Novel oral anticoagulation treatment is not associated with recurrent or severe epistaxis*

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To the Editor:

So far, a number of risk factors for epistaxis such as thrombocyte aggregation inhibitors (TAI) with aspirin or clopidogrel as well as classic oral anticoagulation (cOAC) treatment with vitamin K antagonists (VKA) have been identified [1-3]. With the advent of novel oral anticoagulant drugs (NOAC) [4] and due to the guideline changes in the treatment of venous thromboembolism and atrial fibrillation [5,6], patients on NOAC are becoming increasingly more common in the ED [2]. Few publications exist that evaluate the impact of NOAC on epistaxis and its complications. Hence, the aim of our large retrospective study was to analyze whether the treatment with NOACs is associated with recurrent or more severe epistaxis events especially when compared to patients with cOAC, TAI or without such medication.

We reviewed the history of 675 patients treated for epistaxis in our ENT emergency clinic with a total of 1606 epistaxis episodes in the period between April 2015 until end 2018. Data of 487 patients, who met the inclusion criteria, with a total of 745 documented epistaxis episodes were analyzed. Exclusion criteria were nasal trauma, sinonasal carcinoma, hereditary hemorrhagic teleangiectasia (HHT), vasculitis, surgical intervention of the upper respiratory tract up to 6 months before the epistaxis event as well as age < 18 years. Ethical approval was obtained from the ethical committee of the Kanton Zurich (BASEC-Nr. 2018-01768). Statistical analyses were performed with R software version 3.5.2. Continuous data are presented as mean (± standard deviation (SD)) and in non- Gaussian distribution as median and range. To analyze associations between different medication groups and epistaxis events as well as interventions (age-adjusted) odds ratios (OR) are used. Additionally, p-values of generalized linear models are reported. A p-value < 0.05 was considered statistically significant.

In our cohort, the median age was 71 years with 61.4% male and 38.6% female patients. In total, 56.5% of patients were on some form of anticoagulation. In the subgroup analysis, 31.2% of the patients were on TAI whereas 21.8% on oral anticoagulation. The ratio of cOAC and NOAC patients was almost balanced with 1.2 : 1, which is lower than previously published [7,8]. We see this most likely due to the expanded indications and usage of NOACs in recent years. In line with previous studies [8,9], approximately 85% of our patients presented with anterior, 15 % with posterior epistaxis and that ratio stayed constant in the first and second relapse potentially indicating true relapses in the Kiesselbachii locus as a region of minor resistance (data and other demographics see supplementary Table 2 and 3).

We did not find an association of any of the analyzed medications, especially the usage of NOACs with posterior bleedings, which are generally considered more severe and difficult to manage (supplementary Table 3). A recent retrospective study similar to ours could not identify an association of NOAC treatment with more complicated or severe epistaxis but rather with recurrent bleedings [8]. In our study we could only confirm increased odds for recurrent epistaxis in patients treated with cOAC but not in case of regular NOAC intake (Figure 1A). This is in line with reports assessing the safety profile of NOAC treatment describing an overall lower rate of minor and major bleeding events compared to classic oral anticoagulation [10,11]. Interestingly, only half of the patients on cOAC and with an INR above target range in our study presented with recurrent epistaxis suggesting mechanisms other than overdosage in cOAC associated epistaxis.

In contrast to cOAC, regular TAI intake was associated with increased odds for nasal packing, alone or in combination with other treatment modalities (Figure 1B). Furthermore, we could observe the highest rate of surgical interventions in the patient group with TAI treatment, which also reached statistical significance in the multivariable model (Table 1). By irreversible inhibiting the cyclooxygenase (COX) enzyme or the P2Y12 receptor, TAI treatment induces platelet dysfunction [12]. As

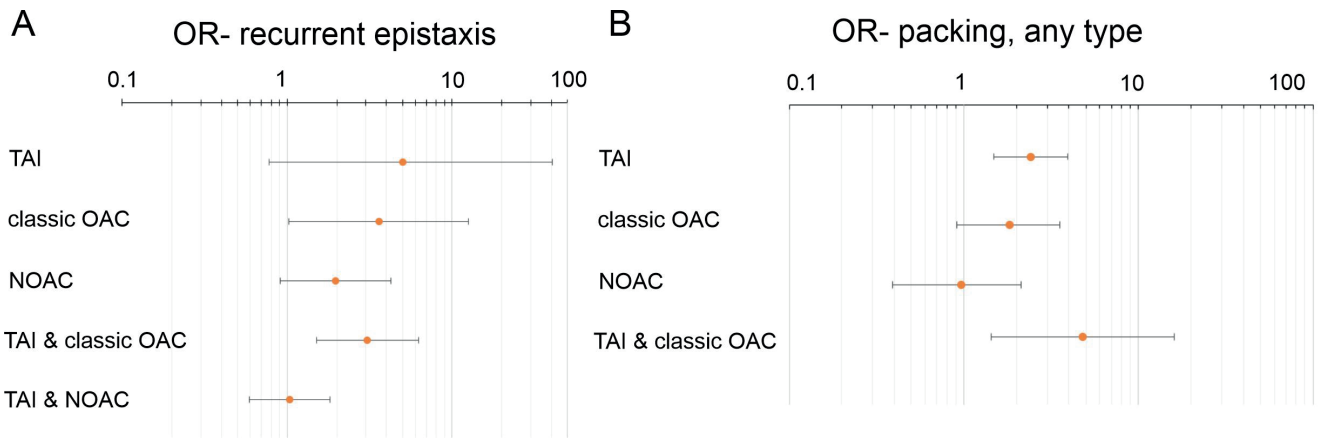

Figure 1. A) Forest Plot showing age adjusted ORs with 95% CI for recurrent epistaxis in patients treated with TAI, classic OAC, NOAC or a combination of TAI and classic OAC as well as TAI and NOAC, if compared to epistaxis patients without such medication. Number n and percentage % of patients with recurrent epistaxis: all cases 131 (26.5%), no medication 42 (19,8%), TAI 36 (23,7%), cOAC 26 (44,8%), NOACs 18 (37,5%), TAI & cOAC 6 (50%) TAI & NOACs 3 (60%). B) Forest plot showing age adjusted ORs with 95% CI for necessity of nose packing (alone or in combination with other treatment modalities) in patients on TAI, classic OAC, NOAC or a combination of TAI and classic OAC if compared to the group without such medication. The OR of the group of patients with a combination of TAI and NOAC was deliberately not included due to the very low number of patients. Number and percentage of patients with nose packing: all cases 120 (24.6%), no medication 38 (17.9%), TAI 51 (33.5%), cOAC 16 (27.6%), NOACs 8 (16.7%), TAI & cOAC 6 (50%) TAI & NOACs 1 (25%), $p < 0.001$, TAI (thrombocyte aggregation inhibitor), classic OAC (classic oralanticoagulation), NOAC (novel oral anticoagulation)

previously proposed, an explanation of the increased odds for packing and a higher rate of surgical intervention could be that the initial aggregation of thrombocytes is of more importance in controlling epistaxis than the following formation of a fibrin clot [3]. Another explanation could be a certain selection bias with patients on OAC in general being sicker and with more severe comorbidities. Hence, such patients might be treated with a more conservative approach in case of posterior bleedings to prevent further risk of general anesthesia. Our study showing no evidence for more invasive surgical treatment in patients on NOACs is also in line with a previous study that directly compared the rate of surgical intervention for epistaxis in patients on cOAC or NOAC [9]. Without specifically considering the effect of TAI, no increased rate of invasive treatments for epistaxis was found for the group on NOAC if compared to classic VKA [9].
As for other complications of epistaxis such as a lower hemoglobin levels or longer hospital stays after admission, we could not find any differences between the different medication groups (Table 1, supplementary Table 3). Previous data by Sauter et al. even suggest rivaroxaban to be associated with fewer hospital admissions in case of severe epistaxis if compared to phenprocoumon although effects of other drugs such as TAIs have not been specifically considered in that study [7].

There are some limitations of our study. Data collection was done in a retrospective setup and despite careful review, data are limited to the information documented in the patients file. Another limitation of this study is that it was performed in the setting of a tertiary referral institute at our university hospital as a single center study resulting in a further selection bias.
In conclusion, our study suggests, in line with previous reports, no increased odd for severe or recurrent epistaxis as well as its complications in case of NOAC treatment especially if compared to subjects without such medication. Therefore, from an ENT perspective NOAC treatment would be preferable over cOACs (and TAIs) if medical indications allow its use. Owing to the high proportion of NOAC use in the epistaxis population, it should still be considered a risk factor for the event of non-severe nose bleeds.

Conflict of interest

We do not have any financial relationships or activities with any organizations that might have an interest in the submitted work. Furthermore, there is no conflict in interest for any of the stated authors.

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Authorship contribution

DR: designed study, collected data, performed statistical analysis, wrote manuscript; VS: analyzed data and performed statistical analysis, edited the manuscript; YL: collected and analyzed data; TK: edited and approved manuscript; MBS: designed study, edited and approved manuscript.

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Table 1. Summarizing treatment modalities in the different groups such as patients without medication, with thrombocyte aggregation inhibitor (TAI), classical anticoagulation (cOAC), novel oral anticoagulation (NOAC) or combinations of these drugs. The highest percentage of surgical interventions was found in the group of patients on TAI and in patients without any type of medication which was statistically significant in a multivariable model considering age and gender.

	All Cases	No medication	TAI	classic OAC	NOAC	TAI & classic OAC	TAI & NOAC
Electrocauterization, n (%)	373 (76.5)	160 (75.5)	107 (70.4)	48 (82.6)	45 (93.8)	9 (75)	4 (80)
Chemical cauterization, n (%)	49 (10.0)	25 (11.8)	11 (7.2)	7 (12.1)	5 (10.4)	1 (8.3)	0 (0)
Any type of packing (w/o other treatment modality), n (%)	120 (24.6)	38 (17.9)	51 (33.5)	16 (27.6)	8 (16.7)	6 (50)	1 (25)
Packing with any type of Rapid RhinoTM, one side, n (%)	49 (10.0)	14 (6.6)	23 (15.1)	6 (10.3)	3 (6.25)	2 (16.7)	1 (20)
Packing with Rapid RhinoTM, both sides, n, (%)	6 (1.2)	2 (0.9)	2 (1.3)	1 (1.7)	0 (0)	1 (9.1)	0 (0)
Packing with any type of Rapid RhinoTM, age adjusted OR (95% CI)		1	3.39 (1.50-8.20)	2.48 (0.72-8.29)	1.71 (0.33-7.47)	3.98 (0.53-20.21)	5.01 (0.23-43.32)
Any type of packing, age adjusted OR (95% CI)		1	2.42 (1.49 - 3.95)	1.82 (0.91 - 3.54)	0.96 (0.39 - 2.12)	4.79 (1.43 - 16.1)	1.19 (0.06-8.37)
Surgical intervention, n (%)*		15 (6.8)	13 (8.5)	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)
Patients hospitalized, n (%)		17 (8.1)	17 (11.2)	6 (10.5)	2 (4.2)	1 (8.3)	0 (0)
Hospitalization, age adjusted OR (95%)		1	0.35 (0.05 - 1.43)	1.05 (0.33 - 3.05)	1.15 (0.53 - 2.53)	n. a.	n. a.

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SUPPLEMENTARY DATA

Supplementary Table 1. A summary of patients characteristics and demographics in the different groups such as patients without medication, with thrombocyte aggregation inhibitor (TAI), classical anticoagulation (classical OAC), novel oral anticoagulation (NOAC) or combinations of these drugs.

	All Cases	No medication	TAI	classic OAC	NOAC	TAI & classic OAC	TAI & NOAC	p-value
Number, n	487	212	152	58	48	12	5	
Proportion of Total (%)	100	43.5	31.2	11.9	9.9	2.4	1..1	
Age, yr (Median, range)	71, 18 - 100	57.5, 18 -100	73 , 29 -98	80.5, 48 -98	77, 53 -93	75.5, 55 -94	78, 72 - 86	< 0.001
Gender, Female (%)	38.6	41	30.9	44.8	50	16.7	16.7	0.887
Coronary artery disease (%)	19.5	1.4	40.1	13.8	31.3	50	80	<0.001
Atrial fibrillation (%)	20.1	1.9	6.6	58.6	79.2	66.7	20	<0.001
Diabetes (%)	13.1	8.1	18.4	19	10.4	16.7	40	0.041
Renal insufficiency (%)	16.9	4.7	16.4	27.6	33.3	66.7	80	<0.001

Supplementary Table 2. An overview of the clinical presentation of epistaxis in the different groups. p-value based on multivariate analysis considering age and gender.

	All Cases	No medication	TAI	classic OAC	NOAC	TAI & classic OAC	TAI & NOAC	p-value
Proportion of total cases (%)	487	212	152	58	48	12	5	
Recurrent epistaxis, n, (%)	100	43,5	31,2	11,9	9,9	2,5	1	
Number with single epistaxis episode, n, (%)	131 (26.5)	42 (19,8)	36 (23,7)	26 (44,8)	18 (37,5)	6(50)	3 (60)	<0.001
two epistaxis episode, n, (%)	81	26 (12.3)	23 (15.1)	14 (24.1)	13 (27.1)	3 (25)	2 (40)	
three or more episode, n, (%)	50	16 (7.5)	13 (8.6)	12 (20.7)	5 (10.4)	3 (25)	1 (20)	
Relapse within one month after first bleed, n, (% of tot recurrent epist in group)	81 (61.4)	33 (78.6)	20 (55.6)	13 (50)	11 (61.1)	2 (33.3)	2 (66.6)	
Relapse within six month after first bleed, n, (% of tot recurrent epist in group)	86 (65.2)	33 (78.6)	22 (61.1)	15 (57.7)	11 (61.1)	3 (50)	2 (66.6)	
Mean number bleeding episodes, n, SD	1.47 (0.991)	1,32 (0.804)	1,38 (0.853)	1,83 (1.201)	1,66 (1,26)	2,25 (2,05)	1,8 (0,837)	<0.001
Recurrent epistaxis, age adjusted OR (95% CI)		1	5.03 (0.78-40.18)	3.6 (1.03-12.52)	1.96 (0.91-4.23)	3.06 (1.51-6.27)	1.038 (0.59-1.82)	
Site of bleeding, left n, %	223 (46.6)	97 (45.8)	63 (41.4)	30 (51.7)	21 (43.8)	5 (41.7)	1 (20)	0.591
right n, %	244 (46.9)	101 (47.6)	82 (53.9)	23 (39.7)	26 (54.2)	5 (41.7)	3 (60)	
unclassified (e.g. both sides) n, %	31 (6.5)	14 (6.6)	7 (4.6)	5 (8.6)	1 (2.1)	2 (16.7)	1 (20)	
Location all events, ant. n, %	412 (86.4)	184 (88)	119 (79.9)	50 (90.9)	45 (95.7)	10 (83.3)	4 (80)	
post. n, %	65 (13.6)	25 (12)	30 (20.1)	5 (9.1)	2 (4.3)	2 (16.7)	1 (20)	
Posterior epistaxis, age adjusted OR (95% CI)		1	2.21 (0.08 - 65.35)	1.27 (0.11 - 12.43)	0.6 (0.12 - 2.92)	n. a.	n. a.	
Mean Hb	125.2 (25.6)	131	130,5	137,5	129,5	93	128	0.49
Mean Thrombocyte count	233.8 (98.4)	240	250	188	243	201	293	0.582
INR	1.7 (1.26)	1.1	1.1	2.6	1.4	2.6	1.25	<0.001
Glomerular filtration rate (GFR)	74.9 (25.0)	91.5	74.5	54	61	69.5	NA	<0.001