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The European Rare Disease Network for HHT Frameworks for management of hereditary haemorrhagic telangiectasia in general and speciality care

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A B S T R A C T

Hereditary haemorrhagic telangiectasia (HHT) is a complex, multisystemic vascular dysplasia affecting approximately 85,000 European Citizens. In 2016, eight founding centres operating within 6 countries, set up a working group dedicated to HHT within what became the European Reference Network on Rare Multisystemic Vascular Diseases. By launch, combined experience exceeded 10,000 HHT patients, and Chairs representing 7 separate specialties provided a median of 24 years' experience in HHT. Integrated were expert patients who focused discussions on the patient experience. Following a 2016–2017 survey to capture priorities, and underpinned by more than 40 monthly meetings, and new data acquisitions, VASCERN HHT generated position statements that distinguish expert HHT care from non-expert HHT practice. Leadership was by specialists in the relevant sub-discipline(s), and 100% consensus was required amongst all clinicians before statements were published or disseminated. One major set of outputs targeted all healthcare professionals and their HHT patients, and include the new Orphanet definition; Do's and Don'ts for common situations; Outcome Measures suitable for all consultations; COVID-19; and anticoagulation. The second output set span aspects of vascular pathophysiology where greater understanding will assist organ-specific specialist clinicians to provide more informed care to HHT patients. These cover cerebral vascular malformations and screening; mucocutaneous telangiectasia and differential diagnosis; anti-angiogenic therapies; circulatory interplays between anaemia and arteriovenous malformations; and microbiological strategies to counteract loss of normal pulmonary capillary function. Overall, the integrated outputs, and documented current practices, provide frameworks for approaches that augment the health and safety of HHT patients in diverse health-care settings.

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Abbreviations

ACMG	American College of Medical Genetics and Genomics
ACVRL1	Official symbol for gene encoding activin receptor-like kinase 1- a heterozygous loss-of-function variant causes HHT type 2
AHP	Association for Molecular Pathology
ARUP	Name of laboratory curating the HHT Mutation Database
AVF	Arteriovenous fistula
AVM	Arteriovenous malformation
BTS	British Thoracic Society
COVID-19	Disease caused by coronavirus SARS-CoV-2
DVA	Developmental venous anomaly
EASL	European Association for the Liver
ENG	Official symbol for gene encoding endoglin (CD105)- a heterozygous loss-of-function variant causes HHT type 1
ENT	Ear Nose and Throat Surgery (Otorhinolaryngology)
ePAG	European Patient Advisory Group
ERN	European Reference Network
HCP	Health care provider (hospital)
HHT	Hereditary haemorrhagic telangiectasia
NIPAP	Mnemonic to remember nosebleeds, iron deficiency, pulmonary AVMs, antibiotics and pregnancy
SMAD4	Official symbol for gene encoding SMAD4- a heterozygous loss-of-function variant causes HHT in association with juvenile polyposis
VASCERN	The European Reference Network on Rare Multisystemic Vascular Diseases

1. Overview of hereditary haemorrhagic telangiectasia

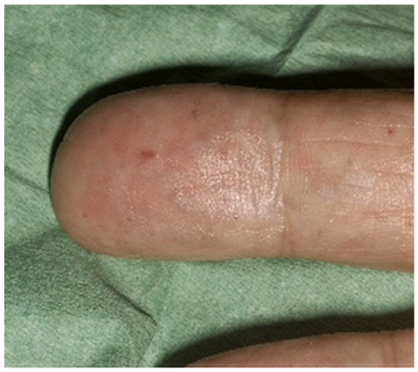
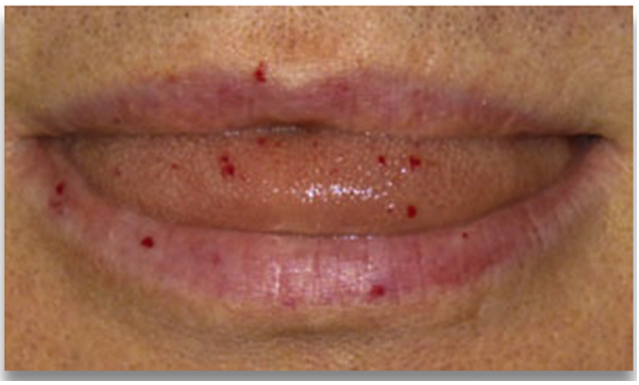
Hereditary haemorrhagic telangiectasia (HHT, syn. Osler-Weber-Rendu syndrome) is a complex multisystemic vascular dysplasia that leads to telangiectasia and arteriovenous malformations (AVMs) in visceral and mucocutanous vascular beds [VASCERN HHT 2019a; Shovlin, 2010], and downstream physiological perturbations. Based on a conservative European population prevalence of 1 in 6000 [Bideau et al., 1989; Kjeldsen et al., 1999], HHT is estimated to affect approximately 85,000 European citizens.

HHT is diagnosed clinically by the Curacao Criteria [Shovlin et al., 2000], specifically, the presence of at least 3 of recurrent spontaneous nosebleeds; mucocutaneous telangiectasia at characteristic sites; visceral vascular abnormalities; and an affected first degree relative according to these criteria (Table 1). HHT-affected individuals are at risk of two major types of vascular abnormalities. The first group increase with age, and consist of small telangiectasia that develop at characteristic sites, particularly in the nose (causing nosebleeds [epistaxis]), mouth, finger tips and gastrointestinal tract (Table 1). The second group are larger arteriovenous malformations in the lungs, liver, brain and other viscera. For these, development is predominantly completed by the end of puberty. There are other inherited vascular dysplasias, and non-inherited states that may result in vascular abnormalities reminiscent in distribution and appearances to those observed in HHT. These issues are outlined in Table 1, and discussed further in *Section 4.2*.

HHT is inherited as an autosomal dominant trait, classically due to a heterozygous loss-of-function allele in one of 3 different genes- *ENG* (HHT type 1), *ACVRL1* (HHT type 2), or *SMAD4* (HHT associated with juvenile polyposis) [VASCERN HHT 2019a]. While not a focus of the current article, it is important to recognise recent advances that emphasise not all DNA sequence variants in these genes cause HHT. The increasing stringency required to assign pathogenic or likely pathogenic status to variants since the publication of ACMG/AHP standards [Richards et al., 2015] has resulted in many variants in these genes in

Table 1
The Curaçao Criteria. The HHT diagnosis is **definite** if 3 of the 4 criteria are present, **possible or suspected** if 2 criteria are present, and **unlikely** if fewer than 2 criteria are present. A pathogenic (null) sequence variant in *ENG, ACVRL1* or *SMAD4* also defines definite clinical HHT according to current understanding. A negative HHT gene test does not exclude HHT unless the gene variant causing HHT has been identified in another affected family member.

Criterion	Curaçao Criteria Definition	Distinguishable from non HHT?
1. Epistaxis	Spontaneous, recurrent nose bleeds	Not possible by history- range from nil/minor to extreme. For patients with recurrent epistaxis, nasal examination by an otorhinolaryngologist can identify other causes for epistaxis and exclude HHT.
2. Telangiectases	Multiple, at characteristic sites • Lips • Oral cavity • Fingers • Nose	Yes - only some telangiectasia at characteristic sites are diagnostic, e.g **Finger pads** not nailfold or dorsum of hand. Examples are shown below. Note that arms, chest and legs are **not** characteristic sites: telangiectasia at these sites are not a diagnostic criterion.
3. Visceral lesions	Such as gastrointestinal telangiectasia (with or without bleeding); pulmonary AVM; hepatic AVM; cerebral AVM; spinal AVM	Multiple AVMs at a particular site are more likely to be due to HHT than a single AVM
4. Family history	A first degree relative with HHT according to these criteria	Yes, by an *ENG, ACVRL1* or *SMAD4* pathogenic or likely pathogenic DNA variant

HHT patients left as being of uncertain significance, or "pending assignment", i.e. not for use in diagnostic testing [HHT Mutation Database, 2021; Shovlin et al., 2020]. Recent data also emphasise that affected individuals, if the first in their family, may be mosaic for their causal HHT gene and initially have a negative HHT gene test [Tørring et al., 2018; McDonald et al., 2018; Clarke et al., 2020]. There is also evidence that one reason why individual vascular abnormalities develop at a particular site in someone affected by HHT may be due to somatic loss of the second wildtype allele [Snellings et al., 2019].

2. VASCERN HHT overview, goals, and delivery methods

The goal of VASCERN HHT is to maximize the number of affected individuals receiving safe and effective preventative and therapeutic strategies in order to limit the number and severity of HHT complications. The expertise required to best manage HHT patients spans numerous clinical disciplines, frequently involving pathologies that are not mainstream within these specialities, and requiring long-term, specific patient exposures to appropriately contextualise and assimilate new evidence to improve patient care.

Recognising similar patterns for all rare diseases, the European Commission established 24 European Reference Networks (ERNs). These included the European Reference Network on Rare Multisystemic Vascular Diseases (VASCERN) that was initiated in 2016, and formally launched on March 9th 2017 [VASCERN 2017]. VASCERN HHT, the working group within VASCERN that is dedicated to hereditary haemorrhagic telangiectasia (HHT), was built upon Multidisciplinary HHT Centres of Excellence that have been collaborating since an inaugural international meeting in 1996.

2.1. Expertise in VASCERN HHT

The eight founder health care providers (HCPs, "Expert Centres") in VASCERN HHT were from 6 different health care systems (Denmark, France, Germany, Italy, the Netherlands, and the UK). At the time of application for ERN Status in 2016, these providers had more than 10,000 HHT patients on their individual databases. Each HCP provided a Chair with a median of 24 years' experience in HHT, and the Chairs represent 7 separate specialties in Medicine (Adult and Paediatric) and Surgery (specifically ENT Surgery and Neurosurgery). Additional HCP members (>10 per HCP) provided expertise that was shared at appropriate times. Thus, the functional working VASCERN unit over the past 5 years has comprised expert HHT clinicians from Adult Internal Medicine, Cardiology, Clinical Genetics, Gastroenterology, Haematology; Hepatology, Interventional Radiology (Thoracic and Neuro-interventional Radiology); Microbiology; Neonatology, Neurology; Obstetrics and Gynaecology, Paediatrics, Pulmonology, and Surgery (ENT, Neurosurgery and Liver Transplantation).

Separately, there were multiple HHT patient advocates operating both independently within the European Patient Advisory Group (ePAG), and within the monthly VASCERN HHT meetings. These expert patients conveyed the experiences of those with HHT, and ensured the discussions were always focussed on the patient experience, mindful of off-target consequences such as radiation exposure and unintended lifestyle impacts.

2.2. Goals and priorities

As detailed on our website [VASCERN 2020], the goal of VASCERN HHT is to harness expertise across Europe to provide optimal guidance to maximize patient health and safety.

To set appropriate priorities, between November 2016 and January 2017, members were surveyed and in free text, asked what they considered to be the 3 most important problems for HHT. The full data from the 4 groups of respondents (Clinicians, Patients, Patient Advocates and Scientists) and the subsequent discussion framework are provided in *Appendix 1*. Over the next 4 years, more than 40 monthly meetings and a similar number of supplementary communications, the priorities were addressed, and additional priorities incorporated as they emerged, including COVID-19.

The fundamental driver within VASCERN HHT has been that the most important material to generate and share is that which distinguishes expert HHT care from non-expert HHT practice. Thus, emphasis is on:

- Generating statements that exemplify and encourage good HHT practice;
- Reaching 100% agreement across all expert authors;
- Leadership by experts in the relevant sub-discipline(s), with their voices carrying greater weight than HHT experts from different disciplines. This has been particularly important for cerebral, haemorrhagic, microbiological, obstetric and paediatric discussions, when relevant experts have been brought in from the wider Consultant membership of the VASCERN HHT HCPs.

2.3. VASCERN HHT dissemination approach

VASCERN HHT materials are released only if 100% agreement is reached from all experts participating in the VASCERN HHT group at the time, each with either a very high level of HHT-specific experience, and/or relevant speciality expertise. Topics are removed from priority lists when it becomes clear after initial discussions that extra data/discussion will not be able to provide a "one size fits all" approach at the initial level of detail. In these cases, a higher level topic that might enable 100% agreement to be reached across all members is considered. Where this is not possible, differences between experts are acknowledged and respected. For a Rare Disease field where randomised controlled trial evidence is sparse, this approach to generate Clinical Consensus Statements appears to VASCERN HHT to be at least as powerful as Clinical Practice Guidelines that do not require 100% agreement, and where high quality evidence and individual expertise is not always as evident.

Box 1
European Commission Definitions.

"Clinical practice guidelines are statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options." [Graham et al., 2011]

"A clinical consensus statement is the end product developed by an independent panel of (at least 3) subject matter experts convened specifically to perform a systematic review of the available literature, for the purpose of understanding a clinically relevant issue or surgical procedure." It offers specific recommendations on a topic. Compared to Clinical Practice Guidelines and Clinical Practice Recommendations, Clinical Consensus Statements undergo a less rigorous peer review process.

Engagement has been encouraged with separate groupings and structures generating alternate Clinical Practice Guidelines that advocate recommendations approved by the majority (which are thus able to address additional questions with less convincing evidence), or other Consensus Statements. Thus VASCERN HHT Leads played major roles in shaping the outputs from, for example, the European Association for the Liver (EASL [European Association for the Study of the Liver, 2016]) and the French Association for the Study of the Liver (AFEF) [Silvain et al., 2020]) regarding hepatic AVMs; the British Thoracic Society (BTS [Shovlin et al., 2017a]) regarding pulmonary AVMs, and the Second International Guidelines for HHT [Faughnan et al., 2020]. The latter had 6 working groups: nosebleeds, gastrointestinal bleeds, hepatic AVMs, anaemia, pregnancy and paediatrics [Faughnan et al., 2020]). Through 2019–2020, seven HHT centre lead clinicians, and 2 further VASCERN HHT members (patient ePAG representative, and clinician) participated, providing an opportunity to shape the discussions for all of the 2019 guideline working groups [Faughnan et al., 2020]).

The remainder of this article focuses on the detail of the VASCERN Statements, targeting two separate readership groups:

- All clinicians and healthcare professionals and their patients affected by HHT (Section 3)
- Organ-specific clinicians with and without HHT-specific expertise (Section 4)

There is then a fifth section that documents current practice across the VASCERN HHT centres, as reviewed in our October 2020 meeting following publication of the Second International HHT Guidelines.

3. HHT management relevant to all clinicians taking care of HHT patients

HHT is estimated to affect 85,000 European citizens, and each of these will see a variety of healthcare professionals over their lifetime.

As emphasised by VASCERN's HHT patient pathway (presented elsewhere in this series), for most HHT patients, most of their care will be conducted by local clinicians and healthcare practitioners. HHT patients may need HHT-specific advice (or reassurance to follow normal advice) whenever they encounter a healthcare professional. This could be from pregnancy to dental care, emergency care to surgery, concerning what tablets to take or not to take, and what treatments to have or not to have.

While patients ideally will have ongoing access to HHT-specific services on demand, and their clinicians will ideally have ongoing support from HHT specialist teams, realistically most immediate management decisions and interventions will be performed by healthcare professionals who are not experts in HHT. They may require confidence and guidance as to why and when to modify their usual practices, especially in the setting when the patient is more HHT-informed than they are.

For the patients and their usual or emergency general healthcare providers, VASCERN HHT developed resources to efficiently support all stages of the pathway, and prevent unnecessary delays in provision of urgent care (Fig. 1).

3.1. Orphanet Definition of HHT

OUTPUT 3.1	*Hereditary haemorrhagic telangiectasia.*	*Published online Jan 2019* [VASCERN HHT 2019a]

As detailed at [VASCERN 2019] the entry on Hereditary Haemorrhagic Telangiectasia (HHT) in the Orphanet Encyclopedia for Professionals was reviewed and updated by VASCERN HHT [VASCERN HHT 2019a]. Primary references are provided in VASCERN HHT's Outcome Measures manuscript [Shovlin et al., 2018], as detailed in Section 3.3.

The agreed clinical description and prognosis sections of the Orphanet Definition provide a succinct overview of HHT suitable for all clinicians:

> "The most common clinical signs of hereditary hemorrhagic telangiectasia (HHT) include recurrent epistaxis (nosebleeds), frequently from childhood, and cutaneous or mucosal telangiectases generally presenting later, and increasing with age, where anemia may become an important part of the disease. Visceral arteriovenous malformations (AVMs) are usually asymptomatic but can lead to complications that produce highly variable manifestations. The age of onset of AVM-related complications is variable, ranging from childhood to geriatric age, with a few cases reported during the neonatal period. Pulmonary AVMs may manifest with brain abscesses, strokes,

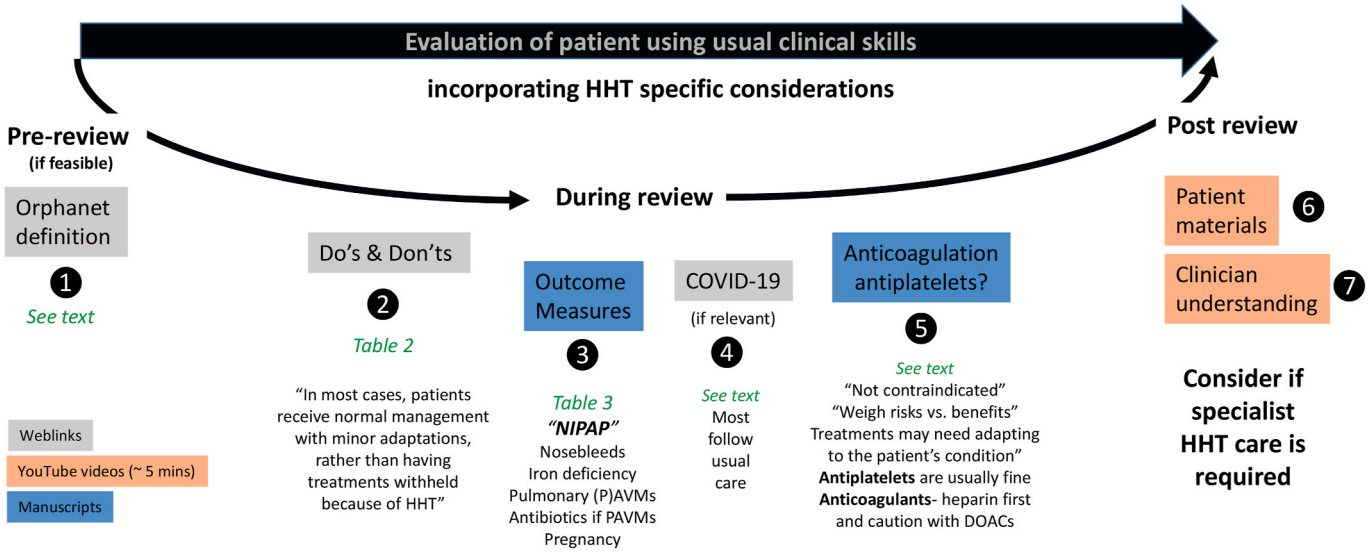


Fig. 1. VASCERN HHT outputs for general care of HHT patients, positioned in suggested order across a generic consultation with a healthcare provider. The black circle numbers indicate the outputs addressed in Section 3: Sections 3.1 [VASCERN HHT 2019a]; 3.2 [Dupuis-Girod et al., 2018]; 3.3 [Shovlin et al., 2018]; 3.4 [VASCERN HHT 2020; VASCERN HHT, 2021]; 3.5 [Shovlin et al., 2019a]; and 3.6/3.7 [VASCERN HHT 2019b; Shovlin 2018; Kjeldsen 2018]. These provide a suggested framework to assist clinicians and patients, rather than a blueprint for management. As for all guidance and support tools, material should be interpreted in the patient and healthcare-specific context, and can be supplemented by country and speciality documents such as those outlined in Sections 3 and 4.

transient ischemic attacks, signs of chronic hypoxaemia or, rarely, haemorrhagic rupture. AVMs of the central nervous system can be haemorrhagic or, rarely, produce signs of slow compression. Hepatic AVMs, which can remain latent for a long time, in a limited proportion of patients become severe leading to high-output cardiac failure, portal hypertension, pulmonary hypertension or ischemic cholangitis. Hemorrhagic digestive telangiectases increase with age and can worsen chronic anemia.

Life expectancy is reduced in unscreened patients. In patients assessed and treated for pulmonary AVMs in an HHT Center, life expectancy is comparable to the general population. Pregnancy-related death has been reported, and is a particular risk for women with pulmonary arteriovenous malformations."

The definition also includes brief sections on HHT etiology, diagnosis (including methods, differential and antenatal), management, and genetic counselling that are more relevant to specialist clinicians [VASCERN HHT 2019a].

3.2. Do's and Don'ts

OUTPUT 3.2	*Hereditary haemorrhagic telangiectasia: VASCERN Do's and Don'ts Factsheets for Rare Vascular Disease Patients Facing Frequent Situations.*	*Published online Feb 2018*: [Dupuis-Girod et al., 2018]

A core recommendation of the ERN auditing authority adopted by the ERN for Rare Multisystemic Vascular Diseases (VASCERN) was to foster information on safety standards for rare disease patients. To address general issues that may be encountered over a patient's lifetime, multiple Do's and Don'ts statements were generated [Dupuis-Girod et al., 2018] and are summarised in Table 2. The key messages are that:

- In most cases, patients receive normal medical management with minor adaptations rather than having treatments withheld because of HHT;
- Nasogastric intervention requires extreme caution due to the risk of triggering a severe episode of epistaxis related to the presence of mucous telangiectases, with nasal manipulations (eg intubation) contraindicated where there are alternative routes;
- Apart from the risk of bleeding related to the presence of mucous telangiectases (nasal, gastrointestinal), there are no coagulation anomalies associated with hereditary haemorrhagic telangiectasia and no surgical bleeding risk connected with this pathology.

3.3. HHT Outcome Measures

OUTPUT 3.3	*European Reference Network For Rare Vascular Diseases (VASCERN) Outcome Measures For Hereditary Haemorrhagic Telangiectasia (HHT).*	*Orphanet J Rare Dis. 2018 Aug* [Shovlin et al., 2018]

If Outcome Measures are selected carefully, their dissemination and implementation can directly improve patient care, including that from health care providers with limited prior exposure or training on the specific disease. Simple, clinical practice-based Outcome Measures are particularly important for rare multisystemic conditions. With these considerations in mind, HHT Outcome Measures were developed to be applicable to every encounter with a healthcare professional, specifically targeting areas where optimal management reduces morbidity and mortality in HHT, and where the measures would be robust to emerging new evidence.

At the simplest level, the Outcome Measures provide a reminder for all patients and healthcare practitioners of essential considerations in HHT [Shovlin et al., 2018]. They span nosebleeds (epistaxis); iron deficiency (anaemia); pulmonary AVMs; antibiotic prophylaxis if pulmonary AVMs are present; and pregnancy. The items (remembered by the mnemonic NIPAP) encourage care improvement by all healthcare providers, and if considered, should increase the number of patients receiving good care. (Table 3).

Originally developed as metrics to identify healthcare providers of good care in specialised settings, more broadly, the 5 principles will facilitate good care in all healthcare settings. In keeping with the wider principles of the Curaçao Criteria [Shovlin et al., 2000], where HHT is suspected (two Curaçao criteria) and there is no molecular test to confirm or refute the diagnosis, the five measures are also extremely appropriate to apply.

More details regarding each of these measures, and primary references, are provided in reference [Shovlin et al., 2018]. Overall, the Outcome Measures ensures that for any HHT patient, irrespective of their presentation pattern to the healthcare practitioner:

Table 2
Summary of HHT Do's and Don'ts in common medical situations. Several separate entries emphasise the contraindication to unnecessary nasal manipulations (nasal intubation, aspirations, etc.) due to the significant risk of triggering sometimes very severe episodes of epistaxis linked to mucous telangiectases. If the patient's clinical condition requires the insertion of a nasogastric tube, it should be soft, small diameter (unless clinical circumstances demand a large bore tube), and put in place with extreme caution due to the risk of triggering a severe episode of epistaxis related to the presence of mucous telangiectases. † Addressed further in Section 4.5.

Situation	Core Message (extracts, full text in [Dupuis-Girod et al., 2018])
1. Physical Activity	No restrictions, other than scuba diving with a diving tank in patients with pulmonary AVMs
2. Breast feeding	No need to restrict
3. Contraindicated medications	No medication is formally contraindicated. Risks and benefits should be discussed, and treatments may need adapting
4. Antiplatelets and anticoagulants	Not contraindicated, though antiplatelet agents and anticoagulants should only be prescribed after weighing the risks and benefits
5. Thromboses and pulmonary emboli	Generally follow standard treatment, even when hereditary hemorrhagic telangiectasia is present
6. Haemorrhagic stroke	Generally follow standard emergency treatment, and look for underlying cerebral AVMs to prevent recurrence.
7. Brain abscess	Generally follow standard emergency treatment, and look for underlying pulmonary AVMs to prevent recurrence.
8. Heart failure	This is most commonly seen in the context of high output states due to hepatic AVMs and anaemia, which should be sought to optimize management. Vasodilators are not recommended to treat pulmonary hypertension secondary to hepatic vascular malformations.†
9. Kidney failure	Renal biopsy possible if AVMs excluded by doppler sonography.
10. Multiple traumatic injuries; 11. Aortic dissection; 12. Pneumothorax	Apart from the risk of bleeding related to the presence of mucous telangiectases (nasal, gastrointestinal), there are no coagulation anomalies associated with hereditary haemorrhagic telangiectasia and no surgical bleeding risk connected with this pathology.
13. Bronchoscopies	Follow standard fibroscopy technique, but care with nasal manipulations that may trigger severe nosebleeds, and pre biopsy, use antibiotic prophylaxis if pulmonary AVMs present

- Nosebleeds (epistaxis) are not overlooked as a potential cause of iron deficiency anaemia whether already diagnosed or not. It is poorly appreciated that severe recurrent HHT nosebleeds can generate acute haemodynamic compromise and/or chronic cardiac failure in addition to being the most common cause of iron deficiency anaemia in HHT patients [Finnamore et al., 2013].
- Iron deficiency, which is commonly indolent and not appreciated by the patient until after correction, is promptly identified, enabling optimal management, with evidence that even low dose oral iron supplements (ferrous gluconate 300 mg od, with 35 mg elemental iron) can correct anaemia in HHT patients [Rizvi et al., 2017].
- The possibility of PAVMs is remembered and addressed, since this can be the unusual cause (due to paradoxical embolism) of multiple presentations in general medical care, most commonly migraine [Post et al., 2006], ischaemic stroke, angina, myocardial infarction, deep seated infections, and abscesses, particularly cerebral abscesses [Boother et al., 2017].
- All PAVM patients, their dentists, primary care physicians and other healthcare practitioners are aware of the current situation where European patients refused or not considered for prophylaxis go on to develop a cerebral abscess [Boother et al., 2017; Shovlin et al., 2018]. The rationale for prophylactic antibiotics is discussed further in Section 4.4 [Shovlin et al., 2019b].
- The potential risks of pregnancy for European women with HHT [Shovlin et al., 2008; Dupuis et al., 2020] are appreciated, and obstetric care pathways modified.

3.4. COVID-19 and HHT

OUTPUT 3.4a	*VASCERN Hereditary Haemorrhagic Telangiectasia (HHT) Statement on COVID-19*	Published online March 2020: [VASCERN HHT 2020]

The late 2019 advent of infection by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) brought additional complexities for HHT patients in 2020. Early in the pandemic, VASCERN issued a statement for people with HHT, and their doctors, based on our knowledge on HHT and the follow up of HHT patients with COVID [VASCERN HHT 2020]. The key elements were 4 evidence-based statements:

- People with HHT should follow the standard Public Health Measures as recommended in their specific country.
- People with HHT should be no more and no less concerned about COVID-19 than the general population without HHT.
- The presence of HHT or AVMs in someone who currently has a normal or high exercise tolerance should not limit their access to medical treatment compared to someone without HHT or AVMs of the same age.
- Those obliged to self-isolate because of the general situation are advised to maintain normal treatment regimes if possible (particularly iron supplements for anaemia), and avoid sedentary states.

As the pandemic progressed, first Italian, then all health care provider services reported reductions in new patient numbers. At VASCERN Days October 2020 [VASCERN 2020], VASCERN HHT presented their data on annual number of new HHT patients seen for 2017/2018/2019 (N = 679/686/726) and 2020 (312 predicted, i.e. 60% "missing"). Combining with the HHT-specific data extracted from the European Patent Advisory Group (ePAG) Rare Barometer survey on Covid-19 impact on the rare disease community [Rare Barometer Voices 2020] identified factors including both operation of healthcare services and patient preference to defer elective assessments.

A new issue arose as it became apparent that the commonest cause of death in COVID-19 is through thromboembolic disease [Wichmann et al., 2020], and that enhanced prophylactic and therapeutic anticoagulation is associated with improved survival in the general population [Vizcaychipi et al., 2020]. There is evidence that both HHT patients and their healthcare practitioners can be over-cautious about use of anticoagulants [Devlin et al., 2013]. This is one reason why VASCERN HHT had already prioritised a European-wide Drug Registry on anticoagulants, discussed in the next section.

OUTPUT 3.4b	*VASCERN Hereditary Haemorrhagic Telangiectasia (HHT) Statement concerning COVID-19 vaccination for patients with HHT*	Published online January 2021: *[VASCERN HHT 2021]*

Following the progression of the pandemic, and development then regulatory approval of COVID-19 vaccines, expert recommendations were drafted and posted online. The following points were highlighted:

- A reminder to follow the national safety advice for social distancing, mask wearing etc.
- Vaccination is important for the whole population but it remains patient's choice.
- Recommendation for vaccination: follow the national guidelines concerning vaccination. SARS-CoV-2 vaccination was encouraged in patients with HHT, particularly if patients required regular hospital attendance (e.g. for blood transfusions or iron), were older (>50 years old), or had comorbidities such as chronic respiratory disease, cardiovascular diseases, obesity or diabetes.
- Vaccination during pregnancy should follow national guidelines for pregnancy.
- There are no data to exclude HHT patients from receiving any of the vaccines currently in use.

3.5. Anticoagulants: DOAC registry data imply that heparin and warfarin remain first choice in HHT

OUTPUT 3.5	*Safety of direct oral anticoagulants in patients with hereditary hemorrhagic telangiectasia*	*Orphanet J Rare Dis. 2019 Aug* [Shovlin et al., 2019a]

It was recognised that while the Do's and Don'ts were written based

Table 3
VASCERN HHT Outcome Measures. The outcome measure thresholds are the percentage of adult patients in particular settings who have been recommended screening, or provided with written advice following on from an established diagnosis of HHT (†3 Curaçao Criteria; ‡*ENG, ACVRL1 or SMAD4* pathogenic or likely pathogenic variant), or pulmonary AVMs.

	Target Population	Estimated cases in Europe	Measure	Target threshold
1	All individuals with HHT- either by a clinical† or	85,000	Screen for pulmonary AVMs	≥90%
2	molecular‡ diagnosis.		Receive nosebleed advice in writing	≥90%
3			Assessment of iron deficiency *at each consultation*	≥70%
4	Pulmonary AVMs (+/− HHT)	196,000	Receive written advice on antibiotic prophylaxis prior to dental and surgical procedures	100%
5	Pregnant women with pulmonary AVMs (+/− HHT)	~1000	Receive written advice on PAVM/HHT pregnancies	100%

on evidence from ~200 published cases of HHT-affected users who had used anticoagulation, the published evidence was almost exclusively based on use of warfarin or heparin [Devlin et al., 2013]. Recent years have seen a switch to anti-coagulation strategies using direct oral anticoagulants (DOACs) that do not require regular blood test monitoring. There was no published series of HHT cases treated using such agents, though VASCERN HCP Leads were aware of such patients through their clinical practice.

In keeping with the core recommendation of the ERN auditing authority to foster information on safety standards for rare disease patients, VASCERN HHT instituted a retrospective registry audit to evaluate the safety of DOACs in HHT across the eight HHT centres in Denmark, France, Germany, Italy, the Netherlands and the UK [Shovlin et al., 2019a]. Although the HHT Centres had not recommended DOAC use, 32 treatment episodes had been initiated by other clinicians who were providing local care of the HHT patients. DOAC anticoagulation was commenced for one of two clinical indications- venous thromboembolism or atrial fibrillation, with differing age profiles. HHT nosebleeds increased in severity in 75% (24/32 treatment episodes) leading to treatment discontinuation in 34.4% (11/32 episodes). Patients who had failed to tolerate one agent were commonly able to use a different anticoagulant [Shovlin et al., 2019a].

Of most concern, extreme haemorrhagic responses were reported at higher rates than historically seen by VASCERN HHT Leads in HHT patients receiving anticoagulation: While the adverse responses appeared limited to nosebleeds, these were commonly described as worse than anything experienced previously, lasting hours and requiring hospital admissions, blood transfusions in addition to treatment discontinuation. Such extreme haemorrhagic responses occurred in 5/14 (35.7%) Rivaroxaban episodes compared to 3/15 (20%) Apixaban episodes and published rates of ~5% for warfarin and heparin. Potential explanations for such differences were provided [Shovlin et al., 2019a].

It was concluded that although numbers were small, conventional heparin and warfarin remain first choice anticoagulants in HHT [Shovlin et al., 2019a]. If newer anticoagulants are considered, at this stage Apixaban appears to be associated with lesser bleeding risk than Rivaroxaban, although there are individuals who experience the converse – unable to tolerate Apixaban but able to tolerate Rivaroxaban.

These data and conclusions were incorporated into the second international HHT guidelines [Faughnan et al., 2020]. They are also relevant to emergency management in the setting of COVID-19.

3.6 and 3.7. Supplementary information for patients and general clinicians

OUTPUT 3.6	*HHT from VASCERN HHT*	***Published online March 2019***: [VASCERN HHT 2019b] 2046 *views to date*
OUTPUT 3.6/3.7	*An overview of Hereditary Haemorrhagic Telangiectasia*	*Published online January 2018*: [Shovlin 2018] 13624 *views to date*
OUTPUT 3.7	*Hereditary Haemorrhagic Telangiectasia (HHT) for ENT doctors*	*Published online January 2018:* [Kjeldsen 2018] 3904 *views to date*

Although the measures detailed in Sections 3.1-3.5 are simple and easy to implement, conveying their importance is more challenging. In order to try to encourage clinicians to acquire sufficient information, three short (5–8 min) YouTube videos were generated providing an introduction to HHT explaining its etiology and main features [VASCERN HHT 2019b; Shovlin 2018; Kjeldsen 2018], and these have been viewed more than 19,000 times to date.

The most recent video [VASCERN HHT 2019b] was generated to be particularly well suited to an HHT patient's first exploration of online materials, following their diagnosis.

4. HHT management and principles for organ-specific specialists

New statements were generated for 5 specialist aspects of HHT vascular pathophysiology and treatments where greater understanding would assist other clinicians to provide more informed care of HHT patients.

These are summarised in Fig. 2, and fall into two categories. The first primarily address the abnormal vascular structures of HHT (cerebral vascular malformations, mucocutaneous telangiectasia, and anti-angiogenic therapies). The second address major elements of abnormal circulatory physiology, particularly in relation to the interplay

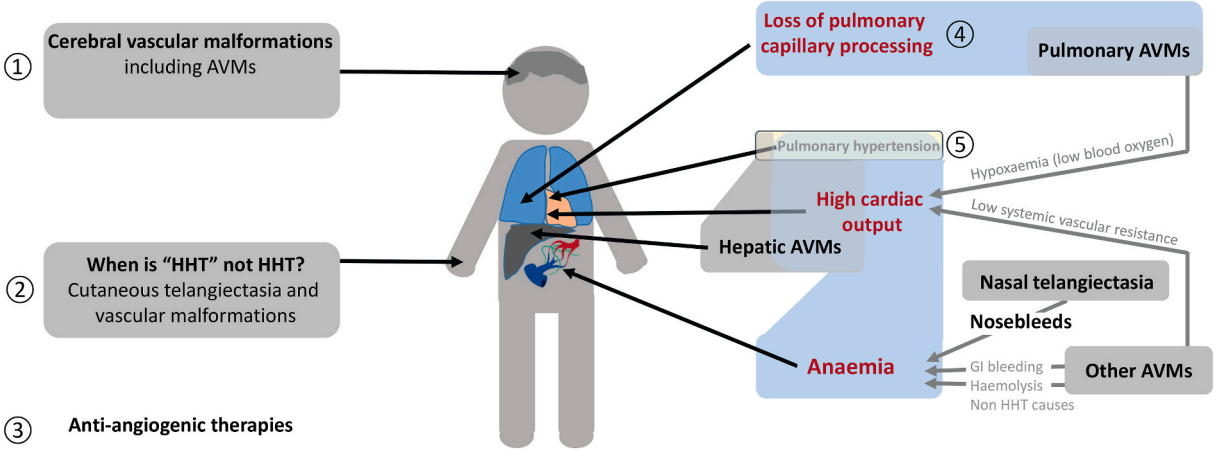


Fig. 2. VASCERN HHT outputs for organ-specific specialist consultations. The categories primarily addressing the abnormal vascular structures and HHT diagnostic criteria are indicated by black text and grey boxes. Categories addressing major elements of abnormal circulatory physiology are indicated by red/grey text and blue boxes. The white circle numbers indicate the outputs addressed in Section 4, i.e. Sections 4.1 [Eker et al., 2020]; 4.2 [VASCERN 2018]; 4.3 [Buscarini et al., 2019]; 4.4 [Shovlin et al., 2019b], and 4.5 [Boother et al., 2019]. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

between anaemia and AVMs in leading to high cardiac outputs and consequences, and the effect of the loss of normal pulmonary capillary function for patients with pulmonary AVMs.

4.1. Cerebral screening in HHT adults and children

OUTPUT 4.1	European Reference Network for Rare Vascular Diseases (VASCERN) Position Statement on cerebral screening in adults and children with hereditary haemorrhagic telangiectasia (HHT).	*Orphanet J Rare Dis. 2020 Jun* [Eker et al., 2020]

- This field is challenged by a complexity of cerebral vascular abnormality definitions and nomenclature, with differing reporting, natural history and treatment success rates.
- At least 6 different cerebrovascular abnormalities contribute to the ~10% rate of cerebrovascular malformations in HHT.
- Through neurosurgical and neuro-interventional leadership, mindful of the full pathway for diagnosed patients, it was possible for 28 VASCERN HHT co-authors from 6 different countries to approve four statements on cerebral screening with 100% consensus.

At the time of generating the Outcome Measures (Section 3.3 [Shovlin et al., 2018]), it was recognised that cerebral screening could not be included in a simple metric, because considerations continue to challenge the HHT community. The online methodological notes highlighted the lack of consensus in the first international HHT Guidelines (2006 agreement only 77% on Level III evidence [Faughnan et al., 2011]), alongside the need to incorporate newer evidence such as from the ARUBA trial [Mohr et al., 2014].

The major reason why cerebral screening approaches have been such a matter of controversy in HHT is the complexity of the field in terms of cerebral vascular abnormality definitions/nomenclature, natural history and treatments. Overall, cerebrovascular malformations affect approximately 10% of HHT patients, differing by HHT genotype. However, they span multiple subtypes including not only cerebral arteriovenous malformations (AVMs) but also, less frequently, arteriovenous fistulae, capillary telangiectases, and cavernous malformations. HHT patients can also have developmental venous anomalies (DVA) and/or intracranial aneurysms. It is poorly appreciated that haemorrhagic risks from these lesions differ markedly in the general population. For example, arteriovenous fistulae, and large and giant aneurysms have a very high risk of rupture; the rupture rate for the more common arteriovenous malformations (AVMs) are usually in the 1–2% per year range of rupture rate; cavernous malformations lower, and telangiectases/DVA almost zero. Differing inclusion of subcategories in HHT data series (summarised in [Eker et al., 2020]) result in prevalence and haemorrhage rates that are difficult to compare. Were treatments to be completely safe and efficacious, such considerations would matter less. However, as VASCERN HHT was advised by its expert neurosurgical and interventional neuroradiology lead authors, currently available therapies for these cerebral vascular malformations, and particularly AVMs, are not trivial and carry a non-negligible risk of complications. This is why the Orphanet Definition statement in relation to cerebral AVMs was limited to the post-diagnostic state: "Usually, cerebral AVMs that have not bled are not treated, whereas cerebral AVMs that have already bled or have become symptomatic usually require treatment" [VASCERN HHT 2019a].

In order to explore the possibility of achieving 100% consensus on cerebral screening in HHT, i.e. detection of lesions that had not already presented due to symptoms or bleeding, VASCERN HHT undertook 24 months of structured discussions. Following the above brief consensus statement that was included in the 2019 Orphanet Definition of HHT [VASCERN HHT 2019a], the number of neurovascular leads was expanded [Eker et al., 2020]. In order to arrive at the final consensus, three key steps were followed. First, the published literature on prevalence and bleeding risk in 6 different types of vascular abnormalities encountered in people with and without HHT was summarised. Second, the neurosurgical and neurovascular intervention lead authors provided a discussion on the treatments available, including risks and benefits. Third, published and unpublished data from across the VASCERN HCPs were summarised, including genotype distinctions, and how the vascular abnormalities were classified (Fig. 3).

In generating the final statements which were approved with 100% consensus, discussions were aided not only by the extensive specialty-specific expertise of the neurosurgical and neuro-interventional lead authors, but also, because 6 of the 8 HCP Leads were able to draw on decades of discussing these critical decisions with patients both

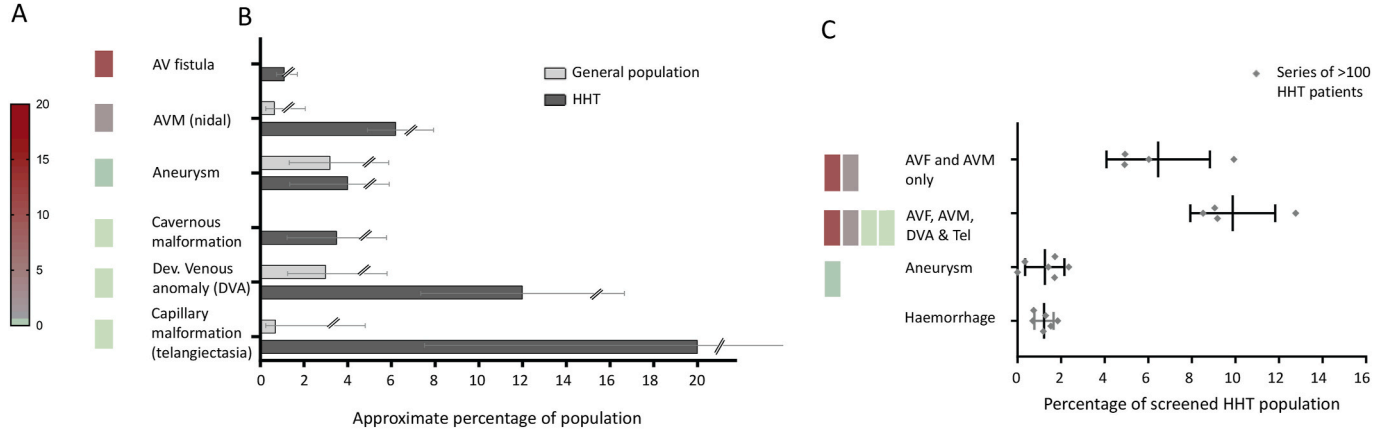


Fig. 3. Graphical representation of data tabulated in reference [Eker et al., 2020]. A) Heatmap of risk of published haemorrhage rates for the 6 types of cerebral vascular abnormalities discussed, where green represents vascular lesions with a low (near to 0%) risk of haemorrhage; grey an intermediate risk, and red a high risk: Numerical value represents estimated rate of haemorrhage per annum (full data in Table 3 of [Eker et al., 2020]). **B)** Bar graph of published approximate prevalence (with indicative error bars) comparing prevalence rates of respective abnormalities in HHT and the general population (full data in Table 3 of [Eker et al., 2020]). **C)** Individual data, mean and standard deviations for series from the VASCERN HHT centres, restricted to data series with >100 HHT patients (141–1742 cases/series, full data in Table 4 of [Eker et al., 2020]). The data restricting findings to AVF and AVM are presented separately to data series that also included DVA and telangiectasia. The heat map data from **A)** is included for ease of reference, noting that the top group contains two separate vascular abnormalities, the second group four separate vascular abnormalities, and the colour codes from the heatmap are provided for each. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

individually (hundreds per HCP Lead), and at respective national Patient Meetings. It was this enormously wide experience, in addition to familiarity with the relevant academic literature, that enabled 100% consensus to be reached amongst the HHT clinicians [Eker et al., 2020]. We recognise that while the European Reference Network achieved 100% consensus on these issues based on 2020 evidence, other experts disagree based on evidence available in 2006 and in 2019.

The 4 core statements in the VASCERN Position Statement on cerebral screening in adults and children with hereditary haemorrhagic telangiectasia were:

1) Individual situations encompass a wide range of personal and clinical states. In order to avoid conflicting advice, particularly arising from non-neurovascular interpretations of the evidence base, we suggest that all HHT patients should have the opportunity to discuss knowingly brain screening issues with their healthcare provider.
2) Any screening discussions in asymptomatic individuals should be preceded by informed pre-test review of the latest evidence regarding preventative and therapeutic efficacies of any interventions. The possibility of harm due to detection or intervention on a vascular malformation that would not have necessarily caused any consequence in later life should be stated explicitly.
3) Neurological symptoms suggestive of cerebral AVMs in HHT patients should be investigated as in general neurological and emergency care practice. This is separate to screening discussions. Management approaches should rely on expert discussions on a case-by-case basis and individual risk-benefit evaluation of all therapeutic possibilities for a specific lesion (neurosurgery, embolization, stereotactic radiosurgery).
4) The current evidence base does not favour the treatment of unruptured cerebral AVMs [Cenzato et al., 2017], and therefore cannot be used to support widespread screening of asymptomatic patients.

4.2. When is HHT not HHT?

OUTPUT 4.2	*VASCERN HHT and VASCA Joint Workshop*	Published online October 2018: [VASCERN 2018]

- Not all familial cutaneous telangiectasia and AVMs are due to HHT.
- In the absence of clinical experience in distinguishing lesion morphologies, genetic testing is recommended.

As noted in Section 1, there are other inherited vascular dysplasias, and non-inherited states that may result in vascular abnormalities reminiscent in distribution and appearances to those observed in HHT. During a workshop held during the October 2018 VASCERN Days meeting, 3 vasculopathies were compared with our colleagues in the VASCERN VASCA working group – HHT, *RASA1,* and *CM-AVM2*. [VASCERN 2018].

4.3. Antiangiogenic use for bleeding in HHTs

OUTPUT 4.3	Safety of thalidomide and bevacizumab in patients with hereditary hemorrhagic telangiectasia	Orphanet J Rare Dis. 2019 Feb 4 [Buscarini et al., 2019]

- In a VASCERN HHT Drug Registry, only a small proportion of the 10,000+ patients known to the HCP Centres had used these agents.
- For the 138 treated patients by late 2018 providing 63.8 person/ys per agent, adverse event rates were 0.40 and 0.44 per patient for bevacizumab and thalidomide respectively.
- There were significant differences in adverse event profiles according to sex and genotype.
- The findings resulted in recommendations for appropriate weighing of the toxicities, which can arise from these drugs, and practice recommendations for prevention and management.

As noted above, a core recommendation of the ERN auditing authority adopted by the ERN for Rare Multisystemic Vascular Diseases (VASCERN), was to foster information on safety standards for rare disease patients. For HHT, anti-angiogenic agents bevacizumab and thalidomide were prioritised as both have a potential for adverse events, and in the last decade, they have been increasingly used off-label in HHT patients, within and outside expert HHT-centres. Therefore an early priority of VASCERN HHT was to set up a Drug Registry, focusing on safety profiles in this specific condition, where toxicity profiles may differ from those reported in the general population. The captured adverse events were classified using the Common Terminology Criteria for Adverse Events [Buscarini et al., 2019].

Strikingly, and in contrast to numbers published from particularly North American Centres [Al-Samkari et al., 2020], relatively few patients used these agents in the major European centre - 69 received bevacizumab for high output cardiac failure/hepatic AVMs, or severe bleeding and 69 received thalidomide for severe epistaxis or gastrointestinal bleeding. It was noted that in the VASCERN HHT centres, the use of bevacizumab or thalidomide is generally proposed when these severe HHT complications are refractory to other, often multiple, therapeutic attempts. These vary depending on the type of complication, and are frequently associated with substantial red cell transfusion requirements [Buscarini et al., 2019]. The publication reported that in the October 2018 VASCERN Meeting, the clinical experts within VASCERN HHT estimated that the patients with HHT complications sufficiently severe to warrant bevacizumab or thalidomide represent fewer than 5% of HHT patients seen by them.

Altogether, the datasets comprised 63.8 person/years treatment with bevacizumab and 75 person/years treatment with thalidomide, and the respective adverse event rates were 0.40 and 0.44 per patient. Adverse events of lesser grade (1–2) were common; included somnolence and drowsiness (typical of the sedative properties of thalidomide); were important for patients, affecting quality of life during these long term treatments; and were the reason for treatment interruption. 39% of patients reported grade 2-3 adverse events - joint pain and peripheral neuropathy were the most frequent for bevacizumab and thalidomide respectively [Buscarini et al., 2019]. There were 4 Grade 5 (fatal) adverse events - one an ischaemic stroke during thalidomide treatment, one due to cardiac failure, and two resulting from catastrophic bleeds, with further details presented in [Buscarini et al., 2019]. Female and genotypic differences were identified: Women were more likely to have reported adverse events with bevacizumab (58.7% compared to 26.1% in men, $p < 0.001$), although the only fatal event occurred in a male. There was a trend for *ENG* patients to have more adverse events reported when on thalidomide (17 events in 17 patients) compared to 14 in 34 *ACVRL1* patients ($p < 0.001$).

With potential increase in use of bevacizumab and thalidomide in HHT patients, and detailed discussions presented in [Buscarini et al., 2019], the data were considered to support appropriate weighing of the toxicities that can arise from these drugs and resulted in practice recommendations for their prevention and management (Table 4).

4.4. Antibiotic prophylaxis for HHT patients with pulmonary AVMs

OUTPUT 4.4	Prevention of serious infections in hereditary hemorrhagic telangiectasia: roles for prophylactic antibiotics, the pulmonary capillaries-but not vaccination.	Haematologica. 2019 Feb; [Shovlin et al., 2019b]

- The deep-seated infections that occur at increased frequency in HHT patients with pulmonary AVMs, are caused by the same flora that are isolated in transient bacteraemias following tooth extraction in the general population.

Table 4
Summary of Recommendations for antiangiogenic use in HHT.

Issue	Core Message (extracts, full text in [Buscarini et al., 2019])
Expertise	In severe HHT-related conditions, specific expertise on HHT is required to appropriately weigh benefits and risks of different available treatments in terms of survival and quality of life, including those conferred by the addition of bevacizumab or thalidomide in critically ill HHT patients.
Indications	For refractory HHT bleeding, bevacizumab or thalidomide could be proposed equally, after a careful evaluation of risk-benefit balance on an individual basis, but when discussing potential risks of treatment, clinicians may prefer to direct males with *ENG* variants to bevacizumab, and females with non *ENG* variants to thalidomide, pending further data.
Thrombosis	Patients at high risk for thromboembolic events should be excluded from these treatments.
Pulmonary AVMs-pre treatment	Screening and treatment of pulmonary AVMs should be performed before commencing treatment, according to established recommendations.
Pulmonary AVMs-surveillance	Enhanced surveillance of pulmonary AVMs during treatment to check for unusual growth, and potentially more careful surveillance of thrombotic complications, is encouraged.
Haemoptysis	Even minimal hemoptysis in an HHT patient on an antiangiogenic drug should prompt intensive management with thoracic CT scan, bronchoscopy, and embolization of pulmonary AVMs if needed. Discontinuation of the antiangiogenic drug is mandatory in such settings.
Hepatic AVMs	After a careful evaluation of cost-benefit balance, bevacizumab represents an interesting option for patients with complicated liver AVMs, refractory to first-line treatment and not amenable to orthotopic liver transplantation (OLT), either because over the age of 65 years or a poor candidate for surgery). If they respond to the drug, they should be re-evaluated for OLT with a "fast-track" to minimize the potential for adverse events due to prolonged bevacizumab use.

- Such bacteraemias can be prevented by a single dose of appropriate prophylactic antibiotics, and are also cleared rapidly in the general population.
- The exact clearance mechanism bypassed for blood flowing through pulmonary AVMs is not yet known, but possibilities include mechanical filtration of bacterial-cellular/embolic aggregates, and close vicinity to pulmonary capillary macrophages.

Patients with HHT are at a significantly increased risk of polymicrobial deep-seated infections and abscesses, especially if they have pulmonary AVMs. As detailed in Section 3.3, one of the 5 VASCERN Outcome Measures for HHT was that 100% of patients with pulmonary AVMs should receive written advice on antibiotic prophylaxis prior to dental and surgical procedures [Shovlin et al., 2018].

Over the last 5 years, recognising that existing recommendations to use antibiotic prophylaxis for patients were not fully implemented [Boother et al., 2017; Shovlin et al., 2018], reducing the risk of abscesses and other infections appeared to demand a fundamental education of healthcare professionals on the existence of transient dental and surgical bacteraemias, the pulmonary AVM-derived focus on pulmonary capillary clearance functions, and the distinction to rationales for prevention of bacterial endocarditis. The topic was initially ran as a VASCERN workshop at the 12th International HHT Scientific Conference in 2017 [Shovlin and Botella, 2017]. Following publication of a review article also suggesting that the rationale was not widely understood, VASCERN HHT updated the workshop materials for formal publication [Shovlin et al., 2019b], emphasising that:

- The deep-seated infections that occur at increased frequency in HHT patients with pulmonary AVMs, are caused by heterogenous flora, usually anaerobic and aerobic commensals of the gastrointestinal and periodontal spaces.
- Transient bacteraemias with these flora are frequent in the general population after dental and other invasive procedures: A key study demonstrated that positive blood cultures increased from 4–9% to 96% within 30 s of a tooth extraction [Limeres Posse et al., 2016]. Crucially, the species isolated from the 421 positive cultures overlapped with those cultured from cerebral abscesses in HHT patients with pulmonary AVMs [Boother et al., 2017], and could be prevented by appropriate antibiotic prophylaxis [Limeres Posse et al., 2016].
- In the absence of antibiotics, bacteraemias were also cleared rapidly in the general population (positive blood cultures fell to 18% at 1 h [Limeres Posse et al., 2016]). The relevant part of the "reticulo-endothelial system" that is bypassed in pulmonary AVM patients at such high risk from deep seated infections from these organisms is the normal pulmonary capillary bed [Shovlin et al., 2017].

As highlighted in Fig. 3, pulmonary AVMs (present in approximately half of all HHT patients), modify the circulation by bypassing normal capillaries. While thrombotic "paradoxical embolic" sequelae of right-to-left shunts from pulmonary AVMs are reasonably well appreciated, there is hesitation in supposing there may be similar roles for the pulmonary capillaries in clearing microbes of smaller individual diameter than a normal pulmonary capillary. As stated in [Shovlin et al., 2019b], both mechanical filtration of bacterial-cellular/embolic aggregates, and close vicinity to pulmonary capillary macrophages would be impaired in patients with pulmonary AVMs, and a better focus on these processes was suggested to improve prevention of prolonged bacteraemias from causing life altering, deep-seated infections.

4.5. Pulmonary hypertension in HHT

OUTPUT 4.5	International similarities and differences in hereditary hemorrhagic telangiectasia (HHT) pathways reported by patients and clinicians.	Thorax 2019 [Boother et al., 2019]

- No VASCERN HHT centre screens asymptomatic patients for pulmonary hypertension.
- All recognise the data from French/Dutch series of 3176 HHT patients [Revuz et al 2017; Vorselaars et al 2017], indicating that when pulmonary hypertension is present, it is usually part of a broader picture of hepatic AVMs, anaemia, atrial fibrillation and symptoms.

In January 2018, VASCERN HHT were made aware that due to a Web Appendix Table from the 2015 European Society of Cardiology (ESC) and European Respiratory Society (ERS) Guidelines for the diagnosis and treatment of pulmonary hypertension [Galiè et al., 2016], at least two European pulmonary hypertension centres were screening HHT patients for pulmonary hypertension on an annual basis. Further investigation revealed many publications were suggesting that pulmonary arterial hypertension affects 10% or more of HHT patients. These issues were discussed across two of the monthly meetings, culminating in the statements within [Boother et al., 2019].

It remains unclear why there have been such statements on pulmonary arterial hypertension, when in French/Dutch series of 3176 HHT patients, prevalence of pulmonary arterial hypertension (pre-capillary pulmonary hypertension) was <2% [Revuz et al., 2017; Vorselaars et al., 2017].

The higher order term "pulmonary hypertension" refers to elevated pulmonary artery pressures irrespective of cause, and pulmonary hypertension is present in many HHT patients. In the French and Dutch series, pulmonary hypertension was usually part of a broader picture of hepatic AVMs, anaemia, atrial fibrillation and symptoms [Revuz et al., 2017; Vorselaars et al., 2017]. Hepatic AVMs are more prevalent in

ACVRL1 patients, the group where PAH is also more common, and a helpful pictorial presentation of the situation is conveyed in a 2017 manuscript from two VASCERN members [Dupuis-Girod et al., 2017].

5. Review of HHT screening and management practice across VASCERN HHT centres specialists taking care of HHT patients

Following publication of the Second International HHT Guidelines [Faughnan et al., 2020], current practice across the VASCERN HHT centres was reviewed in the VASCERN Days October 2020 meeting, and key statements are included here for transparency.

5.1. Nosebleeds

Four HCPs in Denmark, France, Germany and the UK had ENT Leads participating at VASCERN Days, enabling an informed sub-specialty discussion about approaches to ENT treatments that was open to the participating patient representatives. The importance of topical, local non-invasive measures was emphasised by all, with the next stage laser therapy via the nares, then systemic antiangiogenics or Young's procedure (nostril closure). Pathways were similar in the centres reporting the procedures of their ENT colleagues. There were two important discussion points:

1) The HCP ENT experts judged that it would never be possible to be homogeneous in approach, due to the varying nature of disease and treatment responses, with suggestions being framed on a case-by-case basis.
2) The patient representatives expressed surprise that sclerotherapy (injection of a sclerosing agent into nasal arteries) was not being offered, given this was specifically mentioned in the Second HHT Guidelines [Faughnan et al., 2020]. The VASCERN ENT Surgeons emphasised reluctance to take on a new procedure without published evidence of benefit and both theoretical and published evidence of major complications (blindness) due to arterial anastomoses, when there was an alternate approach that had evidence of both safety and efficacy (laser therapy).

5.2. Gastrointestinal bleeds

All HCPs agreed that, except for patients with known or suspected *SMAD4* HHT, they only screened for gastrointestinal bleeding if anaemia was out of proportion to the severity of nosebleeds. All also agreed with the standard methods of assessment (oral gastroduodenoscopy, colonoscopy ± capsular enteroscopy), but emphasised the differences with non-expert centres where colonoscopy appears to be a reflex response to iron deficiency anaemia in HHT. Since there are benefits from a single colonoscopy, the first investigation, particularly if prompting referral to an HHT centre, would not be an issue, but there remained concerns that the anaemia-provoking nosebleeds would not be addressed in such circumstances.

For patients, VASCERN HHT suggested

- They should not accept a proposed upper gastrointestinal endoscopy just "because you have HHT/are anaemic"
- Antibiotics should be administered prophylactically for patients with pulmonary AVMs.

These statements will be added to the 2021 Update of the HHT Do's and Don'ts.

5.3. Hepatic AVMs

All HCPs offered similar responses to their approaches to hepatic AVM screening, and there were surprisingly high levels of agreement on elements not previously discussed through VASCERN. All except one used Doppler sonography as a first line screen for hepatic AVMs, with Doppler ultrasonography "as normal as a stethoscope" in several European countries. CT and MR were offered as second choices, and noted to be potentially better suited to the specific situation during COVID-19.

5.4. Anaemia, pregnancy and paediatrics

The new incorporation of blood transfusions alongside iron replacement therapies for severe anaemia in the Second International HHT Guidelines [Faughnan et al., 2020] was welcomed. New data are pending regarding pregnancy outcomes in France to add to earlier European studies [Shovlin et al., 2008; Dupuis et al., 2020]. Paediatric cerebral screening was addressed as part of [Eker et al., 2020] (see Section 4.1 above). New data are pending on paediatric pulmonary AVM screening and management. It is anticipated that the second five years cycle of VASCERN will conclude these and other data collections before final statements are issued.

6. Summary and reflections

Modifying and transmitting expertise in rare disease management is thwarted by the paucity of randomised control trials set against a plethora of circumstances in which disease-specific advice would be helpful. HHT is no exception. The first five years of VASCERN HHT provided an opportunity to bring together on a more than monthly basis, experience and expertise transcending international boundaries, and to distil the essence of expertise into statements and evidence synthesis to assist other clinicians and patients in their decisions about appropriate health care for specific clinical circumstances. The HCP Leads wish to thank the European Commission and the wider members of VASCERN (see Acknowledgements) for making this possible.

Benefits of such position documents are only as good as the quality of the position documents themselves. Efficacy must be reconstructed on a case-by-case basis, depending on their suitability and adequacy to guide the medical action in the specific act and in the specific context. Wherever possible, VASCERN HHT has sought to prioritise statements for practice that can be achieved in all member states.

All are aware that new evidence, and new treatments may alter the character of good practice in time. In November 2021, VASCERN HHT believes that integrating their 2016–2021 Outputs provides helpful frameworks for approaches, and necessary understanding, that will augment existing general and speciality-specific knowledge and enable a broader cohort of health care professionals to deliver good care to people affected by hereditary haemorrhagic telangiectasia.

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Credit author statement

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Declaration of competing interest

The authors have no competing interest to declare.

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Appendix A. Supplementary data

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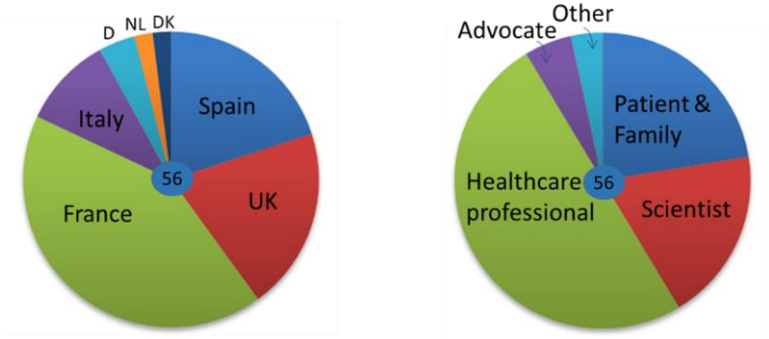
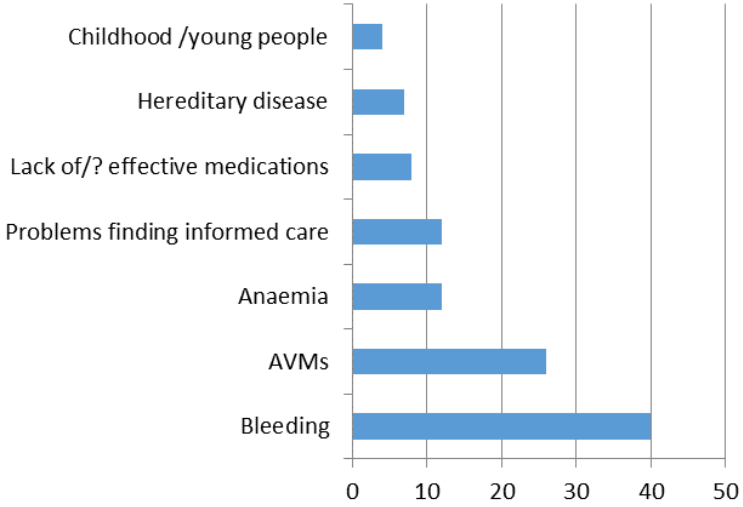
Appendix 1 Methodological Notes

1. Setting Priorities: The 2016-7 VASCERN HHT Survey:

Between November 2016 and January 2017, members were surveyed and in free text, asked what they considered to be the 3 most important problems for HHT. 58 responses were received from 7 countries. Details of the respondents are presented in *Supplementary Fig 2A*. The seven most commonly suggested problems are tabulated in *Supplementary Fig. 2B.*



Supplementary Fig 2A: VASCERN HHT 2016 Survey respondents



Supplementary Fig 2B: VASCERN HHT 2016 Survey responses.

Bleeding most frequently referred to nosebleeds, followed by gastrointestinal and intractable internal bleeding. **Anaemia** was recognised to cause tiredness..

AVMs most frequently referred pulmonary AVMs and complications, with hepatic AVMs and the uncertainty of screening for CAVMs also mentioned.

Problems finding informed care encompassed difficulties in obtaining a diagnosis, lack of health professional understanding, discrepancies in approaches between Europe and North America, in addition to lack of expert centres.

Lack of effective medications referred to both the lack of effective medications and the paucity of data to guide decision making.

In addition to the general concerns regarding transmission to relatives (**hereditary disease**), and care of **children/young people**, There were smaller numbers of comments on:

- Travel/life insurance, quality of life, disability, lack of social resources, psychological stress, and the difficulties in having a social life;.
- Esthetic prejudice and telangiectasia cosmetic appearances;
- Pregnancy
- Concerns regarding research funding, registries, and visibility;
- Single references to other aspects of HHT including brain abscess, dental care, heart failure, pulmonary hypertension, and stroke.

THE EUROPEAN RARE DISEASE NETWORK FOR HHT FRAMEWORKS FOR MANAGEMENT OF HEREDITARY HAEMORRHAGIC TELANGIECTASIA IN GENERAL AND SPECIALITY CARE.
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Appendix 1 Methodological Notes

General Topic	Detailed Topics proposed	Consensus in 2017 ?	Reached 100% consensus	Primary VASCERN HHT output	Other materials with VASCERN HHT input
Problems finding informed care	Clinician education- general HHT	Yes	Yes	Sections 3/ 4: 3.1- 3.7; 4.1-4.5	
	Patient education - general HHT	Yes	Yes	Section 3: 3.2, 3.4, 3.6	
Anaemia	Evaluation for iron deficiency	Yes	Yes	Section 3: 3.3	
	Management of anaemia	No	No	No	a.
Bleeding	Epistaxis	Yes	Yes	Section 3: 3.3, and Section 5	(b)
	Gastrointestinal bleeding	No	Yes	Section 5	(c)
	Severe bleeding- Anticoagulants	No – but acquired	Yes	Section 3: 3.2, 3.5	
	Severe bleeding Anti-angiogenics	No – but acquired	Yes	Section 4: 4.3	
Pulmonary AVM	Importance of screening	Yes	Yes	Section 3: 3.3	
	Precise methods of screening, treatments	No	No	Requested as European guideline topic for 2021	g
	Ischemic stroke prevention	No	No		g
	Brain abscess prevention	Yes	Yes	Sections 3/ 4: 3.3 and 4.4	
Cerebral AVM	Cerebral haemorrhage from CVM	No- but acquired	Yes	Section 4: 4.1	
Hepatic AVM	Hepatic AVM Screening	No	No- in process	No - in process, Section 5	d
	General care	No.	No	No - in process	d
Pregnancy	Pregnancy- mother successful, complication	Yes		Section 3: 3.3	(e)
Children/Young people	Cerebral screening	No	Yes	Section 4: 4.1	
	Pulmonary AVM screening	No	No - in process	No - in process	(f)
Hereditary Nature	Recommendations for use of genetic testing	No- but acquired	Yes	Sections 3/4: 3.1, and 4.5	
	Access to genetic information	No	No - in process	No - in process	
COVID-19	Advice for patients	Not relevant	Yes	Section 3: 3.4	

Table 2: Overview of how Priorities were addressed. Rows are shaded in grey for provision of general information; green if there was sufficient data in 2017 for 100% consensus on an outcome metric to be reached, and yellow if there was insufficient data for consensus in 2017, but this was achieved through the acquisition of new data by VASCERN HHT. Primary VASCERN HHT outputs are referenced in the main text. The consensus materials with VASCERN HHT member input referenced in the final column include the Second International Guidelines for HHT [19] (a, anaemia section; (b) nosebleeds, (c) gastrointestinal bleeding, d, hepatic AVM, (e) pregnancy, and (f) paediatric sections), and g, the BTS clinical statement on pulmonary AVMs [18], where () indicates lower European consensus.

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