

# Effect of Topical Intranasal Therapy on Epistaxis Frequency in Patients With Hereditary Hemorrhagic Telangiectasia

## A Randomized Clinical Trial

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**IMPORTANCE** Epistaxis is a major factor negatively affecting quality of life in patients with hereditary hemorrhagic telangiectasia (HHT; also known as Osler-Weber-Rendu disease). Optimal treatment for HHT-related epistaxis is uncertain.

**OBJECTIVE** To determine whether topical therapy with any of 3 drugs with differing mechanisms of action is effective in reducing HHT-related epistaxis.

**DESIGN, SETTING, AND PARTICIPANTS** The North American Study of Epistaxis in HHT was a double-blind, placebo-controlled randomized clinical trial performed at 6 HHT centers of excellence. From August 2011 through March 2014, there were 121 adult patients who met the clinical criteria for HHT and had experienced HHT-related epistaxis with an Epistaxis Severity Score of at least 3.0. Follow-up was completed in September 2014.

**INTERVENTIONS** Patients received twice-daily nose sprays for 12 weeks with either bevacizumab 1% (4 mg/d), estriol 0.1% (0.4 mg/d), tranexamic acid 10% (40 mg/d), or placebo (0.9% saline).


**MAIN OUTCOMES AND MEASURES** The primary outcome was median weekly epistaxis frequency during weeks 5 through 12. Secondary outcomes included median duration of epistaxis during weeks 5 through 12, Epistaxis Severity Score, level of hemoglobin, level of ferritin, need for transfusion, emergency department visits, and treatment failure.

**RESULTS** Among the 121 patients who were randomized (mean age, 52.8 years [SD, 12.9 years]; 44% women with a median of 7.0 weekly episodes of epistaxis [interquartile range {IQR}, 3.0-14.0]), 106 patients completed the study duration for the primary outcome measure (43 were women [41%]). Drug therapy did not significantly reduce epistaxis frequency ( $P = .97$ ). After 12 weeks of treatment, the median weekly number of bleeding episodes was 7.0 (IQR, 4.5-10.5) for patients in the bevacizumab group, 8.0 (IQR, 4.0-12.0) for the estriol group, 7.5 (IQR, 3.0-11.0) for the tranexamic acid group, and 8.0 (IQR, 3.0-14.0) for the placebo group. No drug treatment was significantly different from placebo for epistaxis duration. All groups had a significant improvement in Epistaxis Severity Score at weeks 12 and 24. There were no significant differences between groups for hemoglobin level, ferritin level, treatment failure, need for transfusion, or emergency department visits.

**CONCLUSIONS AND RELEVANCE** Among patients with HHT, there were no significant between-group differences in the use of topical intranasal treatment with bevacizumab vs estriol vs tranexamic acid vs placebo and epistaxis frequency.

**TRIAL REGISTRATION** clinicaltrials.gov Identifier: [NCT01408030](https://clinicaltrials.gov/ct2/show/study/NCT01408030)

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 Supplemental content

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**H**ereditary hemorrhagic telangiectasia (HHT) is a hereditary vascular condition characterized by the development of arteriovenous malformations throughout the body.<sup>1</sup> The most common manifestation of HHT is recurrent and spontaneous epistaxis, which is seen in 90% to 95% of patients and is due to fragile telangiectases on the nasal mucosa.<sup>1,2</sup> HHT-related epistaxis (HRE) is the most important determinant of quality of life in patients with HHT and is the leading reason given by patients for switching to another profession.<sup>3</sup>

**ESS** Epistaxis Severity Score

**HHT** hereditary hemorrhagic telangiectasia

**HRE** HHT-related epistaxis

To date, randomized clinical trials for HRE have studied oral estrogen,<sup>4</sup> topical estriol plus argon plasma coagulation,<sup>5</sup> oral tamoxifen,<sup>6</sup> oral tranexamic acid,<sup>7,8</sup> submucosal bevacizumab,<sup>9</sup> topical bevacizumab,<sup>10</sup> and sclerotherapy.<sup>11</sup> Even though several of these studies have suggested modest benefit, they also have demonstrated conflicting results, and the majority have included small numbers of patients and have several methodological weaknesses. Nonrandomized clinical trials of endonasal coagulation suggest short-term benefit in a large percentage of patients; however, this therapy is invasive, is costly, and must be repeated intermittently. Therefore, the optimal treatment for HRE remains uncertain.

Given that 80% to 90% of nasal telangiectases are in a location accessible to topical treatment,<sup>12</sup> and the desire to avoid the risks of systemic therapies, this randomized clinical trial was designed to assess topical therapies for HRE. Based on published data and anecdotal experience, 3 agents with theoretically differing mechanisms of action were selected for further study. The first is bevacizumab, which is a recombinant humanized antibody directed against vascular endothelial growth factor that may attenuate angiogenesis. The second is estriol, which induces squamous metaplasia of the nasal mucosa.<sup>13</sup> The third is tranexamic acid, which can stabilize blood clots through inhibition of fibrinolysis and upregulate endoglin and ACVRL1 expression in endothelial cells.<sup>14</sup> The objective of this randomized clinical trial was to determine whether compared with placebo, topical therapy with bevacizumab, estriol, or tranexamic acid would reduce epistaxis frequency and severity in patients with HHT.

## Methods

### Study Design and Oversight

The study design committee chose the 3 drugs judged to have the greatest likelihood of benefit to compare with placebo. The dose of bevacizumab was chosen based on 1 case report in the literature<sup>15</sup> and the anecdotal experiences of the design committee, suggesting a dose of 4 mg/d to 10 mg/d for 7 to 14 days. Balancing potential off-label patient costs and study design considerations, a dose of 4 mg/d of bevacizumab for 7 days was chosen. The dose of estriol was based on the study of Sadick et al.<sup>13</sup> The dose of tranexamic acid was based on extensive literature and experience in the compounding pharmacy world. The treatment duration was cho-

### Key Points

**Question** Will topical medical therapy with either bevacizumab, estriol, or tranexamic acid improve epistaxis severity in patients with hereditary hemorrhagic telangiectasia (HHT) compared with a saline placebo?

**Findings** In this double-blind randomized clinical trial including 121 patients with HHT, the median epistaxis frequency was 7.0 bleeding episodes per week for bevacizumab, 8.0 per week for estriol, and 7.5 per week for tranexamic acid compared with 8.0 per week with placebo, which is a nonsignificant difference.

**Meaning** There was no advantage to topical therapy with these medications in these doses compared with frequent saline sprays for reducing the frequency of epistaxis in patients with HHT.

sen because the committee judged that patients would need to see benefit within 3 months to realistically continue with a treatment. An effect size of 50% improvement in the frequency of epistaxis was chosen based on several studies showing a similar benefit<sup>5,6,8,15</sup> and what would be clinically significant to the patient. All sites received approval from their local institutional review boards and all patients provided written informed consent. Augusta University was the coordinating center and together with the University of Utah prepared all data for the analysis. A data and safety monitoring board of 4 physicians convened every 6 to 12 months to review data on adverse effects and study progress.

### Patient Selection

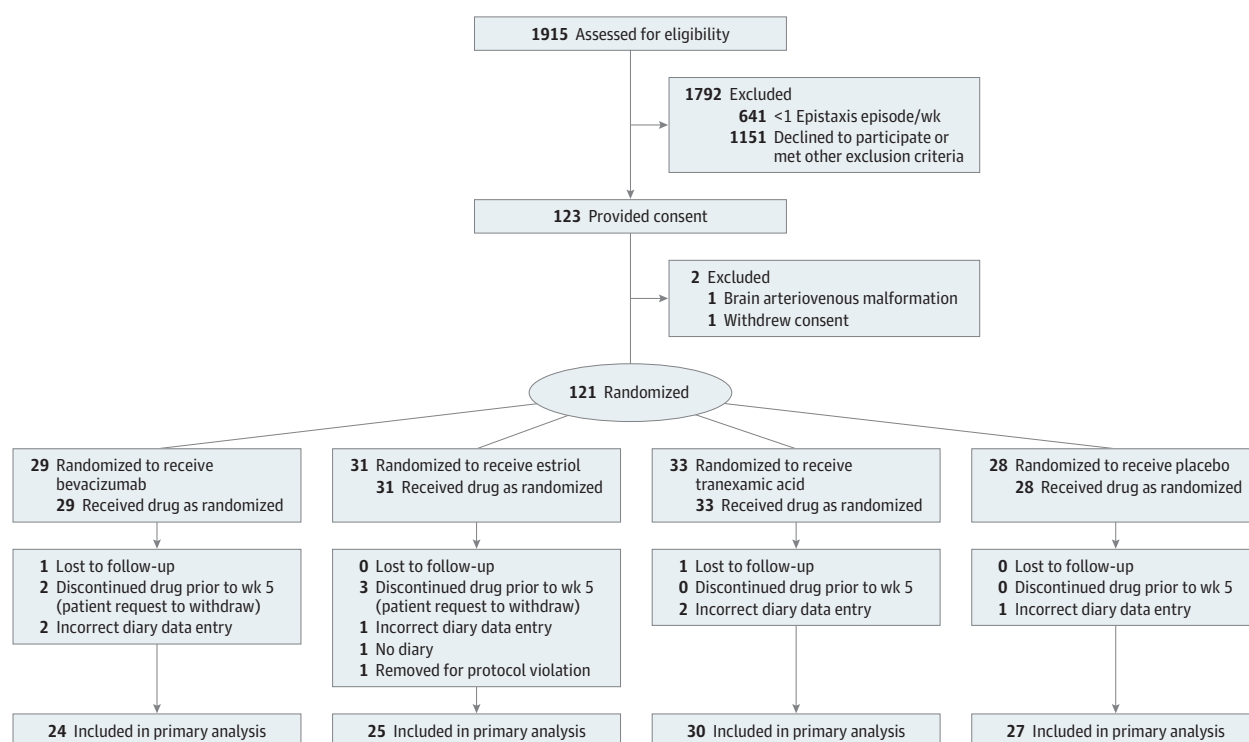
Patients were recruited at 6 participating sites from August 2011 through March 2014 (Figure 1). Eligible patients had to meet all of the following inclusion criteria: (1) aged 18 years or older; (2) had a diagnosis of definite or possible HHT<sup>16</sup>; (3) experienced epistaxis lasting at least 1 minute, occurring at least once weekly, and clinically stable during the preceding 8 weeks; and (4) had an Epistaxis Severity Score (ESS) of at least 3.0.<sup>17</sup> Major exclusion criteria included (1) estimated life expectancy of less than 1 year; (2) a history of arterial or venous thromboembolism within the past 6 months; (3) uncontrolled hypertension; (4) presence of untreated brain arteriovenous malformation; (5) active malignancy in the brain, lung, or colon; (6) symptomatic heart failure; and (7) current or recent use of any of the study treatments.

Patients of all races and ethnicities were eligible because little is known about the role of race and ethnicity in the manifestations of HHT. The categories of white, black, Hispanic, Asian, and other were used and were assigned by the investigator or patient. Additional inclusion and exclusion criteria and the complete research protocol appear in Supplement 1.

### Randomization and Treatment

The North American Study of Epistaxis in HHT (NOSE) was a multicenter, double-blind, randomized phase 2 trial of the active treatment spray bevacizumab 1% (4 mg/d), estriol 0.1% (0.4 mg/d), or tranexamic acid 10% (40 mg/d) compared with a placebo spray (0.9% saline). Patients were stratified by baseline epistaxis frequency (<7 bleeding episodes per week

Figure 1. Flow Diagram of Patients in the North American Study of Epistaxis in HHT



Patients were screened for eligibility at the 6 participating hereditary hemorrhagic telangiectasia (HHT) centers of excellence. The number assessed for eligibility is an estimate based on the number of patients with HHT-related epistaxis (HRE) seen annually at each site and the number of months each site

was enrolling patients. The specific reasons for exclusion were not prospectively recorded. The number of exclusions is an estimate based on data from the Augusta University center of excellence showing that 89% of patients with HRE have 1 or more epistaxis episodes per week.

vs  $\geq 7$  bleeding episodes per week) and study site. The randomization codes were issued in permuted blocks of 4 for each stratification level within each site and were known only to the dispensing pharmacy (O'Brien Pharmacy) and the statistician (M.H.J.). All drugs were prepared by the pharmacy and shipped directly to the patient.

Bevacizumab and tranexamic acid were prepared in 0.9% saline. Estriol was prepared in 0.5% carboxymethylcellulose sodium suspension. All sprays included benzalkonium chloride 0.013% as a preservative and were dispensed in identical-appearing, opaque, polyethylene-metered dose, spray bottles (0.1 mL per spray, Letco Medical). Even though the estriol liquid appeared to be more foamy than the other treatments, this effect was hidden by the opaque bottles. Spray consistency and spray appearance were identical for all treatments. Patients in all 4 treatment groups administered 1 spray (0.4 mL/d) in each nostril twice daily for 12 weeks.

Anecdotal experience with bevacizumab suggested that a topical nasal exposure lasting 1 to 2 weeks would result in a treatment response lasting at least 3 to 4 months. Accordingly, patients randomized to bevacizumab took active drug for 1 week (total dose of 28 mg) followed by 0.9% saline for 11 weeks. Patients randomized to estriol, tranexamic acid, or placebo took the corresponding drug for the full 12 weeks. Adherence was assessed at the end of the study by subtracting the measured residual volume from the original fill vol-

ume for each bottle, then dividing by the prescribed volume (0.4 mL/d = 2.8 mL for bottle 1; 8.4 mL for bottle 2; and 11.2 mL for bottles 3 and 4), and then multiplying by 100. All patients were followed up for an additional 12 weeks after stopping treatment. The use of any estrogen, tranexamic acid, epsilon aminocaproic acid, or vascular endothelial growth factor inhibitor outside the study protocol was forbidden.

### Outcomes and Assessments

The primary outcome was median weekly epistaxis frequency during weeks 5 through 12 for each patient obtained from the daily epistaxis diary. This period was chosen because drugs such as estriol may take several weeks for the onset of action to occur. An episode of epistaxis was defined as blood dripping from the nose or down the back of the throat. Secondary outcomes included median duration of epistaxis for each person from the epistaxis diary during weeks 5 through 12, ESS, hemoglobin and ferritin levels, need for transfusion, emergency department visits, and treatment failure. Additional secondary outcomes including quality-of-life measures and satisfaction with treatment in relationship to other HHT and epistaxis variables will be addressed in a subsequent report.

Patients were given a paper epistaxis diary at enrollment and instructed to fill out the number of separate episodes and total duration of bleeding on a daily basis starting with day 1

of taking the drug and continuing for 24 weeks or until study withdrawal. Baseline epistaxis diary data were not collected prior to initiating drug therapy.

Treatment failure was defined as the occurrence of any of the following during the 12-week treatment period: transfusion of more than 12 units of blood; electrocautery, chemical cautery, or laser ablation of nasal telangiectases; nasal septal dermoplasty; Young nasal closure surgery; initiation of a new treatment modality for epistaxis; withdrawal from the study due to treatment adverse effects; or death related to epistaxis or the study protocol. Additional assessment information and a full discussion of ESS derivation appear in [Supplement 2](#).

### Statistical Analysis

Epistaxis frequency was originally hypothesized to be 7 episodes per week with an SD of 5 episodes per week based on the recent experience at the Augusta University HHT center of excellence. The frequency of epistaxis was calculated so that a sample size of 30 patients in each of the 4 groups would provide 85% power at an level of .05 to detect a 50% reduction<sup>8,15</sup> (mean, 3 episodes per week; SD, 5 episodes per week) in the 3 treatment groups and no change in patients in the placebo group. After the first 66 patients had been enrolled, an unplanned analysis of self-reported frequency of epistaxis per week at enrollment showed that the epistaxis frequency was actually 11 episodes per week with an SD of 7 episodes per week. A revised power calculation found that a sample size of 25 patients in each of the 4 groups would provide 85% power at an level of .05 to detect a 50% reduction in epistaxis frequency in the 3 treatment groups (mean, 5 episodes per week; SD, 7 episodes per week) and no change in the placebo group. A total sample size of 120 was determined to allow for dropout and was agreed on by the investigators.

Continuous data were summarized using means and 95% CIs unless skewed in which case medians and interquartile ranges (IQRs) were used. Categorical data are presented as frequencies and percentages for each drug group. The primary outcome variable for each patient was derived from the epistaxis diary as the median weekly epistaxis count for weeks 5 through 12. This variable was skewed so a log transformation was performed prior to the analysis. Analysis of variance was used to analyze the primary outcome variable for the effect of each drug while accounting for clinical site as a random effect. Exploratory subgroup analyses for epistaxis frequency and nasal irrigation use also were performed. The secondary outcome of total duration was derived from the epistaxis diary as the median weekly epistaxis duration for weeks 5 through 12 for each patient. The duration per bleeding episode was calculated as the duration per week divided by the count for each week for weeks 5 through 12. The median total duration of bleeding episodes per week for weeks 5 through 12 was obtained in a similar manner for each patient.

A log transformation was used prior to the analysis of these variables. Analysis of variance was used to analyze the duration outcomes for the effect of each drug while accounting for clinical site as a random effect. Analysis of covariance was used to analyze hemoglobin and ferritin levels at week 12 for drug effects while adjusting for baseline values and accounting for

clinical site as a random effect. A log transformation was used for ferritin level prior to analysis. Fisher exact tests were used to analyze categorical secondary outcomes and adverse drug effects. A mixed-model repeated-measures analysis of variance was used to analyze ESS for drug and time (baseline, week 12, and week 24) effects in which clinical site and patient were included in the model as random effects. A compound symmetric error structure was used to model the within-patient correlation.

Data were considered missing at random and were not imputed for this analysis; least-squares means with 95% CIs are reported. A Tukey test was used to compare means from significant analyses of variance. Two-sided testing was performed for all analyses with a significance level of .05. All statistical analyses were performed using SAS version 9.3 (SAS Institute Inc).

## Results

Consecutive patients were screened for eligibility at 6 participating HHT centers of excellence (Figure 1). Of 123 willing patients who met initial inclusion criteria, 1 was found to have a brain arteriovenous malformation prior to randomization and was excluded. Another patient withdrew consent prior to randomization, leaving a total of 121 patients who were randomized to topical therapy or placebo (Figure 1 and [Table 1](#)). A total of 29 patients were randomized to bevacizumab, 31 patients to estriol, 33 patients to tranexamic acid, and 28 patients to placebo. After randomization, a patient from the estriol group was excluded for the protocol violation of using of an estrogen-containing medication, leaving 120 patients.

Among the 121 patients who were randomized (mean age, 52.8 years [SD, 12.9 years]; 44% women with a median of 7.0 weekly episodes of epistaxis [IQR, 3.0-14.0]), 106 patients completed the study duration for the primary outcome measure (43 were women [41%]). There were 14 patients with missing data for the primary outcome due to misunderstanding the diary instructions ( $n = 6$ ), dropping out of the study prior to week 5 ( $n = 7$ ; 5 treatment failure and 2 lost to follow-up), or no diary provided ( $n = 1$ ). There were an additional 6 patients for whom the median was calculated based on partial data (range, 3-7 weeks out of 8 weeks). The baseline characteristics of the enrolled patients appear in [Table 1](#). Most patients had moderate epistaxis with a mean ESS between 5.2 and 5.7 for the 4 groups. The majority of patients experienced greater than 7 episodes of epistaxis per week. Based on self-reported age of onset of epistaxis, the patients had experienced a mean of 37.9 years (95% CI, 35.3-40.5 years) of intermittent epistaxis.

Adherence was reviewed at interim telephone follow-up visits, and was assessed by measuring the residual volume in the study bottles following the active treatment phase. Because bevacizumab was only present in bottle 1, the residual volume in bottle 1 and bottles 2 through 4 were compared separately. The patients randomized to bevacizumab used 110% of the expected volume of drug, whereas the other 3 groups used between 85% and 89% of the expected volume ( $P < .05$  for

Table 1. Baseline Demographics and Disease Characteristics of Patients in the North American Study of Epistaxis in HHT<sup>a</sup>

	Bevacizumab (n = 29)	Estriol (n = 30) <sup>b</sup>	Tranexamic Acid (n = 33)	Placebo (n = 28)
Age, mean (95% CI), y	47.8 (42.8-52.9)	56.6 (52.0-61.2)	53.0 (48.2-57.8)	53.0 (48.6-57.3)
Male sex	16/29 (55)	18/30 (60)	19/33 (58)	15/28 (54)
Race/ethnicity				
White	27/29 (93)	29/30 (97)	29/33 (88)	27/28 (96)
Black	0/29	0/30	0/33	0/28
Hispanic	1/29 (3)	1/30 (3)	3/33 (9)	1/28 (4)
Asian	0/29	0/30	1/33 (3)	0/28
Missing	1/29 (3)	0/30	0/33	0/28
Hereditary hemorrhagic telangiectasia history				
Definite	26/29 (90)	29/30 (97)	32/33 (97)	26/28 (93)
Mucocutaneous telangiectases	27/28 (96)	28/30 (93)	33/33 (100)	27/28 (96)
Treated brain arteriovenous malformation	1/25 (4)	2/27 (7)	0/28	1/25 (4)
Lung arteriovenous malformation	10/25 (40)	13/28 (46)	14/28 (50)	7/25 (28)
Liver arteriovenous malformation	3/14 (21)	8/17 (47)	5/20 (25)	4/17 (24)
Gastrointestinal arteriovenous malformation	4/20 (20)	6/25 (24)	7/27 (26)	5/23 (22)
History of gastrointestinal bleeding	5/29 (17)	4/30 (13)	8/33 (24)	3/28 (11)
Family history	27/29 (93)	25/29 (86)	30/32 (94)	26/27 (96)
Genetic testing				
Not done	20/29 (69)	18/30 (60)	19/33 (58)	20/28 (71)
ENG mutation	3/29 (10)	4/30 (13)	3/33 (9)	3/28 (11)
ACVRL1 pathogenic mutation	3/29 (10)	7/30 (23)	9/33 (27)	5/28 (18)
ACVRL1 variant of unknown significance	2/29 (7)	0/30	1/33 (3)	0/28
SMAD4 mutation	0/29	0/30	0/33	0/28
No mutation found	1/29 (3)	1/30 (3)	1/33 (3)	0/28
Epistaxis history				
Age at onset, mean (95% CI), y	14.9 (10.5-19.3)	17.6 (12.7-22.4)	9.1 (7.0-11.2)	17.9 (12.7-23.2)
Bleeding episodes/wk, median (IQR)	10.0 (5.0-14.0)	7.0 (7.0-14.0)	7.8 (5.5-14.5)	7.0 (5.0-15.0)
≥7 Bleeding episodes/wk	21/29 (72)	23/30 (77)	24/33 (73)	21/28 (75)
Nasal irrigation use at baseline	13/29 (45)	8/28 (29)	17/32 (53)	8/27 (30)
Epistaxis Severity Score, mean (95% CI) <sup>c</sup>	5.16 (4.75-5.57)	5.19 (4.71-5.68)	5.43 (4.94-5.91)	5.71 (5.04-6.38)
Hemoglobin level, median (IQR), g/dL	12.6 (11.5-13.9)	13.7 (11.5-14.9)	12.7 (11.0-12.9)	13.9 (11.6-15.0)
Ferritin level, median (IQR), ng/mL	17.7 (5.9-31.6)	29.5 (14.9-68.0)	25.0 (12.0-35.5)	26.5 (18.0-54.0)

SI conversion factors: To convert ferritin to pmol/L, multiply by 2.247; hemoglobin to g/L, multiply by 10.

<sup>a</sup> Data are expressed as No./total No. of patients (%) unless otherwise indicated.

<sup>b</sup> After randomization, 1 patient was excluded for the protocol violation of using an estrogen-containing medication, leaving 30 patients in this group.

<sup>c</sup> This is a validated tool to quantify hereditary hemorrhagic telangiectasia-related epistaxis severity on the basis of the responses to 6 weighted questions.<sup>17</sup> Scores range from 0 to 10 (higher scores reflecting greater epistaxis severity). A score between 0 and 3.99 indicates mild epistaxis; between 4 and 6.99 indicates moderate epistaxis; and between 7 and 10 indicates severe epistaxis.

comparison across groups). All groups used 90% to 97% of the total expected volume from all 4 bottles during the full 12-week period without any other significant differences. A total of 108 patients (90%) successfully completed the 12-week treatment protocol, with 10 (8%) experiencing treatment failure and 2 (2%) lost to follow-up. The epistaxis diary used for the primary outcome was completely filled out for 100 patients (83%) and 106 patients (88%) had at least partial data during weeks 5 through 12. A total of 87 patients (73%) also completed the subsequent 12-week observation phase of the trial.

The primary outcome of epistaxis frequency between weeks 5 through 12 was not significantly different between any of the active drug groups and the placebo group or between any of the therapeutic agents ( $P = .97$  for drug effect; Table 2 and eFigure in Supplement 2). Patients receiving placebo had

a median of 8.0 episodes (IQR, 3.0-14.0 episodes) of epistaxis per week. After 12 weeks of treatment, the median weekly number of bleeding episodes was 7.0 (IQR, 4.5-10.5) for patients in the bevacizumab group, 8.0 (IQR, 4.0-12.0) for the estriol group, 7.5 (IQR, 3.0-11.0) for the tranexamic acid group, and 8.0 (IQR, 3.0-14.0) for the placebo group. The outcome was similar for patients based on the subgroup analysis using the prespecified stratification of baseline epistaxis frequency.

For the secondary outcome of epistaxis duration, no drug treatment was significantly different from placebo (Table 2 and eFigure in Supplement 2). The median epistaxis duration in minutes per bleeding episode was not significantly different for patients receiving bevacizumab (3.0; IQR, 1.6-5.5), estriol (4.0; IQR, 1.6-6.3), tranexamic acid (6.2; IQR, 3.0-9.4), and placebo (5.0; IQR, 3.0-9.8).



Table 2. Intention-to-Treat Analysis of Primary and Secondary Outcomes in the North American Study of Epistaxis in HHT

	Bevacizumab (n = 29)		Etiol (n = 30) <sup>a</sup>		Tranexamic Acid (n = 33)		Placebo (n = 28)		P Value for Drug Effect
	No. of Patients	Median (IQR) <sup>b</sup>	No. of Patients	Median (IQR) <sup>b</sup>	No. of Patients	Median (IQR) <sup>b</sup>	No. of Patients	Median (IQR) <sup>b</sup>	
<b>Primary outcome</b>									
No. of bleeding episodes/wk during wks 5-12	24	7.0 (4.5-10.5)	25	8.0 (4.0-12.0)	30	7.5 (3.0-11.0)	27	8.0 (3.0-14.0)	.97 <sup>c</sup>
Subgroup analyses by baseline status									
High epistaxis frequency (≥7 episodes/wk)	19	8.0 (5.0-16.0)	20	8.5 (6.0-14.5)	22	9.5 (3.0-13.0)	20	10.3 (4.5-14.5)	.99 <sup>c</sup>
Low epistaxis frequency (<7 episodes/wk)	5	5.0 (4.0-5.3)	5	4.0 (3.0-4.0)	8	6.5 (4.0-8.0)	7	2.0 (1.0-10.0)	.73 <sup>c</sup>
Irrigation	13	8.0 (5.3-11.0)	17	8.0 (4.0-15.0)	14	7.5 (5.0-10.0)	18	6.0 (2.0-15.0)	.71 <sup>c</sup>
No irrigation	11	6.0 (3.0-8.0)	6	6.5 (3.0-12.0)	15	10.0 (3.0-13.0)	8	10.3 (7.0-13.0)	.56 <sup>c</sup>
<b>Secondary outcomes</b>									
Total duration of bleeding episodes/wk during wks 5-12, min <sup>d</sup>	26	23.5 (13.0-40.0)	26	36.5 (7.0-70.0)	32	44.5 (13.5-87.5)	28	46.0 (10.0-84.0)	.47 <sup>c</sup>
Duration of individual bleeding episode during wks 5-12, min <sup>d</sup>	24	3.0 (1.6-5.5)	25	4.0 (1.6-6.3)	30	6.2 (3.0-9.4)	27	5.0 (3.0-9.8)	.09 <sup>c</sup>
Treatment failure <sup>e</sup>		2/29 (7) <sup>f</sup>		5/30 (17) <sup>f</sup>		0/33 <sup>f</sup>		3/28 (11) <sup>f</sup>	.08 <sup>g</sup>
Hemoglobin level, g/dL	23	12.8 (11.7-14.1)	22	13.1 (12.3-14.9)	31	11.4 (10.0-13.6)	23	13.8 (12.6-14.9)	.43 <sup>h</sup>
Ferritin level, ng/mL <sup>d</sup>	23	14.0 (7.0-34.4)	22	18.0 (12.0-39.0)	31	25.0 (12.0-49.0)	23	24.0 (18.0-42.0)	.10 <sup>h</sup>
Patients requiring transfusion during wks 1-12 <sup>i</sup>		1/29 (3) <sup>f</sup>		2/30 (7) <sup>f</sup>		5/33 (15) <sup>f</sup>		3/28 (11) <sup>f</sup>	.42 <sup>g</sup>
No. of units of blood transfused per individual patient		2 <sup>j</sup>		2, 1 <sup>l</sup>		2, 2, 2, 4, 10 <sup>l</sup>		6, 6, 18 <sup>j</sup>	<sup>k</sup>
Needed emergency department care during wks 1-12		1/29 (3) <sup>f</sup>		1/30 (3) <sup>f</sup>		3/33 (9) <sup>f</sup>		1/28 (4) <sup>f</sup>	.72 <sup>g</sup>

SI conversion factors: To convert ferritin to pmol/L, multiply by 2.247; hemoglobin to g/L, multiply by 10.

<sup>a</sup> After randomization, 1 patient was excluded for the protocol violation of using an estrogen-containing medication, leaving 30 patients in this group.

<sup>b</sup> Unless otherwise indicated.

<sup>c</sup> Assessed using analysis of variance for which clinic site was included as a random effect.

<sup>d</sup> A log transformation was used on the data prior to analysis.

<sup>e</sup> Defined as the occurrence of any of the following during the 12-week treatment period: transfusion of more than 12 units of blood; electrocautery, chemical cautery, or laser ablation of nasal telangiectases; nasal septal dermoplasty; Young nasal closure surgery; initiation of a new treatment modality for epistaxis; withdrawal from the study due to treatment adverse effects; or death related to epistaxis or the study protocol.

<sup>f</sup> Data are expressed as No. of patients/total No. of patients (%).

<sup>g</sup> Assessed using the Fisher exact test.

<sup>h</sup> Assessed using analysis of covariance to adjust for baseline values and the random effect of clinic site.

<sup>i</sup> The decision to have a blood transfusion, visit the emergency department, or seek any other type of care was at the discretion of the patient and the investigator. In practice, a patient with hereditary hemorrhagic telangiectasia does not usually receive a transfusion unless his or her hemoglobin level decreases to less than 7 g/dL or 8 g/dL.

<sup>j</sup> Patients rarely received blood transfusions during the study. The data listed are the entire number of units transfused for each affected patient, rather than an estimate of center (mean or median) and estimate of variability that would be imprecise due to the small number of events.

<sup>k</sup> Not included due to the lack of statistical power to make meaningful comparisons for this measure.

All 4 groups experienced a significant decline in ESS from baseline to week 12 (Figure 2 and eTable 1 in Supplement 2;  $P < .001$  for time effect). The placebo group decreased from a median ESS of 5.71 (95% CI, 5.04-6.38) to a median ESS of 3.74 (95% CI, 3.17-4.31). Similar declines in ESS were seen for bevacizumab from 5.16 (95% CI, 4.75-5.57) to 3.54 (95% CI, 3.00-4.08); estriol, from 5.19 (95% CI, 4.71-5.68) to 3.56 (95% CI, 2.81-4.30); and tranexamic acid, from 5.43 (95% CI, 4.94-5.91) to 4.06 (95% CI, 3.50-4.61). There was no significant drug effect. The improvement in ESS was clinically significant.

All groups worsened by week 24 ( $P = .01$  for time effect vs week 12) but remained significantly improved from baseline ( $P < .001$  for time effect) with a median ESS of 4.26 (95% CI, 3.65-4.88) for the placebo group, 3.88 (95% CI, 3.28-4.47) for the bevacizumab group, 3.83 (95% CI, 2.61-5.04) for the estriol group, and 4.40 (95% CI, 3.67-5.12) for the tranexamic acid group. The improvement for each group exceeded the minimally important difference for the ESS<sup>18</sup> at weeks 12 and 24 relative to baseline. However, the change from week 12 to 24 did not meet the minimally important difference.

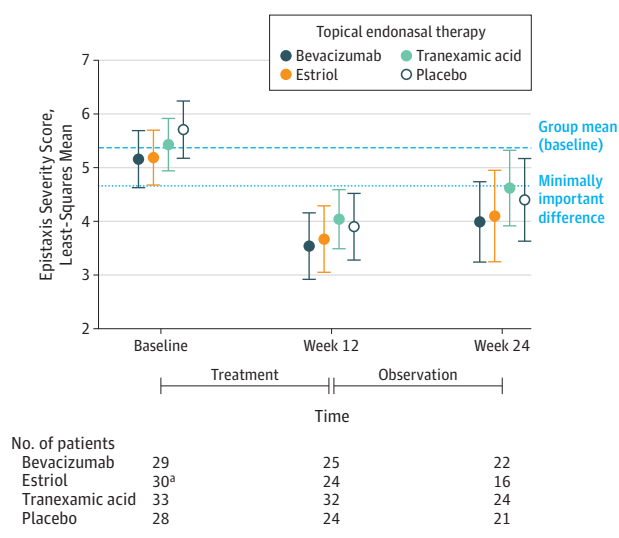
There were 10 patients who experienced treatment failure with no between-group differences (Table 2). The reason for 8 of the 10 patients experiencing treatment failure was due to patient preference to pursue laser therapy or open-label treatments. There was no significant drug effect on level of hemoglobin or ferritin. Two patients exceeded the transfusion limit and were withdrawn from the trial. There was no drug effect on transfusion requirements or differences in the amount of patients seeking emergency department care.

Given the improvement in ESS seen for the placebo group (Figure 2 and eTable 1 in Supplement 2) and the possibility that saline irrigation had a therapeutic effect, an exploratory subgroup analysis of the primary outcome was performed based on nasal irrigation status at baseline (Table 2). No drug effect was observed in either group.

The study therapies were generally well tolerated (Table 3 and eTable 2 in Supplement 2). Nasal symptoms were the most common concern for patients in all 4 study groups. Significant drug effects were seen for patients with gastrointestinal

symptoms including abdominal pain and nausea or vomiting ( $P < .05$  for comparison across groups), and these were most commonly experienced by patients receiving tranexamic acid.

**Figure 2. Change in Epistaxis Severity Score With Topical Endonasal Therapy in the North American Study of Epistaxis in HHT**



Data markers indicate least-squares means and 95% CIs. Patients reported epistaxis severity using the Epistaxis Severity Score (ESS), which is a validated tool to quantify hereditary hemorrhagic telangiectasia-related epistaxis on the basis of responses to 6 weighted questions. The scores range from 0 to 10 with higher scores reflecting greater epistaxis severity. The overall mean ESS at baseline for the combined groups is shown for reference, together with the established threshold for the minimally important difference (0.71).<sup>18</sup> No treatment group differences were significant. Groups were compared using a mixed-model repeated-measures analysis of variance to analyze ESS for treatment and time effects. Each treatment group experienced a significant improvement from baseline (week 0) to the end of the active treatment phase at week 12 ( $P < .001$ ). Compared with week 12, all groups had worsened by the end of the observation phase at week 24 ( $P = .01$ ), but this remained an improvement compared with baseline ( $P < .001$ ). The degree of improvement compared with baseline remained greater than the established minimally important difference for all groups by the end of week 24.

<sup>a</sup> After randomization, 1 patient was excluded for the protocol violation of using an estrogen-containing medication, leaving 30 patients in this group.

**Table 3. Most Frequent Adverse Effects Observed During the North American Study of Epistaxis in HHT<sup>a</sup>**

	No. of Patients Who Experienced an Adverse Effect/Total No. of Patients (%)			
	Bevacizumab	Estriol <sup>b</sup>	Tranexamic Acid	Placebo
Nasal symptoms	11/29 (38)	12/30 (40)	10/33 (30)	10/28 (36)
Headache	10/29 (34)	12/30 (40)	10/33 (30)	6/28 (21)
Nausea and vomiting <sup>c</sup>	4/29 (14)	1/30 (3)	10/33 (30) <sup>d</sup>	8/28 (29) <sup>d</sup>
Abdominal pain <sup>c</sup>	5/29 (17)	2/30 (7)	10/33 (30) <sup>e</sup>	1/28 (4)
Diarrhea	4/29 (14)	3/30 (10)	9/33 (27)	2/28 (7)
Cough	4/29 (14)	2/30 (7)	8/33 (24)	4/28 (14)
Musculoskeletal pain	3/29 (10)	5/30 (17)	5/33 (15)	4/28 (14)
Upper respiratory tract infection	3/29 (10)	5/30 (17)	3/33 (9)	4/28 (14)
Hot flash	3/29 (10)	4/30 (13)	3/33 (9)	3/28 (11)
Vaginal bleeding	2/13 (15)	3/12 (25)	0/14	0/13
Vision problem	2/29 (7)	2/30 (7)	5/33 (15)	1/28 (4)
Breast pain	2/29 (7)	2/30 (7)	4/33 (12)	1/28 (4)
Dizziness	1/29 (3)	0/30	3/33 (9)	2/28 (7)
Edema	2/29 (7)	0/30	2/33 (6)	2/28 (7)

<sup>a</sup> There was a minimum of 5 observations. A full list of adverse effects appears in eTable 2 in Supplement 2.

<sup>b</sup> After randomization, 1 patient was excluded for the protocol violation of using an estrogen-containing medication, leaving 30 patients in this group.

<sup>c</sup> The comparison across the 4 groups yielded a  $P$  value of less than .05 using the Fisher exact test.

<sup>d</sup> Had significantly greater numbers of adverse effects compared with patients in the estriol group after Bonferroni correction.

<sup>e</sup> Had significantly greater numbers of adverse effects compared with patients in the estriol and placebo groups after Bonferroni correction.

Breast pain and hot flashes were no more common in patients receiving estriol than in patients in any other group. There were no thrombotic complications, episodes of severe hypertension, deaths, or drug-related serious adverse effects.

## Discussion

Patients with HHT have impaired quality of life that is driven primarily by HRE.<sup>3</sup> Therapy for HRE has evolved over the years through mostly trial and error, supported by anecdotal reports of benefit.<sup>15</sup> NOSE was a randomized double-blind placebo-controlled trial of therapy for HRE conducted at 6 North American HHT centers of excellence, with power to identify a clinically meaningful improvement in HRE for any of 3 putative topical (nasal spray) therapies: bevacizumab, estriol, or tranexamic acid. None of the 3 topical therapies was any better at decreasing epistaxis frequency than twice-daily saline sprays. No serious adverse effects were seen in this study. The placebo intervention of twice-daily saline sprays is frequently recommended for patients with HRE<sup>19</sup> but has not previously been studied.

Bevacizumab is a recombinant humanized antibody directed against vascular endothelial growth factor, and is approved by the US Food and Drug Administration for use in patients with colorectal or other cancers. After initial case reports that intravenous bevacizumab with oncology dosing improves bleeding in patients with HHT,<sup>20,21</sup> subsequent reports suggest efficacy at lower doses<sup>22,23</sup> or with submucosal<sup>24</sup> or topical treatment.<sup>15</sup> While the NOSE trial was in progress, a phase 1 study of 1-time dosing of topical bevacizumab for HRE was reported.<sup>10</sup> This study demonstrated safety across a range of doses but lacked power to demonstrate efficacy. The dose of bevacizumab (4 mg/d) was chosen based on a case report<sup>15</sup> and the anecdotal experiences of the design committee, and may have been inadequate. Future trials should consider a baseline run-in period with placebo spray and active therapy at a higher dose, longer duration, or both.

There was no significant benefit to the use of topical estriol compared with placebo. As with bevacizumab, there was no effect on epistaxis frequency. Therapy with estriol was generally well tolerated. The use of estriol was not restricted to females, yet no greater estrogen adverse effects were experienced by males in the trial. It is possible that 12 weeks is too soon to judge the efficacy of estriol. A prior study of estriol ointment in 12 patients found that conversion of the nasal mucosa to a stratified squamous epithelium was not complete until 12 months,<sup>13</sup> with some significant changes occurring by 6 months. However, it was judged that for a treatment to be clinically

acceptable for patients, it would have to be effective within 3 months.

Although oral tranexamic acid has been previously shown to improve epistaxis duration for HRE,<sup>7,10</sup> there was no benefit to topical tranexamic acid in this study. Furthermore, systemic adverse effects in the trial tended to be mild and overall showed no difference for any group, whereas gastrointestinal adverse effects were more common for patients who received tranexamic acid than those who received estriol or bevacizumab. Oral tranexamic acid is associated with gastrointestinal adverse effects.<sup>7</sup> Despite the lower overall dose with topical therapy, patients who received tranexamic acid reported a significantly higher likelihood of abdominal pain than those who received placebo or estriol (Table 3). Nausea and vomiting were more common in patients who received tranexamic acid or placebo than in those who received estriol (Table 3). There were more overall gastrointestinal adverse effects in patients who received tranexamic acid than those who received bevacizumab or estriol (eTable 2 in Supplement 2). These adverse effects were not offset by any efficacy to justify therapeutic use.

This study has several important limitations. One key limitation is the lack of a baseline epistaxis diary, which would have allowed a comparison for each patient's epistaxis parameters between baseline and while receiving treatment and an assessment of the placebo effect of saline. Topical therapy has unique challenges relative to systemic therapy. It is possible that drug absorption may have been hampered because of local scab and crust formation causing a barrier to drug penetration to the mucosa. The use of saline or carboxymethylcellulose may have provided only transient exposure of the drug to the mucosa, whereas a gel, ointment, or mucoadhesive polymer may have allowed for better absorption. In this study, it was not possible to directly assess tissue drug levels, and there is no direct pharmacokinetic data for this mode of delivery. Of the 3 drugs, the recombinant antibody bevacizumab is the largest molecule and the agent with most concern for drug absorption. In support of this mode of delivery, an *ex vivo* study of topical bevacizumab penetration into porcine nasal mucosa found that the majority of a 0.5-mg dose delivered to the mucosa could be recovered, including 40% of the dose either within or across the mucosal barrier.<sup>25</sup>

## Conclusions

Among patients with HHT, there were no significant between-group differences in the use of topical intranasal treatment with bevacizumab vs estriol vs tranexamic acid vs placebo and epistaxis frequency.

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