Management and outcome of epistaxis under direct oral anticoagulants: a comparison with warfarin

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Background: Epistaxis is one of the more common reasons for emergency room visits. The main risk factor for epistaxis is anticoagulant therapy. Until recently, the main culprit was oral intake of a vitamin K antagonist, such as warfarin, which has a number of side effects. Even more recently, several direct oral anticoagulants, rivaroxaban and dabigatran, have been approved for use. We investigated the possible differences between treatment of epistaxis with direct oral anticoagulants and vitamin K antagonists.

Methods: We conducted a retrospective cohort study at a tertiary referral center in Germany. All patients who were admitted within a 1-year period were included. Patient files were used to obtain the information.

Results: Overall, 677 patients were included in our study. Of these, 159 had been treated with vitamin K antagonists and 49 with direct oral anticoagulants. There were no significant differences in terms of age (p = 0.592), sex (p = 0.372), vital signs, bloodwork, or location of bleeding (p = 0.372). Management of epistaxis between the groups was also comparable (p = 0.399), with similar hospital admission rates (37.1% vs 24.5%; p = 0.145) and duration of stay (3.5 ± 2.1 days vs 3.8 ± 3.3 days; p = 0.650).

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Conclusion: We found no evidence to suggest epistaxis is more severe or requires more invasive therapy in patients given direct oral anticoagulants. A significant proportion of patients on vitamin K antagonists were not within the target range for international normalized ratio, highlighting one of the main issues with oral anticoagulation by vitamin K antagonists. ©2018 ARSAAOA,

Key Words: epistaxis; hemorrhagic disorders; nose models

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The average person has a probability of approximately 60% of having epistaxis at
least once during their lifetime. Although this number is relatively high, only 6% of cases require professional medical attention. Nonetheless, epistaxis makes up 0.5-1% of all emergency department visits. There are several risk factors for developing epistaxis and requiring medical attention, but the major cause of severe epistaxis is compromised hemostasis. The severe version of the condition is associated with more aggressive local hemostatic measures as well as more frequent and prolonged hospital stays.

This is usually a desired therapeutic effect and can be achieved by preventing either the aggregation of thrombocytes, as is done by antithrombocytic medication such as acetylsalicylic acid or clopidogrel, or inhibition of plasmatic hemostasis. Until recently, the latter was mainly achieved by oral intake of vitamin K antagonists (VKAs) like warfarin or phenprocoumon, derivates of coumarin that prevent recycling of vitamin K and thus decrease the synthesis of vitamin K–dependent hemostatic proteins. However, in recent years, the United States Food and Drug Administration and respective national authorities have approved new direct oral anticoagulants (DOAs). These agents are considered "direct" because these act by directly inhibiting the plasmatic coagulant factors Xa (eg, rivaroxaban) or IIa (eg, dabigatran). Because management of oral plasmatic anticoagulation by VKAs is known to have a number of side effects due to a narrow therapeutic range, DOAs are believed to have a better risk profile in this respect.

There are few data available addressing the topic of epistaxis under DOAs, so we investigated the characteristics of patients admitted to the emergency department of the University Hospital Bonn for treatment of epistaxis and who were being treated with DOAs.

Patients and methods

This study was registered with the ethics committee of the University of Bonn under ongoing file number 199/17. The ethics committee waived the need for informed consent because the study was limited to sole data collection during regular standard practice. Further, there were no changes in treatment as a consequence of this investigation.

Data collection

Our study included all patients who were treated in the emergency department or the ear, nose, and throat (ENT) clinic at the University Hospital Bonn during the period from May 1, 2013 to April 30, 2014. The University Hospital Bonn is a tertiary referral hospital that has a catchment area of approximately 1 million people and serves up to 5500 ENT emergencies per year.
To identify patients who had been treated for epistaxis, any patient who had been registered with the ICD-10 code for epistaxis (R04.0) upon admission was included in the study. Patients’ files were then used for data collection. Overall, 677 patients were treated for epistaxis in the given period.

Patients under 18 years of age who had previously suffered nasal trauma or who had inherent or acquired hemorrhagic diathesis were excluded from the study.

After each patient was identified, patients’ files were used to acquire data regarding age, sex, medication, mode of transportation to the clinic, whether there was active bleeding upon admission, vital signs (systolic and diastolic blood pressure, pulse, oxygen saturation, respiratory rate, body temperature), bloodwork (creatinine, international normalized ratio [INR], hemoglobin [Hb], thrombocytes), and location and treatment of the bleeding. Only the data collected upon admission were included in the study.

The data of the patients without oral anticoagulation are included in the Supplementary Material online.

All patients were treated by an ENT physician either in the ENT clinic or the emergency room, depending on the time of day when the patient presented. There were no differences in terms of technical setup between the ER or the ENT clinic.

We classified both the endoscopic endonasal surgery administered to stop the bleeding and the radiologic intervention as “surgery,” as both treatment forms involve invasive action with considerable sedation or even general anesthesia. If the surgery is performed to control epistaxis, the vessel in charge for blood supply of the region of nasal mucosa where the bleeding took place is ligated—in this study, this was exclusively the sphenopalatine artery. Concomitant septoplasty was performed if necessary for surgical access to the vessel.

Nasal packing was performed exclusively in an anterior fashion; routinely, a commercial nasal tamponade is installed (Latex Schaumstoff-Nasentamponaden, Spiggle & Theis, Overath, Germany). If installation of this tamponade was not possible, nasal packing with cotton strips imbued with petroleum jelly was performed. The packing was left in the nasal cavity and routinely removed after 2 days. During this time, the nasal packing was left in place, and no antimicrobial agents were prescribed.

Statistics

Statistical analysis was carried out using Project R for Macintosh (Build version 3.4.1 for El Capitan, R Project for Statistical Computing, http://www.r-project.org/). To detect significant differences between the 2 groups, the Wilcoxon-Mann-Whitney test was used for comparison of mean
values, and Pearson’s chi-square test was used to assess distribution of characteristics.</p>

## Results

### Demographics

During the study period, 677 patients were admitted to the University Hospital Bonn with the diagnosis of epistaxis. Among these, 159 received treatment with oral VKAs and 49 were treated with DOAs (42 rivaroxaban, 6 dabigatran, 1 apixaban). The groups had no statistical differences in terms of age (75.3 ± 11.0 years vs 76.8 ± 9.8 years; p = 0.592) and sex (101 male [63.5%] vs 27 male [55.1%]; p = 0.372; \{TBL 1\}Table 1). In addition, treatment with antiplatelet medication was comparable between the 2 groups (acetylicsalicylic acid [ASA]: 23 [14.5%] vs 4 [8.2%]; clopidogrel: 7 (4.4%) vs 2 (4.1%); combination of antiplatelet drugs: 13 [8.2%] vs 4 [8.2%]; p = 0.711).

### Presentation of patients

In the VKA treatment group, 78 (49.7%) patients were transported to the clinic by ambulance, whereas, in the DOA group, 17 (34.7%) patients were transported by ambulance. This difference was not significant (p = 0.110). Active bleeding upon physician consultation occurred in 115 (72.3%) and 35 (71.4%) patients, respectively. This difference was also not significant (p = 1.000; \{TBL 2\}Table 2).

### Vital signs upon admission

Systolic (151.5 ± 28.7 mmHg, n = 141 vs 149.4 ± 23.2 mmHg, n = 47; p = 0.814) and diastolic (86.4 ± 17.0 mmHg, n = 140 vs 84.2 ± 12.9 mmHg, n = 44; p = 0.403) blood pressures were comparable for the 2 groups. This was also the case for pulse (84.3 ± 16.8 min⁻¹, n = 138 vs 84.3 ± 17.9 min⁻¹, n = 43; p = 0.936), partial pressure of oxygen (97.0 ± 3.0%, n = 138 vs 97.0 ± 1.9%, n = 43; p = 1.000), respiratory rate (15.7 ± 1.6 min⁻¹, n = 138 vs 15.3 ± 1.5 min⁻¹, n = 43; p = 0.334), and body temperature (36.2 ± 0.5°C, n = 135 vs 36.3 ± 0.4°C, n = 43; p = 0.414).</p>

### Bloodwork upon admission

Bloodwork upon admission showed no significant differences in hemoglobin (13.1 ± 2.1 g/dL, n = 140 vs 12.8 ± 1.8 g/dL, n = 40; p = 0.219), thromboocytes (234.1 ± 84.5 × 10⁸/µL, n = 97 vs 236.6 ± 69.3 × 10⁸/µL, n = 25; p = 0.650), or creatinine (1.5 ± 1.4 mg/dL, n = 78 g/dL, n = 40; p = 0.219).
vs 1.3 ± 0.4 mg/dL, n = 24; p = 0.322). Two patients in the DOA group had a creatinine of >2.0 mg/dL.

INR was significantly different between the VKA and DOA groups (3.0 ± 1.2 vs 1.2 ± 0.2, n = 139 vs 26; p < 0.001). In particular, 53 patients had an INR outside the therapeutic target range: 13 with an INR < 1.5 and 40 with an INR of > 3.5.

**Location of bleeding**

Bleeding sites were comparable between the groups, with 75 (48.4%) and 22 (44.9%) bleeding sites, respectively, located on the right side; 73 (47.1%) and 22 (44.9%), respectively, on the left; and 7 (4.5%) and 15 (30.2%), respectively, on either both sides or caused by a perforation. The bleeding sites were distributed independently (p = 0.336).

For endonasal localization of bleeding in VKA patients, 82 had anterior bleeding (51.6%), 18 had diffuse bleeding (11.3%), 21 had posterior bleeding, and the bleeding site could not be located or was undocumented in 38 patients (23.9%). In the DOA patients, 29 presented with anterior bleeding (59.2%), 7 with diffuse bleeding (14.3%), and 6 with posterior or unlocated bleeding, respectively (12.2% each). There was no association between location of bleeding site and treatment (p = 0.372).

**Therapy of bleeding**

Of the patients in the VKA group, 104 (66.2%) had their epistaxis treated by cauterization of the bleeding site, 34 (21.7%) needed nasal packing, and 7 (4.5%) needed a combination of both cauterization and nasal packing. Two (1.3%) patients had to undergo surgery and 10 (6.4%) did not require invasive treatment. In the DOA group, 30 (61.2%) patients underwent local coagulation to control the bleeding, 8 (16.3%) needed nasal packing, and 3 (6.1%) were treated with a combination of coagulation and nasal packing. Further, 2 (4.1%) patients had to undergo surgery to control the bleeding, whereas 6 (12.2%) required no invasive measurements at all. There were no significant differences between type of bleeding therapy between the VKA and DOA groups (p = 0.399).

**Patient follow-up**

Of the patients who received VKA oral anticoagulation, 59 (37.1%) needed to be hospitalized. Of the patients with DOA treatment, 12 (24.5%) required hospitalization. This difference was not significant (p = 0.145). The length of hospital stay was similar between the groups (3.5 ± 2.1 days vs 3.8 ± 3.3 days; p = 0.650). No patients died during their hospital stay and only 1 patient, from the VKA cohort, needed a single transfusion of 2 erythrocyte...
concentrates.

Discussion

General characteristics of anticoagulated patients

Overall, the general characteristics of patients with DOA treatment are in line with previous findings. The fact that there were more than 3 times as many patients on VKA agonist therapy compared with DOA therapy can be explained by the relative novelty of DOA utilization when this study was conducted and in part by physicians being more comfortable handling oral VKA therapy than DOA therapy. In addition, DOA therapy continues to be more expensive than VKA therapy, although the number of DOA prescriptions has been rising.

Age, sex, and concomitant antiplatelet therapy were comparable between the 2 groups. In terms of bloodwork upon admission, both groups were also comparable, apart from INR, which was significantly lower in the DOA group. This was attributable to the different modes of action of DOAs and VKAs. VKA anticoagulation inhibits the synthesis of clotting factors X, IX, VII, and II, and therefore directly affects INR. DOAs, on the other hand, directly inhibit the activated forms of factors II or X, respectively, and therefore may, but do not regularly affect INR.

Overall, we found no evidence that epistaxis was more severe in either of the 2 groups examined. In particular, the numbers of patients treated with nasal packing or surgery, the more invasive forms of epistaxis management, were comparable between the groups. This finding contradicts earlier findings. Similarly, there was no difference between the 2 groups with regard to other forms of management.

The locations of epistaxis in terms of site and intranasal location were comparable between the DOA and VKA groups. The hospital admission rate was considerably lower in the DOA group, yet not to a significant extent. However, Sauter and colleagues showed that hospital admission rates were actually lower in DOA recipients in their somewhat larger study. The relatively high admission rate in our study groups may be attributed to the national legislation that effectively requires admission of every patient for inpatient treatment with nasal packing. In addition, all patients showing signs of overdose of an oral anticoagulant agent were also admitted and oral anticoagulation was then subsequently switched to a low-molecular-weight heparin, so that patients could be referred to a cardiologist for reevaluation of their anticoagulant medication.

Unfortunately, we cannot account for the overall risk of any form of epistaxis under DOA or VKA therapy, as no data on their overall prescription rates were available for the period of study.
However, there is evidence in the literature suggesting that the general risk for bleeding events, which include but are not limited to epistaxis, is significantly lower in DOA patients compared with VKA patients.\(^\text{12,13}\)

**VKA vs DOAs**

We found that almost one third of patients presenting with epistaxis while on a VKA exhibited INR values outside the target range (\(<1.5\) or \(>3.5\)). This finding replicates the results of 2 large studies.\(^\text{14,15}\) INR values \(<1.5\) may be due to circadian oscillations in INR under oral anticoagulation by warfarin and are most likely not indicative of unsuccessful anticoagulation. Values \(>3.5\) highlight one of the main difficulties in oral anticoagulation with VKA: the dosing is difficult and needs constant monitoring. We found indications of DOA overdose in only 2 patients, who presented with considerably elevated serum creatinine, suggesting DOA accumulation caused due to renal insufficiency.

In addition, VKAs have a considerable half-life, and there is no direct VKA antidote if severe bleeding of any kind occurs. Phyllochinon can be substituted orally or intravenously and, in severe cases, fresh-frozen plasma may be transfused. In contrast, DOAs are eliminated quickly from the body by renal and hepatic pathways. In addition, DOA dosing is straightforward and comfortable for the patient. Finally, in the case of severe bleeding, fast-acting antidotes have been introduced, like idarucizumab, and others are in the process of being developed, like andexanet-alfa\(^\text{17}\) or ciraparantag.\(^\text{18}\)

**Limitations**

There are some limitations to this study. First, data collection was conducted in a retrospective fashion and limited to what had been noted in the patient file. In addition, the data were collected at a single institution. Although our institution is situated in an urban area, some of its catchment includes rural areas, which may have different prescription practices for DOAs.

**Conclusion**

We have succeeded in showing that epistaxis and its management under DOA therapy is no more severe or invasive than under VKA therapy. As in other studies, we found that stationary admission of epistaxis under DOA therapy was lower, yet in this case not statistically significant.

**References**


{\text{TBL1}}<\text{TC}>

\textbf{TABLE 1.} Age, sex, and concomitant antiplatelet medication of patients

<table>
<thead>
<tr>
<th>No plasmatic anticoagulation (n &amp;= 469)</th>
</tr>
</thead>
</table>
| **Age** | 60.5 &plusmn; 19.8  
| **Gender (male)** | 321 (68.4%)  
| Additional anticoagulation |  
| Acetylsalicylicacid | 52 (11.1%)  
| Clopidogrel | 5 (1.1%)  
| Combination | 15 (3.2%)<\text{TB}>  

\text{a} Wilcoxon-Mann-Whitney test.

\text{b} Pearson’s chi-square test.<\text{TF}>

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{TBL1}</TC>

<<enote>>AQ1: AU: Please indicate where superscripts should position in table.
TABLE 2. Vital signs, bloodwork, and bleeding features of patients

<table>
<thead>
<tr>
<th>No plasmatic anticoagulation (n = 469)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transportation to clinic by ambulance</td>
</tr>
<tr>
<td>Active bleeding upon consultation</td>
</tr>
<tr>
<td>Vital signs</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
</tr>
<tr>
<td>Pulse</td>
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<tr>
<td>Partial pressure of oxygen</td>
</tr>
<tr>
<td>Breathing frequency</td>
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<tr>
<td>Body temperature</td>
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<tr>
<td>Bloodwork upon admission</td>
</tr>
<tr>
<td>Creatinine</td>
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<tr>
<td>International normalized ratio</td>
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<tr>
<td>Hemoglobin</td>
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<tr>
<td>Thrombocytes</td>
</tr>
<tr>
<td>Location</td>
</tr>
<tr>
<td>Left</td>
</tr>
<tr>
<td>Right</td>
</tr>
<tr>
<td>Both/perforation</td>
</tr>
<tr>
<td>Anterior</td>
</tr>
<tr>
<td>Diffuse</td>
</tr>
<tr>
<td>Posterior</td>
</tr>
<tr>
<td>Not located/documented</td>
</tr>
</tbody>
</table>

*a* Wilcoxon-Mann-Whitney test.

*b* Pearson’s chi-square test.

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TABLE 3. Therapy and patient follow-up

<table>
<thead>
<tr>
<th>Therapy and Follow-up</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>No invasive therapy</td>
<td>80 (17.1%)</td>
</tr>
<tr>
<td>Cauterization</td>
<td>248 (53.1%)</td>
</tr>
<tr>
<td>Nasal packing</td>
<td>113 (24.1%)</td>
</tr>
<tr>
<td>Cauterization and nasal packing</td>
<td>8 (1.7%)</td>
</tr>
<tr>
<td>Surgery</td>
<td>20 (4.3%)</td>
</tr>
</tbody>
</table>

Follow-up

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Hospital admission</td>
<td>99 (21.1%)</td>
</tr>
<tr>
<td>Length of hospital stay</td>
<td>4.0 ± 2.4 days</td>
</tr>
<tr>
<td>Erythrocyte transfusions</td>
<td>6 (1.3%)</td>
</tr>
<tr>
<td>Number of erythrocytes transfused</td>
<td>2 ± 0</td>
</tr>
</tbody>
</table>

<sup>a</sup> Wilcoxon-Mann-Whitney test.

<sup>b</sup> Pearson’s chi-square test.

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