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# Hereditary Angioedema on Long-Term Prophylaxis: A Narrative Review of Attack Prevention and What Treatment Changes for Daily Life

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## Abstract

*Hereditary angioedema produces swelling that is disfiguring, painful and, when it involves the larynx, occasionally fatal. Until recently the disease was managed by treating attacks. It can now be managed by largely preventing them, which changes what the condition is rather than merely how it is treated.*

***Objectives:*** *To review the published evidence on long-term prophylaxis in hereditary angioedema: how far attack rates fall, how many patients become attack-free, how the available agents compare, and what remains unaddressed once attacks stop.*

***Material and Methods:*** *Narrative review of randomised trials, open-label extensions, real-world cohorts, network meta-analysis and international guidance indexed in PubMed and the major allergy and immunology journals. No new patient data were generated; every estimate quoted is one published by the original investigators.*

***Results:*** *In the pivotal randomised trial, a monoclonal plasma kallikrein inhibitor reduced attack rates by approximately 87 per cent against placebo, with around 44 per cent of patients attack-free over 26 weeks and 77 per cent attack-free for 16 weeks once steady state was reached. Secondary outcomes fell correspondingly: attacks requiring acute treatment by 74 to 87 per cent and moderate or severe attacks by 71 to 83 per cent. In the open-label extension of 212 patients followed for a mean of 29.6 months, attack rate fell 87.4 per cent overall, 37.3 per cent were attack-free throughout, and 97.7 per cent of days were attack-free.*

***Conclusion:*** *Prophylaxis converts a disease of recurrent emergencies into one of occasional events for most patients, and the open-label data suggest the effect is durable. The remaining questions are about access, cost and the smaller group who continue to have attacks, none of which the efficacy trials address.*

***Abbreviations:*** *C1-INH – C1 Inhibitor, HAE – Hereditary Angioedema, LTP – Long-Term Prophylaxis, NMA – Network Meta-Analysis, OLE – Open-Label Extension, q2wks – Every Two Weeks, TEAE – Treatment-Emergent Adverse Event.*

**Keywords:** *Hereditary Angioedema; Long-Term Prophylaxis; Plasma Kallikrein Inhibition; Attack-Free Interval; Quality of Life*

## Introduction

Hereditary angioedema is a rare autosomal dominant disorder, most often caused by deficiency or dysfunction of C1 inhibitor, producing bradykinin-mediated swelling without urticaria [1,2]. Affected sites include the face, extremities, genitals, abdominal viscera and the upper airway; laryngeal attacks can be fatal through asphyxiation [3,4].

Untreated patients experience on average around two attacks per month, though frequency ranges from very rare to twice weekly [4,5]. Abdominal attacks mimic a surgical abdomen and have historically led to unnecessary laparotomy, and the unpredictability of attacks imposes a burden on patients and families that attack counts capture poorly [6,7,29,35], and quality-of-life gains have been reported separately for replacement therapy [34].

Management has three components: on-demand treatment of attacks, short-term prophylaxis before procedures, and long-term prophylaxis to prevent attacks occurring [8,9]. On-demand options include bradykinin receptor antagonism, kallikrein inhibition and C1 inhibitor concentrate [24,25,26]. The last of these has changed substantially with the arrival of plasma kallikrein inhibitors and subcutaneous C1 inhibitor replacement [10,11,12]. This review examines what long-term prophylaxis achieves.

## Material and Methods

**Search strategy:** PubMed and the archives of the major allergy, immunology and general medical journals were searched for studies of prophylaxis in hereditary angioedema. Search terms combined hereditary angioedema with long-term prophylaxis, lanadelumab, berotralstat, C1 inhibitor, plasma kallikrein, attack rate and attack-free. Reference lists of international guidance [8,9] were screened by hand for primary sources.

**Eligibility:** Studies were included if they reported attack rates or attack-related outcomes on prophylactic treatment, characterised the burden of the untreated disease, or compared available agents. On-demand treatment trials are cited where they establish the comparator and are identified as such.

**Data extraction and handling:** Design, sample size, baseline attack rate, treatment duration and the reported outcome were extracted as published. The baseline attack rate required for trial entry is reported alongside every efficacy figure, because relative reductions of similar size mean very different things depending on where the patient started. No pooling or re-analysis was performed. Figures 1 to 4 and Tables 1 and 2 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

## Results

**The pivotal randomised evidence:** In the phase 3 double-blind trial, the monoclonal plasma kallikrein inhibitor lanadelumab given at 300 mg every two weeks reduced attack rates by approximately 87 per cent compared with placebo ($p < 0.001$), and around 44 per cent of patients were attack-free across the 26-week treatment period [10,13]. Once steady state was reached in that dosing group, 77 per cent were attack-free for 16 weeks [13]. Efficacy was evident from the first two weeks and sustained [14].

**Secondary outcomes:** All dosing regimens produced statistically significant reductions across secondary endpoints: attacks requiring acute treatment fell by 74 to 87 per cent, moderate or severe attacks by 71 to 83 per cent, and attacks from day 14 to day 182 by 75 to 89 per cent, with adjusted $p < 0.001$ for all comparisons (Figure 3) [13]. These matter because they describe the attacks that generate emergency attendance rather than the total count.

**Durability:** The open-label extension enrolled 212 patients, 109 continuing from the randomised trial and 103 newly started, of whom 81.6 per cent completed at least 30 months, with a mean exposure of 29.6 months. Mean attack rate fell 87.4 per cent against baseline overall, 92.4 per cent in those continuing and 82.0 per cent in those newly started (Figure 1) [15,16]. Across the whole cohort 37.3 per cent were attack-free for the entire treatment period, and 97.7 per cent of days were attack-free (Figure 2) [16].

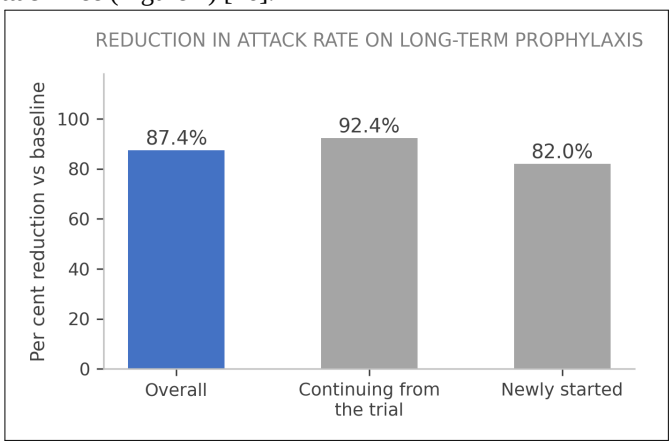


**Figure 1:** Reduction in attack rate against baseline in the open-label extension, overall and by prior exposure [15,16]

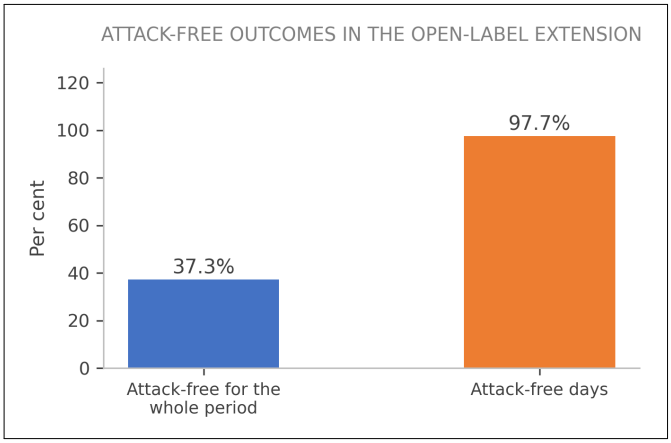


**Figure 2:** Attack-free patients and attack-free days in the open-label extension [16]

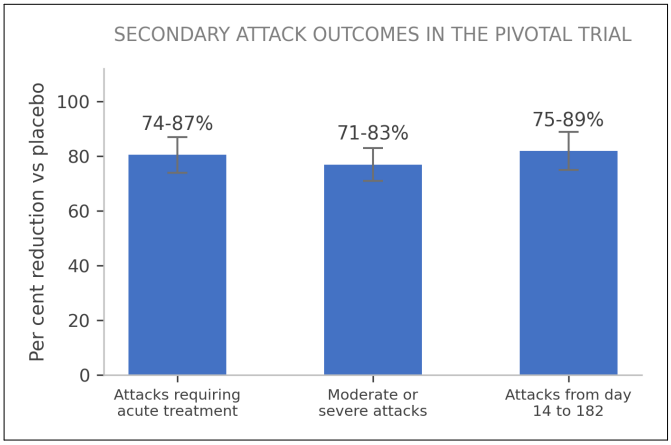


**Figure 3:** Reductions in secondary attack outcomes against placebo in the pivotal trial [13]

**What that means in absolute terms:** The relative figures are easier to quote than to picture. An untreated patient averaging two attacks per month, which is the reported typical burden, moves to a modelled 0.26 attacks per month on treatment in the randomised trial and 0.06 per month among newly treated patients in the extension (Figure 4) [4,17]. That is the difference between something happening most fortnights and something happening once or twice a year.

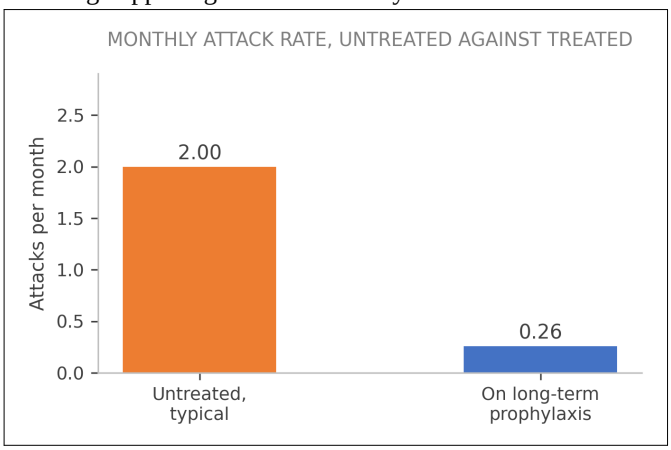


**Figure 4:** Monthly attack rate untreated against treated [4,17]

| Study | Design and cohort | Principal reported finding |
|---|---|---|
| HELP trial [10,13] | Phase 3 RCT, 26 weeks | Attack rate reduced ~87% vs placebo; 44% attack-free |
| HELP OLE [15,16] | Open-label extension, 212 patients, mean 29.6 months | 87.4% reduction overall; 37.3% attack-free throughout |
| Longhurst et al. 2017 [11] | RCT, subcutaneous C1 inhibitor | Established replacement therapy for prophylaxis |
| Zuraw et al. 2021 [12] | APeX-2, oral berotralstat | Once-daily oral kallikrein inhibitor reduces attacks |
| APeX-2 extension [18] | Open-label, up to 4 further years | Long-term safety and tolerability of oral prophylaxis |
| Network meta-analysis [19] | Indirect comparison of agents | Favoured the monoclonal over the oral agent on attack rate |
| EMPOWER [20] | Phase 4 real-world, 109 patients, 36 months | Attack rate reduction maintained outside trial conditions |

**Table 1:** Principal studies reviewed, with the finding as reported by the original investigators

**The available agents:** Long-term prophylaxis can now be delivered by subcutaneous C1 inhibitor replacement, by a subcutaneous monoclonal antibody against plasma kallikrein given every two to four weeks, or by an oral once-daily kallikrein inhibitor [10,11,12]. Attenuated androgens, the previous mainstay, have been displaced by agents without their endocrine and hepatic effects [8,21,30], and current management options have been reviewed in detail [32]. No head-to-head randomised comparison exists between the newer agents; an indirect network meta-analysis favoured the monoclonal antibody over the oral inhibitor on 28-day attack rate and on the proportion achieving a 90 per cent or greater reduction, while noting that both source trial populations were small [19].

**Real-world and dose reduction:** A phase 4 real-world study followed 109 patients for up to 36 months and reported maintained attack rate reduction in those newly treated and continued low rates in those already established, without new safety signals [20]. Claims-based analysis found that a quarter of patients on the monoclonal reduced dosing frequency during months 7 to 12, which is consistent with the observed durability and has cost implications [22]. Adolescent data show a comparable pattern, with attack-free rates similar to the adult cohort [17,23].

| Question | What the evidence shows | Caution |
|---|---|---|
| How much do attacks fall? | About 87% against baseline or placebo | Trial entry required frequent attacks [10,15] |
| How many become attack-free? | 44% in the trial; 37.3% over 30 months | So roughly six in ten still have attacks [13,16] |
| Does it last? | Maintained to a mean of 29.6 months | Open-label, no concurrent control [15,16] |
| Which agent is best? | Indirect comparison favours the monoclonal | No head-to-head trial; small populations [19] |
| Does it work outside trials? | Real-world reduction maintained at 36 months | Observational, 109 patients [20] |
| What about the airway? | Laryngeal attacks can be fatal | Trials are not powered for mortality [3,4] |

**Table 2:** Practical questions in long-term prophylaxis and what the evidence supports

## Discussion

The size of the effect here is unusual. An 87 per cent reduction in the defining event of a disease, sustained across a mean of thirty months, is not a marginal therapeutic gain [10,15]. For a condition in which the previous options were androgens with substantial endocrine effects or repeated intravenous replacement, this is a change in what the illness is.

The figure that deserves equal attention is the one that is less often quoted. In the open-label extension, 37.3 per cent of patients were attack-free for the whole treatment period [16]. That is a remarkable result and it means that roughly six patients in ten continued to have attacks, fewer and further apart, but still occurring. Prophylaxis does not remove the need for on-demand treatment or for a plan for laryngeal involvement, and a patient told that the drug prevents attacks may reasonably conclude otherwise [8,9].

Two features of the evidence structure should temper the numbers. Trial entry required a substantial baseline attack rate, at least one attack every four weeks for those continuing from the randomised study [15]. Relative reductions are largest in the most frequently affected, so the 87 per cent figure describes a selected population. And the extension is open-label without a concurrent control, in a disease where attack frequency varies spontaneously and where enrolment itself tends to follow a bad period [15,20]. National cohorts describe the same variability [31].

On choosing between agents, the honest position is that nobody knows. The indirect comparison favouring the monoclonal antibody is a network meta-analysis of small trials with no head-to-head data, and its authors said so [19]. An oral once-daily tablet and a fortnightly injection differ in ways that matter to patients independently of attack counts, and the choice reasonably rests there. What the efficacy literature does not address at all is cost and access, which in a rare disease with high-cost biologics determines who actually receives any of this [27,33]. Surveys of patients and of prescribing physicians document persistent gaps between guideline and practice [28,33].

## Study limitations

The limitations belong to the underlying literature. Trial populations are small, as the network meta-analysis explicitly noted, and entry criteria selected frequently affected patients [15,19]. The long-term data are open-label without a concurrent control arm, so regression to the mean cannot be excluded [15,16]. Attack ascertainment is patient-reported, and patients on effective prophylaxis may reclassify mild swelling they previously recorded as an attack. Follow-up of around thirty months is short against a lifelong condition [16]. No trial is powered for laryngeal attack or mortality, which are the outcomes that make the disease dangerous [3,4]. Comparative evidence between agents is indirect [19]. Real-world cohorts are predominantly North American and over 90 per cent white [20]. And economic and access data sit outside this literature entirely [22].

## Conclusion

Long-term prophylaxis in hereditary angioedema reduces attacks by roughly 87 per cent and holds that reduction for at least two and a half years, moving a typical patient from something happening most fortnights to something happening once or twice a year. That is among the larger treatment effects in medicine and it should be described without hedging. It should also be described completely: fewer than four in ten patients become entirely attack-free, the trials enrolled the most frequently affected, and nothing in this evidence removes the need for on-demand treatment or an airway plan. Which agent to use is not yet answerable from trials, and on current evidence the decision belongs with the patient who has to take it.

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## Conflict of Interest

The authors declare no competing interests.

## Ethics Statement

This article reviews previously published studies only. No new patient data were collected and no participants were recruited, so ethical approval was not required.

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