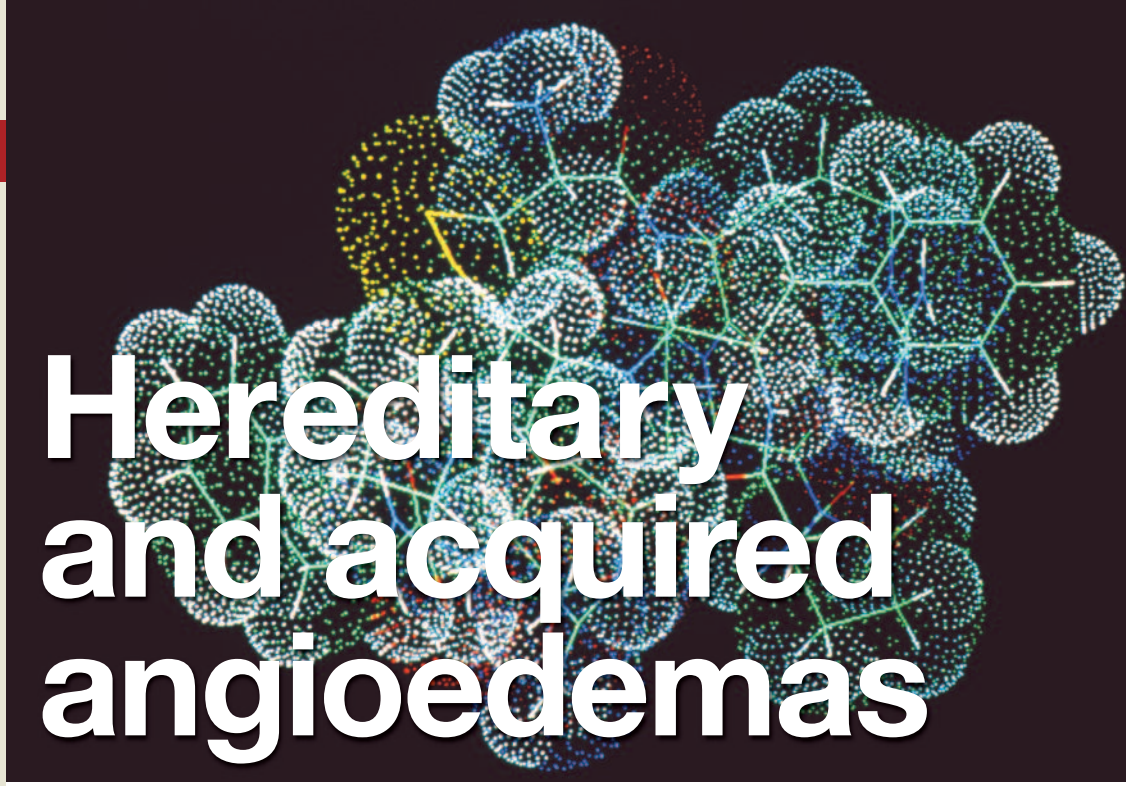
MedicineToday 2013; 14(4): 26-32

PEER REVIEWED FEATURE
POINTS: 2 CPD/2 PDP



Hereditary and acquired angioedemas

Rare but potentially life-threatening

CONSTANCE H. KATELARIS MB BS, PhD, FRACP

Angioedema without urticaria should prompt consideration of hereditary, or acquired, C1 inhibitor deficiency-associated and ACE inhibitor-induced angioedema. These rare forms require different management to urticaria-associated angioedema as they do not respond to antihistamines, corticosteroids and adrenaline.

Key points

- **Angioedema most often occurs in association with urticaria and usually then responds to treatments used for the urticaria.**
- **When angioedema occurs without urticaria, consider hereditary angioedema, acquired angioedema associated with C1 inhibitor deficiency and ACE inhibitor-induced angioedema.**
- **Hereditary angioedema is rare but must be identified as it can be life-threatening. Treatments include C1 INH concentrates, icatibant and ecallantide. Danazol and tranexamic acid are used for prophylaxis.**
- **Treatment of the underlying disease generally relieves symptoms in patients with the very rare acquired angioedema associated with C1 inhibitor deficiency.**
- **ACE inhibitor-induced angioedema is an important cause of angioedema in older people, and may be life-threatening.**

Angioedema may be defined as a sudden and pronounced swelling of the deep dermis and subcutaneous tissue or mucous membranes, with a painful rather than itching sensation, and a slower resolution than for urticaria, taking up to 72 hours for complete settling. It may be mediated by histamine following mast cell activation, or it may result from bradykinin accumulation by various mechanisms (see the box on page 27).[1]

Of patients with angioedema and/or chronic idiopathic urticaria (also known as chronic spontaneous urticaria), up to 50% have both conditions, up to 20% have angioedema alone and about 40% have urticaria alone.[2] Recently, an increase in the rate of hospital admissions for angioedema (3.0% per year) and urticaria (5.7% per year) has been observed in Australia.[3] The greatest increase in hospitalisations for urticaria was in those aged 15 to 34 years (7.8% per year). For angioedema, the rate of hospitalisation was highest in persons aged 65 years and older. It is not known if this increase has occurred in other countries. Among older persons, angioedema is becoming an increasing problem.[3] Angioedema of the upper airway can be life-threatening, and in rare cases, angioedema may progress to anaphylaxis.[3]

In patients with angioedema without urticaria, hereditary angioedema (HAE), acquired angioedema associated with complement

Professor Katelaris is Senior Staff Specialist, Department of Medicine, and Head of Unit, Division of Allergy and Clinical Immunology at Campbelltown Hospital; and Professor of Immunology and Allergy, University of Western Sydney, Sydney, NSW.

component 1 inhibitor (C1 INH) deficiency (AAE) and ACE inhibitor-induced angioedema should be considered (see the box on this page).[1] Unlike the angioedema associated with allergic or chronic idiopathic urticaria, these rarer types of angioedema have poor or no response to the antihistamines and corticosteroids used to treat urticaria, and require other management.

This article will discuss HAE, AAE and ACE inhibitor-induced angioedema. (Much of the article is based on the *ASCIA Position Paper on Hereditary Angioedema,* authored by the Australasian Society of Clinical Immunology and Allergy [ASCIA] HAE Working Party chaired by this author – see http://www.allergy.org.au/health-professionals/papers/hereditary-angioedema.[1])

HEREDITARY ANGIOEDEMA

HAE is a rare autosomal dominant disorder that has been described in three forms: types 1, 2 and 3. Type 1 HAE (about 85% of cases) and type 2 HAE (about 15% of cases) result from deficiency in functional C1 INH, either from low absolute levels (type 1) or production of a dysfunctional protein (type 2).[4] In types 1 and 2 HAE, in the absence of adequate levels or function of C1 INH, subcutaneous and submucosal oedema results from the uninhibited action of vasoactive mediators, the most important of which is considered to be bradykinin. Type 3 HAE is now known as HAE with normal C1 INH levels. Reported mostly in females, it is very rare, and in some families it may be caused by a mutation in the factor XII gene.

HAE is characterised by recurrent nonitchy and nonpitting oedema of the limbs, trunk, face and sometimes genitals, without urticaria, that typically takes 24 hours to peak and resolves over 48 to 72 hours. Visceral swelling of the gastrointestinal tract results in abdominal pain, vomiting and, when severe, shock. Laryngeal swelling is the most serious manifestation, and may be life-threatening. Attacks may be preceded by a prodrome of tingling or nonitchy rash anywhere on the body.

The true prevalence of HAE remains unknown; estimates range from one case in 10,000 individuals to one in 150,000 individuals.[4] There are no known ethnic or gender differences seen with types 1 and 2 HAE.

C1 INH is a protein that inhibits the action of serine proteases. Its major activity is inhibition of several complement components (C1r, C1s and mannose-binding lectin associated-serine protease [MASP]) and contact system proteases (plasma kallikrein and coagulation factor XIIa). During episodes of HAE, these plasma proteolytic cascades are activated and several vasoactive substances are released. Studies have shown that bradykinin is the predominant mediator of enhanced vascular permeability. Bradykinin is generated by activation of the contact system. It binds to its cognate receptor (the bradykinin B2 receptor) on vascular endothelial cells, thereby mediating its effects of increasing vascular permeability, activating inflammation and producing pain and swelling.

HAE should be suspected when a patient presents with recurrent angioedema without urticaria that is unpredictable in its onset but often follows a trigger such as trauma and is associated with recurrent abdominal pain and upper airway swelling.

Clinical presentation of HAE

HAE attacks in an individual follow a typical but not invariable pattern. Prodromal symptoms such as fatigue, flu-like symptoms, indigestion, tingling and, sometimes, a nonurticarial, nonpruritic macular serpiginous erythema (erythema marginatum) may precede the onset of swelling.

Cutaneous angioedema and abdominal pain are the most frequent clinical manifestations of HAE, occurring in about 50% and 48% of episodes, respectively;

CLASSIFICATION OF ANGIOEDEMA[1]*

Histamine-induced angioedema (mast cell-dependent) – most cases

- Idiopathic histamine-induced angioedema
- Allergic angioedema (e.g. IgE-mediated food or drug allergy)
- Drug-induced histamine-dependent angioedema (e.g. NSAID intolerance)

Suspect mast cell-dependent angioedema when:

- Accompanied by urticaria or other features of anaphylaxis
- Has obvious trigger (i.e. drug, food)
- Responds to antihistamines (for treatment or prevention)

Bradykinin-induced angioedema

- Hereditary angioedema (HAE) type 1 – due to C1 inhibitor (C1 INH) deficiency
- HAE type 2 – due to C1 INH dysfunction
- HAE type 3 – with normal C1 INH levels and function†
- Acquired angioedema associated with C1 INH deficiency (AAE)
- ACE inhibitor-induced angioedema – acquired but not due to C1 INH deficiency
- Idiopathic bradykinin-induced angioedema

Trial of antihistamines and corticosteroids is indicated in patients with bradykinin-induced angioedema until diagnosis is confirmed.

* Adapted with permission from *ASCIA Position Paper on Hereditary Angioedema.*[1]

† HAE type 3 is now known as HAE with normal C1 INH levels.

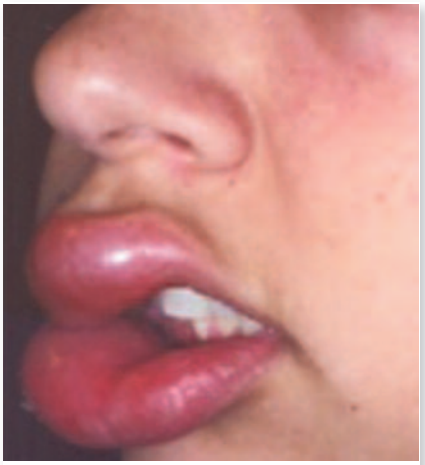


Figure 1. Cutaneous angioedema.

oropharyngeal swelling is a much less frequent manifestation.[5] Cutaneous angioedema, a nonpitting and nonpruritic swelling, usually affects the face, limbs or genitals (Figure 1). Nausea, vomiting, dehydration, diarrhoea or constipation frequently accompany the abdominal pain, and acute attacks can mimic surgical emergencies and result in unnecessary appendectomy or exploratory laparotomy. Laryngeal swelling, which occurs in about 0.9% of episodes, can cause death from asphyxiation.

The features of HAE that distinguish it from other forms of angioedema are summarised in the Table.[1]

Testing for HAE

Testing for HAE should be carried out if there is a clinical suspicion of the disorder in a patient of any age. If the diagnosis is confirmed, family members should be screened as well.

The tests available for screening and diagnosis of HAE include measurement of complement component 4 (C4) and C1 INH serum levels and C1 INH functional activity. The C4 level is used in screening, and in an untreated patient, a normal C4 level makes the diagnosis of HAE unlikely. Serum C4 levels are invariably low during attacks but may be normal in about 2% of cases between attacks.[6]

In patients with isolated angioedema where clinical suspicion of HAE is low, screening with C4 levels may be adequate.

Management of HAE

Many patients who present with recurrent angioedema before the diagnosis of HAE is made will receive a variety of treatments, including antihistamines, corticosteroids and adrenaline. None of these drugs are effective in the management of HAE attacks, and this lack of efficacy should alert the clinician to a possible diagnosis of HAE.

Management of HAE consists of treatment of acute attacks as well as planned prophylaxis for patients with frequent attacks. More information on management of HAE is available on the ASCIA website (http://www.allergy.org.au/-health-professionals/papers/hereditary-angioedema).

Prophylaxis

Two drugs are available for long-term prophylaxis of angioedema in patients with HAE: danazol and tranexamic acid. In addition, short-term prophylaxis is given before procedures such as invasive dental work or surgery to prevent the possibility of swelling triggered by these interventions. Traditionally, C1 INH concentrate has been used for short-term prophylaxis, although an increased dose of danazol can be used instead.

Treatment of acute episodes

The options available for the treatment of severe acute episodes of angioedema in patients with HAE include two replacement C1 INH preparations (C1 INH concentrates), a bradykinin receptor antagonist (icatibant) and a kallikrein inhibitor (ecallantide). Fresh frozen plasma has been used for the management of acute attacks but has had a detrimental effect in some patients because it provides not only C1 INH but also more substrate. The use of fresh frozen plasma cannot be recommended now there are specific therapies available.

C1 INH concentrates

The human C1 INH concentrate Berinert was for many years the only C1 INH product available in Australia. It is a highly purified, freeze-dried C1 INH derived from human plasma, and contains 500 units (U) of C1 INH per vial (50 U/mL). Administration to patients with C1 INH deficiency replaces the missing or malfunctioning C1 INH protein, resulting in relief from the symptoms of HAE. Berinert is administered intravenously.

Berinert has been used for over 30 years in more than 400,000 treatments and has an excellent safety record.[7] It was approved by the TGA in January 2010 for the treatment of acute attacks in patients with HAE, and the recommended dose is 20 U/kg body weight. Berinert is expensive (A$1700 per vial) and is usually funded through hospital budgets. National Blood Authority (NBA) funding is being sought.

The human nanofiltered C1 INH concentrate Cinryze is, like Berinert, purified from human plasma. Although not approved by the TGA for use in Australia, Cinryze achieved orphan drug designation in this country in 2010 for the treatment, routine prevention and pre-procedure prevention of angioedema attacks in adults, adolescents and children from 6 years of age with C1 INH deficiency. This designation was the result of evidence of efficacy from international studies showing Cinryze's efficacy in prophylaxis and treatment of HAE attacks.[8] It is also indicated for the routine prevention of angioedema in adults and adolescents with frequent attacks of HAE who are intolerant to or insufficiently protected by oral therapy. Currently, Cinryze is not funded in Australia and is similar in price to Berinert.

There are no contraindications to use of either Berinert or Cinryze in children or during pregnancy or lactation.

TABLE. FEATURES DISTINGUISHING HEREDITARY ANGIOEDEMA FROM OTHER FORMS OF ANGIOEDEMA[1]*

Symptoms/signs	Hereditary angioedema	Acquired angioedema	Allergic/IgE-mediated angioedema
Angioedema	Yes	Yes	Yes
Urticaria	No	No	Usually
Age of onset (most frequent)	6 to 20 years	Over 50 years	Anytime
Family history	Usually	No	Variable
Underlying disease	No	Yes	No
Location of swelling	All	All	Especially face, lips
Precipitation by trauma	Yes	Yes	No
Duration of swelling	48 to 72 hours	48 to 72 hours	2 to 48 hours
Response to treatment with antihistamine, corticosteroids, adrenaline	No	No	Yes

* Reproduced with permission from *ASCIA Position Paper on Hereditary Angioedema*.[1]

A future use of C1 INH concentrate may be its 'on demand use' as individual replacement therapy. This would involve individuals having prompt access to the product for administration at the earliest sign of an attack. Ideally, patients or family members would be trained to administer the product at home.

Bradykinin receptor antagonist

Icatibant (Firazyr) is a synthetic peptidomimetic bradykinin B2 receptor antagonist with high specificity. Its mode of action, therefore, is to prevent binding of bradykinin to the receptor and the subsequent increased vascular permeability, inflammation, pain and swelling associated with HAE.

Icatibant was registered in Australia in 2010 and as of 1 August 2012 has been funded by the PBS as an authority item. It can be supplied to patients via community pharmacies.

Patients may hold their own icatibant supply (a prefilled syringe) either for self-administration or for administration by a trained companion or a medical professional at a clinic or hospital. It is administered subcutaneously, and can be stored at room temperature and therefore taken when travelling. As such, icatibant is a major step forward in the management of patients with HAE.

Efficacy of icatibant has been examined in several clinical trials.[9-11] The latest of these, the For Angioedema Subcutaneous Treatment (FAST-3) study, was a placebo-controlled randomised double-blind trial in 88 patients with HAE presenting with acute episodes affecting the abdomen, periphery or airway.[11] The primary endpoint of median time to 50% or more reduction in symptom scores was significantly different between active treatment (two hours) and placebo (19.8 hours), without significant adverse events. The time to initial symptom relief was 0.8 hour for active treatment versus 3.5 hours for placebo.

The parameters of efficacy of icatibant (time to effect, degree of effect and adverse effects) are broadly similar to those of C1 INH products, although direct comparisons have not been made. Icatibant has the advantages of lack of blood product-associated risks, lower cost and subcutaneous administration. It has the potential for use in acquired forms of angioedema and, in particular, ACE inhibitor-induced angioedema (it is, however, not approved for this application).

Kallikrein inhibitor

Ecallantide (Kalbitor) is a potent and specific inhibitor of plasma kallikrein, which plays a major role in the contact (kallikrein–kinin) cascade producing bradykinin. Ecallantide is given via the subcutaneous route and is a nonplasma-derived therapy. Because it bypasses the C1 INH pathway, it shows potential in treating not just HAE but also the acquired forms of angioedema that can occur secondary to blood malignancies or autoimmune disease (i.e. AEE; see below).

Ecallantide has been approved by the Food and Drug Administration in the USA for the treatment of acute attacks of angioedema in adults but is not yet available in Australia.

General management recommendations for HAE

Individuals with HAE should be counselled about avoiding and managing triggers for their angioedema episodes. Specific advice about oestrogen-containing oral contraceptive pills (OCPs), ACE inhibitors, acute stress and trauma is given below.

- OCPs – progesterone-only pills, such as levonorgestrel, are generally preferred.

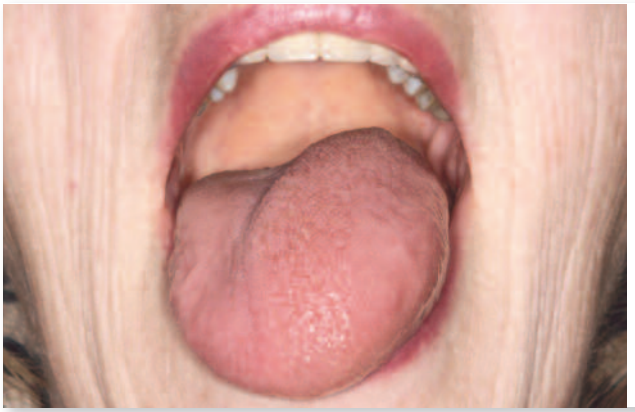


Figure 2. Swollen tongue in a 70-year-old woman, probably caused by the ACE inhibitor she was taking.

- ACE inhibitors – use of alternative antihypertensive agents is strongly recommended (angiotensin-converting enzyme is involved in the breakdown of bradykinin, hence its inhibition causes accumulation of bradykinin).
- Doses of danazol, if used as prophylaxis, should be increased during infections and times of acute stress or trauma.
- Stress management techniques should be used if stress is an identified factor in an individual.
- Trauma such as prolonged pressure on the skin (e.g. when using tools) should be avoided.

As mentioned earlier, patients may now have the opportunity to keep individual supplies of icatibant for use for significant acute attacks. They should receive training on its administration at the time of prescription.

ASCIA has produced an individualised care plan, the *ASCIA Hereditary Angioedema (HAE) Action Plan 2012*, which lists symptoms and appropriate treatment for HAE of different degrees of severity (see http://www.allergy.org.au/health-professionals/papers/hereditary-angioedema). Patients can give this plan and an accompanying letter from their specialist to any treating physician unfamiliar with the individual and the condition. Ideally, a patient's local emergency department will have an alert system in place to fast-track the patient when they present.

Patients should be advised of the HAE patient advocacy organisation, HAE Australia, which may be contacted via its website (http://www.haeaustralia.org.au).

ACQUIRED ANGIOEDEMA ASSOCIATED WITH C1 INHIBITOR DEFICIENCY

Acquired angioedema associated with C1 INH deficiency (AAE) usually has its onset in middle age, with those affected experiencing symptoms similar to those of HAE attacks (see the Table). However, there is no family history. As in HAE, the attacks do not respond to antihistamines or corticosteroids.

AAE results from increased destruction or metabolism of C1 INH. Two types of AEE are described:[4]

- type 1 – typically occurs in association with B-cell lymphoproliferative and rheumatological disorders. Patients have circulating anti-idiotypic antibodies to immunoglobulins on the surface of B cells. Complexes formed between these antibodies and immunoglobulins continuously activate C1. C1 INH is consumed as it inactivates this C1, and C1 INH levels decline below normal as synthesis cannot keep up with consumption
- type 2 – characterised by formation of autoantibodies directed against C1 INH. Binding of these to C1 INH results in its inactivation.[12]

The prognosis for patients with AAE is variable and depends on effective control of the underlying disorder. Even with appropriate treatment of the underlying disease, patients may only temporarily be free of symptoms.

ACE INHIBITOR-INDUCED ANGIOEDEMA

ACE inhibitor-induced angioedema (also known as ACE inhibitor angioedema) is now, anecdotally, the most common exogenous cause of angioedema seen in emergency departments. Studies have shown that it develops in 0.1 to 0.5% of patients receiving ACE inhibitors, with up to 20% of presentations being life-threatening.[13,14] With many older people now taking ACE inhibitors, ACE inhibitor-induced angioedema has become an important cause of angioedema in this age group. Genetic factors may be important. Patients with a history of angioedema from other causes are more susceptible to this form of angioedema.

ACE inhibitor-induced angioedema can cause dramatic swelling of the tongue, pharynx or larynx, and patients may require urgent intubation or tracheostomy (Figure 2). There is usually no associated urticaria, and symptoms resolve within 24 to 48 hours of cessation of the drug. ACE inhibitor-induced angioedema can occur at any time during use of the drug, from the first week of use to after many years of use, and may follow a dose change. Several risk factors have been identified, including obesity, prior endotracheal intubation and face and neck surgery. The condition is more common in females and in African Americans, but the reasons for these factors predisposing to angioedema are not known.[13]

ACE inhibitor-induced angioedema is most commonly seen with captopril and enalapril but has been described with all drugs within the class. It occurs as a consequence of increased bradykinin levels resulting from inhibition of angiotensin-converting enzyme-mediated degradation of kinin.

Because ACE inhibitors are likely to trigger attacks in patients with HAE,

acquired C1 INH deficiency or a history of idiopathic urticaria, this class of drug should be avoided in these patients.[14]

Management of patients presenting with ACE inhibitor-induced angioedema is generally supportive, with preparedness to intubate if necessary. Generally there is a poor response to antihistamines and adrenaline. Icatibant and ecallantide, although not approved for this indication, appear very effective.

Angiotensin receptor antagonists are considered to be safe in patients who have had ACE inhibitor-induced angioedema, and offer an alternative treatment when ACE inhibitors are withdrawn.

SUMMARY

HAE, AAE and ACE inhibitor-induced angioedema are rare forms of angioedema that should be considered in patients with angioedema without urticaria. Although angioedema associated with allergic or chronic idiopathic urticaria generally resolves with antihistamine treatment of the associated urticaria, these other forms have no or poor response to antihistamines, corticosteroids and adrenaline, and require other management.

In patients with HAE, danazol and tranexamic acid are appropriate for prophylaxis, and C1 INH concentrates (expensive and not PBS listed), icatibant (PBS listed) and ecallantide (not available in Australia) are appropriate for the treatment of severe episodes. In patients with AAE, treatment of the underlying disease generally relieves symptoms. In patients with ACE inhibitor-induced angioedema, withdrawal of the ACE inhibitor and supportive management is appropriate, with intubation if necessary. Angiotensin receptor antagonists may be used as an alternative when ACE inhibitors are withdrawn. MT

REFERENCES

1. Katelaris C, Smith W, Mullins R, Gillis D; Australasian Society of Clinical Immunology and Allergy (ASCIA). ASCIA position paper on hereditary angioedema. Sydney: 2012. Available online at: http://www.allergy.org.au/health-professionals/papers/hereditary-angioedema (accessed March 2013).
2. Kaplan A. Clinical practice. Chronic urticaria and angioedema. N Engl J Med 2002; 346: 175-179.
3. Poulos LM, Waters AM, Correll PK, Loblay RH, Marks GB. Trends in hospitalizations for anaphylaxis, angioedema and urticaria in Australia, 1993-1994 to 2004-2005. J Allergy Clin Immunol 2007; 120: 878-884.
4. Nzeako UC, Frigas E, Tremaine WJ. Hereditary angioedema: a broad review for clinicians. Arch Intern Med 2001; 161: 2417-2429.
5. Bork K, Meng G, Staubach P, Hardt J. Hereditary angioedema: new findings concerning symptoms, affected organs, and course. Am J Med 2006; 119: 267-274.
6. Bowen T, Cicardi M, Bork K, et al. Hereditary angioedema: a current state-of-the-art review, VII: Canadian Hungarian 2007 international consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. Ann Allergy Asthma Immunol 2008; 100: (1 Suppl 2): S30-S40.
7. Bernstein JA, Levy R, Wasserman A, et al. Treatment of acute abdominal and facial attacks of hereditary angioedema (HAE) with human C1-esterase inhibitor (C1-INH): results of a global, multicenter, randomized, placebo-controlled, phase II/III study (I.M.P.A.C.T.1). [Abstract LB16.] J Allergy Clin Immunol 2008; 121: 795.
8. Craig T, Levy RJ, Wasserman RL, et al. Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema. J Allergy Clin Immunol 2009; 124: 801-808.
9. Bork K, Frank J, Grundt B, Schlattmann P, Nussberger J, Kreuz W. Treatment of acute edema attacks in hereditary angioedema with a bradykinin receptor-2 antagonist (Icatibant). J Allergy Clin Immunol 2007; 119: 1497-1503.
10. Cicardi M, Banerji A, Bracho F, et al. Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. N Engl J Med 2010; 363: 532-541.
11. Lumry WR, Li HH, Levy RJ, et al. Randomized placebo-controlled trial of the bradykinin B_2 receptor antagonist icatibant for the treatment of acute attacks of hereditary angioedema: the FAST-3 trial. Ann Allergy Asthma Immunol 2011; 107: 529-537.
12. Zuraw BL. Urticaria, angioedema, and autoimmunity. Clin Lab Med 1997; 17: 559-569.
13. Vleeming W, van Amsterdam JG, Stricker BH, de Wildt DJ. ACE inhibitor-induced angioedema. Incidence, prevention and management. Drug Saf 1998; 18: 171-188.
14. Sabroe RA, Black AK. Angiotensin-converting enzyme (ACE) inhibitors and angio-oedema. Br J Dermatol 1997; 136: 153-158.

COMPETING INTERESTS: Professor Katelaris previously participated in multicentre trials of C1 INH concentrate and icatibant in patients with hereditary angioedema.