NHS England Evidence Review:

Icatibant for the treatment of moderate to severe acute swellings due to bradykinin-mediated angioedema with normal C1 inhibitor

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Prepared by Solutions for Public Health (SPH) on behalf of NHS England Specialised Commissioning

Contents

1. Introduction

This evidence review examines the clinical effectiveness, safety and cost effectiveness of icatibant plus current standard care compared with current standard care alone in patients who have bradykinin-mediated angioedema with normal C1 inhibitor.

Icatibant is currently licensed for symptomatic treatment of acute attacks of hereditary angioedema (HAE) with C1 deficiency (types I and II) in adults, adolescents and children aged two years and older. HAE (types I and II) is the most common bradykinin-mediated angioedema, where patients do not have sufficient levels of functional C1-esterase inhibitor (C1-INH). The population in this proposed policy is patients with a distinct form of bradykinin-mediated angioedema that is not associated with C1-INH abnormalities (i.e. HAE-nC1 INH).

Current standard care during acute episodes often involves hospital admission. There are no licensed treatment options for prophylaxis or for acute swellings. Furthermore, some of the unlicensed prophylactic treatments used are not efficacious, have unacceptable side effects or are contraindicated, for instance in patients with a history of thromboembolism or in patients under 18 years. Current standard care during acute swellings involves observation and if the airway is involved then intensive care admission may be required for intubation to prevent asphyxiation.

Icatibant is not currently commissioned for treatment of bradykinin-mediated angioedema with normal C1 inhibitor. Off-label use is therefore proposed for patients with bradykinin-mediated angioedema but a normal C1 function who are aged two years and over.

In addition, the review scope included the identification of possible subgroups of patients within the included studies who might benefit from treatment with icatibant plus current standard care more than others, as well as the doses, frequency and route of administration of icatibant used by the included studies, and the duration of treatment.

2. Executive summary of the review

This evidence review examines the clinical effectiveness, safety and cost effectiveness of icatibant plus current standard care compared with current standard care alone in patients who have bradykinin-mediated angioedema with normal C1 inhibitor. The searches for evidence published since January 2013 were conducted on 15 August 2023 and identified 439 references. The titles and abstracts were screened and 33 full text papers were obtained and assessed for relevance.

Eight papers were identified for inclusion: one systematic review and meta-analysis (SRMA) of three randomised controlled trials (RCTs), the three RCTs that were also included in the SRMA and four retrospective cohort studies. The SRMA included 179 patients and compared icatibant plus current standard care to current standard care, with or without placebo, in patients with angiotensin-converting enzyme inhibitor (ACEI) induced angioedema. The three RCTs included in the SRMA were also included in this review because they reported results for additional outcomes that were not presented in the SRMA. Two of the RCTs compared icatibant plus current standard care to placebo with current standard care and one RCT compared icatibant plus current standard care to current standard care in patients with ACEI induced angioedema. The RCTs ranged in size from 27 to 121 patients. One RCT assessed outcomes up to 48 hours after treatment initiation (but also reported a mean follow-up duration of 4.36 (standard deviation (SD) 2.19) years). A second RCT reported outcome assessments up to eight hours after treatment initiation (or up to 24 hours and every three hours thereafter in patients who had not met discharge criteria or were not discharged by hour eight after treatment initiation) and a safety follow-up on day three after study treatment, or approximately two days after discharge from hospital if the patient was discharged on or after day three. The remaining RCT reported outcome assessments up to 48 hours after treatment initiation and a follow-up visit 14 days after hospital admission.

Two papers analysed data retrospectively from the same prospective, international, multicentre, observational study (Icatibant Outcome Survey Registry Study) with each paper reporting results for a different country. Both of these studies reported total attack/swelling duration in eight and ten icatibant patients with hereditary angioedema and normal C1 inhibitor levels (HAE-nC1 INH). These two studies also included individuals who did not meet the PICO criteria (i.e. patients with hereditary angioedema with C1-INH abnormalities) for whom data were not extracted for this review. The remaining two papers were retrospective cohort studies. One of these studies reported total attack/swelling duration after icatibant treatment compared to previously untreated attacks in the same 13 patients with HAE and variant in the plasminogen gene (PLG). It was not clear from the paper whether the previously untreated attacks related to attacks that were not treated at all, or whether patients received current standard care, without icatibant. The other study reported total attack/swelling duration in five patients with HAE PLG. These two studies also included individuals (i.e. patients with HAE C1-INH abnormalities) and interventions (e.g. plasma-derived C1 INH or long-term prophylaxis) that did not meet the PICO criteria, and these data were therefore not extracted for this review. Where reported in the four observational studies, follow-up assessments were at six monthly intervals (mean follow-up duration of 4.3 [SD 1.42] years reported in one study).

The included papers were published between 2015 and 2022. One study was conducted in each of the following countries: Brazil, France, Russia and the USA, one study was conducted in multiple countries (including Canada, Israel, the UK and USA), and two studies were conducted in Germany.

In terms of clinical effectiveness:

- **Total attack/swelling duration (critical).**

- Four retrospective cohort studies provided very low certainty evidence on total attack/swelling duration in patients with idiopathic/hereditary angioedema with normal C1 inhibitor. Two studies compared the duration of attacks treated with icatibant versus untreated attacks; one study reported a statistically significant 88% reduction in total attack/swelling duration in patients with HAE PLG when treated with icatibant (mean 4.3 hours [SD 2.6]) compared to previously untreated attacks in the same patients (mean 44.7 hours [SD 28.6]); p<0.0001. The same study also reported that the duration of attacks was reduced by >50% in 197 of 201 icatibant treated attacks. The second of these studies reported a mean attack duration of 12 hours in patients with HAE PLG who were treated with icatibant, and a 71.4% reduction in attack duration compared to attack duration in a comparison group but this group was not clearly defined. The two remaining studies were non-comparative and reported differing total attack/swelling durations, based on time from symptom onset to complete symptom resolution after initiation of treatment with icatibant; median attack durations were 7.0 and 32.5 hours in patients with HAE-nC1 INH.

- **Time to resolution (critical).**
  - One SRMA of three RCTs provided very low certainty evidence on time to complete resolution of symptoms or time to meeting discharge criteria in patients with ACEI-induced angioedema. Time to resolution of symptoms was found to be shorter in patients treated with icatibant plus current standard care compared to patients treated with current standard care or placebo with current standard care, but the difference was not statistically significant (MD -7.77, 95% CI -25.18 to 9.63 hours; p=0.38). The SRMA of three RCTs also provided very low certainty evidence that there was no statistically significant difference in the number of patients exhibiting complete resolution of symptoms within four hours after initiation of treatment with icatibant plus current standard care compared to current standard care or placebo with current standard care (RR 1.20, 95% CI 0.48 to 3.04; p=0.70).

- **Treatment response (critical).**
  - Three RCTs provided very low to high certainty evidence on outcomes related to treatment response in patients with ACEI-induced angioedema. Two RCTs provided moderate to high evidence that there was no statistically significant difference (p-values ranging from 0.14 to 0.80) in the number of patients with ACEI-induced angioedema who required additional treatment up to 48 hours, or on day three after administration of icatibant plus current standard care compared to current standard care or placebo with current standard care. One RCT provided very low certainty evidence that no icatibant plus current standard care treated patients with ACEI-induced angioedema required rescue treatment up to six hours after initiation of icatibant plus current standard care compared to three out of 14 patients who received current standard care alone. No statistical measures were reported.

- **Time to the onset of symptom regression (important).**
  - One SRMA of three RCTs provided very low certainty evidence that there was no statistically significant improvement in time to onset of symptom relief in ACEI-induced angioedema patients treated with icatibant plus current standard care compared to current standard care or placebo with current standard care (MD -0.50, 95% CI -1.30 to 0.30; p=0.22).

- **Symptom progression (important).**
  - Three RCTs provided very low to moderate certainty evidence on symptom progression in patients with ACEI-induced angioedema. One RCT reported that there was no statistically significant difference between the icatibant plus current standard

care and placebo with current standard care groups in terms of patients with ACEI-induced angioedema requiring intubation (p=0.32). The remaining two RCTs reported that a single patient with ACEI-induced angioedema in either the icatibant plus current standard care group or current standard care alone group required intubation or tracheotomy, but no statistical measures were reported.

- **Health related quality of life (HRQoL) (important).**
    - No evidence was identified for important outcome HRQoL.

- **Hospital attendances (important).**
    - Two RCTs reported moderate to high certainty evidence relating to the number of patients with ACEI-induced angioedema requiring hospital or ICU admission between icatibant plus current standard care and placebo with current standard care groups. One RCT reported that the difference was not statistically significant (p=0.36), the remaining RCT did not report statistical measures but showed that the same number of patients in each treatment group required hospital admission.

In terms of safety:

- One SRMA of three RCTs provided very low to moderate certainty evidence on safety in patients with ACEI-induced angioedema. No statistically significant differences were found between ACEI-induced angioedema patients treated with icatibant plus current standard care versus current standard care or placebo with current standard care in the occurrence of any adverse events (RR 0.95, 95% CI 0.43 to 2.10; p=0.90) or drug-related adverse events (RR 1.29, 95% CI 0.58 to 2.87; p=0.53). In addition, there were no statistically significant differences between icatibant plus current standard care versus current standard care or placebo with current standard care groups in terms of a reaction at the injection site (swelling) (RR 1.52, 95% CI 0.89 to 2.61; p=0.13). There was a statistically significant difference in the number of patients with ACEI-induced angioedema reporting reactions at the injection site (erythema), with reactions occurring more often in patients treated with icatibant plus current standard care (RR 2.47, 95% CI 1.56 to 3.90; p=0.0001).

In terms of cost effectiveness:

- No evidence was identified for cost effectiveness.

In terms of subgroups:

- No evidence was identified regarding any subgroups of patients that would benefit more from treatment with icatibant plus current standard care.

Icatibant regimen and treatment duration:

- Three RCTs reported doses, frequency and route of administration of icatibant; two RCTs administered a single subcutaneous injection of icatibant 30 mg within 12 hours after symptom onset and one RCT administered 30 mg subcutaneous injection (delivered in two 1.5 ml syringes) at 0 and six hours. Two retrospective cohort studies reported the number of injections required for angioedema attacks; the majority of patients required one injection (70.0% and 96.7%), with the remaining patients requiring between two and four injections. Two retrospective cohort studies reported that icatibant was self-administered in 15.4% and 96.1% of patients.

Please see the results table (section 5) in the review for further details of outcomes and definitions.

Limitations:

Although this review includes a SRMA of three RCTs (Jeon et al 2019), the three RCTs that were also included in the systematic review (Bas et al 2015, Sinert et al 2017, Straka et al 2017) and four retrospective cohort studies (Bork et al 2020, Bouillet et al 2017, Grumach et al 2022, Manto et al 2021), there are a number of factors that have increased the uncertainty of the results.

The SRMA was limited by the small number of available RCTs and the small sample sizes of the included RCTs. Although the individual RCTs calculated sample sizes prior to the start of the studies, two RCTs (Bas et al 2015, Straka et al 2017) were underpowered, which limits the ability to draw accurate conclusions about the findings. The SRMA reported heterogeneity between the included studies for some outcomes (i.e. complete resolution of symptoms, complete resolution within four hours of treatment, and time to the onset of symptom relief) which may have been partly due to differences between the trials in the time from symptom onset to initiation of treatment, how outcomes were defined and measured and whether or not the trial was blinded. Furthermore, differences between treatment groups were highlighted in the three RCTs, including differences in demographic characteristics and clinical histories.

As no randomised evidence was identified for the critical outcome total attack/swelling duration, four cohort studies were included in this evidence review to provide evidence for this outcome. These studies provided retrospective, observational evidence only and therefore cannot conclusively establish causality or rule out the potential for confounding variables. The studies involved only small subgroups of patients relevant to this evidence review with limited demographic or clinical information provided on these patients, and only two studies provided comparative data. Factors relating to the design and conduct of these studies meant that they were at high risk of bias.

The studies included in this evidence review did not comment on the minimum clinically important difference thresholds for the outcomes reported. Statistical measures were not reported for the outcome total attack/swelling duration, and reporting of statistical measures was limited in the RCTs for treatment response, symptom progression, or hospital/ICU attendances.

Conclusion

This review included one SRMA of three RCTs, the three RCTs that were also included in the SRMA, and four retrospective cohort studies. The SRMA and the three RCTs provide very low to high certainty evidence on critical and important outcomes following treatment with icatibant plus current standard care compared to current standard care or placebo with current standard care in patients with ACEI-induced angioedema. The four retrospective cohort studies provide very low certainty evidence on a critical outcome in patients with idiopathic/hereditary angioedema with normal C1 inhibitor, following treatment with icatibant (with no comparison group) or icatibant compared to no treatment or compared to an unclear patient population who may not have received any treatment or may have received current standard care, without icatibant. No evidence was available for one important outcome (HRQoL) and no evidence was available for cost effectiveness. No evidence was identified regarding relevant subgroups of patients that would benefit more from treatment with icatibant plus current standard care.

The SRMA found no statistically significant difference in time to resolution of symptoms, the number of patients exhibiting complete resolution of symptoms within four hours of treatment, or time to the onset of symptom regression for ACEI-induced angioedema patients receiving icatibant plus current standard care compared to current standard care or placebo with current

standard care. The SRMA also found no statistically significant difference in safety outcomes in patients with ACEI-induced angioedema, with the exception of injection site reactions (swelling), which occurred significantly more often in patients receiving icatibant plus current standard care.

The evidence from the three RCTs regarding treatment response, symptom progression and hospital/ICU admissions indicated no differences between ACEI-induced angioedema patients receiving icatibant plus current standard care compared to patients receiving current standard care or placebo with current standard care. However, only two of the RCTs provided statistical measures for treatment response and one RCT reported statistical measures for symptom progression and hospital/ICU attendances.

No randomised evidence was found that reported on total attack/swelling duration. Four retrospective cohort studies were identified that reported on this outcome in patients with idiopathic/hereditary angioedema with normal C1 inhibitor, but were limited by the lack of a relevant treatment comparison group and small sample sizes (ranging from five to 13 patients).

Given the limitations of the evidence about the clinical effectiveness and safety of icatibant plus current standard care in patients with different subtypes of bradykinin-mediated angioedema with normal C1 inhibitor, it is difficult to assess the validity of the findings or their generalisability to the wider population of interest.

3. Methodology

Review questions

The review questions for this evidence review are:

1. In people with bradykinin-mediated angioedema with normal C1 inhibitor, what is the clinical effectiveness of icatibant plus current standard care compared with current standard care alone?
2. In people with bradykinin-mediated angioedema with normal C1 inhibitor, what is the safety of icatibant plus current standard care compared with current standard care alone?
3. In people with bradykinin-mediated angioedema with normal C1 inhibitor, what is the cost effectiveness of icatibant plus current standard care compared with current standard care alone?
4. From the evidence selected, are there any subgroups of patients that may benefit from icatibant plus current standard care more than the wider population of interest?
5. From the evidence selected, what doses, frequency and route of administration of icatibant were used and what was the duration of treatment?

See Appendix A for the full PICO document.

Review process

The methodology to undertake this review is specified by NHS England in its 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020).

The searches for evidence were informed by the PICO document and were conducted on 15th August 2023.

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO document. Full text references of potentially relevant studies were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE profiles.

4. Summary of included studies

Eight papers were identified for inclusion (Bas et al 2015, Bork et al 2020, Bouillet et al 2017, Grumach et al 2022, Jeon et al 2019, Manto et al 2021, Sinert et al 2017, Straka et al 2017). One was a systematic review and meta-analysis (SRMA) (Jeon et al 2019) which included three randomised controlled trials (RCTs) (Bas et al 2015, Sinert et al 2017, Straka et al 2017). These three RCTs were also included in this review where additional relevant outcomes were provided but not reported in the SRMA. Two papers related to a prospective, international, multicentre, observational study (Icatibant Outcome Survey Registry Study) and analysed outcomes retrospectively for both in scope and out of scope populations from different countries, i.e. France (Bouillet et al 2017) or Brazil (Grumach et al 2022). Two papers were retrospective cohort studies that assessed both in scope and out of scope populations and interventions (Bork et al 2020, Manto et al 2021).

No studies were identified that reported health-related quality of life (HRQoL). No cost effectiveness studies were identified for inclusion in this review. No studies were identified reporting on relevant subgroups of patients that would benefit more from treatment with icatibant plus current standard care.

Table 1 provides a summary of these included studies and full details are given in Appendix E.

Table 1: Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported

Bas et al 2015
 	
Multicentre RCT
 	
Germany
	• Total sample size: N=30
	• Icatibant: n=15
	• Control: n=15
	• Adults with ACEI-induced angioedema of the upper aerodigestive tract; race: white (100%)
	• No subgroups reported
		Intervention
		• Single subcutaneous injection of icatibant 30 mg into the abdominal wall 10 hours after symptom onset, plus IV normal saline
		
		Comparison
		• Current standard care (intravenous prednisolone 500 mg plus clemastine 2 mg) administered 10 hours after symptom onset, plus subcutaneous normal saline
		
		Rescue medication (prednisolone 500 mg and icatibant 30 mg) could be administered to patients in either treatment group 6 hours after initiation of treatment if symptoms had not improved
			Follow-up duration: 14 days after hospital admission, unless otherwise stated
			
			Critical outcomes
			• Time to resolution
			  ○ Time to complete resolution of oedema, assessed by investigators and patients at 1, 2, 3, 4, 6, 8, 12, 24, and 48 hours after initiation of treatment (included in SRMA by Jeon et al 2019)
			  ○ Proportion of patients exhibiting complete resolution of symptoms within 4 hours after initiation of treatment (included in SRMA by Jeon et al 2019)
			• Treatment response
			  ○ Number of patients who had no reduction in symptoms by 6 hours after treatment (i.e. patients who required rescue medication)
			
			Important outcomes
			• Time to onset of symptom regression

Study	Population	Intervention and comparison	Outcomes reported
			○ Time to onset of symptom relief, assessed by investigators and patients at 1, 2, 3, 4, 6, 8, 12, 24, and 48 hours or up to 14 days (included in SRMA by Jeon et al 2019) • Symptom progression ○ Tracheotomy by 6 hours after initiation of treatment • Safety (included in SRMA by Jeon et al 2019)
Bork et al 2020 **Retrospective, single centre, cohort study** **Germany**	• Total sample size: N=111 (n=22 families) • Icatibant: n=13 (n=201 treated attacks/swellings) • Control: n=13 (same patients with 149 previously untreated attacks) • Adults with a confirmed diagnosis of PLG gene variant c.988A > G (p.K330E) • No subgroups reported	**Intervention** • Icatibant treated attacks (administered at home by 2 patients; no other details provided) **Comparison** • Untreated attacks	Follow-up duration: not reported **Critical outcomes** • Total attack/swelling duration ○ Patient assessed attack duration (no further details provided)
Bouillet et al 2017 **Retrospective, multicentre, cohort study** **France**	• Total sample size: N=182 (n=22 in scope patients with HAE-nC1 INH) • Icatibant: n=10 (90 attacks) • Control: None • Symptomatic adults diagnosed with HAE type I or II, or HAE-nC1 INH (normal C1 INH level) • No subgroups reported	**Intervention** • Icatibant (healthcare professional or self-administered; 96.1% of attacks were self-administered) • 70.0% of attacks required one injection, 24.4% required two injections and 5.6% required 3 injections **Comparison** • None	Follow-up duration: not reported (assessments at 6-month intervals) **Critical outcomes** • Total attack/swelling duration ○ Time from symptom onset to complete symptom resolution[a]
Grumach et al 2022 **Retrospective, multicentre, cohort study** **Brazil**	• Total sample size: N=42 (n=16 in scope patients with HAE-nC1 INH) • Icatibant: n=8 (45 attacks) • Control: None • Adults with HAE nC1-INH (normal C1 INH level) or HAE type I or II No subgroups reported	**Intervention** • Icatibant (concomitant rescue therapy was permitted for the treatment of HAE attacks) • 96.7% of attacks required one injection, 1.7% required two injections and 1.7% required four injections Comparison • None	Follow-up duration: mean 4.3 (SD 1.42) years (assessments at 6-month intervals) **Critical outcomes** • Total attack/swelling duration ○ Time between the onset of an attack and complete resolution of all symptoms (no further details provided)
Jeon et al 2019	• Total sample size: N=179; sample sizes ranged from 27 to 121 individuals • Icatibant: n=87 • Control: n=92	**Intervention** • Single subcutaneous injection of icatibant 30 mg (2 RCTs); Subcutaneous injection of	Follow-up duration: see individual RCTs **Critical outcomes** • Time to resolution[b]

Study	Population	Intervention and comparison	Outcomes reported
SRMA (including 3 RCTs) **Study locations: Canada, Germany, Israel, UK, USA**	• Adults with ACEI-induced angioedema: 1 RCT included white patients only; 2 RCTs included mainly black patients • No subgroups reported	icatibant 30 mg at 0 and 6 hours (1 RCT) • Plus antihistamines, corticosteroids and epinephrine (2 RCTs); rescue therapy (prednisolone and icatibant 6 hours after treatment if no reduction in symptoms; 1 RCT) **Comparison** • Single subcutaneous injection of placebo 30 mg (2 RCTs) plus treatments including antihistamines, corticosteroids and epinephrine • Current standard care (prednisolone 500 mg plus clemastine 2 mg IV; 1 RCT), plus rescue therapy (prednisolone and icatibant 6 hours after treatment if no reduction in symptoms)	○ Time to complete resolution of symptoms (or time to meeting discharge criteria) ○ Proportion of patients exhibiting complete resolution of symptoms (or those meeting discharge criteria) within 4 hours after initiation of treatment[c] **Important outcomes** • Time to onset of symptom relief ○ Time to decrease of at least one point in symptom score or scale • Safety ○ Any adverse events ○ Drug-related adverse events ○ Injection site reactions (erythema and swelling)
Manto et al 2020 **Retrospective, single centre, cohort study** **Germany**	• Total sample size: N=208 (n=14 in-scope patients; 10 families) • Icatibant: n=5 (29 attacks) • Control: None • Adults with HAE with the c.988A>G (p.Lys330Glu; p.K330E) variant in the PLG gene • No subgroups reported	**Intervention** • Icatibant (no further details provided) **Comparison** • None	Follow-up duration: not reported **Critical outcomes** • Attack/swelling duration (not clearly defined)
Sinert et al 2017 **Multicentre RCT** **Canada, Israel, UK, USA**	• Total sample size: N=121 • Icatibant: n=61 • Control: n=60 • Adults with at least moderately severe ACEI-induced angioedema of the head and/or neck; race – black or African American (69.4%), other (30.6%) • No relevant subgroups reported	**Intervention** • Single subcutaneous injection of icatibant 30 mg, plus conventional treatments (including antihistamines, corticosteroids and epinephrine) **Comparison** • Single subcutaneous injection of placebo (isotonic acetate-buffered solution) 30 mg, plus current standard care (including antihistamines, corticosteroids and epinephrine)	Follow-up duration: day 3 after study treatment, or approximately 2 days after discharge, if patient discharged on or after day 3, unless otherwise stated **Critical outcomes** • Time to resolution ○ Time to meeting discharge criteria, assessed by investigators at 30 and 60 minutes after treatment initiation and hourly thereafter up to 8 hours, or in patients who did not meet the primary outcome or were not discharged from hospital by hour 8, assessments continued every 2 hours up to 24 hours, and every 3 hours thereafter[b] (included in SRMA by Jeon et al 2019)

Study	Population	Intervention and comparison	Outcomes reported
			○ Proportion of patients exhibiting complete resolution of symptoms within 4 hours after initiation of treatment (included in SRMA by Jeon et al 2019) • Treatment response ○ Use of corticosteroids, antihistamines, or epinephrine after initiation of treatment **Important outcomes** • Time to onset of symptom regression ○ Time to onset of symptom relief, assessed by investigators at 30 and 60 minutes after treatment initiation and hourly thereafter up to 8 hours, or in patients who did not meet the primary outcome or were not discharged from hospital by hour 8, assessments continued every 2 hours up to 24 hours, and every 3 hours (included in SRMA by Jeon et al 2019) • Symptom progression ○ Number of patients requiring airway intervention after study treatment • Hospital attendances ○ Number of hospital admissions after initiation of treatment • Safety (included in SRMA by Jeon et al 2019)
Straka et al 2017 **Multicentre RCT** **USA**	• Total sample size: N=30 • Icatibant: n=12 • Control: n=18 • Adults with ACEI-induced angioedema of the face, lips or pharynx; race – white (33.33%), black (66.66%) • No relevant subgroups reported	**Intervention** • Subcutaneous injection of icatibant 30 mg (delivered in two 1.5 ml syringes at 0 and 6 hours) plus standard care (including antihistamines, steroids, or epinephrine) **Comparison** • Subcutaneous injection of placebo 30 mg (delivered in two 1.5 ml syringes at 0 and 6 hours) plus current standard care (including	Follow-up: up to 48 hours after initiation of treatment or at discharge from hospital, unless otherwise stated **Critical outcomes** • Time to resolution ○ Time to complete resolution of symptoms (included in SRMA by Jeon et al 2019) ○ Proportion of patients exhibiting complete resolution of symptoms within 4 hours after

Study	Population	Intervention and comparison	Outcomes reported

		antihistamines, steroids, or epinephrine)	initiation of treatment (included in SRMA by Jeon et al 2019)
			• Treatment response
			  ○ Use of H1 and H2 blockers, corticosteroids, and epinephrine
			
			Important outcomes
			• Symptom progression
			  ○ Number of patients requiring intubation after initiation of treatment
			• Hospital attendances
			  ○ Number of patients admitted to ICU after initiation of treatment
			• Safety (included in SRMA by Jeon et al 2019)

Abbreviations
ACEI: angiotensin-converting enzyme inhibitor; HAE: hereditary angioedema; HAE-nC1 INH: hereditary angioedema with normal C1 inhibitor; ICU: intensive care unit; IQR: interquartile range; ITT: intention-to-treat; IV: intravenous; NA: not applicable; PICO: population, intervention, comparator, outcome; PLG: plasminogen; RCT: randomised controlled trial; SRMA: systematic review and meta-analysis.

a Defined as time to administration (from symptom onset to first subcutaneous icatibant injection) and time to resolution (duration from icatibant injection to complete symptom resolution)
b Defined as absence of symptoms of oedema in Jeon et al (2019). Primary study definitions: Bas et al (2015) – time to complete resolution of oedema; Sinert et al (2017) – time to meeting discharge criteria (i.e. absence of breathing and swallowing difficulty, and mildness or absence of voice change and tongue swelling); Straka et al (2017) – time to complete resolution of symptoms
c Defined as absence of breathing and swallowing difficulty, and mildness or absence of voice change and tongue swelling.

5. Results

In people with bradykinin-mediated angioedema with normal C1 inhibitor, what is the clinical effectiveness and safety of icatibant plus current standard care compared with current standard care alone?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Total attack/swelling duration **Certainty of evidence:** Very low	This outcome is important to patients as attacks/swellings in this condition are frequent, unpredictable and potentially fatal, and if untreated may last for 3-4 days; therefore, a rapid response to treatment is likely to mitigate the morbidity and mortality associated with this condition. In total, four retrospective cohort studies provided evidence relating to total attack/swelling duration in patients with idiopathic/hereditary angioedema with normal C1 inhibitor. The studies included patients that met the PICO criteria (i.e. patients with HAE PLG or HAE-nC1 INH) but also patients who did not meet the PICO criteria (i.e. patients with C1-INH abnormalities) and/or interventions that did not meet the PICO criteria. However, results were reported separately for patients and interventions that were in scope for this review. Two studies provided comparative evidence on the duration of attacks in patients with HAE PLG. One study compared icatibant treated attacks to previously untreated attacks in the same patients and the other study compared icatibant treated attacks to attacks not treated with icatibant, but the comparator group population was not clearly defined.[1] The two remaining studies provided non-comparative evidence on the duration of icatibant treated attacks in patients with HAE-nC1 INH. **Total attack/swelling duration** • One retrospective cohort study (Bork et al 2020) (n=13 in scope patients) reported an 88% reduction in duration of attacks2 in icatibant treated attacks (201 attacks; mean 4.3, SD 2.6 hours) compared to previously untreated attacks in the same patients with HAE PLG (149 attacks; mean 44.7, SD 28.6 hours). The difference was statistically significant, favouring treatment with icatibant (p<0.0001). **(VERY LOW)** • One retrospective cohort study (Manto et al 2021) (n=5 in scope patients; 29 attacks) reported a 71.4%1 reduction in total attack/swelling duration[3] after treatment with icatibant in patients with HAE PLG (mean attack/swelling duration of 12 hours). Statistical measures were not reported. **(VERY LOW)** **Time from symptom onset to complete symptom resolution** • Two non-comparative retrospective cohort studies (Bouillet et al 2017 [n=10 in scope patients; 90 attacks] and Grumach et al 2022 [n=8 in scope patients; 45 attacks]) reported median total attack/swelling durations of 32.5 (IQR 12.0 to 47.3) hours and 7.0 (range 0.3 to 99.0) hours, respectively, after treatment with icatibant in patients with HAE-nC1 INH. **(VERY LOW)** **Number of attacks shortened with icatibant treatment by >50%, 20% to 50%, <20%** • One retrospective cohort study (Bork et al 2020) (n=13 in scope patients) reported that 197 of 201 attacks were reduced in duration by more than 50%

[1] It was unclear how the reduction in duration of attacks was calculated for Manto et al (2021) in terms of whether the comparison was between icatibant-treated vs untreated attacks in the same five patients with HAE PLG, or the comparison was between 5/14 patients with HAE PLG who were treated with icatibant vs 9/14 patients with HAE PLG who were not treated with icatibant.
[2] Defined as swellings attacks, with duration of attacks recorded by patients.
[3] Not clearly defined; Manto et al (2021) stated that data on disease manifestation (defined as the incidence of clinical symptoms [peripheral oedema, abdominal attacks, oedema of the face and neck, oedema of the tongue, oedema of the larynx, marginal erythema]) and outcomes were obtained from medical records of patients and the database of NRC Institute of Immunology FMBA of Russia.

Outcome	Evidence statement
	after treatment with icatibant, two out of 201 attacks were reduced by 20% to 50% and two out of 201 attacks were reduced by <20% after treatment with icatibant. **(VERY LOW)** **Four retrospective cohort studies provide very low certainty evidence on the effect of icatibant on total attack/swelling duration in patients with idiopathic/hereditary angioedema with normal C1 inhibitor. One study reported a *statistically significant* reduction in total attack/swelling duration after treatment with icatibant compared to previously untreated attacks in the same patients with HAE PLG. One study reported a reduction in total attack/swelling duration in patients with HAE PLG treated with icatibant but it was unclear how the reduction was calculated in terms of the comparison population and statistical significance was not reported. The remaining two studies were non-comparative and reported very different total attack/swelling durations in patients with HAE-nC1 INH.**
Time to resolution **Certainty of evidence:** Very low	This outcome is important to patients as attacks/swellings in this condition are frequent and unpredictable and potentially fatal, and if left untreated may last for an average of 3-4 days; therefore, a rapid response to treatment is likely to mitigate the morbidity and mortality associated with this condition. One SRMA (Jeon et al 2019) of three RCTs (n=179[4]) provided evidence relating to time to complete resolution of symptoms after initiation of treatment and resolution of symptoms within four hours after treatment in patients with ACEI-induced angioedema. The SRMA of three RCTs compared results between patients with ACEI-induced angioedema who were treated with icatibant plus current standard care versus those treated with current standard care or placebo with current standard care. Two of the RCTs included in the SRMA defined time to resolution as 'time to complete resolution of symptoms or oedema' and one RCT defined this outcome as 'time to meeting discharge criteria'[5]. **Time to complete resolution of symptoms or time to meeting discharge criteria[5]:** • The SRMA of three RCTs (Jeon et al 2019) (n=179 patients[4]) reported that there were *no statistically significant* differences between patients with ACEI-induced angioedema treated with icatibant plus current standard care compared to current standard care or placebo with current standard care in time to complete resolution: MD -7.77 (95% CI -25.18 to 9.63); p=0.38. There was evidence of considerable heterogeneity (I^2=83%). **(VERY LOW)** **Proportion of patients exhibiting complete resolution of symptoms (or meeting discharge criteria[5]) within four hours after initiation of treatment:** • The SRMA of three RCTs (Jeon et al 2019) (n=176 patients[4]) reported that in patients with ACEI-induced angioedema complete resolution of symptoms within four hours after initiation of treatment was achieved in 41 patients treated with icatibant plus current standard care compared to 39 patients treated with current standard care or placebo with current standard care. The difference in favour of icatibant plus current standard care was *not statistically significant*: RR 1.20 (95% CI 0.48 to 3.04); p=0.70. There was evidence of moderate heterogeneity (I^2=46%). **(VERY LOW)** **One SRMA of three RCTs provides very low certainty evidence that there is *no statistically significant* difference in time to complete resolution of symptoms after initiation of treatment or resolution of symptoms within four hours of treatment with icatibant plus current standard care versus current standard care or placebo with current standard care in patients with ACEI-induced angioedema.**
Treatment response	This outcome is important to patients as these attacks/swellings are debilitating and potentially fatal; therefore, a response to treatment is likely to mitigate the morbidity

[4] Although Straka et al (2017) stated that their final analysis was based on ITT, they excluded one patient in the icatibant group from the final analysis due to the patient being unable to complete the visual analogue scale. Jeon et al (2019), however, included this patient in their ITT analysis.

[5] Defined as absence of breathing and swallowing difficulty and mildness or absence of voice change and tongue swelling.

Outcome	Evidence statement
Certainty of evidence: Very low to High	and mortality associated with this condition. Untreated attacks may otherwise last for 3-4 days. In total, three RCTs comparing icatibant plus current standard care to current standard care or placebo with current standard care reported outcomes related to treatment response in patients with ACEI-induced angioedema. **Number of patients who did not have a response to treatment (use of rescue medication)[6] up to six hours after initiation of study treatment** • One RCT (Bas et al 2015) (n=27) reported that 0 of 13 patients with ACEI-induced angioedema did not have a response to treatment with icatibant plus current standard care after six hours compared to three of 14 patients with ACEI-induced angioedema who received current standard care. No statistical measures were reported. **(VERY LOW)** **Number of patients who required additional medication** *Up to 48 hours after initiation of study treatment:* • One RCT (Straka et al 2017) (n=30) reported the frequency of administering additional treatments in patients with ACEI-induced angioedema. Epinephrine was used by 17% of patients in the placebo with current standard care group compared to 0% in the icatibant plus current standard care group. 92% of icatibant plus current standard care treated patients required H1 blockers, H2 blockers or corticosteroids compared to 88.9%, 78% and 88.9% of patients in the placebo with current standard care group, respectively. The differences between treatment groups were *not statistically significant* (p-values ranged from 0.14 for epinephrine to 0.80 for H1 blockers and corticosteroids). **(MODERATE)** *Day three after study treatment, or approximately two days after discharge, if patient discharged on or after day three:* • One RCT (Sinert et al 2017) (n=118) reported that 58.3% of 60 patients with ACEI-induced angioedema used corticosteroids, antihistamines, or epinephrine after initiation of icatibant plus current standard care compared to 60.3% of 58 ACEI-induced angioedema patients in the placebo with current standard care group. The difference was *not statistically significant* (p≥0.58). **(HIGH)** **Three RCTs provide very low to high certainty evidence on outcomes related to treatment response in patients with ACEI-induced angioedema. Two RCTs provide moderate to high evidence that there was *no statistically significant* difference in the number of patients with ACEI-induced angioedema who required additional treatment up to 48 hours or three days after administration of icatibant plus current standard care compared to current standard care or placebo with current standard care. One RCT provides very low certainty evidence that no patients with ACEI-induced angioedema required rescue treatment up to six hours after initiation of icatibant plus current standard care compared to three out of 14 patients who received current standard care alone. No statistical measures were reported.**
Important outcomes	
Time to the onset of symptom regression **Certainty of evidence:** Very low	This outcome is important to patients as attacks/swellings in this condition are frequent and unpredictable and potentially fatal, and untreated may last for several days; therefore, a rapid response to treatment is likely to mitigate the morbidity and mortality associated with this condition. One SRMA (Jeon et al 2019) included two RCTs (n=148) comparing time to onset of symptom regression between icatibant plus current standard care and current standard care or placebo with current standard care in patients with ACEI-induced angioedema; follow-up durations were not reported. **Time to decrease of at least one point in symptom score or scale**

[6] 30 mg of icatibant with 500 mg of prednisolone.

Outcome	Evidence statement
	• The SRMA (Jeon et al 2019) reported that there was *no statistically significant difference* in time to the onset of symptom relief between ACEI-induced angioedema patients treated with icatibant plus current standard care compared to current standard care or placebo with current standard care: MD -0.50 (95% CI -1.30 to 0.30), p=0.22. There was evidence of considerable statistical heterogeneity (I^2=96%). **(VERY LOW)** **One SRMA including two RCTs provides very low certainty evidence that there is *no statistically significant* difference in time to the onset of symptom relief between patients with ACEI-induced angioedema treated with icatibant plus current standard care compared to current standard care or placebo with current standard care.**
Symptom progression **Certainty of evidence:** Very low to Moderate	This outcome is important to patients because it provides a holistic evaluation and indication of the patient's general health and their perceived well-being and their ability to participate in activities of daily living. This outcome is both a key indicator of the effectiveness of treatment and provides an insight into the patient's perception of the effectiveness of treatment. In total, three RCTs provided evidence on symptom progression in patients with ACEI-induced angioedema, measured up to six or 48 hours after treatment. One RCT compared icatibant plus current standard care versus current standard care and two RCTs compared icatibant plus current standard care to placebo with current standard care. **Progression of symptoms leading to airway intervention** • One RCT (Bas et al 2015) (n=27) reported that one of 14 ACEI-induced angioedema patients in the current standard care group were classified as having treatment failure and required tracheotomy for dyspnoea by six hours after treatment compared to 0 of 13 patients with ACEI-induced angioedema in the icatibant plus current standard care treatment group. No statistical measures were reported. **(VERY LOW)** • One RCT (Sinert et al 2017) (n=118) reported that one of 60 patients with ACEI-induced angioedema who received icatibant plus current standard care required endotracheal intubation 1.5 hours after receiving treatment and 4.75 hours after attack onset compared to 0 of 58 patients with ACEI-induced angioedema who received placebo with current standard care. No statistical measures were reported. **(MODERATE)** • One RCT (Straka et al 2017) (n=30) reported that two of 12 patients with ACEI-induced angioedema in the icatibant plus current standard care treatment group and one of 18 patients with ACEI-induced angioedema in the placebo with current standard care group required intubation up to 48 hours after treatment. The difference between the two treatment groups was *not statistically significant* (p=0.32). **(MODERATE)** **Three RCTs provide very low to moderate certainty evidence that a similar number of patients with ACEI-induced angioedema required airway intervention after administration of icatibant plus current standard care compared to current standard care or placebo with current standard care; one of the RCTs reported statistical measures indicating that the difference was *not statistically significant*.**
HRQoL **Certainty of evidence:** Not applicable	This outcome is important to patients as attacks/swellings can progress to the extent that fatal airway obstruction can occur; therefore, a reduction in progression is likely to mitigate the morbidity and mortality associated with this condition. **No evidence was identified for this outcome.**
Hospital attendances **Certainty of evidence:** Moderate to High	This outcome is important to patients because severe acute episodes most often require hospital admission, including intensive care monitoring. However, not all acute episodes require hospital admission and if they do not, this signifies reduced severity. Two RCTs provided evidence on the number of hospital/ICU admissions required by patients with ACEI-induced angioedema up to 48 hours after treatment with icatibant plus current standard care or placebo with current standard care on day three after

Outcome	Evidence statement
	treatment with icatibant plus current standard care or placebo with current standard care, or approximately two days after discharge, if patient discharged on or after day three. Hospital attendances after initiation of treatment (excluding patients hospitalised before initiation of treatment) • One RCT (Sinert et al 2017) (n=96) reported the same proportions of patients with ACEI-induced angioedema who were admitted to hospital in the icatibant plus current standard care compared to placebo with current standard care groups on day three after treatment and after hospital discharge, or two days after discharge, if patient discharged on or after day three (45.8% in each group). No statistical measures were reported. **(HIGH)** **Hospital attendances after initiation of treatment (ICU admission)** • One RCT (Straka et al 2017) (n=30) reported that a higher proportion of patients with ACEI-induced angioedema treated with icatibant plus current standard care required admission to ICU compared to patients with ACEI-induced angioedema in the placebo with current standard care group up to 48 hours after initiation of treatment (50% versus 33%, respectively). The difference between treatment groups was *not statistically significant* (p=0.36). **(MODERATE)** **Two RCTs provide moderate or high certainty evidence relating to the number of patients with ACEI-induced angioedema who required admission to hospital/ICU after administration of icatibant plus current standard care or placebo with current standard care; one of the RCTs reported statistical measures indicating that the difference was *not statistically significant* and the second RCT showed that the same number of patients in both treatment arms required hospital admissions, but no statistical measures were reported.**
Safety	
Complications of icatibant treatment **Certainty of evidence:** Very low to Moderate	Safety is important to patients as it reflects the risks involved in a treatment that may be required multiple times. This allows a risk benefit assessment to be undertaken. One SRMA of three RCTs (Jeon et al 2019) provided evidence on safety in patients with ACEI-induced angioedema. One of the included RCTs compared icatibant plus current standard care to current standard care and two RCTs compared icatibant plus current standard care to placebo with current standard care in patients with ACEI-induced angioedema. **Any adverse events:** • One SRMA of three RCTs (Jeon et al 2019) (n=179) reported that, of 88 patients with ACEI-induced angioedema in the icatibant plus current standard care group, 29 experienced an adverse event. Of 91 patients with ACEI-induced angioedema in the current standard care or placebo with current standard care group, 27 experienced an adverse event. The difference between the treatment groups was *not statistically significant*: RR 0.95 (95% CI 0.43 to 2.10); p=0.90. There was evidence of low statistical heterogeneity (I^2=20%). **(LOW)** **Drug-related adverse events:** • One SRMA of three RCTs (Jeon et al 2019) (n=179) reported that, of 88 patients with ACEI-induced angioedema in the icatibant plus current standard care group, 12 experienced a drug-related adverse event. Of 91 patients with ACEI-induced angioedema in the current standard care or placebo with current standard care group, nine experienced a drug-related adverse event. The difference between the treatment groups was *not statistically significant*: RR 1.29 (95% CI 0.58 to 2.87); p=0.53. There was no evidence of statistical heterogeneity (I^2=0%). **(VERY LOW)** **Injection site reactions (erythema):** • One SRMA of two RCTs (Jeon et al 2019) (n=178) reported that, of 75 patients with ACEI-induced angioedema in the icatibant plus current standard care group, 43 experienced erythema. Of 73 patients with ACEI-induced angioedema in the current standard care or placebo with current standard

Outcome	Evidence statement
	care group, 17 experienced erythema. The difference between the treatment groups was *statistically significant*, favouring the current standard care or placebo with current standard care group: RR 2.47 (95% CI 1.56 to 3.90); p=0.0001. There was no evidence of statistical heterogeneity (I^2=0%). **(MODERATE)** **Injection site reactions (swelling):** • One SRMA of two RCTs (Jeon et al 2019) (n=178) reported that, of 75 patients with ACEI-induced angioedema in the icatibant plus current standard care group, 25 experienced swelling. Of 73 patients with ACEI-induced angioedema in the current standard care or placebo with current standard care group, 16 experienced swelling. Although fewer swellings were reported in the current standard care or placebo with current standard care group compared to icatibant plus current standard care group, the difference was *not statistically significant*: RR 1.52 (95% CI 0.89 to 2.61); p=0.13. There was evidence of low statistical heterogeneity (I^2=23%). **(LOW)** **The SRMA of three RCTs provides very low to low certainty evidence that there is *no statistically significant* difference in the number of patients with ACEI-induced angioedema experiencing any adverse event or drug-related adverse event after treatment with icatibant plus current standard care compared to current standard care or placebo with current standard care. The SRMA, including two of the RCTs, provides moderate certainty evidence that there is *no statistically significant* difference in the number of patients with ACEI-induced angioedema experiencing injection site reactions (defined as swelling) after treatment with icatibant plus current standard care compared to current standard care or placebo with current standard care. However, the SRMA, including two of the RCTs, reported a *statistically significant* difference in the number of injection site reactions (defined as erythema), favouring the current standard care or placebo with current standard care group compared to icatibant plus current standard care group.**
Abbreviations ACEI: angiotensin-converting enzyme inhibitor, CI: confidence interval, HAE-nC1 INH: hereditary angioedema with normal C1-esterase inhibitor, HAE PLG: hereditary angioedema with variant plasminogen gene, HRQoL: health-related quality of life, ICU: intensive care unit, IQR: interquartile range, MD: mean difference, PROM: patient- reported outcome measures, RCT: randomised controlled trial, RR: risk ratio, SD: standard deviation, SRMA: systematic review and meta-analysis.	

In people with bradykinin-mediated angioedema with normal C1 inhibitor, what is the cost effectiveness of icatibant plus standard care compared with current standard care alone?

Outcome	Evidence statement
Cost effectiveness	**No evidence was identified for cost effectiveness.**

From the evidence selected, are there any subgroups of patients that may benefit from icatibant plus current standard care more than the wider population of interest?

Outcome	Evidence statement
Subgroups – adults and children or patients with differing number of attacks per patient	**No evidence was identified for subgroups of patients.**

From the evidence selected, what doses, frequency and route of administration of icatibant were used and what was the duration of treatment?

Outcome	Evidence statement
Icatibant regimens	Three RCTs (Bas et al 2015, Sinert et al 2017, Straka et al 2017) provided details on doses, frequency and route of administration of icatibant in patients with ACEI-induced angioedema. In two RCTs, a single subcutaneous injection of icatibant 30 mg was administered within 12 hours after symptom onset. In one RCT, icatibant 30 mg subcutaneous injection was delivered in two 1.5 ml syringes at 0 and six hours. Two retrospective cohort studies (Bouillet et al 2017, Grumach et al 2022) reported the number of injections required for attacks in patients with HAE-nC1 INH. Bouillet et al (2017) reported that 70.0% of attacks required one injection, 24.4% required two injections and 5.6% required 3 injections (ranging between one and four injections). Grumach et al (2022) reported that 96.7% of attacks required one injection, 1.7% required two injections and 1.7% required four injections. One retrospective cohort study (Bork et al 2020) reported that two of 13 patients with HAE PLG administered icatibant at home. A second retrospective cohort study (Bouillet et al 2017) reported that icatibant was self-administered for attacks in 96.1% patients with HAE-nC1 INH.

Abbreviations

ACEI: angiotensin-converting enzyme inhibitor, HAE-nC1 INH: hereditary angioedema with normal C1-esterase inhibitor, HAE PLG: hereditary angioedema with plasminogen gene variant, RCT: randomised controlled trial.

6. Discussion

This review examined the clinical effectiveness, safety and cost effectiveness of icatibant plus current standard care compared to current standard care alone in patients who have bradykinin-mediated angioedema with normal C1 inhibitor. The critical outcomes of interest were total attack/swelling duration, time to resolution, and treatment response. The important outcomes of interest were time to the onset of symptom regression, symptom progression, health related quality of life (HRQoL), hospital attendances, and safety.

Evidence for the clinical effectiveness of icatibant plus current standard care (including time to resolution, treatment response, the time to the onset of symptom regression, symptom progression, hospital attendances) and safety was available from one systematic review of three RCTs (Jeon et al 2019) and the three RCTs also included in the SRMA (Bas et al 2015, Sinert et al 2017, Straka et al 2017). No randomised evidence was identified for the critical outcome total attack/swelling duration, and four retrospective cohort studies were therefore included as they provided evidence for this outcome in subgroups of patients relevant to this evidence review (Bork et al 2020, Bouillet et al 2017, Grumach et al 2022, Manto et al 2021). The three RCTs included in the SRMA (Bas et al 2015, Sinert et al 2017, Straka et al 2017) were also included individually in this evidence review because they provided additional evidence for in scope outcomes that were not presented in the SRMA (i.e. treatment response, symptom progression and hospital attendances). No studies were identified that reported HRQoL. No studies were identified that reported on relevant subgroups of patients that would benefit more from treatment with icatibant plus current standard care, and no cost effectiveness studies were identified.

The three individual RCTs (sample size range: 27 to 121 patients) and four retrospective cohort studies (sample size range of in-scope patients: 5 to 13 patients) included in this evidence review were all undertaken in adults and were conducted in Brazil; France; Germany (two studies); Russia; the USA; Canada, Israel, the UK and the USA. The study populations included patients with different types of bradykinin-mediated angioedema with normal C1 inhibitor. The three RCTs included patients with ACEI–induced angioedema affecting the head and/or neck. Two of the retrospective studies included patients with a confirmed diagnosis of PLG gene variant c.988A > G (p.K330E or p.Lys330Glu;K330E). The two remaining retrospective cohort studies included patients with hereditary angioedema (HAE) and normal levels of C1 INH (defined as C1 INH level normal or above normal [≥15 to 50 mg/dL] and function normal or above normal levels [≥70 to 130%]); one study reported confirmed Factor XII mutation or family history of HAE in patients, whilst this information was not available for the second study. Follow-up assessments were performed on day three after treatment initiation (or approximately two days after discharge in patients who were discharged on or after day three) or 14 days after hospital admission in two of the RCTs, with the third RCT reporting assessments up to 48 hours after treatment and a mean follow-up duration of 4.36 (SD 2.19) years. Two of the four retrospective cohort studies reported six monthly follow-up assessments, with one of the studies reporting a mean follow-up of 4.3 (SD 1.42) years.

The SRMA (Jeon et al 2019), including 179 patients with ACEI-induced angioedema, compared icatibant plus current standard care to off-label standard care, i.e. prednisolone plus clemastine (Bas et al 2015) or placebo with current standard care (Sinert et al 2017, Straka et al 2017). The two studies comparing icatibant plus current standard care versus placebo with current standard care (Sinert et al 2017, Straka et al 2017) permitted patients in both groups to receive additional treatments, such as antihistamines, corticosteroids and epinephrine, at the discretion of the study investigators. The study comparing icatibant plus current standard care versus current standard care (Bas et al 2015) did not provide additional treatment to patients other than rescue therapy which could be given six hours after initiation of treatment if symptoms had not

improved. The four retrospective cohort studies reported the use of concomitant rescue medications to help alleviate symptoms rather than treat the attack, but details were not reported separately in the subgroup populations relevant to this evidence review.

The three individual RCT publications provided demographic details and clinical histories for patients with ACEI-induced angioedema (Bas et al 2015, Sinert et al 2017, Straka et al 2017). Where demographic details and clinical histories were reported, this highlighted some potential differences between the studies. For example, Bas et al (2015) included a white European population, whereas Sinert et al (2017) and Straka et al (2017) included mainly black populations and/or African Americans; 69.4% and 67%, respectively. Baseline severity of angioedema symptoms appeared to differ between studies, with one RCT including only patients with at least moderate severity ACEI-induced angioedema (Sinert et al 2017). However, severity of symptoms was measured using different methods (i.e. investigator or patient assessed).

One placebo controlled RCT of 33 patients with ACEI-induced angioedema (Straka et al 2017) was discontinued early due to a decline in recruitment following publication of the Bas et al (2015) trial. Although the required number of patients were recruited to the placebo with current standard care group, this was not the case for the icatibant plus current standard care group. The imbalance in patient numbers resulted from randomisation blocks within strata not being fully completed, meaning that the icatibant plus current standard care treatment group was not powered to detect the main endpoint. In addition, two out of 18 patients in the placebo with current standard care group did not receive a second dose of study treatment at six hours but were included in the analyses and one out of 15 patients in the icatibant plus current standard care group was unable to complete the visual analogue scale (VAS) for severity of swelling and other symptoms and was excluded from the final analysis, resulting in the analysis not being based on true ITT. The effect of this is likely to be small, but remains unclear.

The SRMA (Jeon et al 2019) combined data from the three RCTs to provide evidence on time to resolution, time to the onset of symptom regression, and safety outcomes. The SRMA showed no benefit of icatibant plus current standard care treatment compared to current standard care or placebo with current standard care for the time to complete resolution of symptoms (MD -7.77, 95% CI -25.18 to 9.63; p=0.38), complete resolution of symptoms within four hours (RR 1.20, 95% CI 0.48 to 3.04; p=0.70), or time to the onset of symptom relief (MD -0.50, -1.30 to 0.30; p=0.22) in patients with ACEI-induced angioedema. There was a wide variance in median times reported by the individual RCTs, which ranged from four to 25 hours, but it is unclear how this may have affected the pooled results. Bas et al (2015) was the only RCT that reported a significant decrease in time to complete resolution of symptoms and time to onset of symptom relief for the icatibant plus current standard care group. However, there was a discrepancy in the results reported for Bas et al (2015) in the SRMA with the actual results reported in the RCT publication for time to complete resolution of oedema. The SRMA reported that the mean (±SD) for icatibant plus current standard care was 9.1 (10.8) hours and for the comparator group 32.2 (22.8) hours, while the individual RCT reported the mean (±SD) for Icatibant plus current standard care was 15.4 (18.8) hours and for the comparator group 33.2 (18.0) hours. The discrepancy was not discussed in the SRMA but may have been due to the different methods used in the SRMA and RCT to convert medians (IQRs) to means (SDs). The larger discrepancy in means reported for the icatibant plus current standard care group between the SRMA and RCT is unclear, as is the impact this may have had on the overall pooled results reported in the SRMA in terms of the mean difference between treatment groups.

The SRMA (Jeon et al 2019) also reported safety outcomes using combined data from the RCTs. Combined evidence from all three RCTs showed no statistically significant differences between treatment groups for any adverse events, drug-related adverse events, or injection site reactions (swelling). Combined evidence from two of the RCTs showed a significantly greater

number of injection site reactions (erythema) were reported in the icatibant plus current standard care group compared to the placebo with current standard care group: RR 2.47 (95% CI 1.56 to 3.90); p=0.0001.

Treatment response (defined as use of rescue medications after initiation of treatment or use of additional medications) was reported in the three RCTs (Bas et al 2015, Sinert et al 2017, Straka et al 2017). All three RCTs indicated that there were no differences between the treatment groups in the number of patients requiring additional treatments but only two RCTs reported p-values. The three RCTs (Bas et al 2015, Sinert et al 2017, Straka et al 2017) reported that there were no significant differences between icatibant plus current standard care treated patients and current standard care or placebo with current standard care treated patients in terms of progression of symptoms leading to airway intervention, or need for hospital/ICU admission, but statistical measures were not always reported.

The four retrospective cohort studies provided limited details for the subgroups of patients relevant to this review (Bork et al 2020, Bouillet et al 2017, Grumach et al 2022, Manto et al 2021). Of the four retrospective cohort studies, two studies related to the same prospective, international, multicentre, observational study (Icatibant Outcome Survey Registry Study) but data were analysed retrospectively for both in scope and out of scope populations from different countries, i.e. France (Bouillet et al 2017) or Brazil (Grumach et al 2022). Both of these studies reported total attack/swelling duration in eight and 10 icatibant plus current standard care treated patients with HAE and normal C1 INH levels. These two studies also included out of scope individuals (i.e. patients with HAE and C1-INH abnormalities) for whom data were not extracted for this review. The two remaining retrospective cohort studies (Bork et al 2020, Manto et al 2021) included five and 13 patients with HAE PLG and compared total attack/swelling duration for treated attacks versus untreated attacks (untreated attacks were not clearly defined in Bork et al (2020) and it was therefore unclear whether patients did not receive any treatment at all or received current standard care, without icatibant). These two studies also included out of scope individuals (i.e. patients with HAE and C1-INH abnormalities) and out of scope interventions (e.g. plasma-derived C1 INH or long-term prophylaxis) for which data were not extracted for this review.

One retrospective cohort study (Bork et al 2020) reported a statistically significant 88% reduction in the total attack/swelling duration between attacks treated with icatibant in 13 patients with HAE PLG compared to previously untreated attacks in the same patients (4.3 vs 44.7 hours respectively; p<0.0001). One retrospective cohort study (Manto et al 2021) reported a 12 hour total attack/swelling duration in five icatibant treated patients, indicating a 71.4% reduction in attacks. However, it was unclear how the reduction was calculated; whether the comparison was between icatibant-treated vs untreated attacks in the same five patients with HAE PLG, or the comparison was between 5/14 patients with HAE PLG who were treated with icatibant vs 9/14 patients with HAE PLG who were not treated with icatibant. The two remaining retrospective cohort studies (Bouillet et al 2017, Grumach et al 2022) reported diverse total attack/swelling durations, with median durations reported as 32.5 hours in 10 patients with HAE-nC1 INH and 7.0 hours in eight patients with HAE-nC1 INH, respectively. The difference may have been due to the severity of attacks whereby Bouillet et al (2017) reported severe/very severe attacks in 94.7% of patients compared to 60.7% of patients in Grumach et al 2022 considered severe/very severe attacks. There may also have been a difference in medications used in addition to icatibant between the two studies, but this is uncertain as the use of these medications was only reported in Grumach et al (2022) and not mentioned by Bouillet et al (2017).

The SRMA (Jeon et al 2019) was limited by the small number of available RCTs and their small sample sizes. Although the individual RCTs calculated sample sizes prior to the start of the studies, based on previous studies, two RCTs (Bas et al 2015, Straka et al 2017) were underpowered, which limits the ability to draw accurate conclusions about the findings. A further

limitation with the SRMA was the heterogeneity between the included studies for some outcomes, which the authors suggested may have been due to factors such as the use of a placebo and how outcomes were defined and measured (i.e. time to complete resolution vs time to meeting discharge criteria). Other factors that may have contributed to the differences in outcomes among the RCTs include differences in baseline severity of angioedema symptoms and different methods used to measure severity, and differences in population characteristics such as inclusion of only a white European population in one RCT compared to mainly black populations and/or African Americans in two RCTs. Further differences between the three RCTs included time from symptom onset to medication administration: Bas et al (2015) reported a median of 6.1 hours (range 3.0 to 10.0) in the icatibant plus current standard care group and 5.1 hours (range 2.0 to 9.3) in the current standard care group, whilst Sinert et al (2017) reported a median of 7.9 hours (range 2.0 to 12.4) in the icatibant plus current standard care group and 7.8 hours (range 1.7 to 12.4) in the placebo with current standard care group. Although patients in Straka et al (2017) received study treatment within six hours of presentation to the hospital, the mean time from onset of symptoms to administration of treatment was 10.3 hours in the icatibant plus current standard care group.

Limitations of the retrospective cohort studies include their observational nature which means that there is uncertainty around whether the effects observed may have been due to confounding factors. Further limitations include the lack of a treatment comparator in two of the four studies, small sample sizes, post hoc analyses and limited demographic or clinical information about the subgroups of patients that were relevant to this evidence review. Sample sizes in the subgroup populations of relevance to the PICO criteria were small in all four retrospective cohort studies, partly due to the small number of patients with HAE PLG and HAE-nC1 INH subtypes in the populations of interest.

Four of the studies included in this evidence review reported patient reported outcome measures (PROMs). Whilst there are benefits in using PROMs to enhance patient care, there are also limitations such as reliance on patient recall, which can result in risk of bias and the potential for under- or over-reporting of their symptom severity. This is particularly relevant in unblinded RCTs and observational studies as this may introduce bias due to the subjective nature of reporting. Two of the RCTs (Sinert et al 207, Straka et al 2017) addressed the risk of bias by blinding patients and outcome assessors by administering a matching placebo.

The evidence provided by the four retrospective cohort studies regarding the effect of icatibant on total attack/swelling duration should be considered as very low certainty due to very serious risk of bias and very serious indirectness due to lack of a relevant treatment comparison. The evidence provided by the SRMA regarding time to complete resolution of symptoms, complete resolution within four hours, and time to onset of symptom relief for icatibant plus current standard care compared to current standard care or placebo with current standard care should be considered as very low certainty due to serious risk of bias, serious or very serious inconsistency due to heterogeneity and serious or very serious imprecision in the findings. The evidence provided by the SRMA regarding safety ranged from very low to moderate certainty due to serious risk of bias, and serious or very serious imprecision. The evidence provided by the three individual RCTs regarding treatment response and symptom progression for icatibant plus current standard care compared to current standard care or placebo with current standard care ranged from very low to high certainty, due to serious or very serious risk of bias, or zero events in one treatment arm. The evidence regarding hospital attendances, provided by two individual RCTs, was moderate or high certainty due to serious risk of bias in one RCT.

The studies included in this evidence review did not comment on minimum clinically important difference thresholds for the outcomes reported.

7. Conclusion

This review included one SRMA of three RCTs, the three RCTs that were also included in the SRMA and four retrospective cohort studies. The SRMA and the three RCTs provide very low to high certainty evidence on critical and important outcomes following treatment with icatibant plus current standard care compared to current standard care or placebo with current standard care in patients with ACEI-induced angioedema. The four retrospective cohort studies provide very low certainty evidence on a critical outcome in patients with idiopathic/hereditary angioedema with normal C1 inhibitor, following treatment with icatibant (with no comparison group) or icatibant compared to no treatment or compared to an unclear patient population who may not have received any treatment or may have received current standard care, without icatibant. Evidence was available for the three critical outcomes (total attack/swelling duration, time to resolution of symptoms, treatment response) and four important outcomes (time to the onset of symptom regression, symptom progression, hospital attendances, safety). No evidence was available for one important clinical effectiveness outcome (HRQoL) and no evidence was available on cost effectiveness. No evidence was identified regarding any subgroups of patients that would benefit more from treatment with icatibant plus current standard care.

The SRMA found no statistically significant difference in time to resolution of symptoms, the number of patients exhibiting complete resolution of symptoms within four hours of treatment, or time to the onset of symptom regression for ACEI-induced angioedema patients receiving icatibant plus current standard care compared to current standard care or placebo with current standard care. The evidence from the SRMA for these outcomes should be considered as very low certainty due to lack of details on review methodology, serious to very serious imprecision and/or inconsistency. The SRMA also found no statistically significant difference in safety outcomes for patients receiving icatibant plus current standard care compared to patients receiving current standard care or placebo with current standard care, with the exception of injection site reactions in the form of swelling, which was reported statistically significantly more often in patients receiving icatibant plus current standard care. The evidence from the SRMA on safety ranged from low to moderate due to serious to very serious imprecision and/or lack of details on the review methodology.

Although not reported by the SRMA, the three RCTs included in the SRMA separately reported on treatment response, symptom progression and hospital attendances for icatibant plus current standard care compared to current standard care or placebo with current standard care in patients with ACEI-induced angioedema. The RCTs provided very low to high certainty evidence which suggested no differences between patients receiving icatibant plus current standard care compared to patients receiving current standard care or placebo with current standard care for these outcomes. The findings were limited by the small sample sizes and reporting of statistical comparisons was only reported in two of the RCTs for treatment response and one RCT for symptom progression and hospital/ICU attendances.

No randomised evidence was found that reported on total attack/swelling duration. Four retrospective cohort studies were identified that reported on this outcome in patients with idiopathic/hereditary angioedema with normal C1 inhibitor, but were limited by the lack of a relevant treatment comparison group and small sample sizes (ranging from five to 13 patients).

Given the limitations of the evidence about the clinical effectiveness and safety of icatibant plus current standard care compared to current standard care or placebo with current standard care in patients with different subtypes of bradykinin-mediated angioedema with normal C1 inhibitor, it is difficult to assess the validity of the findings or their generalisability to the wider population of interest.

Appendix A PICO document

The review questions for this evidence review are:

1. In people with bradykinin-mediated angioedema with normal C1 inhibitor, what is the clinical effectiveness of icatibant plus current standard care compared with current standard care alone?
2. In people with bradykinin-mediated angioedema with normal C1 inhibitor, what is the safety of icatibant plus current standard care compared with current standard care alone?
3. In people with bradykinin-mediated angioedema with normal C1 inhibitor, what is the cost effectiveness of icatibant plus current standard care compared with current standard care alone?
4. From the evidence selected, are there any subgroups of patients that may benefit from icatibant plus current standard care more than the wider population of interest?
5. From the evidence selected, what doses, frequency and route of administration of icatibant were used and what was the duration of treatment?

P-Population and Indication	Adults and children aged 2 years and over with bradykinin-mediated angioedema with normal C1 inhibitor, including HAE with normal C1 (HAE-n-C1) and idiopathic non-histaminergic angioedema (INHA), with acute swellings. [Terms used to describe this patient population also include, but are not limited to, HAEnC1, HAE-nC1 INH, hereditary angioedema type III, HAE with normal C1-INH. C1 inhibitor may also be referred to as C1-INH, C1 esterase inhibitor. Patients with drug induced bradykinin-mediated angioedema with normal C1 are also relevant to this policy] [Acute swellings may also be referred to as acute attacks. The relevant indication is any attack of sufficient severity to prevent normal function, including attacks requiring admission/injection treatment on risk assessment. These include moderate and severe attacks, or as defined in the literature. For example, but not limited to, attacks involving the airway] Subgroups of interest include: • Adults and children • Patients with differing number of attacks per patient (within a given window of time) as defined by the relevant studies [for example, patients with a high frequency of attacks vs patients with a lower frequency of attacks]
I-Intervention	Icatibant (a bradykinin-2 receptor antagonist) plus standard care, either self-administered via subcutaneous injection, or healthcare professional- administered. Repeated administrations may be required. [The licensed frequency of administration is 6 hourly and a maximum of 3 administrations per 24 hours. Standard care for acute swellings includes admission, intensive care admission, observation, airway support, for example intubation and supportive treatment including analgesia. Standard care may also include prophylactic treatments

	such as tranexamic acid, C1esterase Inhibitor infusion and attenuated androgens, however the evidence is limited and practice varies. Prophylactic treatments such as lanadelumab and berotralstat may be used in this patient group in the international literature]
C – Comparator(s)	Standard care [Standard care for acute swellings includes admission, intensive care admission, observation, airway support for example intubation and supportive treatment including analgesia. Standard care may also include prophylactic treatments such as tranexamic acid, C1INH C1esterase Inhibitor infusion and attenuated androgens, however the evidence is limited and practice varies. Prophylactic treatments such as lanadelumab and berotralstat may be used in this patient group in the international literature]
O-Outcomes	**Clinical Effectiveness** *Unless stated for the outcome, minimum clinically important differences (MCIDs) are unknown. Time frame for outcomes is likely to be hours to days unless stated otherwise.* Critical outcomes • **Total attack/swelling duration** *This is important to patients as attacks/swellings in this condition are frequent, unpredictable and potentially fatal, and if untreated may last for 3-4 days; therefore, a rapid response to treatment is likely to mitigate the morbidity and mortality associated with this condition.* [This can be defined by the duration from symptom onset to complete resolution of symptoms] [The terms “attack” and “swelling” are used interchangeably in the literature] • **Time to resolution** *This is important to patients as attacks/swellings in this condition are frequent and unpredictable and potentially fatal, and if left untreated may last for an average of 3-4 days; therefore, a rapid response to treatment is likely to mitigate the morbidity and mortality associated with this condition.* [This can be defined by the time from icatibant administration or comparator administration to complete resolution of symptoms] • **Treatment response** *This is important to patients as these attacks/swellings are debilitating and potentially fatal; therefore, a response to treatment is likely to mitigate the morbidity and mortality associated with this condition. Untreated attacks may otherwise last for 3-4 days.* [Treatment response may be a binary outcome, or may be ascertained using PROM qualitative data]

	Important outcomes • **Time to the onset of symptom regression** *This is important to patients as attacks/swellings in this condition are frequent and unpredictable and potentially fatal, and untreated may last for several days; therefore, a rapid response to treatment is likely to mitigate the morbidity and mortality associated with this condition.* [This can be defined by the time from icatibant administration or comparator administration to the beginning of symptom resolution. Some papers may define this as time from icatibant onset to the beginning of resolution of the index symptom] • **Symptom progression** *This is important to patients as attacks/swellings can progress to the extent that fatal airway obstruction can occur; therefore, a reduction in progression is likely to mitigate the morbidity and mortality associated with this condition.* [This refers to symptom progression during attacks/swellings, for example if attack severity progresses from moderate to severe. Other methods of assessing symptom progression include but are not limited to subjective/self-reported/clinician reported progression.] • **Health related quality of life (HRQoL)** *This outcome is important to patients because it provides a holistic evaluation and indication of the patient's general health and their perceived well-being and their ability to participate in activities of daily living. This outcome is both a key indicator of the effectiveness of treatment and provides an insight into the patient's perception of the effectiveness of treatment* [Methods of assessing quality of life include but are not limited to subjective/self-reported/carer reported quality of life experiences. This outcome is ideally measured longer term, for example over months to years] • **Hospital attendances** *This outcome is important to patients because severe acute episodes most often require hospital admission, including intensive care monitoring. However, not all acute episodes require hospital admission and if they do not, this signifies reduced severity.* [Attendances include Emergency Department attendance, admission to secondary care, or admission to intensive care] [Terms used to describe or indicate admissions include but are not limited to; binary yes/no admission, binary yes/no intensive care, total hospital bed days, total admission duration, total intensive care bed days, total intensive care admission duration, number of admissions to hospital, number of admissions to intensive care]

	<u>Safety</u> • **Complications of icatibant treatment** *Safety is important to patients as it reflects the risks involved in a treatment that may be required multiple times. This allows a risk benefit assessment to be undertaken* [Other terms used to describe or indicate safety include, but are not limited to; adverse events, serious/ major adverse events. Adverse events may include but are not limited to; death, anaphylaxis, injection site reactions including erythema, swelling, pain or burning sensation] **<u>Cost effectiveness</u>** Factors to consider for the associated potential cost effectiveness are as follows: drug cost (available generic brand), associated cost for reduced hospital attendances, alleviate nurse shortage if patients are trained to self-administer; cost and time efficient for patients able to self-administer on demand treatment.
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher-level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	All ages
Date limits	2013 - 2023
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, preprints and guidelines.
Study design	Case reports, resource utilisation studies.

Appendix B Search strategy

Medline, Embase, the Cochrane Library and TRIP database were searched limiting the search to papers published in English language in the last 10 years. Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-publication prints, guidelines, case reports and resource utilisation studies were excluded.

Search dates: 1 January 2013 to 15 August 2023

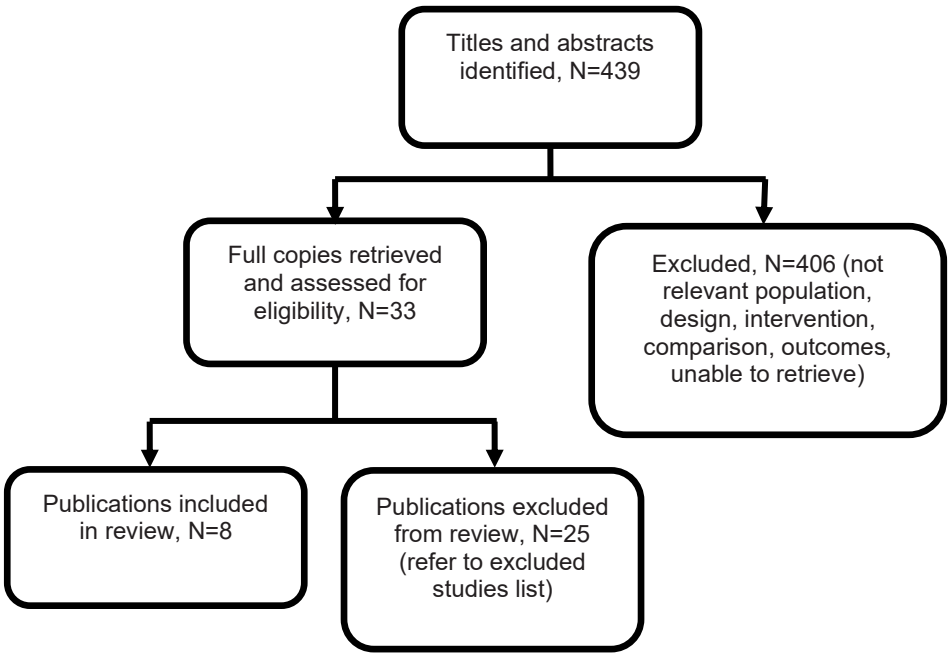
Medline search strategy

1	exp Angioedema/
2	(angi?oedema* or angio-edema* or angio-oedema* or (angioneurotic adj2 (edema* or oedema*))).ti,ab,kf.
3	((c1 adj2 inhibitor deficienc*) and (edema* or oedema*)).ti,ab,kf.
4	(hae or haes or haenc1).ti,ab,kf.
5	1 or 2 or 3 or 4
6	Bradykinin B2 Receptor Antagonists/
7	(icatibant or firazyr or sajazir).ti,ab,kf.
8	6 or 7
9	5 and 8
10	exp animals/ not humans/
11	9 not 10
12	limit 11 to (meta analysis or "systematic review" or "reviews (maximizes specificity)")
13	(comment or editorial or letter or review).pt.
14	11 not 13
15	12 or 14
16	limit 15 to (English language and yr="2013 -Current")

Appendix C Evidence selection

The literature searches identified 439 references. These were screened using their titles and abstracts and 33 references were obtained in full text and assessed for relevance. Of these, 8 references are included in the evidence summary. The remaining 25 references were excluded and are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection - decision and rationale if excluded
Bouillet, L., Boccon-Gibod, I., Launay, D., Gompel, A., Kanny, G., Fabien, V., Fain, O. and IOS Study Group, 2017. Hereditary angioedema with normal C1 inhibitor in a French cohort: clinical characteristics and response to treatment with icatibant. *Immunity, Inflammation and Disease,* 5(1), pp.29-36.	Included
Jones, D.H., Bansal, P., Bernstein, J.A., Fatteh, S., Harper, J., Hsu, F.I., O'Connor, M., Park, N. and Suez, D., 2022. Clinical profile and treatment outcomes in patients with hereditary angioedema with normal C1 esterase inhibitor. *World Allergy Organization Journal,* 15(1), p.100621.	Excluded No in-scope comparison (n=11/23 patients received icatibant alone or in combination; in-scope comparison studies identified through our literature search that report relevant outcomes; no data reported for total attack/swelling duration or HRQoL.
Grumach, A.S., Henriques, M.T., Bardou, M.L., Pontarolli, D.A., Botha, J. and Correa, M., 2022. Icatibant use in Brazilian patients with hereditary angioedema (HAE) type 1 or 2 and HAE with normal C1-INH levels: findings from the Icatibant Outcome Survey Registry Study. *Anais Brasileiros de Dermatologia*, 97, pp.448-457.	Included

Appendix D Excluded studies table

Study reference	Reason for exclusion
Aberer W, Maurer M, Reshef A, Longhurst H, Kivity S, Bygum A, et al. Open-label, multicenter study of self-administered icatibant for attacks of hereditary angioedema. Allergy. 2014;69(3):305-14.	No in-scope population (patients with HAE types I or II)
Bas M, Greve J, Hoffmann TK, Reshef A, Aberer W, Maurer M, et al. Repeat treatment with icatibant for multiple hereditary angioedema attacks: FAST-2 open-label study. Allergy. 2013;68(11):1452-9.	No in-scope population (patients with HAE types I or II)
Beyaz S, Demir S, Oztop N, Colakoglu B, Buyukozturk S, Gelincik A. How satisfactory is on-demand icatibant from the patients' perspective in real life? Allergy & Asthma Proceedings. 2022;43(2):148-54.	No in-scope population (patients with HAE types I or II)
Bova M, Guilarte M, Sala-Cunill A, Borrelli P, Rizzelli GM, Zanichelli A. Treatment of ACEI-related angioedema with icatibant: a case series. Internal & Emergency Medicine. 2015;10(3):345-50.	No in-scope comparison (n=13 in-scope patients); in-scope comparison studies identified through our literature search that report relevant outcomes; no data reported for total attack/swelling duration or HRQoL
Bygum A. Hereditary angioedema - consequences of a new treatment paradigm in Denmark. Acta Dermato-Venereologica. 2014;94(4):436-41.	No in-scope population (patients with HAE types I or II), or acquired C1INH deficiency)
CADTH. Icatibant for Patients with Type III Hereditary Angioedema: An Updated Review of Clinical Effectiveness and Harms. Canadian Agency for Drugs and Technologies in Health - Rapid Review. 2017.	Non-systematic review (rapid response summary report)
Cai G, Barber C, Kalicinsky C. Review of icatibant use in the Winnipeg Regional Health Authority. Allergy, Asthma, & Clinical Immunology : Official Journal of the Canadian Society of Allergy & Clinical Immunology. 2020;16(1):96.	No in-scope comparison (n=23 in-scope patients); in-scope comparison studies identified through our literature search that report relevant outcomes; no data reported for total attack/swelling duration or HRQoL
Deroux A, Boccon-Gibod I, Fain O, Pralong P, Ollivier Y, Pagnier A, et al. Hereditary angioedema with normal C1 inhibitor and factor XII mutation: a series of 57 patients from the French National Center of Reference for Angioedema. Clinical & Experimental Immunology. 2016;185(3):332-7.	No in-scope outcomes reported
Fok JS, Katelaris CH, Brown AF, Smith WB. Icatibant in angiotensin-converting enzyme (ACE) inhibitor-associated angioedema. Internal Medicine Journal. 2015;45(8):821-7.	No in-scope comparison (n=13 in-scope patients); in-scope comparison studies identified through our literature search that report relevant outcomes; no data reported for total attack/swelling duration or HRQoL
Hide M, Wang Y, Dote N, Miyakawa K, Sugiura K, Ishida K. Safety, efficacy, and pharmacokinetics of icatibant treatment in Japanese pediatric patients with hereditary angioedema: A phase 3, open-label study. Journal of Dermatology. 2023;29:29.	No in-scope population (patients with HAE types I or II)
Javaud N, Achamlal J, Reuter PG, Lapostolle F, Lekouara A, Youssef M, et al. Angioedema Related to Angiotensin-Converting Enzyme Inhibitors: Attack Severity, Treatment, and Hospital Admission in a Prospective Multicenter Study. Medicine. 2015;94(45):e1939.	No in-scope comparison (n=62 in-scope patients); in-scope comparison studies identified through our literature search that report relevant outcomes; no data reported for total attack/swelling duration or HRQoL
Javaud N, Gompel A, Bouillet L, Boccon-Gibod I, Cantin D, Smaiti N, et al. Factors associated with hospital admission in hereditary angioedema attacks: a multicenter prospective study. Annals of Allergy, Asthma, & Immunology. 2015;114(6):499-503.	No in-scope comparison (n=13 in-scope patients); in-scope comparison studies identified through our literature search that report relevant outcomes; no data reported for total attack/swelling duration or HRQoL, data not reported separately for hospital admissions
Jones DH, Bansal P, Bernstein JA, Fatteh S, Harper J, Hsu FI, et al. Clinical profile and treatment outcomes in patients with hereditary angioedema with normal C1 esterase inhibitor. World Allergy Organization Journal. 2022;15(1):100621.	No in-scope comparison (n=1 in-scope patients); in-scope comparison studies identified through our literature search that report relevant outcomes; no data reported for total attack/swelling duration or HRQoL

Study reference	Reason for exclusion
Lawlor CM, Ananth A, Barton BM, Flowers TC, McCoul ED. Pharmacotherapy for Angiotensin-Converting Enzyme Inhibitor-Induced Angioedema: A Systematic Review. Otolaryngology - Head & Neck Surgery. 2018;158(2):232-9.	Systematic review - one in-scope controlled trial identified through literature search and included in this evidence review
Le TA, Smith W, Hissaria P. Real-world off-label use of icatibant for acute management of non-hereditary angioedema. Internal Medicine Journal. 2021;51(3):419-23.	No in-scope comparison (n=16 in-scope patients); in-scope comparison studies identified through our literature search that report relevant outcomes; no data reported for total attack/swelling duration or HRQoL
Malbran A, Riedl M, Ritchie B, Smith WB, Yang W, Banerji A, et al. Repeat treatment of acute hereditary angioedema attacks with open-label icatibant in the FAST-1 trial. Clinical & Experimental Immunology. 2014;177(2):544-53.	No in-scope population (patients with HAE types I or II)
McKibbin L, Barber C, Kalicinsky C, Warrington R. Review of the Manitoba cohort of patients with hereditary angioedema with normal C1 inhibitor. Allergy, Asthma, & Clinical Immunology : Official Journal of the Canadian Society of Allergy & Clinical Immunology. 2019;15:66.	No in-scope comparison (n=6 in-scope patients); in-scope comparison studies identified through our literature search that report relevant outcomes; no data reported for total attack/swelling duration or HRQoL
Riedl MA, Banerji A, Manning ME, Burrell E, Joshi N, Patel D, et al. Treatment patterns and healthcare resource utilization among patients with hereditary angioedema in the United States. Orphanet Journal Of Rare Diseases. 2018;13(1):180.	No in-scope population (patients with HAE and C1-esterase inhibitor deficiency)
Riha HM, Summers BB, Rivera JV, Van Berkel MA. Novel Therapies for Angiotensin-Converting Enzyme Inhibitor-Induced Angioedema: A Systematic Review of Current Evidence. Journal of Emergency Medicine. 2017;53(5):662-79.	Systematic review - one in-scope controlled trial identified through literature search and included in this evidence review
Rosi-Schumacher M, Shah SJ, Craig T, Goyal N. Clinical manifestations of hereditary angioedema and a systematic review of treatment options. Laryngoscope Investigative Otolaryngology. 2021;6(3):394-403.	Systematic review - included studies do not report useable data for relevant outcomes
Tachdjian R, Johnson KE, Casso D, Oliveria SA, Devercelli G, Jain G. Real-world cohort study of adult and pediatric patients treated for hereditary angioedema in the United States. Allergy & Asthma Proceedings. 2020;41(3):172-82.	Relevant outcomes not reported separately for in-scope population
van den Elzen M, Go M, Knulst AC, Blankestijn MA, van Os-Medendorp H, Otten HG. Efficacy of Treatment of Non-hereditary Angioedema. Clinical Reviews in Allergy & Immunology. 2018;54(3):412-31.	Systematic review - one in-scope controlled trial identified through literature search and included in this evidence review
Xu YY, Buyantseva LV, Agarwal NS, Olivieri K, Zhi YX, Craig TJ. Update on treatment of hereditary angioedema. Clinical & Experimental Allergy. 2013;43(4):395-405.	Non-systematic review (narrative review/overview)
Zanichelli A, Maurer M, Aberer W, Caballero T, Longhurst HJ, Bouillet L, et al. Long-term safety of icatibant treatment of patients with angioedema in real-world clinical practice. Allergy. 2017;72(6):994-8.	No in-scope comparison (n=140 in-scope patients); in-scope comparison studies identified through our literature search that report relevant outcomes; no data reported for total attack/swelling duration or HRQoL
Zarnowski J, Rabe M, Kage P, Simon JC, Treudler R. Prophylactic Treatment in Hereditary Angioedema Is Associated with Reduced Anxiety in Patients in Leipzig, Germany. International Archives of Allergy and Immunology. 2021;182(9):819-26.	No in-scope comparison (n=4 in-scope patients); in-scope comparison studies identified through our literature search that report relevant outcomes; no data reported for total attack/swelling duration, QoL data not reported separately for in-scope population

Appendix E Evidence table

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Bas M, Greve J, Stelter K, Havel M, Strassen U, Rotter N, et al. A randomized trial of icatibant in ACE-inhibitor-induced angioedema. New England Journal of Medicine. 2015;372(5):418-25. **Study location** Germany **Study type** Phase II, multicentre, double-blind RCT **Study aim** To assess the effectiveness and safety of icatibant compared to standard combination treatment in patients with ACEI-induced angioedema of the upper aerodigestive tract **Study dates** July 2010 to December 2011	**Inclusion criteria** Patients aged 18 to 95 years presenting to the emergency department with ACEI–induced angioedema affecting the upper aerodigestive tract (including the face, lips, cheeks, tongue, soft palate or uvula, pharynx, and larynx) **Exclusion criteria** Patients with angioedema considered to be caused by factors other than ACEIs; history of angioedema before treatment with ACEIs; acute urticaria; unstable angina; acute myocardial ischemia; acute heart failure with a New York Heart Association class of III or IV; pregnancy and lactation **Total sample size** N=30 (all patients as treated) N=27 (per protocol analysis)	**Interventions** Single subcutaneous injection of icatibant 30 mg into the abdominal wall 10 hours after symptom onset, plus normal saline administered intravenously **Comparators** Off-label standard care (intravenous prednisolone 500 mg plus clemastine 2 mg) administered 10 hours after symptom onset, plus normal saline administered subcutaneously If symptoms had not reduced after 6 hours, rescue medication (30 mg of icatibant with 500 mg of prednisolone) could be administered to patients in either treatment group	Outcomes were assessed at 14 days after hospital admission, unless otherwise stated **Critical outcomes** **Time to resolution** Time to complete resolution of oedema, assessed by investigators and patients at 1, 2, 3, 4, 6, 8, 12, 24, and 48 hours after initiation of treatment See Jeon et al 2019 Proportion of patients exhibiting complete resolution of symptoms within 4 hours after initiation of treatment See Jeon et al 2019 **Treatment response** Patients who had no reduction in symptoms by 6 hours after initiation of treatment[10] – n/N (per protocol analysis) Icatibant plus current standard care: 0/13 Current standard care: 3/14 **Important outcomes** **Time to onset of symptom regression** Defined as time to onset of symptom relief, assessed by investigators and patients at 1, 2, 3, 4, 6, 8, 12, 24, and 48 hours or up to day 14 after initiation of treatment See Jeon et al 2019	This study was appraised using the JBI checklist for RCTs. 1. Yes 2. Yes 3. Yes 4. Yes 5. No 6. Yes 7. Yes 8. Yes 9. Unclear 10. No 11. No 12. No 13. Yes Other comments: Patients who received current standard care were older than patients who received icatibant plus current standard care, but otherwise there were no significant differences between the treatment groups in any baseline characteristics. Investigators who were responsible for randomisation, study-drug administration, and assessment of injection-site reactions were aware of the study assignments. Limited details were provided on the methods used to measure outcomes in terms of number of raters and rater reliability.

[10] Defined as patients who required administration of rescue therapy (30 mg of icatibant with 500 mg of prednisolone).

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	No. of participants in each treatment group Icatibant plus current standard care: n=13 Current standard care: n=14 **Baseline characteristics – per-protocol population** Age (mean, ± SD): Icatibant plus current standard care 62.4 (9.7) years; Current standard care 69.4 (16.6) years Sex (male), n (%): Icatibant plus current standard care 9 (69); Current standard care 8 (57) Race, n (%): White 27 (100) Previous episode of ACEI-induced angioedema – n (%): Icatibant plus current standard care 5 (38); Current standard care 5 (36) Severity of symptoms (mean, ± SD) Composite investigator-assessed symptom		**Symptom progression** Defined as tracheotomy by 6 hours after initiation of treatment (n/N) Icatibant plus current standard care: n=0/13 Current standard care: n=1/14 **Safety** See Jeon et al 2019	N=30 patients were enrolled in the study. Treatment decisions were made by the investigator before randomisation in the case of 3 patients (2 patients received icatibant plus current standard care and one patient received current standard care); these 3 patients were excluded from the per-protocol efficacy analyses; per-protocol analysis was conducted, including all patients who underwent randomisation and received the study treatment (n=27). Given the sample size calculation required 15 patients in each treatment group to detect the primary efficacy outcome, both treatment groups were underpowered which may have impacted on the validity of the findings. Safety analyses were performed in the as-treated population (n=30), although the authors stated that the sample size was too small to allow for a robust evaluation of safety. For the 3 patients in the current standard care group who required rescue therapy, the maximum recorded time to complete resolution of oedema (61.2 hours) was used to replace the data for these 3 patients in the primary efficacy analysis; there was, therefore, an imbalance in the number of missing data between treatment groups.

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	score[7]: Icatibant plus current standard care 1.1 (0.2); Current standard care 1.2 (0.2) Composite investigator-assessed angioedema score[8]: Icatibant plus current standard care 1.1 (0.2); Current standard care 1.1 (0.2) Composite patient-assessed VAS score[9]: Icatibant plus current standard care 2.9 (0.6); Current standard care 3.5 (0.6)			All patients were hospitalised and patients were followed up 14 days after hospital admission. No patients discontinued study treatment due to adverse events, but n=4 patients in the current standard care group were lost to follow-up. Source of funding: Shire and the Federal Ministry of Education and Research of Germany.
Bork K, Wulff K, Witzke G, Machnig T, Hardt J. Treatment of patients with hereditary angioedema with the c.988A>G (p.Lys330Glu) variant in the plasminogen gene. Orphanet Journal Of Rare Diseases. 2020;15(1):52.	**Inclusion criteria** Patients with a confirmed diagnosis of PLG gene variant c.988A > G (p.K330E) **Exclusion criteria** Not stated **Total sample size**	**Interventions** Icatibant (administered at home by 2 patients; no other details provided) **Comparators** Untreated attacks	Follow-up duration was not reported **Critical outcomes** **Total attack/swelling duration[12] – hours (mean, ± SD)** Icatibant treated attacks (n=13 patients): 4.3 (2.6) Untreated attacks (same n=13 patients): 44.7 (28.6)	This study was appraised using the JBI checklist for cohort studies 1. Yes 2. Yes 3. Yes 4. No 5. No 6. No 7. Unclear 8. No

[7] The intensity of six symptoms (pain, shortness of breath, dysphagia, change in voice, sensation of a foreign body, and feeling of pressure) was assessed by investigators before treatment and 1, 2, 3, 4, 6, 8, 12, 24, and 48 hours after treatment, using a scale from 0 (no symptoms) to 3 (severe symptoms); the average of the six symptom scores was calculated to determine the composite symptom score.
[8] The severity of angioedema at four locations (lips and cheeks, tongue, oropharynx, and hypopharynx or larynx) was assessed by investigators using a scale from 0 (no angioedema) to 4 (very severe angioedema). An ear, nose and throat specialist assessed angioedema of the oropharynx and hypopharynx, and an endoscopy was performed when necessary. The average of the four symptom scores was calculated to determine the composite angioedema score.
[9] The intensity of six symptoms (pain, shortness of breath, dysphagia, change in voice, sensation of a foreign body, and feeling of pressure) was assessed by patients before treatment and 1, 2, 3, 4, 6, 8, 12, 24, and 48 hours after treatment, with the use of a VAS (scores ranged from 0 to 10 and higher scores indicated more severe symptoms). A composite score on the VAS was calculated as the average of the measurements for the six symptoms.
[12] Patients recorded their attack duration in a patient diary; no further details were provided.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Study location Germany **Study type** Retrospective, single centre, cohort study **Study aim** To assess and compare the effectiveness of on-demand treatments and long-term prophylaxis in patients with HAE-PLG **Study dates** January 1999 to July 2019	N=111 symptomatic individuals with HAE-PLG (n=22 families); n=59 patients had received treatment, n=52 patients had not received treatment for acute attacks **No. of participants in each treatment group** Icatibant plus current standard care: n=13 (treated attacks; 201 acute facial and abdominal attacks and tongue swellings) Control: n=13 (same patients with previously untreated attacks; 149 acute facial and abdominal attacks and tongue swellings)[11] **Baseline characteristics** All patients had normal C1-INH activity, C1-INH protein, and C4 in plasma Of the n=13 patients who received icatibant, 1 patient experienced facial attacks, abdominal attacks and tongue swellings; 1 patient experienced facial and		*Difference between treated vs untreated attacks: p<0.0001* On average, icatibant treated attacks reduced the duration of swellings/attacks by 88% <u>Number of attacks shortened with icatibant treatment (n=13) by:</u> >50%: 197 20% to 50%: 2 <20%: 2	9. Yes 10. Not applicable 11. Yes Other comments: This was a retrospective cohort study from which only a subgroup of patients were in-scope for this review as they received icatibant; out-of-scope patients received plasma-derived C1 INH, corticosteroids and antihistamines with or without epinephrine, fresh frozen plasma, or long-term prophylaxis (including progestins, tranexamic acid, danazol, corticosteroids or antihistamines). Limited baseline characteristics were reported for the in-scope subgroup. No attempts were made to identify confounding factors or implement strategies to deal with them. Patients recorded their attack symptoms in a patient diary and the treatment effect was assessed by an intra-individual comparison of the attack duration of treated versus untreated attacks in the same patients receiving icatibant. It was unclear whether the previously untreated attacks related to attacks that were not treated at all, or whether patients received current standard care, without icatibant.

[11] Last 10 attacks before treatment or all if less than 10.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	abdominal attacks; 1 patient experienced facial attacks alone; 10 patients experienced tongue swellings alone Other characteristics for the population of interest were not presented			Before 2017, patients with HAE-PLG were classified as having HAE-nC1 INH and an unknown genetic background (HAE-unknown) or idiopathic angioedema. Source of funding: CSL Behring.
Bouillet L, Boccon-Gibod I, Launay D, Gompel A, Kanny G, Fabien V, et al. Hereditary angioedema with normal C1 inhibitor in a French cohort: Clinical characteristics and response to treatment with icatibant. Immunity, Inflammation and Disease. 2017;5(1):29-36. **Study location** France **Study type** Retrospective, multicentre, cohort study (Icatibant Outcome Survey registry) **Study aim** To compare disease characteristics and the safety and efficacy of icatibant in the treatment of acute attacks in patients	**Inclusion criteria** Symptomatic patients diagnosed with HAE type I (C1 INH deficiency) or II (normal levels of C1 INH, but with dysfunctional protein), or HAE-nC1 INH (C1 INH level normal or above normal [≥15 to 50 mg/dL] and function normal or above normal levels [≥70 to 130%]) **Exclusion criteria** Patients with other conditions such as acquired angioedema (i.e. unassociated with HAE) **Total sample size** N=182 (n=22 in-scope patients with HAE-nC1 INH and a family history of HAE; n=160 out-of-	**Interventions** Icatibant (healthcare professional or self-administered; 96.1% of attacks were self-administered) 70.0% of attacks required one injection, 24.4% required two injections and 5.6% required 3 injections No further information provided **Comparators** None	Outcomes were assessed at 6-month intervals but follow-up duration was not reported **Critical outcomes** **Total attack/swelling duration** Defined as time from symptom onset to complete symptom resolution in patients providing complete information[13] – hours (median, IQR) HAE-nC1 INH patients treated with icatibant (n=10 patients; n=90 attacks): 32.5 (12.0 to 47.3)	This study was appraised using the JBI checklist for cohort studies 1. Not applicable 2. Not applicable 3. Unclear 4. No 5. No 6. No 7. Unclear 8. Yes 9. Yes 10. Not applicable 11. Yes Other comments: This was a retrospective cohort study from which only a subgroup of patients were in-scope for this review. No attempts were made to identify confounding factors or implement strategies to deal with them. The authors reported that validated measures were used to assess attack duration, but no further details were provided on measures of reliability (i.e. inter- or intra-observer reliability).

[13] Defined as time to administration (from symptom onset to first subcutaneous icatibant injection) and time to resolution (duration from icatibant injection to complete symptom resolution).

Study details	Population	Interventions	Study outcomes	Appraisal and funding
with HAE-nC1 INH, HAE with C1 INH deficiency (type I), or dysfunction (type II) **Study dates** July 2009 to September 2013	scope patients with HAE I or II) **No. of participants in each treatment group** Icatibant: n=10 patients with HAE-nC1 INH providing complete information for outcome data Control: None **Baseline characteristics – n=22 in-scope patients with HAE-nC1 INH** Age at enrolment (years) – median (IQR): 35.1 (28.0 to 42.8) Sex (male) n (%): 4 (18.2) Of the 22 in-scope patients, 16 patients were tested for the presence of a Factor XII (FXII) mutation. Of these 16 patients, 4 were confirmed as having this mutation and 9 patients were found to not have this mutation. Of the remaining patients tested for the FXII mutation, 1 patient had a single nucleotide polymorphism (c.2399C>A), 1 patient			Follow-up assessments were performed by physicians at a minimum of 6-month intervals, and outcomes were reported in patients providing complete information only. In addition to diagnosis of HAE-nC1 INH, evidence that conventional treatment with antihistamines and corticosteroids was unsuccessful was required, and either a confirmed Factor XII mutation or family history of HAE. Source of funding: Shire Development LLC.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	did not have a large deletion or rearrangement in the FXII gene but had the p.Thr328Lys variant in FXII, and 1 patient had an unknown genetic cause			
Grumach AS, Henriques MT, Bardou MLD, Pontarolli DA, Botha J, Correa M. Icatibant use in Brazilian patients with hereditary angioedema (HAE) type 1 or 2 and HAE with normal C1-INH levels: findings from the Icatibant Outcome Survey Registry Study. Anais Brasileiros de Dermatologia. 2022;97(4):448-57. **Study location** Brazil **Study type** Retrospective, multicentre, cohort study (Icatibant Outcome Survey registry) **Study aim** To compare the effectiveness and tolerability of icatibant in	**Inclusion criteria** Patients with HAE nC1-INH or HAE type I or II; aged ≥18 years; received at least one dose of icatibant **Exclusion criteria** Not stated **Total sample size** N=42 (n=16 in-scope patients with HAE-nC1 INH; n=26 out-of-scope patients with HAE I or II) **No. of participants in each treatment group** Icatibant: n=10 HAE-nC1 INH patients (63 attacks) Control: None **Baseline characteristics – n=16**	**Interventions** Icatibant Concomitant rescue therapy was permitted for the treatment of HAE attacks 96.7% of attacks required one injection, 1.7% required two injections and 1.7% required four injections No further information provided **Comparators** None	Outcomes were assessed at 6-month intervals and mean follow-up was 4.3 (SD 1.42) years **Critical outcomes** **Total attack/swelling duration** <u>Defined as time between the onset of an attack and complete resolution of all symptoms – hours (median, range)</u> HAE-nC1 INH patients treated with icatibant (n=8 patients; n=45 attacks)[14]: 7.0 (0.3 to 99.0) <u>Defined as time between the onset of an attack and complete resolution of all symptoms – hours (mean, ±SD)</u> HAE-nC1 INH patients treated with icatibant (n=8 patients; n=45 attacks)[14]: 18.4 (24.8)	This study was appraised using the JBI checklist for cohort studies 1. Not applicable 2. Not applicable 3. Unclear 4. No 5. No 6. No 7. Unclear 8. Yes 9. Yes 10. Not applicable 11. Yes Other comments: This was a retrospective cohort study from which only a subgroup of patients were in-scope for this review. No attempts were made to identify confounding factors or implement strategies to deal with them. The authors acknowledged the limitations associated with relying on patient recall and potential for incomplete reporting of symptoms; no further details were provided on measures of

[14] N=16 patients with HAE-nC1 INH were enrolled in the Icatibant Outcome Survey registry, frequency of attacks and icatibant administrations were reported in n=10 patients with HAE-nC1 INH (60 attacks; data were missing for 3 attacks), and outcome data on total attack duration was available for n=8 patients with HAE-nC1 INH (45 attacks).

Study details	Population	Interventions	Study outcomes	Appraisal and funding
the treatment of patients with HAE-nC1 INH and HAE type I or II **Study dates** Up to September 2019	**patients with HAE-nC1 INH** Age at enrolment (years) – mean (±SD): 42.1 (13.8) Sex (male) n (%): 0 (0) Family history of HAE – n (%): 15 (93.8) Patients with HAE nC1-INH who experienced severe or very severe attacks prior to treatment: 61.7% Number of patients with HAE-nC1 INH experiencing ≥1 icatibant-treated HAE attack: n=10 Number of attacks per patient with HAE-nC1 INH (n=10): Mean (± SD): 6.3 (4.5) Median (IQR): 6.0 (5.0 to 8.0) Range: 1 to 17			reliability (i.e. inter- or intra-observer reliability). At the time of data cutoff, information on the specific genetic mutations in patients with HAE nC1-INH was incomplete and findings from that analysis were therefore not reported in the publication. Source of funding: Shire Human Genetic Therapies, Inc.
Jeon J, Lee YJ, Lee SY. Effect of icatibant on angiotensin-converting enzyme inhibitor-induced angioedema: A meta-analysis of randomized controlled trials. Journal of Clinical Pharmacy &	**Inclusion criteria** RCTs comparing icatibant to current standard care or placebo in patients with ACEI-induced angioedema and reporting the time taken	**Interventions** **Icatibant** 2 RCTs administered a single subcutaneous injection of icatibant 30 mg (steroids, antihistamines and epinephrine were permitted in 1 RCT and	Follow-up durations: See individual RCTs **Critical outcomes** **Time to complete resolution of oedema** Defined as complete resolution of symptoms or time to meeting discharge criteria[15] - hours MD (95% CI) Random effects model	This study was appraised using the JBI checklist for systematic reviews 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes

[15] Defined as absence of breathing and swallowing difficulty, and mildness or absence of voice change and tongue swelling.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Therapeutics. 2019;44(5):685-92. **Study location** Germany (1 RCT), USA (1 RCT), Canada, Israel, the UK and USA (1 RCT) **Study type** SRMA **Study aim** To assess the effectiveness and safety of icatibant compared to placebo or conventional therapy in the treatment of ACEI-induced angioedema **Study dates** Database searches were conducted through to 2017	to achieve complete resolution of oedema **Exclusion criteria** None stated **Total sample size** N=179 patients included in 3 RCTs **No. of participants in each treatment group** Icatibant plus current standard care: n=87 Current standard care or placebo with current standard care: n=92 **Baseline characteristics** Age (mean, ± SD): Icatibant plus current standard care 56.3 (13.4) to 62.4 (9.7) years; Current standard care or placebo with current standard care 60.7 (10.8) to 69.4 (16.6) years Sex (male, %): Icatibant plus current standard care 42 to 69; Current standard care or	rescue medications (icatibant and prednisolone) were permitted 6 hours after treatment in 1 RCT); 1 RCT administered icatibant 30 mg subcutaneously at 0 and 6 hours (steroids, antihistamines and epinephrine were permitted) **Comparators** **Current standard care or placebo with current standard care** 2 RCTs administered placebo – normal saline subcutaneously once in 1 RCT and isotonic acetate-buffered solution subcutaneously at 0 and 6 hours in 1 RCT (steroids, antihistamines and epinephrine were permitted in both RCTs); 1 RCT administered prednisolone 500 mg and intravenous clemastine 2 mg (rescue medications (icatibant and prednisolone) were permitted 6 hours after treatment)	3 RCTs (n=179)[16]: -7.77 (95% CI -25.18 to 9.63, I^2=83%; p=0.38) Fixed effect model 3 RCTs (n=179)[16] 0.16 (95% CI -1.06 to 1.38, I^2=83%; p=0.80) **Proportion of patients exhibiting complete resolution within 4 hours after initiation of treatment** Defined as complete resolution of symptoms or those meeting discharge criteria[15] within 4 hours after initiation of treatment, n/N events (3 RCTs) Icatibant plus current standard care: 41/86 Current standard care or placebo with current standard care: 39/90 *Difference between treatment groups - RR (95% CI)* 3 RCTs (n=176)[16]: 1.20 (95% CI 0.48 to 3.04, I^2=46%; p=0.70) **Important outcomes** **Time to onset of symptom relief** Defined as time to decrease of at least one point in symptom score or scale – hours, MD (95% CI) 2 RCTs (n=148): -0.50 (-1.30 to 0.30, I^2=96%; p=0.22) **Safety** Any adverse events, n/N events (3 RCTs) Icatibant plus current standard care: 29/88	6. Unclear 7. Unclear 8. Yes 9. No (<10 studies) 10. Not applicable 11. Not applicable Other comments: Individual studies included in the SRMA reported differing exclusion criteria, including, for example, causes other than ACEI angioedema, acute MI, HF NYHA III to IV, pregnancy, family history, anaphylaxis, abscess, >12 hours after attack, response to 1 of the current standard care treatments. The review methodology, in terms of decisions on study inclusion, study appraisal and data extraction, was not clearly described. It was therefore unclear whether methods were used to minimise errors in study selection, critical appraisal and data extraction. Recommendations for policy and/or practice, and specific directives for new research were not discussed by the review authors. The review authors contacted the primary study authors for further information. There was an unexplained discrepancy in the results reported for 1 RCT (Bas et al

[16] Although Straka et al (2017) stated that their final analysis was based on ITT, they excluded one patient who received icatibant from the final analysis due to the patient being unable to complete the visual analogue scale. Jeon et al 2019 include this patient in their intention-to-treat analysis.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	placebo with current standard care 33 to 57 Race (black or African American, %): Icatibant plus current standard care 0 to 75; Current standard care or placebo with current standard care 0 to 71.7 Race (white, %): Icatibant plus current standard care 25 to 100; Current standard care or placebo with current standard care 28.3 to 100 Severity was reported differently in the 3 RCTs but all patients had moderate to severe symptoms		Current standard care or placebo with current standard care: 27/91 *Difference between treatment groups, RR (95% CI)* 3 RCTs (n=179)[18]: 0.95 (0.43 to 2.10, I^2=20%; p=0.90) <u>Drug-related adverse events, n/N events (3 RCTs)</u> Icatibant plus current standard care: 12/88 Current standard care or placebo with current standard care: 9/91 *Difference between treatment groups, RR (95% CI)* 3 RCTs (n=17**9**)[18]: 1.29 (0.58 to 2.87, I^2=0%; p=0.53) <u>Injection site reactions (erythema), n/N events (2 RCTs)</u> Icatibant plus current standard care: 43/75 Current standard treatment or placebo with current standard treatment: 17/73 *Difference between treatment groups, RR (95% CI)* 2 RCTs (n=148): 2.47 (1.56 to 3.90, I^2=0%; p=0.0001) <u>Injection site reactions (swelling), n/N events (2 RCTs)</u> Icatibant plus current standard care: 25/75 Current standard treatment or placebo with current standard treatment: 16/73	2015) in the SRMA with the actual results reported in the RCT publication for time to complete resolution of oedema. The SRMA reported mean ± SD as Icatibant plus current standard care 9.095 ± SD 10.7972 hours; Control 32.2314 ± SD 22.8176 hours while the individual RCT reported Icatibant plus current standard care 15.4 ± SD 18.8 hours; Control 33.2 ± SD 18.0 hours. The discrepancy may have been due to the different methods used by the different authors to convert medians (IQRs) to means (SDs). However, the greater discrepancy in converted means reported for the icatibant plus current standard care treatment groups are unclear, and this may have impacted on the overall result in terms of indicating greater benefit with icatibant plus current standard care compared to standard treatment. Jeon et al 2017 stated that “if the study population also included some patients with histamine-mediated angioedema, use of antihistamines could lead to shorter recovery time”. The authors considered the 3 RCTs to be of moderate quality according to GRADE assessment.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Difference between treatment groups, RR (95% CI) 2 RCTs (n=148): 1.52 (0.89 to 2.61, I^2=23%; p=0.13)	Source of funding: Dankook University.
Manto IA, Latysheva EA, Bliznetz EA, Timoshenko DO, Aleshina LV, Bocherova YA, et al. Hereditary angioedema with a mutation in the plasminogen gene: A retrospective study of a cohort of 14 patients from Russia. Russian Journal of Allergy. 2021;18(2):5-19. **Study location** Russia **Study type** Retrospective, single centre, cohort study **Study aim** To assess and compare the efficacy of on-demand treatments and long-term prophylaxis for angioedema in patients with HAE-PLG versus	**Inclusion criteria** Patients with an identified mutation c.988A>G (p.Lys330Glu;K330E) in the PLG gene or HAE type I or II in accordance with the WAO/EAACI criteria, plus clinical symptoms of HAE (recurrent angioedema of various localisation and/or abdominal attacks) **Exclusion criteria** Individuals without HAE symptoms **Total sample size** N=208 (n=14 in-scope patients with HAE-PLG [n=10 families]; n=194 out-of-scope patients with HAE I/II [124 families])	**Interventions** Icatibant (Firazyr®: no other details provided) **Comparators** None	Follow-up duration was not reported **Critical outcomes** **Total attack/swelling duration[17] – hours (average)** Icatibant treated attack durations (n=5; 29 attacks): 12 On average, icatibant reduced the duration of attacks by 71.4%[18]	This study was appraised using the JBI checklist for cohort studies 1. Not applicable 2. Not applicable 3. Unclear 4. No 5. No 6. No 7. Unclear 8. No 9. Yes 10. Not applicable 11. Yes Other comments: This was a retrospective cohort study from which only a subgroup of patients were in-scope for this review. Out-of-scope patients received long-term prophylaxis (including tranexamic acid). No attempts were made to identify confounding factors or implement strategies to deal with them. No details were provided on measures of reliability (i.e. inter- or intra-observer reliability).

[17] Total attack/swelling duration was not clearly defined. Data on disease manifestation (defined as the incidence of clinical symptoms (peripheral oedema, abdominal attacks, oedema of the face and neck, oedema of the tongue, oedema of the larynx, marginal erythema) and outcomes were obtained from medical records of patients and the database of NRC Institute of Immunology FMBA of Russia.

[18] It was unclear how the reduction in duration of attacks was calculated in terms of whether the comparison was between icatibant-treated vs untreated attacks in the same five patients with HAE PLG, or the comparison was between 5/14 patients with HAE PLG who were treated with icatibant vs 9/14 patients with HAE PLG who were not treated with icatibant.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
patients with HAE types I or II **Study dates** 2009 to 2020 (collection and processing of data between October and December 2020)	**No. of participants in each treatment group** Icatibant: n=5 (29 attacks) Control: None **Baseline characteristics – n=14 patients with HAE-PLG** Age (mean ± SD): 51.64 (± SD 13.55) years Sex (female, n/N, %): 13/14 (92.9) All patients with HAE-PLG had a positive family history (100%)			Source of funding: The study received no funding.
Sinert R, Levy P, Bernstein JA, Body R, Sivilotti MLA, Moellman J, et al. Randomized Trial of Icatibant for Angiotensin-Converting Enzyme Inhibitor-Induced Upper Airway Angioedema. The Journal of Allergy & Clinical Immunology in Practice. 2017;5(5):1402-9.e3. **Study location** Canada, Israel, the UK, the USA **Study type** Phase III, multicentre, double-blind RCT	**Inclusion criteria** Patients aged ≥18 years and being treated for ACEI–induced angioedema of the head and/or neck, with at least moderately severe symptoms of <12 hours' duration **Exclusion criteria** Patients with angioedema considered to be caused by factors other than ACEIs (e.g. hereditary, acquired or allergic angioedema; patients with a family history of recurrent angioedema or a history	**Interventions** Single subcutaneous injection of icatibant (Firazyr) 30 mg **Comparators** Single subcutaneous injection of placebo (isotonic acetate-buffered solution) 30 mg Antihistamines, corticosteroids, and epinephrine were permitted in both treatment groups	Outcomes were assessed on day 3 after study treatment, or approximately 2 days after discharge, if patient discharged on or after day 3, unless otherwise stated **Critical outcomes** **Time to resolution** Defined as time to meeting discharge criteria[15], assessed by investigators at 30 and 60 minutes after treatment initiation and hourly thereafter up to 8 hours, or in patients who did not meet the primary outcome or were not discharged from hospital by hour 8, assessments continued every 2 hours up to 24 hours, and every 3 hours thereafter See Jeon et al 2019 Proportion of patients exhibiting complete resolution of symptoms within 4 hours after initiation of treatment	This study was appraised using the JBI checklist for RCTs 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Yes 7. Yes 8. Yes 9. Yes 10. Yes 11. Yes 12. Yes 13. Yes Other comments: There was a greater proportion of patients weighing ≤75 kg in the placebo with current standard care group compared to icatibant plus current

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Study aim To assess the effectiveness of icatibant in patients with ACEI-induced angioedema of at least moderate severity **Study dates** December 2013 to August 2015	of angioedema attacks before staring ACEI treatment); patients with a vascular condition that contraindicated participation **Total sample size** N= 121 (ITT analysis) N=118 (modified ITT and safety analysis) **No. of participants in each treatment group** Icatibant plus current standard care: n=61 (ITT analysis); n=60 modified ITT and safety analysis) Placebo with current standard care: n=60 (ITT analysis); n=58 modified ITT and safety analysis) **Baseline characteristics** Age (mean, ± SD): Icatibant plus current standard care 60.9 (12.1) years; Placebo with current standard care 61.8 (13.4) years Sex (male, n, %): Icatibant plus current standard care 34 (55.7); Placebo with current standard care 25 (41.7)		See Jeon et al 2019 **Treatment response (modified ITT analysis)** Defined as use of corticosteroids, antihistamines, or epinephrine after initiation of treatment (n, %) Icatibant plus current standard care (n=60): 35 (58.3) Placebo with current standard care (n=58): 35 (60.3); p≥0.58 **Important outcomes** **Time to onset of symptom regression** Defined as time to onset of symptom relief, assessed by investigators at 30 and 60 minutes after treatment initiation and hourly thereafter up to 8 hours, or in patients who did not meet the primary outcome or were not discharged from hospital by hour 8, assessments continued every 2 hours up to 24 hours, and every 3 hours thereafter See Jeon et al 2019 **Symptom progression** Defined as number of patients requiring airway intervention (n, %) Icatibant plus current standard care (n=60): n=1 (1.7) (patient was admitted to ICU and received airway intervention 1.5 hours after receiving icatibant plus current standard care and 4.75 hours after attack onset [symptoms were considered moderate at baseline]) Placebo with current standard care (n=58): n=0 (0) **Hospital attendances**	standard care group, but otherwise there were no significant differences between the treatment groups in baseline characteristics. A single physician assessed the severity of the four primary symptoms using a validated clinical rating scale; investigators were trained on the scoring measure. The authors excluded patients with either mild angioedema or the most severe angioedema and stated that eligible patients who were rapidly worsening also were likely underrepresented in the study population. Therefore, the study population in whom the angioedema attack was plateauing, may have contributed to an overall shorter duration of symptoms than is typically seen with ACEI-induced angioedema attacks. No patients discontinued study treatment due to adverse events, but n=3 patients did not receive study treatment and n=1 patient in the placebo with current standard care group was lost to follow-up. Source of funding: Shire HGT.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Race, Black or African American n (%): Icatibant plus current standard care 41 (67.2); Placebo with current standard care 43 (71.7) <u>Weight (kg), n (%)</u> ≤75: Icatibant plus current standard care 9 (14.8); Placebo with current standard care 20 (33.3) >75 to 100: Icatibant plus current standard care 31 (50.8); Placebo with current standard care 24 (40.0) >100: Icatibant plus current standard care 21 (34.4); Placebo with current standard care16 (26.7) <u>Severity of attacks[19] (n, %)</u> Moderate: Icatibant plus current standard care 45 (73.8); Placebo with current standard care 42 (70.0) Severe or very severe: Icatibant plus current standard care 16 (26.2);		<u>Defined as number of hospital admissions after initiation of treatment – excluding patients hospitalised before initiation of treatment (n, %)</u> Icatibant plus current standard care (n=48): 22 (45.8) Placebo with current standard care (n=48): 22 (45.8) **Safety** See Jeon et al 2019	

[19] The severity of the ACE-I-induced angioedema attacks were assessed by the enrolling physician and determined by the patient's worst severity rating at baseline, measured using 4 clinical domains (difficulty breathing, difficulty swallowing, voice changes, and tongue swelling).

<table>
<tr><th>Study details</th><th>Population</th><th>Interventions</th><th>Study outcomes</th><th>Appraisal and funding</th></tr>
<tr><td></td><td>Placebo with current standard care 18 (30.0)</td><td></td><td></td><td></td></tr>
<tr><td>Straka BT, Ramirez CE, Byrd JB, Stone E, Woodard-Grice A, Nian H, et al. Effect of bradykinin receptor antagonism on ACE inhibitor-associated angioedema. Journal of Allergy & Clinical Immunology. 2017;140(1):242-8.e2.

Study location
USA

Study type
Phase IV, multicentre, double-blind RCT

Study aim
To assess whether icatibant decreases the severity and duration of ACEI-associated angioedema

Study dates
October 2007 to September 2015</td><td>Inclusion criteria
Patients aged 18 to 65 years with ACEI-associated angioedema (defined as swelling of lips, tongue, pharynx or face during ACEI use and no swelling in the absence of ACEI use)

Exclusion criteria
Patients with HAE and C1 deficiency; patients with bowel oedema; patients presenting for care >6 hours prior to screening and randomisation; pregnancy

Total sample size
N=33 (randomised)[20]
N=30 (ITT analysis)[21]

No. of participants in each treatment group
Icatibant plus current standard care: n=12 (ITT analysis)[23]
Placebo with current standard care: n=18 (ITT analysis)</td><td>Interventions
Subcutaneous injection of icatibant plus current standard care (Firazyr) 30 mg (delivered in two 1.5 ml syringes at 0 and 6 hours)

Comparators
Subcutaneous injection of matching placebo (normal saline) 30 mg (delivered in two 1.5 ml syringes at 0 and 6 hours)

Standard-of-care treatment (e.g. antihistamines, steroids, or epinephrine) was permitted at the discretion of the treatment team</td><td>Outcomes were assessed up to 48 hours after initiation of treatment or at discharge from hospital, unless otherwise stated

Critical outcomes

Time to resolution
<u>Defined as time to complete resolution of symptoms</u>

See Jeon et al 2019

<u>Proportion of patients exhibiting complete resolution of symptoms within 4 hours after initiation of treatment</u>

See Jeon et al 2019

Treatment response (ITT analysis)
<u>Defined as use of H1 and H2 blockers, corticosteroids, and epinephrine (n, %)</u>

<table><tr><th></th><th>Icatibant plus current standard care</th><th>Placebo/current standard care</th><th>p-value</th></tr><tr><td>H1 blocker</td><td>11 (92)</td><td>16 (88.9)</td><td>0.80</td></tr><tr><td>H2 blocker</td><td>11 (92)</td><td>14 (78)</td><td>0.32</td></tr><tr><td>Corticosteroids</td><td>11 (92)</td><td>16 (88.9)</td><td>0.80</td></tr><tr><td>Epinephrine</td><td>0</td><td>3 (17)</td><td>0.14</td></tr></table>
Important outcomes

Symptom progression</td><td>This study was appraised using the JBI checklist for RCTs

1. Yes
2. Yes
3. Yes
4. Yes
5. Yes
6. Yes
7. Yes
8. Yes
9. Unclear
10. Yes
11. Yes
12. No
13. Yes

Other comments: The study was terminated based on DSMC recommending discontinuation due to futility and feasibility.

There were no significant differences between the treatment groups in baseline characteristics (although there was a greater number of patients in the placebo with current standard care group which the authors stated was due to incompletely filled randomisation blocks within strata [randomisation was stratified by race]). N=2 patients in the placebo with current standard</td></tr>
</table>

[20] Two patients randomised to icatibant withdrew consent prior to initiation of treatment.
[21] Although Straka et al 2017 reported ITT analysis, they excluded one patient who was intubated and unable to complete the VAS score from their final analysis.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Baseline characteristics Age (mean, ± SD): Icatibant plus current standard care 56.3 (13.4 years; Placebo with current standard care 60.7 (10.8) years Sex (female, n, %): Icatibant plus current standard care 7 (58); Placebo with current standard care 12 (67) Race (white, n, %): Icatibant plus current standard care 3 (25); Placebo with current standard care 7 (39) Race (black, n, %): Icatibant plus current standard care 9 (75); Placebo with current standard care 11 (61) Immunosuppressed (n, %)[22]: Icatibant plus current standard care 1 (8); Placebo with current standard care 5 (28)		<u>Defined as number of patients requiring intubation after initiation of treatment (n, %)</u> Icatibant plus current standard care (n=12): n=2 (17) Placebo with current standard care (n=18): n=1 (6); p=0.32 **Hospital attendances** <u>Defined as number of patients admitted to ICU after treatment initiation (n, %)</u> Icatibant plus current standard care (n=12): 6 (50) Placebo with current standard care (n=18): 6 (33) *Difference between treatment groups: p=0.36* **Safety** See Jeon et al 2019	care group did not receive a second dose of treatment at six hours, but were included in the final analysis. N=1 patient in the icatibant plus current standard care group was excluded from the final analysis due to the inability to complete the VAS. Given the sample size calculation required 16 patients in each treatment group to detect the primary efficacy outcome, the icatibant plus current standard care treatment group was underpowered which may have impacted on the validity of the findings. It was unclear whether the outcomes were measured in a reliable way due to limited details provided by the authors (i.e. "the investigator or research nurse independently assessed the severity of angioedema"). The mean (SD) follow-up duration was 4.36 (2.19) years. Source of funding: National Institutes of Health and Jerini AG/Shire Pharmaceuticals, Inc.
Abbreviations ACEI: angiotensin-converting enzyme inhibitor, CI: confidence interval, FX11: factor XII, GRADE: Grading of Recommendations Assessment, Development and Evaluation, HAE: hereditary angioedema, HAE-nC1 INH: hereditary angioedema with normal C1 esterase inhibitor, ICU: intensive care unit, IQR: interquartile range, ITT: intention-to-treat, MI:				

[22] Immunosuppressants in the placebo with standard care group were prednisone (n=4), methotrexate (n=1), tacrolimus (n=1). One patient in the icatibant group had the human immunodeficiency virus (HIV).

Study details	Population	Interventions	Study outcomes	Appraisal and funding
myocardial infarction, HF: heart failure, MD: mean difference, NYHA: New York Heart Association, PLG: plasminogen, RCT: randomised controlled trial, RR: risk ratio, SD: standard deviation, SRMA: systematic review/meta-analysis, VAS: visual analogue scale, WAO/EAACI: World Allergy Organisation/European Academy of Allergy and Clinical Immunology.				

Appendix F Quality appraisal checklists

JBI Critical Appraisal Checklist for Systematic Reviews and Research Synthesis

1. Is the review question clearly and explicitly stated?
2. Were the inclusion criteria appropriate for the review question?
3. Was the search strategy appropriate?
4. Were the sources and resources used to search for studies adequate?
5. Were the criteria for appraising studies appropriate?
6. Was critical appraisal conducted by two or more reviewers independently?
7. Were there methods to minimize errors in data extraction?
8. Were the methods used to combine studies appropriate?
9. Was the likelihood of publication bias assessed?
10. Were recommendations for policy and/or practice supported by the reported data?
11. Were the specific directives for new research appropriate?

JBI Critical Appraisal Checklist for Randomised Controlled Trials

1. Was true randomisation used for assignment of participants to treatment groups?
2. Was allocation to treatment groups concealed?
3. Were treatment groups similar at the baseline?
4. Were participants blind to treatment assignment?
5. Were those delivering treatment blind to treatment assignment?
6. Were treatment groups treated identically other than the intervention of interest?
7. Were outcome assessors blind to treatment assignment?
8. Were outcomes measured in the same way for treatment groups?
9. Were outcomes measured in a reliable way?
10. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?
11. Were participants analysed in the groups to which they were randomised?
12. Was appropriate statistical analysis used?

13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomisation, parallel groups) accounted for in the conduct and analysis of the trial?

JBI Critical Appraisal Checklist for Cohort studies

1. Were the two groups similar and recruited from the same population?
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?
3. Was the exposure measured in a valid and reliable way?
4. Were confounding factors identified?
5. Were strategies to deal with confounding factors stated?
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?
7. Were the outcomes measured in a valid and reliable way?
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?
10. Were strategies to address incomplete follow up utilized?
11. Was appropriate statistical analysis used?

Appendix G GRADE profiles

Table 2: In people with bradykinin-mediated angioedema with normal C1 inhibitor, what is the clinical effectiveness and safety of icatibant plus current standard care compared with current standard care alone?

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Icatibant plus current standard care	Current standard care/ Placebo with current standard care	Result		
Clinical effectiveness									
Total attack/swelling duration (patient recorded or not clearly defined)[a] – hours, mean (SD) [lower value indicates benefit]									
1 retrospective cohort study Bork 2020	Very serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	13 (201 treated attacks)	13 (149 untreated attacks)	Treated attacks: 4.3 (2.6) Untreated attacks: 44.7 (28.6) *Difference between treatment groups: 88% reduction; p<0.0001*	Critical	Very low
1 retrospective cohort study Manto 2021	Very serious limitations[1]	Very serious indirectness[3]	Not applicable	Not calculable	5 (29 attacks)	None	Treated attacks: 12 On average, icatibant reduced the duration of attacks by 71.4%[b]	Critical	Very low
Total attack/swelling duration (defined as time from symptom onset to complete symptom resolution[c]) – hours, median									
1 retrospective cohort study Bouillet 2017	Very serious limitations[4]	Very serious indirectness[3]	Not applicable	Not calculable	10 (90 attacks)	None	32.5 (IQR 12.0 to 47.3)	Critical	Very low
1 retrospective cohort study	Very serious limitations[4]	Very serious indirectness[3]	Not applicable	Not calculable	8 (45 attacks)	None	7.0 (range 0.3 to 99.0)	Critical	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Icatibant plus current standard care	Current standard care/ Placebo with current standard care	Result		
Grumach 2022									
Total attack/swelling duration (defined as number of attacks shortened with icatibant treatment by >50%, 20% to 50%, <20%)									
1 retrospective cohort study Bork 2020	Very serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	13 (201 treated attacks)	None	>50%: 197 20% to 50%: 2 <20%: 2	Critical	Very low
Time to resolution of symptoms (defined as complete resolution of symptoms or time to meeting discharge criteria[d]) – hours, MD (95% CI) [negative mean difference indicates shorter time for icatibant plus current standard care patients]									
1 systematic review (3 RCTs) Jeon 2019	Serious limitations[5]	No serious indirectness	Very serious inconsistency[6]	Serious imprecision[7]	87	92	-7.77 (-25.18 to 9.63, I^2=83%; p=0.38)[e]	Critical	Very low
Proportion of patients exhibiting complete resolution of symptoms (or those meeting discharge criteria[d]) within 4 hours after initiation of treatment - RR (95% CI) [RR greater than 1 favours icatibant plus current standard care]									
1 systematic review (3 RCTs) Jeon 2019	Serious limitations[5]	No serious indirectness	Serious inconsistency[8]	Very serious imprecision[9]	86	90	1.20 (0.48 to 3.04, I^2=46%; p=0.70)	Critical	Very low
Treatment response (defined as patients who did not have a response to treatment up to 6 hours after initiation of study treatment and required administration of rescue intervention[f]) – n/N [lower value indicates benefit]									
1 RCT Bas 2015	Very serious limitations[10]	No serious indirectness	Not applicable	Serious imprecision[11]	13	14	Icatibant plus current standard care: 0/13 Current standard care: 3/14	Critical	Very low
Treatment response (defined as use of corticosteroids, antihistamines, or epinephrine on day 3 after initiation of study treatment, or approximately 2 days after discharge if patient discharged on or after day 3) – n (%) – [lower value indicates benefit]									

<table>
<tr><th colspan="5">QUALITY</th><th colspan="3">Summary of findings</th><th rowspan="2">IMPORTANCE</th><th rowspan="2">CERTAINTY</th></tr>
<tr><th colspan="4"></th><th colspan="2">No patients</th><th>Effect</th></tr>
<tr><th>Study</th><th>Risk of bias</th><th>Indirectness</th><th>Inconsistency</th><th>Imprecision</th><th>Icatibant plus current standard care</th><th>Current standard care/ Placebo with current standard care</th><th>Result</th></tr>
<tr><td>1 RCT
Sinert 2017</td><td>No serious limitations</td><td>No serious indirectness</td><td>Not applicable</td><td>Not calculable</td><td>60</td><td>58</td><td>Icatibant plus current standard care: 35 (58.3)
Placebo with current standard care: 35 (60.3)
Difference between treatment groups: p>0.58</td><td>Critical</td><td>High</td></tr>
<tr><td colspan="10">Treatment response (defined as use of H1 or H2 blockers, corticosteroids, or epinephrine up to 48 hours after initiation of study treatment) – n (%) – [lower value indicates benefit]</td></tr>
<tr><td>1 RCT
Straka 2017</td><td>Serious limitations[12]</td><td>No serious indirectness</td><td>Not applicable</td><td>Not calculable</td><td>12</td><td>18</td><td><table><tr><th></th><th>Icatibant/current standard care</th><th>Placebo/current standard care</th><th>p-value</th></tr><tr><td>H1 blocker</td><td>11 (92)</td><td>16 (88.9)</td><td>0.80</td></tr><tr><td>H2 blocker</td><td>11 (92)</td><td>14 (78)</td><td>0.32</td></tr><tr><td>Steroids</td><td>11 (92)</td><td>16 (88.9)</td><td>0.80</td></tr><tr><td>Epinephrine</td><td>0</td><td>3 (17)</td><td>0.14</td></tr></table></td><td>Critical</td><td>Moderate</td></tr>
<tr><td colspan="10">Time to onset of symptom relief (defined as time to decrease of at least one point in symptom score or scale) – hours, MD (95% CI) [negative mean difference indicates shorter time for icatibant plus current standard care]</td></tr>
<tr><td>1 systematic review (2 RCTs)
Jeon 2019</td><td>Serious limitations[5]</td><td>No serious indirectness</td><td>Very serious inconsistency[6]</td><td>Serious imprecision[7]</td><td>74</td><td>74</td><td>-0.50 (-1.30 to 0.30, I^2=96%; p=0.22)</td><td>Important</td><td>Very low</td></tr>
<tr><td colspan="10">Symptom progression (progression of symptoms leading to airway intervention) – n (%) [lower value indicates benefit]</td></tr>
<tr><td>1 RCT
Bas 2015</td><td>Very serious limitations[10]</td><td>No serious indirectness</td><td>Not applicable</td><td>Serious imprecision[11]</td><td>13</td><td>14</td><td>Icatibant plus current standard care: 0
Placebo with current standard care: 1</td><td>Important</td><td>Very low</td></tr>
</table>

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Icatibant plus current standard care	Current standard care/ Placebo with current standard care	Result		
1 RCT Sinert 2017	No serious limitations	No serious indirectness	Not applicable	Serious imprecision[13]	60	58	Icatibant plus current standard care: 1 Placebo with current standard care: 0	Important	Moderate
1 RCT Straka 2017	Serious limitations[12]	No serious indirectness	Not applicable	Not calculable	12	18	Icatibant plus current standard care: 2 (17) Placebo with current standard care: 1 (6) *Difference between treatment groups: p=0.32*	Important	Moderate
Hospital attendances after initiation of treatment (excluding patients hospitalised before initiation of treatment) - n (%) [lower value indicates benefit]									
1 RCT Sinert 2017	No serious limitations	No serious indirectness	Not applicable	Not calculable	48	48	Icatibant plus current standard care: 22 (45.8) Placebo with current standard care: 22 (45.8)	Important	High
Hospital attendances after initiation of treatment (ICU admission) - n (%) [lower value indicates benefit]									
1 RCT Straka 2017	Serious limitations[12]	No serious indirectness	Not applicable	Not calculable	12	18	Icatibant plus current standard care: 6 (50) Placebo with current standard care: 6 (33) *Difference between treatment groups: p=0.36*	Important	Moderate
Safety – complications of icatibant treatment									
Any adverse events – RR (95% CI) [RR lower than 1 favours icatibant plus current standard care]									
1 systematic review (3 RCTs)	Serious limitations[5]	No serious indirectness	No serious inconsistency	Very serious imprecision[9]	88	91	0.95 (0.43 to 2.10, I^2=20%; p=0.90)	Important	Low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Icatibant plus current standard care	Current standard care/ Placebo with current standard care	Result		
Jeon 2019									
Drug-related adverse events – RR (95% CI) [RR greater than 1 favours current standard care/placebo with current standard care]									
1 systematic review (3 RCTs) Jeon 2019	Serious limitations[5]	No serious indirectness	No serious inconsistency	Very serious imprecision[9]	88	91	1.29 (0.58 to 2.87, I^2=0%; p=0.53)	Important	Very low
Injection site reactions (erythema) – RR (95% CI) [RR greater than 1 favours current standard care/placebo with current standard care]									
1 systematic review (2 RCTs) Jeon 2019	Serious limitations[5]	No serious indirectness	No serious inconsistency	No serious imprecision	75	73	2.47 (1.56 to 3.90, I^2=0%; p=0.0001)	Important	Moderate
Injection site reactions (swelling) – RR (95% CI) [RR greater than 1 favours current standard care/placebo with current standard care]									
1 systematic review (2 RCTs) Jeon 2019	Serious limitations[5]	No serious indirectness	No serious inconsistency	Serious imprecision[14]	75	73	1.52 (0.89 to 2.61, I^2=23%; p=0.13)	Important	Low

Abbreviations
CI: confidence interval, IQR: interquartile range, MD: mean difference, RCT: randomised controlled trial, RR: risk ratio.

1 Very serious limitations due to lack of identification of and adjustment for potential confounding factors and unclear follow-up.
2 Very serious indirectness due to no relevant comparison across treatment arms (out-of-scope comparator included plasma-derived C1 INH, corticosteroids and antihistamines with or without epinephrine, fresh frozen plasma, or long-term prophylaxis); comparison reported is between treated versus untreated attacks in the same patients.
3 Very serious indirectness due to no treatment comparison (outcomes were compared to out-of-scope patients [i.e. patients with C1 INH abnormalities; the PICO states patients with normal C1 inhibitor]).
4 Very serious limitations due to lack of identification of and adjustment for potential confounding factors, unclear methods used to assess the reliability of measuring attack duration, and limited statistical analysis.
5 Serious limitations due to unclear review methodology in terms of whether methods were used to minimise errors in study selection, critical appraisal and data extraction.
6 Very serious inconsistency due to considerable heterogeneity (I^2>75%).

7 Serious imprecision due to wide 95% CIs that cross the default minimal clinically important difference lower threshold based on half the standard deviation of the control group at baseline.
8 Serious inconsistency due to moderate heterogeneity (I^2=46%).
9 Very serious imprecision due to wide 95% CIs that cross the default minimal clinically important difference upper and lower thresholds.
10 Very serious limitations due to uncertainties surrounding statistical methods, unclear methods used to assess reliability of outcome measures, and an imbalance in patients lost to follow-up between treatment groups.
11 Serious imprecision due to 0 events in the intervention arm.
12 Serious limitations due to an imbalance in the number of patients in the icatibant plus current standard care treatment group, and uncertainties surrounding the reliability of outcome measures due to limited information provided.
13 Serious imprecision due to 0 events in the comparator arm.
14 Serious imprecision due to wide 95% CIs that cross the default minimal clinically important difference upper threshold.

a Total attack/swelling duration was not clearly defined: Bork et al (2020) defined this outcome as patient recorded attack duration (no further details provided); Manto et al (2021) stated that data on disease manifestation (defined as the incidence of clinical symptoms [peripheral oedema, abdominal attacks, oedema of the face and neck, oedema of the tongue, oedema of the larynx, marginal erythema]) and outcomes were obtained from medical records of patients and the database of NRC Institute of Immunology FMBA of Russia.
b It was unclear how the reduction in duration of attacks was calculated in terms of whether the comparison was between icatibant-treated vs untreated attacks in the same five patients with HAE PLG, or the comparison was between five of 14 patients with HAE PLG who were treated with icatibant vs nine of 14 patients with HAE PLG who were not treated with icatibant.
c Defined as time to administration (from symptom onset to first subcutaneous icatibant injection) and time to resolution (duration from icatibant injection to complete symptom resolution) in Bouillet et al (2017); no further details were provided in Grumach et al (2022).
d Defined as absence of breathing and swallowing difficulty, and mildness or absence of voice change and tongue swelling.
e Random effects model; analysis using a fixed effect model also reported no statistically significant difference (MD 0.16 (95% CI -1.06 to 1.38; p=0.80).
f Defined as patients who required administration of rescue therapy (30 mg of icatibant with 500 mg of prednisolone).

Glossary

Adverse event	Any undesirable event experienced by a person while they are having a drug or any other treatment or intervention, regardless of whether the event is suspected to be related to or caused by the drug, treatment or intervention.
Allocation concealment	The process used to prevent (conceal) advanced knowledge of what intervention group people have been assigned to in a randomised controlled trial. It should be done by someone who is not responsible for recruiting people into the trial. The process prevents researchers from (unconsciously or otherwise) influencing which people are assigned to a given intervention group. Allocation concealment is different from blinding or masking; a double blind study can have unconcealed allocation and an open-label (unblinded) study can have concealed allocation.
Baseline	The set of measurements at the beginning of a study (after any initial 'run-in' period with no intervention), with which subsequent results are compared.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results, which is caused by the way the study is designed or conducted.
Blinding or masking	A way to prevent researchers, doctors and patients in a clinical trial from knowing which study group each patient is in so they cannot influence the results. The best way to do this is by sorting patients into study groups randomly. The purpose of 'blinding' or 'masking' is to protect against bias.
Comparator	The standard (for example, another intervention or usual care) against which an intervention is compared in a study. The comparator can be no intervention (for example, best supportive care).
Confidence interval (CI)	A way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. A wide confidence interval indicates a lack of certainty about the true effect of the test or treatment - often because a small group of patients has been studied. A narrow confidence interval indicates a more precise estimate (for example, if a large number of patients have been studied).
Confounding	In a study, confounding occurs when the effect of an intervention on an outcome is distorted because of an association between the population or intervention or outcome and another factor (the 'confounding variable' or 'confounder') that can influence the outcome independently of the intervention under investigation.
Cost effectiveness analysis	An analysis that assesses the cost of achieving a benefit by different means. The benefits are expressed in non-monetary terms related to health, such as life years gained (that is, the number of years by which life is extended as a result of the intervention). Options are often compared on the cost incurred to achieve 1 outcome (for example, cost per life year gained).

GRADE (Grading of recommendations assessment, development and evaluation)	A systematic and explicit approach to grading the quality of evidence and the strength of recommendations developed by the GRADE working group.
Heterogeneity	A term used in meta-analyses and systematic reviews to describe when the results of a test or treatment (or estimates of its effect) differ significantly in different studies. Such differences may occur as a result of differences in the populations studied, the outcome measures used or because of different definitions of the variables involved. It is the opposite of homogeneity.
Intention-to-treat analysis (ITT)	An assessment of the people taking part in a trial, based on the group they were initially (and randomly) allocated to. This is regardless of whether or not they dropped out, fully adhered to the treatment or switched to an alternative treatment. Intention-to-treat analysis (ITT) analyses are often used to assess clinical effectiveness because they mirror actual practice, when not everyone adheres to the treatment, and the treatment people have may be changed according to how their condition responds to it. Studies of drug treatments often use a modified ITT analysis, which includes only the people who have taken at least 1 dose of a study drug.
Meta-analysis	A method often used in systematic reviews to combine results from several studies of the same test, treatment or other intervention to estimate the overall effect of the treatment.
Off-label prescribing	A medicine with an existing marketing authorisation that is used outside the terms of its marketing authorisation, for example, by indication, dose, route or patient population.
PICO (population, intervention, comparison and outcome) framework	A structured approach for developing review questions that divides each question into 4 components: the population (the population being studied); the interventions (what is being done); the comparators (other main treatment options); and the outcomes (measures of how effective the interventions have been).
P-value (p)	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that 1 seems to be more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance), it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 0.1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Per protocol analysis (PP)	A comparison of treatment groups in a trial that includes only those patients who completed the treatment they were originally allocated to. If done alone, this analysis leads to bias.
Randomised controlled trial (RCT)	A study in which a number of similar people are randomly assigned to two (or more) groups to test a specific drug, treatment or other intervention. One group (the experimental group) has the intervention being tested, the other (the

	comparison or control group) has an alternative intervention, a dummy intervention (placebo) or no intervention at all. The groups are followed up to see how effective the experimental intervention was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias.
Relative risk/risk ratio	The probability of an event occurring in the study group compared with the probability of the same event occurring in the control group, described as a ratio. If both groups face the same level of risk, the relative risk is 1. If the first group had a relative risk of 2, subjects in that group would be twice as likely to have the event happen. A relative risk of less than 1 means the outcome is less likely in the first group. Relative risk is sometimes referred to as risk ratio. It will be very similar to the odds ratio when events are rare.
Reliability	The ability to get the same or similar result each time a study is repeated with a different population or group.
Retrospective study	A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected.
Standard deviation (SD)	A measure of the spread, scatter or variability of a set of measurements. Usually used with the mean (average) to describe numerical data.
Statistical significance	A statistically significant result is one that is assessed as being due to a true effect rather than random chance.
Systematic review	A study which involves systematically searching for evidence using pre-defined criteria. Relevant studies are selected and quality appraised. Evidence from multiple studies is extracted and reported and may be combined in a meta-analysis.
Validity	Whether a test or study actually measures what it aims to measure. Internal validity shows whether a study or test is appropriate for the question, for example, whether a study of exercise among gym members measures the amount of exercise people do at the gym, not simply whether people join. External validity is the degree to which the results of a study hold true in non-study situations, for example, in routine NHS practice. It may also be referred to as the generalisability of study results to non-study populations.

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NHS England
Wellington House
133-155 Waterloo Road
London
SE1 8UG