Original Article

Trends in Treatments With Disease-Specific and Interfering Drugs in Patients With Hereditary Angioedema in Sweden

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What is already known about this topic? Recent decades have seen progress in both the long-term prophylaxis and the emergency treatment of hereditary angioedema (HAE). Drug treatment of other diseases may interfere with disease control. To what extent disease-specific and possibly interfering medications are used in HAE has not been investigated previously.

What does this article add to our knowledge? This study shows a high use of attenuated androgens and increasing use of C1 inhibitor as long-term prophylaxis in HAE. Common use of the emergency medication icatibant indicates poor disease control in many patients.

How does this study impact current management guidelines? The study indicates an unmet need for long-term prophylaxis in patients with HAE, particularly middle-aged women. The relatively high use of attenuated androgens and increase in intravenous C1 inhibitor for long-term prophylaxis is also notable.

BACKGROUND: Hereditary angioedema (HAE) is caused by low levels of or defects in C1 inhibitor. Although disease activity may be modified by prophylaxis, emergency treatment, treatment for comorbidities, and oral contraceptives, the extent of their use is unclear.

OBJECTIVE: To investigate trends in the use of disease-specific and interfering drugs in patients with HAE compared with the general population in Sweden.

METHODS: In a nationwide, longitudinal study, 239 patients with HAE and 2 383 controls were compared with the Prescribed Drug Register (2005−2019). These data reflect rates of dispensed prescriptions from pharmacies in Sweden.

RESULTS: Attenuated androgens were used by approximately 10% of patients with HAE. The number of individuals treated with prophylactic plasma-derived C1 inhibitor increased during this period to reach almost 25% in men and 35% in women in 2019. Tranexamic acid was prescribed to 5% to 15% of patients, primarily children and young adults. Rates of prescriptions for icatibant, an emergency medication, showed a steady increase since its introduction in 2010, in particular among middle-aged women, suggesting poorly controlled disease. The use of diuretics, calcium channel blockers, and gestagens was more common in patients with HAE than in controls, whereas angiotensin-converting enzyme inhibitors were rarely collected.

CONCLUSIONS: Despite concerns regarding side effects, approximately 10% of patients with HAE received attenuated androgens for long-term prophylaxis. The common use of emergency medication also suggests poorly controlled disease in many patients, highlighting the need for increased focus on prophylactic treatment. **(J Allergy Clin Immunol Pract 2023;11:621-8)**

Key words: *Androgens; C1-INH; Hereditary angioedema (HAE); Icatibant; Tranexamic acid*

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INTRODUCTION

Hereditary angioedema (HAE) is caused by germline or *de novo* mutations in the *SERPING1* gene, which encodes C1 inhibitor (C1-INH).[1] This results in low levels of (type 1) or defect function of (type 2) C1-INH, which leads to dysregulation of

Abbreviations used
ACE- Angiotensin-converting enzyme
ARBs- Angiotensin II receptor blockers
BKB2R- Bradykinin B2 receptor
C1-INH- C1 inhibitor
CVD- Cardiovascular disease
DPP4- Dipeptidyl peptidase-4
HAE- Hereditary angioedema
LTP- Long-term prophylaxis

plasma kallikrein, an enzyme that generates bradykinin from high molecular weight kininogen.[2,3] Activation of the bradykinin type B2 receptor (BKB2R) results in typical manifestations of HAE, of which laryngeal edema, and consequent asphyxia, is the most serious complication.[4] Gastrointestinal angioedema, presenting as painful subileus, is another important disease manifestation along with swellings in the face and limbs, causing functional impairments. In addition, the appearance of swellings may cause psychosocial stress.[5,6] Hereditary angioedema can limit a patient's activities because even minor physical trauma or emotional stress may precipitate episodes of angioedema, resulting in avoidance of physical and social activities, and thus affecting the career and quality of life.

Considering the impact of the disease, there is an important unmet need for efficient long-term prophylaxis (LTP), as well as emergency medications for the treatment of HAE. Fresh-frozen plasma was previously used to treat angioedema episodes, although this has gradually been replaced by purified, plasma-derived C1-INH.[7-12] In Sweden, plasma-derived C1-INH was approved for emergency use in 2009 and as LTP in 2011. In addition to C1-INH, icatibant, a competitive BKB2R antagonist, was approved in Sweden in 2010 for use as an emergency medication.[13,14]

Attenuated androgens have been used off-label for long- and short-term prophylaxis since the 1970s in Sweden (personal communication in 2022: Dr. Janne Björkander, Jönköping, Sweden).[15,16] Their mechanisms of action are largely unknown but are thought to involve induction of metallopeptidases that inactivate bradykinin and increase production of C1-INH.[17,18] There are concerns that the use of androgens for LTP may increase the risk of cardiovascular disease (CVD) and cancer.[19-25] Tranexamic acid is also used as LTP in HAE. This antifibrinolytic agent reduces bradykinin production by blocking the conversion of plasminogen to plasmin, and subsequently prekallikrein to kallikrein, thereby preventing the generation of bradykinin.[1] Tranexamic acid was reported to have a prophylactic effect in HAE in 1972 and has been prescribed ever since in Sweden, although its efficacy remains unproven in controlled studies.[26,27] It is sometimes associated with side effects such as headache, nausea, various gastrointestinal symptoms, and a potentially increased risk of thromboembolism.

Treatment for comorbidities, including angiotensin-converting enzyme (ACE) inhibitors used to treat CVD may increase the risk of angioedema, and when used in combination with dipeptidyl peptidase-4 (DPP4) inhibitors (used to treat diabetes), the risk is further increased.[28] Both ACE and DPP4 participate in the degradation of bradykinin and substance P.[28,29] In women, the manifestations of HAE often start at puberty, indicating that estrogen is a promoter of angioedema.[30] Therefore, there is general consensus not to use oral contraceptives containing estrogens in patients with HAE.[31]

The aim of this study was to investigate the use of LTP and emergency treatments for HAE from 2005 to 2019 in Sweden. Rates and patterns of prescriptions for the treatment of CVD and oral contraceptives were also investigated.

MATERIALS AND METHODS

Study design and setting

This was a nationwide, longitudinal study investigating prescribed drugs for the LTP and emergency treatment of HAE, as well as drugs that may interfere with HAE disease control (eg, medications used to treat CVD and oral contraceptives) in Sweden.[32] A personal identity number allows cross-referencing with national databases. Prescription of pharmaceutical drugs in both primary and secondary care is registered in the Prescribed Drug Register (Läkemedelsregistret) from July 2005 to the end of 2019.[33]

Study population

Patients with HAE (type 1 or 2) were identified by contacting physicians caring for patients with HAE as well as physicians responsible for diagnostic testing at all clinical immunology laboratories in Sweden. Diagnosis was based on a history of angioedema, low concentrations of complement C4, and either low levels of C1-INH (type 1) or normal/increased levels of C1-INH with impaired function (type 2). A rare subset of HAE with normal C1-INH (HAE-nC1-INH) can be caused by mutations in several other genes including those encoding coagulation factor XII, plasminogen and high molecular weight kininogen. However, in the current study, only individuals with HAE types 1 and 2 were included. A control cohort was selected using the National Population Register at Statistics Sweden (SCB). This cohort comprised a random sample (n = 2,383) of the Swedish general population (~10 controls per 1 patient with HAE) matched for age, sex, and county of residence.

Assessments

Medication data including the number of packages, drug strength, volumes, expedition dates, and collection were obtained for each individual and Anatomical Therapeutic Chemical code using the Prescribed Drug Register. The World Health Organization (WHO) long-term Anatomical Therapeutic Chemical classification (https://www.whocc.no) was used to categorize the following pharmacological agents: androgens (danazol, G03XA01; oxandrolone, A14AA08; stanozolol, A14AA02), C1-esterase inhibitor (human plasma–derived, B06AC01; human recombinant, B06AC04), tranexamic acid (B02AA02), icatibant (B06AC02), combined gestagen/estrogen contraceptives (G03AA), combined gestagen/estrogen contraceptives in sequence (G03AB), gestagen contraceptives (G03AC), nonselective beta-blockers (C07AA), selective beta-1-blockers (C07AB), combined alpha- and beta-adrenergic blockers (C07AG), thiazide diuretics (C03A, C03B, C03EA), loop diuretics (C03C), potassium-sparing diuretics (C03D), ACE inhibitors (C09AA), angiotensin II receptor blockers (ARBs; C09CA), calcium channel blockers (C08C), neprilysin inhibitors (C09DX04), and dipeptidyl peptidase-4 inhibitors (A10BH).

The percentage of individuals obtaining prescribed drugs during each quarter was determined. To assess the age and gender distribution in 2019, drugs dispensed from pharmacies over 3 quarters or more were analyzed. In Sweden, drugs for continuous treatment are

TABLE I. Demographic characteristics of the study population

Characteristics	Patients with HAE (n = 239)	Reference population* (n = 2,383†)
Male/female	111/128 (46%/54%)	1,103/1,280 (46%/54%)
HAE type 1	216 (90.4%)	
Male/female	102/114 (47%/53%)	
HAE type 2	23 (9.6%)	
Male/female	9/14 (39%/61%)	
Age (y)‡	Male/female (n)	
0–9	10/6	100/60
10–19	15/21	150/209
20–39	31/35	301/348
40-59	27/37	260/376
≥60	26/19	162/248

*Control subjects were matched for year of birth, gender, and county of residence.
†For 1 HAE patient, only 3 control individuals could be identified.
‡Age of individuals alive at date of enrollment in the study (January 1, 2020). Twelve patients with HAE and 169 individuals in the control group were deceased as of January 1, 2020.

prescribed for 3 months at a time, to be collected 4 times a year. Consequently, dispensed prescriptions may be delayed at the turn of the year. Therefore, continuous treatment was defined as obtaining a prescribed drug for 3 or more quarters in 2019. In the case of C1-INH, a dose of 24,000 IU/quarter or more was considered prophylactic treatment. Poorly controlled HAE was defined as 6 or more doses (30 mg/dose in a disposable syringe) of icatibant dispensed per quarter.

All plots were created using R v4.1.2 and ggplot2.[34,35] Smoothed trend lines were fitted using LOESS.[36]

Ethical considerations

The study was approved by the Swedish Ethical Review Authority (2019-01623) and conducted in accordance with the amended Declaration of Helsinki.

RESULTS

Demographic characteristics

This study was based on a cohort of 239 individuals with HAE previously described.[37] In this cohort, 216 individuals (90.4%) suffered from HAE type 1 and 23 individuals (9.6%) were characterized as having HAE type 2. As of January 2020, 227 individuals in the HAE cohort were alive. Demographic data relating to patients and controls, as well as the age stratification used, are presented in Table I.

Long-term prophylaxis

The use of attenuated androgens for LTP remained unchanged over the period investigated (2005–2019; Figure 1, *A*). The most frequently prescribed drug was danazol, oxandrolone was much less common, and stanozolol was not dispensed at all (data not shown). Prescriptions for androgens were obtained by approximately 10% of patients with HAE, with a slight male predominance. Age stratification showed that, in 2019, men between 20 and 59 years old were primarily treated with androgens, whereas an increasing proportion of women received androgen treatment from the age of 60 years (Figure 1, *B*).

The use of plasma-derived C1-INH as LTP showed a steady increase from 2005 to 2019. This was particularly notable in women because more than 30% received plasma-derived C1-INH in 2019 (Figure 1, *C*). The age and sex distribution analysis revealed that C1-INH was predominantly used by women between the ages of 20 and 59 years. In children, there was a predominance of females collecting C1-INH whereas it was rarely prescribed to individuals aged 60 years or older (Figure 1, *D*). Recombinant human C1-INH (expressed in transgenic rabbits) is not used to a significant extent in Sweden despite being available since 2011, and ecallantide, an inhibitor of plasma kallikrein, has not been introduced to the Swedish market. Tranexamic acid was used by 5% to 10% of males and 10% to 15% of females, with its use showing a slight decline in recent years. This drug was used mainly by children and young adults (Figure 1, *E, F*).

Emergency medication

In 2010, the BKB2R antagonist icatibant was introduced in Sweden for use as emergency medication to relieve angioedema episodes in HAE. The proportion of patients with HAE collecting icatibant at least once per year during 2005 to 2019 showed a steady increase, reaching approximately 45% of women and 35% of men in 2019 (Figure 2, *A*). Of these individuals, there was a relatively high proportion of young girls and markedly few teenagers of both sexes. In addition, there was a high proportion of individuals aged 20 years or older and a slight decline among men aged 60 years or older (Figure 2, *B*).

To determine the proportion of patients with poorly controlled HAE, we categorized individuals according to the number of doses prescribed during each quarter (1–5 doses or ≥6 doses; Figure 2, *C*). There was an overall increase in the number of individuals collecting 6 or more doses each quarter during 2005 to 2019 (Figure 2, *C*). These were predominantly female patients. The sex and age of individuals collecting 6 or more doses at least once during 2019 were also investigated (Figure 2, *D*). A large proportion of patients, particularly women, aged 20 years or older, were prescribed icatibant at this volume. There was also a relatively high percentage of young girls collecting this drug. However, surprisingly few female teenagers were prescribed 6 or more doses of icatibant, considering the fact that puberty can exacerbate manifestations of HAE (Figure 2, *D*).

Treatment of CVD

In recent years, the use of medication for the treatment of CVD was slightly higher among individuals with a diagnosis of HAE than that in the reference population (Figure 3, *A*). The percentage of individuals with HAE collecting medication for CVD increased steadily with age, mainly from the age of 40 years for both males and females, with a slight predominance among males (Figure 3, *B*).

The age and sex distribution of individuals who were prescribed beta-blockers was similar in both individuals with a diagnosis of HAE and the reference population, with the exception of males suffering from HAE in which greater variation was observed (Figure 3, *C*). The use of diuretics among individuals with a diagnosis of HAE was higher than that in the reference population (Figure 3, *D*). Calcium channel blockers were more commonly used by males with a diagnosis of HAE than controls, although there was no differences in use between women with HAE and controls (Figure 3, *E*). The use of ACE inhibitors by patients with HAE was very low compared with that by the reference population (Figure 3, *F*). In contrast, the

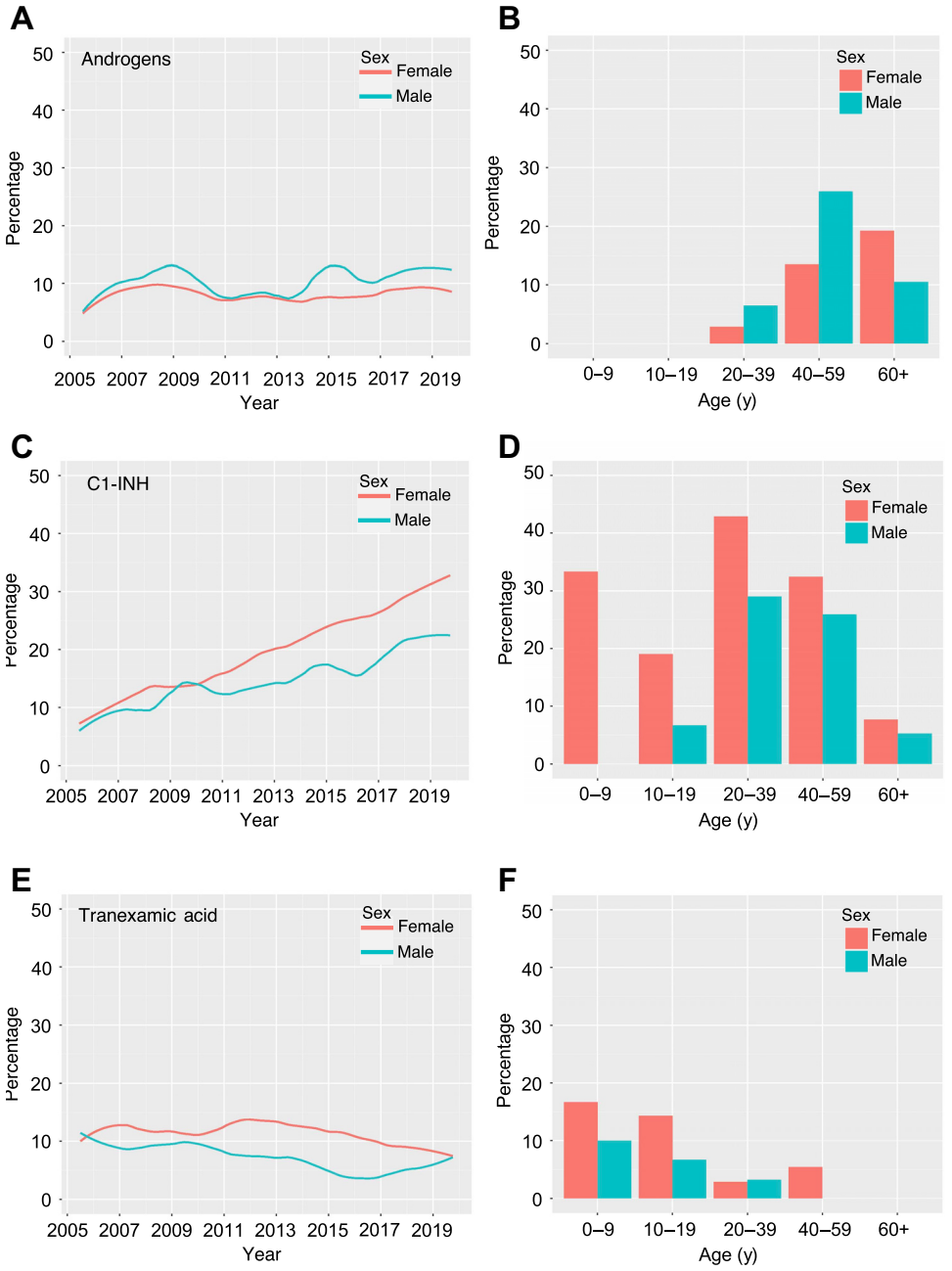

FIGURE 1. Long-term prophylaxis of HAE (2005−2019). (**A**) Individuals who obtained prescriptions for attenuated androgens (danazol/oxandrolone) each quarter. (**B**) Age/sex of individuals treated with attenuated androgens in 3 or more quarters in 2019. (**C**) Prophylactic C1-INH (≥24,000 IU/quarter). (**D**) Age/sex of individuals treated with C1-INH in 2019. (**E**) Tranexamic acid. (**F**) Age/sex of individuals who obtained prescriptions for tranexamic acid in 2019.

use of ARBs showed a steady and parallel increase in both patients with HAE and controls (Figure 3, *G*).

Oral contraceptives

Estrogens can precipitate angioedema and, in women, the first episodes of angioedema often occur at puberty.[30,38] Combined birth control pills (containing estrogens and gestagens) were rarely prescribed to individuals with HAE during the period investigated (2005−2019) and not at all in 2019 (Figure 4, *A, B*). In contrast, gestagens do not promote angioedema.[30] The prescription increased during the observation period, surpassing that in the reference population in 2010 (Figure 4, *C*). In 2019, teenage girls with HAE collected more gestagens than their matched controls (Figure 4, *D*).

Dipeptidyl peptidase-4 inhibitors

The DPP4 inhibitors (or gliptins) belong to a novel class of orally administrated antihyperglycemic substances used to treat

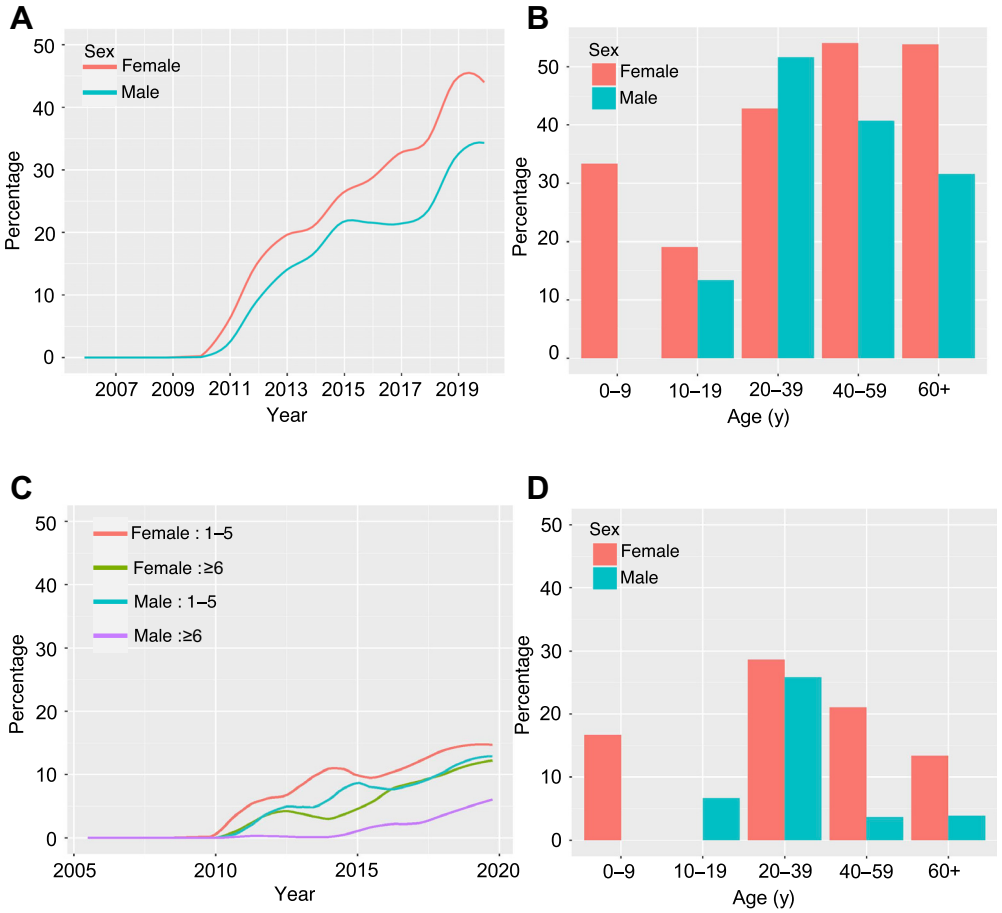

FIGURE 2. Emergency medication of HAE (icatibant; 2010−2019). (**A**) Proportion of individuals who collected icatibant at least once per year. (**B**) Age/sex of individuals who obtained a prescription for icatibant at least once during 2019. (**C**) Age/sex of individuals who obtained 1 to 5 or 6 or more doses each quarter. (**D**) Age/sex of individuals who obtained 6 or more doses in at least 1 quarter in 2019.

diabetes mellitus type 2 by inhibiting the degradation of incretin.[39] This class of drugs may induce angioedema when used in combination with ACE inhibitors because they also participate in the degradation of bradykinin.[28] There were very few prescriptions for these drugs by patients with HAE in the current study (data not shown).

Neprilysin inhibitors

Sacubitril is a neprilysin inhibitor used in combination with valsartan for heart failure. A well-known side effect of this treatment is angioedema because the inhibition of neprilysin by sacubitril increases bradykinin concentrations.[32] In this study, sacubitril was rarely prescribed to patients with HAE (data not shown).

DISCUSSION

In this nationwide study, longitudinal rates and patterns of prescriptions for disease-modifying drugs and other pharmacological treatments that may interfere with the course of HAE were investigated. To the best of our knowledge, this is the first study of this kind. The most striking findings were the high use of attenuated androgens and increasing use of C1-INH as LTP in certain patient subgroups, and more worryingly, the frequent collection of icatibant, implying that poor disease control may exist in a relatively high number of patients.

Although androgens have long been used as LTP for HAE, concerns have been raised regarding side effects such as weight gain, virilization, menstrual irregularities, headache, depression, liver adenomas, increased creatine phosphokinase concentrations, liver function test results, and serum lipid concentrations.[17,20,23,24] Despite this, the use of androgens remained unchanged during the period investigated in this study. Interestingly, a relatively high number of middle-aged and older women received LTP with androgens. This may indicate that these drugs provide both high clinical efficacy and fewer side effects than anticipated. However, a more likely explanation is the lack of alternative drugs available for LTP in HAE during the time period investigated in this study, a situation that probably will change in years to come.

Substitution with plasma-derived C1-INH should be the most appropriate physiological approach to treating HAE. It is interesting to see that there was a steady increase in C1-INH use in this study. However, to date, C1-INH may only be administered intravenously. Because administration is repeated 2 or 3 times per week, problems with access to veins may occur, and the use of indwelling intravenous catheters for permanent access may lead to thromboembolic events and risk of infection.[22]

Despite being introduced a relatively long time ago, tranexamic acid remains an important agent for LTP in HAE in

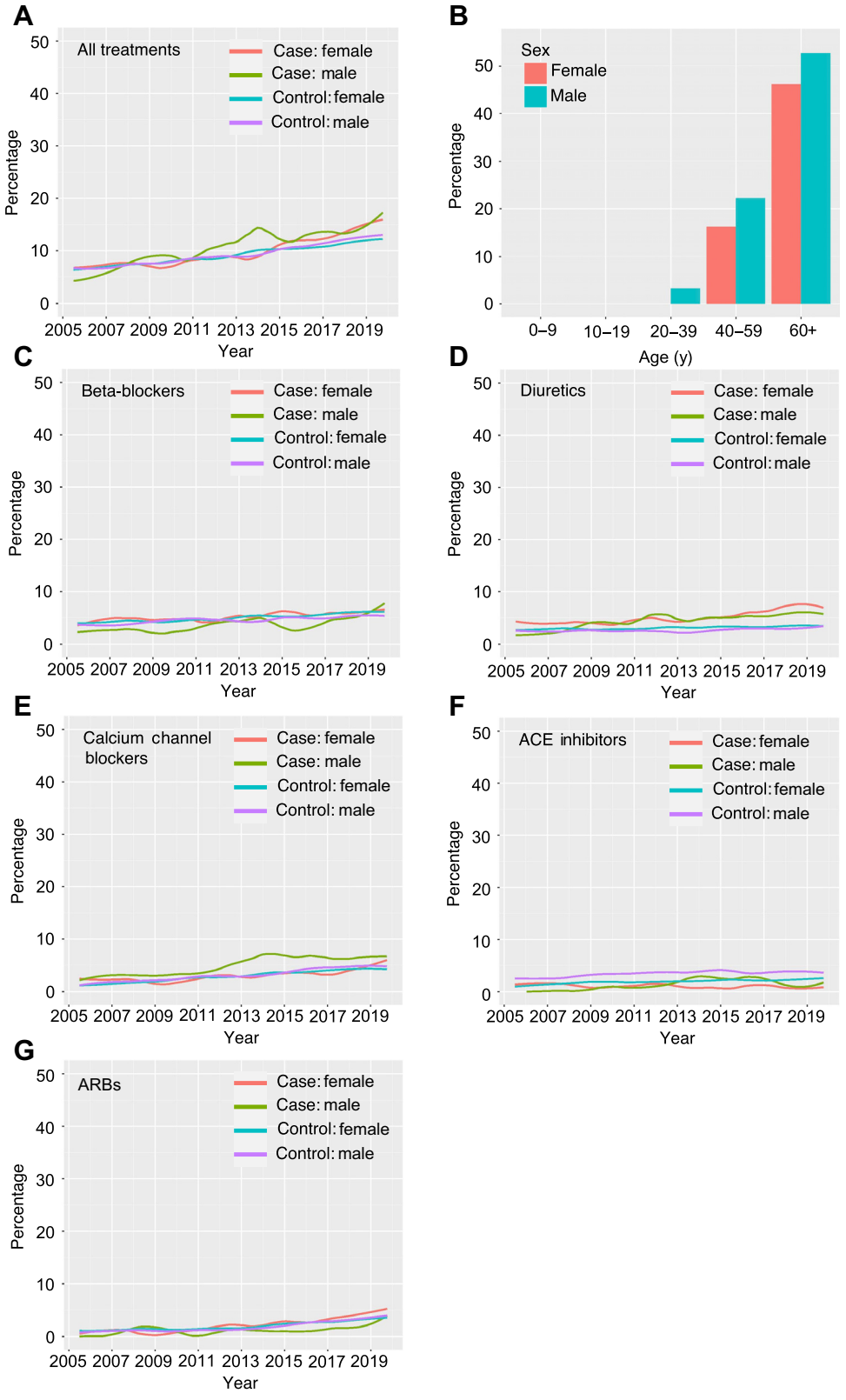

FIGURE 3. Medication for CVD among individuals with HAE and the reference population (2005–2019). (**A**) Individuals who were prescribed any medication for CVD each quarter. (**B**) Age/sex of individuals who collected medication for CVD in 3 or more quarters in 2019. (**C**) Beta-blockers. (**D**) Diuretics (thiazide/loop/potassium-sparing). (**E**) Calcium channel blockers. (**F**) ACE inhibitors. (**G**) ARBs.

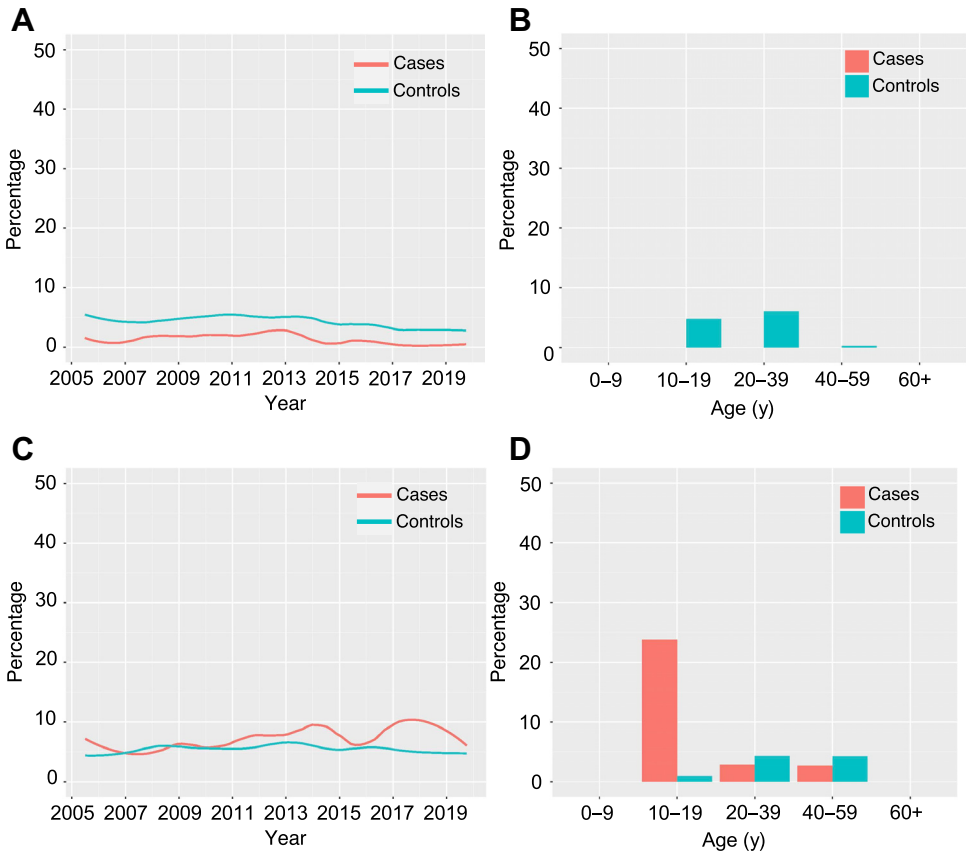

FIGURE 4. Use of oral contraceptives among women with HAE and the reference population (2005−2019). (**A**) Prescription of combined estrogens/gestagens each quarter. (**B**) Age of individuals who were prescribed combined estrogens/gestagens in 2019. (**C**) Gestagens. (**D**) Age of individuals who were prescribed gestagens in 2019.

Sweden, particularly in children and young adults. Angioedema episodes typically become more severe and frequent during and after puberty.[5] In this study, attenuated androgens were rarely used in children whereas both plasma-derived C1-INH and tranexamic acid were commonly collected for use in children and teenagers. The use of androgens may be avoided in children because of potential side effects. Tranexamic acid may be favored because of its oral administration and it is inexpensive.

According to the current study, it has taken almost a decade for icatibant to be established as a commonly prescribed emergency medication for patients with HAE. Even so, it was only collected by half of the patient population in 2019. This may be explained by efficient LTP or stable disease, making such patients less prone to collect this emergency drug. Furthermore, plasma-derived C1-INH may be preferred by some patients as emergency medication. Icatibant was also collected by fewer teenagers than other patient groups. Young women especially may experience HAE episodes because of increasing estrogen levels.[40] There was an increase in the number of individuals who collected 6 or more doses of icatibant each quarter during the period investigated. This is worrying because it likely indicates poor disease control and the need for more effective LTP. Other possible explanations may include improved diagnosis and knowledge of the disease, resulting in more prescriptions for the treatment of attacks. A high rate of dispensed prescriptions was most notable among women aged 20 years or older with a decline after menopause, possibly indicating the positive effects of decreasing estrogen levels on disease activity. Whether the introduction of icatibant affected the use of C1-INH as an on-demand medication is not reflected in the Drug Prescription Register, because in Sweden, it is mainly used in emergency departments.

The higher use of CVD medication among patients with HAE compared with that in the reference population may reflect the greater prevalence of CVD among patients with HAE.[37] The most striking differences between patients with HAE and the control cohort was the greater use of diuretics in both sexes and the higher use of calcium channel blockers among men with HAE. It is also interesting to see that ARBs are used to a similar extent in patients with HAE and the reference population. This may be explained by the low/absent use of ACE inhibitors, which may necessitate substitution with alternative drugs. The ACE inhibitors are known to trigger episodes of angioedema by impairing the degradation of bradykinin and substance P.[41] However, it is concerning that ACE inhibitors were prescribed at all to individuals suffering from HAE.

Women with HAE commonly present with more frequent and more severe attacks than men. The disease is often affected by estrogenic status because estrogens increase kininogenase activity.[40] It is interesting that the use of gestagens increased among fertile women suffering from HAE, in particular among teenagers, to exceed that in the reference population. Gestagens are known to decrease the risk of angioedema attacks.[42]

A limitation of the current study is that patterns of adherence to the medications could not be determined. Being a register-based study, only data reflecting dispensed prescriptions from the pharmacies were possible to obtain. One should also bear in mind that the findings of the current study may not be generalizable because there are large variations in access to medications among countries for example, depending on reimbursement policies, commercial marketing, national treatment guidelines, and general welfare.

Currently, the LTP of HAE is on the threshold of a paradigm shift. Both orally administrated small-molecule compound inhibitors and subcutaneously administered monoclonal antibodies against plasma kallikrein were recently introduced.[1] However, they were not marketed in Sweden until 2021. It will be important to follow how these novel pharmaceuticals will affect current treatment strategies and the need for emergency medications in HAE.

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