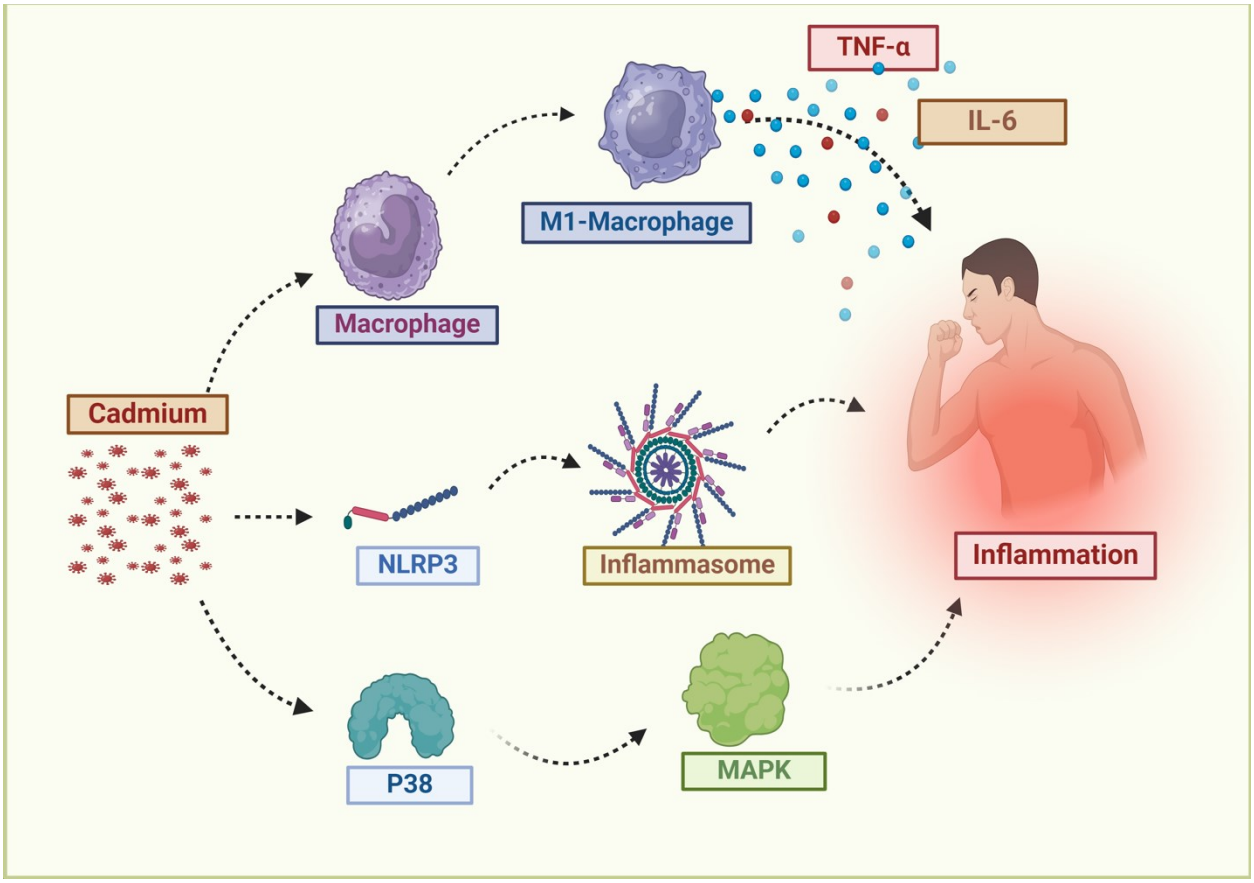

Fig. 2: Cadmium mediated-cardiotoxicity: Cadmium causes cardiotoxicity primarily by activating mTOR and MAPK, as well as inducing ca2+ efflux. Cadmium stimulates ca2+ influx by interacting with a G-protein-coupled receptor, leading to the activation of phospholipase C. This enzyme then generates IP3 from PIP2, which subsequently binds to its specific receptor on the endoplasmic reticulum, resulting in ca2+ influx

Cardiomyocyte regeneration

Following postnatal physiological changes in the human body, cardiomyocytes experience significant alterations, such as a reduction in their ability to regenerate and an enhancement in their functionality (53, 54). However, the regenerative capability of cardiomyocytes can be enhanced by various factors, such as ischemia, certain hormones like platelet-derived growth factor, and vasoactive peptides (55). Moreover, the transformation of other cell types, such as fibroblasts, into functional cardiomyocytes and the differentiation of stem cells into cardiomyocytes, serve as additional mechanisms for cardiomyocyte regeneration (56, 57). Several molecular mechanisms are involved in the proliferation of cardiomyocytes. One of these mechanisms is the PI3K/AKT signaling pathway, which plays a crucial role in enhancing the proliferation and survival of cardiomyocytes (58). There is evidence suggesting that cadmium inhibits the activation of this signaling pathway (13). This inhibition not only reduces the reproductive capability of cardiomyocytes but also affects their energy homeostasis, leading to a decrease in functionality and cardiac contractile tension. Conversely, PI3K/AKT is an important pathway in which suppression of this pathway inhibit the cadmium mediated cardiotoxicity (14). Therefore, cadmium can potentially interfere with cardiomyocyte regeneration.

Strategy to cardiotoxicity inhibition

Exposure to cadmium has been linked to various harmful effects. Numerous studies have been conducted to explore potential methods of inhib-

iting cadmium-induced toxicity, particularly in relation to cardiotoxicity. These methods include preventive measures such as the use of chemical and natural decontamination agents (59), nanoparticles (60), as well as treatment options following cadmium exposure, such as the use of chelating agents (Table 1) (61) and plasma exchange-hemodialysis-plasmapheresis (3). Contaminated water poses a significant risk for cadmium exposure, leading to the utilization of various decontaminating agents to minimize this risk. Some of these agents are Moringa oleifera seeds, peanuts (Arachis hypogaea), cowpeas (Vigna unguiculata), urad (Vigna mungo), and corn (Zea mays). These seeds work by filtering contaminated water through different mechanisms, including neutralizing colloidal positive charge and absorbing heavy metals in their tissues (3). Detoxifiers can also be used to remove soil contamination. Upon exposure to cadmium, the initial approach to treating poisoned patients with heavy metal involves the sequential removal of circulating cadmium and the subsequent neutralization of its harmful impact on various organs, particularly the cardiovascular system. Hemodialysis and chelating agents, such as Ethylenediaminetetraacetic acid (EDTA), are viable options for eliminating cadmium from the bloodstream (3). The subsequent step entails counteracting the adverse effects of cadmium. Given that oxidative stress plays a central role in cadmium-induced cardiotoxicity, the utilization of antioxidant agents such as vitamin C and vitamin D serves as an appropriate strategy for mitigating this toxicity (62). Roflumilast can effectively reduce cadmium-induced cardiotoxicity by inhibiting oxidative stress in a rat mode (63)l. Hence, it proves to be a successful approach to initially eliminate cadmium from the bloodstream and the human system, subsequently counteracting its detrimental consequences like oxidative stress through the utilization of antioxidants.

Conclusion and future perspective

Cadmium is a hazardous heavy metal present in contaminated air, soil, and potentially in vegetables (64). Even minimal exposure to cadmium can cause serious damage to various organs (65, 66). The primary mechanisms responsible for cadmium toxicity are primarily linked to oxidative stress and the Ca2+ ions efflux (67). These conditions give rise to toxic effects such as severe damage to cardiomyocytes and an increased likelihood of thrombosis, thereby increasing the risk of cardiovascular disease (66). Furthermore, an increasing amount of evidence suggests that cadmium also induces inflammation, further worsening its toxic effects on the cardiovascular system (18).

Numerous investigations have been conducted to explore potential techniques for mitigating the harmful effects caused by cadmium. The appropriate course of action following cadmium exposure consists of two main components. Firstly, the primary concern is to eliminate cadmium from the patient's body (68). Two approved methods for achieving this objective are chelation therapy utilizing agents and hemodialysis (3). Subsequently, the focus shifts towards alleviating the adverse impacts of cadmium on the individual's body. Although some studies propose the utilization of antioxidants to counteract cadmium toxicity, there is limited evidence supporting the use of anti-inflammatory medications or a combination of antioxidants and anti-inflammatory agents to reduce cadmium-induced cardiotoxicity (3, 69). Considering that inflammation and the production of ROS play crucial roles in cadmium-mediated toxicity, it is suggested that a more effective approach would involve targeting both inflammation and oxidative stress.

Table 1: Heavy metal chelating agents

Chelating Agents	Mechanisms	Type	Side Effects	Ref
EDTA	Bind to heavy metals via four carboxylate and two amine groups	hydrophile	low blood sugar, diminished calcium levels, headache, nausea, dangerously low blood pressure, kidney failure, organ damage, irregular heartbeat, and seizures	(70, 71)
Penicillamine (DPA)	Binding to divalent and three valent ions	hydrophile	Abdominal or stomach pain, chest pain, and dark urine	(72, 73)
Dimercaprol	Bind through thiol group to cadmium and other heavy metal	hydrophile	nausea, vomiting, abdominal pain, tachycardia, hypertension, headache, burning sensation in the eyes, nose, and mouth	(74)
Dithiocarbamates	Bind to heavy metal through by its thiol group	hydrophobic	flushing, nausea and tachycardia.	(75)
Meso 2, 3-dimercaptosuccinic acid (Succimer, DMSA)	Chelating heavy metal by its sulfur and capping agents feature.	hydrophile	Nausea, vomiting, diarrhea, and anorexia are common.	(76)
dimercapto-1-propane sulfonic acid (Unithiol, DMPS)	Chelating heavy metal by their sulfur group,	hydrophile	nausea, vertigo, headache, weakness, pruritus, and allergic reactions, such as rashes	(77)
monoisoamyl DMSA *(MiADMSA)*	Bind to heavy metal through its thiol groups	hydrophobic	mild gastrointestinal discomfort, fatigue, mental fuzziness, headache, and diuresis.	(78)
Monocyclohexyl DMSA (McbDMSA)	Bind to heavy metal through its thiol groups	hydrophobic	-	(79)

Conclusion

Cadmium exerts significant cardiotoxic effects through oxidative stress, inflammation, and cellular activation. Future therapeutic strategies should target these pathways, particularly the activation of platelets, leukocytes, and endothelial cells, to reduce cadmium-induced cardiovascular damage and improve long-term outcomes.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or

submission, redundancy, etc.) have been completely observed by the authors.

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Data availability

This is a review study, and it is not an original. Data availability is corresponding author responsibility.

Consent for publication

Not applicable.

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Conflict of interest

The authors declare that they have no conflict of interest.

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