Association of Epistaxis With Atherosclerotic Cardiovascular Disease

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**Objectives/Hypothesis:** To investigate the association between epistaxis and atherosclerotic cardiovascular disease.

**Study Design:** Case-control cohort study.

**Methods:** This study included patients from the tertiary-care ear, nose, and throat department at the University Hospital of Zurich between December 1, 2016 and June 1, 2017. We assessed the cardiovascular risk profiles in a group of 41 patients presenting with epistaxis, and a group of 41 matched controls, focusing on a surrogate parameter for atherosclerosis: the carotid intima-media thickness (CIMT).

**Results:** With a mean of 1.06 mm (standard deviation [SD] = 0.17), CIMT values were on average 26% higher in epistaxis patients than in their controls, with a mean of 0.84 mm (SD = 0.14; \( P < .001 \)). Occurrence of severe epistaxis was also associated with lower ankle–brachial index values at 0.96 (SD = 0.12) versus 1.05 (SD = 0.17) (\( P < .001 \)) and significantly higher QRISK2 relative risks (an algorithm for predicting cardiovascular risk) than found in the control group (1.81, SD = 0.97 vs. 1.35, SD = 0.28; \( P = .028 \)). A binary logistic regression model, adjusted for possible confounders, showed an odds ratio of 2.5 for the occurrence of epistaxis per increase in CIMT of 0.1 mm in the study population (95% confidence interval: 1.56–4.11; \( P < .001 \)).

**Conclusions:** The occurrence of severe epistaxis was shown to be closely associated with the prevalence of atherosclerotic cardiovascular disease. Accordingly, patients affected by epistaxis should be regarded as at an elevated cardiovascular risk, which indicates the need for appropriate further medical assessment and preventive measures.

**Key Words:** Epistaxis, atherosclerosis, cardiovascular disease, carotid intima-media thickness.

**Level of Evidence:** 3b

**Trial Registration:** Clinical trials NCT03092973

**INTRODUCTION**

Atherosclerotic cardiovascular disease (CVD) is still the main reason for mortality worldwide, causing nearly 801,000 deaths per year in the United States alone.1 CVD is a chronic disease of the arterial tree that often develops over decades without any symptoms until a major cardiovascular event, such as a stroke or myocardial infarction, occurs.2 This is why it is crucial to identify individuals with an increased atherosclerotic burden before such a possibly life-threatening event takes place.2 Current guidelines recommend against screening of asymptomatic patients, but propose medical prophylaxis in patients with known risk factors for CVD and stroke, such as hypertension and dyslipidemia.3–5

Epistaxis has been linked to long-term hypertension and diabetes, and both are known to induce atherosclerotic changes in blood vessels. Although the direct connection of epistaxis and CVD has not yet been made, these changes could lead to a friability of the nasal vessels and therefore a predisposition for nosebleed.6,7 Approximately 60% of the population is affected by nosebleed at least once in their lifetime, which makes epistaxis a very common reason for visits not only to otorhinolaryngologic emergency departments but also to primary care physicians.8

However, the extent to which epistaxis is connected to atherosclerosis must still be investigated. If epistaxis turns out to be a sign of subclinical atherosclerosis, the assumption could be made that patients affected are at a higher risk for CVD and therefore major cardiovascular events.

Presumptive risk factors for epistaxis include trauma, inflammation of the nasal mucosa, the cold season, alcohol overuse, abnormalities in hemostasis, and antithrombotic or antiplatelet medication.9–11 The exact role of hypertension in the development of epistaxis is still unclear, although severe epistaxis has been shown to be more common in patients with long-term hypertension.9,12–15 High blood pressure and diabetes have also been associated with high recurrence rates of epistaxis, possibly because they are promoters of atherosclerotic cardiovascular disease.9

To investigate the relation between epistaxis and atherosclerosis, we used a well-established surrogate parameter for generalized atherosclerosis: the carotid-artery intima-media thickness (CIMT).16–18 This measurement shows arterial wall alteration and can safely and efficiently be performed by ultrasound, is noninvasive, reproducible, and has a positive association with future cardiovascular events.19,20 Numerous studies have shown a correlation between the CIMT and CVD.19,21–23 Lorenz et al. stated that for each increase in CIMT by...
0.1 mm, the risk for myocardial infarction rises by 10% to 15% and the risk for stroke by 13% to 18%.19,24 By assessing the CIMT in a group of epistaxis patients and in a group of matched controls, along with additional parameters such as the ankle–brachial index (ABI),25,26 we determined a relationship between nosebleeds and atherosclerosis. Those findings may justify a more in-depth look at cardiovascular risk factors in patients presenting with epistaxis and initiation of preventive measures if needed.

MATERIALS AND METHODS

Study Design and Population

The design of this project was an observational case-control cohort study at the University Hospital of Zurich performed in 2016 and 2017. The study population consisted of patients presenting with spontaneous epistaxis, and they were recruited directly after their outpatient treatment or during their inpatient stay. Inclusion criterion was adult patients with active spontaneous epistaxis, whereas patients with traumatic or postsurgical nosebleed, patients currently undergoing chemotherapy, and patients with a known bleeding disorder were excluded.

The control group also consisted of patients at the otorhinolaryngologic department of the University Hospital Zurich and was matched for age, sex, and antiplatelet and anticoagulant drugs. Patients with a history of recurrent epistaxis (more than two episodes in the last 10 years) were excluded from the control group. We chose not to exclude head and neck cancer patients from the control group to avoid a selection bias, leading to less comparability between the groups.

Informed consent was obtained from every patient, and the study was conducted in accordance with the latest version of the Helsinki declarations and with the permission of the local ethics committee (ID: KEK 2016-01227). Patients were involved in neither the setting of the research question nor the design or conduct of this study.

Data Collection

Procedures. The CIMT of all patients was measured by ultrasound with a high-resolution B-mode system (Logiq S8; GE Medical Systems Ltd., Little Chalfont, United Kingdom) by a trained examiner (S.M.K.). The patients were asked to lie on the examination couch with their heads slightly reclined and turned away from the side that was assessed.20,27 CIMT was measured manually in triplicates in three different angles (anterior, lateral, posterior) at the far wall of the left and right common carotid artery (CCA) 1 cm proximal of the carotid bulb. The measurements were made in plaque-free sequences of the CCA. The distance between the leading edges of the lumen-intima and media-adventitia ultrasound interfaces was assessed in each angle.22

According to the European Mannheim consensus, plaques were defined as focal structures encroaching into the arterial lumen by at least 0.5 mm or 50% of the surrounding intima-media thickness value, or a total CIMT value of at least 1.5 mm, and recorded as either present or absent.25,26 The ABI, defined as the ratio of the systolic blood pressure of the vessels at the ankle to that at the brachial artery, is a tool for the detection of lower-extremity peripheral artery disease (PAD), and has been shown to indicate the presence of atherosclerosis at other vascular sites as well. Due to this fact, it can be used as a predictor for cardiovascular events.30,31 For ABI measurement, the systolic blood pressure was determined using Doppler ultrasound (Dopplex MD2; Huntleigh Healthcare Ltd., Cardiff, United Kingdom).

The ABI was calculated for each leg individually, using the higher value of either the tibialis posterior artery or the dorsalis pedis artery as the numerator and the higher value of brachial arteries as the denominator.30 An ABI value below 0.9 is a sign for a stenosis greater than 50% between the aorta and distal leg arteries, and therefore the presence of PAD, even if the patient does not report any symptoms.2

Questionnaire. The clinical history of all patients was completed by the same medical doctor (S.M.K.) in individual interviews following an epidemiological questionnaire. Patient history was obtained regarding epistaxis, CVD (myocardial infarction, angina pectoris, stroke, transient ischemic attack [TIA], PAD), arterial hypertension (defined as currently using antihypertensive medication), diabetes mellitus, atrial fibrillation, rheumatoid arthritis, and chronic kidney disease. The questionnaire further assessed demographic and lifestyle information (e.g., current cigarette smoking habits and packs per year), family history regarding CVD, and current medication intake, focusing on anticoagulant and antiplatelet medication, statins, and blood pressure treatment. The smoking status was defined as either nonsmoker, ex-smoker, light (<10 cigarettes/day), moderate (10–19 cigarettes/day), or heavy smoker (>20 cigarettes/day). Family history regarding CVD was considered positive if a first degree relative of the patient had a heart attack or angina before the age of 60 years. The physical examination profile included—besides the CIMT and ABI measurements—height, weight and blood pressure.

We used the QRISK2 score to calculate the 10-year risk for CVD and the relative risk for CVD (defined as the patient’s risk divided by a healthy person’s risk). It is the second version of the QRISK score, an algorithm for predicting an individual’s cardiovascular risk. It was established for the contemporary Northern European population and has been proven to have a high accuracy in predicting major cardiovascular events.32–34

Statistical Analysis

The sample size was planned using a power analysis with a power of 90% and an a-error of 5%, considering a difference in CIMT of 0.1 mm (standard deviation [SD] = 0.1) as relevant. A sample size of at least 24 patients per group resulted, but because the examined individuals were expected to be rather heterogeneous, we aimed for 80 patients in total. Despite unchanged outcome results, the analysis of 80 individuals revealed imperfect matching for age; therefore, two additional patients were recruited.

The CIMT, ABI, blood pressure, and pulse were defined as continuous variables, whereas the occurrence of epistaxis, drug treatment, positive family history, and presence of plaques were defined as dichotomous data. Continuous values were presented as mean with SD, whereas binary data were presented as percentages or odds ratio (OR) with confidence interval (CI), if applicable.

The normality of distribution was checked using the Kolmogorov-Smirnov test. If no serious deviation from a bell-shaped distribution was observed, the Student t test was used to compare continuous variables, whereas Pearson χ² tests were performed for categorical data. For non-normally distributed continuous variables, a Mann-Whitney U test was used. We completed a binary logistic regression analysis to investigate factors influencing the occurrence of epistaxis; placing CIMT and possible confounders like body mass index (BMI) or pack-years as covariates. These independent variables were chosen according to
significance in the previously performed simple correlation analyses. The SPSS software version 24.0 (IBM, Armonk, NY) was used for all statistical analyses, and a two-sided P value of < .05 was considered significant.

### RESULTS

In total, 41 patients and 41 matched, healthy controls were included in the present study. The patient group consisted of 14 females and 27 males, whereas there were 13 females and 28 males in the control group. The mean age in these study groups was 74.2 ± 13.6 years (range, 37–93 years) and 71.2 ± 10.4 years (range, 49–95 years), respectively (Mann-Whitney U test: P = .1). The distribution of hemostasis-compromising medication is shown in Table I. Participants of the control group were presenting at the hospital for reasons in the field of otology (16/41; including hearing loss and otitis), rhinology (9/41; including chronic rhinosinusitis and postsurgical care after rhinoplasty), and head and neck cancers (16/41; including various skin cancers and carcinoma of the tongue). Treatment modalities used in epistaxis patients included in this study are shown in Figure 1. Out of those 41 patients, 61% could be managed in an outpatient setting, whereas 39% were hospitalized (25 vs. 16).

Positive patient history for stroke was found three times in the epistaxis group (7.3%) and one time in the control group (2.4%). For known coronary heart disease, smoking habits, antihypertensive medication, presence of atherosclerotic plaques, BMI, family history, smoking habits, antihypertensive medication, statins, or the prevalence of coronary heart disease or arterial hypertension. An overview of results from clinical examination and ultrasound is shown in Table II.

### DISCUSSION

In this study, we investigated the relationship between atherosclerotic cardiovascular disease and the occurrence of epistaxis, showing an overall higher atherosclerotic burden in patients needing treatment for nasal bleeding. These findings strongly suggest that, on the one hand, atherosclerosis might be a risk factor for epistaxis, and on the other hand, epistaxis could likely be a

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**TABLE I.** Distribution of hemostasis impairing medication (VKA: Vitamin K Antagonist, NOAC: novel oral anticoagulants).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Epistaxis (n = 41)</th>
<th>Control (n = 41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No medication</td>
<td>15/41 (36.6%)</td>
<td>18/41 (43.9%)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>13/41 (31.7%)</td>
<td>12/41 (29.2%)</td>
</tr>
<tr>
<td>VKA</td>
<td>6/41 (14.6%)</td>
<td>5/41 (12.2%)</td>
</tr>
<tr>
<td>NOAC</td>
<td>4/41 (9.8%)</td>
<td>3/41 (7.3%)</td>
</tr>
<tr>
<td>Aspirin &amp; Clopidogrel</td>
<td>1/41 (2.4%)</td>
<td>2/41 (4.9%)</td>
</tr>
<tr>
<td>Aspirin &amp; NOAC</td>
<td>1/41 (2.4%)</td>
<td>1/41 (2.4%)</td>
</tr>
<tr>
<td>Aspirin &amp; Clopidogrel &amp; NOAC</td>
<td>1/41 (2.4%)</td>
<td>none</td>
</tr>
</tbody>
</table>

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Fig. 1. Treatment modalities used in participants of the epistaxis group.

CIMT values in epistaxis patients had a mean of 1.06 mm (± 0.17) and a median of 1.07 mm, which made them 26.2% higher than the CIMT in the control group, with a mean of 0.84 mm (± 0.14) and a median of 0.85 mm (Student t test: P < .001). Thirty-three out of 41 epistaxis patients had CIMT values above the threshold for atherosclerosis (0.9 mm), whereas among controls, only 14 patients showed values beyond that cutoff value (χ²: P < .001). Out of the 28 epistaxis patients with no history of CVD manifestation, 23 patients had mean CIMT values at or above 0.9 mm.

When only taking the patients currently using acetysalicylic acid into consideration, the epistaxis patients (n = 16) still had CIMT values with means 31% higher (1.14 mm ± 0.16 vs. 0.87 mm ± 0.14, Student t test: P < .001) than the control group (n = 15). Among those participants without any hemostasis-impairing drugs, CIMT values in the epistaxis group still showed significantly higher values, with a mean of 0.98 mm (± 0.15, n = 15), whereas the control group had a mean CIMT of 0.83 mm (± 0.14, n = 18; P < .005). The abovementioned results are shown in Figure 2. The ABI was 8.6% lower in the epistaxis group (0.96 ± 0.12 vs. 1.05 ± 0.17, Mann-Whitney U test: P = .002), whereas the heart rate was 16.3% higher than in the control group (78.7 ± 12.0 vs. 67.7 ± 11.1, Student t test: P < .001).

Because the QRISK2 score cannot be evaluated in patients over 85 years old and those with a positive history for coronary heart disease, stroke, and TIA, it could only be determined for 26 epistaxis patients and 30 controls. In these individuals, the QRISK2 relative risk was 34.1% higher in the epistaxis group (1.81 ± 0.97 vs. 1.35 ± 0.28, Mann-Whitney U test: P = .028), but there was no significant difference in the 10-year QRISK2 score (25.9 ± 14.5 vs. 29.7 ± 17.1, Mann-Whitney U test: P = .38).

The binary logistic regression confirmed that CIMT is a strong predictor of the occurrence of epistaxis, with an odds ratio of 2.5 for each increase of 0.1 mm (95% CI: 1.56–4.11, P < .001). Model fit was assessed using the Hosmer-Lemeshow test (P = .779).

No statistically significant difference was observed between the two groups in regard to age, sex, blood pressure, presence of atherosclerotic plaques, BMI, family history, smoking habits, antihypertensive medication, statins, or the prevalence of coronary heart disease or arterial hypertension. An overview of results from clinical examination and ultrasound is shown in Table II.
symptom of manifest, as well as of subclinical CVD. This link highly indicates that spontaneous epistaxis is a sign for an increased overall cardiovascular risk, and thus might justify further medical assessment in affected patients.

Strengths and Limitations

This study proves a connection between epistaxis and atherosclerosis, which is of high clinical importance and impact on everyday practice. A strength of this study was the performed matching for age, sex and antiplatelet and anticoagulant drugs; being important risk factors for epistaxis and often getting prescribed for already known CVD. This allowed us to focus on atherosclerosis as the main endpoint, with as little influence of potential confounders as possible. Another strength was the choice of a highly reliable and reproducible surrogate parameter for CVD, the CIMT,16 supported by several additional measurements and demographic values, therefore allowing us to characterize the patients’ cardiovascular risk profile.

However, there are also several limitations to consider. Firstly, the sample size was small, but the power reached was high, and results of the primary outcomes were statistically significant. Secondly, we only defined atherosclerotic plaques as being present or absent, without further classification with a plaque score or defining the extent of carotid stenosis. This needs to be considered in future studies on this topic. Thirdly, risk calculation was not possible in 15/41 cases of the epistaxis group and 11/41 cases of the control group, because the QRISK2 score is only applicable for patients below the age of 85 years and without any personal history of coronary heart disease.34 Finally, both study groups exclusively consisted of white European women and men, so it remains unclear to what extent our findings are generalizable to other ethnic groups.14

Interpretation

Our results show a significant relation between spontaneous epistaxis and a high atherosclerotic burden, because the majority of included patients with epistaxis had mean CIMT values above the threshold of 0.9 mm, defining them as affected by CVD.16–18 Even among the participants of the epistaxis group without any known manifestation of CVD, the majority showed values above 0.9 mm (23 out of 28). The findings of this study, therefore, suggest that CVD might possibly be an important risk factor for epistaxis. This appears to be the case even in people not yet affected by any other manifestation of CVD. However, to further investigate the strength of the association of atherosclerosis and epistaxis, a larger study sample is needed.

As mentioned above, this assertion is mainly based on CIMT measurements, but it is supported by significantly lower ankle–brachial index, as well as significantly higher QRISK2 relative risks in the epistaxis group compared to the matched control group. Hemostasis-impairing medication, most importantly aspirin, had the potential to be a very strong confounder in this study.

TABLE II.
Comparison of Parameters Among Epistaxis Patients and Controls.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Epistaxis (n = 41)</th>
<th>Control (n = 41)</th>
<th>P Value (Two Sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIMT mean (mm)</td>
<td>1.06 ± 0.17</td>
<td>0.84 ± 0.14</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ABI</td>
<td>0.96 ± 0.12</td>
<td>1.05 ± 0.17</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>144.8 ± 3.76</td>
<td>136.6 ± 2.72</td>
<td>.08</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>81.8 ± 1.78</td>
<td>79.9 ± 1.99</td>
<td>.48</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>78.7 ± 1.87</td>
<td>67.7 ± 1.74</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Plaques (yes/no)</td>
<td>32/8</td>
<td>25/16</td>
<td>.09</td>
</tr>
<tr>
<td>Hypertension (yes/no)</td>
<td>20/21</td>
<td>17/24</td>
<td>.66</td>
</tr>
</tbody>
</table>

Continuous variables are stated as mean ± standard deviation.

ABI = ankle–brachial index; CIMT = carotid intima-media thickness; DBP = diastolic blood pressure; SBP = systolic blood pressure.
Due to adequate matching of both groups, this bias could be overcome.

Patients already being treated with aspirin very likely have a history of cardiovascular disease, and are therefore already being monitored by a medical professional, in most cases their primary care physician. Epistaxis patients not being treated with aspirin or other hemostasis impairing medication presumably are not diagnosed with CVD yet. In those cases, further medical assessment to determine the patients’ overall cardiovascular risk is indicated, considering the results of the current study. Initiation of appropriate preventive measures might not only lead to less frequent and possibly less severe epistaxis incidents, but also an overall reduction of an individual’s cardiovascular risk. The goal of this study was to investigate the relationship between CVD and epistaxis. Nevertheless, to further define the clinical relevance of epistaxis in regard to CVD, additional research with a more invasive approach and long-term follow-up is suggested.

CONCLUSION
Epistaxis patients showed significantly higher mean CIMT values compared to the matched control group. Therefore, atherosclerotic CVD can be seen as an independent major risk factor for the occurrence of epistaxis. Patients with spontaneous nasal bleeding consequently are at a higher risk for CVD than their nonaffected peers, thus justifying a thorough clinical workup and adequate preventive measures.

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BIBLIOGRAPHY