Balkan Med J 2024;41:83-4

Comment on "Risk of Venous Thromboembolism with Statins: Evidence Gathered via a Network Meta-analysis"

Levent Pay

Clinic of Cardiology, Ardahan State Hospital, Ardahan, Türkiye

To the Editor

I have read the meta-analysis by Birdal et al.[1] with great interest; the study compared the effectiveness of lipid-lowering agents in patients with venous thromboembolism (VTE) and examined the evidence in literature regarding reducing the risk of VTE. They demonstrated that compared with a placebo, rosuvastatin significantly reduced the risk of VTE and fenofibrate increased the risk of VTE. I would like to appreciate the authors' explanatory analysis and share my thoughts for a better understanding of the article.

Statins have become the focus of attention for preventing VTE owing to their effectiveness in preventing cardiovascular diseases and the common etiological risk factors for venous and arterial thromboses. In the JUPITER study, the initial randomized controlled trial that assessed the use of statins for VTE prevention in healthy patients, daily administration of 20 mg rosuvastatin was compared to administration of a placebo. The findings indicated that statin treatment might lower the risk of VTE.[2] However, the limitation of this study, which included approximately 18,000 patients, was the low number of VTE events (rosuvastatin group, n = 34 and placebo group, n = 60). The current meta-analysis is significant because its results support those of the JUPITER study regarding the effects of rosuvastatin.

The efficacy of rosuvastatin in lowering low-density lipoprotein cholesterol (LDL-C) and apolipoprotein (Apo) B levels, while simultaneously increasing Apo A1 levels, could be a contributing factor in reducing the risk of VTE.[3] Furthermore, the preventive advantages of rosuvastatin against VTE may arise from its impact on lipid levels and its ability to suppress thrombosis and inflammation.[4,5] Fenofibrate is associated with a higher incidence of VTE.[6] However, the pathophysiological pathway between fenofibrate and VTE is not yet fully understood. A possible mechanism is thought to be increased plasma homocysteine levels, a known risk factor for VTE.[7] Furthermore, fenofibrate's effects on elongation of fatty acid chains and desaturase, which are important factors in fatty acid metabolism, may lead to changes in the lipid profile that supports clot formation.[8] Pemafibrate, a specific modulator of peroxisome proliferator-activated receptor α, lowers triglyceride levels and enhances various lipid parameters. Pemafibrate demonstrated more advantageous outcomes than fenofibrate does with respect to lowering triglyceride levels and increasing high-density lipoprotein cholesterol levels.[9] A study among patients with type-2 diabetes mellitus demonstrated that although pemafibrate reduced the levels of triglycerides, very-low-density lipoprotein cholesterol, remnant cholesterol, and Apo C-III, it did not significantly affect the incidence of cardiovascular events.[10] The study results indicate that pemafibrate is associated with a higher incidence of VTE, which is consistent with the results of previous studies. Proprotein convertase subtilizin/kexin type 9 (PCSK9) inhibitor, a newer lipid-lowering agent, reduces LDL-C and lipoprotein(a) levels. Increased plasma levels of lipoprotein(a) appear to be significantly associated with an increased risk of VTE.[11] PCSK9 inhibition reportedly significantly reduces the risk of VTE, and the reduction of lipoprotein(a) levels may be an important mediator of this effect.[12] Furthermore, the non-lipid effects of PCSK9 monoclonal antibodies, which reduce platelet aggregation and activation, may contribute to this protective effect.[13] However, further studies are required to understand these mechanisms.

REFERENCES

1. Birdal O, Saygı M, Doğan R, Tezen O, Karagöz A, Tanboğa İH. Risk of Venous Thromboembolism with Statins: Evidence Gathered via a Network Meta-analysis. *Balkan Med J.* 2023;40:324-332. **[CrossRef]**
2. Glynn RJ, Danielson E, Fonseca FA, et al. A randomized trial of rosuvastatin in the prevention of venous thromboembolism. *N Engl J Med.* 2009;360:1851-1861. **[CrossRef]**
3. Zhang X, Xing L, Jia X, et al. Comparative Lipid-Lowering/Increasing Efficacy of 7 Statins in Patients with Dyslipidemia, Cardiovascular Diseases, or Diabetes Mellitus: Systematic Review and Network Meta-Analyses of 50 Randomized Controlled Trials. *Cardiovasc Ther.* 2020;3987065. **[CrossRef]**
4. Undas A, Brummel-Ziedins KE, Mann KG. Statins and blood coagulation. *Arterioscler Thromb Vasc Biol.* 2005;25:287-294. **[CrossRef]**

Corresponding author: Levent Pay, Clinic of Cardiology, Ardahan State Hospital, Ardahan, Türkiye
e-mail: leventpay@hotmail.com

Received: October 04, 2023 Accepted: October 23, 2023 Available Online Date: January 03, 2024 • DOI: 10.4274/balkanmedj.galenos.2023.2023-10-17

Available at www.balkanmedicaljournal.org

ORCID iDs of the authors: L.P. 0000-0002-7491-8119.

Cite this article as:
Pay L. Comment on "Risk of Venous Thromboembolism with Statins: Evidence Gathered via a Network Meta-analysis". *Balkan Med J.*; 2024; 41(1):83-4.

5. Kaba NK, Francis CW, Moss AJ, et al. Effects of lipids and lipid-lowering therapy on hemostatic factors in patients with myocardial infarction. *J Thromb Haemost*. 2004;2:718-725. **[CrossRef]**
6. Dolladille C, Humbert X, Faucon M, et al. Association between venous thromboembolism events and fibrates: A comparative study. *Therapie.* 2019;74:421-430. **[CrossRef]**
7. Herrmann M, Whiting MJ, Veillard AS, Ehnholm C, Sullivan DR, Keech AC; FIELD study investigators. Plasma homocysteine and the risk of venous thromboembolism: insights from the FIELD study. *Clin Chem Lab Med.* 2012;50:2213-2219. **[CrossRef]**
8. Oosterveer MH, Grefhorst A, van Dijk TH, et al. Fenofibrate simultaneously induces hepatic fatty acid oxidation, synthesis, and elongation in mice. *J Biol Chem.* 2009;284:34036-34044. **[CrossRef]**
9. Yamashita S, Rizzo M, Su TC, Masuda D. Novel Selective PPARα Modulator Pemafibrate for Dyslipidemia, Nonalcoholic Fatty Liver Disease (NAFLD), and Atherosclerosis. *Metabolites.* 2023;13:626. **[CrossRef]**
10. Das Pradhan A, Glynn RJ, Fruchart JC, et al. Triglyceride Lowering with Pemafibrate to Reduce Cardiovascular Risk. *N Engl J Med.* 2022;387:1923-1934. **[CrossRef]**
11. Dentali F, Gessi V, Marcucci R, Gianni M, Grandi AM, Franchini M. Lipoprotein(a) as a Risk Factor for Venous Thromboembolism: A Systematic Review and Meta-analysis of the Literature. *Semin Thromb Hemost.* 2017;43:614-620. **[CrossRef]**
12. Marston NA, Gurmu Y, Melloni GEM, et al. The Effect of PCSK9 (Proprotein Convertase Subtilisin/Kexin Type 9) Inhibition on the Risk of Venous Thromboembolism. *Circulation.* 2020;141:1600-1607. **[CrossRef]**
13. Ugovšek S, Šebeštjen M. Non-Lipid Effects of PCSK9 Monoclonal Antibodies on Vessel Wall. *J Clin Med.* 2022;11:3625. **[CrossRef]**