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American Society of Hematology
2021 L Street NW, Suite 900,
Washington, DC 20036
Phone: 202-776-0544 | Fax 202-776-0545
bloodadvances@hematology.org

Cost-effectiveness of bevacizumab therapy in the care of patients with hereditary hemorrhagic telangiectasia

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Daniel Wang (Yale University School of Medicine, United States) Satoko Ito (Yale University School of Medicine, United States) Christina Waldron (Yale University School of Medicine, United States) Ayesha Butt (Yale University, United States) Ellen Zhang (Stanford University Medical Center, United States) Harlan Krumholz (Yale, United States) Hanny Al-Samkari (Massachusetts General Hospital, Harvard Medical School, United States) George Goshua (Yale University School of Medicine, United States)

Abstract:
No FDA or EMA approved therapies exist for bleeding due to hereditary hemorrhagic telangiectasia (HHT), the second-most-common inherited bleeding disorder worldwide. The current standard-of-care (SOC) includes iron and red cell supplementation, alongside the necessary hemostatic procedures, none of which target underlying disease pathogenesis. Recent evidence has demonstrated that bleeding pathophysiology is amenable to systemic antiangiogenic therapy with the anti-VEGF bevacizumab. Despite its high cost, the addition of longitudinal bevacizumab to the current SOC may reduce overall healthcare resource utilization and improve patient quality-of-life. We conducted the first cost-effectiveness analysis of IV bevacizumab in patients with HHT with the moderate-to-severe phenotype, comparing 1) bevacizumab added to SOC versus 2) SOC alone. The primary outcome was the incremental net monetary benefit (iNMB) reported over a lifetime time horizon and across accepted willingness-to-pay thresholds, in USD per quality-adjusted-life-year (QALY). Bevacizumab therapy accrued 9.3 QALYS while generating $428,000 in costs, compared to 8.3 QALYs and $699,000 in costs accrued in the SOC strategy. The iNMB of bevacizumab therapy versus the standard of care was $433,000. No parameter variation and no scenario analysis, including choice of iron supplementation product, changed the outcome of bevacizumab being a cost-saving strategy. Bevacizumab therapy also saved patients an average of 133 hours spent receiving HHT-specific care per year of life. In probabilistic sensitivity analysis, bevacizumab was favored in 100% of all 10,000 Monte Carlo iterations across base-case and all scenario analyses. Bevacizumab should be considered for more favorable formulary placement in the care of patients with moderate-to-severe HHT.

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Authors: Daniel Wang, BS[1], Satoko Ito, MD, PhD[2], Christina Waldron, BS[1], Ayesha Butt, MD[3], Ellen Zhang, MD[4], Harlan M. Krumholz, MD, SM[5,6], *Hanny Al-Samkari, MD[7] and *George Goshua, MD, MSc[2,6]

*Co-senior authors.

[1]Yale School of Medicine, New Haven, CT; [2]Section of Hematology, Department of Internal Medicine, Yale School of Medicine, New Haven, CT; [3]Department of Internal Medicine, Yale University School of Medicine, New Haven, CT; [4]Department of Medicine, Stanford University Medical Center, Palo Alto, CA; [5]Section of Cardiovascular Medicine, Yale School of Medicine, New Haven, CT; [6]Center for Outcomes Research and Evaluation, Yale New Haven Hospital, New Haven, CT; [7]Division of Hematology Oncology, Massachusetts General Hospital, Cambridge, MA

Corresponding Author Contact:

Full Name: George Goshua, MD, MSc, FACP

Address: 333 Cedar St, New Haven, CT

Email: george.goshua@yale.edu

For original data, please email the corresponding author.

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1. Longitudinal systemic bevacizumab is a cost-saving therapeutic option in the care of HHT patients with moderate-to-severe bleeding
2. Cost savings are mediated by decreased need for iron and RBC supplementation, hemostatic procedures, and hospitalizations

ABSTRACT (250-word limit)

No FDA or EMA approved therapies exist for bleeding due to hereditary hemorrhagic telangiectasia (HHT), the second-most-common inherited bleeding disorder worldwide. The current standard-of-care (SOC) includes iron and red cell supplementation, alongside the necessary hemostatic procedures, none of which target underlying disease pathogenesis. Recent evidence has demonstrated that bleeding pathophysiology is amenable to systemic antiangiogenic therapy with the anti-VEGF bevacizumab. Despite its high cost, the addition of longitudinal bevacizumab to the current SOC may reduce overall healthcare resource utilization and improve patient quality-of-life. We conducted the first cost-effectiveness analysis of IV bevacizumab in patients with HHT with the moderate-to-severe phenotype, comparing 1) bevacizumab added to SOC versus 2) SOC alone. The primary outcome was the incremental net monetary benefit (iNMB) reported over a lifetime time horizon and across accepted willingness-to-pay thresholds, in USD per quality-adjusted-life-year (QALY). Bevacizumab therapy accrued 9.3 QALYS while generating $428,000 in costs, compared to 8.3 QALYs and $699,000 in costs accrued in the SOC strategy. The iNMB of bevacizumab therapy versus the standard of care was $433,000. No parameter variation and no scenario analysis, *including choice of iron supplementation product*, changed the outcome of bevacizumab being a cost-saving strategy. Bevacizumab therapy also saved patients an average of 133 hours spent receiving HHT-specific care per year of life. In probabilistic sensitivity analysis, bevacizumab was favored in 100% of all 10,000 Monte Carlo iterations across base-case and all scenario analyses. Bevacizumab should be considered for more favorable formulary placement in the care of patients with moderate-to-severe HHT.

Introduction

Hereditary hemorrhagic telangiectasia (HHT) is the second-most-common inherited bleeding disorder worldwide, afflicting 1 in 5,000 or 1.4 million persons, or twice the prevalence of hemophilia A and twelve times the prevalence of hemophilia B.[1] Vascular lesions that develop with disease progression result in recurrent mucosal bleeding, leading to iron deficiency anemia in most patients.[2–4] As such, HHT is associated with substantial morbidity and mortality at every year lived, with significant decreases in both quality of life and life expectancy.[5–8] Unlike the inherited bleeding disorders hemophilia and von Willebrand disease, there are no FDA or EMA approved therapies for HHT-associated bleeding.[9] The current standard-of-care (SOC) consists of red blood cell (RBC) transfusion, intravenous (IV) iron supplementation, and local hemostatic procedures (i.e., nasal, gastrointestinal).[1,4] Such interventions may help manage the symptoms of HHT but do not target its underlying pathogenesis – burdening patients with the need for lifelong, recurrent exposure to the risks of repeat iron and RBC support, as well as surgical procedures, all alongside an increasing age-dependent hazard of bleeding and bleeding-associated complications.[10]

Bleeding pathophysiology in HHT is amenable to vascular endothelial growth factor (VEGF) inhibition and the monoclonal anti-VEGF antibody bevacizumab has shown great promise as a disease-modifying therapeutic.[4] The multisite, international, observational InHIBIT-Bleed study (International HHT Intravenous Bevacizumab Investigative Team Study of Bleeding) was the largest clinical study evaluating a therapeutic intervention in HHT (n=238) to date and employed a retrospective pre- versus a prospective post-bevacizumab intra-patient comparison study design.[9] InHIBIT-Bleed demonstrated that longitudinal IV bevacizumab significantly improved clinical symptoms, raised hemoglobin levels, and nearly abrogated the need for IV iron infusions and RBC transfusions for patients with HHT. Although bevacizumab is an expensive biologic agent with a financial barrier to access in the United States, we hypothesized that reduction in healthcare resource utilization and improvement

in transfusion-dependence would improve quality of life for patients with HHT at costs commensurate with added clinical value (i.e., that bevacizumab is a cost-effective intervention).[11] Accordingly, we conducted the first cost-effectiveness analysis of IV bevacizumab therapy in HHT.

Methods

Model Structure

We built a Markov cohort simulation model of adult patients with a diagnosis of HHT to examine the cost-effectiveness of treatment with 1) bevacizumab added to the current standard-of-care (hereon referred to as "bevacizumab" for simplicity) versus 2) the current standard-of-care alone. Rates of RBC transfusion, iron infusion, and healthcare resource utilization in both treatment arms was informed by InHIBIT-Bleed study intra-patient comparison data for pre- versus post-bevacizumab that included descriptive statistics for 1) RBC transfusions, 2) IV iron infusions, 3) hemostatic procedures (number and type), 4) hospitalizations (number and length), and 5) emergency department visits.[9] During each model cycle, patients may experience RBC- and iron-related adverse events including delayed hemolytic transfusion reactions (DHTR), transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI), post-transfusion purpura (PTP), or iron infusion-related anaphylaxis, which may lead to death. Transition probabilities for these adverse events were sourced from hemovigilance reports including the 2015 National Blood Collection and Utilization Survey, 2008-2018 World Health Organization (WHO) Vigibase data, 2014-2019 FDA Adverse Event Reporting System, Medicare data (2010-2013), and the 2021 Serious Hazards of Transfusion report.[12–16] These adverse events were also nullified in a scenario analysis to show the effect of the complete absence of RBC and iron-related adverse events on whether the model result changed.

In addition, patients may also discontinue bevacizumab due to adverse events (AEs), after which they return to the SOC treatment paradigm, no longer receiving bevacizumab and so experiencing a return of bleeding events to the status quo (i.e., standard of care). All transition probabilities were directly informed by InHIBIT study data. Treatment-specific patient time and lost wages (up to age 65, representing the assumed age of retirement in the United States) were also accounted for across IV infusions, emergency department visits, hospitalizations, and hemostatic procedures.

We assumed a starting age of 63 years to reflect the mean age of patients enrolled in InHIBIT-Bleed, and further explored the effect of earlier bevacizumab initiation in sensitivity analysis. Transition-state cycles were 6 months in duration, in line with the lengths of the pre- and post-bevacizumab portions of the InHIBIT study, with a lifetime time-horizon and a 62:38 male:female sex mix, reflecting the study results. The primary outcome was either the incremental cost-effectiveness ratio (ICER), or the incremental net monetary benefit (iNMB) if intervention was found to be cost-saving (i.e., intervention saves costs while yielding increased quality-adjusted life expectancy). The secondary outcome was the aggregated patient time spent receiving HHT-specific care. We performed this analyses from both the US healthcare system and societal perspectives (i.e., incorporating wages lost due to time spent on HHT-specific care as part of overall costs),[17] doing so across a range of conventionally accepted willingness-to-pay (WTP) thresholds in the United States ($50,000-$150,000 per quality-adjusted life year [QALY]), and discounting cost and effectiveness by 3% annually, as recommended in the US context.[17,18] We constructed our model using TreeAge Pro Healthcare 2023 (TreeAge Software, Williamstown, MA). Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines were implemented where applicable.

Model Assumptions

Age- and disease-specific annual background mortality probabilities for patients living with HHT were informed by 2022 United States Life Tables and a population-based study comparing mortality risk in an HHT cohort with that of a matched cohort of individuals without HHT.[5,19] Base-case estimates and ranges for all input parameters used in the model are reported in Table 1. Ferric carboxymaltose was chosen as the base-case iron supplement given its market dominance among IV iron products, estimated at over 47% US market share.[20–23] We explored this assumption extensively both in sensitivity analyses and also scenario analyses which employed use of ferumoxytol and iron dextran in place of ferric carboxymaltose, as described below (see *"Sensitivity and Scenario Analyses"*). To account for aggregated patient time spent received HHT-related care, we assumed that all infusion types (RBC, iron, and bevacizumab) cost patients half of one working day, or 4 hours of wages; with hemostatic procedures costing 1 working day (8 hours) and hospitalization costing 5.5 days. In addition, although patients who undergo bevacizumab discontinuation largely do so in the first few months of drug use, we extrapolated bevacizumab discontinuation to continue beyond the first year of its successful use, doing so at 10% of the initial discontinuation rate annually. All of these assumptions were extensively tested in sensitivity analysis to see if any affect model results (i.e., which strategy is the cost-effective strategy).

Costs

All costs were adjusted to 2023 US dollars using the medical component of the consumer price index.[24] The costs of bevacizumab, RBCs, iron supplementation, emergency department visits, and endoscopic hemostatic procedures were obtained from the 2023 Centers for Medicare & Medicaid Services (CMS) Hospital Outpatient Prospective Payment System.[11] We assumed a mean patient body weight of 84.05kg, as per the January 2021 US Vital and Health Statistics Report.[25] HHT-specific hospitalization costs were sourced from a retrospective cross-sectional analysis of 2000-2014 Nationwide Impatient Sample discharge

data.[26] The cost of intranasal hemostatic procedures (including embolization, passage ablation, and arterial ligation) were sourced from Healthcare Bluebook and previous economic evaluations of epistaxis treatment in the US.[27–29]

Quality-adjusted life-years

Health outcomes estimated by our model were expressed in quality-adjusted life-years (QALYs), a measure that accounts for both health-related quality of life and length of life. QALYs were informed by age-specific EQ-5D index values derived from one of the only large (n=187) quality of life studies in HHT patients worldwide.[6] The EQ-5D (EuroQol-5d) is a preference-based health-related-quality-of-life tool used by patients to measure self-reported health across the dimensions of mobility, self-care, usual activities, pain or discomfort, and anxiety or depression.[30,31] Its use has been validated in variety of clinical settings, including in multiple hematologic malignancies and bleeding disorders such as hemophilia.[32,33] To capture the utility increment for patients in the bevacizumab treatment arm we employed anemia-severity-specific (i.e., patient population improved from severe to moderate anemia) utilities derived from the 2019 Global Burden of Disease Study.[34] The Global Burden of Disease Study estimates the incidence, prevalence, mortality, years of life lost, and disability-adjusted life-years due to over 360 disease and injuries across 204 countries and territories. Principle input data include censuses, civil registration and vital statistics, disease registries, and household surveys.[35,36] Please see the Appendix for further detail.

Sensitivity and Scenario Analyses

We quantified the sampling uncertainty within the parameters of our Markov model by performing one-way (deterministic) and probabilistic sensitivity analyses (PSA). In deterministic sensitivity analyses, utilities and non-utility parameters were varied by +/-10% and +/-50%, respectively. In the PSA, data-driven probability distributions for input

parameters with probabilistic uncertainty were assigned (Table 1). We employed β-PERT distributions for utilities and transition probabilities, and γ distributions for costs, while simultaneously ensuring random draws from each distribution via 10,000 second order Monte Carlo simulations. γ distributions were employed to best model the RBC and iron supplementation count requirements reported for pre- (retrospective) and post- (prospective) bevacizumab treatment in InHIBIT-Bleed patients. We concluded by examining scenario analyses using iron dextran and ferumoxytol for IV iron supplementation as alternative formulations. This purposefully covers a range of choices that include the least costly per infusion product (i.e., dextran) and most (i.e., ferric carboxymaltose from base-case). The costs of all IV iron products were sourced from the CMS Hospital Outpatient Prospective Payment System, while the rates of anaphylaxis (and subsequent mortality) were informed by the WHO VigiBase and data from the FDA Adverse Event Reporting System, which as noted before (see "*Model Structure*") were separately nullified in an additional scenario analysis. [14,16]

Results

Base-case cost-effectiveness analysis

The estimated total cost, QALYs, and net monetary benefit associated with each treatment strategy at a lifetime-time horizon are reported in Table 2. In the base-case, bevacizumab versus SOC alone costs $428,000 and $699,000 while accruing 9.3 and 8.3 QALYs, respectively. The iNMB with bevacizumab was $433,000 [95% credible interval $215,000-$942,000] from the US health system perspective and $444,000 [95% CI $217,000-$973,000] from the societal perspective, at a WTP of $150,000/QALY. Bevacizumab is also predicted to save patients 2,034 hours over a lifetime, or 133 hours per year lived compared to the SOC alone.

Sensitivity Analyses

One-way sensitivity analyses identified no parameter changed that caused the iNMB to fall below $0, always favoring bevacizumab (Figure 1). The top 5 parameters to which the model was most sensitive to were, in order: patient age at treatment initiation, the number of hospitalizations experienced under the current SOC, the cost of hospitalization, the cost of bevacizumab, and patient weight. No change in any of these parameters changed the model outcome to favor SOC (Figure 1). Of note, varying the rate of bevacizumab discontinuation did not change the model outcome; in fact, it did not affect the iNMB by more than 10% (Figure 1). In probabilistic sensitivity analyses, bevacizumab was favored over SOC alone in 100% of the 10,000 Monte Carlo iterations: cost-saving in 99.4% and, at worst, cost-effective in the remaining 0.6% of iterations (Figure 2).

Scenario Analyses

Our scenario analyses for different iron products (i.e., rather than ferric carboxymaltose) all show that bevacizumab continues to be the cost-effective strategy (Table 3). Specifically, with ferumoxytol as the choice of iron supplementation, bevacizumab costs $407,000 and accrues 9.3 QALYs, compared to $598,000 in costs and 8.3 QALYs in the SOC alone. The iNMB with bevacizumab was $354,000 [95% CI $181,000-$652,000] and bevacizumab was preferred in 100% of 10,000 Monte Carlo iterations in PSA. When iron dextran is used as the choice of iron supplementation, bevacizumab costs $398,000 and generates 9.3 QALYs, compared to $552,000 in costs and 8.3 QALYs accrued in the SOC alone. The iNMB with bevacizumab was $316,000 [95% CI $147,000 - $567,000] and bevacizumab was preferred in 100% of 10,000 Monte Carlo iterations in PSA.

In a third scenario analysis when RBC- and iron-related adverse events were nullified, bevacizumab remains the cost-effective strategy, accruing 9.3 QALYs at $428,000 in costs compared to 8.3 QALYs and $700,000 in the SOC alone (Table 4). The iNMB with

bevacizumab was $432,000 [95% CI $217,000 – 941,000] and was preferred over the SOC alone in 100% of 10,000 Monte Carlo iterations in PSA.

Discussion

To our knowledge, this is the first cost-effectiveness analysis of any therapeutic in HHT, a multisystem disease with significant population health impact and documented prior inequities.[37,38] Our findings suggest that, regardless of the willingness-to-pay threshold, bevacizumab appears to be a cost-saving intervention that also improves the quality-adjusted life expectancy of patients with HHT.[39,40] This overwhelming benefit is mediated by a reduction in the need for all hemostatic procedures, hospitalizations, emergency department visits, RBC transfusions, and iron infusions in a vulnerable patient population. Beyond cost-effectiveness, bevacizumab also saves patients over 100 hours per year lived spent on receiving HHT-related care. Moreover, these effects are consistent regardless of the choice of IV iron supplementation.

These results are impactful for several reasons and extend the literature in several ways. First, our model adds to the growing body of clinical evidence, including the InHIBIT-Bleed study and the Second International Guidelines for the Diagnosis and Management of HHT, supporting the use of IV bevacizumab in HHT patients with a defined phenotype of moderate to severe bleeding.[9,41] The clinical improvement seen with bevacizumab treatment stands in stark contrast to other systemic agents that were less efficacious when evaluated for HHT-associated bleeding, such as tranexamic acid and oral estrogen.[42–44] Nasal pharmacotherapy with timolol, tranexamic acid, and even nasal bevacizumab has also shown no improvement in epistaxis severity compared to placebo.[45–47] Estrogen nasal pharmacotherapy has garnered mixed results with no conclusive evidence of benefit.[47,48] As such, IV bevacizumab should be strongly considered as a best-choice agent for the treatment of moderate-to-severe HHT-associated bleeding.

Second, while patients seen at an HHT Center of Excellence will be treated according to the International Guidelines, only 30 such centers currently exist in North America and the majority of community-based physicians remain less familiar with bevacizumab use in HHT or HHT itself.[4] This lack of awareness, combined with under-recognition and delayed diagnosis – a substantial problem in HHT care – means that many patients currently experience worse outcomes and quality of life than is necessary, at an increased cost to all payers.[49,50] Our work highlights the importance of educating both physicians and patients about the benefit of bevacizumab therapy in HHT, as well as providing a quantitative, value-based analysis for the inclusion of an HHT-specific bevacizumab indication for those making coverage decisions. Finally, our analysis further supports the value of decision science and cost-effectiveness studies in evaluating therapeutic options in multisystemic, rare disease spaces such as HHT, especially as patients would benefit before large randomized controlled trials can accrue and reach completion.

Because of its wide variety of symptoms ranging from epistaxis and GI bleeding to less specific signs such as dyspnea from lung AVMs or headaches, local and community physicians – including primary care doctors, cardiologists, pulmonologists, gastroenterologists, otolaryngologists, and neurologists – should all be prepared to serve as primary points of contact and care for patients with HHT.[4,51] As such, our results have broad implications for providers across the country, regardless of specialty. However, many are unfamiliar with the important, multisystem manifestations of the disease, which may lead to delayed screening, diagnosis, and initiation of guideline-directed therapies.[51,52] Therefore, bridging this gap in knowledge while continuing to advocate for multispecialty, interdisciplinary collaboration in the treatment of patients with HHT remains of utmost importance in improving overall quality of care.

Our model has several strengths. First, our model parameters are directly informed by the real-world clinical outcomes of the largest (n = 238) reported cohort of patients, serving as their own controls with a retrospective pre- and prospective post-treatment study design in the multicenter, international InHIBIT-Bleed study. The structure of our model also accounts for a wide variety of possible adverse events – including to RBCs, iron, and bevacizumab – whose probabilities are scaled on an exposure-dependent basis so as to best approximate the risks that real patients face with repeated infusions (see Appendix for more details). Additionally we performed scenario analyses to examine the impact of varying iron supplementation products on our model results, purposefully selecting from commonly used agents across low (iron dextran), medium (ferumoxytol), and high (ferric caroxymaltose) price points on a per-infusion basis. We found that regardless of iron product, bevacizumab continues to produce cost-savings and increase quality-adjusted-life-years when added to the current SOC. A separate scenario analysis adjusts our model to further favor the null hypothesis by eliminating any iron- or RBC-associated adverse events (which patients in the SOC have greater exposure to), finding that bevacizumab remains a cost-saving intervention even in this case. Finally, another strength of our model is its incorporation of a societal cost perspective, through the quantification of wages and hours lost by patients and caregivers to HHT-related care.

We also recognize several limitations in our model. While our model is based on prospectively collected health resource utilization data across multiple international centers, the health resource utilization data from these same patients (i.e. intrapatient comparison) prior to initiating bevacizumab was retrospective. Although it is subject to the typical limitations of retrospective data collection, the data was directly pulled by investigators from physician records over the past year. Second, these results only apply to HHT patients with a strictly defined moderate to severe phenotype (see Appendix for clinical definition). We also acknowledge that, on a population level, the severity of bleeding symptoms in HHT

generally increase with age, and older patients bear a significantly greater burden of disease and subsequent degree of healthcare resources utilization compared to their younger counterparts.[10,53] As such, the results of our one-way sensitivity analysis on age must be carefully interpreted in this context – while severe symptoms (epistaxis and GI) can and does occur in patients as young as 18, the majority of those experiencing moderate-to-severe bleeding are of an older age, where the base-case and scenario analyses are all focused. Furthermore, alternative oral antiangiogenic agents that are currently under-investigated for the treatment of HHT-associated bleeding, including pomalidomide, are outside the scope of this analysis.[54,55]

Third, our model does not explore all the possible choices of IV iron supplementation available to treat HHT-associated bleeding under the current SOC, although it specifically targets the entire range by examining the lowest and highest cost products with consistent results across all tested formulations. Fourth, all economic models are specific to their specific country context and this model is specific to the United States' context. Analyses of bevacizumab for HHT outside of the US context may not reach the same conclusion given different country-specific costs. Fifth, since there is no on-treatment specific utility data for patients with HHT undergoing bevacizumab treatment, we estimated an incremental utility increase for patients on bevacizumab based on their degree of anemia improvement rather than direct patient reporting of quality of life, although we addressed this limitation in extensive sensitivity analyses. Future, longitudinal quality-of-life studies of systemic bevacizumab treatment in the HHT patient population will reflect an even more accurate depiction of its utility and impact on individuals living with HHT, although the investment into these would be first best adjudicated with value-of-information analysis, as was recently done in the evaluation of potential future studies for study prioritization in the peripartum thromboprophylaxis space.[56]

In summary and to the best of our knowledge, we performed the first cost-effectiveness analysis of systemic bevacizumab therapy in HHT. We found that, regardless of the willingness-to-pay, the addition of longitudinal, intravenous bevacizumab to the current standard of care improves the quality-adjusted life expectancy of patients with HHT and appears to be a cost-saving intervention, as compared to the current standard of care alone. Separately, bevacizumab also saves patients at least 133 hours in HHT-specific care per year lived in the form of reduced RBC transfusions, IV iron infusions, emergency department visits, hospitalizations, and hemostatic procedures. In the United States' context, these results strongly suggest that bevacizumab tier placement should be favorably prioritized across all commercial and public funders in the care of individuals living with HHT.

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Table 1 Base-case input parameters and probability distributions.

Input Parameter	Value	Probability Distribution Used in Probabilistic Sensitivity Analysis	Data Source
Cohort age at start	63	Fixed	InHIBIT-Bleed
Discount rate	0.03	Fixed	Sanders et al.
Patient weight, mean (kg)	84.05	Fixed	CDC

Mean US hourly wage (USD)	34.10	Fixed	US Bureau of Labor Statistics
Hazard ratio of mortality, HHT : non-HHT individuals	2.0	Fixed	Donaldson et al.
Median number of RBC units transfused, 6 months pre-treatment	9	γ (0.9138, 0.06741)	InHIBIT-Bleed
Median number of RBC units transfused, first 6 months on Bev	0	γ (0.3832, 0.1571)	InHIBIT-Bleed
Median number of iron units infused, 6 months pre-treatment	8	γ (1.680, 0.1472)	InHIBIT-Bleed
Median number of iron units infused, first 6 months on Bev	2	γ (0.6645, 0.2086)	InHIBIT-Bleed
Mean number of ED visits or admissions, 6 months pre-treatment	0.96	β-PERT (0.48, 1.44)	InHIBIT-Bleed
Mean number of ED visits or admissions, first 6 months on Bev	0.30752	β-PERT (0.1538, 0.4613)	InHIBIT-Bleed
Mean number of endoscopic hemostatic procedures, 6 months pre-treatment	0.60123	β-PERT (0.3006, 0.9018)	InHIBIT-Bleed
Mean number of endoscopic hemostatic procedures, first 6 months on Bev	0.06641	β-PERT (0.0332, 0.0996)	InHIBIT-Bleed
Mean number of ENT hemostatic procedures, 6 months pre-treatment	0.47573	β-PERT (0.0996, 0.7135)	InHIBIT-Bleed
Mean number of ENT hemostatic procedures, first 6 months on Bev	0.14740	β-PERT (0.073698002, 0.221094006)	InHIBIT-Bleed
Transition Probabilities			
Probability of major AE leading to Bev discontinuation, first year of treatment	0.02363	β-PERT (0.0118, 0.0354)	InHIBIT-Bleed
Assumed of major AE leading to Bev discontinuation, all subsequent years	0.00239	β-PERT (0.001194, 0.003582)	Assumed - 10% of first year probability
Probability of Delayed Hemolytic Transfusion Reaction	4.55E-05	β-PERT (2.27E-05, 6.82E-05)	Goel et al.

Probability of Transfusion Associated Circulatory Overload	0.000111	β-PERT (5.56E-05, 1.67E-04)	Goel et al.
Probability of Transfusion Related Acute Lung Injury	1.67E-05	β-PERT (8.33E-06, 2.50E-05)	Goel et al.
Probability of Post-transfusion Purpura	7.69E-08	β-PERT (3.85E-08, 1.15E-07)	Goel et al.
Probability of Ferric Carboxymaltose Anaphylaxis	3.31E-05	β-PERT (1.66E-05, 4.97E-05)	Durup et al.
Probability of Ferumoxytol Anaphylaxis	3.41E-04	β-PERT (1.71E-04, 5.12E-04)	Wang et al.
Probability of Iron Dextran Anaphylaxis	7.90E-06	β-PERT (3.95E-06, 1.19E-05)	Durup et al.
Probablity of Death from DHTR	0.038	β-PERT (0.019, 0.057)	Davies et al., 2006
Probability of Death from TACO	0.084	β-PERT (0.042, 0.13)	2021 SHOT Report
Probability of Death from TRALI	0.075	β-PERT (0.0375, 0.1125)	Popovsky
Probability of Death from PTP	0.046	β-PERT (0.023, 0.069)	Davies et al., 2006
Probability of Death due to Ferric Carboxymaltose Anaphylaxis	0.002	β-PERT (0.001, 0.003)	Trumbo et al.
Probability of Death due to Ferumoxytol Anaphylaxis	0.13	β-PERT (0.067, 0.20)	Trumbo et al.
Probability of Death due to Iron Dextran Anaphylaxis	0.045	β-PERT (0.022, 0.068)	Trumbo et al.
Utility Values			
Utility of HHT disease state	Age-dependent	β-PERT	Zarrabeitia et al.
Utility increment of anemia improvement (severe -> moderate)	0.05	β-PERT (0.045, 0.055)	GBD 2019
Estimated disutility of major AE due to Bev	-0.00261	β-PERT (-0.00288, -0.00235)	Assumed
Disutility of Transfusion Related Acute Lung Injury	-0.01538	β-PERT (-0.01692, -0.0547)	van Eerd et al.
Disutility of Delayed Hemolytic Transfusion Reaction	-0.00608	β-PERT (-0.00668, -0.00547)	Lloyd et al.

Disutility of Transfusion Associated Circulatory Overload	-0.01538	β-PERT (-0.01692, -0.0547)	van Eerd et al.
Disutility of Post-transfusion Purpura	-0.00885	β-PERT (-0.00973, -0.00796)	Di Minno et al.
Disutility of Iron Anaphylaxis	-0.000740	β-PERT (-0.000814, -0.000665)	Shaker et al.
Costs (USD)			
Cost of Bevacizumab / mg	7.0752	Fixed	HCPCS 44363
Cost per unit of RBC	135.52	Fixed	HCPCS P9021
Cost of Ferric Carboxymaltose per infusion	826.5	Fixed	HCPCS J1439
Cost of Ferumoxytol per infusion	283.56	Fixed	HCPCS Q0138
Cost of Iron Dextran per infusion	33.16	Fixed	HCPCS J1750
Cost of ED visit	381.61	γ (16, 0.04192)	HCPCS 99284
Cost of hospital admission	37266.09	γ (16, 0.0004293)	Harder et al.
Cost of endoscopic hemostatic procedure	1412.25	γ (16, 0.01133)	HCPCS 44391
Cost of ENT hemostatic procedure	8501.26	γ (16, 0.001882)	Rudmik et al., Healthcare Bluebook
Cost of Delayed Hemolytic Transfusion Reaction treatment	1537	γ (16, 0.01041)	Janssen et al.
Cost of Transfusion Associated Circulatory Overload treatment	4830	γ (16, 0.003313)	Janssen et al.
Cost of Transfusion Related Acute Lung Injury	9959	γ (16, 0.001607)	Janssen et al.
Cost of Post-transfusion Purpura treatment	2536.58	γ (16, 0.006308)	Davies et al.
Cost of Ferric Carboxymaltose Anaphylaxis treatment	2124.61	γ (16, 0.007531)	Trumbo et al.
Cost of Ferumoxytol Anaphylaxis treatment	9491.83	γ (16, 0.001686)	Trumbo et al.
Cost of Iron Dextran Anaphylaxis treatment	10016.19	γ (16, 0.001597)	Trumbo et al.

Table 2 Base-case results and net monetary benefits for bevacizumab plus the standard-of-care (SOC) versus SOC alone, from a US health system and societal perspective. Bevacizumab is a cost-saving treatment strategy that accrues net monetary benefits.
Legend: QALY = quality-adjusted life-year; USD = United States dollar

Strategy	Cost (USD)	Incremental Cost (USD)	Effectiveness (QALY)	Incremental Effectiveness (QALY)	Net Monetary Benefit (USD)	Incremental Net Monetary Benefit [95% Credible Interval] (USD)
Base Case Model (Health System Perspective)						
Bevacizumab	428,000	--	9.3	1.0	973,000	433,000 [215,000 - 942,000]
Standard of Care	699,000	271,000	8.3	--	540,000	
Base Case Model (Societal Perspective)						
Bevacizumab	435,000	--	9.3	1.0	967,000	444,000 [217,000 - 973,000]
Standard of Care	717,000	281,000	8.3	--	523,000	

Table 3 Scenario analyses base-case results and net monetary benefits using alternative IV iron supplementation (Ferumoxytol and Iron Dextran). Bevacizumab remains a cost-saving treatment with added net monetary benefit regardless of choice of iron supplementation.
Legend: QALY = quality-adjusted life-year; USD = United States dollar

Strategy	Cost (USD)	Incremental Cost (USD)	Effectiveness (QALY)	Incremental Effectiveness (QALY)	Net Monetary Benefit (USD)	Incremental Net Monetary Benefit [95% Credible Interval] (USD)
Health System Perspective - Ferumoxytol						
Bevacizumab	407,000	--	9.3	1.0	994,000	354,000 [181,000 - 652,000]
Standard of Care	598,000	191,000	8.3	--	640,000	
Societal Perspective - Ferumoxytol						
Bevacizumab	414,000	--	9.3	1.0	987,000	364,000 [182,000 - 680,000]
Standard of Care	615,000	201,000	8.3	--	623,000	
Health System Perspective - Iron Dextran						
Bevacizumab	398,000	--	9.3	1.0	1,003,000	316,000 [147,000 - 567,000]
Standard of Care	552,000	154,000	8.3	--	687,000	
Societal Perspective - Iron Dextran						

Bevacizumab	405,000	--	9.3	1.0	996,000	326,000 [151,000 - 592,000]
Standard of Care	569,000	164,000	8.3	--	670,000	

Table 4 Scenario analysis base-case results and net monetary benefits assuming no adverse events from iron or RBC supplementation. Bevacizumab remains a cost-saving treatment even when the rates of adverse events from iron and RBC supplementation are reduced to zero.
Legend: QALY = quality-adjusted life-year; USD = United States dollar

Strategy	Cost (USD)	Incremental Cost (USD)	Effectiveness (QALY)	Incremental Effectiveness (QALY)	Net Monetary Benefit (USD)	Incremental Net Monetary Benefit [95% Credible Interval] (USD)
Base Case Model (Health System Perspective)						
Bevacizumab	428,000	--	9.3	1.0	973,000	432,000 [215,000 - 941,000]
Standard of Care	700,000	272,000	8.3	--	541,000	
Base Case Model (Societal Perspective)						
Bevacizumab	435,000	--	9.3	1.0	967,000	443,000 [218,000 - 973,000]
Standard of Care	717,000	282,000	8.3	--	524,000	

Figures Legends

Figure 1 One-way sensitivity analysis tornado diagram demonstrating net monetary benefits produced with bevacizumab compared to SOC alone. Each row illustrates analysis results when one parameter is varied across its range. Parameters that produced >10% change in the incremental net monetary benefit (iNMB) when varied were included. Ranges utilized in analyses are detailed in Table 1. Blue denotes iNMB changes associated with lower values, while red denotes iNMB changes associated with higher values. Legend: WTP = willingness-to-pay; EV = expected value; SOC = standard-of-care

Figure 2 Cost-effectiveness acceptability curve of probabilistic sensitivity analysis for bevacizumab added to the SOC versus SOC alone, across a range of willingness-to-pay thresholds. Ranges utilized in analysis are detailed in Table 1.

Figure 1 One-way sensitivity analysis tornado diagram demonstrating net monetary benefits produced with bevacizumab compared to SOC alone. Each row illustrates analysis results when one parameter is varied across its range. Parameters that produced >10% change in the incremental net monetary benefit (iNMB) when varied were included. Ranges utilized in analyses are detailed in Table 1. Blue denotes iNMB changes associated with lower values, while red denotes iNMB changes associated with higher values. Legend: WTP = willingness-to-pay; EV = expected value; SOC = standard-of-care

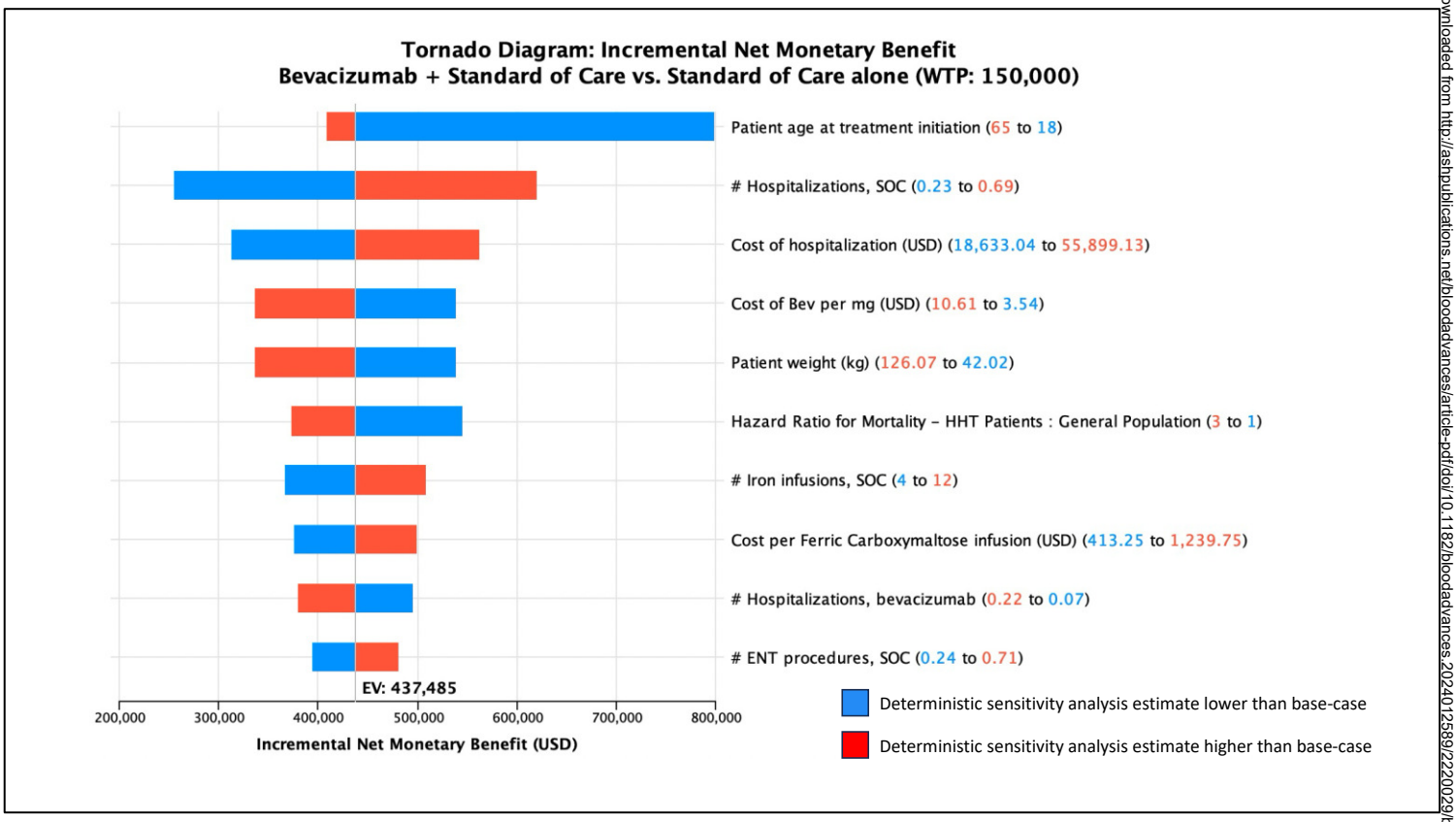

Figure 2 Cost-effectiveness acceptability curve of probabilistic sensitivity analysis for bevacizumab added to the SOC versus SOC alone, across a range of willingness-to-pay thresholds. Ranges utilized in analysis are detailed in Table 1.