Statin use and bleeding risk during vitamin K antagonist treatment for venous thromboembolism: a multicenter retrospective cohort study

Statins have several pleiotropic effects, beyond cholesterol synthesis inhibition, including anti-inflammatory and antithrombotic properties.[1] They have been shown to reduce the rate of venous thromboembolism (VTE), but whether this beneficial effect is counterbalanced by an increased hemorrhagic risk is still a subject of debate. Here, we report the results of a multicenter retrospective cohort study of patients taking vitamin K antagonists (VKA) for VTE. Our results suggest that statins do not increase the risk of bleeding during long-term VKA treatment.

Statin therapy may affect several steps of the blood coagulation cascade, including downregulation of tissue factor expression, increased protein C activity and factor Va inactivation, and enhanced thrombomodulin expression.[2] The effects are reduced thrombin generation and, therefore, decreased fibrinogen cleavage and platelet activation.[2] In a recent meta-analysis, the use of statins for primary or secondary cardiovascular prevention has been shown to reduce the risk of VTE by approximately 20%.[3] Furthermore, there is evidence that high-potency statins might give greater protection against recurrent VTE than low-potency statins.[4,5] On the other hand, high-dose atorvastatin was associated with increased rates of hemorrhagic stroke in a large randomized controlled trial of patients with previous stroke or transient ischemic attack (TIA).[6] However, these findings were not confirmed in a meta-analysis assessing the efficacy and safety of statins in patients with acute ischemic stroke or TIA.[7] Thus, the aim of this study was to evaluate the influence of statins on the risk of bleeding in VTE patients taking VKA.

This study is part of a project that has been described in detail in a previous publication.[8] We retrospectively included consecutive adult patients with acute VTE, either deep vein thrombosis or pulmonary embolism, who had been referred to five Italian anticoagulation clinics (Cuneo, Livorno, Mantova, Napoli, Varese) for VKA monitoring between January 2010 and August 2012. Baseline patient characteristics and the use of concomitant medications (statin and antiplatelets) were collected at the time of VTE diagnosis. Patients were included from the beginning of VKA and were followed-up for one year or until the end of treatment, whichever came first. All bleeding events were reviewed by a central adjudication committee and classified as major bleeding (MB), according to the International Society on Thrombosis and

Table 1. Characteristics of the study population divided by statin use.

	Statin-users (n=136)	Non-statin users (n=545)	*P*
Age (years), median (IQR)	60.5 (46-73.5)	63 (46-74)	0.725
Males, n (%)	61 (44.9%)	266 (48.8%)	0.409
Classic provoking factors			
Active neoplasm, n (%)	17 (12.5%)	61 (11.2%)	0.668
Recent trauma, n (%)	15 (11.0%)	47 (8.6%)	0.383
Recent surgery, n (%)	11 (8.1%)	43 (7.9%)	0.939
Unprovoked VTE, n (%)	79 (58.1%)	316 (58.0%)	0.982
Other co-morbidities			
Arterial hypertension, n (%)	75 (55.2%)	226 (41.5%)	0.004
Diabetes mellitus, n (%)	15 (11.0%)	52 (9.5%)	0.602
Dyslipidemia, n (%)	114 (83.8%)	84 (15.4%)	<0.001
Obesity, n (%)	33 (24.3%)	77 (14.1%)	0.004
Active or past smoker, n (%)	46 (33.8%)	94 (17.3%)	<0.001
Previous stroke or TIA, n (%)	13 (9.6%)	20 (3.7%)	0.004
Coronary artery disease, n (%)	23 (16.9%)	19 (3.5%)	<0.001
Atrial fibrillation, n (%)	9 (6.6%)	28 (5.1%)	0.496
Peripheral artery disease, n (%)	3 (2.2%)	4 (0.7%)	0.147
Severe renal failure*, n/N (%)	4/133 (3.0%)	9/519 (1.7%)	0.314
Thrombocytopenia**, n/N (%)	1/135 (0.7%)	11/538 (2.0%)	0.476
Treatment			
Vitamin K antagonist			
TTR (%), median (IQR)	82.5 (65-92.2)	71 (56-83.1)	<0.001
Treatment duration (months), median (IQR)	12 (6-12)	10.8 (6-12)	0.314
Concomitant antiplatelet, n (%)	19 (14.0%)	27 (5.0%)	<0.001
Statin			
Atorvastatin 10/20/40 mg, n	9/36/5	–	–
Fluvastatin 80 mg, n	3	–	–
Lovastatin 20 mg, n	1	–	–
Pravastatin 20/40 mg, n	6/1	–	–
Rosuvastatin 5/10/20 mg, n	2/21/3	–	–
Simvastatin 10/20/40 mg, n	5/38/6	–	–

*IQR: interquartile range; NA: not applicable; TIA: transient ischemic attack; TTR: time within therapeutic range; VTE: venous thromboembolism. *Severe renal failure was defined as creatinine clearance <30 mL/min (MDRD equation). **Thrombocytopenia was defined as platelet count <100*10³/mm³.*

Table 2. Statin use and bleeding complications in patients treated with vitamin K antagonists.

	N. events/ N. patients	Incidence rate (95%CI) per 100 patient-years	Crude HR (95%CI)	Adjusted HR * (95%CI)
Composite outcome				
Non-statin users	39/545	9.8 (7.2-13.4)	1.0	1.0
Statin users	11/136	10.7 (5.9-19.3)	0.93 (0.46-1.87)	0.91 (0.43-1.93)
MB only				
Non-statin users	11/545	2.8 (1.5-5.0)	1.0	1.0
Statin users	2/136	1.9 (0.5-7.8)	0.67 (0.15-3.01)	0.48 (0.10-2.44)
CRNMB only				
Non-statin users	28/545	7.0 (4.9-10.2)	1.0	1.0
Statin users	9/136	8.7 (4.5-16.8)	1.04 (0.47-2.29)	1.11 (0.47-2.63)

Sensitivity analyses for the composite outcome, divided by statins' potency

	N. events/ N. patients	Incidence rate (95%CI) per 100 patient-years
According to Biere-Rafi *et al.*[4]		
Potency I	0 / 6	–
Potency II	11 / 121	12.1 (6.7-21.8)
Potency III	0 / 8	–
According to Schmidt *et al.*[5]		
Low potency	5 / 60	10.6 (4.4-25.5)
High potency	6 / 76	10.7 (4.8-23.8)

**Adjusted for age, gender, antiplatelet treatment, TTR and stratified by Center. Biere-Rafi et al.[4] divided statins' potency in 3 classes: potency I (fluvastatin 10-20 mg, pravastatin 10-20 mg), potency II (atorvastatin 10-20 mg, fluvastatin 40-80 mg, pravastatin 40-80 mg, rosuvastatin 10 mg, simvastatin 10-80 mg) and potency III (atorvastatin 40-80 mg, rosuvastatin 20-40 mg). Schmidt et al.[5] divided statins' potency in 2 classes: low potency (fluvastatin, lovastatin, pravastatin, simvastatin) and high potency (atorvastatin, rosuvastatin).*

Haemostasis criteria,[9] or clinically-relevant non-major bleeding (CRNMB). We defined CRNMB as any overt bleeding requiring a medical intervention (hospitalization, surgical procedure, diagnostic imaging, laboratory test or specialist evaluation) and/or treatment discontinuation, and not meeting any of the criteria for MB. The primary outcome was the composite of MB and CRNMB events during VKA treatment and up to three days after discontinuation. This study was approved by the local ethics committees and is reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for observational studies.[10]

Continuous variables were reported as median with interquartile range (IQR); categorical variables as counts and percentages. The base-line characteristics of statin users and non-users were compared using the Mann-Whitney U test (for continuous variables) and the χ^2 or Fischer's exact test (for dichotomous variables). Bleeding was expressed as the number of events per 100 patient-years of observation with 95% confidence interval (CI), and compared in the two groups using the Kaplan-Meier analysis and the log rank test. The effect of statin was expressed as hazard ratio (HR) with 95%CI, and a multivariable Cox regression model was used to adjust for potential confounders [age, gender, antiplatelet treatment, time within therapeutic range (TTR)] and to stratify according to center. Missing data were managed by multiple-imputation in order to prevent the exclusion of observed data.[11] We performed two sensitivity analyses dividing statins' potency according to Biere-Rafi *et al.*[4] and Schmidt *et al.*[5] All analyses were conducted using STATA SE 12 (StataCorp LP, College Station, TX, USA).

Among the 681 patients included in our cohort, 136 (20.0%) received statins. Median age of statin-users was 60.5 years and 44.9% were males; 40.4% had pulmonary embolism. Base-line characteristics of the population are reported in Table 1. The most commonly prescribed statins were: atorvastatin (36.8%), simvastatin (36.0%), and rosuvastatin (19.1%). Apart from dyslipidemia, statin-users were also more likely to have arterial hypertension, obesity, coronary artery disease and previous stroke or TIA, than non-users. All patients received VKA, either warfarin (97%) or acenocumarol, with INR target range 2.0-3.0. Statin-users had a significantly higher median TTR (82.5% *vs.* 71%) and were also more likely to receive concomitant antiplatelet therapy (14.0% *vs.* 5.0%).

The total follow up on VKA treatment was 500.59 patient-years (pt-y) and the median VKA treatment duration was 11.1 (IQR 6-12) months. The high prevalence of unprovoked VTE and VTE secondary to permanent risk factors (such as cancer) in our cohort can explain the need for long-term secondary prevention of VTE. The composite outcome of MB and CRNMB occurred in 50 patients, 11 statin-users and 39 non-users, corresponding to bleeding incidence rates of 10.7 (95%CI: 5.9-19.3) per 100 pt-y and 9.8 (95%CI: 7.2-13.4) per 100 pt-y, respectively. The number of MB and CRNMB separately and the respective incidence rates are reported in Table 2. Twenty-three of these events (8 in statin-users and 15 in non-users) occurred with INR in therapeutic range. There was no significant difference in Kaplan-Meier curves for the composite outcome in statin-users *versus* non-users (log rank test χ^2=0.04; *P*=0.843) (Figure 1). The sensitivity analyses did not show any increasing trend according to statins' potency (Table 2).

In multivariable analysis, adjusted for potential con-

founders and stratified by center, statin use did not correlate with the risk of any bleeding, MB or CRNMB only (Table 2), while the use of antiplatelet drugs at baseline emerged as independent predictor for the composite bleeding outcome (HR 2.62; 95%CI: 1.06-6.50; *P*=0.038).

In this study, we aimed to evaluate the risk of bleeding associated with the use of statins during long-term VKA treatment for VTE. Despite the reported anticoagulant properties of statins, we found that bleeding rates were not significantly different in statin-users *versus* non-users.

Approximately one-fifth of our cohort received concomitant treatment with statins and VKAs. As expected, these patients were more likely to have cardiovascular risk factors and to receive antiplatelet treatment. Previous studies evaluating VTE patients, concurrently prescribed with statins, showed similar characteristics; however, they only assessed the risk of recurrent venous or arterial thrombotic events.[4,12] More recently, Schmidt *et al*. reported that statin use, along with oral or parenteral anticoagulation, was associated with an approximately 25% reduction in the risk of recurrent VTE at 3-year follow up, without increasing the risk of bleeding (HR 1.09; 95%CI: 0.95-1.26).[5] Nonetheless, hemorrhagic complications were identified from registry codes.[5]

Douketis *et al*. explored the relationship between statin use and the risk of bleeding in patients treated with VKA for atrial fibrillation.[13] Findings that emerged from this study were the opposite, since long-term statin use seemed to be associated with a significantly reduced risk of hospitalization for upper gastrointestinal or intracranial hemorrhage (OR 0.80; 95%CI: 0.66-0.97). However, in the absence of a biologically plausible explanation, the authors concluded that these results might be due to potential confounders, such as the "healthy-user effect", expressed in this context by a lower personal risk of bleeding.[13] Similarly, Wells *et al*. reported a modest non-significant reduction of MB with the use of statin in VTE patients randomized to VKA (HR 0.69; 95%CI: 0.36-1.32) or rivaroxaban (HR 0.92; 95%CI: 0.43-1.98).[14] In this *post hoc* analysis of randomized controlled trials, statin use was rigorously defined as a time-dependent variable, but the rate of MB in statin-users was no different to that in our cohort (2.3 per 100 pt-y).[14]

Our study has potential limitations that need to be acknowledged. First, the observational design lacks the advantage of random treatment allocation. Although it is expected that statin-users have more cardiovascular risk factors than non-users (confounding by indication), we could not exclude the presence of the "healthy-user effect". Among patients with vascular history or dyslipidemia, who indeed might benefit from statins, this treatment is usually prescribed only to those with a better life expectancy, thus the nomenclature of "healthy-users". However, in our cohort of VTE patients, bleeding risk factors appeared to be well distributed between the two groups. There was no significant difference in age and VTE provoking factors; statin-users had a greater prevalence of concurrent antiplatelet therapy, but also better anticoagulation control. Second, the use of statin was assessed at baseline, while information on the starting date and effective treatment duration was not available. Therefore, we could not perform a time-varying regression analysis. Third, cholesterol levels were available only in a minority of patients. Despite the retrospective data collection, patients included in our cohort were routinely followed by the anticoagulation clinics, providing detailed follow ups. However, unlike full blood count or renal function, lipid profile is not usually required during anticoagulant treatment. Finally, our follow-up time was not sufficiently long to evaluate the impact of statin use on the risk of recurrent VTE, which is very low during VKA treatment.

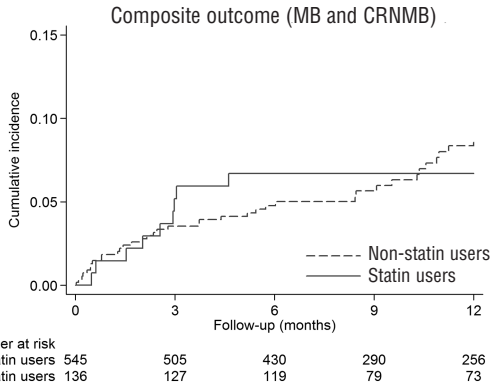

Figure 1. Kaplan-Meier curves for the cumulative incidence of bleeding events during vitamin K antagonist treatment in statin-users and non-statin users.

The main strength of our study was the specific focus on overall clinically-relevant bleeding complications during long-term VKA treatment for VTE secondary prevention in real life clinical practice. All bleeding events were centrally reviewed and rigorously classified as MB or CRNMB. In addition, the three most commonly used statins (atorvastatin, rosuvastatin and simvastatin), although administered at moderate doses, were well represented in our cohort, allowing our findings to be generalized to a statin class effect.

In conclusion, the concomitant use of statin and vitamin K antagonist appeared to be safe. This finding needs to be confirmed in larger prospective cohort studies.

Nicoletta Riva,[1] Matteo N.D. Di Minno,[2,3] Nicola Mumoli,[4] Fulvio Pomero,[5] Massimo Franchini,[6] Marta Bellesini,[1] Roberta Lupoli,[2] Silvia Sabatini,[4] Valentina Borretta,[5] Carlo Bonfanti,[6] Walter Ageno,[1] and Francesco Dentali[1]

[1]Department of Clinical and Experimental Medicine, University of Insubria, Varese; [2]Department of Clinical Medicine and Surgery, Federico II University, Naples; [3]Unit of Cell and Molecular Biology in Cardiovascular Diseases, Centro Cardiologico Monzino, IRCCS, Milan; [4]Department of Internal Medicine, Ospedale Civile Livorno; [5]Department of Internal Medicine, 'S. Croce e Carle' Hospital, Cuneo,; [6]Department of Transfusion Medicine and Haematology, Carlo Poma Hospital, Mantua, Italy

Correspondence: nico.riva@hotmail.it
doi:10.3324/haematol.2015.127183

Key words: statins, vitamin K antagonist, venous thromboembolism, bleeding, cohort study.

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

References

1. Arslan F, Pasterkamp G, de Kleijn DP. Unraveling pleiotropic effects of statins: bit by bit, a slow case with perspective. Circ Res. 2008; 103(4):334-336.
2. Undas A, Brummel-Ziedins KE, Mann KG. Anticoagulant effects of

statins and their clinical implications. Thromb Haemost. 2014; 111(3):392-400.
3. Squizzato A, Galli M, Romualdi E, et al. Statins, fibrates, and venous thromboembolism: a meta-analysis. Eur Heart J. 2010;31(10):1248-1256.
4. Biere-Rafi S, Hutten BA, Squizzato A, et al. Statin treatment and the risk of recurrent pulmonary embolism. Eur Heart J. 2013;34(24): 1800-1806.
5. Schmidt M, Cannegieter SC, Johannesdottir SA, Dekkers OM, Horváth-Puhó E, Sørensen HT. Statin use and venous thromboembolism recurrence: a combined nationwide cohort and nested case-control study. J Thromb Haemost. 2014;12(8):1207-1215.
6. Amarenco P, Bogousslavsky J, Callahan A 3rd, et al; Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med. 2006;355(6):549-559.
7. Squizzato A, Romualdi E, Dentali F, Ageno W. Statins for acute ischemic stroke. Cochrane Database Syst Rev. 2011;8:CD007551.
8. Riva N, Bellesini M, Di Minno MN, et al. Poor predictive value of contemporary bleeding risk scores during long-term treatment of venous thromboembolism. A multicentre retrospective cohort study. Thromb Haemost. 2014;112(3):511-521.
9. Schulman S, Kearon C; on behalf of the Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost. 2005;3(4):692-694.
10. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med. 2007; 147(8): 573-577. Erratum in: Ann Intern Med. 2008;148(2):168.
11. Janssen KJ, Donders AR, Harrell FE Jr, et al. Missing covariate data in medical research: to impute is better than to ignore. J Clin Epidemiol. 2010;63(7):721-727.
12. Nguyen CD, Andersson C, Jensen TB, et al. Statin treatment and risk of recurrent venous thromboembolism: a nationwide cohort study. BMJ Open. 2013;3(11):e003135.
13. Douketis JD, Melo M, Bell CM, Mamdani MM. Does statin therapy decrease the risk for bleeding in patients who are receiving warfarin? Am J Med. 2007;120(4):369.e9-369.e14.
14. Wells PS, Gebel M, Prins MH, Davidson BL, Lensing AW. Influence of statin use on the incidence of recurrent venous thromboembolism and major bleeding in patients receiving rivaroxaban or standard anticoagulant therapy. Thromb J. 2014;12:26.