MANAGEMENT OF THYROID DISORDERS

A Review of Controversies and Challenges

April 2026

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DISCLOSURES

- Research on thyroid nodules with Interpace Inc
- Data safety monitoring on Graves eye disease with Amgen

2

LEARNING OBJECTIVES

1) Identify clinical contexts in which TSH interpretation should informed by additional information to optimize treatment decisions.

2) Evaluate the risks and benefits of different thyroid hormone preparations for treatment in different populations.

3) Assist patients in evaluating among the options for treatment of thyrotoxicosis.

3

THYROID DISEASE DEFINITION CHALLENGES

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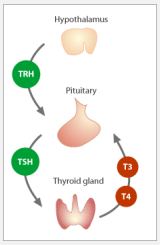
THE HYPOTHALAMIC PITUITARY THYROID AXIS IS A **NON-LINEAR**, NEGATIVE FEEDBACK SYSTEM



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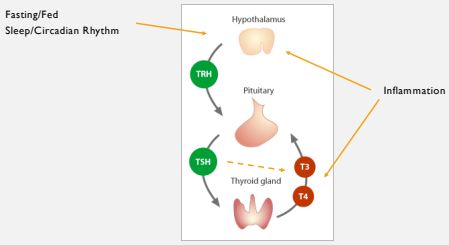
ADDITIONAL REGULATION OF THE HPT AXIS



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TFT CHALLENGES

- Genetics (e.g. TH resistance)
- Non-thyroidal Illness
- Medications
  - Steroids
  - Estrogenic compounds
  - Lithium
  - Amiodarone
- Assay interference
  - Biotin
  - HAMA antibodies
- Other setpoint populations
  - Pregnancy
  - Aging

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CHALLENGES IN HYPOTHYROIDISM

1) Should patients be treated for symptoms?
2) Are there appropriate uses of combination therapy?
3) What are the risks and causes of over treatment?

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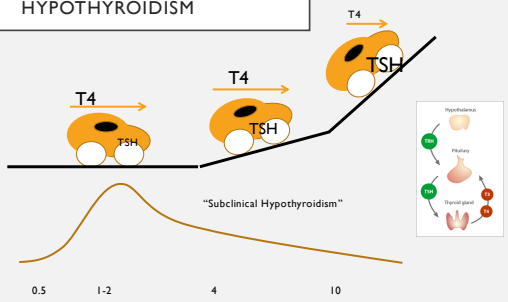
PROGRESSION OF PRIMARY HYPOTHYROIDISM



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THE COLORADO THYROID DISEASE PREVALENCE STUDY

- 4+ symptoms of hypothyroidism
  - 25% of those with overt hypothyroidism,
  - 20% of those with subclinical hypothyroidism
  - 17% of euthyroid patients.
- Total population: 88% euthyroid, 9% had subclinical hypothyroidism, 0.4% were overtly hypothyroid
  - 1000 people: 90 SCH, 4 Overt hypothyroidism, 880 euthyroid
- 1 symptomatic with overt disease, 18 symptomatic SCH, 149 symptomatic with normal thyroid function
- **Positive Predictive Value for 4+ symptoms: 11%**

Canaris GJ, et al. 2000 Arch Intern Med 160:526–534

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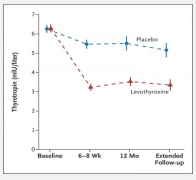
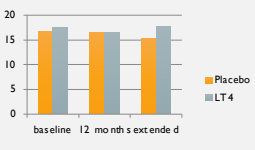
TRUST TRIAL OF LT4 TREATMENT IN OLDER ADULTS

- Mean age 74, Mean baseline TSH=6.4 mIU/L
- Screened 2647, to find 737 untreated patients with persistent TSH elevation

TSH Goals Achieved



Hypothyroid Symptom Scores Not Different



Stott et al, N Engl J Med 2017; 376:2534

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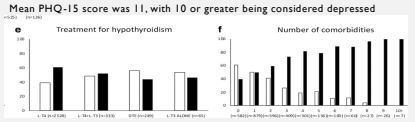
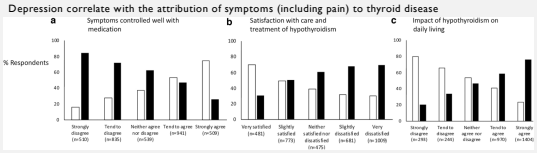
HIGH PREVALENCE OF DEPRESSION AND DIS-SATISFACTION IN SURVEY PARTICIPANTS

Mean PHQ-15 score was 11, with 10 or greater being considered depressed



Saravanan 2002, Clin Endo 57(5)
Mitchell 2021, Clin Endo 94(3)
Peterson 2018, Thyroid 28(6)
Perros et al, 2023 Thyroid 33(8)

Depression correlate with the attribution of symptoms (including pain) to thyroid disease



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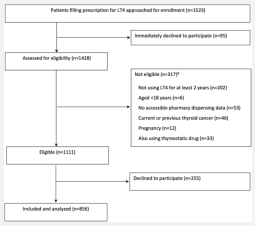
RANDOM SAMPLING – NO CORRELATIONS BETWEEN THERAPY AND SYMPTOMS/QUALITY OF LIFE

- The median TSH level 1.50 (IQR 0.63–2.84) mU/L
- 138/563 had out-of-range TSH levels
  - 14.6% [82/563] below
  - 9.9% [56/563] above
- Self-rated thyroid symptoms were generally not bothersome (median VAS: 1.0 mm, IQR 0.0–5.0; 0-100 possible).
  - 4.1% had a VAS score >50 (poor symptom control)
  - ThyPRO-39 and VAS scores were correlated ($r = 0.277$, $p < 0.01$).
  - ThyPRO-39 did not significantly correlate with TSH values ($r = 0.052$, $p = 0.222$).



Mehuys et al, 2023 Thyroid 33(8)

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ALTERNATIVE EXPLANATIONS

- Sleep apnea
- Menopause
- Post-infectious fatigue syndromes

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HOW TO DO AN N-OF-ONE TRIAL

- Explain subclinical hypothyroidism
  - I draw the cars and the hill
  - Treatment will bring the TSH down, but T4 levels should be relatively stable
- Set expectations
  - Treatment will bring the TSH down,
  - There may be a burst of over treatment in the first weeks as the pituitary adjusts and their own thyroid makes less hormone to compensate for the pill
  - Wait to get to steady state at 3 months
  - Wait 3 months at steady state to assess for benefit

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A BRIEF HISTORY OF DESICCATED THYROID

- 1891 DTE isolated from pigs to treat myxedema
- Grandfathered under the 1938 law founding the FDA – no new drug approval process
- The USP-based doses by iodine content, not active hormone.
- 1950 LT4 synthesis – levothyroxine available
- 1980 JAMA study demonstrated the presence of inactive tablets marketed as DTE
- 2000s Armour thyroid reformulated to monitor hormone levels

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POPULAR CULTURE AROUND DTE

Quote from the Dr Oz website:

"***the current blood testing misses the majority of people who need thyroid hormone treatmen***t. Sadly, many physicians don't know that the testing is unreliable, and continue to treat the tests instead of the person. Holistic physicians know how to treat taking both your symptoms and labs into account. ***Anyone with even 2 of the above symptoms should consider a trial of natural prescription thyroid*** (e.g., Armour Thyroid or a mix of T3 and T4 thyroid hormone)."

-Dr Jacob Teitelbaum on www.doctoroz.com 11/12/2009

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DOES ADDING T3 IMPACT MOOD, QUALITY OF LIFE, OR COGNITION?

- **Positive studies** (Bunevicius 1999, 2000, 2002; Escobar-Morreal, 2005 higher doses; Nygaard, 2010)
  - **Cross over designs**
  - **5-8 weeks** (one is 12 weeks).
  - **Suppressed TSH by T3 addition (except Nygaard, same TSH)**
- **Negative studies** (Smith, 1970; Sawaka 2003; Walsh 2003; Clyde, 2003; Siegmund, 2004; Rodriguez, 2005; Escobar-Morreal, 2005 lower doses; Appelhof 2005; Saravanan, 2005 Regalbuto, 2007; Fadeyev, 2007)
  - **Randomized control trials** including two large ones: 141 people over 15 weeks (Appelhof 2005) and 697 people over one year (Saravanan, 2005)
  - **8-52 weeks**
  - **Similar or increased TSH** (except Siegmund, Appelhof and Regalbuto, suppressed)

Reviewed in Biondi and Wartofsky, 2012 JCEM97(7):2256

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PATIENT PREFERENCE FOR T3 – associated with weight loss

- Appelhof (2005) RTC of LT4 v T3 at two doses
  - In LT4 (control) group : 29% prefer "study medication" compared to baseline (there was no actual change in the dose of medication)
  - In HIGH DOSE T3 group: 51% prefer the study medication
  - Excluding the hyperthyroid subjects, there is no significant preference (n=90).
  - Weight loss on excess T3 was the only significant predictor of preference

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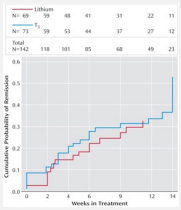
T3 IN TREATMENT RESISTANT DEPRESSION

- Data on standalone therapy is poor quality
  - Patients don't meet criteria for depression
  - Small, heterogenous samples with poor design.
- Might be equal to lithium for tricyclic-resistant depression
  - 4 RTCs, one negative so pooled effect negative
- STAR*D trial of 4000 patients with depression -
  - Failure at each treatment level lead to randomization at the next –L3 for Li v T3
  - Similar response rates (some side effects)



Nierenberg et al 2006 JAMA Psych 163(9)

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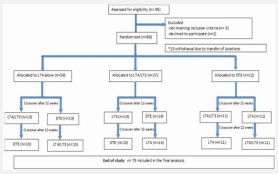
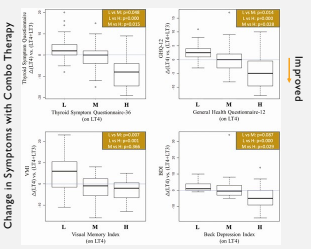
SUBSET OF POOR LT4 RESPONDERS?



Primary analyses all negative – no difference in symptoms, weight, QoL or cognitive testing across the treatments



Shakir et al 2021 JCEM 106(11)

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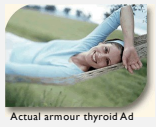
CHALLENGES OF COMBINATION THERAPY

- Short Half-life:
  - Q8 hour dosing for steady state
  - Long acting formulas are not yet available
- Physiologic ratios are hard to achieve:
  - DTE ratio of T3:T4 is 1:4 (pig) compared to 1:14 for human thyroid
  - Cytomel tablets are 5, 25 and 50 mcg, hard to cut
  - 4-5x as potent so physiologic conversion of 112 mcg total LT4 dose would be 100 mcg LT4 plus 2.5 T3.



Actual armour thyroid Ad

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TO T3 OR NOT TO T3?

- Maybe:
  - DTE formulations with adequate production controls allows stable dosing
  - Targeting physiologic TSH is possible (BID dosing)
  - Subgroups that benefit?
  - Malabsorbing patients that can benefit
  - May exert a strong placebo effect in a subset of patients eager to try it.
- Maybe not:
  - No demonstrated benefit in RTCs
  - Harder to avoid over treatment and the harm associated with that

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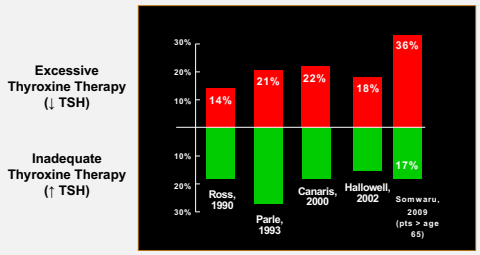
PREVALENCE OF SUBOPTIMAL THYROXINE THERAPY



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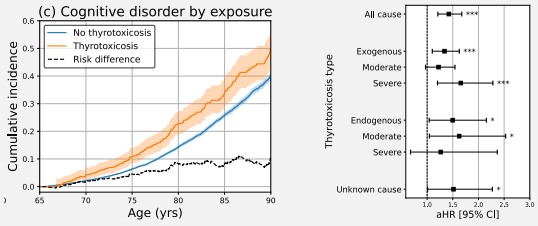
THYROTOXICOSIS FROM ANY SOURCE IS ASSOCIATED WITH A HIGHER INCIDENCE OF COGNITIVE DISORDERS



Adams et al, JAMA Int Med 2023

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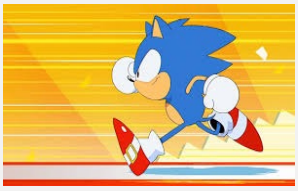
WHY ARE SOME PEOPLE OVERTREATED?



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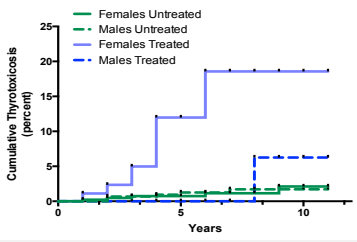
Incidence of Thyrotoxicosis By Treatment Status and Sex In the Baltimore Longitudinal Study of Aging



Mammen et al, 2015 Thyroid 25(9) 979-986

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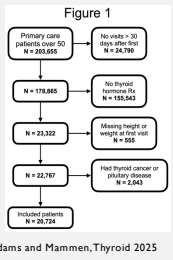
IATROGENIC THYROTOXICOSIS IN REAL WORLD DATA



Adams and Mammen, Thyroid 2025

Women and men are different for almost all tested risk factors

	All	Female	Male	p-value
N	20,724 (100.0%)	15,894 (100.0%)	4,830 (100.0%)	< 0.001
Female	15,894 (76.7%)	15,894 (100.0%)	0 (0.0%)	< 0.001
Age at first visit (y)				
55-60	7,454 (36.0%)	5,958 (37.5%)	1,496 (31.0%)	< 0.001
60-70	6,228 (30.1%)	4,817 (30.3%)	1,411 (29.2%)	< 0.001
70-80	4,405 (21.3%)	3,240 (20.4%)	1,165 (24.1%)	< 0.001
80+	2,637 (12.7%)	1,879 (11.8%)	758 (15.7%)	< 0.001
Race				
White	15,846 (76.5%)	12,014 (75.6%)	3,832 (79.3%)	< 0.001
Black	2,656 (12.8%)	2,155 (13.6%)	501 (10.4%)	< 0.001
Other	2,222 (10.7%)	1,725 (10.9%)	497 (10.3%)	< 0.001
Hispanic	647 (3.1%)	511 (3.2%)	136 (2.8%)	< 0.001
Years followed	4.7 (3.3)	4.7 (3.3)	4.5 (3.2)	< 0.001
TSH measures per year	1.6 (3.3)	1.6 (3.6)	1.6 (1.9)	0.089
Height (m)*	65.0 (3.8)	63.6 (2.8)	69.3 (3.1)	< 0.001
BMI* (kg/m²)*	30.2 (7.2)	30.2 (7.5)	29.9 (6.2)	0.909
TSH > 10 m IU/L*	5,174 (25.0%)	3,790 (23.8%)	1,384 (28.7%)	< 0.001
Iatrogenic hyperthyroidism*	6,995 (33.8%)	5,840 (36.7%)	1,155 (23.9%)	< 0.001
Severe*	2,871 (13.9%)	2,419 (15.2%)	452 (9.4%)	< 0.001
Comorbidities*				
Diabetes	5,952 (28.7%)	4,273 (26.9%)	1,679 (34.8%)	< 0.001
Fatigue/chronic pain	11,828 (57.1%)	9,384 (59.0%)	2,444 (50.6%)	< 0.001
Obesity	6,922 (33.4%)	5,462 (34.4%)	1,460 (30.2%)	< 0.001
Depression	6,616 (31.9%)	5,524 (34.8%)	1,092 (22.6%)	< 0.001
Atrial fibrillation	2,827 (13.6%)	1,803 (11.3%)	1,024 (21.2%)	< 0.001
Ischemic heart disease	3,909 (18.9%)	2,363 (14.9%)	1,546 (32.0%)	< 0.001
Heart failure	2,644 (12.8%)	1,836 (11.6%)	808 (16.7%)	< 0.001
Medications*				
Calcium	8,410 (40.6%)	6,825 (42.9%)	1,585 (32.8%)	< 0.001
Estrogen	3,529 (17.0%)	3,524 (22.2%)	5 (0.1%)	< 0.001
GLP-1RA*	2,516 (12.1%)	1,990 (12.5%)	526 (10.9%)	< 0.001
Iron	4,086 (19.7%)	3,116 (19.6%)	970 (20.1%)	< 0.001
Magnesium	6,694 (32.3%)	5,118 (32.2%)	1,576 (32.6%)	< 0.001
PPI*	10,852 (52.4%)	8,314 (52.3%)	2,538 (52.5%)	< 0.001

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NO RISK FACTORS EXPLAINED INCREASED RISK OF IATROGENIC THYROTOXICOSIS IN WOMEN

	All patients
Model	HR for female sex [95% CI]
Unadjusted	1.67 [1.56 - 1.79]
Fully Adjusted	1.50 [1.34 - 1.68]

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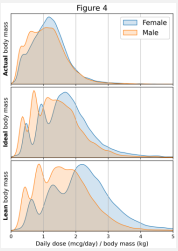
RISK DIFFERENCE IS A FUNCTION OF DOSING DIFFERENCES BECAUSE OF BODY COMPOSITION

Figure 4



		All patients	
Model		HR[a] for female sex [95% CI[b]]	p-value
Unadjusted for dose		1.55 [1.41 - 1.69]	Ref
Adjusted for dose/body mass	Actual	1.50 [1.34 - 1.68]	0.404
	Ideal	1.30 [1.16 - 1.46]	< 0.001
	Lean	1.06 [0.95 - 1.19]	< 0.001

[a] Hazard ratio
[b] Confidence interval

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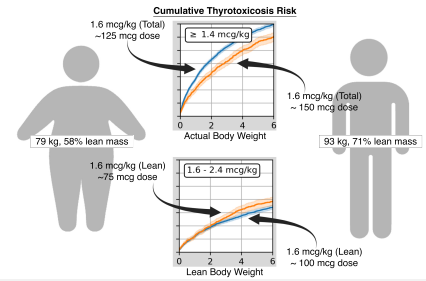
Women are at increased risk of thyrotoxicosis compared to men at similar actual body weight doses, but not similar lean body weight doses



Adams and Mammen, Thyroid 2025

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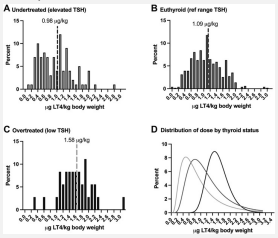
OLDER ADULTS AND OBESITY ADJUSTMENTS

Euthyroid doses in the BLSA



Gavigan et al 2023 Endo Clin Prac.

Euthyroid doses after surgery across BMI range

Table 2. Levothyroxine Dosing to Achieve Euthyroidism

Variable	BMI					
	<25	26–30	31–35	35–40	>40	p
Stable LT4 dose (mcg/kg)	1.76	1.47	1.42	1.27	1.28	<0.01
Stable LT4 dose (mcg)	111.5	112.9	128.7	131.4	152.3	<0.01
Weeks to stable dose	37.8	60.7	46.5	51.2	50.9	0.58
Weight change (kg)	−4.23	−2.73	−4.48	−0.7	−2.4	0.61

Papoian et al, 2019 Thyroid 29(11)

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CHALLENGES IN HYPERTHYROIDISM

1) How long can medical therapy be used?
2) How should we understand cancer risk with RAI?

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HYPERTHYROIDISM HAS NEGATIVE OUTCOMES, ESPECIALLY WITH AGE

- Thyroid storm: mortality rate is 10-15% over age 60. (Thiyagarajan, Thyroid 2022)
- Mortality is increased even without storm: OR=1.14 (95% CI 1.04–1.24; Franklyn, JAMA 2005)
- Atrial fibrillation in 20% of patients (64/312) without underlying heart disease (Sandler and Wilson, Q J Med 1959)
- Excesses hip fracture risk is age dependent (Vestergaard and Mosekilde, Thyroid 2003)

Review: Chaker et al, Lancet 2024 402(10428):768

Cardiac complications by age

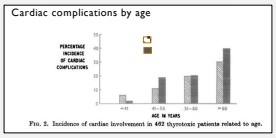
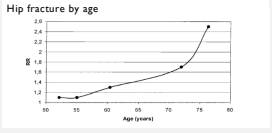


Fig. 2. Incidence of cardiac involvement in 402 thyrotoxic patients related to age.

Hip fracture by age



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ATA HYPERTHYROIDISM GUIDELINES TREATMENT THRESHOLDS BASED ON RISK

- Subclinical hyperthyroidism should be treated in individuals with serum TSH levels persistently <0.1 mU/L who are over age 65, postmenopausal or have risk factors for cardiac arrhythmias.
- Treatment of subclinical hyperthyroidism should be considered in individuals with serum TSH persistently between 0.1 and 0.5 mU/L who are over age 65 or have cardiac disease.

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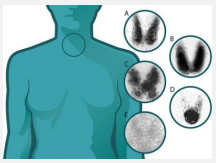
TREATMENT OPTIONS

- Symptom control with beta blocker (outpatient)
  - Lets you make a diagnosis
- Thionamide compounds
  - Take several weeks to work
  - Methimazole: longer half life
  - PTU: less trans-placental transfer; blocks de-iodinase
- Radioactive Iodine
- Surgery
- Emerging non-surgical management of nodules with RFA)



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TREATMENT COMPARISON

	Advantages	Hypothyroidism	Other Disadvantages	Cost
Antithyroid Drugs	Nonablative	Low frequency	Not definitive, side-effects	+
Radioiodine	Definitive	100%	Fear/cancer?	++
Surgery	Definitive	100%	complications, discomfort	+++

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A 2011 Survey of Clinical Practice Patterns in the Management of Graves' Disease

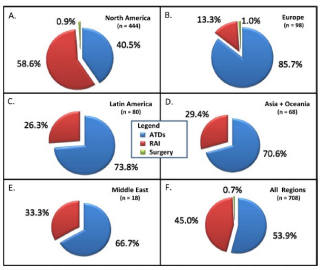

FIG. 3. International differences in the selection of primary treatment modality for the index case of uncomplicated GD.

Burch H et al.
J Clin Endocrinol Metab. 2013

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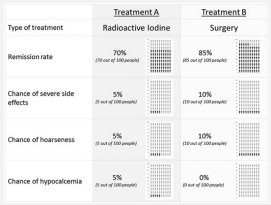
GRAVES TREATMENT PREFERENCES

- Discrete choice experiment
  - 3 treatments, 5 attributes
  - 48 pairs of possible choices (4 sets of 12)
- 286 patients, 61 clinicians
- Remission rate is most important factor, but ATD still preferred
- Subgroup of patients with negative feelings about RAI
- Clinicians prefer RAI to surgery



	Treatment A	Treatment B
Type of treatment	Radioactive Iodine	Surgery
Remission rate	70% (70 out of 100 people)	85% (85 out of 100 people)
Chance of severe side effects	5% (5 out of 100 people)	10% (10 out of 100 people)
Chance of hoarseness	5% (5 out of 100 people)	10% (10 out of 100 people)
Chance of hypocalcemia	5% (5 out of 100 people)	0% (0 out of 100 people)

Van Kinschot et al 2021 Eur J Endo 184 (6)

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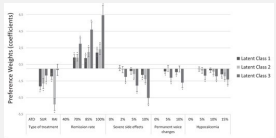
ATD PREFERRED BY PATIENTS



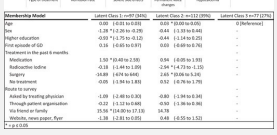


Table 4
Willingness to trade remission rate (%).

Attribute	Patients	Clinicians
Treatment type		
ATD instead of surgery	−38.4	−25.5
ATD instead of RAI	−43.0	−6.1
Severe side effect*	−3.1	−4.1
Permanent voice changes*	−0.8	−1.8
Hypocalcemia*	−1.3	−1.8

* 1% less risk.

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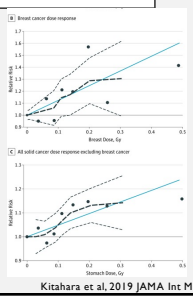
RAI AND CANCER RISKS
COOPERATIVE THYROTOXICOSIS THERAPY FOLLOW UP STUDY

- 35,000 patients, half treated with RAI in the 1950s
- Initial reports were negative
  - No difference in total and site specific CA compared to general population
  - No dose response
- Revised study in 2019 – new calculation of delivered dose
  - Dose-response increase in solid tumor risk combined,
  - Only significant individually for breast cancer
    - RR=1.12 p=0.04
    - 3 excess breast cancer deaths for every 1000 patients with a tissue dose of 100 mGy (mean 150)
  - No effect on thyroid cancer risk
  - No effect on leukemia



Kitahara et al, 2019 JAMA Int Med 179(8)

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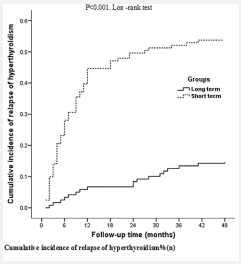
LONG TERM USE OF MME AND REMISSION

- 258 patients randomized after 18 months to continue (15-24 more months)or stop.
- 4 year follow up
- 56/123 (45%) versus 101/121 (83%) were still euthyroid at 4 years
- No good predictors of relapse at the time of stopping therapy (TFTS all the same).



Azizi 2019,Thyroid 29(9)

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