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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.