JHWCR JOURNAL OF HEALTH, WELLNESS AND COMMUNITY RESEARCH 3007-0570

https://doi.org/10.61919/6d7ehw77

Review Article

Medical Treatments of Epistaxis in Hereditary Hemorrhagic Telangiectasia: An Updated Systemic Review and Meta-Analysis of Randomized Control Trials

Abdul Manan Dero[1], Falak Naz[2], Hassan Khan[3], Muhammad Saqib[4], Shakira Razick[5], Nirma Naz Abro[6], Asadullah[1], Abdul Rauf[1], Zubair Ahmed[2], Fareeha Hasan[7]

[1] Chandka Medical College, Larkana, Pakistan
[2] Richmond University Medical Center, Staten Island, New York, USA
[3] Changsha Medical University, Hunan, China
[4] Khyber Medical College, Peshawar, Pakistan
[5] Wyckoff Heights Medical Center, Brooklyn, New York, USA
[6] Jinnah Postgraduate Medical Centre, Karachi, Pakistan
[7] Dow University of Health Sciences, Karachi, Pakistan

***Corresponding author: Abdul Manan Dero, manandero45@gmail.com**

"Cite this Article" Received: 07 January 2026; **Accepted**: 19 February 2026; **Published**: 27 February 2026

Author Contributions: Concept: AMD; Design: AMD, FNS, HK; Data Collection: FNS, HK, MS, SR, NNA; Analysis: AMD, MS, A, AR; Drafting: AMD, FNS, ZA, FH; all authors contributed to review and finalization of the manuscript. **Ethical Approval**: Chandka Medical College, Larkana, Pakistan. **Informed Consent**: Written informed consent was obtained from all participants; **Conflict of Interest**: The authors declare no conflict of interest. **Funding**: No external funding; **Data Availability**: Available from the corresponding author on reasonable request; **Acknowledgments**: N/A.

ABSTRACT

Background: Epistaxis is the most frequent and clinically burdensome manifestation of hereditary hemorrhagic telangiectasia (HHT), yet pharmacological trials vary considerably in intervention class, route of administration, study design, and outcome definition. Objective: To evaluate the efficacy and safety of pharmacological treatments for HHT-related epistaxis and to integrate pooled treatment effects with complementary randomized evidence across the evolving therapeutic landscape. Methods: This systematic review was registered in PROSPERO (CRD420251013449) and reported in accordance with PRISMA 2020. PubMed, Scopus, and Web of Science were searched from inception to February 2025. Meta-analysis was performed in RevMan 5.4.1 using random-effects models, mean differences (MDs) for continuous outcomes, risk ratios (RRs) for binary outcomes, and I^2 to quantify heterogeneity. Risk of bias was assessed using the Cochrane RoB 1 tool, and certainty of evidence was evaluated using GRADE. Quantitative estimates were derived from the predefined meta-analytic dataset, while additional eligible randomized trials were synthesized narratively when they were not incorporated into the pooled analyses. Results: The quantitative synthesis comprised 12 comparative studies, including one retrospective comparative study. Bevacizumab did not significantly reduce epistaxis frequency (MD −0.30, 95% CI −5.17 to 4.58) or duration (MD −26.87 min/month, 95% CI −112.32 to 58.58), and no significant improvement was observed in hemoglobin concentration (MD 0.37, 95% CI −0.86 to 1.60) or overall adverse-event risk (RR 1.00, 95% CI 0.85 to 1.19). A small but statistically significant reduction in Epistaxis Severity Score (ESS) favored bevacizumab (MD −0.22, 95% CI −0.38 to −0.05; I^2=14%). Tranexamic acid showed no significant pooled effects on epistaxis frequency, duration, or hemoglobin concentration, with considerable heterogeneity in the primary analyses (I^2=92%–94%). Timolol showed no significant pooled differences in adverse events or hemoglobin concentration, while estrogen/estriol did not significantly reduce epistaxis frequency. GRADE certainty ranged from moderate to very low across outcomes. Complementary randomized evidence expanded the therapeutic profile: topical propranolol produced a significant ESS benefit in a small randomized trial; pomalidomide reduced ESS by 0.94 points versus placebo at 24 weeks in PATH-HHT; and nintedanib did not meet its primary responder endpoint in EPICURE, although favorable secondary changes were observed in epistaxis duration and hemoglobin concentration. Conclusions: The pooled evidence demonstrates limited and inconsistent benefit for several established pharmacological interventions, with the clearest quantitative signal being a small reduction in ESS with bevacizumab. The broader randomized evidence indicates that clinically meaningful pharmacological benefit is achievable with selected therapies, particularly pomalidomide, while treatment effects vary according to drug mechanism, route of administration, disease severity, and outcome definition. Management of HHT-related epistaxis should therefore remain individualized, integrating bleeding burden, therapeutic mechanism, safety profile, route of administration, and certainty of evidence. Keywords: hereditary hemorrhagic telangiectasia; epistaxis; bevacizumab; tranexamic acid; timolol; pomalidomide; meta-analysis; systematic review

INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT), also known as Rendu–Osler–Weber disease, is an autosomal dominant vascular disorder characterized by mucocutaneous telangiectasias and visceral arteriovenous malformations (AVMs) resulting from abnormal vascular development and maintenance (1-3). The disorder has an estimated prevalence of approximately 1 in 5,000 individuals, although

underdiagnosis is common because manifestations are age dependent, clinical severity is highly variable, and affected individuals may remain unrecognized until recurrent bleeding or complications from visceral AVMs become clinically apparent (1-3). HHT is therefore not confined to mucosal bleeding but represents a multisystem vasculopathy in which vascular malformations may involve the nasal and gastrointestinal mucosa, lungs, liver, brain and spinal circulation, with complications arising from either hemorrhage or abnormal vascular shunting (1-3).

The molecular basis of HHT is closely linked to dysregulation of endothelial signalling pathways responsible for angiogenesis and vascular maturation. Pathogenic variants in ENG, which encodes endoglin, and ACVRL1, which encodes activin receptor-like kinase 1, account for the majority of genetically confirmed cases, while variants involving SMAD4 and less frequently other genes contribute to additional HHT phenotypes (2,3). ENG, ACVRL1 and SMAD4 participate in transforming growth factor-β/bone morphogenetic protein signalling in vascular endothelial cells, and loss of normal signalling contributes to impaired vascular stabilization, abnormal endothelial responses and formation of structurally fragile telangiectasias and AVMs (2,3). Experimental and translational evidence also implicates dysregulated angiogenic signalling, including altered vascular endothelial growth factor activity, in the persistence and remodeling of these abnormal vessels, thereby providing a biological rationale for antiangiogenic treatment strategies in HHT (4).

Epistaxis is the most common and characteristic manifestation of HHT, affecting more than 90% of patients during their lifetime and frequently beginning during childhood or adolescence (1,3,5). The severity of epistaxis varies considerably between individuals: some experience brief and infrequent bleeding, whereas others develop recurrent and prolonged episodes resulting in substantial cumulative blood loss (5,6). Nasal telangiectasias are particularly susceptible to mechanical disruption because of their fragile architecture and superficial location within the nasal mucosa, and repeated bleeding may become progressively more clinically consequential as patients age (3-5). Consequently, epistaxis frequently becomes the dominant symptomatic problem in HHT and a major determinant of treatment requirements, healthcare utilization and patient-reported disease burden (1,5,6).

Chronic blood loss from recurrent epistaxis, often compounded by gastrointestinal telangiectatic bleeding, is an important cause of iron deficiency and anaemia in HHT (1,7). In a large multicentre HHT cohort, approximately half of evaluable patients reported a history of anaemia, and both epistaxis and gastrointestinal bleeding were associated with its occurrence; more severely affected patients may require repeated intravenous iron supplementation or red-cell transfusion (7). Anaemia and iron deficiency may in turn contribute to fatigue, reduced exercise tolerance, impaired concentration and diminished functional capacity, magnifying the clinical consequences of otherwise intermittent bleeding (1,7). These findings reinforce the importance of evaluating pharmacological therapies not only in relation to the number or duration of nosebleeds, but also with respect to haemoglobin concentration, iron requirements, transfusion burden and broader patient functioning.

The burden of HHT-related epistaxis is also strongly reflected in health-related quality of life. Studies using both generic and disease-specific instruments have shown that recurrent epistaxis interferes with social functioning, vitality, emotional well-being, sleep, daily activity and occupational participation (8-10). Pasculli et al. demonstrated that the frequency of epistaxis was independently associated with impairment across several quality-of-life domains, while subsequent studies confirmed that increasing epistaxis severity correlates with poorer patient-reported health status (8,9). Epistaxis-specific quality-of-life instruments have further shown that both bleeding frequency and duration are associated with worse patient experience, supporting the view that treatment outcomes should extend beyond binary assessments of bleeding cessation (10).

The need for reproducible outcome assessment led to development of the Epistaxis Severity Score (ESS), a standardized patient-reported instrument specifically designed for HHT-related epistaxis (11). The ESS incorporates several clinically relevant dimensions of bleeding, including frequency, duration, intensity,

anaemia and treatment requirements, and has subsequently become one of the most widely used endpoints in HHT clinical trials (11-13). Subsequent validation work has demonstrated strong test–retest reliability and meaningful relationships between ESS, haemoglobin, ferritin and other measures of clinical burden, although the score captures several related dimensions of epistaxis rather than a single homogeneous construct (12,13). Other instruments, including the NOSE-HHT questionnaire and detailed bleeding diaries, have also been developed to capture functional, physical and emotional consequences of HHT-associated epistaxis (14). The increasing use of standardized outcomes has improved clinical-trial interpretability but has also highlighted substantial heterogeneity between older and newer studies.

Management of HHT-related epistaxis is generally stepwise and must be individualized according to bleeding severity, anaemia, previous treatment response, comorbidity and patient preference (1). International HHT guidelines recommend nasal humidification and moisturizing topical therapies as initial measures, followed by pharmacological or procedural interventions when bleeding remains clinically significant (1). Oral tranexamic acid may be considered in patients with persistent epistaxis, while ablative procedures such as laser treatment, electrosurgery or sclerotherapy may be employed for more substantial local disease; systemic antiangiogenic therapy and more invasive surgical strategies may be considered in selected patients with refractory or severe bleeding (1). The persistence of multiple therapeutic options rather than a universally effective standard treatment reflects the marked heterogeneity of HHT-associated epistaxis and the incomplete comparative evidence supporting individual interventions (1,15).

Pharmacological treatment has attracted particular interest because it offers the potential to reduce bleeding without repeated destructive or invasive nasal procedures. The therapeutic approaches investigated in HHT encompass several mechanistically distinct classes, including antifibrinolytic agents such as tranexamic acid, antiangiogenic agents such as bevacizumab, β-adrenergic antagonists including timolol and propranolol, hormonal and selective estrogen-receptor therapies, immunomodulatory agents such as tacrolimus, tetracycline derivatives such as doxycycline, and more recently systemic agents targeting pathological vascular remodelling and angiogenic signalling (15-17). Antiangiogenic therapy has been of particular interest because dysregulated angiogenesis is central to HHT pathophysiology and because reduction or stabilization of telangiectatic vascular lesions may provide a disease-modifying approach rather than transient local hemostasis alone (4,16).

However, randomized evidence for many of these treatments has historically been inconsistent. Trials of tranexamic acid demonstrated variable effects depending on formulation, route and outcome definition; Gaillard et al. reported a reduction in cumulative epistaxis duration with oral tranexamic acid in a randomized crossover design, whereas the multicentre North American trial of topical intranasal tranexamic acid did not demonstrate significant superiority over saline for weekly epistaxis frequency (18,19). Similarly, randomized studies of intranasal bevacizumab have not consistently demonstrated significant improvements over placebo despite promising biological rationale and observational experience (19-21). A systematic review focused specifically on intranasal bevacizumab concluded that available randomized and nonrandomized evidence did not establish a consistent benefit for local bevacizumab across epistaxis duration, frequency, severity or quality of life (21).

β-adrenergic blockade has also been investigated as an alternative antiangiogenic and vasoactive strategy. A randomized placebo-controlled trial of topical propranolol demonstrated a significantly greater reduction in ESS than placebo, while randomized trials of intranasal timolol have produced more modest and less consistent effects, with some improvement in patient-reported outcomes but substantial imprecision because of small sample sizes (22-24). Likewise, trials of estrogenic or anti-estrogenic therapies, tacrolimus and doxycycline have produced heterogeneous results across epistaxis frequency, bleeding duration, ESS and hematologic outcomes (15,25). The diversity of therapeutic mechanisms is therefore paralleled by substantial diversity in trial design and endpoint selection.

The first quantitative attempts to synthesize this evidence emphasized these limitations. Hsu et al. identified eight randomized studies evaluating medical treatments for HHT-related epistaxis and found no consistent pooled benefit of bevacizumab, tranexamic acid or estrogen for several major outcomes, although tamoxifen and submucosal bevacizumab showed signals of benefit in selected analyses (26). The authors also found no clear pooled improvement in haemoglobin concentration or quality of life, underscoring the limited and heterogeneous nature of the available randomized evidence at that time (26). Earlier evidence-based and pharmacological reviews similarly emphasized small study samples, inconsistent outcome definitions, variation in drug formulation and route of administration, and frequent dependence on nonrandomized evidence (15,17).

The evidence base subsequently expanded substantially. A 2023 systematic review and network meta-analysis identified 21 randomized controlled trials evaluating HHT-related epistaxis treatments, of which 15 trials involving 697 participants and seven pharmacological interventions were included in quantitative synthesis (27). In that analysis, propranolol demonstrated the largest estimated improvement in ESS compared with placebo, followed by timolol, while tranexamic acid was associated with a reduction in epistaxis frequency; other treatments produced less consistent comparative effects (27). Importantly, six additional randomized studies could not be incorporated quantitatively and were instead evaluated qualitatively, illustrating that the existence of multiple randomized trials does not necessarily imply statistical comparability when intervention routes, study designs and outcome constructs differ substantially (27).

The therapeutic landscape has continued to evolve with larger and more methodologically rigorous systemic-treatment trials. The PATH-HHT randomized placebo-controlled trial enrolled 144 participants and demonstrated that pomalidomide produced a statistically significant and clinically relevant improvement in ESS at 24 weeks together with improvement in HHT-specific quality of life (28). This trial is particularly important because it represents one of the largest randomized studies of systemic pharmacological treatment in HHT and provides evidence that pharmacological benefit may extend beyond the older topical and local treatment paradigms (28). Similarly, the EPICURE multicentre randomized double-blind trial evaluated oral nintedanib in 60 patients with moderate-to-severe HHT-related epistaxis. Although the prespecified primary responder endpoint was not statistically significant, nintedanib was associated with greater reductions in epistaxis duration and improvements in haemoglobin concentration in secondary analyses, illustrating the importance of differentiating primary efficacy outcomes from supportive secondary findings (29).

Collectively, the literature demonstrates that HHT-related epistaxis is supported by an expanding but methodologically heterogeneous randomized evidence base. Differences in study design—including parallel versus crossover trials—are accompanied by variations in route of administration, dose, duration of treatment, comparator, baseline bleeding severity, follow-up period and outcome measurement (18-29). Some studies report raw episode counts, others cumulative bleeding duration or model-based rates, while contemporary trials increasingly use ESS, clinically meaningful responder thresholds, hematologic support requirements and disease-specific quality-of-life measures (11-14,18-29). These differences complicate direct pooling and may explain why apparently similar interventions have produced discordant results across conventional meta-analyses, network meta-analyses and individual randomized trials (26,27).

A further methodological consideration is that statistical synthesis should not obscure the distinction between evidence that is quantitatively compatible and evidence that remains clinically informative but cannot validly be combined. This is particularly relevant in HHT because several important trials use crossover designs, multi-arm placebo comparisons, shared procedural co-interventions or non-normally distributed epistaxis outcomes, while newer systemic-treatment trials frequently report adjusted treatment effects and responder analyses rather than simple post-treatment means (18,19,22-24,28,29). Interpretation of the evidence therefore requires attention not only to whether an intervention produced

a statistically significant result, but also to study architecture, outcome definition, precision of effect estimates, certainty of evidence and the clinical relevance of observed treatment differences (26-29).

Against this background, the present systematic review evaluates the efficacy and safety of pharmacological treatments for HHT-related epistaxis, with particular attention to epistaxis frequency, cumulative bleeding duration, ESS, haemoglobin concentration and treatment-related adverse events. The manuscript retains the quantitative meta-analytic synthesis for the comparative dataset from which the existing pooled estimates and figures were generated, while incorporating additional randomized evidence identified into an expanded narrative evidence update. Accordingly, the pooled estimates are interpreted as representing the

quantitative subset, rather than the totality of contemporary randomized evidence. This distinction permits the analyses to be presented transparently while placing their findings within the substantially broader therapeutic evidence now available (26-29).

The objective of this review is therefore to critically synthesize the efficacy and safety of pharmacological interventions for HHT-related epistaxis, to characterize the magnitude and consistency of effects across clinically relevant outcomes, and to contextualize the pooled findings within the evolving randomized evidence base. Particular emphasis is placed on distinguishing statistically significant effects from clinically meaningful changes, identifying sources of heterogeneity between trials, and evaluating how differences in intervention class, route of administration, trial design and outcome measurement influence interpretation of the available evidence (1,15,26-29).

MATERIALS AND METHODS

Study Design and Reporting Framework

This study was conducted as a systematic review with meta-analysis and an updated contextual synthesis of randomized evidence evaluating pharmacological treatment of epistaxis in patients with hereditary hemorrhagic telangiectasia (HHT). The conduct and reporting of the review were structured according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement, which provides contemporary guidance for transparent reporting of study identification, selection, appraisal and synthesis in systematic reviews (30). Reporting of the literature-search process was additionally informed by the PRISMA-S extension, which emphasizes reproducible reporting of information sources, complete search strategies, search dates, supplementary searches and management of retrieved records (31).

The review was registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD420251013449). The principal review question concerned the efficacy and safety of pharmacological interventions for HHT-associated epistaxis. The pooled estimates were preserved rather than retrospectively recalculated while incorporating additional contextual evidence.

To ensure transparent interpretation, the review distinguishes between two evidence components: the quantitative synthesis, represented by the existing meta-analytic figures and pooled estimates, and an updated contextual evidence synthesis, comprising additional randomized evidence identified during the supplementary evidence update. This distinction prevents studies identified subsequently from being represented inaccurately as contributors to pooled analyses in which they were not included. Contemporary systematic-review methodology emphasizes transparent documentation of analytical decisions and separation of analyses from subsequent evidence updates when quantitative reconstruction is not undertaken (30,32).

Review Question and Eligibility Framework

The review question was structured according to a Population–Intervention–Comparator–Outcome framework. The population comprised patients diagnosed with HHT who experienced recurrent

epistaxis. HHT was principally defined according to the Curaçao diagnostic criteria, comprising spontaneous and recurrent epistaxis, multiple mucocutaneous telangiectasias at characteristic sites, visceral vascular lesions and a first-degree family history of HHT. A definite clinical diagnosis is supported by the presence of at least three of these four criteria (33). Molecular confirmation of HHT was also considered acceptable when explicitly reported by the primary study, particularly in more recent randomized trials.

Eligible interventions comprised pharmacological therapies administered with the objective of reducing HHT-associated epistaxis, improving bleeding-related clinical outcomes or reducing hematological consequences of recurrent bleeding. Relevant pharmacological classes included antiangiogenic therapies such as bevacizumab, antifibrinolytic treatment with tranexamic acid, β-adrenergic antagonists such as timolol and propranolol, estrogenic or anti-estrogenic therapies, and other pharmacological interventions directed toward hemostasis, vascular stability or abnormal angiogenic signaling. Contemporary HHT guidelines recognize pharmacological therapy as an important component of escalating treatment for persistent or clinically significant epistaxis (1).

Acceptable comparators included placebo, saline, vehicle, usual care or an appropriate active comparator. Trials in which an identical procedural co-intervention was administered to both randomized groups were considered pharmacologically informative when the randomized difference between groups was the drug intervention itself. In contrast, studies in which surgery, laser ablation or another procedure constituted the principal randomized treatment and no independent pharmacological effect could be isolated were outside the principal pharmacological review question.

The principal outcomes were prespecified as epistaxis duration, epistaxis frequency, mean hemoglobin concentration, Epistaxis Severity Score (ESS), and adverse events. These outcomes were retained because they represented the endpoints incorporated into the quantitative synthesis and together capture bleeding burden, disease severity, hematological consequences and treatment safety.

The ESS was considered separately from simple bleeding frequency and duration because it is a multidimensional HHT-specific patient-reported measure rather than a simple event count. Its development and subsequent use in HHT therapeutic research were described in the Introduction under reference (11); accordingly, that citation number is reused rather than reassigned.

Inclusion and Exclusion Criteria

The principal quantitative eligibility framework was directed toward randomized controlled trials or randomized comparative trials investigating pharmacological treatment of HHT-associated epistaxis. Studies were eligible when they: enrolled participants with clinically or genetically confirmed HHT; evaluated an eligible pharmacological intervention against placebo, saline, vehicle or another appropriate control; reported at least one prespecified outcome; and provided sufficient information for extraction or derivation of comparative outcome data.

Studies were excluded from the randomized evidence framework when they were case reports, case series, uncontrolled cohorts, retrospective observational studies without random allocation, studies involving non-HHT epistaxis, purely procedural or surgical studies without an isolatable pharmacological contrast, duplicate reports without additional relevant data, or reports from which treatment outcomes could not be adequately determined.

The review included only English-language publications and imposed no lower publication-date restriction. The language restriction has been retained transparently in the Methods.

A specific methodological inconsistency identified is concerned Simonds et al., which had entered the quantitative dataset but was subsequently confirmed to be a retrospective comparative study rather than an RCT (34). The study evaluated submucosal bevacizumab combined with potassium titanyl phosphate

laser treatment against historical laser-treated controls. Because the existing forest plots and quantitative outputs could not be regenerated, the study remains visible in the legacy quantitative figures where it appeared.

Information Sources and Literature Search

The systematic search was conducted independently by two reviewers using PubMed, Scopus and Web of Science. The search documentation and PRISMA flow diagram identify these three databases; consequently. The search combined HHT terminology with treatment-related concepts. The recorded principal search expression was based on:

"Hereditary Hemorrhagic Telangiectasia" AND ("Treatment" OR "drugs")

Searches were conducted from database inception through February 2025, with no lower date restriction. Reference lists of potentially relevant primary studies, systematic reviews and meta-analyses were additionally examined to identify eligible studies not retrieved electronically. Supplementary reference searching is recommended as an adjunct to database searching because indexing and terminology may differ across databases, publication eras and uncommon clinical conditions (31,32).

The manuscript reports search strategy transparently, however, because PRISMA-S recommends complete database-specific and reproducible search reporting, the limitations of the relatively simple query are acknowledged (31). Either place the search strategy in the supplement or state factually that it is provided there

The search identified 2,240 records, comprising 2,220 from PubMed, 18 from Scopus and 2 from Web of Science. After removal of duplicates, 1,850 records underwent title and abstract screening. A total of 48 reports progressed to full-text assessment, and 12 comparative studies entered the quantitative synthesis. These counts correspond to the existing PRISMA figure and therefore describe the historical search and selection process, not the later contextual evidence audit.

Because additional eligible randomized studies were identified during the supplementary evidence update, the PRISMA flow should not be interpreted as representing a newly rerun February 2025 search. Instead, the figure documents how the quantitative dataset was assembled.

Evidence Audit and Contextual Evidence Update

A structured evidence audit was undertaken to determine whether the quantitative subset represented the broader randomized pharmacological evidence available within the stated February 2025 evidence window. This audit did not replace or rerun the systematic search and did not alter the numerical meta-analysis. The study list was cross-checked against previous high-level evidence syntheses, particularly the conventional meta-analysis by Hsu et al. and the subsequent systematic review and network meta-analysis by Chitsuthipakorn et al. (26,27). The Second International HHT Guidelines were also consulted to contextualize the therapeutic evidence base and clinical treatment framework (1).

Hsu et al. identified eight randomized studies evaluating medical treatments for HHT-related epistaxis and demonstrated the limited and heterogeneous nature of the randomized evidence available at that time (26). The later network meta-analysis by Chitsuthipakorn et al. identified 21 randomized treatment trials, with 15 studies involving 697 participants contributing to quantitative synthesis and six additional randomized trials evaluated qualitatively (27). This discrepancy demonstrated that the forest plots in the present manuscript did not encompass the entirety of randomized evidence available within the broader therapeutic field.

Therefore, randomized studies identified during the audit that met the broader pharmacological eligibility criteria were incorporated into a contextual narrative evidence update but were not inserted retrospectively into the existing forest plots or pooled effect estimates. This preserves the integrity of the analysis.

The evidence audit remained anchored to the February 2025 cutoff. Studies published subsequently may be consulted to clarify study reports or trial characteristics where necessary, but they are not treated as newly eligible intervention studies within the formal evidence window.

Study Selection

The records retrieved during the search were managed and screened using Rayyan, a web-based systematic-review application designed to facilitate collaborative study selection and resolution of independent screening decisions (35).

Two reviewers independently screened titles and abstracts against the eligibility criteria. Reports considered potentially eligible were retrieved for full-text review. Full-text publications were subsequently evaluated according to study design, HHT diagnosis, pharmacological intervention, comparator and availability of at least one prespecified outcome.

Disagreements between reviewers were resolved by discussion. Where consensus could not initially be reached, a third reviewer adjudicated the decision. Independent duplicate screening is recommended in systematic reviews because it reduces the probability that potentially eligible studies are excluded as a consequence of individual reviewer error or subjective interpretation (30,32).

Multiple reports describing the same underlying trial were treated as multiple publications of a single study, rather than independent trials. Where several reports arose from the same participant cohort, the report providing the most complete or relevant outcome data was used for the corresponding analysis, while companion reports could be used to clarify intervention protocols, methodological details or longer-term follow-up.

Data Extraction and Management

Two reviewers independently extracted data from studies included in the synthesis. Extracted variables included author, publication year, study design, study population characteristics, HHT diagnostic criteria where available, sample size, number randomized, number analyzed, intervention, comparator, dose, route of administration, duration of treatment, follow-up period, co-interventions, study inclusion and exclusion criteria, baseline clinical characteristics, outcome definitions, post-treatment findings and adverse events. Any disagreement in extracted information was resolved through reviewer discussion, with consultation of the primary study report and, where necessary, adjudication by an additional reviewer.

Particular attention was given to distinguishing between participants randomized, participants completing treatment or follow-up, and participants contributing to a particular outcome. These denominators are methodologically distinct and should not be used interchangeably, particularly in small randomized trials and crossover designs.

Data were retained in their source-native format whenever possible. Continuous outcomes could therefore be represented as mean and standard deviation, median and interquartile range, median and range, or an adjusted/model-derived treatment estimate according to the reporting method of the primary trial. Binary outcomes were extracted as the number of participants experiencing an outcome and the relevant denominator when available. Counts of multiple adverse-event episodes were distinguished from the number of individual patients experiencing at least one adverse event. This distinction is important because repeated events cannot validly be analyzed as if each constituted an independent patient in a conventional risk-ratio analysis.

Conversion of Non-Parametric Summary Data

In the quantitative analysis, when a study reported a median, range and/or interquartile range rather than a mean and standard deviation, approximate means and variances were derived when required for

inclusion in a continuous-outcome meta-analysis. The approach was based on established statistical methods for estimating sample means and standard deviations from limited summary statistics (36).

Wan et al. demonstrated that such transformations can facilitate meta-analysis when primary studies report non-parametric summaries, although their performance depends on sample size and the underlying distribution of the data (36). Accordingly, the review distinguishes between ly reported statistics and derived values used for meta-analysis. Converted means and standard deviations are not described as though they were directly reported by the source investigators.

Management of Parallel, Multi-Arm and Crossover Trials

Parallel-group trials were synthesized according to the comparison represented in the quantitative dataset. Multi-arm trials were counted as one unique randomized study when describing the number of trials or participants, even when they contributed more than one active treatment comparison. This distinction is particularly important in HHT trials in which multiple drug doses or different active nasal treatments share a single placebo arm.

Contemporary Cochrane methodology recommends accounting appropriately for shared comparator groups to avoid double counting participants and artificially increasing statistical precision (32). Because the meta-analysis was not rerun. Instead, this issue is acknowledged explicitly when interpreting relevant pooled estimates.

Crossover trials were handled in the analysis using data from the initial treatment period where suitable first-period information was available. Restricting a crossover trial to first-period data can avoid potential carry-over effects and permits analysis as a parallel-group comparison, although it reduces the efficiency normally gained from within-participant crossover analysis (32).

The published crossover results were additionally considered in their source-reported paired or model-based form when interpreting the wider evidence base. However, these published paired effects were not substituted retrospectively into the forest plots.

Outcomes and Effect Measures

Five principal outcomes were evaluated.

Epistaxis duration was defined according to the reporting metric used by individual trials. This could include cumulative bleeding duration over a specified period or duration per episode. Where the quantitative synthesis standardized results to minutes per month, this unit is stated explicitly.

Epistaxis frequency represented the number or rate of bleeding episodes during the trial-defined observation period. Because events per week, events per month and modeled event-rate ratios represent different statistical constructs, study units were preserved in the contextual narrative evidence update.

Epistaxis Severity Score was considered a separate continuous patient-reported outcome. Because ESS integrates several dimensions of bleeding burden, it was not treated as interchangeable with simple episode frequency or cumulative duration.

Hemoglobin concentration represented the principal hematological outcome and was analyzed as a continuous measure. Trial-specific units were retained or converted where required to permit interpretation.

Adverse events represented the principal safety outcome. Conventional binary comparisons were interpreted using patient-level event incidence when that information was available. Recurrent event counts were reported descriptively when they could not be translated reliably into the number of affected participants.

Quantitative Synthesis

The meta-analysis was conducted using Review Manager (RevMan), version 5.4.1, developed by the Cochrane Collaboration (37). Meta-analysis was undertaken when at least two studies in the analytical dataset reported an outcome considered sufficiently comparable for quantitative combination. For continuous outcomes, the analysis used the inverse-variance method and expressed treatment effects as mean differences (MDs) with 95% confidence intervals (CIs). Mean difference is appropriate when studies measure an outcome using sufficiently comparable units and scales (32).

For binary outcomes, the Mantel-Haenszel method was used to estimate risk ratios (RRs) with 95% CIs. Statistical significance was evaluated using two-sided tests with $p<0.05$.

Random-effects models were used for the principal pooled comparisons presented in the existing forest plots. The use of random-effects models is clinically plausible in the HHT literature because substantial variability exists in intervention route, dose, study population, baseline bleeding severity, treatment duration and follow-up. The results related to additional randomized trials were reported using the published treatment effects, confidence intervals, p values and clinically relevant outcome measures provided by the primary investigators.

Assessment of Statistical Heterogeneity

Statistical heterogeneity was assessed using the I^2 statistic, which describes the proportion of variability in observed effect estimates that is attributable to between-study heterogeneity rather than sampling error (32).

Interpretation of I^2 was aligned with contemporary Cochrane guidance. Values of approximately 0–40% may indicate heterogeneity that is not important; 30–60% may represent moderate heterogeneity; 50–90% substantial heterogeneity; and 75–100% considerable heterogeneity. These ranges are not interpreted mechanically and are considered alongside effect direction, clinical diversity and the number of contributing studies (32).

The review undertook subgroup or sensitivity analyses where heterogeneity was substantial, particularly when I^2 exceeded approximately 50%. Those pre-existing analyses are retained.

However, merely because I^2 decreased after exclusion of an individual study. Where substantial variability remains clinically plausible, pooled results are interpreted cautiously.

Risk-of-Bias Assessment

Two reviewers independently assessed methodological risk of bias in the studies represented in the quantitative synthesis using the Cochrane Risk of Bias tool (RoB 1) (38).

- The assessed domains comprised:
- random sequence generation;
- allocation concealment;
- blinding of participants and personnel;
- blinding of outcome assessment;
- incomplete outcome data;
- selective outcome reporting; and
- other potential sources of bias.

Each domain was categorized as low, unclear, or high risk of bias, consistent with the RoB 1 framework (38).

The existing graphical risk-of-bias summary and study-level matrix are retained unchanged because they were produced as part of the quantitative analysis. They are therefore explicitly described as RoB 1 figures, not as assessments performed using the newer RoB 2 tool.

The presence of Simonds et al. in the historical risk-of-bias matrix is acknowledged as a methodological artifact because the study was later confirmed to be retrospective rather than randomized (34). Its risk-of-bias representation is therefore not interpreted as a valid randomized-trial assessment in the updated narrative.

Small-Study Effects and Publication Bias

Funnel plots were generated during the analysis for selected treatment-outcome comparisons and are retained in the manuscript as exploratory descriptive figures.

Funnel-plot asymmetry cannot be equated directly with publication bias because asymmetry may arise from between-study heterogeneity, methodological differences, selective reporting, chance or other small-study effects (39).

Methodological guidance cautions against formal interpretation of funnel-plot asymmetry when fewer than approximately 10 studies are included because statistical power is low and apparent asymmetry may be unreliable (39). The principal drug-specific meta-analyses in this review contain substantially fewer than 10 studies. They are retained only to document the analysis, and any consideration of publication bias is incorporated cautiously within the broader certainty-of-evidence assessment.

Certainty of Evidence

The certainty of evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework (40,41).

GRADE categorizes certainty as high, moderate, low or very low and evaluates five principal domains that may reduce confidence in randomized evidence:

- risk of bias;
- inconsistency;
- indirectness;
- imprecision; and
- publication bias (40,41).

Randomized evidence begins at high certainty and may be downgraded when limitations within these domains reduce confidence that the estimated effect approximates the true treatment effect (40,41).

GRADE judgments were interpreted at the outcome level, rather than assigning one overall certainty designation to an intervention or to the review as a whole. This is important because the certainty associated with epistaxis frequency may differ substantially from that associated with duration, hemoglobin concentration, ESS or adverse events. Wide confidence intervals crossing the null and encompassing potentially meaningful benefit or harm warrant cautious interpretation under GRADE (40,41).

Similarly, publication bias was not regarded as “strongly suspected” solely because a funnel plot containing only a few studies appeared visually asymmetric. Such an inference would be inconsistent with accepted guidance on funnel-plot interpretation and GRADE assessment (39-41).

The existing GRADE Summary-of-Findings tables are therefore interpreted as relating specifically to the quantitative comparisons rather than as representing the certainty of the entire pharmacological evidence base.

Integration of the Meta-Analysis With the Updated Evidence

The forest plots, pooled effect estimates, heterogeneity statistics and associated graphical analyses remain unchanged. They are explicitly described throughout the manuscript as the quantitative synthesis.

The additional randomized evidence identified during the supplementary evidence update is presented separately as an updated contextual synthesis. This evidence is used to determine whether newer randomized findings support, qualify or differ from the patterns observed in the pooled subset, but it is not represented as contributing statistically to those historical pooled estimates.

This distinction is particularly important because earlier and contemporary HHT trials differ substantially in route of administration, drug formulation, duration of follow-up, crossover versus parallel design and outcome definition. Previous systematic reviews have demonstrated that not all randomized HHT epistaxis trials are statistically combinable even when they address the same overall clinical problem (26,27).

Accordingly, a nonsignificant pooled result is interpreted as failure to demonstrate a statistically clear effect within the quantitative subset, rather than evidence that the treatment has been conclusively shown to be ineffective. Conversely, a favorable newer trial is not described as altering a pooled estimate unless that trial actually contributed to the meta-analysis.

Ethical Considerations

The review synthesized aggregate information from previously published studies and did not involve recruitment of new participants, collection of identifiable personal data or direct intervention by the review authors. Separate institutional ethical approval and individual informed consent were therefore not required for the systematic review itself.

RESULTS

Study Selection and Composition of the Evidence Base

The database search identified 2,240 records: 2,220 from PubMed, 18 from Scopus, and 2 from Web of Science. After removal of 390 duplicate records, 1,850 records underwent title and abstract screening. Of these, 1,802 were excluded and 48 reports proceeded to full-text assessment. The source PRISMA record documented 36 full-text exclusions and 12 studies entering the quantitative synthesis. The explicitly listed exclusion categories accounted for 21 reports (no control group, n=2; different intervention, n=4; case reports, n=10; case series, n=5), while the remaining 15 exclusions were grouped under other reasons in the source record. These figures are retained as the historical study-selection pathway shown in Figure 1.

Accordingly, all pooled estimates reported below refer only to the studies represented in the figures, whereas additional eligible randomized trials are summarized separately in the contextual evidence update.

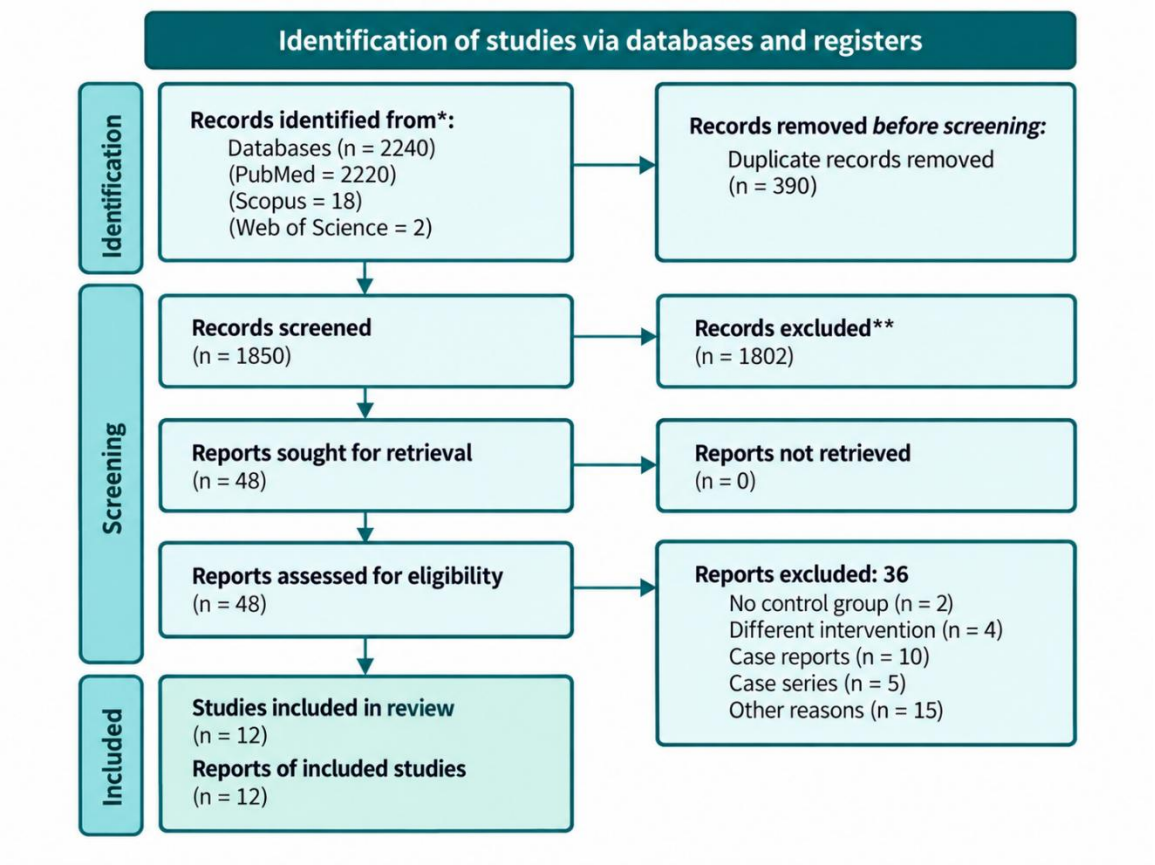

Figure 1. PRISMA-style flow diagram documenting the historical search and study-selection process.

The figure is reproduced unchanged. The "reports not retrieved" field was left blank and the listed full-text exclusion reasons account for 21 of 36 exclusions; these limitations are clarified in the accompanying Results narrative rather than retrospectively altering the legacy figure.

Characteristics of the Quantitative Subset

The quantitative subset comprised comparative studies of bevacizumab, tranexamic acid (TXA), timolol, and estrogen-based therapy. It included the North American multi-arm trial by Whitehead et al. (19), the randomized bevacizumab trial by Dupuis-Girod et al. (20), the submucosal bevacizumab trial by Riss et al. (42), the crossover TXA trial by Geisthoff et al. (43), the European crossover TXA trial by Gaillard et al. (18), the ELLIPSE bevacizumab dose-escalation trial by Dupuis-Girod et al. (44), the estrogen trial by Vase (45), the bevacizumab/electrocautery trial by Khanwalkar et al. (46), the intravenous bevacizumab trial by Dupuis-Girod et al. (47), and the timolol trials by Dupuis-Girod et al. (23) and Peterson et al. (24). The dataset also contained Simonds et al. (34), which source-level reassessment confirmed to be a retrospective comparative study rather than a randomized trial. It is therefore retained only as part of the legacy quantitative subset and is not counted as randomized evidence in the updated interpretation.

Table 1. Characteristics of studies represented in the quantitative synthesis

Study / design	Randomized or analyzed sample	Intervention and comparator	Follow-up	Principal outcomes represented
Whitehead et al., 2016 (19) Multicenter double-blind RCT	121 randomized BV 29; estriol 31; TXA 33; placebo 28	Intranasal BV 1%, estriol 0.1%, or TXA 10% vs saline placebo	12 weeks treatment; later follow-up	Epistaxis frequency and duration, ESS, hemoglobin, ferritin, transfusion, adverse events
Dupuis-Girod et al., 2016 (20) Multicenter phase 2/3 RCT	80 randomized BV 59; placebo 21	BV nasal spray 25, 50, or 75 mg vs placebo	6 months	Monthly epistaxis duration, safety, hematologic outcomes
Riss et al., 2015 (42) Double-blind RCT	15 randomized BV 9; placebo 6	Single intranasal submucosal BV 100 mg vs placebo	12 weeks	Epistaxis duration, VAS, ESS

Study / design	Randomized or analyzed sample	Intervention and comparator	Follow-up	Principal outcomes represented
Geisthoff et al., 2014 (43) Double-blind crossover RCT	22 in intention-to-treat analysis	Oral TXA 1 g three times daily vs placebo	3 months per period	Hemoglobin and epistaxis score
Gaillard et al., 2014 (18) Multicenter crossover RCT	135 randomized; 118 contributed to modified ITT analysis	Oral TXA 3 g/day vs placebo	3 months per period	Epistaxis duration and frequency, hemoglobin, safety
Dupuis-Girod et al., 2014 (44) Phase 1 randomized dose-escalation trial	40 randomized	Single-dose BV nasal spray 12.5-100 mg vs placebo	Approximately 3 months	Safety; exploratory epistaxis efficacy
Vase, 1981 (45) Double-blind RCT	31 randomized Estrogen 17; placebo 14	Oral estradiol valerate 4 mg/day vs placebo	3-month treatment after control period	Bleeding frequency/intensity, hemoglobin, transferrin
Khanwalkar et al., 2022 (46) Double-blind RCT	39 enrolled; 37 completed	Submucosal BV vs saline; both groups received bipolar electrocautery	6 months	ESS and quality of life
Dupuis-Girod et al., 2023 (47) Multicenter phase 2 RCT	24 randomized 12 per group	IV BV 5 mg/kg every 14 days for six doses vs placebo	6 months	Transfusion requirement, hemoglobin, ESS, epistaxis duration/frequency, adverse events
Dupuis-Girod et al., 2019 (23) Double-blind RCT	58 randomized	Timolol 0.5% nasal spray vs placebo	28-day treatment; assessment to 4 months	Monthly epistaxis duration, adverse events
Peterson et al., 2020 (24) Double-blind RCT	27 randomized; 23 completed primary outcome	Timolol 0.1% thermosensitive intranasal gel vs placebo gel	8 weeks	ESS, NOSE-HHT, hemoglobin, adverse events
Simonds et al., 2009 (34) Retrospective comparative study	19 total BV+KTP 10; historical KTP control 9	KTP laser + submucosal BV 100 mg vs historical KTP laser control	Pre/post follow-up	Epistaxis frequency/severity, transfusion requirement, quality of life

Abbreviations: BV, bevacizumab; ESS, Epistaxis Severity Score; IV, intravenous; KTP, potassium titanyl phosphate; NOSE-HHT, Nasal Outcome Score for Epistaxis in HHT; RCT, randomized controlled trial; TXA, tranexamic acid; VAS, visual analog scale. Simonds et al. is shown because it contributed to the legacy quantitative figures.

Risk of Bias in the Quantitative Subset

The Cochrane RoB 1 assessment showed that random-sequence generation, allocation procedures, participant/personnel blinding, outcome-assessor blinding, and selective reporting were judged predominantly at low risk across the included randomized studies. The principal concentration of high-risk judgments occurred in incomplete outcome data, while the other-bias domain was more variable. The study-level matrix also demonstrated that several trials had high-risk attrition judgments despite otherwise favorable assessments across blinding and selection domains. These patterns are consistent with the small, longitudinal HHT trial literature, in which loss to follow-up and incomplete outcome measurement can materially affect precision.

The legacy matrix includes Simonds et al. (34); however, because that study is retrospective, its RoB 1 row is retained only as a record of the analysis and should not be interpreted as a randomized-trial risk-of-bias assessment. Vase (45) also had limited reporting across several methodological domains in the matrix, reducing confidence in domain-level judgments for that older trial.

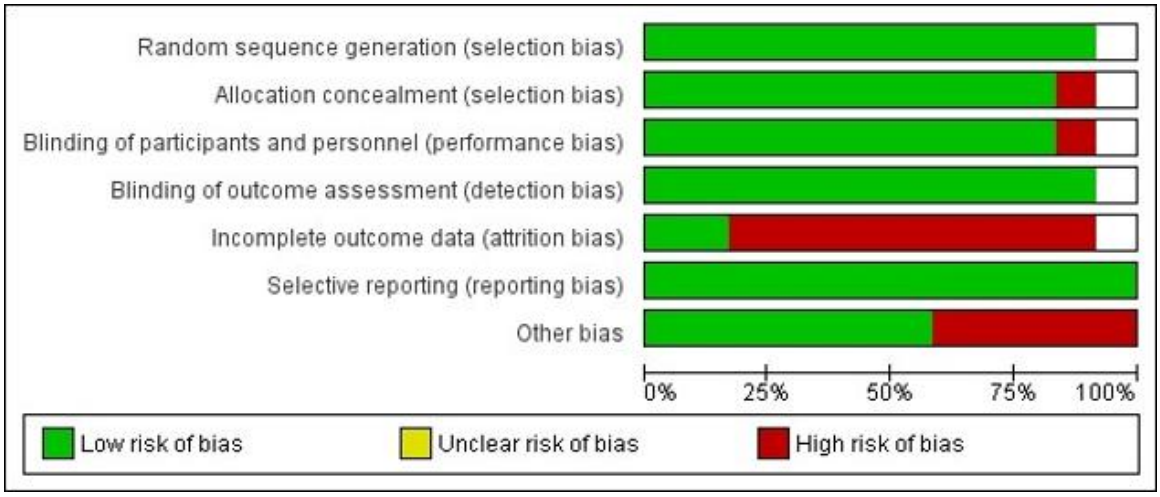

Figure 2A. Domain-level summary of risk-of-bias judgments in the quantitative evidence set.

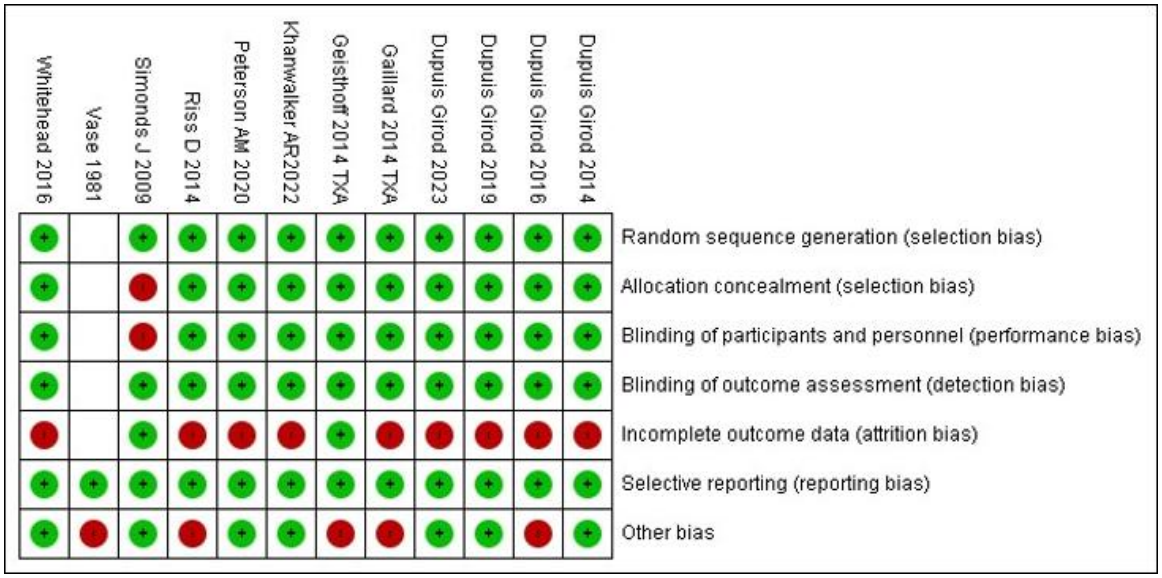

Figure 2B. Study-level risk-of-bias judgments for studies represented in the quantitative synthesis. The Simonds 2009 row is retained, however, the study is retrospective rather than randomized.

Quantitative Synthesis

The following estimates reproduce the existing RevMan outputs without recalculation. Because the quantitative dataset could not be rerun, the numerical estimates, study weights, and heterogeneity statistics are reported as displayed in the forest plots. For hemoglobin outcomes, clinical direction should be interpreted from the sign and magnitude of the mean difference rather than from generic inherited axis labels in the legacy plots.

Bevacizumab

Epistaxis frequency was pooled across four bevacizumab comparisons involving 134 participants represented in Dupuis-Girod 2014, Dupuis-Girod 2016, Whitehead 2016, and Dupuis-Girod 2023 (19,20,44,47). The pooled mean difference (MD) was -0.30 episodes in the analysis scale (95% CI -5.17 to 4.58; p=0.90), with no observed statistical heterogeneity (I^2=0%). The confidence interval crossed the null and encompassed both possible reduction and possible increase, providing no statistically significant evidence of a frequency benefit within the pooled subset.

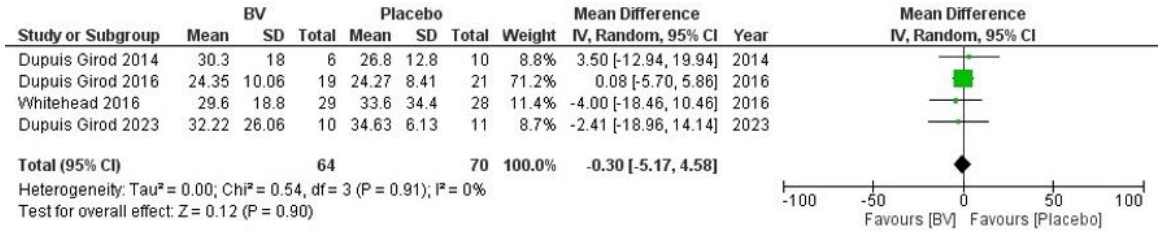

Figure 3. Epistaxis frequency: bevacizumab versus placebo in the quantitative synthesis.

Epistaxis duration was pooled across five bevacizumab comparisons involving 149 participants (19,20,42,44,47). The random-effects estimate favored bevacizumab numerically but was not statistically significant (MD -26.87 minutes/month, 95% CI -112.32 to 58.58; p=0.54). Heterogeneity was moderate (I^2=47%), and the wide confidence interval indicates substantial uncertainty around the magnitude and direction of the average effect. The result therefore supports a possible reduction in duration but does not establish superiority over placebo in the pooled dataset.

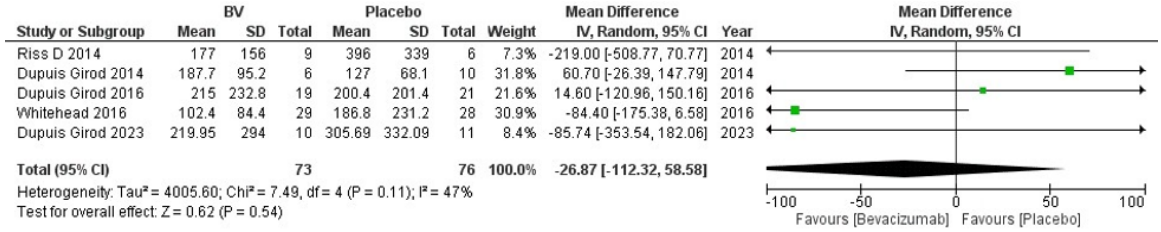

Figure 4. Epistaxis duration: bevacizumab versus placebo in the quantitative synthesis

The legacy bevacizumab safety pool contained four comparative datasets with 60 participants in the bevacizumab groups and 55 in the control groups, with 42 and 37 events, respectively (42).. The pooled risk ratio (RR) was 1.00 (95% CI 0.85 to 1.19; p=0.97; I^2=0%), indicating no detectable difference in the pooled event incidence as represented in the figure (19,34,42,47). Interpretation requires caution because Simonds et al. (34) is nonrandomized and because adverse-event definitions and routes of bevacizumab administration differed across studies.

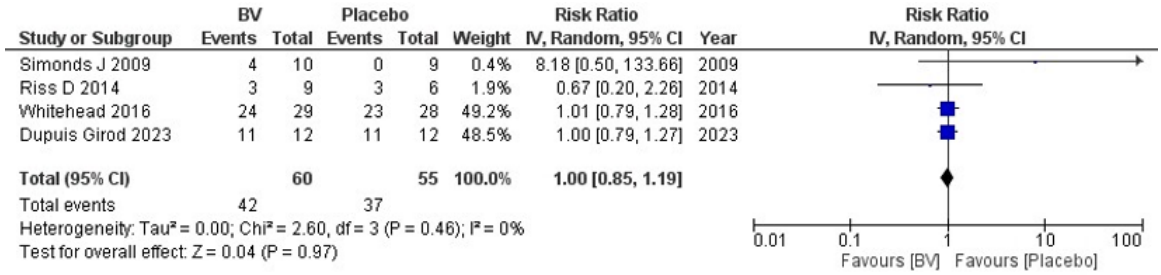

Figure 5. Adverse events: bevacizumab versus placebo in the quantitative synthesis. The pooled figure includes Simonds et al. 2009 (34), a retrospective comparative study; this limits randomized-evidence interpretation of the pooled safety estimate.

Three studies contributed to the primary bevacizumab hemoglobin analysis (19,20,47), comprising 120 participants. The pooled MD was 0.37 (95% CI -0.86 to 1.60; p=0.56), with substantial heterogeneity (I^2=69%). Thus, the pooled analysis did not demonstrate a statistically significant between-group difference in hemoglobin concentration. In the existing sensitivity analysis, one study was assigned zero weight, leaving 97 participants; the pooled estimate shifted to -0.17 (95% CI -1.31 to 0.98; p=0.78) and heterogeneity decreased to I^2=40%. The sensitivity analysis therefore reduced inconsistency but did not alter the conclusion of statistical nonsignificance.

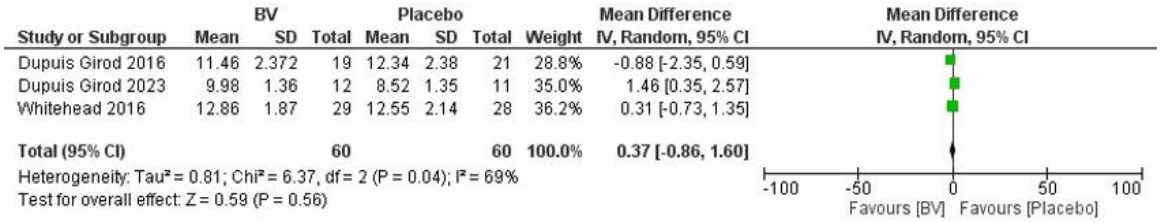

Figure 6. Mean hemoglobin concentration: bevacizumab versus placebo.

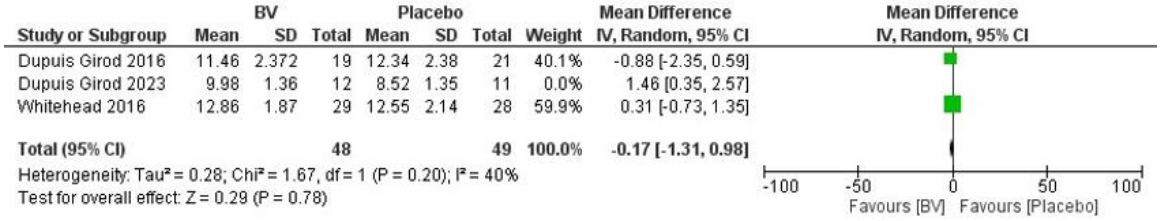

Figure 7. Sensitivity analysis of mean hemoglobin concentration: bevacizumab versus placebo.

ESS was pooled across four bevacizumab comparisons involving 123 participants from Riss, Whitehead, Khanwalkar, and Dupuis-Girod 2023 (19,42,46,47). In contrast to the earlier prose version of the manuscript, the forest plot shows a pooled MD of -0.22 points (95% CI -0.38 to -0.05; p=0.010), with low heterogeneity (I^2=14%). This represents a statistically significant but small average reduction in ESS favoring bevacizumab within the pooled subset. The magnitude should nevertheless be interpreted in the context of differences in route, co-intervention, baseline severity, and study design.

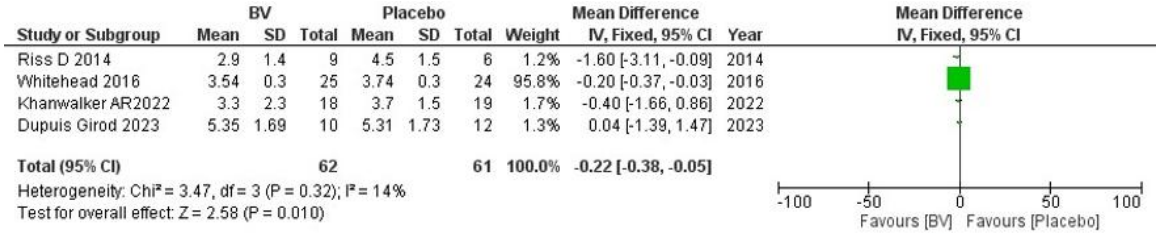

Figure 8. Epistaxis Severity Score: bevacizumab versus placebo.

Timolol

Two timolol comparisons contributed to the legacy adverse-event analysis, with 42 participants in each group and 23 versus 18 adverse events. The pooled RR was 1.33 (95% CI 0.67 to 2.67; p=0.41), with moderate heterogeneity (I^2=38%). The confidence interval was wide and included both lower and substantially higher event risk, so the pooled analysis does not establish a difference in overall adverse-event risk (23,24).

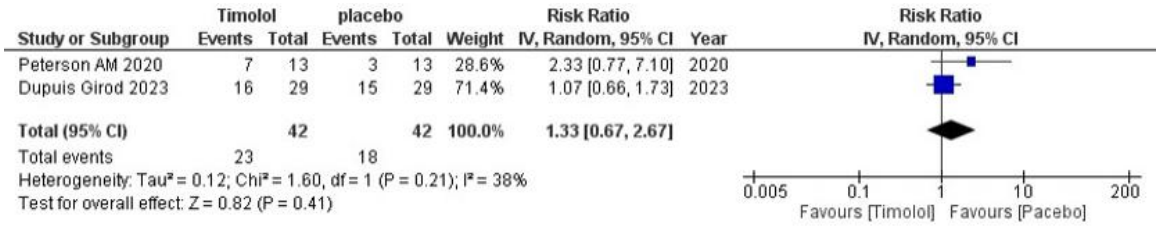

Figure 9. Adverse events: timolol versus placebo. The legacy figure labelled Dupuis Girod 2023 represents the relevant timolol randomized trial is Dupuis-Girod et al. 2019 (23).

For mean hemoglobin concentration, the two timolol trials contributed 85 participants. The pooled MD was 0.80 (95% CI -0.52 to 2.11; p=0.24), with no observed heterogeneity (I^2=0%). Although the point estimate was positive, the confidence interval crossed zero and the analysis did not demonstrate a statistically significant hematological advantage of timolol over placebo (23,24).

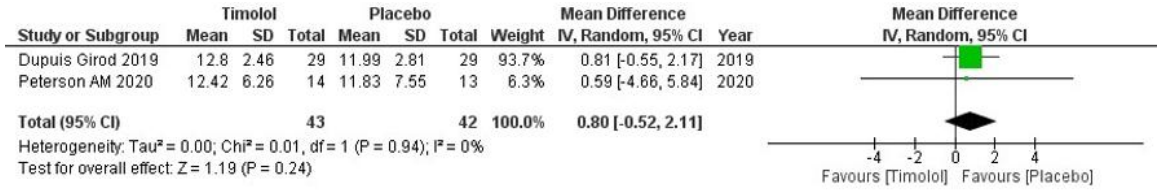

Figure 10. Mean hemoglobin concentration: timolol versus placebo.

Tranexamic Acid

The primary legacy analysis of epistaxis frequency combined three TXA datasets from Gaillard, Geisthoff, and Whitehead, representing 99 intervention-period/arm observations and 100 placebo-period/arm observations in the displayed forest plot (18,19,43). The pooled MD was -7.36 (95% CI -20.20 to 5.48; p=0.26), but heterogeneity was considerable (I^2=94%). The pooled point estimate therefore suggested fewer episodes with TXA, but the uncertainty was wide and the studies were highly inconsistent.

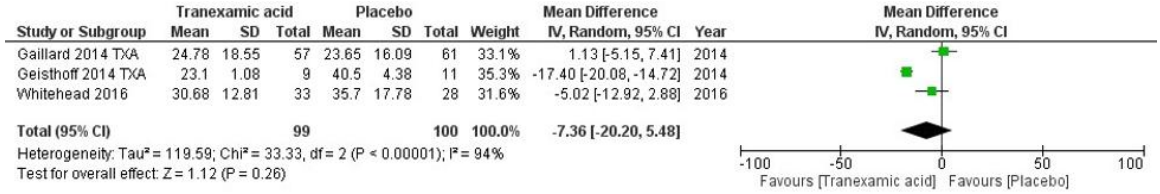

Figure 11. Epistaxis frequency: tranexamic acid versus placebo, primary legacy analysis.

In the corresponding sensitivity analysis, the Geisthoff dataset was assigned zero weight, leaving 90 TXA and 89 placebo observations in the pooled calculation. The resulting MD was -1.46 (95% CI -7.41 to 4.49; p=0.63), and heterogeneity fell to I^2=30%. This analysis substantially reduced statistical inconsistency but also moved the point estimate closer to the null; the between-group effect remained nonsignificant (18,19,43).

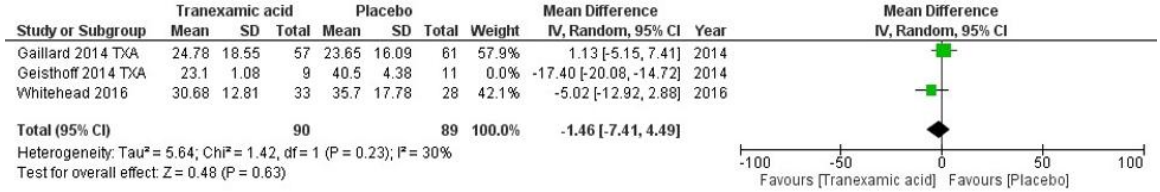

Figure 12. Sensitivity analysis of epistaxis frequency: tranexamic acid versus placebo.

For epistaxis duration, the primary three-study TXA analysis included 99 TXA and 100 placebo observations and produced an MD of -54.67 minutes/month (95% CI -176.12 to 66.79; p=0.38), with considerable heterogeneity (I^2=93%) (18,19,43). A route-oriented sensitivity analysis excluded the Whitehead intranasal dataset from the pooled weight, leaving the two oral crossover trials; the resulting MD was -86.82 minutes/month (95% CI -288.00 to 114.37; p=0.40), but heterogeneity remained very high (I^2=96%). Thus, neither the primary nor sensitivity analysis established a statistically significant effect on epistaxis duration, and the large between-study inconsistency remained unresolved.

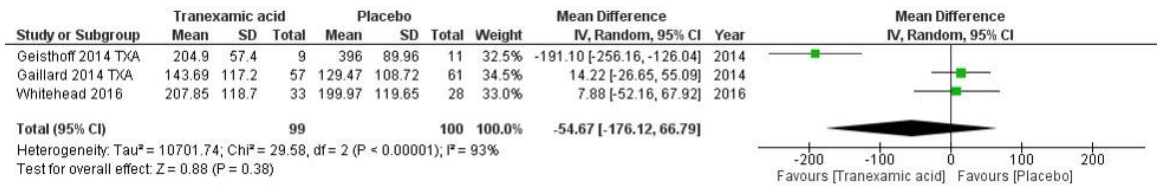

Figure 13. Epistaxis duration: tranexamic acid versus placebo, primary legacy analysis.

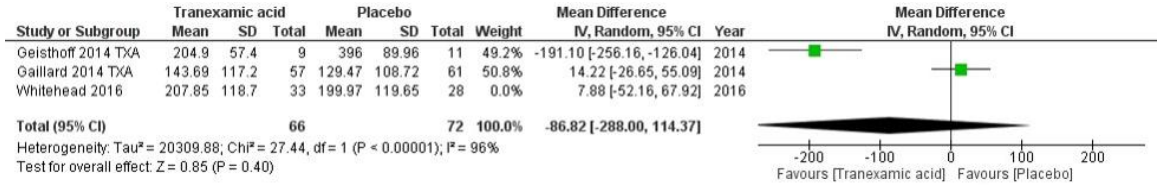

Figure 14. Sensitivity analysis of epistaxis duration after exclusion of the intranasal TXA dataset.

Mean hemoglobin concentration was also pooled across the same three TXA datasets. The primary estimate was MD -1.18 (95% CI -2.81 to 0.45; p=0.16), with considerable heterogeneity (I^2=92%). When the Whitehead intranasal dataset was excluded from the pooled weight, the sensitivity estimate was MD -0.32 (95% CI -0.98 to 0.34; p=0.34) and heterogeneity decreased to I^2=0%. The sensitivity analysis therefore removed the statistical inconsistency apparent in the primary analysis, but neither estimate demonstrated a significant difference in hemoglobin concentration (18,19,43).

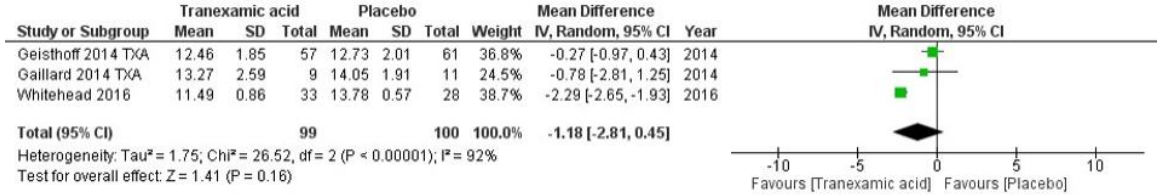

Figure 15. Mean hemoglobin concentration: tranexamic acid versus placebo, primary legacy analysis.

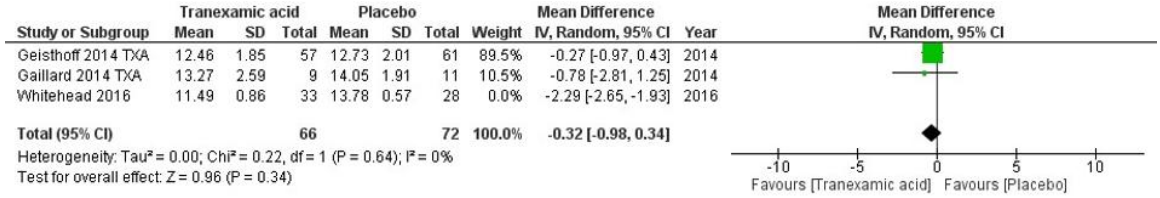

Figure 16. Sensitivity analysis of mean hemoglobin concentration after exclusion of the intranasal TXA dataset.

Estrogen / Estriol

Two estrogen/estriol datasets, from Vase and Whitehead, contributed to the epistaxis-frequency analysis (19,45). Across 46 intervention and 41 placebo participants, the pooled MD was -2.70 episodes in the analysis scale (95% CI -8.76 to 3.36; p=0.38), with no observed heterogeneity (I^2=0%). The confidence interval crossed zero, and the pooled result did not demonstrate statistically significant superiority of estrogen-based treatment over placebo.

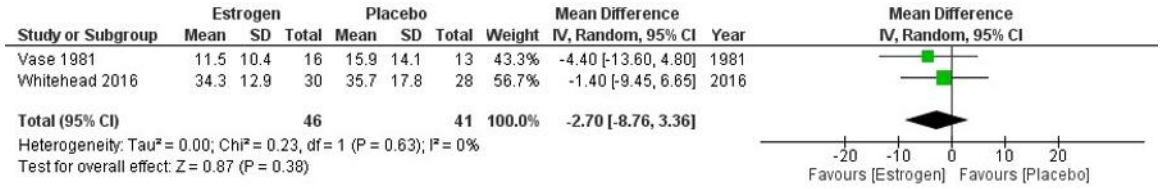

Figure 17. Epistaxis frequency: estrogen/estriol versus placebo.

Adverse-Event Profile Across Drug Classes

The categorical adverse-event table compared selected symptom groups across estriol, TXA, bevacizumab, and timolol. Most estimates were imprecise, with confidence intervals crossing 1.00. Two comparisons were statistically distinguishable from the null: estriol was associated with a lower risk of nausea and vomiting (RR 0.12, 95% CI 0.02 to 0.87), whereas TXA was associated with a higher risk of gastrointestinal symptoms (RR 2.34, 95% CI 1.51 to 3.64). Point estimates for timolol were comparatively high for nasal and cardiac symptoms, but confidence intervals were extremely wide and did not establish

a significant increase. The table should therefore be interpreted symptom-by-symptom rather than as evidence of an overall safety ranking among drugs (19,23,24).

Table 2. Adverse-event profile of pharmacological treatments versus placebo in the analysis

Adverse-event category	Estriol RR (95% CI)	TXA RR (95% CI)	Bevacizumab RR (95% CI)	Timolol RR (95% CI)
Nasal symptoms	1.03 (0.52-2.04)	0.79 (0.39-1.60)	1.19 (0.62-2.28)	3.32 (0.87-12.64)
Nausea and vomiting	0.12 (0.02-0.87)	1.20 (0.62-2.34)	0.59 (0.22-1.59)	2.80 (0.12-63.20)
Gastrointestinal symptoms	1.56 (0.41-5.91)	2.34 (1.51-3.64)	2.90 (0.87-9.61)	NA
Cardiac symptoms	NA	NA	0.82 (0.11-5.91)	6.59 (0.37-117.77)
Drowsiness and dizziness	0.19 (0.01-3.73)	2.05 (0.92-4.60)	0.48 (0.05-5.03)	1.26 (0.34-4.65)
Headache	1.87 (0.81-4.30)	1.25 (0.71-2.20)	0.61 (0.17-2.22)	1.45 (0.26-8.09)
Respiratory symptoms	0.82 (0.34-1.96)	1.17 (0.55-2.49)	0.84 (0.35-2.02)	1.61 (0.22-11.66)

Values are risk ratios with 95% confidence intervals. Bold values indicate confidence intervals excluding 1.00. NA, not available. These symptom-specific estimates reproduce the adverse-event table and should not be interpreted as a unified drug-level safety ranking.

Small-Study Effects and Funnel Plots

Five funnel plots were generated in the analysis for bevacizumab duration, bevacizumab frequency, timolol adverse events, TXA frequency, and estrogen frequency. Each comparison contained far fewer than 10 contributing studies. Consequently, the plots are retained as descriptive records of the analysis but are not used to make formal claims of publication bias or small-study effects. Apparent asymmetry in such sparse plots can arise from chance, clinical heterogeneity, or differences in study precision and cannot reliably distinguish publication bias from other explanations (39).

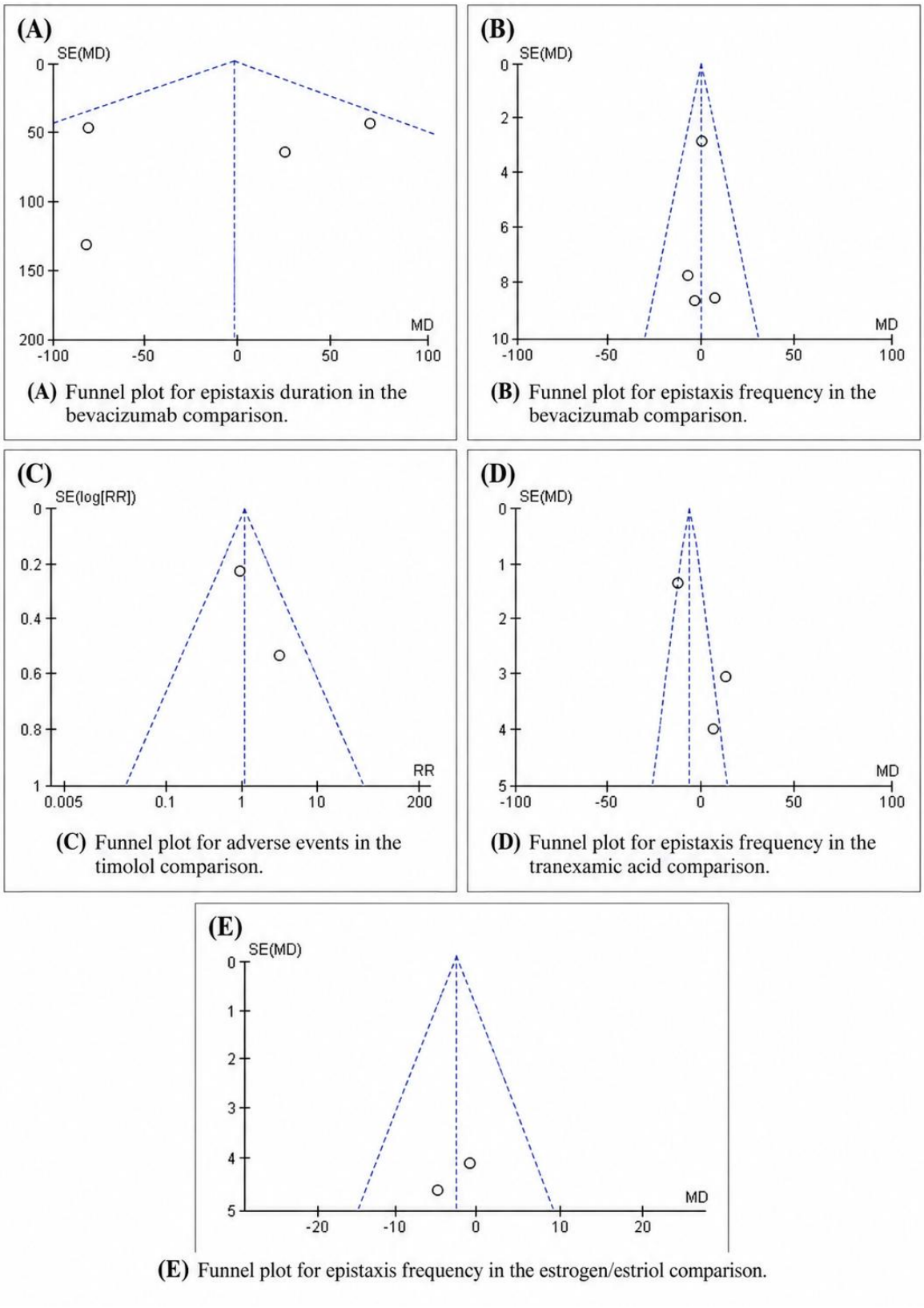

Figure 18. Funnel plots for selected bevacizumab, timolol, tranexamic acid, and estrogen/estriol outcomes.

Certainty of Evidence for the Quantitative Comparisons

The legacy GRADE assessments ranged from moderate to very low certainty across outcomes. Bevacizumab frequency, duration, and ESS were rated as moderate-certainty evidence in the GRADE outputs, while bevacizumab hemoglobin and adverse-event outcomes were rated low certainty. TXA duration, frequency, and hemoglobin; timolol adverse events and hemoglobin; and estrogen frequency were rated very low certainty. The numerical effects in Table 3 are aligned to the forest plots reproduced

above. Because the legacy GRADE files included publication-bias downgrading in several comparisons with only two or three studies, those publication-bias judgments are not treated as independently; the certainty labels are presented as the GRADE classifications rather than as a newly rerun GRADE assessment (39-41).

Table 3. Summary of pooled effects and legacy GRADE certainty

Intervention / outcome	Studies; participants	Pooled effect (95% CI)	I^2	Legacy GRADE certainty
Bevacizumab - epistaxis frequency	4; 134	MD -0.30 (-5.17 to 4.58)	0%	Moderate
Bevacizumab - epistaxis duration	5; 149	MD -26.87 (-112.32 to 58.58)	47%	Moderate
Bevacizumab - adverse events	4; 115	RR 1.00 (0.85 to 1.19)	0%	Low
Bevacizumab - hemoglobin	3; 120	MD 0.37 (-0.86 to 1.60)	69%	Low
Bevacizumab - ESS	4; 123	MD -0.22 (-0.38 to -0.05)	14%	Moderate
TXA - epistaxis frequency	3; 199	MD -7.36 (-20.20 to 5.48)	94%	Very low
TXA - epistaxis duration	3; 199	MD -54.67 (-176.12 to 66.79)	93%	Very low
TXA - hemoglobin	3; 199	MD -1.18 (-2.81 to 0.45)	92%	Very low
Timolol - adverse events	2; 84	RR 1.33 (0.67 to 2.67)	38%	Very low
Timolol - hemoglobin	2; 85	MD 0.80 (-0.52 to 2.11)	0%	Very low
Estrogen/estriol - frequency	2; 87	MD -2.70 (-8.76 to 3.36)	0%	Very low

ESS, Epistaxis Severity Score; MD, mean difference; RR, risk ratio; TXA, tranexamic acid. The certainty categories reproduce the legacy GRADE outputs. For bevacizumab ESS, the pooled numerical estimate is taken from Figure 8 because the legacy GRADE file contained a discordant effect estimate. The bevacizumab adverse-event pool includes the nonrandomized Simonds study (34), which limits interpretation of its legacy certainty classification.

Stage Contextual Randomized Evidence

The evidence audit identified randomized pharmacological evidence not represented in the forest plots. These trials were not added retrospectively to the meta-analysis; their results are reported as study-level randomized evidence to place the legacy pooled findings in the wider therapeutic context. The additional evidence included tamoxifen, postoperative topical estriol, propranolol, tacrolimus, two doxycycline trials, an additional timolol crossover trial, pomalidomide, and nintedanib (22,25,28,29,48-52). This broader randomized landscape is consistent with the subsequent network meta-analysis, which identified substantially more randomized HHT epistaxis trials than were represented in the historical pooled subset (27).

Table 4. Additional randomized pharmacological evidence identified in the contextual audit

Study / intervention	Design and sample	Principal randomized outcome	Objective result
Yaniv et al., 2009 (48) Tamoxifen 20 mg/day	Double-blind placebo-controlled RCT; 25 randomized, 21 completed	Epistaxis frequency and severity	Improvement favored tamoxifen; frequency p=0.01 and severity p=0.049 in the reported trial analysis.
Bergler et al., 2002 (49) Topical estriol after APC	Randomized comparative trial; n=26	Bleeding frequency/intensity at 12 months	Both arms received APC; postoperative estriol produced lower bleeding frequency/intensity than dexpanthenol and higher treatment satisfaction (93% vs 42%).
Mei-Zahav et al., 2020 (22) Topical propranolol 1.5% gel	Double-blind placebo-controlled RCT; 23 initially randomized, 20 completed	Change in ESS	ESS change was -2.03 +/- 1.70 with propranolol versus -0.35 +/- 0.68 with placebo; between-group difference was significant (p=0.009).
Dupuis-Girod et al., 2020 (25) Tacrolimus 0.1% nasal ointment	Multicenter double-blind placebo-controlled RCT; n=50	Epistaxis duration	The post-treatment primary between-group comparison was not significant (p=0.77), although a during-treatment time effect was reported.
McWilliams et al., 2022 (50) Oral doxycycline (NOSTRIL)	Randomized placebo-controlled crossover RCT; n=22	ESS, epistaxis frequency and duration	The prespecified primary outcomes were not significantly improved; reported p values included frequency p=0.16, duration p=0.05, and ESS p=0.19.
Thompson et al., 2022 (51) Oral doxycycline	Double-blind placebo-controlled crossover RCT; n=13	Weekly epistaxis duration and frequency	No significant treatment effect on duration (p=0.136) or frequency (p=0.261); hemoglobin was higher

Study / intervention	Design and sample	Principal randomized outcome	Objective result
			during doxycycline exposure (p=0.0499).
Andorfer et al., 2022 (52) Timolol nasal spray plus standard laser	Randomized double-blind placebo-controlled crossover RCT; 20 treated, 18 completed both sequences	ESS at 3 months	The 3-month primary ESS comparison favored timolol numerically but was not significant (p=0.084); the 1-month ESS comparison favored timolol (p=0.010).
Al-Samkari et al., 2024 (28) Pomalidomide 4 mg/day	Multicenter randomized placebo-controlled trial; n=144	Change in ESS at 24 weeks	Pomalidomide reduced ESS versus placebo by MD -0.94 (95% CI -1.57 to -0.31; p=0.004) and improved HHT-specific quality of life.
Hermann et al., 2024 (29) Nintedanib	Multicenter phase 2 randomized double-blind placebo-controlled trial; n=60	>=50% reduction in mean monthly epistaxis duration	Primary responder outcome: 43.3% vs 26.7% (p=0.28). Secondary analyses showed greater median epistaxis reduction (57% vs 27%; p=0.013) and hemoglobin change (+18 vs -1 g/L; p=0.02).

APC, argon plasma coagulation; ESS, Epistaxis Severity Score; HHT, hereditary hemorrhagic telangiectasia; MD, mean difference; RCT, randomized controlled trial. These studies are presented as contextual randomized evidence and were not incorporated into the forest plots.

The contextual randomized evidence therefore broadens the pharmacological landscape beyond the four drug classes emphasized in the meta-analysis. In particular, the large PATH-HHT trial provides randomized evidence of a clinically relevant ESS reduction with pomalidomide, whereas EPICURE did not meet its primary binary responder endpoint despite favorable secondary changes in epistaxis duration and hemoglobin (28,29). The additional propranolol, tacrolimus, doxycycline, and TIM-HHT trials likewise show that treatment effects differ according to drug, formulation, outcome definition, and follow-up period (22,25,50-52). These findings are reported descriptively and do not modify the pooled effect estimates.

DISCUSSION

Principal Findings

This systematic review demonstrates that the pharmacological evidence for HHT-related epistaxis is broader and more heterogeneous than the meta-analytic dataset alone suggests. In the preserved quantitative synthesis, most pooled comparisons did not demonstrate statistically significant superiority over placebo for epistaxis frequency, epistaxis duration, hemoglobin concentration, or overall adverse-event risk. The most consistent pooled efficacy signal was a small reduction in ESS with bevacizumab (MD -0.22, 95% CI -0.38 to -0.05; I2=14%). By contrast, the TXA analyses were characterized by very high heterogeneity, the timolol analyses were imprecise, and the estrogen/estriol frequency analysis crossed the null. These findings broadly reinforce earlier conventional and network meta-analyses showing that no single pharmacological intervention has demonstrated uniform benefit across all clinically relevant HHT epistaxis outcomes (26,27).

The interpretation is intentionally more cautious because evidence audit identified an important distinction between the historical quantitative subset and the wider randomized literature. The pooled figures remain useful as a record of the analyses that were actually performed, but they should not be interpreted as a complete meta-analysis of every eligible randomized trial available by February 2025. This distinction is clinically important because newer randomized evidence includes treatment classes and outcome structures not represented in the legacy forest plots, including propranolol, tacrolimus, doxycycline, additional timolol data, pomalidomide, and nintedanib (22,25,28,29,50-52).

Bevacizumab: Route-Dependent Signals Within an Inconsistent Evidence Base

Bevacizumab has the largest representation in the quantitative synthesis and illustrates the central problem of combining clinically diverse HHT trials. The pooled analyses did not demonstrate statistically significant reductions in epistaxis frequency or duration, nor a significant improvement in

hemoglobin concentration. The ESS analysis, however, favored bevacizumab by a small but statistically significant amount. Importantly, this ESS estimate is concordant with the later bevacizumab-specific meta-analysis by Chen et al., which also reported an ESS reduction of approximately 0.22 points while finding no significant pooled benefit for epistaxis frequency or duration (53). Earlier systematic review evidence likewise concluded that intranasal bevacizumab had not shown a consistent advantage for frequency, duration, severity, or quality of life (21).

Trial-level findings help explain why a single pooled summary can obscure route-specific effects. Intranasal spray studies, including the multicenter trial by Dupuis-Girod et al. and the North American multi-arm trial by Whitehead et al., did not demonstrate clear superiority over placebo for their principal epistaxis endpoints (19,20). The ELLIPSE study established tolerability of intranasal bevacizumab across escalating doses but did not demonstrate efficacy in that phase 1 setting (44). Riss et al. reported a numerically favorable but imprecise response after submucosal bevacizumab injection, while Khanwalkar et al. evaluated bevacizumab as an adjunct to a common electrocautery procedure and observed clinically relevant ESS improvement at selected follow-up points without establishing an unequivocal independent treatment effect across all analyses (42,46). These trials differ in formulation, local exposure, background treatment, baseline bleeding burden, and outcome measurement, making a universal route-independent effect biologically and statistically unlikely.

The randomized trial of intravenous bevacizumab published by Dupuis-Girod et al. in 2023 is particularly relevant to contemporary interpretation because it evaluates systemic therapy in patients with severe HHT-associated bleeding rather than simply local nasal drug delivery (47). Although the primary randomized endpoint did not provide definitive evidence of superiority, secondary hematological and epistaxis-related signals favored systemic treatment in selected analyses. This pattern is compatible with the broader clinical literature in which systemic bevacizumab is used for severe bleeding phenotypes and other HHT complications, but such evidence should not be extrapolated to imply that intranasal, submucosal, and intravenous administration are therapeutically equivalent (1,16,47). The current review therefore does not support a blanket statement that bevacizumab is a first-line epistaxis therapy; rather, the evidence suggests that route, disease severity, clinical objective, and safety profile should determine where bevacizumab fits within an individualized treatment pathway (1,16).

Tranexamic Acid: Statistical Heterogeneity and the Importance of Trial Design

The legacy TXA analyses produced nonsignificant pooled effects for epistaxis frequency, duration, and hemoglobin concentration, with I2 values of 92%-94% in the primary analyses. Such heterogeneity is not a minor statistical inconvenience; it reflects fundamental differences in route, endpoint structure, and study design. Gaillard et al. and Geisthoff et al. used randomized crossover designs with oral TXA, whereas Whitehead et al. evaluated intranasal TXA in a parallel multi-arm trial (18,19,43). The native trial analyses therefore do not represent interchangeable parallel-group mean differences.

The individual oral TXA trials nevertheless provide evidence of biological and clinical activity. Gaillard et al. reported a significant reduction in cumulative monthly epistaxis duration under oral TXA, while Geisthoff et al. reported improvement in an epistaxis score despite no significant hemoglobin effect (18,43). In contrast, topical intranasal TXA in the Whitehead trial did not significantly reduce the primary frequency endpoint relative to saline placebo (19). The later network meta-analysis also found a significant reduction in epistaxis frequency with TXA compared with placebo, although its pooled framework and included trial set differed from the legacy analysis reproduced here (27). These findings support the interpretation that the apparent conflict between the present pooled null effect and positive trial-level findings is driven partly by analytical incompatibility rather than by a simple absence of pharmacological activity.

This distinction is also consistent with the Second International HHT Guidelines, which recommend consideration of oral tranexamic acid for epistaxis that does not respond adequately to moisturizing

topical therapy (1). The guideline position should not be interpreted as proof that all formulations are effective or that every patient will respond. Instead, the available data support oral TXA as a reasonable option in selected patients with persistent bleeding, while the highly heterogeneous meta-analytic estimates in the present review should be interpreted with low confidence and without assuming equivalence between oral and topical administration (1,18,19,27,43).

Beta-Blockers: Promising ESS Effects but Limited Precision

The beta-blocker evidence illustrates the difference between class-level promise and treatment-specific certainty. In the quantitative subset, timolol did not significantly alter hemoglobin concentration and the adverse-event RR was imprecise, with a confidence interval compatible with both lower and substantially higher event risk. The principal randomized timolol nasal-spray trial also failed to demonstrate a significant improvement in its primary epistaxis-duration endpoint (23). Peterson et al. reported improvement in both the timolol gel and placebo gel groups, with numerically greater patient-reported improvement in the timolol group but insufficient precision to establish definitive superiority (24).

The later TIM-HHT crossover trial added evidence that the effect of timolol may be time dependent: the primary three-month ESS comparison favored timolol numerically but was not statistically significant, whereas a one-month comparison was significant (52). This temporal pattern argues against interpreting timolol as uniformly effective and suggests that formulation, adjunctive laser therapy, duration of use, and background nasal care may modify treatment response. By comparison, the small randomized propranolol trial demonstrated a substantially larger ESS improvement than placebo, with a between-group change consistent with the favorable estimate reported in the subsequent network meta-analysis (22,27). Thus, beta-blockade remains a plausible therapeutic strategy, but current evidence is stronger for a signal of symptom improvement than for durable hematological benefit or a clearly established class-wide effect (22-24,27,52).

Hormonal and Anti-Estrogen Therapies: Heterogeneous Mechanisms Should Not Be Collapsed

The estrogen/estriol frequency meta-analysis did not show a statistically significant reduction in epistaxis frequency. This finding is consistent with the older double-blind trial by Vase, in which oral estradiol valerate did not significantly reduce bleeding frequency or intensity and did not improve hemoglobin concentration (45). Whitehead et al. likewise did not show a significant frequency benefit for intranasal estriol compared with saline placebo (19). These findings argue against treating estrogen-based therapies as a homogeneous evidence category with a reliably positive effect.

However, the contextual evidence demonstrates that other hormonal approaches cannot be dismissed on the basis of this pooled result alone. Yaniv et al. reported significant improvement in epistaxis frequency and severity with tamoxifen compared with placebo, while Bergler et al. found that postoperative topical estriol after argon plasma coagulation produced greater improvement in bleeding frequency and intensity than dexpanthenol after the same procedure (48,49). Tamoxifen is pharmacologically distinct from estrogen replacement, and Bergler evaluated estriol as an adjunct to a procedural co-intervention; neither study is directly interchangeable with the legacy estrogen frequency pool. The network meta-analysis similarly treated these interventions separately and identified qualitative benefit for tamoxifen and estriol in selected studies (27). Accordingly, the present review supports treatment-specific interpretation rather than a global conclusion for all hormone-related therapies.

Tacrolimus and Doxycycline: Negative or Inconclusive Randomized Evidence

The audit identified additional randomized evidence for tacrolimus and doxycycline that was not represented in the forest plots. The multicenter tacrolimus trial did not show a significant post-treatment between-group difference in its primary epistaxis-duration comparison, despite a signal during

treatment (25). Two randomized crossover trials of doxycycline likewise failed to demonstrate convincing improvement in the prespecified epistaxis outcomes. The NOSTRIL trial did not significantly improve ESS, frequency, or duration, and the Thompson trial found no significant treatment effect for weekly epistaxis duration or frequency, although hemoglobin was higher during doxycycline exposure in a secondary analysis (50,51).

These findings are important because they demonstrate that plausible antiangiogenic or vascular-remodeling mechanisms do not necessarily translate into clinically meaningful epistaxis control. They also reinforce the need to privilege prespecified primary endpoints over isolated favorable secondary findings. On the current evidence, tacrolimus and doxycycline should be regarded as investigational or selectively considered therapies rather than as interventions with established efficacy for routine HHT epistaxis management (25,27,50,51).

Newer Systemic Therapies: A Shift in the Randomized Evidence Landscape

The most consequential development in the evidence update is the emergence of larger randomized trials of systemic therapy. PATH-HHT enrolled 144 participants and demonstrated that pomalidomide reduced ESS by 0.94 points relative to placebo at 24 weeks (95% CI -1.57 to -0.31; p=0.004), with accompanying improvement in HHT-specific quality of life (28). Unlike many earlier HHT epistaxis trials, PATH-HHT was sufficiently large to provide a comparatively precise treatment estimate and used a validated patient-centered bleeding outcome. Its findings materially broaden the therapeutic landscape and show that clinically relevant pharmacological benefit can be demonstrated when adequately powered trials use standardized outcomes.

EPICURE provides a complementary but more nuanced example. Nintedanib did not significantly improve the prespecified primary responder endpoint, although secondary analyses suggested greater reductions in epistaxis duration and improvement in hemoglobin concentration (29). The appropriate interpretation is therefore not that nintedanib was unequivocally effective, but that it generated a mixed signal requiring confirmation. Together, PATH-HHT and EPICURE show why contemporary HHT evidence should be interpreted trial by trial, with explicit distinction between primary and secondary endpoints, rather than being reduced to a binary classification of effective versus ineffective therapy (28,29).

These newer systemic trials also expose a limitation of the historical pooled analyses: the latter largely reflect older local or repurposed therapies and therefore do not capture the full therapeutic direction of the field. Contemporary management is increasingly influenced by systemic antiangiogenic and immunomodulatory approaches for patients with moderate-to-severe bleeding phenotypes, particularly when recurrent epistaxis is accompanied by iron deficiency, transfusion dependence, or other clinically significant HHT manifestations (1,16,28). The present review therefore positions the meta-analysis as one component of an evolving evidence base rather than as the final comparative assessment of pharmacological treatment.

Safety and Tolerability

Safety findings in the quantitative subset were generally imprecise. The pooled bevacizumab adverse-event RR was close to the null, but interpretation is weakened by route heterogeneity and by inclusion of the nonrandomized Simonds study in the legacy figure. The timolol adverse-event estimate was also imprecise, and the wide confidence interval precludes a reliable conclusion about overall risk. In the symptom-specific adverse-event table, TXA was associated with more gastrointestinal symptoms, whereas most other category-specific confidence intervals crossed the null. These results should not be converted into a simplistic ranking of drug safety because event definitions, exposure periods, and ascertainment differed substantially between trials.

Clinical safety also depends on route and systemic exposure. Topical and intranasal therapies cannot be assumed to share the same risk profile as systemic bevacizumab or newer systemic antiangiogenic agents. Contemporary HHT guidance therefore emphasizes individualized treatment selection, careful assessment of bleeding severity and comorbidity, and appropriate monitoring when systemic antiangiogenic therapy is used (1,16). Similarly, the absence of a statistically significant adverse-event difference in a small trial should not be interpreted as proof of equivalence or long-term safety. The limited sample sizes and short follow-up of many HHT trials mean that uncommon but clinically important harms may remain undetected.

Risk of Bias, Certainty of Evidence, and Publication Bias

The legacy RoB 1 assessment showed generally favorable judgments for randomization and blinding but frequent concerns regarding incomplete outcome data. Attrition is particularly important in rare-disease trials because even a small number of withdrawals can materially change precision and may introduce bias if dropout is related to treatment response or adverse effects. The presence of Simonds et al., a retrospective study, in the historical RoB matrix further illustrates why the legacy figure should be interpreted as a record of the analysis rather than a contemporary assessment of a purely randomized evidence set (34,38).

The GRADE assessments ranged from moderate to very low certainty, which is consistent with the small number of trials, wide confidence intervals, outcome heterogeneity, and methodological limitations identified throughout the review (40,41). The TXA, timolol, and estrogen outcomes were generally graded very low in the legacy assessment, while several bevacizumab outcomes were graded moderate or low. These categories should nevertheless be interpreted cautiously because the GRADE tables themselves were produced from the evidence subset and were not regenerated after the audit.

The funnel plots should likewise be regarded as descriptive only. None of the drug-specific comparisons approached the number of studies usually required for meaningful evaluation of funnel-plot asymmetry, and apparent asymmetry in sparse plots may reflect chance, heterogeneity, or differences in precision rather than publication bias (39).

Clinical Implications

The clinical implications of this review are best understood within a stepped and individualized HHT treatment framework. The Second International HHT Guidelines recommend nasal humidification and moisturizing topical measures as initial management, followed by oral TXA for persistent epistaxis and escalation to ablative procedures, systemic antiangiogenic therapy, septodermoplasty, or nasal closure according to disease severity, prior response, and patient preference (1). The findings of the present review do not justify replacing this individualized framework with a universal pharmacological hierarchy.

For patients with mild-to-moderate epistaxis, the evidence supports consideration of less invasive pharmacological approaches while acknowledging that treatment response is variable and that topical formulations often have limited trial-level superiority over placebo. Oral TXA has the strongest guideline-supported role among the older systemic hemostatic options despite heterogeneous trial results (1,18,27,43). Beta-blocker therapies may provide symptomatic benefit in selected patients, particularly when ESS is a clinically relevant target, but the current trials remain too small to establish a definitive class effect (22-24,52). Hormonal and anti-estrogen approaches should be interpreted by agent and patient context rather than pooled as a single category (19,45,48,49).

For more severe bleeding phenotypes, especially when recurrent epistaxis contributes to iron-deficiency anemia, transfusion requirement, or substantial quality-of-life impairment, the expanding evidence for systemic antiangiogenic or immunomodulatory therapy becomes increasingly relevant (1,16,28). PATH-HHT provides particularly important randomized support for pomalidomide, while systemic

bevacizumab remains supported by a combination of randomized and broader clinical evidence in selected severe HHT populations (16,28,47). These therapies require consideration of systemic toxicity, comorbidity, monitoring burden, and treatment goals and therefore should not be presented as interchangeable first-line options.

Strengths of the Review

This review has several strengths. First, it evaluates multiple clinically relevant dimensions of HHT epistaxis rather than relying on a single bleeding endpoint, including frequency, duration, ESS, hemoglobin concentration, and adverse events. Second, results narrative links with the actual forest plots, including the bevacizumab ESS estimate. Third, it transparently distinguishes the quantitative synthesis from the contextual evidence update, avoiding the misleading implication that newly identified randomized trials contributed to analyses that were not rerun. Fourth, the interpretation integrates risk of bias, heterogeneity, GRADE certainty, and the limitations of sparse funnel plots rather than treating statistical significance as the sole determinant of evidence quality (30,32,39-41).

An additional strength is the use of primary randomized evidence to contextualize treatment-specific conclusions. This is particularly important in HHT because route, formulation, crossover design, adjunctive procedures, and outcome definitions vary substantially across trials. The audit therefore improves clinical interpretability even though it does not alter the preserved numerical meta-analysis (18-29,42-52).

Limitations

The most important limitation is that the meta-analysis itself could not be rerun after the evidence audit. Consequently, additional eligible randomized trials are not incorporated into the forest plots, pooled effect estimates, heterogeneity statistics, or GRADE tables. The quantitative estimates should therefore be interpreted as the results of the historical analytical subset rather than a complete quantitative synthesis of all randomized pharmacological evidence available by the final search date.

Second, one retrospective comparative study, Simonds et al., was included in the quantitative dataset and appears in the historical risk-of-bias matrix and bevacizumab safety figure (34). Because the analysis could not be regenerated, this study could not be removed without altering the figures. Its presence reduces the methodological purity of the legacy randomized evidence set and limits interpretation of pooled safety and risk-of-bias results in which it appears.

Third, the search strategy was relatively simple, was limited to English-language publications, and produced a PRISMA flow in which the explicitly listed full-text exclusion reasons did not account for all excluded reports. The evidence clarified these issues but could not reconstruct every historical screening decision. The subsequent identification of additional randomized trials confirms that the quantitative subset was incomplete. Although the audit improves contextual completeness, it is not equivalent to rerunning the full systematic search and screening workflow from inception (30,31).

Fourth, the legacy meta-analysis included crossover and multi-arm studies whose source-native statistical structures differ from conventional independent parallel-group comparisons. In addition, some medians and dispersion measures were transformed to approximate means and standard deviations for pooling. Such transformations can be useful but may be sensitive to skewed distributions, which are plausible for epistaxis frequency and duration. Shared placebo groups and within-participant correlation in crossover trials also require careful handling to avoid artificial precision (32,36). Because these analyses were not reconstructed, residual analytical uncertainty remains.

Fifth, clinical and methodological heterogeneity was substantial. Drug route, dose, treatment duration, baseline epistaxis severity, follow-up interval, background procedures, and endpoint definitions varied across studies. The TXA analyses were especially heterogeneous, and route-oriented sensitivity analyses

did not consistently eliminate inconsistency. Heterogeneity also limits the meaning of an average pooled effect when individual treatment contexts differ clinically.

Finally, many trials were small and short, limiting precision for efficacy and particularly for uncommon adverse events. Publication bias could not be assessed reliably because each drug-specific comparison contained far fewer than 10 studies (39). The legacy GRADE ratings therefore appropriately range from moderate to very low, and even statistically significant findings should be interpreted in the context of magnitude, precision, clinical relevance, and reproducibility (40,41).

Implications for Future Research

Future HHT epistaxis trials should prioritize adequately powered multicenter randomized designs, prospective registration, transparent statistical analysis plans, and standardized outcome definitions. ESS is useful because it captures several dimensions of disease burden, but it should be accompanied by objectively interpretable measures such as cumulative bleeding duration, episode frequency, hemoglobin, ferritin, intravenous iron requirement, red-cell transfusion burden, and HHT-specific quality of life (11-14). Core outcome harmonization would substantially improve the feasibility and validity of future meta-analysis.

Future studies should also predefine clinically meaningful treatment thresholds and distinguish primary from supportive secondary outcomes. Route and formulation should be treated as potential effect modifiers rather than automatically combined. Crossover trials should report paired treatment effects and within-participant variance, while multi-arm trials should report data in a form that permits correct handling of shared controls. Longer follow-up is required to define durability of response and delayed toxicity, particularly for systemic antiangiogenic and immunomodulatory therapies.

As the randomized evidence base expands, a fully updated systematic review should ultimately rerun the search, reconstruct the complete study-level dataset, apply contemporary outcome-specific risk-of-bias assessment, and perform new quantitative synthesis using methods appropriate to parallel, crossover, and multi-arm designs. Such an update would allow the newer systemic therapies to be compared formally with the older topical and repurposed interventions rather than being confined to narrative contextualization.

CONCLUSION

The preserved meta-analysis indicates that the older pharmacological evidence for HHT-related epistaxis is characterized more by uncertainty and treatment-specific signals than by a single consistently effective therapy. Within the quantitative subset, bevacizumab did not significantly improve pooled epistaxis frequency, duration, hemoglobin concentration, or overall adverse-event risk, although it produced a small statistically significant reduction in ESS. TXA showed nonsignificant pooled effects with considerable heterogeneity, timolol did not demonstrate clear pooled hematological or safety superiority, and estrogen/estriol did not significantly reduce epistaxis frequency. These findings are consistent with the broader literature showing substantial heterogeneity in formulation, route, trial design, and outcome measurement (21,26,27,53).

The evidence update substantially broadens this interpretation. Randomized evidence supports clinically relevant benefit from selected therapies, including propranolol in a small trial and, most notably, pomalidomide in the larger PATH-HHT trial, while other interventions such as tacrolimus, doxycycline, and nintedanib have produced negative, inconclusive, or mixed primary results (22,25,28,29,50-52). Consequently, absence of statistical significance in the historical pooled analyses should not be interpreted as proof that pharmacological treatment is ineffective; rather, treatment effects appear to depend on drug mechanism, route, disease severity, outcome definition, and patient selection.

Clinical management should therefore remain individualized and aligned with contemporary HHT guidance, progressing from conservative nasal care and oral antifibrinolytic therapy toward local procedures or systemic antiangiogenic/immunomodulatory treatment according to bleeding severity, hematological consequences, prior response, comorbidity, and patient preference (1,16). The pooled estimates should be regarded as an exploratory synthesis of a historical quantitative subset, whereas the newer randomized evidence signals a transition toward better powered, mechanism-directed systemic treatment. A future fully updated meta-analysis that reconstructs the complete randomized dataset will be necessary to provide definitive comparative estimates across this rapidly evolving therapeutic landscape.

REFERENCES

1. Faughnan ME, Mager JJ, Hetts SW, Palda V, Lang-Robertson K, Buscarini E, et al. Second International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia. Ann Intern Med. 2020;173(12):989-1001. doi:10.7326/M20-1443.

2. McDonald J, Bayrak-Toydemir P, Pyeritz RE. Hereditary hemorrhagic telangiectasia: an overview of diagnosis, management, and pathogenesis. Genet Med. 2011;13(7):607-616. doi:10.1097/GIM.0b013e3182136d32.

3. Dupuis-Girod S, Bailly S, Plauchu H. Hereditary hemorrhagic telangiectasia: from molecular biology to patient care. J Thromb Haemost. 2010. doi:10.1111/j.1538-7836.2010.03860.x.

4. Ardelean DS, Letarte M. Anti-angiogenic therapeutic strategies in hereditary hemorrhagic telangiectasia. Front Genet. 2015;6:35. doi:10.3389/fgene.2015.00035.

5. Sautter NB, Smith TL. Hereditary hemorrhagic telangiectasia-related epistaxis: innovations in understanding and management. Int Forum Allergy Rhinol. 2012. doi:10.1002/alr.21046.

6. Cuesta AM. Hereditary hemorrhagic telangiectasia: diagnosis and management. J Clin Med. 2022;11(16):4698. doi:10.3390/jcm11164698.

7. Kasthuri RS, Montifar M, Nelson J, Kim H, Lawton MT, Faughnan ME. Prevalence and predictors of anemia in hereditary hemorrhagic telangiectasia. Am J Hematol. 2017. doi:10.1002/ajh.24832.

8. Pasculli G, Resta F, Guastamacchia E, Di Gennaro L, Suppressa P, Sabba C. Health-related quality of life in a rare disease: hereditary hemorrhagic telangiectasia. Qual Life Res. 2004. doi:10.1007/s11136-004-7865-y.

9. Merlo CA, Yin LX, Hoag JB, Mitchell SE, Reh DD. The effects of epistaxis on health-related quality of life in patients with hereditary hemorrhagic telangiectasia. Int Forum Allergy Rhinol. 2014. doi:10.1002/alr.21374.

10. Ingrand I, Ingrand P, Gilbert-Dussardier B, et al. Altered quality of life in Rendu-Osler-Weber disease related to recurrent epistaxis. Rhinology. 2011. PMID:21743869.

11. Hoag JB, Terry P, Mitchell S, Reh D, Merlo CA. An epistaxis severity score for hereditary hemorrhagic telangiectasia. Laryngoscope. 2010. doi:10.1002/lary.20818.

12. Beckman JD, Li Q, Hester S, et al. Integration of clinical parameters, genotype and epistaxis severity score to guide treatment for hereditary hemorrhagic telangiectasia-associated bleeding. Orphanet J Rare Dis. 2020. doi:10.1186/s13023-020-01453-1.

13. Gong A, Linares Bolsegui M, Lee EE, Mathai S, Weiss CR. Assessing the psychometric validity of the Epistaxis Severity Score: internal consistency and test-retest reliability. Am J Rhinol Allergy. 2023. doi:10.1177/19458924231207137.

14. Peterson AM, Kallogjeri D, Spitznagel EL, Chakinala MM, Schneider JS, Piccirillo JF. Development and validation of the Nasal Outcome Score for Epistaxis in Hereditary Hemorrhagic Telangiectasia. JAMA Otolaryngol Head Neck Surg. 2020. doi:10.1001/jamaoto.2020.3040.

15. Halderman AA, Ryan MW, Clark CM, Sindwani R, Reh DD, Poetker DM, et al. Medical treatment of epistaxis in hereditary hemorrhagic telangiectasia: an evidence-based review. Int Forum Allergy Rhinol. 2018. doi:10.1002/alr.22094.

16. Al-Samkari H. Systemic antiangiogenic therapies for bleeding in hereditary hemorrhagic telangiectasia: a practical, evidence-based guide for clinicians. Semin Thromb Hemost. 2022. doi:10.1055/s-0042-1743467.

17. Radwi M, Ponnampalam A, Faughnan M, Shehata N. A systematic review on the use of pharmacological agents in patients with hereditary hemorrhagic telangiectasia. Blood. 2013;122:4745. doi:10.1182/BLOOD.V122.21.4745.4745.

18. Gaillard S, Dupuis-Girod S, Boutitie F, Riviere S, Moriniere S, Hatron P, et al. Tranexamic acid for epistaxis in hereditary hemorrhagic telangiectasia patients: a European cross-over controlled trial in a rare disease. J Thromb Haemost. 2014. doi:10.1111/jth.12654.

19. Whitehead KJ, Sautter NB, McWilliams JP, Chakinala MM, Merlo CA, Johnson MH, et al. Effect of topical intranasal therapy on epistaxis frequency in patients with hereditary hemorrhagic telangiectasia: a randomized clinical trial. JAMA. 2016. doi:10.1001/jama.2016.11724.

20. Dupuis-Girod S, Ambrun A, Decullier E, Fargeton AE, Roux A, Breant V, et al. Effect of bevacizumab nasal spray on epistaxis duration in hereditary hemorrhagic telangiectasia: a randomized clinical trial. JAMA. 2016. doi:10.1001/jama.2016.11387.

21. Stokes P, Rimmer J. Intranasal bevacizumab in the treatment of HHT-related epistaxis: a systematic review. Rhinology. 2018. doi:10.4193/Rhin17.166. PMID:29166422.

22. Mei-Zahav M, Gendler Y, Bruckheimer E, et al. Topical propranolol improves epistaxis control in hereditary hemorrhagic telangiectasia: a randomized double-blind placebo-controlled trial. J Clin Med. 2020;9:3130. doi:10.3390/jcm9103130.

23. Dupuis-Girod S, Pitiot V, Bergerot C, Fargeton AE, Beaudoin M, Decullier E, et al. Efficacy of timolol nasal spray as a treatment for epistaxis in hereditary hemorrhagic telangiectasia: a double-blind, randomized, placebo-controlled trial. Sci Rep. 2019. doi:10.1038/s41598-019-48502-9.

24. Peterson AM, Lee JJ, Kallogjeri D, Schneider JS, Chakinala MM, Piccirillo JF. Efficacy of timolol in a novel intranasal thermosensitive gel for hereditary hemorrhagic telangiectasia-associated epistaxis: a randomized clinical trial. JAMA Otolaryngol Head Neck Surg. 2020. doi:10.1001/jamaoto.2020.3025.

25. Dupuis-Girod S, Fargeton A, Grobost V, et al. Efficacy and safety of a 0.1% tacrolimus nasal ointment as a treatment for epistaxis in hereditary hemorrhagic telangiectasia: a randomized placebo-controlled trial. J Clin Med. 2020;9:1262. doi:10.3390/jcm9051262.

26. Hsu YP, Hsu CW, Bai CH, Cheng SW, Chen C. Medical treatment for epistaxis in hereditary hemorrhagic telangiectasia: a meta-analysis. Otolaryngol Head Neck Surg. 2018. doi:10.1177/0194599818797316.

27. Chitsuthipakorn W, Hoang MP, Kanjanawasee D, Seresirikachorn K, Snidvongs K. Treatments of epistaxis in hereditary hemorrhagic telangiectasia: systematic review and network meta-analysis. Curr Allergy Asthma Rep. 2023. doi:10.1007/s11882-023-01116-8.

28. Al-Samkari H, Kasthuri R, Iyer VN, Pishko A, Decker J, Weiss CR, et al. Pomalidomide for epistaxis in hereditary hemorrhagic telangiectasia. N Engl J Med. 2024. doi:10.1056/NEJMoa2312749.

29. Hermann R, Grobost V, Le-Guillou X, Lavigne C, Parrot A, Riviere S, et al. Effect of oral nintedanib versus placebo on epistaxis in hereditary hemorrhagic telangiectasia: the EPICURE multicenter randomized double-blind trial. Angiogenesis. 2024. doi:10.1007/s10456-024-09962-4.

30. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi:10.1136/bmj.n71.

31. Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al. PRISMA-S: an extension to the PRISMA Statement for reporting literature searches in systematic reviews. Syst Rev. 2021;10:39. doi:10.1186/s13643-020-01542-z.

32. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors. Cochrane Handbook for Systematic Reviews of Interventions. Version 6.2. Cochrane; 2021.

33. Shovlin CL, Guttmacher AE, Buscarini E, Faughnan ME, Hyland RH, Westermann CJJ, et al. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). Am J Med Genet. 2000;91(1):66-67. doi:10.1002/(SICI)1096-8628(20000306)91:1<66::AID-AJMG12>3.0.CO;2-P.

34. Simonds J, Miller F, Mandel J, Davidson TM. The effect of bevacizumab (Avastin) treatment on epistaxis in hereditary hemorrhagic telangiectasia. Laryngoscope. 2009;119:988-992. doi:10.1002/lary.20159.

35. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016;5:210. doi:10.1186/s13643-016-0384-4.

36. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014;14:135. doi:10.1186/1471-2288-14-135.

37. The Cochrane Collaboration. Review Manager (RevMan). Version 5.4.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2020.

38. Higgins JPT, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928. doi:10.1136/bmj.d5928.

39. Sterne JAC, Sutton AJ, Ioannidis JPA, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ. 2011;343:d4002. doi:10.1136/bmj.d4002.

40. Guyatt GH, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383-394. doi:10.1016/j.jclinepi.2010.04.026.

41. Balshem H, Helfand M, Schunemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401-406. doi:10.1016/j.jclinepi.2010.07.015.

42. Riss D, Burian M, Wolf A, Kranebitter V, Kaider A, Arnoldner C. Intranasal submucosal bevacizumab for epistaxis in hereditary hemorrhagic telangiectasia: a double-blind, randomized, placebo-controlled trial. Head Neck. 2015;37(6):783-787. doi:10.1002/hed.23655.

43. Geisthoff UW, Seyfert UT, Kubler M, Bieg B, Plinkert PK, Konig J. Treatment of epistaxis in hereditary hemorrhagic telangiectasia with tranexamic acid: a double-blind placebo-controlled cross-over phase IIIB study. Thromb Res. 2014;134(3):565-571. doi:10.1016/j.thromres.2014.06.012.

44. Dupuis-Girod S, Ambrun A, Decullier E, Samson G, Roux A, Fargeton AE, et al. ELLIPSE Study: a phase 1 study evaluating the tolerance of bevacizumab nasal spray in the treatment of epistaxis in hereditary hemorrhagic telangiectasia. mAbs. 2014;6(3):794-799. doi:10.4161/mabs.28025.

45. Vase P. Estrogen treatment of hereditary hemorrhagic telangiectasia: a double-blind controlled clinical trial. Acta Med Scand. 1981;209(5):393-396. doi:10.1111/j.0954-6820.1981.tb11614.x.

46. Khanwalkar AR, Rathor A, Read AK, Paknezhad H, Ma Y, Hwang PH. Randomized, controlled, double-blinded clinical trial of effect of bevacizumab injection in management of epistaxis in hereditary hemorrhagic telangiectasia patients undergoing surgical cauterization. Int Forum Allergy Rhinol. 2022;12(8):1034-1042. doi:10.1002/alr.22961.

47. Dupuis-Girod S, Riviere S, Lavigne C, Fargeton AE, Gilbert-Dussardier B, Grobost V, et al. Efficacy and safety of intravenous bevacizumab on severe bleeding associated with hereditary hemorrhagic telangiectasia: a national, randomized multicenter trial. J Intern Med. 2023;294(6):761-774. doi:10.1111/joim.13714.

48. Yaniv E, Preis M, Hadar T, Shvero J, Haddad M. Antiestrogen therapy for hereditary hemorrhagic telangiectasia: a double-blind placebo-controlled clinical trial. Laryngoscope. 2009;119(2):284-288. doi:10.1002/lary.20065.

49. Bergler W, Sadick H, Gotte K, Riedel F, Hormann K. Topical estrogens combined with argon plasma coagulation in the management of epistaxis in hereditary hemorrhagic telangiectasia. Ann Otol Rhinol Laryngol. 2002;111(3 Pt 1):222-228. doi:10.1177/000348940211100306.

50. McWilliams JP, Majumdar S, Kim GH, Lee J, Seals K, Tangchaiburana S, et al. North American Study for the Treatment of Recurrent Epistaxis with Doxycycline: the NOSTRIL trial. J Thromb Haemost. 2022;20(5):1115-1125. doi:10.1111/jth.15662.

51. Thompson KP, Sykes J, Chandakkar P, Marambaud P, Vozoris NT, Marchuk DA, Faughnan ME. Randomized, double-blind, placebo-controlled, crossover trial of oral doxycycline for epistaxis in hereditary hemorrhagic telangiectasia. Orphanet J Rare Dis. 2022;17:405. doi:10.1186/s13023-022-02539-8.

52. Andorfer KEC, Zeman F, Koller M, Zeller J, Fischer R, Seebauer CT, et al. TIMolol nasal spray as a treatment for epistaxis in hereditary hemorrhagic telangiectasia (TIM-HHT)-a prospective, randomized, double-blind, controlled, cross-over trial. Pharmaceutics. 2022;14(11):2335. doi:10.3390/pharmaceutics14112335.

53. Chen H, Zhang Z, Chen X, Wang C, Chen M, Liao H, et al. Meta-analysis of efficacy and safety of bevacizumab in the treatment of hereditary hemorrhagic telangiectasia epistaxis. Front Pharmacol. 2023;14:1089847. doi:10.3389/fphar.2023.1089847.