

# Physician and patient perspectives on the management of hereditary angioedema: a survey on treatment burden and needs

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## ABSTRACT

*Hereditary angioedema (HAE) is a rare disorder caused by genetic mutations that lead to recurrent episodes of swelling in various parts of the body. Prophylactic treatment is common for patients with HAE, and the therapeutic options have expanded in recent years. The current standard of care for prophylactic HAE therapies is subcutaneous treatment, which can be self-administered at home, greatly improving patient quality of life. As new therapies emerge, it is important for patients and physicians to discuss the risks and benefits associated with each treatment to develop an individualized approach to HAE management. We conducted surveys of patients with HAE and physicians who treat patients with HAE to identify prescribing trends for prophylactic HAE treatments and the impact that such treatments has on patients. Our results confirmed that newer, subcutaneous therapies are prescribed for HAE prophylaxis more frequently than other therapies in the United States and that treatment burdens still exist for patients with HAE. We found that physicians and patients were not always aligned on how treatment choices affect patients' lives, which may mean that there are opportunities for enhanced patient-physician dialog and shared decision-making in HAE management in the United States.*

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**H**ereditary angioedema (HAE) is a rare, genetic disease characterized by recurrent, unpredictable, and potentially life-threatening angioedema attacks in various parts of the body. The HAE treatment landscape is rapidly evolving to include new therapies with various mechanisms of action, routes of administration, and dosing schedules.<sup>1–4</sup> With this expanding

armamentarium, it is important to understand how physicians' prescribing practices are changing and how these may affect patient treatment burden and satisfaction. A physician survey conducted in 2019 in the United States identified several prescribing trends over the past decade, including a preference toward prescription of newer subcutaneous (SC) prophylaxis options over older intravenous (IV) prophylaxis options; reduced use of androgens for prophylaxis; and less concern for adverse events in general.<sup>5</sup> The study also described high levels of physician-reported patient satisfaction with their current treatment.<sup>5</sup>

Personalized therapy is essential to optimizing HAE treatment because symptoms, lifestyle, and characteristics are unique to each individual.<sup>4,6</sup> The decision to use prophylactic HAE medication should be shared between a patient and his or her physician, and tailored to the needs of the individual patient.<sup>4,6</sup> Demonstrated benefits of shared decision-making in other disease states include patients identifying treatment options based on their personal preferences and treatment goals, and patients developing a better understanding of the therapy options available to them (including the risks and benefits associated with each treatment).<sup>6–9</sup>

To better understand patients' and physicians' experiences with prophylactic HAE treatment, we conducted, in the United States, two separate but parallel surveys of patients with HAE and physicians who treat patients with HAE. The objectives of the surveys were to identify

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Table 1 Physician characteristics

	Physicians by Specialty		Number of Patients with HAE Treated per Year		Total (N = 109)
	A/I (n = 77)	Other (n = 32)	≥6 (n = 63)	0–5 (n = 46)	
Men, n (%)	60 (77.9)	21 (65.6)	47 (74.6)	34 (73.9)	81 (74.3)
Age, mean ± SD, y	51.8 ± 10.6	48.2 ± 9.7	50.8 ± 11.1	50.7 ± 9.4	50.8 ± 10.4
Region, n (%)					
South	28 (36.4)	8 (25.0)	14 (22.2)	22 (47.8)*	36 (33.0)
Midwest	19 (24.7)	13 (40.6)	24 (38.1)	8 (17.4)*	32 (29.4)
Northeast	18 (23.4)	6 (18.8)	17 (27.0)	7 (15.2)	24 (22.0)
West	12 (15.6)	5 (15.6)	8 (12.7)	9 (19.6)	17 (15.6)
Years in practice, mean ± SD	18.4 ± 7.8	16.7 ± 7.7	17.6 ± 7.6	18.3 ± 8.1	17.9 ± 7.8
Primary medical specialty, n (%)					
A/I	77 (100.0)	0	40 (63.5)	37 (80.4)	77 (70.6)
Other	0	32 (100.0)	23 (36.5)	9 (19.6)	32 (29.4)
Primary setting, n (%)					
Private practice/clinic	71 (92.2)	27 (84.4)	55 (87.3)	43 (93.5)	98 (89.9)
Academic hospital	5 (6.5)	4 (12.5)	6 (9.5)	3 (6.5)	9 (8.3)
Community hospital	1 (1.3)	1 (3.1)	2 (3.1)	0	2 (1.8)
Familiarity with HAE					
Score#, mean ± SD	6.4 ± 0.7	5.5 ± 0.8§	6.2 ± 0.8	6.1 ± 0.8	6.1 ± 0.8
No. patients with HAE seen per year, mean ± SD	7.0 ± 5.3	8.9 ± 6.9	11.9 ± 6.0	3.9 ± 1.2*	7.4 ± 5.7
Type I	4.9 ± 4.0	4.6 ± 3.6	7.8 ± 4.2	2.5 ± 1.2*	4.8 ± 3.9
Type II	1.3 ± 1.7	3.2 ± 3.0§	2.9 ± 2.7	0.8 ± 0.9*	1.7 ± 2.2
With normal C1-INH (formerly known as type III)	0.8 ± 1.4	1.2 ± 1.5	1.3 ± 1.9	0.5 ± 0.7*	0.9 ± 1.4
No. patients with HAE actively treated, mean ± SD	7.0 ± 5.3	7.1 ± 6.6	11.4 ± 6.0	3.7 ± 1.3*	7.0 ± 5.6
No. patients with HAE referred to another physician, mean ± SD	0	1.8 ± 2.4§	0.6 ± 1.9	0.2 ± 0.7	0.4 ± 1.3

HAE = hereditary angioedema; A/I = allergy/immunology; SD = standard deviation; C1-INH = C1-inhibitor.

\* $p < 0.05$  for ≥6 versus 0–5 patients with HAE per year.

§Based on a rating scale ranging from 1 (lowest, not at all familiar) to 7 (highest, extremely familiar).

§ $p < 0.05$  for A/I specialists vs other specialists.

HAE prescribing practices, prophylaxis-associated treatment burden, and treatment preferences. Here, we report results from the physician survey regarding their perceptions of prophylactic HAE treatments and how physician and patient perspectives differ. The complete results of the patient survey can be found in Radojicic *et al.*<sup>10</sup>

## METHODS

### Study Design and Participants

The physician survey was conducted as part of a series of three blinded online surveys in 2020 that examined the perceptions of HAE-related burdens and treatment preferences from perspectives of patients, caregivers, and physicians. The complete methodology of all three surveys is reported in Radojicic *et al.*<sup>10</sup> This article describes the responses obtained from physicians and patients. As described in Radojicic *et al.*,<sup>10</sup> this study was reviewed by the Western Institutional Review Board and was found to qualify for exempt status. Before release of the surveys, the survey instruments were pilot tested with five patients and five physicians (four allergy/immunology [A/I] specialists and one primary care physician) to evaluate their face validity. Minor wording changes to improve clarity and relevance were made to the surveys based on feedback from these participants.

Physicians were eligible for the study if they met the following inclusion criteria: board certified in A/I, internal medicine, primary care, general practice, family practice, pulmonology, rheumatology, or hematology/oncology; worked in an academic or community hospital, or private practice in the United States; had been in practice for 2–35 years; saw at least 300 patients per year; actively treated patients with HAE and saw two or more patients with type I or type II HAE per year; and prescribed prophylactic medication for HAE. Patients were eligible for the study if they met the following inclusion criteria:  $\geq 18$  years of age, resident of the United States, a diagnosis of type I or type II HAE by a health care professional as reported by the patient, and currently receiving HAE prophylaxis (defined as medication taken on a regular schedule to prevent HAE attacks before they start).

### Measures

The physician survey included 14 screening items, 30 base items that all respondents were asked, and 4 additional items with conditional bases. The patient survey included 13 screening items, 49 base items that all respondents were asked, and 16 additional items with conditional bases.

### Data Analysis

All data were anonymized and analyzed in aggregate, and a descriptive statistical analysis of the data was performed. Data were analyzed for all physicians,

Table 2 Patient characteristics

	Total (n = 75)
Age, mean $\pm$ SD, y	44.1 $\pm$ 13.4
Region, n (%)	
South	32 (43)
Midwest	14 (19)
Northeast	17 (23)
West	12 (16)
Years since diagnosis, mean $\pm$ SD	24.6 $\pm$ 14.4
HAE type, n (%)	
Type I	58 (77)
Type II	17 (23)
No. HAE attacks in the past 6 months, mean $\pm$ SD	6.1 $\pm$ 6.3
Duration of treatment for HAE, mean $\pm$ SD, y	15.1 $\pm$ 12.0
Primary HCP specialty for HAE treatment, n (%)	
Allergy/immunology	64 (85)
Internal medicine	5 (7)
Primary care, general, family practice	3 (4)
Pulmonology	1 (1)
Rheumatology	1 (1)
Other	1 (1)

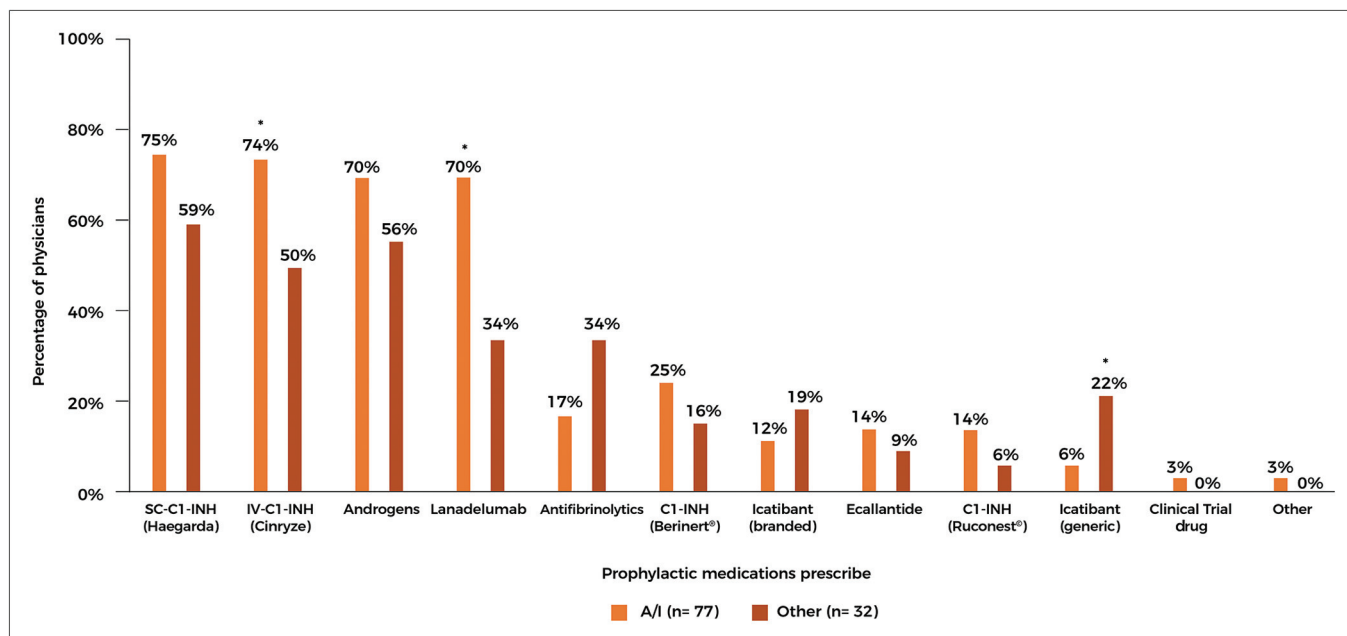
SD = standard deviation; HAE = hereditary angioedema; HCP = health care professional.

and for subgroups defined as A/I specialists versus all other specialists (“other”), and physicians who treated six or more patients versus zero to five patients with HAE per year. For comparisons between physician and patient responses, all surveyed physicians were compared with all surveyed patients. Student’s *t*-tests and *z*-tests were used to assess statistical significance between means and percentages, respectively. Statistics were unweighted and did not account for demographic variation. Extreme outliers were removed from mean calculations. Percentile values were rounded to the nearest whole number.

## RESULTS

### Respondent Characteristics

A total of 109 physicians (77 A/I specialists and 32 other physicians) completed the survey between May 19 and June 14, 2020. The mean length of time that the physicians had spent in clinical practice was 17.9 years, and the mean number of patients with HAE treated per year was 7.4 (4.8 type I, 1.7 type II, and 0.9 HAE with normal C1-inhibitor [C1-INH]). Sixty-three respondents (58%) reported treating six or more patients with HAE per year. The physicians reported a mean score of 6.1 on



**Figure 1.** Prophylactic medications prescribed for HAE by physicians by specialty type (\* $p < 0.05$ ). HAE = hereditary angioedema; A/I = allergy/immunology; C1-INH = C1-inhibitor; IV = intravenous; SC = subcutaneous.

a 7-point scale of self-reported familiarity with HAE; the mean score  $\pm$  standard deviation was significantly higher for A/I specialists compared with other specialists ( $6.4 \pm 0.7$  versus  $5.5 \pm 0.8$ ;  $p < 0.05$ ). Physician characteristics are displayed in Table 1.

Seventy-five patients completed the survey between May 20 and June 10, 2020. Eighty percent of the respondents were women, the mean age was 44.1 years, and the mean time since diagnosis of HAE was 24.6 years. Seventy-seven percent of the respondents had type I HAE and 23% had type II HAE. Eighty-five percent of patients were treated for their HAE primarily by A/I specialists, and most patients reported using lanadelumab (53%), SC C1-INH (25%) (Haegarda; CSL Behring, King of Prussia, PA), or IV C1-INH (8%) for prophylaxis at the time of the survey. The complete results of the patient survey have been reported separately and can be found in Radojicic *et al.*<sup>10</sup> Patient characteristics are displayed in Table 2.

### Prophylactic Prescribing Practices

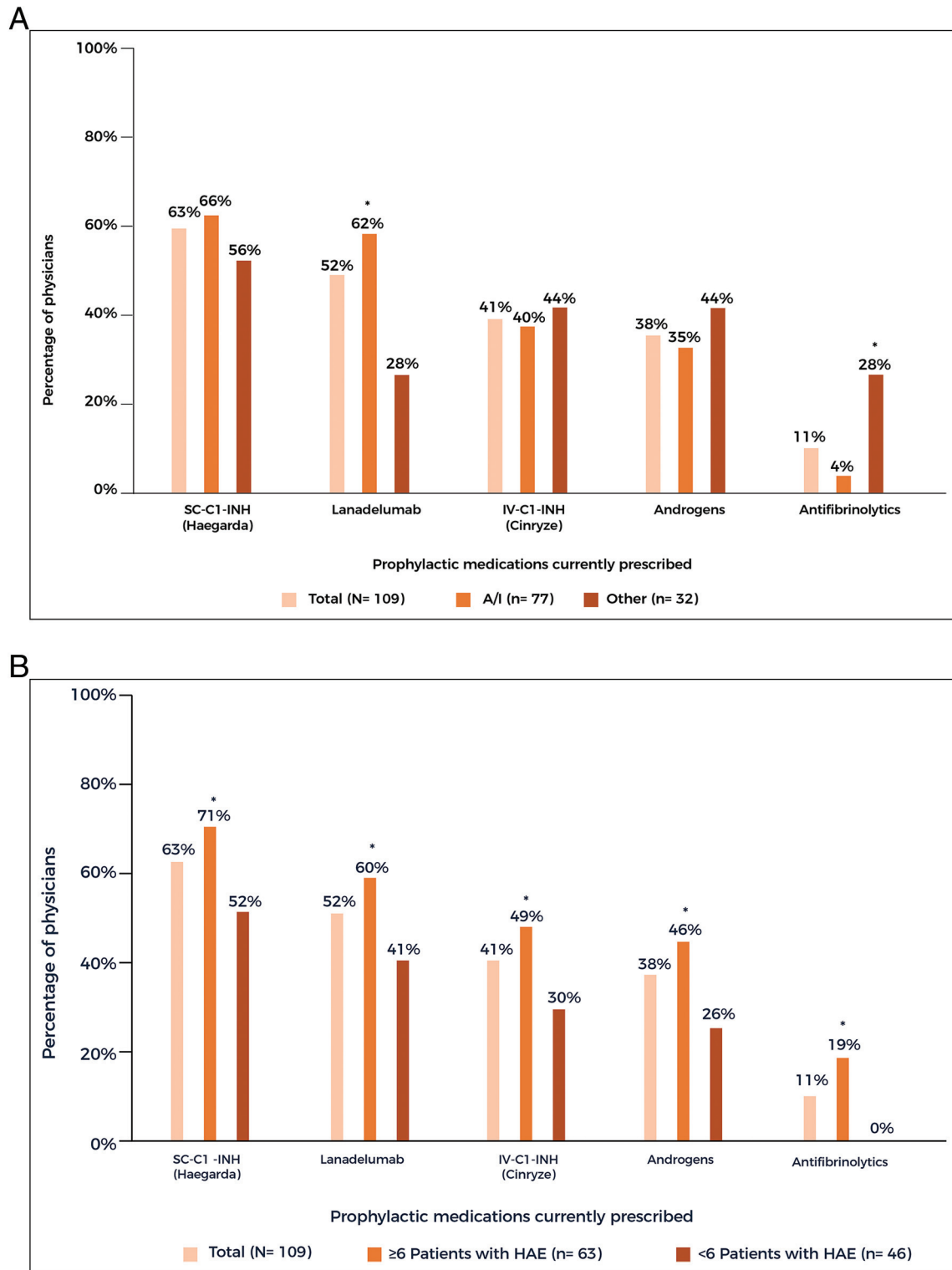
Physicians reported familiarity with the medications commonly used to manage HAE, having experience in prescribing SC C1-INH (71%), IV C1-INH (67%), androgens (66%), and lanadelumab (60%). Although all the physicians surveyed had experience with HAE medications, A/I specialists were significantly more likely than other specialists to have prescribed IV C1-INH (74% versus 50%;  $p < 0.05$ ) and lanadelumab (70% versus 34%;  $p < 0.05$ )

(Fig. 1), and to report that they are aware of the latest HAE medications (99% versus 84%;  $p < 0.05$ ).

Sixty-three percent of physicians currently prescribe SC C1-INH, 52% currently prescribe lanadelumab, 41% currently prescribe IV C1-INH, and 38% currently prescribe androgens for HAE prophylaxis (Fig. 2A). The A/I specialists were more likely than other specialists to currently be prescribing lanadelumab (62% versus 28%;  $p < 0.05$ ), whereas other specialists are more likely than the A/I specialists to be prescribing antifibrinolytics (28% versus 4%;  $p < 0.05$ ) (Fig. 2A). In addition, physicians who treated six or more patients with HAE are significantly more likely than physicians who treated fewer than six patients with HAE to currently be prescribing SC C1-INH (71% versus 52%), lanadelumab (60% versus 41%), or IV C1-INH (49% versus 30%) for prophylaxis (all  $p < 0.05$ ) (Fig. 2B).

### Treatment Burden

Physicians and patients agreed on certain aspects of prophylactic HAE medications that contribute to the burden of treatment. The majority of physicians (77%) and patients (76%) agreed that most patients try not to think about the demanding nature of their treatment, find injections or infusions unpleasant (79% of physicians and 68% of patients), and are tired of injections or infusions (70% of physicians and 58% of patients) (Fig. 3A). Furthermore, most physicians and patients indicated that patients would prefer to administer their treatment when and where they need it (90% of physicians and 84% of patients) (Fig. 3A).

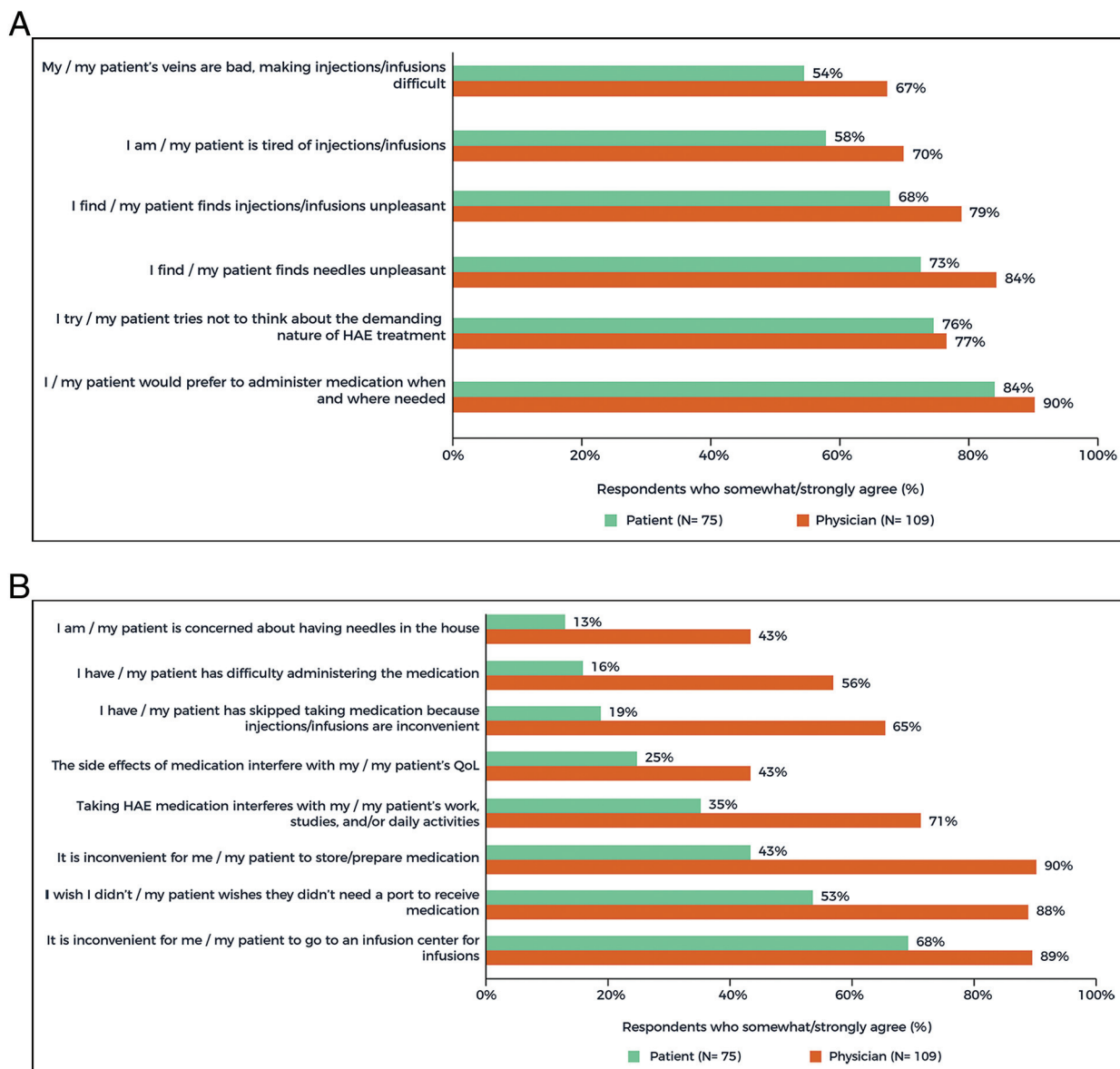


**Figure 2.** Top five prophylactic medications currently prescribed by physicians by (A) specialty type, and (B) number of patients with HAE treated per year (\* $p < 0.05$ ). HAE = hereditary angioedema; A/I = allergy/immunology; C1-INH = C1-inhibitor; IV = intravenous; SC = subcutaneous.

Although physicians and the patients were generally aligned on the burden associated with current prophylactic treatments, perceptions of the impact of treatment burden on patients differed

between the groups. Physicians considered several aspects of treatment to be significantly more burdensome on the patients than the patients inter-





**Figure 3.** Factors contributing to HAE treatment burden according to physicians and patients by (A) areas of agreement, and (B) areas of disagreement. HAE = hereditary angioedema; QoL = quality of life.

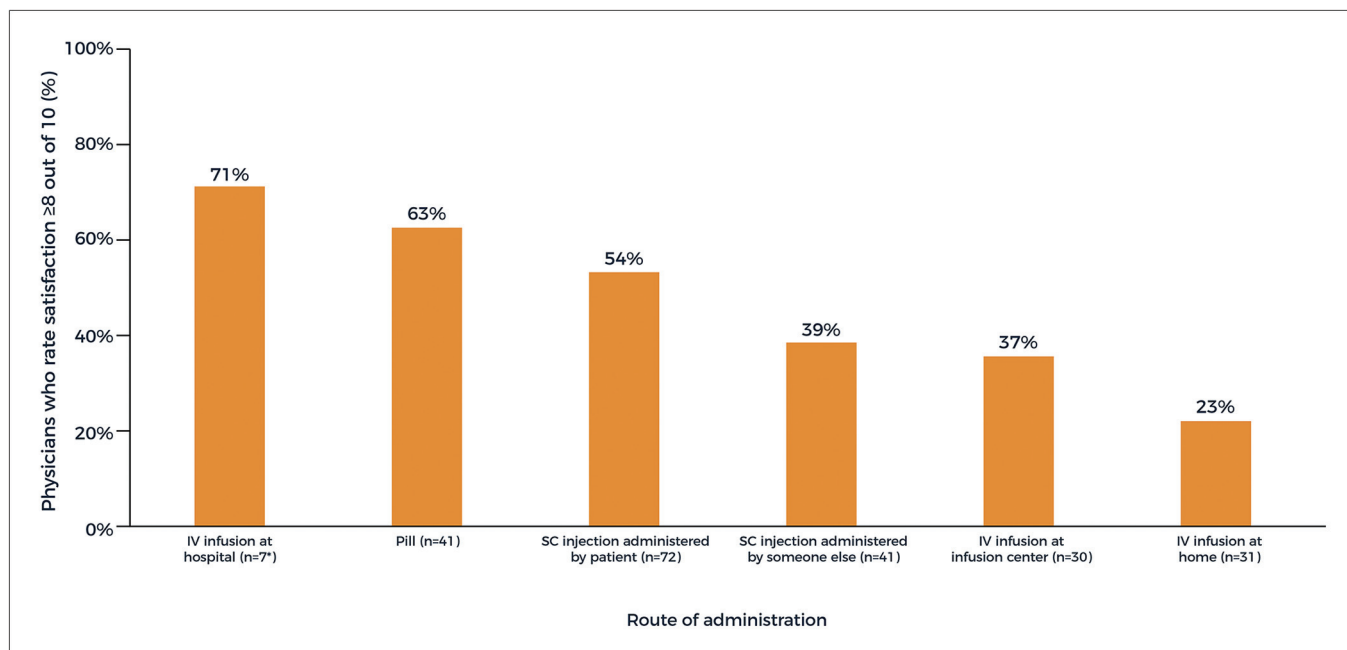
fering with a patient's daily life (71% of physicians versus 35% of patients;  $p < 0.05$ ); patients having skipped taking their medication because injections or infusions are inconvenient (65% of physicians versus 19% of patients;  $p < 0.05$ ); and storage and preparation of medication being inconvenient (70% of physicians versus 43% of patients;  $p < .05$ ) (Fig. 3B).

Physicians were more likely than patients to agree that becoming comfortable with needles is intimidating (77% versus 61%;  $p < 0.05$ ) and that learning to self-administer medication is challenging (77% versus 51%;  $p < 0.05$ ). However, physicians underestimated the time required to prepare and administer SC C1-INH, which was reported, on average, as 16.6 minutes by

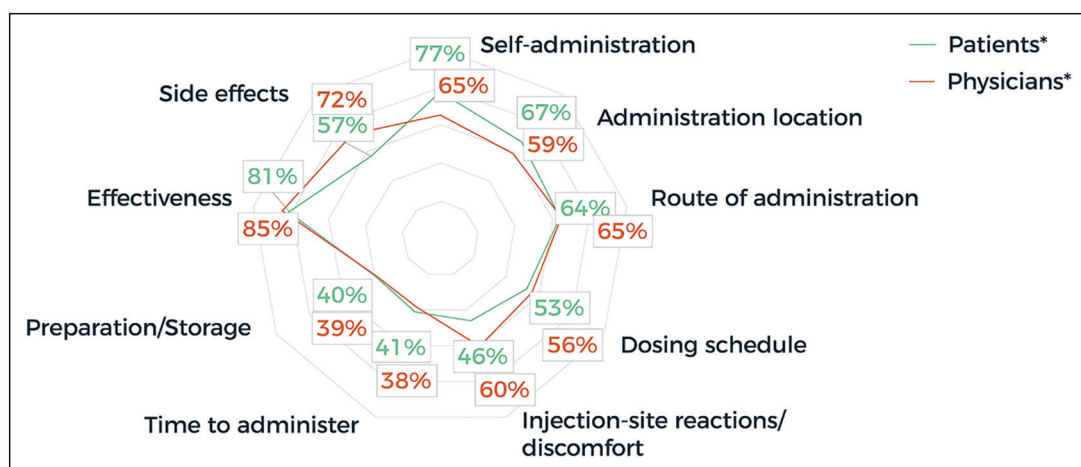
physicians, compared with an average of 30.4 minutes reported by patients.

### Patient-Physician Interactions

The physician and the patient responses on care practices showed notable differences. For example, 61% of physicians reported seeing their patients with HAE at least three times a year, whereas only 27% of the patients reported seeing their physician at this frequency ( $p < 0.05$ ). Similarly, most physicians (80%) reported initiating conversations with patients with regard to the challenges of HAE prophylaxis, whereas most patients (72%) reported initiating these conversations with their physicians.



**Figure 4.** Proportion of physicians satisfied (rate satisfaction  $\geq 8$  of 10) with each route of administration they prescribe. \*Small sample size. IV = intravenous; SC = subcutaneous.



**Figure 5.** Level of impact on willingness to switch hereditary angioedema (HAE) prophylaxis medication. Percentage of respondents who rated 8–10 on a scale of 0 (not at all impactful) to 10 (extremely impactful). \*Base values vary; responses of “not sure” have been excluded.

### Physician and Patient Preferences for Prophylactic Treatment

Sixty-seven percent of physicians ( $n = 72$ ) reported self-administered SC injection as the most common route of administration of prophylactic treatments they prescribed; however, only 54% of those physicians ( $n = 39$ ) are satisfied with that route of administration, based on an 11-point Likert scale (Fig. 4). These data align closely with patient satisfaction data because 54% of the patients who self-administer SC injection for prophylaxis reported being satisfied with this route of administration.

Physicians and patients were generally aligned on the treatment attributes (including efficacy, adverse effects, ability to self-administer, and route of administration) that are most likely to prompt a switch in prophylactic medications (Fig. 5). The A/I specialists were significantly more likely than other specialists to rate the potential for injection-site reactions (68% versus 42%;  $p < 0.05$ ) and challenges of self-administration (72% versus 48%;  $p < 0.05$ ) as being extremely influential on the decision to switch prophylactic treatments.

The survey results highlight various unmet needs for patients with HAE. Despite physician and patient

satisfaction with current therapies (81% versus 85% for lanadelumab, and 67% versus 58% for SC C1-INH, respectively), 93% of physicians and 86% of patients reported an interest in treatments that were easier to administer, and 94% of physicians and 84% of patients reported a need for more novel treatments.

## DISCUSSION

Based on the results of this study, the U.S. physicians treating HAE prescribed more SC C1-INH and lanadelumab for HAE prophylaxis compared with IV C1-INH or androgens. This finding is consistent with the 2019 survey mentioned previously, which also concluded that SC prophylactic therapies were most frequently prescribed by U.S. physicians.<sup>5</sup> A significantly higher percentage of A/I specialists reported that they were aware of the latest HAE medications compared with the other specialists, which was demonstrated by their prescription of SC C1-INH and lanadelumab over older therapies for HAE prophylaxis.

A comparison of the survey results demonstrated that physicians and patients were generally aligned on the treatment burden associated with current prophylactic agents. The majority in both survey groups agreed that patients try not to think about the nature of their treatment, find injections or infusions unpleasant, and would prefer to administer prophylaxis themselves when and where needed. In other chronic disease states, such as diabetes, asthma, and macular degeneration, physicians and patients felt that the inconvenience and unpleasantness associated with repeated injections were often barriers to treatment.<sup>11–13</sup> The resolution of these burdens may increase patient adherence to long-term treatment regimens.

The surveyed physicians perceived a greater negative impact on patients' lives due to prophylactic treatment burden compared with that reported by the surveyed patients. The reasons for this were unclear but may be related to the adaptability of individuals with HAE over time because many patients grow accustomed to self-administering medication and incorporating treatment into their normal activities.<sup>4,14</sup> In addition, patients may readily accept and accommodate some treatment burdens, given the significant benefits and improvements in quality of life experienced with modern, effective HAE treatments.<sup>15,16</sup> In fact, an important finding from the companion patient survey is that patients learn to cope with the difficult aspects of their disease and treatment over time (Radojicic *et al.*).<sup>10</sup>

This study uncovered differences in physician and patient perceptions related to HAE care practices. For example, physicians reported seeing their patients more often than the patients reported seeing their physician. In addition, the physicians believed that they initiated conversations about the challenges of prophylaxis more frequently than did the patients, whereas patients believe

the opposite. Both perspectives may be true, given that the surveys did not contain a matched cohort survey, *i.e.*, the physician respondents may not have been involved in the care of any of the patient respondents. Both patients and physicians believe that these conversations on the challenges of prophylactic treatment are helpful, which highlights the importance of patient-physician dialog and a need for conversation aids to assist in shared decision-making to drive greater alignment on the goals of treatment between patients and their physicians.<sup>6,17</sup> The survey results further demonstrate that most physicians and patients are satisfied with current prophylactic therapies but would be interested in new treatment options.

## STUDY LIMITATIONS

Limitations common across patient, caregiver, and physician surveys are reported in Banerji *et al.*<sup>17</sup> In addition to those limitations, the sample size of the physicians who completed the survey was small ( $N = 109$ ), particularly for the two subpopulations (A/I specialists [ $n = 77$ ] and other physicians [ $n = 32$ ]), which resulted in a lack of statistically significant outcomes; however, a comprehensive cross section of specialists who treat patients with HAE were represented in this survey.

## CONCLUSION

Both physicians and patients agree that substantial burdens exist with current prophylactic treatments but are not fully aligned on the impact that these burdens have on patient well-being. Therefore, an effective dialog with regard to treatment burden and patient preference should be the goal of treatment discussions between physicians and patients. In addition, implementation of shared decision-making may promote an individualized approach to HAE management. An understanding of the totality of both disease and treatment burden may improve patient-centered treatment decisions and lead to better health outcomes for patients with HAE.

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