Thyroid disorders – what's new?

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Royal Free Hampstead NHS Trust

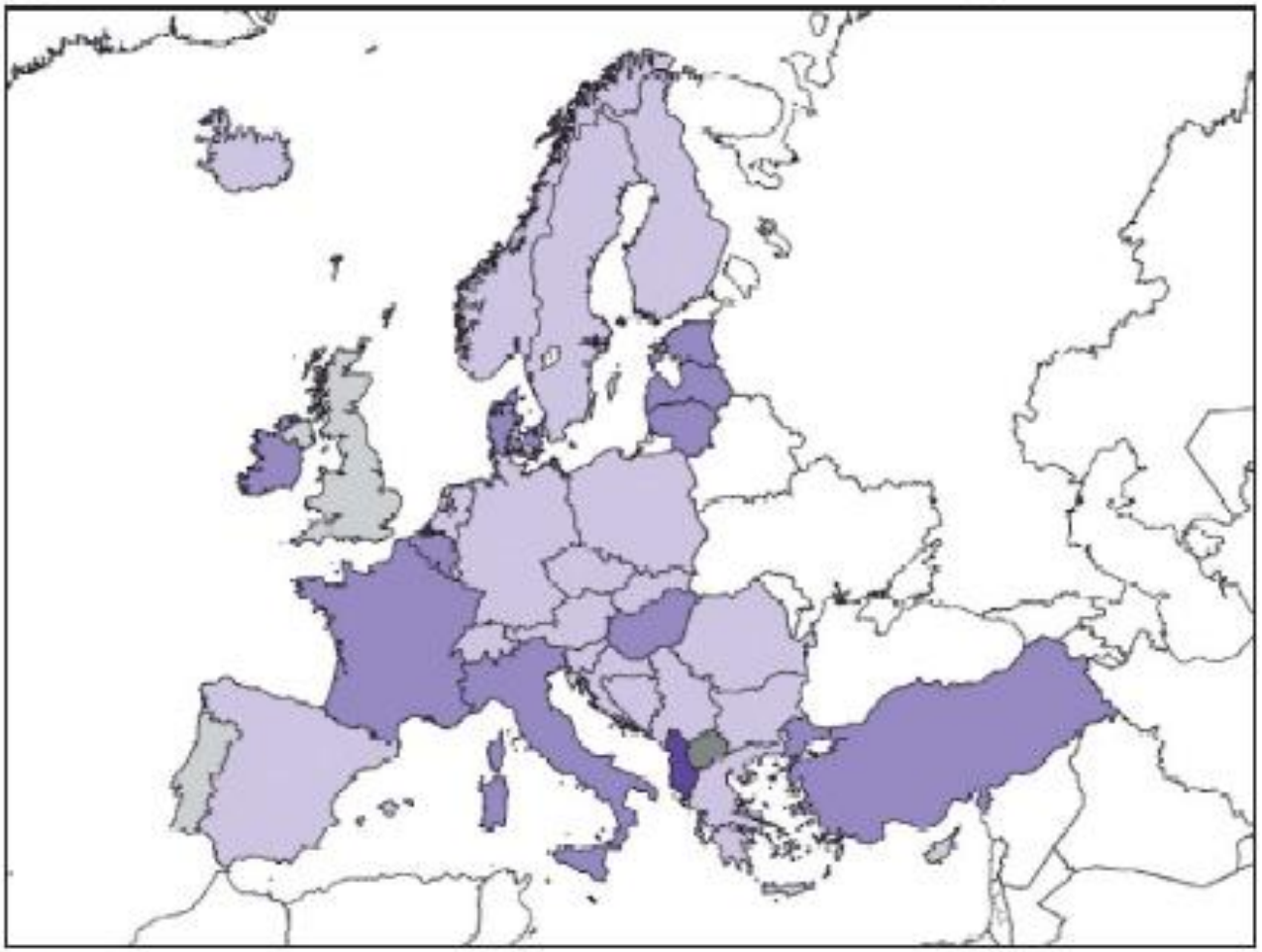
Copenhagen Consensus 2008

Costs and benefits of proposals for confronting ten great global challenges

- 1 Micronutrient supplements for children (vitamin A and zinc) (60) Malnutrition
- 2 The Doha development agenda (0) Trade
- 3 Micronutrient fortification (iron and salt iodization) (286) Malnutrition
- 4 Expanded immunization coverage for children (1,000) Diseases
- 5 Bio fortification (60) Malnutrition
- 6 Deworming and other nutrition programs at school (27) Malnutrition/Education
- 7 Lowering the price of schooling (5,400) Education
- 8 Increase and improve girls' schooling (6,000) Women
- 9 Community-based nutrition promotion (798) Malnutrition
- 10 Provide support for women's reproductive role (4,000) Women

(Annual cost in million USD)

Figure 3.2: **National iodine nutrition based on median UI in Europe**



Moderate iodine deficiency (20-49 µg/l), 1 country

Mild iodine deficiency (50-99 µg/l), 10 countries

Optimal (100-199 µg/l), 20 countries

Risk of iodine-induced hyperthyroidism (200-299 µg/l), 1 country

No data

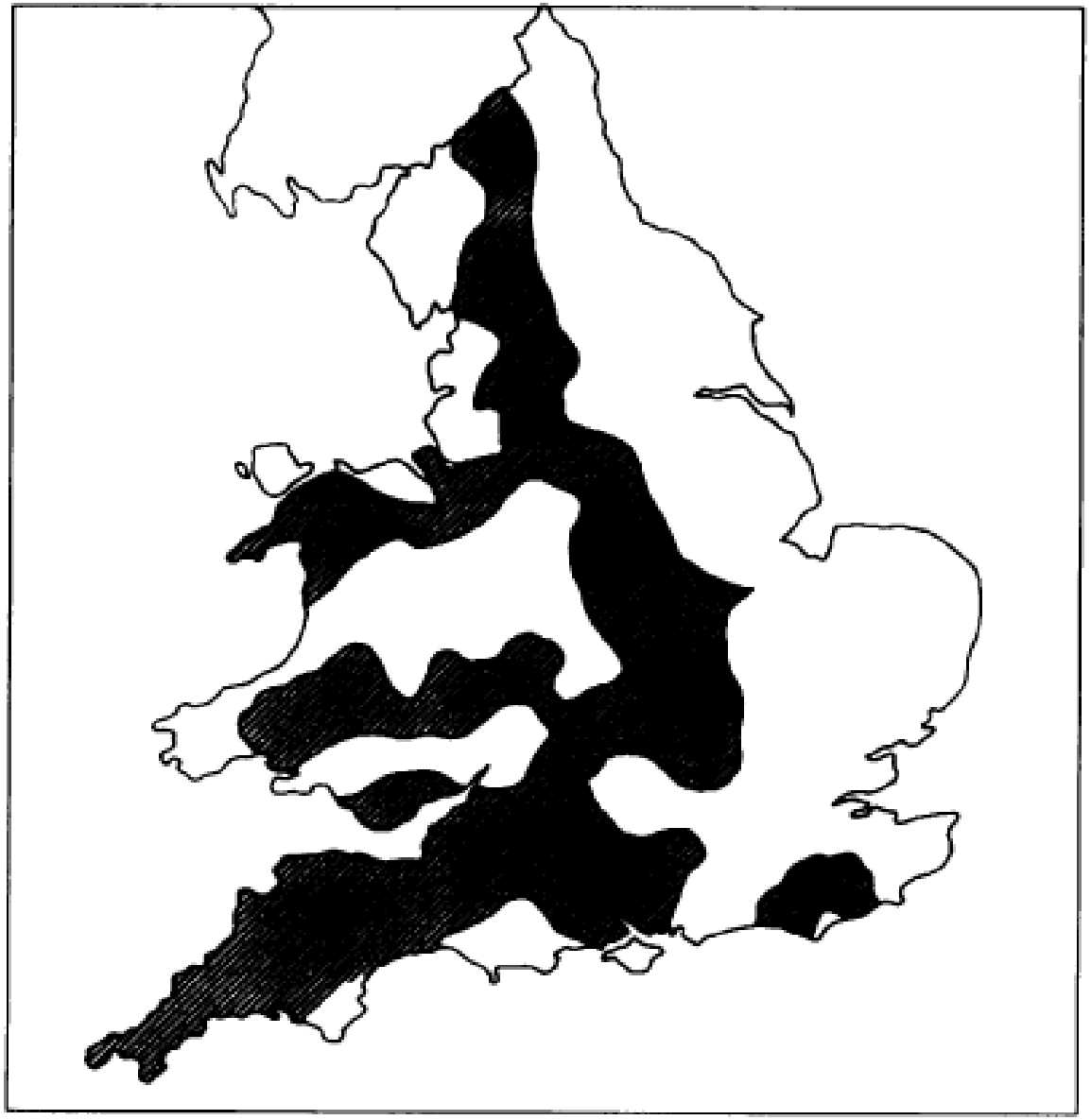


Figure 1 Areas of England and Wales where endemic goitre has been prevalent in the past.[24].

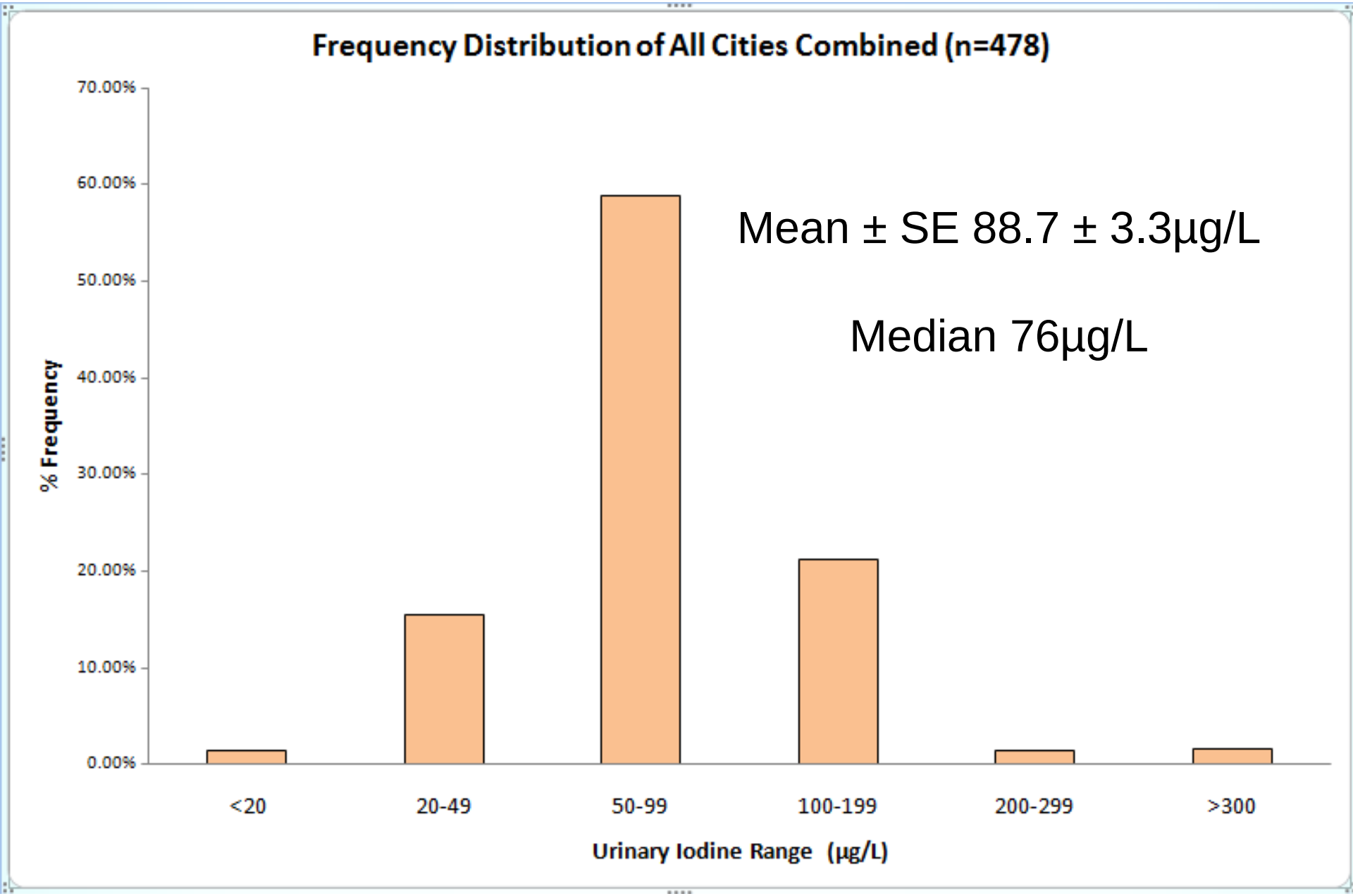

Frequency Distribution of All Cities Combined (n=478)
70.00%
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
% Frequency
Mean ± SE 88.7 ± 3.3µg/L
Median 76µg/L
<20
20-49
50-99
100-199
200-299
>300
Urinary Iodine Range (µg/L)

Table 1. Prevalence of amiodarone-induced thyroid dysfunction in areas of different environmental iodine intake and underlying thyroid status.[1,2]

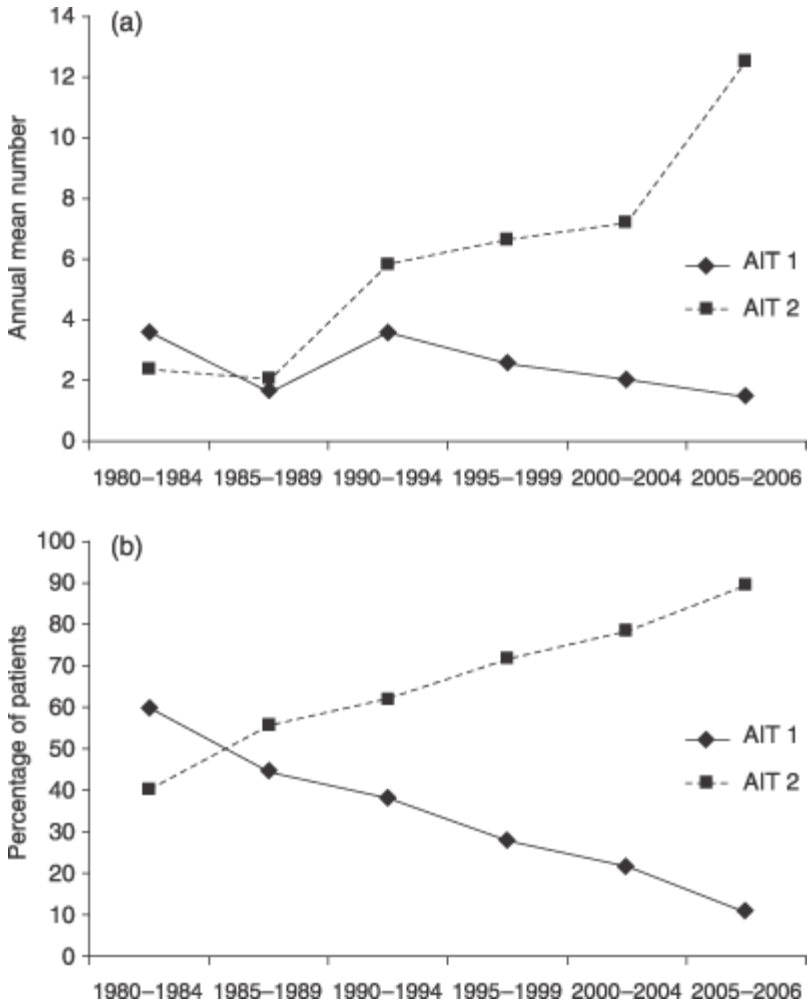
	Geographical iodine status	
	Sufficient (%)	Deficient (%)
Prevalence of AIH	22	5
Prevalence of AIT	2	10

Table 2. Some characteristic differences between type I and type II AIT

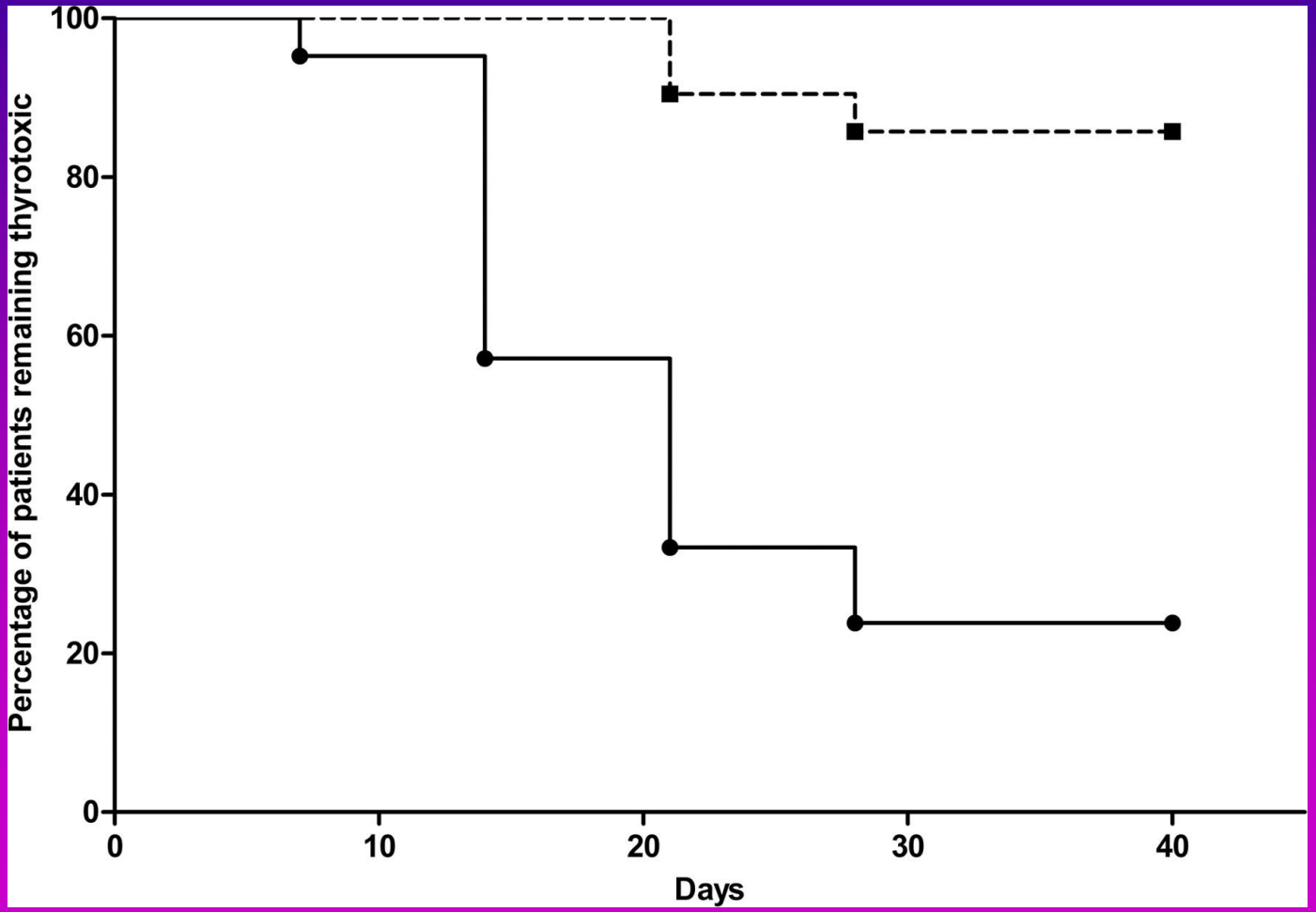
	Type I	Type II
Useful tests		
Goitre (diffuse of nodular)	Often present	Often absent
Thyroid Auto-antibodies	Often present	Often absent
Colour flow Doppler sonography	Pattern I–IV	Pattern 0
Less useful tests		
Interleukin-6 levels	Often normal	>2-fold of upper normal
24-h RAI uptake	>3%	<1%
Response to perchlorate within 8 weeks	Yes	No
Other characteristics		
Response to steroids within 4 weeks	No	Yes
Subsequent hypothyroid	No	Yes

Prevalence of Amiodarone-induced thyrotoxicosis

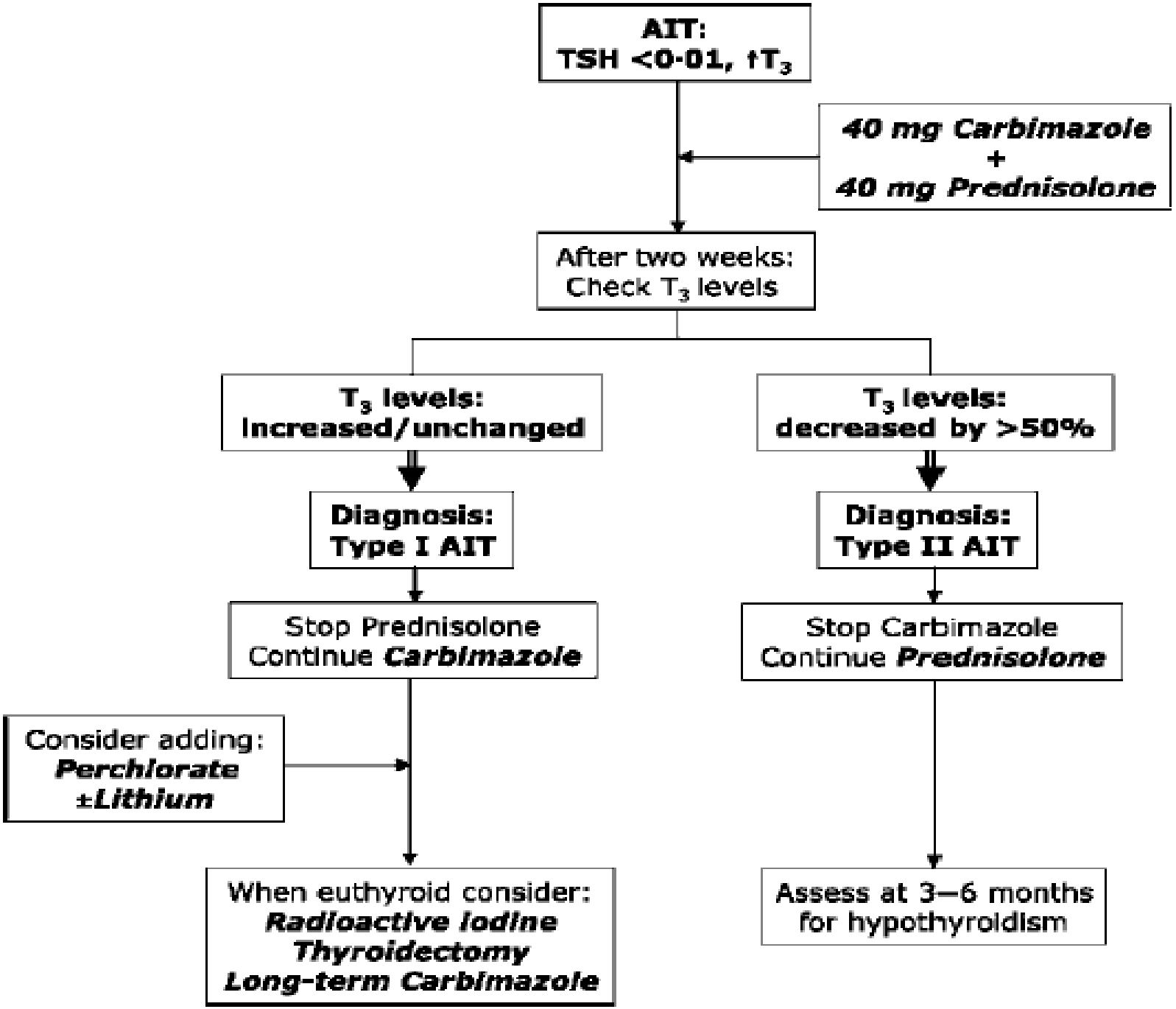
(Bogazzi et al, 2007)



Proportion of patients remaining thyrotoxic during the first 40 days of therapy



Bogazzi, F. et al. J Clin Endocrinol Metab 2009;94:3757-3762


AIT:
TSH <0-01, ↑T3
40 mg Carbimazole
+
40 mg Prednisolone
After two weeks:
Check T3 levels
T3 levels:
Increased/unchanged
T3 levels:
decreased by >50%
Diagnosis:
Type I AIT
Diagnosis:
Type II AIT
Stop Prednisolone
Continue Carbimazole
Stop Carbimazole
Continue Prednisolone
Consider adding:
Perchlorate
±Lithium
When euthyroid consider:
Radioactive Iodine
Thyroidectomy
Long-term Carbimazole
Assess at 3—6 months
for hypothyroidism

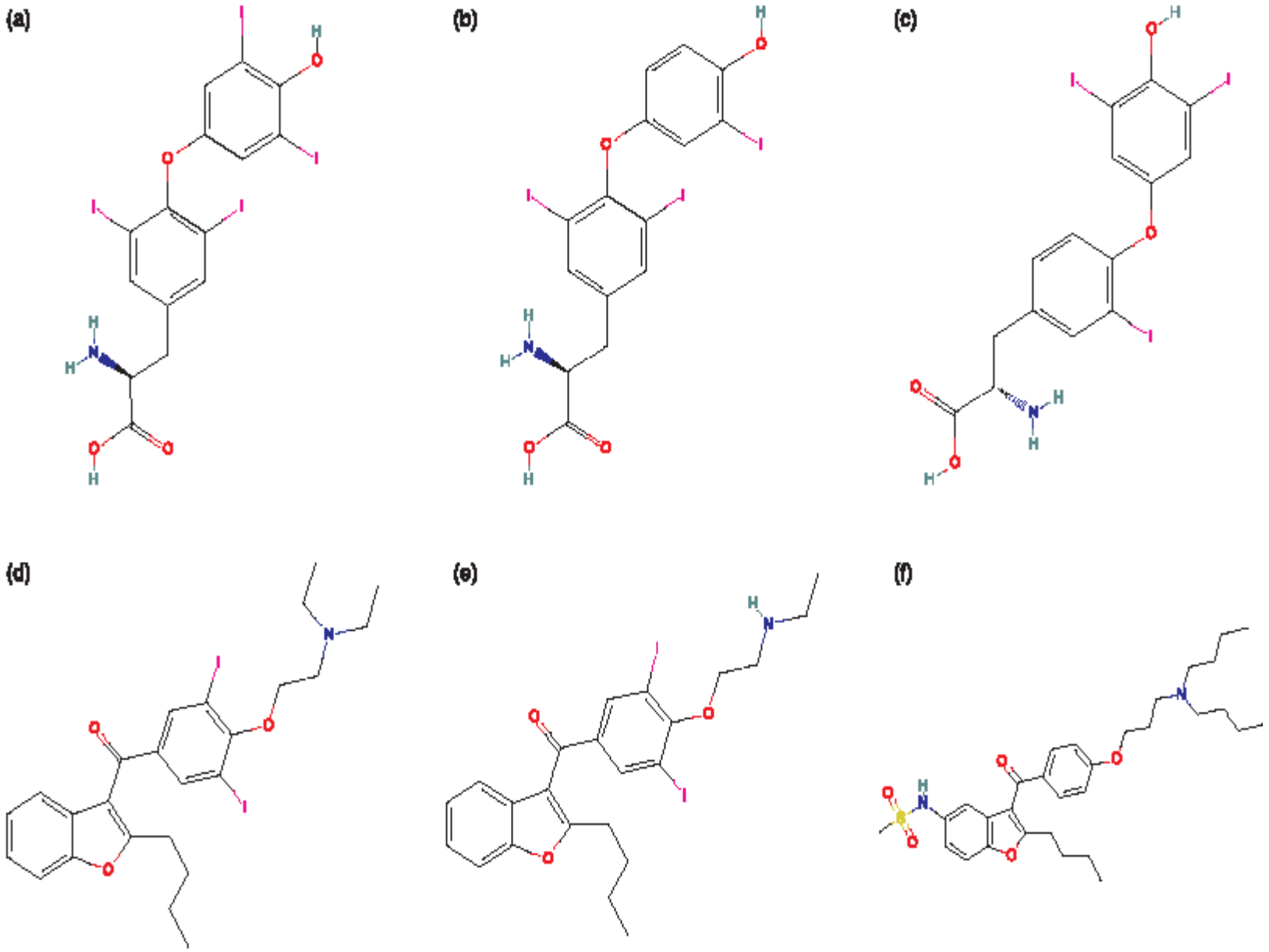
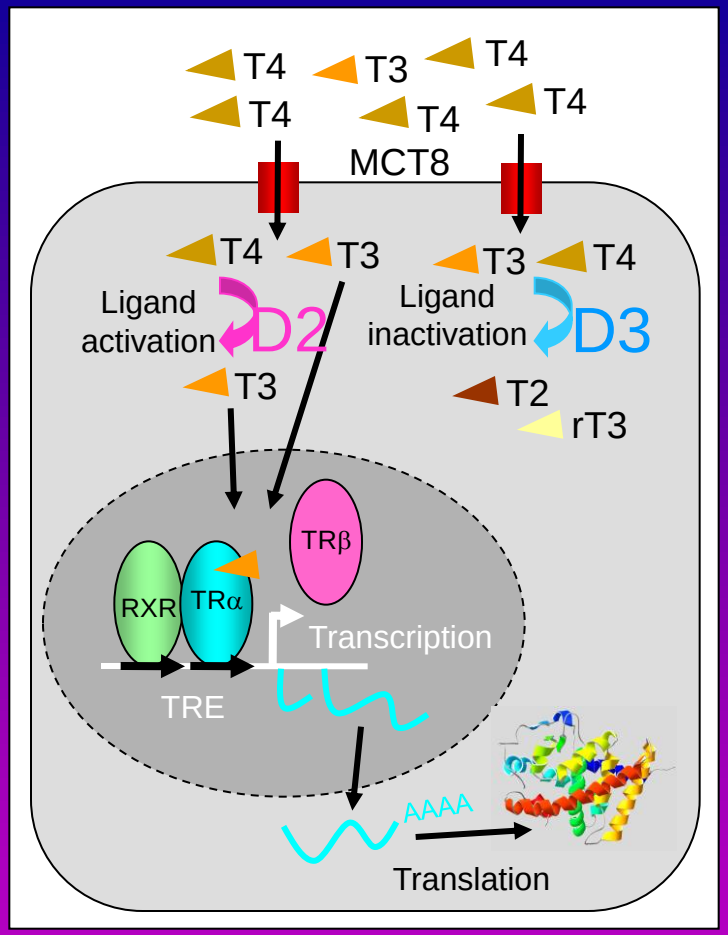


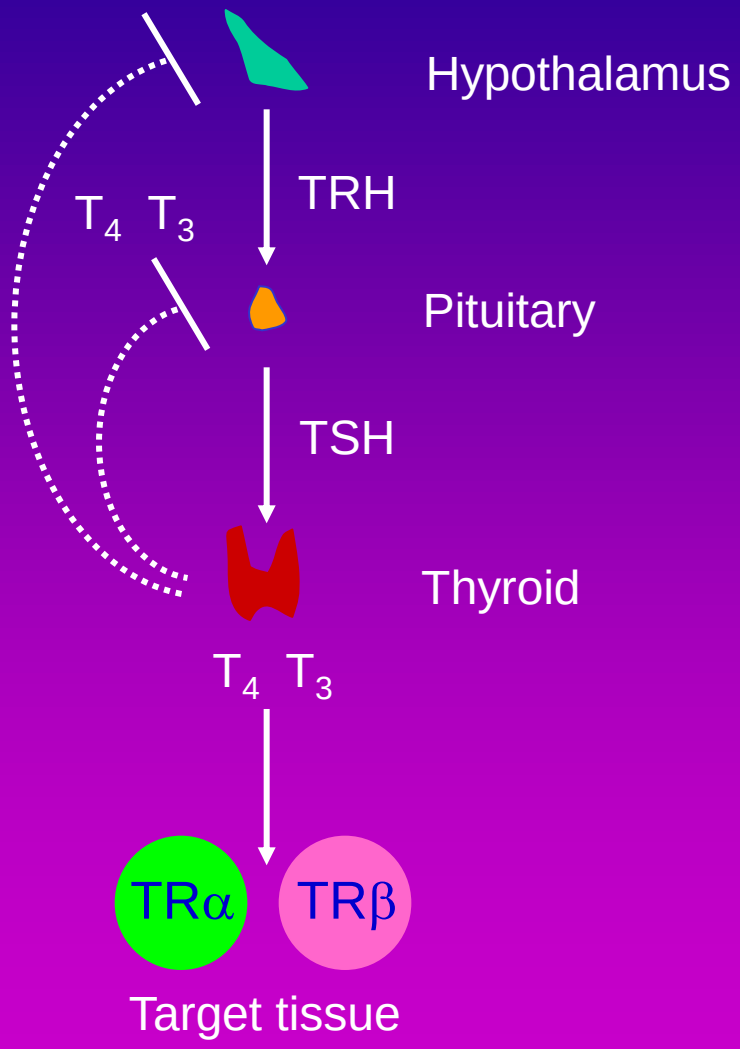
Fig. 2 Structures of T_4 (a), T_3 (b), rT_3 (c), amiodarone (d), DEA (e) and dronedarone (f) (Source: http://pubchem.ncbi.nlm.nih.gov).

Dronadarone

- Non-iodinated benzofuran derivative
- Less lipophilicity due to methane sulphonyl group, shorter t1/2
- Multi-channel blocking effects and anti-adrenergic properties
- Antagonist of $TR\alpha_1$ and $TR\beta_1$ isoforms
- Little impact on thyroid hormones
- Minor TSH changes of no significance
- Marginally less effective at preventing recurrence of AF and caution in CCF

Thyroid hormone action





- TRα and TRβ
  - Sensitive to ligand availability
  - +ve and –ve target gene responses
  - Spectrum of sensitivity to T3
  - Expression varies during development & between tissues

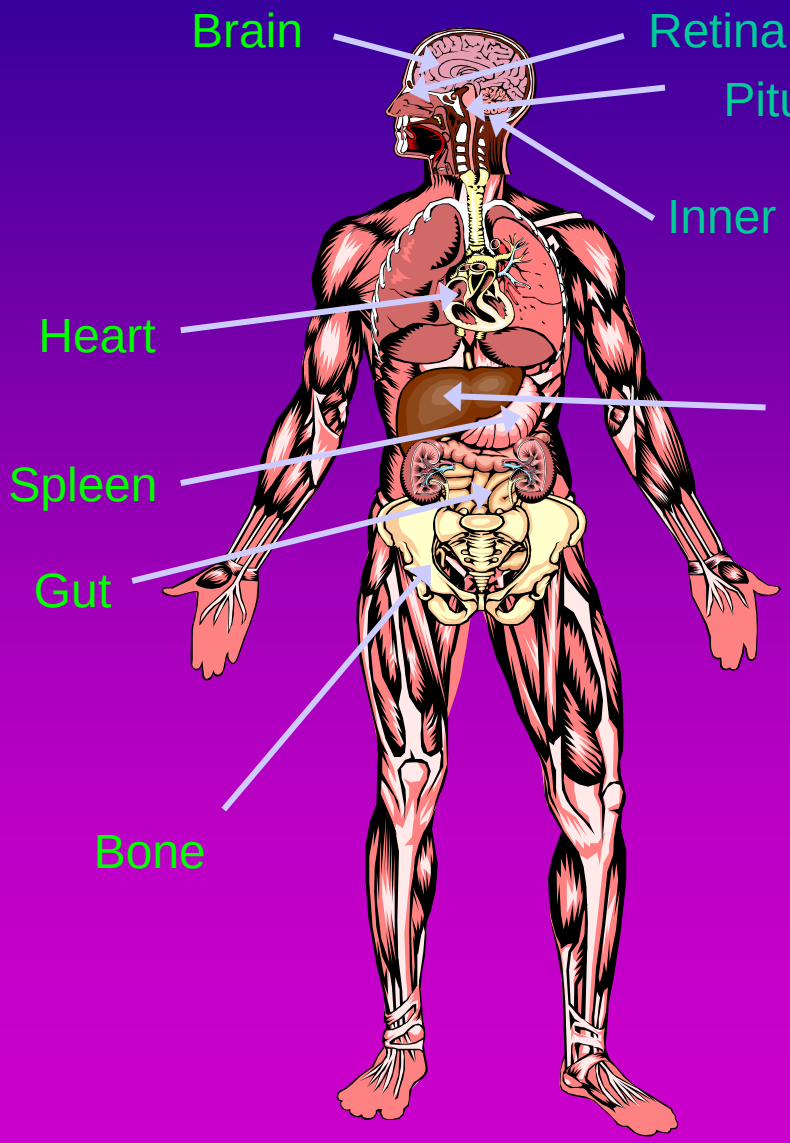
T3 responses tightly regulated and tissue-specific

Yen 2001 Physiol Rev 81:1097-11142
Harvey & Williams 2002 Thyroid 12:441-446

TR isoform-specific target tissues

TRα

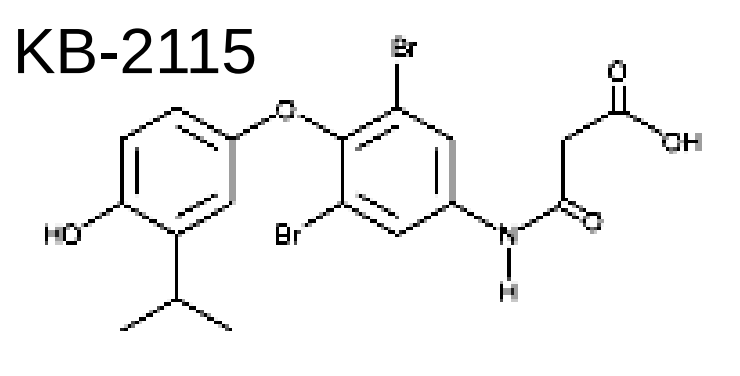
TRβ



Mixed TRα and TRβ or unknown

- BMR
- Thermogenesis
- Adipogenesis
- Vasculature
- Skin
- Hair
- Muscle
- Bone marrow
- Kidney
- Lung

KB-2115 (Eprotirome)



KB-2115
- TRβ-selective agonist
- Tissue-selective uptake in liver

3 Phase 2 trials of TR modulator in humans
- Dose related reductions
  - LDL cholesterol (40% after 1 week versus 11% response to placebo)
  - Total cholesterol and apoB (similar responses)
- No effect on TGs, lipoprotein (a), BMR or weight
- Increased bile acid synthesis independent of cholesterol synthesis
  - Mechanism different to statin
- No apparent adverse events or effects on heart, bone or TSH suppression
- 3 trials: Epiterome alone, +statin, + ezetimide
- 21-26% reduction in LDL

Berkenstam et al 2008 PNAS 105:663-667
Ladenson, ATA 2009

The Association for Clinical Biochemistry

Royal College of Physicians
Setting higher medical standards

British Thyroid Association

BRITISH THYROID FOUNDATION

B S P E D

Society for Endocrinology

The Diagnosis and Management of Primary Hypothyroidism

A statement made on behalf of

The Royal College of Physicians

in particular its Patient and Carer Network and the Joint Specialty Committee for Endocrinology & Diabetes

The Association for Clinical Biochemistry

The Society for Endocrinology

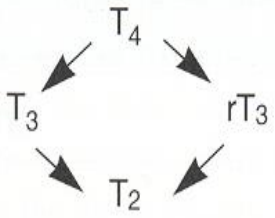
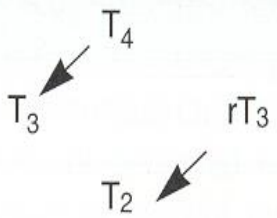
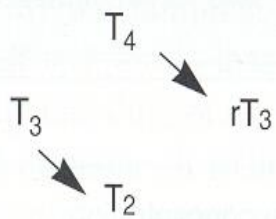
The British Thyroid Association

The British Thyroid Foundation Patient Support Group

The British Society of Paediatric Endocrinology and Diabetes

Endorsed by
the Royal College of General Practitioners

Iodothyronine deidonase isoenzymes

	Type I	Type II	Type III
			
Molecular weight (kD)	55 (dimer of ~27)	200 (multimer of ~29)	Unknown
Tissue distribution	Liver, kidney, thyroid	Brain, pituitary, brown adipose tissue	Brain, skin, placenta
Subcellular location	Endoplasmic reticulum (liver); basolateral plasma membrane (kidney)	Microsomal membranes	Microsomal membranes
Effect of thiouracils	Inhibition	Almost none	None
Effect of thyrotoxicosis	Increase	Decrease	Increase
Effect of hypothyroidism	Decrease	Increase	Decrease

D2 is major source of plasma T3 in euthyroidism

	extrathyroidal T3 production	D1 mediated	D2 mediated
hypothyroidism	7 nmol/day	29%	71%
euthyroidism	44 nmol/day	34%	66%
hyperthyroidism	224 nmol/day	67%	33%

Maia et al. JCI 2005

TAO and Etanercept

- 56-year old women diagnosed 20 years ago with hypothyroidism post-partum
- On T4 100mcg daily many years
- Diagnosed rheumatoid arthritis 2005
- Commenced on Etanercept May 2008
- Within 1 month, eye pain and oedema and right proptosis
- MRI scan increased retrorbital fat
- ?significance of anti-TNF-α effect

TABLE 1. SELECTED BIOLOGICAL AGENTS IN CLINICAL TRIALS OR WITH POTENTIAL FOR TREATING TAO

Method of action	*Name*	*Structure*	*Target*	*Current experience in patients with TAO*	*FDA-approved indications*[a]
B-lymphocyte depletion	Rituximab (Rituxan®/MabThera®)	Monoclonal antibody	CD20	El Fassi, 2006 ($n=2$) (64) Salvi, 2007 ($n=7$) (65)[b]	Non-Hodgkin B-cell lymphomas, RA
B-cell Survival	Belimumab (LymphoStat-B®)	Monoclonal antibody	BAFF[c]		None
Inhibition of T-lymphocyte activation	Abatacept (Orencia®)	CTLA-4/ immunoglobulin fusions molecule	CD28	None	RA
Anticytokines	Etanercept (Enbrel®)	TNF-receptor/ immunoglobulin fusion molecule	TNF-α	Paridaens, 2005 ($n=10$) (80)	RA, juvenile RA, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis
	Infliximab (Remicade®)	Monoclonal antibody	TNF-α	Durrani, 2005 ($n=1$) (81)	RA, psoriatic arthritis, plaque psoriasis, Crohn's disease, ulcerative colitis
	Adalimumab (Humira®)	Monoclonal antibody	TNF-α	None	RA, juvenile RA, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis Crohn's disease
	Tocilizumab (Actemra®)	Monoclonal antibody	IL-6	None	None
	Anakinra (Kineret®)	IL-1 receptor antagonist	IL-1	None	RA

Cytokines in TAO

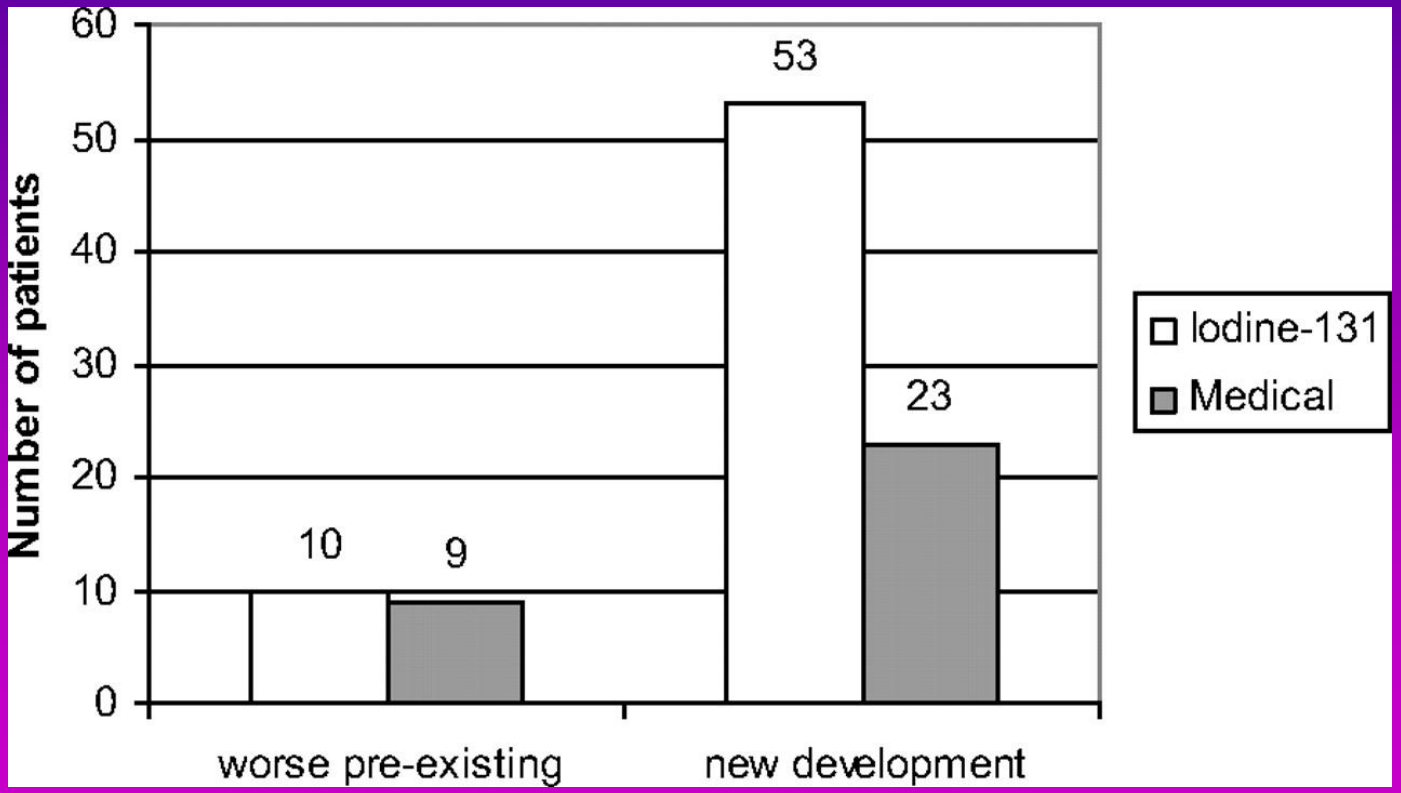
- Orbital connective tissue remodelling - cytokine-dependent fibroblast activation
- Accumulation of GAG
- Infiltration mast cells/T and B cells
- TNFα and IL1 stimulate ICAM1/GAG
- IL1 promotes whilst TNFα inhibits adipogenesis in vitro

(Cawood et al, Eur J Endo 2006)

Radioiodine effects on TAO
(Traisk et al, JCEM 2009)

- Multicentre randomised trial in Graves' disease pts: I131 (n=163) and ATDs (n=150)
- Early use of T4
- At 1 year follow-up risk of de novo TAO was 31% of I131 pts and 16% of ATD
- Worsening in those with pre-existing disease was not more common in I131
- Smoking influenced risk of TAO
- Pre-treatment FT3 and TSHRAb titre?

Worsening of pre-existing TAO and de novo development of TAO

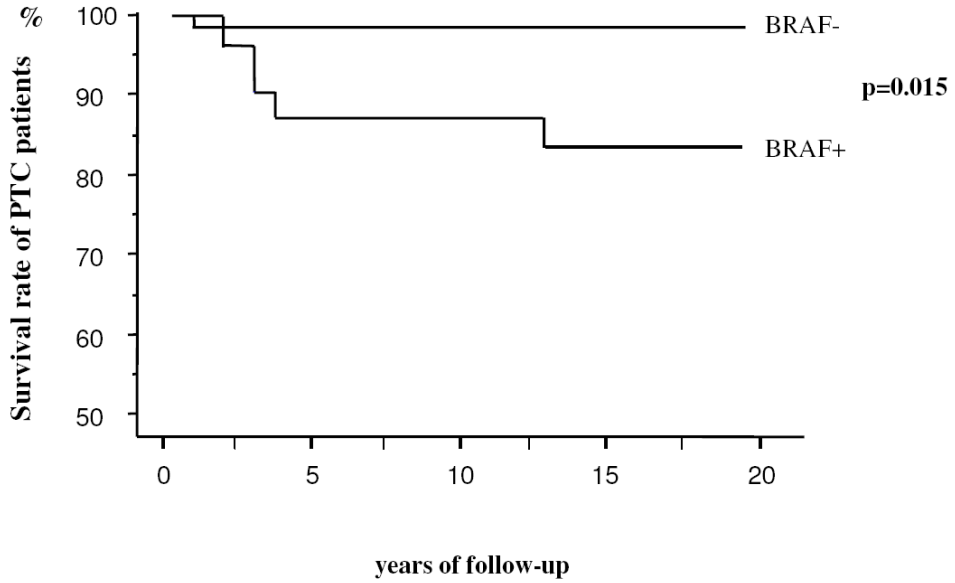


Traisk, F. et al. J Clin Endocrinol Metab 2009;94:3700-3707

Revised ATA guidelines (Thyroid, 2009)

- U/S characteristics of nodules and what to FNA?
- Extent of surgery and role of prophylactic neck dissection
- Remnant ablation – patient selection and use of rhTSH
- Assessment of cure – low/high risk
- TG and U/S in monitoring long-term
- T4 therapy and TSH suppression

Prognostic value of BRAF*V600E*



Clinical features	Odds ratio	95% CI	p-value
Age at diagnosis >60	1.25	0.08-19.28	0.87
Tumor Size (continuous variable)	0.51	0.25-1.04	0.06
De Groot's classes	10.97	0.72-166.84	0.08
Stage (TNM)	1.02	0.89-1.16	0.73
VEGF (score 2-3)	1.20	0.95-1.51	0.12
Vascular invasion	0.97	0.10-9.00	0.98
BRAF mutation	14.63	1.28-167.29	***0.03***

N=102 PTC

Elisei, JCEM 2008

Tyrosine kinase inhibitors

Compound	Target	Published	Author	# DTC	CR/PR/SD
Gefitinib	EGFR	Thyroid 2007	Pennell	25	12%
Axitinib	VEGFR	J Clin Oncol 2008	Cohen	45	73%
Motesanib	RET- PDGF – VEGFR-KIT	NEJM 2008	Sherman	93	12%
Sorafenib	RET-RAS-RAG- VEGF-VEGFR-PDGF-cKIT	J Clin Oncol 2008	Gupta	30	23%
		J Clin Oncol 2009	Kloos	52	15%
		Eur J Endocrinol 2009	Smit	32	24%

Summary

- UK appears to now be iodine deficient
- Use steroids early in Amiodarone-induced thyrotoxicosis
- Thyroid hormone analogues may be future addition to statin therapy in DM
- T4 remains only treatment for hypothyroidism
- No new therapies for TAO but cautious with I131 in Graves' and use steroids
- Ongoing trials of TK inhibitor therapies for non-responsive patients with DTC