

Statins for Preventing Venous Thrombosis: For or Against?

Giuseppe Lippi, MD^{1,2} Emmanuel J. Falavero, PhD, FFSc (RCPA)^{1,2}

¹Section of Clinical Biochemistry, University of Verona, Verona, Italy

²Department of Haematology, Sydney Centres for Thrombosis and Haemostasis, Institute of Clinical Pathology and Medical Research, NSW Health Pathology, Westmead Hospital, Westmead, NSW, Australia

Address for correspondence Prof. Giuseppe Lippi, MD, Section of Clinical Biochemistry, University Hospital of Verona, Piazzale LA Scuro, 37100–Verona, Italy (e-mail: giuseppe.lippi@univr.it).

Semin Thromb Hemost 2019;45:834–836.

The basic assumption beneath the use of a common therapy for preventing both arterial and venous thrombosis is that the biology of blood clot formation expresses some overlap, so that thrombus structure and composition would not be markedly different when developing in arterial or venous blood vessels.¹ Briefly, both arterial and venous thrombi are largely composed of platelets and fibrin, although the main components of the so-called Virchow's triad (i.e., hypercoagulability, venous stasis, and endothelial injury) may have some differential impact on thrombus formation in arteries versus veins. Thrombosis in arterial vessels mostly results from fissuration, ulceration, or complete rupture of pre-existing atherosclerotic plaques, thus leading to local release of several prothrombotic substances, which may finally promote both platelet aggregation and blood clotting. Unlike this process in the arteries, the pathogenesis of vein thrombosis is more profoundly influenced by a pre-existent prothrombotic milieu in the circulation, which interplays with the lower blood pressure present in these vessels (up to venous stasis) to trigger blood coagulation and platelet activation. Atherosclerotic plaques are typically absent in normal veins,² and can only develop once these vessels are implanted, as bypass conduits, to replace important arteries (typically coronaries) irreversibly occluded or injured.³ Based on this premise, it seems at first glance counterintuitive to conclude that lowering atherogenic lipoproteins (i.e., mostly low-density lipoproteins) would not have the same favorable effect against thrombosis in both arteries and veins. This conceptual dichotomy has been firmly endorsed by epidemiological studies, showing that serum levels of atherogenic lipoproteins are not associated with the risk of developing either incident⁴ or recurrent⁵ venous thrombosis.

Statins, which mainly act as competitive inhibitors of the enzyme 5-hydroxy-3-methylglutaryl-coenzyme A reductase, have become a mainstay for treatment of patients with cardiovascular disease, although their use in primary prevention of cardiovascular disorders remains largely debated.⁶ Several lines of evidence, as reviewed in this issue

of the journal by Orsi et al,⁷ seemingly demonstrate that these drugs are also effective to dampen platelet function and may also interfere with blood coagulation, thus representing potentially suitable agents for also lowering the risk of venous thrombosis. However, some clinical studies, also reviewed by Orsi et al,⁷ have provided controversial evidence on the role of statins for reducing the risk of venous thromboembolism (VTE). For example, the recent systematic review and meta-analysis published by Kunutsor et al concluded that the risk of VTE was 15% lower (relative risk [RR], 0.85; 95% confidence interval [95% CI], 0.73–0.99) with statin therapy compared with no treatment, but no clear risk reduction was seen for pulmonary embolism (RR, 1.02; 95% CI, 0.74–1.40).⁸ Interestingly, a similar lack of significant effect was noted in a recent study in a high-risk population (i.e., cancer patients), in which these drugs were shown not to prevent either deep vein thrombosis (hazard ratio [HR], 0.96; 95% CI, 0.88–1.05) or pulmonary embolism (HR, 0.91; 95% CI, 0.79–1.05).⁹

Thus, statins still have an uncertain role in primary prevention of VTE; however, what cannot be discounted is the fact that all drug use carries some risks for adverse effects. With the anticoagulant agents, the main adverse risk factor is bleeding (–Fig. 1).^{10–12}

Statin use does not seem to confer an increased risk of bleeding, and thus may be seen as an attractive alternative to anticoagulant use. Nevertheless, statin use still carries significant potential for side effects, especially in the general population. These adverse effects include muscle injury (up to rhabdomyolysis), pancreatic and liver impairment, neuropathy, cognitive loss, and sexual dysfunction.^{13,14} Importantly, a recent cross sectional study of the National Health and Nutrition Examination Survey concluded that statin intake was associated with significantly enhanced prevalence of musculoskeletal pain in all body areas (prevalence ratios comprised between 1.3 and 1.6).¹⁵ As regards statin-induced rhabdomyolysis, safety data identifies the prevalence of this severe

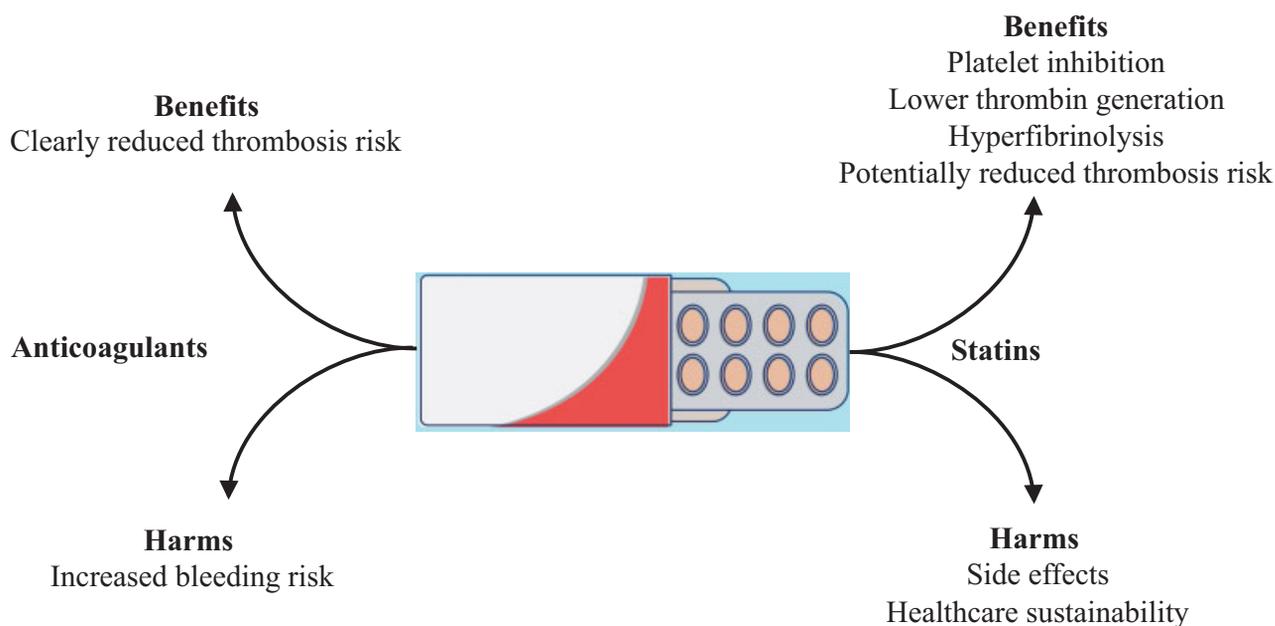


Fig. 1 Possible harms and benefits of statins in primary prevention of venous thromboembolism, as compared with anticoagulant use.

and often life-threatening condition to be as high as 1.35 cases per 100,000 prescriptions,¹⁶ and this is consistently magnified by concomitant use of statins with fibrate.¹⁷ In another retrospective study, including 32,225 subjects (10,247 with diabetes and 21,978 without), Nichols and Koro reported a prevalence of severe myositis and rhabdomyolysis of 0.4 to 0.8 and 0.1 to 0.2 per 1000 person-years, respectively.¹⁸

Thus, the use of statins for primary prevention would notably not only be associated with a significant clinical risk of side effects for patients but also raise issues of healthcare sustainability, since such treatment would entail larger healthcare expenditures for both administering the drug to the general population and for managing potential complications.¹⁹ More epidemiological evidence is therefore advisable to prove both cost-effectiveness and safety of statins in primary and secondary prevention of VTE.²⁰ For the interim, our conviction remains that the balance between possible harms and benefits of using statins in the general population would currently make their widespread usage unwarranted (► **Fig. 1**), while their impact on risk reduction of recurrent VTE, ranging between 26 and 38%, was found to be limited to long-term statin users.⁷ It is understandable that clinicians and patients alike desire a magic bullet to treat and prevent thrombosis. It is unclear if statin use will find a place in treatment of select patient groups. However, for most patients, lifestyle changes based on appropriate nutrient intake and preventing a sedentary lifestyle²¹ may still be the best options to reducing primary thrombosis risk. Although, like statins, focusing on individual foods or nutrients may not provide the answer either.^{22–24} We eagerly await further advances in the field.

Conflict of Interest
None.

References

- 1 Lippi G, Favaloro EJ. Venous and arterial thromboses: two sides of the same coin? *Semin Thromb Hemost* 2018;44(03):239–248
- 2 Agnelli G, Becattini C. Venous thromboembolism and atherosclerosis: common denominators or different diseases? *J Thromb Haemost* 2006;4(09):1886–1890
- 3 Mautner SL, Mautner GC, Hunsberger SA, Roberts WC. Comparison of composition of atherosclerotic plaques in saphenous veins used as aortocoronary bypass conduits with plaques in native coronary arteries in the same men. *Am J Cardiol* 1992;70(18):1380–1387
- 4 Morelli VM, Lijfering WM, Bos MHA, Rosendaal FR, Cannegieter SC. Lipid levels and risk of venous thrombosis: results from the MEGA-study. *Eur J Epidemiol* 2017;32(08):669–681
- 5 Morelli VM, Lijfering WM, Rosendaal FR, Cannegieter SC. Lipid levels and risk of recurrent venous thrombosis: results from the MEGA follow-up study. *J Thromb Haemost* 2017;15(04):695–701
- 6 Lippi G, Plebani M. Statins for primary prevention of cardiovascular disease. *Trends Pharmacol Sci* 2017;38(02):111–112
- 7 Orsi FA, Cannegieter SC, Lijfering WM. Statin therapy to revert hypercoagulability and prevent venous thromboembolism: a narrative review. *Semin Thromb Hemost* 2019;45(08):825–833
- 8 Kunutsor SK, Seidu S, Khunti K. Statins and primary prevention of venous thromboembolism: a systematic review and meta-analysis. *Lancet Haematol* 2017;4(02):e83–e93
- 9 El-Refai SM, Black EP, Adams VR, Talbert JC, Brown JD. Statin use and venous thromboembolism in cancer: a large, active comparator, propensity score matched cohort study. *Thromb Res* 2017; 158:49–58
- 10 Schulman S. Bleeding complications and management on anticoagulant therapy. *Semin Thromb Hemost* 2017;43(08):886–892
- 11 Gómez-Outes A, Terleira-Fernández AI, Lecumberri R, Suárez-Gea ML, Calvo-Rojas G, Vargas-Castrillón E. Causes of death in patients with venous thromboembolism anticoagulated with direct oral anticoagulants: a systematic review and meta-analysis. *Semin Thromb Hemost* 2018;44(04):377–387
- 12 Blennerhassett R, Favaloro EJ, Pasalic L. Novel (Oral) anticoagulant challenges in surgery. *Semin Thromb Hemost* 2017;43(07):706–715
- 13 Golomb BA, Evans MA. Statin adverse effects: a review of the literature and evidence for a mitochondrial mechanism. *Am J Cardiovasc Drugs* 2008;8(06):373–418

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

- 14 Cervellin G, Comelli I, Benatti M, Sanchis-Gomar F, Bassi A, Lippi G. Non-traumatic rhabdomyolysis: background, laboratory features, and acute clinical management. *Clin Biochem* 2017;50(12):656–662
- 15 Buettner C, Rippberger MJ, Smith JK, Leveille SG, Davis RB, Mittleman MA. Statin use and musculoskeletal pain among adults with and without arthritis. *Am J Med* 2012;125(02):176–182
- 16 Davidson MH, Clark JA, Glass LM, Kanumalla A. Statin safety: an appraisal from the adverse event reporting system. *Am J Cardiol* 2006;97(8A):32C–43C
- 17 Amend KL, Landon J, Thyagarajan V, Niemcryn S, McAfee A. Incidence of hospitalized rhabdomyolysis with statin and fibrate use in an insured US population. *Ann Pharmacother* 2011;45(10):1230–1239
- 18 Nichols GA, Koro CE. Does statin therapy initiation increase the risk for myopathy? An observational study of 32,225 diabetic and nondiabetic patients. *Clin Ther* 2007;29(08):1761–1770
- 19 Lippi G, Mattiuzzi C. Application of the new cholesterol guidelines. *N Engl J Med* 2014;371(01):78
- 20 Lippi G, Falavaro EJ, Sanchis-Gomar F. Venous thrombosis associated with HMG-CoA reductase inhibitors. *Semin Thromb Hemost* 2013;39(05):515–532
- 21 Crous-Bou M, Harrington LB, Kabrhel C. Environmental and genetic risk factors associated with venous thromboembolism. *Semin Thromb Hemost* 2016;42(08):808–820
- 22 Lippi G, Mattiuzzi C, Franchini M. Vegetables intake and venous thromboembolism: a systematic review. *Blood Coagul Fibrinolysis* 2016;27(03):242–245
- 23 Lippi G, Cervellin G, Mattiuzzi C. Red meat, processed meat and the risk of venous thromboembolism: friend or foe? *Thromb Res* 2015;136(02):208–211
- 24 Mattiuzzi C, Cervellin G, Franchini M, Lippi G. Fish intake and venous thromboembolism: a systematic literature review. *Clin Appl Thromb Hemost* 2016;22(04):309–313