Editorial / Editöryal Yorum

Pleiotropic effects of statins: New evidences

Statinlerin pleitropik etkileri: Yeni kanıtlar

Kaan Okyay, M.D.

Department of Cardiology, Başkent University School of Medicine, Ankara, Turkey

Statins (3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA] reductase inhibitors) decrease blood cholesterol, particularly low density lipoprotein (LDL) cholesterol levels. Since more than three decades, clinical trials have demonstrated the efficacy of statins for both primary and secondary prevention of coronary heart disease (CHD). Some of these beneficial effects are independent from LDL-C lowering and called as pleiotropic effect.[1,2] Statin pleiotropy is not solely shown in cardiovascular system, it has also been studied in many non-cardiovascular conditions. By means of some "yet uncertain" cellular and molecular properties, statins have been demonstrated to have beneficial effects on kidney functions, infectious diseases including sepsis, rheumatic diseases, gastrointestinal diseases, neurological disorders, periodontal diseases, malignancies etc.[1-3] Not surprisingly, statins are even offered to be beneficial in patients with COVID-19, suffering from increased microvascular and macrovascular thrombosis, and uncontrolled inflammation including cytokine storm.[4]

Owing to pleiotropic properties such as improvement of endothelial dysfunction, antioxidant effects, atherosclerotic plaque stabilization, and inhibition of inflammatory responses, statins are the mainstay agents used in cardiovascular diseases.[1] The cardioprotective effects of statins are tested in many clinical trials. The preoperative use of statins before non-cardiac, non-vascular surgery was associated with lower rate of major adverse events.[5] Statins are widely studied to prevent for cardiac and non-cardiac adverse events in patients undergoing cardiac surgery. Atorvastatin for reduction of myocardial dysrhythmia after cardiac surgery (ARMYDA-3 study), a randomized, placebo-controlled study revealed that treatment with atorvastatin (40 mg/day for seven days) before cardiac surgery reduced the incidence of postoperative atrial fibrillation (AF) by 61%.[6] In recent meta-analysis of 12 randomized controlled trials (RCT) including 2980 patients, statin treatment before coronary artery by-pass surgery (CABG) reduced the incidence of postoperative AF by 58%. Interestingly, atorvastatin reduced the risk by 65%, whereas rosuvastatin was not protective for AF.[7] In the Statin Therapy In Cardiac Surgery (STICS), a large Chinese RCT including 1922 patients, rosuvastatin did not reduce the incidence of post-CABG AF.[8] Worse still, compared with placebo, the incidence of postoperative acute kidney injury was higher in patients randomised to rosuvastatin.[8] The reason for the different outcomes between atorvastatin and rosuvastatin is mainly unknown. Different studies evaluating the potantial effects of statins on hospital and intensive care unit stay, renal failure, myocardial infarction (MI), stroke,

Abbreviations:

ACS	*Acute coronary syndrom*
AF	*Atrial fibrillation*
CABG	*Coronary artery by-pass surgery*
CHD	*Coronary heart disease*
FFR	*Fractional flow reserve*
HMG-CoA	*3-hydroxy-3-methylglutaryl coenzyme A*
hsTnT	*High sensitivity troponin T*
IMR	*Index of microcirculatory resistance*
LDL	*Low density lipoprotein*
MI	*Myocardial infarction*
PCI	*Percutenous coronary interventions*
RCT	*Randomized controlled trials*
STICS	*Statin Therapy in Cardiac Surgery*

Correspondence: Kaan Okyay, M.D. Department of Cardiology, Başkent University School of Medicine, Ankara, Turkey
Tel: +90 312 203 68 68/1501 e-mail: drokyay@yahoo.com

and mortality after CABG demonstrated conflicting results and randomized data comparing the different statin types and dosages are still lacking.[9-11] According to the recent guidelines, statins should be initiated as early as possible particulary before coronary and vascular surgeries, and statins should not be discontinued prior or after surgery.[12]

Likewise, myocardial protection is of great importance during percutenous coronary interventions (PCI). Auguadro et al.[13] studied cardioprotective effect of the statins in 552 patients underwent elective PCI. They divided the patients into two groups according to the presence or absence of statins in the last 3 months before PCI and provided that patients under statin treatment had lower release of troponins compared with patients who were not using statin.[13] In another study,[14] the effects of high-dose atorvastatin pretreatment on microvascular function and myocardial injury after elective PCI were determined. Patients were randomly assigned to high-dose atorvastatin (40 mg/d) and low-dose atorvastatin (20 mg/d) treatment for 7 days before PCI. The index of microcirculatory resistance (IMR) was measured after PCI. Fractional flow reserve (FFR) was calculated before and after procedure. Troponin I levels were studied at baseline and 24 h after procedure. IMR values were significantly lower in high-dose atorvastatin group, and pre-PCI troponin I levels were similar However, post-PCI troponin I levels in high-dose group were significantly lower. Ari et al.[15] randomly recruited 172 patients with stable angina pectoris underwent elective PCI with pretreatment of Cilostazol 200 mg and Rosuvastatin 40 mg or rosuvastatin 40 mg. At the end of the study, adjunct cilostazol and rosuvastatin pre-treatment did not significantly reduce myocardial injury.[15] In a recent meta-analysis, effect of high-dose statin pretreatment to prevent myocardial perfusion was evaluated in patients undergoing PCI. Fifteen RCTs with 4240 individuals were included. The pooled analysis (consisted of stable and acute coronary syndrom [ACS] patients) showed that high-dose statin pretreatment before PCI significantly improved the final TIMI flow grade, and reduced incidence of subsequent cardiac events. In subgroup analysis, the beneficial effect of high-dose statin was significant in statin-naive treatment patients, ACS patients, and patients on atorvastatin therapy, but not in rosuvastatin therapy, previous statin therapy, and stable angina patients.[16]

In the present study published in the current issue of the Archives of the Turkish Society of Cardiology, Koçak et al.[17] investigated the effects of long term statin usage on myocardial injury related with elective PCI. 102 patients were divided in three groups based on the statin usage at least 8 weeks before PCI; "potent statin" group (n=26) that means of usage of atorvastatin 40 mg, rosuvastatin 20 mg or higher doses of these statins, "weak statin" group (n=23) consisted of patients using other doses or different statins, and "statin free" group (n=53). The procedural complications were noted and myocardial injury was evidenced by elevation of high sensitivity troponin T (hsTnT) levels after the procedure. They provided that increases in hsTnT values were significantly lower in the potent statin group. In patients with procedural complications using potent statins, rise in hsTnT levels was also lower. Additionally, in case of procedural complication, hsTnT levels exceeding the myocardial infarction limit was decreased in the potent statin group. Accordingly, the authors concluded that hsTnT release after elective PCI was less frequent in patients using potent statins, and this benefical effect was pronounced in patients suffered from complicated procedures. The authors justifiably declared small number of patient population and a lack of clinical follow-up as the limitations of their study. However, there are some notable drawbacks in this trial. According to the contemporary literature (mentioned above), there is an "unexplained" heterogeneity in rosuvastatin and atorvastatin molecules in term of myocardial protection both after PCI and surgical procedures. In this study, the ratio of different types and doses of statins were not shared. Even so, due to small population size, further subgroup analyses are not possible. The authors experienced relatively higher percentage of complications (almost 1/3 of the patients) for elective PCIs. The complications listed by the authors require distinct and individual approaches as well as different medications including antitrombotic therapy all of which could influence the findings of this study. The data of PCI-treated vessel, type of lesions, use of stents and anti-IIb/IIIa inhibitors were also not shown. Despite all these limitations, there are important strengths of the current study. First, patients had been using statins for at least 8 weeks before the procedure (median time was not presented). On the other hand, most of the previous studies have evaluated the effect of statin therapy

initiated as a loading dose or a few days before the procedure. In this manner, Koçak et al.[17] supported the findings of Auguadro et al.[13] by demonstating the cardioprotective effects of mid-or-long term use of statins. Second, it can be argued that a mildly increase in troponins after PCI would not have any prognostic value. However, in this trial, the investigators found that high dose statin usage might not only prevent for occurrence of periprocedural myocardial injury but also for occurrence of periprocedural MI, particulary in the presence of interventional complications. This result is realy exciting and I hope, that would inspire further clinical researches aimed at this topic.

Conflict-of-interest: None.

REFERENCES

1. Oesterle A, Laufs U, Liao JK. Pleiotropic effects of statins on the cardiovascular system. Circ Res 2017;120:229-43. [Crossref]
2. Murphy C, Deplazes E, Cranfield CG, Garcia A. The role of structure and biophysical properties in the pleiotropic effects of statins. Int J Mol Sci 2020;21:8745. [Crossref]
3. Zhang Q, Dong J, Yu Z. Pleiotropic use of Statins as non-lipid-lowering drugs. Int J Biol Sci 2020;16:2704-11. [Crossref]
4. Olszewska-Parasiewicz J, Szarpak Ł, Rogula S, Gąsecka A, Szymańska U, Kwiatkowska M, et al. Statins in COVID-19 therapy. Life (Basel) 2021;11(6):565. [Crossref]
5. Raju MG, Pachika A, Punnam SR, Gardiner JC, Shishehbor MH, Kapadia SR, et al. Statin therapy in the reduction of cardiovascular events in patients undergoing intermediate risk noncardiac, nonvascular surgery. Clin Cardiol 2013;36:456-61. [Crossref]
6. Patti G, Chello M, Candura D, Pasceri V, D'Ambrosio A, Covino E, et al. Randomized trial of atorvastatin for reduction of postoperative atrial fibrillation in patients undergoing cardiac surgery: results of the ARMYDA-3 (Atorvastatin for reduction of myocardial Dysrhythmia after cardiac surgery) study. Circulation 2006;114:1455-61. [Crossref]
7. Elgendy IY, Mahmoud A, Huo T, Beaver TM, Bavry AA. Meta-analysis of 12 trials evaluating the effects of statins on decreasing atrial fibrillation after coronary artery bypass grafting. Am J Cardiol 2015;115:1523-8. [Crossref]
8. Zheng Z, Jayaram R, Jiang L, Emberson J, Zhao Y, Li Q, et al. Perioperative Rosuvastatin in cardiac surgery. N Engl J Med 2016;374:1744-53. [Crossref]
9. Siskos D, Tziomalos K. The role of statins in the management of patients undergoing coronary artery bypass grafting. Diseases 2018;6:102. [Crossref]
10. Galyfos G, Sianou A, Filis K. Pleiotropic effects of statins in the perioperative setting. Ann Card Anaesth 2017;20:S43-8. [Crossref]
11. Nomani H, Mohammadpour AH, Reiner Ž, Jamialahmadi T, Sahebkar A. Statin therapy in post-operative atrial fibrillation: focus on the anti-ınflammatory effects. J Cardiovasc Dev Dis 2021;8:24. [Crossref]
12. Kristensen SD, Knuuti J, Saraste A, Anker S, Bøtker HE, Hert SD, et al. 2014 ESC/ESA Guidelines on non cardiac surgery: Cardiovascular assessment and management: The Joint Task Force on non cardiac surgery: Cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). Eur Heart J 2014;35:2383-431. [Crossref]
13. Auguadro C, Manfredi M, Scalise F, Mortara A, Specchia G. Protective role of chronic statin therapy in reducing myocardial damage during percutaneous coronary intervention. J Cardiovasc Med (Hagerstown) 2006;7:416-21. [Crossref]
14. He GX, Tan W. High-dose atorvastatin pretreatment could diminishes microvascular impairment in patients undergoing elective percutaneous coronary intervention. J Geriatr Cardiol 2013;10:355-60.
15. Ari H, Emlek N, Ari S, Cosar S, Doganay K, Aydin C, et al. The effect of high dose cilostazol and rosuvastatin on periprocedural myocardial ınjury in patients with elective percutaneous coronary ıntervention. Acta Cardiol Sin 2015;31:292-300.
16. Xiao Y, He S, Zhang Z, Feng H, Cui S, Wu J. Effect of high-dose statin pretreatment for myocardial perfusion in patients receiving percutaneous coronary ıntervention (PCI): A meta-analysis of 15 randomized studies. Med Sci Monit 2018;24:9166-76. [Crossref]
17. Koçak A, Ünlü S, Gökalp G, Yılmaz NS, Gülbahar Ö, Abacı A. The relationship between long term statin usage and myocardial injury related to percutaneous coronary interventions evaluated by high sensitivity troponins. Turk Kardiyol Dern Ars 2021;49:536-44.