Accepted: 9 May 2017

DOI: 10.1111/coa.12904

ORIGINAL ARTICLE

WILEY

Epistaxis in anticoagulated patients: Fewer hospital admissions and shorter hospital stays on rivaroxaban compared to phenprocoumon.

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Abstract

Objectives: Treatment of epistaxis in patients on anticoagulants is challenging and associated with higher admission rates and longer hospital stays compared with patients without anticoagulation. However, there is little information about epistaxis in patients taking new direct oral anticoagulants such as rivaroxaban compared with patients on traditional vitamin K antagonists such as phenprocoumon.

Design: Retrospective cohort study.

Setting: The study was conducted at the emergency department of the University Hospital Inselspital, Bern, Switzerland.

Participants: All admissions to the emergency department of the University Hospital Inselspital, Bern, Switzerland from 1st July 2012 to 30th June 2016 with non-traumatic epistaxis on anticoagulant therapy with phenprocoumon or rivaroxaban were included.

Main outcome measures: We compared clinical outcome parameters (admission rates, length of hospital stay and mortality) for both anticoagulant groups.

Results: We included 440 patients with epistaxis, 123 (28%) on rivaroxaban and 317 (72%) on phenprocoumon. Fewer hospital admissions and shorter hospital stays were found in patients under rivaroxaban (12 (10.4%) vs 57 (18.0%) patients, P=.033; 0.7±2.2 vs 1.5±3.7 days, P=.011) compared with phenprocoumon. Anterior epistaxis was more common in the rivaroxaban group in contrast to posterior epistaxis in patients on phenprocoumon (74 (60.2%) vs 139 (43.8%) patients, P=.002; 7 (5.7%) vs 39 (12.3%) patients, P=.042).

Conclusions: Our data suggests that epistaxis on direct oral anticoagulation with rivaroxaban is associated with shorter hospital stays and fewer hospital admissions than epistaxis on vitamin K antagonist phenprocoumon.

1 | INTRODUCTION

Epistaxis is a common reason for emergency department (ED) attendance, accounting for up to 1 in 200 ED visits in the United States.[1] With 20,000 hospital admissions and 36 000 hospital bed days from 2014 to 2105 in the United Kingdom, epistaxis represents a relevant burden to a medical system.[2] Antithrombotic therapy was previously found to be present in 60% of patients admitted to an ED with epistaxis.[2] Specifically, epistaxis under anticoagulant therapy with the vitamin K antagonist (VKA) warfarin is known to be associated with

an increased hospital admission rate and length of hospital stay as well as more surgical interventions compared with patients without anticoagulant therapy.[2,3]

Current guidelines on anticoagulant treatment in venous thromboembolism and atrial fibrillation recommend new direct oral anticoagulants (DOACs) over traditional anticoagulation treatment with VKAs..[4,5] As such it seems likely that patients taking DOACs will become increasingly common in the ED. However, a recent review of epistaxis patients found a lack of studies including patients treated with DOAC and could not identify a direct comparison of patients under DOAC or VKAs.[2] Only a few case reports about the management of patients with epistaxis on DOAC therapy exist.[6,7] Although severe bleeding complications in DOAC patients are rare, epistaxis was found to be one of the most frequent minor bleeding complication in patients on DOAC therapy.[8]

To our knowledge, no study has yet described the characteristics of ED patients with epistaxis during DOAC therapy, nor did we find a direct comparison of DOACs and VKAs in patients presenting with epistaxis.

Our study seeks to describe the characteristics of ED patients with epistaxis treated with rivaroxaban compared to those with phenprocoumon.

Additionally this study aims to identify differences in outcome (admission rate, length of hospital stay and mortality) associated with the two different types of anticoagulant therapy in this population.

Keypoints

- Epistaxis is a common reason for emergency department attendance and a relevant burden to a medical system.
- Epistaxis on direct oral anticaogulation with rivaroxaban is associated with shorter hospital stays and fewer hospital admissions than epistaxis on vitamin K antagonist phenprocoumon.

2 | METHODS

2.1 | Ethical considerations

This retrospective cohort study is registered with the ethics committee of the Canton Bern, Switzerland (Number 073/2015).The responsible ethics committee of the Canton Bern, Switzerland waived the need for informed consent because of the sole use of anonymised data collected during routine patient care.

2.2 | Study design

The study population included all admissions to the emergency department (ED) of the University Hospital Inselspital, Bern, Switzerland from 1st July 2012 to 30th June 2016. The ED has a catchment area of about 2 million people in the Canton Bern, Switzerland and treats about 40 000 patients per year.[9]

To include all anticoagulant patients older than 18 years of age who were treated for epistaxis, a full-text search in the emergency department information system (E.care, Turnhout, Belgium) was performed for the medications "phenprocoumon" and "rivaroxaban" and then screened for the keywords "epistaxis" or "nosebleed" and variations in spelling. Because diagnoses and procedures are documented in free text in our ED and ICD or OPCS codes are generated only afterwards for billing purposes, free text arguably reflects the medical conditions and necessities more closely and free of economic considerations. As rivaroxaban is by far the DOAC with the highest prevalence in our emergency patient population, our investigation focused on patients taking this DOAC. Similarly phenprocoumon is the coumarin most commonly prescribed in our catchment area. Patient without documented anticoagulant therapy or those without epistaxis at the time of admission were excluded (Figure 1). We further excluded all trauma patients due to the different mechanism of epistaxis in this population.

2.3 | Variables

We collected demographic data (age, gender, nationality), patient outcome data (hospital admission, length of hospital stay, ED- and in-hospital mortality), medical data (indication for anticoagulant therapy, additional platelet-anticoagulation therapy, blood pressure), specific factors concerning epistaxis (location of bleeding, ED

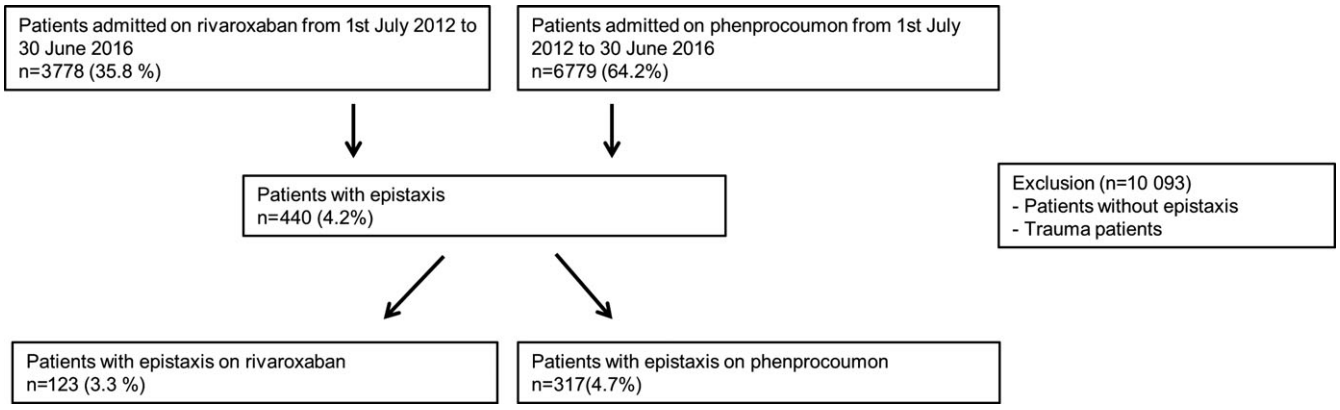

FIGURE 1 Flow chart

therapy, need for blood transfusion) and laboratory results at admission (creatinine, international normalised ratio (INR), haemoglobin (Hb), thrombocytes). In our university, ED patients with epistaxis are treated by otolaryngologists. Thus, for the majority of patients the location of bleeding could be detected by nasal endoscopy and documented in the medical records.

2.4 | Statistical analysis

Statistical analysis was performed in SPSS Statistics version 22 (IBM Zurich, Switzerland) with statistical significance defined as a *P*-value <.05.

Descriptive statistics were used to describe patient's baseline characteristics. Patient demographic data, administrative data, medical data and laboratory results were compared using Mann-Whitney U, Pearson's chi-squared and Fisher's exact test, as applicable.

3 | RESULTS

The database search of about 160 000 ED admissions total during 4 years returned 3778 patients on DOAC anticoagulant therapy with rivaroxaban and 6779 patients on VKA therapy with phenprocoumon (see Figure 1). These included 440 epistaxis patients of which 123 patients were on DOAC therapy (28%) and 317 patients on VKA (78%).

The demographic characteristics of both groups are summarised in Table 1. Groups were found to be comparable regarding age (75.8±11.2 years [DOAC] vs 75.2±11.7 years [VKA]; *P*=.727) and gender (78 male DOAC patients (63%) vs 196 male VKA patients (62%); *P*=.758). There was no significant difference in the indications for anticoagulation therapy between the DOAC and VKA group apart from the group of patients with mechanical heart valves, for which the use of DOACs is currently not approved (0 patients (%) vs 21 patients (7%); *P*=.003*). To assess whether or not differences between groups were due to a higher target-INR in patient anticoagulated for mechanical heart valves, we tested for differences in INR between VKA patients with (INR mean 2.58±0.78) and without (INR mean 2.63±0.88) mechanical heart valve and found no significant difference (*P*=.818).

TABLE 1 Baseline characteristics of the study cohort according to type of anticoagulant (n=440)

Characteristics	Rivaroxaban n=123 (28%)	Phenprocoumon n=317 (78%)	*P*-value
Patient data			
Age (y)	75.8 ± 11.2	75.2 ± 11.7	.727
Gender (male)	78 (63%)	196 (62%)	.758
Nationality (Swiss)	113 (92%)	302 (95%)	.167
Indication for anticoagulant therapy(%)			
Atrial fibrillation	55 (45)	120 (38)	.187
Thromboembolic event	15 (12)	50 (16)	.343
Post-surgery	2 (2)	11 (4)	.530
Mechanic heart valve	0 (0)	21 (7)	.003*
Not documented	50 (41)	122 (39)	.676
Additional platelet-aggregation-inhibitor therapy(%)			
Acetylsalicylate acid	16 (13.0)	25 (7.9)	.097
Clopidogrel	5 (4.1)	5 (1.6)	.151
Acetylsalicylate acid and clopidogrel	1 (0.8)	9 (2.8)	.296
Prasugrel	1 (0.8)	0 (0)	.280

Mean ±standard deviation or percentage (%) as appropriate, Mann-Whitney U, Pearson's Chi-Square or Fisher's exact test as applicable. *$P<.05$.

Additional platelet-aggregation-inhibitor therapy was documented in 23 (18.7%) patients with DOACs and 39 (12.3%) patients with VKAs (*P*=.084). For details about antiplatelet medication see Table 1. Vital signs and blood results of both groups at admission are summarised and compared in Table 2.

Comparing the location of epistaxis as documented in transnasal endoscopy, we found a larger proportion of anterior epistaxis in DOAC patients. In contrast, more VKA patients presented with posterior epistaxis (anterior: 74 (60.2%) DOAC vs 139 (43.8%) VKA; *P*=.002*; posterior: 7 (5.7%) DOAC vs 39 (12.3%) VKA, *P*=.042*). Regarding emergency treatment, no significant difference was found (Table 2).

The comparison of outcome parameters revealed an increased hospital admission rate in VKA patients with epistaxis (12 (10.4%) DOAC vs 57 (18.0%) VKA, *P*=.033*).

Of those admitted, the length of hospital stay was significantly shorter in epistaxis patients on DOACs in comparison with patients on VKAs (0.7±2.2 days [DOAC] vs 1.5±3.7 days [VKA], *P*=.011*).

No patient died in the ED and there was no significant difference regarding in-hospital mortality (one patient (0.8%) [DOAC] vs three patients (0.9%) [VKA], *P*=1.000).

4 | DISCUSSION

4.1 | Synopsis of key findings

This retrospective cohort study demonstrates a significantly lower hospital admission rate and a significantly reduced length of hospital stay in patients on rivaroxaban compared with those treated with phenprocoumon. Furthermore, we found that anterior epistaxis in patients treated with the DOAC rivaroxaban is significantly more likely than in patients with the VKA phenprocoumon. In contrast to this, the prevalence of posterior epistaxis was found to be significantly higher in patients on phenprocoumon compared with rivaroxaban.

4.2 | Characteristics of ED patients with epistaxis on the DOAC rivaroxaban compared to patients with epistaxis on the VKA phenprocoumon

The patient groups included in our analysis are similar in demographic characteristics. However, the sample age overall is older than a previously published population of unselected patients with

TABLE 2 Clinical characteristics, treatment and outcome of patients according to type of anticoagulant (n=440)

Variables	Rivaroxaban n=123 (28%)	Phenprocoumon n=317 (78%)	*P*-value
Vital signs			
BPsys (mm Hg)	145.6±36.8	146.4±34.1	.838
BPdia (mm Hg)	73.1±24.1	80.9±20.2	.056
Blood results			
Creatinine (μmol/l)	104.5±42.5	113.1±58.5	.665
INR	1.28±0.28	2.63±0.87	<.001*
Haemoglobin (g/L)	125.4±17.7	124.7±23.4	.826
Thrombocytes (G/L)	209.9±87.0	212.1±76.7	.883
Location of epistaxis(%)			
Anterior	74 (60.2)	139 (43.8)	.002*
Diffuse	1 (0.8)	16 (5.0)	.050
Posterior	7 (5.7)	39 (12.3)	.042*
Not documented or not visualised in endoscopy	41 (33.3)	123 (38.8)	.287
Treatment(%)			
No therapy needed	0 (0)	6 (1.9)	.192
Cauterisation	39 (31.7)	86 (27.1)	.339
Nasal packing	29 (23.6)	85 (26.8)	.487
Cauterisation and nasal packing	22 (17.9)	42 (13.2)	.216
Surgery	0 (0)	2 (0.6)	1.000
Not documented	33 (26.8)	96 (30.3)	.475
Blood transfusion needed	2 (1.6)	3 (0.9)	.622
Outcome parameter			
Hospital admissions	12 (10.4%)	57 (18.0%)	.033*
Length of hospital stay (days)	0.7±2.2	1.5±3.7	.011*
ED mortality	0 (0%)	0 (0%)	1.000
In-hospital mortality	1 (0.8%)	3 (0.9%)	1.000

Mean ±standard deviation or percentage (%) as appropriate, independent samples *t*-test, Mann-Whitney U and Pearson's Chi-Square or Fisher's exact test as applicable.

INR, International normalised ratio; BPsys, systolic blood pressure; BPdia, diastolic blood pressure; bpm, beats per minute; ED, emergency department. *$P<.05$.

epistaxis in general.[10] This older age of epistaxis patients on anticoagulant therapy is consistent with the findings of Smith et al.[3] The main indication for anticoagulation in our study was atrial fibrillation (regardless of which anticoagulant was used). Increasing prevalence of atrial fibrillation with older age may explain the relatively older age of our population.

Laboratory results at admission were similar in both groups, apart from the INR. This is not surprising, given the fact that rivaroxaban has no linear effect on the INR and cannot be monitored using the INR. Nevertheless, the low INR values documented in patients with prescribed rivaroxaban are interesting, given the fact that normally INR raises 2-12 hours after rivaroxaban intake. With our retrospective data it remains unclear if patients on rivaroxaban were undertreated or if the time point of rivaroxaban intake was too long before ED admission. Therefore, further prospective investigations including rivaroxaban activity measurements and the exact time point of last DOAC intake would be valuable. Impaired renal function could potentially lead to an accumulation of DOACs in contrast to VKA, but creatinine was similar in both patient groups.

A number of patients in both groups were treated with additional antiplatelet medication. Antiplatelet medications have been shown to result in more complicated and longer hospital stays in epistaxis patients.[3] A previous study showed an increased length of hospital stay for patients on VKA and antiplatelet medication as compared to VKA alone.[3] To our knowledge, a comparable investigation about the combination of antiplatelet therapy with DOAC therapy in epistaxis patients does not yet exist. In our population, we could not demonstrate a significant difference between the VKA and DOAC group regarding additional antiplatelet use. Thus, differences in outcomes observed between the two groups most likely result from treatment with either a VKA or a DOAC, not from differences in antiplatelet co-medication.

4.3 | Differences in outcome between patients on the DOAC rivaroxaban compared with patients on the VKA phenprocoumon

Fortunately, no patient died in the ED. The mortality rate during hospital stay was not significantly different and equally low in both groups.

The hospital admission rate was significantly lower and the length of hospital stay significantly shorter in patients with epistaxis under the DOAC rivaroxaban compared with VKA epistaxis patients.

The primary reason for these differences may be the much shorter half-life of rivaroxaban compared with phenprocoumon.

Although no specific antidote for rivaroxaban is available at the moment, stopping the DOAC leads to a rapid normalisation of haemostasis, and therefore, treatment may be faster and early removal of nasal packing is more likely to be successful compared to patients on VKA. Furthermore, restarting or adjusting the therapeutic range of VKAs is more complex than for DOACs and may thus contribute to the longer hospital stay and higher admission rate in the former group.

The difference in bleeding location may contribute as well to the differences in outcome observed in this study. While anterior bleedings are (i) easily accessible to the physician and (ii) usually well treatable with local coagulation, anterior tamponade or other conservative measures, posterior lesions are harder to reach and posterior packs are more difficult to place and more uncomfortable for the patient. Posterior packing is therefore likely to require an increasing number of hospital admissions for monitoring purposes.[11,12]

4.4 | Clinical applicability of the study

Minor bleeding complications such as epistaxis are frequent in patients under anticoagulant medication and thus pose a relevant medical, social and economic challenge. The differences in outcome between patients with epistaxis treated with either the DOAC rivaroxaban or the VKA phenprocoumon have not previously been described and should now add further weight to the evidence for prescribing DOACs in preference over VKAs. Further research regarding the transferability of these results to patients treated with other VKAs like warfarin is recommended.

4.5 | Limitations

Despite a careful review of all available documentation, it is possible that not all eligible patients were included in this study due to potential documentation biases. However, this bias can reasonably be expected to be evenly distributed between groups and thus should not affect the conclusions of this study. As our hospital is a university hospital, epistaxis patients that are treated in our ED are most likely subject to a selection bias. This limitation should however be the same for both anticoagulants investigated in this study as well. Because we excluded traumatic epistaxis from our study to avoid a too heterogeneous patient population with different mechanisms of epistaxis, the role of anticoagulation in this patient group should be subject to further research. Furthermore the different size of groups compared with our investigation reflects the lower prevalence of DOACs compared to VKAs in our consecutive sample of ED admissions.

Due to the retrospective study design, no comparison of patient groups with different dosages of rivaroxaban and different time points of last intake was possible, because neither of these information is routinely documented. Future studies should address the possibility that the differences observed in this study are ascribable to patients having a very distant intake of the last dose of DOAC compared to patients on VKAs.

One key difference between both groups is that patients with mechanical heart valves are often anticoagulated with a VKA. To assess the suspicion that these patients might be targeted towards a higher INR and that this may in turn explain the differences observed in this study, we compared INR in patients with and without mechanical heart valves. Failure to find a difference between these patients may however be due to a lack of power as the group with mechanical valves is comparatively small (only about 10% of all patients under VKA).

The number of cases with incomplete documentation of some parameters, owed to the retrospective study design, was not significantly different between the compared groups and therefore should not compromise the results. Nevertheless, further prospective studies should be conducted to confirm our results.

Inclusion of other DOACs than rivaroxaban in such a study would be desirable. It was not possible in our analysis due to the small number of patients on other DOAC medications admitted to our ED. Further research should be performed in the future, including a comparison of patients treated with different DOACs.

In our population, no standardised approach to the treatment of epistaxis in patients with DOAC anticoagulation was used. Therefore, we can only describe the treatment in our patients and are unable to recommend a best therapeutic approach in epistaxis patients under DOAC anticoagulant therapy. Further prospective research about specific therapies of epistaxis in patients with such anticoagulant treatment is needed.

5 | CONCLUSION

Our study suggests that epistaxis on the DOAC rivaroxaban is associated with shorter hospital stays and less hospital admissions compared to epistaxis on vitamin K antagonist phenprocoumon. The increased number of anterior and lower number of posterior epistaxis in rivaroxaban compared to patients treated with phenprocoumon may partially contribute to this observed outcome differences.

Further research on epistaxis on anticoagulants and specifically on DOAC therapy as well as other VKAs like warfarin is necessary.

ACKNOWLEDGEMENTS

The authors want to thank the Gottfried und Julia Bangerter-Rhyner Foundation for their funding of DOAC research at the Inselspital, University Hospital Bern.

CONFLICT OF INTEREST

TCS has received research grants or lecture fees from Bayer, Boehringer Ingelheim, and Daiichi-Sankyo and Gottfried und Julia Bangerter-Rhyner Foundation. MN has received research grants or lecture fees from Bayer, CSL Behring, Roche diagnostics, and Instrumentation Laboratory. WEH has received financial compensation for educational consultancies from the AO Foundation, Zurich. AKE is member of the advisory boards of all registered DOACs. No conflicts of interest are reported from GK, MER, KH and UB.

AUTHOR CONTRIBUTION

TS designed the study, drafted the manuscript and performed statistical analyses of data. MN contributed to the study design and critically revised the manuscript. WEH contributed to the study design, performed statistical analyses and helped with the interpretation of data and critically revised the manuscript. MER helped with the study design, and helped with the interpretation of data. KH collected data, helped with the interpretation of data and critically revised the manuscript. AKE helped with the study design, helped with the interpretation of data and critically revised the manuscript. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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How to cite this article: Sauter TC, Hegazy K, Hautz WE, et al. Epistaxis in anticoagulated patients: Fewer hospital admissions and shorter hospital stays on rivaroxaban compared to phenprocoumon.. *Clin Otolaryngol*. 2017;00:1–6. https://doi.org/10.1111/coa.12904