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REVIEW

HMG-CoA Reductase Inhibitors for Traumatic Brain Injury

Kalman Katlowitz[1] · Shankar Gopinath[1] · Jovany Cruz Navarro[1] · Claudia Robertson[1]

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Abstract
Traumatic brain injuries (TBIs) are associated with high morbidity and mortality due to both the original insult as well as the destructive biological response that follows. Medical management aims to slow or even halt secondary neurological injury while simultaneously laying the groundwork for recovery. Statins are one class of medications that is showing increased promise in the management of TBI. Used extensively in cardiovascular disease, these drugs were originally developed as competitive inhibitors within the cholesterol production pipeline. They are now used in diverse disease states due to their pleiotropic effects on other biological processes such as inflammation and angiogenesis. Preclinical studies, retrospective reviews, and randomized clinical trials have shown a variety of benefits in the management of TBI, but to date, no large-scale randomized clinical trial has been performed. Despite this limitation, statins' early promise and well-tolerated side effect profile make them a promising new tool in the management of TBIs. More bench and clinical studies are needed to delineate proper treatment regimens as well as understand their true potential.

Keywords Traumatic brain injury · Statins · Trauma · Inflammation · Concussion · Inflammation · Cholesterol

Introduction

Traumatic brain injury (TBI) is a leading health problem in both developing and high-income countries. Over 50 million TBIs occur internationally each year, causing one-third of injury-related deaths and costing 0.5% of worldwide GDP [1]. TBI-related disability has an incidence of approximately 4 million people in the USA. This disease disproportionally affects the young, with peaks in the adolescent and the elderly stages of life [2]. These numbers underestimate the true impact of TBIs, with an order of magnitude more going unreported and unnoticed [2, 3].

Traumatic brain injury is a complex heterogeneous pathology with a wide clinical impact, ranging from asymptomatic to a neurologically devastating disease. Severe TBI has been estimated to have a mortality rate of almost 40%. Those who survive are often debilitated with severe physical, emotional, and economic burdens [4]. Nearly half of TBI survivors develop depression and later in life suffer from dementia at five times the average rate [5]. Even mild TBIs can have long-term impacts including increased risk of dementia, seizures [6], functional limitations, disability, mood disorders [7], and reduced quality of life [8].

Crucial to the management of TBI is recognition that it is not an acute condition, but a chronic and evolving disease process. The "second hit" model posits that damage continues even after the original injury, as swelling and inflammation sets in. Additionally, the recovery process is a complex, poorly understood process dependent on the reshaping or reformation of the damaged neural networks [9].

The standard of care for TBI management is a constantly changing field. In the acute period, surgical intervention such as placement of a ventriculostomy or craniectomy can have a significant impact on morbidity and mortality [10, 11]. However, the vast majority of cases are managed conservatively [10]. In addition to long-term support including physical and occupational therapy, many different medical interventions have been tried. Aside from antiepileptics prevention of early-onset seizures [12] and multimodal therapy for intracranial pressure control [13], no other regimen has been codified in the management of TBI sequelae [14, 15].

This large divide between a clear clinical need and a lack of solution has driven an enormous amount of research into potential treatments. Clinical trials have investigated a wide variety of known medications [15], such as magnesium [16] and cyclosporine-A [17]. One class of medications receiving

✉ Kalman Katlowitz
Kalman.katlowitz@bcm.edu

[1] Department of Neurosurgery, Baylor College of Medicine, Houston, TX 77030, USA

increased interest is statins. Statins classically impact physiology as inhibitors of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase), the rate-controlled step within the mevalonate pathway. This interrupts the metabolic chain reaction that eventually produces cholesterol and other organic isoprenoid derivates such as steroids and vitamins. However, further investigations have revealed many alternative impacts of statins, including stimulating angiogenesis, anti-inflammatory effects, and influence of neural circuit formation (Fig. 1) [18].

History

In the late twentieth century, researchers began to elucidate the role of cholesterol in cardiovascular disease and looked for ways to control cholesterol levels. The first statin was actually a byproduct of antibiotic research. Inspired by the discovery of penicillin, researchers were culturing fungi at a large scale to find new compounds. Mevastatin, also known as compactin, was isolated in 1971 from the fungus *Penicillium citrinum* by researchers looking for an enzyme that might target microbes that depended on sterols or other isoprenoids [19, 20]. Lovastatin was isolated by Merck in 1978 from *Aspergillus terreus* and in 1987 became the first statin to be approved by the FDA. The incredible results of early trials [21] caused a wave of public interest in statins, leading to the development of many alternative compounds. In the early 2000s, blockbuster drugs such as simvastatin, pravastatin, and atorvastatin had an average annual cost of nearly $25 billion in the USA alone [22].

Mechanism of Action

Statins were originally discovered for their ability to competitively inhibit HMG-CoA reductase due to their molecular similarity to HMG-CoA (Fig. 2). This competition for the enzyme's active site allows it to compete with the native substrative and reduce the rate that mevalonate is produced. The lower availability of mevalonate decreases the body's ability to generate cholesterol (a downstream molecule). This impact is compounded by the liver, which increases the production of LDL receptors to harvest circulating cholesterol, further lowering bloodstream levels [23].

Yet as their use became more widespread, new findings began to suggest that this is not the only action of statins in the body. In fact, a large part of its impact may actually be derived from other sources. For example, simply lowering cholesterol by other means does not have the same benefit, and these drugs have been shown to have a benefit in disease processes not classically associated with elevated lipid levels [24].

More than 20 years since statins were put on the market, new findings demonstrated that many of their health benefits may be through their immunomodulatory impact. For example, they are known to inhibit the inductive effect of interferon-γ on major histocompatibility class II (MHC-II), thereby repressing MHC-II-medicated T-cell activation [25]. They have also been shown to lower C reactive protein (CRP) levels by one-third [26], as well as other inflammatory markers such as inducible nitric oxide synthase (iNOS), tumor necrosis factor alpha (TNF-α), and interleukin-1β (IL-1β) [27]. Other studies have shown a disruption of lipid

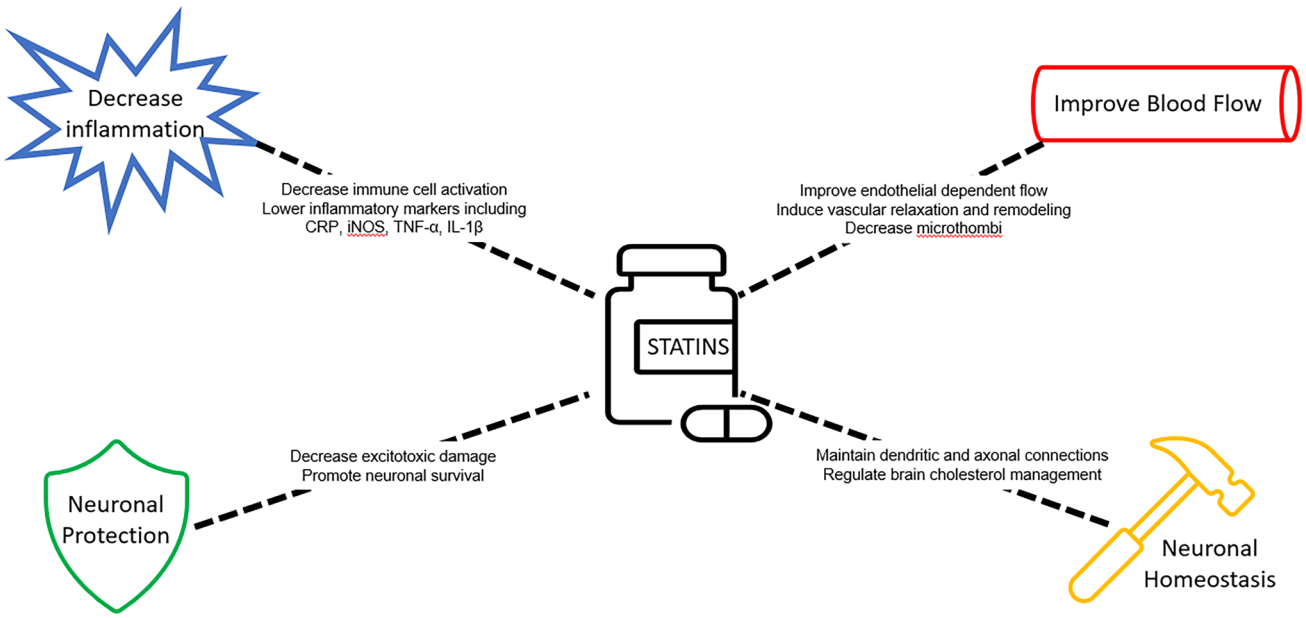

Fig. 1 The putative beneficial effects and proposed mechanisms of statin therapy for TBI

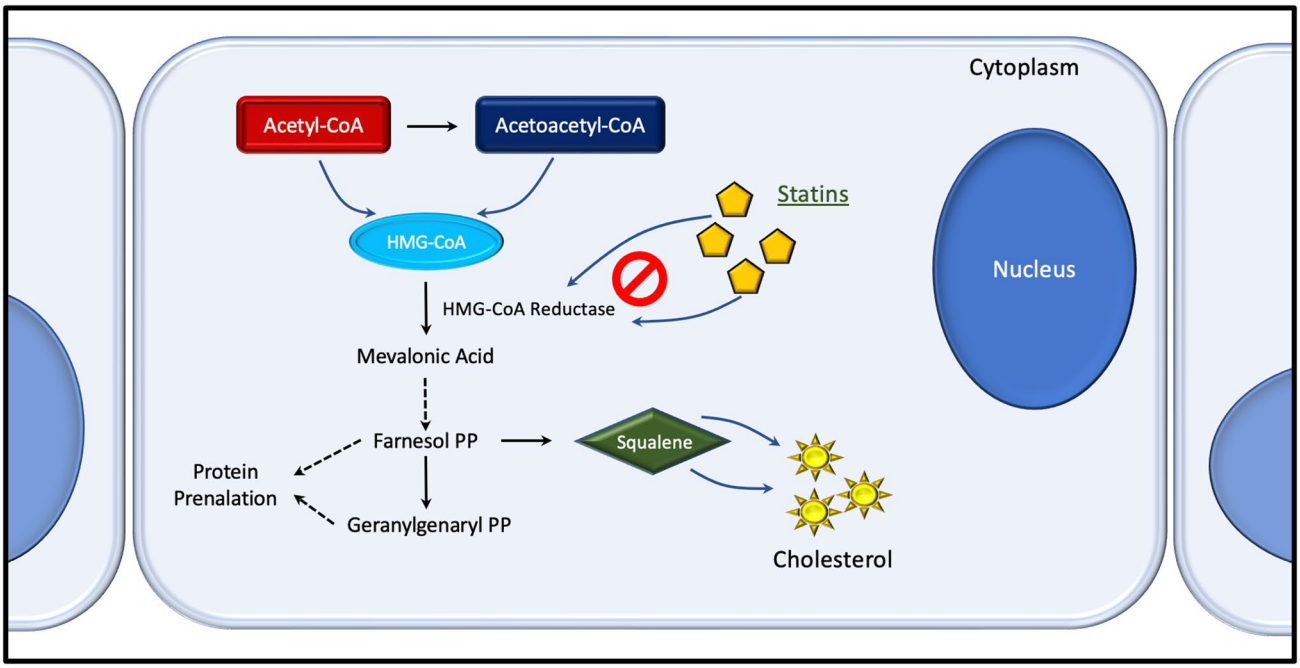

Fig. 2 The cholesterol synthetic pathway, highlighting the effects of statins on the mevalonate pathway. PP pyrophosphate, HGM 3-hydroxy-3-methylglutaryl, CoA coenzyme A

rafts, preventing the organization of proteins necessary for the activation of immune cells [28]. Natural killer cells have lower cytotoxicity in patients on statins, leading to their use in preventing organ rejection [29]. Other autoimmune disorders that have been treated with statins include multiple sclerosis, rheumatoid arthritis, and osteoporosis [25].

Further investigations have also shown a direct impact on vasculature. Endothelial-dependent flow significantly improves after statin treatment [30]. Statins induce endothelial nitric oxide synthase (eNOS), an enzyme that generates nitric oxide (NO) within vessel walls to promote vascular relaxation and decrease interactions with circulating leukocytes and platelets [31]. They also induce the expression of various genetic profiles involved in the remodeling of both endothelial and smooth muscle cells [24].

Lastly, there may be direct neurological impacts both cholesterol and non-cholesterol mediated. Cholesterol is a major component of neural membranes and is a rate-limiting step in synaptogenesis [32]. Compactin has been shown to promote the maintenance of dendritic and axonal connectivity patterns [33]. Statins can protect neurons from excitotoxic damage, such as NMDA-mediate excitotoxic cell death [34]. Simvastatin in particular has been shown to stimulate the Bcl-2 gene, promoting neuronal survival [35] and attenuating axonal injury [36]. Many other enzymes with key roles in the maintenance of neural homeostasis have been shown to be modulated by statins [18].

Pharmacology

Statins can be broadly divided into two categories. Type 1 statins such as lovastatin, pravastatin, and simvastatin are fungal-derived and share structural similarities to the original mevastatin. Type 2 statins such as atorvastatin and rosuvastatin are synthetically derived and have highly variable properties [37]. All statins are absorbed by the intestines and have a bioavailability between 5 and 50%. Most (but not all) are metabolized by cytochrome P-450 (CYP 450) [38]. Lipophilic statins such as atorvastatin and simvastatin passively cross the blood–brain barrier [39]. There is some concern that hydrophilic statins do not have as large of an impact [39], but there is evidence that they also enter the cerebrospinal fluid space, possibly through active transport [40]. The wide diversity of molecular profiles begs the question of the efficacy of each variation. Unfortunately, research is still lacking on how to maximize benefits.

Despite their potency, statins are often very well tolerated. Myopathy has been classically associated with statin use in 1–5% of patients [41], though the incidence is controversial with many studies demonstrating no increased risk relative to placebo [42]. Hepatic dysfunction (as defined by elevated transaminases) has also been reported in up to 3% of patients [43], especially within the first few months of initiation. However, clinically significant liver injury is rare, and regular monitoring is not required [44]. Lastly, there may be a small

increased risk in the long-term development of type 2 diabetes [45]. Notably, some of the reported side effects may be due to cognitive biases, with one large-scale study finding discontinuation rates to be similar between statins and placebo [46].

Animal Studies

Early animal models showed significant promise in the role of statins in traumatic neurological injuries. Using simple tasks as proxies for both motor and cognitive function, researchers examined the impact of the administration of statins on TBI outcomes. Table 1 demonstrates select highlighted studies but are not an exhaustive list. Simvastatin was most commonly used, but other statins were tested as well. While not every study showed a definite improvement [47], decades of studies have shown that even a short course of statins can have significant motor [47–52] and cognitive [36, 52–57] benefits. These benefits may have long-term impacts, as one study showed improved functional outcomes up to 3 months with the administration of a variety of statins [58].

The use of an animal model allowed these studies to further look into the putative mechanisms of these benefits. Findings supported many of the in vitro and in vivo hypotheses. Many showed a reduced inflammatory profile [48, 49, 52, 59]. Other studies showed that the vascular impact of statins may provide further benefit, with reduced thromboses [53, 60] and

Table 1 Selected animal studies

Author/date	Study design	Treatment	Clinical outcome	Physiological outcomes
Lu et al. 2004 [53, 54, 60, 61]	CCI rats	Atorvastatin × 7–15 days	Improved Corner scores, mNS scores, improved spatial memory	Increased neurogenesis, increased angiogenesis, reduced intracranial hematoma volume, decreased vessel thrombosis
Chen et al. 2007 [48]	CCI rats	Lovastatin × 5 days prior to injury	Improved rotarod and adhesive removal tests	Decreased contusion volume and degenerating neurons Decreased TNF-α, IL-1β
Lu et al. 2007 [55]	CCI rats	Atorvastatin and simvastatin × 14 days	Improved spatial learning	Reduced neuronal loss and increased neurogenesis in hippocampus
Wang et al. 2007 [49]	CCI mice	Atorvastatin or Simvastatin × 14 prior to injury and 3 days after	Improved rotarod	Reduced neuronal loss, decreased CNS inflammation, improved cerebral hemodynamics
Mahmood et al. 2009 [58]	CCI rats	Simvastatin × 14 days	Improved motor function up to 90 days	Increased proliferation in lesional zone
Wu et al. 2011 [50]	CCI rats	Simvastatin × 14 days	Decreased falls	Increased angiogenesis
Wu et al. 2012 [36]	CCI rats	Simvastatin × 14 days	Improved mNS scores	Decreased axonal injury, increased neurite growth, via mTOR and APC pathways
Abrahamson et al. 2013 [62]	CCI Human Amyloid-β mice	Simvastatin × 3 weeks		Decreased Amyloid-β, brain tissues loss, improved blood flow
Darwish et al. 2014 [56]	CCI rats	Simvastatin × 14 days	Decreased memory deficits	
Wang et al. 2014 [51]	CCI rats	Simvastatin × 7 days	Improved grip strength	Decreased cerebral vascular endothelial inflammation
Xie et al. 2015 [57]	CCI rats	Simvastatin × 35 days	Decreased mNS scores	Increased neurogenesis via Notch-1
Mountney et al. 2016 [59]	PBBI rats	Simvastatin × 10 days	No benefit on rotarod, improved water maze test	Decreased GFAP, IL-1α, I1-17
Mountney et al. 2016 [47]	FPI, CCI, and PBBI rats	Simvastatin × 14 days	Mild benefit on grid walk, balance beam, and rotarod, worsened water maze	Worse cortical loss in FPI model
Xu et al. 2017 [52]	CCI mice	Atorvastatin × 3 days	Improved mNS, latency to falls	Decreased neuronal apoptosis, WBC invasion, IFN-γ, IL-6, chemokines

CCI controlled cortical impact, *mNS* modified neurological severity, *WBC* white blood cells, *FPI* fluid percussion injury, *PBBI* penetrating ballistic-like brain injury

intracranial hematoma volumes [61]. A direct neuronal impact was noted in some instances, with increased neurogenesis and reduced neuronal loss [36, 52, 54, 55, 57, 58].

Human Trials

In one of the first large-scale studies, Khokhar et al. looked at the impact of prior statin use on outcomes in TBI in over 100,000 medicare beneficiaries over 65. They showed that statin used was associated with an approximate 0.85 long-term relative risk of dementia, stroke, and depression [63]. While not consistently replicated [64], at least two other studies since then have showed similar outcomes with respect to the risk of dementia even when looking only at mild concussions [65, 66]. Interestingly, this was true even if they were not on a statin prior to their TBI though the effect disappeared if the patient did not continue taking the statin. Additionally, there was no significant difference in the class (lipophilic vs. hydrophilic) or dose of statin prescribed, though rosuvastatin did seem to perform the best [65].

Table 2 Human studies of TBIs

Author/date	Study design	Patient population	Intervention	Clinical outcome	Physiological outcomes
Tapia-Perez et al. 2008 [68]	RCT	Age 16–50, GCS 9–13 ($n=21$)	Rosuvastatin 20 mg × 10 days	Decreased amnesia. No difference in disability at 3 months	increased IL6. No difference in TNF-α, IL-1β,
Schneider et al. 2011 [74]	RCS	Age > 65 head AIS > 2 ($n=523$)	Prior statin use	Decreased in-hospital death, improved outcomes at 1 year	
Sanchez-Aguilar et al. 2013 [67]	RCT	Moderate to severe TBI ($n=36$)	20 mg rosuvastatin × 10 days	Decreased disability	Decreased TNFα, no effect on IL-1β, IL-6, IL-10
Naghibi et al. 2016 [69]	RCT	Severe TBI ($n=44$)	40 mg simvastatin	Higher GCS at discharge, similar mortality rate and ICU course	Lower CRP at 48 h, no difference in IL6
Nielson et al. 2016 [75]	RCS	Severe TBI	Prior statin use	No decreased mortality at 2 weeks, or changes in GOS at 6 months	
Govindarajan et al. 2016 [78]	RCT	Mild TBI ($n=75$)	Atorvastatin		Protection from cortical thinning seen in placebo group
Farzanegan et al. 2017 [73]	RCT	Severe TBI ($n=65$)	20 mg atorvastatin × 10 days	Improved mRS, GOS and DRS at 3 months	No difference in contusion volume
Robertson et al. 2017 [77]	RCT	Age 18–50, Mild TBI ($n=52$)	Atorvastatin 1 mg/kg × 7 days	No difference for the first 3 months in post-concussion syndrome nor many other cognitive tests	
Khkohar et al. 2018 [63]	RCS	Age > 65 hospitalized for TBI ($n=100{,}515$)	Prior statin use	Decreased mortality, depression, stroke, dementia	
Lokhandwala et al. 2019 [72]	RCS	Age > 18, severe TBI ($n=270$)	Prior statin use	Lower mortality, decreased SNF disposition, higher GOS	
Redelmeier et al. 2019 [65]	RCS	Age > 66 with concussion ($n=28{,}815$)	Statin prescribed within 90 days of injury	Decreased dementia	
Mansi et al. 2020 [64]	RCS	TBI diagnosis ($n=140$)	Prior statin use	No difference in neurological outcomes	
Li et al. 2020 [66]	RCT	Age 50–89 with TBI ($n=733{,}920$)	Statin prescribed after injury	Decreased dementia	
Soltani et al. 2020 [70]	RCT	Age 15–50, moderate to severe TBI ($n=60$)	Atorvastatin 40 mg daily during hospitalization	Increased GCS at discharge, decreased ICU stay	Decreased CRP, ESR, WBC at 14 days,
Shafiee et al. 2021 [71]	RCT	Severe TBI, GCS < 9 ($n=98$)	40 mg simvastatin × 10 days	Increased GCS scores at discharge and 1 month	

GOS Glasgow Outcome Score, *MRS* modified Rankin scale, *DRS* Disabilitiy Rating Scale, *SNF* skilled nursing facility, *AIS* Abbreviated Injury Score, *RCT* randomized control trial, *RCS* retrospective cohort study, *CRP* C reactive protein

More rigorous studies have been performed, albeit with lower patient numbers. In a randomized control trial of a small population, Sanchez-Aguilar et al. showed that starting rosuvastatin after TBI can reduce disability scores at 3 and 6 months. This study did not show any improvement in amnesia and disorientation, though that could be due to low power or short-term follow-up [67]. In a similar study, Tapia-Perez did find a small reduction in amnesia time but no difference in disability at 3 months [68]. Other metrics of function such as Glasgow Coma Score (GCS) at discharge [69–71], Glasgow Outcomes Scale [72], Disability Rating Scale, and modified Rankin sale [73] are also improved by statins. Data on the impact of statins on mortality is mixed, with some showing a decreased risk [63, 72, 74], others no impact [64, 69, 75], and one demonstrating that stopping statins can increase mortality [76]. However, not all studies are uniformly positive. Robertson et al. performed a phase II clinical trial and found that atorvastatin for 7 days had no difference in the Rivermead score (a post-concussive assessment) at 3 months post-injury [77]. Notably, as with some of the animal studies, these trials have shown the effective time window to be as long as 24 h post-injury, increasing the clinical utility of statins in real-world situations.

Other studies aimed to correlate these outcomes with physiologic parameters of injury. From the inflammatory perspective, statins were shown to reduce levels of tumor necrosis factor- α (TNF-α), with mixed results on interleukin (IL) levels [67, 68]. Similarly, simvastatin has been shown to lower CRP in severe TBIs requiring ICU admission [69]. Interestingly, even in patients that show long-term benefits, it is difficult to notice any immediate difference on cranial imaging, with similar contusion volumes and rates of expansion [73], though one study showed decreased cortical loss [78].

Lastly, atorvastatin will be tested in a multi-arm, multi-stage adaptive platform trial for the acute treatment of TBI by the TRACK-TBI network. This will be a multi-center, double-blind, placebo-controlled adaptive platform, precision medicine trial conducted under a single multi-arm, multi-stage (MAMS) study with parallel groups. Subjects will be randomized to receive one of four possible treatments, being atorvastatin a study drug. It is expected that the findings of this study will assist in clarifying the potential beneficial effect of statins in the management of TBI (Table 2).

Conclusion

TBI is a significant and growing public health problem. There is no current standard of care regimen in the medical management of TBI. Statins are a well-studied popular class of medication with minimal side effect profile relative to the proposed benefits. Recent research has demonstrated that their benefits are not limited solely to the cardiovascular outcomes. In vitro, animal, retrospective, and randomized control studies have all demonstrated the potent for multimodal impact on both motor and cognitive outcomes. Further work is needed to clarify how to maximize its impact to ensure that its putative and potential benefits are realized.

Declarations

Conflict of Interest None.

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