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European Reference Network for Rare Vascular Diseases (VASCERN): When and how to use intravenous bevacizumab in Hereditary Haemorrhagic Telangiectasia (HHT)?

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ABSTRACT

Hereditary haemorrhagic telangiectasia (HHT) is a rare vascular multisystemic disease that leads to epistaxis, anaemia due to blood loss, and arteriovenous malformations (AVMs) in organs such as the lungs, liver and brain. HHT prevalence is estimated at 1/6000, i.e. around 85,000 European citizens, and is served by the European Reference Network for Rare Multisystemic Vascular Diseases (VASCERN). HHT treatments depend on clinical manifestations, and span multiple different medical, surgical and interventional disciplines. Separate to local treatments in the nose, in severe settings, intravenous bevacizumab has been proposed as treatment option, and the purpose of the current article is to assess the use of intravenous bevacizumab in patients with HHT in 2022 according to available data.

1. Background

Rendu-Osler disease or Hereditary Haemorrhagic Telangiectasia (HHT) affects one in 5000–8000 individuals (around 85,000 European citizens). It is characterised by the existence of recurrent epistaxis, cutaneous-mucosal telangiectasias and arteriovenous malformations (AVMs) in the lungs, liver, nervous system and digestive tract. Epistaxis is the major expression of mucous telangiectases and >68% of HHT patients exhibit telangiectases on the mucous membranes of the nose (Shovlin, 2010). It is spontaneous, recurrent with fluctuations, diurnal, and nocturnal; it can provoke iron deficiency and anemia of various degrees of severity, and it is the HHT sign most frequently associated with impaired quality of life in HHT(Pasculli et al., 2004). For each

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List of abbreviations

ACVRL1	gene encoding the ALK-1 protein
AVM(s)	arteriovenous malformation(s)
BMP9	Bone Morphogenetic Protein 9
CAVMs	cerebral arteriovenous malformations
ENG	gene encoding the endoglin protein
ERNs	European Reference Networks
HAVMs	hepatic arteriovenous malformations
HHT	hereditary haemorrhagic telangiectasia
PAVMs	pulmonary arteriovenous malformations
PTEN	Phosphatase and TENsin homolog
SMAD4	gene encoding the SMAD4 protein
VASCERN	European Reference Network for Rare Vascular Diseases
VEGF	Vascular endothelial growth factor

individual, nosebleed severity exhibits major waxing and waning.

Loss-of-function variants in three major genes cause HHT: *ENG* encoding endoglin, *ACVRL1* encoding the type 1 receptor ALK1 and *SMAD4* (previously known as *MADH4)* encoding the transcription factor SMAD4. Each of these three genes encodes proteins involved in the TGF/BMP superfamily signaling pathways. These proteins have an important role in the angiogenic balance. The receptor ALK1 plays a key role in inhibiting the proliferation, migration and budding of endothelial cells in vitro, as well as neo-angiogenesis in vivo. The best-known ligand for ALK1, BMP9 may thus be a key factor in the maturation phase of angiogenesis and its presence in the blood suggests it plays a role in maintaining vascular quiescence in adults(David et al., 2008). When the BMP9/ALK1/endoglin pathway is disturbed, the quiescence maintenance as well as the vessel maturation are thought to be disrupted, resulting in the dysregulation of this angiogenic balance, and thus an excessive neo-angiogenic proliferation and/or a failure in vessel stabilization during neo-angiogenesis maturation(Park et al., 2009; Ricard et al., 2021). Vascular endothelial growth factor (VEGF) is one of the key factors in the activation phase of angiogenesis. This phase is followed by a maturation phase in which the endothelial cells stop migrating and proliferating, the cellular matrix is reconstituted and there is recruitment of mesenchymatous cells which differentiate into pericytes or smooth muscle cells, depending on the type of vessel(Carmeliet, 2000; Gaengel et al., 2009). Dysregulation of proper angiogenic remodelling, potentially due to excessive VEGF-mediated angiogenic activation, has been proposed as the underlying mechanism ultimately leading to AVM onset in HHT, although these aspects are still to be better elucidated or confirmed.

To date, AVM regression cannot be achieved by any available mechanism-based treatment in HHT. Hence, treatments in HHT depend on clinical manifestations, and address anaemia, prevention and treatment of epistaxis, and management of AVMs. There is no current surgical treatment that cures the nosebleeds definitively, although several procedures can lead to short and long-term improvements. The repetition of these treatments can entail significant iatrogenic conditions, including the perforation of the nasal septum, resulting in a worsening of the nosebleeds(Presutti et al., 2007). No studies with a "high level of proof" have shown the efficacy of any medical or surgical treatments on epistaxis. The management of AVMs is based on interventional radiology for pulmonary AVMs; regarding neurological AVMs the picture is much more complex and management depend on individual case considerations(Eker et al., 2020; Faughnan et al., 2020). In cases of liver AVMs associated with severe complications refractory to medical treatment, liver transplantation may be necessary.

1.1. Rationale for antiangiogenic treatments in HHT

An efficacy of antiangiogenic treatments involved in this signaling pathway has therefore been considered (Fig. 1) (Robert et al., 2020). If HHT *de facto* leads to, or is exacerbated by, deregulation of signaling and/or activity of VEGF, a key angiogenic factor resulting in abnormal endothelial cell proliferation, the use of anti-VEGF antibodies could inhibit this activation of angiogenesis and return the endothelium to a quiescent state.

1.2. History of bevacizumab treatment in HHT

Anti-angiogenic therapies including bevacizumab have been developed and tested in oncology. It is in this context that the first HHT patient with severe digestive (gastrointestinal) bleeding was treated in 2006, in order to treat a malignant mesothelioma(Flieger et al., 2006). In 2008 a dramatic improvement after intravenous bevacizumab treatment was also reported in the clinical conditions of a patient whose HHT was complicated by severe liver AVMs with cardiac failure(Mitchell et al., 2008). Bevacizumab is a humanised monoclonal antibody produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cells. Bevacizumab binds to VEGF, thereby inhibiting the binding of VEGF to its receptors on the surface of endothelial cells, and neutralising the biological activity of VEGF, inhibiting the formation of new vessels.

A prospective study using intravenous bevacizumab in HHT was conducted in France between March 2009 and November 2012 to study the efficacy of bevacizumab in HHT with severe hepatic AVMs (Dupuis-Girod et al., 2012). This study highlighted the efficacy of this treatment, in decreasing the cardiac output secondary to liver AVMs, but also by inducing a significant decrease of nosebleeds, which considerably improved the quality of life of the patients. No severe adverse events related to bevacizumab were observed in this study. Orphan drug designation was obtained in 2014 by Dr S. Dupuis-Girod for bevacizumab in HHT (EMA/3/14/1390). Since this first study, retrospective studies and surveys (Al-Samkari et al., 2021, 2020; H.A. Al-Samkari et al., 2019; H. Al-Samkari et al., 2019; Buscarini et al., 2019; Chavan et al., 2017, 2013; Desroches-Castan et al., 2019; Dupuis-Girod et al., 2012; Guilhem et al., 2017; Iyer et al., 2018; Rosenberg et al., 2019;

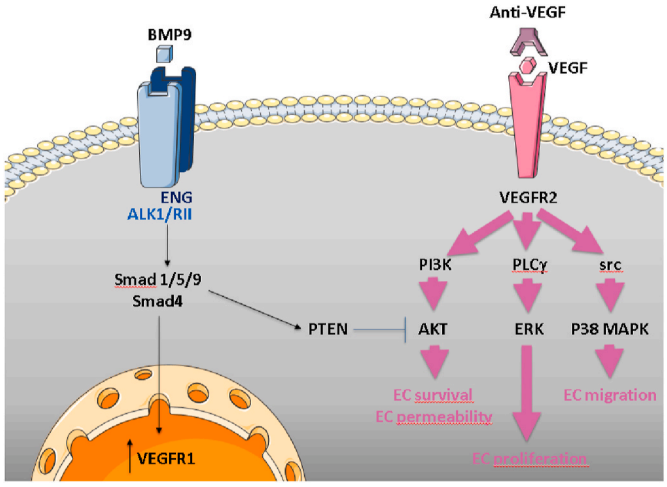

Fig. 1. BMP9 induces vascular quiescence. Through ALK1 phosphorylation of Smad1/5/9, BMP9 or BMP10 triggers transcriptional effects that induce vascular quiescence, including induction of VEGFR1 expression. In parallel, BMP9 inhibits the phosphorylation of the phosphatase PTEN (which is active in its unphosphorylated form), thereby inhibiting the activity of PI3K, a downstream effector of VEGF. VEGF activates different signaling pathways (PI3K/AKT, PLCγ/ERK, src/p38MAPK), which trigger a variety of biological responses (EC (endothelial cell) survival, permeability, proliferation and migration).

Thompson et al., 2014; Vázquez et al., 2020) (Table 1) and many case reports (Albitar et al., 2020b; Amann et al., 2015; Amanzada et al., 2010; Bennesser Alaoui et al., 2015; Bernardes et al., 2018; Bose et al., 2009; Brinkerhoff et al., 2012; Chavan et al., 2013; Cruikshank and Chern, 2011; Epperla and Hocking, 2015; Fleagle et al., 2012; Flieger et al., 2006; Fodstad et al., 2011; Föllner et al., 2012; Huemer et al., 2017; Kochanowski et al., 2015; Lazaraki et al., 2011; Lb et al., 2020; Lupu et al., 2013; Maestraggi et al., 2015; Mitchell et al., 2008; Oosting et al., 2009; Sehl et al., 2015; Suppressa et al., 2011; Vlachou et al., 2013; Wee et al., 2014) have documented effectiveness of bevacizumab in HHT patients with nose and digestive bleeding, and high cardiac output secondary to liver AVMs. Relapse after bevacizumab withdrawal is almost universal by one year.

Safety has to be carefully considered. The most frequent adverse event, as previously described is arterial hypertension which must be regularly monitored. In most cases, mild grade adverse events have been recorded, and these may rarely lead to discontinuation of what was effective treatment at the time. Additionally, severe adverse events have been reported, including deep venous thrombosis and hemoptysis from pulmonary AVMs(Al-Samkari et al., 2021; Buscarini et al., 2019). In HHT, the nasal septum perforation is frequent and related to iterative surgical procedures and has been described following intra-mucosal injections of bevacizumab.

Efficacy of anti-VEGF therapy was also demonstrated in mouse models of HHT (Eng $^{\pm}$ and Alk1$^{+/-}$ mice) (Han et al., 2020). The effect of systemic anti-VEGF therapy in multiple organs in Eng $^{\pm}$ and Alk1$^{+/-}$ mice was tested. In these models, anti-VEGF treatment normalized pulmonary peripheral microvessel density and attenuated right ventricular hypertrophy in adult Eng and Alk1 heterozygous murine models (Ardelean et al., 2014; Ardelean and Letarte, 2015).

1.3. Current status

It is therefore understandable that medical experts and patient organizations are now receiving many questions about the possibility and benefit of receiving bevacizumab to improve quality of life for patients with HHT. The use of intravenous bevacizumab has been cited in International Guidelines for HHT published in 2020 for the treatment of severe epistaxis and GI bleeding as well as severe liver involvement (Al-Samkari, 2021; Faughnan et al., 2020).

The setting up of the ERN for Rare Vascular Diseases (VASCERN) network in 2016 was at the origin of a discussion within the HHT group on the improvement of patient care. The first element was a Drug Registry to capture potential adverse events related to anti-angiogenic treatments. The conclusion of this evaluation was to underscore that antiangiogenic drugs are generally reserved for patients with severe conditions (either severe nose or gastrointestinal bleeding, or high output cardiac failure) and refractory to other therapies.

In this article, we assess the use of bevacizumab in patients with HHT in 2022 according to available data, the experience of VASCERN HHT centers, and with the input from patient associations who carried out a survey which will be reported in part 1.

1.3.1. Part 1: The patient voice

The HHT European population is represented by 13 National HHT Patient Organizations which are involved in patient advocacy, support groups, disseminating information and collecting needs. Most of the organizations have been operating in the continent for over 15 years and

Table 1
Studies performed on efficacy and safety of systemic bevacizumab in HHT patients.

Authors	Study design	n	Dosage	Mean follow-up (months)	Results
Dupuis-Girod S, 2012	Prospective phase 2, open-labeled	25	6 × 5 mg/kg/inj/2 wks	12	↘ CI ($p < 0.001$) ↘ Epistaxis duration ($p < 0.008$) Safety: 2 cases of grade 3 high blood pressure
Thompson A, 2014	Prospective open-labeled	6	6 × 0.125 mg/kg/inj/4 wks	3	↘ ESS Safety: Minimal AE
Chavan A, 2013	Prospective, case series	3	6 × 5 mg/kg/inj/2 wks + maintenance therapy	3	↘ Epistaxis, abdominal pain, NYHA stage ↗ Hb
Guilhem A, 2017	Retrospective	46	6 × 5 mg/kg/inj/2 wks + maintenance therapy	NA	Improvement in 74% cases Safety: infections (22%), high blood pressure (11%); wound healing with 2 amputations
Chavan A, 2017	Prospective	21	6 × 5 mg/kg/inj/2 wks + maintenance therapy	33	↘ Epistaxis, abdominal pain, NYHA stage ↗ Hb AE: hypertension (n = 4), epistaxis (n = 1), hematemesis (n = 2), pulmonary embolism (n = 1).
Iyer V, 2018	Retrospective	34	4 × 5 mg/kg/2 wks then 4 × 5 mg/kg/2 or 4 wks or 4 × 7.5 mg/kg or 10 mg/kg/2 wks	17.6	↘ ESS $p < 0.01$) ↘ RBC transfusions Safety: 5 cases of high blood pressure
Al-Samkari H, 2020	Retrospective	238	4 to 6 × 5 mg/kg/inj/2 wks	12	↗ Hb ↘ ESS score ↘ RBC transfused ($p < 0.0001$) ↘ Iron infusions ($p < 0.0001$) Safety: VTE (2%), high blood pressure, fatigue, proteinuria
Al-Samkari H, 2019	Survey-based	150	6 × 5 mg/kg/inj/2 wks + maintenance therapy	NA	↘ CI (55%) Safety: rare AE
Buscarini E, 2019	Survey-based	69	6 × 5 mg/kg/inj/2–3 wks + maintenance therapy	NA	Safety: 1 death possibly related to drug (hemoptysis), Joint pain (10%), proteinuria (3%)
Rosenberg T, 2019	Retrospective	12	6 × 5 mg/kg/inj/3 wks + maintenance therapy		↘ RBC transfusion, Epistaxis and GI bleeding ↗ Hb Safety: facial pain, hairloss, fatigue
Al-Samkari H, 2020	Survey-based	291	6 × 5 mg/kg/inj/2 wks + maintenance therapy	NA	↘ Epistaxis and GI bleeding ↗ Hb
Vazquez C, 2020	Retrospective	20	6 × 5 mg/kg/inj/2 wks ± maintenance therapy	13.5	↗ Hb ↘ RBC units transfused ↘ ESS score Safety: poor wound healing (n = 4) worsening of previous hypertension (n = 2), asthenia/myalgia (n = 4), ischemic non-cardioembolic stroke (n = 1)

have developed strong channels of communication with the patient body they represent.

The patient organizations were involved in this study from the very first steps as it was paramount to collect the level of queries and interest of the European patient community around bevacizumab. The method used by the organizations was a centralized retrospective survey run by HHT Europe (Federation of Patient Organizations) involving national volunteers in charge of Help Lines, Social Media and Events asking them to outline the perception of interest and quality of questions around the drug. Thirteen Patient Organizations participated in the survey (Questionnaire in supplementary materials) and the results that emerged are as follow:

Frequency of bevacizumab queries from the HHT Patient Community:

- Help line: 25% often - 33,3% occasionally
- Social Media: 8,3% Very frequently - 16,7% Often 33,3% Occasionally
- Online and face-to-face events: 16,7% Very frequently - 25% Often - 25% Occasionally

Summing all channels of communication with the patient community we can observe that questions on bevacizumab arise from occasionally to very frequently in a range from 58,3% to 66,7% of cases proving a general interest towards the topic.

The most common questions on Bevacizumab are: is it effective, what are the risks and how to access the drug in Europe (equal amount of questions for all three topics).

The consistency of interest from the patient population and specific topics of the queries encouraged the present European expert analysis and statement on the drug.

1.3.2. Part 2: Where we are (the clinicians)

The first phase II study was a prospective, open-label, non-comparative study evaluating the efficacy and safety of bevacizumab IV in 25 patients with HHT with liver AVMs and high cardiac output. The dose of bevacizumab used was 5 mg/kg every 14 days for a total of 6 injections. The results, published in JAMA, highlighted several points(Dupuis--Girod et al., 2012): (1) a significant improvement in the cardiac index three months after the start of treatment, confirmed at six months; (2) a decrease in the average duration of epistaxis (from 221 min/month to 43 min/month; $p = 0.008$) and (3) an improvement in the quality of life score. Given the size of this study, data on safety were limited. No patients experienced thromboembolic events, haemorrhage, gastrointestinal perforation or reversible posterior encephalopathy syndrome. Out of a total of 89 adverse events (AEs) there were 21 AEs reported as related to bevacizumab. One patient had a grade 3 systemic hypertension controlled on antihypertensive therapy and 21 patients had at least 1 AE possibly related to bevacizumab; all AEs occurred within 90 days after the first injection; reported AEs were: headache, nausea and vomiting, asthenia, abdominal pain, muscle pain, diarrhoea and rash.

The second prospective study was limited by the number of patients included(Thompson et al., 2014). To date, no randomized prospective study has been published.

Based on the data summarized above, the prescription of bevacizumab has come into practice for HHT, but to date, bevacizumab is not market-authorized in HHT andthere is no evidence from randomized control trials. Furthermore, the rate of relapse after treatment withdrawal is high, and may require maintenance therapy or new treatment courses. For this reason, patients should be properly informed that initiating this therapy might involve repeated administration cycles, and become a lifelong treatment.

In addition, concerns about a potentially life-long therapy with monoclonal antibodies arise. Despite a relatively safe profile of this drug, at the utilized dosages, the long-term safety profile is unknown. An additional risk of wider prescription, apart from the risk of adverse events and cost, is to miss the right time to propose a liver transplant in severe complicated hepatic AVMs(Dupuis-Girod et al., 2016).

These considerations may provide a rationale for suggesting bevacizumab as a treatment option, for those patients with refractory and transfusion-requiring manifestations, rather than those with moderate bleeding (see indications).

For these reasons, it seems necessary that all prescriptions are discussed/authorized by expert centers and are monitored strictly for side effects. The expert centers include Centers of the European Reference Network (ERN) or centers officially appointed by National Networks for rare diseases, or acknowledged by the ERNs (as listed in the VASCERN app).

1.3.3. What VASCERN-HHT experts suggest

1. Before considering treatment with bevacizumab in HHT patients:
   - Special attention to skin wound and surgery. It is recommended to stop bevacizumab 6–8 weeks before surgery and to restart it at least 4 weeks thereafter and only if the wound is totally healed. In case of acute surgery treatment must be stopped until complete healing
   - Women of childbearing potential should use effective contraceptive measures during treatment and for 6 months after discontinuation.
   - In case of hereditary pulmonary arterial hypertension (WHO class 1.2), without high cardiac outflow, bevacizumab should be used with caution, based on mouse models(Winter et al., 2020), and scant human data regarding VEGF signaling inhibition. This does not apply to the more usual post-capillary pulmonary hypertension secondary to severe hepatic AVMs.
2. The prescription should be discussed and confirmed within HHT expert centers.
3. Evaluation of prothrombotic conditions should be considered before treatment with bevacizumab is started. In HHT patients with high risk for thromboembolic events, the risk-benefit balance should be discussed, and co-application with tranexamic acid is not recommended (Roberts et al., 2020). However, the randomized ATERO study published in 2014 (Gaillard et al., 2014) studied per os administration of 3 g/d tranexamic acid for 3 months and no cases of deep vein thrombosis were observed.
4. The prescription of the treatment must be preceded by accurate history collection and physical examination to exclude contraindications:
   - Severe arteriopathy (i.e. atherosclerotic disease with a history of ischemic complications) as well as recent thrombotic events are highly risky situations
   - Recent deep venous thrombosis (<6 months)
   - Recent Severe Infectious disease(<1 month)
5. Screen and treat pulmonary AVMs according to current guidelines, as for every HHT patient, before considering bevacizumab treatment;
6. Indications:
   - Bevacizumab can be effective for treatment of HHT-related digestive bleeding resistant to standard therapies especially when it causes chronic severe anaemia despite iron supplementation
   - Bevacizumab can be effective for treatment of HHT-related severe epistaxis resistant to standard therapies especially in case of chronic severe anaemia despite iron supplementation.
   - For HHT-related severe liver AVMs when complicated and refractory to medical management, bevacizumab may be considered

Table 2
Bevacizumab in HHT: Monitoring.

Bevacizumab 5 mg/kg/injection	Initiation (D0) Or retreatment[d]	D14	D28	D42	D56	D70	M6	M12	M24	M36	In case of maintenance therapy[e]
RBC transfusion recording: date and number of RBC	X[c]	X	X	X	X	X	X	X	X	X	X
Iron infusion recording: date and mg of iron	X[c]	X	X	X	X	X	X	X	X	X	X
Epistaxis grids filling[a]	X[c]	X	X	X	X	X	X	X	X	X	X
Epistaxis score ESS evaluation	X						X	X	X	X	X
Clinical examination	X[c]	X	X	X	X	X	X	X	X	X	X
Blood pressure	X	X	X	X	X	X	X	X	X	X	X
Proteinuria (dipstick)	X	X	X	X	X	X					X
Biology Hemoglobinemia, Ferritinemia	X	X	X	X	X	X	X	X	X	X	X
Natremia, kaliemia, creatininemia	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]					X[c]
Liver function	X[c]	X	X	X	X	X	X	X	X	X	X
Echocardiography[b]	X[c]						X	X	X	X	X
Adverse events collection Treatment related[f] or led to the discontinuation of treatment	X	X	X	X	X	X	X	X	X	X	X
Also need to be mindful of risks of thrombosis, PAVM growth; stop 28 days prior to planned surgery, and stop in any situation where normal wound healing is required.											

Legends: RBC red blood cell.

[a] Epistaxis monitoring records (paper sheet, electronic App, or other).
[b] Echocardiography with cardiac index measurement. For HHT patients with severe liver involvement combined with a high cardiac output and dyspnea.
[c] Before treatment.
[d] In case of retreatment specify the rank (2nd cycle, 3rd etc).
[e] For maintenance therapy, record infusion frequency.
[f] To declare to pharmacovigilance.

by expert teams either for patients over 65 years old, or those who are no candidates for liver transplant or as bridge to transplant; All potential liver transplant candidates should be re-evaluated for liver transplant (with a "fast-track") as the prognosis of severe complicated liver VMs is very poor and liver transplantation is still the treatment of choice(Buscarini et al., 2011). This choice involves the risk of missing the "transplant window" for patients less than 65 years and the decision to treat with bevacizumab must be carefully considered in this context.

7. In all cases, a monitoring scheme should be proposed and a national register should be set up (Table 2).
8. The dosage and administration proposed in HHT patients:
   - Bevacizumab infusions should be administered under the supervision of a physician. In the absence of a dose finding study in the different indications and based on published data, a dosage of 5 mg/kg body weight administered as an intravenous infusion at 14 day–21 day intervals is recommended.
   - Mode of administration: The initial dose should be given as a 90-min intravenous infusion. If the first infusion is well tolerated, the second infusion may be given over 60 min. If the 60-min infusion is well tolerated, all subsequent infusions may be given over 30 min.
   - The recommended duration of induction treatment with bevacizumab is 6 infusions at 14 day–21 day intervals therefore resulting in 2.5–4 months induction time. If bleeding control is achieved after 3 infusions, the patient can be shifted on maintenance treatment.
   - In the event of objective response, maintenance treatment may be proposed, and inherent risks and benefits discussed with the patient. To date, no prospective studies concerning maintenance treatment have been performed and no long-term results are available for bevacizumab treatment in HHT, so the need for life-long regimen therapy cannot be excluded. The dose schedule should be considered on a case-by-case basis and is generally adapted according to the patient's response and tolerance(Albitar et al., 2020a). In all cases, it seems reasonable to stop maintenance treatment upon occurrence of a serious (grade 3) adverse event.

2. In conclusion

Bevacizumab can help control severe bleeding in HHT patients and can add in controlling large hepatic AVMs. Although there have not been conducted any randomized controlled trials on the efficacy, we believe bevacizumab plays an important role, and in this paper we have tried to outline how to use bevacizumab in care of HHT patients.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

Not applicable.

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SDG is the Chair and EB the CoChair of VASCERN HHT; CLS is an invited expert, and was the Chair of VASCERN HHT until January 2021. The discussion text was developed during monthly telecons, face to face meeting and by email June 2021–June 2022.

CRediT authorship contribution statement

Sophie Dupuis-Girod: Writing – original draft, wrote the first draft, developed the discussions, Writing – review & editing, all authors reviewed and approved the final manuscript. **Claire L. Shovlin:** developed the discussions, Writing – review & editing, all authors reviewed and approved the final manuscript. **Anette D. Kjeldsen:** developed the discussions, Writing – review & editing, all authors reviewed and approved the final manuscript. **Hans-Jurgen Mager:** developed the discussions, Writing – review & editing, all authors reviewed and approved the final manuscript. **Carlo Sabba:** developed the discussions, Writing – review & editing, all authors reviewed and approved the final manuscript. **Freya Droege:** developed the discussions, Writing – review & editing, all authors reviewed and approved the final manuscript. **Anne-Emmanuelle Fargeton:** Writing – review & editing, all authors reviewed and approved the final manuscript. **Annette D. Fialla:** Writing – review & editing, all authors reviewed and approved the final manuscript. **Silvia Gandolfi:** Writing – review & editing, all authors reviewed and approved the final manuscript. **Ruben Hermann:** Writing – review & editing, all authors reviewed and approved the final manuscript. **Gennaro M. Lenato:** Writing – review & editing, all authors reviewed and approved the final manuscript. **Guido Manfredi:** Writing – review & editing, all authors reviewed and approved the final manuscript. **Marco C. Post:** Writing – review & editing, all authors reviewed and approved the final manuscript. **Catherine Rennie:** Writing – review & editing, all authors reviewed and approved the final manuscript. **Patrizia Suppressa:** Writing – review & editing, all authors reviewed and approved the final manuscript. **Ulrich Sure:** Writing – review & editing, all authors reviewed and approved the final manuscript. **Claudia Crocione:** developed the discussions, Writing – review & editing, all authors reviewed and approved the final manuscript.

Declaration of competing interest

Authors have no competing interest to declare.

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Appendix A. Supplementary data

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