

# Urticaria og angioødem update – præsentation af UCARE og ACARE



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# *Disclosures*

Foredrag, konsulent, advisory boards, investigator, forskningsstøtte:

AbbVie, Ammirall, Celgene, CSL, Eli Lilly, Janssen, LEO Pharma, Novartis, Pfizer, Roche, Sanofi, UCB Pharma og Union Therapeutics

# Urticaria

- Hudsygdom forårsaget af overaktive mastceller
- Kvadler og/eller angioødem
- Kløe (og brændende/pressende fornemmelse) i huden
- Kvadler til stede under 24 timer / angioødem til stede under 72
- Livstidsprævalens af urticaria er ~25%
- Livstidsprævalens af kronisk urticaria er ~1%
- Angioødem til stede hos ~40% med urticaria (eneste manifestation hos 5%)

# Klassifikation af urticaria

**Kvadler og/eller angioødem i under 6 uger  
= akut urticaria**

**Kvadler og/eller angioødem i over 6 uger  
= kronisk urticaria**

# Klassifikation af kronisk urticaria

## Chronic Urticaria Subtypes

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### Chronic Spontaneous Urticaria (CSU)

Spontaneous appearance of wheals, angioedema, or both for >6 weeks due to known<sup>a</sup> or unknown causes.

### Inducible Urticaria

Symptomatic dermographism<sup>b</sup>  
Cold urticaria<sup>c</sup>  
Delayed pressure urticaria<sup>d</sup>  
Solar urticaria  
Heat urticaria<sup>e</sup>  
Vibratory angioedema<sup>f</sup>  
Cholinergic urticaria  
Contact urticaria  
Aquagenic urticaria

# UCARE (Urticaria Centers of Reference and Excellence)

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**Registration for expert panel and author group for urticaria guideline now open!**  
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We provide excellence in urticaria management

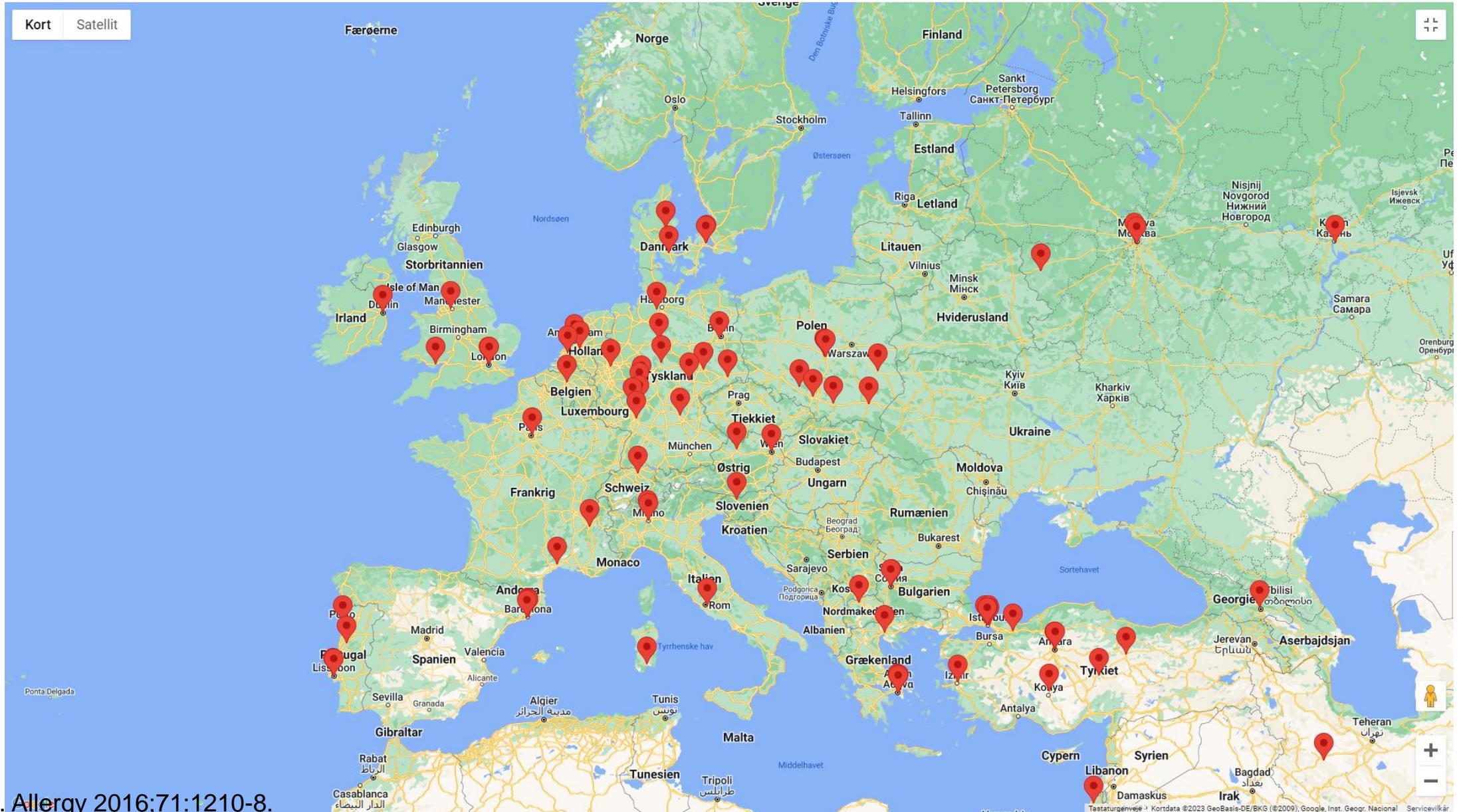
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# UCARE (Urticaria Centers of Reference and Excellence)



# UCARE

# (of Reference and Excellence)



Network of Excellence

## 32 Requirements to be met to become a GA²LEN Urticaria Centers of Reference and Excellence (UCARE)

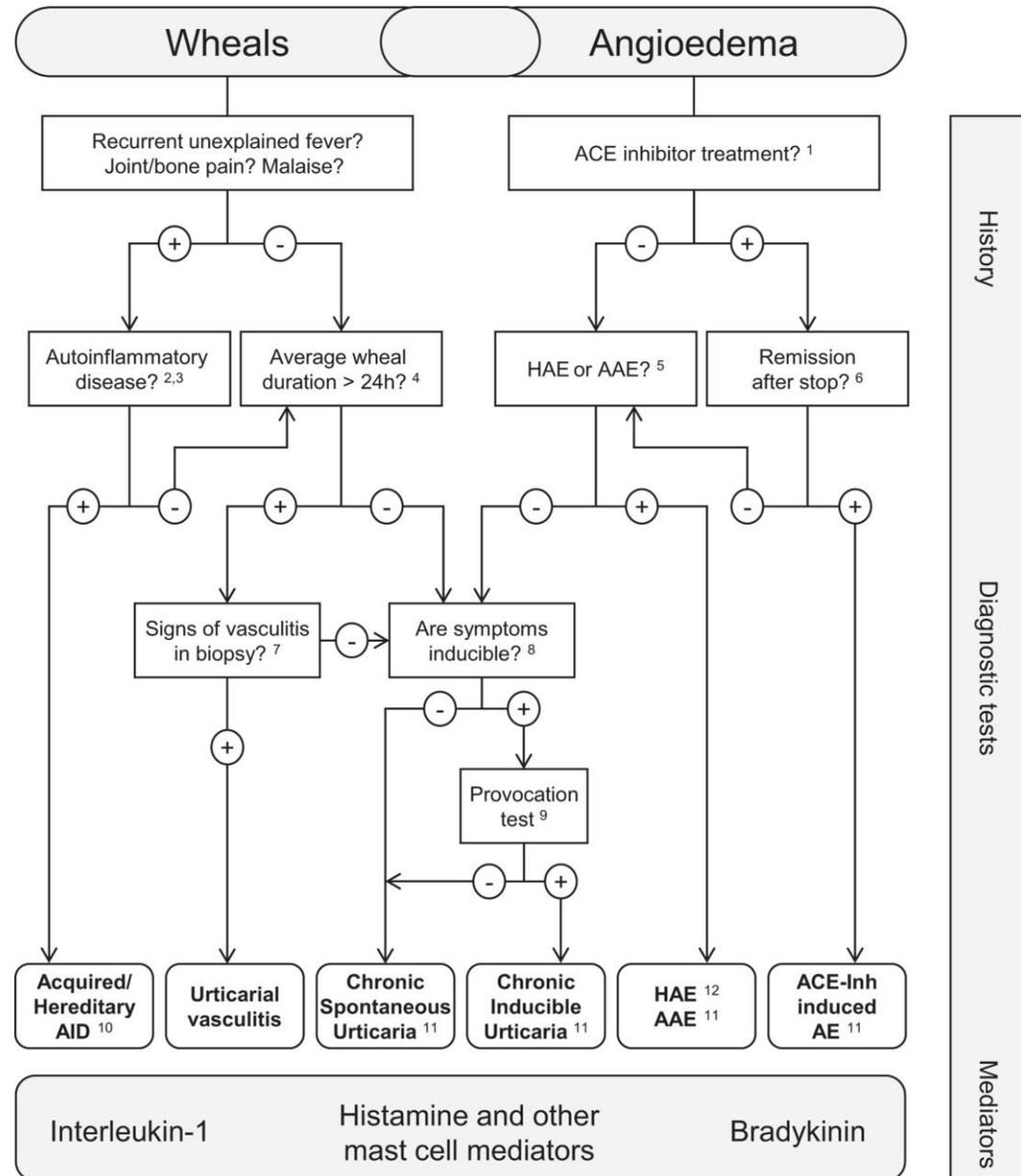
Requirement	Explanation	Infrastructure / Set up		Deliverable(s)	Yes /No	Cat.
1. Hospital setting	Center needs to be in a hospital or affiliated with a hospital with inpatient facilities to allow for extended diagnostic work up and management of exacerbation			Evidence of hospital setting or affiliation with hospital	<input type="checkbox"/> <input type="checkbox"/> _____	B
2. Outpatient clinic with separate clinic hours for urticaria patients headed by expert	Center needs to have designated and expert leadership (experienced specialist physician) and to offer a minimum number of consultation hours per week exclusive for urticaria patients			Lead by experienced physician (board certified specialist) ≥4h / week of dedicated urticaria clinic (physician contact time)	<input type="checkbox"/> <input type="checkbox"/> _____ <input type="checkbox"/> <input type="checkbox"/> _____	A
3. Open to children and adult patients	Centers need to be able to provide care for urticaria patients of any age, either by center staff or affiliated			Evidence that urticaria patients of any age are provided with state of the art care	<input type="checkbox"/> <input type="checkbox"/> _____	A
4. Team of dedicated staff, with specific urticaria training	Center staff needs to comprise more than one physician and at least one nurse. All center staff needs to be specifically and regularly trained in urticaria			≥2 physicians and ≥1 nurse	<input type="checkbox"/> <input type="checkbox"/> _____	A
5. Multidisciplinary approach	Center needs to be able to interact with other specialties for the management of comorbidities, the treatment of patients with differential diagnoses, and to perform extended diagnostics			Record of ≥1 urticaria training per staff member per year, e.g. GA²LEN school on urticaria, urticaria CME activity, etc.	<input type="checkbox"/> <input type="checkbox"/> _____ <input type="checkbox"/> <input type="checkbox"/> _____	A
				Evidence of interaction with other specialists	<input type="checkbox"/> <input type="checkbox"/> _____	B

# Urticaria guideline 2021

**The International EAACI/GA<sup>2</sup>LEN/EuroGuiDerm/APAAACI  
Guideline for the Definition, Classification, Diagnosis and  
Management of Urticaria**

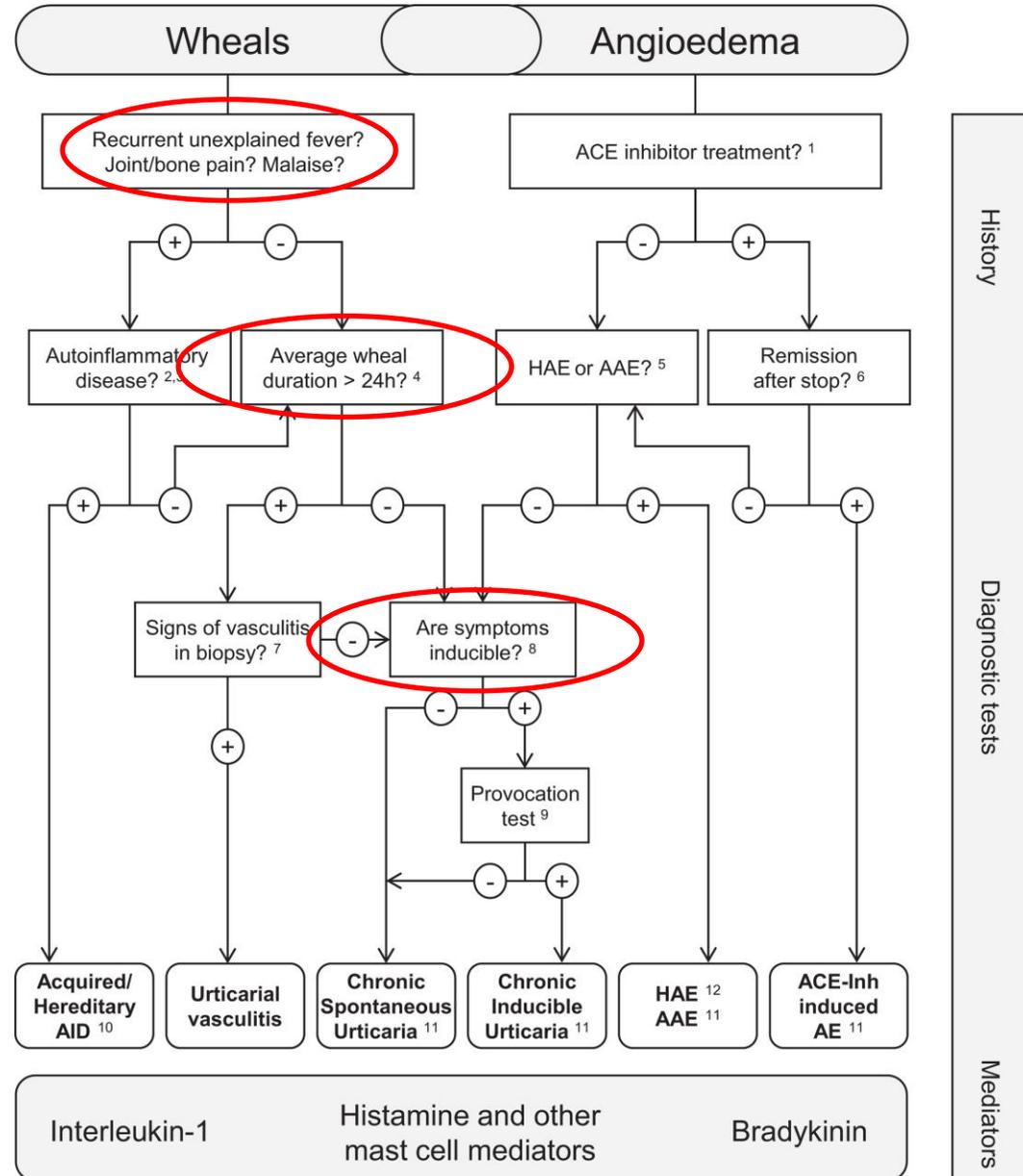


# Diagnostisk algoritme ved kronisk urticaria



# Diagnostisk algoritme ved kronisk urticaria

Stil 3 spørgsmål til din patient med formodet kronisk urticaria....:



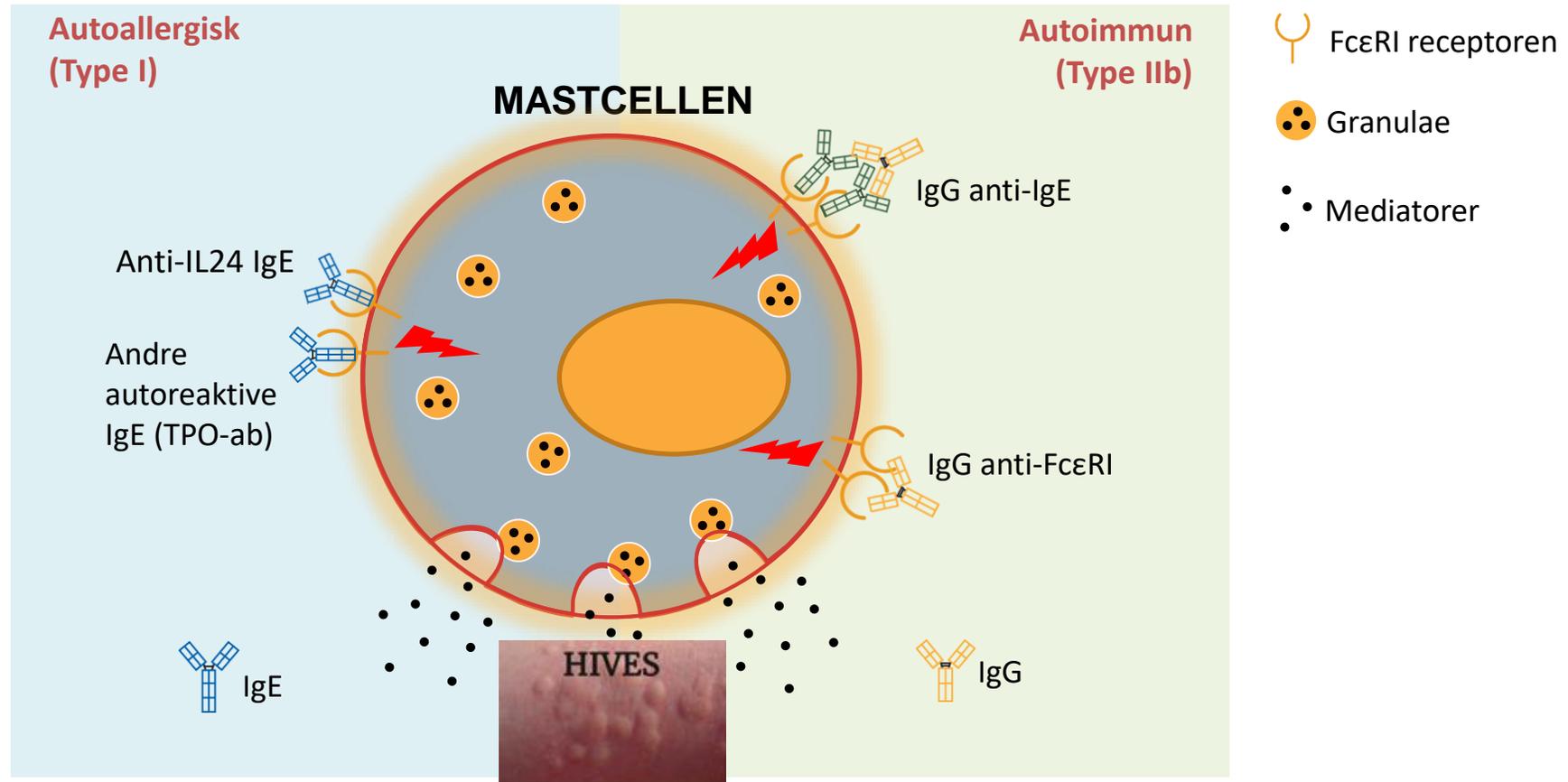
# Hvorfor får man urticaria?

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Everyday life events that occurred immediately before onset of CU, <i>n</i> (%)	
Experienced emotional stress	37 (43.5)
Travelling abroad	17 (20.0)
Had an infection	16 (18.8)
Had a new job	14 (16.5)
Weight changes	12 (14.1)
Experienced unusual physical symptoms	9 (10.6)
Moved house	9 (10.6)
Initiated new medication(s)	7 (8.2)
Changes in physical activity habits	7 (8.2)
Major dietary changes	6 (7.1)
Eaten new foodstuff	3 (3.5)
Changes in smoking habits	3 (3.5)
Changes in alcohol drinking habits	3 (3.5)
Onset of another chronic illness	3 (3.5)
Been pregnant or tried to become pregnant	2 (2.4)

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# Type I (autoallergisk) og Type IIb (autoimmun) kronisk urticaria



# Hvordan skelner man mellem Type I og Type IIb kronisk urticaria?

Type I (85%)	Type IIb (15%)
Negativ urticaria HR test	Positiv urticaria HR test

# Hvordan skelner man mellem Type I og Type IIb kronisk urticaria?

Type I (85%)	Type IIb (15%)
<b>Negativ urticaria HR test</b>	<b>Positiv urticaria HR test</b>
Normal/Høj total IgE	Lav total IgE (typisk under 10-40)
Normalt basofiltal	Lavt basofiltal
Normalt eosinofiltal	Lavt eosinofiltal
Normal thyroideaperoxidase (TPO-ab)	Høj thyroideaperoxidase (TPO-ab)
Sjældnere angioødem (40%)	Ofte angioødem (80%)
Lavere sygdomsaktivitet	Højere sygdomsaktivitet
God prognose	Dårlig prognose
God respons på behandling	Dårlig respons på behandling

# Potentielle undersøgelser ved kronisk urticaria

- Thyroidea hormoner / thyroidea autoantistoffer
- Basofil histamin release test / ASST / BAT
- Helicobacter pylori og parasitter i afføring
- CRP, leucocytter, sænkning
- Hepatitis B og C
- Standard / fødevarer prik og RAST tests
- Serum tryptase
- Serum total IgE
- Hudbiopsi
- CINDU provokationstests
- C1-esterase inhibitor
- ANA
- D-dimer
- Urinstix
- Røntgen af thorax
- Interferon gamma release assay (TB)
- PET/CT scanning
- Flåtoverførte infektioner / Borrelia burgdorferi



# Anbefalede diagnostiske tests ved kronisk urticaria

Types	Subtypes	Routine diagnostic tests (recommended)	Extended diagnostic programme <sup>a</sup> (based on history) – For identification of underlying causes or eliciting factors and for ruling out possible differential diagnoses if indicated
Spontaneous urticaria	Acute spontaneous urticaria	None	None <sup>b</sup>
	CSU	Differential blood count. ESR and/or CRP IgG anti-TPO and total IgE <sup>e</sup>	Avoidance of suspected triggers (eg, drugs); diagnostic tests for (in no preferred order): (i) infectious diseases (eg, <i>Helicobacter pylori</i> ); (ii) functional autoantibodies (eg, basophil test); (iii) thyroid gland disorders (thyroid hormones and autoantibodies); (iv) allergy (skin tests and/or allergen avoidance test, eg, avoidance diet); (v) concomitant CIndU, see below <sup>45</sup> ; (vi) severe systemic diseases (eg, tryptase); and (vii) other (eg, lesional skin biopsy)
Inducible urticaria	Cold urticaria	Cold provocation and threshold test <sup>c,d</sup>	Differential blood count and ESR or CRP, rule out other diseases, especially infections <sup>160</sup>
	Delayed pressure urticaria	Pressure test and threshold test <sup>c,d</sup>	None
	Heat urticaria	Heat provocation and threshold test <sup>c,d</sup>	None
	Solar urticaria	UV and visible light of different wavelengths and threshold test <sup>c</sup>	Rule out other light-induced dermatoses
	Symptomatic dermographism		
	Elicit dermographism and threshold test <sup>c,d</sup>	Differential blood count, ESR or CRP	
	Vibratory angioedema	Test with vibration, for example, Vortex-mixer <sup>d</sup>	None
	Aquagenic urticaria	Provocation testing <sup>d</sup>	None
	Cholinergic urticaria	Provocation and threshold testing <sup>d</sup>	None
Contact urticaria	Provocation testing <sup>d</sup>	None	

# Kliniske træk ved inducérbar urticaria (CIndU)



A



B



C



D



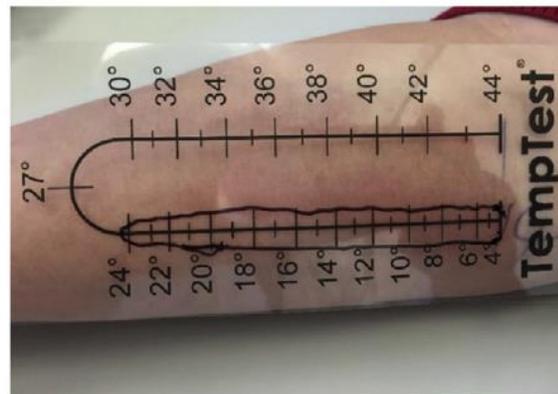
E



F



G



H

## Fysisk CIndU:

- Symptomatisk dermografisme (A)
- Trykurticaria (B)
- Kuldeurticaria (D-F)
- Varmeurticaria
- Solurticaria (C)
- Vibratorisk angioødem

## Andre CIndU:

- Kolinerg urticaria (G-H)
- Kontakturticaria
- Aquagen urticaria

# Provokationstests ved inducérbar urticaria (CIndU)



## CIndU:

A: Kulde/Varme urticaria

B: Solurticaria

C-D: Symptomatisk dermografisme

E: Trykurticaria

F: Vibratorisk angioødem

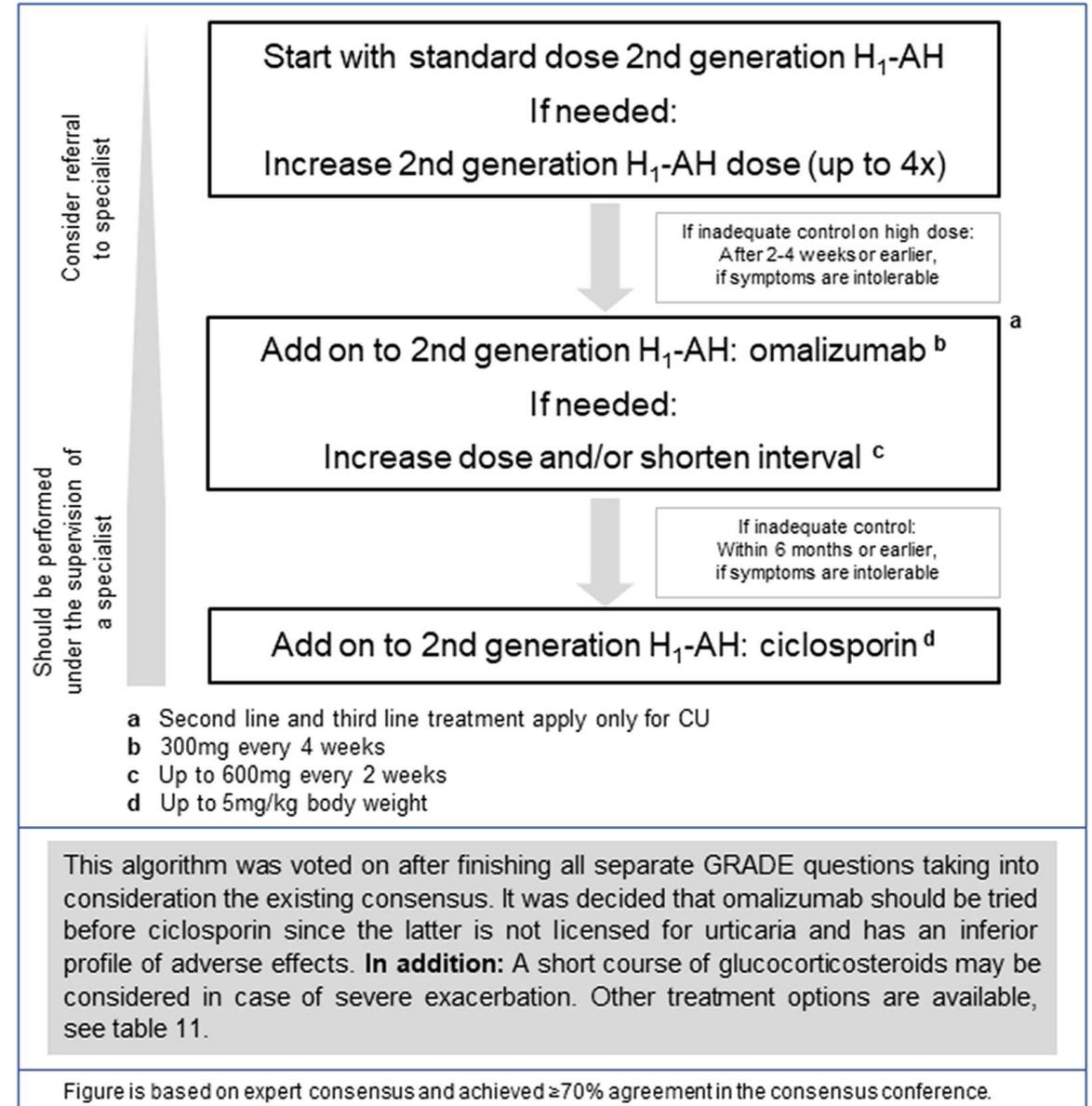
G: Kolinerg urticaria

Patients	True Positive	False Positive	True Negative	False Negative	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
<b>Provocation</b>								
<b>Probable diagnosis</b>								
Heat	0	1	183	14	0	99.5	0	92.3
Cold	9	7	205	8	52.9	96.7	56.3	96.2
Pressure	0	1	188	23	0	99.5	0	89.1
<b>Possible diagnosis</b>								
Heat	1	1*	183	55	1.8	99.5	50	76.9
Cold	4	7*	205	21	16	96.7	36.4	90.7
Pressure	1	1*	188	41	2.4	99.5	50	82.1

Maurer M. J Allergy Clin Immunol Pract 2018;6:1119-30.

Holm JG. Eur J Dermatol 2017;27:406-8.

# Behandling af kronisk urticaria



# Behandling af kronisk urticaria

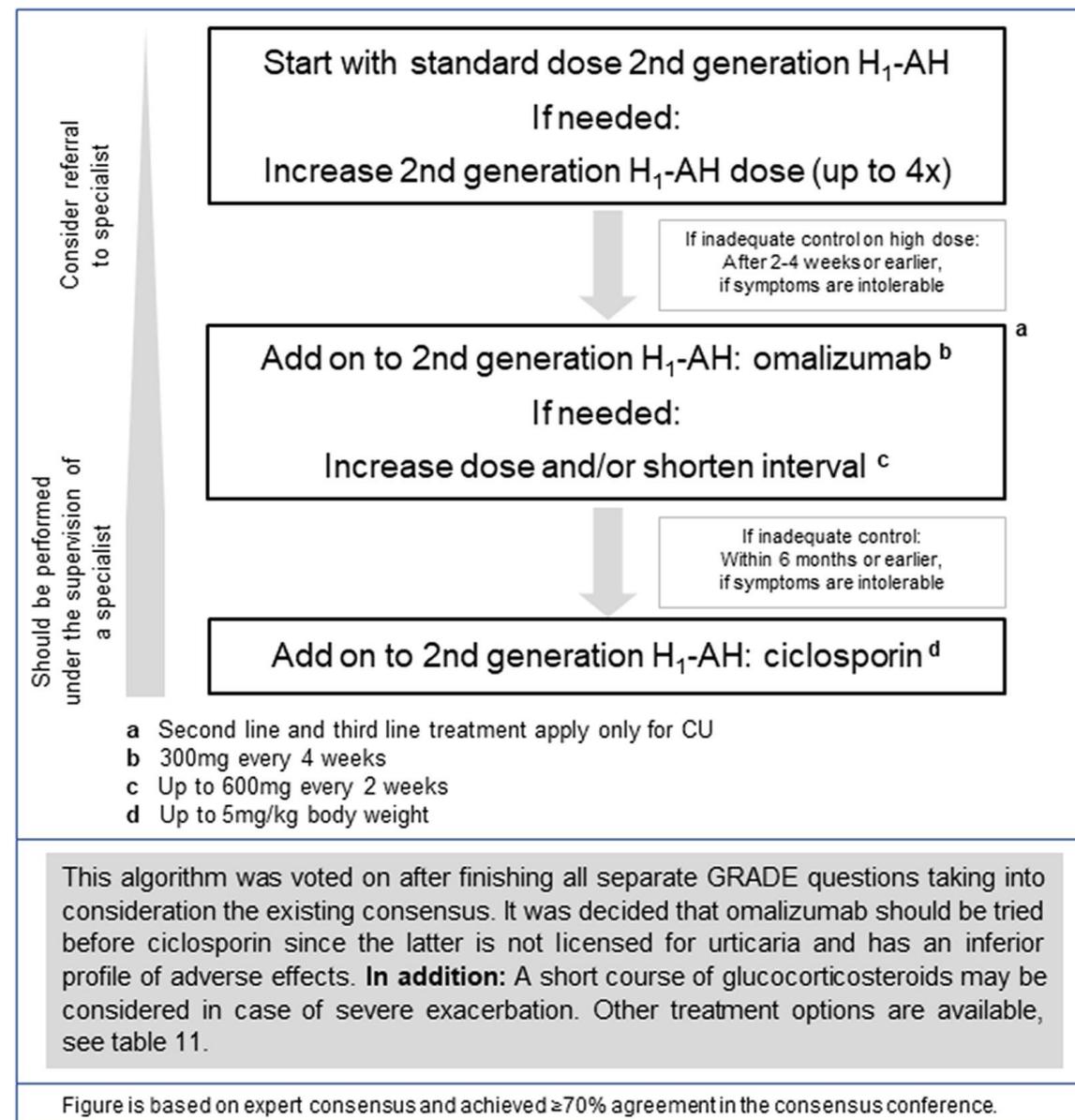
men...

Hvornår skal man starte?

Hvornår og hvordan ned/optrappes behandlingen?

Hvornår stoppes?

Hvad skal man forvente af effekt?



# Omalizumab (Xolair)

Humaniseret monoklonalt antistof rettet mod C $\epsilon$ 3 på IgE

Neutraliserer frit cirkulerende IgE (indenfor timer)  
og medfører nedregulering af IgE-receptorer på  
mastceller, basofile og dendritceller

Godkendt i:

2003 til svær allergisk astma

2014 til kronisk urticaria

2020 til kronisk bihulebetændelse

Administreres s.c. hver 4. uge, 300 mg



# Krav til sygdomsaktivitet for at få omalizumab

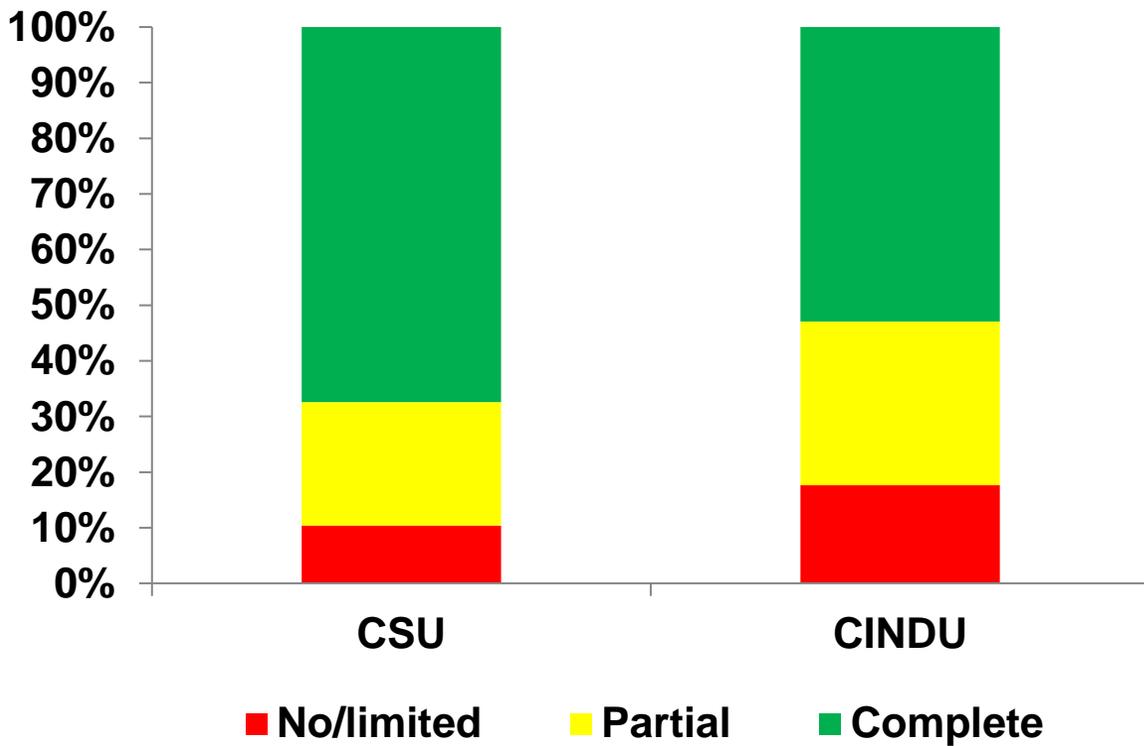
Denne kalender (urticaria aktivitetsscore) kan hjælpe dig med at overvåge forløbet af din urticaria (nældefeber).

Angiv én gang om dagen og på omtrent samme tidspunkt hver dag (f.eks. om aftenen), hvor mange nælder der er fremkommet i løbet af de sidste 24 timer, og hvor meget din hud har kløet i løbet af de sidste 24 timer.

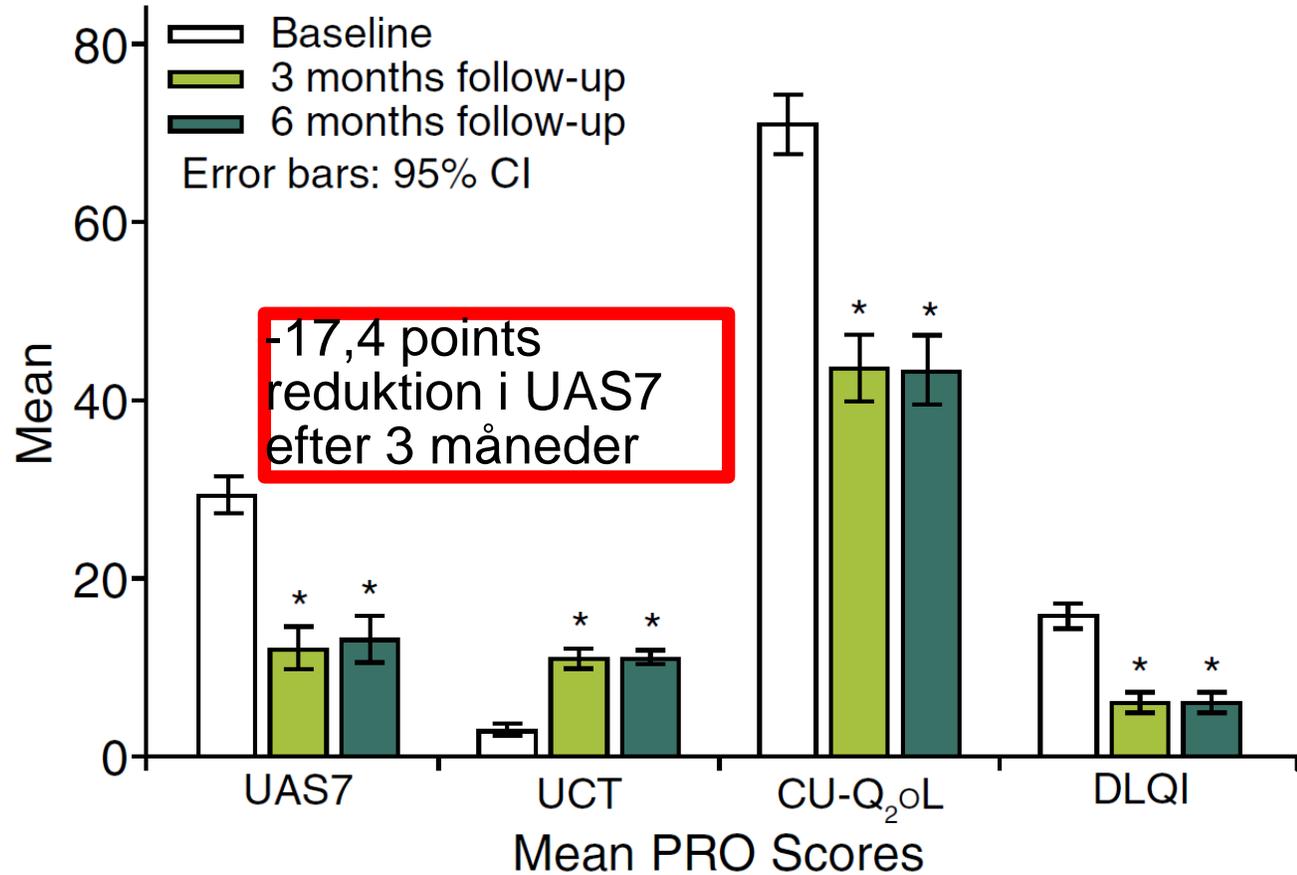
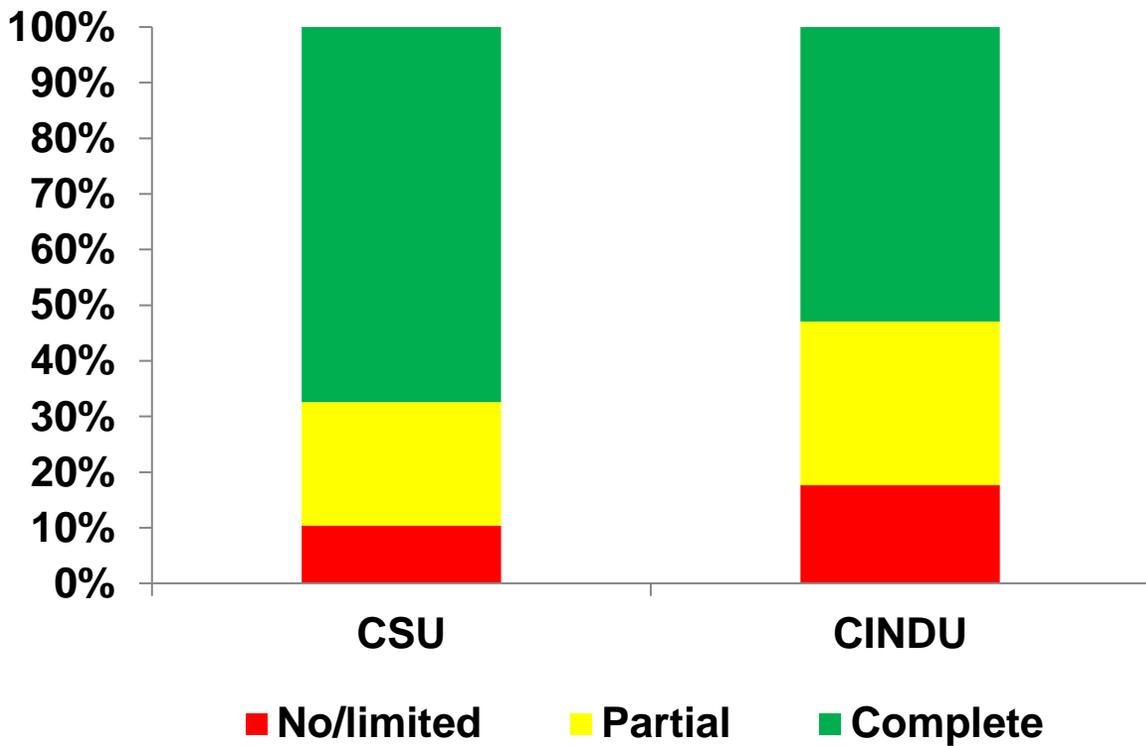
Dato	Dag	Nælder				Kløe			
		Ingen	< 20	20-50	> 50	Ingen	Mild	Moderat	Svær
	1								
	2								
	3								
	4								
	5								
	6								
	7								

**UAS7  $\geq$  16 trods opdoseret antihistamin**

# Effekt af omalizumab på kronisk urticaria



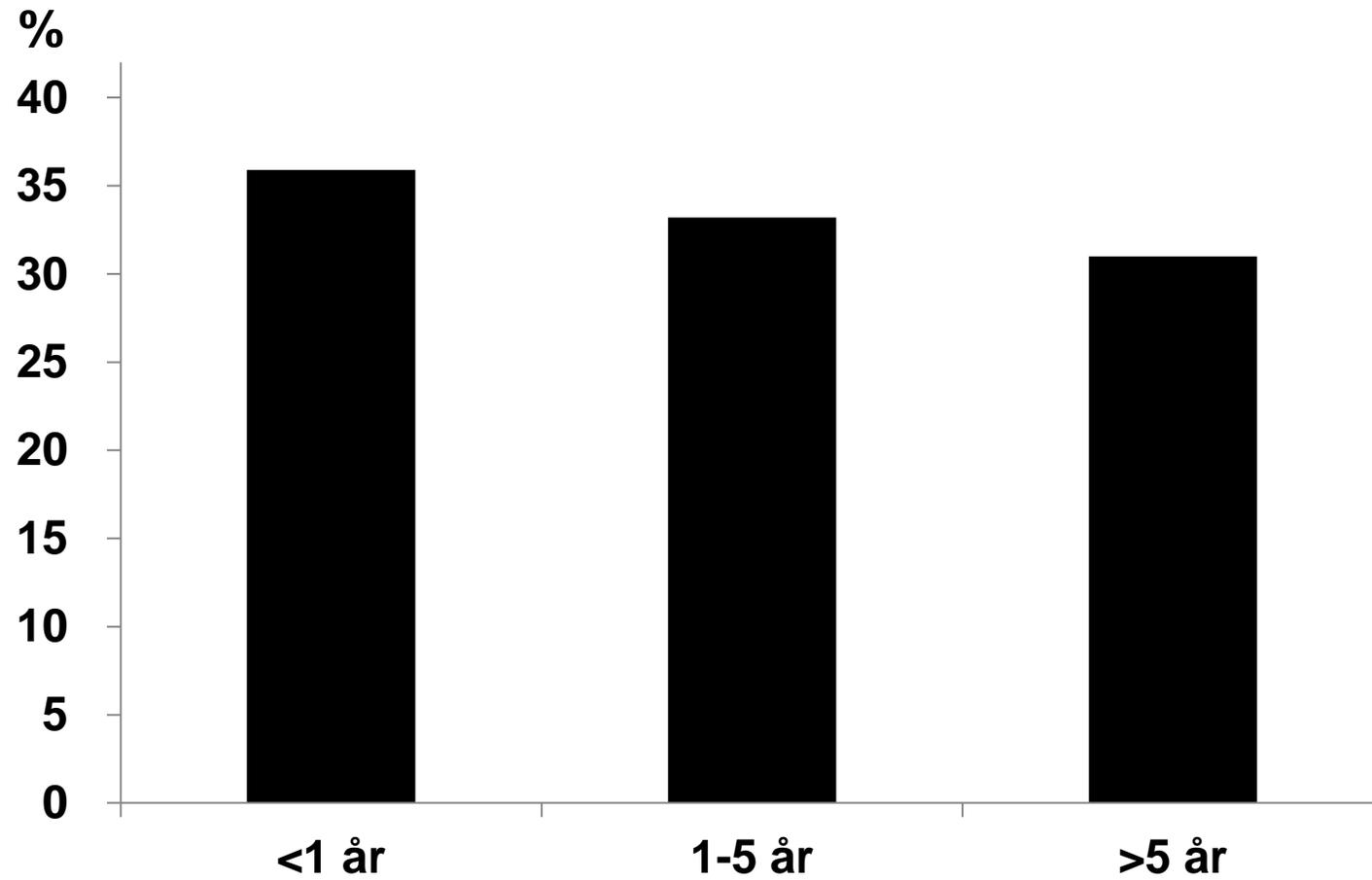
# Effekt af omalizumab på kronisk urticaria



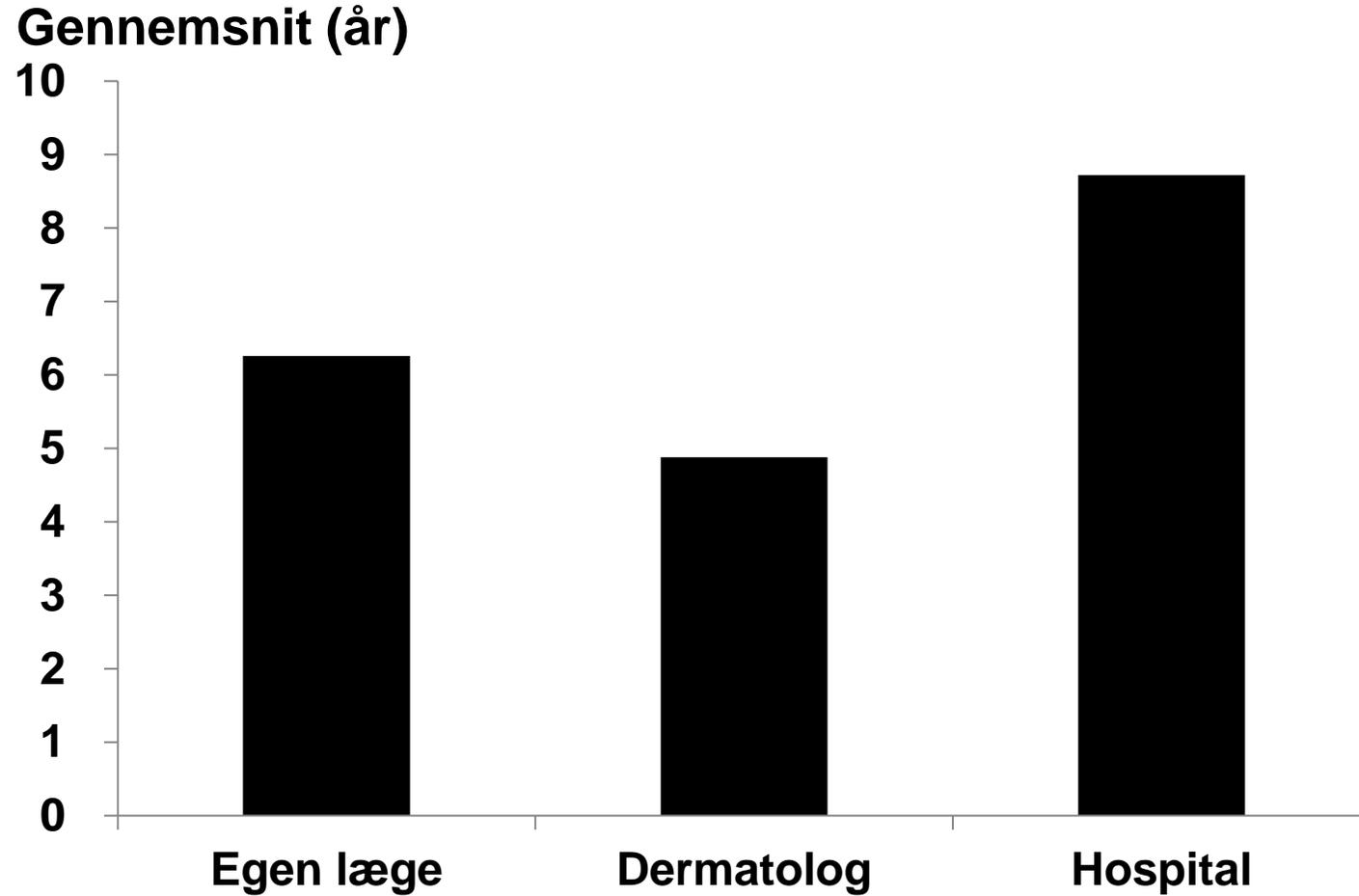
# Nyhenviste patienter med kronisk urticaria

<b>N=800 (~200 nye patienter om året)</b>	
<b>Køn (kvinder)</b>	68%
<b>Alder</b>	38 år
<b>Varighed</b>	5,5 år
<b>CINDU</b>	35%
<b>Angioødem</b>	42%
<b>Thyroidas sygdom</b>	10%
<b>Psykisk sygdom</b>	18%
<b>Astma</b>	15%
<b>Positiv urticaria HR test</b>	11%
<b>UAS7 (0-42 point)</b>	22,0
<b>DLQI (0-30 point)</b>	9,2
<b>Omalizumab ordineret ved første kons.</b>	39%

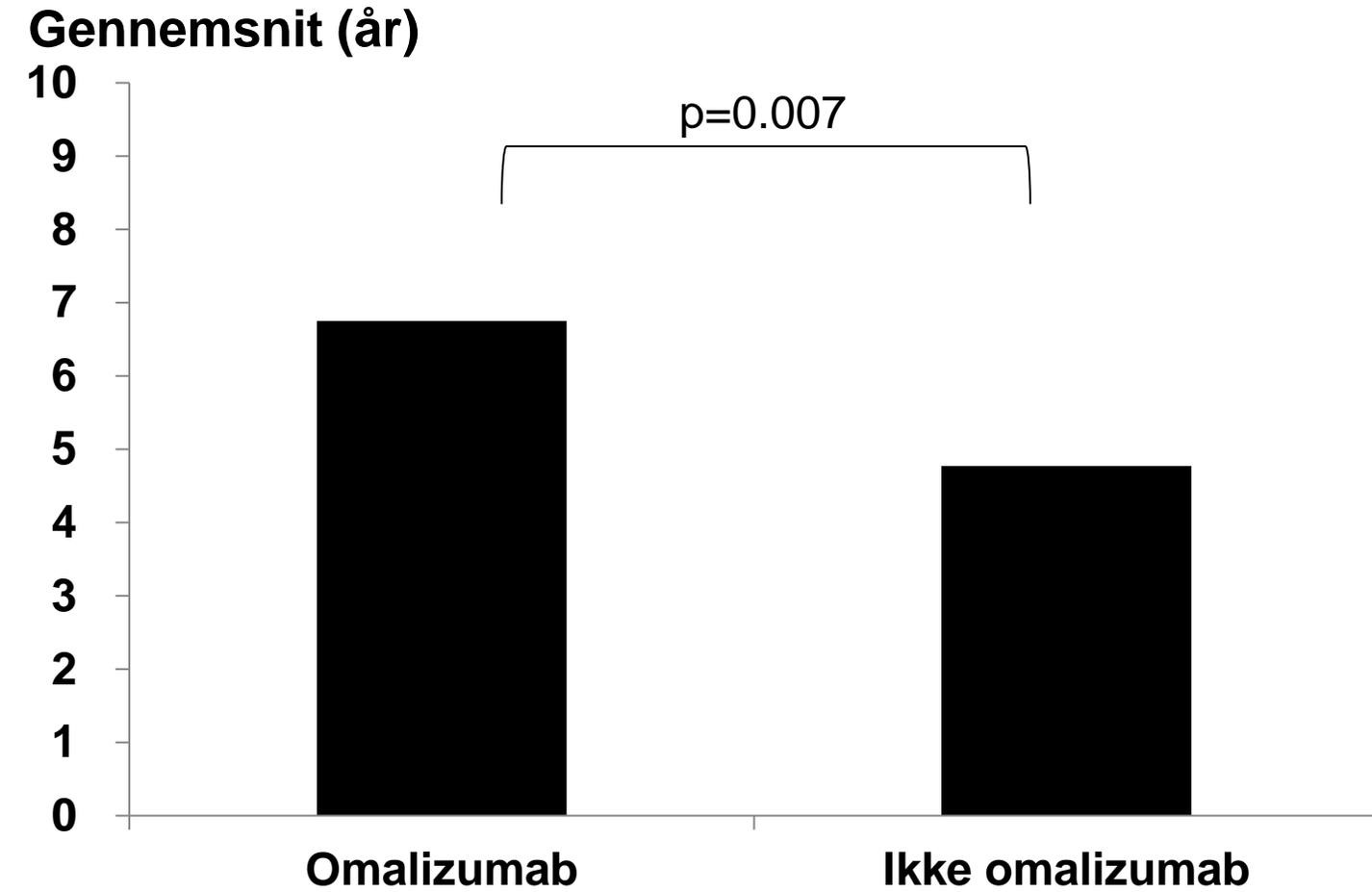
# Varighed af kronisk urticaria hos nyhenviste patienter



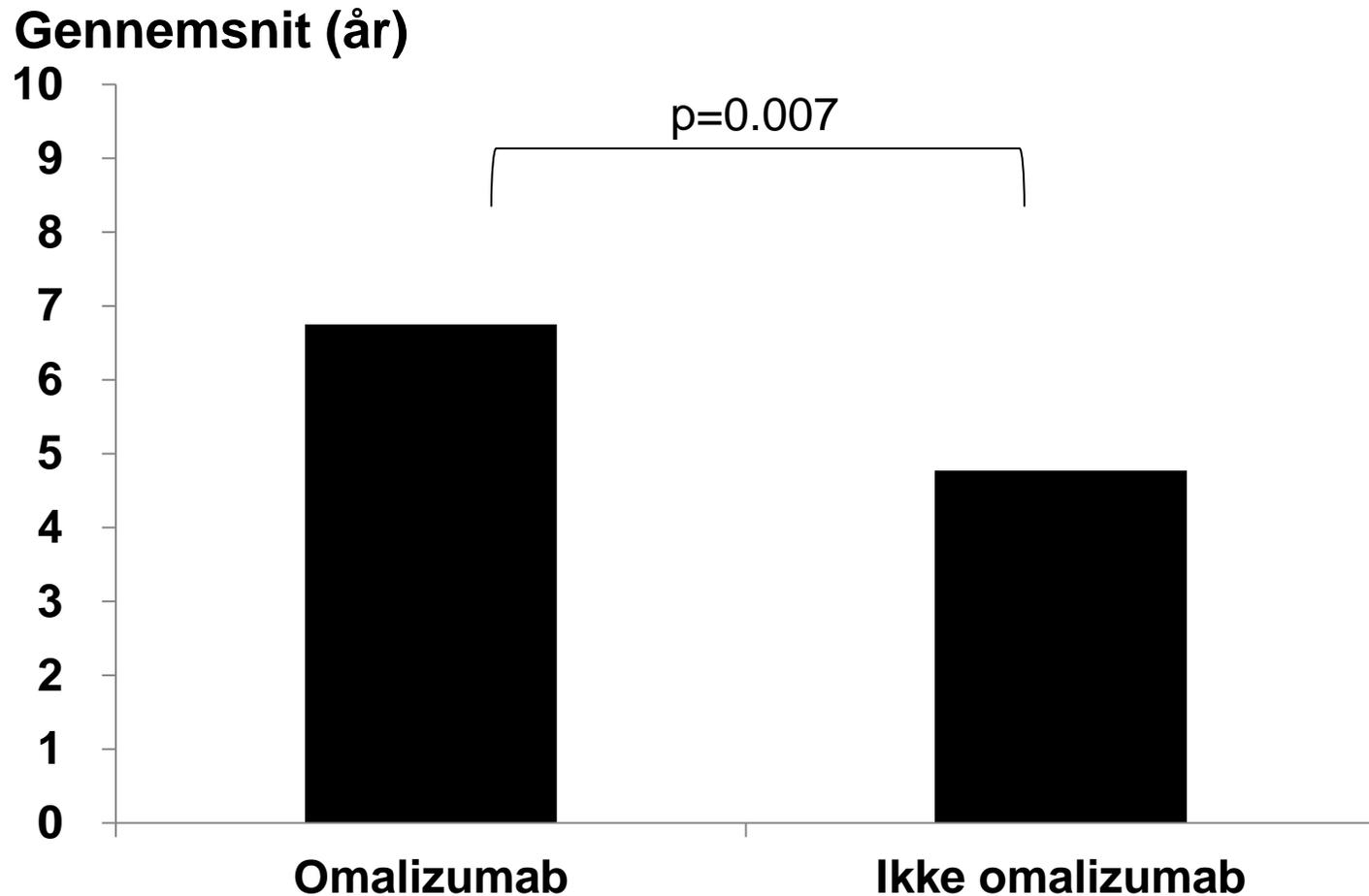
# Varighed af kronisk urticaria afhængig af henviser



# Varighed af kronisk urticaria vs. udskrevet omalizumab

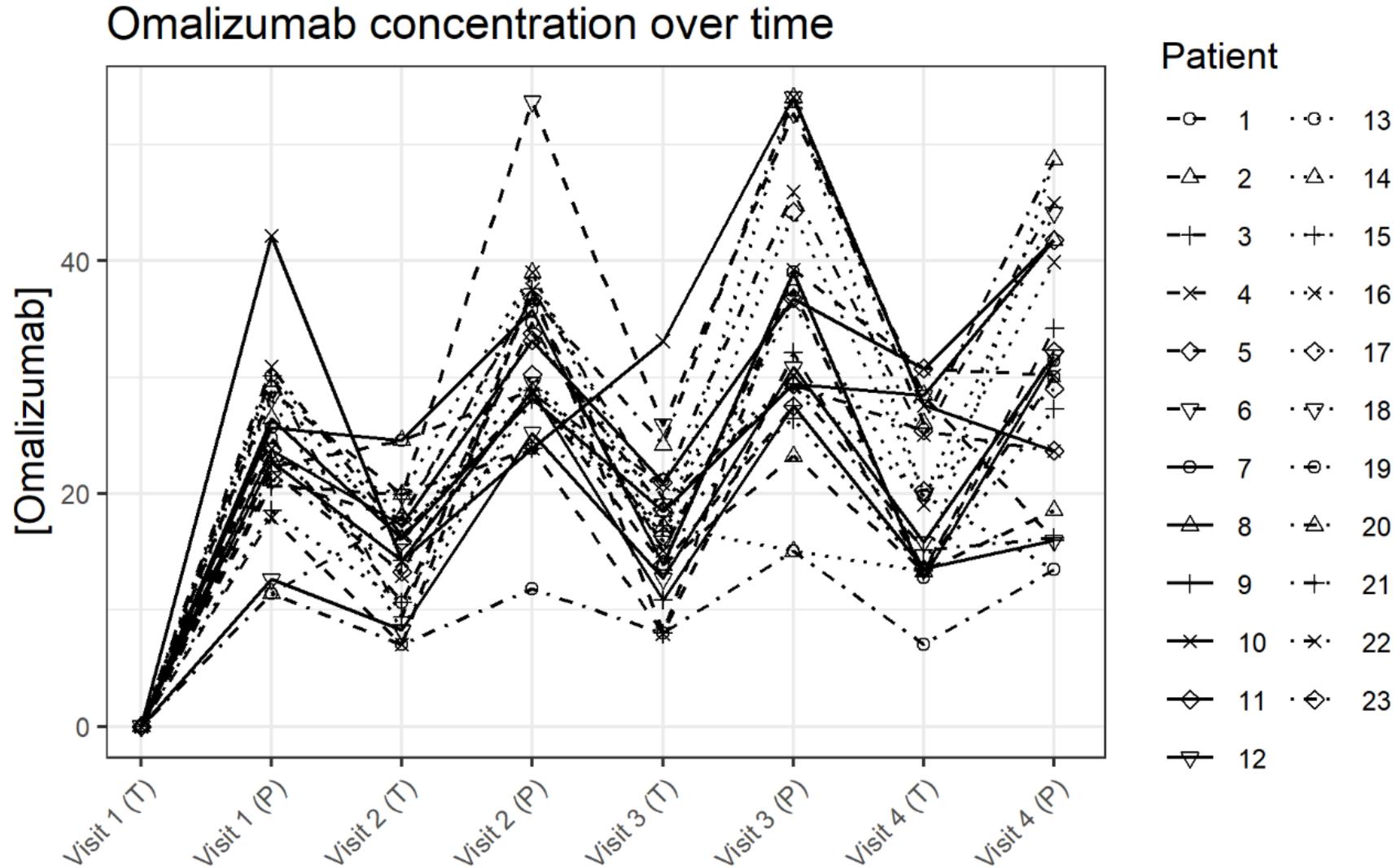


# Varighed af kronisk urticaria vs. udskrevet omalizumab

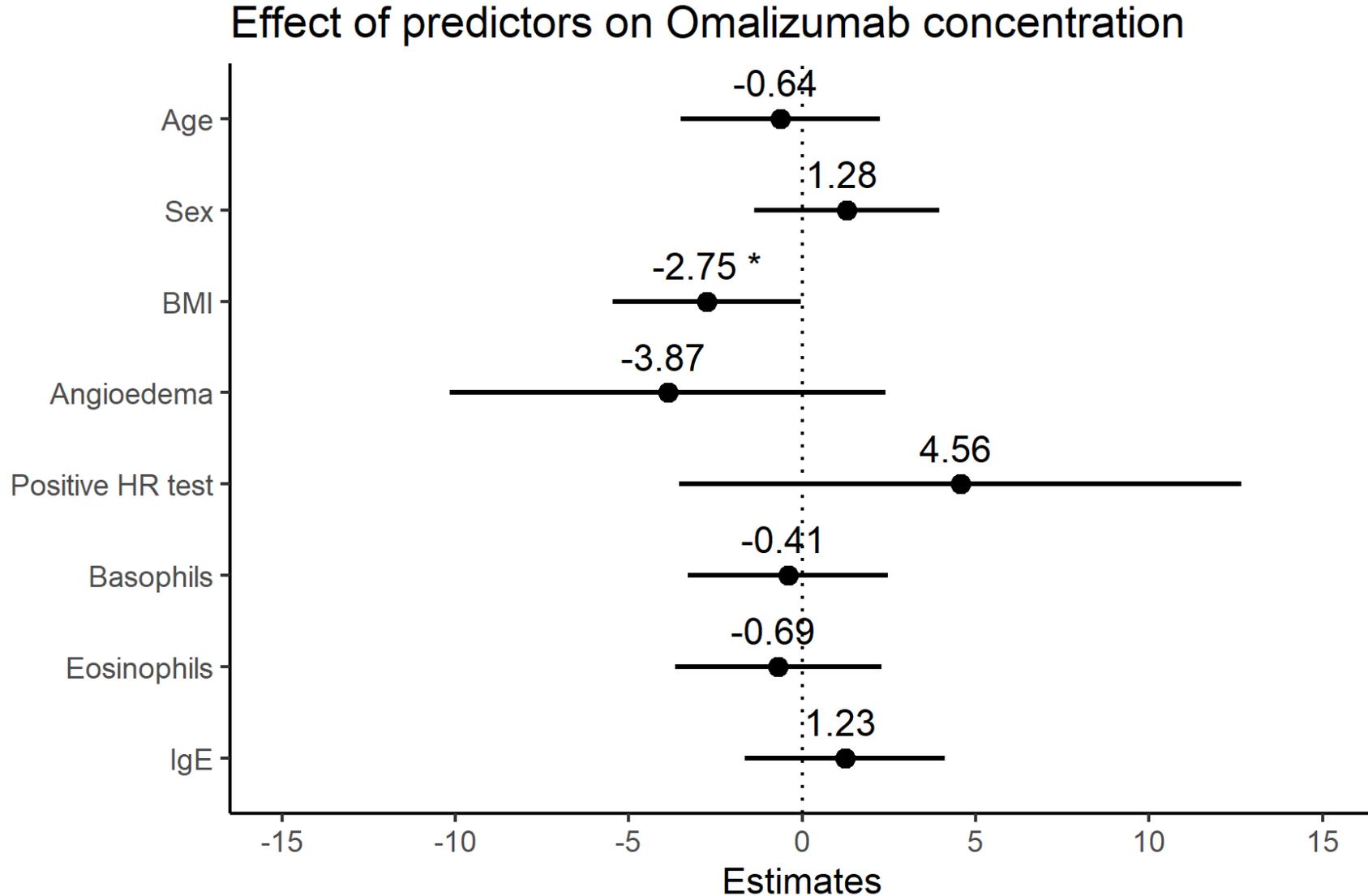


<b>Prediktorer for påbegyndelse af omalizumab</b>
Høj UAS7
Høj DLQI
Lang varighed
Angioødem
Psykisk sygdom
Henvist fra dermatolog
Tidligere anvendt systemisk steroid

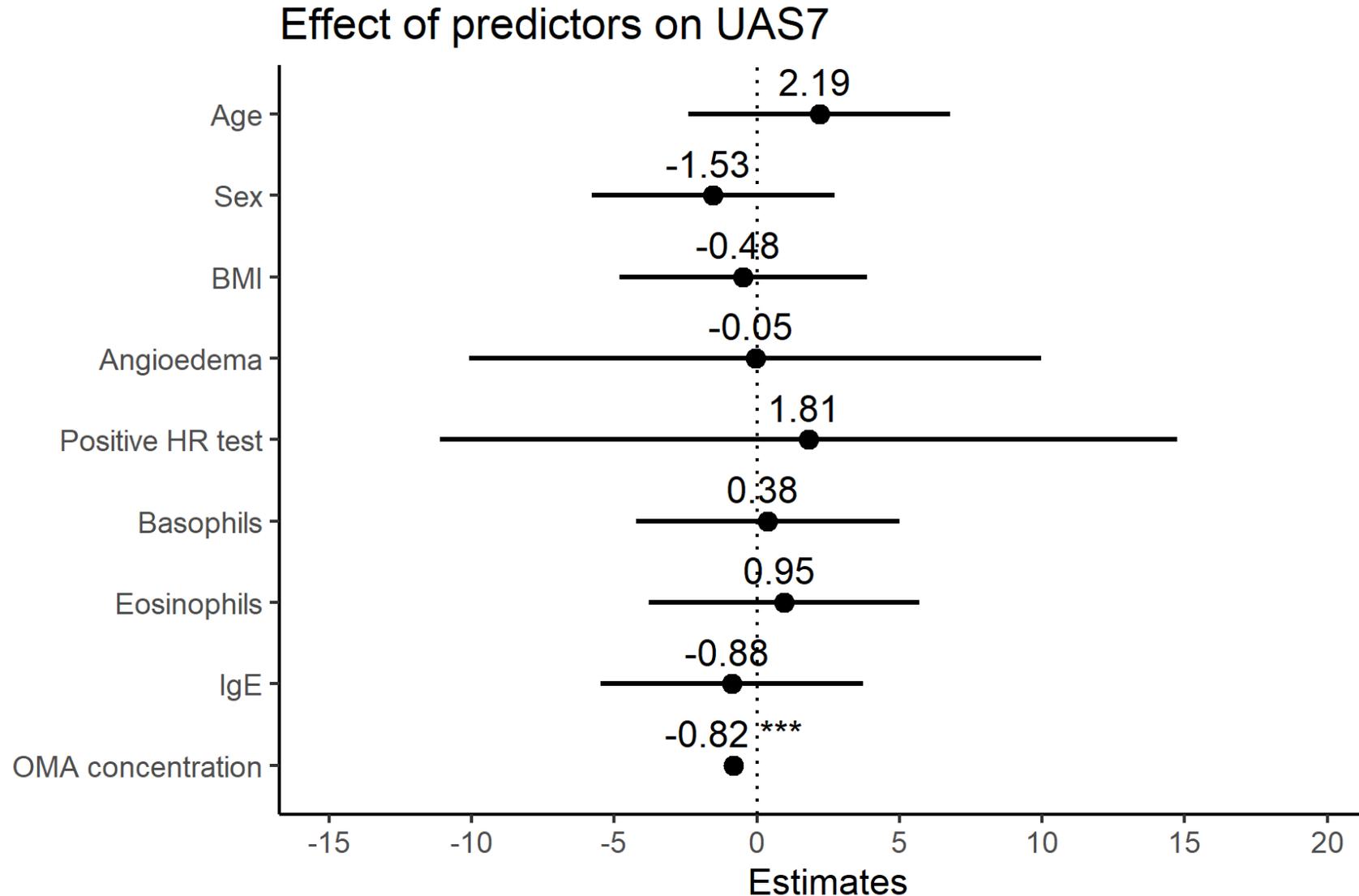
# Tid til opnåelse af peak omalizumab koncentration



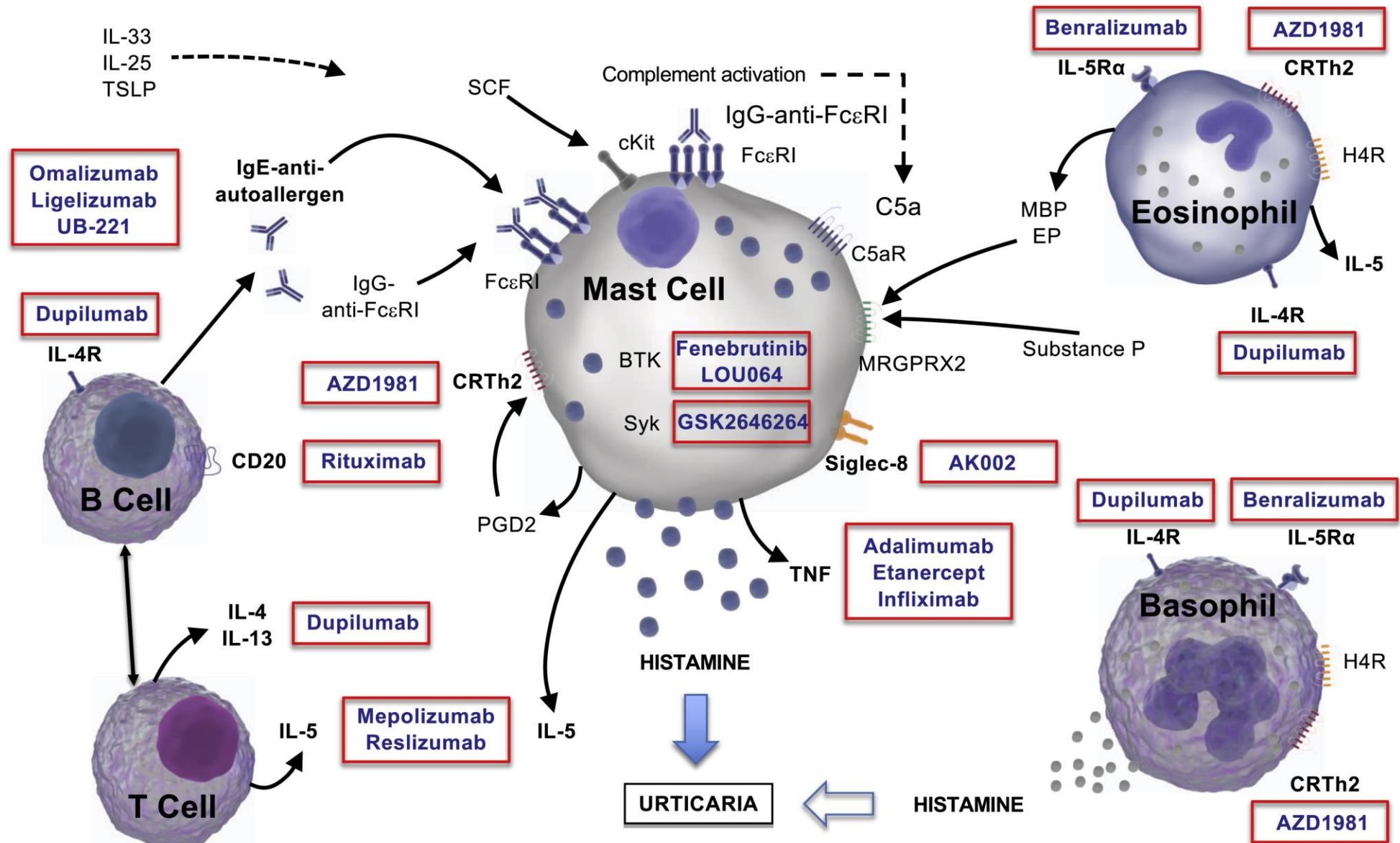
# Faktorer af betydning for omalizumab peak koncentration



# Faktorer af betydning for omalizumab effektivitet



# Lægemedler til kronisk urticaria



# Urticaria og graviditet

## The PREG-CU study



21 UCAREs  
13 countries



Pregnant woman  
with chronic urticaria  
n= 288



47-item-  
questionnaire

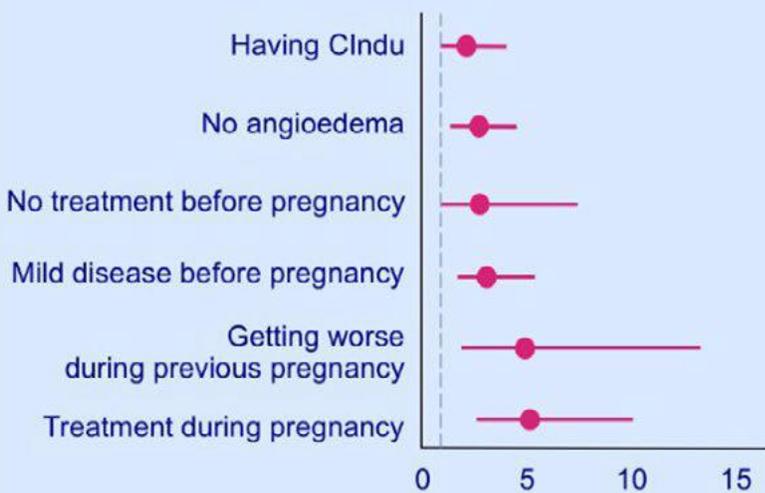
## Course of CU during pregnancy



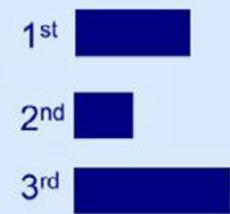
10% pregnant CU patients require emergency care



## Risk factors



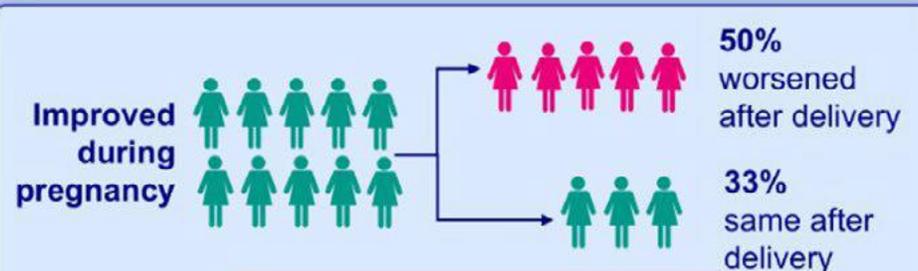
## Exacerbations per trimester



## Angioedema frequency



## Worsening of CU during pregnancy



## Course of CU after delivery

# Urticaria og graviditet

**TABLE I.** Serum total IgE levels and their association with disease activity changes during pregnancy

CSU disease parameters		Total IgE level, median (range)	<i>P</i>
Diagnosis	CSU	103 (3-1664)	.971
	CSU + CIndU	103 (19-672)	
Severity before pregnancy	Mild	112* (3-967)	.009*
	Moderate	128† (4-1664)	.018†
	Severe	68*† (11-347)	
Angioedema during pregnancy	Unchanged	115 (3-1664)	.539
	Got better	100 (4-515)	
	Got worse	60 (37-379)	
Emergency referral during pregnancy	Yes	89 (10-406)	.953
	No	106 (3-1664)	
Disease activity during pregnancy	Got better	82.2‡ (4-672)	.033‡
	Got worse	154‡ (3-967)	
	Did not change	120 (10-1664)	
Disease activity after birth	Got better	120 (3-967)	.501
	Got worse	84.3 (4-1664)	
	Did not change	128 (7-965)	

# Behandling af urticaria før og under graviditet

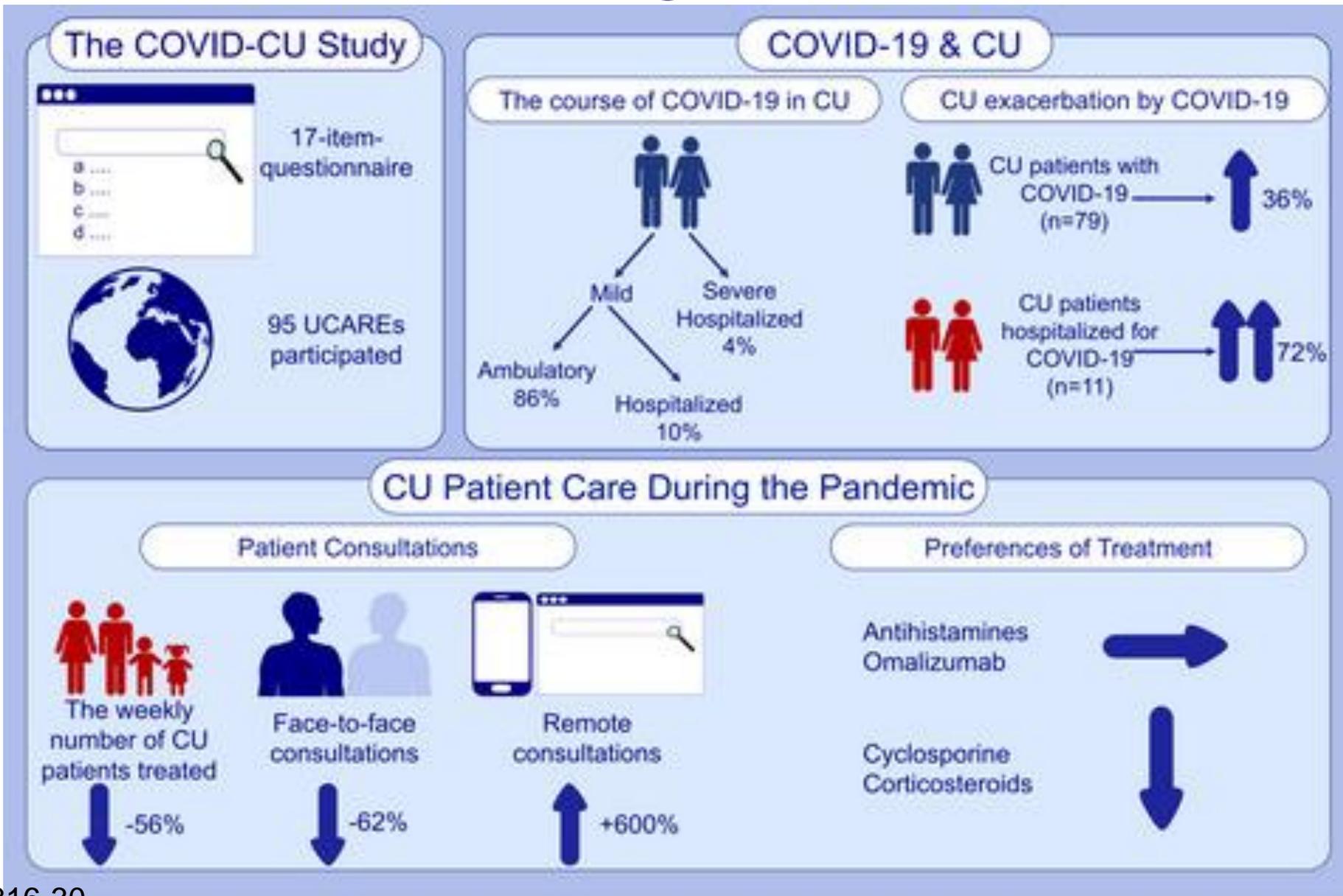
Treatments used before pregnancy, <i>n</i> (%)	Continued use during pregnancy, <i>n</i> (%)	Stopped and did not switch to other regular medication, <i>n</i> (%)	Stopped and switched to other regular medication							
			Total, <i>n</i> (%)	SD-sgAH, <i>n</i>	HD-sgAH, <i>n</i>	fgAH, <i>n</i>	AH-comb, <i>n</i>	Oma, <i>n</i>	GCS, <i>n</i>	Other, <i>n</i>
Total, <i>n</i> = 166, 100%	60 (36.1)	47 (28.3)	59 (35.5)	35	5	11	4	1	3	0
SD-sgAH, <i>n</i> = 65, 39.1%	35 (53.8)	22 (33.8)	8 (12.3)	-	2	4	0	1	1	0
HD-sgAH, <i>n</i> = 38, 22.9%	5 (13.1)	8 (21)	25 (65.8)	17	-	5	2	0	1	0
fgAH, <i>n</i> = 10, 6%	6 (60.0)	1 (10.0)	3 (30.0)	2	1	-	0	0	0	0
AH-comb, <i>n</i> = 7, 4.2%	0	4 (57.1)	3 (42.8)	3	0	0	-	0	0	0
LTRA-comb, <i>n</i> = 11, 6.6%	0	3 (27.3)	8 (72.7)	3	1	2	1	0	1	0
Oma, <i>n</i> = 22, 13.2%	10 (45.4)	3 (13.6)	9 (40.9)	9	0	0	0	-	0	0
GCS, <i>n</i> = 8, 4.8%	3 (37.5)	3 (37.5)	2 (25.0)	1	0	0	1	0	-	0
Other <sup>a</sup> , <i>n</i> = 5, 3%	1 (20.0)	3 (60.0)	1 (20.0)	0	1	0	0	0	0	-

# Behandling af urticaria før og under graviditet og amning

Treatments used before pregnancy, <i>n</i> (%)	Continued use during pregnancy, <i>n</i> (%)	Stopped and did not switch to other regular medication, <i>n</i> (%)	Stopped and switched to other regular medication							
			Total, <i>n</i> (%)	SD-sgAH, <i>n</i>	HD-sgAH, <i>n</i>	fgAH, <i>n</i>	AH-comb, <i>n</i>	Oma, <i>n</i>	GCS, <i>n</i>	Other, <i>n</i>
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fgAH, <i>n</i> = 10, 6%	6 (60.0)	1 (10.0)	3 (30.0)	2	1	-	0	0	0	0
AH-comb, <i>n</i> = 7, 4.2%	0	4 (57.1)	3 (42.8)	3	0	0	-	0	0	0
LTRA-comb, <i>n</i> = 11, 6.6%	0	3 (27.3)	8 (72.7)	0	0	0	0	0	0	0
Oma, <i>n</i> = 22, 13.2%	10 (45.4)	3 (13.6)	9 (40.9)	0	0	0	0	0	0	0
GCS, <i>n</i> = 8, 4.8%	3 (37.5)	3 (37.5)	2 (25.0)	0	0	0	0	0	0	0
Other <sup>a</sup> , <i>n</i> = 5, 3%	1 (20.0)	3 (60.0)	1 (20.0)	0	0	0	0	0	0	0

Treatments	<i>n</i>	%
SD-sgAH	85	61.5
HD-shAH	19	13.7
fg- AH	7	5.1
AH-comb/LTRA-comb	4	2.8
Oma	11	8.0
GCS	6	4.3
Other <sup>a</sup>	6	4.3
Total	138	100

# Urticaria og COVID-19



# Kronisk urticaria og alfa-gal allergi

	Private allergology practice, <i>n</i> = 450				Dermatology hospital department, <i>n</i> = 283	
	Chronic urticaria, <i>n</i> = 373		Non-urticaria, <i>n</i> = 77		Chronic urticaria, <i>n</i> = 283	
	$\alpha$ -gal sensitized <i>n</i> = 21 (5.6%)	$\alpha$ -gal non-sensitized <i>n</i> = 352 (94.4%)	$\alpha$ -gal sensitized <i>n</i> = 4 (5.2%)	$\alpha$ -gal non-sensitized <i>n</i> = 73 (96.1%)	$\alpha$ -gal sensitized <i>n</i> = 11 (3.9%)	$\alpha$ -gal non-sensitized <i>n</i> = 272 (96.1%)
Sex, <i>n</i> (%)						
Female	11 (52.4)	265 (75.3)	2 (50.0)	40 (54.8)	3 (27.3)	196 (72.1)
Male	10 (47.6)	87 (24.7)	2 (50.0)	33 (45.2)	8 (72.7)	76 (27.9)
Age (years), mean (SD)	54.0 (16.1)	45 (17.8)	68.2 (16.8)	48.1 (17.0)	33.8 (16.2)	38.2 (17.1)
Obesity (BMI $\geq$ 30.0 kg/m <sup>2</sup> ), <i>n</i> (%)	7 (33.3)	83 (23.6)	0 (0)	18 (24.7)	N/A	N/A
Angioedema, <i>n</i> (%)	13 (61.9)	181 (51.4)	0 (0)	0 (0)	5 (45.5)	119 (43.8)
PRO-score, mean (SD)	N/A	N/A	N/A	N/A		
UAS7					24.3 (16.6)	21.4 (14.1)
UCT					4.3 (3.9)	6.0 (4.2)
Total IgE (KU/L)	233 (28–4.840)		103 (103–103)		168 (15–1.280)	70.50 (1.00–12.800)
Clinically relevant, <i>n</i> (%)		N/A		N/A		N/A
Yes	8 (38.1)		0		2 (18.2)	
No	6 (28.6)		3 (75.0)		7 (63.6)	
Information unavailable	7 (33.3)		1 (25.0)		2 (18.2)	