HAEi Newsletter

IN THIS NEWSLETTER

VERY SUCCESSFUL HAE GLOBAL CONFERENCE

THE SCIENTIFIC PROGRAM

THE PATIENT PROGRAM

THE POSTER SESSION

THE GENERAL SESSION

COUNTRY PRESENTATIONS

REGIONAL PRESENTATION

CLOSING REMARKS

A Message from the President

Dear HAE Friends,

Judging from the overwhelmingly positive feedback we have received, the 2014 HAE Global Conference that took place in Washington D.C. in mid May was an unconditional success. With around 450 attendees from more than 30 countries, it qualifies as the largest worldwide gathering of HAE patients that has ever been organized!

This edition of the HAEi newsletter is solely devoted to this exciting and informative conference.

Before you proceed to the meeting highlights, however, I would like to take a moment to announce the results of HAEi Research Grant Program. As mentioned in previous newsletters, the HAEi Executive Committee developed this initiative to encourage the discovery of new information that contributes to understanding the basic etiology and pathogenesis of HAE.

In response to a request for proposals, HAEi received sixteen grant applications, which were turned over to an independent selection committee that evaluated the submissions and chose two for funding:

- ***Regulation of B1 bradykinin receptors in HAE.*** Prof. Bruce Zuraw, US HAEA Angioedema Center at UCSD, San Diego, California, USA.
- ***One cut too many: Factor XII mutations that cause hereditary angioedema enhance activation by plasmin.*** Assistant Professor Coen Maas, University Medical Center Utrecht, Department of Clinical Chemistry and Hematology, Utrecht, The Netherlands.

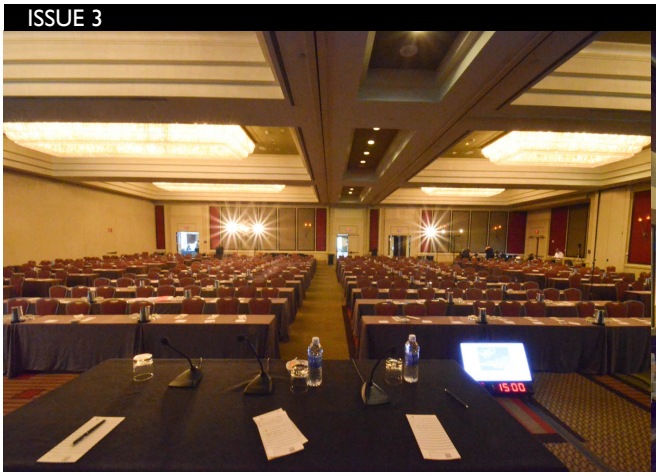
The independent review committee commented that their decision was not easy because the applications were quite impressive. We wish we could have funded all of them.

Enjoy the 2014 HAE Global Conference overview!

Warm regards,
Anthony J. Castaldo
President, HAEi

HAE GLOBAL CONFERENCE
WASHINGTON DC
15-18 MAY 2014

"We had a groundbreaking global conference in Washington DC - with 450 HAE friends from more than 30 countries."



2014 HAE Global Conference - A Positive Experience for the World's HAE Community

With about 450 delegates from more than 30 countries the HAE Global Conference in Washington D.C., USA (15-18 May 2014) was by all measures a great success.

With a focus on 'Setting New Standards', the conference provided HAE advocates from all over the globe with an opportunity to assess the state of HAE care in their countries and discuss strategies for making improvements with colleagues from other countries. The active participation of the delegates lead to productive interactions between patients, the scientific/medical community, and the pharmaceutical companies.

The conference was designed to serve as an incubator for developing creative collaborations and innovative approaches to improving HAE care throughout the world. The overall aim was to inspire delegates to translate the knowledge and motivation gained during the conference into systematic action aimed at improving diagnosis and access to life saving HAE therapies.

The conference began with two tracks - a scientific program for physician/researchers and a patient track that covered the fundamentals of understanding HAE. The rest of the conference consisted of sessions with all attendees participating. The welcome reception as well as a conference dinner and a guided bus city tour around Washington D.C provided ample opportunities to meet, greet, and exchange thoughts and ideas with fellow attendees. Furthermore, participants had the opportunity to interact with representatives from the conference sponsors: **Shire, ViroPharma, CSL Behring, Dyax Corp., BioCryst Pharmaceuticals** and **Salix Pharmaceuticals.**

This newsletter is dedicated to give an overview of conference highlights.

From the scientific program

The Scientific Program was co-chaired by Prof. Bruce Zuraw, USA and Prof. Konrad Bork, Germany and took place in the morning of Friday 16 May 2014 with a focus on "Understanding Angioedema: How Do We Differentiate Different Forms?" and "Treating Angioedema Due to C1 Inhibitor Deficiency. "

Prof. Jonathan Bernstein (University of Cincinnati, USA): Optimizing the diagnosis of HAE

The mean age of onset of HAE is 11 years, with a significant lag between onset and diagnosis that may extend up to 22 years; the average time to diagnosis is 8.3 years. 65 % of HAE patients have been previously misdiagnosed, most often with allergy/allergic reaction or appendicitis. About 19-24 % of the patients have undergone unnecessary surgical procedures. Surveys show that only 51-64 % of physicians use C4 levels to aid diagnosis of HAE.

Dr. Andrea Zanichelli (University Hospital Luigi Sacco Milan, Italy): Approaching the diagnosis of aquired angioedema

Coexistence in C1-INH-aquired angioedema patients of B cell malignancy, non-malignant B cell proliferation and autoantibodies suggest that the pathogenesis is dominated by an altered control of B cell proliferation. The possibility to cure C1-INH-aquired angioedema treating the underlying B-cell proliferation indicates a direct causative role.

Prof. Christian Drouet (University Hospital Grenoble, France): HAE with SERPING1 and F12 mutations – distinct modifying factors

HAE associated with SERPING1 (HAE-C1Inh) and F12 (HAE-FXII) mutations presents with highly variable clinical expression. Based on data gathered from a very large carrier cohort, we assessed the modifiers affecting the clinical phenotype. Metalloprotease activities involved in the inactivation of kinins play a significant role in the pathophysiology of HAE associated with both causative genes; importantly kinin forming proteases are involved in the responsibility of HAE-FXII. The HAE-C1Inh and HAE-FXII are associated with very distinct modifiers of the kinin catabolism enzymes: (1) APP for HAE-C1Inh, a condition to desArg9-BK accumulation, (2) ACE and CPN for HAE-FXII, a condition for sustained BK accumulation.

Dr. Alejandro Malbran (British Hospital Buenos Aires, Argentina): Epidemiology of angioedema without wheels in an allergy and immunology clinic

We reviewed the case records of all patients consulting our office from January 1997 to April 2013, finding 303 patients (of a total of 17,823) with a presumptive diagnose of angioedema without wheels (AWW). AWW is a rare consultation cause. Women prevail over men. Most patients have anti-H1 responsive idiopathic angioedema. Family history and age at onset of symptoms varies among different types of angioedema.

Angioedema is an infrequent clinical situation. Half are histamine responsive idiopathic angioedema. Drugs are responsible for a quarter of the cases. Other angioedema causes are even more rare.

Dr. Camila Lopes Veronez (Federal University Sao Paolo, Brazil): Next generation sequencing as a new tool for research and molecular diagnosis of HAE

We have performed the genetic analysis by using next generation sequencing of the coding region of 15 genes involved in BK release pathway, from C1-INH to B2R. We analyzed a family composed by 23 individuals, nine of them presenting HAE symptoms and found around 80 alterations per patient. One specific mutation found in the SERPING1 gene in the nine patients, p.Ala457Pro, was considered probably pathogenic and is the main candidate to be responsible for HAE in these patients.

Next generation sequencing might be an efficient tool for the diagnosis of HAE, helping to find the main genes responsible for the disease and the genes modulating the clinical symptoms. The knowledge and experience generated using next generation sequencing technologies is necessary to expand our understanding in the sensitivity of specific mutations to individualized therapies. Gathering a complete profile of mutations in genes related to HAE for the application of personalized and tailored targeted therapy is critical to developing more specific treatments.

We believe a faster and cost effective genotyping tool such as next generation sequencing technology will be greatly beneficial for the assignment of such specific therapeutics in the near future use for HAE and other diseases.

Dr. Hilary Longhurst (Barts Health NHS Trust, United Kingdom): How do we improve the treatment of HAE attacks?

What has changed in the last 10 years in HAE treatment? In 2004 it was mostly about prevention of death (laryngeal attacks), treatment of unbearable symptoms, and limited treatments due to few studies. By 2014 the treatment of HAE has developed into prevention of disability, patient empowerment through home therapy and self-administration, several treatments, many studies, and optimized dose/timing.

All attacks, irrespective of location, are eligible for treatment as soon as they are clearly recognized by the patient, ideally before visible or disabling symptoms develop.

Assoc. Prof. Marc Riedl (US HAEA Angioedema Center San Diego, USA): Selecting the proper patients and drugs for long-term prophylaxis

Several studies have demonstrated the efficacy of attenuated androgens in preventing HAE attacks.

However, there are some contraindications to the use of androgens, including pregnancy, lactation, hepatic disease, children, cancer of the breast or prostate, and nephrotic syndrome.

Androgens can be enormously useful in HAE therapy, but they also have a variety of potential side effects, including virilization, hepatotoxicity, headache, hypertension, weight gain, menstrual abnormalities, acne, altered mood, and altered libido. Liver adenomas or even carcinomas have been linked to androgen therapy.

The antifibrinolytics epsilon aminocaproic acid and tranexemic acid tend to be less effective than the androgens for long-term HAE prophylaxis. Nevertheless, many HAE patients have benefited from them. Common side effects from the antifibrinolytics include nausea and diarrhea, vertigo, postural hypotension, and fatigue. Muscle cramps and weakness are particularly common. Other concerns include risk of vascular thrombosis and teratogenicity.

There are a number of patient and medication factors that should influence the decision to prescribe therapy, for instance frequency of attacks, rapidity of attack progression, history of laryngeal attacks, patient access to medical care, history of frequent hospitalization, treatment complications, and patient quality of life. Medication factors include efficacy, safety, cost, route of administration, and patient preference/tolerability.

HAE patients who should be considered for long-term prophylaxis include those who fail on-demand therapy and those who suffer from HAE with decreased quality of life such as anxiety, frequent attacks, intubation or intensive care unit stay, upper airway edema, loss of school or work, narcotic dependence, or limited access to healthcare or rapid onset of attacks.

The only treatment option for long-term prophylaxis in children is plasma derived C1-INH – attenuated androgens are not recommended. As for attenuated androgens adverse effects are common and lengthy, and it is contraindicated in several populations, for instance children and pregnant or lactating women. Attenuated androgens are frequently intolerable for female patients and only an option for patients who accept the risks and tolerate the side effects.

Dr. Yung Chyung (Dyax Corp., USA):
DX-2930 – discovery and characterization of a highly specific antibody inhibitor of plasma kallikrein for investigation in HAE prophylaxis

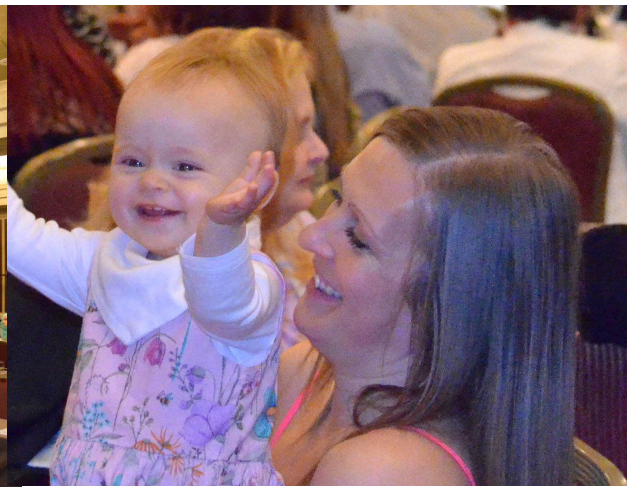
Due to the unmet medical need for a long-lasting prophylactic therapy and given the established relevance of plasma kallikrein as a drug target in HAE, we have developed a fully humanized antibody inhibitor (DX-2930) specific for plasma kallikrein.
In vitro enzyme inhibition and affinity assays demonstrate that DX-2930 is a potent antibody inhibitor of plasma kallikrein. Following a single or repeat subcutaneous dose of 5, 25 or 50 mh/kg DX-2930 in cynomolgus monkeys, we observed dose and time-dependent inhibition of plasma kallikrein activity, confirming the bioactivity of DX-2930. It has a prolonged serum residence time (301 hours) in cynomolgus monkeys following a single dose administration, supporting the potential of DX-2930 for long-term prophylaxis of HAE. DX-2930 is now being investigated for this indication through the following clinical trial program:
• Phase 1b (Initiation in mid-2014): Multiple ascending dose study in patients with HAE; assessing safety, tolerability, PK, exploratory biomarker
• Phase 2 (Planned for 2015): Proof of concept and dose-ranging study; assessing safety and efficacy in long-term prophylaxis of HAE.

Prof. Timothy Craig (Penn State University, USA):
Assessment of HAE treatment risks

Therapies used for HAE have been associated with adverse events such as thrombosis, emboli, hepatocellular carcinoma, exacerbation of attacks, and anaphylaxis.
After surveying multiple HAE physicians to determine the risk associated with HAE therapies we recommend that indwelling catheters when administering C1-INH be avoided due to the risk of a thrombotic events. Fresh frozen plasma is no longer advised when Icatibant, Ecallantide, or C1-INH are available. Androgens carry their own set of adverse effects including hepatocellular carcinoma, therefore screening is important. Adverse events to drugs should be reported so that the true incidence of adverse events can be determined – and as all therapies have potential for adverse events. HAE patients should be monitored closely and seen by an HAE expert every 6 to 12 months.

Dr. Inmaculada Martinez-Saguer (Hämophilie-Zentrum Rhein Main, Germany): Severe side effects in 22 patients with HAE using different dosages of Danazol – how to switch to other treatment regimen?

Danazol can reduce the frequency and severity of HAE attacks. However, it is associated with multiple adverse events, and drug interactions and contraindications which limits its use. Current WAO guidelines recommend C1-INH concentrate or androgens for long-term prophylaxis. Long-term prophylaxis with androgens must be regarded critically because of their side effects. Withdrawing androgens immediately when a patient is switched to another therapy puts the patient at risk. The androgen dose must be tapered over weeks (or months) of introducing a new therapeutic regimen. Switching from Danazol to C1-INH may reduce the frequency of HAE attacks and improve the patients' quality of life, but the switch requires that the patient is willing and able to learn self-administration and recognize early signs of an attack. Also it is important that training of self-administration is completed prior to the stepwise reduction of the Danazol dosage. The duration of this tapering period depends on the initial Danazol dose.
C1-INH-IRT is a suitable alternative in patients with severe HAE who present with intolerable side effects to Danazol and/or lack of response to this medication.



From the patient program

Ms. Sarah Smith-Foltz (Spain) and Ms. Alejandra Menendes (Argentina), both from the HAEi Executive Committee: Ten Things Every Patient and Caregiver Should Know About HAE

1. HAE is caused by a genetic defect that results in a deficiency of the blood protein C1 inhibitor.
- The absence of family history does not rule out the HAE diagnosis.

2. HAE does not skip generations.

3. In most cases blood tests confirm the HAE diagnosis and genetic testing is not required.

4. HAE swellings are not caused by an allergic reaction.
- Most cases of angioedema are not HAE and are caused by an allergic reaction.
- Unlike the swellings experienced by HAE patients, allergic angioedema happens when the immune system detects a foreign substance which causes the body to release histamine and other chemicals that cause swelling.
- Anyone with a chronic swelling disorder should receive a full work up that includes testing for HAE.

5. Antihistamines, epinephrine, and corticosteroids do not stop or prevent HAE attacks.

6. An explanation of how the deficiency of C1 Inhibitor leads to swelling attacks.
- The genetic defect inherited by HAE patients results in production of either inadequate or non-functioning C1-Inhibitor protein.
- Normal C1-Inhibitor helps to regulate the complex biochemical interactions of blood-based systems involved in disease fighting, inflammatory response, and coagulation.
- Because defective C1-Inhibitor does not adequately perform its regulatory function, a biochemical imbalance can occur and produce unwanted biological reactions that cause the release of plasma fluids into surrounding tissues, thereby causing swelling.

7. Swelling of the mouth, tongue, and throat are medical emergencies that require immediate attention.

8. In addition to anabolic steroids which are prescribed to prevent attacks, there are five products being manufactured to treat HAE:
- Berinert: C1-inhibitor; EMA/FDA-approved for treating acute abdominal, facial or laryngeal HAE attacks; intravenous,
- Cinryze: C1-inhibitor; EMA/FDA-approved for preventing HAE attacks and for preventing and treating attacks in Europe; intravenous,
- Firazyr: Bradykinin receptor antagonist; EMA/FDA-approved for treating acute HAE attacks in patients 18 years and older; subcutaneous,
- Kalbitor: Plasma kallikrein inhibitor; FDA-approved to treat acute HAE attacks in patients 12 years of age and older; subcutaneous, and
- Ruconest (Rhucin outside Europe): Recombinant human C1 inhibitor EMA-approved for the treatment of angioedema attacks in patients with HAE.
FDA-approval is pending in the USA.

9. Promising new therapies are on the horizon
- CSL Behring: Ongoing clinical trial testing a subcutaneous formulation of Berinert.
- Shire: Ongoing clinical trial testing a subcutaneous formulation of Cinryze.
- Dyax Corp.: Clinical trial testing of DX-2930, a subcutaneously administered fully human monoclonal antibody inhibitor of plasma kalikrein as a potential long-acting medicine to attacks.
- BioCryst Pharmaceuticals: Phase 2B of testing BCX4161, an oral plasma kalikrein inhibitor for preventing HAE attacks.

10. Patient organizations can make their voices heard and spark dramatic improvements in HAE awareness, diagnosis, and treatment.



From the poster session

The following are the main conclusions presented in posters displayed during the conference.

HAE in children *(Gregory H. Bennett, Penn State Hershey Children's Hospital, USA and Timothy Craig, Penn State University, USA)*
Accurate and timely diagnosis of HAE is imperative for children. With a prompt diagnosis and the availability of targeted and appropriate medications, therapy should be prescribed at the time of diagnosis so that the patient is adequately prepared to treat attacks.

Assessment of HAE treatment risks *(Shana Kalaria, Penn State University, USA)*
The incidence of hepatocellular carcinoma is rare. The incidence of adverse effects to fresh frozen plasma is greater than the literature suggests. Patients with HAE should avoid indwelling catheters, use fresh frozen plasma only when other therapies are unavailable, and use androgens with caution. Most importantly, adverse events to drugs should be reported so that the true incidence of adverse events can be determined.

Emergency angioedema: A 24/7 phone call service *(Isabelle Boccon-Gibod, National Reference Center of Angioedema, France et al.)*
The countrywide implementation of a 24/7 phone call service enables daily 'remote expertise' in the context of rare disease. It allows healthcare professionals to benefit direct advices from experts. It is a training platform to help healthcare professionals with their diagnosis practice and care handling. It contributes to improving early diagnosis and care, potentially saving more HAE patients from a fatal asphyxiation, thanks to effective treatment available in France since 2008.

The need for individualized HAE acute action plans: Two case studies of misdiagnosed attacks and unnecessary surgeries *(Melanie C. Dispenza, Northwestern University Chicago, USA et al.)*
It is prudent to test all relatives of HAE patients, whether they are symptomatic or not. All HAE patients, including those with no history of attacks, should be provided with an individualized action plan and prescribed on-demand therapy. These simple steps could prevent significant morbidity and mortality in the event of a suspected attack.

Therapy for HAE: barriers to teaching self-administration in the USA *(Linh-An C. Tuong, Penn State University, USA et al.)*
In the USA, specially trained nurses are essential for home-based teaching of the skills required for injection/infusion and for addressing patient's concerns regarding treatment. They have reported that challenges to self-administered therapy go beyond a patient's skill set. Barriers include coordinating care between patient and health-care providers, acquiring necessary medications and equipment, scheduling of sessions, distance to a patient's home and having adequate nursing follow-up. Further work on identified areas will enhance home-based treatment and will lead to earlier therapy, reduce cost associated with care, and improve patients' quality of life.

Treatment of HAE at the time of prodromal symptoms: An international survey of physicians *(Neelu Kalra and Timothy Craig, Penn State University, USA)*
A majority of physicians perceive that treating HAE at the time of prodrome in patients who are able to predict attacks may lead to reduced morbidity and mortality and improve quality of life. The major barrier to using this approach is the lack of data on specificity.

Delayed diagnosis of HAE: A case report of 39 years of misdiagnosis and inadequate treatment *(I. Martinez-Saguer, Hämophilie-Zentrum Rhein Main, Germany et al.)*
Early diagnosis of HAE could have prevented the patient from inadequate treatment and unnecessary surgical interventions. Furthermore, it could have facilitated appropriate treatment not only of painful gastrointestinal attacks but also of potentially fatal airway obstruction. It is therefore important to raise awareness of HAE among healthcare professionals.

Management of the pregnancies of a HAE patient treated with attenuated androgens since childhood *(Henriette Farkas, Semmelweis University, Hungary et al.)*
Our case illustrates that – notwithstanding the long-term use of attenuated androgens introduced as early as during childhood – pregnancy can be successful following appropriate planning and preparation. Irregular menstruation associated with Danazol therapy could delay the recognition of pregnancy. Further, Danazol taken during early pregnancy might contribute to spontaneous abortion. Pregnancy may have a different influence on disease symptoms. However, family planning, individualized management, and close patient surveillance are indispensable to success. In agreement with the data from the literature, plasma derived C1-INH was effective and well tolerated when administered as prophylaxis, as Individual Replacement Therapy, or for the acute treatment of edematous attacks – both during pregnancy and during breastfeeding.

Biochemical comparison of four commercially available C1 esterase inhibitor concentrates for treatment of HAE *(Thomas Machnig, CSL Behring, Germany et al.)*
The four commercially available C1-INH concentrates differ in their biochemical composition. Ruconest has the highest purity profile, followed by Berinert. However, due to glycosylation modifications, the C1-INH protein in Ruconest is not identical to the human C1-INH protein. This lack of glycosylation is associated with a considerably shorter half-life of Ruconest compared with plasma derived C1-INH concentrates. Cinryze and Cetor have more non-therapeutic proteins compared with Ruconest and Berinert. Currently, it is not known if long-term prophylaxis of these other plasma proteins may have an impact on treatment effects and/or side effects.
In order to harmonize the analysis for drug release testing, we recommend the strict adherence to existing international standards and the establishment of regulatory requirements for the determination of purity of C1-INH products by size exclusion chromatography.

Sustained response following acute treatment of HAE attacks with recombinant human C1 esterase inhibitor *(H. Henry Li, Institute for Asthma and Allergy Chevy Chase, USA et al.)*
Treatment with rhC1-INH resulted in a high response rate, assessed as the number of attacks with beginning relief within four hours. Most of these attacks were treated effectively with a single rhC1-INH dose. No significant relapses occurred within 24 hours for attacks with relief within four hours.
Incidence of recurrent or new attack symptoms within three days of rhC1-INH treatment is low. Single doses of rhC1-INH provide sustained and durable responses in the treatment of acute attacks.

Diagnosis and pathogenesis of HAE with normal C1-inhibitor: Role of molecular analysis *(Adriana Moreno, University of Sao Paolo, Brazil et al.)*
The Thr328Lys mutation in Coagulation Factor XII was identified in four Brazilian families with normal C1-Inhibitor. Molecular modeling studies suggested that mutations Thr328Lys and Thr328Arg may cause marked change in three-dimensional structure of FXII, and may lead to stronger binding to C1-INH.

Survey to evaluate the nurses' education and role in HAE self-/home treatment *(Karin Andritschke, HZRM, Germany et al.)*
To find out the actual status of the nurses' qualifications, education and responsibilities we want to carry out a survey among nurses caring for HAE patients. The aim is to characterize the situation of HAE nurses in different countries, to identify points of improvement, and to provide a basis to be used by nurses in different countries or internationally for the development of specialized educational programs or curricula. A questionnaire will be developed and we will ask the physicians to inform their nurses about this project. Interested nurses can contact us at karin.andritscke@hzrm.de.

Safety of C1-esterase inhibitor in acute and prophylactic therapy of HAE: Findings from the ongoing international Berinert® patient registry *(P. Busse, Mount Sinai School of Medicine New York, USA et al.)*
Results from the ongoing registry support the safety of Berinert in prophylactic and on-demand treatment of HAE. Berinert is not an independent causative risk factor for thromboembolic events. Abdominal attacks are most common but a significant share of subjects suffers from potentially life-threatening laryngeal and/or facial attacks. Home administration is a suitable and safe option. Individual dosing is commonly used for treatment of acute attacks and prophylaxis. Doses used are close to the currently recommended 20 LU/kg body weight.

International practice of self-administration in the management of HAE: Survey results and discussion from an international expert panel *(Timothy Craig, Penn State University, USA et al.)*
Internationally, the number of patients being offered and opting for self-administration therapy is increasing. All HAE patients who are willing and able should be considered for self-administration. The key to successful self-administration appears to be training in the technical skills required for infusion coupled with the availability of nurse/physician support. The outcome of self-administration is to improve time to treatment, quality of life, self-confidence and independence of HAE patients.

Practicalities of intravenous C1-inhibitor concentrate self-administration for HAE: Discussion from an international HAE expert meeting *(Timothy Craig, Penn State University, USA et al.)*
More needs to be done to encourage further uptake and adequate training in HAE centers. Patient training is not consistent across different countries due to varying levels of experience and resources. Setting up national centers of excellence could be a method of standardizing training internationally. Effective communication of key points of advice for self-administration to patients will help to build patient confidence in managing their disease by self-administration.
Several initiatives were suggested regarding practicalities and support networks for patients who self-administer treatment. These include a 24-hour helpline (as available for hemophilia patients), individual disease management programs and dedicated community training staff.

Recombinant human C1 inhibitor treatment does not affect D-dimer levels and is not associated with thromboembolic events in HAE patients *(Avner Reshef, Tel Aviv University, Israel et al.)*
Consistent with previous findings, D-dimer, an activation marker of coagulation/fibrinolysis, was elevated during HAE attacks compared with remissions. D-dimer levels were higher with submucosal compared with subcutaneous attacks. Elevated D-dimer levels were associated with acute attacks, but not with rhC1-INH treatment. High D-dimer levels during attacks imply that the parameter might be a biomarker of disease activity. No thromboembolic events were observed with rhC1-INH.

HAE nationwide study in Belarus *(Irina E. Guryanova, Belarusian Research Center for Pediatric Oncology, Hematology and Immunology, Belarus et al.)*
The ratio of symptomatic patients in Belarus is about 1:300,000. That is lower than, for example, the 1:50,000 reported by a nationwide study in Switzerland. Nearly four times more HAE patients have been diagnosed over the past two years than before, which shows the overall improvement of diagnostics.

Country presentations

During the general sessions representative of seven national HAE organizations provided valuable insights into the present state in their respective corners of the globe:

Germany
A group of young members of HAE Germany focused their presentation on the first HAE Youngsters Meeting that took place in Berlin in October 2013. The participants in the meeting gathered for workshops on topics such as Anxieties and Distresses, For girls only, For boys only, and How to learn self-administration. Also, they listened to lectures and they spent time together as tourists in the German capital.

This remarkable group of youngsters concluded their presentation with inspiring advice and a suggestion:

"Our advice to the youngsters: Tackle your future – its yours! You need to work on that every day! Just like we do and like we have done in the past. It is worth fighting for your future and therapy! It is your life! Tackle it to the best! With good treatment, you can reach everything!"

The German youth delegation suggested (1) an international meeting with affected children and adolescents to enable an exchange of experiences and mutual support, and (2) the idea of an International HAE Youngsters' Exchange allowing young people with HAE to visit HAE families around the world.

Australia and New Zealand
Ms. Fiona Wardman, President of HAE Australasia, spoke of both achievements so far and plans for the future.

HAE Australasia's presence on Facebook, a dedicated website, and media coverage have resulted in a doubling of membership. The organization has held national patient meetings, arranged patient meet ups around Australia, presented at Clinical Insights meetings – and helped Firazyr become accessible and reimbursed for patients in Australia.

Among the future projects of HAE Australasia are: A C1 Inhibitor submission support; helping patients in New Zealand get access to better treatment options; continued HAE educational outreach to the community and to healthcare professionals; patient meet ups around Australia and New Zealand; and the National Patient Meeting in 2015.

Macedonia

Even though HAE Macedonia is a small organization – 10 members – it is very active and has achieved at lot in a short period of time.

In her introduction to the situation in her country, HAE Macedonia President Ms. Natasha Jovanovska, said that general practitioners are not informed on this condition – and if they are, their hands are tied because there is neither a national solution, nor treatment for HAE.

Below are excerpts from Ms. Jovanoska's presentation:

There are frequent cases of misdiagnosis and patients often obtain medications from other countries even though this is not legal.

HAE Macedonia has been very active lobbying with government officials and other influential people. For instance the organization has met with the Director of the Pediatric Clinic, the Manager of the Health Insurance Fund, and the wife of the US ambassador to Macedonia who has shown a great interest in helping rare disease patients in Macedonia.

Among the other most recent activities in Macedonia are: The first Macedonian HAE symposium held in April 2013, the annual marathon in the capital Skopje in both 2013 and 2014, a concert in a public park in Skopje, and the production of two videos for YouTube. In one of these videos, aimed at informing the general public and raising awareness, HAE Macedonia managed to get support from people such as a famous Macedonian jazz composer, a European karate champion, the first Macedonian woman to climb Mount Everest, and a well-known rock musician from Macedonia.

Among the organization's plans are a HAE Caravan to medical clinics in order to educate medical staff in smaller towns in Macedonia, lobbying for a patient register for rare diseases, increased public pressure through traditional and social media, and a new approach to the Ministry of Health if it continues to ignore HAE patients.

Poland

Mr. Michal Rutkowski, President of HAE Poland, informed the delegates that the Polish organization since its foundation in 2005 has grown to 270 members – both patients and relatives – and that there are by now 142 women and 85 men diagnosed with HAE in Poland. However, there is only one HAE clinic center in the country, located in Krakow.

Below are excerpts from Mr. Rutkowski's remarks: 1 March 2013 was a ground-breaking date in the history of HAE Poland: After several years of fight the Ministry of Health officially approved the Swedish Orphan Biovitrum application, and issued a two year reimbursement permission for Ruconest. Another ground-breaking date in our history was 1 March 2014 when the ministry also officially approved the CSL Behring application, and issued a two year reimbursement permission for Berinert. Before these two events, HAE Poland had been in dialogue with the Ministry of Health regarding the possibility of drug reimbursement.

Although we frequently and consistently underscored that HAE is not an ordinary disease, but a complex disorder, the ministry turned a deaf ear. It was the death of two patients due to lack of access to medication in December 2012 and February 2013 that forced the ministry to listen. Why so late? Is death the only reason to respond?

HAE Poland held its first ever HAE workshop dedicated to physicians in May 2013, attracting 21 attendees from all over Poland as well as Belarus and Czech Republic, Sweden, and Italy. Mid October 2014, HAE Poland will be hosting the first Polish HAE patients and physicians conference, expected to attract some 100 participants from Poland as well as neighboring countries.

United Kingdom

In her presentation Ms. Ann Price, Chair of Trustees of the HAE UK, informed the audience that the UK National Health Service (NHS) has developed a strategy for management of rare conditions and established Clinical Review Groups to identify 'Specialized Conditions' and to develop new policies for treatment. HAE has been designated as a "Specialized Condition," and in April 2013 NHS issued a policy with service specifications for the management of acute HAE attacks. The policy includes accredited specialist centers, equality of access, and a five-year plan for the development and amendment of policies.

Ann told the audience that "The policy sets out the treatments that will be centrally commissioned and funded by the NHS. Under the policy, HAE attacks can be treated at the earliest possible stage with C1 Inhibitor or Icatibant. Suitable patients who experience frequent attacks affecting abdomen or airway should be offered training in home therapy."

Recently HAE UK has been involved in producing a patient summary of the NHS policy, a QIPP (Quality, Innovation, Productivity and Prevention) for home therapy, and a patient information booklet in line with NHS policy.

In 2005 HAE UK produced the first Consensus Document of Guidelines for the treatment of HAE. Now, the organization together with the UK Primary Immunodeficiency Network (a multidisciplinary organization of those caring for patients with primary immunodeficiencies) has commissioned the writing of a revised consensus document and HAE UK is represented on the writing panel. The new document will inform the level of HAE management in the UK over the next few years.

Japan

"It is nothing short of a miracle that we came here given that self-possession and self-infusion of Berinert is not authorized. Some of the patients who came with me signed up for this trip despite having never travelled overseas before, and the two doctors, who have accompanied us, worked tirelessly in the months leading up to the trip to cover all bases into terms of safety."

This is how Prof. Beverley Yamamoto, President of HAE Japan, described the efforts the Japanese delegation had to go through in order to attend the conference. As if that wasn't enough, the group got stranded in Canada on the way to Washington D.C. and arrived just in time for the time slot allotted to the Japanese delegation.

Below are excerpts from Prof. Yamamoto's presentation:

HAE Japan was established in 2013. Regarding the present situation in Japan, the total number of patients diagnosed with HAE in Japan were 292 as per March 2014 but there could be close to 5,000 undiagnosed patients out there. Although patients in Japan gained access to Berinert in 1990 – which is 19 years earlier than in the US – no other medications have been approved since. Japan is now behind many other countries with similarly high levels medical care infrastructure and with a similarly well-developed health care system. This leaves patients with no access to long-term prophylaxis other than attenuated androgens. Short-term prophylactic use of Berinert, which has been approved in Europe for example, is not approved in Japan. Perhaps even more constraining is that self-possession is not authorized.

This makes it very hard for patients to travel, whether for work, leisure of family reasons. Travelling in Japan has been made possible by the dedication of doctors and CSL Behring Japan staff who ensured that medication was on hand at the destination that a patient goes to. Travelling abroad is highly problematic as this trip made clear – and not all of us were issued with Berinert for travel, so we made the trip with very limited supplies. Patients I have spoken to to-date have either curtailed all travel overseas and in Japan as well, or they have travelled without an effective emergency medication for an acute attack. The current situation severely impacts quality of life and places patients at risk. It also overburdens doctors with HAE patients.

According to Prof. Yamamoto, tranexamic acid has been used widely and is still recommended in the only Japan-based HAE guidelines. This can cause a delay in appropriate treatment and provides doctors and patient information that many involved in HAE advocacy and care would probably find problematic.

According to Prof. Yamamoto, the short term goals of HAE Japan is self-infusion and self-possession of Berinert, recognition of Berinert for short-term prophylactic use, raising awareness so there is faster diagnosis, and increasing the range of authorized effective medications.

Argentina

As part of her presentation regarding South America as a whole, (see below) Ms. Alejandra Menendez, President of HAE Argentina, gave a brief overview of the situation in her home country. Ms. Menendez noted that Argentina holds a privileged position within the region because patients have access to two of the current treatments and there is progress being made in the acceptance of self-treatment.

According to Ms. Menendez, "What still has to be worked on is the fact that there are reimbursement difficulties as HAE is not included on the list of rare conditions in Argentina. As a consequence, the transition to self-treatment is still rather slow."

Regional presentation: Latin America

Ms. Menendez reported that the first Latin American Patient Advocacy Forum took place in Buenos Aires, Argentina (December 2013). Delegates from nine countries (Argentina, Brazil, Chile, Colombia, Ecuador, México, Panamá, Uruguay, and Venezuela) with approximately 15,000 people affected by HAE took part. The purpose of the meeting was to achieve a better understanding of the current HAE situation in Latin America, to agree on activities to improve patients' quality of life, and to initiate a report on the state of HAE management in the region.

While Argentina, Brazil and Mexico are the only countries with legally constituted HAE patient groups, Colombia and Chile are in their initial stages of organizing HAE groups, and hopefully Venezuela will also form an HAE organization.

Fresh frozen plasma is still very much used for emergency situations in all the countries where no other therapies are available. Nadroprarine (heparin) is prescribed in Mexico when none of the other treatments are available.

Ms. Menendez stated that, "The biggest challenges for HAE patients in the Latin American region is the lack of recognition by health authorities that it is indeed a serious, rare, debilitating, life threatening condition. There is a need to facilitate diagnosis and patient identification, raise awareness among the medical community, and promote the creation of national patient groups. Furthermore, there is much work to be done in order to guarantee accessibility as treatments become available, educate patients and promote self-treatment aiming at an optimal management of the condition.

The lack of knowledge about HAE and the lack of acute treatments poses an alarming threat to the patients. There is a huge amount of work to be done – and only creating a good synergy among all the parties involved would help gradually revert this devastating situation.

From the general session

President Anthony J. Castaldo, HAEi: Because it's personal
In his presentation, Mr. Castaldo asked patients to think about the very personal pain and suffering caused by HAE and stressed that there is only one way for us to prevent or eradicate HAE and that is by taking action. He then went to challenge HAE friends to build their local organization because there is strength in numbers. Mr. Castaldo then discussed the importance of forging partnerships to sharpen advocacy efforts, finding and working with doctors who show an interest in helping HAE patients, and seeking out industry representatives to collaborate on raising awareness and broadening access to life saving medicines. He advised fellow patients to, "Never take no for answer, be creative, and don't hesitate to ask HAEi for advice and assistance…and never forget: HAE is personal!"

Prof. Bruce Zuraw (University of California San Diego, USA): HAE – a scientific-medical perspective
Prof. Zuraw provided the audience with an insightful overview of HAE science. Below are excerpts from the non-scientific part of Prof. Zuraw's presentation.
HAE is a rare disease with a widely dispersed patient population. As such, the logistic and financial barriers to studying rare diseases are amplified. The ability to utilize the Internet to create a cohesive interactive patient registry transcends these obstacles. The establishment of a defined patient cohort naturally facilitates scientific investigation to establish biologic mechanisms, diagnostic testing and enhance competitiveness for external funding. A partnership created between the physician and patient community can then effectively network with the pharmaceutical industry to develop targeted management strategies. Much of the progress made to date results from patient centered organizations (such as HAEi and its NMOs) that unify patient communities and advocate for treatment and scientific advancement.

Prof. Michael Frank (Duke University, USA): HAE – background and treatment in America
Prof. Frank who is HAE pioneer in the United States provided a fascinating overview of the scientific history of HAE. Prof. Frank introduced us to the key scientists whose work established the framework for modern HAE diagnosis and therapy.

Prof. Henriette Farkas (Semmelweis University, Hungary): The challenges of treating children and women with HAE
Below is a brief summary of Prof. Farkas' presentation:
Women are more likely to experience symptoms of HAE than men and it may worsen during the premenstrual period. Estrogen-containing combined contraceptives and estrogen replacement therapy may exacerbate the symptoms just as pregnancy and breastfeeding can aggravate them. Many patients experience worsening during menopause.
For long-term prophylaxis plasma derived C1-INH concentrate is safe and effective during both pregnancy and lactation. As for antifibrinolytic, these agents can be used when plasma derived C1-INH is unavailable, but are not recommended during breastfeeding. Attenuated androgens are not recommended during pregnancy. Plasma derived C1-INH is the drug of choice before amniocentesis, surgical abortion, forceps delivery or vacuum extraction as well as cesarean section.
Plasma derived C1-INH concentrate is recommended as first line acute therapy for women with HAE during both pregnancy and lactation.
Because of their superior safety profile, antifibrinolytic agents are preferred to attenuated androgens when it comes to long-term prophylaxis for children. Attenuated androgens influence the development of secondary sexual characteristics, psychic functions and behavior as well as premature closure of epiphyseal growth plates. Plasma derived C1-INH concentrate is an effective and safe agent for acute attacks in children.


BRUCE ZURAW
abranghe

Assoc. Prof. Aleena Banerji (Harvard Medical School, USA):
HAE into the future

Below is a summary of Assoc. Prof. Banerji's presentation:

• **Individualized Management Plans:** Every HAE patient is different with unique needs, experiences and perspectives; all patients should have on-demand treatment available; patients should be counseled to treat as soon as the attack is clearly recognized; all patients should be trained in self-administration; treating physician and patient must establish a strong partnership with regular clinical follow-up; the physicians' knowledge of when patients require on-demand treatment is a key aspect of optimal management of HAE; all patients taking HAE medications need to be periodically monitored for potential adverse effects of the medications

• **Home Based Therapy:** Home therapy improves patient quality of life; reduces use of emergency services; lowers the number of absences from work or school; and should be considered for all patients because attacks should be treated as early as possible

• **Evidence Based Guidelines:** Useful, among other things, as a tool for increasing knowledge of treatment options and optimizing HAE management.

Continued development of novel therapies:

• **Subcutaneous C1 Inhibitor replacement therapy:** Clinical trials being conducted by two manufacturers.

• **DX-2390 – Plasma Kallikrein Inhibitor (subcutaneous):** In single dose escalating trial in healthy subjects DX-2930 was well tolerated at all dose levels with no serious adverse events.

• **BCX4161 – Kallikrein Inhibitor (oral):** Successful Phase IIb clinical trial with positive proof of concept--additional trials are being planned.

Future novel diagnostics/therapeutics:

• **Factor XIIa inhibitor:** Fully human function-neutralizing antibody that binds into the FXIIa enzymatic pocket

There a still many unanswered questions: Why is there only local bradykinin during an HAE attack? Why are HAE symptoms of swelling intermittent? What is the mechanism of bradykinin generation in nonhistaminergic angioedema? What would be a better diagnostic tool? Can we consider gene therapy?

President Anthony J. Castaldo and Executive Director Henrik Balle Boysen, HAEi:
A global assessment of HAE management

The HAE patient organization leaders from 26 countries provided data in response to an HAEi online global assessment survey that addressed a variety of issues related to HAE management. Below are some of the findings from the survey.

Of the 26 countries included in the survey, we found that in :

• 25 % there is no modern therapy registered,
• 30 % there is no reimbursement for HAE therapies,
• 55 % patients do not have at least two treatments available to treat acute attacks,
• 60 % patients are not allowed to self-administer,

"The global assessment confirmed that there still is much to be done!"

• 60% emergency room doctors have poor or very poor knowledge of HAE,
• 70 % patients are not allowed to treat all attacks,
• 75 % the average physician (including family doctors) has poor or very poor knowledge of HAE,
• 80 % patients have limited influence on their choice of therapy, and
• 88 % HAE has a moderate to severe impact on quality of life.

In two thirds of the countries where modern therapies are available, medications may only be used for life-threatening or severe attacks and treatment of extremity attacks is discouraged.

One of the survey respondents summed it up best:

"The HAE patients themselves count for the biggest challenge. We have to realize that they need to be better informed about their disease, as they can't expect physicians to carry the knowledge. Also there is a need for the patients to realize that it is okay to treat attacks – to remove the 'guilt' they feel about 'spending money'."

From the general session

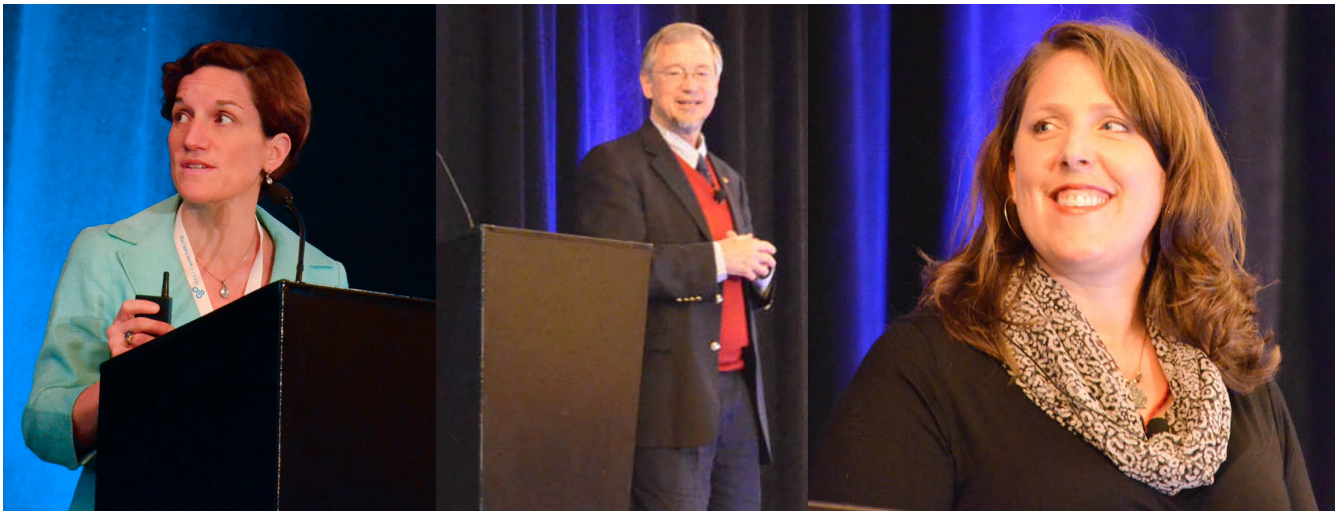
Suzanne Wait, Phd. (SHW Health Ltd., United Kingdom):
Significant findings from the European burden of illness study
The key messages from the study are that HAE is an unpredictable and serious disease, there is no 'typical' HAE patient, and that the disease impacts people not just during, but also in between attacks. Furthermore, HAE results in missed opportunities in terms of school and career, and has a significant impact on the entire family. The study also supports the notion that treatment of HAE varies across countries and across patients. Dr. Wait stated that in order to make policymakers listen patients must provide clear messages supported by strong evidence. She also made some recommendations: Patients and family members should always tell persona stories that reveal the devastating human impact of this disease. Use personal stories together with any available guidelines as your advocacy tools. Educate the policymakers to dispel any lingering myths. Demonstrate inequalities in access to care. Clearly show what is being done wrong and where improvements are needed. Also, remember to show the economic impact. Propose an easy to understand approach that helps the policymakers feel that they can make a difference.

The ultimate goal is to enable every patient to lead a normal life by limiting, and if possible preventing, the pain and suffering caused by HAE attacks. Each patient should have an individualized treatment plan and access to the most effective and appropriate treatment at all times.

The European burden of illness study can be used to help raise awareness of HAE with policymakers, to communicate to doctors the impact of HAE on the lives of those affected, and to improve awareness and understanding of HAE among the general public. Also, the study can be used to support the fact that HAE patients can lead a relatively normal life when provided access to appropriate treatment and care.

Frank J. Sasinowski, Board Member, National Organization for Rare Diseases (USA):
Patient power on the rise!
Mr. Sasinowski discussed, among other things, the growing role that patients are playing in the drug regulatory process. He cited the Food and Drug Administration Safety and Innovation Act (signed by President Obama in July 2012) which requires the US Food and Drug Administration (FDA) to "implement strategies to solicit the views of patients ... and consider the perspectives of patients during regulatory discussions." Mr. Sasinowski believes that we are on the threshold of a whole new era in which the patient's voice is finally getting heard. He urged the global HAE patient community to petition their governments and demand a greater voice for patients in (1) regulatory decisions governing licensing of medicines, and (2) decisions regarding access to and reimbursement for medicine.

Melissa Hogan, Patient Advocate, Blogger, Saving Case & Friends Website (USA):
An advocate by necessity – a mother's story
Ms. Hogan is the mother of a little boy with a rare disease called Hunter's Syndrome. She is an indefatigable patient rare disease patient advocate who has not only helped her son, but inspires many others suffering from Hunter's Syndrome and other rare diseases.
Ms. Hogan provided the HAE community with some invaluable recommendations on how to be an effective advocate:
"My advice for advocacy in health care could be summed up in four steps:
- Educate yourself – how can you argue for something that you don't know about?
- Educate those you are dealing with
- Ask for what you need – kindly, but firmly, assert your rights
- Effectively assert your influence
Patients are the key. Doctors may know the disease medically; the pharmaceutical companies may know the drugs pharmaceutically; but only patients and caregivers know the life, the abilities and challenges of patients, the disease in action, and the drugs in action."



From the general session

Assoc. Prof. Marc Riedl (US HAEA Angioedema Center San Diego, USA):

The importance of patient advocacy – a physician's perspective

Dr. Riedl's presentation is summarized below:

"A correct and timely diagnosis is a key step in proper management of HAE. Unfortunately, there is often a long interval between onset of symptoms and establishment of the diagnosis. It is likely that a significant number of HAE patients remain improperly diagnosed. Considering the unique treatment strategies required and the potential morbidity and mortality associated with attacks, it is critical to establish the correct diagnosis of HAE as early as possible.

Understand that it may take some effort to find a doctor for your condition, needs, and personality. It is important that patients recognize that there are options for treatment and that they should obtain information about the options and discuss them with their family. In preparation for a visit with the doctor, patients should write down questions in advance and be clear about their goals and expectations for treatment. Patients should tactfully, but confidently assert their views about which treatment plan would be a good fit - and understand that the doctor may need some time to gather information or pursue the treatment that is requested. Patients must be willing to do their part of the 'legwork' in arranging a treatment plan.

Do not expect the health care system to automatically be prepared for your treatment needs - or your doctor to 'fix' all past difficulties. Don't underestimate the complexity of treating HAE and don't be alarmed if your physician wishes to get input from other specialists.

Patients are their own best advocates, but the physician is an essential partner for successful management – so find a good match. Patients know their situation and needs better than anyone; and your physician will value clear, concise information and communication. Keep in mind that treatment plans require teamwork, planning, and effort by both you and your physician."

The Final Session - A Patient-Physician Q&A Session

During the last conference session, the audience had 90 minutes to ask HAE world class HAE physician/scientists questions about any topic related to HAE. This was a highly successful segment that produced important information about the HAE diagnosis and treatment as well as tangible suggestions for solving real world HAE-related problems.

A Closing Message

Before adjourning the 2014 HAE Global Conference, HAEi President Anthony Castaldo thanked the patients, caregivers, and medical professionals for attending and also thanked the pharmaceutical companies for their generous support.

Mr. Castaldo summed things up with a call to action that challenged each attendee to use some of the insights and ideas learned during the conference to "Set New Standards" and improve the lives of HAE patients in their respective countries.

Your feedback is very welcome

Please let us know what you believe should be included in future newsletters. You can do that by providing feedback to Executive Director Henrik Balle Boysen or Communications Manager Steen Bjerre. In addition, we invite you to submit articles on any topics that you believe would be of interest to other readers. We look forward to your comments and working with you on future newsletters.

We hope to see all of you at the 2016 HAE Global Conference

A warm thank you to the 2014 HAE Global Conference Supporters:

Diamond Supporters:

Shire

ViroPharma Incorporated

Gold Supporter:

CSL Behring
Biotherapies for Life™

Silver Supporter:

Dyax

Basic Supporters:

BioCryst Pharmaceuticals, Inc.

Salix Pharmaceuticals, Inc.
Advancing Treatment in Gastroenterology™

HAEi is a global non-profit umbrella organization dedicated to working with its network of national HAE patient organizations to raise awareness of HAE.

NEWSLETTER STAFF

Steen Bjerre
Communications Manager
E: s.bjerre@haei.org
P: +45 22 20 46 01

Henrik Balle Boysen
Executive Director
E: h.boysen@haei.org
P: +45 31 591 591

Subscription
if you would like to subscribe to our Newsletter - please send us an email: info@haei.org - or register directly on our website www.haei.org

HAEi Newsletter
HAEi - Hereditary Angioedema International Association

HAEi

hae day :-)
MANY FACES ONE FAMILY