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To the Editor,

Hereditary angioedema (HAE) is a rare disease characterized by spontaneous and recurrent subcutaneous and submucosal swellings, caused by autosomal dominant inheritance of C1-inhibitor (C1-INH) deficiency. Acquired angioedema (AAE) is an acquired form of C1-INH deficiency with similar symptoms. HAE with normal C1-INH levels can be caused by mutation in the gene encoding coagulation factor XII, angiopoietin-1, or plasminogen(1).

To improve patient care and research, a set of variables should be recorded for every angioedema attack(2). Reporting these variables can be challenging for patients, so we developed an electronic reporting platform available for smartphone in 2013, hypothesizing it would increase compliance in documentation and make real-time registration easier. The platform content was constructed according to international guidelines(2). This method has yielded detailed real-time and real-life data, and we wish to present our findings. This is the first publication reporting the use of such a method in AAE and HAE.

This observational study took place at the HAE Centre Denmark between September 2013 and September 2016. Patients were instructed to make real-time entries on their smartphones - or computer if a smartphone was not accessible - of the following events: symptom onset, treatment, change of severity, and resolution of the attack. The application would automatically log the timing of entries and ask for additional data on anatomical location, treatment, hours of absence from work/school, efficiency and side effects of treatment, and if the attack prompted contact with healthcare providers.

All patients signed an informed consent. Permission for access to data was granted by the Danish Data-Protection Agency (14/46172).

All analyses were performed using Stata (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

The study population comprised 44 patients (21 women) who had consistently utilized the application for at least eight months. Forty-two patients suffered from HAE, two suffered from AAE.

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Patients reported 2148 attacks, with an average of 1.9 attacks/month per patient (range 0.2-5.5). Attack frequency was significantly lower among males than among females with an incidence rate ratio (IRR) of 0.62 ( $p<0.001$  and 95%CI 0.52;0.73). For each year of delay in disease debut, attack frequency was significantly lower, IRR 0.97 ( $p<0.001$  and 95%CI 0.96;0.98). Analyses were performed using Poisson regression on the last eight months of data from all HAE patients, due to varied follow-up times. Mean attack duration was 19.4 hours (SD 19.1), calculated from 1047 correctly recorded attacks (both attack onset and resolution were recorded). Eighty-eight percent of attacks were treated. Based on 1770 attacks correctly recorded, the average time from symptom onset of an attack until treatment was 2.9 hours (SD 9.4). All patients were offered C1-INH concentrate and adults were further suggested to use icatibant. Twenty-four patients treated acute attacks with C1-INH concentrate, while 12 patients used icatibant. Eight patients alternated between icatibant and C1-INH concentrate, and treated a total of 15 attacks with both icatibant and C1-INH concentrate. Forty HAE patients reported 934 attacks with data on both attack duration and corresponding time to treatment. Multilevel mixed-effects linear regression was performed on this data, to test the effect of time to treatment on attack duration. Attacks were stratified as treated before or after one, two and six hours in three separate models (Figure 1).

Attacks treated within one, two and six hours of symptom onset were 6.5 (95%CI 4.2;8.8), 8.3 (95%CI 6.0;10.5) and 13.5 (95%CI 10.7;16.3) hours shorter than when treated after these time points ( $p<0.001$ ). Potential confounders were included in the models, but were not significant (Figure 1).

Multilevel mixed-effects linear regression was also performed on data from the 934 attacks to explore variables affecting time from symptom onset to treatment (Figure 2). Average attack frequency experienced by individual patients was significantly correlated to time to treatment of attacks. As attack frequency increased by one attack/month, time to treatment decreased by 2.1 hours ( $p=0.01$  and 95%CI (-3.6;-0.5)). Potential confounders were included in the model, but were not significant (Figure 2).

Angioedema attacks resulted in 4310 hours of absence from work/school and caused 98 emergency department visits, five hospitalizations and five visits to general practitioners.

The average attack frequency was 1.9/month, which is higher than many studies using retrospective reporting, but similar to other studies using prospective reporting (3-6). This could be because it can be hard to motivate patients with less impact on quality of life to participate in prospective studies, or due to recall bias in retrospective studies.

Being female and having an early disease debut are predictors of a higher attack frequency in HAE. A German study made similar findings(7).

Mean attack duration was 19.4 hours in this study. The IMPACT2 study(8), found a median attack duration of 15.5 hours (patients exclusively used C1-INH concentrate).

We found a significant correlation between time to treatment and attack duration. Similar trends were described by Maurer et al., who reported attack durations of 6.1, 7.2 and 8.0 hours when attacks were treated before one, two and five hours respectively(9). The shorter attack durations described by Maurer could be related to attacks being treated with icatibant. We had the impression, that patients in our cohort using both C1-INH concentrate and icatibant preferred to treat less severe attacks with icatibant. Squeglia et al. reported that being able to self-administer C1-INH concentrate was correlated with a shorter time from symptom onset to treatment, though not statistically significant(4).

We found that average attack frequency, and not the ability to self-administer therapy, predicted time to treatment. Possibly because patients who experienced fewer attacks did not recognize the very early symptoms of an attack, due to less experience with angioedema attacks.

Using the application did not guarantee perfect compliance, as fifty-one percent of attacks had missing data on the resolution of attacks. We believe that increased focus on applying personalized attack-data in consultations could help physicians and patients optimize disease understanding and treatment, and thus motivate greater compliance in registrations.

In conclusion, real-time reporting through smartphone yielded clinically relevant information on attacks and treatment. We recommend using this method in research and clinical settings.

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## Conflict of Interest Statement

Kristian Kreiberg:

Has attended an advisory board for CSL Behring; received funding to attend conferences and other educational events from CSL Behring, Shire and Biocryst; received speaker fees from CSL Behring and Shire; participated as a study coordinator in a clinical study performed by Biocryst.

Anette Bygum:

Has been involved in clinical research and educational events involving CSL Behring, Shire, Dyax and BioCryst.

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## Figure Legends

### *Figure 1*

Bar graph of predictive margins with 95% confidence intervals illustrating how time to treatment of an attack affects attack duration. Based on Multilevel mixed-effects linear regression of 934 attacks. Further covariates included in the models: using icatibant compared with C1-INH concentrate (at one hour  $p=0.9$ , at two hours  $p=1.0$ , at six hours  $p=0.7$ ), being on prophylactic treatment (at one hour  $p=0.8$ , at two hours  $p=0.8$ , at six hours  $p=0.7$ ), and having a cutaneous or laryngeal attack, as compared to an abdominal attack (at one hour  $p=0.9$  and  $p=0.8$ , at two hours  $p=0.8$  and  $p=0.9$ , at six hours  $p=0.7$  and  $p=0.8$ ).

### *Figure 2*

Predictive margins with 95% confidence interval illustrating the relationship between monthly attack frequency and the time from symptom onset to treatment of an attack. Based on Multilevel mixed-effects linear regression of 934 attacks. Beta = -2.1 hours ( $p=0.01$  and 95%CI (-3.6;-0.5)). Further covariates included in this model: being able to self-administer on demand therapy ( $p=1.0$ ), using icatibant compared with C1-INH concentrate ( $p=0.3$ ), and having a cutaneous or laryngeal attack, as compared to an abdominal attack ( $p=0.5$  and  $p=0.8$ ).



