New Approaches to Treatment of Hereditary Angioedema

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Disclosures

- Shire: Advisory Board, Research
- CSL Behring: Advisory Board
- Dyax: Consulting

Objectives

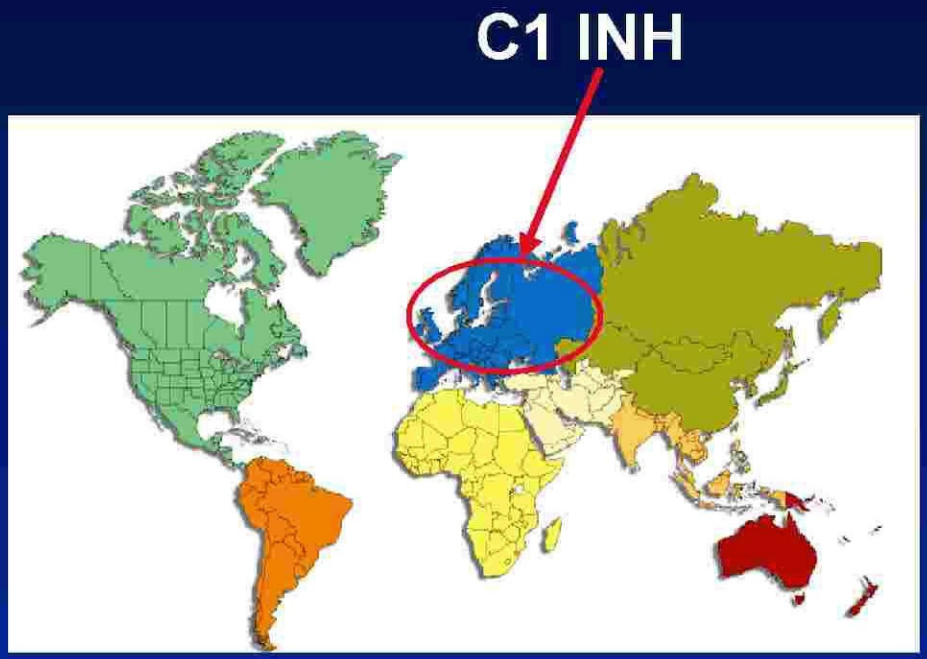
- Discuss novel treatment options for hereditary angioedema
- Review consensus guidelines for the treatment of hereditary angioedema
- Compare long-term prophylaxis vs. on-demand treatment
- Discuss the benefits of self-administration for patients

Hereditary Angioedema Treatment Goals

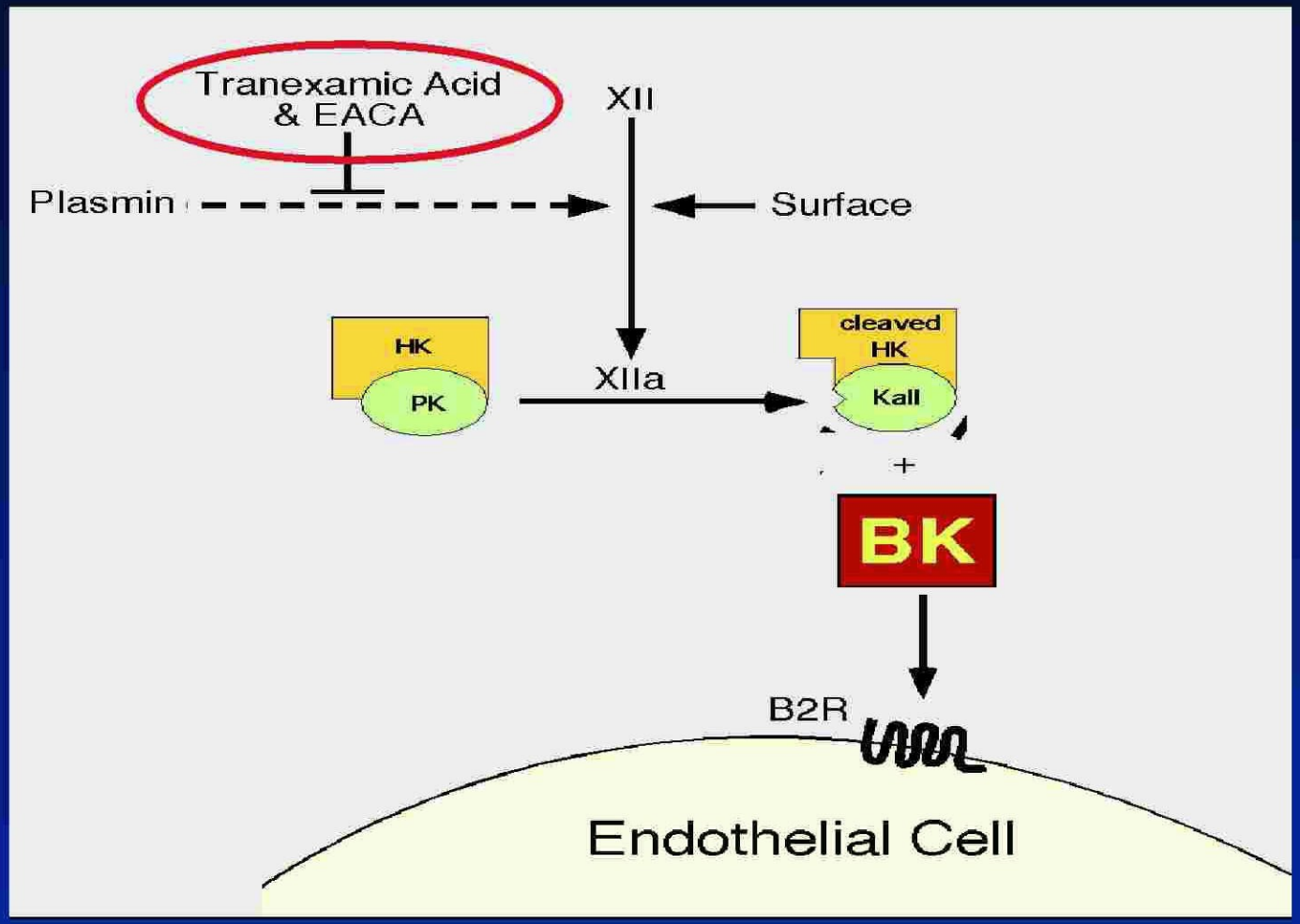
- On-demand treatment of acute attacks
  - To abort an ongoing attack of angioedema
  - To prevent an angioedema attack from affecting quality of life
- Prophylactic treatment
  - Short-term prophylaxis to prevent an expected attack especially in the setting of exposure to known triggers
  - Long-term prophylaxis to minimize the frequency and severity of recurrent attacks

"Older" Options for Treatment of HAE

- Treatment of acute attacks
  - Supportive Care
  - FFP
- Long-term prophylaxis
  - Anabolic Androgens
  - Antifibrinolytics
- Short-term prophylaxis
  - FFP
  - Anabolic androgens



Antifibrinolytics for Hereditary Angioedema



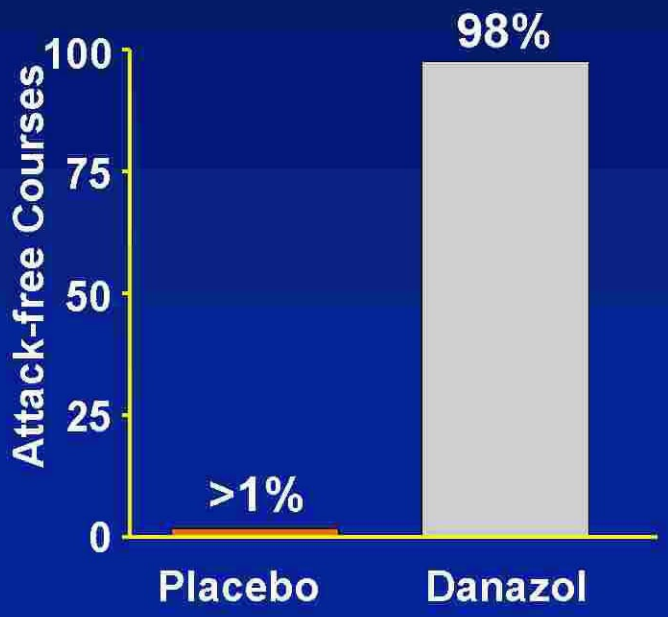
Side Effects of Antifibrinolytic Agents

- Most common side effects
  - Nausea, vomiting and diarrhea
  - Vertigo
  - Postural hypotension
  - Fatigue and myalgias
- Theoretical concerns
  - Risk of vascular thrombosis
  - Teratogenicity

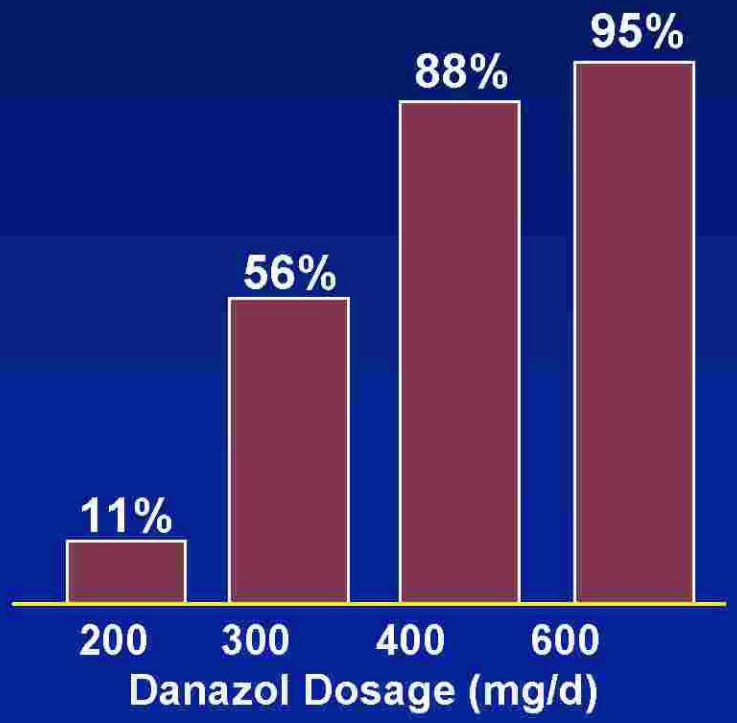
Androgens

Danazol, Stanozolol, Oxandrolone, Methyltestosterone

Danazol: Freedom from HAE Attacks vs Placebo



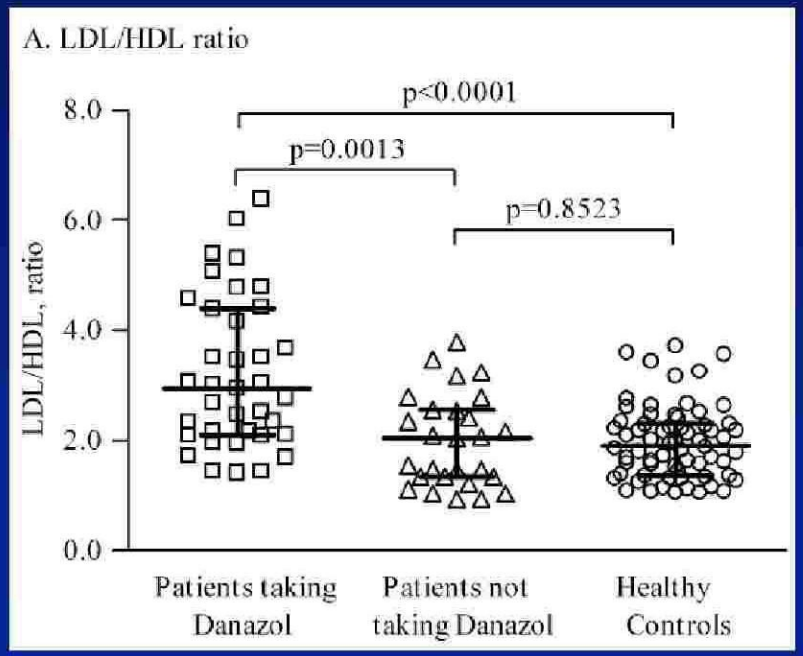
Danazol: Cumulative Freedom from HAE Attacks at Varying Dosages

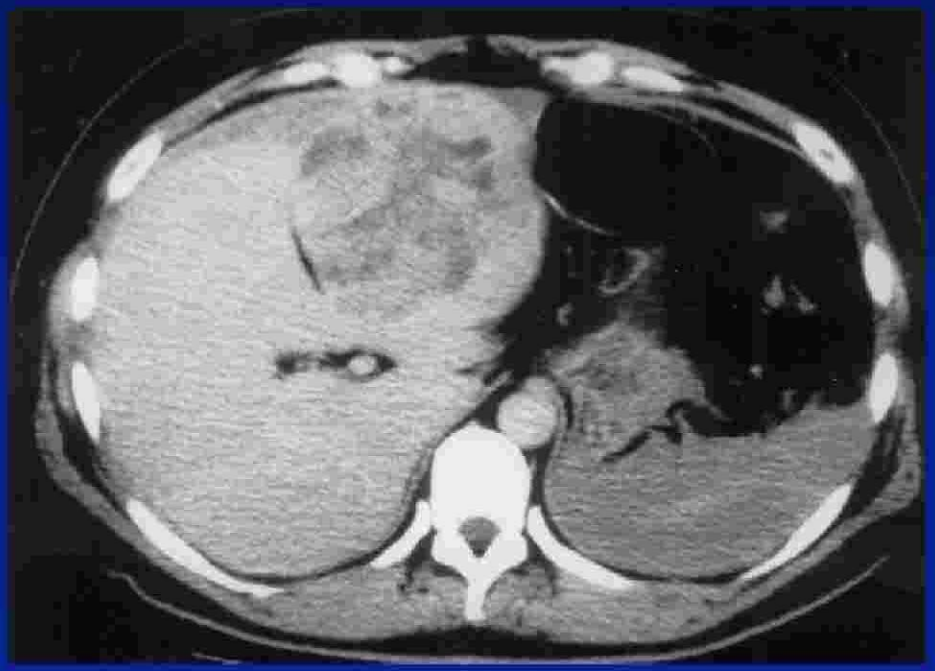


Frank M. Immunol Allergy Clin N Am 2006
Gelfand JA et al., N Engl J Med 1976

Androgens: Adverse Reactions & Side Effects

Virilization, hepatotoxicity, headache, hypertension, weight gain, menstrual abnormalities, acne, altered mood, altered libido



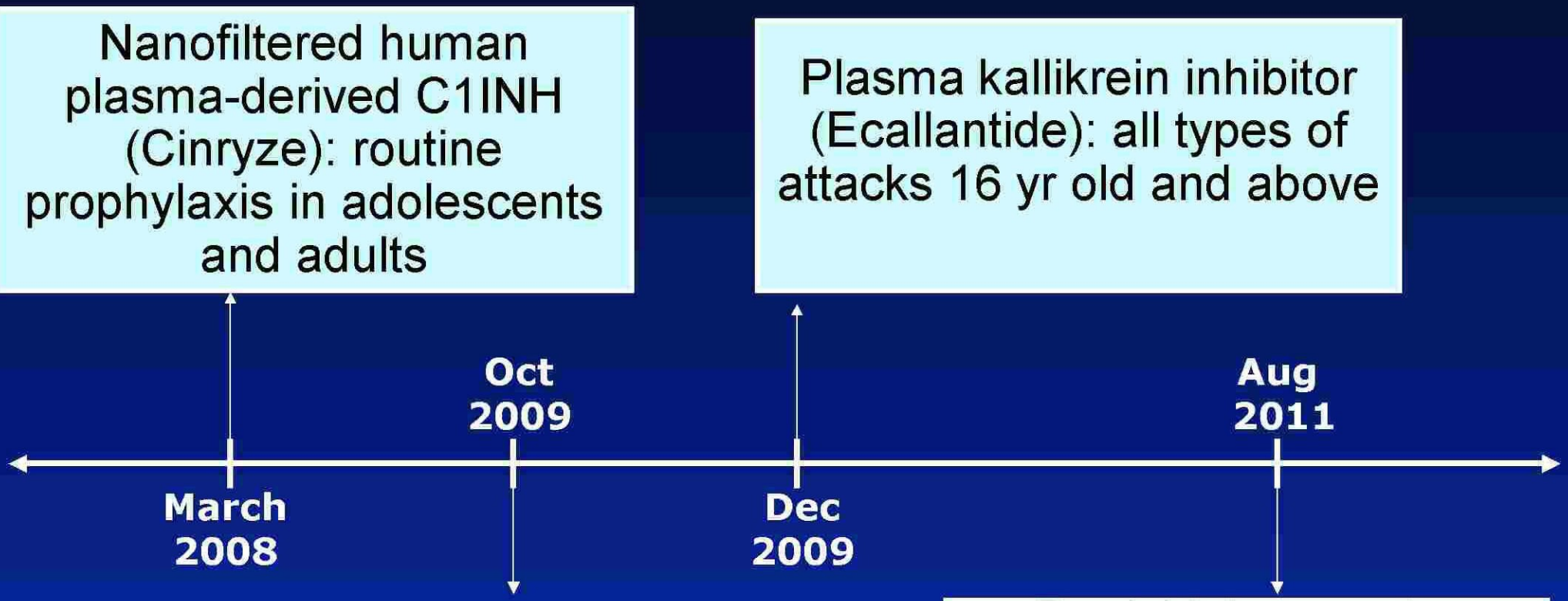


Széplaki et al. J Allergy Clin Immunol 2005
Bork K, Schneiders V. J Hepatol 2002

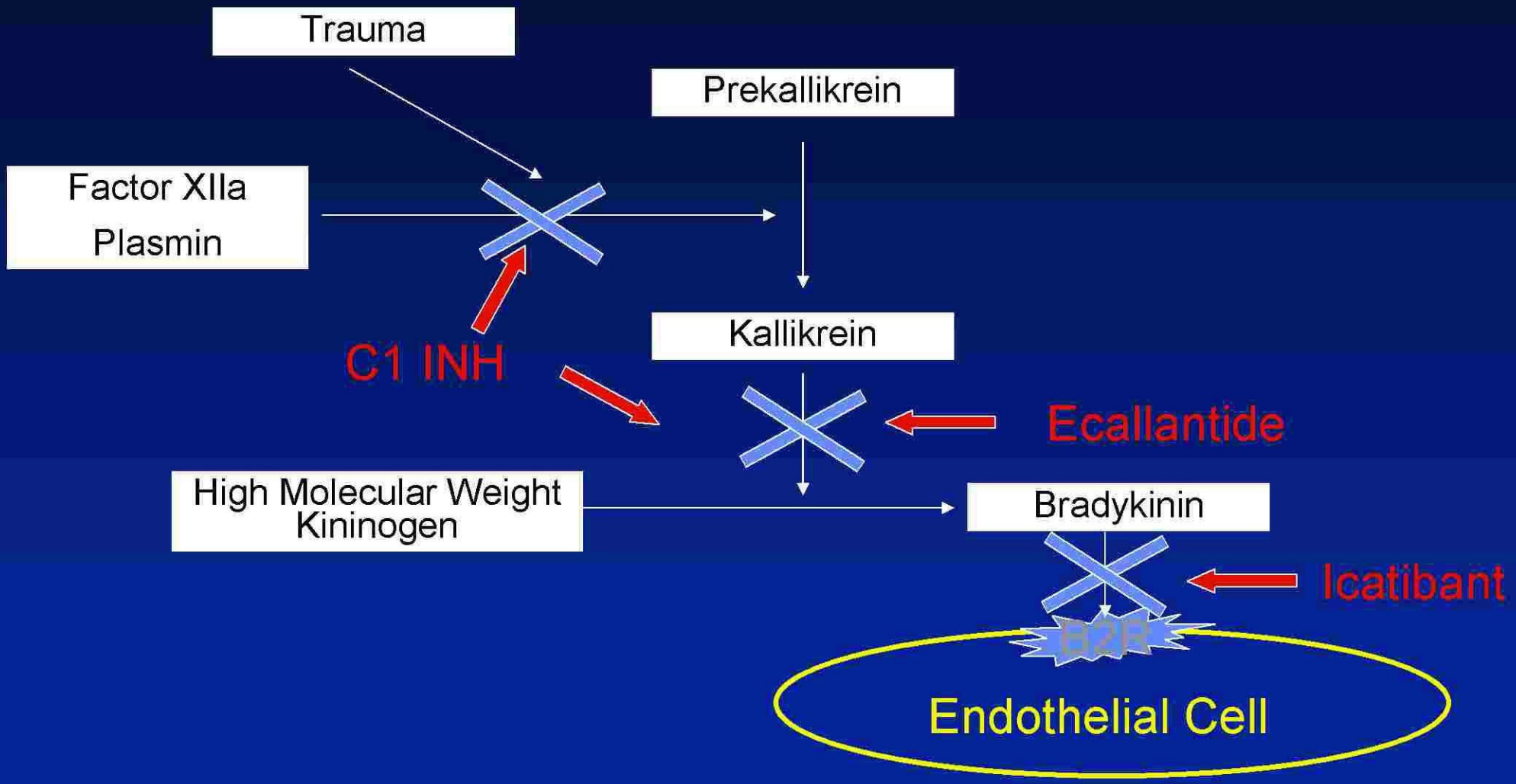
Treatment with Danazol

- Adverse effects increase with dosage and duration of therapy
- The lowest effective dose should be used for maintenance
- Can start with higher dose and taper every 2-4 weeks to achieve symptomatic control
  - Alternatively, start low dose and increase dose every 2-4 weeks to achieve symptom control
- Monitor liver function tests periodically

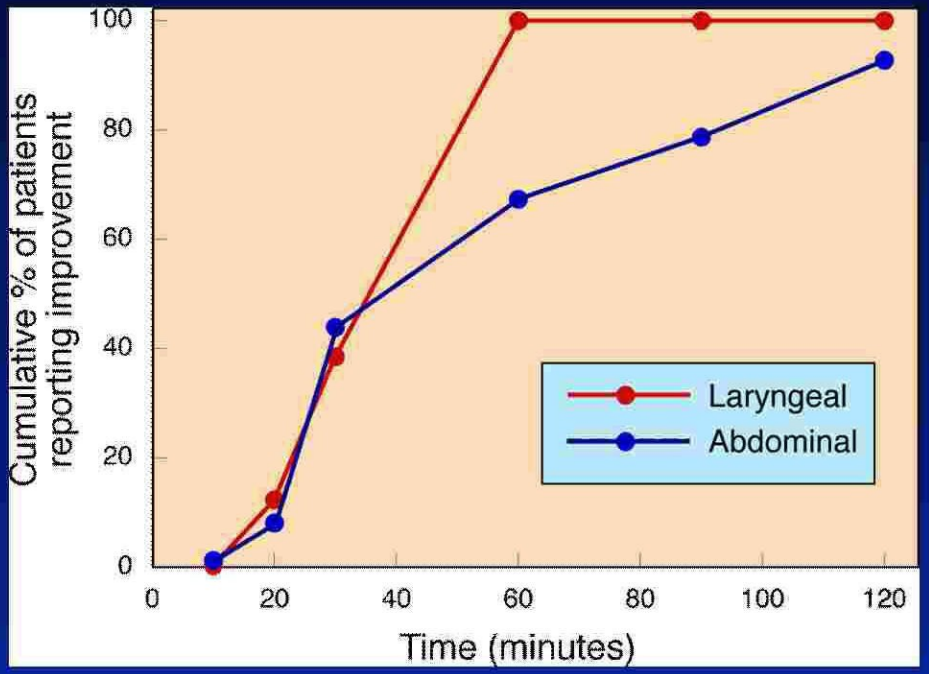
FDA Approval of "Newer" Treatment Options



"Newer" Treatments for Hereditary Angioedema



Plasma C1-INH Replacement Therapy

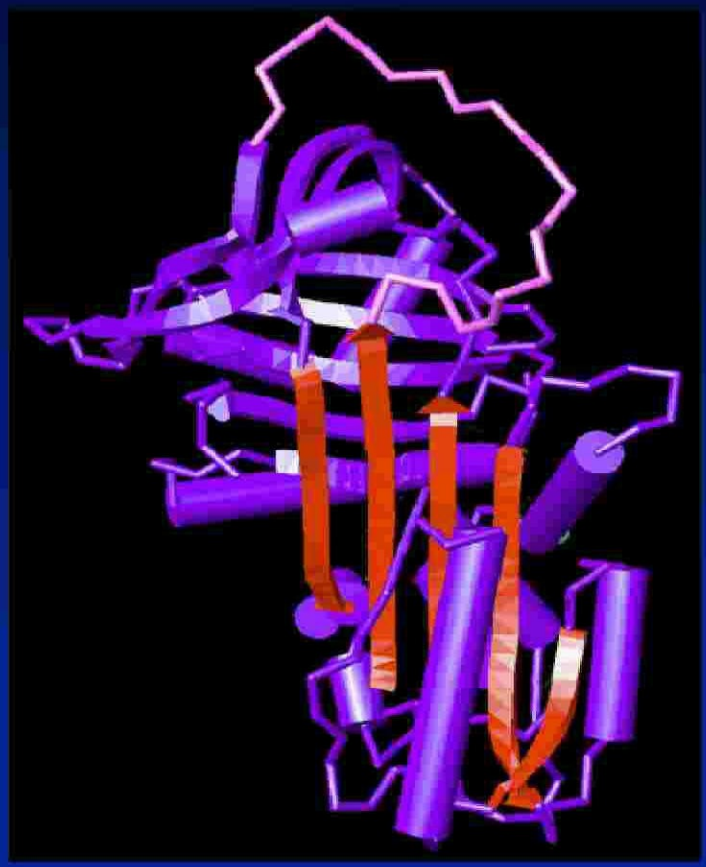


- Efficacy first demonstrated >25 years ago
- Response rate of virtually 100%
  - 629/630 attacks
  - 193/193 laryngeal attacks

Bork K, Barnstedt SE. Arch Intern Med 2001
Bork K, et al. Transfusion 2005

C1INH Concentrate

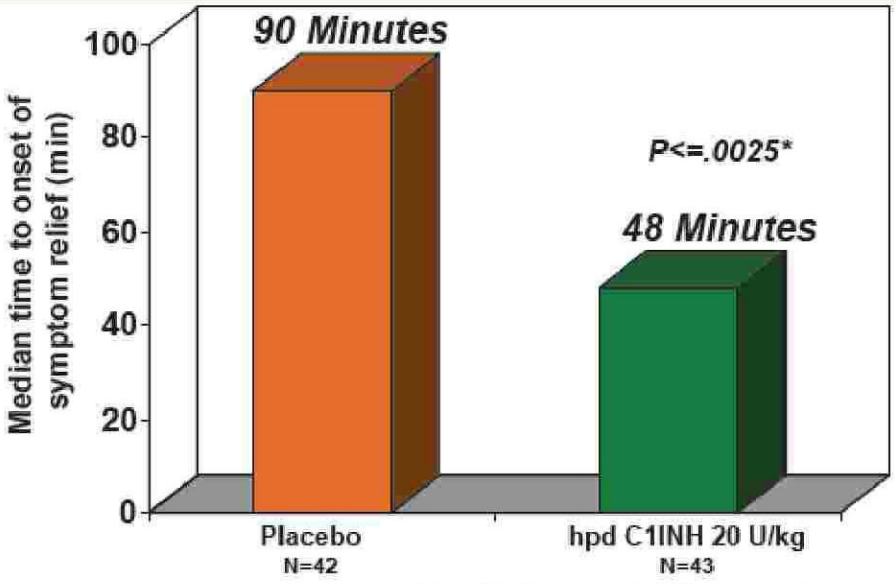
- Pasteurized C1INH Concentrate (Berinert)
- Nanofiltered C1INH Concentrate (Cinryze)
- Recombinant C1INH (Rhucin)



Pasteurized Plasma C1INH Concentrate (Berinert)

Phase III DBPC study: International Multicenter Prospective Angioedema C1INH Trial (IMPACT)

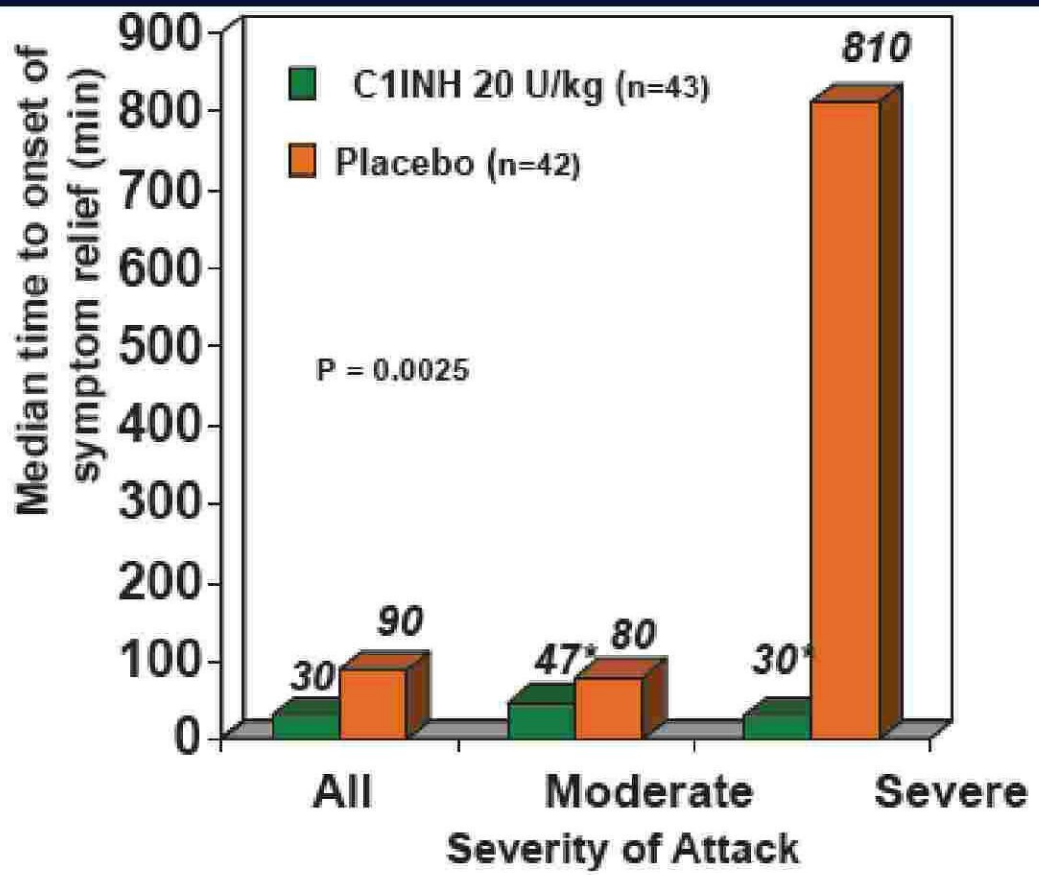
- Pasteurized product used for over 20 years in Europe with >300,000 acute attacks treated
- No drug-related safety issues



Craig TJ et al., *JACI* 2009;124:801-808.

*One-sided two-sample Wilcoxon test for comparison to placebo.
Note: Patient reported. Time to onset of symptom relief was set to 24 hours if a subject received rescue study medication.

Pasteurized Plasma C1INH Concentrate (Berinert)

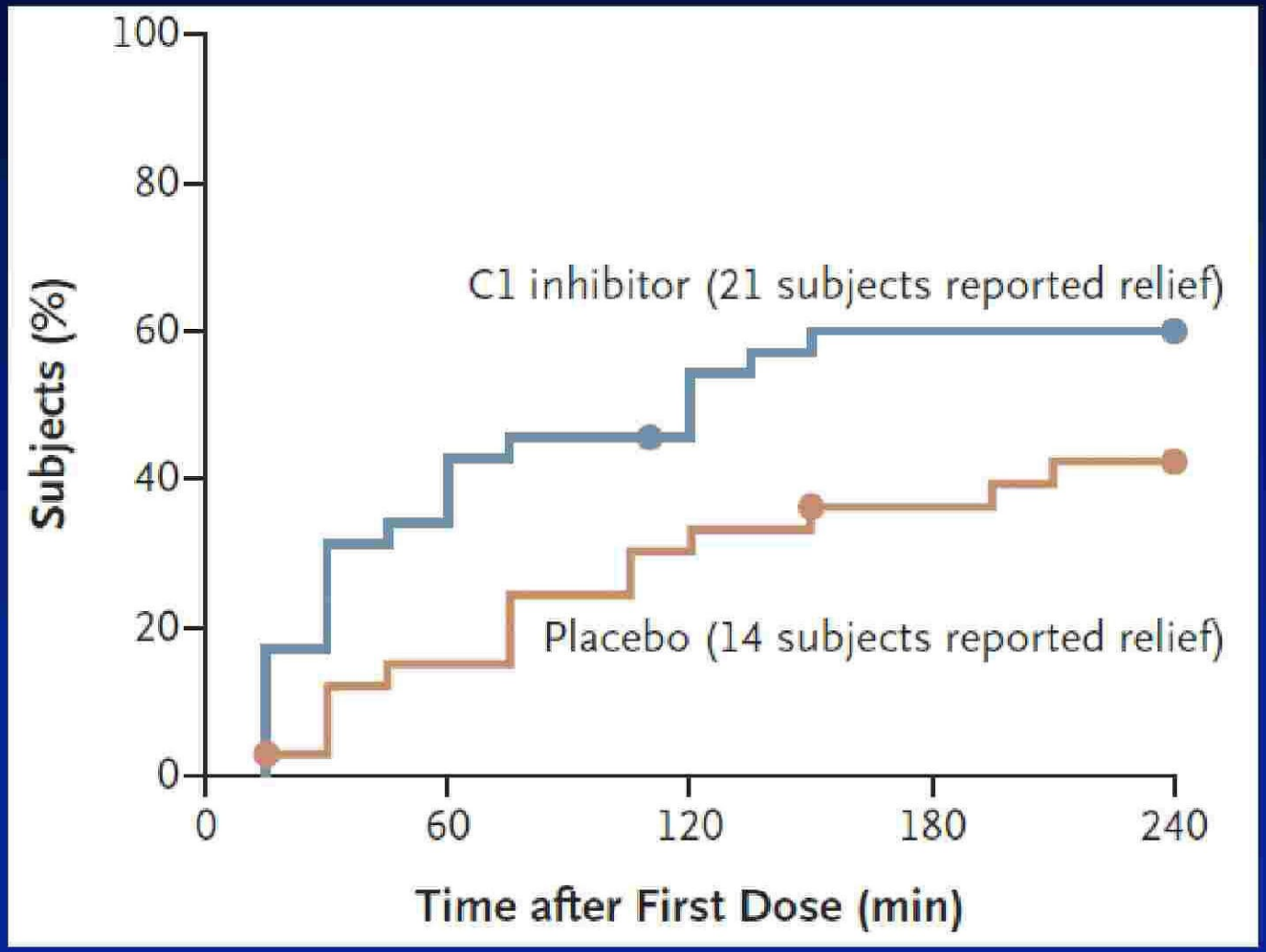


Craig TJ et al., *JACI* 2009;124:801-808.

*Significance testing was applied only for primary endpoints and not for subgroup analyses.

Nanofiltered Plasma C1-INH Concentrate (Cinryze)

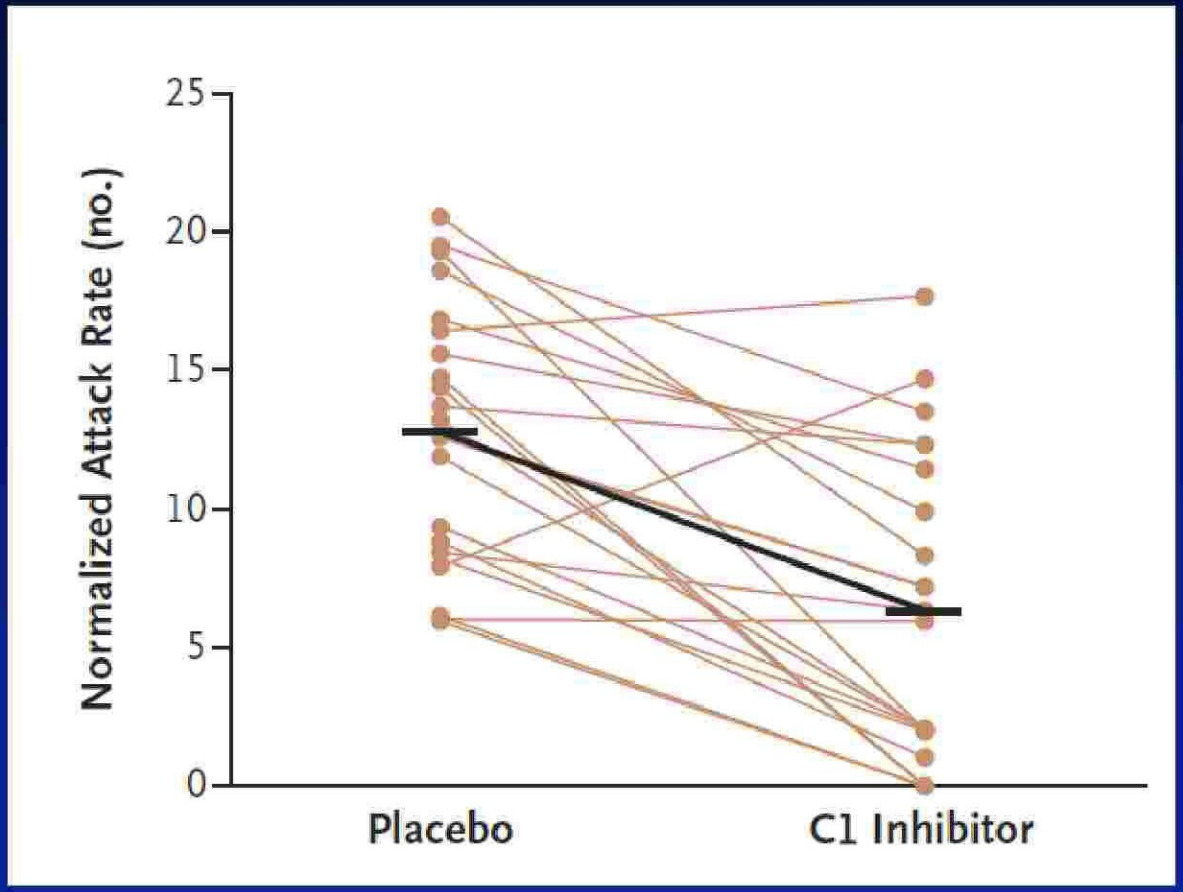
Acute Treatment



Zuraw et al., NEJM 2010

Nanofiltered Plasma C1-INH Concentrate (Cinryze)

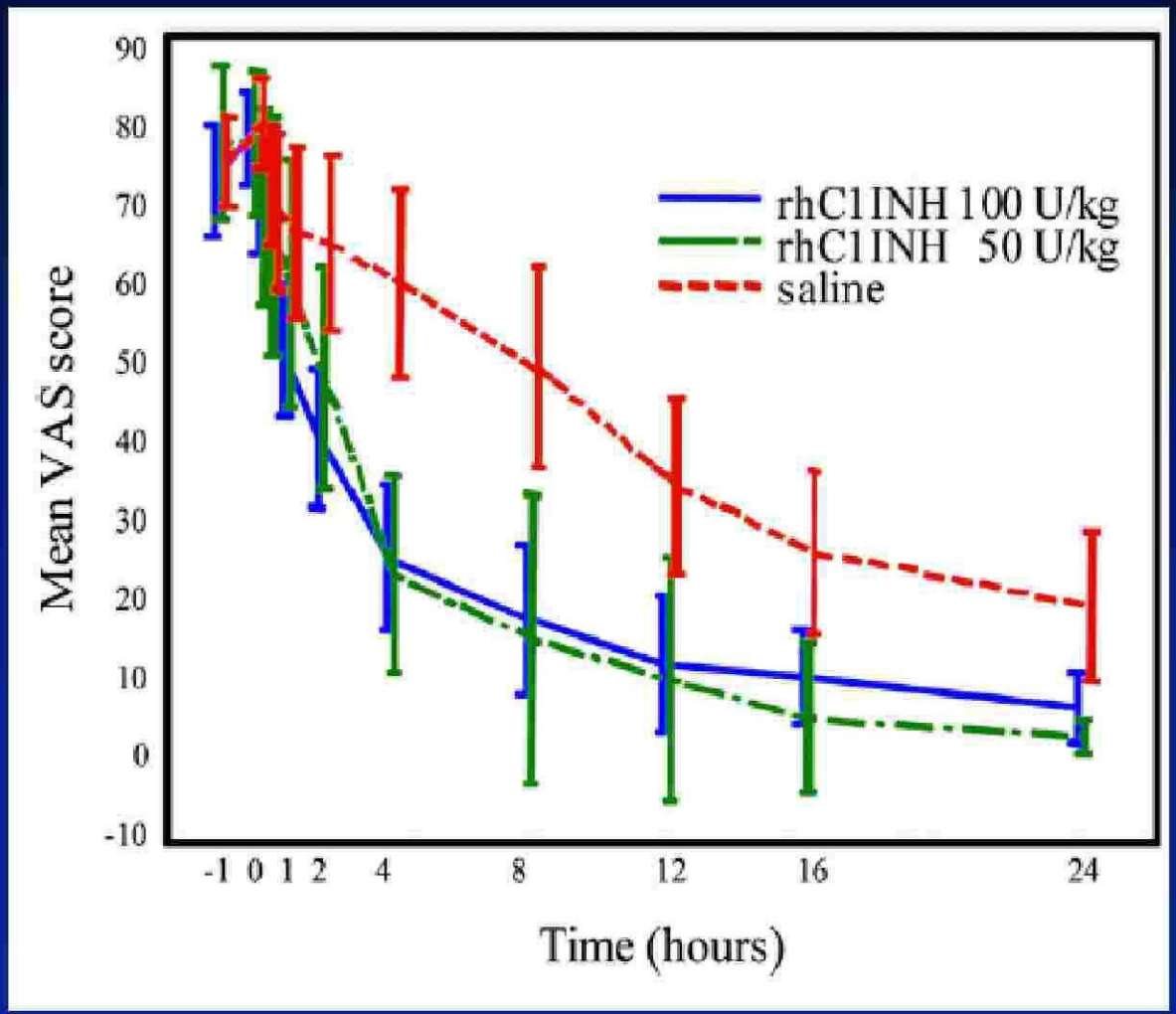
Prophylactic treatment: every 3-4 days



- 22 patients with at least 2 HAE attacks/month enrolled in a 24-week DBPC cross-over study
- Randomized to 12 weeks of C1INH or placebo, after 12 weeks patients switched treatment arms
- 52% reduction with C1INH therapy ($p<0.0001$), 66% reduction in days of swelling ($p<0.0001$)

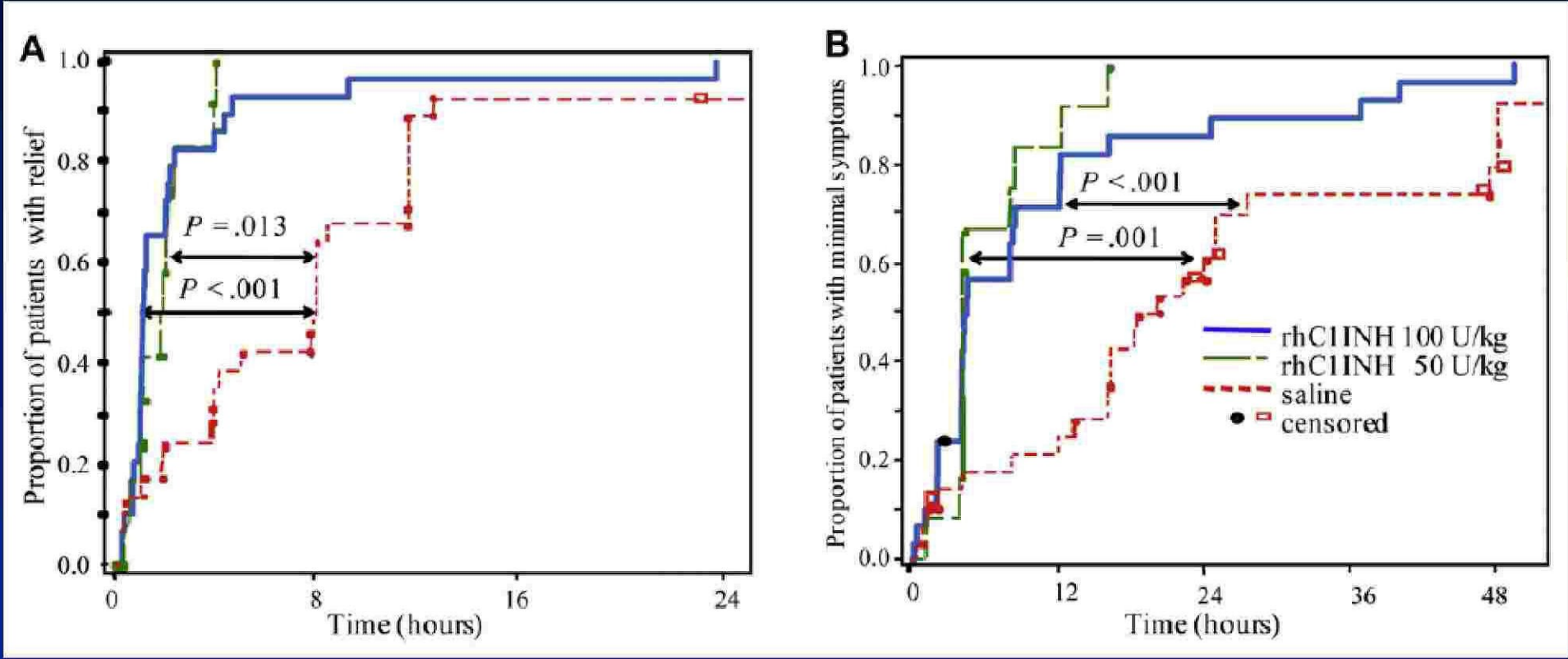
Zuraw et al., NEJM 2010

Efficacy of Recombinant Human C1-INH (Rhucin)



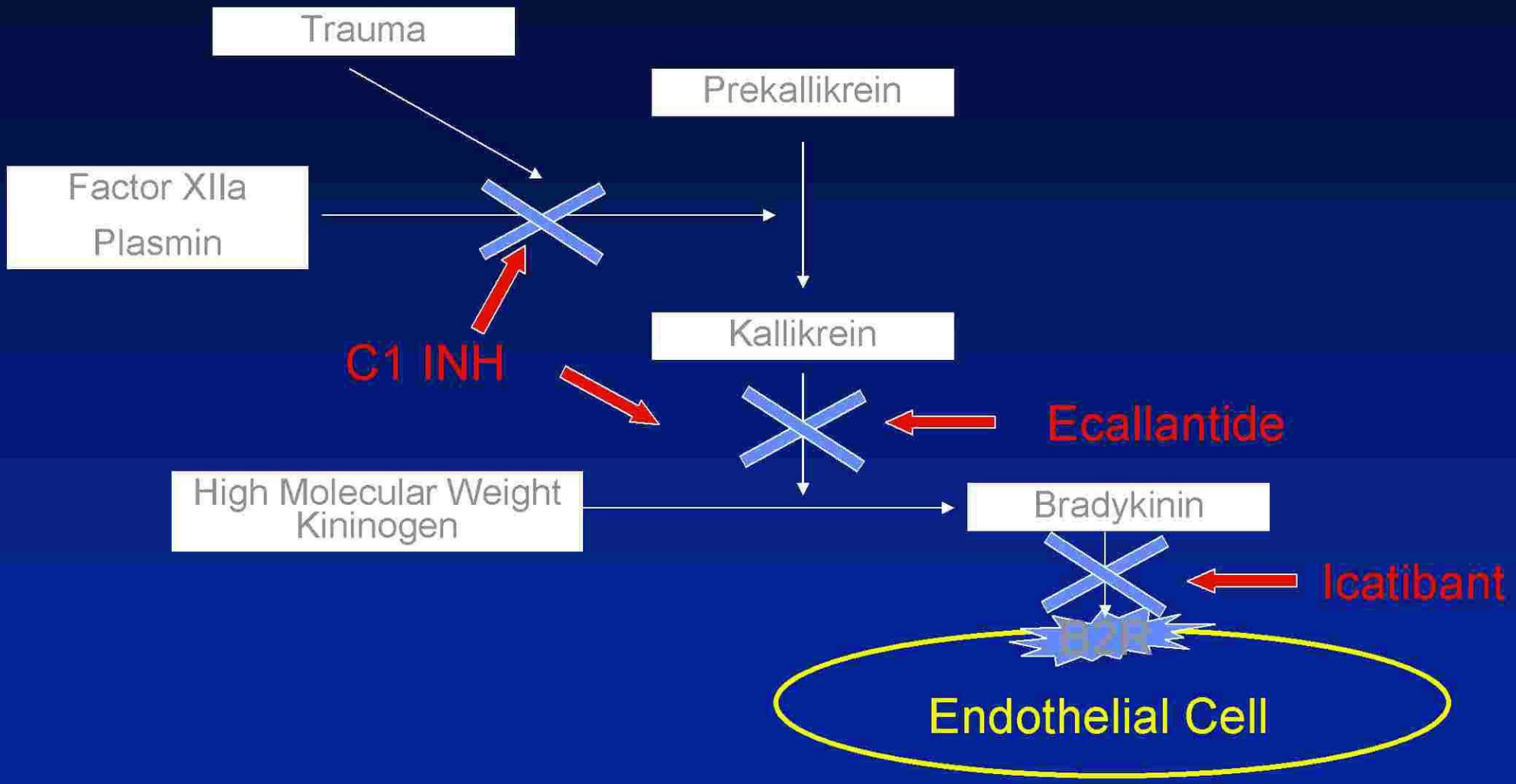
Zuraw et al., JACI 2010

Recombinant C1INH (Rhucin): Time to beginning of relief and significant relief

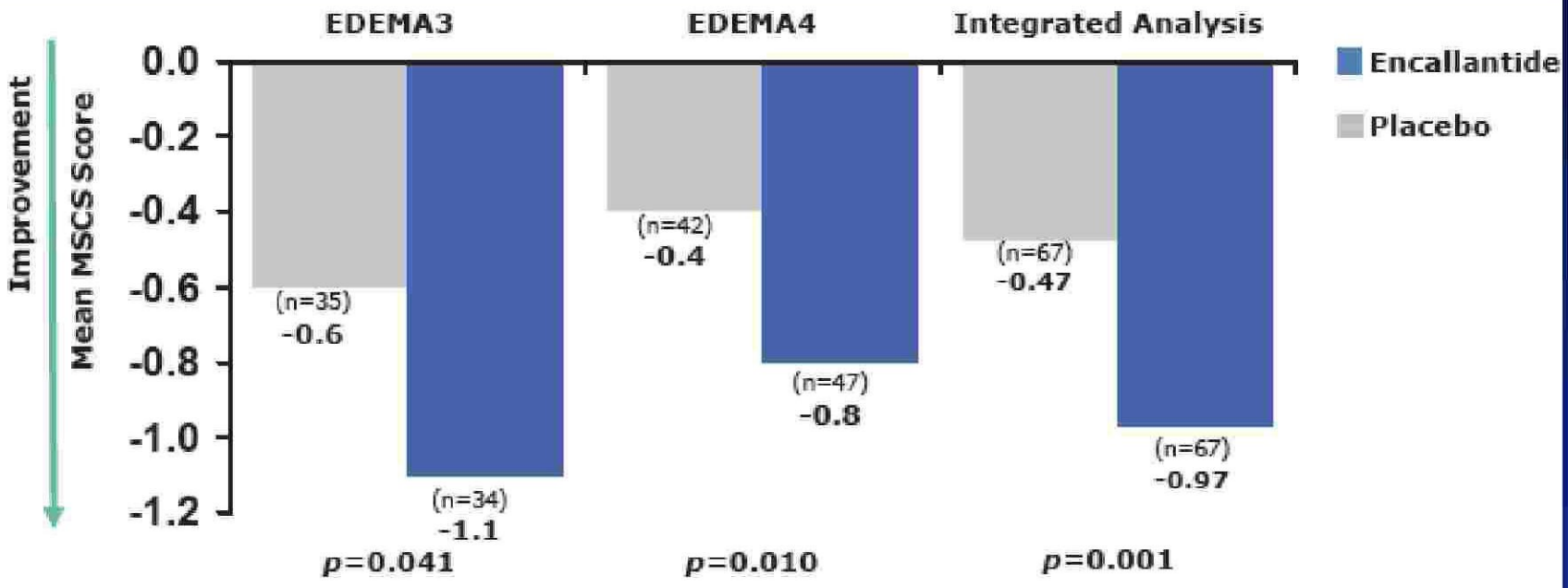


Zuraw et al., JACI 2010

"Newer Treatments" for Hereditary Angioedema



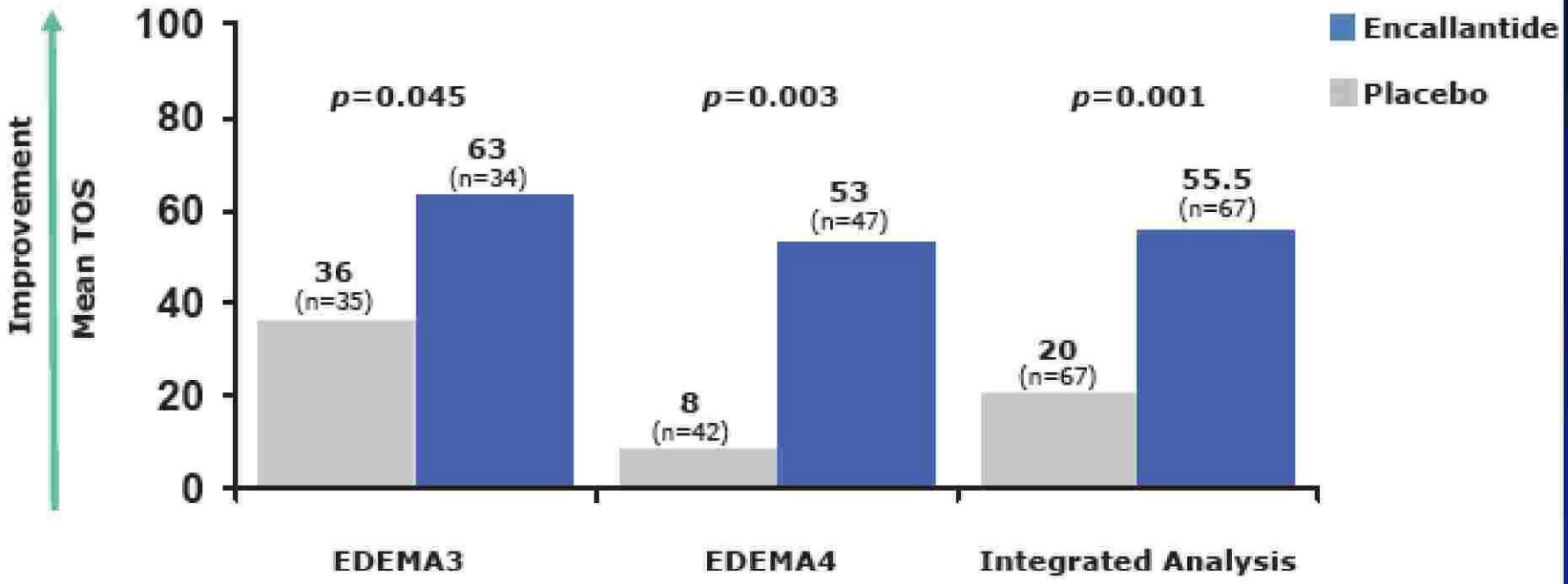
Ecallantide: Improvement of acute attack symptoms at 4 hours



** Mean Symptom Complex Severity (MSCS) score is a point-in-time measure of symptom severity. A decrease in MSCS score reflected an improvement in symptoms.*

Cicardi M, Levy RJ et al.: *N Engl J Med*. 2010 Aug 5;363(6):523-31
Levy RJ, Lumry WR et al.: *Ann Allergy Asthma Immunol*. 2010 Jun;104(6):523-9

Ecallantide: Improvement of acute attack symptoms at 4 hours



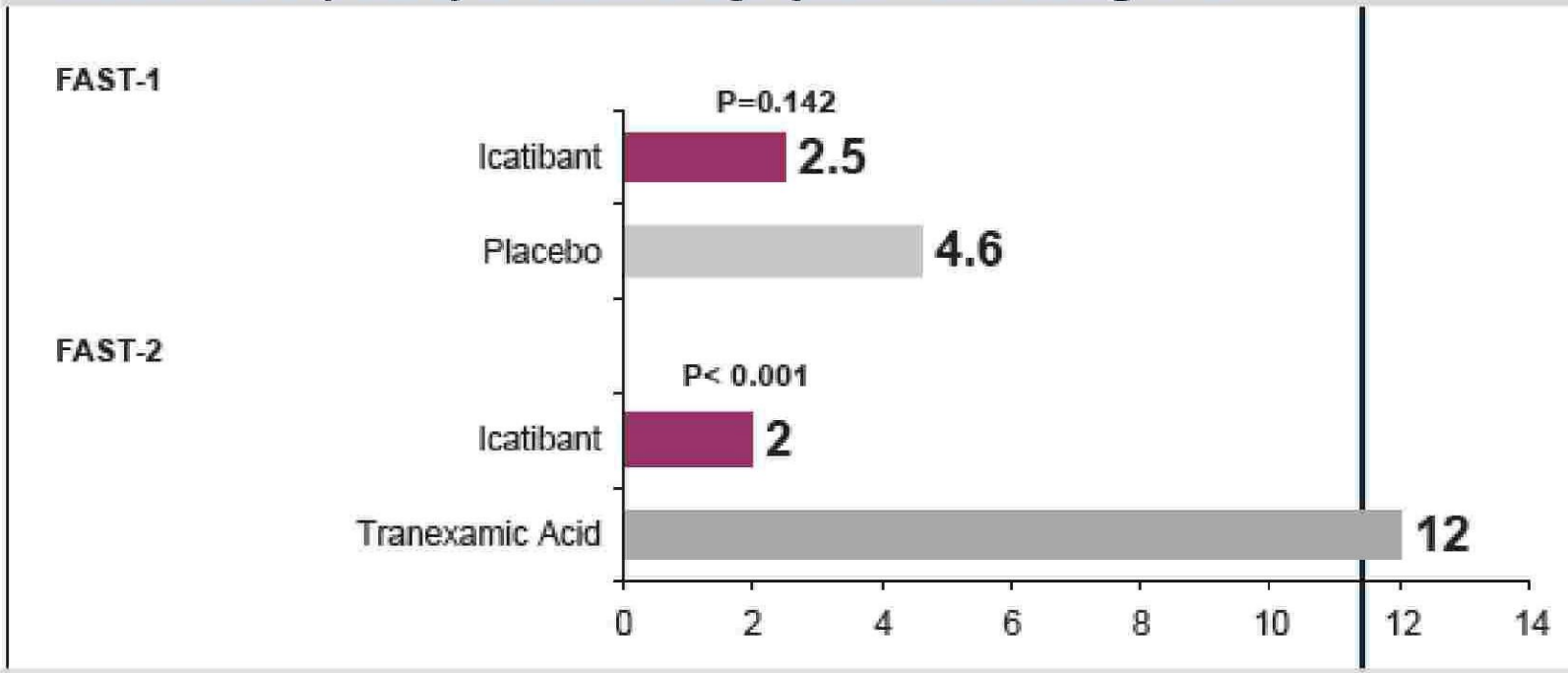
** Treatment Outcome Score (TOS) is a measure of symptom response to treatment. A TOS value >0 reflected an improvement in symptoms from baseline.*

Cicardi M, Levy RJ et al.: *N Engl J Med*. 2010 Aug 5;363(6):523-31

Levy RJ, Lumry WR et al.: *Ann Allergy Asthma Immunol*. 2010 Jun;104(6):523-9

Primary Endpoint: Time to Onset of Symptom Relief

Median time (hours) to onset of symptom relief using VAS

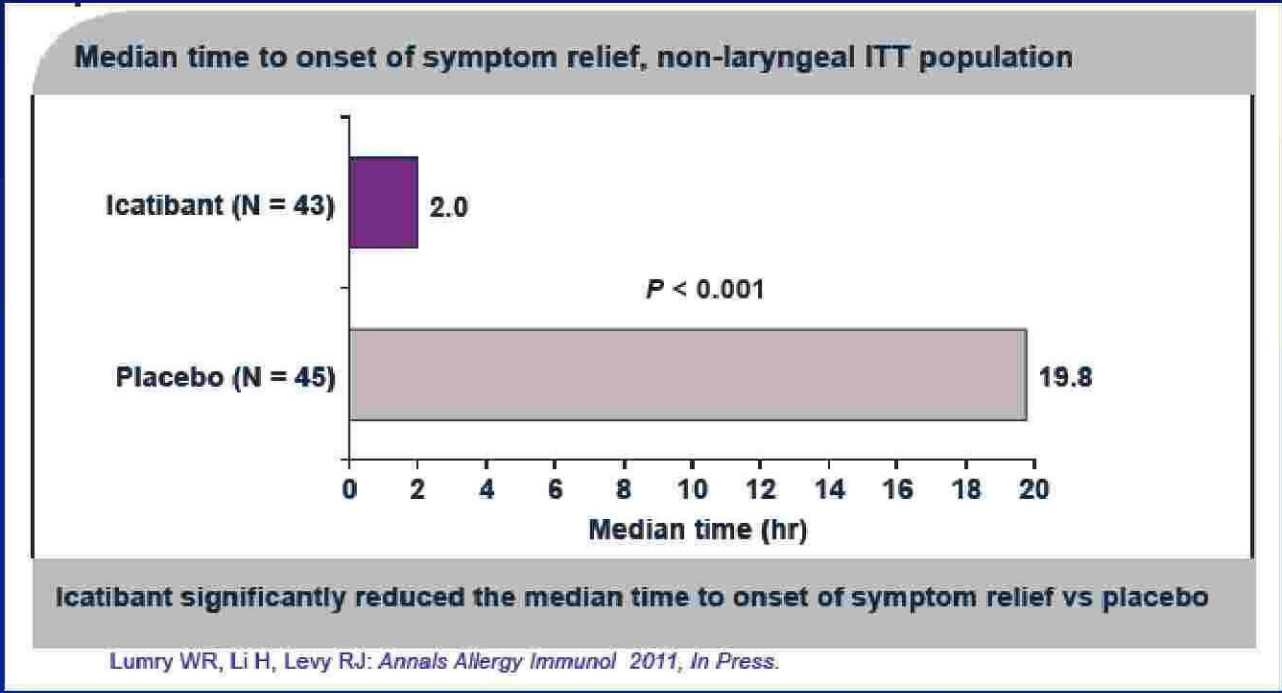


Consistent and clinically relevant results for Icatibant in both trials (Significant only for FAST- 2).

Cicardi M, Banerji A, Bracho F, Lumry W et al.: *N Engl J Med*. 2010 Aug 5;363(6):532-41.

FAST 3: December 2010

- Primary Endpoint: 50% reduction in the composite symptom score ($p<0.001$)
- No reports of anaphylaxis



Lumry WR, Li H, Levy RJ: *Annals Allergy Immunol 2011, In Press.*

How do the newer drugs compare?

Drug	Potential Safety Concerns	Disadvantages	Advantages	Status
Plasma-derived C1-INH (Berinert, Cinryze)	• Infectious risk • Potential infusion reactions	• Needs IV access • Limited supply	• Extensive clinical experience • Corrects the fundamental defect • Relatively long half-life	• **Berinert: FDA approved acute treatment** • **Cinryze: FDA approved prophylaxis**
Recombinant C1-INH (Rhucin)	• Potential allergic reactions • Antibody formation to protein	• Needs IV access • Short half-life	• Corrects the fundamental defect • No human virus risk • Scalable supply	• Awaiting FDA review
Ecallantide	• Allergic reactions • Antibody formation to protein • Local injection reactions	• Short half-life	• No infectious risk • Subcutaneous administration	• **FDA approved acute treatment**
Icatibant	• Local injection reactions	• Short half-life	• No infectious risk • Stable at room temperature • Subcutaneous administration	• FDA approved, acute treatment, self administration

New approaches to HAE Treatment

- Treatment should maximize patient health
  - Effective treatment readily available for attacks
  - Avoid significant side effects
- Treatment should be individualized
  - Based on attack frequency and severity
- Minimize disruption of normal life
  - Home therapy
  - Prophylactic therapy

Adapted from B Zuraw

Long Term Prophylaxis: Who?

- British consensus document 2004:
  - Joint decision between physician and patient
  - Recognition of the role of individualized therapy and burden on QOL
- Gompels et al., 2005:
  - >1 episode of severe abdominal pain or head/neck swelling
  - Frequent peripheral swelling
  - C1INH more than once a year
- Canadian Hungarian consensus document 2007:
  - >1 severe event per month
  - Disabled more than 5 days per month
  - History of airway compromise

Bowen Annals Allergy Asthma Immunol 2008
Agostoni, JACI 2004
Bowen et al., Allergy Asthma Clin Immunol 2010
Gompels et al., Clin Exp Immunol 2005

Consideration Criteria for Prophylactic Therapy
2009

Consideration Criteria	Episodic Therapy	Prophylactic Therapy
Description of HAE Attacks		**ANY ONE OF THESE**
Frequency of Attacks	<1/Month	≥1/Month
Rapid progression of attacks	No	Yes
Timely access to care	Yes	No
Nature of HAE Attacks		
History of laryngeal attacks	No	Yes
Emergency visit to physician/hospital	≤ 3/year	> 3/year
Intubation due to HAE	No	Yes
Hospitalization due to HAE	≤ 1/year	> 1/year
ICU due to HAE	No	Yes
Burden On Activities of Daily Living		
Missed days of school or work	≤10 days/year	>10 days/year
Significant anxiety or compromise in quality of life	possible	consider
Impacts lifestyle (vacation, family, sports)	No	Yes
Analgesic dependency	No	Yes

Craig T et al., Ann Allergy Asthma Immunol 2009

Is Prophylaxis Appropriate?
Individualized Care

- Goal of long-term prophylaxis is to decrease the frequency and severity of attacks
- Evaluate nature and frequency of HAE attacks and associated disease burden of each patient
- Consider access to emergency care, history of ED/physician visits, hospitalizations and intubations due to HAE attacks
- Clinical course is unpredictable

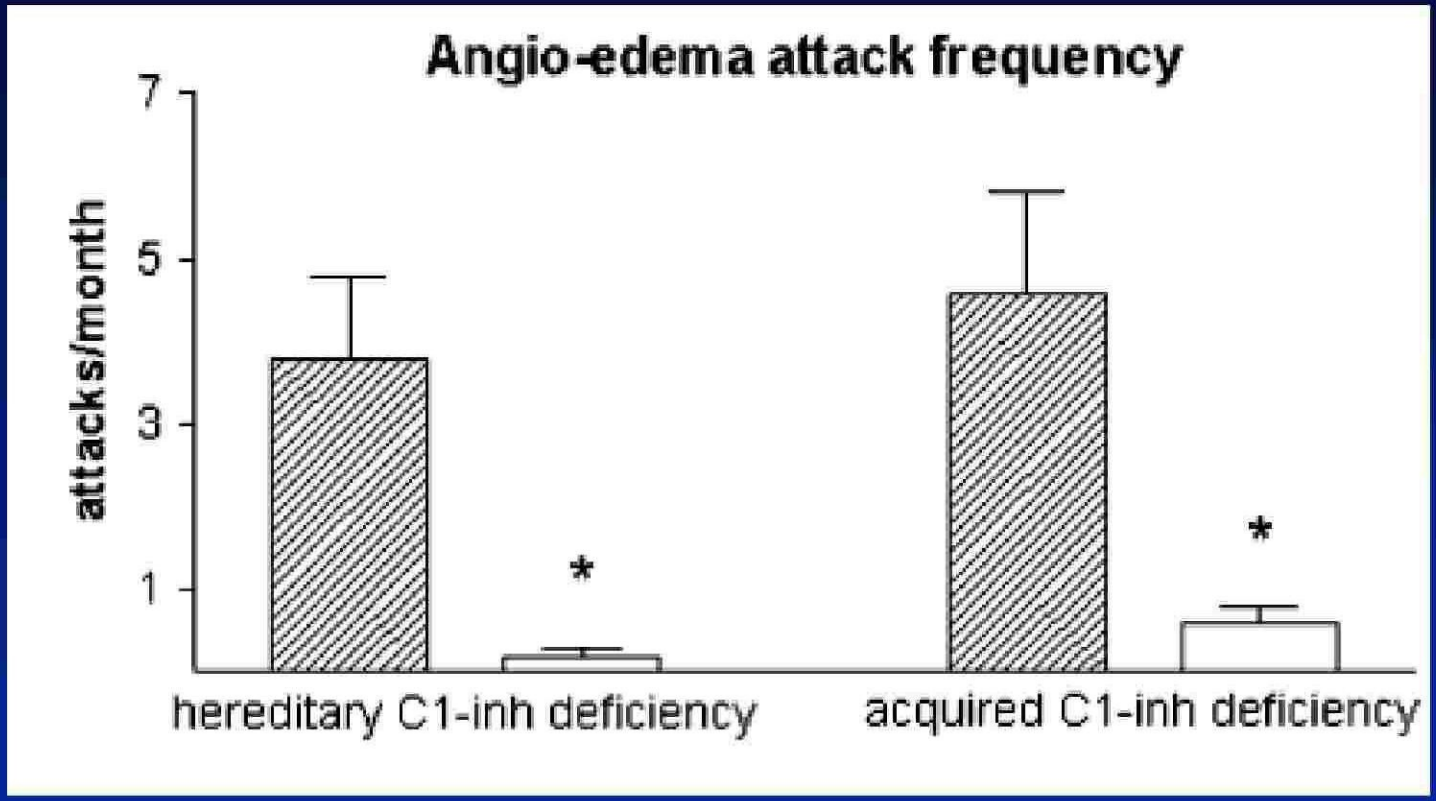
International HAE Conference Consensus

Gargnano, Italy

- All HAE patients should have on-demand treatment available
  - Patients should be trained in self-administration
  - Attacks at all locations are eligible for treatment
  - Attacks should be treated as soon as they are recognized
  - Hospitalize for progressing laryngeal involvement
- Long-term prophylaxis
  - Consider when optimized on-demand therapy fails
  - Androgens are contraindicated in patients who are:
    - ≤16 years old
    - Pregnant/breastfeeding
    - Does not tolerate or accept androgens

Adapted from B Zuraw

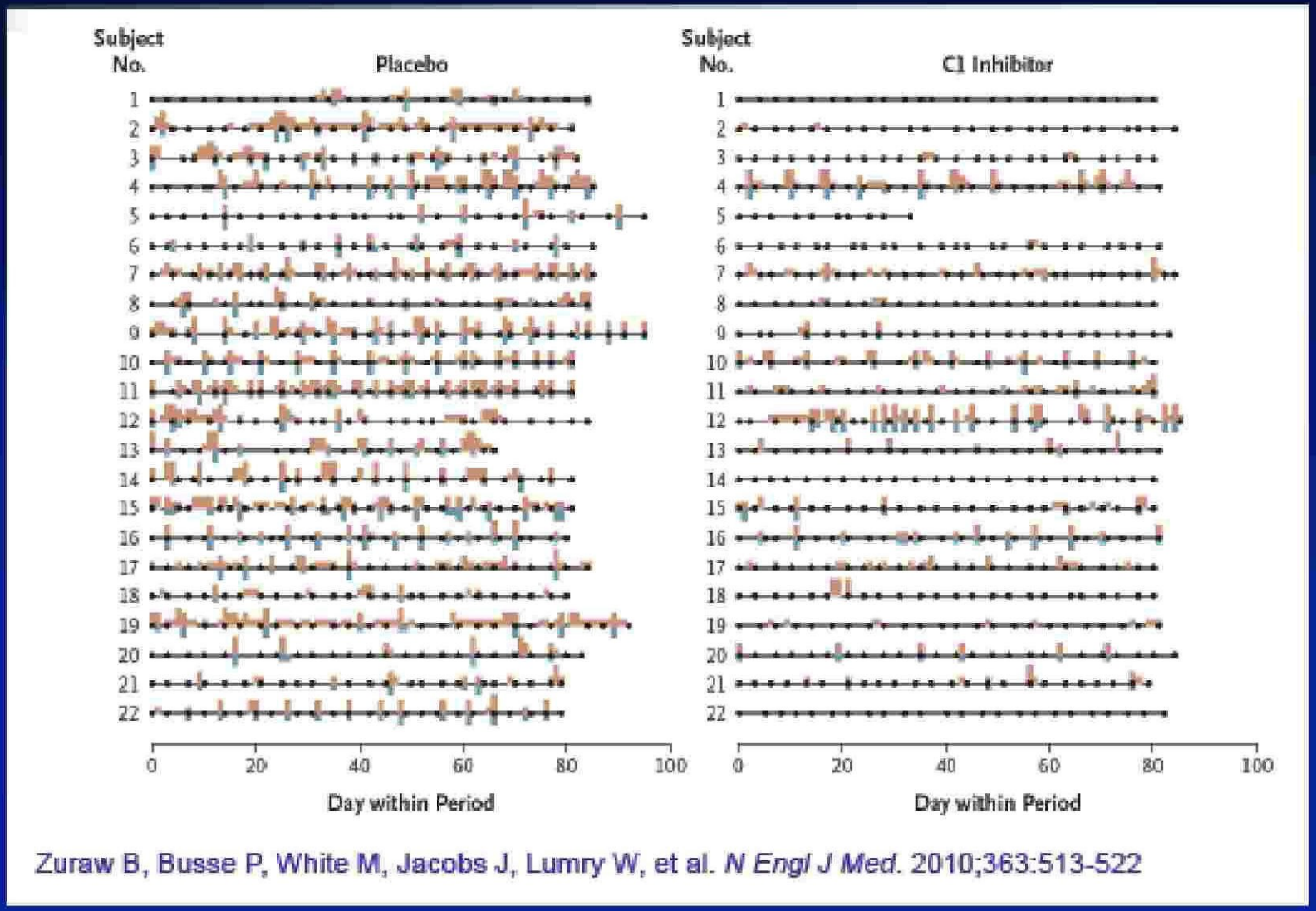
Frequency of HAE Attacks Decreases Significantly After Initiation of Prophylaxis



- Attack frequency decreased from 4 attacks to 0.3 attacks per month

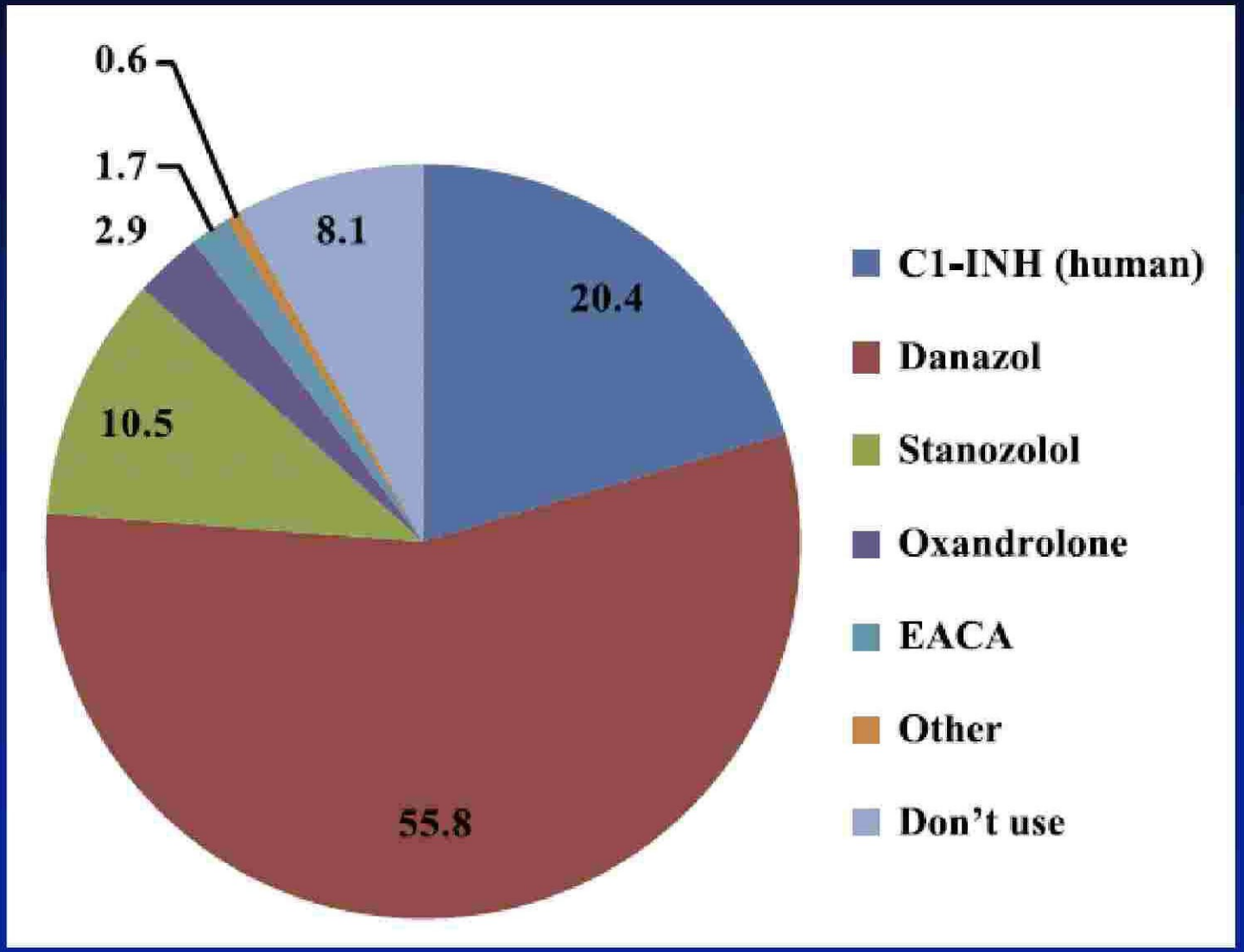
Levi et al., JACI 2006

Efficacy of Prophylactic Nanofiltered Plasma C1-INH Concentrate



Zuraw B, Busse P, White M, Jacobs J, Lumry W, et al. *N Engl J Med.* 2010;363:513-522

Physician reporting of medications prescribed for prophylaxis in HAE



Riedl et al., Ann Allergy Asthma Immunol 2011

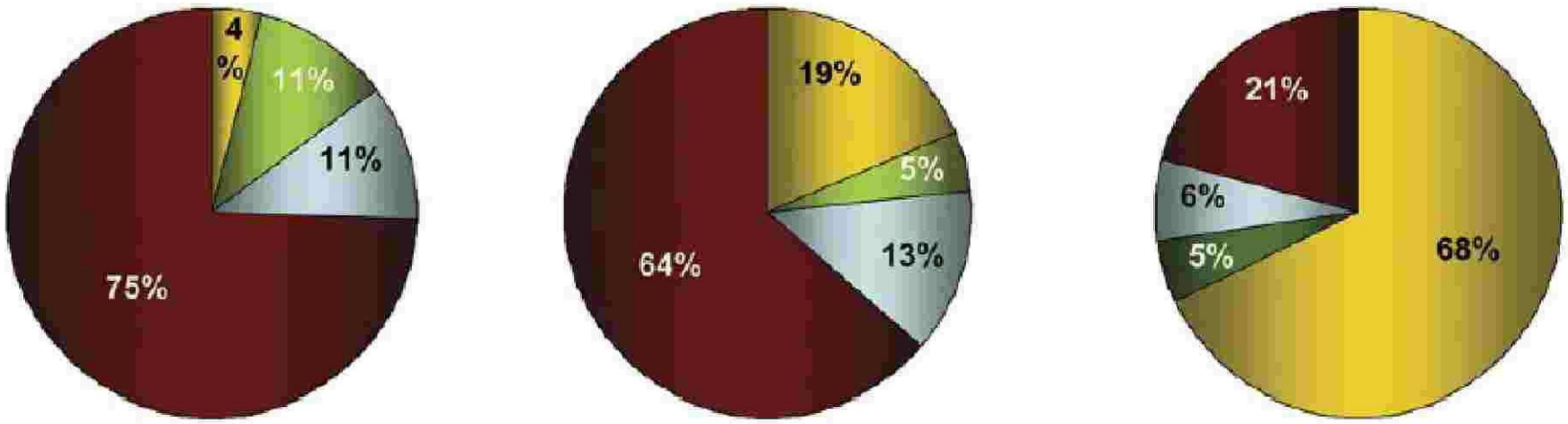
Comparison of Prophylactic Therapies: Attenuated Androgens and C1INH

	Anabolic Androgens	C1 INH
Advantages	Low cost Oral	Replaces abnormal protein
Disadvantages	Adverse effects	Intravenous access High cost
Potential side effects	Weight gain Hepatitis Hyperlipidemia Hepatocellular carcinoma Mood changes	Potential for blood-borne pathogens Port thrombosis and infection
Contraindicated populations	Pregnant women Children	Hypersensitivity to blood products

On-Demand Therapy: Drug Comparisons

	pdC1-INH	rhC1-INH	Ecallantide	Icatibant	Androgen
Acute use efficacy	++++	++++	++++	++++	-
Route	i.v.	i.v.	subQ	subQ	p.o.
Approved in USA	Yes	No	Yes	Yes	Yes
Primary safety issue	infectious (?)	allergic (?)	allergic	? CV	multiple
Tolerability	i.v. stick; veins	i.v. stick; veins	multiple injections	local pain	fair to poor
Home use	++	++	-	+++	++++

Medical Costs of HAE



- Emergency department and hospital visits for acute attacks
- Medications for both acute attacks and long-term disease management
- Clinical care including physician's office visits and any procedures or tests; both short-term and long-term care are included
- Indirect costs, including travel, childcare, and missed work for acute attacks and reduced income and reduced productivity associated with chronic disease

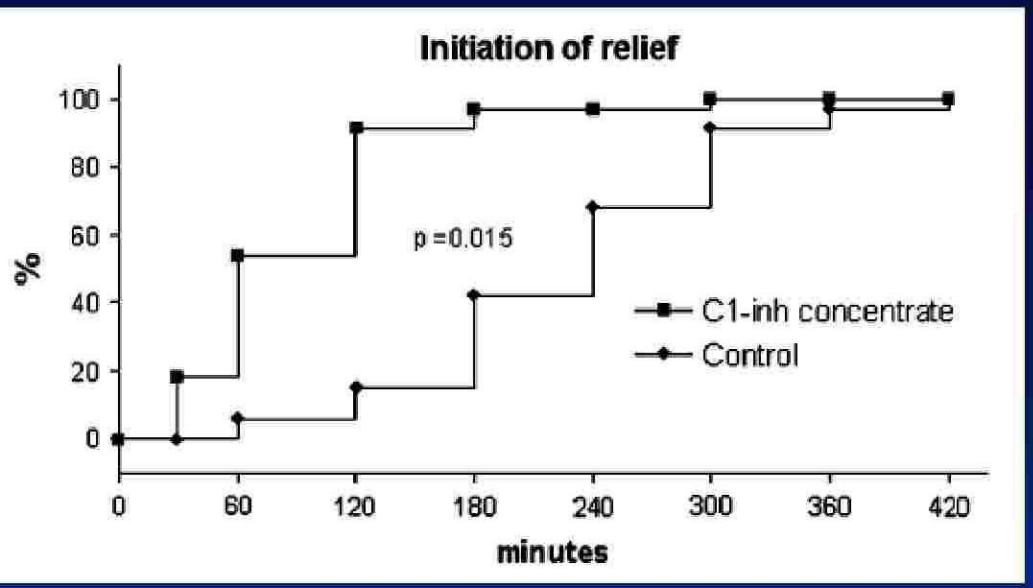
Wilson et al., Ann Allergy Asthma Immunol 2010

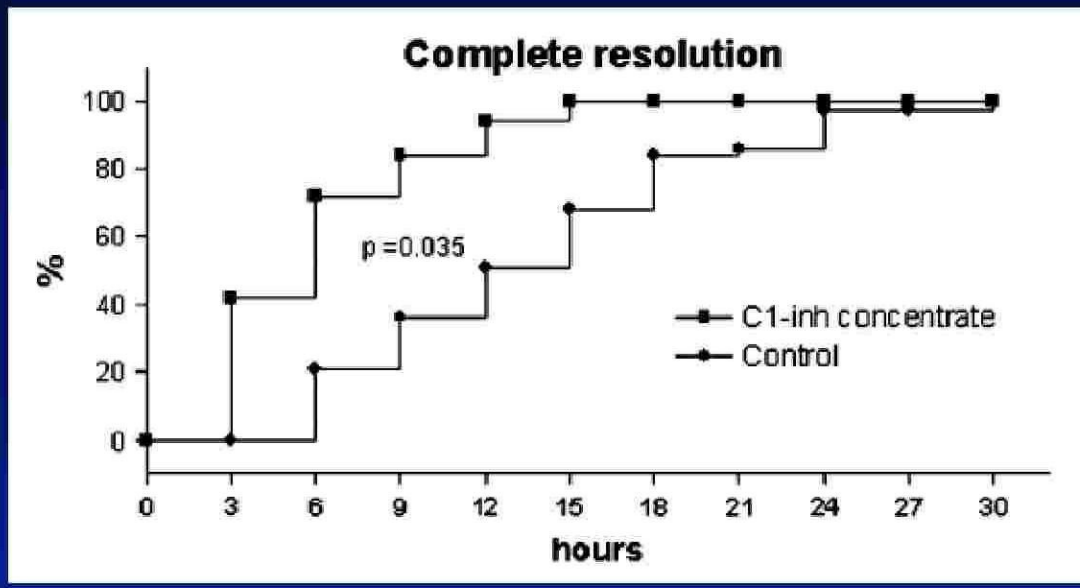
Prophylaxis vs. Acute Treatment: Costs

	Rx type	Agent name	Efficacy	Side effects	Annual cost
Prophylaxis	Androgens	Danazol	+++	+++	$736[a]
	C1 inhibitor (nanofiltered)	Cinryze	+++	+	$486,720[b]
Acute attacks	C1 inhibitor (pasteurized)	Berinert	++[d]	+	$17,868[c]
	Plasma kallikrein inhibitor	Ecallantide (Kalbitor)	+++	++[e]	$47,700[c]
	Bradykinin β2 receptor inhibitor	Icatibant	+++	+	Not FDA approved

Tilles et a., Ann Allergy 2011

Efficacy of Self-Administration of C1 INH

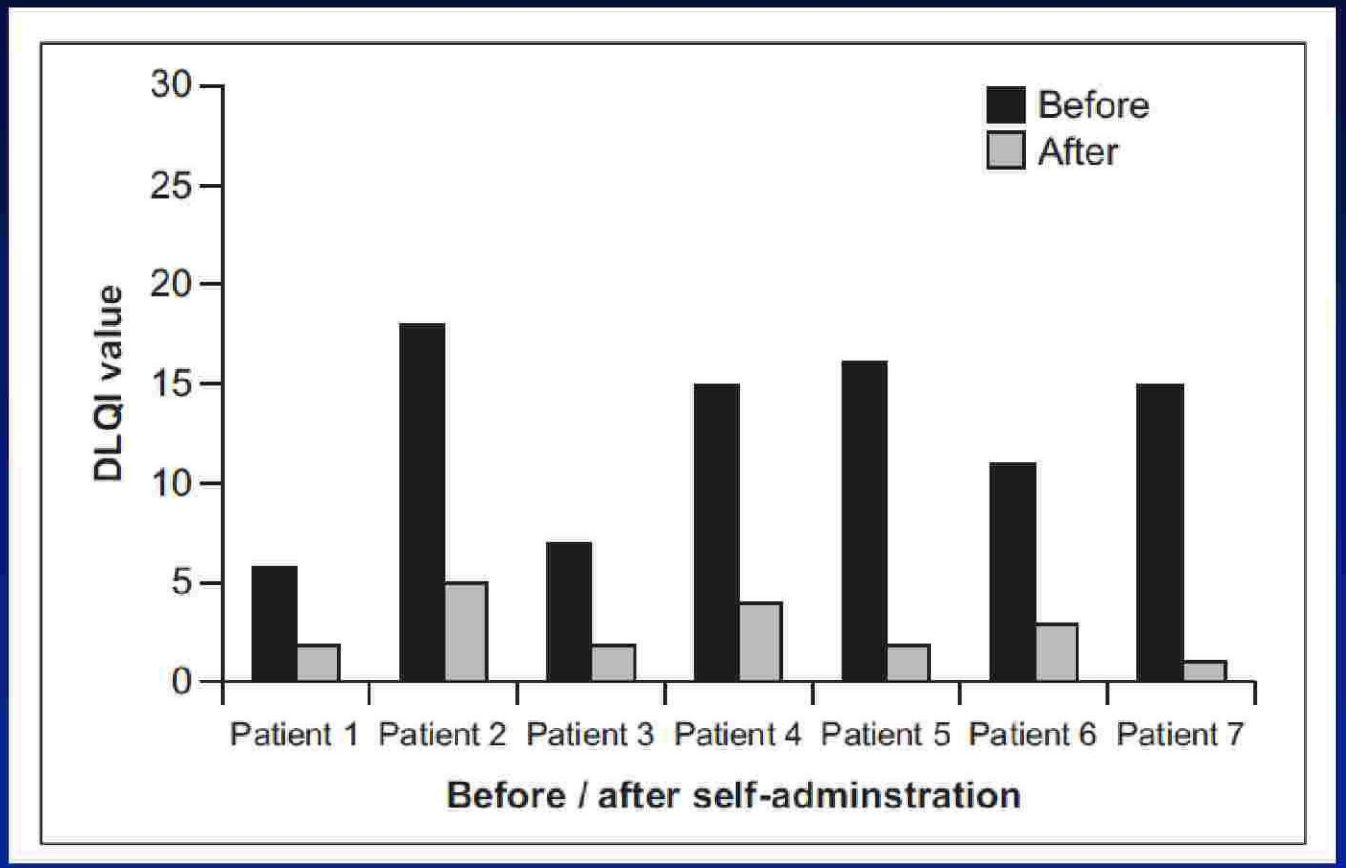




- The time between the onset of a severe attack and self-administration of C1-inhibitor was 1.4 ± 1.0h vs. 3.4 ± 2.1h in historical controls before the start of the self-administration

Levi et al., JACI 2006

Improved QOL with Self-Administration



- Similar improvement in SF-36 parameters
- Reduced use of emergency services ($P<0.05$)

Bygum et al., Eur J Dermatol 2009

Conclusions

- Novel therapies have been developed that are safe and effective
- Consensus guidelines about treatment strategies have emerged
  - All patients should have access to on-demand treatment with a well delineated treatment plan
  - Long-term prophylaxis is best reserved for patients in whom on-demand treatment is not sufficiently effective
  - Aim to minimize any side effects
  - Therapy needs to be individualized for each patient
- Self-administration can offer significant benefits