An international, multicenter study of intravenous bevacizumab for bleeding in hereditary hemorrhagic telangiectasia: the InHIBIT-Bleed study

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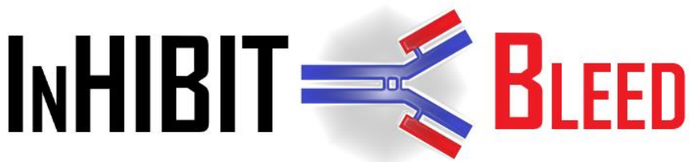
Supplemental Material



The International HHT Intravenous Bevacizumab Investigative Team Study of Bleeding

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Supplemental Methods

Additional Data Collection Information. Patients were excluded from the study if inadequate chart data was available to assess one or more effectiveness measures or safety (which required complete and continuous follow-up data during bevacizumab treatment such that all adverse events were captured). A standard data collection form was developed and used by all the participating sites. The following data was collected retrospectively from the electronic medical record: demographics, baseline HHT characteristics, local hemostatic procedures performed, epistaxis severity score (ESS) measurements, bevacizumab dosing, treatment-emergent adverse events (TEAEs), treatment discontinuation, hematologic parameters and support [including hemoglobin (Hgb) values, RBC transfusions, and iron infusions], administration of antifibrinolytic agents or erythropoiesis-stimulating agents, and total duration of follow-up.

Additional Effectiveness Measures Details. Hemoglobin. The threshold for definition of anemia (Hgb <11 g/dL) was selected for clinical relevance and because of its use in prior studies of non-HHT anemia-directed treatment.[1]

Epistaxis Severity Score Background. The ESS is a well-validated continuous 10-point clinical score to longitudinally assess the severity of nosebleeds in patients with HHT.[2] A score of 0.0-1.0 signifies minimal or no epistaxis, 1.1-4.0 signifies mild epistaxis, 4.1-7.0 signifies moderate epistaxis, and 7.1-10.0 signifies severe epistaxis occurring over the time since the patient's last clinic visit. The minimal clinically-important difference of the ESS is a change of 0.71.[3]

Additional Statistical Analysis Details. For genotype subgroup analysis, the treatment effect (difference between baseline/pretreatment values and on-treatment values) for each effectiveness measure was compared between subgroups using the two-sample t-test (Hgb and ESS) or the Mann-Whitney U test (RBC transfusions and iron infusions). For maintenance dosing subgroup analysis, results in each group were compared using the two-sample t-test (Hgb and ESS) or the Mann-Whitney U test (RBC transfusions, iron infusions). Maintenance dosing subgroup analysis compared the first 6 months of treatment (most reflective of induction treatment) and the second 6 months of treatment (entirely reflective of maintenance strategy) between patients receiving continuous vs. intermittent maintenance.

Missing data were not imputed. For comparisons of means or medians, if the baseline or at least one on-treatment value for a given patient was not available, that patient was omitted from analysis of that particular outcome.

Statistical analysis was performed and graphs for figures were prepared using Stata version 14.2 (StataCorp LLC, College Station, TX), GraphPad Prism 7 (GraphPad, Inc., San Diego, CA), and Microsoft Excel 360 (Microsoft Corp., Seattle, WA).

Supplemental Table 1. General criteria considered by centers in determining whether to offer systemic bevacizumab for the treatment of HHT-associated bleeding. Given the heterogeneity of bleeding manifestations and severity in HHT, criteria are not absolute and ultimately the decision to begin bevacizumab was a shared one between patient and provider with a detailed discussion of the possible risks and benefits.

General Criteria for Systemic Bevacizumab*
Epistaxis • Epistaxis severity score > 7 (severe range) on a consistent basis despite adequate local nasal therapy +/- systemic antifibrinolytic treatment • Need for frequent local nasal procedures to maintain epistaxis control • Significant quality of life impairment (social isolation, work restrictions or psychological distress) regardless of epistaxis severity score
Gastrointestinal bleeding • Hospitalization for GI bleeding • Need for frequent endoscopic procedural treatments • Persistent anemia requiring IV iron infusions and/or blood transfusions
Iron deficiency anemia (from either epistaxis and/or GI bleeding) • Need for regular IV iron infusions and/or blood transfusions to maintain target hemoglobin† • Inability to maintain target hemoglobin† despite regular IV iron infusions and/or blood transfusions

*Patients would typically be eligible to receive systemic bevacizumab if one or more of the criteria below were met.
†The target hemoglobin in HHT patients is generally a normal hemoglobin for gender, unless there is a known condition resulting in reduced baseline hemoglobin (e.g. thalassemia trait).

Supplemental Table 2. Results of mixed linear models of outcome measures. Estimated treatment effect of bevacizumab on hemoglobin, epistaxis severity score, RBC transfusions, and iron infusions over the first year of treatment.

Outcome	3 months	6 months	9 months	12 months
Hemoglobin (g/dL), estimated change of mean from baseline (95% CI) in patients with baseline anemia (Hgb<11) (N=185)	+3.0 (2.7, 3.3; *P*<0.0001)	+3.4 (3.1, 3.7; *P*<0.0001)	+3.3 (3.0, 3.6; *P*<0.0001)	+3.4 (3.1, 3.7; *P*<0.0001)
Epistaxis severity score, estimated change of mean from baseline (95% CI) in patients treated for epistaxis (N=146)	-2.96 (-3.26, -2.66; *P*<0.0001)	-3.73 (-4.05, -3.43; *P*<0.0001)	-3.69 (-4.03, -3.35; *P*<0.0001)	-3.60 (-3.94, -3.26; *P*<0.0001)
Outcome	**First 6 months on treatment**		**Second 6 months on treatment**	
RBC transfusions, units, estimated change of mean from pretreatment* (95% CI) (N=191)	-7.8 (-9.3, -6.3; *P*<0.0001)		-8.5 (-10.1, -7.0; *P*<0.0001)	
Iron infusions, estimated change of mean from pretreatment* (95% CI) (N=183)	-6.4 (-7.5, -5.4; *P*<0.0001)		-7.6 (-8.7, -6.5; *P*<0.00001)	

*Total number of RBC transfusions (in units) or iron infusion events in the 6 months prior to initiation of bevacizumab.

Supplemental Table 3. Subgroup analysis by genotype. PreTx, pretreatment, Tx, treatment.

Outcome	Baseline/PreTx (*ENG*)	Baseline/PreTx (*ACVRL1*)	Mean* or Median† Difference (95% CI)	Change w/Tx (*ENG*)	Change w/Tx (*ACVRL1*)	Mean* or Median† Difference (95% CI)
Hemoglobin (g/dL), mean (95% CI), baseline anemia (Hgb<11)	8.7 (8.3, 9.0)	8.7 (8.4, 9.0)	0.0 (-0.5, 0.4) *P*=0.860*	+3.4 (+2.8, +3.9)	+3.0 (+2.6, +3.4)	-0.4 (-1.0, 0.3) *P*=0.325*
Epistaxis severity score, mean (95% CI), treated for epistaxis	6.43 (5.85, 7.00)	6.94 (6.62, 7.26)	0.52 (-0.08, 1.11) *P*=0.090*	-3.33 (-3.99, -2.67)	-3.41 (-3.89, -2.94)	-0.09 (-0.88, 0.71) *P*=0.831*
RBC transfusions, units, median (interquartile range)	6.0 (0.0-12.25)	8.0 (0.0-13.0)	2.0 (-1.0 , 3.0) *P*=0.601†	-4.0 (-9.0-0.0)	-6.0 (-11.0-0.0)	-2.0 (-4.0, 0.0) *P*=0.247†
Iron infusions, median (interquartile range)	8.0 (2.5-21.0)	7.0 (1.25-22.0)	-1.0 (-3.0, 2.0) *P*=0.721†	-5.0 (-14.0-0.0)	-5.0 (-16.75-0.0)	0.0 (-3.0, 2.0) *P*=0.794†

*By two-sample t-test.
†By Mann-Whitney U test.

Supplemental Table 4. Subgroup analysis by maintenance dosing strategy. CM, continuous maintenance; IM, intermittent maintenance.

Outcome	First 6 Months (CM)	First 6 Months (IM)	Mean* or Median† Difference (95% CI)	Second 6 Months (CM)	Second 6 Months (IM)	Mean* or Median† Difference (95% CI)
Hemoglobin (g/dL), mean (95% CI), baseline anemia (Hgb<11)	11.9 (11.6, 12.2)	11.5 (10.7, 12.2)	-0.4 (-1.2, 0.3) *P*=0.237*	12.3 (11.9, 12.6)	10.8 (10.0, 11.6)	-1.5 (-2.3, -0.7) *P*=0.0002*
Epistaxis severity score, mean (95% CI), treated for epistaxis	3.40 (3.04, 3.76)	3.78 (2.57, 4.99)	0.39 (-0.58, 1.35) *P*=0.432*	2.88 (2.51, 3.25)	4.96 (3.74, 6.18)	2.08 (1.09, 3.07) *P*<0.0001*
RBC transfusions, units, median (interquartile range)	0.0 (0.0-2.0)	0.0 (0.0-0.5)	0.0 (0.0, 0.0) *P*=0.316†	0.0 (0.0-0.0)	0.0 (0.0-0.25)	0.0 (0.0, 0.0) *P*=0.172†
Iron infusions, median (interquartile range)	1.0 (0.0-6.0)	2.0 (0.0-3.0)	-1.0 (0.0, 1.0) *P*=0.472†	0.0 (0.0-3.0)	0.0 (0.0-2.0)	0.0 (0.0, 0.0) *P*=0.520†

*By two-sample t-test.

†By Mann-Whitney U test.

Supplemental Table 5. Bevacizumab-treated patients receiving concurrent treatments for HHT-associated bleeding (CT, N=88) versus those receiving no concurrent treatments (NCT, N=165). RBC transfusion and iron infusion numbers on treatment are for the first 6 months of bevacizumab treatment (for proper comparison with pretreatment numbers, which are for 6 months pretreatment). PreTx, pretreatment, BL, baseline.

Outcome	Baseline/PreTx (CT)	Baseline/PreTx (NCT)	Mean* or Median† Difference (95% CI)	On Treatment (CT)	On Treatment (NCT)	Mean* or Median† Difference (95% CI)
Hemoglobin (g/dL), mean (95% CI), baseline anemia (Hgb<11)	8.7 (8.4, 9.0)	8.7 (8.4, 8.8)	0.1 (-0.3, 0.5) *P*=0.578*	11.4 (10.9, 11.9)	12.0 (11.7, 12.3)	-0.6 (-1.2, -0.1) *P*=0.033*
Epistaxis severity score, mean (95% CI), treated for epistaxis	7.21 (6.71, 7.70)	6.60 (6.32, 6.88)	0.61 (0.08, 1.13) *P*=0.023*	3.93 (3.35, 4.51)	3.22 (2.91, 3.53)	0.71 (0.12, 1.31) *P*=0.019*
RBC transfusions, units, median (interquartile range)	4.0 (0.0-14.25)	6.0 (0.0-12.0)	2.0 (-2.0, 2.0) *P*=0.975†	0.0 (0.0-3.5)	0.0 (0.0-1.0)	0.0 (0.0, 0.0) *P*=0.038†
Iron infusions, median (interquartile range)	4.0 (1.0-12.0)	6.0 (1.0-18.0)	2.0 (0.0, 3.0) *P*=0.157†	2.0 (0.5-6.0)	1.0 (0.0-3.0)	1.0 (0.0, 2.0) *P*=0.011†

*By two-sample t-test.
†By Mann-Whitney U test.

Supplemental Table 6. Venous thromboembolic events in patients treated with bevacizumab. VTE, venous thromboembolism; DVT, deep vein thrombosis.

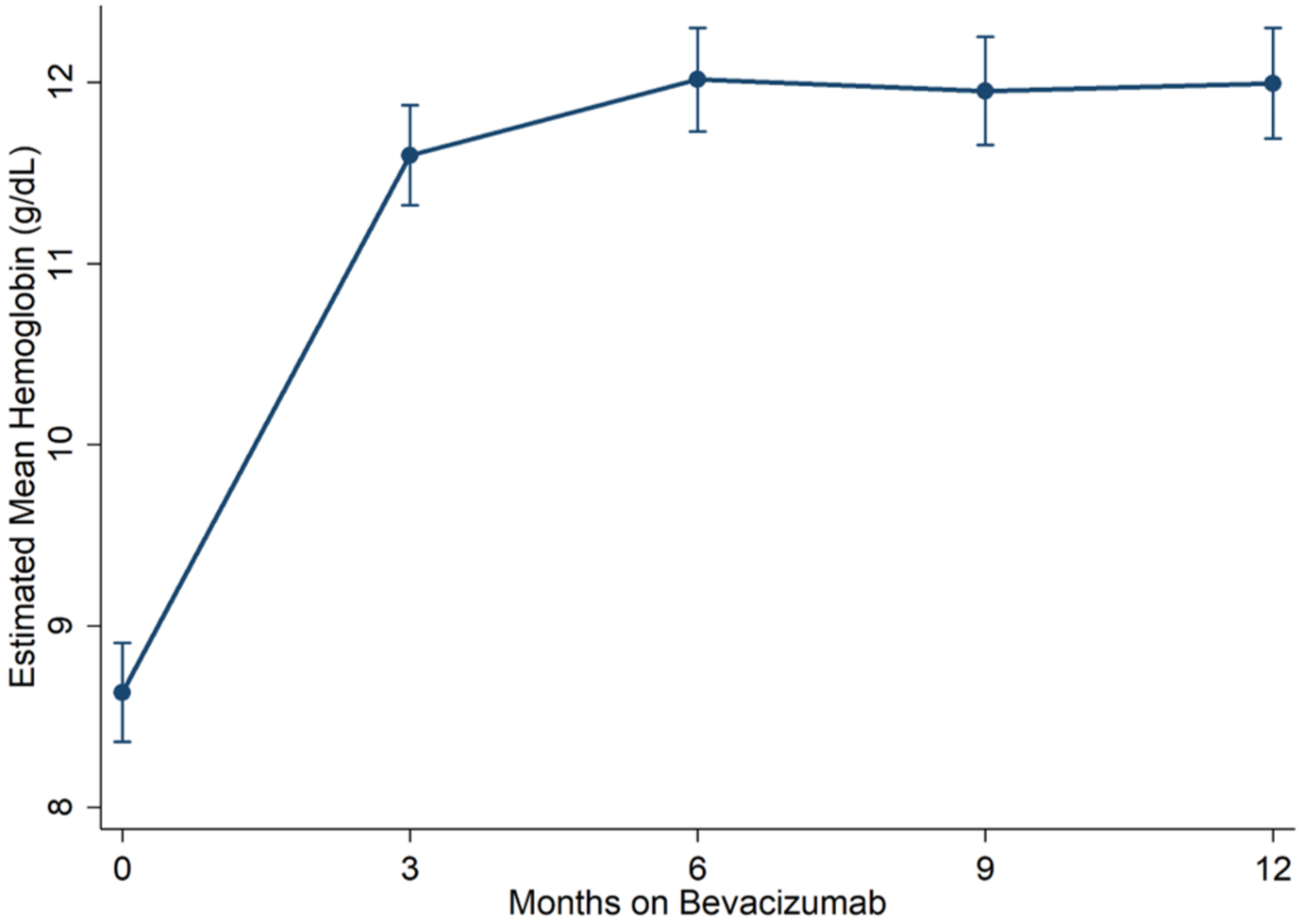
Patient age, sex	Type of VTE	Known provoking factors	#Bevacizumab infusions prior to VTE	Phase of treatment	Notes
68, female	Lobar pulmonary embolus	None	2	Induction	Patient had prior unprovoked pulmonary embolism and known prothrombin G20210 mutation and was on chronic warfarin; recurrent pulmonary embolism occurred during warfarin interruption, and was later resumed on warfarin without increased bleeding symptoms; bevacizumab was not interrupted
70, male	Femoral vein DVT	Hip replacement surgery	6	Induction	Bevacizumab held for 1 month prior to total hip replacement; during the postoperative period 6 weeks following bevacizumab interruption the patient developed femoral vein DVT (postoperative VTE prophylaxis was sequential compression device only), managed with warfarin for 3 months without increased bleeding symptoms; bevacizumab was resumed 1 month following surgery without incident
68, female	Popliteal vein DVT	Knee replacement surgery	6	Induction	Bevacizumab held for 1 month prior to total knee replacement; during the postoperative period 5 weeks following bevacizumab interruption the patient developed popliteal vein DVT (postoperative VTE prophylaxis was sequential compression device only), managed with warfarin for 3 months without increased bleeding symptoms; bevacizumab was resumed 1 month following surgery without incident
56, male	Femoral vein DVT	None	8	Maintenance (continuous)	During a percutaneous lung AVM coiling procedure, patient was found to have an incidentally discovered asymptomatic femoral vein thrombus; because patient had active gastrointestinal bleeding an inferior vena cava filter was placed; bevacizumab was not interrupted
62, male	Popliteal vein DVT	None	9	Maintenance (continuous)	Treated with warfarin without increased bleeding; bevacizumab was not interrupted

Supplemental Table 7. Bevacizumab TEAEs prompting discontinuation. All patients were treated with 5 mg/kg dose for each infusion.

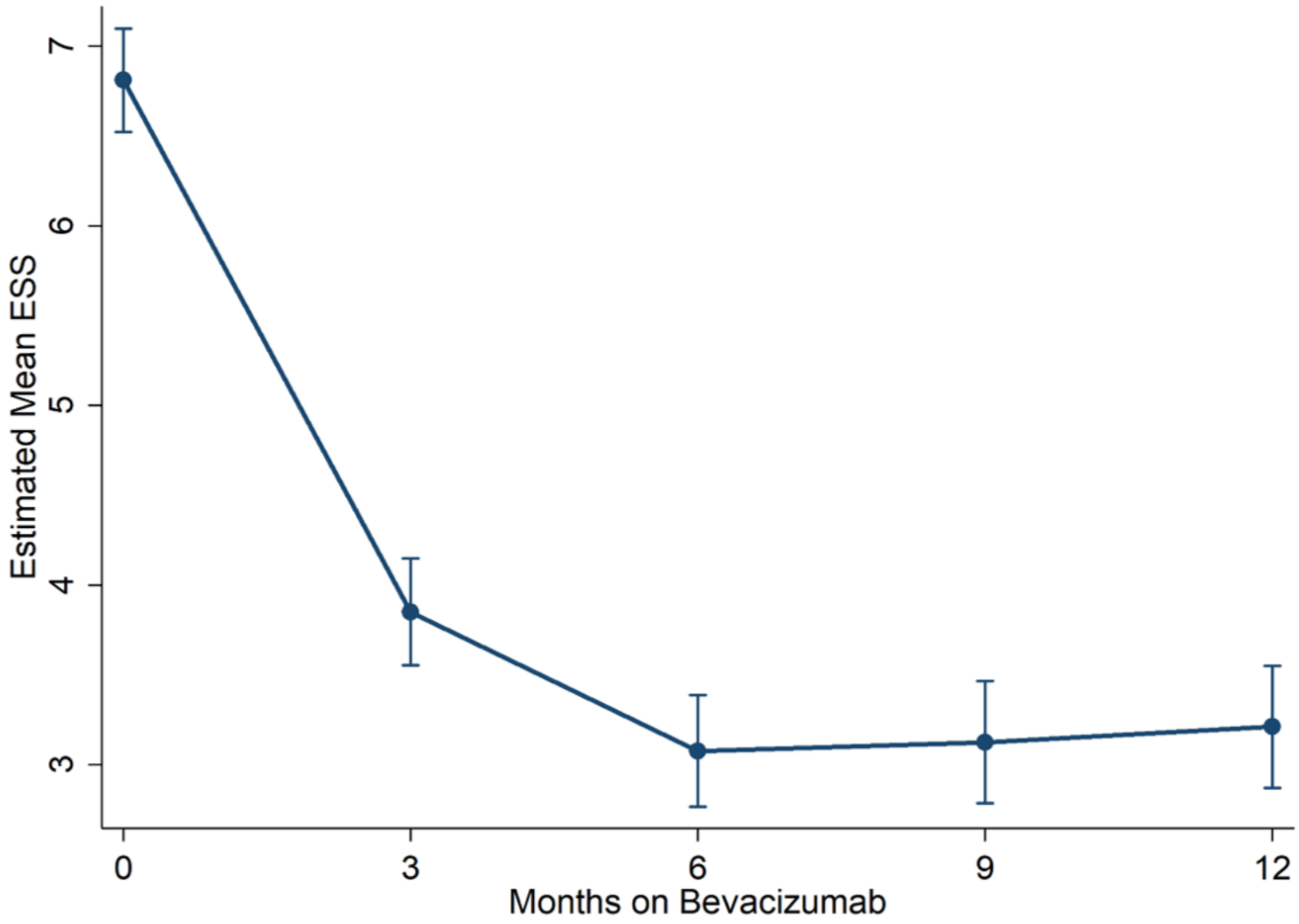
Patient age, sex	Discontinuation event	# Bevacizumab infusions prior to discontinuation	Notes
87, female	Grade 2 myalgia Grade 2 fatigue	5	
53, male	Grade 2 maculopapular rash	9	
54, female	Grade 3 hypertension	1	Medical management of hypertension was not attempted prior to discontinuation
69, female	Grade 3 proteinuria	11	Urinalysis prior to bevacizumab initiation was not done.
50, female	Grade 2 arthralgia	4	
74, female	Grade 2 hoarseness	3	Otolaryngologic evaluation concluded patient had developed mild dysphonia likely unrelated to bevacizumab
76, male	Grade 3 proteinuria	27	Pretreatment urinalysis negative; proteinuria developed after 19 months of bevacizumab treatment
73, female	Grade 3 hypertension	3	Medical management of hypertension was done and was effective, but decision was still made to discontinue treatment due to exacerbated hypertension in setting of other cardiovascular issues
60, female	Grade 1 alkaline phosphatase elevation Grade 1 alanine aminotransferase elevation Grade 1 aspartate aminotransferase elevation	11	Patient had pre-existing liver AVMs and liver disease; after no improvement several months after bevacizumab discontinuation, it was concluded that liver enzyme elevation was likely unrelated to bevacizumab
58, male	Grade 2 hoarseness	6	
54, female	Grade 3 headache	12	
70, male	Grade 2 fatigue	4	

Supplemental Figure 1. Estimated outcome measures on treatment using mixed effects linear regression models. **(A)** Hemoglobin. **(B)** ESS. **(C)** RBC transfusion. **(D)** Iron infusion.

(A)



(B)



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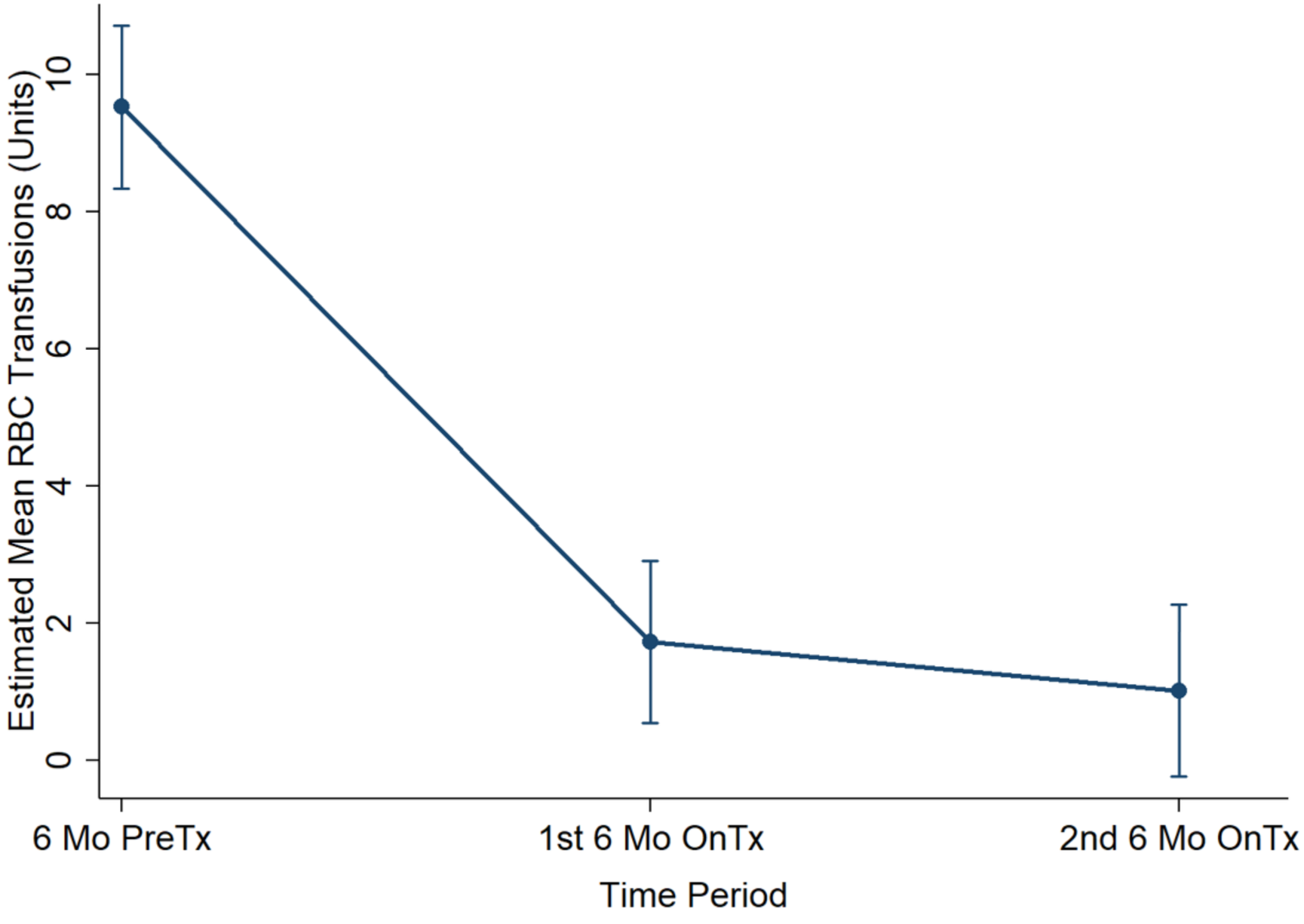
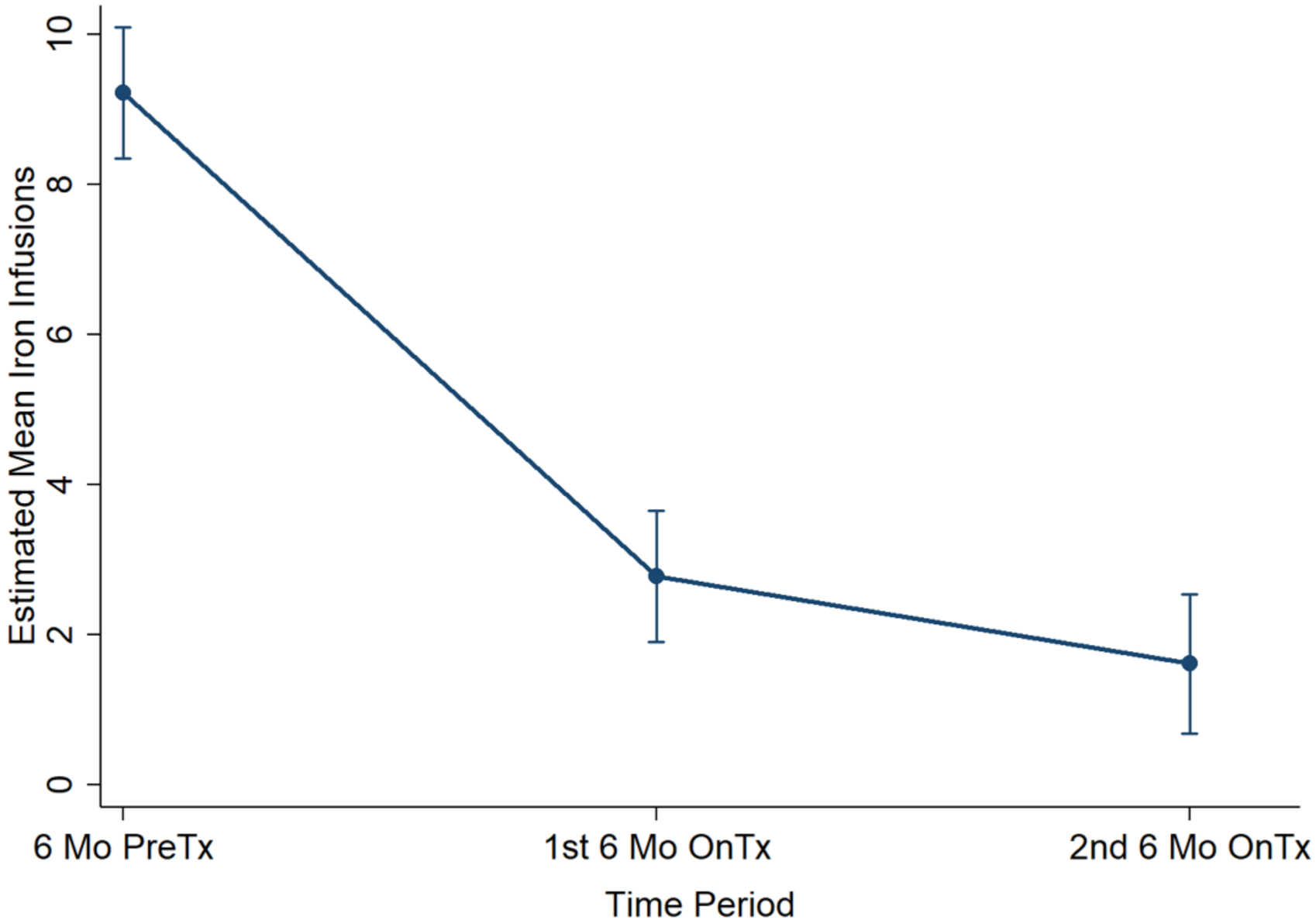

Estimated Mean RBC Transfusions (Units)
0
2
4
6
8
10
6 Mo PreTx
1st 6 Mo OnTx
2nd 6 Mo OnTx
Time Period

(D)


Estimated Mean Iron Infusions
0
2
4
6
8
10
6 Mo PreTx
1st 6 Mo OnTx
2nd 6 Mo OnTx
Time Period

Additional Information

13 of the 238 patients (5.4%) included in this study were previously comprehensively described in a prior case series.[4] An additional 34 patients (14.2%) had been partially described (epistaxis severity score data was described) in a prior case series, but data such as impact on hemoglobin and iron infusions were not described.[5]

Supplemental References

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