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EXECUTIVE SUMMARY

Executive summary of the 15th HHT international scientific conference

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Abstract

Hereditary Hemorrhagic Telangiectasia (HHT) is a rare autosomal dominant vascular disorder characterized by mucocutaneous telangiectasias and visceral arteriovenous malformations (AVMs), which arise due to direct connections between arteries and veins. These vascular lesions are prone to bleeding and vascular shunts, leading to recurrent epistaxis and GI bleeding, among other systemic complications. HHT is caused by heterozygous loss-of-function mutations in genes involved in the BMP9/BMP10 signaling pathway—primarily *ENG*, *ACVRL1* (also known as *ALK1*), and *SMAD4*—which define the major HHT subtypes (HHT1, HHT2, and HHT-JP). HHT has a global prevalence of 1 in 5000 individuals, affecting approximately 1.6 million worldwide. The 15th International HHT Scientific Conference was held in Mandelieu-la-Napoule, France, bringing together over 376 attendees from around the world, including 77 trainees, to share the latest advances in HHT research and clinical care. The conference received 225 abstract submissions, of which 49 were selected for oral presentations and 176 for poster sessions. This gathering marked a significant milestone in the field, not only for its scale but also for the depth and breadth of the scientific discussions. Key highlights included new insights into AVM biology, disease mechanisms, genetic underpinnings, and emerging therapeutic strategies. In addition to oral and poster sessions, two focused workshops provided in-depth discussion on pulmonary arterial hypertension (PAH) and HHT, a rare occurrence of two disease states where treatment for one often worsens the other, and a discussion on the evolving definition of HHT and whether it should be revised in light of recent advances in research, genetic testing, and clinical evidence beyond the Curacao criteria, which were established 25 years ago. This executive summary aims to recapitulate the key scientific and clinical findings presented at the conference and to spotlight areas of continued debate and unmet need. We hope this summary will serve as a resource for experts working in the field and as an invitation for new investigators and clinicians to engage in collaborative efforts to advance the understanding and treatment of HHT.

Keywords HHT - Hereditary haemorrhagic telangiectasia · BMP - Bone morphogenic protein · ENG - Endoglin · ALK1 - Activin receptor-like kinase 1 · AVM - Arteriovenous malformation · Epistaxis

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Summary of clinical talks

Freya Droege and Alexandre Guilhem

New local and systemic treatment options

For the first time at an HHT international conference, an entire session was dedicated to randomized, double-blinded clinical trials. McCrae presented results, already published [1], of a randomized double-blinded trial testing pomalidomide 4 mg/d during 24 weeks. They observed a reduction in the epistaxis severity score (ESS) and significant improvement of hemoglobin level. Neutropenia and constipation were frequently seen but resolved after treatment cessation. However, the study might not have been able to report on side effects occurring with long-term use such as polyneuropathy as seen with other immune modulators given the limited 6 months observation period. Reduced dose of 2–3 mg/day seemed to have a similar efficacy. In O1, Mager reported the results of an allosteric inhibitor of the AKT protein kinase tested at 2 dosages (30 and 40 mg/d orally) vs placebo in a double blinded and randomized international trial. Skin rash was quite frequent (45% in the 40 mg/d group), as well as hyperglycemia (12%). The drug seemed to reduce several epistaxis parameters and improve patients' quality of life. A phase III trial is planned for 2025. Hermann et al. conducted a randomized trial testing nintedanib 150 mg twice a day vs placebo [2]. They observed a reduction of epistaxis duration and a significant improvement of hemoglobin levels although the primary outcome (proportion of patients achieving a reduction of at least 50% in mean monthly epistaxis duration comparing the 8 weeks before treatment to the last 8 weeks of treatment) was not achieved. The most common adverse effect was diarrhea. Gossage et al. presented an update of an ongoing randomized double blinded trial testing pazopanib 150 mg/d orally vs placebo over 24 weeks (clinical trial ID: NCT03850964). As a primary endpoint, the investigators chose a 50% reduction of epistaxis duration, or a 2 g/dl increase of hemoglobin levels compared to the run-in phase. After enrolment of 60 patients (out of 70 required), tolerability seemed good (documented adverse events were high blood pressure, fatigue). Results are planned to be available at the beginning of 2026.

In addition to randomized controlled clinical trials, results from open label trials and preclinical studies were presented. In O2, Faughnan's team treated 10 patients with HHT with low dose tacrolimus over 6 months (0.025 mg/kg/day, individually adjusted to target 2–5 ng/ml trough FK506 levels). Low dose tacrolimus appeared to reduce epistaxis and was reasonably well tolerated (moderate digestive side effects). Bagheri et al. (O3) treated 10 patients with oral sirolimus (dose adjusted to target 6–10 ng/ml blood levels) for a 3-month period. The tolerance was acceptable (upper respiratory infection, headaches, skin reaction/, diarrhea) and epistaxis tended to reduce; however, anemia worsened in 6 of 8 patients, probably due to bone marrow toxicity. Lebrin's team analyzed in O4 a library of 30 new analogues of pomalidomide to identify those with conserved anti-angiogenic and pericytes recruitment capacities but with lower levels of cereblon binding (assumed to be responsible for the drug toxicity). Their objective was to identify beneficial novel immune modulatory drugs (IMiD) for clinical development for HHT treatment.

Studies of large retrospective cohorts provided reassuring data about long-term tolerance and efficacy of routinely used drugs. Dupuis-Girod (O5) reported the long-term outcome of 210 patients with HHT who were treated with bevacizumab from 2009 to 2023 with a median follow up of 3 years. Data confirmed efficacy for the treatment of severe bleedings and high-output cardiac failure. Clinical improvement appeared to be earlier in case of GI bleeding. The decline in efficacy over time appeared to be due to low residual bevacizumab levels. Long-term safety was good (easily manageable arthralgia, hypertension and proteinuria). Kasthuri reported in O6 a retrospective cohort of 102 patients treated with continuous antifibrinolytic therapy over a long time period (71% > 1 year, 31% > 5 years). Data confirmed the efficacy on epistaxis and hemoglobin levels. The tolerance was good and venous thrombotic events were rare (five events, only one without provoking factor).

Regarding novel local treatments, Rimmer (O7) presented data about the use of PuraStat™ after laser ablation for HHT-related epistaxis. This translucent synthetic hemostatic gel mimics the structure of natural collagen and leads to coagulation and hemostasis. It is resorbed in around 30 days. In this prospective case–control study so far data of 25 patients with HHT receiving either the topical application of PuraStat™ or chloramphenicol ointment after laser treatment were analyzed. The preliminary data showed a trend towards a lower 12-week epistaxis severity score and higher scores in health survey (SF-36). Future studies are required to determine if these beneficial effects remain consistent in a larger patient cohort over a longer observation period.

Two major issues emerged from these very rich sessions. Firstly, all double-blind studies were affected by a strong placebo effect, which sometimes made achievements of the primary endpoints difficult. This must be considered for future studies and calls for caution when open label trial results are interpreted. Secondly, the limitations of the epistaxis severity score (ESS) as a primary endpoint in clinical trials were highlighted by many investigators. A study presented by Tarulli et al. in O8 specifically addressed this point. Different self-reported epistaxis measures were collected from the run-in phases of 2 HHT clinical trials and

their statistical performance was compared. Recall based measures were more limited than diary methods. The PRO-CB (weekly epistaxis duration) and PRO-CGB (weekly gushing epistaxis duration) seem to be the two most relevant measures for future HHT clinical trials.

Bleeding, antithrombotic/coagulative, and iron treatment

Recurrent bleedings and the optimal treatment of iron deficiency play a pivotal role in the care of patients with HHT. In his talk, Al-Samkari (O9) pointed out the poor adherence to recommendations for intravenous iron administration by the providers. In his retrospective analysis of 2876 U.S. patients with HHT only about 60% received the optimal iron treatment recommended in the international guidelines. In addition, he emphasized the fact that treatment-emerged hypophosphatemia can be eliminated as unwanted side effects of intravenous iron treatment, when the ferric carboxymaltose formulation is avoided.

Often patients with HHT as well as their physicians are reluctant to prescribe anticoagulative or anti-thrombotic substances out of fear of possibly worsening the patients' bleeding episodes. In a multicentric prospective study, Grobost and his team (O10) presented the results of the PROPLACOTEL study. The bleeding parameters and hospitalization rate in 32 patients with HHT and antithrombotic therapies (antiplatelet and/or anticoagulant) were analyzed. Although there was a discontinuation rate of more than 35%, most patients tolerated the antithrombotic therapy well. There was a higher rate of transfusions and hospitalization rates in patients taking anticoagulants compared to those only taking antiplatelet therapies. However, long-term effects need to be provided in the future.

Although HHT is an autosomal-dominant inherited disease, there seem to be differences between patients' sex. While heavy menstrual bleeding might aggravate the iron deficiency anemia in fertile women, anemia itself facilitates bleedings. A formation of an international multi-task force to study and address sex differences in HHT was suggested by the invited speaker Von Drygalski. Moreover, Zhang (O11) compared women who suffered from two different inherited diseases leading to recurrent bleeding episodes; either HHT or von Willebrand disease, a common bleeding disorder characterized by impaired blood clotting. In this observational study, bleeding manifestations and healthcare utilization rates were higher in women with HHT and therefore, Zhang concluded that HHT might be the most morbid and clinically relevant inherited disease of women [3]. However, the rate of patients with both, HHT and von Willebrand disease, remained unclear. Moreover, although in both diseases, patients often suffer from recurrent bleeding, the disease mechanisms are different and therefore difficult to compare.

Clinical imaging

According to the international guidelines, screening for organ vascular malformations, especially for pulmonary arteriovenous malformations (PAVM), is recommended in all patients with suspected or confirmed HHT [4]. Schneider (O12) presented data from 419 patients with HHT who underwent MRI examinations of the brain, liver and pulmonary vasculature for detection of arteriovenous malformations (AVMs) in a single examination (40–45 min study time). He concluded that the MRI was a feasible, radiation-free and one stop screening method in HHT.

Regarding the value of transthoracic contrast echocardiography after the embolization of PAVM, Hessels (O13) summarized that chest CTs might be forgone in patients with a right-to-left shunt (RLS) grade 0–1 after PAVM embolization. Kirkpatrick (O14) conducted a retrospective, single-center analysis on 327 children. He stated that the earlier a lesion was identified the more rapidly it grew. Similarly, if lesions were diagnosed in children at later age, they were less likely to progress. Additionally, no lesions regressed from initial to final CT in type.

Hepatic vascular malformations might lead to high output heart failure with right ventricular volume overload, pulmonary hypertension (PH), and tricuspid regurgitation. It can be treated off label with bevacizumab [5]. In a single-center retrospective analysis of thirteen patients with HHT type 2 Lawrence (O15) provided an integrated assessment of cardiac remodeling using cardiac MRIs and echocardiography. The cardiac enlargement was proportional to cardiac index; however, the dilation of the right ventricle was greater than the left ventricle in high output heart failure. It was suggested that the improvement in right ventricular dilatation provided a rapid indicator of cardiac remodeling after bevacizumab treatment in those patients.

Pulmonary embolization and complications

PAVMs provide a continuous right to left shunt between pulmonary arteries and veins. They are associated with a range of potential clinical manifestations, from symptomatic hypoxemia to life-threatening septic embolic events, paradoxical embolic stroke, and hemorrhage from vascular rupture especially found in pregnant women. Thus, embolization of PAVMs is recommended whenever possible, even in pregnancy [4, 6]. Among the variety of treatment options, Srinivas (O16) compared the short-term efficacy of microvascular plugs in the distal feeding artery (DFA-MVP) and coils to block the nidus and feeding artery (NiFA-coil).

After short-term follow-up, both techniques showed a high success rate of 97% (defined as s≥70% shrinkage of the size of the nidus or the draining vein on follow-up CT chest imaging). Whereas NiFA-coil embolization might be more expensive per PAVM it was especially useful for PAVM with a complex architecture, a larger feeding artery, and a larger sac size. Complications such as recanalization of the PAVM might occur. Analyzing the long-term effects, Gulich (O17) showed in her study a reperfusion rate of around 36% especially in cases with low packing density. She detected a mean time interval of 5.5 years between embolization and detection of reperfusion which underlined the importance of long-time follow-up imaging preferably with MRI after embolotherapy [7]. Another reason for recanalization was mentioned by Fish (O18). He stated that likely due to high pulmonary artery pressures there was a strong correlation between PH and PAVM recurrence without confounding variables. He suggested measuring pulmonary arterial pressures during the embolization procedures to guide screening intervals [8].

Other aspects of HHT

The conference also addressed aspects of patient care that is often neglected. Given that treatment of rare, heterogeneous disorders like HHT can be challenging, Canaud reported of a success story of getting FDA approval for a drug for the rare disease *PIK3CA*-related overgrowth spectrum (PROS) [9, 10], thereby providing an encouraging example for patients, physicians and scientists living with or working on HHT.

Hessels (O19) conducted a multi-language European survey (including versions for patients and their partners) to study the consequences of HHT on family planning, intimacy and contraception [11]. Although HHT does not strongly affect family planning and sexual activity in most patients, about one quarter of the 572 respondents experienced effect on intimacy mainly due to epistaxis. This point seemed accessible to expert counselling. Tigani reported in O20 the responses of 138 oral health experts to an online survey about HHT recognition and oral management. It revealed a clear need for knowledge improvement, maybe through an educational tool kit. Mathavan (O21) reported a cohort of 29 HHT patients affected by obstructive sleep apnea. The positive airway pressure therapy was not tolerated due to exacerbation of epistaxis in 11 of 21 patients trialed. A treatment strategy specific to HHT was suggested. Wei reported in O22 the results of an online survey about adherence to recommendations on air bubble filter uses according to the HHT international guidelines. By analyzing 431 responses, it appeared that adherent patients experienced more difficulties to timely access to IV treatment while no patient reported permanent neurological defects related to an IV infusion without the use of a filter. It was therefore recommended to update the mention of air bubble filters in the next expert recommendations: *Ensure air-bubble free wet to wet connection before starting IV treatment*.

All the key messages from the clinical sessions of this 15th HHT conference could be effectively disseminated to patients thanks to Marano's team strategy reported in O23. They provided 53 patients with weekly HHT online sessions of expert counselling over a period of 14 weeks, which could serve as a blueprint for distributing this conference's content. This presented approach seemed highly acceptable (100% of adoption and completion) and efficacious (improvement of psychological scores).

Summary of basic science talks

Nicolas Ricard and Edda Spiekerkoetter

Advances in genetic understanding of HHT

Dr. Carmelo Bernabeu gave a summary about the past 30 years of scientific research in HHT. The first gene identified as mutated in patients with HHT was *Endoglin* (*ENG*) (McAllister et al., 1994) encoding for a coreceptor of the Transforming Growth Factor-β (TGF-β) superfamily. Later *Activin-receptor Like Kinase 1* (*ACVRL1*) encoding a receptor of the same family called ALK1 (Johnson et al., 1996) was identified. Once the Endoglin/ALK1 complex is activated, this complex phosphorylates transduction proteins called R-Smad binding to Smad4 to enter the nucleus and modify target gene expressions. Interestingly, 20 years ago, mutations in *MADH4*, encoding Smad4, were found in patients with a combined syndrome of juvenile polyposis and HHT (Gallione et al. 2004). In 2007, Bailly's team identified two members of the TGF-β superfamily, Bone Morphogenetic Proteins (BMP)-9 and 10, as the ligands of the ALK1/ENG complex (David et al. 2007). Since then, mutations in *GDF2*, encoding BMP9, have been described in patients [12, 13].

There are two key challenges in understanding HHT pathogenesis: First, the localized nature of HHT lesions, despite the fact that all endothelial cells carry the germline mutations, and the timeline of symptom development, as clinical manifestations in patients worsen with age. Heterozygosity seems to be a general requirement for lesion development in HHT lesions but is likely not sufficient.

The second-hit hypothesis was proposed as a potential explanation, though the nature of the "additional" hit remained unidentified until a few years ago when the Marchuk's lab identified biallelic second somatic mutations in *ENG* or *ACVRL1* in 50% of dermal telangiectasia from

HHT patients [14]. The remaining question was to determine if this genetic second hit existed in large, visceral arteriovenous malformations (AVMs) in the lung, brain or liver. By pooling tissue samples from patients seen at multiple HHT Centers of Excellence (COE) across the US and Canada, the Marchuk group presented this year that they identified second-hit somatic mutations in 35% of hepatic vascular malformations (7/20), in brain AVMs (2/2), in one craniofacial AVM, and in one pulmonary AVM (1/7) in *ENG*, *ACVRL1*, and *MADH4* mutated patients (O24) [15]. Interestingly, the somatic mutations were different from one AVM to another AVM even in lesions from the same liver. Toydemir's lab equally found biallelic loss of heterozygosity in brain AVMs (2/3), one lung AVM (1/1), but not in liver AVM (0/1) (O25) [16]. They also found somatic mutations in nasal telangiectasia (6/15) and dermal telangiectasia (2/4) from 8 patients out of nine. The somatic mutations were found in less than 2% of the sequenced cells. The low number of cells carrying a somatic mutation, and the possibility to carry somatic mutations in non-coding regulatory regions, intronic regions affecting splicing, or other complex rearrangements may explain that somatic mutations were not detected in some HHT lesions. However, we can conclude from the most recent data that loss of heterozygosity seems to be a general mechanism in most if not all HHT lesions.

Spiekerkoetter's group presented somatic mutations in a patient with both HHT and pulmonary arterial hypertension (PAH) in the setting of a germline *ENG* mutation (O26). They were looking for somatic mutations in *ENG* or genes involved in vascular malformations in PAVMs, the characteristic lesions of HHT, and plexiform lesions, the characteristic lesions of PAH. While they were unable to identify somatic *ENG* mutations neither in PAVM nor plexiform lesions, they found somatic mutations in other genes associated with vascular malformations that likely promote endothelial proliferation [17]. This finding indicates that sequencing to identify acquired somatic mutations in vascular lesions in patients with HHT needs to include genes known to be involved in other types of vascular malformations. It also suggests that not only the disturbance of the main HHT pathway genes may lead to vascular abnormalities, but in addition an interaction with other pathway genes that influence vascular cell function, proliferation and angiogenesis.

The second challenge for our understanding of HHT is the variability in symptom severity between patients, even amongst family members harboring the same mutation. This raises the hypothesis that modifier genes could affect symptom severity. Animal models in which the genetic background greatly influences phenotypic expression supports this possibility [18]. Faughnan's group performed a genome-wide association study to identify genetic modifiers associated with disease severity in 843 patients (O27). They identified 11 single nucleotide polymorphisms significantly associated with disease severity. To advance the understanding of a potential link between these polymorphisms and HHT severity, it is essential to investigate the functional consequences of these polymorphisms in future studies. Shovlin's group offered another explanation for the variability in HHT severity between patients, identifying that mutations causing premature termination codons are more likely to induce severe HHT symptoms than point mutations. This was supported by data from three cohorts, including a total of 704 patients (O28) [19]. The association between premature termination codons and HHT severity was stronger for patients with an *ENG* mutation than for those with an *ACVRL1* or *MADH4* mutation.

Taken together, assessing the functional consequences of identified mutations from HHT patients, whether germline or somatic, is therefore crucial. Previously, Bailly's group already presented functional assays to test the downstream signaling and functional consequences in *ACVRL1* and *ENG* mutations [20, 21]. Here, they presented functional assays to test *MADH4* mutations and *GDF2* (encoding BMP9) mutations. Eleven *MADH4* variants identified in HHT patients were studied. The team created a cellular assay where mutant Smad4 is overexpressed in cells lacking endogenous Smad4 (O29). Then, using a luciferase reporter under a reporter for either a read-out for BMP or TGF-β signaling, they found that the identified HHT-related Smad4 mutants were all loss of function mutations for both pathways. In endothelial cells isolated from patients, heterozygous *MADH4* mutations did not affect BMP9 signaling, a similar finding as in *ACVRL1* heterozygous mutations [22]. This result strongly suggested that a second genetic hit was needed to affect BMP9 signaling pathway in patients carrying *MADH4* mutations. Bailly's lab furthermore performed a functional assay on four *GDF2* (encoding for BMP9) mutations found in HHT patients (O30). They overexpressed these BMP9 mutants in cells that do not express endogenous BMP9 and assessed the mutant gene expression, secretion of ligand, and the ability to induce the ALK1 pathway using their luciferase reporter. Only 2 out of the 4 mutations were loss of function mutations, and none of these patients met the Curaçao criteria for HHT diagnosis. Interestingly two presented with PAVMs suggesting a potential role for *GDF2* mutations in PAVM formation.

Ligand sources and maturation

As mutations in HHT are all located in the BMP9/10-ALK1-ENG-Smad pathway and given the increasing number of publications supporting involvement of *GDF2* and *BMP10*

mutations in HHT and PAH, several groups are working on a better characterization of the endogenous sources of BMP9 and BMP10, their circulating forms and their active forms. In mammals, there are two ALK1 ligands, BMP9 produced by the stellate cells in the liver and BMP10 produced by the cardiomyocytes of the right atria and the stellate cells [23]. Tillet's group sought to decipher hepatic and cardiac BMP10 and BMP9 functions by using tissue specific *Bmp10* knockout in a *Gdf2* knockout mouse models (O31). They showed that mice deficient in *Gdf2* and hepatic *Bmp10* exhibit altered liver sinusoidal endothelial cell identity and intestinal AVMs. Conversely, mice deficient in *Gdf2* and cardiac *Bmp10* did not exhibit any vascular phenotype. This result suggested that active BMP10 originated from the liver and not the heart. Roman's lab presented data to identify the sources of ALK1 ligands in the zebrafish models (O32). In zebrafish, there are three identified ligands: Bmp9, Bmp10, and Bmp10-like. Using individual knockout of each ligands, only *bmp10* knockout fish developed vascular malformations such as edema and bleeding and started to die at 6 weeks of age. These zebrafish exhibit vascular malformations in the skin and liver with enlarged blood vessels and altered arteriovenous specification, which suggested that *bmp10* knockout zebrafishes were valid HHT models. Ultimately, these mutant animals developed high output heart failure. In zebrafish, Bmp9 and Bmp10 were produced by hepatic stellate cells, while Bmp10-like was produced by cardiomyocytes. Transfection of human BMP9 or BMP10 in immortalized hepatic stellate cells and cardiomyocytes showed that while both cell types secreted mature BMP9, cardiomyocytes secreted mature BMP10 whereas hepatic stellate cells secreted full-length uncleaved pro-BMP10. In human plasma, Roman's group found that the major circulating form of ALK1 ligands was a heterodimer composed of a mature BMP9 monomer associated with a full-length pro-BMP10 monomer. These results were in accordance with results from Tillet's group who showed that the circulating forms of ALK1 ligands, heterodimers of BMP9 and 10, were produced in hepatic stellate cells (O31).

To determine whether the BMP9 and BMP10 ligands were redundant in their signaling, Oh's lab generated *ACVRL1* knockout (KO) human induced pluripotent stem cells (iPSCs) and then differentiated them in endothelial cells (iPSC-ECs) (O33). They found that while WT iPSC-ECs exhibited Smad1/5 phosphorylation in response to BMP10 as low as 0.1ng/mL, *ACVRL1* KO iPSC-ECs did not respond to BMP10 even at 5 ng/mL. However, when stimulated by BMP9 at 1 ng/mL and 5 ng/mL, *ACVRL1* KO iPSC-ECs showed some phosphorylation of Smad1/5, although it was lower than in WT iPSC-ECs. Using bulk RNA sequencing, they found similar responses to BMP9 and BMP10 for WT iPSC-ECs, but in *ACVRL1* KO iPSC-ECs, about one third of BMP9 target genes identified in WT cells were regulated in *ACVRL1* KO cells. This response was not observed when cells were stimulated with BMP10. Using single cell RNA sequencing, the Oh group also found similar responses to BMP9 and BMP10 in WT cells, while BMP10 stimulation did not produce any response in *ACVRL1* KO cells. Altogether, these results showed that BMP9 and BMP10 have similar responses when ALK1 are expressed, but when ALK1 is absent, BMP9 is still able to induce some gene expression, yet BMP10 cannot signal, suggesting that BMP10 may have a more significant role in the *ACVRL1* mediated disease mechanism than BMP9.

Although significant progress has been made characterizing the circulating and active forms of ALK1 ligands, uncertainties remain regarding the distinct roles of BMP9 versus BMP10 versus the BMP9/BMP10 heterodimer. However, in animal models, neutralizing BMP9 and BMP10 induces AVM development in mice, providing a valid model for HHT.

Arteriovenous malformations formation in animal models

Injections of neutralizing anti-BMP9 and anti-BMP10 antibody in newborn mice induce AVMs in the retina [24]. This model, in addition to the inducible endothelial *Eng* knockout mouse model, was used by Marambaud's lab as a preclinical model to test if inhibition of cell proliferation could be a therapeutic target to treat AVMs (O34) [25]. Indeed, neutralization of BMP9/10 in pups induced proliferation markers in retinal AVMs. Targeted proteomic analysis on liver endothelial cells from these mice showed that proteins involved in the G1/S restriction point were affected. Expression levels of two cyclin dependent kinases *Cdk-4* and *Cdk-6* were found to be increased, confirming the acceleration of the cell cycle in endothelial cells after BMP9/10 inhibition or *Eng* deletion. Proliferation of endothelial cells in human dermal telangiectasia was also found, validating that targeting endothelial cell proliferation may be beneficial to treat HHT patients. Inhibition of CDK4/6 using palbociclib prevented retinal AVM formation and normalized vascular density and vessel diameter in the retina of mice when BMP9 and BMP10 were neutralized. The involvement of endothelial cell proliferation through CDK4/6 in AVM development was also presented by Hirschi's lab [26]. Hirschi's lab also showed that the cell cycle state affected endothelial cell commitment to a venous or arterial fate [27]. Therefore, by disrupting the normal cell cycle, proper arteriovenous determination could be prevented. Hirschi's lab found that in *Acvrl1* knockout mice arteriovenous identity was affected [26]. Consequently, since cell cycle regulation and arteriovenous differentiation appeared to be interconnected, it

is crucial to understand the molecular mechanism linking the BMP pathway to cell cycle control in HHT. Marambaud's lab showed that Vascular Endothelial Growth Factor (VEGF) is able to induce CDK6 and that BMP9 can prevent it [25]. As the VEGF pathway is known to be involved in HHT and neutralization of VEGF has been effective to treat bleeding [5, 24], data from Marambaud's lab further emphasize the importance of the BMP9/VEGF balance in HHT.

However, neutralization of VEGF does not seem to be able to treat all the vascular malformations observed in HHT. Indeed, Meadows' team showed that in the *Smad4* and in the *Eng* inducible endothelial knockout models, neutralizing VEGF did not prevent AVM formation in the brain of these mice (O35). This lab already published that inhibition of Angiopoietin-2 (Ang-2) improved brain vascular pathologies, albeit to varying degree [28]. Here, they used Faricimab, a bispecific antibody targeting Ang-2 and VEGF in *Smad4* iECKO mice. They found a higher efficiency of Faricimab to prevent brain AVM formation and normalization of brain blood vessel diameters than neutralizing antibody against Ang-2 or VEGF alone. This study, in addition to providing a new therapeutic opportunity to treat HHT patients, underlined that molecular mechanisms and thus therapeutic targets for HHT may be different in different organs.

While loss of BMP9/10 quiescence signaling and increased Ang-2 and VEGF proangiogenic signaling contribute to endothelial cell proliferation and AVM formation, defective shear stress sensing may also play a role. Indeed, Hirschi's lab demonstrated that shear stress induces cell cycle arrest in arterial endothelial cells (Fang et al., 2017), suggesting that this mechanism might also regulate endothelial cell proliferation. Siekmann's lab showed that, in *eng*-/- and *acvrl1*-/- zebrafish models, defective flow sensing affected endothelial cell size leading to AVMs (O36) [29]. They found that arterial endothelial cells were bigger than venous endothelial cells even though the diameters of veins were larger than the ones of arteries. Moreover, arterial endothelial cell size depended on blood flow and correlated with the artery diameter, whereas venous endothelial cell size was not flow dependent and did not correlate with vein diameter. In *eng*-/- zebrafish, venous endothelial cells behaved similarly to arterial endothelial cells in WT zebrafish, meaning they enlarged in response to flow, with venous endothelial cells becoming even larger than arterial endothelial cells. The increase in endothelial cell size was supported by an increase in ribosome gene expressions, improving the cells capacity to synthetize proteins. The increase in endothelial cell size led to increase in vessel diameters, forming AVM.

Taken together, these presentations outlined mechanisms involved in AVM formation. Given that flow can regulate the cell cycle [30], it would be valuable to decipher the exact cascade of events leading to AVM formation. This could involve linking the loss of the BMP9/10 pathway, flow sensing defects, endothelial cell size, cell cycle acceleration, proangiogenic signaling and arteriovenous fate determination.

Workshops

HHT and pulmonary hypertension/pulmonary arterial hypertension (Nick Morrell, Murali Chakinala)

Both diseases HHT and Pulmonary hypertension (PH) are vascular syndromes that are characterized by a complex interplay of the BMPR2-ACVRL1-ENG receptors and BMP/GDF/Activin ligands.

It is important to discriminate the much more rare Group 1 Pulmonary Arterial Hypertension (PAH) characterized by an occlusive pulmonary vasculopathy leading to an increased pulmonary vascular resistance (younger patients) and ultimately right heart failure from Group 2 pulmonary hypertension (PH) due to high output failure in the setting of liver arteriovenous malformations occurring predominantly in middle-aged and older patients. The latter affects about 10–15% of patients with HHT and present with left heart failure and cardiac insufficiency ± pulmonary congestion. It is estimated that only about 1% of all HHT patients develop PAH. Both Groups of PH have more often *ACVRL1* than *ENG* mutations and require specialized treatment. In addition, the most common mutations in PAH are mutations in the Bone Morphogenetic Protein receptor 2 (*BMPR2*) (75% of families).

Anti-angiogenic therapy with bevacizumab reduces bleeding episodes, anemia and improves, at least temporally, hepatic vascular malformations in patients with HHT [5, 31], though their long-term efficacy remains unclear. On the flip side, it was debated whether anti-angiogenic therapy was safe in patients with HHT and PAH, given that some preclinical rodent models use VEGF inhibitors to induce experimental PH [32]. The general consensus was that, based on case reports, the treatment appeared to be safe, but it was suggested to thoroughly study the effect of Bevacizumab in PAH by combing the experience and registries of PAH and HHT centers.

Approved vasodilator therapies for PAH improve right ventricular function but are not believed to alter disease progression. Patients with both, HHT and PAH, respond to pulmonary vasodilators similar to patient with only PAH, yet HHT-PAH patients have an increased risk of developing thrombocytopenia, worsening bleeding events (GI-tract,

epistaxis, hemoptysis), nasal congestion, catheter-related complications (paradoxical emboli, infections) [33, 34] when using pulmonary vasodilators which might limit their use.

Of interest, Sotatercept, an ACVR2A-Fc fusion protein that blocks activin signaling has recently shown great promise in treating PAH remodeling. Paradoxically though, Sotatercept can induce HHT-like symptoms in some patients with development of cutaneous telangiectasia, epistaxis and GI bleeding [35–37]. Sotatercept therefore mimics the HHT 5 phenotype that is linked to variants in BMP9 (GDF2) with earlier onset of epistaxis, cutaneous telangiectasia on the upper forelimbs, trunk and head and cerebrovascular malformations [11, 38]. It was discussed that extreme vigilance is needed regarding the extent of AVM formation in PAH patients, particularly the potential for development of visceral AVMs in the lung, brain and liver as well as the extent of bleeding episodes. It was suggested not to use Sotatercept and other Activin signaling inhibitors in HHT-PAH patients with a significant bleeding history or the need for blood transfusions. In addition, a comprehensive baseline assessment of visceral AVMs was recommended with subsequent close monitoring. Only after gathering and evaluating more data regarding the safety and sided effect profile in PAH as well as HHT-PAH patients can a recommendation be made regarding the use of Sotatercept for patients with PAH and HHT.

It was further discussed that the management of PAVMs in patients with HHT-PAH should involve a joint discussion between the PAH and HHT team to determine the optimal time for embolization, pre-treatment of PAH or augmentation of existing PAH therapy, optimization of right ventricular function, and a discussion about a possible staged procedure when multiple PAVM are present. While some studies did not report a significant change in PAP with embolization in patients with mild PH [39] this is likely not the case for patients with more severe PAH and multiple PAVMs. In addition, the risk of delaying a procedure (risk of rupture and paradoxical emboli) needs to be balanced with the benefits.

What is HHT? Defining HHT after recent updates in research and clinical genetics (Jamie MacDonald and Sabine Bailly)

HHT has long been defined by its characteristic clinical, most notably outlined in the Curaçao criteria and formalized at the 2006 guidelines conference. However, recent advances in clinical genetics, molecular biology, and diagnostic technology have significantly expanded our understanding of the disorder. Initially recognized as a disease involving *ENG* and *ACVRL1* gene mutations, the spectrum has widened with the discovery of atypical variants and rare overlapping syndromes, such as those involving *GDF2* (OMIM-designated HHT5). These cases, although limited in number, demonstrate robust clinical criteria within families and continue to challenge the boundaries of HHT diagnosis.

The current understanding of HHT necessitates a more nuanced and molecularly driven approach to diagnosis. Experts advocate for incorporating genotype–phenotype correlations, especially as expressivity varies widely, and some patients with clear clinical presentations test negative for known HHT mutations. The need for discernment is critical, especially in cases overlapping with conditions such as capillary malformation–arteriovenous malformation (CM-AVM) syndrome or HHT-like systemic disorders. A consensus is forming around the idea that HHT exists on a continuum, and that both formal and informal collaborations—such as within the ClinGen working group or NIH's Undiagnosed Diseases Network—will be instrumental in addressing the growing number of patients who defy classical definitions.

Moving toward precision medicine, there is increasing recognition of the importance of early diagnosis, particularly as patients with HHT might be at risk for life-threatening AVMs. Severe cases may be underrepresented due to survivor bias in adult cohorts, highlighting the need for expanded research to understand progressive cases of HHT and underlying causes of that severity. Future diagnostic frameworks will benefit from comprehensive clinical annotation, especially for rare variants, and from openness to revisiting and redefining disease boundaries as the genetic and phenotypic landscapes continue to evolve.

O1 Novel allosteric AKT inhibitor for the treatment of HHT

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Objective: Hereditary haemorrhagic telangiectasia (HHT) is a debilitating disease for which there are no approved therapies. Patients report recurrent epistaxis as the most frequent and severe manifestation affecting quality of life. The pathogenesis of the disease is due to genetic mutations, which lead to overactivation of AKT causing lesions in mucosal tissue, skin and vital organs. A prospective randomized double-blind, placebo-controlled proof-of-concept study (NCT05406362) investigating two doses of VAD044 has been conducted to evaluate the safety and efficacy of VAD044 in the treatment of HHT. VAD044 is a potent, reversible, allosteric, selective AKT1/2 inhibitor for oral use formulated in gelatin capsules.

Methods: In this double-blind proof of concept study VAD044 was taken orally on a daily basis for 12 weeks. 75 patients were randomised in a 1:1:1 ratio to receive VAD044 30 mg or 40 mg daily or matching placebo. The primary study objective was to evaluate the safety of VAD044. Efficacy parameters were measured as secondary objectives recorded daily using an innovative HHT eDiary App. 66 subjects completed the study across 7 sites in Europe and USA.

Results: Data are currently being analyzed and results of this study will be presented.

Conclusions: VAD044 may offer a novel approach to management of HHT. Safety and efficacy data demonstrating proof-of-principle will be presented and therapeutic implications explored to support next steps in further development.

O2 Low-dose tacrolimus for epistaxis in hereditary hemorrhagic telangiectasia: phase II open label trial

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Objective: Given pre-clinical work in HHT models, we hypothesized that tacrolimus would reduce epistaxis in HHT patients.

Methods: Single-centre, Phase II open-label trial of oral low-dose tacrolimus (target trough 2-5 ng/mL). Primary outcome: weekly epistaxis duration (WED), from patient daily epistaxis diary. Design: 3-month baseline (weeks 1–12), 6-month treatment (weeks 13–36), 3-month follow-up period (weeks 37–48). Linear mixed effects model used to estimate average WED change from baseline to treatment and paired t-test to compare mean difference in Epistaxis Severity Score (ESS).

Results: Ten patients completed the trial (12 enrolled, 2 withdrawn prior to drug):7 females, 3 males, mean age = 60.9 years (SD 6.38, median 59.5, range 52–72). At end-baseline (weeks 9–12), mean WED was 60.4 min (SD 45.7, range 2.8–115.3) and mean ESS was 5.28 (SD 0.92, range 3.4–6.7). At end-treatment (weeks 33–36), mean WED was 44.5 min (SD 39.2, range 0–118.0), with average WED decrease of 15.9 min compared to end-baseline (95% CI: -30.40 to-1.34, $p = 0.033$). Comparing entire baseline to treatment period, average WED decrease 20.45 min (95% CI: -29.93 to -10.98, $p < 0.0001$). At end-treatment, mean ESS was 4.0 (SD 1.48, range 1.9–6.6), significantly lower than end-baseline ($p = 0.002$). Reported Adverse events (AEs) (total = 78): 31 drug-related AEs: 30 mild, 1 severe (otofacial pain), and 47 non-drug related AEs: 44 mild, 2 moderate, 1 severe (worsening anemia). There were no serious adverse events. Nausea (N = 5), diarrhea (N = 4), headaches (N = 4) were most frequent drug-related AEs. No patients stopped study drug due to AEs.

Conclusions: Low-dose tacrolimus significantly reduced epistaxis in HHT patients and was well tolerated.

O3 Sirolimus for epistaxis in hereditary hemorrhagic telangiectasia: a phase II open- label trial

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Objective: To study safety and effectiveness of sirolimus, as a potential pathway-based therapy, for HHT patients with moderate-severe epistaxis.
Methods: Phase II open-label study of oral sirolimus (target trough 6-10 ng/mL) for epistaxis in 10 HHT patients with minimum 15 min epistaxis/week, with 3-month baseline (weeks 1–12), 3- month treatment (weeks 13–24), and 3-month follow-up (weeks 25–36) periods. Primary outcome: PRO-CB (Patient reported outcome of cumulative weekly bleeding) at end- treatment (weeks 21–24) compared to end-baseline (weeks 9–12), from daily epistaxis diary. Adverse event (AE) monitoring occurs every 2 weeks, safety bloodwork every 6 weeks.
Results: Ten patients (5 female, 5 male, mean age = 57 years, SD = 9.7, range 42–71) were enrolled and received treatment. Two patients were withdrawn (by investigator) pre-treatment. One patient withdrew voluntarily after starting treatment. At recruitment, mean Epistaxis Severity Score (ESS) was 4.81 (SD 0.83, range 2.93–5.87).). At end-baseline, mean ESS was 4.78 (SD 0.80, range 3.71–6.45) and mean PRO-CB was 135 min (SD 214, median 61, range 20.5–643.5). AEs to date (total = 38): 20 incidences of drug-related AEs (18 mild, 2 severe: worsened anemia and worsened oral bleeding), and 18 non-drug related AEs (17 mild, 1 moderate). There were no drug-related serious adverse events (SAEs); one non- drug related SAE (worsened anemia). Upper respiratory infection (N = 4), headaches (N = 4), skin reaction/rash (N = 4), diarrhea (N = 3), and worsened epistaxis (N = 3) were the most reported drug-related AEs. One patients stopped study drug due to AE.
Conclusions: To date, sirolimus appears reasonably well tolerated, in this small study. PRO-CB, ESS and additional safety data will be available for analysis after 09/2024, and will be presented.

O4 Towards the development of safe analogues of pomalidomide preserving vascular integrity to treat Hereditary Hemorrhagic Telangiectasia

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Objective: The Immunomodulatory imide drug (IMiD) thalidomide and its derivatives lenalidomide and pomalidomide have emerged as treatments for HHT with reported benefits in animal models and patient case reports. However, clinical translation is impeded by unclear mechanisms of action and adverse effects.
Methods: A structure–activity relationship program (SAR), in combination with omics have been initiated to identify the minimal active group of thalidomide responsible for its ability to enhance blood vessel stability and to decipher its mechanism of action using adult mice depleted for endoglin and human induced pluripotent stem cell-derived vascularized organoids.
Results: Thalidomide was found to modulate WNT signalling pathways to reinforce endothelial cell–cell contacts, and to increase pericyte attachment, thereby limiting vessel alteration. Its vascular protective effect was independent of its anti-angiogenic activity or of Cereblon, the primary target for IMiD adverse effects including teratogenic activity, hematological toxicity and second malignancies. Instead, the vascular protective effects relied on the phthaloyl ring of thalidomide. We also report that IMiDs possess distinct vascular protective properties. We have synthesized new analogues of pomalidomide with a safer profile and have tested them in mice depleted for endoglin demonstrating their efficacy to inhibit retinal AVM formation.
Conclusions: Our findings indicate that the development of analogues of pomalidomide with a safer profile that preserve the vasculature and prevent the development of vascular malformations is possible, opening new avenues for treating chronic conditions.

O5 Intravenous bevacizumab in HHT: A French multicenter real-world data study

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Objective: Hereditary Hemorrhagic Telangiectasia (HHT) is a rare yet ubiquitous hereditary vascular disease caused by an imbalance in angiogenic factors. Since 2009, bevacizumab, a humanized monoclonal antibody targeting and neutralizing the biologic activity of human VEGF (Vascular Endothelial Growth Factor) has been used to treat severe bleeding and hepatic involvement related to HHT as numerous studies and many case reports confirmed its efficacy. Objective: The main objective was to survey and describe the use of bevacizumab in a cohort of HHT patients treated with bevacizumab in France from 2009 to 2024. The secondary objectives were to evaluate the efficacy and safety of bevacizumab in HHT patients according to their clinical profile (severe anemia related to nosebleeds or digestive bleedings, high cardiac output, or both), to the drug used (Avastin® and biosimilars) and to HHT characteristics (gene mutated, pulmonary or liver AVMs). Additionally, pharmacokinetics data, when available, were analyzed.
Methods: This retrospective cohort study utilizes clinical, genetic, and treatment data of French patients with HHT, which are documented in a specialized health data hub registry known as CIROCO. Data regarding intravenous administration of bevacizumab has been prospectively collected since January 2023. To provide a comprehensive analysis, retrospective data from the period spanning 2009 to 2022 has been integrated into the dataset.
Results: 284 patients received bevacizumab induction followed by maintenance therapy in responders.
Conclusions: The meeting will feature presentations on the long-term safety and efficacy, with full results set to be available at the time of the congress.

O6 Efficacy and safety of continuous long-term antifibrinolytic therapy in patients with Hereditary Hemorrhagic Telangiectasia

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Objective: Hereditary Hemorrhagic Telangiectasia (HHT) is an inherited bleeding disorder characterized by mucocutaneous telangiectasias and visceral organ arteriovenous malformations. Affected individuals develop recurrent spontaneous epistaxis and gastrointestinal bleeding. Iron deficiency anemia develops in 50% of individuals requiring frequent iron infusions and occasional blood transfusions. Antifibrinolytics are commonly used to reduce the frequency and severity of bleeding in HHT. However, safety of their long-term use has not been evaluated. The objectives of this study were to determine the long-term efficacy and safety of continuous antifibrinolytic therapy in patients with HHT.

Methods: This is a single institution retrospective study. Electronic medical records were reviewed to obtain patient demographics, antifibrinolytic use, adverse effects, and efficacy (epistaxis severity score, hemoglobin). Only patients on continuous antifibrinolytic therapy were included.

Results: One hundred and two patients met study criteria. Most were female, white, with median age of 66 years. Seventy one percent were on antifibrinolytics for more than a year, with 31% longer than 5 years (Table 1). Antifibrinolytics were associated with significant improvements in ESS and hemoglobin (Table 2). Antifibrinolytics were discontinued in 48% of patients; reasons included lack of efficacy (12%), efficacy (11%), insurance (10%) and treatment-related adverse effects (TAEs; 7%). Incidence of venous thromboembolism was 5%, four of them with presence of risk factors (Table 2). Table 1: Demographic Data, Antifibrinolytics use (n = 102) Age, median (range) 66 years (33–89) Female (%) 59 Race White (%) 81 Black (%) 13 Hispanic (%) 2 Native American (%) 2 Other (%) 2 Antifibrinolytic Use Aminocaproic acid (%) 9 Tranexamic acid (%) 77 Aminocaproic acid and tranexamic acid (%) 14 Duration of Therapy Duration of antifibrinolytic use, median (range) 24 months (1–215) < 1 year, N (%) 29 (29) 1–5 years, N (%) 41 (40) 5–10 years, N (%) 30 (29) > 10 years, N (%) 2 (2) Baseline efficacy outcomes ESS pre- antifibrinolytic therapy, median 5.22 Hemoglobin pre-antifibrinolytic therapy, median (g/dL) 9.8 N = number; ESS = epistaxis severity score Table 2: Safety and efficacy of antifibrinolytic therapy in HHT Safety (N = 102) Number of patients continuing antifibrinolytic therapy, N (%)38 (37) Number of patients who stopped antifibrinolytic, N (%) 49 (48) Number of patients lost to follow-up 15 (15) Reason for discontinuing antifibrinolytic therapy (N = 49) Ineffective, N (% of total treated) 12 (12) No longer indicated due to good response, N (% of total treated) 11(11) Unable to afford due to cost, N (% of total treated) 10 (10) Treatment-related adverse effects, N (% of total treated) 7 (7) Venous thromboembolism, N (% of total treated)

- Pulmonary embolism while recuperating in rehabilitation center after prolonged hospitalization
- Right leg deep vein thrombosis, Left arm deep vein thrombosis while in ICU, intubated
- Superficial thrombophlebitis, hospital admission the previous week
- SVC stenosis, clot at tip of central venous access device
- Right leg deep vein thrombosis, no provoking factors

5 (5) Deceased, N (% of total treated) 7 (7) Efficacy Last ESS while on antifibrinolytic therapy 2.93 Last hemoglobin while on antifibrinolytic therapy, g/dL 12.0 Median decrease in ESS 2.29 Median increase in hemoglobin, g/dL 2.2 N = number; ESS = epistaxis severity score.

Conclusions: This is the largest report on continuous use of antifibrinolytic therapy. Antifibrinolytics were well tolerated with discontinuation due to TAEs occurring in only 7%. Long-term continuous use of antifibrinolytics in patients with HHT is safe and effective.

O7 Novel use of haemostatic gel (PuraStatTM) after laser ablation for HHT-related epistaxis

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Objective: To assess whether a haemostatic gel (PuraStatTM) used topically in the nose after laser ablative therapy for HHT-related epistaxis leads to better symptom control and improved health related quality of life (HR-QOL) over standard therapy.

Methods: Prospective case–control study comparing topical application of PuraStatTM with chloramphenicol ointment after laser ablation of nasal telangiectasia. Patients were recruited from a single tertiary centre in Melbourne. All patients had a diagnosis of HHT and underwent laser ablative treatment for epistaxis. Patients were excluded if they were on anticoagulant/antiplatelet medications. Severity of bleeding was measured with the Epistaxis Severity Scale (scored 0–10; low–high symptom burden) and HR-QOL was measured using the short form-36 (SF-36) questionnaire. Outcomes were measured at baseline, 2, 4 and 12 weeks.

Results: Data collection of 60 patients is in progress; preliminary analysis of 25 patients has been performed. The

average age was 54 ± 17 years; 76% were female. The average age of onset of epistaxis was 19 years. The most common genetic mutation was ACVRL-1 (24%). The mean decrease in epistaxis severity at 12 weeks was 1.9 ± 1.5 vs. 1.1 ± 1.7 for the chloramphenicol and PuraStatTM groups respectively (p = 0.25).
Conclusions: On preliminary analysis, no significant differences was demonstrated in epistaxis severity or HR- QOL scores at 12 weeks between the two preparations although patient preference showed a trend towards PurastatTM. Further data collection, analysis and results are pending.

O8 Characterizing Self-Reported Epistaxis Measures in Hereditary Hemorrhagic Telangiectasia

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Objective: To characterize self-reported epistaxis measures as outcomes measures for clinical trials in HHT.
Methods: Collected data from 3 month "run-in" phase in 2 HHT trials. For inclusion, participants required minimum 15 min/week of nosebleeds for past month. Participants completed daily diary, indicating each bleed's severity (gushing/not) and duration. Nocturnal bleeds without duration were estimated at 5 min. Extreme duration episodes were retained. Duration measures were calculated (minutes) per episode, day, week (PRO-CB, Patient-reported outcome, cumulative weekly bleeding) and month.
Results: 23 patients (9 male, 14 female, mean age = 61 years) included. Epistaxis Severity Score (ESS) mean was 5.3 (SD = 0.99). Episode duration mean was 5.9 min (SD = 12.6, median = 3, IQR = 1- 5, range = 1–300,). Daily duration mean was 10.1 min (SD = 20.1, median = 4, IQR = 0–11, range = 0–310). Weekly duration (PRO-CB) mean was 71.2 min (SD = 81.1, median = 40, IQR = 20–95, range = 0–555). Monthly duration mean was 307.6 min (SD = 311.6, median = 190, IQR = 91–434, range = 16–1667). Coefficient of variation decreased from 214 and 199% in episode and daily durations respectively, to 114% and 101% in weekly and monthly durations respectively. Mean gushing episode duration significantly exceeded non-gushing (11.3 min, SD = 12.8 vs. 6.2 min, SD = 13.5, $P < 0.001$). Gushing bleeds comprised 555/2963 (18.7%) of episodes, ranging from 0–57.4% of episodes across patients. Autocorrelation and partial- autocorrelation plots demonstrated no significant correlation between data points (daily or weekly durations).
Conclusions: Self-reported epistaxis measures are limited by significant variability of duration and intensity. PRO-CB has better operating characteristics than episode and daily bleeding duration. However, cumulative bleeding duration does not reflect intensity and not all nocturnal bleeding, despite potentially impacting quality of life and total blood loss.

O9 Poor adherence to international guidelines for intravenous iron in U.S. patients with hereditary hemorrhagic telangiectasia

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Objective: Iron deficiency anemia (IDA) afflicts most patients with hereditary hemorrhagic telangiectasia (HHT). HHT guidelines recommend treatment with intravenous iron (IVI) in patients with severe anemia and in those for whom oral iron is inadequate. Guidelines recommend repletion in deficient patients with 1000 mg or more of elemental iron and advise against the use of ferric carboxymaltose (FCM), due to the potential for treatment-emergent hypophosphatemia in as high as 75% of patients receiving this formulation. Repeat use of FCM may result in osteomalacia and pathologic fractures. This study evaluated the utilization of IVI in patients with HHT.
Methods: A retrospective analysis of commercial administrative claims data included patients with IDA and HHT who received IVI treatment between January 1, 2016 and August 31, 2023, with the first IVI infusion as the index date. US approved IVI products were evaluated. Adherence was defined as having received ≥ 1,000 mg of IVI over 6 weeks.
Results: 2876 patients with HHT were identified. Adherence to IVI therapy was 61.9% overall and for each IVI product: iron dextran (166/251; 66.1%), iron sucrose (267/811; 32.9%), sodium ferric gluconate (12/157; 7.6%), ferric derisomaltose (14/14; 100.0%), FCM (892/1104; 80.8%), and ferumoxytol (430/539; 79.8%).
Conclusions: Nearly 40% of patients received less elemental IVI than recommended in guidelines. Alarmingly, FCM was used most frequently despite warnings in the guidelines and the established published evidence about FCM-induced hypophosphatemia. U.S. adherence to guideline recommendations for IVI therapy appears poor,

placing large numbers of patients at risk of inadequate therapy and hypophosphatemic complications.

O10 Antiplatelet and anticoagulant therapies in hereditary hemorrhagic telangiectasia: a large French prospective study (PROPLACOTEL)

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Objective: There is no prospective data in hereditary hemorrhagic telangiectasia (HHT) patients expose to antithrombotic therapies (AT), antiplatelet (AP) and/or anticoagulant (AC).To evaluate tolerance in HHT population with newly introduction of AT.
Methods: Multicentric prospective study in French national HHT Registry (Clinical Trials registry NCT05641142).
Results: We include 32 HHT patients (13 males and 19 females). Mean age is 58.3 ± 20 y. Before AT introduction, 20% experience intestinal bleeding, 33% a previous major bleeding event (MBE), 20% hospitalization for hemorrhage and 19.4% transfusions with a median of 4 blood units [2–9] and a median hemoglobin nadir at 11 g/dl [7–14]. AT treatments are: AP in 9 cases (aspirine n = 8), DOA (apixaban = 10 with 7 under 10 mg/d, rivaroxaban n = 1), LMWH (n = 9) and others (n = 3). Indications are venous thromboembolic diseases (n = 13), TIA/stroke (n = 3) or others (n = 14). After AT introduction, 26 patients are analysed with minimal follow-up of 3 months: hospitalization for hemorrhage occurs in 35% (9/26; p = 0.26) in similar proportion under AP versus AC, transfusions in 6/26 (23%, p = 0,65) more frequently under AC (4/14 vs 0 under AP, p = 0,27) with a median of 3 blood units [1–4] and a median of Hb nadir at 9 g/dl [8–14] (p = 0.11 versus before AT). MBE occurs in similar proportion under AP and AC (n = 5/26, 19.2%).
Conclusions: Hospitalization for hemorrhage and MBE seems to be similar under AP versus AC in HHT population in first 3 months of AT. This future powered study is still in progress.

O11 Hereditary hemorrhagic telangiectasia may be the most morbid and clinically significant inherited bleeding disorder of women

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Objective: To examine the relative morbidity and healthcare utilization of HHT and von Willebrand disease (VWD) in women, which has never previously been done.
Methods: We performed an observational cohort study of women with HHT or VWD, comparing a representative sample of 100 randomly selected women with HHT to 100 randomly selected age- matched women with VWD, at an institution that is both an HHT Center of Excellence and a Comprehensive Hemophilia and VWD Treatment Center.
Results: In HHT versus VWD, recurrent epistaxis and GI bleeding were more likely (OR [95% CI] = 32.73 [13.81–71.80], P < 0.0001 and 5.69 [2.59–12.89], P < 0.0001) and heavy menstrual bleeding was less likely (OR 0.32 [0.18–0.57], P < 0.0001). Iron deficiency anemia was significantly more likely, and lowest hemoglobin significantly lower, in HHT versus VWD. Odds of iron infusion dependence, requirement for red cell transfusion, and hemostatic surgical procedures were significantly higher—17-fold, threefold, and eightfold higher, respectively—and hospital admissions to manage disease complications were both approximately 14 times more frequent in women with

HHT versus VWD. Odds of death were fivefold higher in women with HHT.
Conclusions: Much higher disease-related morbidity, mortality, and healthcare utilization was observed in women with HHT versus VWD. HHT, a historically neglected disease, may be the most clinically significant inherited bleeding disorder of women at both the individual and population level. Given the vast gap in research funding for HHT compared with both hemophilia (primarily affecting men) and VWD, these findings have significant implications for gender equity in bleeding disorders.

O12 Screening of patients diagnosed with HHT (hereditary hemorrhagic telangiectasia) or their first-degree relatives for disease expression in brain, liver and lung by Magnetic Resonance Imaging

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Objective: Screening of patients with clinical and/or genetic proven diagnosis of HHT or first-degree relatives of HHT patients for AVMs (arterio-venous malformations) in the brain, liver or lung by MRI.
Methods: 419 patients (3–86 years; mean 42 ± 19 years; male/female 157/262) underwent MRI examinations of the brain, liver and pulmonary vasculature for detection of AVMs in a single examination (40–45 min study time). The imaging protocol included unenhanced MRI of the brain followed by unenhanced liver imaging. This was followed by an unenhanced and CE-MRA of the pulmonary vasculature with time-resolved and high-resolution CE-MR-angiography.
Finally a CE scan of the liver and of the brain was performed.
Results: In 278 of 419 patients (66%) at least one disease expression in either brain, liver or lung was found (mean age at diagnosis of 44 ± 18 years). The total number of patients with cerebral AVMs was 34 (8%), pulmonary AVMs 236 (56%) and liver AVMs 64 (15%). Of these 5 patients only showed AVMs in the brain, 188 only in the lung and 34 only in the liver respectively. 21 patients had simultaneous AVMs in both brain and lung, 3 in both brain and liver and 22 in both lung and liver. Only 5 patients demonstrated AVMs in all evaluated organs. All AVMs detected in the screening MRI were confirmed either by angiography or in follow-up studies.
Conclusions: MRI is a feasible, radiation-free one stop screening method for evaluation of disease expression in brain, liver and lung in HHT-patients, the detection of which is essential to prevent irreversible complications of the disease.

O13 The value of transthoracic contrast echocardiography after pulmonary arteriovenous malformation embolization

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Objective: Pulmonary arteriovenous malformations (PAVMs) are direct connections between the pulmonary artery and vein, creating right-to-left shunting (RLS). Embolization is indicated to prevent complications. Guidelines recommend follow-up chest CTs to confirm persistent occlusion and embolization of all treatable PAVMs. Graded transthoracic contrast echocardiography (TTCE) after PAVM embolization may offer a reliable alternative in a subgroup of patients while preventing radiation exposure. We hypothesized that in patients with a RLS grade 0–1, no indication for additional embolization would be established.
Methods: Since 2018, the standard follow-up protocol after PAVM-embolization includes both TTCE and chest-CT after 6–12 months and long-term follow-up visits. Patients who underwent first or long- term follow-up with TTCE and chest-CT were included. The indication for additional embolotherapy was discussed in a multidisciplinary team meeting. The primary outcome was the indication for additional embolotherapy in each RLS-grade. In addition, the association between the RLS-grade and indication for additional embolotherapy was investigated.
Results: 339 patients with 412 embolization procedures were included, median time to follow-up TTCE was 7.6 months. A RLS was present in 399 post-embolization TTCEs (97%): RLS grade 1 in 93 patients (23%), grade 2 in 149 patients (36%) and grade 3 in 157 patients (38%). In patients with a RLS grade 0–1, no treatable PAVMs were found. In patients with RLS grade 2–3, 22 (15%) and 72 (46%) received additional embolization's.
Conclusions: This study shows chest CT might be forgone in patients with an RLS grade 0–1 after PAVM- embolization.
Please note: part of these results were published as a poster presentation at the HHT conference in 2022.

O14 Evolution of pediatric pulmonary AVMs (PAVMs) in HHT

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Objective: Determine the evolution of PAVM in the pediatric HHT population.

Methods: A retrospective analysis was performed on 327 patients first seen in our HHT Center before age 18 from 2005–2024. Twenty-two patients with two CT scans separated by ≥ 1 year were included. Initial and final CTs were compared for number of PAVMs, PAVM diameter, PAVM type (telangiectasia, vascular, mixed, or indeterminate), Hounsfield units, and feeding artery (FA) diameter.

Results: The average interval between CT scans was 7.2 years (range 1 to 16 years). 142 PAVMs were present in the initial scans. By the final scan 53 new PAVM developed and 17 were embolized. There was an average net PAVM growth of 2.65 mm (–0.9 to 10.5 mm, median 2.15) with growth rate of 0.41 mm/year (-0.33 to 2.12 mm, median 0.35). Non-embolized PAVM that were present on both scans (126 lesions, 89% of initial PAVMs) grew an average of 5.4%/year (-9.9% to 18.4%, median 5.0%). Hounsfield units in the same population increased an average of 61 HU (-273 to 578, median 32). 25 (28.7%) of initially telangiectatic lesions evolved to either mixed or vascular PAVMs by the final CT without any PAVMs regressing. Feeding artery diameter increased from < 2 mm to ≥ 2 mm in 20 PAVM, and increased by at least 1 mm in 56 PAVM.

Conclusions: In this pediatric population, PAVMs increased in number, size, and radiographic density over time. There was also evolution of type from telangiectatic towards vascular, and FA diameter increased into the treatable range in 20 PAVMs.

O15 RV remodeling in high output heart failure in HHT patients with liver AVMs

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Objective: Right ventricular (RV) volume overload, pulmonary hypertension, and tricuspid regurgitation are key factors in the pathogenesis of high output heart failure (HOHF) in patients with Hereditary Hemorrhagic Telangiectasia (HHT) and liver arteriovenous malformations (AVMs). RV remodeling in HOHF is not well characterized.

Methods: A single-center retrospective analysis of RV structural and functional parameters was conducted using cardiac magnetic resonance imaging (CMR) and echocardiography in patients with HHT with liver AVMs and HOHF.

Results: Thirteen patients (mean age 62 years, 92% female, all HHT type 2) were identified. A history of atrial fibrillation was present in 4(31%) patients and 8(62%) were prescribed loop diuretics.

Hemoglobin was < 8.0 g/dL in three patients and >12.0 g/dL in four (mean 10.1 + 2.2 g/dL). Cardiac index (CI) was 5.1 + 2.3 L/min/m2 by CMR. RV and LV dilation was comparable: Mean RV end-diastolic volume index (RVEDVI) was 136 + 24 mL/m2 (1.21 × normal) and LVEDVI was 123 + 17 (1.28 × normal), both correlating with CI (RV: r = 0.71, p = 0.007, LV: r = 0.73, p = 0.005). Twelve (92%) patients had a normal RV ejection fraction (mean 57 + 6.5%). RV systolic pressure (RVSP) by echo was elevated in 5/11(45%) patients. Moderate-severe tricuspid regurgitation was present in all four patients with moderate-severely elevated RVSP, but not with normal RVSP. After bevacizumab treatment, 5/6(83%) patients demonstrated a reduction in RVEDVI from mean 151 + 25 to 124 + 10 mL/m2 ($p < 0.04$).

Conclusions: RV volume overload is characteristic of HOHF in HHT patients, and significant tricuspid regurgitation correlates with pulmonary hypertension in addition to RV dilation, but not RV dilation alone. Treatment with bevacizumab leads to a reduction in RV dilation.

O16 Microvascular plug embolization of the distal feeding artery versus coil embolization of the nidus and feeding artery: which technique is more effective for pulmonary arteriovenous malformations?

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Objective: PAVMs are abnormal connections between pulmonary arteries and veins. Treatment options include microvascular plugs in the distal feeding artery (DFA-MVP) or coils to block the nidus and feeding artery

(NiFA-coil). While both techniques are effective, direct comparative data is lacking. This study compares short-term efficacy of NiFA-coil and DFA-MVP techniques for PAVMs.
Methods: Retrospective chart review of patients who underwent NiFA-coil or DFA-MVP embolization of PAVMs between October 2014 and July 2023 and obtained CT chest imaging within 14 months was performed. PAVMs treated with both embolic agents were excluded. Treatment success was defined as ≥ 70% shrinkage of nidus or draining vein on follow-up CT chest imaging. Statistical analysis included Mann–Whitney U-test to compare continuous variables between treatment groups and Fisher's exact test to compare proportions.
Results: 123 PAVMs (31 DFA-MVP, 92 NiFA-coil) in 69 patients of which 53 had hereditary hemorrhagic telangiectasia (HHT) were included. Treatment success was achieved in 119/123 PAVMs (97%) at median follow-up period of 4.2 months. There was a greater proportion of simple PAVMs in the DFA-MVP group (28/31, 90%) compared to the NiFA-coil group (61/92, 66%) ($p = 0.01$). There was no statistically significant difference in treatment success rate for NiFA-coil (89/92, 97%) compared to DFA-MVP (30/31, 97%) ($p = 1$). On average, patients undergoing NiFA-coil technique had a larger feeding artery (3.7 mm vs 2.4 mm, $p < 0.001$) and sac size (7.2 mm vs 3.4 mm, $p = 0.04$).
Conclusions: NiFA-coil embolization and DFA-MVP embolization both result in high rates of short-term treatment success for PAVMs.

O17 Reperfusion of pulmonary arteriovenous malformations treated by catheter embolization

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Objective: 345 patients with HHT underwent screening for evaluation of disease expression in the lung by contrast-enhanced (CE) MRI. In 154 out of 345 patients at least one clinically relevant PAVM was found and catheter embolization was performed. We investigated these patients for a possible reperfusion of PAVM after embolization, which might occur after initial successful embolization.
Methods: 118 of 154 patients underwent follow-up studies for detection of reperfused PAVM. The mean follow-up period was 6 years and 3 month. For follow-up, a time-resolved dynamic and high resolution CE-MRA were performed. Images were evaluated regarding enhancement of the PAVM and if detected, time of enhancement of the draining vein was further evaluated.
Results: We found no reperfusion in 75 out of 118 patients. 43 patients showed a reperfusion in follow-up studies of which 35 patients showed recanalization and 11 patients demonstrated newly developed collateral vessels, feeding the initially treated PAVM. Mean time between embolization and detection of reperfusion was 5.5 years. 41 of 43 patients underwent re- embolization with confirmation by DSA. Reperfusion occured both after coil and plug embolization. Mean diameter of reperfused vessels was 4.4 mm (SD 2.2).
Conclusions: The rather long time-interval between embolization and detection of reperfusion highlights the importance of regular follow-up studies after embolotherapy. CE-MRA can reliably detect reperfusion of treated malformations if platinum coils or plugs have been used for embolization and evaluation of enhancement kinetics in time resolved CE-MRA helps to distinguish between a true arterial reperfusion and a venous enhancement of a persisting aneurysm sac.

O18 Pulmonary arteriovenous malformation recurrence in patients with pulmonary hypertension

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Objective: To evaluate the correlation between pulmonary hypertension (PH) and post-embolization pulmonary arteriovenous malformation (PAVM) recurrence.
Methods: With IRB approval the records of 377 patients with PAVMs evaluated at single HHT center of excellence between January 1, 2013, and September 10, 2023, were retrospectively reviewed. PAVMs embolized during this time-period were evaluated for recurrence. Patients and lesions not treated during this time-period were excluded. Growth of previously untreated lesions was not considered recurrence. Patients without chest CT follow-up were excluded. General demographics, HHT status as defined by genetic testing or Curacao criteria, presence of PH, history of smoking, anemia, and liver AVMs was documented. Odds ratio and stratified analysis was calculated to assay the correlation between PAVM recurrence, PH and possible confounders.
Results: A total of 151 patients with PAVMs were treated during the study period, including 438 PAVMs, for which follow-up was available. This included 106 patients with definite, 31 doubtful, and 14 possible HHT. The presence of pulmonary hypertension was significantly associated with both PAVM recurrence by patient (OR: 8.13, 95%

CI 3.50 – 19.67) and by lesion (OR: 4.07, 95% CI 2.14 – 7.91). Multivariate analysis demonstrated that this correlation was independent of several variables including HHT status, smoking history, presence of liver AVMs, and anemia.
Conclusions: There is a high correlation between pulmonary hypertension and PAVM recurrence, likely due to high pulmonary artery pressures causing recanalization. Pulmonary arterial pressures should be obtained during embolization procedures as they may help guide screening intervals.

O19 Family planning, intimacy and contraception in hereditary hemorrhagic telangiectasia: a European survey study

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Objective: The presence of HHT symptoms can influence the quality of life and social relationships, but the topics of family planning, intimacy and contraception have not been investigated to date.
Methods: This multi-language inventory European survey study included a patient's and partners' version of a questionnaire designed specifically for this study. HHT patients were informed about the study through HHT expert centres, social media and websites of patient associations. Data collection took place between March- May 2023.
Results: The survey was completed by 572 patients with a definite HHT diagnosis. In most patients, HHT does not affect relationship decisions (62%) and decisions concerning pregnancy and children (50%) and sexual activity (57%). However, 27% of HHT patients did experience effect on sexual activity and may benefit from improved epistaxis management and better awareness of their partners.
Conclusions: HHT does not affect family planning decisions and sexual activity in most patients, but approximately a quarter of patients experience effect on intimacy mainly caused by epistaxis.

O20 Assessment of knowledge of HHT care in a dental setting

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Objective: Oral care needs for HHT patients are greatly under-appreciated. Dental professionals are a vital first line in recognizing manifestations of HHT and directing patients to care. We sought to assess dental professional's recognition of oral lesions associated with HHT.
Methods: Potential participants consisted of dental professionals who were reached via US Midwest state and local dental society and association newsletters and voluntarily completed an online IRB exempt Qualtrics survey.
Results: 38 participants submitted a complete response and were included in this analysis. Of these, 76.3% correctly recognized that oral AVMs are the most common oral manifestations of HHT and 68.4% that HHT is a genetic disorder. Unfortunately, only 36.8% could appropriately identify HHT in a picture, and only 18.4% knew that 75% of HHT patients have oral manifestations by age 40. 47.4% understood which HHT patients require antibiotic

prophylaxis before dental treatment and that it is not routinely indicated for all HHT patients. 10.2% recognized precautions needed for patients receiving VEGF-Inhibitors. Most respondents were dentists (34.2%) or dental hygienists (57.9%) and had been in practice 20 + years (50%) or 1–5 years (21%). Most common practice setting was community suburban (42.1%), urban (21.1%) or rural (15.8%); 13.2% were academic. Only 10.3% of the participants expressed experience treating HHT patients.
Conclusions: While a majority of dental professionals are aware of oral AVMs in HHT and its genetic inheritance, greater awareness in the dental community is clearly needed in the treatment and identification of HHT both in known patients and in those presenting without a confirmed diagnosis.

O21 Clinical characteristics and tolerability of treatment for obstructive sleep apnea (OSA) in patients with hereditary hemorrhagic telangiectasia (HHT)

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Objective: OSA is a common sleep-related breathing disorder with a significant comorbidity profile and its incidence is an important exacerbating condition in patients with HHT, who already have a particularly elevated risk for pulmonary hypertension and venous thromboembolism. We aimed to characterize OSA in this population and assess tolerability of positive airway pressure therapy.
Methods: Analysis of a retrospective cohort of patients with HHT treated at the University of Florida. Patients with OSA diagnosed via polysomnography with an apnea–hypopnea index of ≥ 5 were included in the investigation.
Results: Of 188 patients with HHT, 29 (15.4%) patients had OSA. Average age was 66.9 ± 10.5 years old (range 48 – 91), 13 (44.8%) were female, and average body mass index was 30.5 ± 7.4 kg/m2. Genotypic profile was 11 (37.9%) with *ENG* variant, 7 (24.1%) with *ACVRL1* variant, and 11 (37.9%) with unknown genotype. Average epistaxis severity score was 4.51 ± 2.5. Rates of comorbidities were as follows: 22 (75.9%) hypertension, 12 (41.4%) tobacco use history, 10 (34.5%) coronary artery disease, 8 (27.6%) diabetes mellitus, 7 (24.1%) pulmonary hypertension, 6 (20.7%) atrial fibrillation, 5 (17.2%) heart failure, and 5 (17.2%) venous thromboembolism. Average apnea–hypopnea index was 19.7 ± 10.5. A total of 21 (72.4%) patients trialed positive airway pressure therapy; the remainder declined due to concern for their epistaxis. Of the 21 patients, 17 (81%) experienced treatment failure due to worsening epistaxis (n = 11) or general intolerance (n = 6). When examining failure events, factors associated with discontinuation due to worsening epistaxis included baseline epistaxis severity score > 7 ($p = 0.027$) and tobacco use history ($p = 0.013$). No patients were offered alternative treatment strategies.
Conclusions: OSA is a common disorder in patients with HHT with an extensive comorbidity burden. Positive airway pressure therapy is limited by exacerbation of epistaxis, and alternative treatment strategies should be considered. Further research in this area is needed in this population.

O22 Unanticipated consequences of HHT guidelines bubble filter recommendation for patients with PAVM

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Objective: To evaluate benefits and possible unintended consequences of the International HHT Guidelines air bubble filter recommendation for patients with PAVM.
Methods: An 18-question anonymous survey focusing on filter use, efficacy, and potential downsides was sent to 7000 patients at HHT Centers worldwide. Exclusion criteria were incomplete surveys and age < 18.
Results: 581 responses were received (8%); 150 were excluded, leaving a total of 431 responses (6%). In addition, 80% are aware of the recommendation while 18% are not. 66% adhere while 33% do not. 20% of patients who are aware do not adhere. 17% and 26% of patients have refused or rescheduled/delayed a needed study/treatment because of no filter, respectively. 67% of delays were at the patient's discretion versus 41% at the healthcare provider's. 4% of patients reported having a stroke/TIA while receiving IV therapy. Of these (n = 18), none had a permanent neurological defect. When stratifying difficulty of treatment access based on adherence, a higher proportion of responses in the "half the time," "sometimes," and "never" categories were patients who adhere ($p < 0.05$).

Conclusions: The disadvantages of the HHT Guidelines bubble filter recommendation may outweigh the advantages regarding treatment access and patient experience. No patients had any permanent effect from TIAs. Of patients who adhere, there is increased incidence of delaying/not receiving needed treatments/studies. Adherence to the recommendation not only provides minimal benefit, but actually could cause patients harm. These results suggest a review of the bubble filter recommendation may be in order.

O23 Overcoming barriers to change: the promise of web-mediated counseling for the management and treatment of Hereditary Haemorrhagic Telangiectasia

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Objective: Hereditary hemorrhagic telangiectasia (HHT) is characterized by a high emotional and physical burden caused by the nature of the disease, which can greatly affect quality of life and psychological well-being. Counseling is a therapeutic process that aims to enhance self- awareness and the recognition of internal resources. The goal of the present study was to assess the long-term effects of a web-based counseling intervention for HHT patients.
Methods: Fifty-three subjects diagnosed with HHT received 14 weekly online counseling sessions (Table 1). Questionnaire-based assessments of various clinical outcomes were conducted at pre- treatment, post-treatment, and 6-month follow-up periods. These assessments included measures of depression, state anxiety, trait anxiety, hopelessness, self-efficacy, mental quality of life, and physical quality of life.
Results: This treatment format seems to be feasible and acceptable to participants, with high rates of adoption and completion (100%) and excellent rates of treatment completion and clinical adherence (100%). Participants showed significant reductions in depression, anxiety, and the biopsychosocial impact of HHT both post-intervention and at the 6-month follow-up, as well as significant improvements in self-efficacy and quality of life. Effect sizes from pre- to post- treatment were found to be moderate to large on measures of depression, self-efficacy, mental quality of life, and physical quality of life (Table 2).
Conclusions: An Internet-delivered counseling seems to be an efficacious, ecological and acceptable treatment for the management of HHT. Counseling interventions can play a crucial role in addressing the needs of HHT patients along their care trajectory, developing a personalized treatment plan to address these evolving needs appropriately.

O24 Somatic mutations in hereditary hemorrhagic telangiectasia arteriovenous malformations

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Objective: The Marchuk Laboratory previously showed that HHT telangiectasias develop via a two-hit genetic mechanism resulting from biallelic loss of function (LOF) mutations in either ENG or ACVRL1. This mechanism has never been shown in visceral AVMs. Our objective is to identify the genetic mechanism of AVM genesis in internal HHT lesions.
Methods: We sequenced DNA from 2 HHT BAVMs, 20 HHT HAVMs, 1 HHT craniofacial AVM, and 6 HHT PAVMs using a targeted gene sequencing approach on an Illumina platform. Sequence data were analyzed following GATK best practices for data preprocessing, and somatic

short variant discovery was performed with Mutect2. Potential variants were manually screened in IGV.
Results: We identified second-hit somatic mutations in HHT AVMs. In 7/20 (35%) liver lesions, we identified germline and somatic mutations in either ENG or ACVRL1. We identified distinct somatic mutations in each lesion, even in lesions from the same liver. In one craniofacial AVM, we identified biallelic mutations in SMAD4. In 2/2 (100%) BAVMs, we identified germline and somatic mutations in either ENG or ACVRL1. In one BAVM, we confirmed that the germline and somatic mutations are biallelic.
Conclusions: We identified new somatic mutations that may contribute to the pathogenesis of internal HHT lesions. These data strongly suggest that internal HHT lesions also require biallelic LOF in HHT genes to develop. These novel findings further our understanding of the common genetic etiology underlying HHT AVMs and telangiectasias and have implications for future investigations into therapeutic strategies to treat HHT.

O25 Discovery of biallelic loss of heterozygosity in brain arteriovenous malformation (AVM): somatic second hit mutations drive AVM formation in HHT

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Objective: Somatic second-hit loss of function variations in the HHT causative genes, ENG and ACVRL1, have been described in dermal telangiectasias. It is unclear if somatic second-hit mutations also cause the formation of AVMs and nasal telangiectasias in HHT. To investigate the genetic mechanism of AVM formation in HHT, we evaluated multiple affected tissues from fourteen patients.
Methods: DNA from six formalin fixed paraffin embedded AVM tissues (brain, lung, liver, and gallbladder) from five patients were evaluated. Fresh/frozen tissue biopsies from nine HHT patients were also evaluated: 15 nasal telangiectasia, 4 dermal telangiectasia, and 10 control tissues. DNA was evaluated using a 736 vascular malformation/cancer next-generation sequencing gene panel down to 1% somatic mosaicism.
Results: Somatic second-hit mutations were identified in 4/6 of the AVM biopsies (75%), including the loss of heterozygosity in ENG in one brain AVM sample in which the germline mutation occurred in a different allele than the nearby somatic mutation (both are loss of function mutations). Eight of 9 (88.9%) patients in whom telangiectasia tissues were evaluated had a somatic mutation ranging from 1.03–1.96% in the same gene with the germline mutation. Six of fifteen (40%) nasal and two of four (50%) dermal telangiectasia had a detectable somatic second hit. Additional low level somatic mutations in other genes were identified in several telangiectasias.
Conclusions: This is the first report demonstrating loss of heterozygosity in AVM and nasal telangiectasia tissues in HHT caused by very low level somatic second hit mutations.

O26 Somatic activating mutation in Phosphoinositide 3-kinase in a plexiform lesion of an Endoglin mutation carrier with hereditary hemorrhagic telangiectasia (HHT) and pulmonary arterial hypertension (PAH)

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Objective: The cause of arteriovenous malformations (AVMs) in HHT is unknown. Somatic mutations in the functional allele of HHT causing genes were recently identified in skin telangiectasias of HHT patients. The resulting loss-of-heterozygosity, likely leading to clonally expanding endothelial cells, might be required to drive AVM formation. We here aimed at detecting somatic mutations in pulmonary vascular lesions of a patient with HHT and end-stage PAH caused by an Endoglin mutation. Her lung pathology revealed pulmonary AVMs and plexiform lesions, which are channel-like formations with vascular clonal expansion typical for PAH.
Methods: Targeted deep sequencing of three HHT causing genes and eleven vascular malformation (VM) associated genes was performed on five AVMs and fourteen plexiform lesions of the lung of the patient.
Results: The HHT causing germline mutation in Endoglin, an exon 9–10 deletion, was detected in every sample.

Somatic mutations in VM associated genes were found in four out of fourteen plexiform lesions, but not in unaffected lung regions nor pulmonary AVMs. These included mutations in THBS1 (Thrombospondin-1 and a mutation in PIK3CA (Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Alpha), which is present in the Catalogue Of Somatic Mutations In Cancer and has been previously functionally confirmed as a moderately potent oncogenic mutation.
Conclusions: Targeted deep sequencing of HHT and VM related genes identified somatic mutations in some, but not all plexiform lesions, and in none of the pulmonary AVMs of a patient with HHT and PAH. The confirmed activating somatic mutation in PIK3CA might contribute to excessive cellular proliferation characteristically seen in plexiform lesions.

O27 Shared and distinct circulating microRNome in hereditary hemorrhagic telangiectasia with brain arteriovenous malformations and familial cerebral cavernous malformations, Sturge-Weber Syndrome, and cerebral microbleeds

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Objective: Hereditary hemorrhagic telangiectasia with brain arteriovenous malformations (HHTBAVM) involve inherited genetic mutations as well as other factors triggering brain lesion formation. Familial cerebral cavernous malformations (FCCM) and Sturge-Weber Syndrome (SWS), and are also cerebrovascular disorders driven by genetic mutations while cerebral microbleeds (CMBs) are primarily associated with the aging process. These diseases are characterized by vascular dysmorphism with or without hemorrhagic phenotype. We hypothesized that common and distinct circulating miRNAs in the patients' plasma are altered in HHTBAVM, FCCM, SWS, and CMB compared to age/sex matched controls reflecting shared and different vascular pathologies and serving as potential biomarkers and therapeutic targets.
Methods: Plasma miRNAs from patients with HHTBAVM (n = 10), FCCM (n = 10), SWS (n = 10), and as well as propensity-matched healthy young (HY) subjects (n = 10) were extracted and sequenced. Similarly, plasma miRNome of CMB patients (n = 10) and propensity-matched healthy old (HO) subjects (n = 10) were analyzed. MiRNA expression analysis in each group was performed and DESeq2 identified differentially expressed (DE) miRNAs of FCCM, SWS, and HHT BAVM to HY controls ($p < 0.05$, false discovery rate [FDR] corrected, absolute fold change [|FC|] > 1.5]) as well as CMB to HO controls [$p < 0.1$, FDR-corrected, |FC| > 1.2]. Ingenuity Pathway Analysis (IPA) was conducted to determine associated targets and pathways for each disease DE miRNAs.
Results: Forty one DE miRNAs were identified in HHTBAVM, 11 in FCCM, 40 in SWS ($p < 0.05$, FDR- corrected). In addition, 31 DE miRNAs were identified in CMB ($p < 0.1$, FDR-corrected). Further analyses showed that miR-487b-3p was commonly downregulated in both HHTBAVM and FCCM, while miR-431-5p was upregulated in FCA and downregulated in CMB. Twenty-nine genes targeted by miRNAs and 647 pathways were shared between HHTBAVM, FCCM, SWS, and CMB. CCND2, CDKN1A, SCN8A, and TGFBR2 were targeted by at least two DE miRNA in each of the four cerebrovascular disorders. Chronic myeloid leukemia signaling, GADD45 signaling, molecular mechanisms of cancer, and senescence pathways were linked to three of those four gene targets.
Conclusions: The identification of dysregulated miRNAs across HHTBAVM, FCCM, SWS, and CMB underscores their potential as robust biomarkers and therapeutic targets, reflecting their mechanistic involvement in shared pathophysiological pathways. Furthermore, the commonly targeted genes and implicated pathways suggest shared functionality of miRNA in each disease. These findings

pave the way for further exploration in preclinical studies and human trials, aiming at the clinical application of these miRNAs for disease monitoring and therapeutic intervention.

O28 Mutations causing premature termination codons discriminate clinical variability in three cohorts with HHT haemorrhage

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Objective: Our aim was to better understand the variability of bleeding between patients, in order to improve treatments strategies. We previously showed that haemorrhage severity was not explained by the HHT-causal gene (Shovlin-Blood-2020; Joyce-BloodAdvances-2022) and hypothesized that pathogenic variants generating termination codons (PTCs) may explain some of this variability.
Methods: Obligate PTC-generating variants (frameshift and nonsense) were categorized separately to non- PTC generating (full gene deletions, start loss, missense, inframe indels, and 5' UTR) and splice variants. With ethical approval, we examined associations in 3 essentially non-overlapping Imperial HHT cohorts where haemorrhage phenotyping was completed prior to genotyping of any family member. Cohort 1 (N = 426) discriminated daily severe bleeding, Cohort 2 (N = 256) used a 6-point bleeding score, and Cohort 3 (N = 22) had quantified responses to an ENT-directed rotating nasal antibiotic ointment regime.
Results: The cohorts had similar ENG/ACVRL1/SMAD4 distributions (Cohort 1: 289/122/15; Cohort 2: 191/58/7; Cohort 3: 12/7/2), but these were not associated with differing severity or responses of nosebleeds. The proportion of obligate PTC variants was highest in ENG, and similar between the series. Cohort 1 severe nosebleeds were 3.3-fold more common in ENG PTC than ENG non- PTC-patients ($p = 0.028$). Cohort 2 bleeding scores were higher in ENG PTC than ENG non- PTC-patients (mean 2.41 versus 3.01, $p = 0.05$). Cohort 3 patients with obligate PTC-generating variants were more likely to report beneficial responses to antibiotic-containing creams ($p = 0.0070$).
Conclusions: HHT haemorrhage differs in patients whose HHT is caused by an obligate PTC-generating mutation, particularly in ENG. Mechanistic considerations are presented elsewhere (Bernabéu- Herrero- Blood-2024).

O29 Development of a functional cellular test for the characterization of SMAD4 variants in HHT

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Objective: This project aims to set up a functional test to assess the activity of SMAD4 mutations identified in HHT patients in order to propose a better diagnosis for patients.
Methods: Eleven SMAD4 variants were identified at the French HHT national reference center located in Lyon. SMAD4 mutants were generated by site-directed mutagenesis. We established a cell-based functional assay with a luciferase reporter gene in human breast cancer cells lacking endogenous SMAD4 (MDA-MB468). We tested these mutants in two luciferase reporter assays using either a BMP (BRE) or a TGFß (CAGA) responsive promoter stimulated with BMP9 or TGFß respectively.
Results: We found that all the SMAD4 mutants resulted in loss of function in response to BMP9 or TGFß stimulation, although most of them seemed to be expressed at the protein level. Notably, ten of these mutants were found in the MH2 domain which is involved in the formation of the trimeric active complex of SMAD4 with the regulatory R-SMAD1/5 or R-SMAD2/3. We are thus currently testing the capacities of these SMAD4 mutants to oligomerize with R-SMAD. We also isolated endothelial cells carrying a SMAD4 mutation that we could test for its capacity to respond to BMP9. Interestingly, as previously shown for ALK1 heterozygote mutations, these cells, although expressing half the level of SMAD4 protein, respond like control cells.
Conclusions: We have developed a SMAD4 functional test that allows to discriminate polymorphic from pathogenic variants. This test will be transposable to hospital genetic laboratories and will provide a better diagnosis for HHT patients.

O30 Identification and validation of a novel pathogenic variants in GDF2 (BMP9) responsible for hereditary hemorrhagic telangiectasia

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Objective: The center of reference for HHT in Lyon has recently identified four GDF2 (BMP9) variants in patients suspected of HHT. The aim of this project was to set up a functional test to assess the activity of BMP9 variants.
Methods: BMP9 mutants were generated by site-directed mutagenesis. These mutants were then tested by western blot and ELISA for their expression and secretion. The secreted BMP9 mutant proteins were then tested for their functional activities using a cellular luciferase reporter assay under the control of a BRE (BMP responsive element) promoter.
Results: Two out of the four BMP9 mutations led to the biosynthesis of inactive BMP9. One is a non- sense mutation producing a truncated inactive protein. However, this patient presented a unique PAVM suggesting that he might not be a typical HHT patient. The other BMP9 variant is a missense mutation. In vitro studies showed that, although the mutation did not hamper intracellular precursor biosynthesis, dimerization and processing, mature BMP9 was not secreted, and accordingly no BRE activity could be measured supporting that this mutant led to a loss of function. Notably, this patient presented typical symptoms of HHT (epistaxies and typical telangiectases).
Conclusions: We have developed a functional test for BMP9 mutations. We have identified two new loss of function BMP9 variants. We propose that at least one of these heterozygous BMP9 variant presents typical HHT symptoms further supporting that BMP9 mutations can lead, although very rarely, to HHT.

O31 Deciphering hepatic and cardiac BMP10 functions using tissue-specific Bmp10-KO mouse models

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Objective: BMP9 and BMP10 act as ligands for the ALK1 receptor, whose mutations induce the development of Hereditary Hemorrhagic Telangiectasia (HHT). Understanding ligand biosynthesis and distribution is of major importance for giving some clues on ALK1 activation mechanisms in tissues. Although produced mainly by cardiomyocytes in the right atria, BMP10 is also synthesized to a lesser extent in the liver by hepatic stellate cells. The aim of this work is to determine the respective functions of hepatic versus cardiac BMP10 in vascular homeostasis.
Methods: Murine models with tissue-specific inducible deletion of cardiac Bmp10 or constitutive deletion of hepatic Bmp10 were generated using promoters with specific expression in cardiomyocytes or hepatic stellate cells, respectively. These mice were crossed with Bmp9-KO mice to determine vascular defects in absence of any other ALK1 ligands.
Results: Using these animal models, we show that the circulating and active form of BMP10 originates from the liver rather than the heart. Additionally, mice with hepatic deletion of Bmp9 and Bmp10 exhibited deregulation of endothelial cell-specific markers at a paracrine level in the liver, which were not observed in mice with cardiac deletion. Interestingly, vascular defects were also observed in intestine vessels, one of the most affected organs in HHT patients, supporting a role for hepatic-derived circulating BMP10 ligands on endothelial cells of remote organs.
Conclusions: Active circulating BMP10 originates from the liver and plays a major role in vascular homeostasis both locally and at distance.

O32 Biosynthesis of ALK1 ligands, BMP9 and BMP10

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Objective: Bone morphogenetic protein 9 (BMP9) and BMP10 homodimers or heterodimers serve as high- affinity ligands for the endothelial cell receptors, ALK1 and endoglin (ENG), mutations in which cause HHT. BMP9 is transcribed in hepatic stellate cells (HSCs) and BMP10 in HSCs and cardiomyocytes. BMPs are generated as proproteins: in canonical biosynthesis, the C-terminal growth factor (GF) domains dimerize in the rough ER and cleavage occurs in the trans-Golgi, releasing the N- terminal prodomains. Our objective is to understand BMP9 and BMP10 biosynthesis in physiologically relevant cell types

and to uncover the molecular nature and cellular origin of the dominant ALK1/ENG ligand in human plasma.
Methods: To probe ligand biosynthesis, we transfected immortalized HSCs and cardiomyocytes with human BMP9 and/or BMP10 and assayed protein production by Western blot. To identify the predominant ligand in human plasma, we performed ELISAs and immunoprecipitation/mass spectrometry.
Results: We found that cardiomyocytes secrete cleaved BMP9 or BMP10, whereas HSCs secrete mostly cleaved BMP9 but full-length pro-BMP10. Additionally, we found that full-length pro-BMP10, heterodimerized with cleaved BMP9 GF domain, is the most abundant ALK1 ligand in human plasma. Finally, we found that HSCs co-transfected with BMP9 and BMP10 secrete pro- BMP10/BMP9 GF, whereas co-transfected cardiomyocytes do not.
Conclusions: HSCs are the likely source of the abundant half-processed ALK1 ligand, pro-BMP10/BMP9 GF. We speculate that the peptide-bonded BMP10 PD might confer solubility, stability, and latency to this ligand, with activity enabled by cleavage at the endothelial cell surface.
This new insight may inform development of ligand-based therapeutics for HHT.

O33 The higher specificity of BMP10 towards the ALK1 receptor compared to BMP9 may explain BMP10's primary role in forming the proper arteriovenous network

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Objective: Disruption of TGF-β/BMP signaling, mediated by ENG/ALK1 in endothelial cells (EC), is implicated in the development of arteriovenous malformations (AVMs). Although both BMP9 and BMP10 activate ALK1/ENG signaling in ECs, knockout (KO) of Bmp10, but not Bmp9, in mice replicates AVM phenotypes observed in other HHT mouse models. However, the specific mechanism underlying this specificity remains unclear.
Methods: We established ALK1-KO human induced pluripotent stem cells (iPSCs) using CRISPR/Cas9 and then differentiated wildtype (WT) and ALK1-KO iPSCs into ECs (iPSC-ECs). We investigated the distinct downstream gene expression responses to BMP9 or BMP10 in WT and ALK1-KO iPSC-ECs using both bulk- and single-cell(sc)-RNA sequencing analyses.
Results: Both WT and ALK1-KO iPSC-ECs exhibited strong expression of EC markers, along with typical cobblestone-like morphology and EC characteristics. Interestingly, BMP10-responsive SMAD1,5,8 activation in WT iPSC-ECs was completely abolished in ALK1-KO cells, whereas BMP9 treatment sustained minimal active SMAD1,5,8 even in ALK1-deficient cells.
Furthermore, bulk-RNAseq data revealed that BMP10 signaling relied entirely on the ALK1 receptor, whereas some gene expression induced by BMP9 can occur independently of ALK1. Sc-RNAseq also indicated that while both BMP9 and BMP10 treatments altered clusters of WT iPSC-ECs, the responsiveness to BMP10, but not by BMP9, was completely blunted by ALK1 deficiency.
Conclusions: These findings underscore the higher specificity of BMP10 for the ALK1 receptor compared to BMP9, implying the crucial role of BMP10 in the formation of healthy arteriovenous networks.
This suggests that BMP10 serves as the primary physiological ligand for ENG and ALK1 receptor complexes in ECs.

O34 CDK6 controls endothelial cell proliferation and AVM pathology in HHT

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Objective: To understand the mechanism underlying endothelial cell (EC) proliferation deregulation in HHT and investigate the effectiveness of targeting AVM EC proliferation in HHT as a therapeutic strategy.
Methods: BMP9/10 blocking antibody-treated and inducible EC-specific Eng KO mice, as well as human skin telangiectasias, were utilized to study abnormal EC proliferation and its relationship to a deregulation of the cell cycle in HHT. Pharmacological inhibition and genetic deletion of CDK4 and CDK6 were investigated. HUVEC cultures were used to elucidate the underlying molecular mechanism.
Results: We report the identification of a CDK6-driven mechanism of cell cycle progression deregulation involved in EC proliferation and HHT vascular pathology. HHT

mouse liver and retina ECs exhibited a G1/S checkpoint bypass and cell cycle acceleration. Phosphorylated retinoblastoma (p-RB1), a marker of G1/S transition through the restriction point, significantly accumulated in retinal AVM ECs of HHT mouse models and in ECs of HHT patient skin telangiectasias.
Mechanistically, ALK1 loss of function increased the expression of key restriction point mediators, and treatment with palbociclib or ribociclib (two CDK4/6 inhibitors) blocked p-RB1 increase and retinal AVMs in HHT mice. Specific deletion of Cdk6 in ECs was sufficient to protect HHT mice from AVM pathology. In HUVECs, VEGF controlled CDK6 expression via PI3K/mTOR signaling, and ALK1 activation blocked this pathway.
Conclusions: A VEGF- and CDK6-mediated mechanism of endothelial cell cycle acceleration controls EC proliferation in AVMs and is a central determinant of HHT pathogenesis. We propose that CDK6 inhibition has therapeutic potential in HHT.

O35 Pre-clinical assessment of ANG2-VEGFA bispecific inhibitor on AVM formation in HHT mouse models

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Objective: Bevacizumab, an IgG-VEGF inhibitor, is used to manage epistaxis and chronic bleeding from telangiectasias in HHT patients. However, its effect on arteriovenous malformations (AVMs), a serious complication in HHT, is not well characterized. Our lab has previously published beneficial effects of an IgG-Angiopoietin-2 (ANG2) inhibitor on prevention of cerebrovascular abnormalities, including AVM development in HHT mouse models. Our study aims to compare and determine the beneficial effects of the ANG2 and VEGFA monotherapies, as well as a novel IgG CrossMab ANG2-VEGFA bispecific inhibitor on prevention of cerebrovascular defects in Smad4 and Eng HHT mouse models.
Methods: The phenotypic benefits of the anti-angiogenic inhibitors were assessed in the HHT mouse models using latex vascular perfusion and light sheet microscopy for surface and deeper cerebrovascular defects, and immunofluorescence staining for retinal vasculature. We will further analyze molecular transcriptomic changes brought about by the minimal effective dosage of the bispecific inhibitor compared to the monotherapies via RNA sequencing.
Results: Our very preliminary data suggests the combined effect of the bispecific inhibitor in smaller doses improves brain vasculature defects in HHT mice more robustly than the individual inhibitors alone, while not negatively affecting control littermates. We further expect ANG2-VEGFA dual inhibition to normalize the transcriptomic signature of mutants to mimic more closely the control setting compared to monotherapies.
Conclusions: We provide a pre-clinical assessment indicating the repurposing of FDA approved bispecific inhibitor (Faracimab) may have beneficial effects for AVM management. These studies may further our mechanistic understanding of AVM development and management in HHT.

O36 Alk1/Endoglin signaling restricts vein cell size increases in response to hemodynamic cues and limits ribosomal biogenesis

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Objective: Hemodynamic cues influence blood vessel hierarchy by regulating diameter in response to flow changes. Arteriovenous malformations (AVMs) may stem from aberrations in this control, but it is unclear if all vessel types respond similarly to flow changes and where AVMs originate.
Methods: Using zebrafish embryos with mutations in endoglin (eng) or alk1 (acvrl1) along with cell transplantations and time lapse imaging we investigate AVMs causes and the roles of alk1 and eng in arterial and venous cells.
Results: Arteries adhere to the shear stress set point model, while veins behave differently due to distinct endothelial cell (EC) shapes and sizes. Arterial ECs enlarge more strongly when experiencing higher flow, as compared to vein cells. Mutant eng or alk1 vein cells enlarge in normal flow conditions, while we do not observe a phenotype in arteries. We further show that an increase in vein diameters initiates AVMs in eng mutants, secondarily transmitting higher flow to arteries. These enlarge in response to higher flow through increasing arterial EC sizes, fueling the AVM. Finally, single cell sequencing results and immunofluorescence analysis indicate that increases in vein EC sizes in eng mutants are likely caused by increases in ribosome biogenesis and downregulation of the translational inhibitor dap1b.
Conclusions: This study elucidates how BMP signaling limits vein EC size increases in response to flow and provides a framework for our understanding of how mutant vein cells can trigger AVMs through flow-mediated effects on arterial ECs.

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Author contributions FD, AG, NR, and ES wrote the main text. RH, ER, SDG, and SB provided edits. MC and CF provided edits preparation of materials. All authors reviewed.

Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

References

1. Al-Samkari H et al (2024) Pomalidomide for Epistaxis in Hereditary Hemorrhagic Telangiectasia. N Engl J Med 391(11):1015–1027
2. Hermann R et al (2024) Effect of oral nintedanib vs placebo on epistaxis in hereditary hemorrhagic telangiectasia: the EPICURE multicenter randomized double-blind trial. Angiogenesis 28(1):9
3. Zhang E et al (2024) Hereditary hemorrhagic telangiectasia may be the most morbid inherited bleeding disorder in women. Blood Adv 8(12):3166–3172
4. Faughnan ME et al (2011) International guidelines for the diagnosis and management of hereditary haemorrhagic telangiectasia. J Med Genet 48(2):73–87
5. Dupuis-Girod S et al (2012) Bevacizumab in patients with hereditary hemorrhagic telangiectasia and severe hepatic vascular malformations and high cardiac output. JAMA 307(9):948–955
6. Gossage JR, Kanj G (1998) Pulmonary arteriovenous malformations. A state of the art review. Am J Respir Crit Care Med 158(2):643–661
7. Gulich B, Buecker A, Schneider G (2024) Reperfusion of pulmonary arteriovenous malformations treated by catheter embolization. J Clin Med 13(24):7812
8. Fish A et al (2024) Recurrence of pulmonary arteriovenous malformation after embolization in patients with pulmonary hypertension. J Vasc Interv Radiol 35(8):1148–1153
9. Venot Q et al (2019) Author Correction: Targeted therapy in patients with PIK3CA-related overgrowth syndrome. Nature 568(7752):E6
10. Canaud G et al (2023) Alpelisib for treatment of patients with PIK3CA-related overgrowth spectrum (PROS). Genet Med 25(12):100969
11. Hessels J et al (2025) Family planning, sexual activity and contraception in hereditary hemorrhagic telangiectasia: a European survey study. Orphanet J Rare Dis 20(1):395
12. Wooderchak-Donahue WL et al (2013) BMP9 mutations cause a vascular-anomaly syndrome with phenotypic overlap with hereditary hemorrhagic telangiectasia. Am J Hum Genet 93(3):530–537
13. Balachandar S et al (2022) Identification and validation of a novel pathogenic variant in GDF2 (BMP9) responsible for hereditary hemorrhagic telangiectasia and pulmonary arteriovenous malformations. Am J Med Genet A 188(3):959–964
14. Snellings DA et al (2019) Somatic mutations in vascular malformations of hereditary hemorrhagic telangiectasia result in bi-allelic loss of ENG or ACVRL1. Am J Hum Genet 105(5):894–906
15. DeBose-Scarlett E et al (2024) Somatic mutations in arteriovenous malformations in hereditary hemorrhagic telangiectasia support a bi-allelic two-hit mutation mechanism of pathogenesis. Am J Hum Genet 111(10):2283–2298
16. Whitehead KJ et al (2024) Investigation of the genetic determinants of telangiectasia and solid organ arteriovenous malformation formation in hereditary hemorrhagic telangiectasia (HHT). Int J Mol Sci 25(14):7682
17. Castillo SD, Baselga E, Graupera M (2019) PIK3CA mutations in vascular malformations. Curr Opin Hematol 26(3):170–178
18. Desroches-Castan A et al (2019) Differential consequences of Bmp9 deletion on sinusoidal endothelial cell differentiation and liver fibrosis in 129/Ola and C57BL/6 mice. Cells 8(9):1079
19. Bernabeu-Herrero ME et al (2024) Mutations causing premature termination codons discriminate and generate cellular and clinical variability in HHT. Blood 143(22):2314–2331
20. Mallet C et al (2015) Functional analysis of endoglin mutations from hereditary hemorrhagic telangiectasia type 1 patients reveals different mechanisms for endoglin loss of function. Hum Mol Genet 24(4):1142–1154
21. Ricard N et al (2010) Functional analysis of the BMP9 response of ALK1 mutants from HHT2 patients: a diagnostic tool for novel ACVRL1 mutations. Blood 116(9):1604–1612
22. Al Tabosh T et al (2024) Impact of heterozygous ALK1 mutations on the transcriptomic response to BMP9 and BMP10 in endothelial cells from hereditary hemorrhagic telangiectasia and pulmonary arterial hypertension donors. Angiogenesis 27(2):211–227
23. Tillet E et al (2018) A heterodimer formed by bone morphogenetic protein 9 (BMP9) and BMP10 provides most BMP biological activity in plasma. J Biol Chem 293(28):10963–10974
24. Ola R et al (2016) PI3 kinase inhibition improves vascular malformations in mouse models of hereditary haemorrhagic telangiectasia. Nat Commun 7:13650
25. Dinakaran S et al (2024) CDK6-mediated endothelial cell cycle acceleration drives arteriovenous malformations in hereditary hemorrhagic telangiectasia. Nat Cardiovasc Res 3(11):1301–1317
26. Genet G et al (2024) Induced endothelial cell cycle arrest prevents arteriovenous malformations in hereditary hemorrhagic telangiectasia. Circulation 149(12):944–962
27. Chavkin NW et al (2022) Endothelial cell cycle state determines propensity for arterial-venous fate. Nat Commun 13(1):5891
28. Zhou X et al (2023) ANG2 blockade diminishes proangiogenic cerebrovascular defects associated with models of hereditary

hemorrhagic telangiectasia. Arterioscler Thromb Vasc Biol 43(8):1384–1403
29. Diwan Z et al (2024) Alk1/Endoglin signaling restricts vein cell size increases in response to hemodynamic cues. Angiogenesis 28(1):5
30. Fang JS et al (2017) Shear-induced Notch-Cx37-p27 axis arrests endothelial cell cycle to enable arterial specification. Nat Commun 8(1):2149
31. Al-Samkari H et al (2021) An international, multicenter study of intravenous bevacizumab for bleeding in hereditary hemorrhagic telangiectasia: the InHIBIT-Bleed study. Haematologica 106(8):2161–2169
32. Abe K et al (2010) Formation of plexiform lesions in experimental severe pulmonary arterial hypertension. Circulation 121(25):2747–2754
33. Li W et al (2018) The clinical characteristics and long-term prognosis of pulmonary arterial hypertension associated with hereditary hemorrhagic telangiectasia. Pulm Circ 8(2):2045894018759918
34. Abston E et al (2021) Treatment of pulmonary hypertension in patients with Hereditary Hemorrhagic Telangiectasia—A case series and systematic review. Pulm Pharmacol Ther 68:102033
35. Hoeper MM et al (2023) Phase 3 trial of sotatercept for treatment of pulmonary arterial hypertension. N Engl J Med 388(16):1478–1490
36. Hoeper MM et al (2025) Efficacy and safety of the activin signalling inhibitor, sotatercept, in a pooled analysis of PULSAR and STELLAR studies. Eur Respir J 65(5):2401424
37. Souza R et al (2023) Effects of sotatercept on haemodynamics and right heart function: analysis of the STELLAR trial. Eur Respir J 62(3):2301107
38. Farhan A et al (2022) Clinical manifestations of patients with GDF2 mutations associated with hereditary hemorrhagic telangiectasia type 5. Am J Med Genet A 188(1):199–209
39. Shovlin CL et al (2008) Embolisation of pulmonary arteriovenous malformations: no consistent effect on pulmonary artery pressure. Eur Respir J 32(1):162–169