

Statin as an Anti-Inflammatory Agent in Sepsis

Sepsiste Anti-İnflamatuar Bir Ajan Olarak Statin

Statin ve Sepsis / Statin and Sepsis

Zekeriya Arslan[1], Mustafa Aparcı[1], Murat Ünlü[2]
[1]Etimesgut Military Hospital, Cardiology Department,
[2]Beytepe Military Hospital, Cardiology Department, Ankara, Türkiye

Özet

Statinler, HMG-CoA redüktaz inhibitörleri, yalnızca kardiyovasküler hastalıklarda değil, pnömoni ve sepsis gibi önemli infeksiyonlarda da anti-inflamatuar pleiotropik etkileri nedeniyle morbidite ve mortaliteyi azaltmada son zamanlarda kullanılmaktadır. Ancak statinlerin bu etkilerini nasıl başardıkları halen tam açıklanmış değildir. Karmaşık inflamatuar süreçleri etkilemeleri yalnızca LDL kolesterol düşürme etkisi ile ilişkili değil, aynı zamanda NO dengesi, lökosit-endotel ilişkileri, inflamatuar hücre sinyalizasyon ve gen ekspresyonu, mononükleer hücre aktivitesi, pıhtılaşma, fibrinoliz ve oksidatif stres gibi dengeler üzerindeki etkilerine bağlanmaktadır. Ümit verici birçok çalışma statinlerin umulandan daha fazla rol oynayabildiğini göstermiştir. Biz bu derlemede statinlerin sepsisteki inflamatuar süreç üzerindeki etki mekanizmaları ve klinik sonuçlara olan etkilerini ele aldık.

Anahtar Kelimeler

Statin; HMG-CoA Redüktaz İnhibitörü; Sepsis; İnflamasyon

Abstract

Statins, inhibitors of HMG-CoA reductase, have been used for decrease morbidity and mortality not only in cardiovascular disease, but also in important infectious disease like pneumonia and sepsis recently through the anti-inflammatory pleiotropic effects. But it is stil not clear that how statins accomplish these effects. They affect the complex inflammatory cascade mostly regarded as not related to lowering LDL cholesterol, but changing in NO balance, leucocyte–endothelium interactions, and inflammatory cell signaling or gene expression, affecting mononuclear-cell activity, coagulation, fibrinolysis and oxidative stress. Several promising publications demonstrated that statins could get in role in sepsis besides that we expected. In this review, we evaluate the mechanism of action of statins on inflammatory cascade of sepsis and their effects on clinical outcomes.

Keywords

Statin; HMG-CoA Reductase Inhibitor; Sepsis; Inflammation

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Corresponding Author: Zekeriya Arslan, Etimesgut Asker Hastanesi, Kardiyoloji Servisi, 06790 Etimesgut, Ankara, Türkiye.
GSM: +905415669093 E-Mail: zekeriya.arslan@gmail.com

Introduction

There is an imbalance between extensive triggering of defense mechanisms and the effects of invaded microorganisms or their products in the systemic inflammatory response syndrome (SIRS), called sepsis. Complex pro- and anti-inflammatory events eventually result in widespread tissue injury[1]. The pathophysiological process starts from infection, and continues with sepsis, severe sepsis, and multi-organ dysfunction.

Sepsis is getting more important all over the world due to its high morbidity and mortality. 68% of the patients with severe sepsis requires intensive care unit (ICU) treatment and the mortality rate passes through the rate of 70%[2]. The increase of prevalence is probably the result of general population aging and improved survival with chronic diseases that predispose sepsis.

It is obvious that the need for new treatments and management strategies to be developed. Although a great amount of researches into the mechanisms of sepsis published recently, only few new antibiotics and some medications, like drotrecogin-alfa[3], were added to this era. Statins (HMG-CoA reductase inhibitors), may be useful for sepsis treatment with anti-inflammatory (pleiotropic) effects [4-8]. We evaluated the essential mechanisms of sepsis and potential role of statins on sepsis treatment.

Inflammatory Changes In Sepsis

A complex immunologic process helps for protecting from invasion of microorganisms in humans. A lack of defense may lead to develop infection. On the other hand, an excessive or poorly regulated response may be harmful to host by releasing of endogenous inflammatory compounds.

Microcirculation;

During sepsis, microcirculation is the place where the pathophysiological processes mostly occur in. Changes in arteriolar tone influencing blood pressure, adaptations to endothelial cell integrity causing leakage of proteins and macromolecules, adhesion and migration of leucocytes through the vascular endothelium, and also changes in coagulation system are the most common sequences of events in sepsis. Such processes contribute to widespread tissue damage, multiple organ failure and death. Meanwhile, endothelium serves as an important autocrine and paracrine organ regulating this condition.

Nytric oxide (NO);

Altered balance between inducible nitric oxide synthase (iNOS), providing inflammatory overproduction of NO, and endothelial nitric oxide synthase (eNOS), providing physiological production of NO, may be the most important responsible microvascular mechanism. With the activation of EC after developing sepsis, EC participates in the inflammatory process and generates multiple inflammatory mediators and up-regulating adhesion molecule expression. EC adhesion molecules activate the signalling cascades required for successful leucocyte transmigration. Normally, eNOS is activated by protein kinase Akt which produce NO for controlling vasomotor activity(Figure1) [9]. NO then diffuses into adjacent smooth muscle cells, activating guanyl cyclase and producing cyclic GMP that mediates vascular relaxation via protein kinase G. Sepsis results in a decrease in eNOS function and an increase in iNOS expression, leading to the vasodilation induced hypotension and resistance to vasopressor drugs in severe sepsis [5;10;11]. That also results in coagulopathy, endothelial dysfunction, vascular instability, and eventually apoptosis (ie programmed cell death) and multi-organ failure.

Cytokines;

Inflammation is mediated by a number of mediators including proinflammatory molecules, consist of cytokines [such as interleukin (IL)-1, IL-6, IL-8, tumor necrosis factor (TNF)-α], lysosomal enzymes, superoxide-derived free radicals, vasoactive substances,such as platelet-activating factor (PAF), tissue factor (TF), and plasminogen activator inhibitor-1 (PAI-1); and anti-inflammatory cytokines such as IL-1Ra, IL-10 and transforming growth factor (TGF)-β [12] (Figure 1). Although cytokines are necessary for appropriate function of the system; over or inappropriate expression of them may result in severe tissue destruction. Microbial components reacting with specific toll receptors were reported to trigger monocytes, neutrophils, and endothelial cells (EC) to initiate an inflammatory cascade [13]. Such a trigger stimulates the TF and PAI-1 produced by EC, compelements produced by monocytes, and also cytokines TNF-α and IL-1. Cytokines also stimulate oxygene radical production, lipid mediators and hence lead to vascular instability. Similar to cytokines, the inflammatory cells, including EC, also promote oxygene radical production; leading to microvascular occlusion with TF and PAI-1 [14]. Then, microvascular occlusion and vascular instability cause coagulopathy, fever, vasodilation and the capillary leak. Eventually multi-organ failure and sepsis will be developed.

Cytokines have the key role on early biochemical events in sepsis. It has been revealed that increasing of the TNF-α leads to sepsis and organ failure, and decreases the survival [15]. However, anti-TNF-α strategies with monoclonal antibodies were only slightly effective in increasing survival, not denoted dramatic clinical benefit as expected. Because, they neutralize already produced TNF-α, instead of suppressing ongoing production, and affect the intravascular space predominantly instead of extracellular space [16].

TNF-α and IL-1, promote endothelial cell-leucocyte adhesion, release of proteases and arachidonate metabolites, and activation of clotting by synergistic effects. IL-8 is a neutrophil chemotaxin and plays a role in driving sepsis. Additionally, a study of afelimomab targetting another pro-inflammatory cytokine, IL-6, revealed that its therapeutic potential on reduction in TNF-α production [17]. The anti-inflammatory cytokines, IL-1Ra and IL-10 inhibit the generation of TNF-α, T-lymphocyte and macrophage production, and augment the action of acute-phase reactants, like CRP, and immunoglobulins.

Pro/anti-inflammatory response rate may be another important point for this issue. It was demonstrated that impaired mediator production in response to trigger existed in mononuclear immune cells [18]. Thus this ratio, which is measured by TNF-α/IL-10, may be reduced and tends to the anti-inflammatory side, meaning the blunted inflammatory response [19].

Coagulation

Coagulopathy connected with sepsis results from increasing of TF and PAI-1, and decreasing protein C on mononuclear and endothelial cells (Figure1). In the coagulation cascade, TF activates factor X and then increases the conversion of prothrombin to thrombin, which generates fibrin from fibrinogen. On the other hand, increasing of PAI-1 levels results in decrease of plasminogen and plasmin which converts fibrin to fibrin degredation products (FDP). The activated form of protein C (aPC) inactivates factors Va and VIIa, and inhibits PAI-1 activity. Eventually the formation of fibrin clots is enhanced in microcirculation, which leads impaired tissue perfusion.

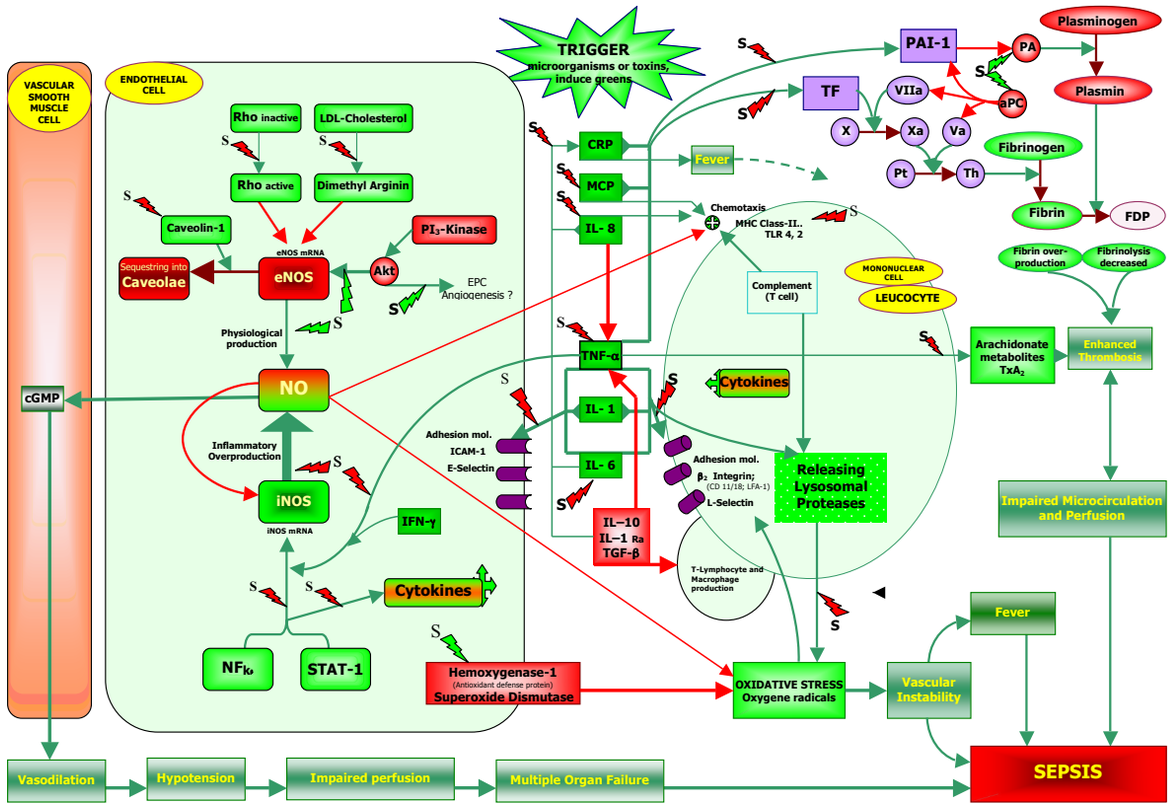


Figure 1. Pathophysiologic events and the effects of statins at the various side of inflammation. For explanations please see text.

Abbreviations and auxiliaries;

Rho	: Small GTP'ases; mediator of tight junctions and permeability, an inhibitor of eNOS
NO	: Nytric oxide
eNOS	: Endothelial nytric oxide synthase, responsible for physiologically NO production.
iNOS	: Inducible nytric oxide synthase, responsible for inflammatory overproduction of NO
Akt	: Akt protein phosphorilates the eNOS
EPC	: Endothelial progenitor cell, produced in bone marrow
IFN-γ	: Interferon gamma
PI_3-Kinase	: Phosphatidil inositole3- kinase
$NF_{k.}$	: Nuclear factor kappa beta
STAT-1	: Signal transducer activator of transcription-1
cGMP	: Cyclic guanosine monophosphate
ICAM-1	: Intracellular adhesion molecule-1
CRP	: C-Reactive protein
MCP	: Monocyte chemoattracatant protein
TNF-α	: Tumor necrosis factor alpha
IL –	: Interleukines
TGF-β	: Transforming growth factor beta
MHC	: Major histocompatibilitiy complex
CD 11,18	: Mononuclear cell cluster of differentiation, functioning on adhesiveness of immune cell
TLR	: Toll like receptors 4 and 2, for recognition of pathogens
LFA-1	: Leucocyte function antigene
TF	: Tissue factor, activator of clotting
PAI-1	: Plasminogen activator inhibitor-1
PA	: Plasminogen activator
aPC	: Activated Protein C
X,Xa,Va,VIIa: Coagulation factors; a: activated	
Pt	: Prothrombin
Th	: Thrombin
FDP	: Fibrin degredation products.

S Statins stimulate or increase of level

S Statins inhibit or decrease of level

Inhibit or decrease of level,

Stimulate or increase of level or result in

Transformation

Having pro-inflammatory state

Having anti-inflammatory state

Because of the complex nature of sepsis, only a single component blockage could not be sufficient to arrest this process. For example, although meta-analysis regarding to TNF-α inhibitors revealed improvement, these trials have been disappointing [20]. Recombinant activated protein C (drotrecogin alfa, rhAPC), is also very expensive and can only be administered IV [3]. Therefore, strategies modifying several arms of the inflammatory cascade may be more succesful and must be taken into consideration in sepsis treatment in the future.

Statins' Mechanism Of Action In Sepsis

Lots of data proved in large trials about statins showed reduce morbidity and mortality and increase survival in patients with coronary artery diseases (CAD) [21;22]. Lowering LDL increases survival not only in individuals with elevated LDL levels, but also in those with average LDL levels in both primary and secondary prevention of CAD. The magnitude of effect of statins on cardiovascular outcomes have been greater than their attributable effect on lowering cholesterol [23]. Statins' several anti-inflammatory and pleiotropic useful effects may beneficially modulate the inflammatory cascades and this make it possible to use in sepsis [24-26]. The mechanism is complex, but mostly regarded as not related to lowering LDL cholesterol. Changes in NO balance, leucocyte–endothelium interactions, inflammatory cell signaling and gene expression, effects on mononuclear-cell activity, coagulation and fibrinolysis, and antioxidant effects are some mechanism pathways which responsible for these effects as was demonstrated in figure 1 [27;28].

Impact of statins on cholesterol metabolism, cell signalling and gene expression

HMG CoA reductase, rate limiting enzyme of cholesterol syn-

thesis cascade, converts HMG-CoA to mevalonate mainly in the liver and other tissues (Figure 2). This enzyme also responds to negative feedback regulation by the products of mevalonate metabolism and can be inhibited by statins. Therefore statins reduce hepatocyte cholesterol content and increase expression

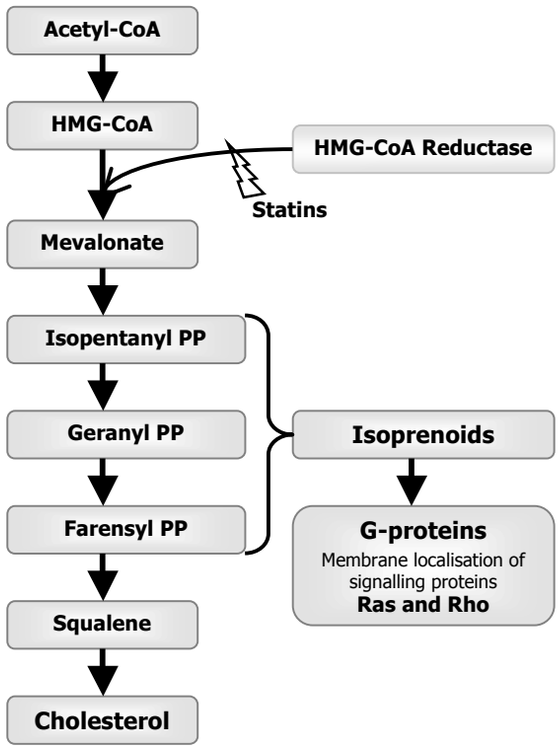


Figure 2. The cholesterole synthesis pathway. HMG-CoA Reductase inhibitors not only reduce the synthesis of cholesterole, but they also reduce the synthesis of isoprenoids.

of low-density lipoprotein (LDL)- receptors, responsible for LDL cholesterol uptake via receptor-mediated endocytosis, leading to reduce total cholesterol, LDL-cholesterol and apolipoprotein B. Besides intracellular decreasing, statins reduce levels of isoprenoids, derived from mevalonate in the cholesterol synthesis cascade (Figure 2). Isopentanyl-PP, geranyl-PP and farensyl-PP, are known as isoprenoids posttranslationally prenylate some adhesion molecules and cellular proteins that play pivotal roles in cell proliferation and signal transduction pathways. Guanine nucleotide binding proteins (G-proteins) have been shown to modulate signal transduction and mitogenic pathways [29]. Statins also decrease peroxisome proliferator-activated receptor (PPAR)-α activation [30], signal transducer activator of transcriptor-1 (STAT-1) and nuclear factor kappa beta (NFκβ) activity in human EC [31:32]; hence reduce iNOS expression. Jacobson et al. [33] also revealed that simvastatin decrease lipopolysaccharide-mediated gene expression and attenuate vascular leak.

Endothelial cell functions and NO balance

Although the entire mechanism remain unclear, the hypotheses of the benefit of statin therapy on endothelial functions center on NO-dependent. Briefly, statins transform the endothelium from predominantly prothrombotic and vasoconstructive to thromboresistant and vasodilatory stage. They reduce iNOS expression by blocking the transcription factors NFκβ and STAT-1, which attenuate the effects of cytokines upon EC [34]. Thus they prevents up-regulation of cell adhesion molecules on both endothelial cells and leucocytes. Enhancing physiological NO production appears to be most important mechanism that regulates the paracrine functions of the EC, including leucocyte and platelet adhesion and chemotaxis, control of vasomotor tone.

Statins have been reported to increase eNOS activity by following mechanisms; inducing Akt-mediated phosphorylation of eNOS [35]; up-regulating eNOS expression [36]; inhibition of Rho, which is an eNOS inhibitor, via blocking of the mevalonate pathway [37]; and inhibition of caveolin-1, which down-regulates NO synthesis through sequestering eNOS into caveolae. Some evidences suggested that increased concentrations of oxidized LDL may directly inhibit NO by excessive production of oxygen-derived free radicals and reduced transcription or increased posttranslational destabilization of eNOS mRNA [38]. Hypercholesterolemia also reduces eNOS activity through cytokine production [39], or increases in dimethyl arginine, an endogenous inhibitor of eNOS [40]. The other effect of statin is to increase the number and survival of circulating endothelial progenitor cells (EPCs) and to induce angiogenesis by promoting the proliferation and migration [41].

Inflammatory cytokines, acute phase proteins and leucocyte adhesion

Investigators revealed that statins influenced the following cytokines or acute phase reactants; IL-1, IL-6, TNF-α [42,43], IL-8 [30:42], monocyte chemoattractant protein-1 (MCP–1) [30;42;44], and C-reactive protein (CRP) [30:32;45;46]. Statins can reduce the proinflammatory cytokines and acute phase reactants, contributing to attenuating of sepsis. Known as an acute phase reactant, CRP is mainly produced by hepatocytes in response to cytokines; majority of IL-6 and partly IL-8, IL-10, and IL-1Ra [47]. Among statins, especially atorvastatin reduces the CRP levels more than that of the others [48]. The TF inducers, CRP and MCP-1, were significantly reduced by simvastatin in another double-blind, plasebo controlled study [49].

Statins also significantly decrease sepsis induced leucocyte recruitment, adhesion and transmigration. These effects were attributed to decrease MCP-1, IL-8, exotoxin induced leucocyte rolling, up-regulation of tol-llike receptors (TLR) 4 and 2 on the surface of monocytes [50], an adhesion molecule E-selectin expression on the EC [51], and direct inhibition of CD11a/CD18 or lymphocyte function antigen-1 (LFA-1)-mediated leucocyte adhesion [52;53]. Suppressed TLR4 and TLR2 expression was associated with decreased circulating concentrations of TNF-α and MCP-1[50]. The direct inhibition of MHC class II antigenes on T-cells is also probable. These pathways may have importance for expected beneficial effects on various side of mechanism of sepsis.

Coagulation and fibrinolysis

Besides enhanced platelet activation and hypercoagulability which is associated with hypercholesterolemia, studies mentioned about procoagulant condition in sepsis, contributing impaired microcirculation [54]. Statins decrease TF expression[49], von Willebrand factor[51], and PAI-1[31]; and increase tissue plasminogen activator (tPA) [55] and thrombomodulin activities [56]. In addition to reduced conversion of prothrombin to thrombin and reduced thrombin activity, the level of fibrinogen also reduces in result of decreased TF expression. On the other hand, statins also seem to stimulate fibrinolysis, which is impaired in sepsis by decreasing the level and activity of PAI-1 and increasing PA [31;54]. Though the effect of statins on plate-

let function is not clear, decreased platelet arachidonate metabolites like TxA2 production may be involved [57]. Through the activation of the protein C, improved outcome has been demonstrated with recombinant thrombomodulin in animal models of sepsis and dretrocogin-α in human being with sepsis and organ failure [3;58;59]. Activated protein C (aPC) actually contributes the anticoagulant state by inhibiting factors V, VIIa and PAI-1. In conclusion, statin therapy ameliorates the enhanced thrombotic and reduced fibrinolytic state in sepsis.

Antioxidant effects and cellular apoptosis

Some of the putative antioxidant effects have been attributed to statins because of decreasing isoprenylation of NADPH oxidase, in which its isoprenylated state generates superoxide anion [60-62]. Statins increase EC superoxide dismutase (SOD) and haemoxygenase-1 [63;64].

TNF-α, IL-1 and TGF-β may increase of the EC apoptosis. However, it is not easy to determine the apoptotic EC with routine methods. Soluble Fas levels increase in patients with sepsis and refall during recovery [65], and nuclear matrix protein level, which is cell death index, is also high in sepsis. These findings making us to think that EC apoptosis is increased in sepsis related multi-organ disease. Statins activate the Akt pathway which is important for reducing EC apoptosis in vitro [66].

Evidences For Statin Use In Sepsis

Although several observational studies reported the statins as protective for sepsis by their pleiotropic effects, the metaanalysis couldn't show the explicit benefit [67]. However, evidence based data derived from those studies revealed that statin use has some beneficial effects on preventing from infectious diseases or sepsis and improving outcomes.

Preventing from sepsis

A great amount of epidemiologic studies demonstrated that the patients hospitalized with bacteremia and pneumonia receiving statins had decreased incidence of sepsis. Evidences suggested that statin therapy reduces six times the incidence in severe sepsis[5], three times developing pneumonia in diabetic patients [68], 2.5 times hospital admission for sepsis in patients with chronic renal failure [69], reduces 7.9 times the developing severe sepsis due to acute bacterial infection[6], reduce 19-25% incidence of sepsis in patients with cardiovascular disease [70]. A recent study also showed that acute atorvastatin administration may prevent sepsis progression in patient with sepsis[71]. However mortality rate didn't reduce by statin using in this study.

Although statins seem to play role on preventing from sepsis, some hazardous effects also were reported. Evidences revealed that low lipoprotein and cholesterol levels may predispose to infection and related mortality [5;72;73]. So it is clear that the need for randomized studies to clarify the net benefit of statins on treatment of sepsis.

Reducing mortality and improving outcomes

Statin use was demonstrated to reduce mortality in patients with bacteremia[4]. They also reduce mortality 4.5 times in septic patients with atherosclerosis [74], 2 times in patients with pneumonia [75], 2.3 times suspected infection releated mortality in the emergency department [76]. In contrast, some other studies reported no improve on clinical outcomes with statins, and are not associated with reduced mortality or need for admission to an ICU in patients with pneumonia; and reports of benefit in sepsis attributed to confounding variables [77;78]. Additionaly, even if they are not frequent, statins are associated with serious organ specific adverse effects, such as muscular system and hepatic toxicity. These harmful effects cannot be ignored. However, we have to remember that how important a catastrophic disease the sepsis is, while making a decision.

In conclusion, the positive evidences derived from these retrospective investigations and observational studies arousing expectation, but couldn't be confirmed by randomized controlled trials to prove the net benefit of statins on sepsis treatment; additionally not all clinical studies showed a positive outcome so far. So it is obvious that randomised controlled large clinical studies are still required for confidently use statins for treatment of sepsis.

Competing interests

The authors declare that they have no competing interests.

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