Brigham and Women's Hospital
Founding Member, Mass General Brigham

Update in thyroid disease

Ole-Petter R. Hamnvik, MB BCh BAO, MMSc
Associate Physician, Brigham and Women's Hospital
Division of Endocrinology, Diabetes and Hypertension
Department of Medicine
Brigham and Women's Hospital
Associate Professor in Medicine
Harvard Medical School

Ole-Petter R. Hamnvik, MB BCh BAO, MMSc

Medical school: **Royal College of Surgeons in Ireland**

Internal medicine residency, chief medical residency, endocrinology fellowship: **Brigham and Women's Hospital**

Current position: Clinician-educator, BWH

- Transgender health, general endocrinology
- Endocrinology fellowship program director
- Education editor, NEJM Group

Disclosures

- None

Learning objectives

- At the end of this activity, participants can:
  - Understand analytical aspects that can affect thyroid function testing
  - Describe novel causes of abnormal thyroid function tests
  - Describe recent progress in the management of thyroid eye disease
  - Outline an approach to management of persistent hypothyroid symptoms

Case 1

- A 44-year-old woman is evaluated for fatigue without any other associated symptoms. Her laboratory evaluation shows normal renal function and liver blood tests, normal electrolytes, a normal complete blood count, but a TSH returns below the limit of detection of the assay (<0.01)
- Her past medical history is notable for relapsing-remitting multiple sclerosis. She currently takes glatiramer acetate, biotin, cholecalciferol and a combined oral contraceptive pill.
- A complete review of symptoms is negative for any other symptoms, including palpitations, weight loss, frequent bowel movements, insomnia, irritability and eye symptoms. Physical exam shows the following vital signs: BP 115/65, HR 73, T36.6. There is no tremor, and her thyroid gland is of normal size with no tenderness or nodules.
- Repeat labs showed: TSH <0.01, free T4 >7.77, and elevated level of thyroid-stimulating immunoglobulin.

Case 1 (continued)

- What is the most likely cause of this patient's laboratory findings?

A. Graves' disease
B. Assay interference
C. Pituitary involvement from MS
D. Drug-induced thyroiditis
E. Altered TBG level

Case 1 (answer)

- What is the most likely cause of this patient's laboratory findings?

A. Graves' disease
   - Unlikely in the absence of any symptoms, thyromegaly.

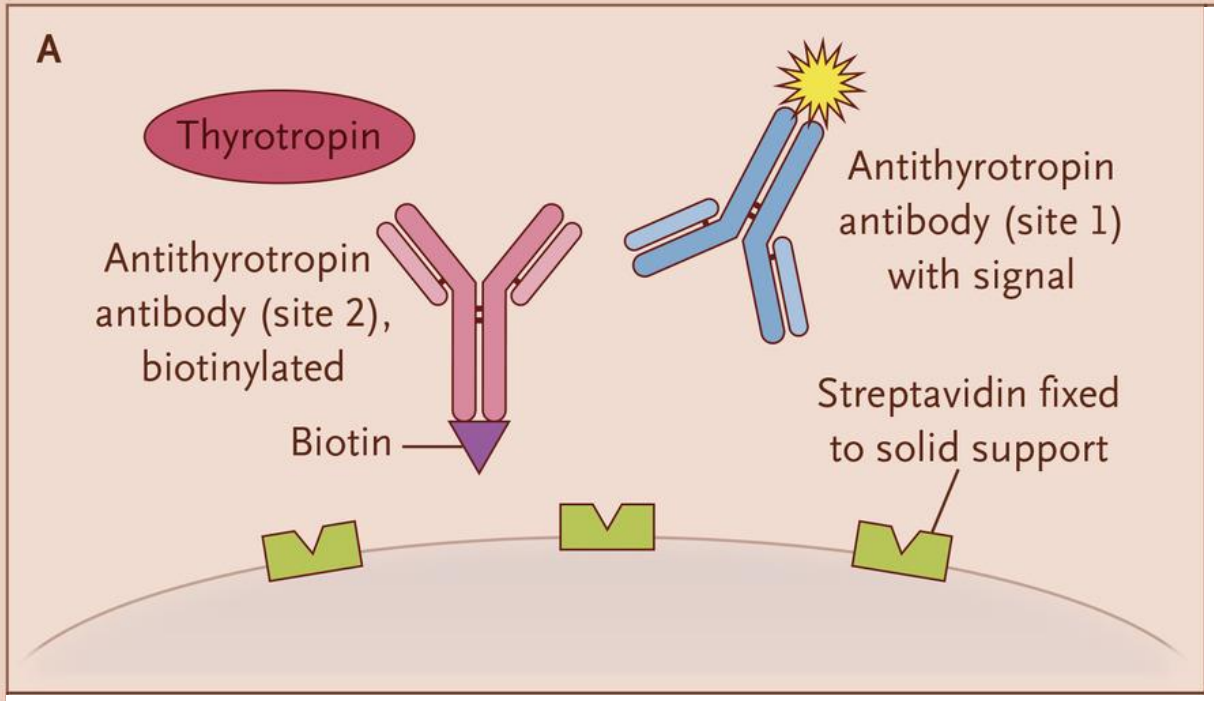
B. Assay interference
   - Biotin interferes with a variety of immunoassays.

C. Pituitary involvement from MS
   - Not a common area of involvement, and would not expect thyrotoxic labs.

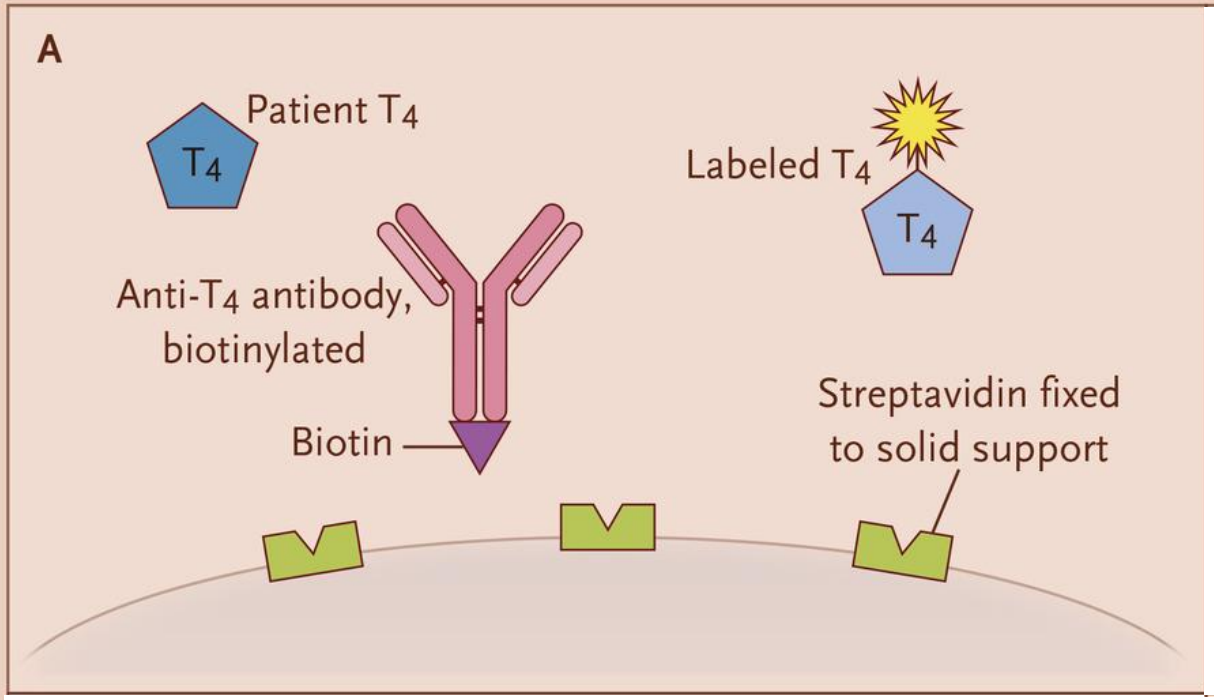
D. Drug-induced thyroiditis
   - Her drugs do not cause thyroiditis. Also unlikely in the absence of symptoms.

E. Altered TBG level
   - TBG likely high from cOCP which might raise total T4, but TSH and free T4 should not be altered.

Kummer et al. N Engl J Med 2016; 375:704-706



N Engl J Med 2019; 381:749-761



N Engl J Med 2019; 381:749-761

Case 2

- A 65-year-old woman is referred urgently for evaluation of abnormal TFTs. She has a history of lung cancer diagnosed 3 years ago, which has been treated with several chemotherapy regimens that have included cisplatin, paclitaxel, pemetrexed and bevacizumab. Due to progression of her disease, she was switched to pemetrexed, carboplatin and pembrolizumab 2 months ago.
- The patient reports symptoms of nausea and malaise after receiving her cancer treatment, but otherwise has no new symptoms and her vital signs and physical exam are normal.
- She had routine TFTs sent 2 days ago, which showed a TSH of 0.02 and a free T4 of 2.9. Her last TFTs sent a month ago showed a TSH of 0.69 and a free T4 of 1.5.

Case 2 (continued)

- In addition to monitoring the TFTs, what is the best next step in the treatment of this patient?

A. No treatment at this point.
B. Methimazole
C. Prednisone
D. Propylthiouracil
E. Metoprolol

Case 2 (answer)

- In addition to monitoring the TFTs, what is the best next step in the treatment of this patient?

A. No treatment at this point.
   - This patient has checkpoint inhibitor-induced thyroiditis. The thyrotoxicosis will resolve spontaneously with development of hypothyroidism; beta-blockers can be used if symptoms (steroids if severe).

B. Methimazole
   - No expected benefit in a thyroiditis.

C. Prednisone
   - Reserved for severe cases. Concern for reducing anti-neoplastic effect.

D. Propylthiouracil
   - No expected benefit in a thyroiditis.

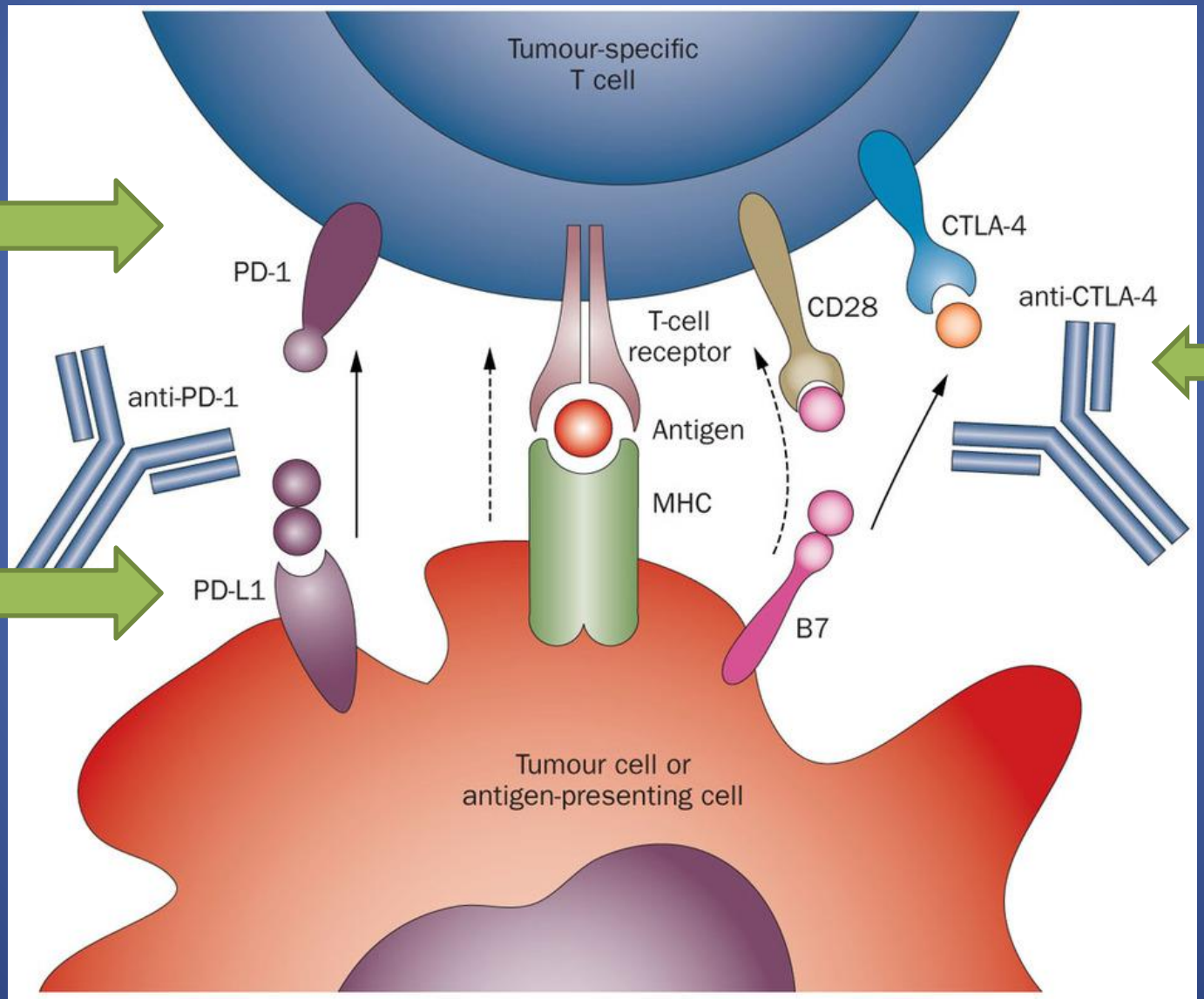
E. Metoprolol
   - Reasonable if symptomatic.

Higham et al. Endocr Connect. 2018 Jul;7(7):G1-G7

Immune checkpoint inhibitors block inhibitory signals to T-lymphocytes

- Nivolumab
- Pembrolizumab

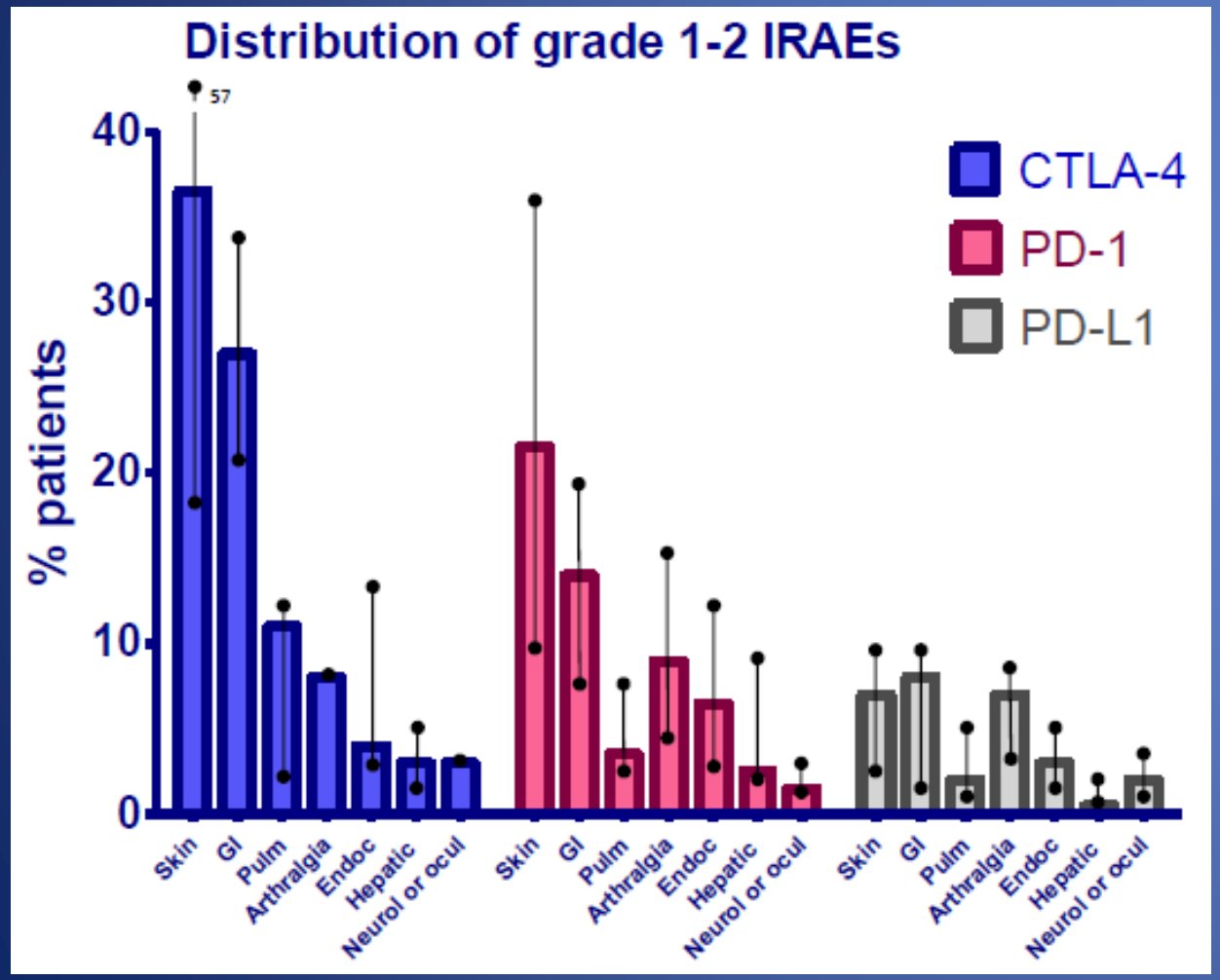
- Atezolizumab
- Avelumab
- Durvalumab

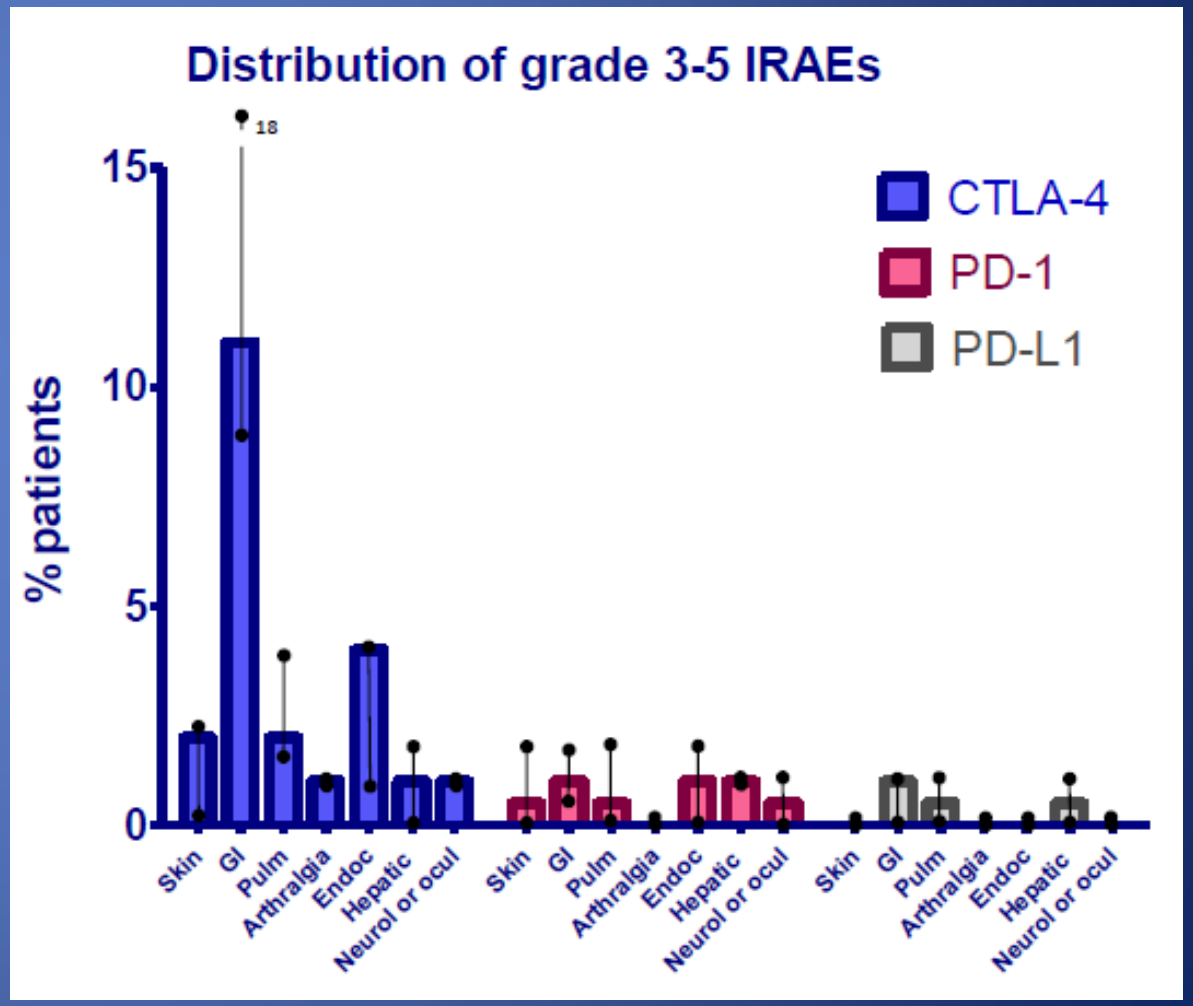


- Ipilimumab

Nature Reviews Clinical Oncology **11**, 24–37 (2014)

Immune-related adverse events are common with immune checkpoint inhibitors





European Journal of Cancer 54 (2016) :139;e148

Thyroid dysfunction is the most common endocrine side effect of PD-1 and PD-L1 inhibitors

	Thyroiditis / hypothyroidism	Hyperthyroidism	Hypophysitis
Ipilimumab (CTLA-4 inhibitor)	6%	2%	8%
Nivolumab (PD-1 inhibitor)	9%	4%	<1%
Ipilimumab + nivolumab	22%	8%	9%
Pembrolizumab (PD-1 inh)	3.9%	0.6%	Rare
Atezolizumab (PD-L1 inh)	13.2%	8%	0.2%

Endocr Relat Cancer. 2014 Apr; 21(2): 371–381.
http://packageinserts.bms.com/pi/pi_opdivo.pdf

Evaluation for thyroid disease – ASCO/NCCN

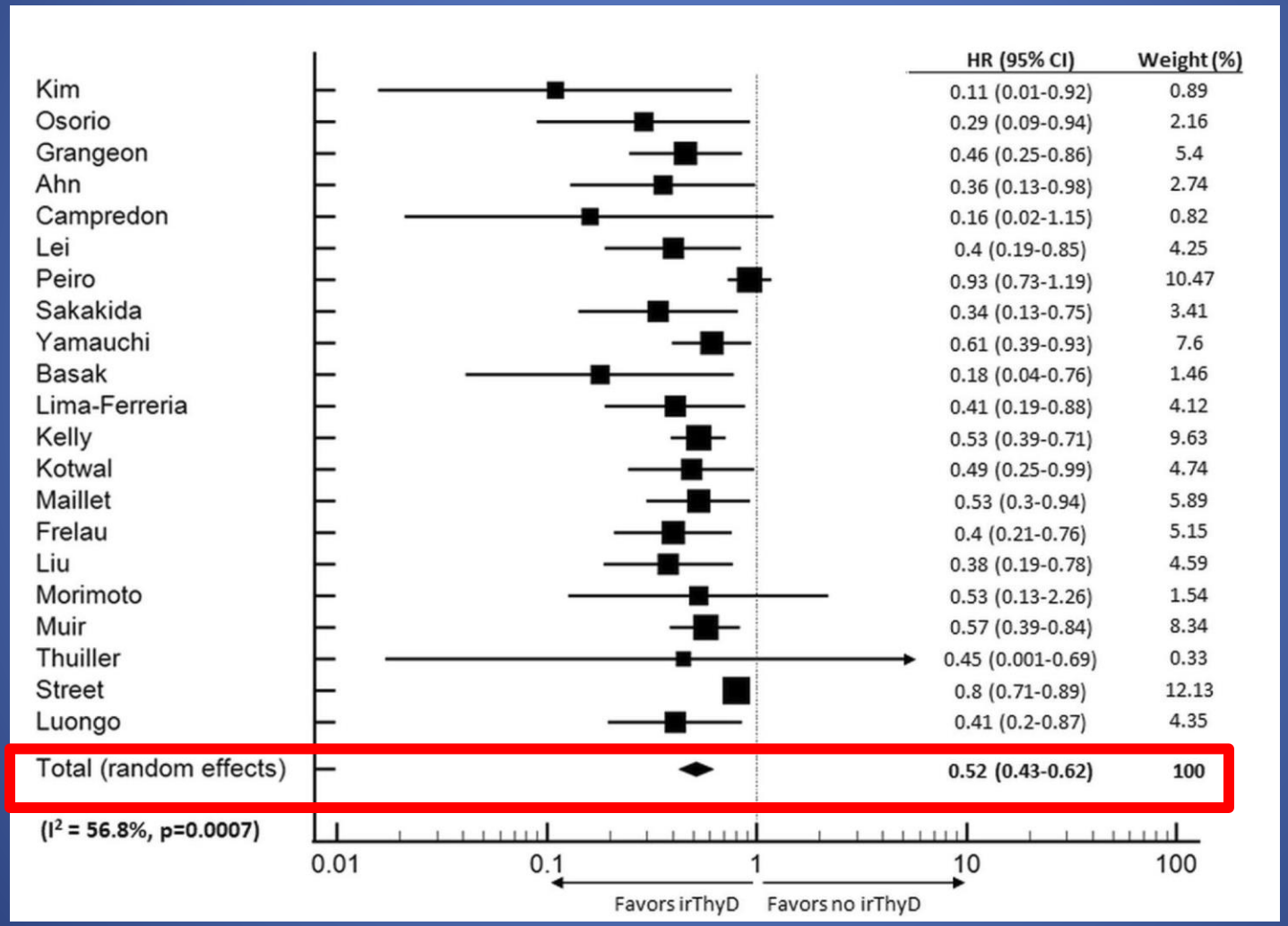
- TSH and free T4 every 4-6 weeks during treatment, then every 12 weeks

Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2021; 39:4073.
Thompson et al. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

Management of immune checkpoint inhibitor-induced thyrotoxicosis

- Destruction of gland – expect thyrotoxicosis followed by hypothyroidism (or euthyroidism)
- Serial thyroid function tests
  - Thyrotoxicosis >6-8 weeks: Evaluate for Graves'
  - Hypothyroidism: Start levothyroxine if TSH>10
- If tachycardic, symptoms: Betablockers are first line
- No role for antithyroid drugs (methimazole / carbimazole / propylthiouracil)
- How about glucocorticoids?

Thyroiditis from ICI is associated with improved survival



Cheung YM, Wang W, McGregor B, Hamnvik OPR. Cancer Immunol Immunother. 2022 Aug;71(8):1795-1812.

Unique aspects of endocrine iRAEs

- High dose glucocorticoids are not usually needed
- Focus is on hormone replacement
- The immune checkpoint inhibitor can be continued once endocrine condition stabilized
- Due to irreversible destruction of the endocrine gland, chronic follow-up is needed

Case 3

- A 42-year-old woman presents with a new diagnosis of thyrotoxicosis – 2 months of palpitations and weight loss, with TSH <assay, free T4 4.9 (elevated), TSI 3.3 (elevated)
- Started on methimazole 20 mg daily, returns for follow-up 1 month later.
- Symptoms have improved, TSH remains <assay, free T4 now 1.9.
- Reports eye symptoms: Mild retroorbital pain, marked diplopia esp. on upgaze, dry and uncomfortable eyes.

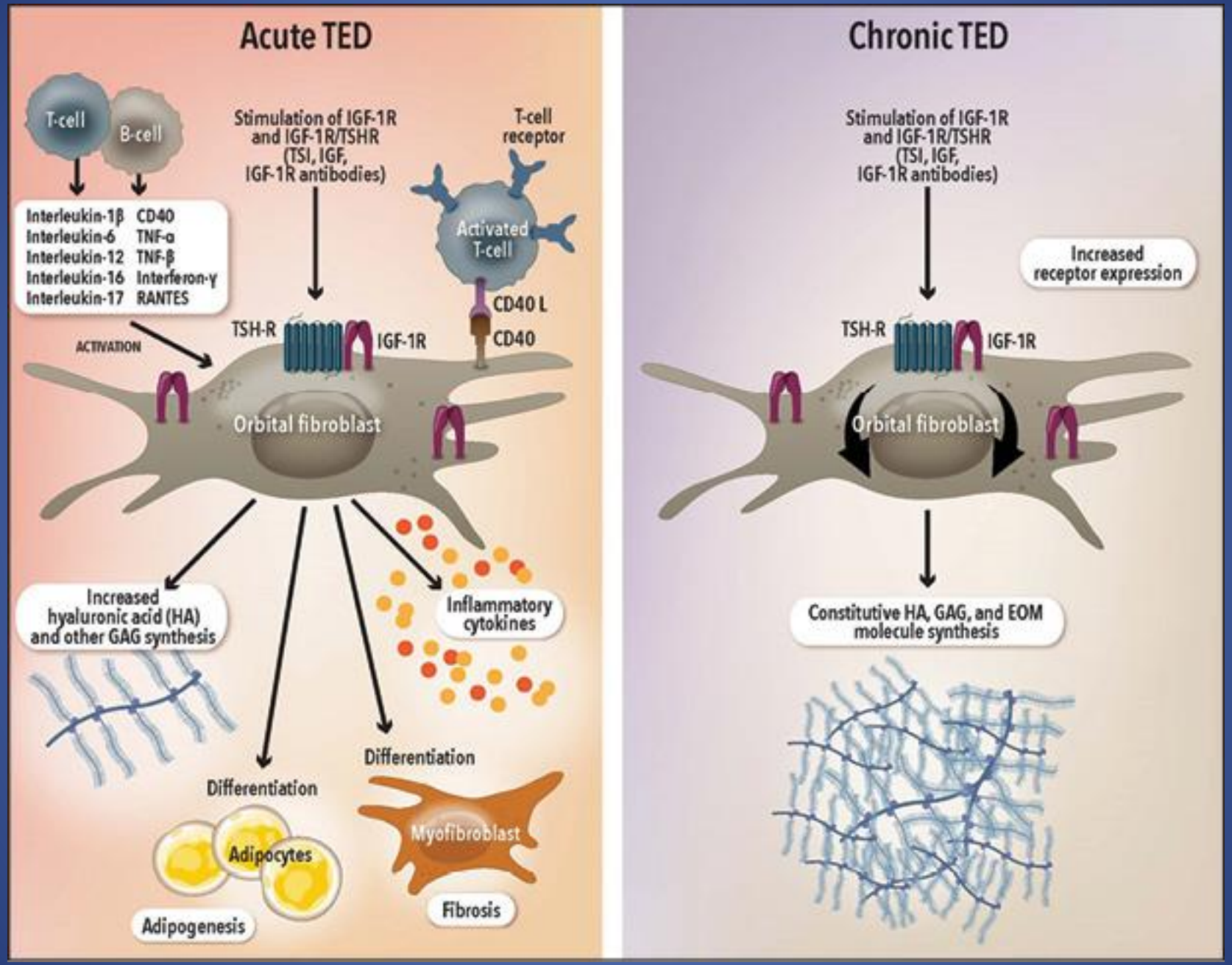
Case 3 (ctd)

- Physical examination:
  - Normal vital signs.
  - Bilateral proptosis, R>L
  - EOM restricted upgaze R>L
  - +chemosis, +eyelid swelling, +conjunctival erythema
  - Moderate thyromegaly
  - Mild tremor to outstretched hand

Case 3 (continued)

- Which one of the following interventions is indicated at this time?

A. Increase dose of methimazole to 40 mg daily
B. Refer for thyroidectomy
C. Refer to ophthalmic surgeon for consideration of strabismus surgery
D. Initiate pulse steroids
E. Initiate teprotumumab



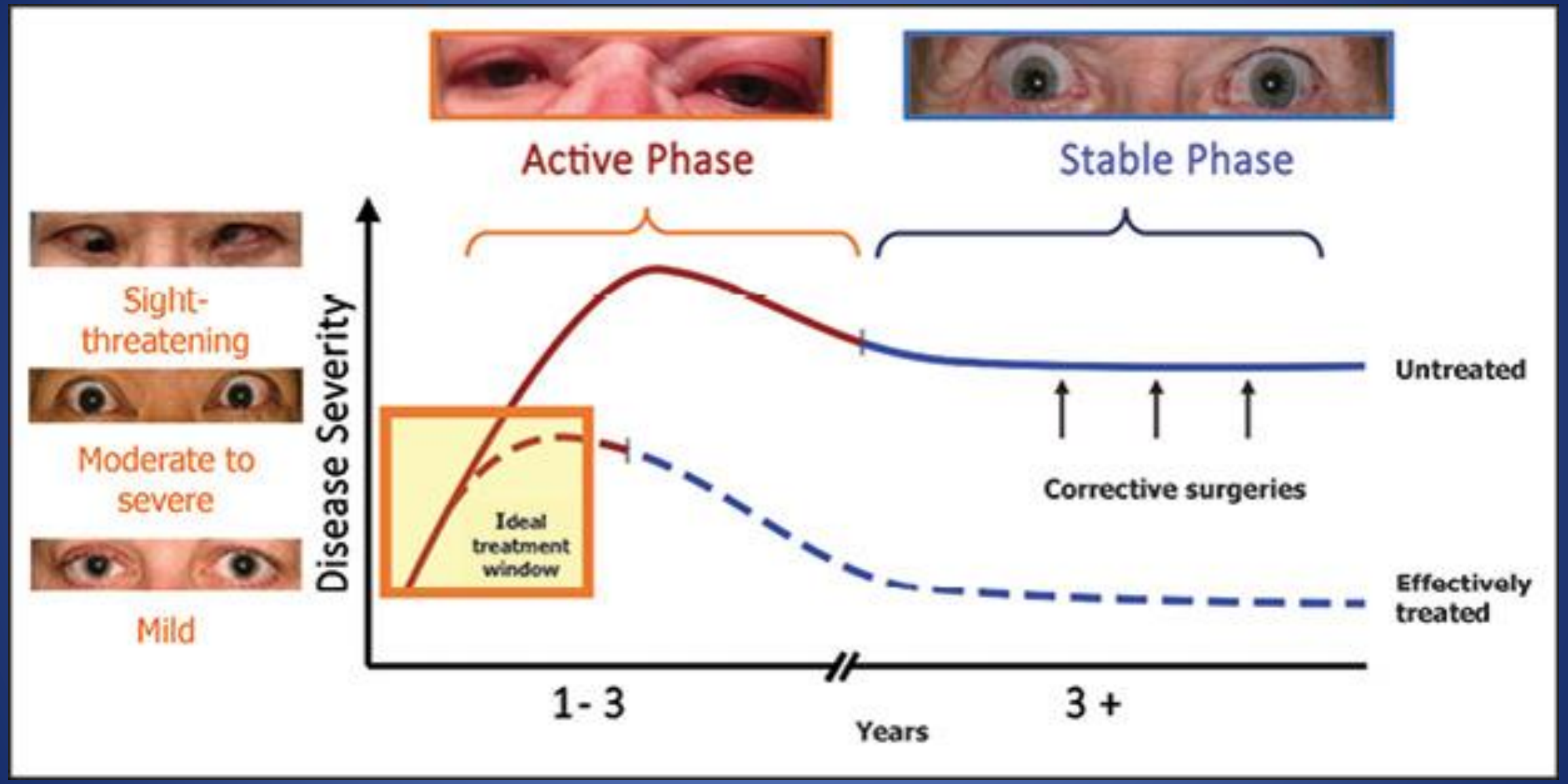
Ugradar S, et al. Eye (Lond). 2022;36(8):1553-1559.

Severity of Graves' orbitopathy

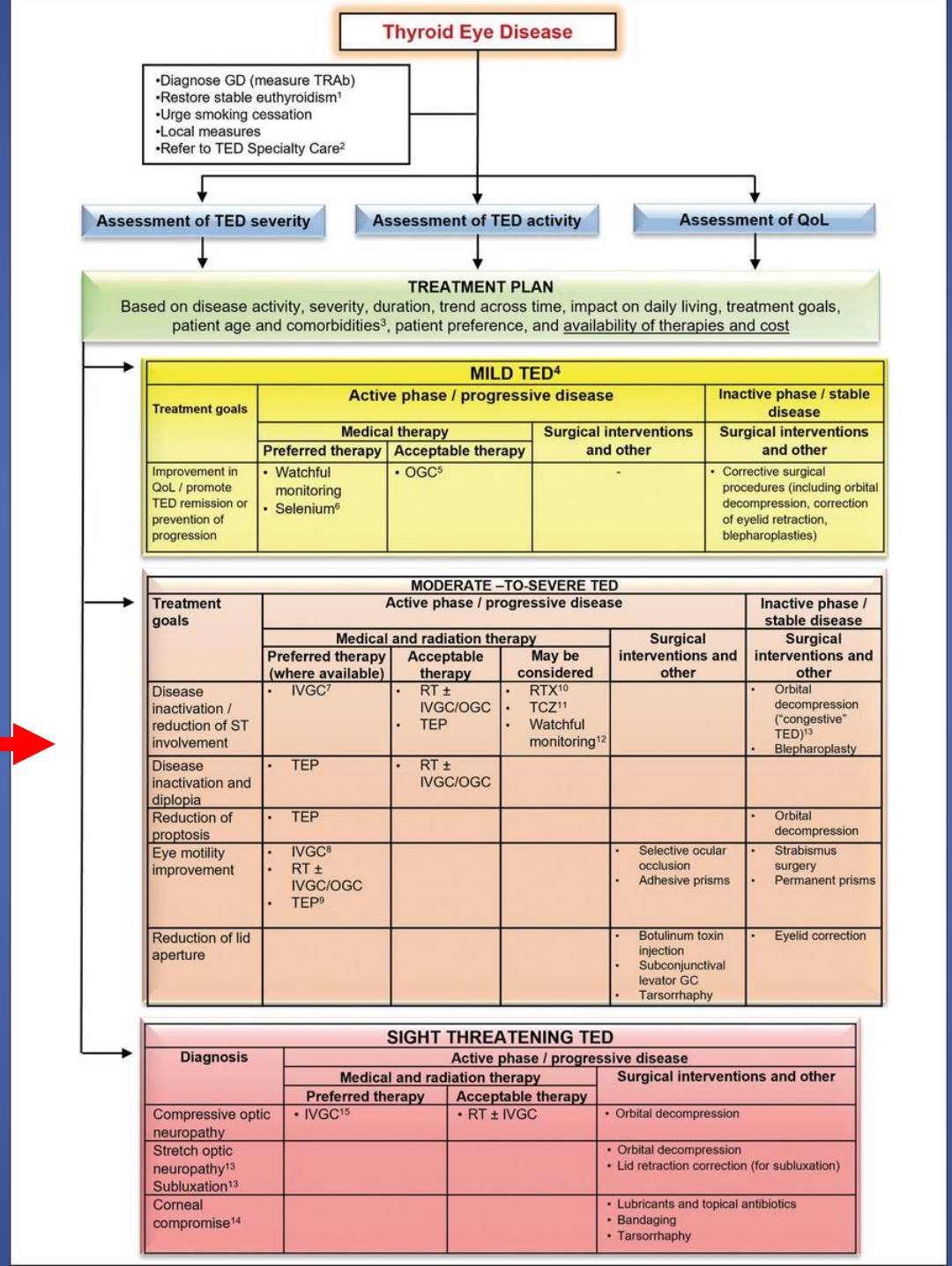
Classification	Lid retraction	Soft tissue involvement	Proptosis[a]	Diplopia	Cornea	Optic nerve
Mild	<2 mm	Mild	<3 mm	Transient or absent	Responsive to topical treatment	Normal
Moderate to severe	≥2 mm	Moderate to severe	≥3 mm	Inconstant or constant		
Sight threatening	—				Breakdown	DON

DON = dysthyroid optic neuropathy.

Bartalena L, et al. Front Endocrinol (Lausanne). 2020;11:615993.
Bartalena L, et al. Eur J Endocrinol. 2021;185(4):G43-G67.



https://webeye.ophth.uiowa.edu/eyeforum/patients/thyroid-eye-disease.htm



MILD TED[4]

Treatment goals	Active phase / progressive disease			Inactive phase / stable disease
	Medical therapy		Surgical interventions and other	Surgical interventions and other
	Preferred therapy	Acceptable therapy		
Improvement in QoL / promote TED remission or prevention of progression	• Watchful monitoring • Selenium[6]	• OGC[5]	-	• Corrective surgical procedures (including orbital decompression, correction of eyelid retraction, blepharoplasties)

MODERATE –TO-SEVERE TED

Treatment goals	Active phase / progressive disease				Inactive phase / stable disease
	Medical and radiation therapy			Surgical interventions and other	Surgical interventions and other
	Preferred therapy (where available)	Acceptable therapy	May be considered		
Disease inactivation / reduction of ST involvement	• IVGC[7]	• RT ± IVGC/OGC • TEP	• RTX[10] • TCZ[11] • Watchful monitoring[12]		• Orbital decompression ("congestive" TED)[13] • Blepharoplasty
Disease inactivation and diplopia	• TEP	• RT ± IVGC/OGC			
Reduction of proptosis	• TEP				• Orbital decompression
Eye motility improvement	• IVGC[8] • RT ± IVGC/OGC • TEP[9]			• Selective ocular occlusion • Adhesive prisms	• Strabismus surgery • Permanent prisms
Reduction of lid aperture				• Botulinum toxin injection • Subconjunctival levator GC • Tarsorrhaphy	• Eyelid correction

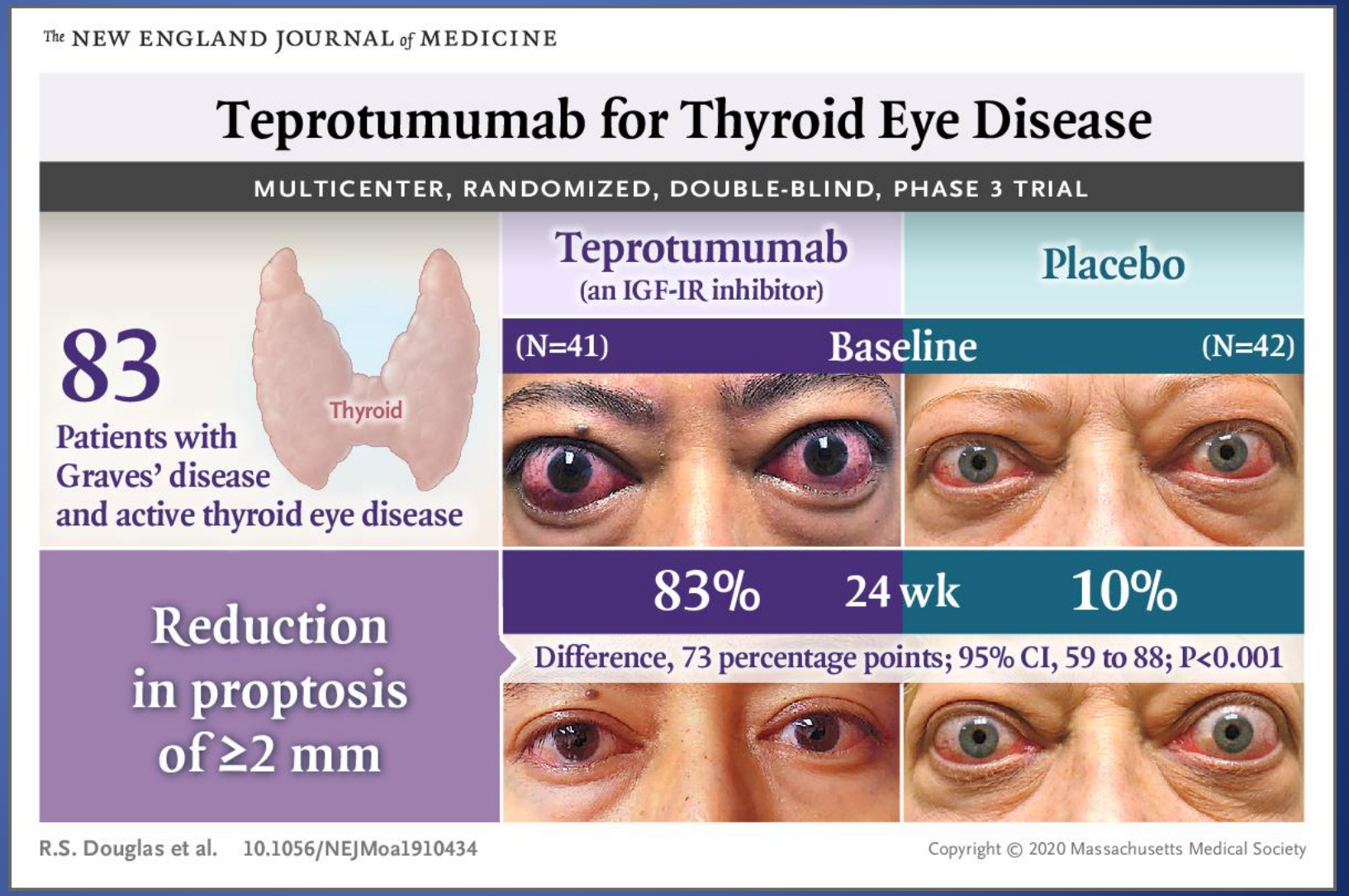
SIGHT THREATENING TED

Diagnosis	Active phase / progressive disease		
	Medical and radiation therapy		Surgical interventions and other
	Preferred therapy	Acceptable therapy	
Compressive optic neuropathy	• IVGC[15]	• RT ± IVGC	• Orbital decompression
Stretch optic neuropathy[13] Subluxation[13]			• Orbital decompression • Lid retraction correction (for subluxation)
Corneal compromise[14]			• Lubricants and topical antibiotics • Bandaging • Tarsorrhaphy

Burch HB, et al. Thyroid. 2022;32(12):1439-1470.

What is teprotumumab?

- IGF-1R inhibitor
- Given q3w for 8 doses
- Key side effects:
  -Hyperglycemia
  -Hearing loss
  -Infusion rxn
  -Diarrhea (IBD)
- Cost: $360K



N Engl J Med 2020; 382:341-352

Case 3 (continued)

- Which one of the following interventions is indicated at this time?

A. Increase dose of methimazole to 40 mg daily
   - Achieving euthyroid state important, but is getting there on 20 mg (TSH lags behind)

B. Refer for thyroidectomy
   - May be needed to control hyperthyroidism but not needed here

C. Refer to ophthalmic surgeon for consideration of strabismus surgery
   - Acutely: Sometimes decompression (sight-threatening) but strabismus surgery limited to chronic phase

D. Initiate pulse steroids
   - Due to balance of efficacy and cost, likely to be best option here, but may not be as effective as TEP and need to consider the potential for s/e with very high dose

E. Initiate teprotumumab
   - First-line had cost not been a hindrance

Case 4

- A 33-year-old woman presents for follow-up of hypothyroidism.
- She reports adherence with generic levothyroxine 75 mcg/day, in morning fasting, with a recent TSH of 0.99 [RR: 0.5-5.5].
- She endorses some fatigue and is asking about whether she should switch to ”the new thyroid drug they’re advertising on TV”

Case 4 (continued)

- Which one of the following is the next best step in evaluation or management of this patient?

A. Change her thyroid hormone replacement to levothyroxine oral solution
B. Switch her to desiccated pork thyroid
C. Send iron studies
D. Prescribe a brand-name thyroid hormone formulation
E. Measure a T3 level

Case 4 (continued)

- Which one of the following is the next best step in evaluation or management of this patient?

A. Change her thyroid hormone replacement to levothyroxine oral solution
   - Benefit is unclear, and cost is real

B. Switch her to desiccated pork thyroid
   - Should not be used (though could consider low-dose T3)

C. Send iron studies
   - Persistent hypothyroid symptoms in patients with normal TSH levels should prompt a search for alternate causes of fatigue

D. Prescribe a brand-name thyroid hormone formulation
   - Increasing data shows no benefit

E. Measure a T3 level
   - No role in hypothyroidism

Hypothyroid symptoms are common in the general population

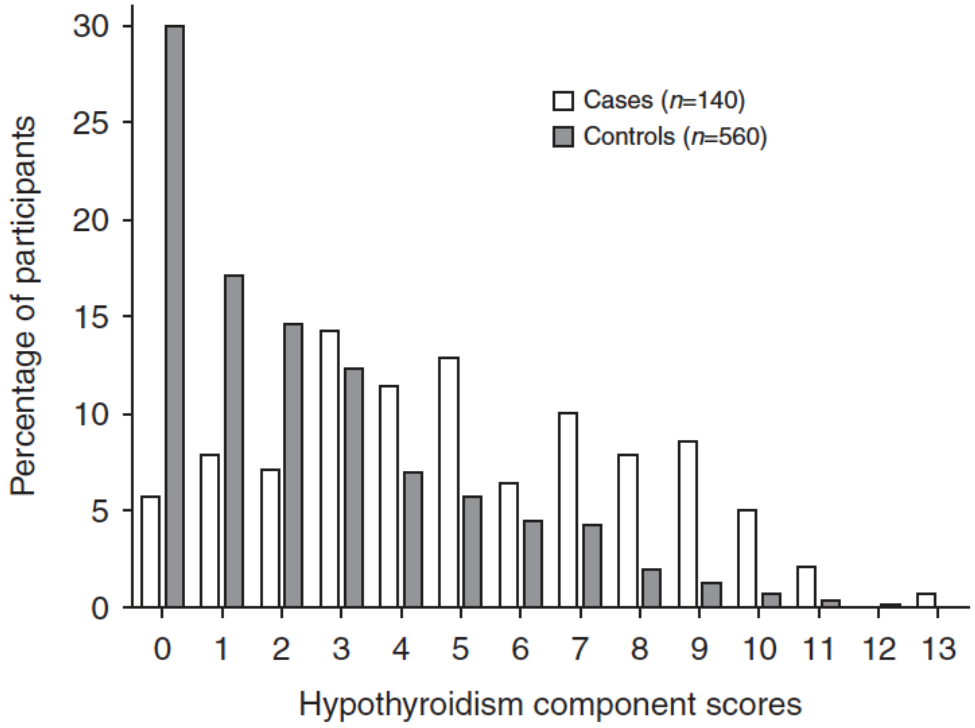


Figure 2

Number of hypothyroidism-associated symptoms as reported by hypothyroid patients at disease onset and by their region-, age- and sex-matched controls.

Eur J Endocrinol. 2014 Nov;171(5):593-602

Hypothyroid patients are more likely to report symptoms even when TSH is normal

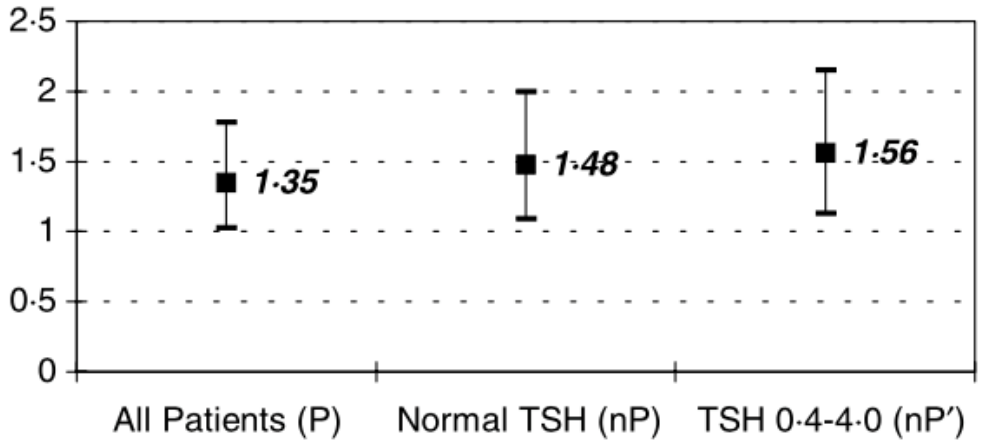
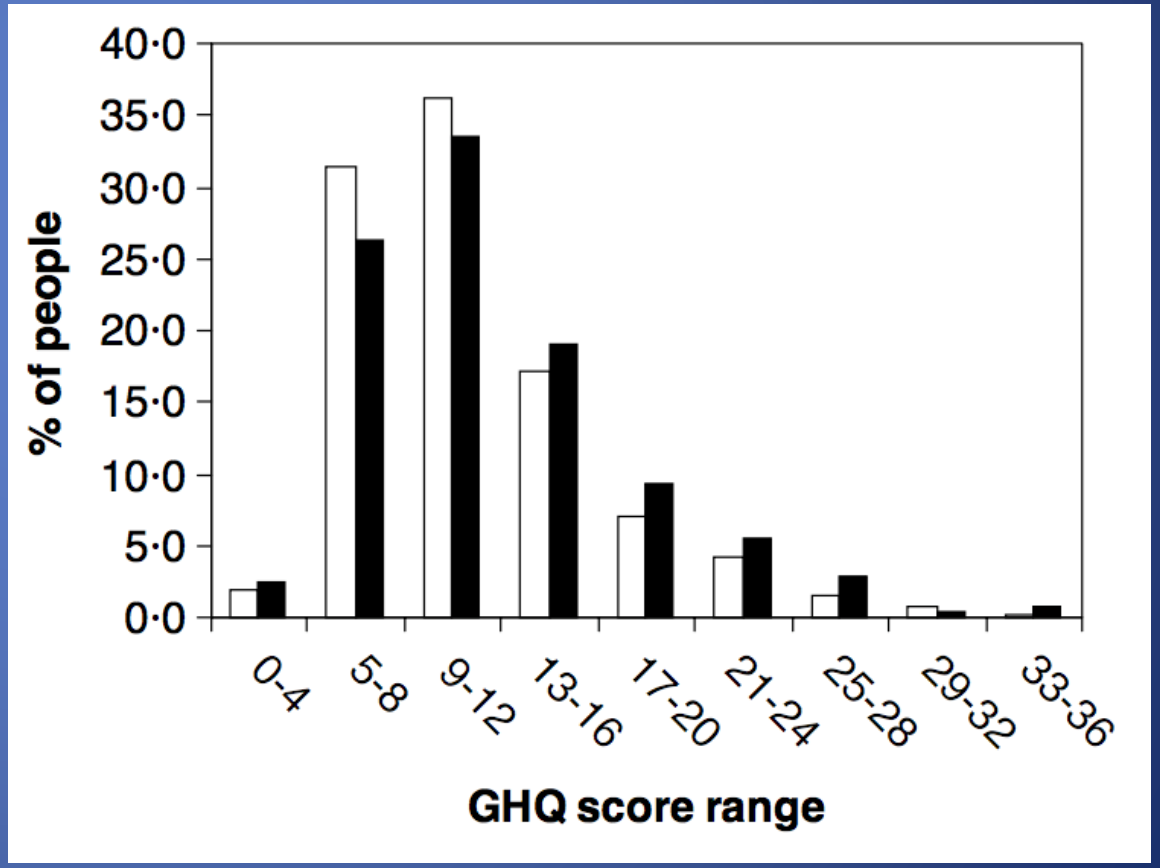


Fig. 3 Odds ratios and confidence intervals for casenesss (GHQ) comparing the patients and patient subgroups with normal TSH to controls. The Y-axis shows odds ratios for caseness using GHQ scores of 3 or more as a threshold. The X-axis shows groups compared with the control group: total responding patient group (P), patient group with TSH in normal laboratory range (nP) and patient group with TSH in a narrow normal range (0·4–4·0 mU/l; nP′).



Clin Endocrinol (Oxf). 2002 Nov;57(5):577-85.

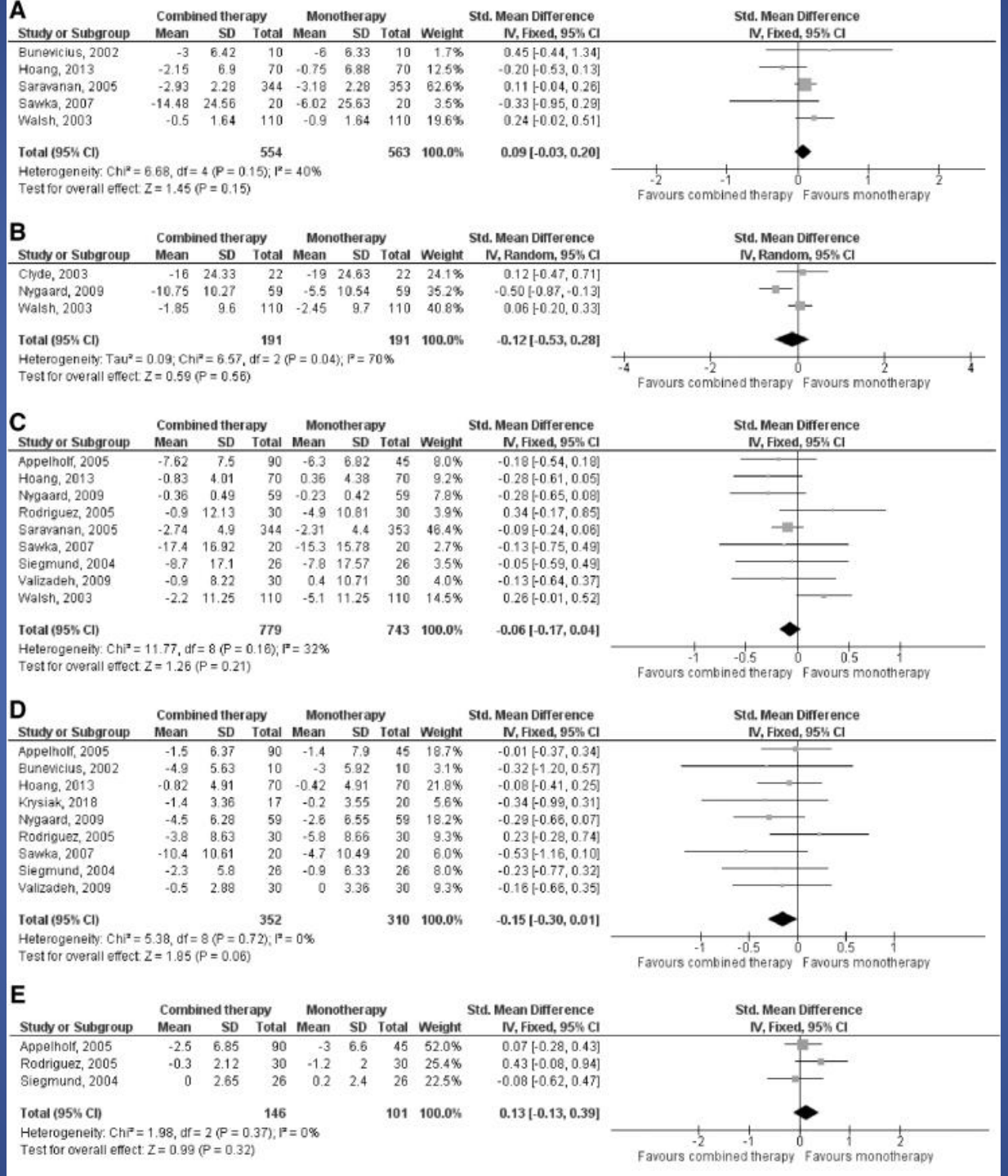
Potential solution #1: Target low-normal TSH

Variable	TSH 2-4.8	TSH 0.3-1.99	TSH <0.3	
General well-being	36.5 ± 3.7	40.0 ± 3.0	40.0 ± 1.9	ns
Tiredness	46.4 ± 5.0	50.2 ± 3.7	51.7 ± 3.9	ns
Aches and pains	35.3 ± 5.8	36.7 ± 3.9	36.5 ± 4.1	ns
SF-36 physical	42.3 ± 0.8	42.5 ± 0.6	42.3 ± 0.7	ns
SF-36 mental	51.2 ± 0.8	49.1 ± 1.0	48.9 ± 1.0	ns
GHQ-28	16.6 ± 1.6	18.3 ± 1.4	19.6 ± 1.7	ns
TSQ	12.5 ± 0.7	13.0 ± 0.6	13.6 ± 0.8	ns
Treatment satisfaction	0.7 ± 0.2	0.8 ± 0.1	0.8 ± 0.1	ns

J Clin Endocrinol Metab. 2006 Jul;91(7):2624-30.

Potential solution #2: Add T3

- 20% of circulating T3 is derived from the thyroid gland.
- Remainder is derived from peripheral deiodination of T4
- Theoretically: Add T3 to compensate for the 20% no longer secreted
- No measurable benefit in studies – though limited in size, outcome measurements, duration
- But **some** studies showed that patients preferred combination therapy
- Specific subgroups?
  - Low T3 values
  - Persistent symptoms
  - Polymorphisms in *DIO2* – Thr92Ala



Thyroid. 2021 Nov;31(11):1613-1625.

T4/T3 combination therapy

- Not recommended by European Thyroid Association or ATA guidelines
- …But do open for a therapeutic trial in patients with persistent symptoms
- Sample protocol (adapted from Bunevicius et al, NEJM, 1999):
  - Reduce LT4 dose by 25 (-50) mcg
  - Add LT3 (liothyronine) 5 (-10) mcg qAM [or 5 mcg qAM + 5 mcg qNoon]

Word of caution

- T4 is needed for fetal brain development – do not use T3 in women of childbearing potential

Potential solution #3: Desiccated thyroid

- Theoretical benefit: T4, T3
- Other molecules? Unclear role, disappear with purification
- Cost: $1-2/dose (Adthyza, Armor, NP Thyroid)
- Sample tablet: 65 **mg** strength, 28 **mcg** T4, 9 **mcg** T3
- Concerns:
  - Ratio of 4.2 : 1 is lower than 14 : 1 ratio of human thyroid gland -> relative excess of T3.
  - Short half-life of T3 – fluctuating levels
- A single RCT – no difference in outcomes, but patients prefer
- Cannot be recommended at this time

Thyroid. 2014 Dec;24(12):1670-751
J Clin Endocrinol Metab. 2013 May;98(5):1982-90.

Potential solution #4: Use new formulations of levothyroxine

- Levothyroxine capsules (Tirosint/generic) and oral solution (Tirosint-SOL)
  - Cost ≈$5/dose (Brand tablets: $1-2; generic 10¢-50¢)
  - Few ingredients (glycerol, levothyroxine, water, ±gelatin – role if allergies, celiac, other dietary restrictions
  - Reportedly less impact of intake with food
- Solution
  - Cost ≈$5-10/dose
  - 2000 mcg vials (20 mcg/mL - Thyquidity) or 2700/5400 mcg vials (30 mcg/mL – Ermeza)
  - More flexible dosing, easier to swallow
- Various claims on symptoms – based on minimal unblinded data

Potential solution #5: Consider brand-name formulations

- Switching between generic and brand-name: No change in TSH
- Switching between different generics: No change in TSH
- Symptoms – no data
- Cost difference: Brand tablets: $1-2; generic 10¢-50¢

JAMA Intern Med. 2022 Apr 1;182(4):418-425. JAMA Netw Open. 2020 Sep 1;3(9):e2017645.

Potential solution #6: Look for alternate causes

Box 1. Some possible causes of persistent symptoms in euthyroid patients on L-T4

Endocrine/autoimmune	Nutritional	Lifestyle
Diabetes mellitus	Vitamin B12 deficiency	Stressful life events
Adrenal insufficiency	Folate deficiency	Poor sleep pattern
Hypopituitarism	Vitamin D deficiency	Work-related exhaustion
Coeliac disease	Iron deficiency	Alcohol excess
Pernicious anaemia	Metabolic	Others
Haematological	Obesity	Obstructive sleep apnoea
Anaemia	Hypercalcaemia	Viral and postviral syndromes
Multiple myeloma	Electrolyte imbalance	Chronic fatigue syndrome
End-organ damage	Drugs	Carbon monoxide poisoning
Chronic kidney disease	Beta-blockers	Depression and anxiety
Chronic liver disease	Statins	Polymyalgia rheumatica
Congestive cardiac failure	Opiates	Fibromyalgia

Symptom review, medical history, physical examination
CBC with diff, renal function, liver blood tests, electrolytes
Iron studies
B12, [folate]
25-OH-vitamin D
[AM cortisol, ACTH]

Clin Endocrinol (Oxf). 2016 Jun;84(6):799-808.

Iron deficiency in hypothyroidism

- 25 women with persistent hypothyroid symptoms despite normal TSH on LT4
- Other causes of hypothyroid symptoms ruled out, incl. no anemia
- Ferritin <15 in 5 patients, 15-60 in 20 patients.
- Treated with oral iron to achieve ferritin >100 mg/L.
- Symptom resolution in 4 of 5 patients with ferritin <15, 14 of 20 patient with ferritin 15-60.

Thyroid 2015:25(suppl 1):A-74.

My approach

- Look for alternate causes first
- If none, discuss with the patient that persistent symptoms are common, that we do not have any proven way to improve this, but that individual patients may find tweaks to regimen helpful even if large trials found no benefit:
  - Aim for TSH 0.5-2.5
  - Switch to brand-name tablets (rarely capsules)
  - Add liothyronine 5 mcg qAM ± 5 mcg qNoon if not pursuing pregnancy

Final take-home points

- If labs don’t make sense, consider lab interference from biotin (or other situations – speak to your lab!)
- Immune checkpoint inhibitors can cause a thyroiditis with transient thyrotoxicosis leading to persistent hypothyroidism; this is associated with improved cancer outcomes
- The management of thyroid eye disease is undergoing a big change with the approval of teprotumumab, although cost and concern for hyperglycemia and hearing loss are limitations
- Persistent symptoms in hypothyroidism is common, but can be addressed by ruling out alternate causes for the symptoms; non-proven adjustments to thyroid replacement can be considered but come with a financial cost

Key references

- Ylli D, Soldin SJ, Stolze B, et al. Biotin Interference in Assays for Thyroid Hormones, Thyrotropin and Thyroglobulin. Thyroid. 2021;31(8):1160-1170. doi:10.1089/thy.2020.0866
- Illouz F, Briet C, Rodien P. Immune checkpoint inhibitor-related thyroid dysfunction. Ann Endocrinol (Paris). 2023;S0003-4266(23)00046-X.
- Kossler AL, Douglas R, Dosiou C. Teprotumumab and the Evolving Therapeutic Landscape in Thyroid Eye Disease. J Clin Endocrinol Metab. 2022;107(Suppl_1):S36-S46.
- Millan-Alanis JM, González-González JG, Flores-Rodríguez A, et al. Benefits and Harms of Levothyroxine/L-Triiodothyronine Versus Levothyroxine Monotherapy for Adult Patients with Hypothyroidism: Systematic Review and Meta-Analysis. *Thyroid*. 2021;31(11):1613-1625.

ohamnvik@bwh.harvard.edu