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استادان و مدعوین محترم

لینک و QR جهت سخنرانی Question Box

استاد دکتر عزیزی می باشد.

Practical Hints for Long-term Antithyroid Drug Treatment

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Disclosure

I declare that I

Have no conflict of

Interest

Case of Hyperthyroidism

32 year old woman with tachycardia, nervousness and weight loss.

Pulse rate 106/minute, BP 110/50, diffuse goiter 45 gm, lid lag, lid retraction, warm and moist skin.

		Normal Range
Serum fT4	**3.5 ng/dl**	**(0.7-2.0)**
	45 pmol/L	**(9-26)**
Serum T3	**360 ng/dl**	**(70-190)**
Serum TSH	**0.05 mIU/l**	**(0.4-5.0)**
Serum TRAb	**10.8 IU/L**	**(<1.75)**

Advantages and indications of three available treatment modalities for thyrotoxicosis

Thianamdes	Radioiodine	Thyroidectomy
✓ High remission chance	❖ Definitive pre-pregnancy treatment	➢ Large glands/ nodules
✓ Elderly, co-morbidities	❖ Elderly, comorbidities	➢ Suspicious nodules
✓ Poor surgical candidate, surgical contraindications, lack of surgical expertise	❖ Poor surgical candidate, surgical contraindications, lack of surgical expertise	➢ Hyperparathyroidism ➢ Orbitopathy ➢ Definitive pre-pregnancy treatment Low RAIU
✓ Orbitopathy		

2016 ATA Guidelines. Thyroid 26: 1343-1421

Which Treatment modality do you prefer

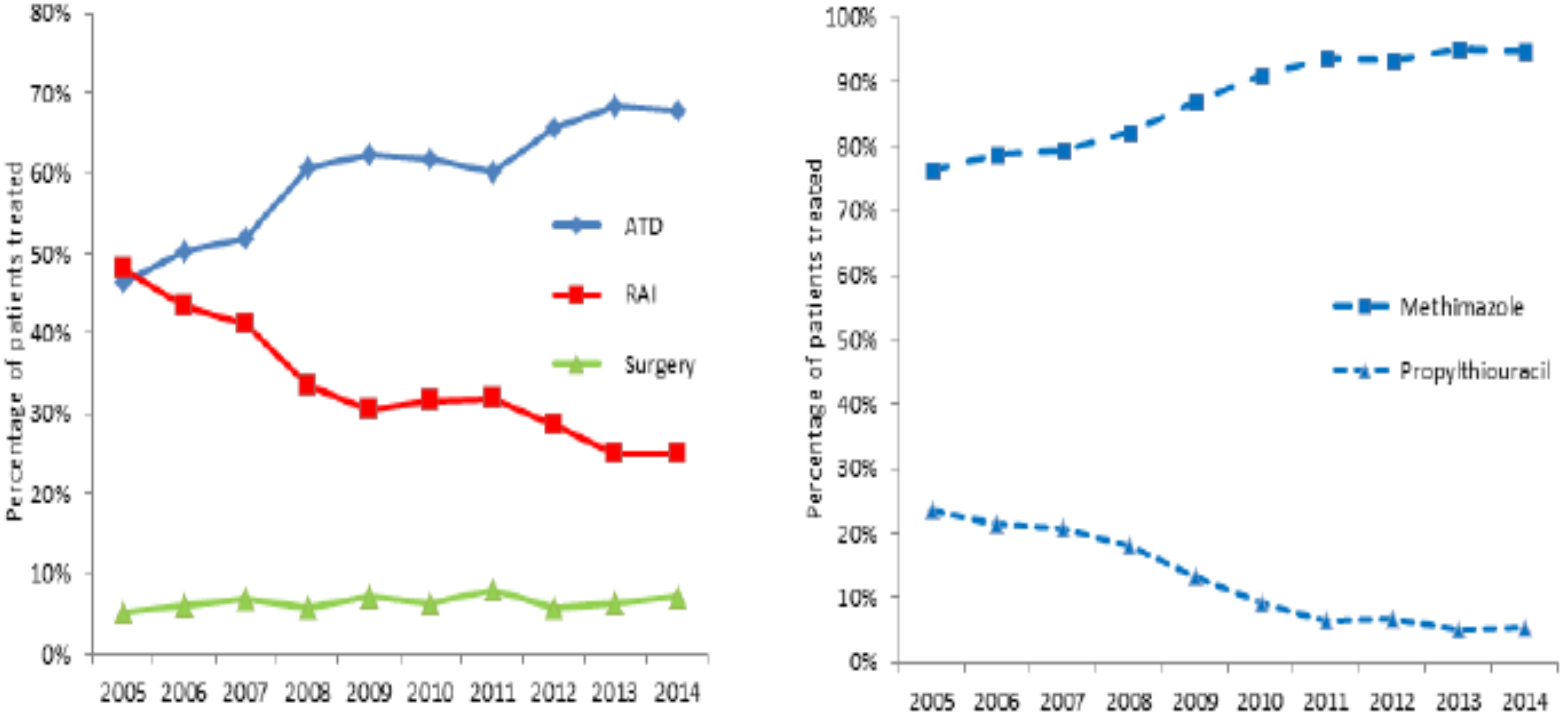
1. **Antithyroid drugs (ATD)**
2. **Radioiodine (RAI)**
3. **Thyroidectomy**
4. **ATD for 3 months then RAI**

Treating physician and patient, should discuss each of the treatment modalities, including the benefits, potential side effects, logistics, expected speed of recovery, drawbacks and costs.

Important issues for making appropriate decision:

- ❖Expected speed of recovery
- ❖Sustained euthyroidism
- ❖Worsening of orbitopathy
- ❖Quality of life
- ❖Ease of treatment & costs
- ❖Adverse events
- ❖Induction of hypo- or hyperthyroidism
- ❖Cancer related mortality
- ❖Cardiovascular risk and events
- ❖Remission rate

Treatment choice for hyperthyroidism (USA, 2005-2014)



Left: Percentage of treatment choice by year. Right: Percentage of ATD treatment drug choice by year.

Brito JP et al. Thyroid 2016; 26: 1144-5

Patient was treated with methimazole (MMI) 20 mg daily for the first month and 10 mg daily for the second month. She is clinically euthyroid.

Serum fT4 and T3 became normal and TSH was <0.1 mU/L after 2 months. Which action do you take

1. **Change to propylthiouracil**
2. **Continue same dose of MMI**
3. **Increase MMI dosage**
4. **Add lithium to MMI**

Cardiovascular safety

- **↑ All-cause mortality is increased**

  Brandt F et al, Thyroid 2013; 23: 408-13.

- **↑ In cardiovascular outcomes with longer durations of suppressed serum TSH**

  Boelaert K, Maisonneuve P, Torlinska B, Franklyn JA. J Clin Endocrinol Metab. 2013;98(5):1869e1882.

- **↑ Risk of mortality and substantial cardiovascular morbidity in uncorrected hyperthyroidism**

  Lillevang-Johansen M, Abrahamsen B, Jørgensen HL, Brix TH, Hegedüs L. J Clinical Endocrin Metab 2017;102(7):2301-9.

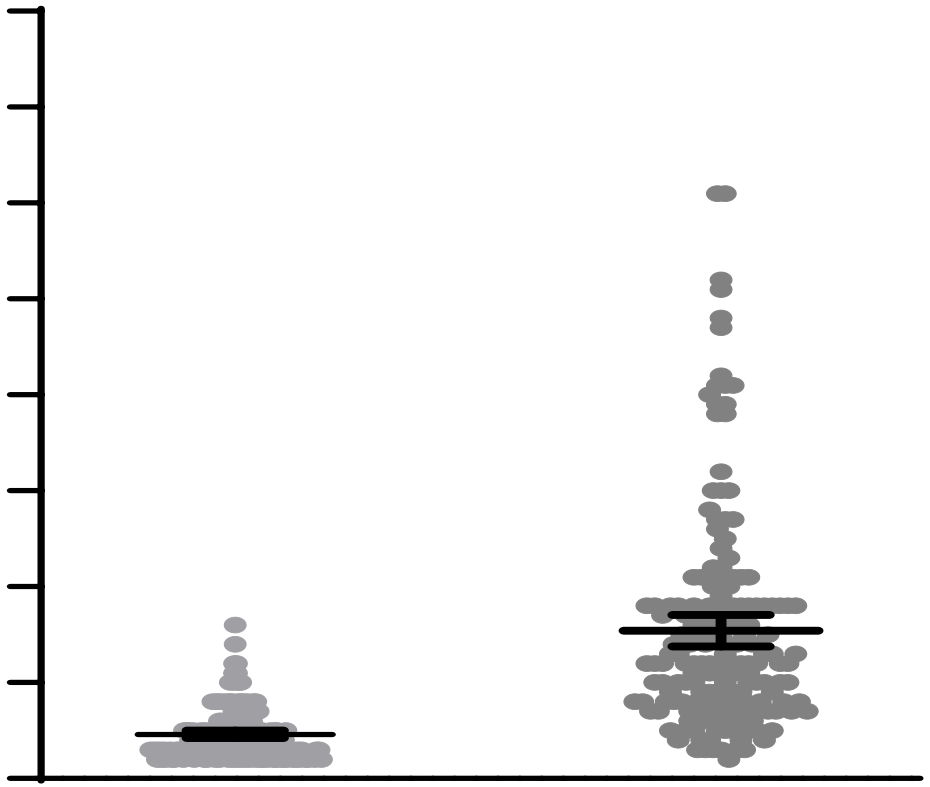
- **↑ All-cause mortality increases in patients with regimens not resulting in hypothyroidism**

  Lillevang-Johansen M, Abrahamsen B, Jørgensen HL, Brix TH, Hegedüs L. Thyroid 2019;29(3):332-40.

- **Early and effective control of the disease is associated with better-improved survival**

  Okosieme OE, Taylor PN, Evans C, et al. Lancet Diabetes Endocrinol 2019;7(4):278e287.

Mean time to euthyroidism after the start of intervention in the methimazole and the radioactive iodine groups



Azizi F et al. Endocrine Practice 2022; 101631

With proper treatment, serum TSH became detectable after 6 months. The dose of MMI decreased to 5 mg daily and was continued for 12 months (total treatment duration=18 months). Goiter was 40 gm, fT4=1.3 ng/dl, T3=145 ng/dl, TSH=0.8 mU/L and TRAb= 1.5 IU/L

What is the best next step?

1. **Discontinue MMI**
2. **Advise RAI therapy**
3. **Continue MMI for another 2 years**
4. **Continue MMI for a total of 5 years**

Factors affecting outcome of antithyroid drug treatment for Graves' hyperthyroidism

Impact on risk of relapse

Strong	Possible	Uncertain
Thyroid volume	Orbitopathy	Age

Any one of these factors are not sufficiently specific or sensitive for remission of hyperthyroidism

Postpartum period

Family history

Stress

Autoimmune disorders

Tc thyroid uptake

Struja T et al. Europ J Endocrine 2017; 176: 87
Piantanida E et al. Horm Metab Res 2015; 47: 767-72.

TRAb:
Positive predictive value of 97% for relapse of hyperthyroidism in 8 weeks
Overall, 53% relapse in TRAb positive and 39% relapse in TRAb negative

THYROID
Volume 26, Number 10, 2016

DOI: 10.1089/thy.2016.0229

2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis

Douglas S. Ross,[1*] Henry B. Burch,[2**] David S. Cooper,[3] M. Carol Greenlee,[4] Peter Laurberg,[5†] Ana Luiza Maia,[6] Scott A. Rivkees,[7] Mary Samuels,[8] Julie Ann Sosa,[9] Marius N. Stan,[10] and Martin A. Walter[11]

❖ Recommendation 21

Measurement of TRAb levels prior to stopping ATD therapy is suggested because it aids in predicting which patients can be weaned from the medication, with normal levels indicating greater chance for remission.

❖ Recommendation 22

If MMI is chosen as the primary therapy for GD, the medication should be continued for approximately 12-18 months, and then discontinued if the TSH and TRAb levels are normal at that time.

> Thyroid. 2006 Mar;16(3):295-302. doi: 10.1089/thy.2006.16.295.

Serum thyrotropin receptor antibodies concentrations in patients with Graves' disease before, at the end of methimazole treatment, and after drug withdrawal: evidence that the activity of thyrotropin receptor antibody and/or thyroid response modify during the observation period

C Carella [1], G Mazziotti, F Sorvillo, M Piscopo, M Cioffi, P Pilla, R Nersita, S Iorio, G Amato, L E Braverman, E Roti

- **55 patients with Graves' disease**
- **12-18 months ATD treatment**

Serum TRAb (IU/L)	Percent patients	Relapse (%)
<0.9	7	0
0.9-4.4	47	53
>4.4	46	85

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If a patient with GD becomes hyperthyroid after completing a course of MMI, consideration should be given to treatment with RAI or thyroidectomy. Continued low-dose MMI treatment for longer than 12–18 months may be considered in patients not in remission who prefer this approach.

Treatment of Graves' disease in Azizi clinic

I used to treat hyperthyroidism with MMI via the titration method for 18 months, recommending radioiodine treatment or occasionally even surgery, if hyperthyroidism relapsed. However, as many patients refused to be treated by radioiodine, long-term MMI treatment was prescribed, since the early 1980s, as an alternative in my practice.

Clinical studies entitled:

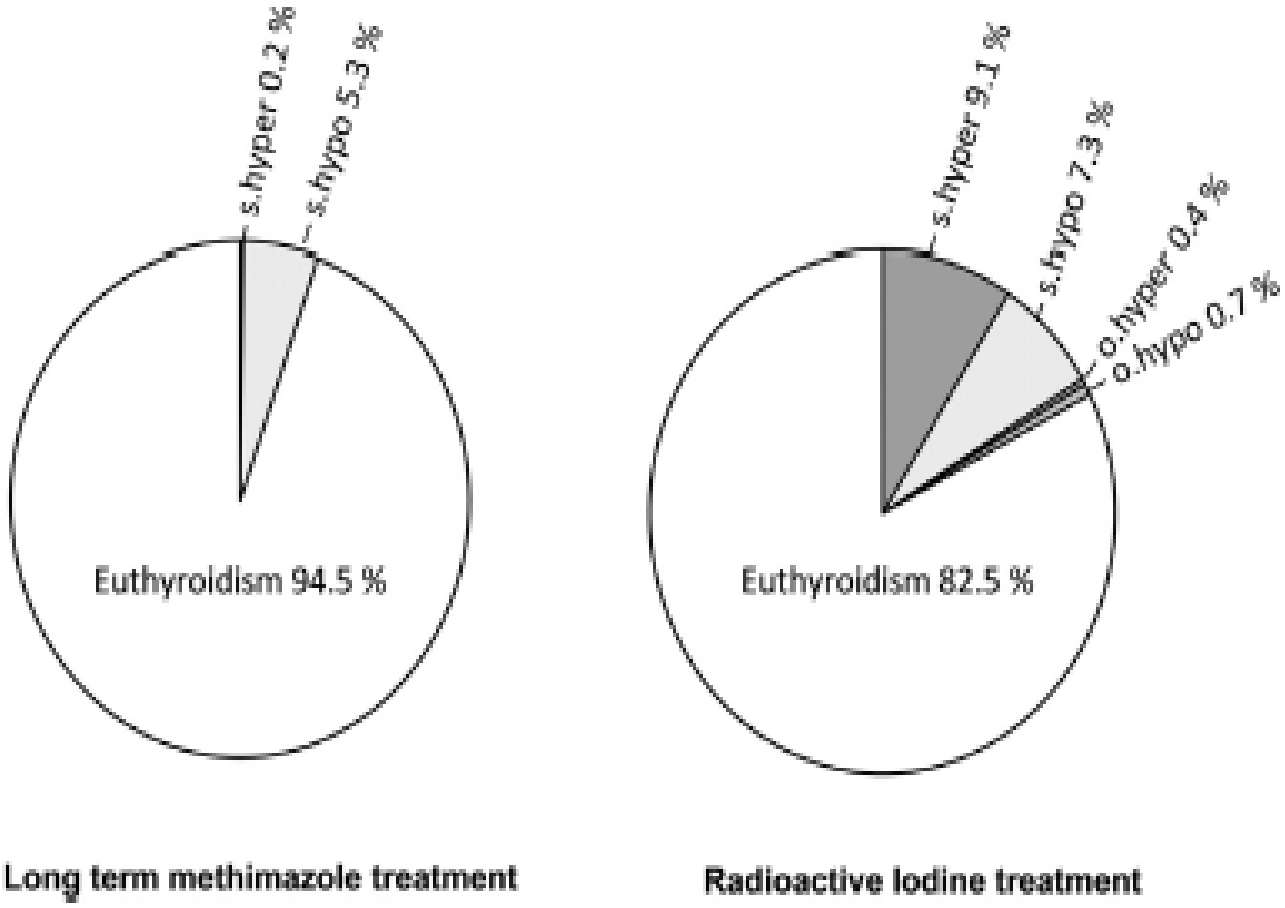
"Towards Outstanding Hyperthyroid Care Induced by Antithyroid Drugs" (TOHID)

www.IRCT.IR/TRIAL/5143

Singerland DW, Barrows BA. Long-term antithyroid treatment in hyperthyroidism. JAMA 1979; 242: 2408

Azizi F. Thyroid 2020; 30: 1451

The time spent in different thyroid function status in the long-term methimazole (LT-MMI) and radioactive iodine (RAI) groups



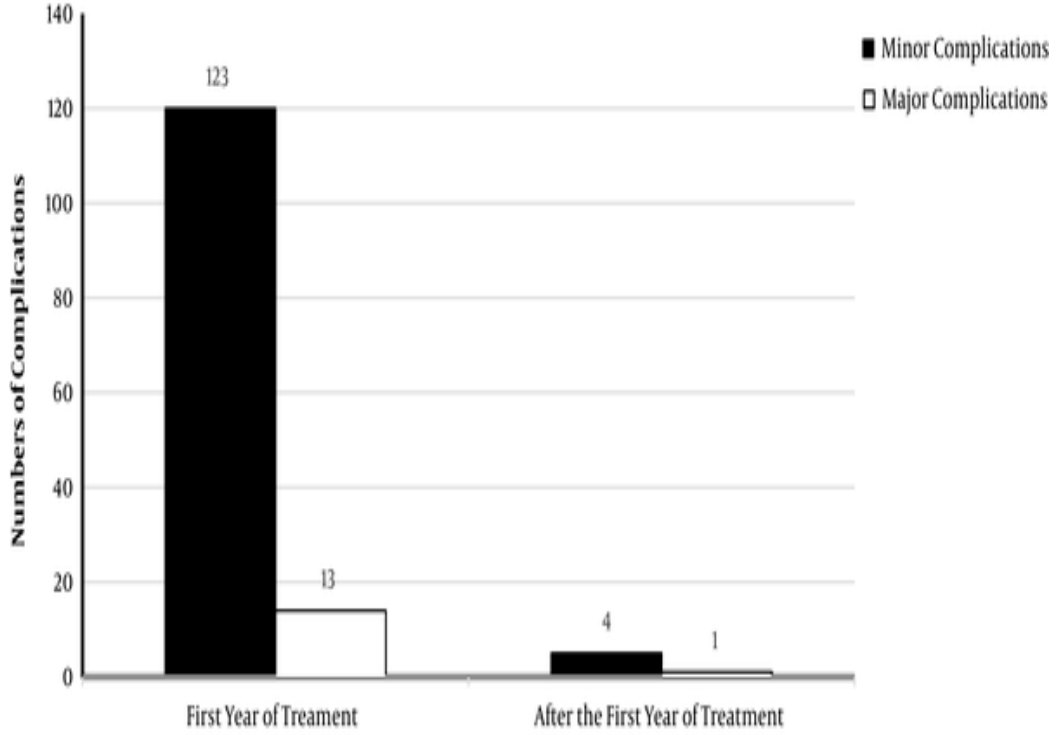
S.hyper: Subclinical hyperthyroid; S.hypo: Subclinical hypothyroid; O.hyper: Overt hyperthyroid; O.hypo: Overt hypothyroid
Azizi F et al. Endocrine Practice 2022; 101631

Comparison of effectiveness of long-term antithyroid drug (LT-ATD) versus radioactive iodine treatment for Graves' hyperthyroidism

Variables	LT-ATD
Shorter time to biochemical improvement	Better
Sustained euthyroidism	Better
Echocardiographic indices of velocity	Better
Quality of life	Better
Recurrence of hyperthyroidism	Less
Abnormal TSH at various times	Less
Worsening of thyroid eye disease	Less
Increased body mass index	Less
Lipid profile derangement	Less
Overall cost	≤ Less

Azizi F et al. Best Practive & Res Clin Endocrinol Metab 2022
EL Kawkgi OM et al. Clinical Endocrinology 2021; 95: 3-12
Torring O et al. Thyroid 2019; 29: 322
Azizi F. Thyroid 2020; 30: 1451
Villagelin D et al. Thyroid 2015; 25: 1282

Relationship between time and antithyroid drugs complications



- **All clinical trials with >18 months ATD therapy**
- **From 1950-2018, from 615 articles 12 were included**
- **1666 patients treated for a mean of 5.8 years (10,000/yr)**
- **123 (97%) minor events during the first year**
- **14 (11%) major events occurred**
- **Only one ANCA vasculitis with PTU after first year**

Malboosbaf R, Azizi F. Int J Endocrinol Metab 2020; 18: 23

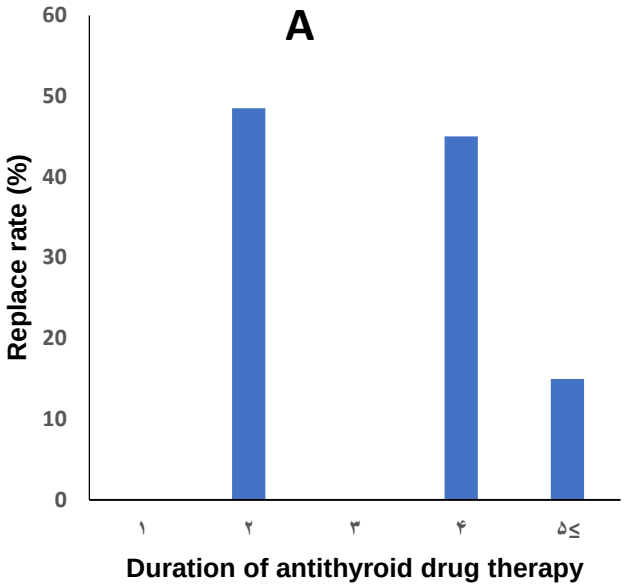
Azizi F, Malbousbaf R. J Endocrinol Invest 2019; 42: 1273

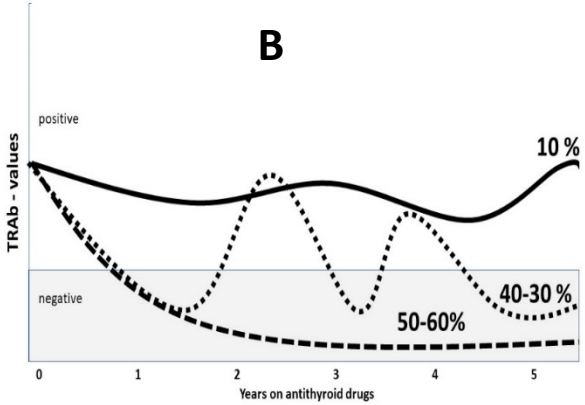
Question?

If long-term ATD therapy is effective and safe, why recommended optimal duration of ATD is 12-18 month?

1. **Studies had poor quality**
2. **Paucity of RCT's in long-term MMI therapy**
3. **Duration was arbitrary chosen**
4. **All of the above**

Trend in serum TRAb and relapse rate during years of ATD treatment

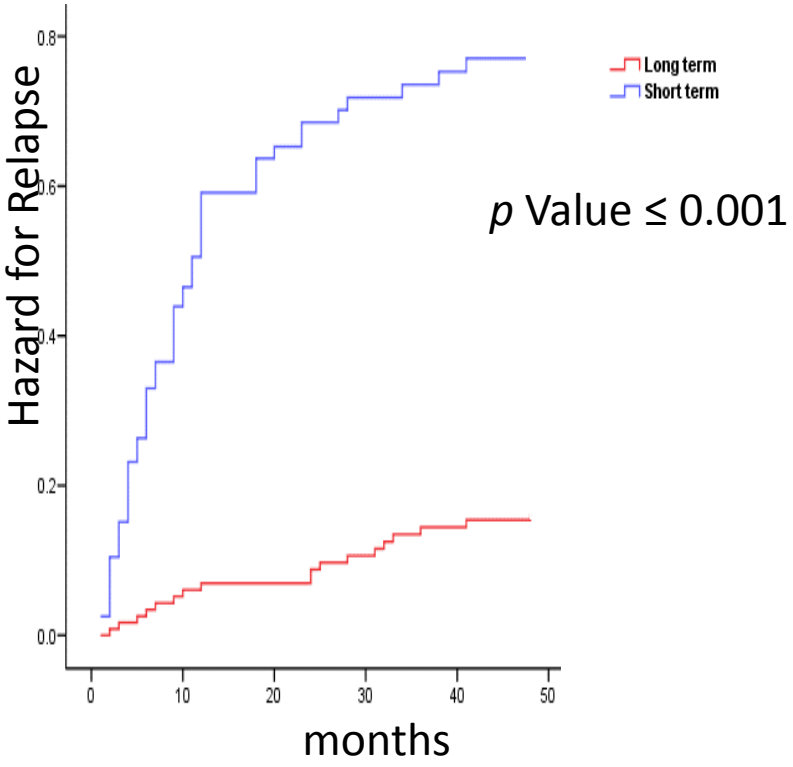




Panel A demonstrates the relapse rate with different duration of ATD therapy; panel B and shows trend of TRAb titers during years of ATD treatment. The remissions seen in approximately half of the patients after 1-2 years of therapy are associated with decrease TRAb in smooth type. Persistent relapse rate by 4 years of ATD therapy is associated with high levels of TRAb in fluctuating type. Fall in relapse rate with ATD therapy of more than 5 years is associated with normalization of TRAb in majority of patients with fluctuating type

Azizi F et al. J Endocrinol Invest 2022; 45: 1139.
Okamura K et al. Int J Endocinol Metab 2020; 18 (suppl): e101139.

Hyperthyroidism relapse rate following MMI discontinuation in LT (>6-120) and ST (15-24 months) groups

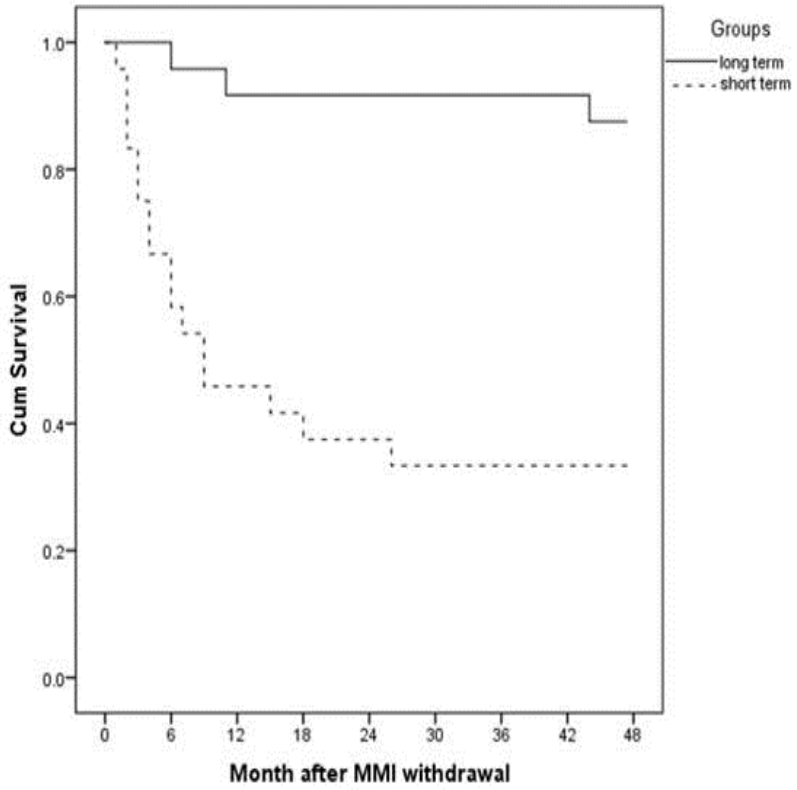


p Value ≤ 0.001

% relapse in ST →	29	51
% relapse in LT →	3.3	16

Azizi F et al. Thyroid 2019; 29:1192-1200

Relapse of hyperthyroidism in Juvenile Graves' patients after long-term methimazole withdrawal



% relapse in ST →	54	67
% relapse in LT →	8	12

Azizi F et al. Pediatrics 2019; 143: 21

❖**Long-term antithyroid drug therapy for both Graves' disease and toxic adenoma / toxic multinodular goiter is preferred by most patients.**

❖**This preference may reflect publications during the last decade that suggest serious side effects from ATD occur predominately during the first 6-9 months of therapy.**

❖**Or it may reflect patient preference to avoid radioiodine or permanent hypothyroidism.**

Ross DS: Meet the Professor Session, 90th ATA Congress, 2021 and symposium lecture, 14th ICED, 2023

Dr. Ross is the first author of 2016 ATA Guidelines

Appropriate management during long-term methimazole therapy

- Change of MMI dosage according to TSH every 6 months
- Rare cases of persistent disease

  ? ablative therapy
- Rare cases of spontaneous hypothyroidism
- Exceptional case of major adverse event
- Desire of pregnancy

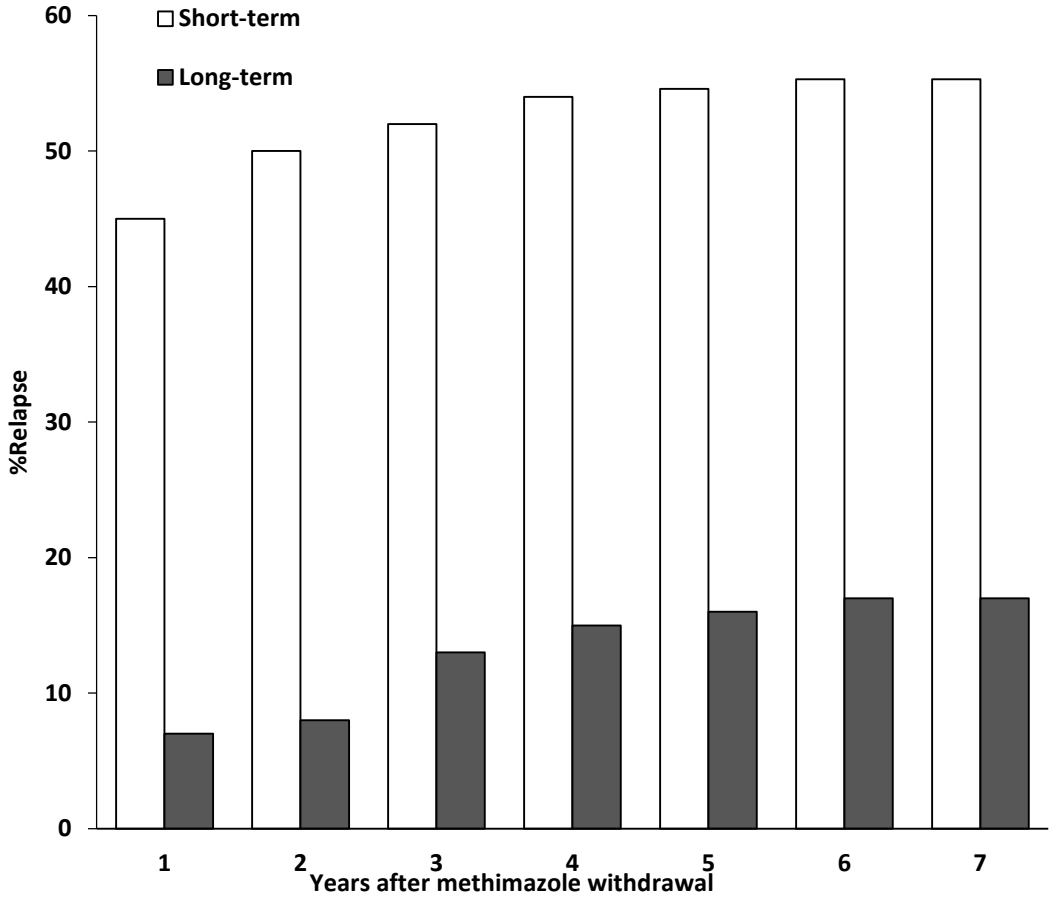
  ?ablation, ?change to PTU, ?discontinue ATD

Patient preferred continuous long-term MMI treatment. Serum fT4, T3 and TSH were WNL for treatment duration. 60 months after LT-MMI she is on daily 2.5 mg MMI; goiter is 35 gm; fT4=1.2 ng/dl, T3=118 ng/dl, TSH=1.2 mIU/L and TRAb= 1.1 IU/L.

Which of the following is the best next step?

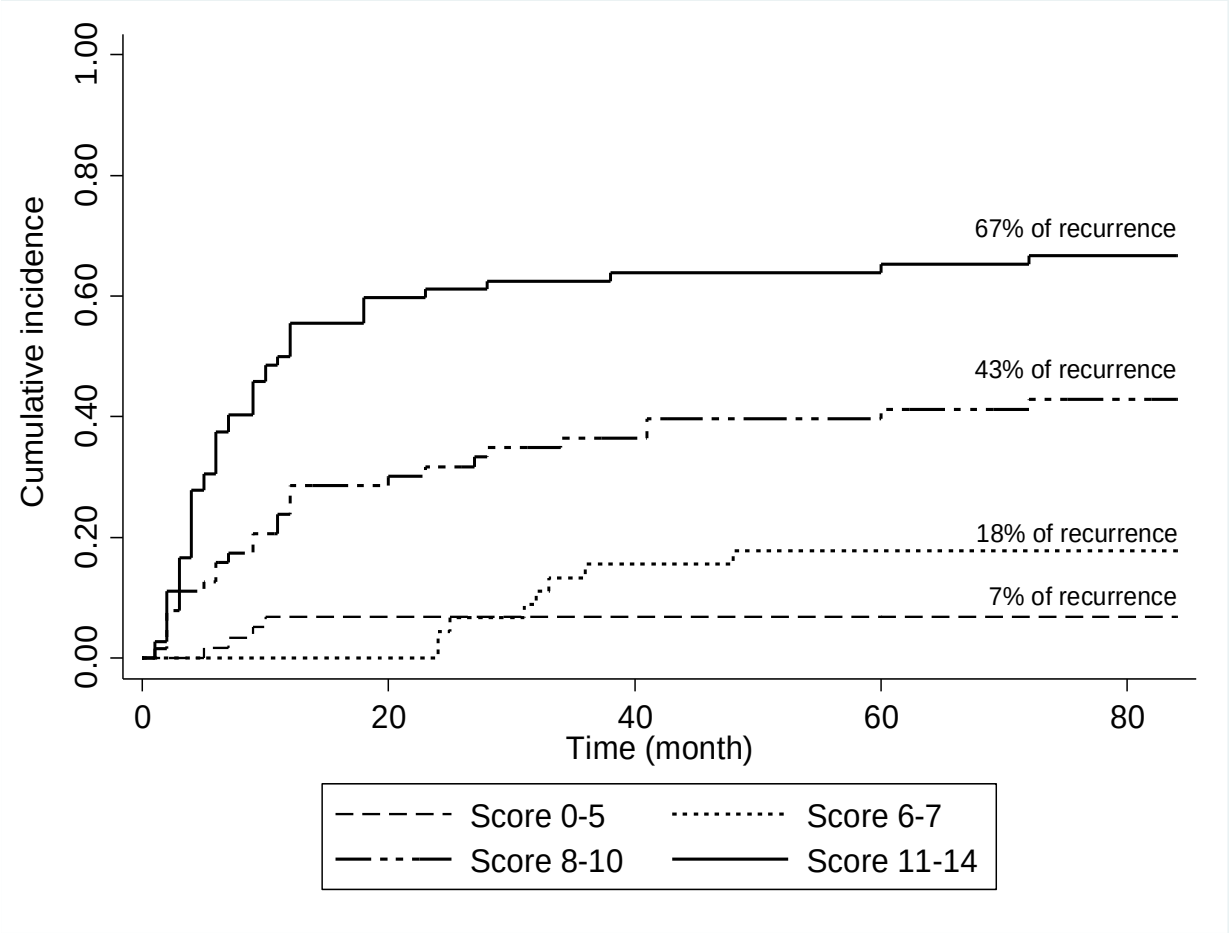
1. **Discontinue MMI**
2. **Continue MMI until TRAb is undectable**
3. **Apply scoring scale for making decision**
4. **Continue MMI therapy for the whole life**

Relapse rate of Graves' hyperthyroidism after discontinuation of methimazole



Azizi F et al. Best Practive & Res Clin Endocrinol Metab 2022

The risk stratification based on the quartile of the individuals' risk scores. The cumulative incidence of recurrence for each risk category is shown on top of the lines. All predefined predictors together including treatment group, sex, age, free thyroxine (fT4), triiodothyronine (T3), thyroid-stimulating hormone (TSH), TSH receptor antibodies (TRAb), and goiter grade, and B. all predictors except T3 and TSH

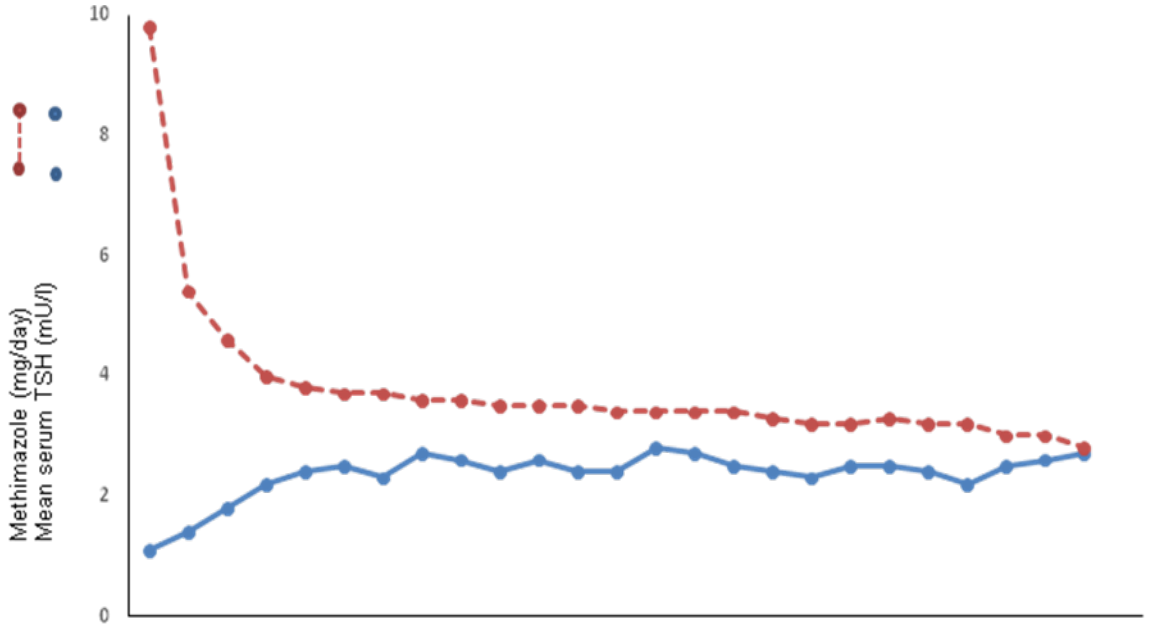


Azizi F et al. Endocrine, Submitted

Control of Graves' hyperthyroidism with very long-term methimazole treatment: a clinical trial

Fereidoun Azizi [1], Hengameh Abdi [2], Atieh Amouzegar [3]

All 27 patients continued therapy for at least 15 years, 16 patients until 20 years and 11 patients until 24 years. Daily doses of methimazole to maintain euthyroidism decreased to mean of 3.4 ± 1.0 and 2.8 ± 1.7 mg daily, by 15 and 24 years of therapy; serum TRAb was normal in all patients during methimazole treatment

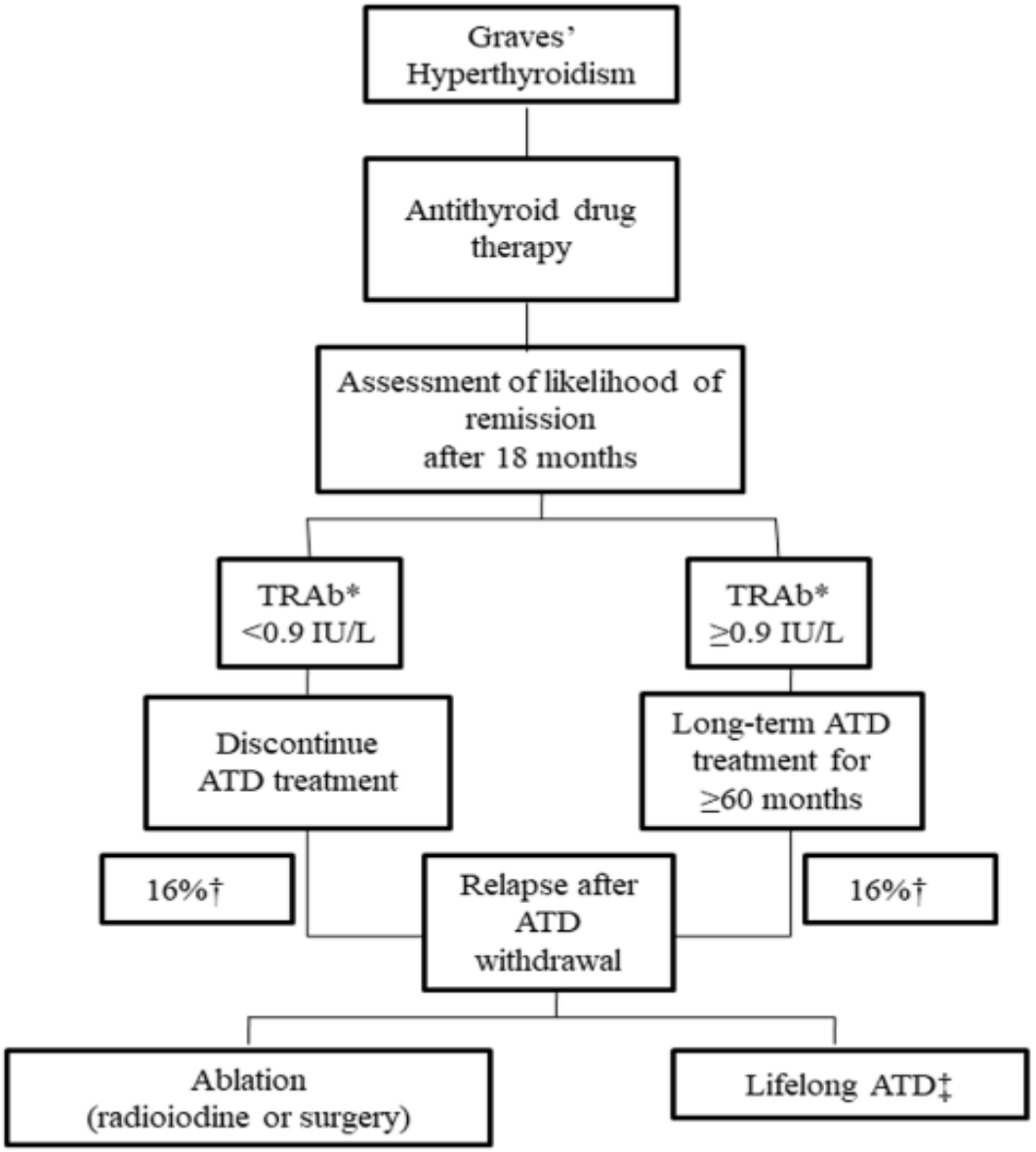


TSH< 0.4 mU/L No		12	11	5	2	4	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Mean serum TRAb (IU/ml)				1.2						1.1								1.0							0.9
Methimazole (mg/day)	Mean	9.8	5.4	4.6	4	3.8	3.7	3.7	3.6	3.6	3.5	3.5	3.5	3.4	3.4	3.4	3.4	3.3	3.2	3.2	3.3	3.2	3.2	3.0	3.0	2.8
	SD	1.0	1.6	1.5	1.2	1.1	1.0	1.1	1.0	0.9	1.1	1.2	1.1	1.0	1.1	1.1	1.0	1.1	1.1	1.1	1.3	1.1	1.1	1.7	1.6	1.7

Azizi F et al. BMC Endocr Disords 2021; 21: 16

Management and monitoring steps during long-term ATD treatment of Graves' disease

*Approximately 10% may have TRAb <0.9 IU/L after 12 months of ATD treatment.
†Equal chance of only 16% remission in each arm after discontinuation of ATD.
‡Yearly check of TRAb and discontinuation of ATD if TRAb would be <0.9 IU/L.
ATD, antithyroid drug; TRAb, TSH receptor antibodies



Azizi F, et al. J Endocrinol Invest 2022; 45: 1139-1150

Practice points

- **Antithyroid drugs are the treatment of choice for Graves' disease.**
- **To avoid relapse of hyperthyroidism, long-term (more than five years) treatment with antithyroid drugs are advised.**
- **The majority of patients with Graves' disease have less likelihood of relapse and benefit from long-term antithyroid drug treatment.**
- **Long-term methimazole therapy is associated with cure of hyperthyroidism in more than 80% of patients.**
- **Long-term therapy with methimazole in adults does not cause additional major adverse events.**

Azizi F et al. Best Pract Res Clin Endocrinol Metab 2022; 101631

Save thyroid, do not ablate

low dose MMI treatment may be prescribed effectively, even throughout the patients' life for those with Graves' hyperthyroidism who do not desire ablation treatment. Low cost, safe and effective drugs are prescribed as lifelong therapy for some specific diseases, such as epilepsy, inflammatory bowel disease and hypothyroidism and MMI may be added to the list of lifelong drugs for control of Graves' hyperthyroidism.

Azizi F et al. BMC Endocrine Disorders 2021; 21: 16

Greatly Indebted to Colleagues Participated in "TOHID" Studies:

- Abdi Hengameh
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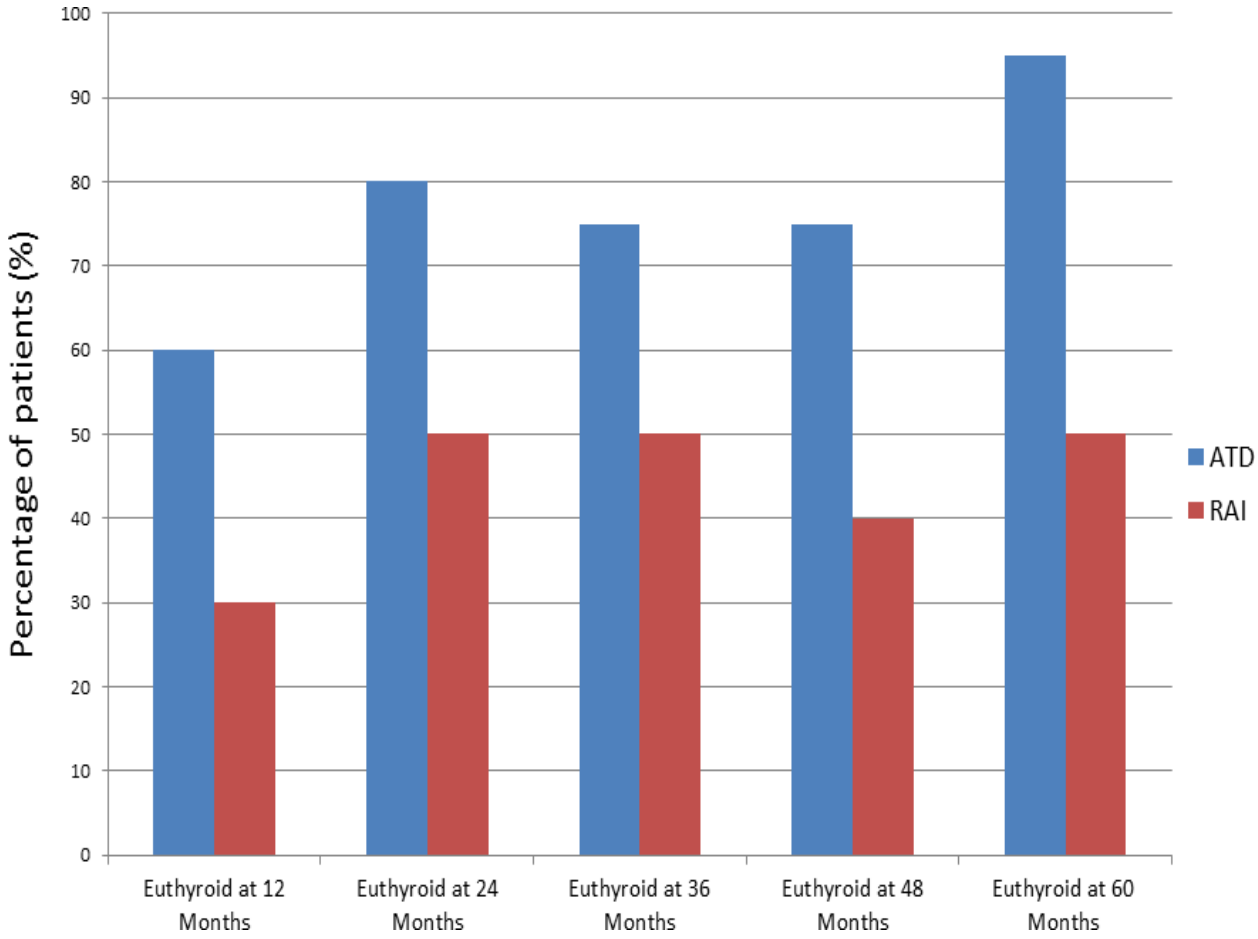
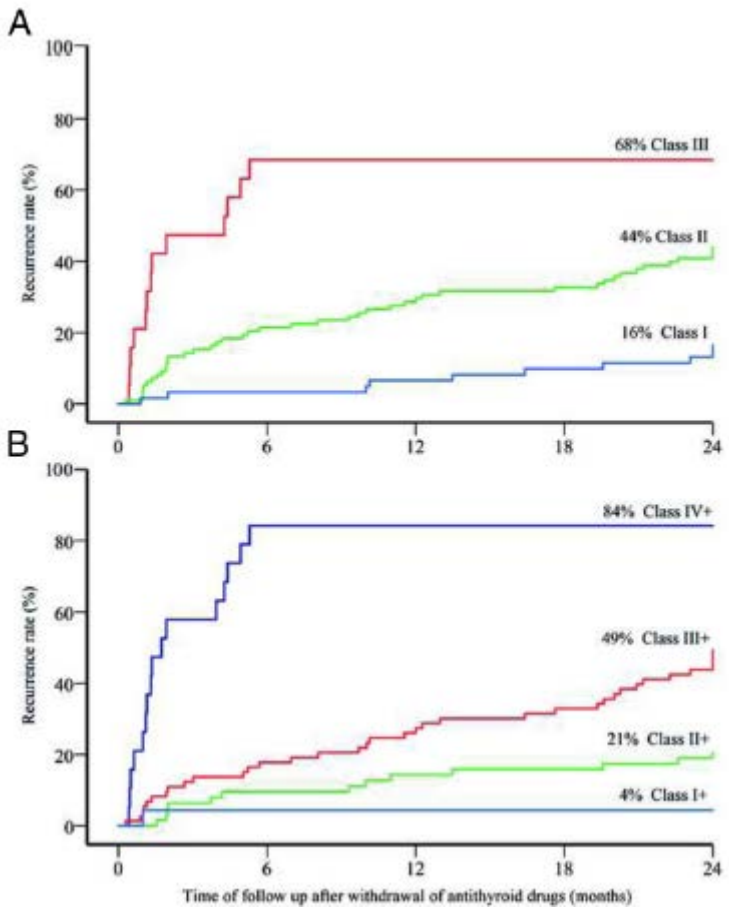
- Ataie Ladan
- Bahrainian Abdolmajid
- Cheraghi Leila
- Habibi Moeini Ali Siamak
- Hedayati Mehdi
- Khalili Davood
- Madresseh Elham
- Malbousbaf Ramin
- Masoumi Safdar
- Mehrabi Yadollah
- Mehran Ladan
- Pasandi Fatemeh
- Perros Petros
- Saadat Navid
- Sheikholeslami Farhad
- Takyar Alireza
- Tohidi Maryam
- Yousefi Vahid

Percentage of patients euthyroid at various time points in use of long-term ATD compared to RAI



Villagelin D et al. Thyroid 2015; 25: 1282

Kaplan-Meier recurrence curves according to risk classes measured with the GREAT score (A) and GREAT score (B)



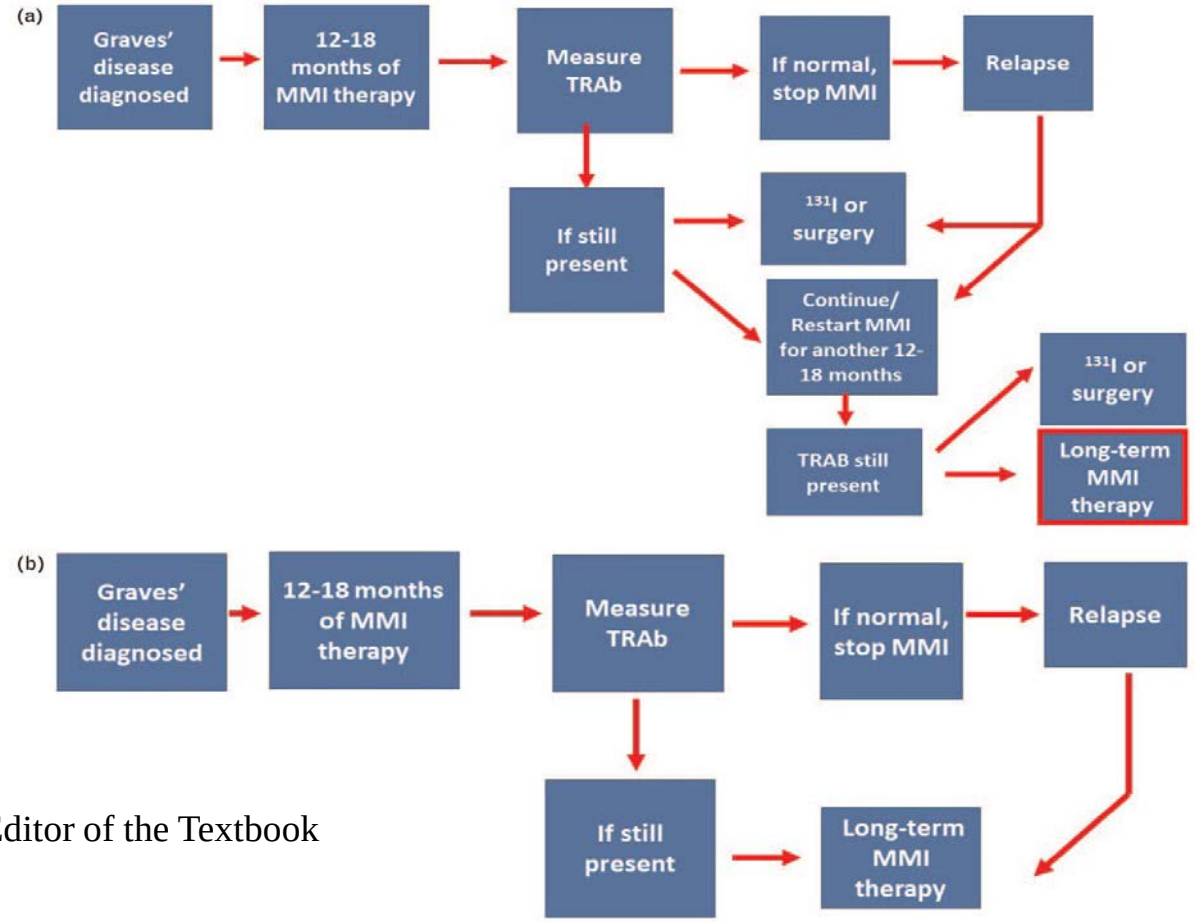
Vos XG et al. J Clin Endocrinol Metab 2016; 101:1381

Review > Curr Opin Endocrinol Diabetes Obes. 2021 Oct 1;28(5):510-516.
doi: 10.1097/MED.0000000000000656.

Long-term antithyroid drug therapy

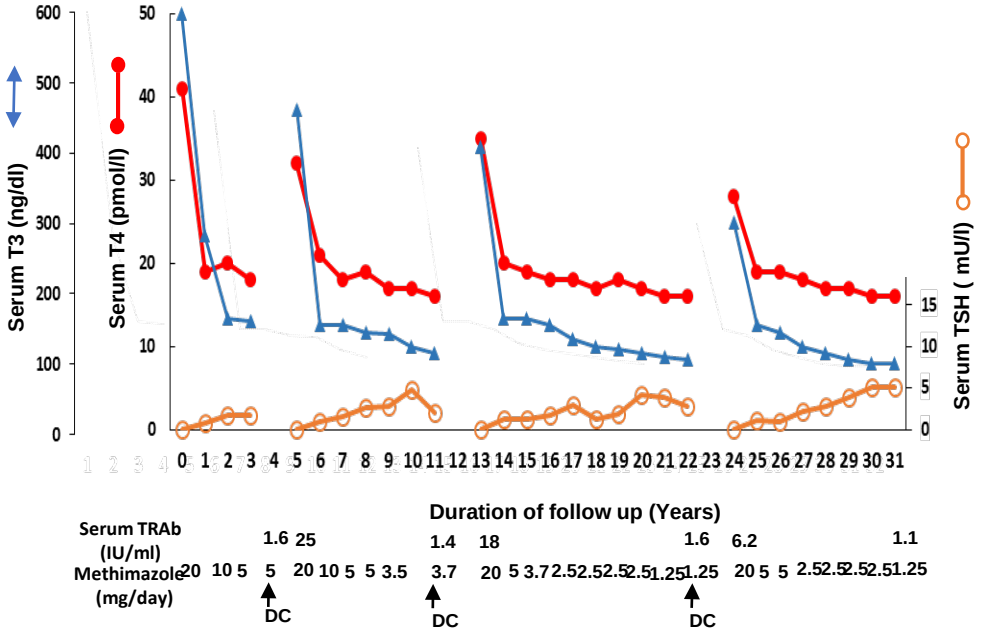
David S Cooper [1]

Algorithms for the management of Graves' disease. (a) Management strategy as recommended by current clinical practice guidelines. (b) Implementation of long-term antithyroid drug therapy



Dr. Cooper is the Editor of the Textbook of the Thyroid

Response to methimazole treatment following 3 recurrences

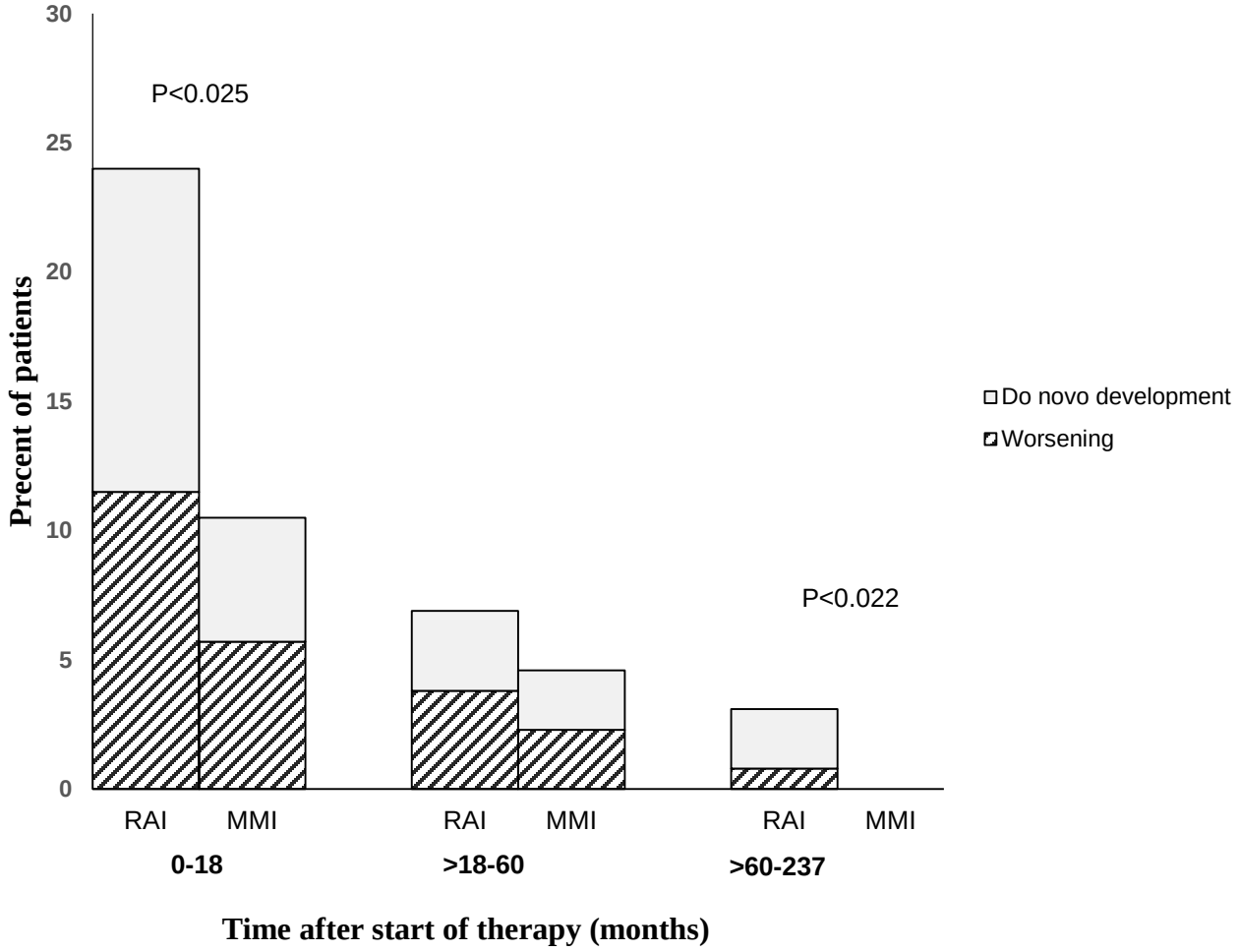


Patient stopped treatment on three occasions. Hyperthyroidism recurred, but was appropriately managed by methimazole therapy, normalizing serum fT4, T3, TSH and TRAb each time; metimazole dose gradually decreased to a minimum of 1.25 mg daily.

Conclusions

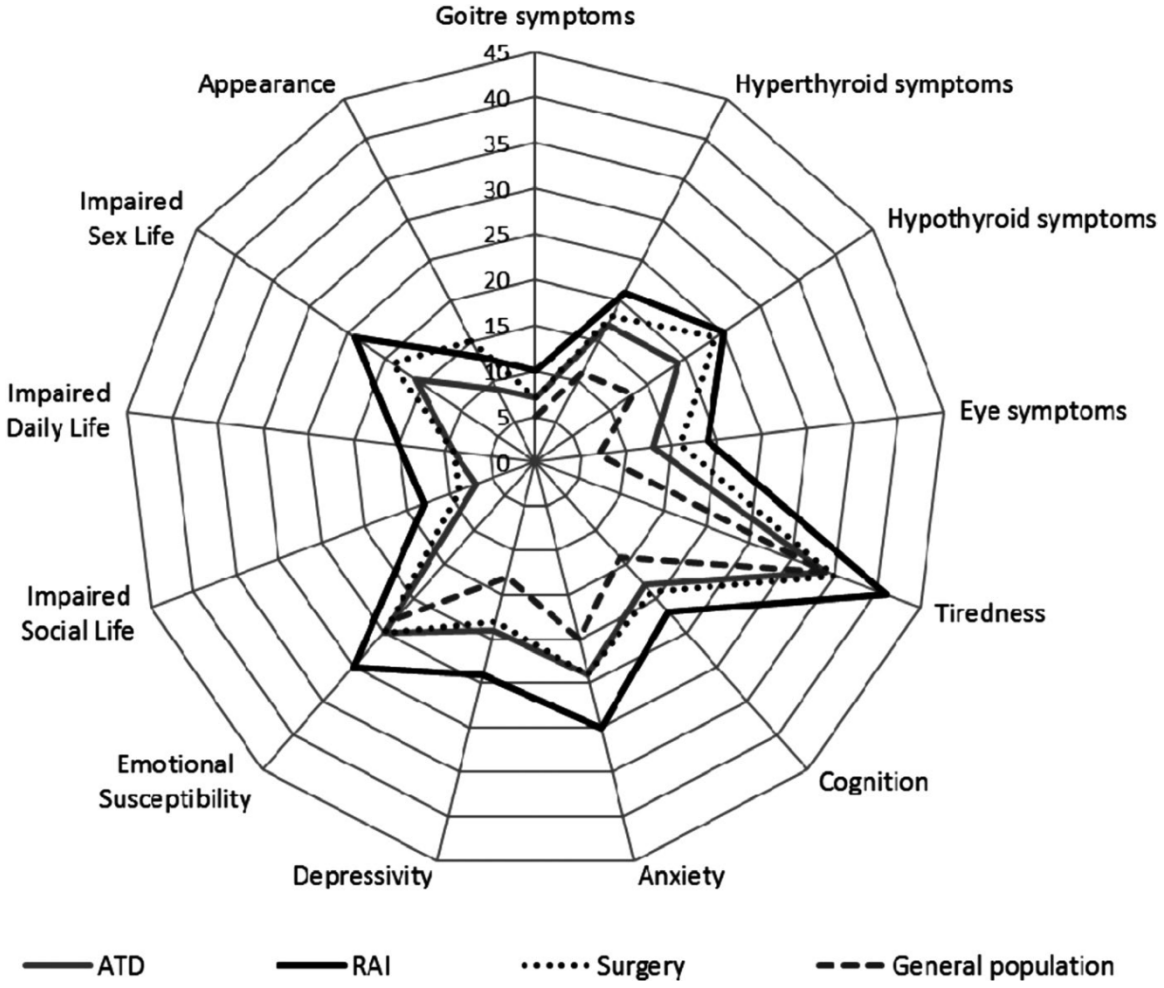
- **Management of Graves' disease is complex and needs to consider various variables and to apply patient centered care.**
- **Many factors influence physicians and their patients in deciding the mode of control of Graves' disease.**
- **Taking all recent evidence based studies, may help choosing the best treatment for each patient.**
- **Long-term ATD therapy should be considered as an appropriate choice for treatment of all patients with hyperthyroidism.**

Frequency of progression and do novo development of Graves' orbitopathy in 1163 patients treated with radioiodine and long-term methimazole



Azizi F et al. Endocrine Practice 2022; 101631

Mean Thyroid-Related Patient-Reported Outcome (ThyPRO) questionnaire scale scores, adjusted for sex and age among patients with Graves' disease, treated with anti-thyroid drugs (ATD), radioactive iodine (RAI) or surgery, as well as scores from a general population sample. Scale scores range from 0 to 100, with higher scores indicating worse health status



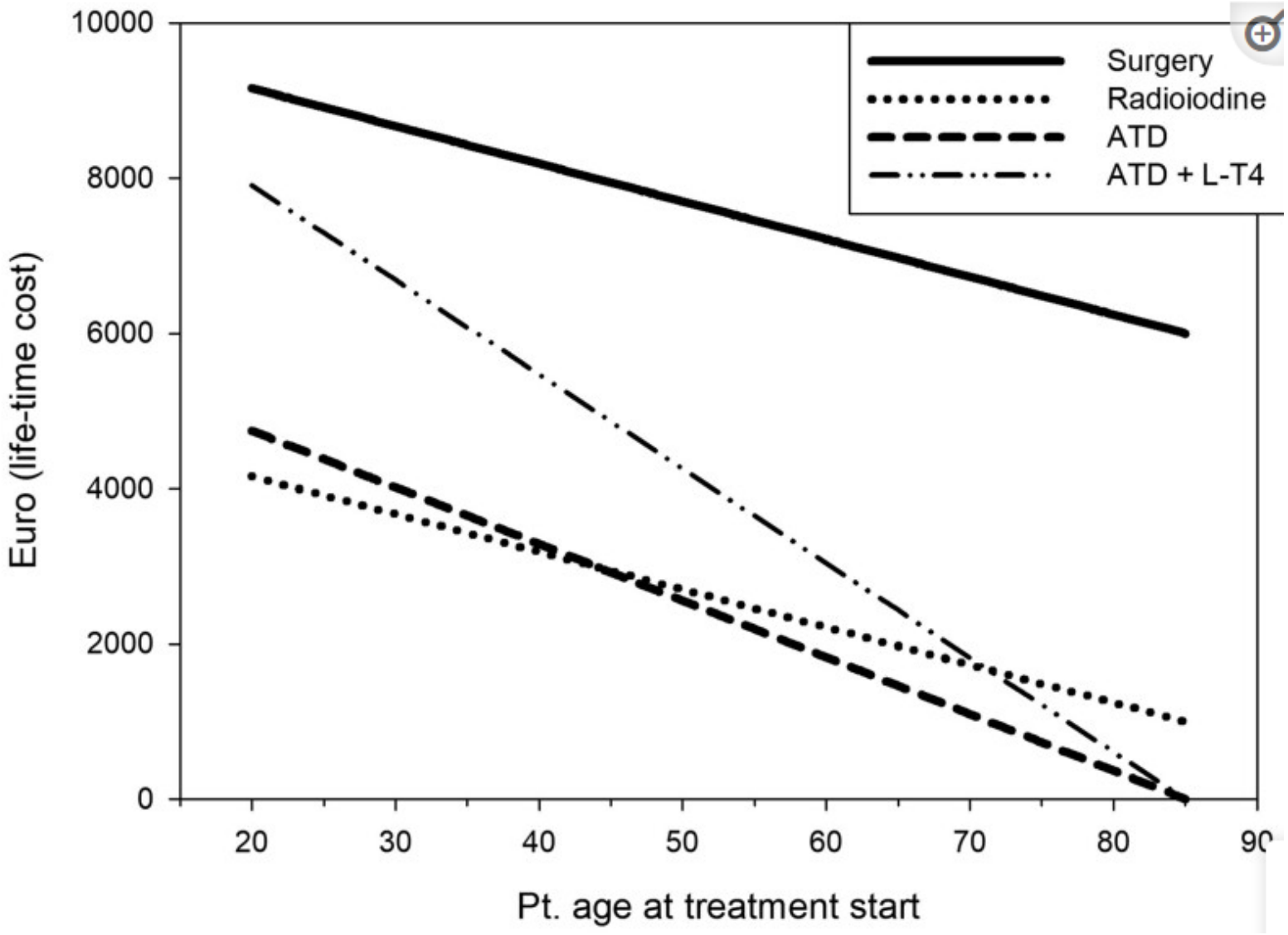
Non-RCT

1186 patients

RAI patients had lower QOL on standardized questionnaires

Torringo et al. Thyroid 2019; 29: 322

Treatment cost of lifelong treatment for three different treatment modalities of Graves' hyperthyroidism



Karmisholt J et al. Eur Thyroid J 2022; 11(3): e220031

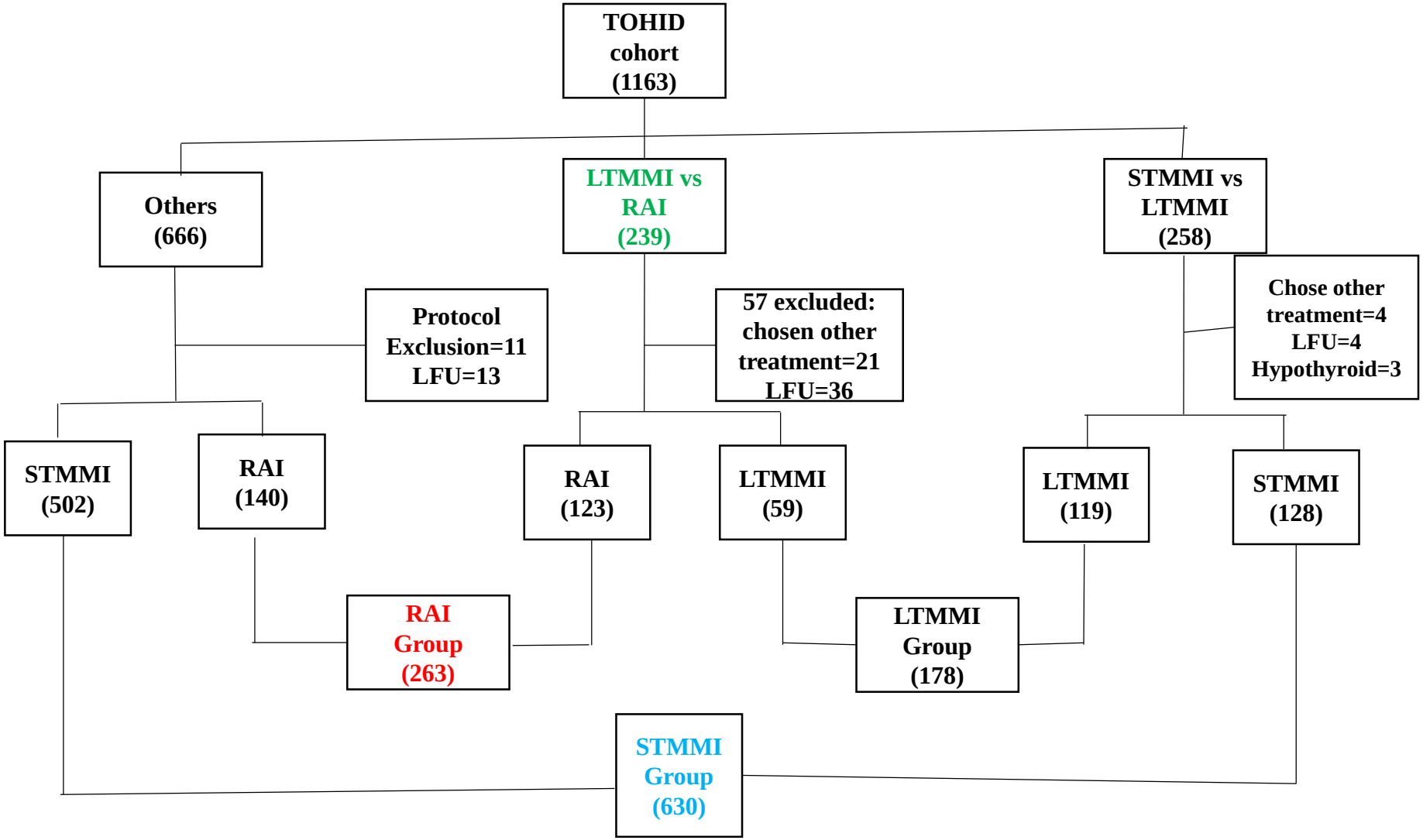
Graves' Recurrent Events After Therapy (GREAT) and GREAT+ Scores

Risk factor	GREAT Score	Our case	GREAT+ Score
Age (y)			
≥ 40	0		
< 40	+1	1+	
fT4 (pmol/L)			
<40	0		
≥ 40	+1	1+	
TBII (U/L)			
<6	0		
6-19.9	+1	1+	
≥ 20	+2		
Goiter size			
0-I	0		
II-III	+2	2+	
		Total 5 points	
HLA polymorphism			
0			0
1-2			+2
3			+3
PTPN22			
Wild type			0
C/T			+1
Risk stratification	Class 1(0-1 points) Class 11(2-3 points) Class III(4-6 points)		0-2 Points 3-4 Points 5-6 Points Class IV (7-10 points)

Vos XG et al. J Clin Endo Metab 2016; 101: 1381-9

Struja T et al. Eur J Endocrinol 2017; 176: 413-9

Study enrolement and follow up of 1163 patients with Graves' disease and outcome of various treatment modalities



TOHID: Towards Outstanding Hyperthyroid Care Induced by Antithyroid Drugs, RAI: Randoactive iodine; STMMI: Short term methimazole; LTMMI: Long-term methimazole

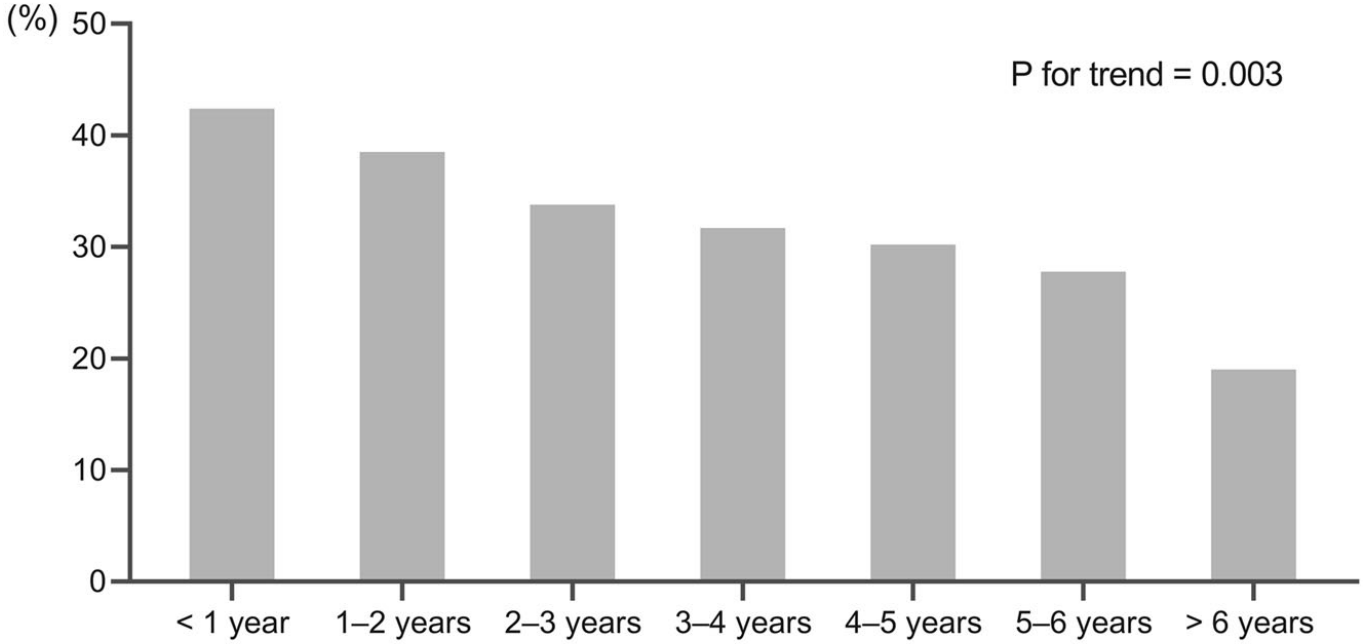
Azizi F. Thyroid 2020; 30: 1451-1457

Endocrine. 2021 Apr 15. doi: 10.1007/s12020-021-02725-x. Online ahead of print.

The longer the antithyroid drug is used, the lower the relapse rate in Graves' disease: a retrospective multicenter cohort study in Korea

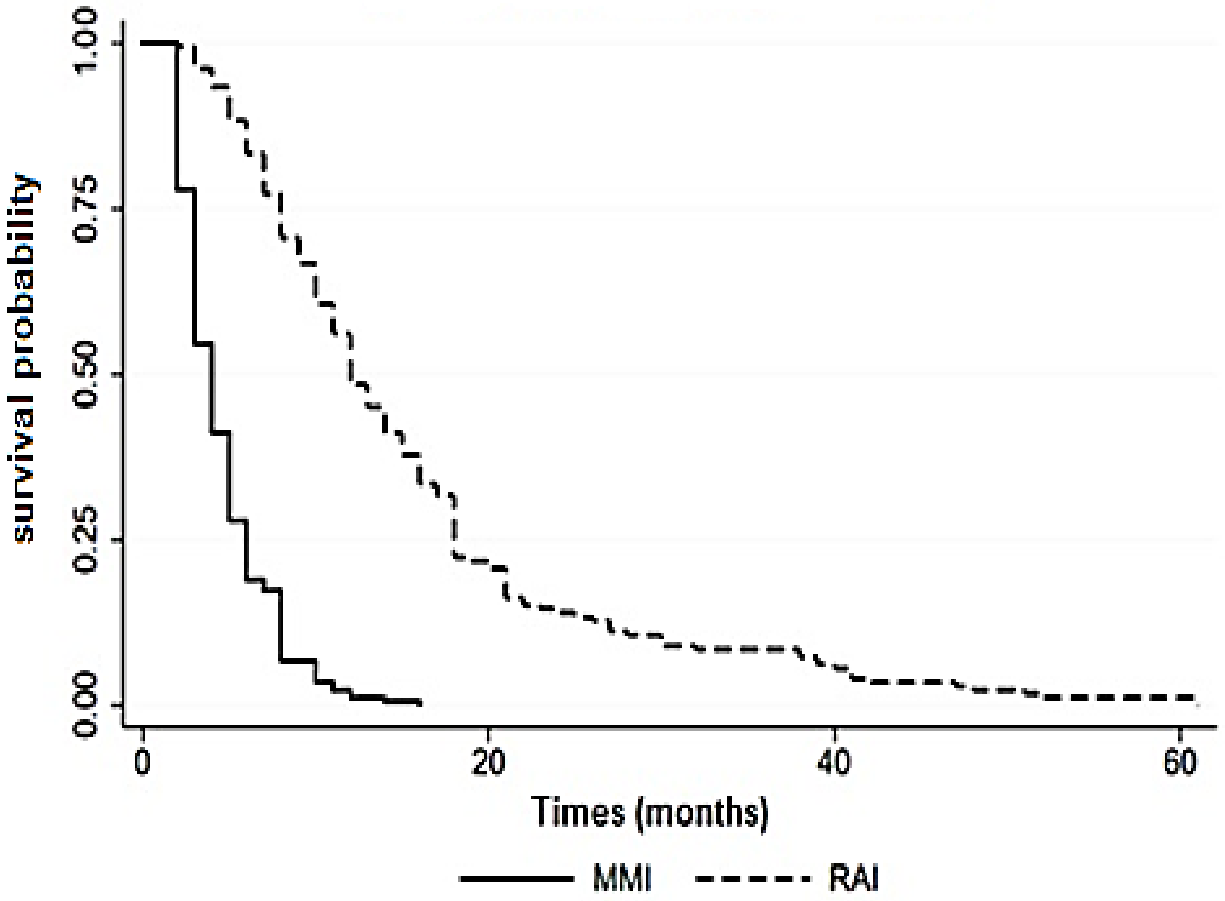
So Young Park [# 1 2], Bo Hyun Kim [# 3], Mijin Kim [3], A Ram Hong [4], Jun Park [1], Hyunju Park [1], Min Sun Choi [1], Tae Hyuk Kim [1], Sun Wook Kim [1], Ho-Cheol Kang [5], Jae Hoon Chung [6]

Relapse rate according to ATD treatment duration (per year)



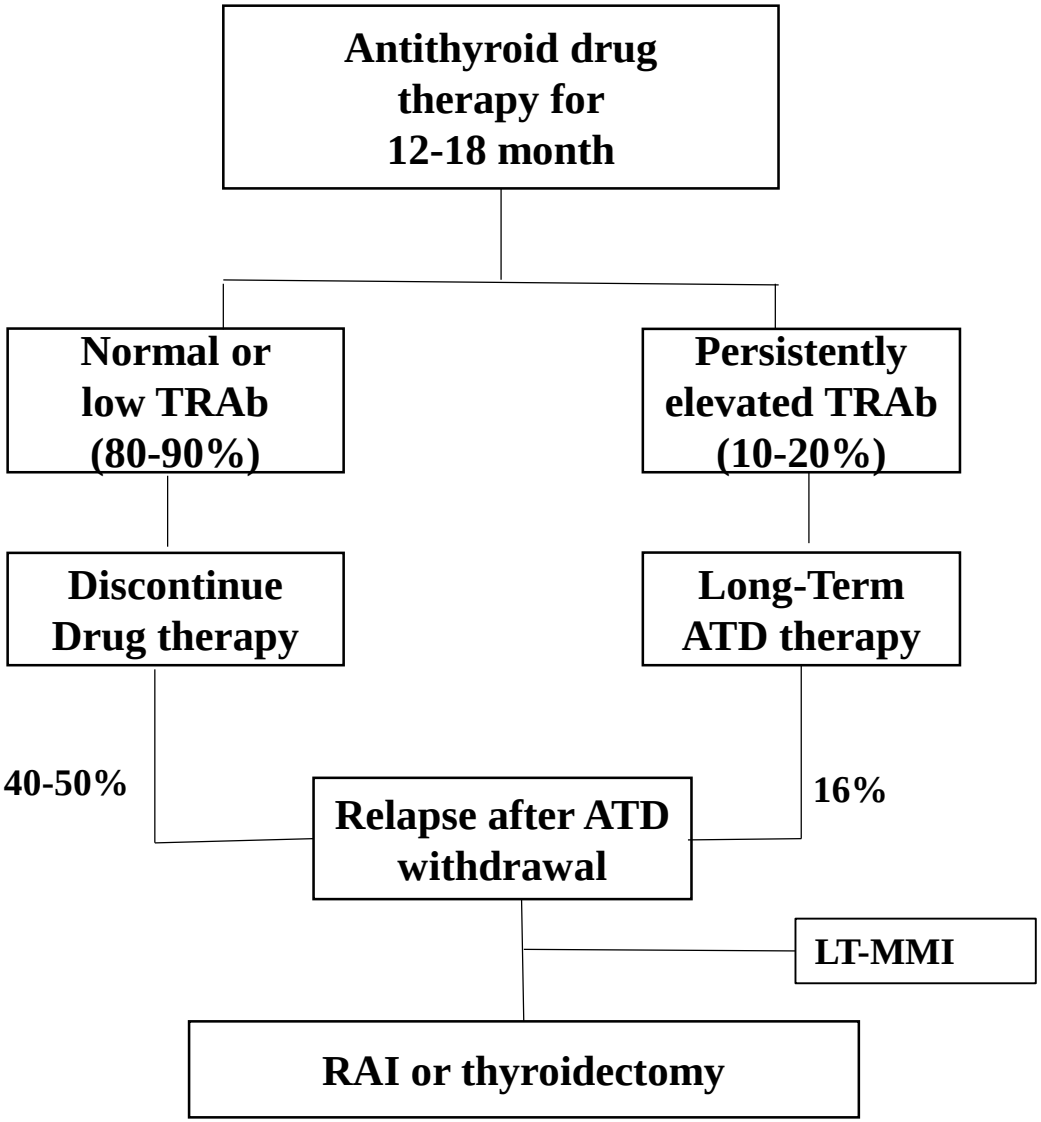
	< 1 year	1–2 years	2–3 years	3–4 years	4–5 years	5–6 years	> 6 years
Total, n	243	371	133	79	43	18	21
Relapse, n	103	143	45	25	13	5	4
Relapse, %	42.4	38.5	33.8	31.7	30.2	27.8	19.0

Time to euthyroidism by Kaplan-Meier analysis in the LT-MMI and the radioactive iodine groups



Azizi F et al. Endocrine Practice 2022; 101631

ATA guidelines for management of Graves' hyperthyroidism



Azizi F. Int J Endocrinol Metab 2020; 67: 53

Very few minor and no major adverse effects of MMI observed during long term therapy

Adverse effects (n= 1660)	Mean Duration of ATD treatment 5.8 years	
	Up to one year	After 12 months
Minbor	**123**	**4**
Cutaneous	**74**	
Elevated liver enzymes	**9**	
Arthralgia	**5**	
Myalgia	**2**	
Thrombocytopenia	**2**	
Fever	**2**	
Nausea	**2**	
Oral ophthous	**1**	
Major	**4**	**1***

* ANCA-associated glumeronephratis due to propyltiouracil treatment

Abraham P, et al. Eur J Endocrinol 2005; 153: 489
Abraham P, et al. Cochrane Dayabase 2010; 1: C01003420
Karmisholt J et al. Europ Thyroid J 2022; e220031
Lertwattana RK et al. Int J Endocrinol 2022; 1705-740

Optimal duration of ATD revisited

Abraham et al. published two articles in 2005 and 2010 and concluded that the optimal duration of ATD therapy was 12-18 months and that treatment over 18 months had no benefit for rise in remission rate.

These two articles have been cited frequently and have been used as basis for many recommendations. In both articles, authors reported only two articles for longer duration of ATD treatment. One compared 12 months versus 24 months and another evaluated 18 months versus 42 months of ATD therapy: Maugendre D et al. Clin Endocrinol 1999; 50: 127

On the basis of these two studied, they found no significant difference between the longer and shorter duration of treatment.

Abraham P, et al. Eur J Endocrinol 2005; 153: 489
Abraham P, et al. Cochrane Dayabase 2010; 1: C01003420

Review > Clin Endocrinol (Oxf). 2021 Jul;95(1):3-12. doi: 10.1111/cen.14374. Epub 2020 Dec 6.

Comparison of long-term antithyroid drugs versus radioactive iodine or surgery for Graves' disease: A review of the literature

Omar M El Kawkgi [1], Douglas S Ross [2], Marius N Stan [1]

Patients who fail to achieve remission after 12-18 months of ATD more frequently opt for long-term ATD treatment over ablative therapy, which results in euthyroidism with minimal complications, low financial cost and an advantageous Qol profile and other biological outcomes.

Causes of Thyrotoxicosis

- **Thyrotoxicosis associated with a normal or elevated RAI uptake over the neck**

  Graves' Disease
  TA or TMNG

  Trophoblastic disease

  TSH-producing pituitary adenomas

  Resistance to thyroid hormone (T3 receptor β mutation)

- **Thyrotoxicosis associated with a near-absent RAI uptake over the neck**

  Painless (silent) thyroiditis

  Aminodarone-induced thyroiditis

  Subacute (granulomatous, de Quervain's) thyroiditis

  Palpation thyroiditis

  Iatrogenic thyrotoxicosis

  Factitious ingestion of thyroid hormone

  Struma ovarii

  Acute thyroiditis

  Extensive metastases from follicular thyroid cancer

2016 ATA Guidelines. Thyroid 26: 1343-1421

Diffuse Toxic Goiter

Avicenna 991-1049
Described already the
Association of goiter and Exophthalmos

Nabipour I, et al. Thyroid 2009; 19: 7

V. Basedow 1799-1854

Robert Graves 1797-1853

C.H. Parry 1755-1822

Guiseppe Flajani 1741-1808

THYROID
Volume 29, Number 9, 2019

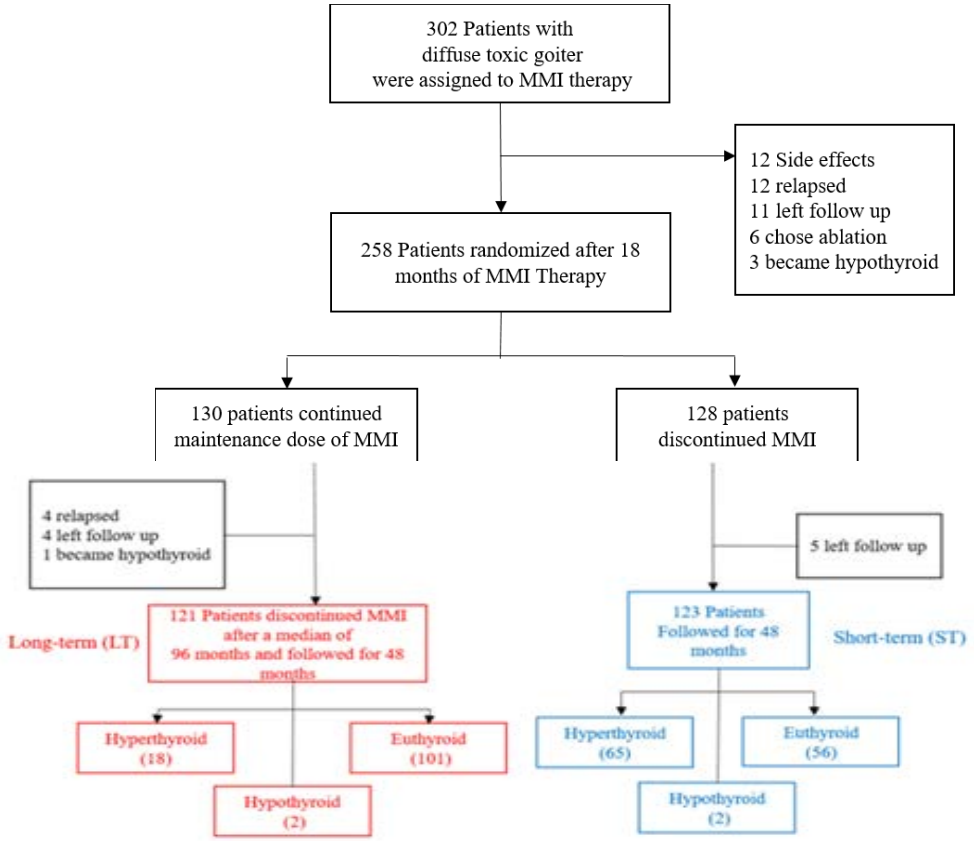
DOI: 10.1089/thy.2019.0180

Increased Remission Rates After Long-Term Methimazole Therapy in Patients with Graves' Disease: Results of a Randomized Clinical Trial

Fereidoun Azizi,[1] Atieh Amouzegar,[1] Maryam Tohidi,[2] Mehdi Hedayati,[3] Davood Khalili,[2,4] Leila Cheraghi,[4] Yadollah Mehrabi,[5] and Miralireza Takyar[1]

METHODS

Study enrollment and follow-up



Limitations and contraindications of three available treatment modalities for hyperthyroidism

Antithyroid drugs	Radioiodine	Surgery
✓ Prior adverse reactions Agranulocytosis Abnormal liver tests ✓ PTU if first trimester pregnancy	❖ Pregnancy, lactation ❖ Orbitopathy ❖ Nodules suspicious for thyroid cancer ❖ Inability to comply with radiation precautions	➢ Elderly, co-morbidities ➢ Poor surgical candidate, surgical contraindications, lack of surgical expertise ➢ Pregnancy

2016 ATA Guidelines. Thyroid 26: 1343-1421

Determinants of Choice of Therapy Discrete Choice Experiment: Hypothetical Cases

286 Patients	61 Clinicians
1. Remission Rates	1. Remission Rates
2. Severe Side Effects	2. Severe Side Effects
• Preferred Antithyroid Drugs	• Preferred Antithyroid Drugs
• Preferred Surgery over RAI	• Preferred RAI over Surgerys

Van Kinschit et al Eur J Endocrin 2021; 184:803

SAFETY

Of long-term ATD therapy

Relapse rate of hyperthyroidism in Graves' patients treated with antithyroid drugs for <50 months

First author (year)	Design	Duration of treatment (months)	Number of patients	Relapse rate* (%)
Shizume K (1970)	Retrospective	12-24	133	78
		24-48	55	84
Maugendre D (1999)	Prospective	18	62	29
		42	72	39
Mazza E (2008)	Retrospective	15.9	121	57
		48.3	115	25
Konishi T (2011)	Retrospective	18-24	87	30
		24->36	20	40

* Mean±SD relapse rate is 48.5±23.6% (range= 29-78%) for 12-24 months and 47.0±25.6 (range= 25-84%) for 24-48 months of ATD treatment.

Azizi F, et al. J Endocrinol Invest 2022; 45: 1139

Summary

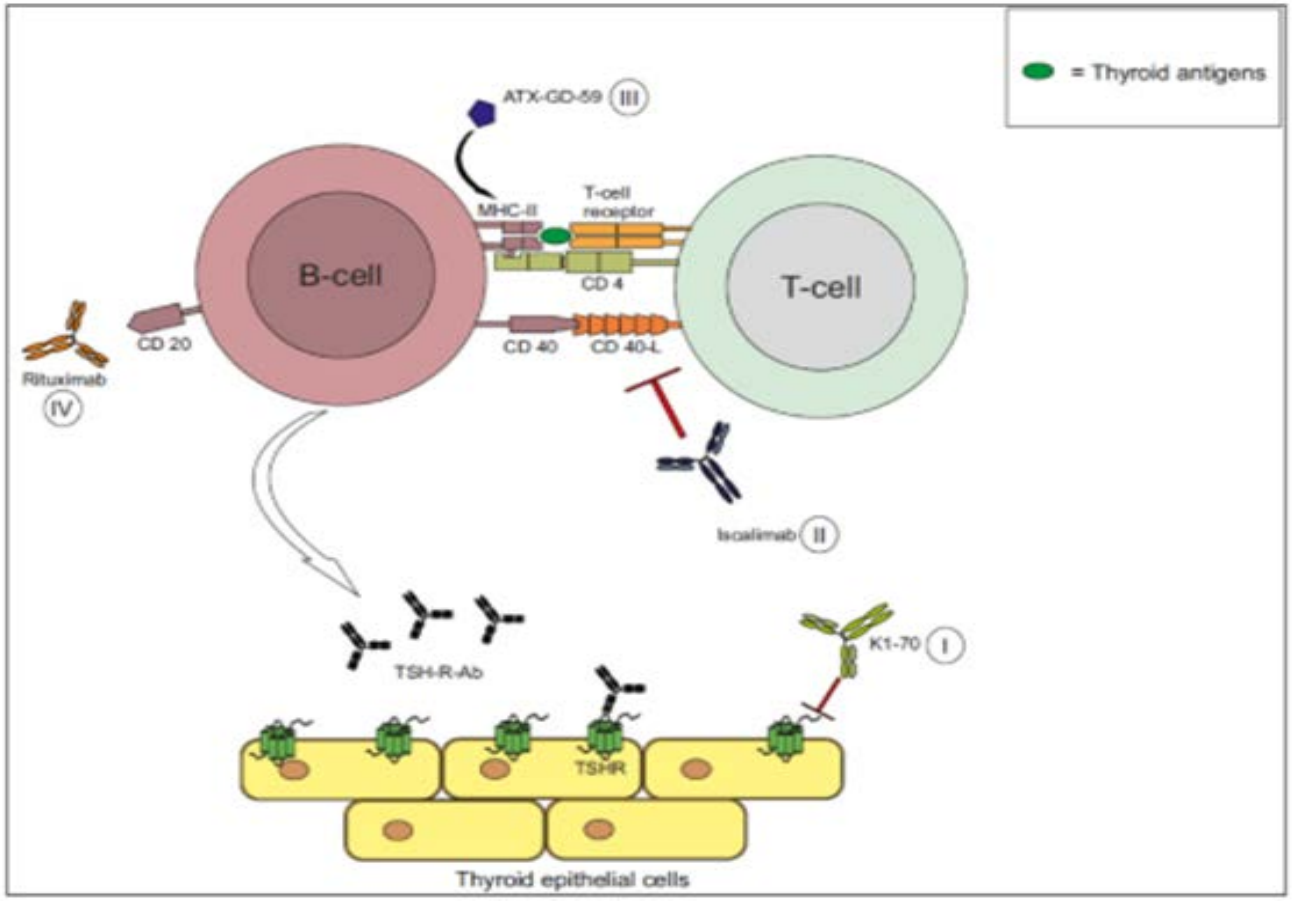
Definition of long-term ATD treatment:

- **Continuous without interruption**
- **At least 60 months of therapy**

Long-term continuous MMI treatment for Graves' disease is the better way:

- **Effective**
- **Safe, rare side effects**
- **High treatment compliance**
- **Comparable expense with RAI therapy**
- **Better quality of life compared to RAI**
- **Longest remission rate after discontinuation**
- **Best cure rate**

Sites of action of novel treatments for Graves' hyperthyroidism



Kahaly GJ. J Clin Endocrinol Metab 2020; 105: dgaa646

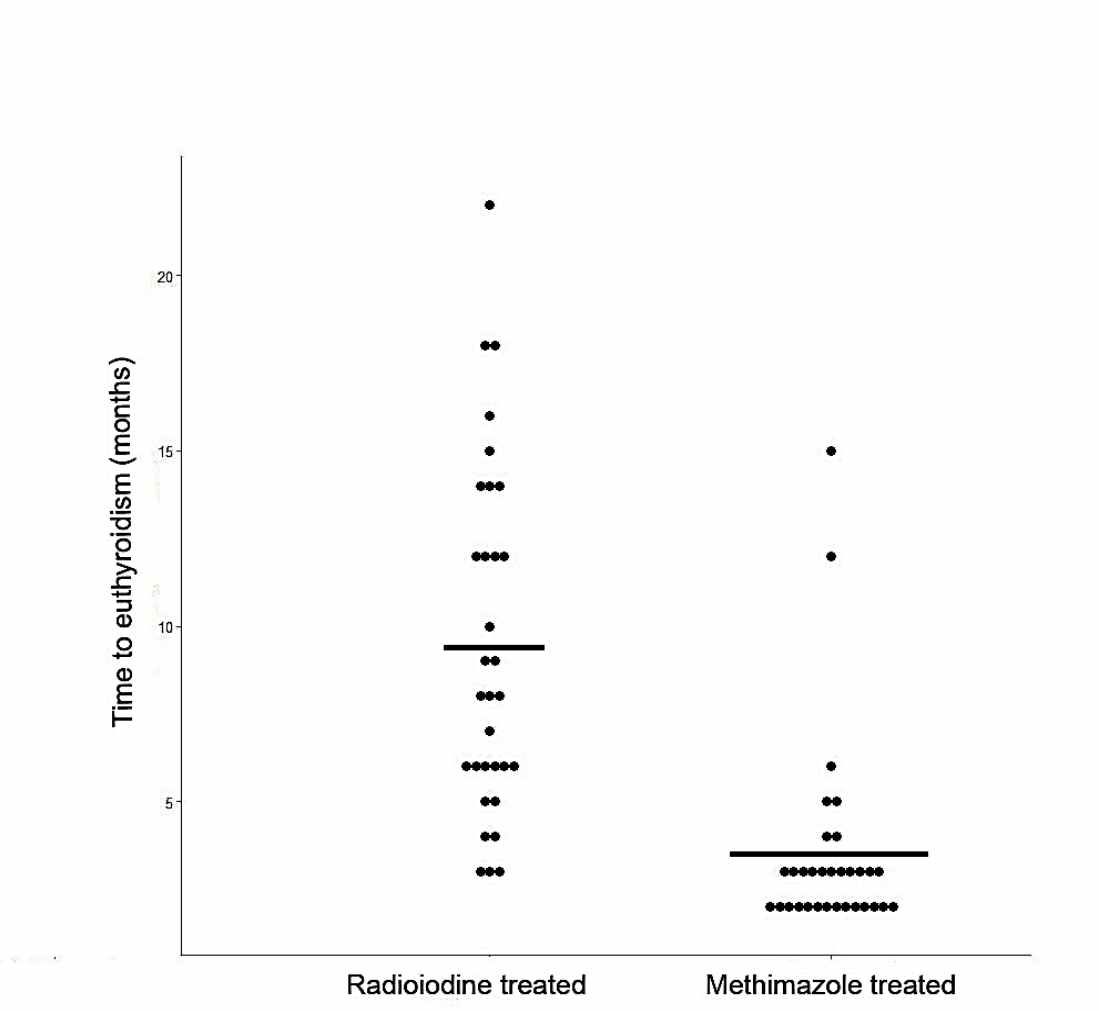
(I) Monoclonal human antibody (K1-70) blocks TSH-R activation by stimulatory TSHRAb

(II) Iscalimab is an anti-CD40 mAb and a potent inhibitor of CD40-CD40 legend pathway

(III) ATX-GD-59 is an "apitope" restoring immune tolerance to the TSH-R, supressing the immune response against the TSH-R and generating regulatory T cells

(IV) Rituximab is an anti-CD20 mAb that inhibits B-cells and reduces autoantibody production.

Time to euthyroidism after radioiodine treatment versus long-term methimazoe therapy in patients with post-radioactive iodine relapsed hyperthyroidism



Saadat N, Azizi F, Abdi H, Amouzegar A. J Endocrinol Invest 2022; 10: 1007

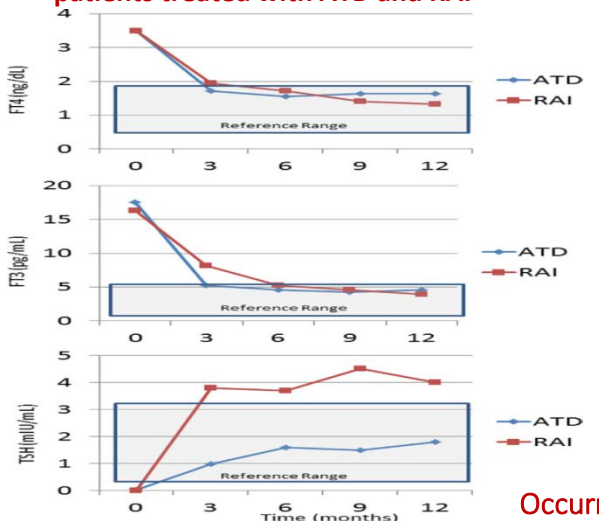
Patient preferred continuous long-term MMI treatment. Goiter is 35 gm. Serum fT4, T3 and TSH were wnl for treatment duration. 60 months after LT-MMI se is on daily 2.5 mg MMI; fT4= 1.2 ng/dl, T3= 118 ng/dl, TSH= 1.2 IU/L and TRAb= 1.1 IU/L. Which of the following is the best next step?

1. **Discontinue MMI**
2. **Continue MMI until TRAb is untestable**
3. **Apply scoring scale for making decision**
4. **Continue MMI therapy for whole life**

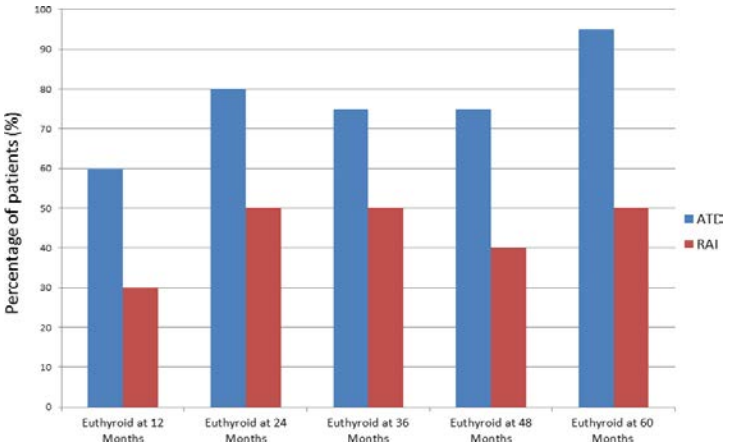
Cardiovascular risks (1)

Comparison of long-term ATD vs radioiodine therapy

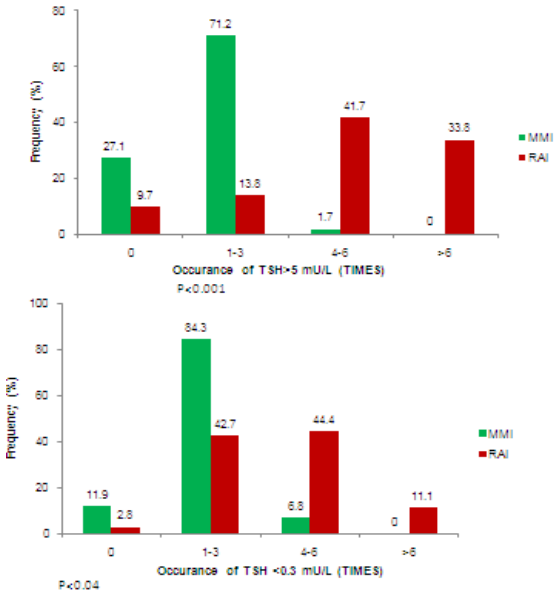
Time to biochemical improvement in hyperthyroid patients treated with ATD and RAI



- **Percentage of patients euthyroid at various time points in use of long-term ATD compared to RAI**



Occurrence of abnormal serum TSH in methimazole and radioiodine treated patients during mean 15 years follow up



Azizi F et al. Arch Iran Med 2012; 15: 477

El Kawkgi OM et al. Clinical Endocrinology 2021; 95: 3-12

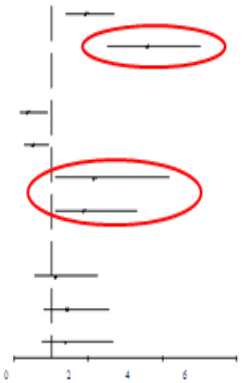
Cardiovascular risks (2)

Comparison of long-term ATD vs radioiodine therapy

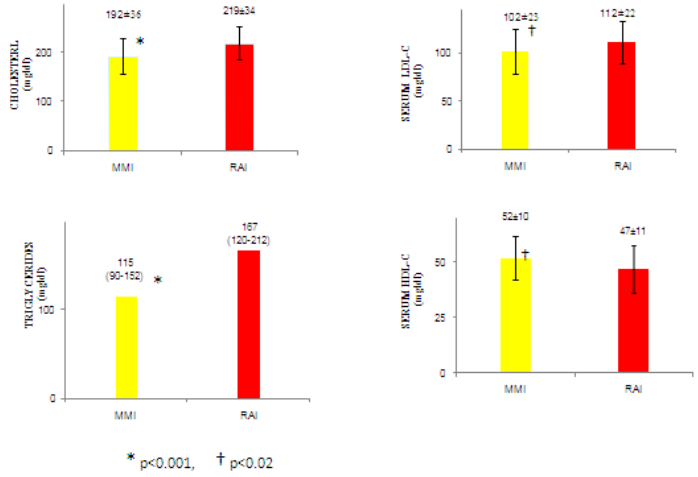
Body weight variation during follow-up and comparison between ATD treated and RAI-treated patients. Data represent mean ± standard deviation. Mann–Whitney U-test *p = .0001; **p = .001.

The relative risk and confidence interval (CI) of variables in the continuous MMI treated (group 1), as compared with the radioiodine induced hypothyroid patients (group 2)

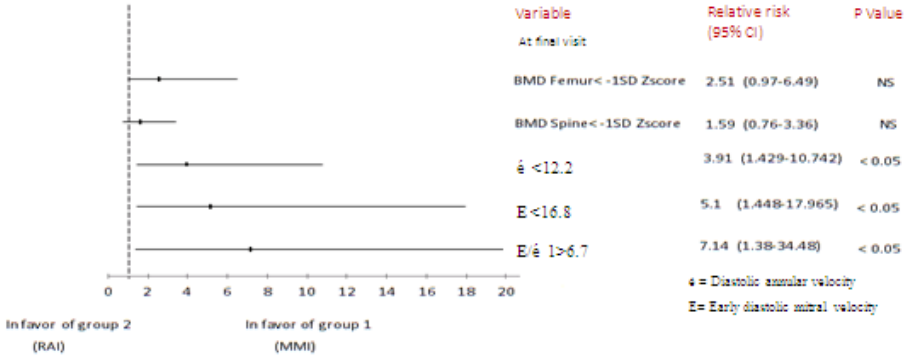
Variable	Relative risk(95%CI)	P Value
During follow up		
TSH<0.3 mU/l	1.95(1.4-2.72)	<0.01
TSH>6 mU/l	3.6 (2.52-5.06)	<0.01
At final visit		
Antithyroperoxidase antibody>100 mU/l	0.38(0.16-0.92)	<0.05
Total goiter rate	0.51(0.27-0.95)	<0.05
Serum cholesterol >200 mg/dl	2.18(1.12-4.22)	<0.03
Serum LDL-C>130 mg/dl	1.9(1.13-3.33)	<0.02
Number BMD<1.5 SD Zscore		
Vertebra	1.12(0.55-2.26)	NS
Hip	1.44(0.81-2.57)	NS
Radius	1.4(0.74-2.68)	NS



Serum lipids and lipoproteines concentrations in methimazole and radioiodine treated patients



The relative risk and confidence interval of the rate of occurrence of bone mineral density <-1 SD Zscore and é velocity <12 and 16.8 cm and early diastolic (E/é ratio <6.7 in continuous MMI- treated, compared to radioiodine-treated patients



Azizi F et al. Arch Iran Med 2012; 15: 477

El Kawkgi Om et al. Clinical Endocrinology 2020; DOI: 10 1111/cen.14374

Cardiovascular safety

- **All-cause mortality is increased in both Graves' disease and toxic nodular goiter**

  Brandt F et al, Thyroid 2013; 23: 408-13.

- **Uncorrected hyperthyroidism have an increased risk of mortality and substantial cardiovascular morbidity, including strokes, heart failure, and cardiac arrhythmias**

  Lillevang-Johansen M, Abrahamsen B, Jørgensen HL, Brix TH, Hegedüs L. J Clinical Endocrin Metab 2017;102(7):2301-9.

- **All-cause mortality increases in patients treated with conventional ATD regimens and after RAI therapy, not resulting in hypothyroidism**

  Lillevang-Johansen M, Abrahamsen B, Jørgensen HL, Brix TH, Hegedüs L. Thyroid 2019;29(3):332-40.

- **Longer durations of suppressed serum TSH levels were associated with rises in cardiovascular outcomes in treated and untreated hyperthyroid patients**

  Boelaert K, Maisonneuve P, Torlinska B, Franklyn JA. J Clin Endocrinol Metab. 2013;98(5):1869e1882.

- **Early and effective control of the disease is associated with better-improved survival**

  Okosieme OE, Taylor PN, Evans C, et al. Lancet Diabetes Endocrinol 2019;7(4):278e287.