Thyroid Eye Disease - Update

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Comon misconceptions about Thyroid Eye Disease

"easily missed, much misunderstood"

Thyroid Eye Disease
Graves Orbitopathy

TED and thyroid dysfunction occur together

- 5-10% euthyroid at presentation
- Anti-TPO antibodies are negative in up to 80% of cases

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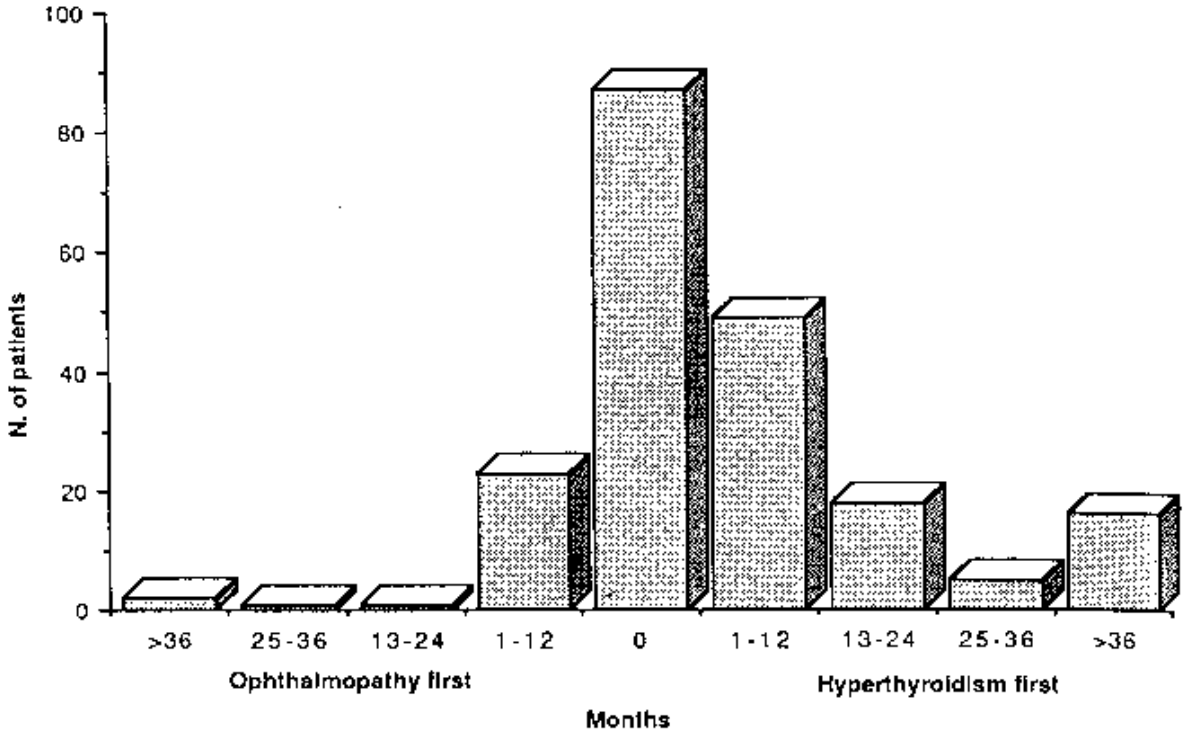
TED and thyroid dysfunction occur together



Marocci et al (1989)

TED gets better by itself

- Only 10-15% of TED is progressive
- 65% improve within 1 year
- 43% still have symptoms after mean of 9 years

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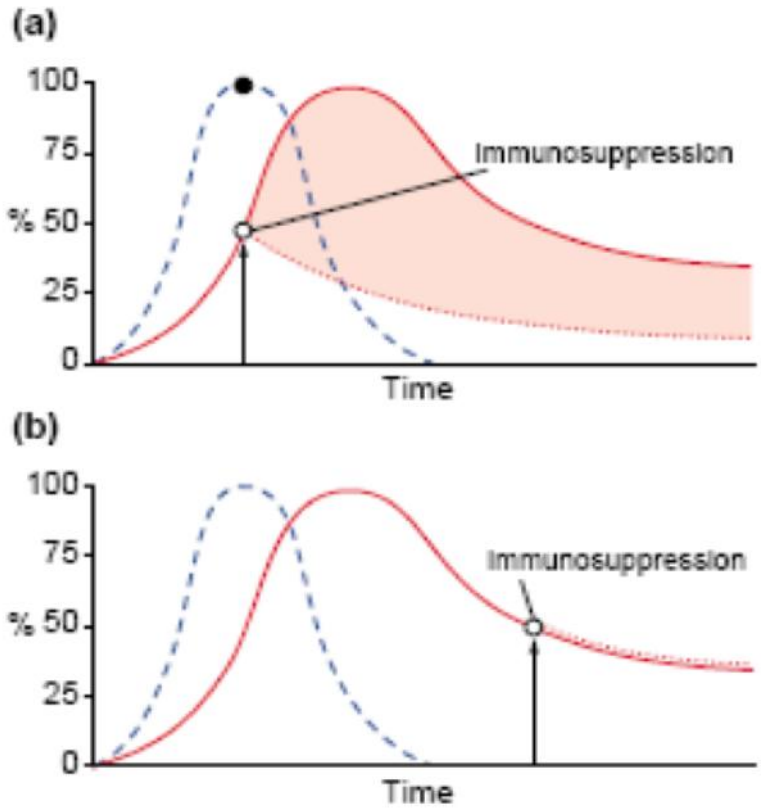
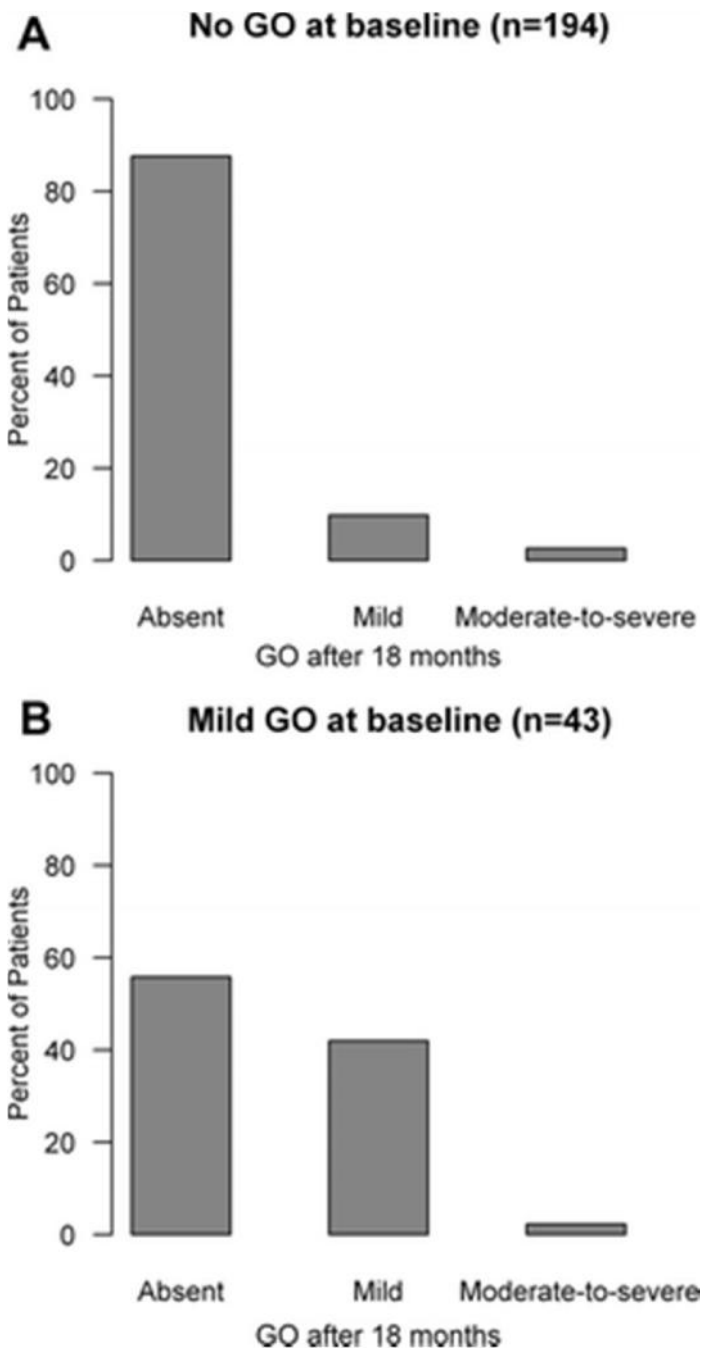
Natural Hx: Active versus inactive disease





The course of GO in 237 patients with no or mild GO. Panel A, patients with no GO at presentation (n = 194). Panel B, patients with initially mild and inactive GO (n = 43)

Tanda et al 2013

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Active versus inactive disease

- Active

- Inactive

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NATIONAL EYE RESEARCH CENTRE

ABOVE & BEYOND

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ABOVE & BEYOND

Clinical Activity Score

PAIN

- Pain on eye movement in the last 4 weeks
- Painful, oppressive feeling on or behind globe in the last 4 weeks

REDNESS

- Conjunctival redness
- Eyelid redness

SWELLING

- Chemosis
- Swollen caruncle
- Eyelid oedema
- Increasing proptosis of > 2mm

IMPAIRED FUNCTION

- Decreasing visual acuity of > 1 snellen line
- Decreasing eye movement of ≥ 8°

Mourits M *et al.* (1997) *Clinical endocrinology*, 47(1): 9-14

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ABOVE & BEYOND

Clinical Assessment:

- I – mild irritation
- II – significant irritation ,red eyes, periorbital oedema
- III – EOM involvement (diplopia)
- IV – optic nerve compression

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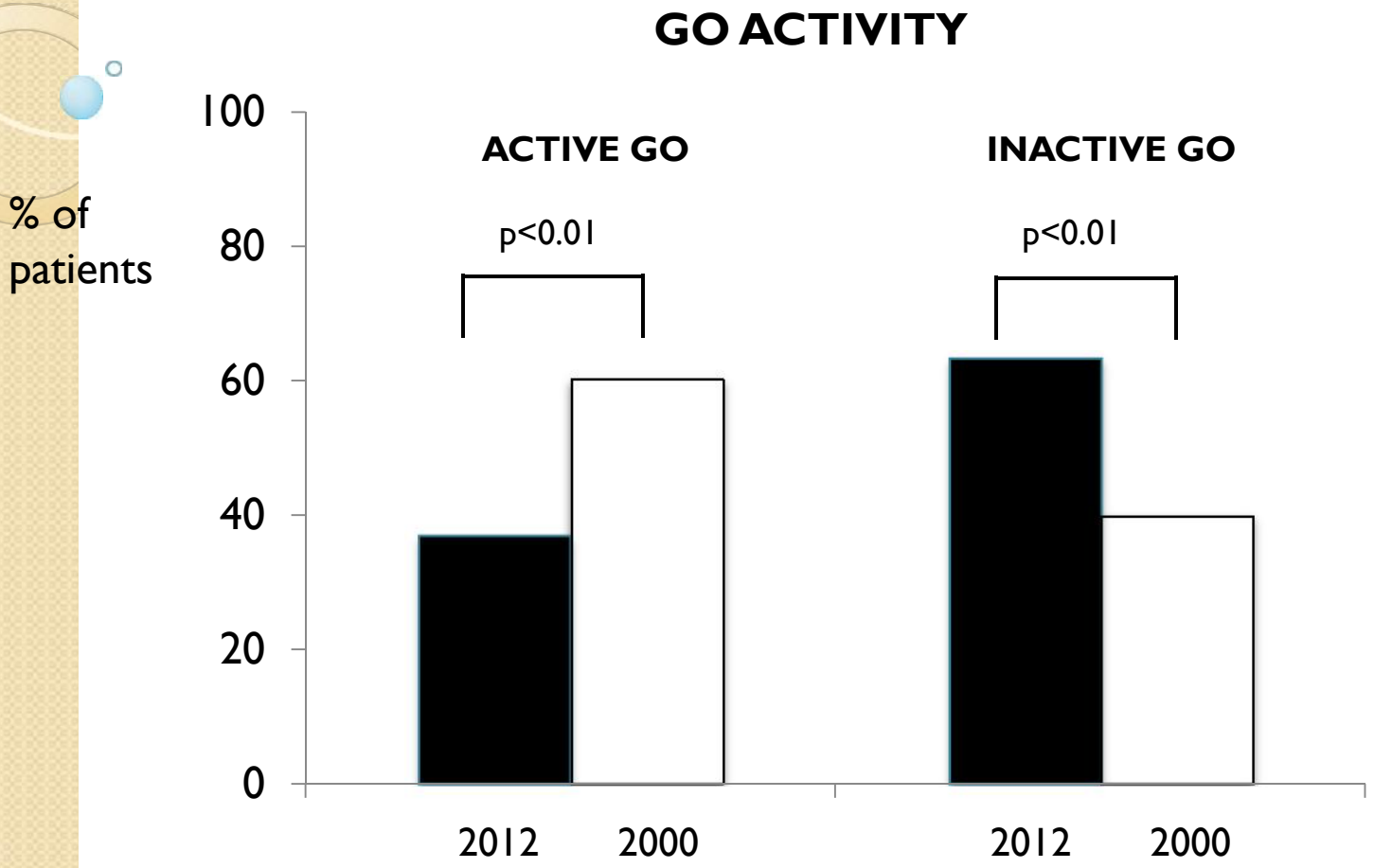
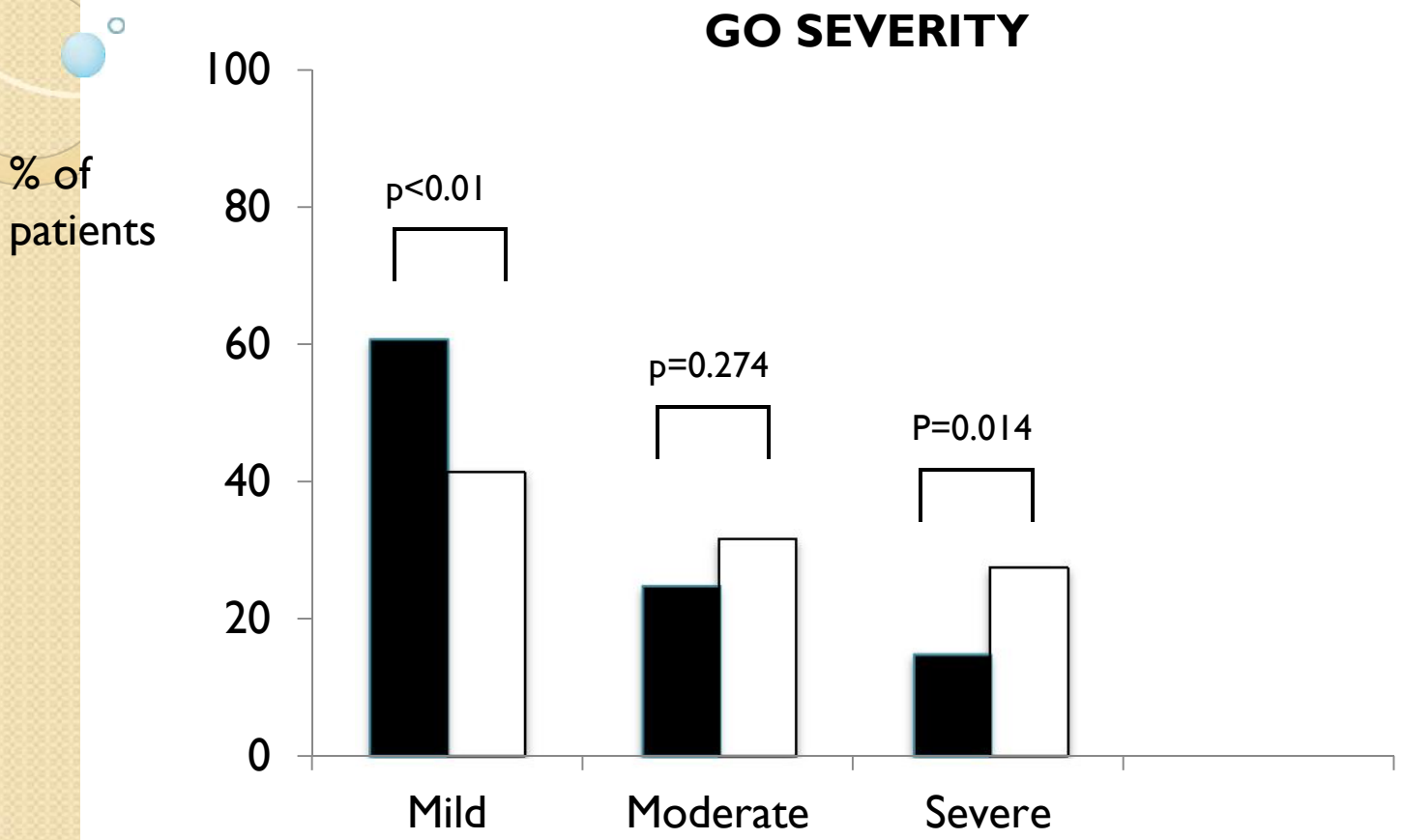
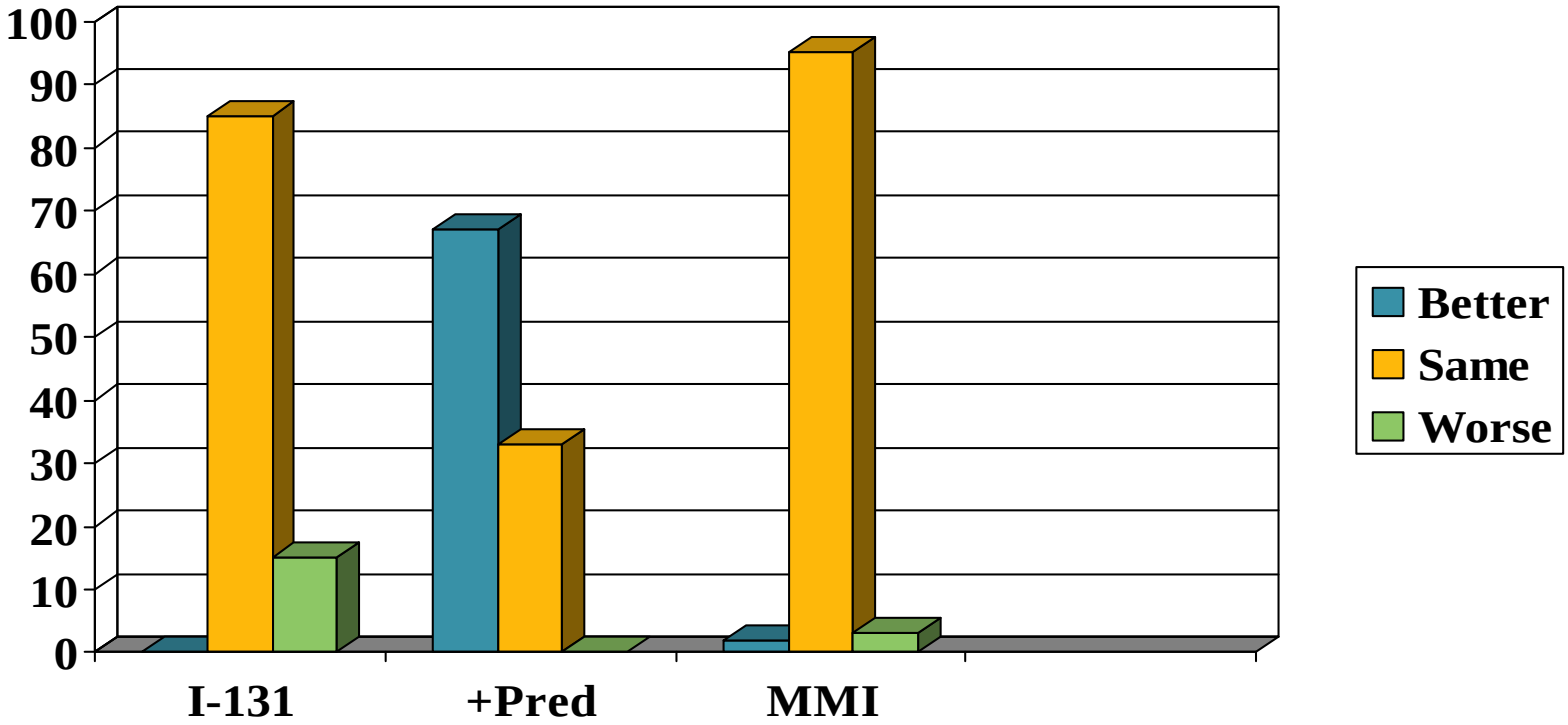

GO ACTIVITY
% of patients
100
80
60
40
20
0
ACTIVE GO
INACTIVE GO
p<0.01
p<0.01
2012
2000
2012
2000



269 patients referred within 4 mths to EUGOGO centres
40% smokers

Perros et al in preparation
Black – 2012;White - 2000

I – 131 and TED



Bartelena et al 1998

Lai et al 2010: 0.2mg/kg or 6 wks sufficient

TSHR antibodies and treatment

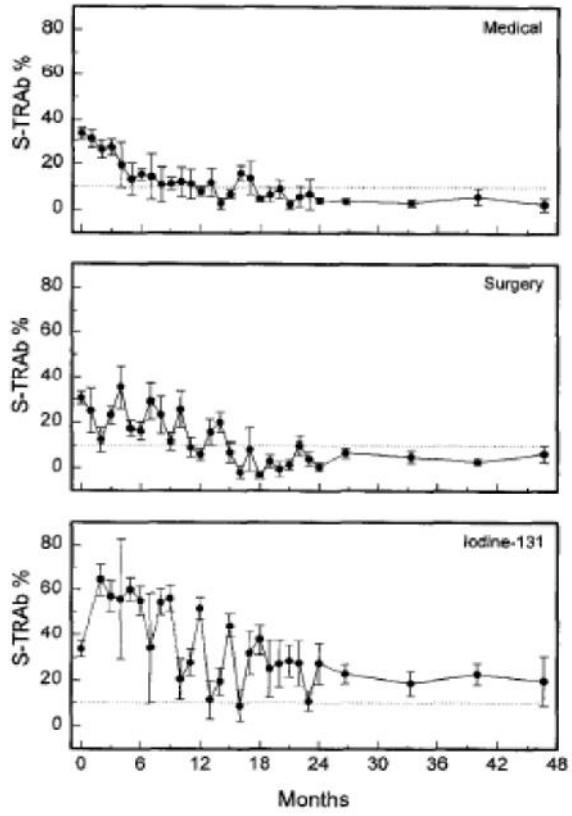


FIG. 2. The serum concentration of TRab during the first 4 yr in the different treatment groups. See also Fig. 1.

Torring et al
1996

Low dose prednisone GO prophylaxis with I-131

- Low-dose prednisone (starting dose, 0.16–0.27 mg/kg bw; mean ± sd, 0.22 ± 0.03 mg/kg bw; group 1);
- Prednisone started 1 d after RAI and withdrawn after 6 wk

Lai et al 2013

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Treatments for TED

- Local
- Systemic
  - Selenium
  - Steroids – p.o., i/v
  - DXT
  - Other immunosuppressants – CyA, Ritux
- Surgical
  - Decompression
  - Strabismus
  - Oculoplastic

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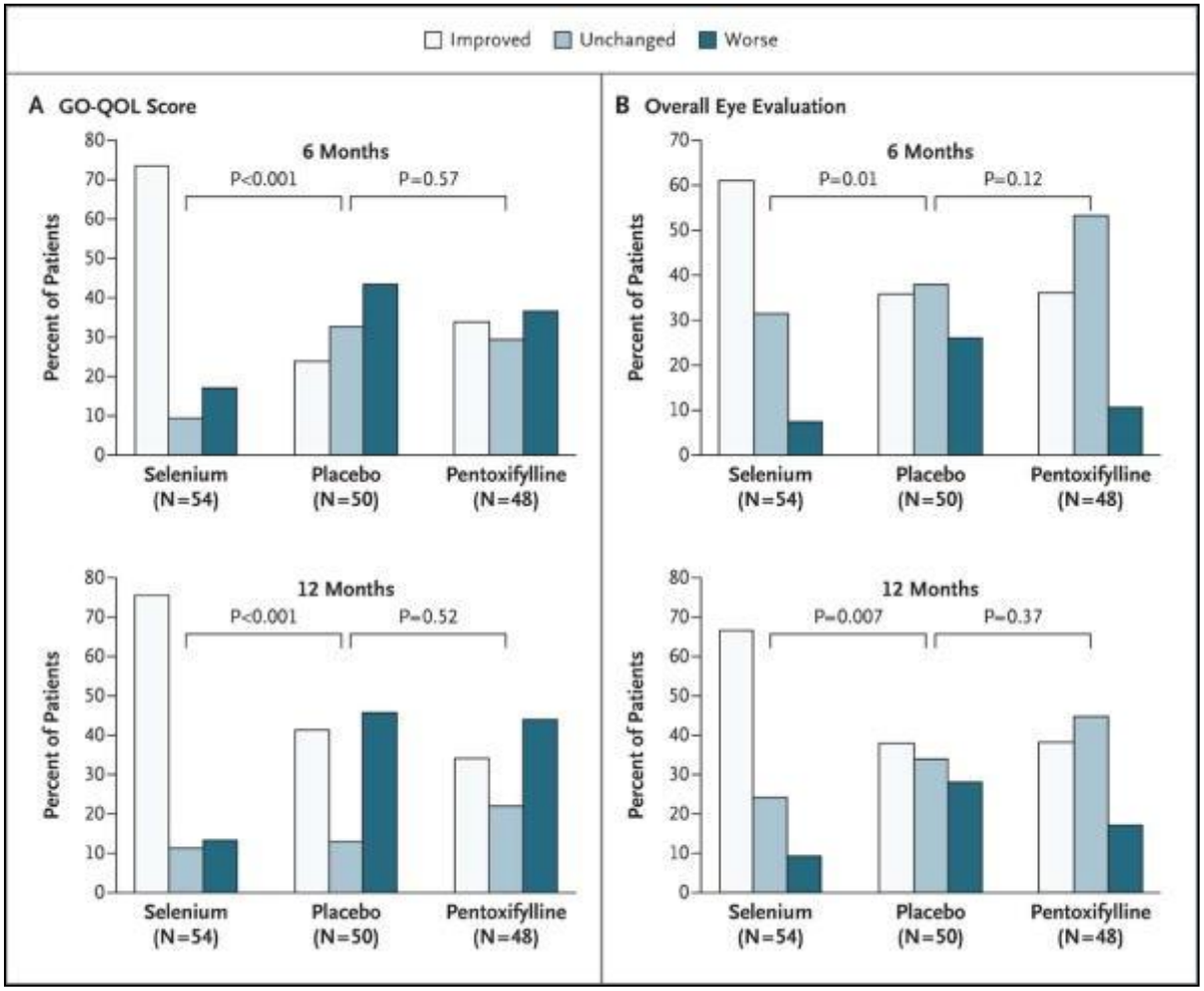
Marcocci et al 2011 - Selenium



Selenium

- Marcocci et al used 100mcg bd o sodium selenite = 105 mcg of elemental selenium
- Lambert selenium = 200mcg – use ½ tablet daily.

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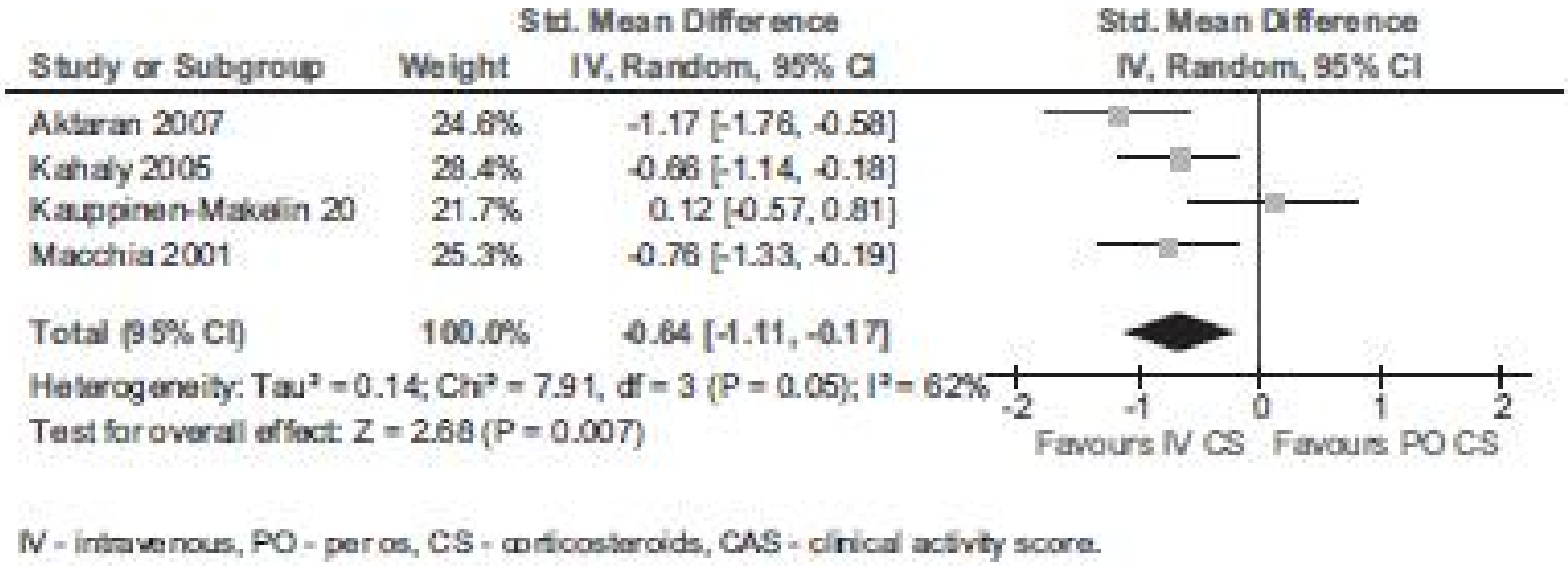
Stiebel-Kalish et al metanalysis 2009: iv vs po steroids



IV - intravenous, PO - per os, CS - corticosteroids, CAS - clinical activity score.

FIG. 2. Intravenous corticosteroids *vs.* oral corticosteroids. The outcome was CAS at the end of follow-up. PO, Per os; CS, corticosteroids.

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Dose of MePred for TED

Parameter	Low dose (2.25 g MP) (n = 53)	Middle dose (4.98 g MP) (n = 54)	High dose (7.47 g MP) (n = 52)
Overall responders, % of patients	28	35	52
Improvement in the quality of life, % of patients	51	48	67
Decrease in the CAS >2 points, n	58	83	81
Absolute decrease in the CAS (points)	−1.8	−2.3	−2.7
Improvement in eye motility, % of patients	21	26	46
Inactive GO at the end of treatment, % of patients	45	60	65
Relapse of GO after treatment, % of improved patients	21	40	33
Occurrence of DON during or after treatment, n of patients	3	4	3
Major adverse events, n of patients	2	3	5

Derived from Bartalena et al. [64]. DON = Dysthyroid optic neuropathy; MP = methylprednisolone.

DO NOT EXCEEED 8g TOTAL DOSE

Bartalena et al 2012

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Stiebel-Kalish et al metanalysis 2009: orbital DXT

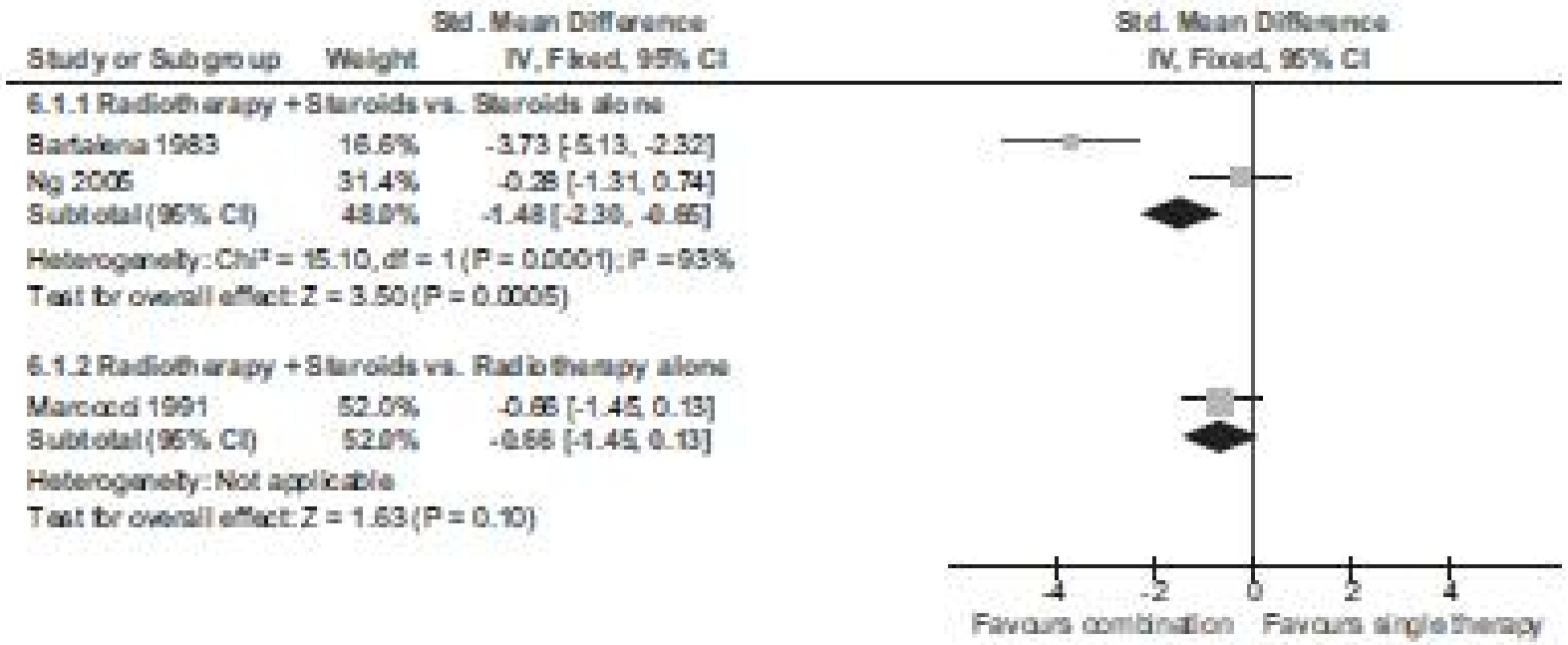

FIG. 4. Orbital radiotherapy plus corticosteroids *vs.* either treatment alone. The outcome was OI/TES at the end of follow-up.

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Stiebel-Kalish et al metanalysis 2009: other treatments

- Total thyroidectomy not better then subtotal
- Steroids better than ciclosporin but Ciclosporin + steroids better.

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Treatment of Dysthyroid Optic Neuropathy

- Iv steroid
- Urgent decompression

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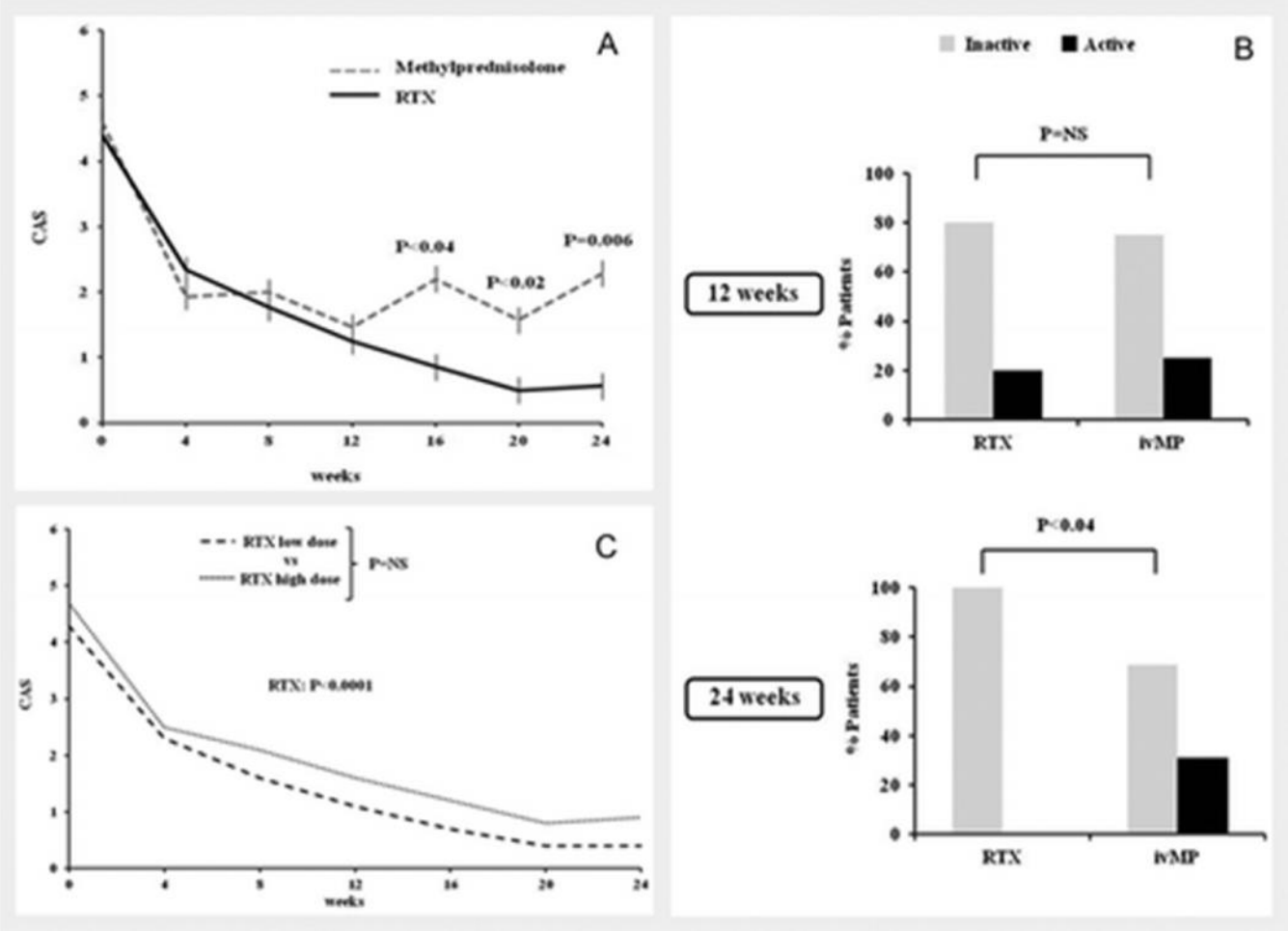
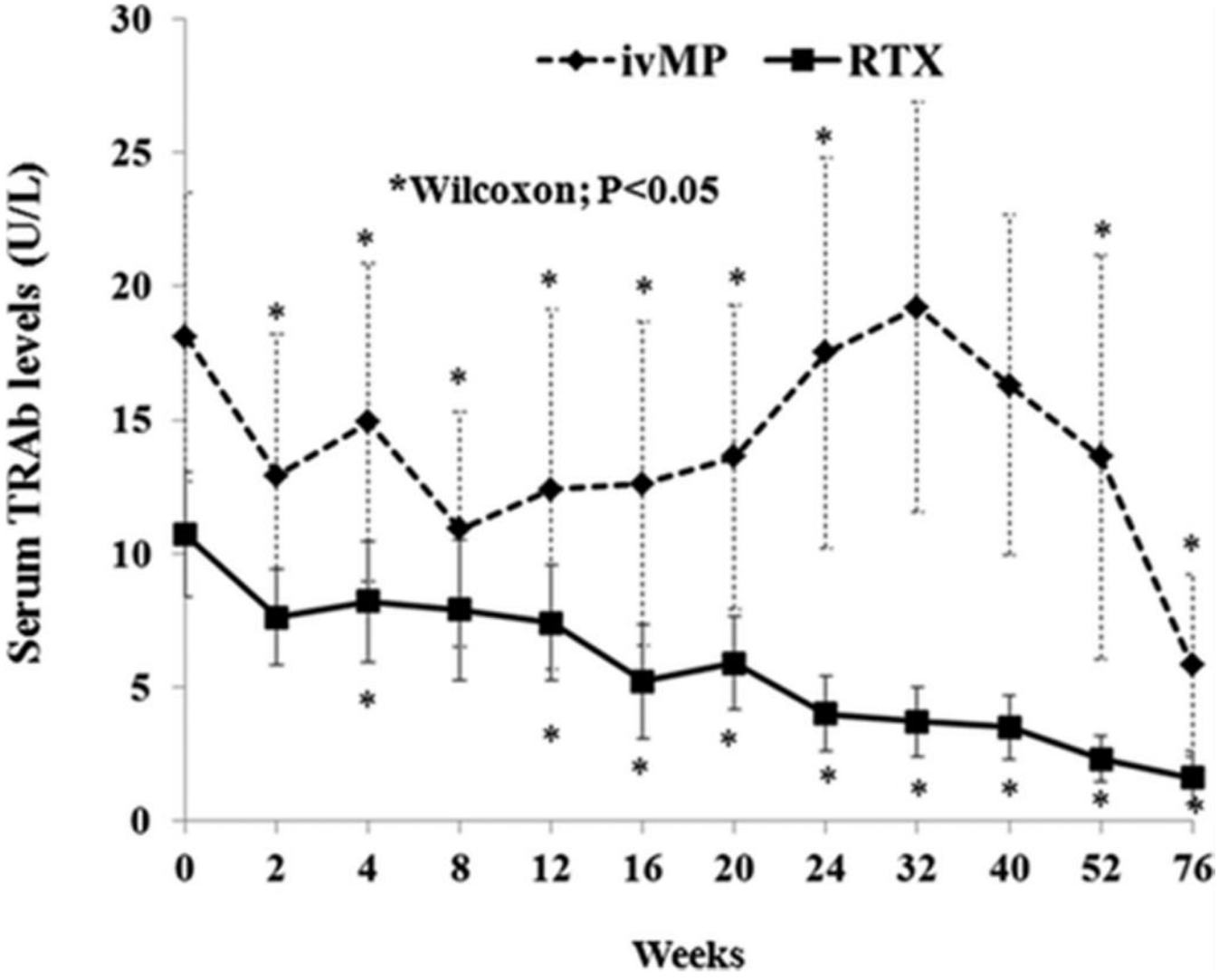
Salvi et al 2015

N= 31



Salvi et al – effects on TRAb



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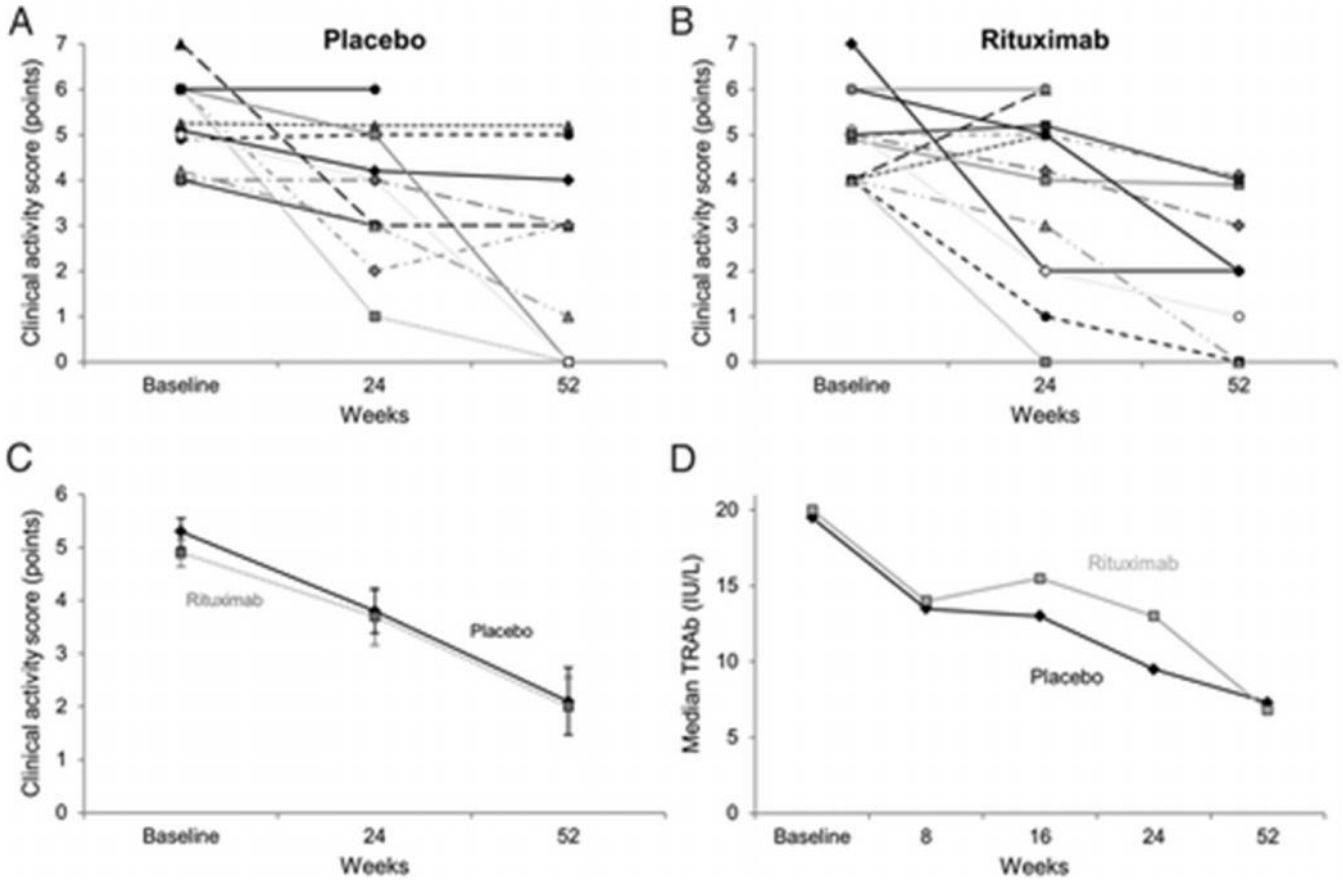
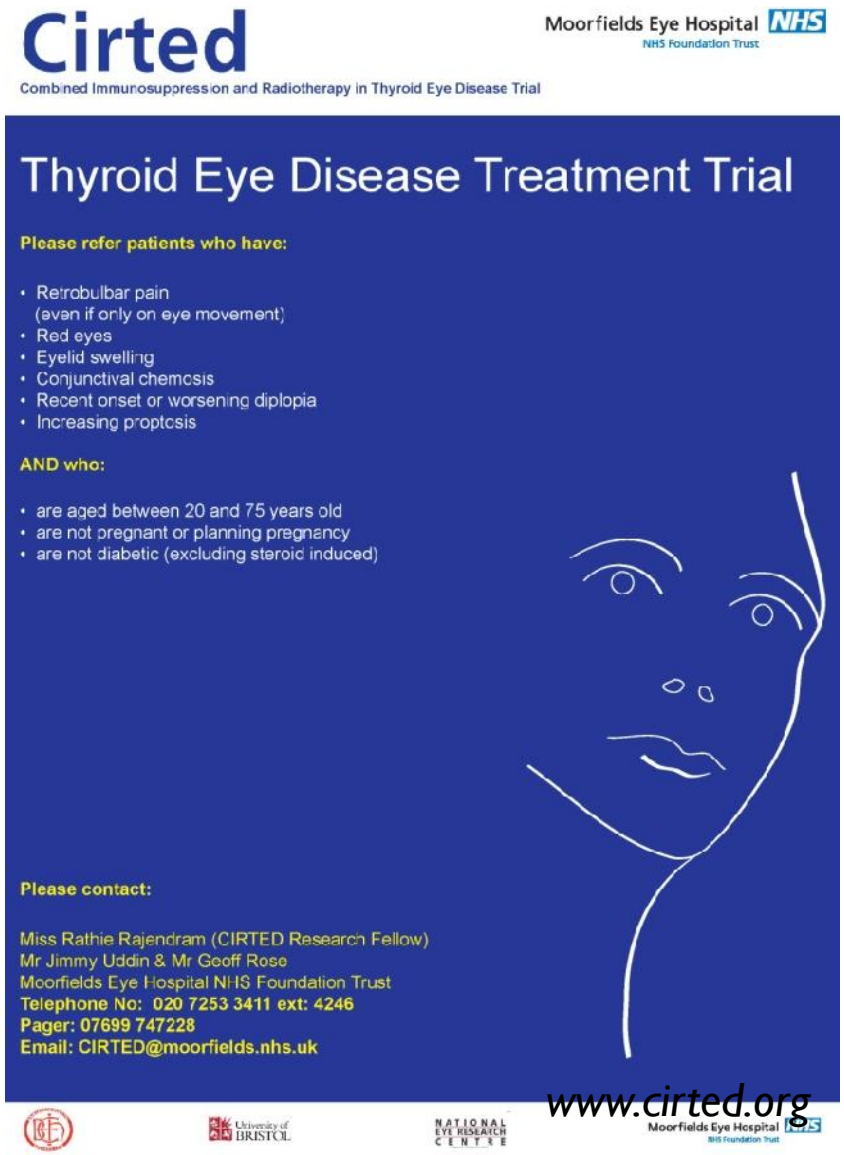
Rituximab – Stan et al 2015

- Underpowered
- N=12/13
- Previous steroid 10
- 50% declined to take part
- 2 worsened with DON



Combination therapy



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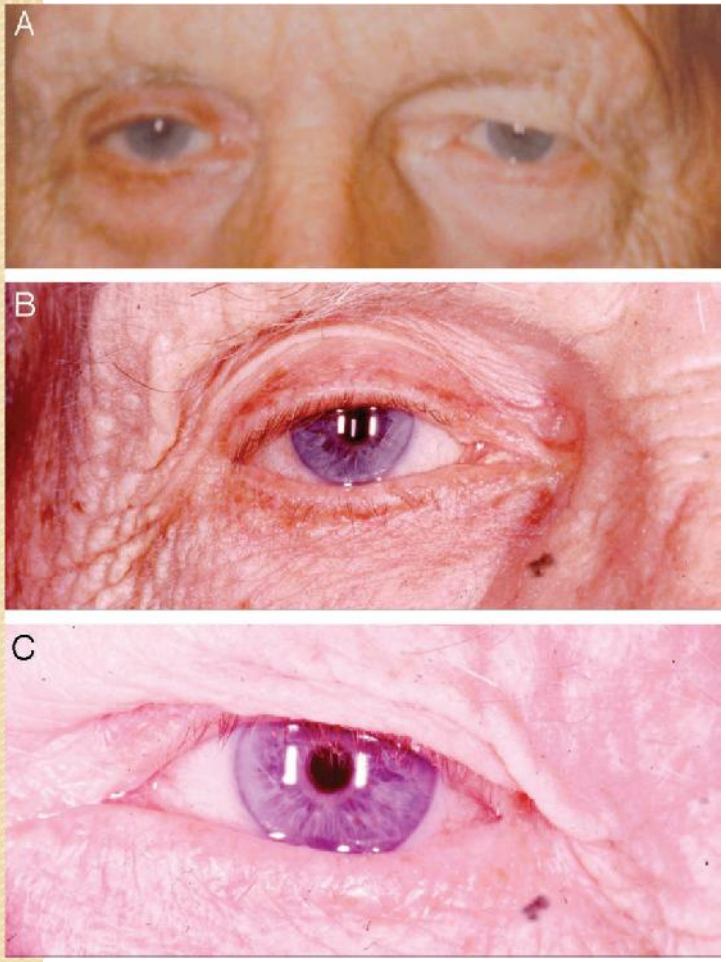
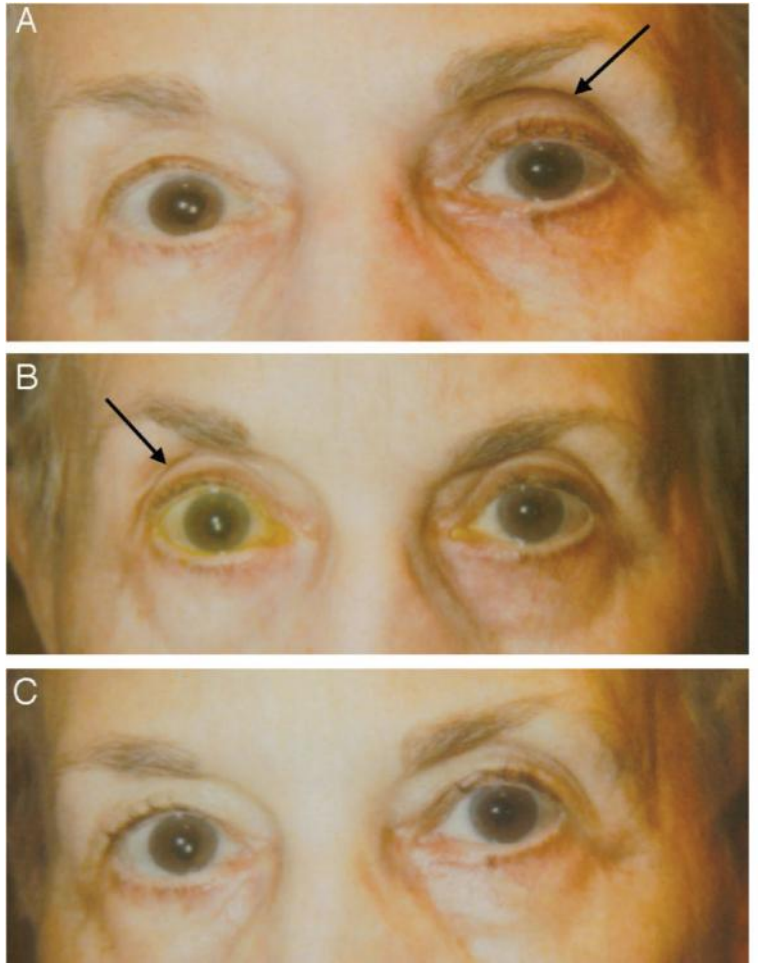
Deepening of Lid Sulcus from Topical Bimatoprost Therapy

LEE S. PEPLINSKI, OD, FAAO and KAREN ALBIANI SMITH, OD





Optometry and Vision Science, Vol. 81, No. 8, August 2004

Surgery in TED

- Orbital surgery (decompression)
- Strabismus surgery
- Oculoplastic surgery

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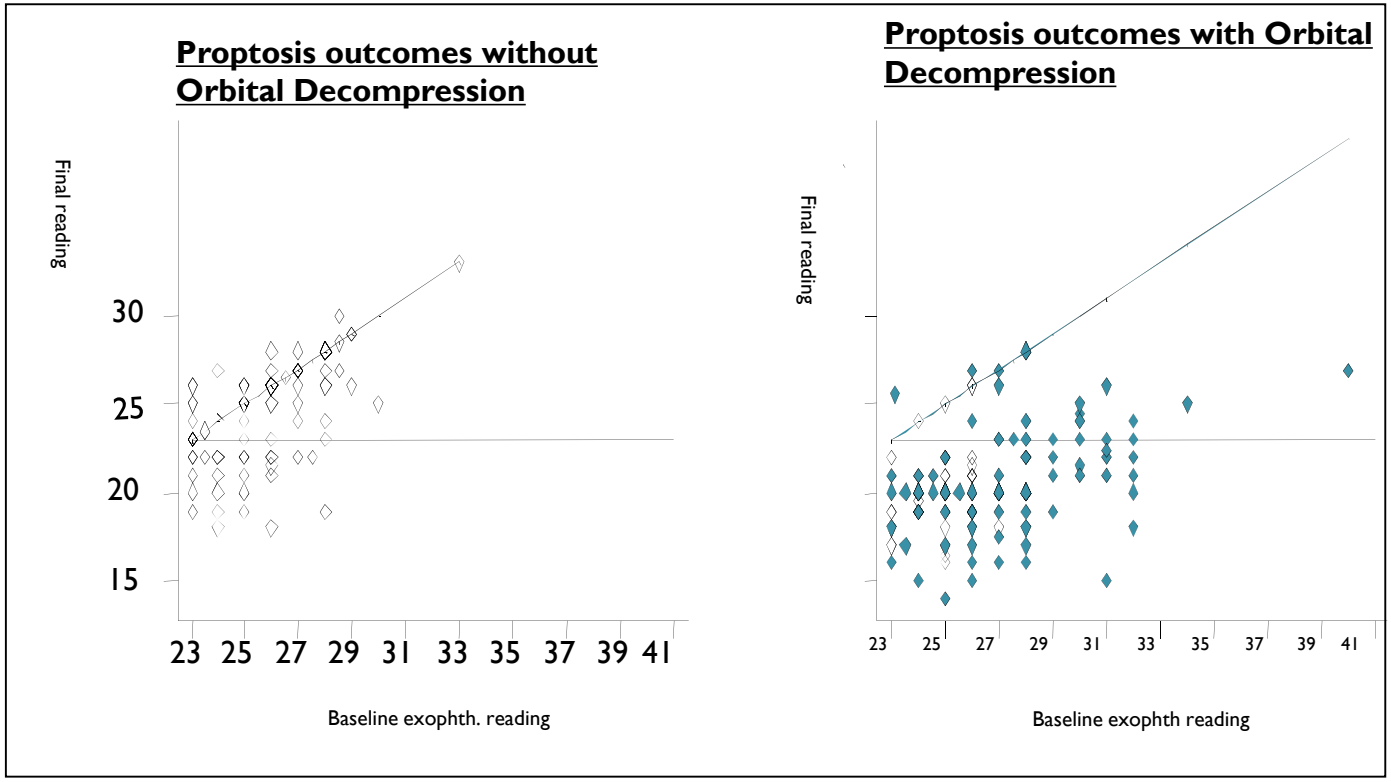
Proptosis outcomes - Moorfields



Rajendram, Rose et al, unpublished

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Diplopia Outcomes (Moorfields series)

	Final diplopia grade[1]				
Initial grade[1]	0	1	2	3	***Total***
1	29 61.70	10 21.28	6 12.77	2 4.26	***47 (n)*** ***(%)***
2	17 41.46	11 26.83	11 26.83	2 4.88	***41(n)*** ***(%)***
3	9 50.00	3 16.77	4 22.22	2 11.11	***18(n)*** ***(%)***
Total	***55*** ***51.89***	***24*** ***22.64***	***21*** ***19.81***	***6*** ***5.66***	***106***

Rajendram, Rose et al, unpublished

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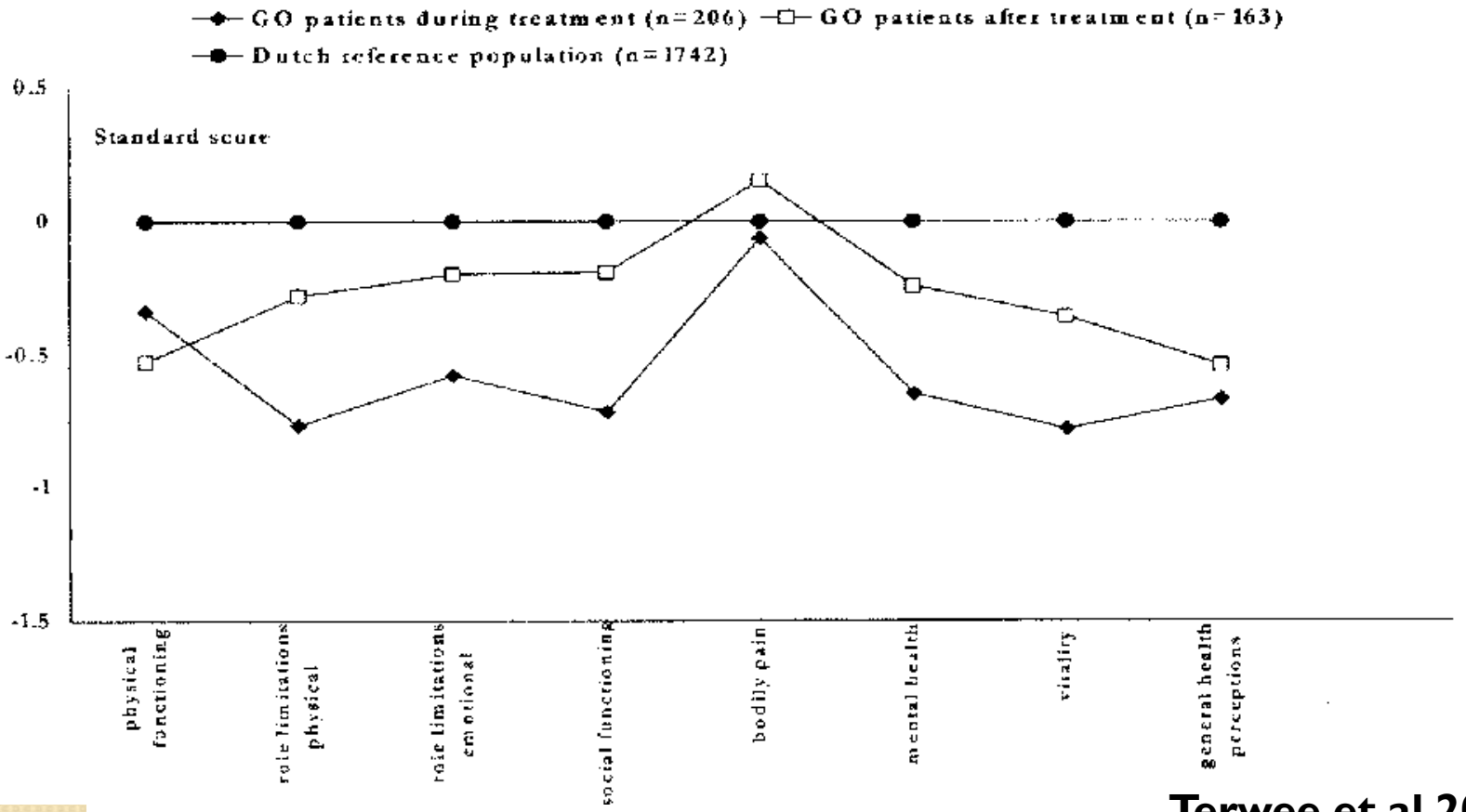
Mild TED is not distressing to patients



Terwee et al 2002

Depression and Anxiety in TED

Table 1: *Comparison of TED group with clinical data on standardised questionnaires*

Study questionnaire	*CIRTED group (n=77)*	*Facial burns (n=32)*	*Head & neck cancer (n=13)*	*Maxillofacial (n=24)*
HADS Dep^{-}	7.47±4.94	4.56±4.67*	5.08±2.40*	4.30±2.53*
HADS Anx^{-}	9.87±4.81	6.31±4.89*	8.08±5.87	6.46±4.07*
DAS-24^{-}	48.52±16.46	32.12±12.25*	41.36±10.08	35.54±9.79*
QoL phys^{+}	12.63±3.52	13.0±2.3	13.3±4.9	15.1±2.7*
QoL psych^{+}	12.40±3.21	14.4±2.5*	12.0±2.6	15.4±2.2*
QoL environment^{+}	13.93±2.89	15.2±3.2	15.4±2.3	15.6±2.3*
QoL social^{+}	14.43±3.28	15.7±3.4	15.0±2.1	15.4±3.2

Key

$^{-}$ = higher scores indicate greater distress

$^{+}$ = higher scores indicate greater satisfaction with life

* = significant correlations, p values in abstract above

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ARVO 2012

Patient support groups

TEDct
Thyroid Eye Disease Charitable Trust
Registered charity in England & Wales 1095967 and Scotland SC042278

www.tedct.co.uk

BRITISH THYROID FOUNDATION
Registered Charity No. 1006391

www.btf-thyroid.org

TED is generally well managed

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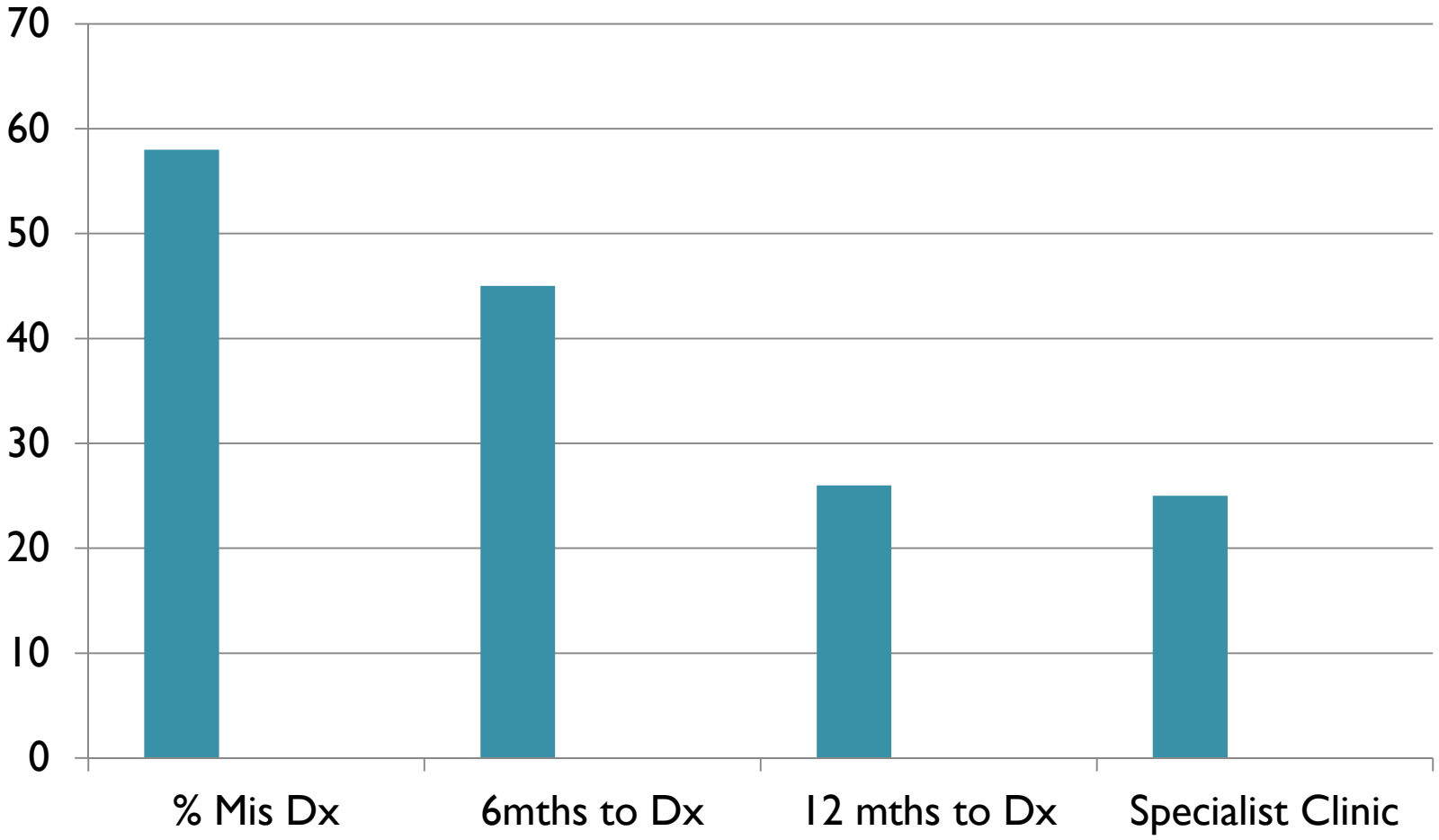
Access to care in TED



Estcourt et al 2009

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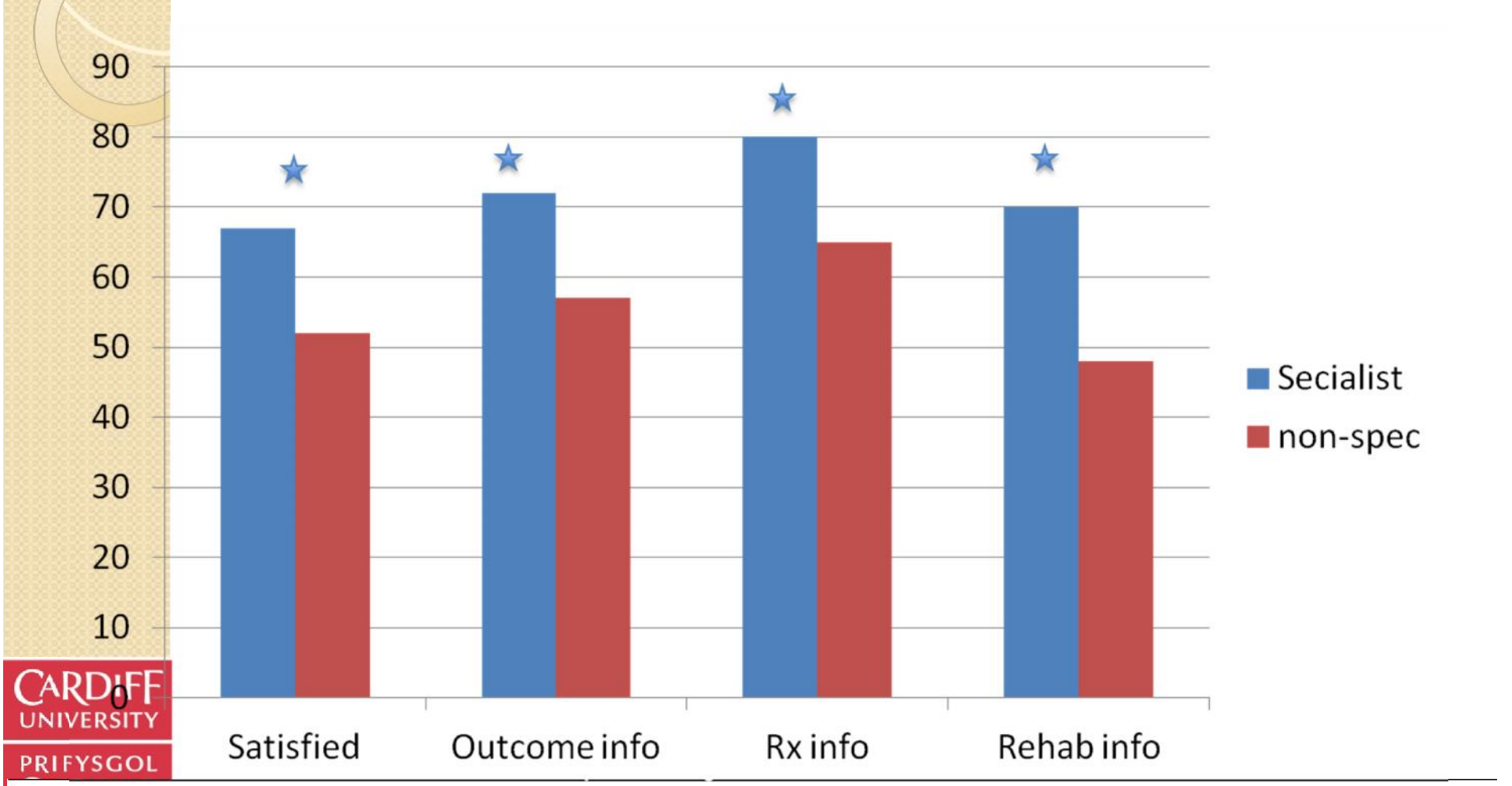
TEAMeD

Thyroid Eye Disease Amsterdam Declaration Implementation Group UK



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BRITISH THYROID FOUNDATION
Registered Charity No. 1106171

TEDct
Registered Charity No: 1095967

British OculoPlastic Surgery Society

British Thyroid Association

Society for Endocrinology

Scottish Ophthalmological Club

THE ROYAL COLLEGE OF OPHTHALMOLOGISTS

Royal College of Physicians

Regional Variation in Specialist Care for TED

Decompressions /year	No. NHS Trusts
> 10	8
5-10	8
< 5	52

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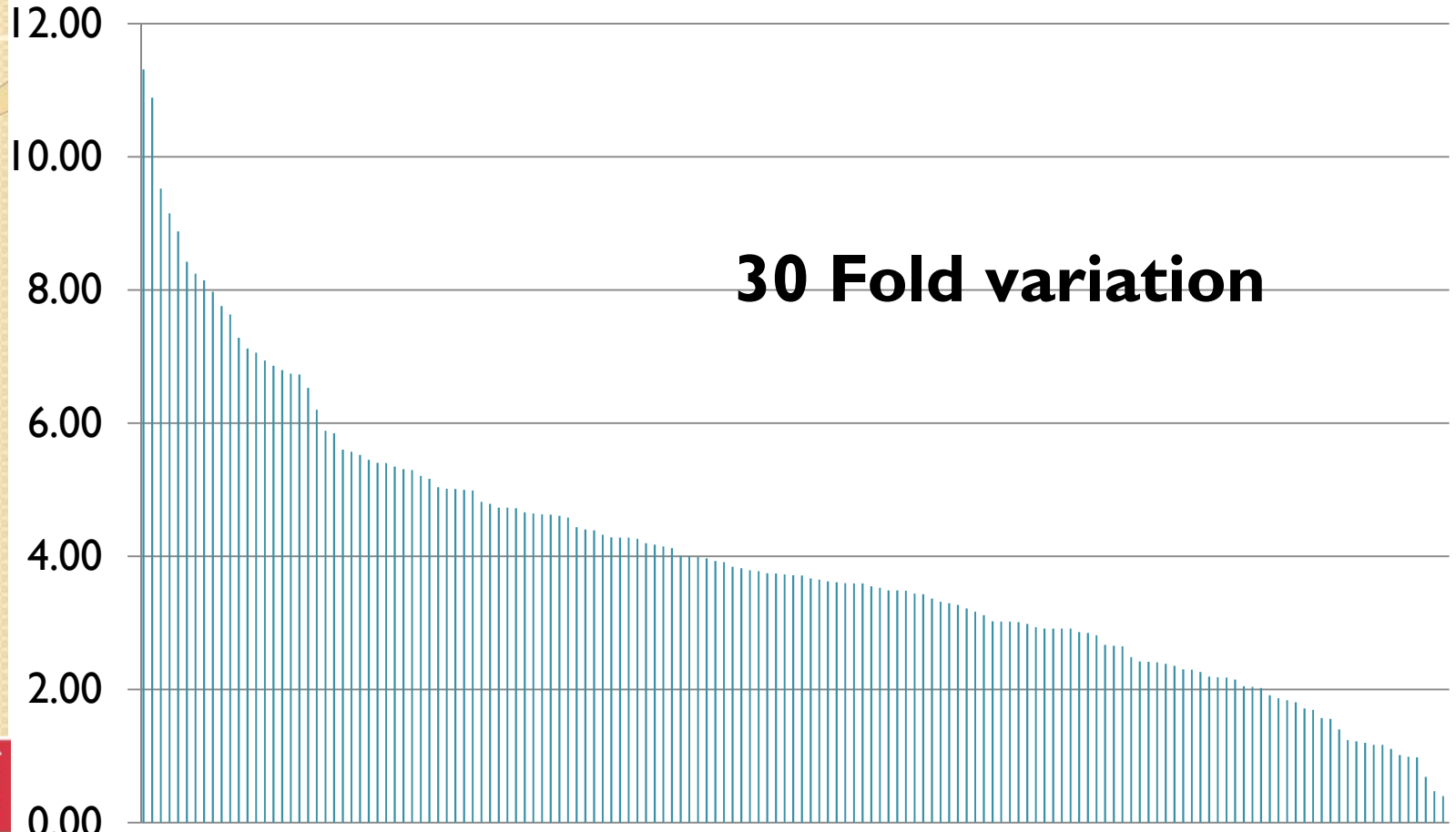
Decompression procedures by PCT (Yearly procedures per 100,000)



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11. Thyroid Eye disease cannot be prevented

- Management of thyroid disease
- Careful use of I-131
- Smoking
- ? Selenium

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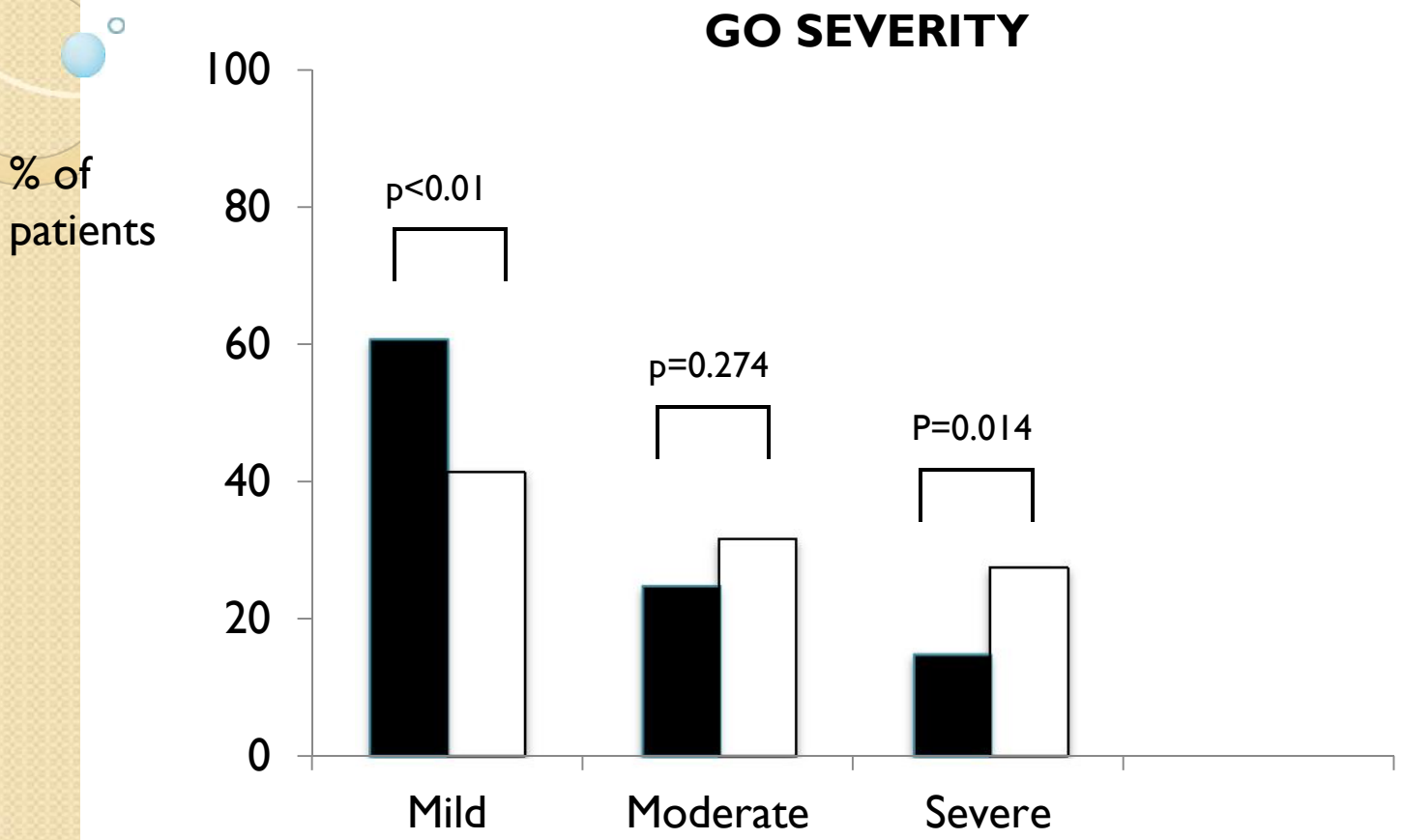

269 patients referred within 4 mths to EUGOGO centres
40% smokers

Perros et al in preparation
Black – 2012;White - 2000

Smoking

- Increase risk of developing TED
- Reduces response to therapy
- Increase requirement for strabismus surgery

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Smoking and TED

Characteristic	Patients undergoing strabismus surgery	Hazards ratio**	Significance (95% confidence interval)
Presenting age 50 years or less	139/342 (41%)	(1.0)	--
Presenting age 51 years or more	49/83 (59%)	1.7	0.01 (1.11 – 2.79)
Female	60/306 (20%)	(1.0)	--
Male	23/119 (19%)	1.1	0.53(0.70 – 1.95)
Non-smoker at presentation	19/138 (14%)	(1.0)	--
Ex-smoker at presentation	7/44 (16%)	1.1	0.82 (0.44 – 2.81)
Active smoker at presentation	51/196 (26%)	1.8	0.02 (1.08 – 3.22)
Euthyroid at presentation	57/278 (21%)	(1.0)	--
Hyperthyroid at presentation	8/58 (14%)	0.6	0.31 (0.32 – 1.43)
Hypothyroid at presentation	8/47 (17%)	0.8	0.70 (0.36 – 1.98)
(Unrecorded status)	10/41 (24%)	--	--
No prior orbital decompression	23 (9%)	(1.0)	--
Prior orbital decompression	60 (35%)	4.0	<0.001 (2.36 – 6.82)

Rajendram et al

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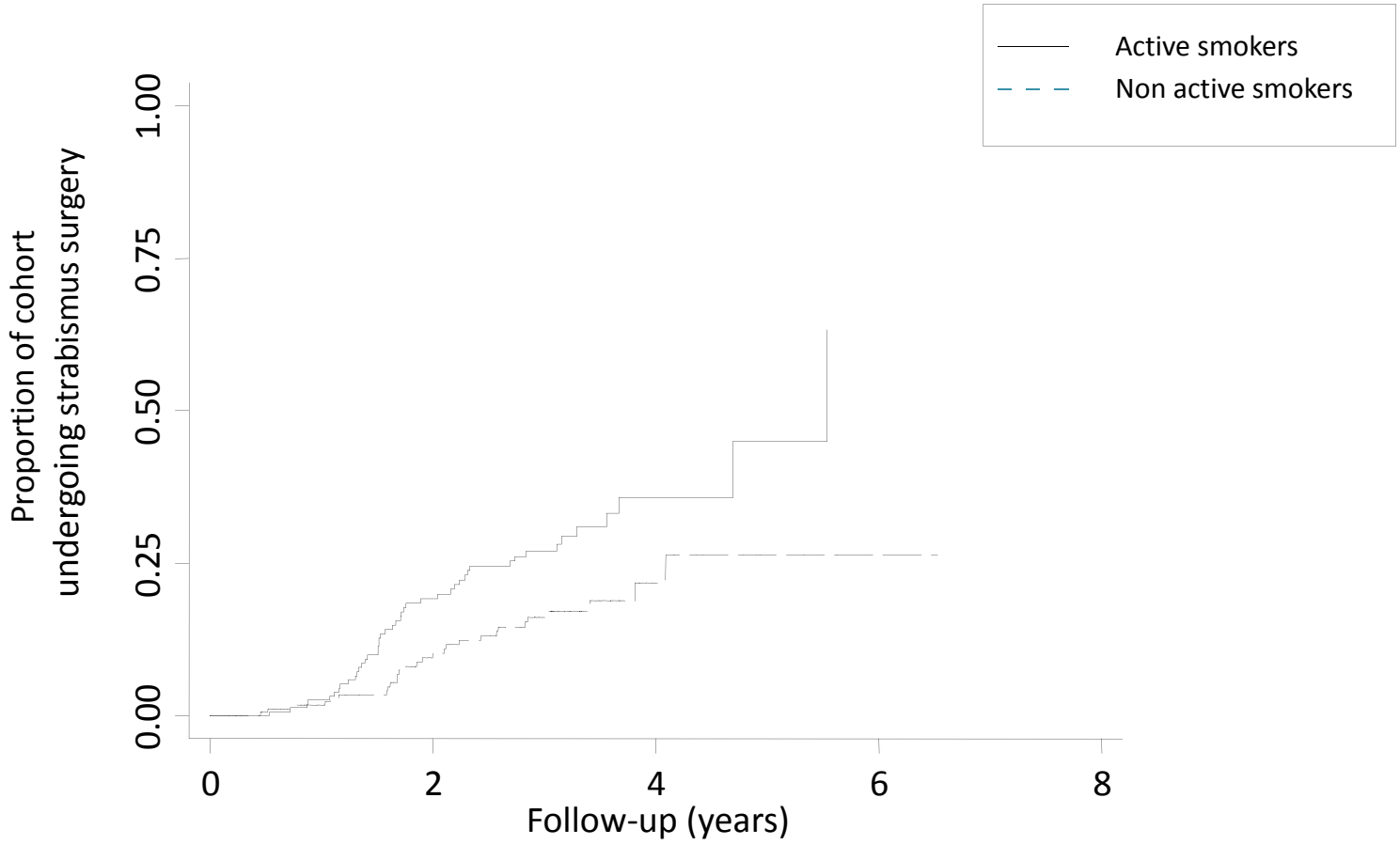
Smoking (& Strabismus surgery)



Number at risk

Non active smokers	192	126	20	4	3
Active smokers	165	108	17	2	2

Figure 2. Proportion of cohort undergoing strabismus surgery according to smoking status at presentation

Rajendram et al 2011

TEAMeD

Thyroid Eye Disease Amsterdam Declaration Implementation Group UK

Thyroid Eye Disease - Early Warning Card

If you have been diagnosed with **Graves' disease** (an overactive thyroid gland) you have a 20% chance of developing **Thyroid Eye Disease** (**TED**).

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BRITISH THYROID FOUNDATION
TEDct Registered Charity No: 1095960
British OculoPlastic Surgery Society
British Thyroid Association
Society for Endocrinology
Scottish Ophthalmological Club
Royal College of Physicians

TEAMeD

Thyroid Eye Disease Amsterdam Declaration Implementation Group UK

What is TEAMeD doing?

1. Collecting and publishing data to show variation in practice across the UK
2. Collecting information and creating a list of all Specialist Clinics in the UK
3. Monitoring current position
    1. Audit of patients arriving at specialist centres
    2. Audit of patient experience through BTF and TEDct websites
4. Creating joint guidelines with the RCP and RCOpth for good referral practice
5. Prevention/early intervention:
    1. Auditing the use of I-131 in Graves' disease
    2. Raising awareness of early disease (endocrine clinic Q)
    3. ? Smoking intervention
6. Surveillance of number of cases of sight threatening TED ("BOSU")

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TEDct Registered Charity No: 10959
British OculoPlastic Surgery Society
British Thyroid Association
Society for Endocrinology
Scottish Ophthalmological Club
Royal College of Physicians

TEAMeD: Key findings so far
Approx 5 month delay to diagnosis
Only ~50% patients seen in specialist clinic
Only ~20% patients seen in a joint clinic
More than 30 UK centres treat moderate – severe eye disease – only 38% have a joint clinic
65% of centres treat $\leq$ 2 severe cases per year
Decompression rates vary more than 30-fold by region
Smoking leaflet now available

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Summary

- Thyroid eye disease is easily missed and underestimated
- Assessment and management is complex
- Refer promptly to specialist centre esp in active phase
- Take active steps to prevent TED in patients diagnosed with Graves' disease
- Do not forget the psychological impact

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Pathophysiology

- TED is an (autoimmune) disease of the retrooribital fat (pre-adipocytes-fibroblast) which secrete GAGs
- Preadipocytes express the TSH receptor
- The eye muscle fibres are intact but swollen
- Smoking worsens TED and prognosis from TED treatment

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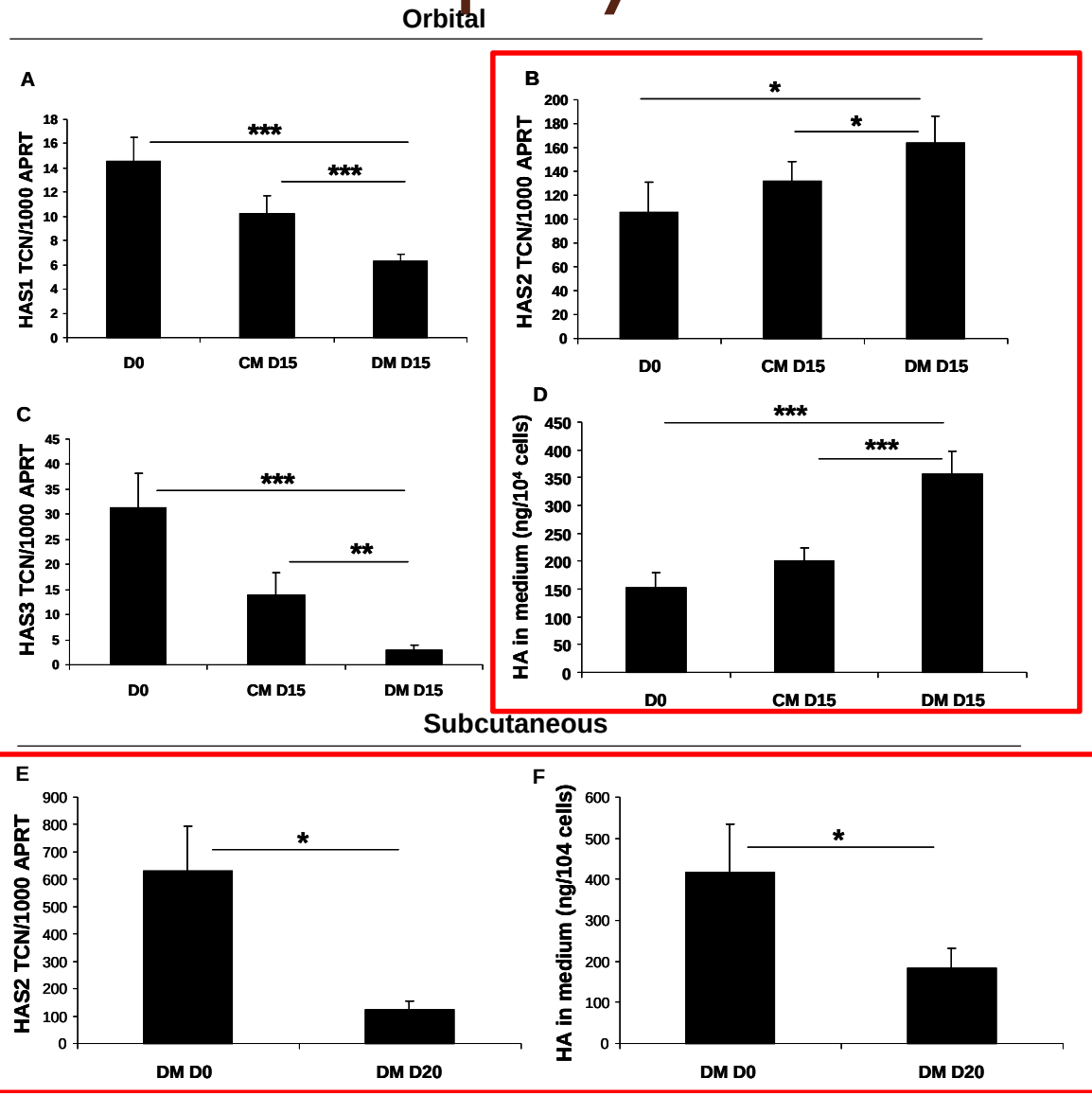
HAS 2 expression in orbital vs subcutaneous adipocytes

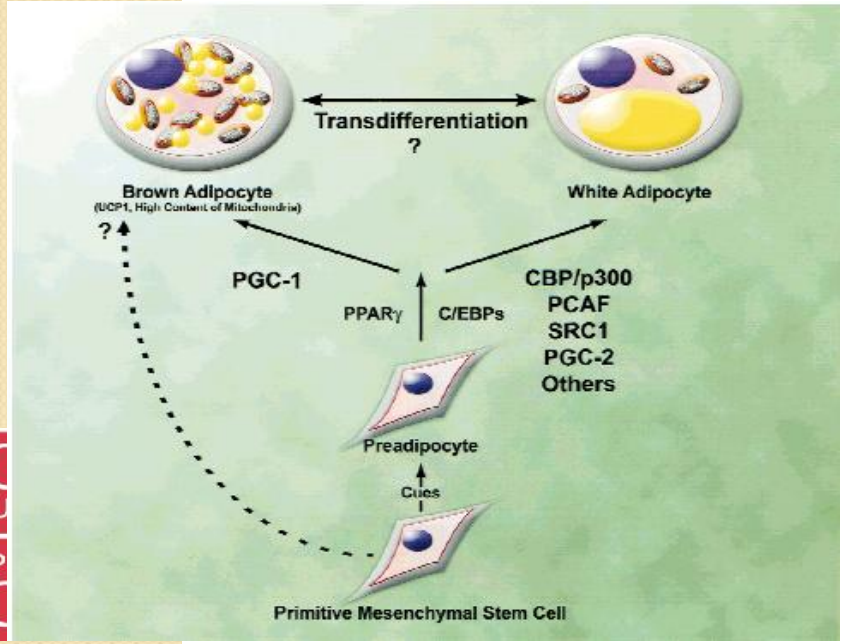
Zhang, Ludgate et al in press

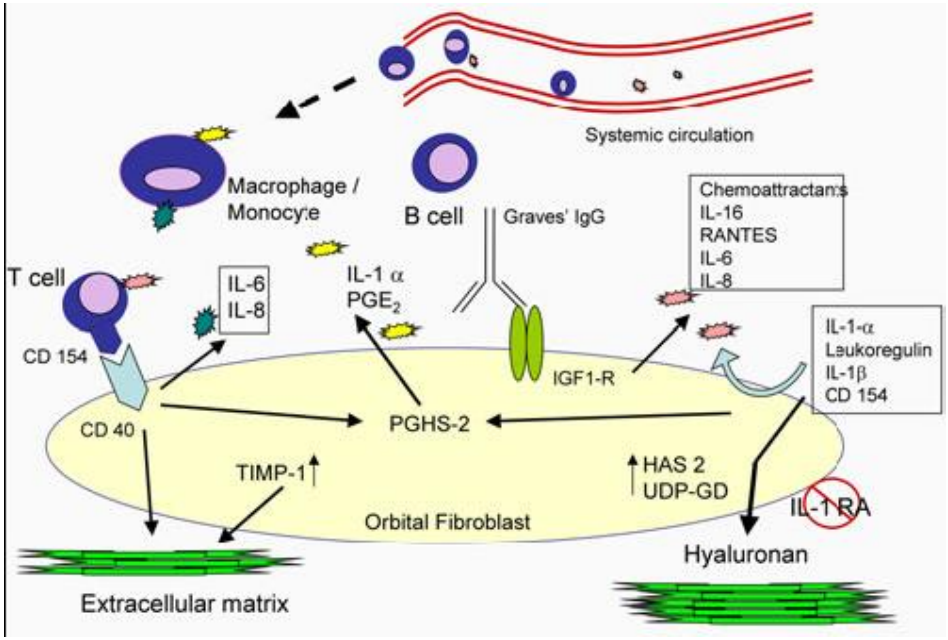


Graves' Orbitopathy (GO) or TED, TAO

- Graves' diseases (GD).
- Patients with euthyroid or Hypothyroid chronic autoimmune thyroiditis.

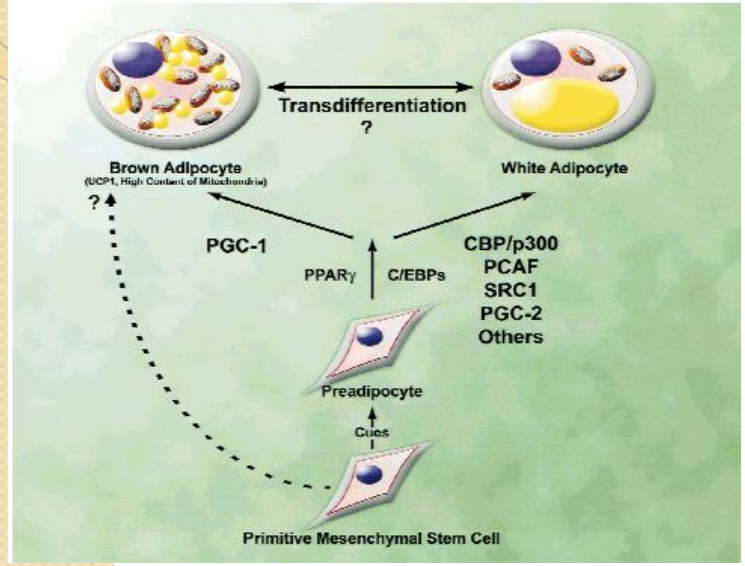
Excess adipogenesis

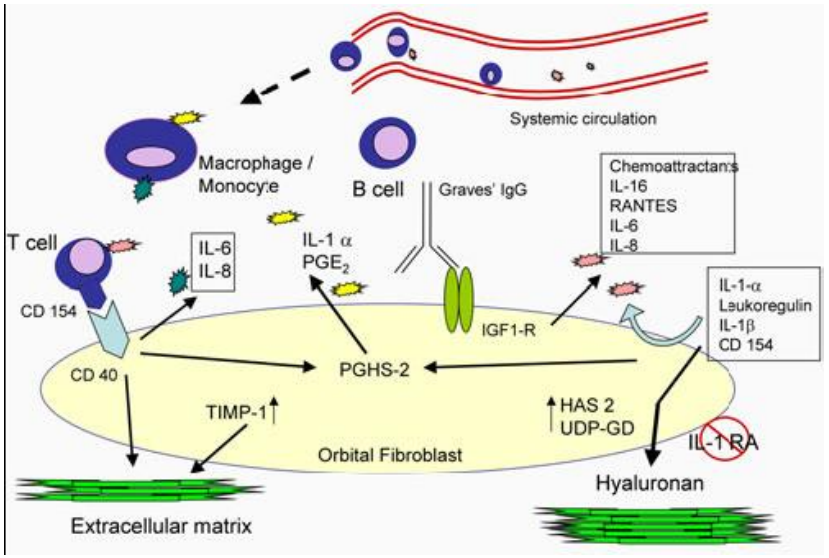




Orbitopathy is the result of:-

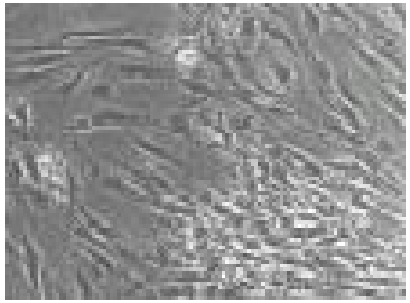
- **Overproduction Glycosa-minoglycans [hyaluronan]**
- **Adipogenesis, process produces new fat.**



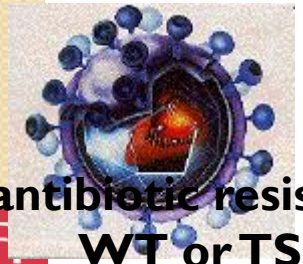


In Vitro Model to investigate effect of TSHR* uses M453T and L629F TSHR*

Preadipocyte Cell Lines



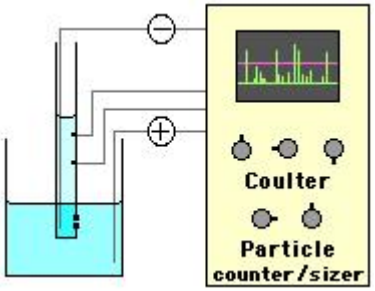
infected with retroviral vectors expressing



antibiotic resistance & WT or TSHR*

Preadipocytes surviving antibiotic selection

Proliferation direct counting



cAMP by RIA

Adipogenesis
Oil Red O
QRT-PCR

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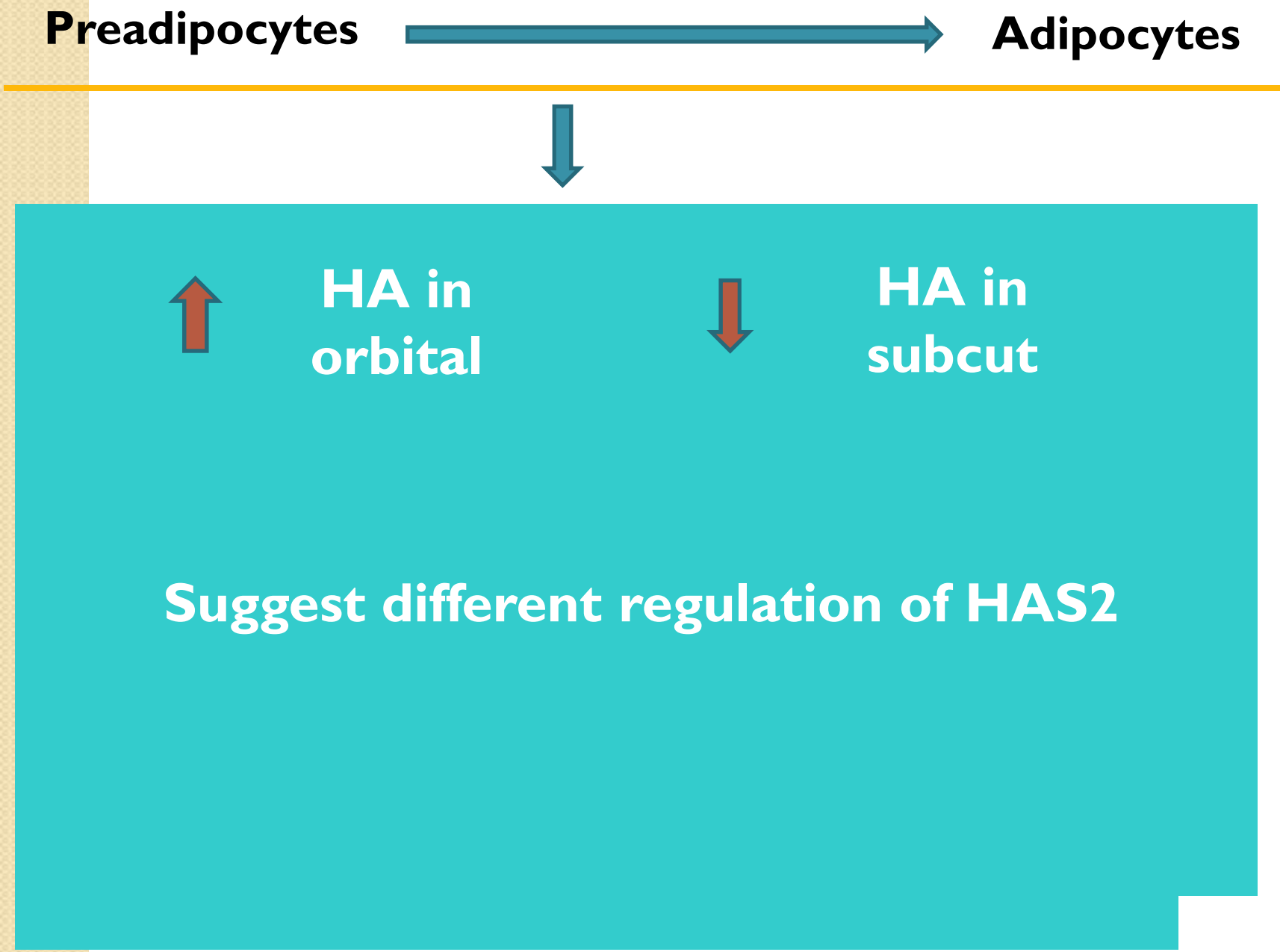
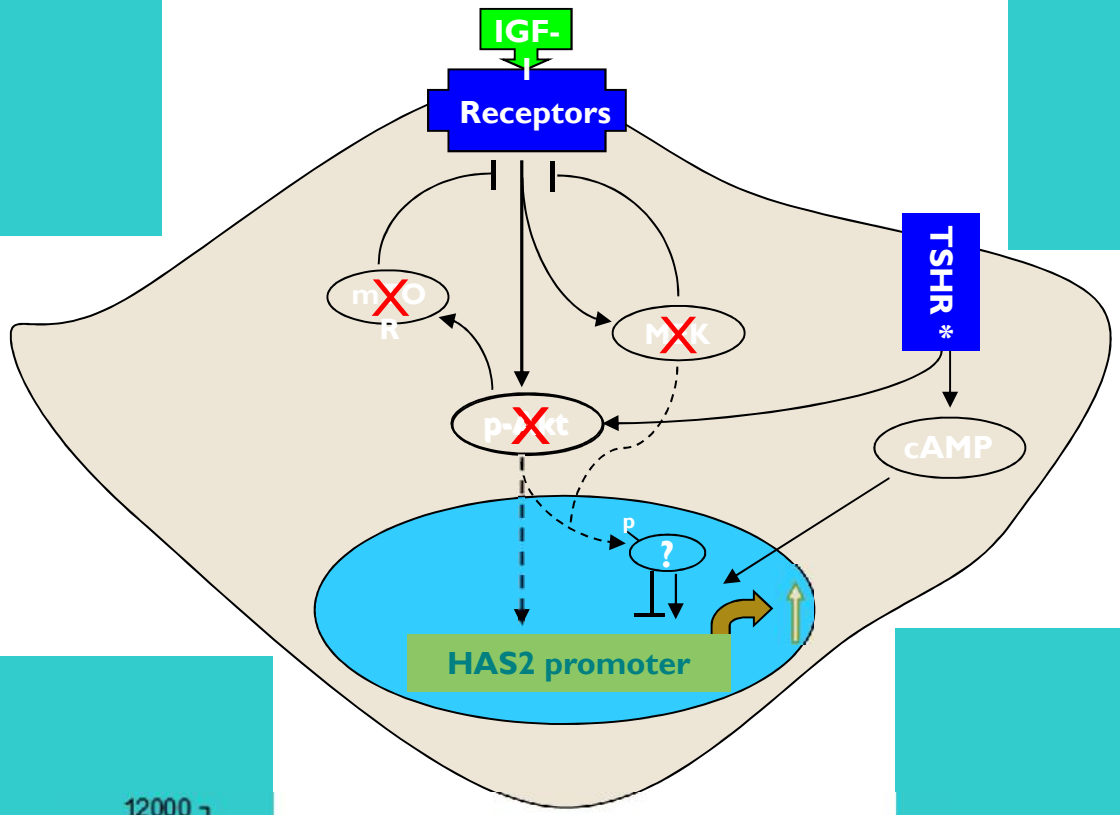
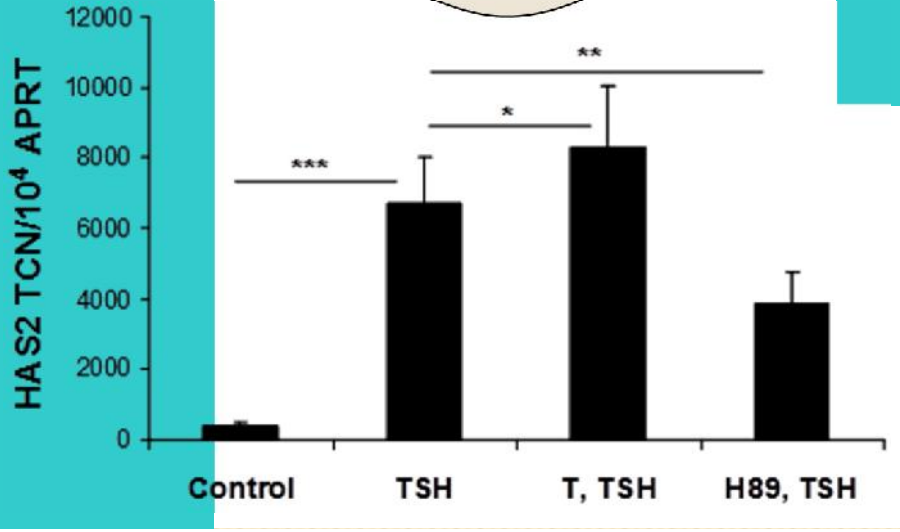
Demonstration that Adipogenesis & HA Production are Linked in Orbit (opposite in Sub-Cutaneous)

(Zhang et al JCEM 2012)


Preadipocytes
Adipocytes
HA in orbital
HA in subcut
Suggest different regulation of HAS2

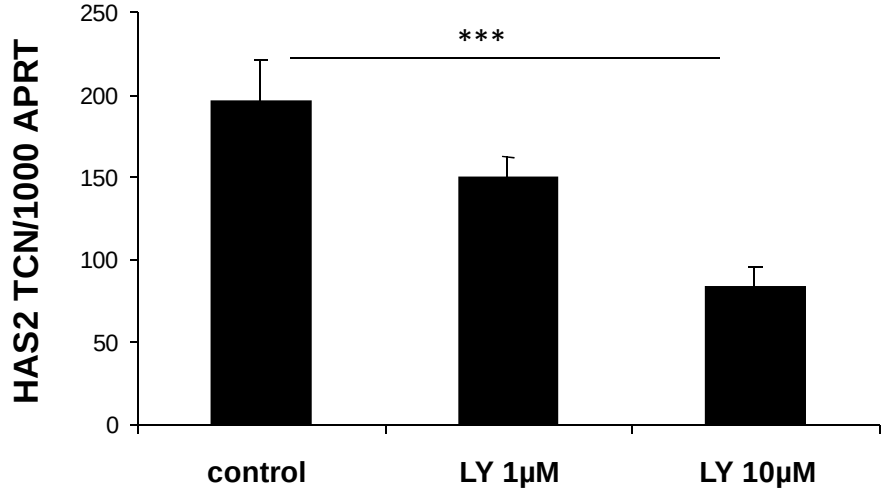

IGF-
Receptors
TSHR *
cAMP
P
?
HAS2 promoter

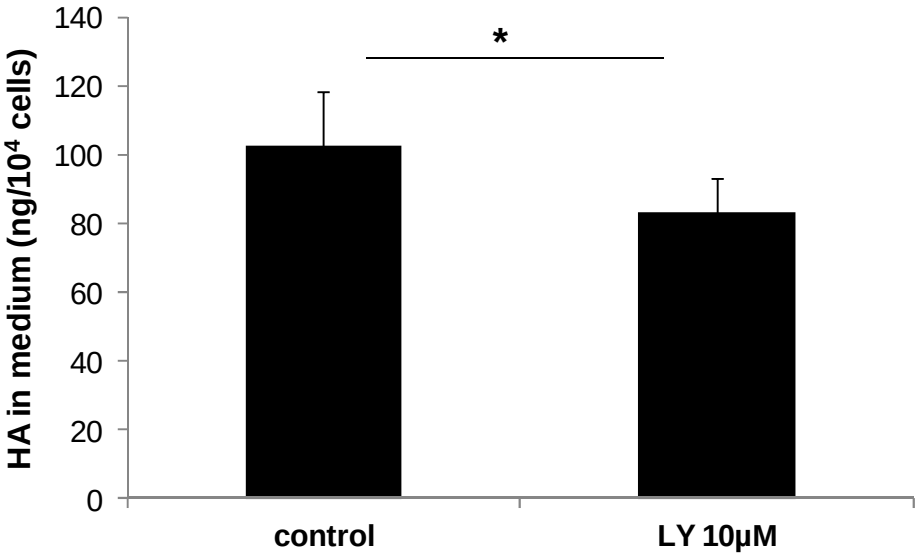

HAS2 TCN/10⁴ APRT
12000
10000
8000
6000
4000
2000
0
***
*
**
Control
TSH
T, TSH
H89, TSH

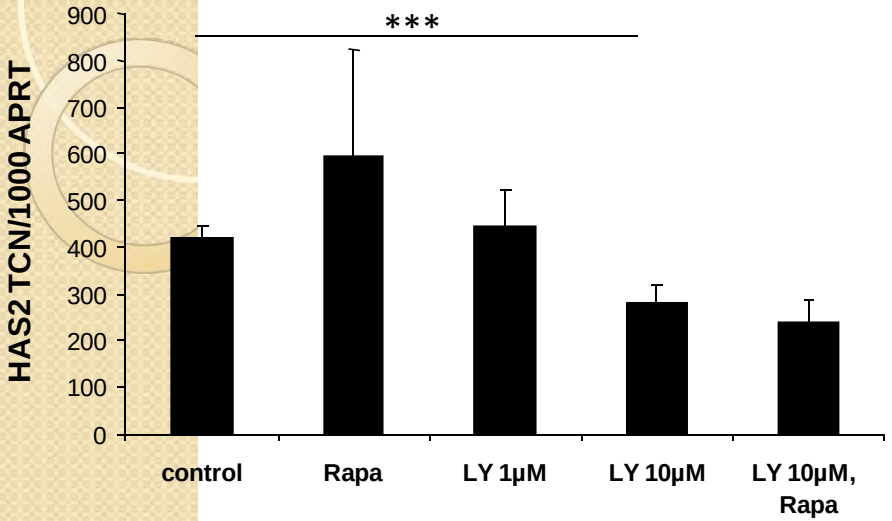
Conclusion

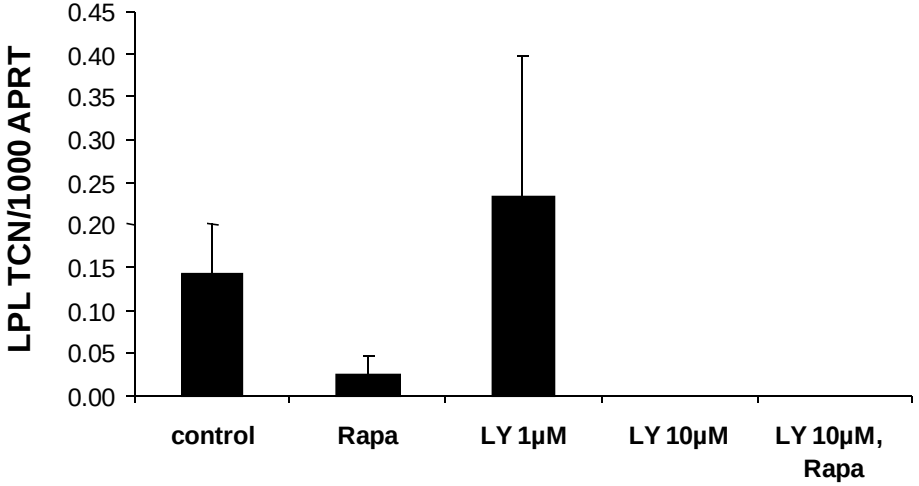
- R
P
s
- A
a
s
d
- T
s
s
- T
C

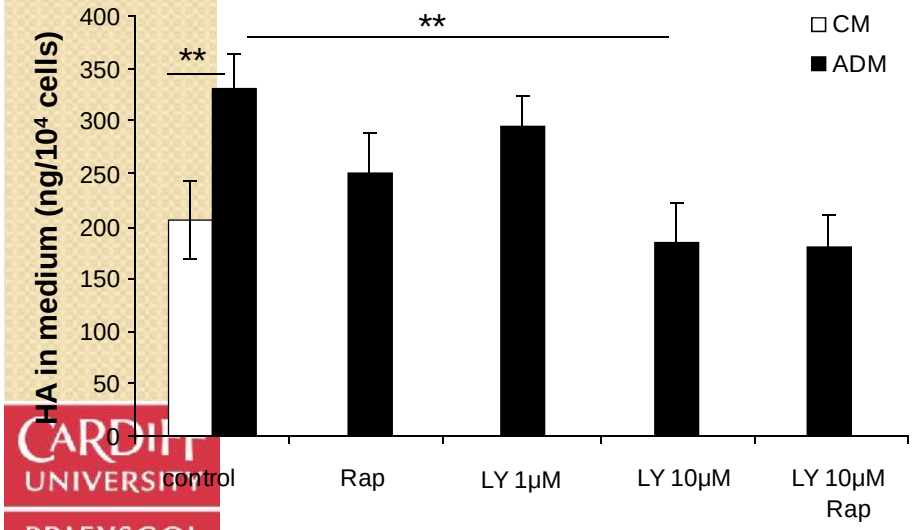
Identification of targets for non-immunosuppressive therapy of Graves' Orbitopathy

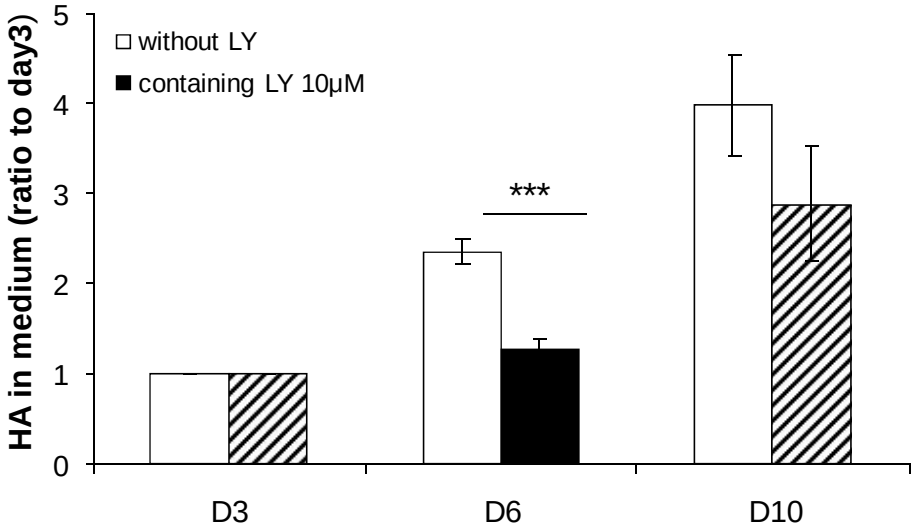

250
200
150
100
50
0
HAS2 TCN/1000 APRT
***
control
LY 1μM
LY 10μM


140
120
100
80
60
40
20
0
HA in medium (ng/10^4 cells)
*
control
LY 10μM

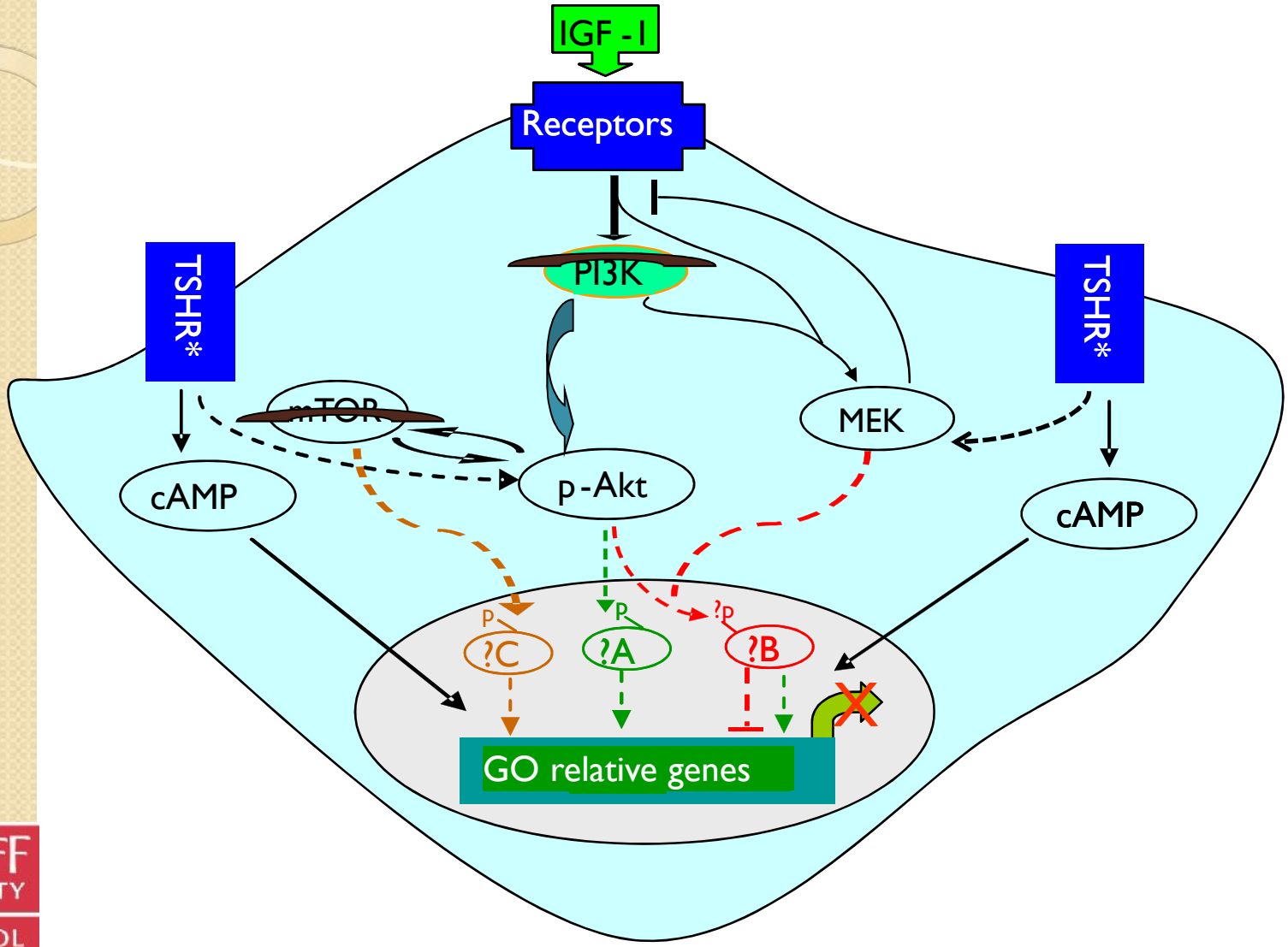

HAS2 TCN/1000 APRT
900
800
700
600
500
400
300
200
100
0
***
control
Rapa
LY 1μM
LY 10μM
LY 10μM, Rapa


LPL TCN/1000 APRT
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
control
Rapa
LY 1μM
LY 10μM
LY 10μM, Rapa


HA in medium (ng/10⁴ cells)
400
350
300
250
200
150
100
50
0
**
**
CM
ADM
control
Rap
LY 1μM
LY 10μM
LY 10μM Rap


HA in medium (ratio to day3)
5
4
3
2
1
0
without LY
containing LY 10μM
***
D3
D6
D10

orbital



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Conclusion:

1. PI3K and mTOR signalling are essential for regulation of Hyaluronan production and adipogenesis in orbital tissue.
2. Possible targets of non-immunosuppressive therapy for GO, PI3K and mTOR.

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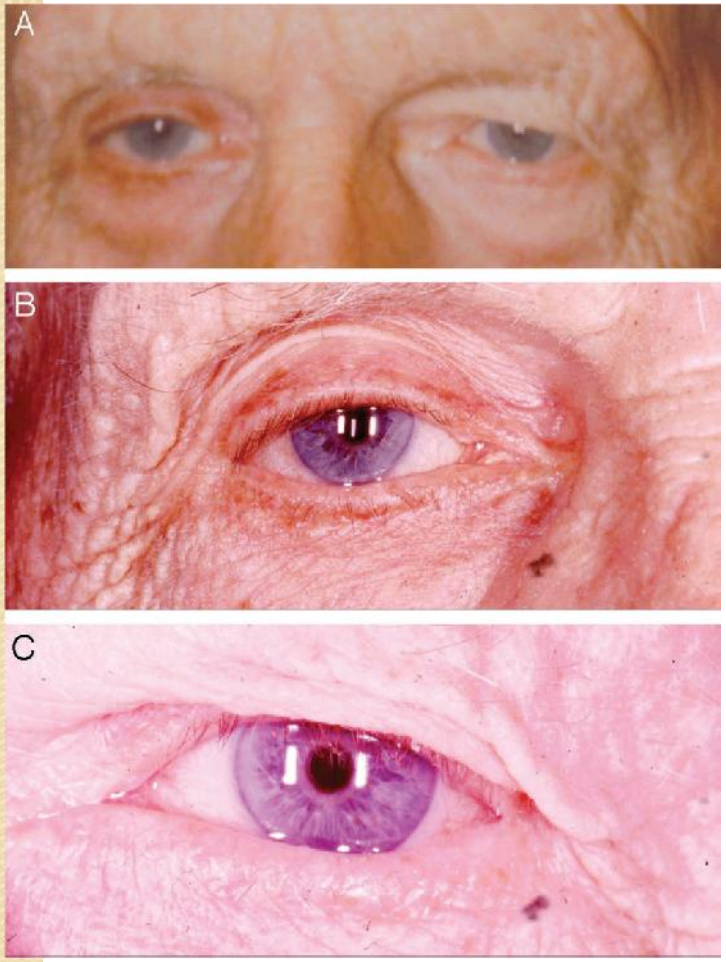
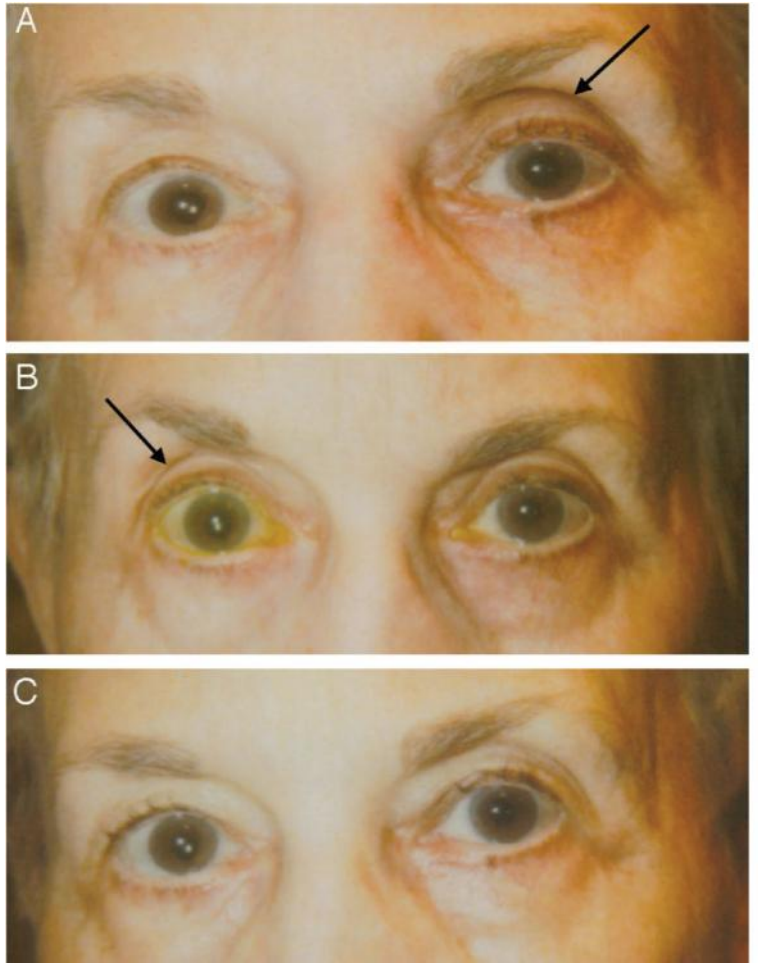
Deepening of Lid Sulcus from Topical Bimatoprost Therapy

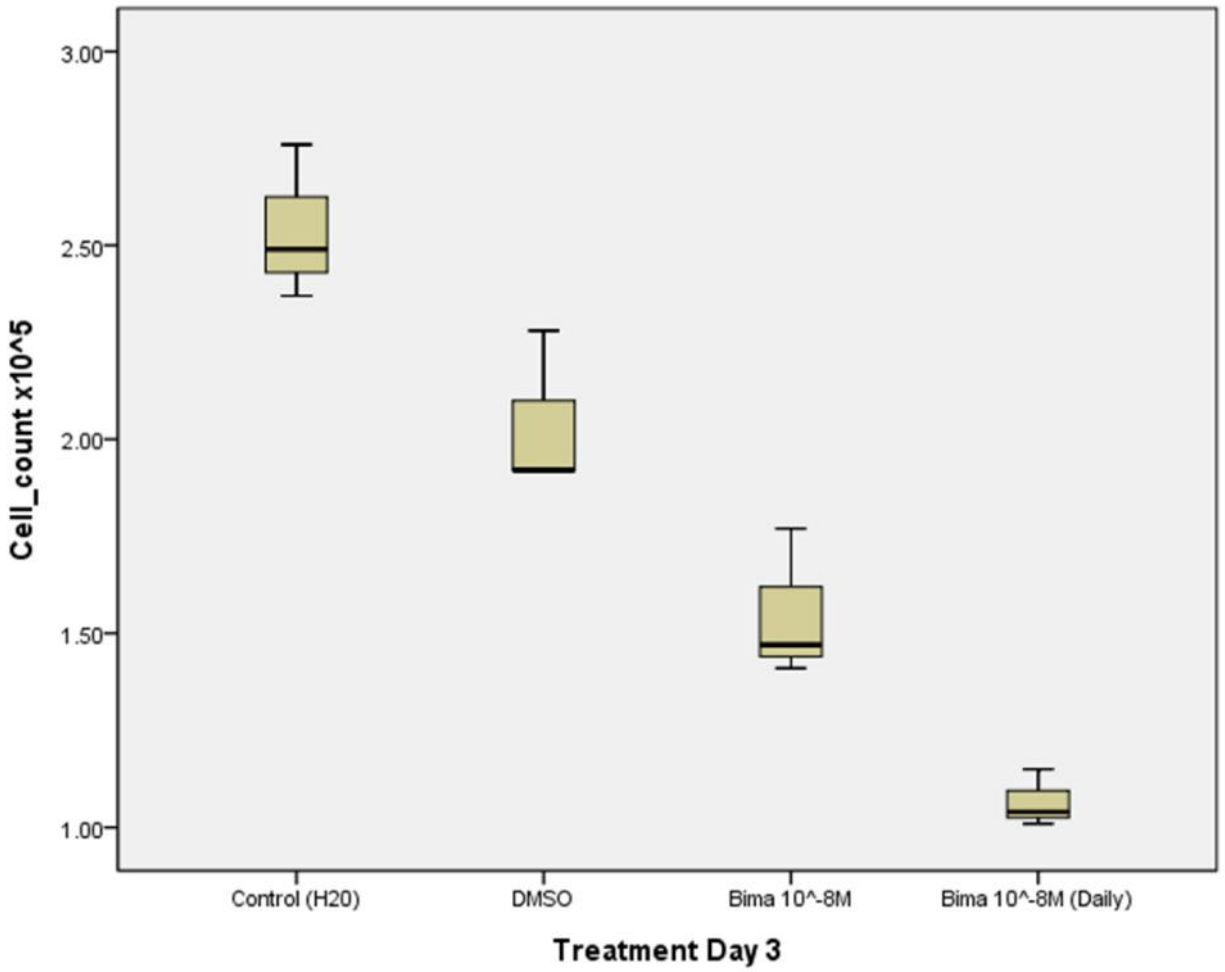
LEE S. PEPLINSKI, OD, FAAO and KAREN ALBIANI SMITH, OD





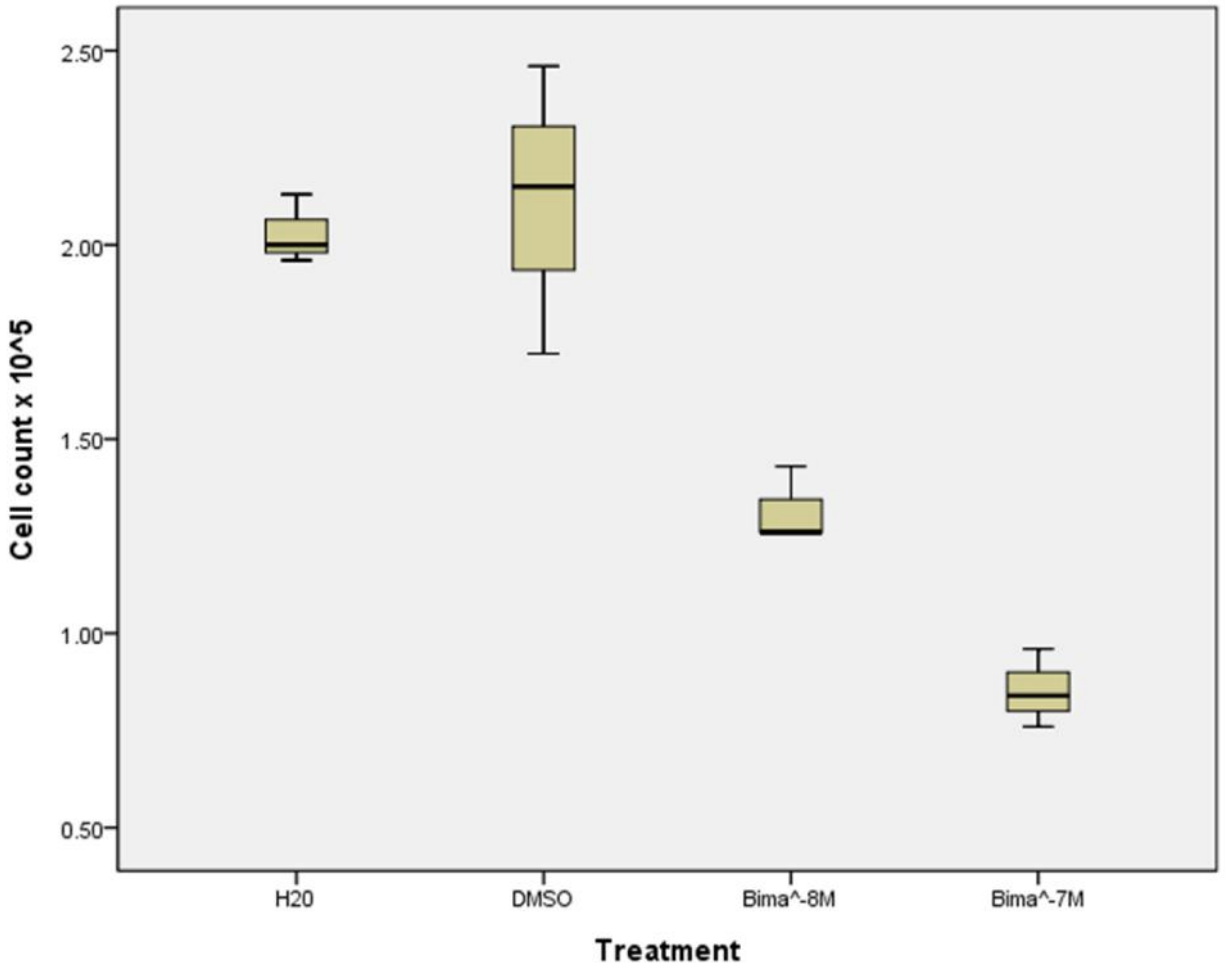
Optometry and Vision Science, Vol. 81, No. 8, August 2004

Proliferation 3T3L1 Day 3 ($0.5x10^4$) seeding (n=3) Control=H20



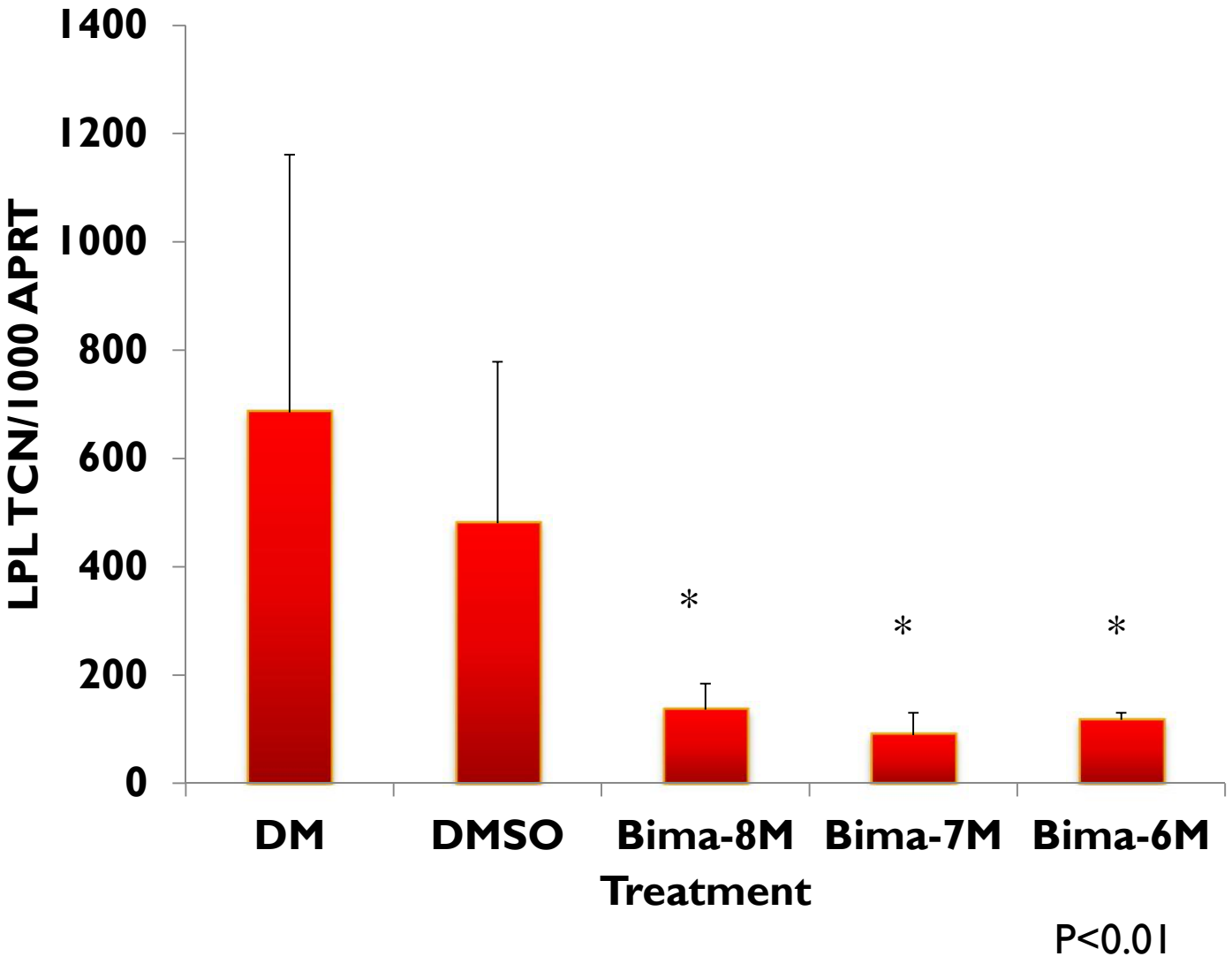
* p=<0.001

Proliferation Graves Orbit Primary Day
5 $0.5x10^5$ seeding



* p=<0.001

GO Patients Adipogenesis Study



Patient screening tool (clinic) - 1

- 1. Do you have redness in your eyes or eyelids?
- 2. Do you have swelling or feeling of fullness in one or both of your upper eyelids
- 3. Do you have bags under the eyes?
- 4. Do your eyes seem to be too wide open?
- 5. Is your vision blurry (even with glasses/contacts?)
- 6. Please have a look at the small print below, with your reading glasses on if you normally them. First cover your right eye and read using your left eye. Then repeat using your right eye to read.
- 7. Please have a look at the red dot below…. Do you think there is a difference in the intensity of the red colour between your two eyes?

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- 8. Are your eyes abnormally sensitive to light?
- 9. Are your eyes excessively gritty?
- 10. Do you have pain in or behind the eyes?
- 11. Has the appearance of the eyes and/or eyelids changed over the past 1–2 months?
- 12. Does the appearance of your eyes cause you concern?
- 13. Can you see two separate images when there should only be one?

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Endocrine clinic screening tool – doctor Qs

- 14. Upper eyelid retraction?
- 15. A history of thyroid dysfunction?
- 16. Abnormal swelling or redness of eyelid(s) or conjunctiva(e)?
- 17. Restriction of eye movements?
- 18. Tilting of the head to avoid double vision?
- 19. Exophthalmos?
- 20. Obvious corneal opacity visible to the naked eye?
- 21. Papilloedema?
- If all negative – no TED

any shaded Qs positive, refer urgently

If other Qs positive, refer routinely to TED clinic

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