THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

"A 54-year-old female with LVAD and weight loss"

OBJECTIVES

- To review thyroid function abnormalities associated with amiodarone use
- Epidemiology and pathophysiology of type 1 and type 2 amiodarone-induced thyrotoxicosis (AIT)
- Treatment of AIT

HPI

- 52yo female with a h/o breast cancer, s/p partial mastectomy, chemo- and RT in 1994, NICM due to anthracycline exposure who was noted to have HF requiring ECMO and had LVAD HM3 placed in 11/2017, complicated by A. flutter/SVT after surgery requiring amiodarone initiation.
- Admitted in March 2020 with MSSA driveline infection
- Presented for a follow up on 5/1/20 complaining of 25 lbs weight loss, decreased appetite, but denied tremors, dyspnea, palpitations; has had baseline constipation with no recent change

Other history and medications

- Past Medical History: breast cancer, bilateral PE, HFrEF, no known thyroid problems
- Past Surgical History: breast lumpectomy, BSO
- Medications: ASA; carvedilol, amiodarone, doxycycline, Lasix, miralax, KCl, warfarin
- FH: negative for thyroid disease

Physical exam and labs

- PE: T 98.1, HR 69-86 bpm; BP 105/60
- HEENT: No exophthalmos or injection, EOMI; No thyromegaly; No hand tremor, Lungs: CTA, CVD: VAD hum
- **LABS prior to presentation to Endocrinology clinic**

	11/14/17	1/16/18	3/23/18	8/3/18
fT4 (0.9-1.7)	0.85	1.56	1.51	1.74
T4 (5-11.6)	5.7	11.7	10.1	11
Total T3 (80-195)	34	68	68	77
Reverse T3 (137-424)	597	1167	972	1061
TSH (0.3-4.0)	5.71	4.31	2.47	1.6

Effect of amiodarone of thyroid hormones

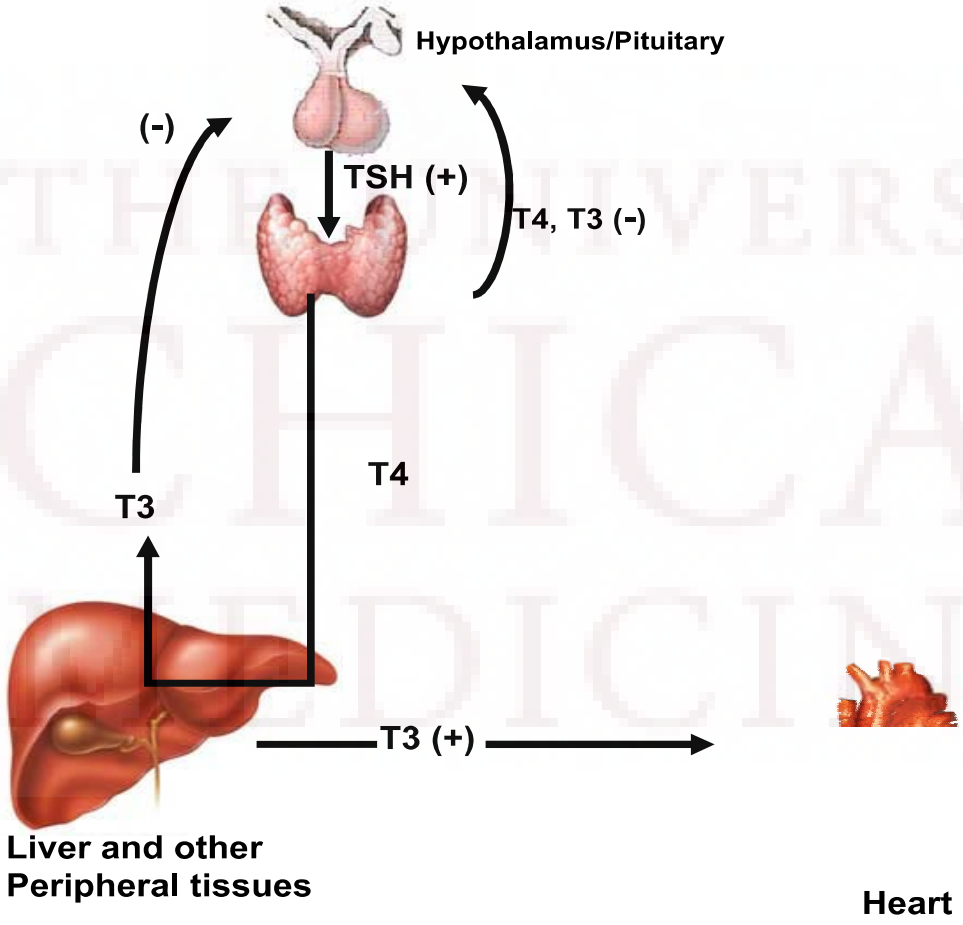


Table 1. Changes in thyroid function tests occurring in euthyroid amiodarone-treated subjects

Assay	Short-term therapy	Underpinning mechanism(s)	Long-term therapy	Underpinning mechanism(s)
Thyrotropin	Increased	Decreased T_4 production (Wolff-Chaikoff effect) (major contribution) Inhibition of pituitary D2 activity (minor contribution) Inhibition of T3 binding to its pituitary receptor (minor contribution)	Normal	Normalized T_4 production (escape from the Wolff-Chaikoff effect)
Thyroxine (T_4): total (TT_4) and free (FT_4)	Increased	Inhibition of hepatic D1 activity	Slightly increased/ high normal	Inhibition of hepatic D1 activity Increased T_4 production rate Decreased T_4 metabolic clearance rate
Triiodothyronine: total (TT_3) and free (FT_3)	Decreased	Inhibition of hepatic D1 activity	Slightly decreased/ low normal	Inhibition of hepatic D1 activity Increased T_4 production rate Decreased T_4 metabolic clearance rate
Reverse T_3	Increased	Inhibition of hepatic D1 activity	Increased	Inhibition of hepatic D1 activity

D1, type 1 iodothyronine deiodinase; D2, type 2 iodothyronine deiodinase.

Bartalena et al. 2018 ETA guidelines for management of amiodarone-associated thyroid dysfunction. Eur Thyroid J, 2018

Endocrine curbside consult on 5/1

	11/14/17	1/16/18	3/23/18	8/3/18	5/1/20
fT4 (0.9-1.7)	0.85	1.56	1.51	1.74	>7.77
T4 (5-11.6)	5.7	11.7	10.1	11	
Total T3 (80-195)	34	68	68	77	
Reverse T3 (137-424)	597	1167	972	1061	192
TSH (0.3-4.0)	5.71	4.31	2.47	1.6	<0.01

Recommended methimazole 10 mg/d, stop amiodarone and outpatient follow up.

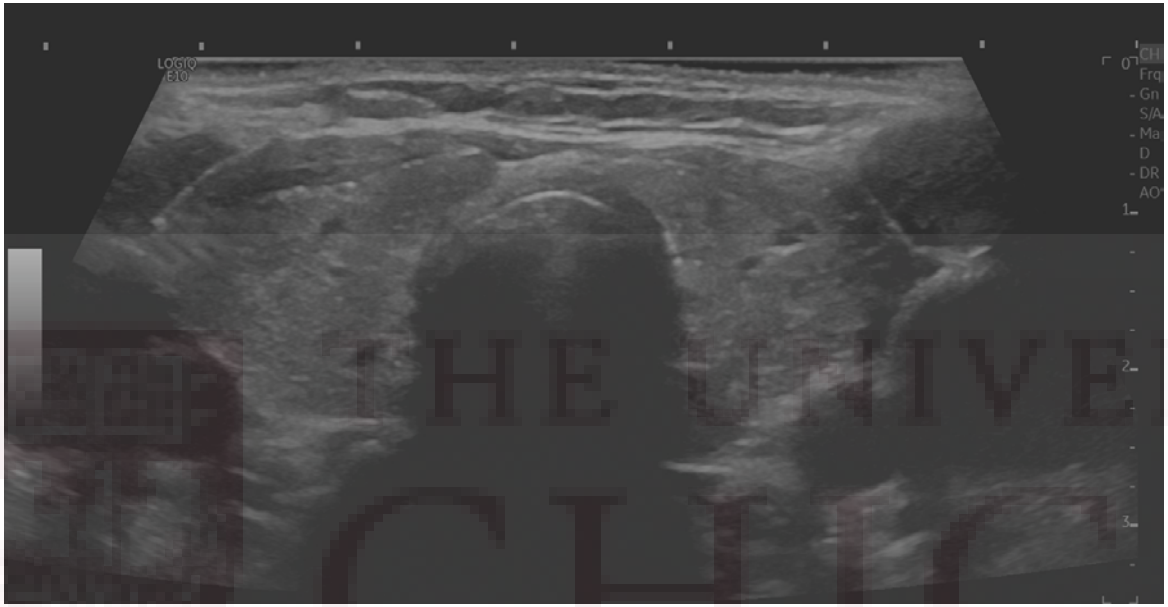
The patient did not start methimazole due to insurance problem.

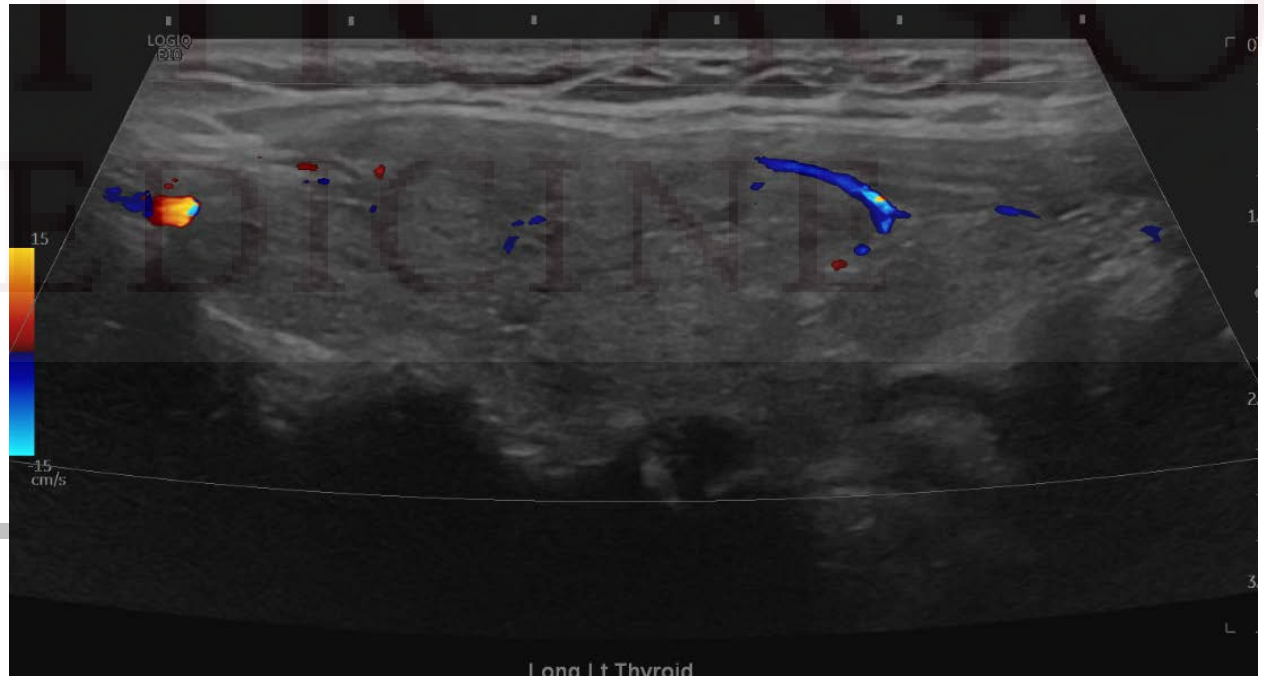
What is the etiology of thyroid function test abnormalities?

What other tests would you order?

1. Graves' disease
2. Toxic nodular goiter
3. Amiodarone-induced thyrotoxicosis
4. Subacute thyroiditis

Thyroid US 5/11/2020





Thyroid US

- **Slightly heterogenous appearance of the thyroid parenchyma without increased color Doppler flow. No discrete suspicious nodule.**
- **These findings are somewhat nonspecific but are suggestive of nonactive parenchymal disease possibly post-thyroiditis sequela.**

Additional tests

- TSI < 1.0
- TPO and thyroglobulin Ab negative

	11/14/17	1/16/18	3/23/18	8/3/18	5/1/20	5/9/20
fT4 (0.9-1.7)	0.85	1.56	1.51	1.74	>7.77	
T4 (5-11.6)	5.7	11.7	10.1	11		>24.9
Total T3 (80-195)	34	68	68	77		181
Reverse T3 (137-424)	597	1167	972	1061	192	
TSH (0.3-4.0)	5.71	4.31	2.47	1.6	<0.01	

Endocrine virtual clinic visit on 5/12

- Patient reported weight loss, but no other symptoms.
- Denies vision problems, voice change, dysphagia, neck pain
- Reported recent need to reduce the dose of coumadin

Warfarin in AIT

- AIT can affect warfarin metabolism and reduce the dose needed to maintain therapeutic INR due to increased degradation of vitamin K-dependent coagulation factors

What type of amiodarone-induced thyrotoxicosis does she have and why do you think so???

Types of AIT

Table 2. Common features of the two main forms of amiodarone-induced thyrotoxicosis (AIT 1 and AIT 2)

	AIT 1	AIT 2
Underlying thyroid abnormalities	Yes	Usually no[a]
Colour-flow Doppler sonography	Increased vascularity	Absent hypervascularity
Thyroidal RAIU	Low/normal/increased[b]	Suppressed
Thyroid autoantibodies	Present if AIT is due to Graves disease	Usually absent[c]
Onset time after starting amiodarone	Short (median 3 months)	Long (median 30 months)
Spontaneous remission	No	Possible
Subsequent hypothyroidism	No	Possible
First-line medical treatment	Antithyroid drugs[d]	Oral glucocorticoids
Subsequent definitive thyroid treatment	Generally yes	No

RAIU, radioiodine uptake. [a] A small goitre may be present. [b] In iodine-replete areas RAIU is always suppressed. [c] Anti-thyroglobulin and anti-thyroid peroxidase antibodies do not allow a diagnosis of AIT 1. [d] Antithyroid drugs (thionamides) may be associated (for a few weeks) with sodium perchlorate.

Bartalena et al. 2018 ETA guidelines for management of amiodarone-associated thyroid dysfunction. Eur Thyroid J, 2018

How to treat???

Physical exam and labs

- Diagnosed with type 2 AIT and started on Prednisone 40 mg daily on 5/12/20. She was supposed to have repeat labs in 2 weeks, but had labs rechecked in 4 days (unchanged??) and she tapered prednisone to 30 mg and 20 mg as she felt weak while on prednisone; increased back to 40 mg on 6/12 after a follow up in clinic

- Admitted 6/15 with syncope, negative Neurology workup

	11/14/17	1/16/18	3/23/18	8/3/18	5/1/20	5/9/20	5/16/20	6/11/20
fT4 (0.9-1.7)	0.85	1.56	1.51	1.74	>7.77		>7.77	>7.77
T4 (5-11.6)	5.7	11.7	10.1	11		>24.9		>24.9
Total T3 (80-195)	34	68	68	77		181	154	181
Reverse T3 (137-424)	597	1167	972	1061	192			
TSH (0.3-4.0)	5.71	4.31	2.47	1.6	<0.01		0.01	<0.01

Endocrinology consulted during this hospitalization

Does the patient really have type 2 AIT?
Should we switch to or add thionamides??

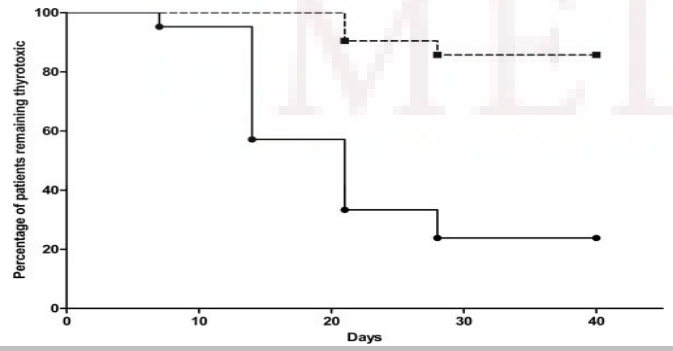
Evidence for using steroids

- Matched retrospective study

Glucocorticoids Are Preferable to Thionamides as First-Line Treatment for Amiodarone-Induced Thyrotoxicosis due to Destructive Thyroiditis: A Matched Retrospective Cohort Study

Fausto Bogazzi, Luca Tomisti, Giuseppe Rossi, Enrica Dell'Unto, Pasquale Pepe, Luigi Bartalena, and Enio Martino

- 21 p treated with Methimazole 40 mg and 21 with prednisone 0.5 mg/kg/d. At 40 days if still thyrotoxic switched from methimazole to prednisone (86%) or prednisone continued if in the steroid group (24%).
- 94% of patients switched from methimazole to steroids became euthyroid at 40 days



Additional evidence for using steroids in AIT type 2

Treatment of Amiodarone-Induced Thyrotoxicosis Type 2: A Randomized Clinical Trial

Silvia A. Eskes, Erik Endert, Eric Fliers, Ronald B. Geskus, Robin P. F. Dullaart, Thera P. Links, and Wilmar M. Wiersinga

TABLE 2. Treatment outcomes in patients with AIT type 2

	Group A (n = 12) prednisone + methimazole	Group B (n = 14) perchlorate + methimazole	Group C (n = 10) prednisone + perchlorate + methimazole
Efficacy of treatment[a]			
TSH ≥ 0.4 mU/liter on initial therapy	12 (100%)	10 (71%)	10 (100%)
TSH ≥ 0.4 mU/liter on additional therapy	NA	4 (29%)	NA
Time to FT_4 ≤ 25 pmol/liter (wk)[b]	4 (4–20)	12 (4–20)	8 (4–20)
Time to TSH ≥ 0.4 mU/liter (wk)[b]	8 (4–20)	14 (4–32)	12 (4–28)
Amiodarone continued	12 (100%)	14 (100%)	10 (100%)
Recurrent thyrotoxicosis	1	0	2
Time of recurrence (wk)	24	NA	12 and 76
Time to TSH ≥ 0.4 mU/liter (wk)	8	NA	4

Hospital course

- Prednisone 40 mg continued, discharged on 6/26 with improving TFTs

	11/14/17	1/16/18	3/23/18	8/3/18	5/1/20	5/9/20	5/16/20	6/11/20	6/20/20	6/26/20
fT4 (0.9-1.7)	0.85	1.56	1.51	1.74	>7.77		>7.77	>7.77	4.45	3.29
T4 (5-11.6)	5.7	11.7	10.1	11		>24.9		>24.9	22.8	18.9
Total T3 (80-195)	34	68	68	77		181	154	181	89	67
Reverse T3 (137-424)	597	1167	972	1061	192					
TSH (0.3-4.0)	5.71	4.31	2.47	1.6	<0.01		0.01	<0.01		0.01

Follow up clinic visit 8/20/20

- No complaints, feels well, still on Prednisone 40 mg/d

	6/11/20	6/20/20	6/26/20	8/3/20	8/17/20
fT4 (0.9-1.7)	>7.77	4.45	3.29	1.46	
T4 (5-11.6)	>24.9	22.8	18.9	9.7	7.8
Total T3 (80-195)	181	89	67	46	43
Reverse T3 (137-424)					
TSH (0.3-4.0)	0.01		0.01	0.02	1.67

Advised to decrease Prednisone to 30 mg/d

Follow up labs

On 9/2 Prednisone tapered to 20 mg/d

	6/11/20	6/20/20	6/26/20	8/3/20	8/17/20	8/28/20	9/2/20	9/9/20	9/16/20	9/24/20
fT4 (0.9-1.7)	>7.77	4.45	3.29	1.46		1.17	1.18	1.18	1.16	1.20
T4 (5-11.6)	>24.9	22.8	18.9	9.7	7.8		8.3	8.5	8.8	9.0
Total T3 (80-195)	181	89	67	46	43	49	65	65	65	82
Reverse T3 (137-424)										
TSH (0.3-4.0)	0.01		0.01	0.02	1.67	3.32	6.01	3.28	6.12	3.14

Amiodarone pharmacology

- 200 mg amiodarone → 75 mg organic iodine daily → 6 mg free iodine into circulation
- 20-40x higher than daily iodine intake in the US (0.15-0.30 mg)
- Amiodarone has a long half-life (~100 days) due to storage in adipose tissue
- Amiodarone is converted by CYP3A4 into an active metabolite D-desethylamiodarone (DEA), which is more concentrated in thyroid and more toxic

Epidemiology of AIT

- Incidence of AIT varies between 0.003% and 10%.
- 3% of patients treated with amiodarone in the North America develop AIT, type 2 more common,
- Up to 10% in countries with low iodine intake, type 1 more frequent in these countries
- M/F 3:1, younger age, presence of thyroid Ab, goiter, low BMI are associated with AIT
- Kinoshita et al identified dilative CMP (OR 3.3, 95% CI 1.26-8.90) and cardiac sarcoidosis (OR 6.47, 95% CI 1.60-25.77) as risk factors for AIT
- Amiodarone induced hypothyroidism is more frequent in iodine-replete regions with prevalence up to 26% for subclinical and 5% of overt

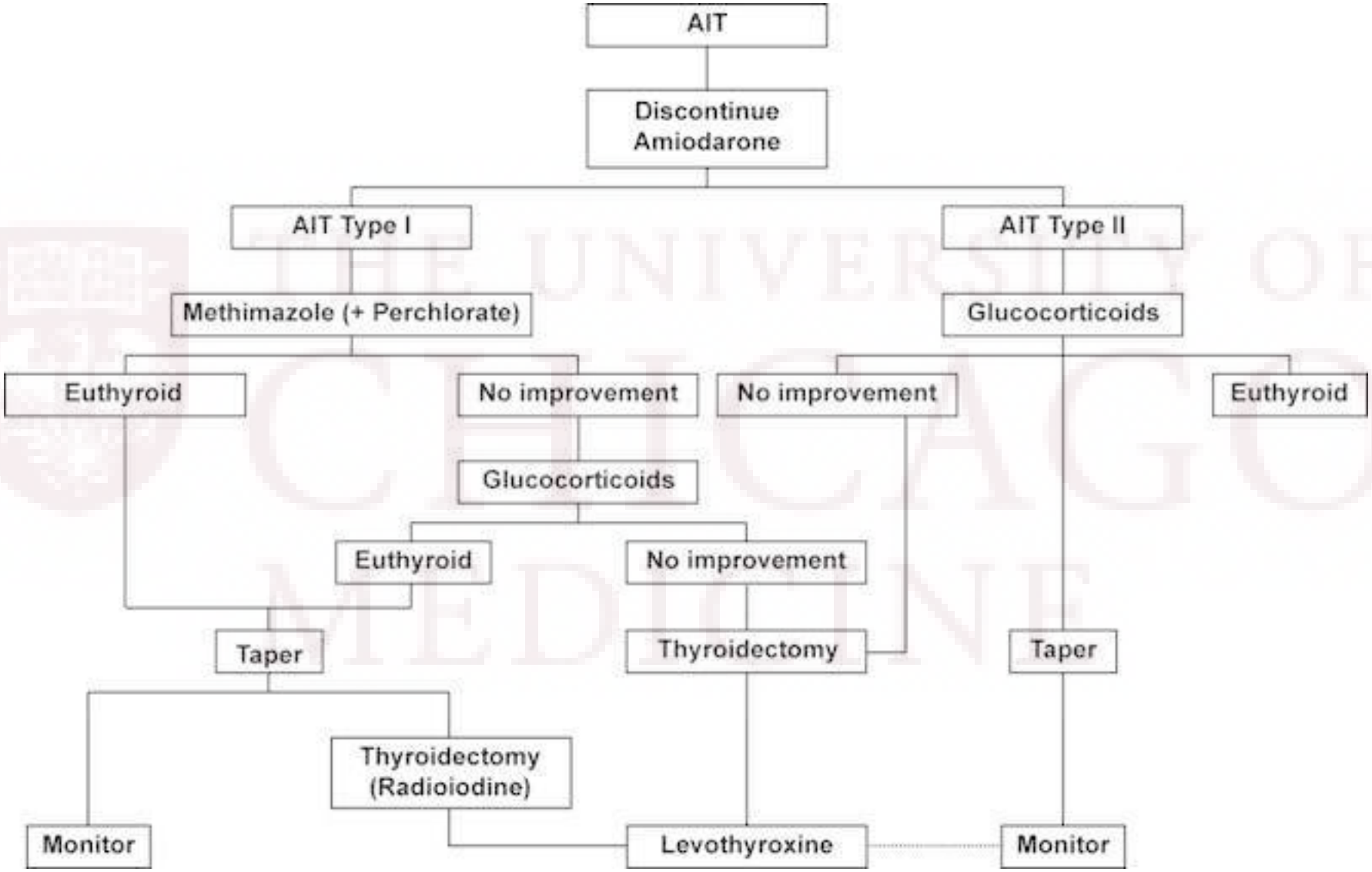
Kinoshita et al. J Arrythm., 2016;
Kinoshita et al. J Clin Pharm Ther., 2020

Treatment

- Type 1 → high dose thionamides (20-60 mg/d methimazole or 400-600 mg PTU) ± KClO4 in a dose <1 g/day no more than 30 days
- Gershinsky et al. noted higher risk for agranulocytosis in patients with AIT on thionamides (HR 9.71; 95% CI 4.28-22.05) vs. those with thyrotoxicosis due to other etiologies (HR 5.70; 95%CI 2.14-15.21)
- Type 2 → prednisone 0.5-0.7 mg/kg/day for ~3 months. May spontaneously resolve and in up to 17% may result in hypothyroidism

Macchia & Feingold, Endotext, 2018
Gershinsky et al, Thyroid, 2019

Algorithm for management of AIT



Thyroidectomy for AIT

- Kotwal et al. retrospective review of 17 p. -> rapid resolution of thyrotoxicosis and improved LVEF, but higher complication rate than other etiologies
- Cappellani et al. compared 156 p. with AIT on medical therapy and 51 p who had thyroidectomy. 4.5% died in the medical therapy group before achieving euthyroidism while 1.9% (1p.) died after surgery. Patients with moderate to severely reduced LVEF had lower mortality with surgery

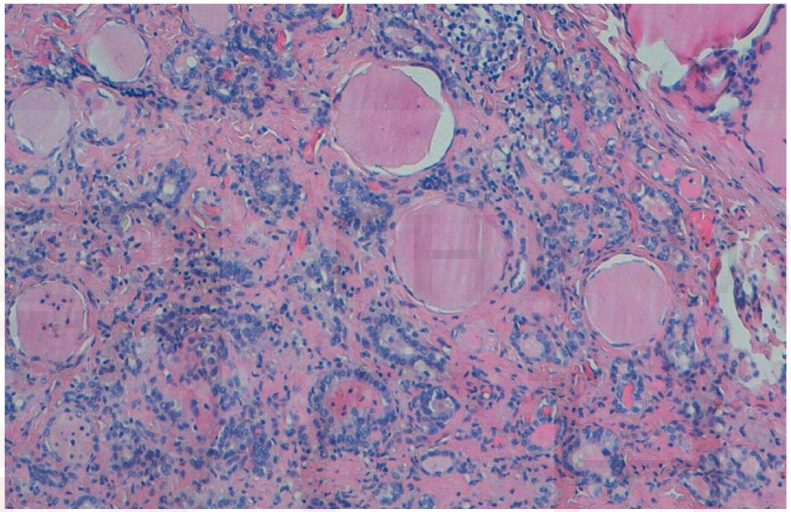
Kotwal et al, J Endocr Soc, 2018
Cappellani et al. J Clin Endocinol Metab, 2020

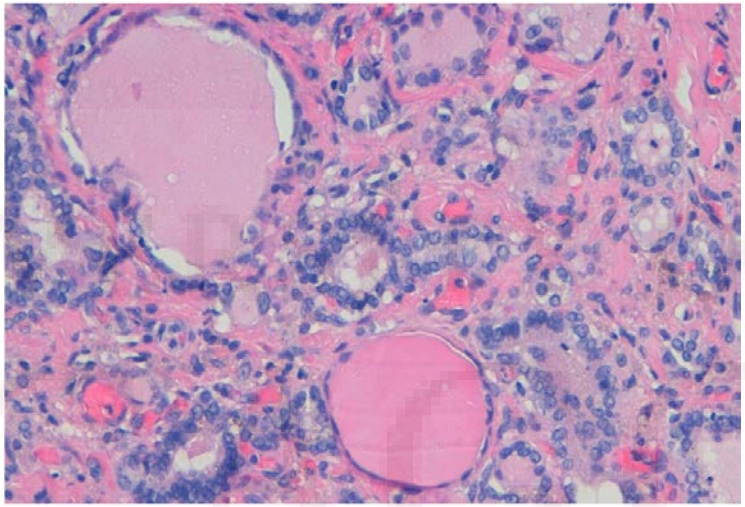
Amiodarone: continue or stop?

Table 3. Advantages and disadvantages of amiodarone withdrawal in patients with amiodarone-induced thyrotoxicosis (AIT)

Disadvantages	Advantages
Efficient drug for life-threatening arrhythmias	Amiodarone and its metabolites have a long half-life, making an immediate exacerbation of cardiac symptoms unlikely
Cardiac protective properties: antagonistic effect on β-adrenergic receptors, inhibition of T_4 deiodination, blockade of T_3 binding to thyroid hormone receptors	Greater chance of achieving euthyroidism and delivering definitive thyroid treatment (particularly radioiodine) at an earlier stage
Amiodarone and its metabolites have a long half-life; thus, discontinuation might be useless, at least in the short term	Continuation of the drug in AIT 2 is associated with a delayed restoration of euthyroidism and a higher chance of recurrence

Bartalena et al. 2018 ETA guidelines for management of amiodarone-associated thyroid dysfunction. Eur Thyroid J, 2018





Thank you!