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2022 14th HHT International Scientific Conference Abstracts

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Contents

Oral presentation abstracts

Medical therapeutics

O1 Cure HHT research network: building the roadmap to cure HHT

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Objective: As a grantee of the Chan Zuckerberg Initiative's Rare as One Project, Cure HHT created a research network (CHRN) to develop a research roadmap for the next 3–5 years. CHRN is led by HHT patients working in collaboration with researchers and clinicians to prioritize research initiatives by order of feasibility, impact, importance, and logical sequence.

Methods: Comprehensive surveys were sent to the HHT patient and professional community to identify perceived gaps in research and treatments. 1,204 patients answered 49 questions, 42 HHT scientists answered 17 questions, and 96 HHT clinicians answered 25 questions. Based on the analyzed results of patient needs, broad-topic work streams were established which included patients, clinicians, and researchers. Work streams performed a comprehensive literature review on their respective topic, discussed gaps in research, and proposed recommendations to fill each knowledge gap. Finally, a 2-day convening was held with all working groups to present recommendations and vote on a consensus for a final research roadmap to meet patient needs over the next 3–5 years.

Results: 8 work streams identified 31 recommendations to address patient needs. Recommendations were selected by anonymous vote after their presentation to the group and ranked by feasibility, impact, and importance. Additionally, resources and tools were identified to achieve all recommendations.

Conclusion: CHRN is poised with specific, actionable goals to address patient priorities. The research roadmap will serve as a guide for next steps, research funding opportunities, and collaboration between patients, clinicians, and researchers at an unprecedented level for the HHT community.

O2 Efficacy and safety of bevacizumab on severe bleedings associated with hemorrhagic hereditary telangiectasia: a national, randomized multicenter phase III study

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Objective: Hereditary Hemorrhagic Telangiectasia is a rare but ubiquitous hereditary vascular disease related to a disequilibrium of the angiogenic balance. Since 2010, bevacizumab, a humanized monoclonal antibody that selectively binds to and neutralizes the biologic activity of human VEGF (vascular endothelial growth factor) has been widely used for the treatment of severe bleeding and hepatic involvement related to HHT as several studies and many case reports are in favor of its efficacy, however, no randomized study has been done. To evaluate the efficacy of intraveinous bevacizumab on blood transfusions in patients with HHT complicated by bleedings responsible for severe anemia.

Methods: Double-blind multi-center randomized phase III trial with an active / placebo ratio 1:1. BABH study was conducted from September 2017 to May 2020 with a 6-months follow-up. Patients were recruited from the French HHT Network. Over 18 years old with confirmed HHT and to epistaxis or digestive bleeding (with the requirement for at least 4 units of blood in the 3-month period before study enrollment) were included. Bevacizumab was given at a dose of 5 mg / kg every 14 days with a total of 6 injections. The primary efficacy criterion was the decrease by at least 50% of the number of red blood cell transfusions 3 months before and after treatment.

Results and Conclusion: 24 patients were included and randomized at 4 different centers 12 in each group. Results will be presented during the meeting.

O3 Safety of long-term systemic bevacizumab use in hereditary hemorrhagic telangiectasia

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Objective: To evaluate the safety profile of long-term systemic bevacizumab use in patients with HHT.

Methods: Patients with HHT managed at the UNC HHT Center of Excellence and treated with bevacizumab were identified in the EMR. Records were reviewed to identify duration of treatment with bevacizumab and documentation of side effects/adverse events/reason for therapy cessation. Search terms included: proteinuria, hypertension, headache, arthralgia, joint pain, DVT, pulmonary embolism, stroke, TIA, dyspnea, hoarseness, and tinnitus.

Results: Forty-eight patients were initially identified. Six were not on systemic bevacizumab, one did not have HHT, and one was lost to follow up. Overall, 40 patients were eligible with a median duration of treatment of 39.5 months with systemic bevacizumab. Side effects data are described in the **Table**. Majority of reactions were transient and associated with infusion. Out of five patients with persistent/worsening hypertension, four cases developed within weeks of their first infusion. One patient developed DVT/PE associated with a Port-a-cath. This subject was on hormonal therapy and symptoms of DVT were noted prior to initiation of bevacizumab. No cases of persistent proteinuria, although one patient briefly held infusions given concern for renal dysfunction of unclear etiology.

Conclusion: In our single-center cohort of HHT patients long-term systemic bevacizumab use was safe and well tolerated overall. Side effects/adverse events were largely infusion-related and appeared early in treatment course. We did not observe thromboembolic events or significant proteinuria. Patients should be monitored acutely for infusion reactions, especially upon initiation of therapy, and chronically for development of hypertension.

O4 Efficacy and safety of tacrolimus as treatment for bleeding caused by hereditary hemorrhagic telangiectasia: an open-label pilot study

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Objective: Haploinsufficiency of Endoglin (ENG) and activin A receptor type II-like I (ALK1) lead to the formation of weak and abnormal vessels in hereditary hemorrhagic telangiectasia (HHT). These cause epistaxis (nosebleeds) and/or gastrointestinal blood loss. In vitro, tacrolimus has been shown to increase ENG and ALK1 expression and is therefore a potential treatment option.

Method: We report here a proof-of-concept study in HHT patients with severe epistaxis and/or gastrointestinal bleeding who were treated daily with orally-administered tacrolimus for twenty weeks.

Results: Twenty-five HHT patients (11 females (44%); 14 males (56%)) with a median age of 59 years, were enrolled. Five patients (20%) stopped the trial prematurely – four due to (serious) adverse events (SAE). 20 patients were included in further analyses. Hemoglobin levels increased during tacrolimus treatment from 6.1 (IQR 5.2 – 6.9) mmol/L at baseline to 6.7 (6.5 – 7.1) mmol/L, $p = 0.003$. In addition, the number of blood transfusions decreased from a mean of 5.0 ($\pm$ 9.2) to 1.9 ($\pm$ 3.5) after treatment, $p = 0.04$. In 64% of the patients, at least one AE occurred.

Conclusion: In summary, oral tacrolimus significantly increased hemoglobin levels and decreased blood transfusion needs in HHT patients with severe epistaxis and/or gastrointestinal bleeding. Side-effects were common, however most patients were content with the effect of treatment. The potential therapeutic benefit should be further investigated.

O5 Randomized, double-blind, placebo-controlled, crossover trial of oral doxycycline for epistaxis in hereditary hemorrhagic telangiectasia

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Funding:US Department of Defense W81XWH-17–1-0429ABSTRACT.

Objective: Vascular malformations in hereditary hemorrhagic telangiectasia (HHT) lead to chronic recurrent bleeding, hemorrhage, stroke, heart failure, and liver disease. There is an unmet need for effective therapies for HHT. We aimed to measure the effectiveness of oral doxycycline for the treatment of epistaxis and explore mechanisms of action on angiogenic, inflammatory and pathway markers in HHT using a randomized controlled trial.

Methods: 13 HHT patients with epistaxis were recruited from the Toronto HHT Center at St. Michael's Hospital. Recruitment was stopped early due to COVID-19-related limitations. The study duration was 24 months. Patients were randomly assigned to the treatment-first or placebo-first study arm. We compared the change in weekly epistaxis duration and frequency, biomarkers, blood measurements, and intravenous iron infusion and blood transfusion requirements between treatment and placebo.

Results: There was no significant difference in the change in weekly epistaxis duration ($p = 0.136$) or frequency ($p = 0.261$) between treatment and placebo. There was no significant difference in the levels of MMP-9, VEGF, ANG-2, IL-6 or ENG with treatment. Hemoglobin levels were significantly higher ($p = 0.0499$) during treatment. On secondary, qualitative analysis, 5 patients appeared to respond to treatment. There was a significant difference ($p = 0.037$) in baseline ANG-2 levels between responders and non-responders.

Conclusion: Overall, our study did not demonstrate effectiveness of doxycycline as a treatment for epistaxis in patients with HHT, though the study was underpowered. Secondary analyses provided new observations which may help guide future trials in HHT.

O6 Oral pazopanib for the management of HHT related bleeding

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Objective: IV bevacizumab has been the preferred anti-angiogenic agent for severe/refractory HHT related bleeding. Oral low-dose (50-200 mg) pazopanib is a promising alternative agent based on initial data. However, the effectiveness of different pazopanib dosages especially in patients previously treated with one/more anti-angiogenic agents requires further study.

Method: We searched a prospectively maintained database of patients with refractory HHT related bleeding treated with anti-angiogenic agents. RBC transfusion, need for ENT procedures, GI endoscopies, and laboratory results were compared before and after initiation of oral pazopanib.

Results: Fourteen patients (57% female) with a median age of 61 (48–82) years were identified (Table 1). Nine (64.25%) patients had been previously treated with other antiangiogenic approaches and were switched to pazopanib (bevacizumab—5, Bevacizumab + Doxycycline—2 & Pomalidomide + bevacizumab + Doxycycline—2). All patients were started on 200 mg OD pazopanib. The dose was reduced to 100 mg daily in five patients due to side effects. Two (14.25%) patients were on antiplatelet therapy and Two (14.25%) patient was on anticoagulation. Cumulative number of transfusions decreased from 0 (0–0.8, min: 0, max: 6) to 0 (0–0, min: 0, max:3), $P = 0.59$. Similarly, total number of upper endoscopies decreased from 0 (0–0, min:0, max:2) vs 0 (0–0, min:0, max:0), $P = 0.35$ at six months. Hemoglobin increased from (11.2 (8.5–13.1, min:6.9, max:15.2) vs 12.7 (9.3–14.5, min:8.3, max:16), $P = 0.22$ at 3 months.

Conclusion: We present our initial experience with pazopanib in a cohort of patients heavily pre-treated with bevacizumab as well as other anti-angiogenic agents. Most patients experienced a good/excellent treatment response to this therapy.

Table 1 .

Age (years)	61 (48 – 82)
Female	7 (57%)
GI telangiectasias (endoscopy confirmed)	4 (25%)
Hypertension	7 (50%)
Diabetes mellitus	4 (28.5%)
Anticoagulation therapy	2 (14.25%)
Antiplatelet therapy	2 (14.25%)
History of smoking	4 (28.5%)
Smoking pack years	23.125 (2.5–30)
Number of patients treated previously with bevacizumab	9
Number of months of bevacizumab treatment	35.33 (7–72)
Number of patients treated with pomalidomide	2(14.25)
Number of patients treated with doxycycline	4 (28.5)
No. of months on Pazopanib	14.5(4–33)
Initial Pazopanib dosing	200 mg OD
Pazopanib dose reduced to 100 mg OD	N = 5

O7 An evaluation of the efficacy and safety Of AKT inhibitors in the prevention of hereditary hemorrhagic telangiectasia

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Objective: HHT pathogenesis strongly relies on an overactivated AKT activity in endothelial cells. Here, we have investigated the therapeutic effects of AKT inhibitors in preclinical models of HHT1.

Method: We compared the effects of Perifosine, Uprosertib and VAD044 on angiogenesis focusing on the neonatal retina of *Cdh5-Cre^{ERT2}; Eng$^{flox/flox}$* mice at P7. Mice received a single dose of 50 µg Tamoxifen at P2 to induce the formation of retinal AVMs and then were treated with AKT inhibitors at P3 and P5. The half maximal concentrations (EC_{50}) were identified in mice and in human in vivo and in vitro by measuring AKT activity in primary endothelial cells and in platelets isolated from blood samples.

Result: VAD044 showed the best efficacy and safety profile. VAD044 at 2.5 mg.kg^{-1} of body weight strongly inhibited the formation of AVMs in *Eng-iKO^{e}* mice. The blood exposure of VAD044 free base in the plasma of mouse neonates corresponded to a concentration of 55.1 nM over 48 h dosing interval. VAD044 IC_{50} on AKT phosphorylation was measured at 55 nM in control mouse endothelial cells and increased to 93 nM in mouse endothelial cells depleted for *Eng*. In human primary endothelial cells, VAD044 IC_{50} was comparable and measured at 87 nM. The values of those IC_{50} were similar to the average plasmatic concentration of VAD044 in mice and in human.

Conclusion: VAD044 showed efficacy in in preclinical models of HHT and was well tolerated. A phase II trial is currently ongoing to evaluate its efficacy to prevent bleeding in patients with HHT.

O8 Evaluating AAV vectors for HHT gene therapy

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Background: Epistaxis from nasal telangiectasias and intracranial hemorrhage from brain arteriovenous malformations (bAVMs) are among the most devastating symptoms of HHT. All available managements for HHT have limitations. Adeno-associated viral vector (AAV) mediates long- term transgene expression with few adverse effects. We showed that intravenous delivery of soluble FMS-related tyrosine kinase 1 using an AAV9 vector (AAV9-sFLT1) reduced bAVM severity of *endoglin* deficient mice. However, minor liver inflammation and growth arrest in young mice were observed.
Objective: Identify AAV vectors and delivery methods that can best transduce brain and nasal tissue with minimum off-target transduction.
Methods: Three engineered AAV capsids (AAV.cc47, AAV.cc84 and AAV1RX) were compared with AAV9. A single-stranded CBA promoter driven tdTomato transgene were packaged in these capsids and delivered intravenously or intranasally to mice. Tissues were collected 4 weeks post-dosing.
Results: After intravenous injection, AAV9 and AAV.cc47 mediated transgene expression in different brain cells and hepatocytes; AAV1RX infected some brain endothelial cells (ECs) but no hepatocytes; and AAV.cc84 transduced a high percentage of brain ECs and a few hepatocytes. After intranasal delivery, AAV9 non-specifically transduced few brain cells and hepatocytes, 1RX transduced a few brain ECs but no hepatocytes, AAV.cc47 dosed animals showed robust transduction in the brain and the liver, while AAV.cc84 transduced brain perivascular cells and nasal epithelial cells, but no hepatocytes.
Conclusion: AAV.cc84 transduces brain perivascular cells and nasal epithelial cells after intranasal delivery without transducing hepatocyte and ECs predominantly after intravenous injection.
Therefore, AAV.cc84 is a promising candidate for HHT gene therapy.
Bleeding, Thrombosis, Anemia, and Iron.

O9 Antithrombotic therapy in hereditary hemorrhagic telangiectasia: a scoping review

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Objective: Data describing safety and tolerability of anticoagulation and antiplatelet therapy in HHT is limited. We sought to better define the state of knowledge in this topic through literature review.

Methods: We performed a scoping review, searching MEDLINE and EMBASE from inception to November 2021 for eligible studies reporting detailed clinical data describing antithrombotic use in HHT. Data extracted included study design, patient population, and characteristics and outcomes of antithrombotic therapy.
Results: Of 575 unique manuscripts identified through database search, 72 manuscripts were included: 60 manuscripts reporting patient-level data on 61 patients and 11 reporting population-level data (**Table**). Inclusive of both patient-level and population-level manuscripts, data were extracted on a total of 401 patients. The most common reasons for antithrombotic therapy were VTE (56.2%), atrial arrythmias (14.4%) and stroke (10.1%). Anticoagulation was used in 287 episodes (76.1%), antiplatelet therapy in 70 episodes (18.6%), and both together in 11 episodes (2.9%). Complications of therapy included worsened HHT-associated bleeding (primarily epistaxis and gastrointestinal bleeding) in 154 antithrombotic treatment episodes (41.1%) and antithrombotic therapy discontinuation in 61 episodes (23.1%). Bleeding- directed therapy (local ablative therapy and systemic therapies) were employed to address worsening bleeding in 8.6% of episodes. No specific complications of therapy were reported in 198 total antithrombotic events (52.5%). Rates of bleeding, therapy discontinuation, and other complications ranged considerably from study to study.
Conclusion: Current publications vary widely on the outcomes and tolerability of antithrombotics in HHT. More formal studies are needed to better guide optimal antithrombotic use in these patients.

O10 Functional alterations involved in increased bleeding in hereditary hemorrhagic telangiectasia mouse models

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Objectives: HHT patients present recurrent and difficult to stop bleeds that compromise patients' life. The aim of this study is to assess possible alterations in hemostasis mechanisms in animal models of HHT.

Methods: Heterozygous murine models of HHT-1 ($Eng^{\pm}$) and HHT-2 ($ALK1^{\pm}$) were used to study different phases of hemostasis in vivo and ex vivo. Moreover, iKO-Eng and ENG^{+} mice were used to confirm the role of endoglin. Primary culture lung endothelial cells were obtained from these mice and in vitro platelet adhesion was assayed under static or shear stress conditions.
Results: Our results show that bleeding time is increased in both animal models of HHT, whereas endothelial-independent hemostasis show normal activity. Endoglin deficiency impairs platelet-endothelial adhesion, consequently, it is observed a reduction in the thrombus stabilization in $Eng^{\pm}$ animals, while it is increased in human endoglin transgenic mice ($hEng^{+}$). On the other hand, the HHT-2 model presents alterations in fibrinolysis, as PAI-1 plasma level is decreased while t-PA is increased.
Conclusion: Both HHT murine models have defects in hemostasis, but the pathophysiologic mechanism underlying this effect seems to be different in HHT-1 and HHT-2. Endoglin deficiency leads to an impaired interaction between platelets and endothelium in HHT-1, resulting in a defective thrombus stabilization that associated with more severe hemorrhages. However, HHT-2 increased susceptibility to bleeding seems to be due to the acceleration of thrombus lysis due to an increased fibrinolysis. Both mechanisms would explain the common bleeding phenotype and should be considered as potential therapeutic targets in future investigations.

O11 Hereditary hemorrhagic telangiectasia is associated with a higher prevalence of heavy menstrual bleeding

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Objective: (1) Determine the prevalence of heavy menstrual bleeding (HMB) and its impact on quality of life (QoL) (2) Compare HMB prevalence in women with HHT to the general population.
Method: A survey study was conducted and members of Cure HHT responded anonymously over 4 weeks. HMB present if: bleeding > 7 days, ≥ 1 product every hour for several consecutive hours, > 1 product-type to control bleeding, or required adult diapers. QoL negatively impacted if missed: work, school, family, or social activities.
Results: There were 633 respondents (**Table**): 352 (55.6%) of childbearing age (Group A). HMB prevalence: entire cohort- 74% and Group A- 72%. In the entire cohort: 9.7% -hysterectomy, 8.7%-uterine AVMs and 23% -post-partum bleeding [4% required blood transfusions, 0.4% required hysterectomy and 5.1% required medications to control bleeding].
Group A: 49%- sought care for HMB, 56%- negative impact on QoL. Prevalence of anemia in the last year was 67% and 79%- used oral iron, 26.5%- IV iron, and 9.5%- RBC transfusion. Interventions to manage HMB: 9.7%-IUD, 6.8%- progestin- only pills, 5.7%-antifibrinolytics, 3%- uterine ablation or equivalent, and 0.3%-hysterectomy.
Significant correlation noted between HMB and QoL ($p < 0.001$), anemia (p- 0.005), OCP use ($p = 0.006$), progestin-only pills ($p = 0.015$), IUD ($p = 0.001$), fibroids ($p = 0.019$), and endometriosis ($p = 0.025$).
Conclusions: We found a prevalence of HMB of 72% among women with HHT (56% reporting an adverse QoL), significantly higher than the reported 53% in the general population. This suggests HMB may be an HHT-related **manifestation that is under-recognized** and warrants further evaluation.

O12 Incidence of spontaneous pulmonary AVM rupture in HHT patients

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Objective: To determine the incidence and prevalence of spontaneous rupture of pulmonary AVMs in HHT patients.
Methods: This study retrospectively reviewed records of 2310 patients with known (1971) or possible (339) HHT according to the Curacao criteria or by genetic testing, referred to a single-center HHT clinic. Patients diagnosed with pulmonary AVMs were evaluated for a single lifetime episode of hemothorax or pulmonary hemorrhage secondary to spontaneous pulmonary AVM rupture. Medical records of the patients with spontaneous rupture were then further evaluated.
Results: Between July 2, 1996 and July 22, 2021, a total of 801 patients with HHT (759 known, 42 possible) were found to have pulmonary AVMs. Spontaneous rupture of the AVM occurred in 22 patients, identified over an average 16.3-year follow-up period (Range 0–25 years). The lifetime prevalence and incidence of spontaneous rupture in HHT patients with pulmonary AVMs was therefore estimated to be 2.7% and 0.16% respectively. Considering all HHT patients, the life-time prevalence was 1.1%. Spontaneous rupture of the AVM represented the initial presentation of 9 cases (40.9%), was life-threatening in 9 cases (40.9%), and occurred during pregnancy in five patients (22.7%). All cases of pulmonary hemorrhage were a result of lobar AVMs and all cases of hemothorax were a result of subpleural AVMs. All cases occurred in virgin lesions, and subsequent embolization was curative.
Conclusion: While a feared complication, pulmonary AVM rupture is rare and is likely effectively revented by existing embolization techniques and indications.

O13 Safety and efficacy of left atrial appendage closure for stroke protection from atrial fibrillation in hereditary hemorrhagic telangiectasia

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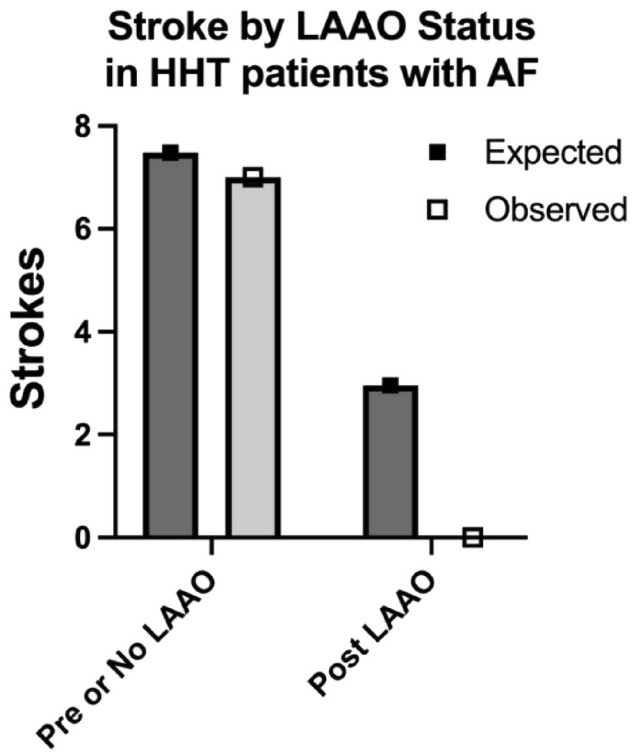
Background: Atrial fibrillation (AF) is a common cause of stroke and occurs with increased incidence in patients with HHT. Anticoagulation can prevent stroke but is poorly tolerated in patients with HHT. Left atrial appendage occlusion (LAAO) is an alternative strategy for stroke prevention.

Objective: Evaluate the safety and efficacy of LAAO for stroke prevention in HHT patient with AF.

Method: Retrospective cohort study.

Results: We observed AF in 31 of 329 consecutive adult patients with definite diagnosis of HHT. A total of 11 patients underwent LAAO (9 AtriClip, 1 Watchman, 1 Lariat). The mean duration of AF in this group was 7.7 ± 4.4 years, with median follow-up post LAAO of 3.3 years (IQR 1.5—5.1 years). Median CHADS-VASc score was 4 (IQR 4—5). Anticoagulation was used by 3 patients (27.3%). The 20 patients without LAAO had a mean duration of AF of 4.4 ± 2.1 years and median CHA2DS2-VASc score of 4 (IQR 2.5—5); 3 patients were treated with anticoagulation (15.0%). We observed 7 ischemic strokes felt to be due to AF in this population, 3 in the control group, and 4 in the LAAO group prior to their procedure. No strokes were observed following LAAO. We expected to observe 7.48 strokes from all patients without or prior to LAAO (observed 7). We expected to observe 2.96 strokes following LAAO (observed 0). This difference approaches statistical significance (P = 0.12).

Conclusion: LAAO is a promising approach to stroke prevention in AF for patients with HHT.



O14 Activation of coagulation and the impact of iron deficiency anemia in hereditary hemorrhagic telangiectasia (HHT)

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Objective: (1) Determine whether there is evidence of coagulation activation in the plasma of patients with HHT; (2) Evaluate the impact of iron deficiency anemia on coagulation activation in the plasma of HHT patients.

Methods: Four groups of subjects were enrolled: HHT patients with and without iron deficiency anemia (IDA), patients with IDA but not HHT, and healthy controls. Pertinent clinical and demographic data were recorded and blood samples collected. The following lab tests were measured: complete blood count, ferritin, D-dimer, E-selectin and vascular endothelial growth factor (VEGF). In a cohort of 8 subjects representing the 4 study groups, differential expression of 55 angiogenesis-related proteins were explored using a protein array assay.

Results: Number of subjects in the 4 groups: HHT with IDA- 24, HHT without IDA- 11, IDA without HHT- 4, controls- 7. D-dimer levels were significantly higher in the HHT with IDA group compared to control (516.52 vs 210.19, p 0.049). VEGF levels were higher in both HHT groups. E-selectin levels were higher in the HHT groups compared to control but did not meet statistical significance. The angiogenesis protein array assay identified 9 upregulated and 11 downregulated proteins that were ≥ 50% control (**Table**), most notably fivefold increase in tissue factor.

Conclusion: We identified a significant increase in D-dimer in iron deficient HHT subjects that was independent of endothelial activation. Angiogenesis protein array reveled upregulation of tissue factor in the HHT cohort supporting a procoagulant state in addition to identifying additional differentially expressed proteins that warrant further study.
Table: Differentially expressed proteins (≥ 50%) in HHT subjects on angiogenesis protein array assay:

Down-regulated	Up-regulated
• Activin A	• Coagulation factor III (tissue factor)
• Angiostatin	• GDNF
• ADAMTS-1	• IL-1 beta
• FGF-4	• Leptin
• GM-CSF	• MCP-1
• HB-EGF	• MIP-1a
• PDGF-AA	• PIGF
• TGF-beta 1	• Serpin-B5
• Thrombospondin-2	• VEGF
• uPA	
• Vasohibin	

O15 Safety, tolerability, and effectiveness of anticoagulation and antiplatelet therapy in hereditary hemorrhagic telangiectasia: a multicenter study

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Objective: Antithrombotic therapy (anticoagulation and antiplatelet therapy) is frequently needed in patients with HHT, but data guiding its use is limited.

Methods: We evaluated outcomes in a 5-hospital observational cohort study of adults with HHT receiving antithrombotic therapy.

Results: 119 patients with 187 discrete antithrombotic therapy episodes were included. Treatment characteristics by patient and episode are given in Table 1 and Table 2. 59 patients (50%) prematurely discontinued and/or dose-reduced therapy (including 52 patients [44%] who discontinued) due to worsening bleeding. Initiation at reduced dose-intensity had a similar premature discontinuation rate (49%) as initiation at standard dose-intensity (43%). Difficulty receiving indicated therapy may have resulted in increased thromboembolic recurrence (20 patients, 17%). In a multivariable logistic model, a history of gastrointestinal bleeding was associated with 3.25-fold odds of discontinuation ($P = 0.001$, Fig. 1). Hemoglobin was significantly lower, and need for intravenous iron and RBC transfusion significantly higher, in the 3 months after antithrombotic therapy initiation versus the 3 months before (**Table 3**); ED visits and hospital admissions due to bleeding also increased. Rates of dose-reduction and/or premature discontinuation were similar regardless of anticoagulant class (warfarin, 46%; heparin- based, 48%; DOAC, 44%) or with multiple simultaneous agents (44%) but slightly lower with single-agent antiplatelet therapy (37%), **Table 4**.

Conclusions: Antithrombotic therapy remains challenging in HHT, resulting in objectively higher morbidity and healthcare utilization from worsened bleeding. Discontinuation rates approached 50% regardless of dose-intensity at initiation or type of antithrombotic agent used and were higher in patients with a history of gastrointestinal bleeding.

O16 Molecular Mechanisms in HHT

Vascular defects associated with hereditary haemorrhagic telangiectasia revealed in patient-derived isogenic iPSCs in 3D vessels-on-chip.

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Objective: Common anti-angiogenic and anti-inflammatory strategies (anti-VEGF, thalidomide) are used to treat patients with Hereditary Haemorrhagic Telangiectasia (HHT). However, some HHT patients do not respond at all to the treatment, others only transiently, as also observed in patients with other vascular conditions who do not always respond to anti-angiogenic therapy. Therefore, a preclinical human model that utilizes cells from HHT patients is needed.

Methods: Previously, we developed a multi-cell type 3D vessel-on-chip (VoC) model based entirely on human induced pluripotent stem cells (hiPSCs) (Vila Cuenca et al., SCR 2021). We have demonstrated that this 3D VoC model can capture vessel wall complexity and model endothelial-pericyte cell interactions. Here, we generated induced pluripotent stem cells (hiPSC) from a rare mosaic HHT1 patient with tissues containing both mutant ($ENG^{c.1678C>T}$) and normal cells, enabling derivation of isogenic diseased and healthy hiPSCs respectively. We showed reduced ENG expression in HHT1-endothelial cells (HHT1-hiPSC-ECs), reflecting haploinsufficiency. $HHT1^{c.1678C>T}$-hiPSC-ECs and the healthy isogenic control behaved similarly in 2D culture, forming functionally indistinguishable vascular networks.

Results: However, when grown in 3D organ-on-chip devices under microfluidic flow, lumenized vessels formed in which defective vascular organization was evident: interaction between inner endothelial cells (ECs) and surrounding pericytes was decreased and there was evidence for vascular leakage.

Conclusion: We are now at the stage when a cohort of HHT1 and HHT2 isogenic iPSC lines generated previously in our group can be tested in the 3D VoC model, and we are also working on the optimization of the throughput of the system for the drug screening.

O17 A cell resolution atlas of the human cerebrovasculature reveals angiogenic and inflammatory cell programs with arteriovenous malformations

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Objective: Cellular dysfunction results in cerebrovascular diseases, a leading cause of death and disability. However, we lack a comprehensive atlas of cerebrovascular cells in the human brain to better understand disease mechanisms and therapeutic strategies.

Methods: To provide a human cerebrovascular cell atlas, we used single-cell mRNA sequencing (scRNAseq) using dissociated vascular cells isolated from the adult human brain and arteriovenous malformations (AVMs). Joint comparative analyses between scRNAseq datasets profiled patterns of aberrant gene expression in AVMs and to resolve cell states enriched in AVMs that bled.

Results: By performing scRNA-seq on 181,388 individual cells, we identified > 40 vascular or neighboring cell states from the human cerebrovasculature and AVMs. We identified an expanded diversity of endothelial and perivascular cells in humans. In AVMs, there was a loss of normal arteriovenous molecular zonation among endothelial cells characterized by the emergence of a distinct cell state with heightened angiogenic potential and immune cell cross-talk spatially confined to the AVM nidus. We characterized the cellular ontology of the cerebrovascularly derived immune cell response and identified infiltration of distinct immune cell states, such as

GPNMB + monocytes, which deplete stabilizing smooth muscle cells in AVMs that bled.

Conclusion: Our single-cell atlas highlights the heterogeneity underlying cell function and interaction in the human cerebrovasculature and defines molecular and cellular perturbations in arteriovenous malformations, a leading cause of stroke in young people. The identified interplay between vascular and immune cells may aid the development of therapeutics targeting angiogenic and inflammatory programs in vascular malformations.

O18 Mutation of platelet-derived growth factor receptor β causes cerebrovascular malformation and enhances brain arteriovenous malformation severity in mice

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Objective: Reduction of pericytes is correlate with brain arteriovenous malformation (bAVM) hemorrhage. The platelet-derived growth factor B and its receptor β (PDGF- B/PDGFRβ) play important roles in regulating pericyte recruitment during angiogenesis. We **hypothesize** that mutation of PDGFRβ causes cerebrovascular malformation and enhances bAVM severity in *endoglin* (*Eng*) deficient mice.
Methods: Three mouse models were used: (1) *Pdgfrβ* F7 (F7) mice that have mutations disrupting Pdgfrβ signaling, (2) *Pdgfb*-icreER;*En*$^{f/f}$ mice that have *Pdgfb* promoter driving, tamoxifen inducible cre expression in endothelial cells and an floxed *Eng* gene; and (3) *Pdgfb*-icreER;*Eng*$^{f/f}$;F7$^{+/-}$ mice. Brain angiogenesis was induced by intra-brain injection of an adeno-associated viral vector expressing vascular endothelial growth factor (AAV- VEGF). Brain AVMs were induced in *Pdgfb*-icreER;*Eng*$^{f/f}$ and *Pdgfb*-icreER;*Eng*$^{f/f}$;F7 mice by tamoxifen induced endothelial *Eng* deletion and intra-brain AAV-VEGF injection. Brain AVM phenotypes were analyzed 8-weeks after model induction by latex vascular cast to detect arteriovenous shunts, immunostaining and Prussian blue staining to quantify dysplasia vessels and hemorrhage.
Results: Compared to WT mice, F7$^{+/-}$ and F7$^{+/+}$ mice have more dysplastic vessels and fewer vascular pericyte before and after AAV-VEGF injection. F7$^{+/-}$ and F7$^{+/+}$ mice showed minor hemorrhage on the AAV-VEGF injection sites and arteriovenous shunts in 40% F7$^{+/-}$ and 86% of F7$^{+/+}$ mice. *Pdgfb*-icreER;*Eng*$^{f/f}$ mice showed dysplastic vessels and hemorrhage at AAV-VEGF injection sites and arteriovenous shunts in 100% of mice. Compared to *Pdgfb*-icreER;*Eng*$^{f/f}$ mice, *Pdgfb*-icreER;*Eng*$^{f/f}$;F7$^{+/-}$ had more dysplastic vessels.
Conclusion: F7 mutation cause AVM like structure in mouse brains and exacerbates bAVM phenotype in *Eng* mutant mice.

O19 Structural basis for biosynthesis of BMP9 and BMP10 in a monomeric form

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Objective: BMP9 and BMP10 activate the ALK1 pathway in endothelial cells (ECs), yet in some cell types they are secreted as monomers. In this study we investigated the structural basis for monomer formation and the signaling activity of monomer relative to dimer in ECs.

Method: proBMP9 and proBMP10 were expressed in expi293 cells and purified from the medium. Monomeric and dimeric BMP9 and BMP10 growth factor were isolated and were characterized using mass spectroscopy (MS), X-ray crystallography, and induction of pSmad1 in human umbilical vein ECs (HUVECS).

Results: proBMP9and proBMP10 were secreted as a mixture of monomers and dimers, but the dimer: monomer ratio was lower for proBMP9 compared to proBMP10. MS analysis showed that BMP9 and BMP10 monomers are cysteinylated and crystallographic analysis of BMP9 showed that attachment is through Cys^{73}. Crystallographic analysis of the BMP9 dimer showed that the inter-chain disulfide is radiation-sensitive. BMP10 monomers retained significant pSmad signaling activity, but their EC_{50} was reduced about 14-fold relative to BMP10 dimers.

Conclusion: X-ray structural studies showed that the interchain disulfide bond is stressed in BMP9, presumably due to a shift in the registration of monomers, and that formation of cysteinylated monomers is a consequence of this. The propensity of BMP9 and BMP10 to form monomers, and the reduced activity of the BMP10 monomer, may be relevant to the formation of the BMP9/10 heterodimer, which has been reported to be the dominant form of BMP9 and BMP10 in the blood.

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Disclosure: The authors have no competing financial interests.

O20 ALK1 heterozygosity is not sufficient for driving hht pathogenesis

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Objective: Heterozygous ALK1 mutations are responsible for nearly half HHT cases and few PAH cases. Here, we aimed to understand the impact of such mutations on the downstream BMP9/10-ALK1-Smad signaling pathway by studying the transcriptome of patient-derived endothelial cells.

Methods: Endothelial colony-forming cells (ECFC) and microvascular endothelial cells (HMVEC) carrying heterozygous loss-of-function ALK1 mutations were isolated from the cord blood of newborn HHT patients and the explanted lungs of PAH patients, respectively. RNA-sequencing was performed on each type of cells compared to control counterparts following an overnight stimulation with BMP9 or BMP10.
Results: In control ECFC, BMP9 and BMP10 stimulations induced around 1200 differentially expressed genes (DEGs). Interestingly, none were differentially regulated between BMP9 to BMP10 stimulation. Comparison of the transcriptome between control and patient ECFC showed very similar profiles at the basal level, and stimulation with BMP9/10 in patients induced a transcriptomic response highly similar to controls. Consistently, patient ECFC displayed a normal Smad response, which could not be explained by a compensation in cell-surface ALK1 level. Conversely, patient HMVEC revealed strong transcriptional deregulations compared with controls with >1600 DEGs at the basal level. Because our study involved two variables (genotype and BMP stimulation), we performed two-factor differential expression analysis and identified 49 genes with impaired BMP9 regulation in patient HMVEC but none in patient ECFC.
Conclusion: ALK1 heterozygosity does not seem sufficient for driving HHT pathogenesis, and the difference observed in patient pulmonary HMVEC could probably be attributed to second hits (mutation/inflammation) found in the sick lung microenvironment.

O21 Hemodynamics, Cell Biology, and Animal Models

An HHT-on-a-chip microphysiological model that recapitulates vascular lesions of patients

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Objective: In Hereditary Hemorrhagic Telangiectasia (HHT), mutations in endothelial-expressed genes such as *ACVRL1* (Alk1) drive vascular malformations (VM) including telangiectasias and arteriovenous shunts in tissues including liver, brain, and skin, and rupture of these aberrant vessels significantly compromises patient quality-of-life. There is currently no cure for HHT and efforts to develop such treatments are challenged by lack of available *in vivo* and *in vitro* models that completely mimic the microenvironment in which healthy and diseased blood vessels form in human HHT patients.
Methods: Here, we present a novel HHT-on-a-chip microfluidic model wherein primary human EC spontaneously self-organize into a perfused blood vessel network. Inclusion of stromal cells from brain (astrocytes, neurons) or liver (hepatocytes) produces microvasculature that exhibits specific characteristics of these respective tissues.
Results: Using this platform, we show that primary human EC engineered (via RNA silencing) to lack *ACVRL1* (Alk1) expression form aberrant blood vessel networks, including structures reminiscent of both telangiectasias and arteriovenous shunts typical of VM in human HHT. We also show compatibility of the HHT-on-a-chip platform with HHT patient-derived cells. Next, we determined that arteriovenous shunts are mosaic structures comprised of both Alk1-intact and Alk1-deficient EC, and that Alk1 is protective against malformations in growth- activated vessels. We also assessed whether the HHT-on-a-chip could detect potentially efficacious HHT drugs and found that VM are prevented following exposure to pazopanib.
Conclusions: Taken together, we describe a robust, scaleable, tissue-specific microphysiological disease model of HHT that will enable further studies into the pathophysiology of HHT as well as drug discovery and testing.
Disclosures: None.

O22 Altered cerebrovascular dynamics in endoglin deficient mice measured by functional ultrasound localization microscopy

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Objective: We have investigated how acute genetic deletion of *Endoglin* in endothelial cells impairs the regulation of cerebral blood flow (CBF) in adult mice.

Method: functional Ultrasound Localization Microscopy (fULM) was introduced to analyze the functional blood capillary response during task-evoked brain activity through the neurovascular coupling. In parallel, electrophysiology and confocal microscopy combined with chemical inhibitors/activators were used to decipher the mechanisms by which endoglin modulates mural cell functions and vasoreactivity along the arteriovenous axis.

Results: Depletion of endoglin had no effect on canonical vascular smooth muscle cells that cover arterioles or on pericytes that extend thin processes longitudinally along capillaries but strongly affected the attachment of Ensheathing (EP) and mesh (MP) pericytes to the endothelium. These cells are located at the pre-capillary arteriolar zone and regulate blood flow. EPs and MPs exhibited a reduced capacity to constrict blood vessels when electrically stimulated *ex vivo* in whole retina, defect that was rescued by exogenous treatment with active TGF-β1. Alk5 and Rho kinase inhibitors blocked the effects of TGF-β1. Finally, genetic deletion of *Endoglin* impaired neurovascular coupling in the barrel cortex of mice under whisker stimulation. Pharmacological treatment with SRI-011381, an orally active TGF-β1 signaling agonist rescued the vasoreactivity of the endothelium to changes in neural activity.

Conclusion: Defective TGF-β1 signaling in mural cells is responsible for the structural defects of the vessel walls in HHT1. Impaired CBF could be detected by fULM opening new avenue for the identification of ultrasound markers to detect microvascular dysfunctions in patients with HHT.

O23 BMP9 deletion induces vessel enlargement and arteriovenous malformations in multiple organs

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Objective: BMP9 and BMP10 are the two high affinity ligands of the ALK1 and endoglin receptors mutated in HHT. We have previously shown that loss of *Bmp9* leads to spontaneous liver fibrosis via capillarization of liver sinusoidal endothelial cells (LSEC) and kidney lesions. Here, we aimed to further characterize the vascular defects in

the kidney, to extend the analysis to other organs and to define the molecular mechanisms by which BMP9 controls endothelial quiescence.

Method: For this, we have studied the vascularization of different organs in adult *Bmp9*-KO mice in the 129/Ola strain by different microscopic approaches. In parallel, we have performed an RNAseq analysis of LSEC from WT and *Bmp9*-KO animals.

Results: We found that loss of BMP9 leads to vessel enlargement in the lungs, brain and kidney glomeruli. In the latter, vascular defects are associated with alteration of the podocytes. Interestingly, the loss of *Bmp9* led to spontaneous arteriovenous malformations (AVM) in the uterus, intestine and liver. RNAseq analysis of LSEC in adult WT versus *Bmp9*-KO mice identified over 2000 differentially expressed genes. Gene ontology analysis showed that *Bmp9* deletion led to a decrease in LSEC differentiation markers, in BMP and Notch signaling as well as an activation of the cell cycle.

Conclusion: Altogether, these results demonstrate that BMP9 plays an important role in vascular quiescence of many organs by regulating endothelial differentiation markers. It also demonstrates that loss of *Bmp9* is sufficient to induce spontaneous AVM, supporting a key role for BMP9 in the pathogenesis of HHT.

O24 Local conditional induction of brain arteriovenous malformations in a HHT mouse model

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Objective: Current mouse models of familial brain arteriovenous malformations (AVMs) have limitations in long-term survival. These drawbacks are mainly attributed to systemic and ubiquitous genetic recombinations with development of AVMs in peripheral organs that result in hemorrhagic conditions. The goal of this project is to develop a novel mouse model with local, conditional induction of brain AVMs.

Methods: Transgenic mice with ubiquitous CreER expression were used (ROSA26CreER;Alk1f/f; Alk1-iKO). 4-hydroxytamoxifen (4-OHTM) was stereotactically delivered into the striatum, parietal cortex, or cerebellum of neonatal mice at postnatal day 1. Mice were evaluated for brain AVMs with systemic latex dye perfusion and 3D time-of-flight magnetic resonance angiography.

Results: *Alk1*-iKO mice injected stereotactically with 4-OHTM developed brain AVMs with 68% (21/31) frequency in the striatum, 72% (13/18) in the parietal cortex, and 44% (4/9) in the cerebellum. Brain AVMs formed in or near the injection site with 95% accuracy (36/38). A subset of mice (8%, [3/38]) presented with a communicating hydrocephalus from CSF malabsorption. The formation of AVMs in these *Alk1*-iKO mice was restricted to the brain, without AVMs developing in peripheral organs (n = 38). The hemoglobin levels were not significantly different between mutant and control *Alk1*-iKO mice after stereotactic, intracerebral 4-OHTM injection ($p = 0.27$). The 4-week mortality was 5% (2/38). Longitudinally monitored mice demonstrated good survival at 3 months of age (86%, [6/7]).

Conclusion: We present the first experimental mouse model with local, CreER-mediated induction of brain AVMs. The model is advantageous in generating brain AVMs with high efficiency, along with an improved long-term survival and reduced early lethality of mice. Collectively, these features may serve as a framework to accelerate the ongoing investigations of brain AVM pathogenesis, rupture, and preclinical testing of novel therapeutics.

O25 Different cardiovascular and pulmonary phenotypes for single- and double-knock-out mice deficient in BMP9 and BMP10

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Objective: BMP9 and BMP10 are the ligands of the receptor ALK1, expressed on endothelial cells. Mutations in this pathway are associated with Hereditary Hemorrhagic Telangiectasia and Pulmonary Arterial Hypertension. *BMP9* and *BMP10* mutations have been reported but their roles in the pathogenesis of these diseases remain unclear.

Methods: We used C57BL/6 single- and double-knockout mice for *Bmp9* (constitutive) and/or *Bmp10* (tamoxifen inducible) to study the roles of BMP9 and BMP10 in angiogenesis and lymphangiogenesis in newborn pups, and in cardiovascular homeostasis and pulmonary hypertension in adult mice.

Results: Single-KO mice presented a lymphatic phenotype but no obvious blood vessel defect. Combined deficiency in *Bmp9* and *Bmp10* led to aberrant postnatal angiogenesis. In adult mice it resulted in a decrease in peripheral vascular resistance and blood pressure and to the progressive development of high-output heart failure and lung inflammation. We next challenged these adult mice to chronic hypoxia to induce pulmonary hypertension. Although deletion of *Bmp9* attenuated the muscularization of pulmonary arterioles induced by hypoxia, we observed no differences in *Bmp10*-cKO mice. Consistent with these results, endothelin-1 levels were reduced in *Bmp9* deficient mice but not *Bmp10*-cKO mice. Furthermore, the effects of BMP9 on vasoconstriction were inhibited by an endothelin receptor antagonist, in a chick chorioallantoic membrane assay.

Conclusion: Our data show redundant roles for BMP9 and BMP10 in cardiovascular homeostasis under normoxic conditions (only combined deletion of *Bmp9* and *Bmp10* was associated with severe defects) but highlight specific roles under chronic hypoxic conditions or in lymphangiogenesis.

BMP9/10 Signaling in HHT

O26 ALK1 is critical for maintenance of pulmonary and liver endothelium integrity

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Objective: HHT symptoms worsen with age with total penetrance by 60-year old, suggesting that ALK1 signaling is critical in the adult endothelium. Here we aimed to characterize the roles of ALK1 in the adult endothelium.

Method: In vitro, we used siRNA against *ACVRL1* in cultured endothelial cells. In vivo, we used inducible *Acvrl1* endothelial knockout (*Alk1*^{iECKO}) mice, focusing on pulmonary and hepatic vasculatures as these organs are widely affected in HHT patients.

Results: We found that endothelial ALK1 deletion in adult mice is lethal within 8 days. Mice present severe pulmonary and gastrointestinal hemorrhages. This phenotype could be related to defects in expression of integrin critical in endothelial adhesion on the basal lamina and of genes involved in endothelial junctions, such as ZO1, ZO2, VE-Cadherin. In the liver, loss of sinusoidal endothelial cell identity occurs, as seen notably by loss of endothelial fenestration, concomitant activation of stellate cells and disorganized hepatocytes. These observations show that loss of endothelial ALK1 leads to phenotypes beyond endothelial cells. 8 days after *Alk1* deletion, these mice exhibit either a severe vasodilation or systemic arteriovenous shunts as fluorescent beads injected in the systemic circulation could reach the lungs. Lastly, to unravel the molecular consequences of endothelial *Alk1* loss in adult mice, we performed single cell RNA sequencing on liver and lung cell suspensions from *Alk1*^{iECKO} mice, which is currently under analysis.

Conclusion: Deletion of endothelial ALK1 in adult leads to severe pulmonary and hepatic phenotypes demonstrating a critical role of ALK1 in the adult endothelium.

O27 PTPN14 interacts with SMAD4 to modify BMP9 signaling in endothelial cells

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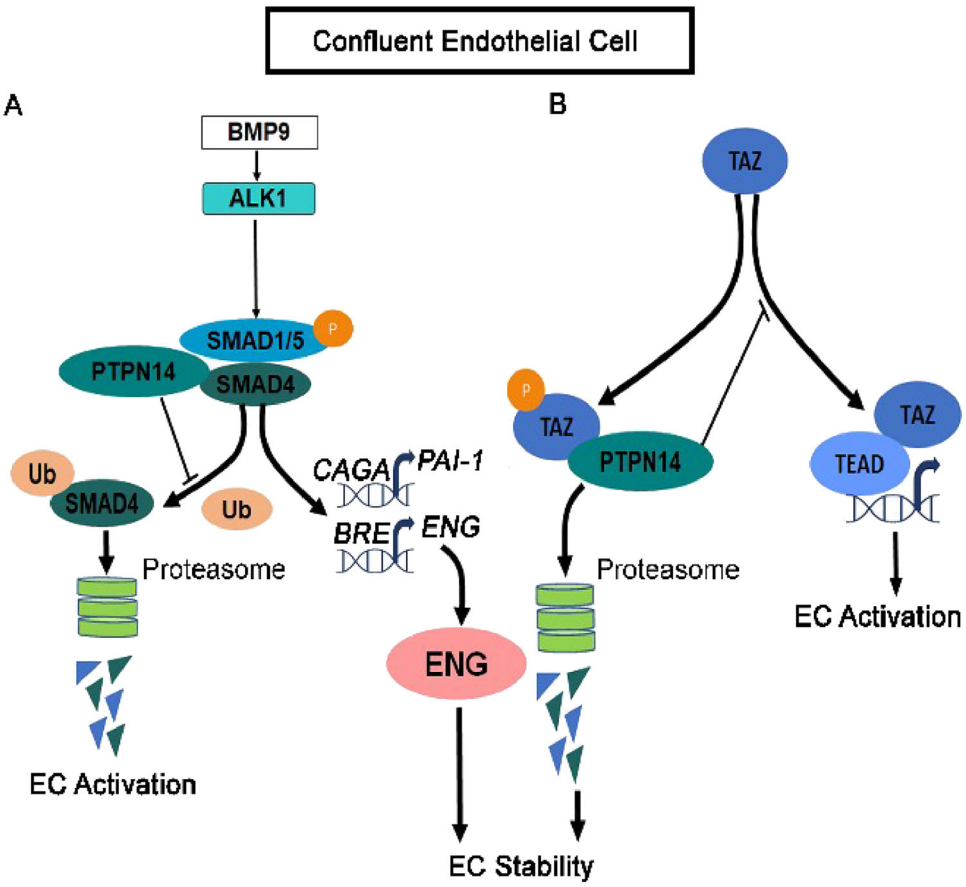
Objective: Telangiectases occur in most HHT patients, and pulmonary, visceral, or cerebral arteriovenous malformations (AVMs) occur in only 20–50%. How AVMs develop and why some patients suffer more severe sequelae are still largely unknown. We hypothesized that PTPN14, a genetic modifier of pulmonary AVM, modulates TGFβ/BMP signaling.

Methods: Gene expression correlation analysis was undertaken by transcriptomic analysis of a panel of lung RNAs isolated from genetically divergent mice, generated by interbreeding two different mouse species, *Mus spretus* and *Mus musculus*, in an F1 backcross to *M. musculus*. In vitro analysis of PTPN14 action on TGFβ/BMP signaling was undertaken in primary HUAECs at high cell density.

Results: Here we show that the HHT genetic modifier, protein tyrosine phosphatase non- receptor, type 14 (PTPN14) modulates the BMP9 signaling pathway through effects on SMAD4. First, the *PTPN14* SNP, *rs2936018*, which is associated with the presence of lung AVMs in HHT, is a cis-eQTL for *PTPN14* expression, with a lower vascular expression of the pulmonary AVM at-risk allele in human vascular tissue. Second: gene expression network analysis of



mouse lung tissue reveals that *Ptpn14* is tightly correlated with *Acvrl1, Eng, Flt1, Ece1, Sash1, and Mapk3k*. At the third level, in primary human endothelial cells, we demonstrate physical interaction between endogenous PTPN14 and SMAD4 proteins that stabilizes SMADs and enhances BMP9 signaling.

Conclusion: PTPN14 suppresses ubiquitylation and turnover of SMAD4, enhancing SMAD4 transcriptional readout. This is the first report that PTPN14 binds and stabilizes SMAD4 and may therefore influence HHT clinical outcomes through this activity.

Graphical abstract: In confluent HUAECS: PTPN14 binds and protects SMAD4 from ubiquitination**.** PTPN14 stabilizes SMAD4 and enhances SMAD4 dependent transcription including *ENG*. PTPN14 maintains endothelial quiescence through SMAD4 stabilization and TAZ degradation. PTPN14-dependent SMAD4 stabilization is independent of its effects on TAZ.

O28 Thresholds of endoglin expression in endothelial cells explains vascular etiology in hereditary hemorrhagic telangiectasia type 1

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Objective: Our aim was to correlate endoglin expression levels in blood vessels and the general prevalence of clinical manifestations in selective organs in HHT1.

Method: Endoglin mRNA and protein expression levels were examined in blood vessels of multiple organs in mice and/or in humans. In parallel, we have investigated how endothelial cells having different tissue of origin responded to endoglin thresholds measuring Akt and smad1/5 phosphorylation following Vascular Endothelial Growth Factor (VEGF) and Bone Morphogenetic Protein 9 (BMP9) stimulation, respectively.

Results: We found a positive correlation between low basal levels of endoglin and the general prevalence of clinical manifestations in selective organs. Endoglin was found particularly low in skin, the earliest site of vascular lesions in HHT1 and even undetectable in arteries and capillaries of heterozygous endoglin mice. Endoglin levels did not appear to be associated with organ specific vascular functions. Instead, our data revealed a critical endoglin threshold compatible with the haploinsufficiency model, below which endothelial cells independent of their tissue of origin exhibited abnormal responses to VEGF.

Conclusion: Our findings explain why only some but not all vascular beds are affected as the causal gene mutations are present in vasculature throughout the body and support the development of drugs promoting endoglin expression as potentially protective.

O29 Loss of paracrine PDGFB-PDGFRß signaling contributes to AVM pathology

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Objective: In the present study we investigated the role of flow induced PDGFB signaling in maintenance of EC quiescence and vascular homeostasis.

Methods: We generated tamoxifen-inducible, endothelial cell (EC) specific *Pdgfb depleted mouse line (Pdgfb*$^{i\Delta EC}$) for our in vivo experiments. The in vitro experiments (q-PCR, immune blotting, western blotting and flow experiments) were performed in HUVECs using the siRNA strategies and mouse lung EC isolated from different genotypes.

Results: In accordance with our previous findings that loss of *Smad4* leads to decreased pericyte coverage within the AVMs, we have now identified that the remaining pericytes have lost the mural Pdgfrß expression. Moreover, in vitro, we found that *PDGFB* mRNA was synergistically upregulated by BMP9 and Flow and this effect was SMAD4 dependent. These results emphasize that SMAD4 signaling is required for flow induced paracrine PDGFB stimulation of pericyte recruitment. To reveal if impaired EC-pericyte crosstalk contributes to AVM formation, we depleted *Pdgfb* in EC and interestingly we found that decreased neonatal *Pdgfb* leads to loss of mural coverage and AVM formation in 50% of retinas. Further analysis found that depletion of Pdgfb in EC disrupted artery-vein identity and EC polarity in arteries and veins. Moreover, ECs were hyper-responsive to low flow in the absence of pdgfb in vitro. RNA sequence data revealed that PI3K pathway was activated and PI3K signaling inhibition could partially prevent AVM formation and normalizes vessel diameters.

Conclusion: Taken together these findings suggest that SMAD4-flow synergy modulate the paracrine PDGFB signaling to maintain EC quiescence.

Diagnostics and clinical imaging

O30 Telangiectatic pulmonary arteriovenous malformations in hereditary hemorrhagic telangiectasia

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Objective: Currently, three subtypes of pulmonary arteriovenous malformations (PAVMs) are defined: simple, complex, and diffuse. However, ground glass densities in Hereditary Hemorrhagic Telangiectasia (HHT) patients have been hypothesized to represent a subtype of PAVM – so called telangiectatic PAVM—that have thus been far

poorly defined. We aim to describe the demographics, clinical features, and imaging characteristics of telangiectatic PAVMs in HHT.

Methods: We reviewed the clinical records and CT chest scans of 50 consecutive patients from two HHT Centers who had definite or suspected HHT. Patients with diffuse PAVM were excluded from analysis. All non-embolized lesions > = 3 mm in diameter were classified as having > 70% ground glass density, > 70% vascular density, or mixed density. Previously embolized PAVM were categorized as to whether they were closed or still perfused.

Results: Of 100 patients, 36% had lesions of ground glass density and 64% did not. Of 214 lesions analyzed, 79 (37%) were ground glass, 104 (49%) were vascular, and 31 (14%) were mixed density [Table]. Among 10 patients who had ground glass lesions but no vascular lesions, mild to moderate pulmonary shunt was typically observed on contrast echocardiography, suggesting that ground glass lesions are likely to be true PAVMs – so called telangiectatic PAVMs.

Conclusion: These findings suggest a distinct subtype of PAVMs, telangiectatic PAVMs, that have unique imaging characteristics and represent pulmonary shunts as seen on contrast echocardiography. Further study is needed to clarify if these lesions have clinical consequences similar to classic vascular lesions and for progression over time.

Table Lesion Characteristics.

Total lesions (not including treated lesions)	Ground glass (n = 79)	Vascular (n = 104)	Mixed (n = 31)	Kruskal–Wallis p-value
Diameter (mm)	7.2 (3.3)	6.5 (4.4)	7.0 (2.4)	0.0018
Mean (SD)				
Feeding artery diameter (mm)	1.4 (0.4)	2.0 (0.9)	1.6 (0.3)	0.0001
Draining vein diameter (mm)	1.5 (0.5)	2.0 (1.1)	1.5 (0.38)	0.0011
Total lesions on contrast enhanced scans (n = 123)	**Ground glass**			
(n = 46)	**Vascular**			
(n = 61)	**Mixed**			
	(n = 16)			
- Lesion HU	-550.5	-6	-393	0.0001
	(-591, -486)	(-93, 151)	(-493.5, -272.5)	
Total lesions on unenhanced scans (n = 91)	**Ground glass**			
(n = 33)	**Vascular**			
(n = 43)	**Mixed**			
	(n = 15)			
- Lesion HU	-583.5	-161	-384	0.0001
	(-680.5, -503)	(-262, -90)	(-501, -166)	

HU = Hounsfield units. Diameter data are presented as mean (SD) and HU are presented as median (interquartile range).

O31 Ultra-low dose chest CT for diagnosis of pulmonary arteriovenous malformation diagnosis in hereditary hemorrhagic telangiectasia

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Objective: To compare the radiation exposure, image quality and the diagnostic value of an ultra-low dose (ULD) chest CT for diagnosing the pulmonary arteriovenous malformation (PAVM) in hereditary hemorrhagic telangiectasia (HHT), compared a reference low-dose (LD) protocol.

Methods: In this prospective board-approved study with informed consent, 45 consecutive patients (67% women, mean (SD) age 42 (16)-year-old) with HHT referred to a reference center for a screening and/or follow-up chest CT were prospectively included from December 2020 to January 2022. Patients underwent 2 consecutive non-contrast chest CT, i.e., an ULD protocol (100 kVp or 80 kVp, 10 mAs) and a reference LD protocol (140 kVp, 10 mAs). Objective image noise measured in carina was compared. Pathologic findings, overall image quality and diagnostic confidence were on a 4-Likert scale (1 = insufficient, 4 = excellent).

Results: 35 PAVM with a feeding artery larger than 2.5 mm diameter were found with LD images versus 39 with ULD images. Sensitivity, specificity, predictive positive value and predictive negative value were of 100%, 86.7%, 89.8% and 100%, respectively. Scores of diagnostic confidence were of 3.0 ± 0.6 vs 3.1 ± 0.6 with ULD and LD images, respectively (*ns*). Scores of overall image quality were of 3.0 ± 0.4 vs 3.1 ± 0.4 with ULD and LD images, respectively (*ns*). Effective radiation dose decreased significantly by 91% in the ULD protocol, without significant difference of image noise in the carina (17.4 HU [15.2–19.6] for ULD and 16.7 HU [13.8–18.4]).

Conclusion: AN ultra-low dose chest CT enabled a sensitivity of 100% and a specificity of 86.7% for PAVM with a feeding artery larger than 2.5 mm diameter, allowing for a 91% dose savings in comparison to a reference low dose protocol.

O32 Phase contrast flow quantification of liver vascular malformations in patients with hereditary hemorrhagic telangiectasia (HHT)

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Objective: Liver arteriovenous malformations (AVMs) are common but often asymptomatic in HHT. MRI with dynamic gadolinium-enhanced T1-weighted sequences is useful for identifying the dominant shunt, which may be either arteriosystemic or arterioportal. Quantification of hepatic blood flow using phase-contrast (PC) MRI sequences may provide an additional metric by which to grade the severity of hepatic involvement.

Methods: Retrospective analysis of 36 patients referred for MRI. 7 patients had exams before and after initiation of anti-angiogenic therapy. 1 exam was excluded for technical reasons. MRI of the liver was performed at 3 T on 6 patients with liver AVMs and a diagnosis of HHT. 2D phase contrast (PC) MRI was performed to quantify flow through the proximal abdominal aorta and hepatic artery (HA). Flow images were processed using clinical software.

Results: All 6 patients had evidence of shunting on liver MRI. Maximum hepatic artery diameters ranged from 10 to 14 mm prior to therapy, and 9 to 11 mm following therapy. Flow volumes in the HA ranged from 2510 to 5142 mL/min prior to initiation of therapy, and 960 to 3550 mL/min following therapy. HA flow volumes measured prior to therapy and at most recent exam decreased in each of the six patients.

Conclusion: PC flow volumes in the HA are elevated in patients with HHT and hepatic AVMs. Quantitative assessment of blood flow to the liver may serve as a useful indicator of the degree of vascular shunting in patients with HHT and has a potential role for monitoring antiangiogenic therapy.

Figure: MR flow measurements in a 51-year-old woman with HHT. Magnitude (a) and phase sensitive (b) sagittal oblique MR images perpendicular to the dilated hepatic artery.

O33 Evolution of pulmonary arteriovenous malformations: the role of contrast echocardiography

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Objective: Pulmonary arteriovenous malformations (PAVMs) are direct connections between the pulmonary artery and the pulmonary vein, mostly associated with hereditary haemorrhagic telangiectasia (HHT). PAVMs can lead to severe neurological complications – such as stroke and brain abscess. Therefore, screening for PAVMs using transthoracic contrast echocardiography (TTCE) is recommended, including a re-screening interval of 5 years. We hypothesized, that the interval for re-screening in patients without a pulmonary right-to-left shunt (RLS) might be extended up to ten years.

Methods: Adult HHT patients with five- and/ or ten-year follow-up TTCE were included. Patients who underwent an embolisation in the past or at baseline were excluded. The RLS grades and presence of a treatable PAVM were compared to baseline.

Results: In total, 387 patients (median age 45 years (IQR 33–54), 56% female) involving five- and ten-year follow up data in respectively 363 and 166 patients were included. None of the patients (n = 148) without a pulmonary RLS at baseline developed a treatable PAVM after five and ten years. Of the patients with a pulmonary RLS at baseline, 20 (9%) and 3 (3%) developed a treatable PAVM at five- and ten-year follow-up respectively. In the majority of patients, the RLS grade remained stable over time.

Conclusion: On the basis of the results of this study, we believe that the rescreening-interval for HHT patients without a pulmonary RLS at initial screening can be extended to ten years. Those with a pulmonary RLS should be rescreened every five years because treatable PAVMs can evolve.

O34 Comparison of graded transthoracic contrast echocardiography and high-resolution chest CT for pulmonary arteriovenous malformation follow-up in the early post-embolization period

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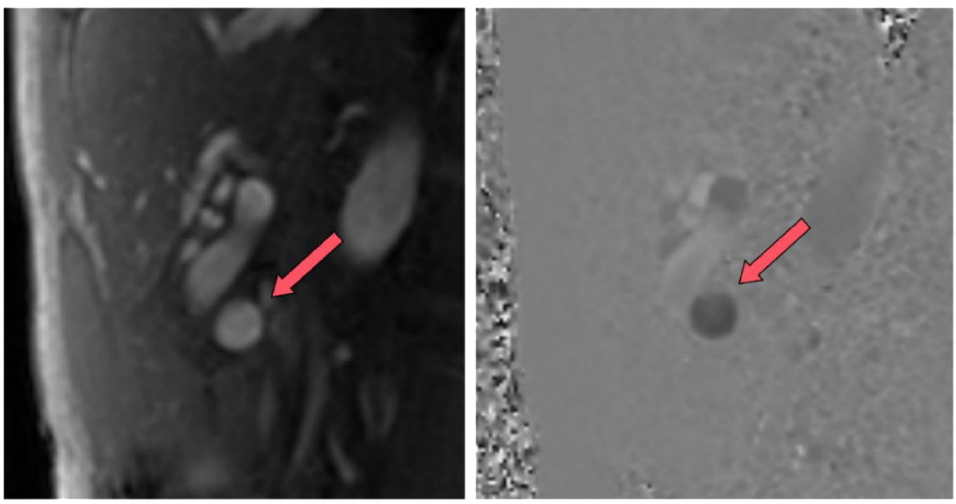

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Objective: Surveillance high-resolution chest CT (HRCT) is the gold-standard for identifying post-embolotherapy pulmonary arteriovenous malformations (PAVMs) requiring retreatment. A prior study demonstrated that graded transthoracic contrast echocardiography (TTCE) can similarly identify PAVMS requiring retreatment, offering a radiation-free alternative. However, most patients included in that study were ≥ 5-years post-embolotherapy. This study sought to better evaluate the ability of graded TTCE to predict the need for repeat embolotherapy in the early post-treatment period, comparing concurrent HRCT and graded TTCE at the six-month follow-up visit.

Methods: Thirty-five patients (6M;29F, mean age 56y, range 27-78y) presenting for six-month post-embolotherapy follow-up between 2017-2021 with concurrent HRCT and graded TTCE were analyzed retrospectively. PAVMs with a feeding artery > 2 mm were considered treatable.

Results: Ninety-four percent of patients (33/35) did not have PAVMs requiring retreatment on HRCT. TTCE was negative (grade 0) in 34% of patients (n=12). Of patients with a positive TTCE (23/35, 66%), 83% had a grade 1 shunt, 13% a grade 2 shunt, and 4% a grade 3 shunt. No patients with a grade 0 or 1 shunt had a treatable PAVM on HRCT. Of the two patients with treatable PAVMs, one had a grade 2 shunt and one had a grade 3 shunt. TTCE grade was significantly associated with the presence of a treatable PAVM on HRCT ($P \leq 0.01$).

Conclusions: Graded TTCE accurately predicts the need for repeat embolotherapy in the early post-embolotherapy period, suggesting graded TTCE can be used as primary surveillance, with HRCT reserved for patients with grade 2 shunt and above.

O35 Long-term systemic collateral supply after embolization of pulmonary arteriovenous malformations in children with hereditary hemorrhagic telangiectasia

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Objectives: To evaluate the frequency of systemic arterial collateral supply in patients with hereditary hemorrhagic telangiectasia (HHT) after embolization of pulmonary arteriovenous malformations (PAVMs) during childhood.

Methods: 27 HHT patients (16% women, age at first embolotherapy: 11.1 (± 4.6) [0.6;16] year-old) from two French centers of reference were retrospectively included.

Clinical and imaging data were reviewed. Imaging data consisted in PAVM characteristics before embolization and identification of collateral supply before embolization and at follow-up on an enhanced chest CT scan.

Results: Follow-up period was 8.2 (± 5.7) years. 10 (37%) patients were asymptomatic. A total of 73 PAVMs were treated with a mean number per patient of 2.7 (± 1.7), corresponding to a mean number of transcatheter embolization of 1.6 (± 3.1). A majority of multiple (51.8%) and simple (60.3%) PAVM types was noted. A high proportion of collateral supply involvement was found in 43.7% of the patients, with 37.5% in asymptomatic patients and 50% in symptomatic patients. One episode of hemoptysis in a patient with a diffuse PAVM type was noted. No other complication was noted.

Conclusions: Collateral supply after embolization of PAVM in HHT is involved in almost fifty percent of the cases, from which risk factors and risk of hemoptysis are still unknown.

O36 Telangiectasia frequency by age and genotype in hereditary hemorrhagic telangiectasia

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Objective: Telangiectasias increase with age but the rate of increase is unknown.

Method: We performed a retrospective review of 184 consecutive patients (age 9.1–86.6 years) with suspected or confirmed HHT, including a complete quantitative telangiectasia exam of the hands and oral cavity.

Results: The family mutation was known for 87.6% (ENG-30.8%, ACVRL1-55.7%, SMAD4-1.1%). The frequency of telangiectasia was expressed as a function of age. Linear regression was used to estimate the age-related change for each region. Total telangiectasia increased by 1.4/year starting at age 21.2 years with no significant difference between ENG (1.3/year starting at age 19.3) and ACVRL1 (1.5/year starting at age 22.7). Oral telangiectasia increased by 0.45/year starting at age 14.3 with no significant difference between ENG (0.58/year starting at age 15.3) and ACVRL1 (0.37/year starting at age 11.6). Hand telangiectasia increased by 1.0/year starting at age 24.2, with a greater rate for ACVRL1 (1.2/year starting at age 26.3) compared to ENG (0.7/year starting at age 22.9, $P = 0.0162$). Only 6 patients had no telangiectasia, none with definite clinical evidence of HHT. Genetic testing was negative for 3 (ruling out HHT for one 22-year-old, unknown family mutation in 2), not done in 1, and confirms HHT in 2 patients with known family history (18-year-old with epistaxis, asymptomatic 27-year-old).

Conclusions: Telangiectasia increase with age by 1.4/year starting at age 21.2 (1.0/year hands, 0.45/year oral). A greater prevalence of hand telangiectasia by age was observed for ACVRL1 in comparison to ENG.

O37 Influence of pregnancy on pulmonary arteriovenous malformations (PAVMs) in HHT

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Objective: Pregnancy in HHT is considered at risk: the most frequent complications for women with HHT during pregnancy are related to PAVMs (haemothorax, hemoptysis, hypoxemia and stroke).

The aim of this retrospective study is to evaluate PAVM size and number on chest CT before and after pregnancy.

Method: We retrospectively studied all CT of our HHT female patients before or during and after pregnancy between October 2009 and April 2022. Women without CT or contrast echocardiography after pregnancy were excluded.

Results: 53 pregnancies occured in 32 HHT women. 30 women (20 with ENG mutation and 10 with ACVLR1 mutation) were followed for HHT in our center and had CT scan before and after pregnancy. Among them, 12/30 had been previously treated with pulmonary embolization for PAVMs. 2 women were not diagnosed with HHT and referred for PAVMs complications occuring during or just after pregnancy. 1 women needed embolization procedure during pregnancy and 8 women after pregnancy: among them 4/ 8 had been treated before pregnancy with embolization, 6/8 of them had CT demonstrating the increase of small PAVMs with feeding arteries > 3 mm diameter, 1/8 had a reperfused PAVM, and one was diagnosed with multiple and large PAVMs inducing severe hypoxemia just after pregnancy and was embolized in our center. 3 women had a stroke related to PAVM.

Conclusion: Our study demonstrates that pregnancy is associated with the increase in size of small PAVMs (6/30) more than reperfusion (1/30) of PAVM.

O38 Validation of a novel simplified nasal endoscopy grading system for HHT patients

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Objective: Nasal endoscopy is the cornerstone of evaluation of HHT patients with epistaxis. Development of a validated and well accepted grading system for endoscopic findings in these patients is crucial for both clinical and research applications. In this study we aimed to validate a novel simplified nasal endoscopic grading system in HHT patients.

Methods: An analysis of the validity of a novel nasal endoscopy grading system during a prospective randomized control trial. The grading was performed by an experienced rhinologist (ES) blinded to the patients' clinical data. The new grading system included three grades- mild (few punctate lesions), moderate (multiple telangiectasias/ large arteriovenous malformations involving the anterior nasal septum) and severe (diffuse involvement of the nasal mucosa with telangiectasias). Patients were examined during three different time points of the study and their grading was further correlated with Epistaxis Severity Score (ESS), quality of life (QoL) and hemoglobin (Hb) levels.

Results: 54 nasal endoscopy scores in 20 patients were available for analysis. A significant association of the endoscopic grading system with ESS ($p < 0.001$), QoL ($p < 0.001$) Hb levels ($p = 0.007$) was observed. Significantly worse ESS, QoL and Hb levels were observed incrementally with a more severe nasal endoscopy grade.

Conclusions: Our novel nasal endoscopy grading system has demonstrated promising results and significant association with crucial clinical variables including ESS, QoL and Hb levels. Further validation of this novel grading system in larger cohorts is needed.

O39 Right atrial dilation assessed on transthoracic echocardiography is associated with the presence of hepatic arteriovenous malformations in hereditary hemorrhagic telangiectasia

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Objective: Hepatic arteriovenous malformations are a well-described manifestation of HHT and can result in high-output cardiac failure and severe liver disease. Routine screening for hepatic AVMs in HHT patients remains controversial. This study evaluated the utility of serum NT-ProBNP and echocardiographic parameters as potential predictors of hepatic AVMs.

Methods: HHT patients treated at a center of excellence were analyzed retrospectively in an observational cohort study. Multivariable logistic models assessed association of echocardiographic characteristics and NT-ProBNP with the presence of imaging-proven liver AVMs. All models included liver AVMs as the dependent variable; model 1 included NT-ProBNP within six months of imaging as the primary independent variable with right atrial dilation, age, and sex as covariates. Model 2 included right atrial dilation as the primary independent variable with NT-proBNP, age, and sex as covariates. Model 3 included elevated tricuspid jet velocity (> 2.8 m/s) as the primary independent variable with age, sex, right atrial dilation, and elevated nt-proBNP as covariates.

Results: 107 patients were analyzed; median age was 63 and 65% were female. We found a predictive association between presence of RA dilation and liver AVMs (adjusted odds ratio 3.76, 95% CI 0.75 to 18.74, $P = 0.11$). No association was observed between elevated NT-ProBNP and elevated tricuspid jet velocity with liver AVMs.

Conclusion: We observed approximately four-fold increased odds of image-proven liver AVMs in patients with RA dilation on echocardiogram. Echocardiography is recommended universally in adults

Characteristic	All patients (N=107)
% Female	65 (61%)
Patients with Liver Imaging (US, CT, or MRI)	52 (49%)
Patients with Hepatic AVM on Imaging	34 (32%)
Patients with Transthoracic Echocardiogram (TTE)	99 (93%)
Patients with RA Dilation on TTE	48 (49%)

Fig. 1 HHT Cohort Baseline Characteristics

with HHT; therefore, presence of RA dilation may be useful in directing patients to undergo liver imaging (Fig. 1).

040 De novo brain vascular malformations in hereditary hemorrhagic telangiectasia

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Disclosures: Dr. Beslow and the Brain Vascular Malformation Consortium (BVMC) are funded by the National Institutes of Health U54-NS065705-13.

Objective: Approximately 10% with hereditary hemorrhagic telangiectasia (HHT) have brain vascular malformations (VMs). Few reports describe de novo brain VM formation. International HHT Guidelines recommend initial brain VM screening upon HHT diagnosis in children but do not address re-screening. We aimed to confirm whether brain VMs can form de novo in patients with HHT.
Method: The BVMC HHT project is a 17-center longitudinal study enrolling since 2010. We queried the database for de novo brain VMs defined as brain VM detected 1) on follow-up neuroimaging in a patient without previous brain VM or 2) in location distinct from previously identified brain VM. An expert neuroradiologist retrospectively reviewed images of reported de novo brain VMs.
Result: Of 1909 patients enrolled, 409 (21%) had brain VMs. Imaging was available in four of seven with reported de novo brain AVMs (BAVM). Patient#1 (no mutation identified) with 2 BAVMs diagnosed at 24 years had a de novo BAVM detected at 37 years. Patient#2 (*ENG* mutation) with negative MRI at age 10 years had a de novo capillary malformation identified on MRI at age 16 years. Patient#3 (10-year-old, *ACVRL1* mutation) had a capillary malformation which was not visualized during infancy on noncontrast MRI. Patient#4 (*ENG* mutation) did not have de novo BAVM, but a small occipital BAVM that increased in size between ages 3 and 6 years.
Conclusion: Brain VMs can, albeit rarely, form de novo in HHT patients. Small lesions may be missed if contrast is not administered. Re-screening may thus be warranted.

Epidemiology and Genetics

O41 Accuracy of the clinical Curaçao criteria at first presentation in children genetically diagnosed with HHT

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Background: Curaçao criteria are the only accepted criteria for the clinical diagnosis of HHT. However, these criteria were established before genetic tests were widely available. The natural course of the disease progresses with age and some characteristics may not be present at time of presentation, especially in the pediatric population.
Objective: To assess the accuracy of Curaçao criteria for the diagnosis of HHT in children with genetically confirmed HHT.
Methods: Retrospective analysis of all patients that were genetically confirmed as having HHT and screened for visceral AVMs at the Hospital for Sick Children between 2000 and 2019.
Results: 367 patients were seen at the HHT clinic between 2000 and 2019. Of those 165 were genetically confirmed with HHT and were included in the analysis (ALK1 – 62, ENG—87, SMAD4 – 16). Mean (SD) age at presentation was 7.7 (5.2) years. At time of presentation, 156 (95%) had at least one first grade relative diagnosed with HHT, 95 (58%) had ongoing epistaxis, and 53 (32%) had typical telangiectasia. 63 (38%) had at least one visceral AVM detected. Altogether, mean (SD) number of criteria met at time of presentation was 1.9 (0.8). 42 (25%) patients met 3–4 criteria, and 66 (40%), 57 (35%) met 2 and less than 2 criteria respectively (Table 1).
Conclusion: Positive family history is seen in the majority of children with HHT and more than half presented with epistaxis. However, about 2/3 of the patients did not present with telangiectasia and more than 60% did not have visceral AVMs. Curaçao criteria may not be as useful in children, thus genetic testing should have an important role in the diagnosis in this age group.

O42 Investigation of the genetic mechanism of telangiectasia formation in hereditary hemorrhagic telangiectasia (HHT)

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Objective: A recent report demonstrated that somatic loss of function variations in the HHT causative genes, *ENG* and *ACVRL1*, are associated with skin telangiectasias (Snellings et al., 2019). Here, we investigated the genetic mechanisms driving nasal telangiectasia formation in HHT patients.
Methods: DNA was extracted from 15 fresh/frozen nasal telangiectasia, 4 dermal telangiectasia, and 10 control tissue biopsies resected from nine unrelated individuals with HHT. DNA was evaluated using a 736 vascular malformation and cancer next-generation sequencing (NGS) gene panel down to 1% somatic mosaicism. Spatial single cell transcriptomic data from nasal telangiectasia and control tissues using the 10 × Genomics Visium platform was also examined.
Results: Heterozygous germline mutations were identified in all tissue specimens. Telangiectasia tissues from 5/9 cases had a pathogenic somatic mutation ranging from 1.03–1.96% in the same gene that had the germline mutation. Four of fifteen (26.7%) nasal telangiectasia and one of four (25%) dermal telangiectasia had a detectable somatic second hit. Surprisingly, additional low level somatic mutations in other genes were identified in several telangiectasias. Spatial single cell sequencing data revealed differential expression patterns in nasal telangiectasia tissues versus controls.
Conclusions: This is the first report that nasal telangiectasia in HHT are caused by very low level somatic second hit mutations. Our data is consistent with previous reports and suggest that bi-allelic loss of *ENG* and *ACVRL1* is required for the development of vascular malformation lesions observed in HHT. Further spatial single cell sequencing data analysis may reveal additional mechanistic insights required for telangiectasia formation.

O43 ClinGen HHT Variant Curation Expert Panel's Modified Variant Interpretation and Classification Guidelines

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Objective: In 2015, the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG-AMP) published a consensus scoring process for systematically analyzing evidence for pathogenicity and classifying variants. Many clinical laboratories have implemented these guidelines, but without additional gene/disease rule specifications there is reviewer subjectivity leading to discrepancies in how laboratories interpret and classify variants. The Clinical Genome Resource (ClinGen) is an NIH-funded program that works to standardize and implement clinical relevance criteria for human disease genes and variants. ClinGen has established expert panels to adapt the ACMG-AMP guidelines for particular genes/diseases. A ClinGen HHT Variant Curation Expert Panel (VCEP) was approved and began actively working in 2019. This panel includes individuals with diverse areas of expertise related to HHT.
Methods:

1. Adapt ACMG-AMP guidelines for standardized HHT variant interpretation.
2. Resolve ClinVar classification discrepancies for variants in *ENG*, *ACVRL1*, and *SMAD4*.
3. Provide 3-star level expert panel classification for HHT variants in ClinVar.
4. Curate ARUP hosted database and submit variants to ClinVar for one centralized HHT variant database.

Result: The HHT VCEP has proposed modified variant interpretation and classification guidelines that include rules with HHT-specific modifications, rules determined not applicable to HHT, and rules that required no modification from the original 2015 guidelines.
Conclusion: This work will aid in the standardization of variant interpretation and data sharing of HHT variants, which will provide a centralized curated resource where clinicians and researchers can go to find the significance of variants associated with HHT.

O44 Whole genome sequencing of patients with hereditary haemorrhagic telangiectasia identifies excess of pro-haemorrhagic variants in patients with more severe bleeding

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Objective: The personalisation of medicine using DNA variant sequences may benefit people with hereditary haemorrhagic telangiectasia (HHT). We tested for chance inheritance and clinical associations of rare deleterious variants where loss-of-function causes bleeding or haemolytic disorders in the general population.
Methods: Literature searches for relevant genes that could impact on HHT phenotypes were performed, and genes of interest investigated in DNA from 104 HHT patients within the Research Environment of the 100,000 Genomes Project using LabKey. For each variant, potential pathogenicity was assigned using gnomAD general

population allele frequencies and Combined Annotation Dependent Depletion (CADD scores). Anonymised, categorised data were integrated with sub-phenotypes assigned blinded to the genomic data.
Results: 75 genes of interest were split into five groups by their roles and disease causation (haemolytic anemias; coagulation and platelet disorders). Fifty-six of these genes (75%) had variants within the 104 participants. All variants were rare with allele frequencies less than 0.003. The categories and genes with a greater variant burden in the study cohort also had higher gene damage indices in the general population. There was no difference in variants or genes according to the HHT gene (most commonly *ENG* or *ACVRL1*), but in blinded analyses, patients with greater haemorrhagic severity that had been attributed solely to HHT vessels had more CADD-deleterious variants in platelet (Spearman $\rho = 0.25$, $p = 0.008$) and coagulation (Spearman $\rho = 0.21$, $p = 0.024$) genes.
Conclusions: Patients with HHT commonly have rare variants in genes of potential relevance to more severe haemorrhagic phenotypes. Joyce et al. Blood Adv. 2022 PMID:35316832.

O45 Iron deficiency responses and compensations – evidence for differences between hereditary hemorrhagic telangiectasia molecular genotypes

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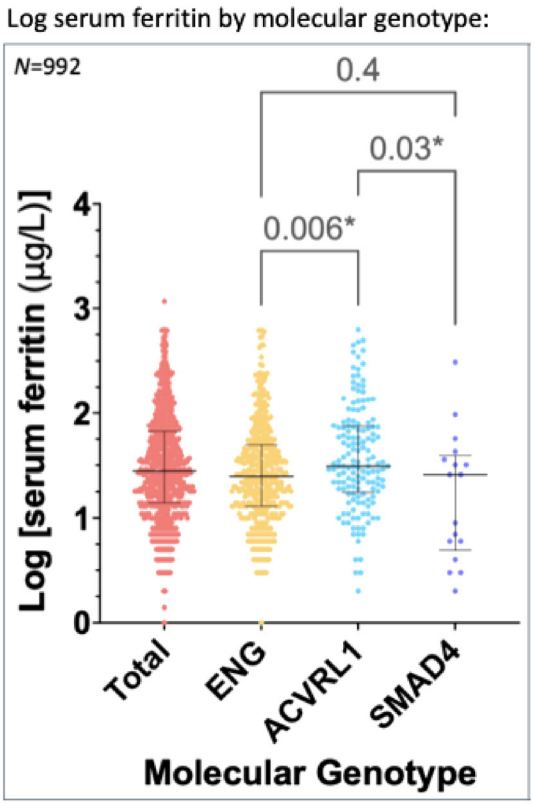
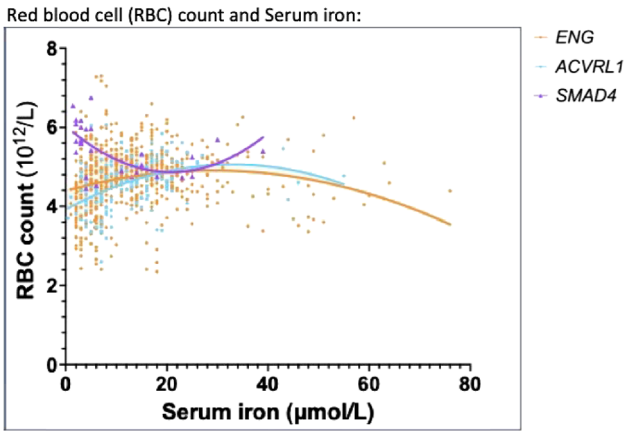
Objective: Hereditary haemorrhagic telangiectasia (HHT) patients are at risk of developing iron deficiency if the iron lost during haemorrhage is not adequately replaced. This study aimed to examine associations between HHT molecular genotype and iron deficiency indices.
Method: A database containing repeated measurements from 426 genotyped HHT patients was retrospectively analysed to compare iron deficiency rates, complications, compensations and responses to iron treatment between molecular genotypes.
Results: Serum ferritin was higher in *ACVRL1* (median 31; IQR 17.5,75) than *ENG* (median 25; IQR 13,50.5; $p = 0.006$) and *SMAD4* (median 26; IQR 5,39.5; $p = 0.03$) patients, as shown by Kruskal–Wallis and Dunn's post-test (Fig. 1). Age and sex-adjusted linear regression analysis found that a *SMAD4* variant was predictive of a decrease in serum iron ($p < 0.0005$). Mean corpuscular volume was lower in *SMAD4* (median 75; IQR 70,87) than *ACVRL1* (median 90; IQR 86,93; $p < 0.0001$) and *ENG* (median 89; IQR 84,93; $p < 0.0001$) patients. Compensating for this, red blood cell counts were higher in *SMAD4* (median 5.4; IQR 5,6) than *ACVRL1* (median 4.7; IQR 4.2,5; $p < 0.0001$)(**Fig. 2**) and *ENG* (median 4.8; IQR 4.3,5.1; $p < 0.0001$) patients. Ultimately, haemoglobin concentrations did not differ significantly between molecular genotypes ($p = 0.39$).
Conclusion: *SMAD4* patients had lower iron indices, more marked indicators of iron deficiency anaemia, and displayed evidence of different compensatory mechanisms to maintain haemoglobin concentration. We speculate that the role of SMAD4 as a hepcidin regulator may explain this unique phenotype. A randomised-control trial assessing differing molecular genotypes' responses to iron treatment would further clarify relationships between iron deficiency and HHT molecular genotype.





O46 Identifying racial disparities in hereditary hemorrhagic telangiectasia

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Francisco, CA, USA; [5]Neurointerventional Radiology, University of California, San Francisco, CA, USA.

Objective: To investigate a racially diverse population at a single HHT center and determine whether epistaxis severity and the incidence of arteriovenous malformations (AVMs) is associated with race, independent of race or demographic differences.

Methods: Retrospective chart review of 429 HHT patients seen at a single academic center between July 1, 2014 and January 1, 2022. The primary outcomes of this study were epistaxis severity score (ESS) and the presence of pulmonary, cerebral, gastrointestinal, spinal, and hepatic AVMs. We studied the associations between predictors and outcomes, predictors and race, and race and outcomes. Racial differences were analyzed using t-tests and analysis of variance (ANOVA) for continuous variables, and chi-squared tests for categorical variables. We then performed multivariate linear and logistic regressions on outcomes.

Results: Through an ANOVA model, race was not significantly associated with ESS (F(6,421) = [0.64], p = [0.70]). Two univariate logistic regression models between race and both pulmonary and brain AVMs showed that race was associated with the incidence of pulmonary AVMs ($p < 0.01$), with Asians at a 2.3 fold risk of pulmonary AVMs compared to Whites ($p = 0.03$). Race was also associated with the incidence of cerebral AVMs ($p < 0.01$) with Hispanic or Latinos at a 4.8 fold risk compared to Whites ($p < 0.01$).

Conclusion: Those who identified as Asian or Hispanic or Latino may have higher rates of pulmonary and cerebral AVMs respectively. The correlations may be important for identifying risk factors in certain populations.

O47 Endoluminal biopsy for molecular classification of human brain arteriovenous malformations

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Objective: Brain arteriovenous malformations (bAVMs) arise from multiple molecular etiologies. Here, we report the first in-human use of endoluminal biopsy of the vessel lumen of bAVMs to characterize gene expression and blood-flow mediated transcriptional changes in living human patients.

Methods: Endoluminal biopsy (EB) and computational fluid dynamic modeling (CFD) was performed during preoperative angiography. Endothelial cells (ECs) were isolated with fluorescence assisted cell sorting (FACS) and sequenced on an Illumina HiSeq 4000 sequencer. Differential gene expression and gene ontology analyses were performed.

Results: EB was successful in 4 patients without complication. FACS sorting detected viable ECs in each patient (control: 309.2 ± 86.6 cells; bAVM: 228.8 ± 133.4 cells). Gene expression profiling identified 106 differentially expressed genes in bAVM ECs (FDR ≤ 0.05) which were enriched in bAVM-related Ras-MAPK signaling and angiogenic cell motility pathways ($p < 0.05$). When compared to cells acquired from resected tissues, EB detected 83.3% of genes and genome-wide expression strongly correlated with ECs from open surgery ($R^2 = 0.8$). CFD modeling of blood flow, including wall shear stress and oscillatory shear index, correlated with EB gene expression and supported evidence of vascular remodeling.

Conclusions: EB allows molecular profiling of bAVMs in living patients. Gene expression profiles are similar to tissues acquired with open surgery and identify potentially targetable Ras-MAPK signaling abnormalities in bAVMs. Integration with CFD allows determination of flow-mediated transcriptomic alterations. Endoluminal biopsy may help facilitate molecular stratification or trials of precision medicine approaches in human bAVMs.

O48 The European rare disease network for HHT frameworks for management of hereditary haemorrhagic telangiectasia in general and specialty care

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Objective: In Europe, the majority of healthcare over a lifetime of hereditary haemorrhagic telangiectasia (HHT) is conducted by non-specialists. Our goal was to guide management in general and speciality care.

Method: In 2016, eight founding centres set up a working group dedicated to HHT within what became the European Reference Network on Rare Multisystemic Vascular Diseases. By launch, combined experience exceeded 10,000 HHT patients, and Chairs representing 7 separate specialties provided a median of 24 years' HHT experience. Integrated were expert patients who focused discussions on the patient experience. Monthly meetings and new data acquisitions were used to support priorities gathered through a 2016–2017 survey. 2021 expansion included a further VASCERN Centre and Collaborating Experts. Leadership is by specialists in the relevant sub-discipline(s). 100% clinician consensus is required before statements are published/disseminated.

Results: One output set targets all healthcare professionals and their HHT patients, and includes the new Orphanet definition; Do's and Don'ts for common situations; Outcome Measures suitable for all consultations; COVID-19; and anticoagulation. The second output set spans aspects of vascular pathophysiology where greater understanding will assist organ-specific specialist clinicians to provide more informed care to HHT patients. These cover cerebral vascular malformations and screening; mucocutaneous telangiectasia and differential diagnosis; anti-angiogenic therapies; circulatory interplays between anaemia and arteriovenous malformations; and microbiological strategies to counteract loss of normal pulmonary capillary function.

Conclusion: The integrated outputs distinguish expert HHT care from non-expert HHT practice. Framework approaches can augment the health and safety of HHT patients in diverse health-care settings.

O49 The QOL-HHT: development and validation of a quality-of-life measurement scale specific to hereditary hemorrhagic telangiectasia

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Objective: Quality of life (QOL) measurement tools are often generic; they do not consider the specificities of diseases, their symptoms and their impact on QOL. To date, no specific scale has been validated to assess the impact of HHT disease on patients' quality of life. This study aims to develop and validate a QOL measurement tool specific to HHT disease: the QoL-HHT.

Method: This study is a prospective non-interventional study involving HHT patients in twenty French HHT expert centers. Duration 36 months. 1. Qualitative phase: The first phase consisted in non-directive interviews with patients and HHT experts. Data saturation was then achieved with13 semi-directive interviews with patients. Thematic content analysis (grounded theory method) was used to develop a 75-item tool addressing all domains of the QOL. 2. Quantitative phase: In the second phase, 415 HHT patients completed the preliminary 75-item version. Statistical analyses provided evidence for a 24-item scale. 228 patients completed the new 24-item version and four other questionnaires: SF36, anxiety-depression scale, social support scale and emotional regulation scale.

Result: Confirmatory factor analyses, re-test and correlational analyses provided evidence for the 24-item scale.

Conclusion: The QoL-HHT scale is able to identify and quantify the aspects of quality of life affected in HHT patients in order to offer them individualized medico-psycho-social support while harmonizing their care. This study was promoted by "Les Hospices Civils de Lyon"; funded by the association AMRO- HHT France and approved by the French research ethics committee. ClinicalTrials NCT03695874.

O50 Clinical Manifestations of Patients with GDF2 Mutations Associated with Hereditary Hemorrhagic Telangiectasia 5

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Objective: Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant fibrovascular dysplasia caused by mutations in *ENG*, *ACVRL1*, and *SMAD4*. Increasingly, there has been an appreciation for vascular conditions with phenotypic overlap to HHT, but which have distinct clinical manifestations and arise from novel or uncharacterized gene variants. This study reported on a cohort of four unrelated probands who were diagnosed with a rare form of *GDF2*-related HHT5, for which only five prior cases have been described.

Methods: Two patients harbored heterozygous missense variants not previously annotated as pathogenic (p.Val403Ile; p.Glu355Gln). Clinically, these patients had features resembling HHT1, including cerebrovascular involvement of their disease (first report documenting cerebral involvement of HHT5), but with earlier onset of epistaxis and a unique anatomic distribution of dermal capillary lesions that involved the upper forelimbs, trunk, and head. The other two patients harbored interstitial deletions larger than five megabases between 10q11.22 to 10q11.23 that included *GDF2*.

Results: To our knowledge, this is the first report detailing large genomic deletions leading to HHT5. These patients also demonstrated mucocutaneous capillary dysplasias, including intranasal vascular lesions complicated by childhood-onset epistasis, with a number a number of extravascular findings related to their 10q11.21q11.23 deletion.

Conclusion: In conclusion, patients with *GDF2*-related HHT may present with a number of unique characteristics that differ from classically reported features of HHT.

O51 Epidemiological, clinical and endoscopic features of epistaxis severity and quality of life in hereditary haemorrhagic telangiectasia: a cross-sectional study

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Objectives: Epistaxis is the main complaint in patients with Hereditary haemorrhagic telangiectasia (HHT). Even though the role of epistaxis in affecting the quality of life (QoL) is well-known, little is known about epidemiological and clinical factors contributing to epistaxis severity and QoL.

Method: This is a cross-sectional study, including adult patients with HHT with epistaxis. All patients underwent an otolaryngological evaluation with nasal endoscopy. Epistaxis severity was graded using the FID score, and QoL was evaluated with the Short-Form Health Survey (SF-36). Descriptive statistics were produced for demographic characteristics; the Shapiro–Wilk test was used to test the normal distribution of quantitative variables. Correlation between the quantitative variables was evaluated with Pearson's correlation coefficient. Both univariate and multivariate linear regression models were fitted to find associations between demographic or clinical factors and the FID score or SF-36.
Results: A total of 234 patients with HHT were included in the study. The univariate analysis highlighted the association between high blood pressure, septal perforation, nocturnal epistaxis, surgery, blood transfusion, hormonal therapy and both FID score and QoL. Sex, allergic rhinitis and nasal polyposis were neither related to epistaxis severity nor perceived health.
Conclusions: Epistaxis severity and QoL in patients with HHT are influenced by several clinical factors both dependent and independent from HHT. Some of the results are consistent with those already published, but for the first time, we extended the analysis to different clinical parameters, such as endoscopic findings, never assessed before.

Procedural and surgical treatments

O52 Characteristics and treatment of brain vascular malformations in children with HHT

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Background: Hereditary hemorrhagic telangiectasia (HHT) is a rare autosomal dominant disease characterized by the development of organ vascular malformations (VMs). Brain VMs can cause intracranial hemorrhage, seizure, and death in adults and children with HHT. Treatment of brain VMs often involves multiple modalities (surgery, stereotactic radiosurgery, embolization) and case-by-case risk assessment.
Objective: To describe the clinical presentations and patterns of treatment of brain VMs in a pediatric HHT cohort, compared to adults.
Methods: Demographic and clinical data were analyzed in 114 pediatric HHT patients with brain VMs and compared with a cohort of 253 adult HHT patients with brain VMs, enrolled in the multicenter Brain Vascular Malformation Consortium.
Results: We demonstrate that a higher proportion of pediatric HHT patients with brain VMs were symptomatic at presentation (60/114, 52.6%) compared to adults (93/253, 36.8%) ($p = 0.003$). Intracranial hemorrhage on presentation was more prevalent in pediatric patients (27/114, 23.7%) compared to adult patients (25/253, 9.9%) ($p < 0.001$). Seizures at presentation were reported in 21/114 (18.4%) pediatric patients, compared to 19/253 (7.5%) adult patients ($p = 0.002$). Surgical resection was the most common brain VM treatment modality in both children (43/69, 62.3%) and adults (66/129, 51.2%). Post treatment hemorrhage was rare in children (3/69, 4.3%) and adults (9/129, 6.9%).
Conclusion: Pediatric patients appear to be more likely to present with symptoms and complications from brain VMs,

O53 Factors associated with pulmonary arteriovenous malformations treated with transcatheter embolization: a retrospective comparative analysis using propensity score weighting

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Objective: Up to 25% of pulmonary arteriovenous malformations (pAVMs) persist after treatment. The definitive treatment for pAVMs is endovascular embolization, and the most commonly used embolization agents are embolic coils or vascular plugs (Micro Vascular Plug System [MVP] or Amplatzer Vascular Plug [AVP]). Our objective was to compare these three embolic agents after matching them by propensity score weighting to account for selection bias.
Materials and Methods: We retrospectively analyzed 112 patients (mean age, 46 years; 70% female) who underwent embolization of 393 pAVMs with MVPs or AVPs from 2003–2020 and who had follow-up chest computed tomography pulmonary angiograms. Median follow-up was.
1.6 years (interquartile range, 0.3–5.7). Persistence was defined as < 70% reduction in pAVM sac size or contrast enhancement of the sac on follow-up computed tomography pulmonary angiograms. Propensity matching score, univariable Cox proportional hazard regression, and a multivariable prediction model were used. Alpha = 0.05.
Results: Of 393 pAVMs, 41 (10%) demonstrated persistence. The following variables were associated with treatment groups with p-values < 0.25: age ($p = 0.02$), gender ($p < 0.001$), whether the

patient was an adult or child ($p < 0.001$), smoking ($p = 0.16$), pAVM complexity (p.
$= 0.08$), lung location of the pAVM ($p = 0.16$), number of feeding arteries ($p = 0.1$), and diameter of the feeding arteries ($p < 0.001$). These variables were included in propensity score weighting analysis and the results of standardized differences before and after propensity score weighting for the aforementioned variables among treatment groups. The results of the Cox regression model with inverse propensity score weighting, after adjustment for artery diameter (due to remaining imbalance after weighting) showed that MVPs had significantly lower risk of persistence compared with both AVP and coils. AVPs were associated with a 63% lower risk of developing persistence compared with coils ($p = 0.03$).
Conclusion: In this retrospective study, MVP alone was superior as a first-line embolic device for embolization of pAVMs compared with coils or AVP.

O54 Double balloon enteroscopy in patients with HHT

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Objective: Double balloon enteroscopy (DBE) with argon plasma coagulation (APC) has been shown to effectively treat small bowel GI bleeding but is not well studied in patients with HHT. We conducted a retrospective study of patients with HHT who underwent DBE at an academic referral center.

Methods: We reviewed medical records of all patients referred to UCSF HHT Center of Excellence who underwent DBE. Hemoglobin, ferritin, and blood transfusion requirements in the year prior and following DBE were collected, as were DBE findings and complications.

Results: The study included 14 patients and 28 procedures. Arteriovenous malformations (AVMs) were identified in the stomach, duodenum, jejunum, and ileum. Number of AVMs ranged from 9 to >100; 21/28 scopes revealed >20 AVMs.

Telangiectasias were treated with APC in all but 3 procedures; gold cautery was used for 4 procedures and clips were placed in 2. There was no significant decrease in hemoglobin or change in transfusion requirements 12 months post-procedure. In patients with ≤20 AVMs, hemoglobin dropped by a mean of 0.97 (95%CI 0.26-1.68) 2 weeks following the procedure but returned to pre-procedure levels by 8 weeks. Those with >20 AVMs experienced no change in hemoglobin levels but had decreased transfusion requirements (mean -4.63u/year, 95%CI 0.73-8.53) post-procedure.

Conclusions: Single and repeat DBE-directed treatment of small bowel telangiectasias is safe in patients with HHT and did not worsen bleeding. Some HHT patients have many lesions; DBE may be particularly helpful in decreasing transfusion requirements in those with >20 small bowel AVMs.

O55 Staging system for longitudinal tracking of endonasal and extranasal mucocutaneous lesions in hereditary hemorrhagic telangiectasia (HHT): Utah telangiectasia assessment for HHT (U.T.A.H.) staging

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Objective: Longitudinal tracking over sequential assessments, whether surgical or clinic-based, has lacked consistent systems for describing the endonasal and extranasal (oral, fingertip, etc.) mucocutaneous lesions of patients with HHT. This lack of common staging or scoring systems has also limited communication among HHT clinical providers regarding shared patients or regarding multi-institutional research protocols. A staging system for describing vascular HHT lesions is proposed for endonasal and extranasal anatomic sites.

Methods: surgical, clinical, and literature reports of common endonasal and other anatomic sites of HHT-associated telangiectasias were incorporated into a standardized staging protocol: the Utah Telangiectasia Assessment for HHT (UTAH) staging. The system includes qualitative and semiquantitative staging for the 1) site, 2) severity, and 3) size of telangiectasias at each endonasal and extranasal location.

Results: examples of UTAH staging assessments and scoring are provided, including representative nasal endoscopy, oral, and cutaneous images.

Conclusions: The UTAH staging system permits longitudinal tracking of telangiectasias across unique anatomic endonasal and extranasal mucocutaneous sites, facilitating standardized research protocol assessments and improving communication among clinical providers who share in the care of HHT patients and families.

O56 Surgical resection for localized diffuse type pulmonary arteriovenous malformations (dPAVMs): further experience

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Objective: Diffuse type PAVMs are difficult to manage. Embolotherapy has been the mainstay of therapy but can require many interventions and is often ineffective in complete eradication. Patients are at risk for life-threatening hemoptysis due to persistent bronchial artery supply to the PAVM. We previously reported three patients with managed surgically and herein we expand that population and report long term follow-up.

Method: The outcomes of 9 patients undergoing embolotherapy and surgery were analyzed retrospectively.

Results: Preoperative symptoms included hemoptysis (n = 2), syncope (n = 2), dyspnea (n = 5), growth retardation (n = 1) and stroke (n = 1). Four patients had embolotherapy (mean 2.8 session, range 0–7) at HHT centers of excellence prior to surgery. Nine patients (median age at surgery 15.1 years, range 18.4–61.6) with dPAVMs limited to one lobe (n = 8) or lung (n = 1), seven with HHT (6 *ENG*,

1 by Curaçao criteria), were treated by partial (n = 3) or complete (n = 5) lobectomy or pneumonectomy with expander (n = 1). Four had surgery without embolization. Mean oxygen saturation improved from 86% (range, 75–96%) to 98% (range, 97–100%). At mean follow-up of 5.1 years (range, 0–12) symptoms have resolved in all patients. No major complications occurred. Only one patient has required treatment of other small preexisting simple PAVMs; no new PAVMs have occurred in the remaining lungs.

Conclusion: In select patients with dPAVM localized to a single lung or lobe, surgery can be curative without risk of late complications such as hemoptysis. With careful patient selection, surgery may be considered front-line therapy in this rare patient population.

O57 Embolotherapy of recurrent pulmonary arteriovenous malformation by ethylene vinyl alcohol copolymer in hereditary hemorrhagic telangiectasia: safety and long-term efficiency

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Objectives: To evaluate short- and long-term safety and efficacy of embolization with a ethylene vinyl alcohol copolymer (Onyx®) for recurrent pulmonary arteriovenous malformations (PAVMs) in hereditary hemorrhagic telangiectasia (HHT).
Methods: 45 consecutive patients (51% women, mean (SD) age 53 (18)-year-old) with HHT referred to a reference center for treatment of recurrent PAVM were retrospectively included from April 2014 to July 2021. Inclusion criteria included evidence of PAVM recurrence on CT or angiography, embolization using Onyx® and a minimal 1-year-follow-up CT or angiography. Success was defined based on standard of reference criteria on unenhanced CT or pulmonary angiography if a recurrence was suspected. PAVMs were analyzed in consensus by 2 radiologists. The absence of safety distance, as defined by a too short distance for coil/plug deployment between the proximal extremity of the primary embolic material used and a healthy upstream artery branch, was reported.
Results: 70 embolizations were analyzed. Mean (SD) follow-up was 3 (1.3) years. Safety distance criteria was missing in 33 (47%) PAVMs. All procedures were technically successful with a short-term occlusion rate of 100% using a mean (SD) of 0.6 (0.5) mL of Onyx®. Long-term occlusion rate was of 60%. No immediate complication directly related to embolization was reported nor any severe long-term complication such as strokes or cerebral abscesses.
Conclusions: In HHT, treatment of recurrent PAVM with Onyx® showed a satisfactory safety and efficacy, with an immediate occlusion rate of 100% and long-term rate of 60%.

Other Vascular Anomalies

O58 Neurologic complications in HHT with pulmonary arteriovenous malformations: database study

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Objective: Hereditary Hemorrhagic Telangiectasia (HHT) is an autosomal dominant genetic disorder affecting vascular maturation, with prevalence of 1 in 3800 in Alberta. Pulmonary arteriovenous malformations (PAVMs) affect 35–40% of individuals with HHT and may lead to embolic neurologic complications, including strokes and transient ischemic attacks (TIAs), and the development of brain abscess due to intrapulmonary right-to-left shunts (RLS). The objective of this study was to assess the prevalence of neurologic complications among HHT subjects in Alberta, Canada.

Methods: Possible or definite HHT consented subjects in the Edmonton HHT Registry were retrospectively assessed for PAVM-related neurologic sequelae.

Results: There were 218 HHT subjects included in the study, 80 of whom had PAVMs. There were 10 (12.5%) stroke cases among HHT-PAVM subjects, though there was no significant association between PAVM and strokes. TIA was twice as common in HHT-PAVM subjects, compared to those without PAVM (11.3% versus 5.1%). Twenty-one PAVM-HHT subjects had migraines, 5 had seizures, and 3 had brain abscess; these associations were not statistically significant. After controlling for age and sex confounders, HHT-PAVM subjects had 2.37 times the odds of associated TIA, compared to those who did not have PAVM (OR = 2.37, 0.85–6.64, p = 0.10).

Conclusion: PAVMs may give rise to embolic complications; therefore, HHT patients are recommended to undergo proper PAVM screening to reduce the risk of developing life-threatening complications. Despite negative findings, our results highlight a further need to evaluate the associations between PAVM and neurologic complications. Future works should evaluate the relationship of PAVM shunt grade on neurologic complications.

O59 Seven cases of HHT-like hepatic vascular abnormalities associated with EPHB4 pathogenic variants

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Objective: to report the characteristics of patients with liver abnormalities initially suggesting of HHT and finally related to RASA1 or EPHB4 after genetic testing.

Methods: After a call for observations in the French HHT network, we analyzed the clinical, radiological and genetic data of the patients.

Results: Seven patients with hepatic vascular abnormalities were identified among 20 patients with a liver imaging in a whole cohort of 43 cases (18 RASA1 and 25 EPHB4). They all had EPHB4 variants (classified as pathogenic for 6, probably pathogenic for 1) without specific hotspot.

Consisting of 5 males and 2 females aged from 43 to 69 years, this group was significantly older than the one with normal liver imaging (median: 51 vs 22 years, p = 0.0004, Mann Whitney test). Epistaxis (without iron deficiency) and atypical telangiectases were noted each in 2 cases. Four patients had a 1^{rst} degree relative affected. No patient had clinical signs of high output cardiac failure.

The liver imaging included 2 ultrasound scans, 6 injected CT scans and 4 MRI. The main hepatic artery were dilated in all the subjects, from 9 to 11 mm. Six patients had hepatic telangiectases, 5 had arterio-venous shunts, 3 had arterio-portal shunts and 4 had porto-venous shunts. The global aspect of the liver was typical of HHT in 6 cases. Five patients had a thoracic CT scan, without vascular malformations.

Conclusion: EPHB4 mutations can be associated to hepatic vascular abnormalities mimicking HHT, especially in older patients. Panel testing including EPHB4 is of great interest for atypical HHT presentations.