Epidemiology of Bradykinin-Mediated Angioedema in the European Population

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Key takeaways

The results of this targeted literature review indicate that bradykinin-mediated angioedema (AE-BK; all types) is a rare condition with prevalence estimates below the threshold of 5 in 10,000 individuals defined by the European Medicines Agency for orphan drug designation.[1]

Literature review

Human studies focused on incidence and/or prevalence estimates for AE-BK in the EU and UK (n=14)

Reported prevalence range per 10,000 individuals

HAE-C1INH (Type 1/2)[a]	HAE-nC1INH[b]	AAE-C1INH[c]
0.05–0.33 (Latvia – Austria)	<0.01–0.07 (UK – Canary Islands, Spain)	0.01–0.02 (Czech Republic – Italy)

AAE-C1INH, acquired angioedema due to C1-inhibitor deficiency; AE-BK, bradykinin-mediated angioedema; C1INH, C1-inhibitor; EU, European Union; HAE-C1INH, hereditary angioedema due to C1-inhibitor deficiency; HAE-nC1INH, hereditary angioedema with normal C1-inhibitor levels; UK, United Kingdom. [a]Based on evidence from 12 population-based studies across 10 European countries. [b]Based on evidence from two studies. [c]Based on evidence from three studies.

Background

- **Angioedema (AE):** a localized, transient swelling of subcutaneous and submucosal tissue mediated by vasoactive compounds, mainly bradykinin or histamine.[2,3]
  - –Angioedema symptoms usually affect upper and lower limbs, face and neck, and genitals, as well as the gastrointestinal and upper respiratory tracts.[4]
  - –Involvement of the upper respiratory tract may be life-threatening.[4-7]
- **Bradykinin-mediated AE (AE-BK):** two types of AE known to be mediated by bradykinin[2,8]:
  - –Hereditary angioedema (HAE), which may be associated with mutations in the C1 inhibitor (C1INH) protein gene (HAE-C1INH) and subclassified as HAE-C1INH Type 1 (deficient C1INH) or HAE-C1INH Type 2 (defective C1INH), or may be associated with other mutations in patients with normal C1INH levels and function (HAE-nC1INH).
  - –Acquired angioedema due to C1INH deficiency (AAE-C1INH) is typically secondary to hematologic and immunologic disorders.
- **Unmet need:** as a rare disease, data are limited on AE-BK prevalence.

Objective

- To summarize epidemiologic data on AE-BK in the European Union (EU) and United Kingdom (UK).

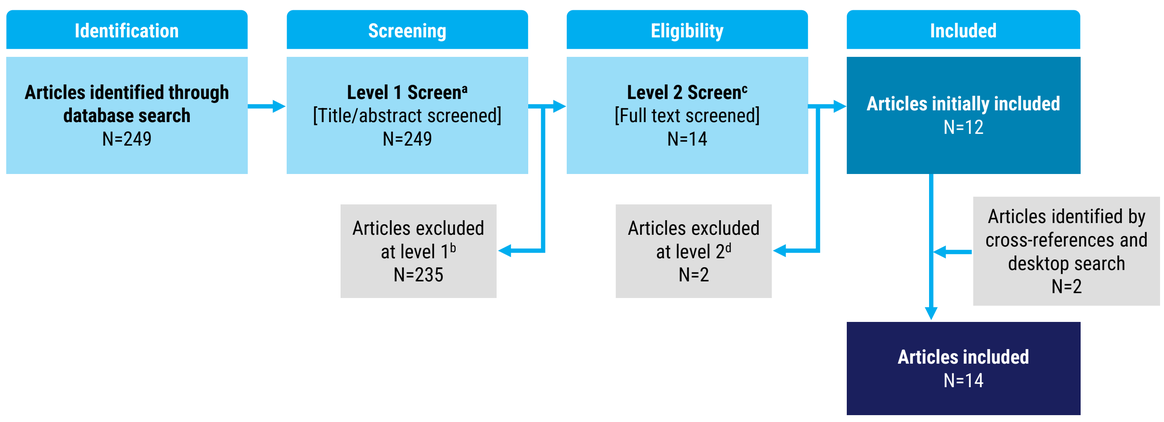
Methods

- **Targeted literature search:** conducted to identify articles published in peer-reviewed journals that provided population-based epidemiology estimates and/or clinical features of AE-BK in the EU and UK.
- **Search terms:** broad to include all types of AE-BK and limited to human studies published in English from 1 January 2014 to 12 June 2024 using MEDLINE (PubMed) and Elsevier Embase databases.
  - –An additional manual review of cross-references from relevant articles was performed to identify other studies that could complement and contextualize the evidence, even if falling outside the targeted region and/or calendar period.
  - –All titles and available abstracts provided by the literature search (n=249) were manually reviewed and based on prespecified criteria, a subset of articles underwent full-text review (n=14).
- **Prevalence estimates:** reported for each AE-BK subtype with the denominator used in each publication (as a fraction of 100,000 or as 1 case over x inhabitants).
  - –Incidence or prevalence estimates among pediatric age groups were also described if available.

Results

- This targeted literature search was performed on 12 June 2024 and provided 249 unique articles, of which 12 articles were included in this analysis.
- Two additional studies were identified through cross-reference checks that contained nationwide prevalence estimates.

Figure 1: Literature search PRISMA chart



AAE-C1INH, acquired angioedema due to C1-inhibitor deficiency; AE-BK, bradykinin-mediated angioedema; EU-27, 27 member states of the European Union; EU, European Union; HAE-C1INH, hereditary angioedema due to C1-inhibitor deficiency; HAE-nC1INH, hereditary angioedema with normal C1 inhibitor levels; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; UK, United Kingdom. [a]Level 1 screening criteria: quantitative, epidemiological data from original research on patients with AE-BK (including HAE-C1INH, AAE-C1INH, HAE-nC1INH in the geographic region of interest (including the EU-27 plus Iceland, Liechtenstein, Norway, and the UK) and written in English; clinical trial data were excluded. [b]132 articles were excluded due to "study design/publication type", 49 due to study population, and 54 due to study outcomes. [c]Level 2 screen criteria: incidence, prevalence, and/or clinical data of AE-BK in the target population. [d]One was excluded due a lack of original research and one did not present data from the targeted European population.

- Fourteen population-based studies reported general population prevalence proportions of HAE-C1INH, AAE-C1INH, and/or HAE-nC1INH from 11 European countries.

Table 1: Details of publications included in analysis

Subtype	Country	Study period	Number of cases	Time point of calculation	Publication
HAE-C1INH (Type 1/2)	Finland	2005–2021	144	2021	Sandberg, et al. *Acta Derm Venereol*. 2024
	Slovakia	2021	132	2021	Markocsy, et al. *World Allergy Organ J*. 2024
	Latvia	2006–2022	10	2022	Kanepa, et al. *Allergy Asthma Clin Immunol*. 2023
	Germany	2020	1350	2020	Martinez-Saguer, et al. *Eur J Dermatol*. 2022
	Canary Islands, Spain	2015–2021	27	2021	Mendoza-Alvarez, et al. *J Clin Med*. 2021
	Spain	1999–2004	444	2001	Roche, et al. *Ann Allergy Asthma Immunol*. 2005
	Austria	2017–2018	294	2018	Schöffl, et al. *J Dtsch Dermatol Ges*. 2019
	Sweden	2007–2011	146	2011	Nordenfelt, et al. *Acta Derm Venereol*. 2016
	Italy	1973–2013	983	2013	Zanichelli, et al. *Orphanet J Rare Dis*. 2015
	Denmark	2001–2009	76	2009	Bygum. *Br J Dermatol*. 2009
	UK	2018–2019	1307[a]	2019	Yong, et al. *J Allergy Clin Immunol Pract*. 2023
	UK	2011–2012	92	2012	Read, et al. *Clin Exp Immunol*. 2014
AAE-C1INH	Czech Republic	2018–2019	14	2018	Sobotkova, et al. *Int Arch Allergy Immunol*. 2021
	Italy	1976–2015	77	2015	Zanichelli, et al. *J Allergy Clin Immunol Pract*. 2017
	UK	2018–2019	91	2019	Yong, et al. *J Allergy Clin Immunol Pract*. 2023
HAE-nC1INH	Canary Islands, Spain	2015–2021	14	2021	Mendoza-Alvarez, et al. *J Clin Med*. 2021
	UK	2018–2019	22	2019	Yong, et al. *J Allergy Clin Immunol Pract*. 2023

AAE-C1INH, acquired angioedema due to C1-inhibitor deficiency; AE-BK, bradykinin-mediated angioedema; HAE-C1INH, hereditary angioedema due to C1-inhibitor deficiency; HAE-nC1INH, hereditary angioedema with normal C1 inhibitor levels; UK, United Kingdom. [a]Number of cases is extrapolated from the reported prevalence of 1:59,000 corresponding to 1152 identified cases and the reported prevalence of 1:52,000 corresponding to the identified cases plus the additional hypothesized unreported cases (1152*(1/52,000)/(1/59,000) = 1307) in the UK.

Results

HAE-C1INH

- Based on evidence from twelve population-based studies across ten European countries, the reported prevalence of HAE-C1INH (Type 1/2) ranged from 0.05/10,000 individuals in Latvia to 0.33/10,000 in Austria.

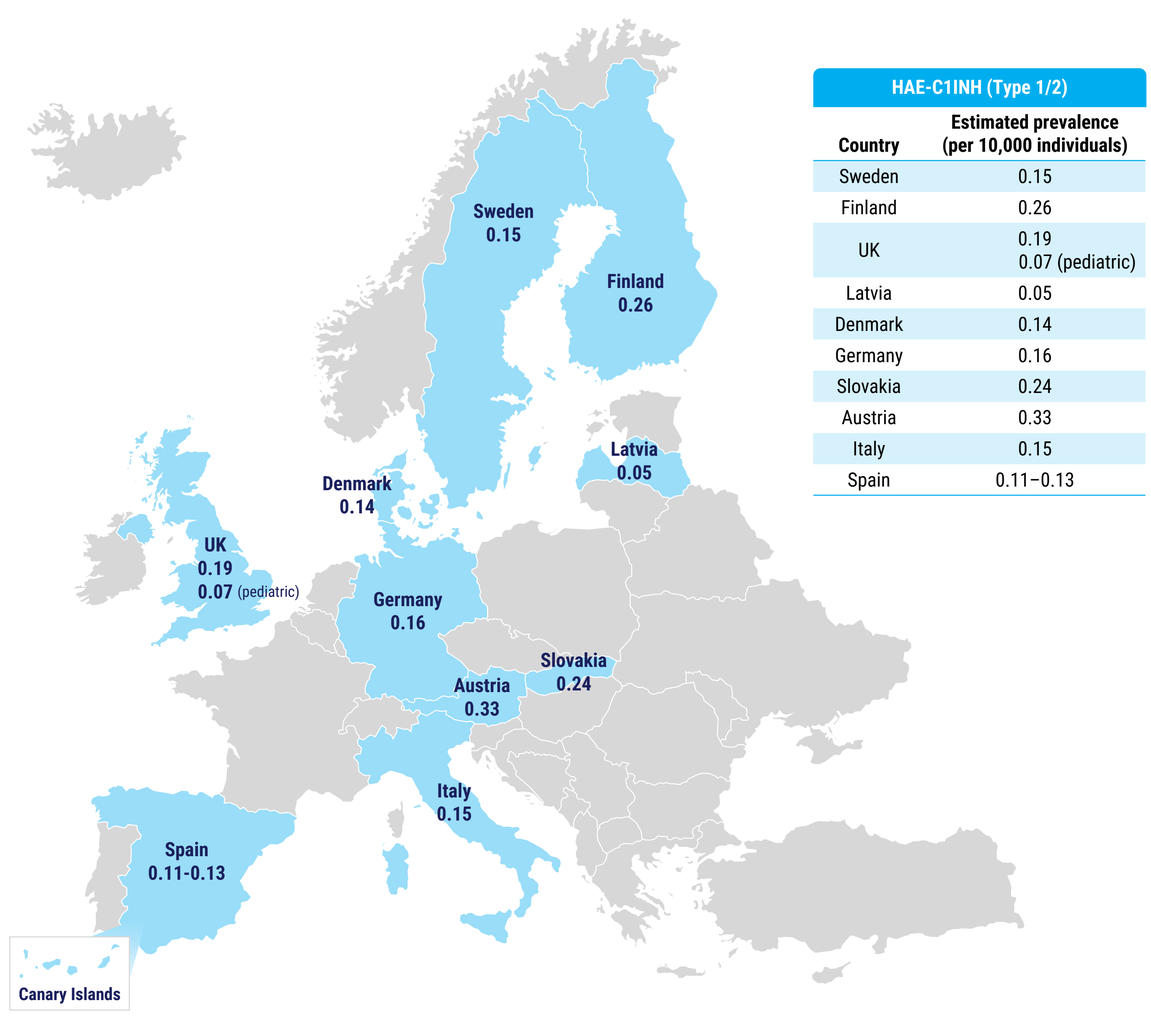
HAE-nC1INH

- Based on evidence from two studies, the reported prevalence of HAE-nC1INH ranged from <0.01/10,000 in the UK to 0.07/10,000 in the Canary Islands, Spain.

AAE-C1INH

- Based on evidence from three studies, the reported prevalence of AAE-C1INH ranged from 0.01/10,000 in the Czech Republic to 0.02/10,000 in Italy.

Figure 2: Prevalence of HAE-C1INH (Type 1/2) in European countries



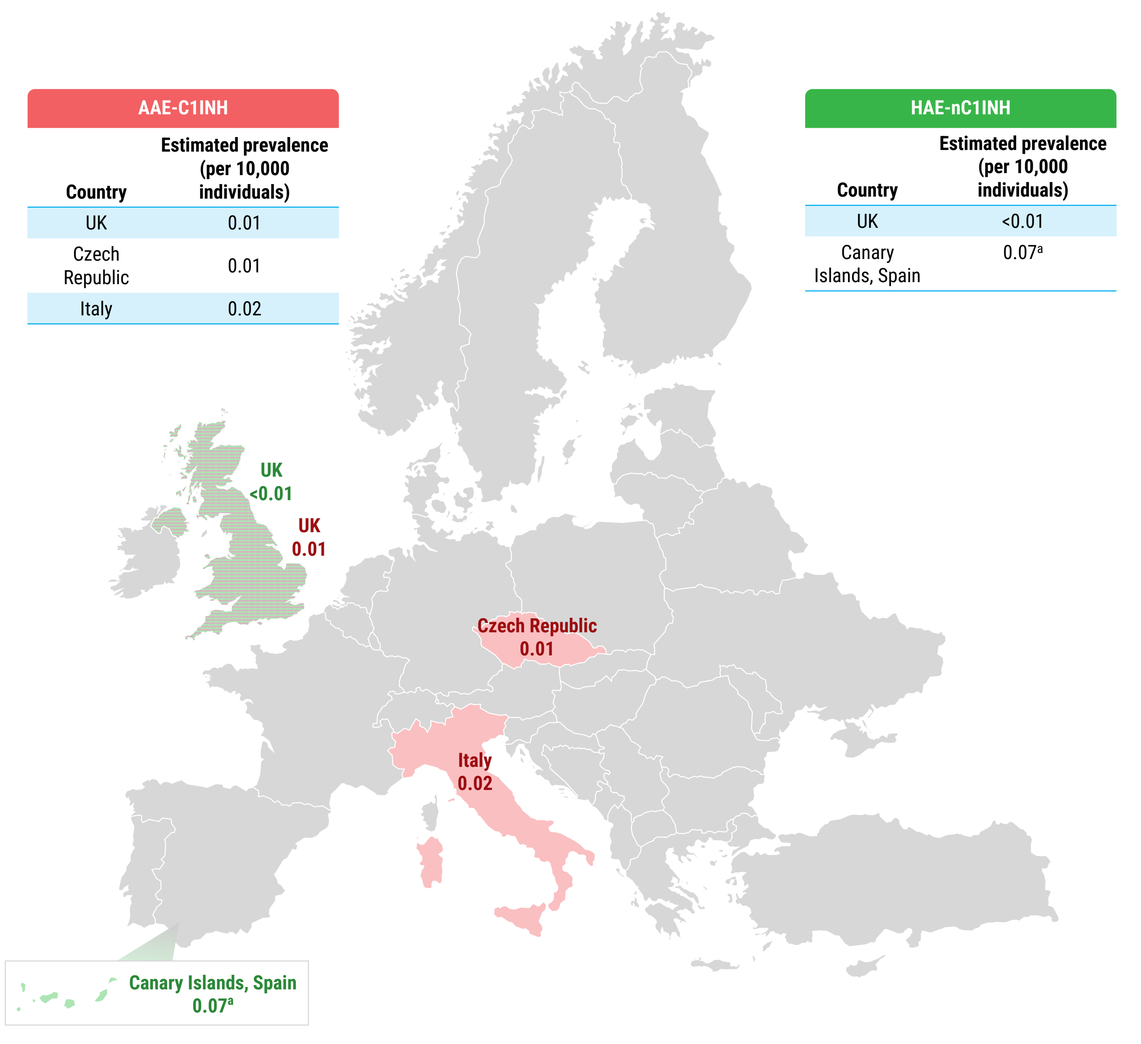
HAE-C1INH (Type 1/2)	
Country	Estimated prevalence (per 10,000 individuals)
Sweden	0.15
Finland	0.26
UK	0.19 0.07 (pediatric)
Latvia	0.05
Denmark	0.14
Germany	0.16
Slovakia	0.24
Austria	0.33
Italy	0.15
Spain	0.11–0.13

HAE-C1INH, hereditary angioedema due to C1-inhibitor deficiency.

Figure 3: Prevalence of AAE-C1INH and HAE-nC1INH in European countries

AAE-C1INH	
Country	Estimated prevalence (per 10,000 individuals)
UK	0.01
Czech Republic	0.01
Italy	0.02

HAE-nC1INH	
Country	Estimated prevalence (per 10,000 individuals)
UK	<0.01
Canary Islands, Spain	0.07[a]



AAE-C1INH, acquired angioedema due to C1-inhibitor deficiency; HAE; hereditary angioedema; HAE-nC1INH, hereditary angioedema with normal C1 inhibitor levels. [a]Indirect prevalence estimate based on subtraction of the reported prevalence of HAE including HAE-C1INH and HAE-nC1INH (0.190 per 10,000) and the reported prevalence of HAE-C1INH alone (0.125 per 10,000), resulting in (0.19-0.125 = 0.065) 0.07 per 10,000.

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