GUIDELINES FOR THE MANAGEMENT OF THYROTOXICOSIS

Contents

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Summary of main recommendations

1. DIAGNOSIS

A thyrotoxicosis proforma is available for use on TRAK including the main aspects of assessment. Examples of TRAK screenshots are provided in Appendix 1.

History

History taking should include:

- Ascertainment of symptoms of thyrotoxicosis, dysthyroid eye disease and goitre
- History of anterior neck pain or recent (within last 6 months) pregnancy (features suggestive of possible thyroiditis)
- Drug history seeking use of specific medications including levothyroxine, amiodarone (N.B. separate amiodarone protocol), iodine-containing contrast, lithium and interferon
- Family history of thyroid disease
- Social history, focusing on smoking status, occupation, presence of children at home and plans for future pregnancy (as appropriate).

Examination

Examination should include:

- Weight/height
- Assessment of thyroid status, including pulse rate/rhythm and CV exam
- Thyroid examination
- Assessment for signs of dysthyroid eye disease – if signs of Graves eye disease present, clinical activity score should be documented
- Assessment of other signs specific to Graves – thyroid acropachy, pretibial myxoedema

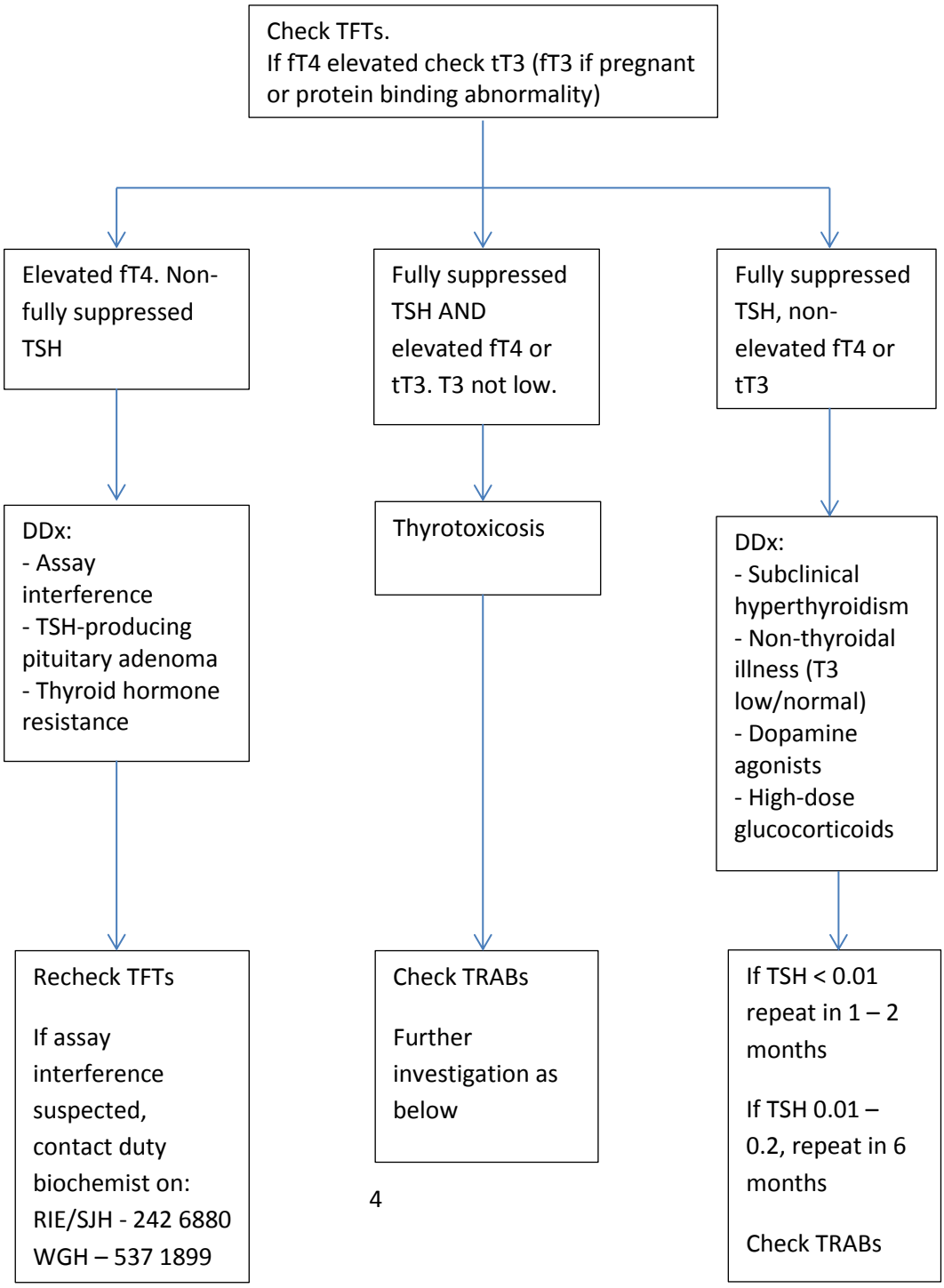
Initial investigation

Thyroid function tests (TFTs) are the first line investigation. Normal values (Table 1) and a flow diagram outlining their interpretation (Figure 1) is shown below.

Table 1. Normal values of thyroid function tests

Thyroid function test	**Normal range (non-pregnant)**	**Pregnancy normal ranges**		
		1st trimester	**2nd trimester**	**3rd trimester**
TSH (mU/l)	0.2 – 4.5	< 0.01 – 3.4	1.3 – 3.3	1.2 – 3.5
Free T4 (pmol/l)	9 – 21	10 – 18	9 – 16	8 - 14
Total T3 (pmol/l)	0.9 – 2.4	N/A	N/A	N/A
Free T3 (pmol/l)	N/A	3.4 – 6.6	3.2 – 6.2	3.2 – 5.6

Figure 1. Interpretation of TFTs



Initial biochemistry

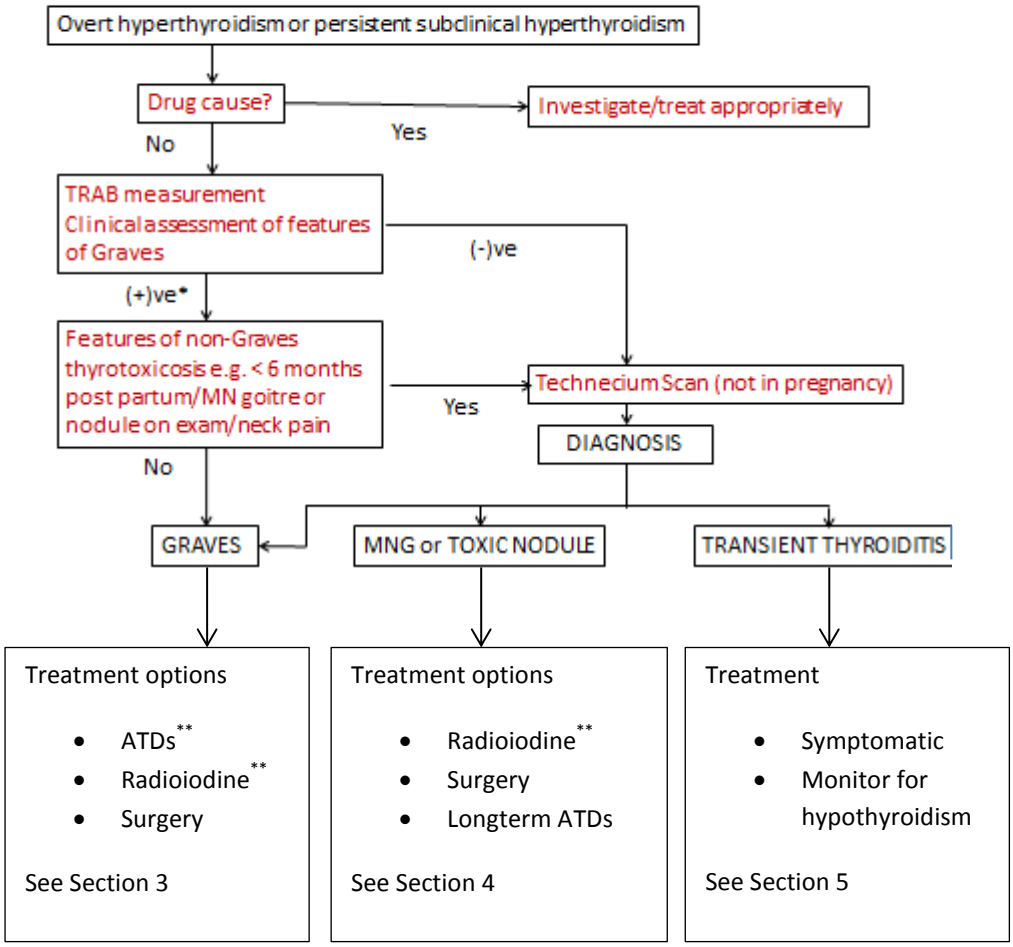
- TSH and T4 will have been checked and the biochemists automatically add tT3 (fT3 if pregnant) and TRABs if TSH suppressed at < 0.01 mu/l and there are no previous results to suggest a diagnosis of thyrotoxicosis.
- If the clinical picture and biochemical tests are felt to be conclusive then treatment after one set of TFTs is reasonable (e.g. in the case of a clinically and biochemically toxic patient with positive TRABs).
- The patterns of tests can be broadly grouped into three categories as above
    - Overt primary hyperthyroidism
    - High T4 with non-fully-suppressed TSH. TFTs should be re-checked and, if assay interference suspected, duty biochemist contacted.
    - Low TSH with normal T4/T3. If TSH < 0.01, repeat in 1-2 months. If TSH 0.01-0.2 repeat in 3-6 months.
- It is recognised that non-thyroidal illness can produce almost any pattern of TFTs, but T3 would be expected to be low or low-normal.

Further investigation of overt and persistent subclinical thyrotoxicosis

An algorithm for further investigation is shown in Figure 2.

Figure 2

Investigation of hyperthyroidism



*Values of TRAB < 1.6 mU/l should be regarded as equivocal and should be interpreted in light of the clinical features.

** Usual first line options for treatment

2. TREATMENT – GENERAL POINTS

In most circumstances specific treatment will be withheld until diagnosis is achieved

Beta-blockers (propranolol 40 mg tds) should be considered for symptom relief and control of tachycardia in the interim period. Calcium channel blockers can be used where beta-blockers are contra-indicated.

3. TREATMENT OF GRAVES' DISEASE

Decision regarding which of the three treatment modalities (antithyroid drugs (ATDs), radioiodine, surgery) is used as first line should be tailored to the patient (see *Background to Recommendations 7.1*). The patient should be informed of risks and benefits of the potential options.

Antithyroid drugs in Graves' disease

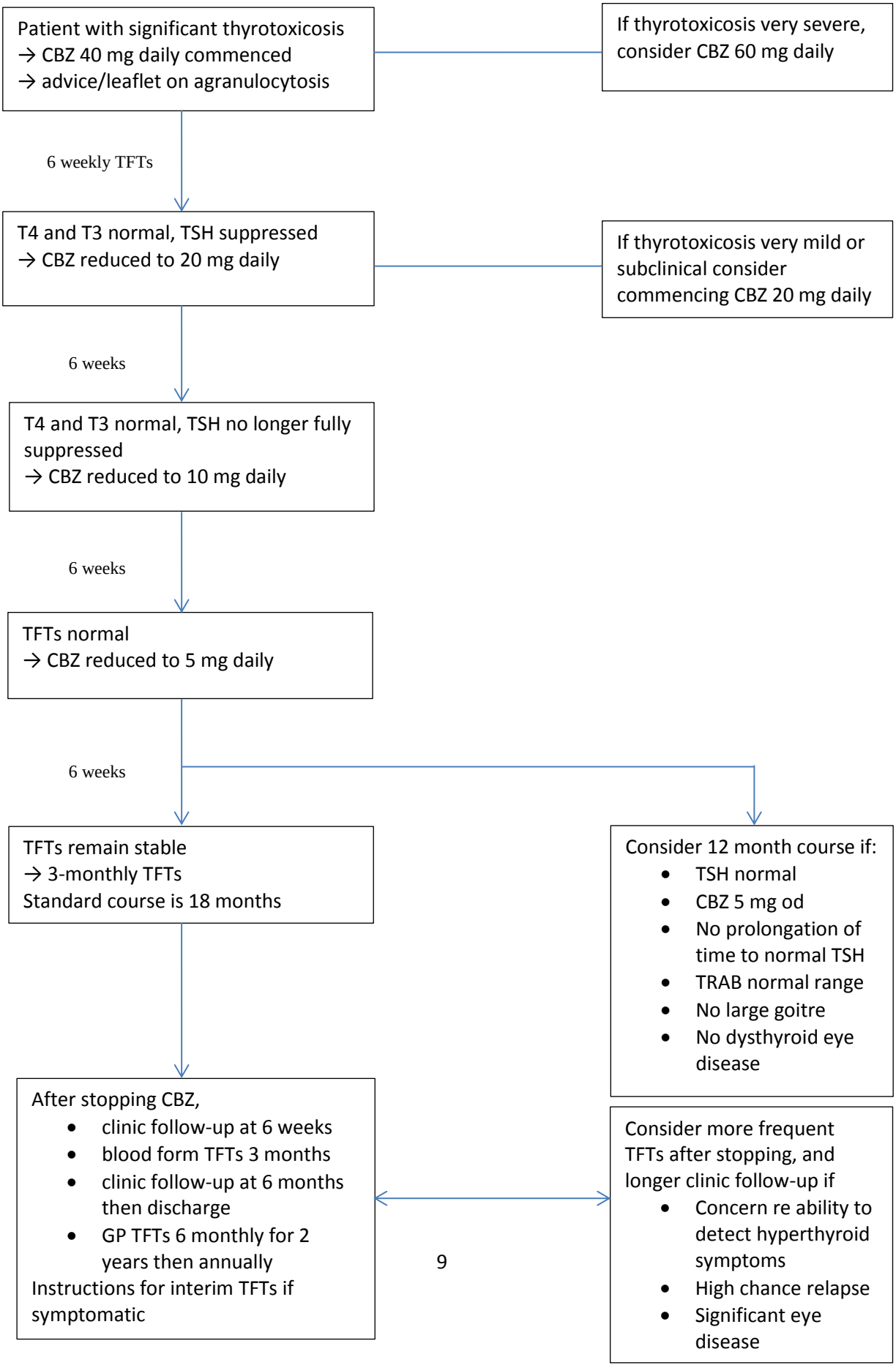
- Carbimazole (CBZ) is advantageous over propylthiouracil (PTU)
    - Once daily dosing
    - Risk of hepatotoxicity with PTU
- On commencing ATD treatment, patients should be warned of risk of relapse after treatment course, risk of agranulocytosis and action to be taken in the event of suggestive symptoms and, in the case of PTU, hepatotoxicity.
- A full blood count should be checked if a patient on ATD treatment develops sore throat, fever or mouth ulcers as these may be indicative of neutropenic sepsis secondary to agranulocytosis. If the neutrophil count is normal, ATD treatment can be continued. If there is clearly agranulocytosis then ATD treatment should be stopped and both carbimazole and PTU will thereafter be contraindicated. There is little evidence as to the appropriate course in the context of a slightly reduced neutrophil count, but it may be appropriate in such patients to continue ATD treatment and monitor patient symptoms and full blood count.
- Carbimazole should be started at a dose of 40 mg daily unless the biochemical picture suggests that another dose is more appropriate – for example, 20 mg daily may be used in mild thyrotoxicosis, up to 60 mg daily in very severe thyrotoxicosis (see *Background Recommendations 7.2*)
- TFTs should be checked 6-weekly initially as standard. Timing for an individual patient may be influenced by the severity of their thyrotoxicosis and initial carbimazole dose (e.g. may consider 4 weekly check if thyrotoxicosis very severe).

- Maintenance dose of carbimazole is typically 5-10 mg. TFTs should be checked 3-6 monthly on maintenance dose once thyroid function is demonstrated (ideally over at least 3 months) to be stable.
- 12-18 month course of ATD initially (see *Background to Recommendations 7.3*)
    - Consider stopping at 12 months if all of the following apply:
        - Normal TSH
        - Carbimazole dose is 5 mg daily or less
        - TRABs within normal reference range
        - No large goitre, no active dysthyroid eye disease
        - Time to TSH normalisation not prolonged
    - Otherwise continue until 18 months
        - Check TRABs at end of course – consider continuing ATD if TRAB remains positive (particularly if > 10 units/l) OR have a plan in place for definitive treatment when relapses.
        - Informed discussion regarding risks of stopping with patient, particularly if TRABs positive (>1.6). Local audit data, as presented in *Background to Recommendations 7.3*, may be used in estimating this risk.
- Follow-up TFTs at the end of a course of ATD treatment should routinely be done as part of clinic follow up at 6 weeks then 6 months. In addition patients should be given a "blood form in hand" for repeat TFTs at 3 months. Patients should be discharged to GP follow-up at 6 months after the end of treatment, although longer hospital-based follow-up may be considered for individual patients, e.g. those with significant eye disease or at very high chance of relapse. GPs should be advised to perform initially 6-monthly TFTs after discharge until two years, then annual TFTs.
- At the time of discharge, patients will be given a leaflet reminding them of the symptoms of hyperthyroidism, need for earlier TFTs if experienced and standard interval between TFTs

Block and replace regimen should be considered in poor attenders, student travellers, those non-tolerant of hypothyroidism, those with eye disease and those with significant fluctuation of TFTs on carbimazole alone (see *Background to Recommendations 7.2*). Carbimazole started at 40mg daily and levothyroxine 100 µg added once T4 in normal range. Contraindicated in pregnancy.

A "standard" patient journey through carbimazole treatment is summarised in Figure 3. It is recognised that there may be departures from this in the case of individual patients.

Figure 3. A standard patient journey for a course of antithyroid drug therapy for first presentation of Graves' Disease.



2nd line treatment for Graves' Disease after relapse following ATD treatment

If a patient becomes hyperthyroid after completing a course of ATDs, consideration should be given to definitive therapy in the form of radioiodine therapy or surgery. An alternative is longterm ATD treatment (see *Background to Recommendations 7.6*).

Radioiodine treatment in Graves' disease

- Consider as 1st, 2nd or 3rd line treatment.
- An 80% cure rate of Graves' with the first dose of radioiodine is expected, with a virtually 100% cure rate in all those given single or multiple doses
- Should be particularly considered as 1st line if high risk of recurrence after ATD therapy, older or cardiac failure/AF.
- Contraindicated if pregnant or planning pregnancy within 6 months or problems with vomiting. Discuss with medical physics if urinary incontinence is an issue.
- Graves' ophthalmopathy is a relative contraindication – consider co-administration of glucocorticoids (see Thyroid Eye protocol)
- Patient should be warned of the high risk of hypothyroidism, possible increased risk of new/worsening eye disease, restrictions re. pregnancy and contact with children/pregnant people
- Consider using non-selective β-blockers in the peri-radioiodine period, especially if at high risk of complications from hyperthyroidism
- Anti-thyroid drugs in the peri-radioiodine period (see *Background to Recommendations 7.5*)
    - Consider using if high risk for complications of worsening hyperthyroidism (elderly, cardiac co-morbidity, fT4 > 2x ULN)
    - Consider avoiding if not high risk due to increased risk of treatment failure
    - It was agreed that the possibility of using radioiodine as "first line" treatment for Graves' disease should NOT deter registrars from giving phone advice to general practitioners to commence ATDs prior to first clinic attendance (waiting times are currently a few weeks for such patients and the symptomatic benefit of improving thyrotoxicosis over this time were felt to outweigh risks of treatment failure)
    - If ATDs are used then they should be discontinued 5 days before radioiodine treatment
    - The decision whether to recommence ATDs post-radioiodine will be individualised to the patient and may be particularly considered if the risk of cardiac complications is high. If ATDs are restarted this should be 3 days post-radioiodine. These patients should be warned of the risks of hypothyroidism, seek earlier TFTs if they develop

symptoms and in this scenario ATD treatment should be discontinued as a first line measure.

- At the time of radioiodine consent a 4-week post-radioiodine review appointment, based on best guess of likely radioiodine administration date, will be made. Scrutiny of the radioiodine administration record, sent from medical physics, will allow accurate determination of the date of radioiodine administration and clarification of when the first (4 week) clinic appointment is due.
- Follow-up post radioiodine (see *Background to Recommendations 7.4*)
    - TFTs at 4 weeks as standard.
    - Patient should be warned of the symptoms of hypothyroidism and told to get earlier TFTs if these develop
    - If hypothyroid (T4 < 9 pmol/l, irrespective of TSH), commence levothyroxine 100 μg daily
    - If TSH detectable and T4 within normal range, TFTs may need to be done more frequently and consideration may be given to commencing levothyroxine **before** T4 drops below the lower limit of normal. This will be a decision made at consultant level and is likely to depend on the absolute T4 level and trajectory of fall.
    - If remains hyperthyroid, repeat TFTs every 4 weeks (form in hand for 8 week test, clinic appointment at 12 weeks with prior TFTs)

Surgery for Graves' disease

- Surgery may be the preferred treatment for Graves' disease in a minority of cases: patient choice; large goitre with compressive symptoms; poorly controlled thyrotoxicosis in pregnancy; severe ophthalmopathy; significant side effects with ATDs and unwilling to have radioiodine
- If thyroid for surgery for Graves' disease is warranted, then near-total thyroidectomy is the procedure of choice
- Permanent hypothyroidism is expected. Other side-effects occur in under 1% of cases and include hypoparathyroidism and recurrent laryngeal nerve palsy.
- Preparation for surgery:
    - Beta-blockade (propranolol 40 mg tds) assuming no contraindication
    - Potassium iodide 60 mg tds for 5-10 days prior to surgery
    - ATD therapy to render patient euthyroid prior to surgery. If ATD treatment is inappropriate (significant side-effects) then pre-operative preparation with beta-blockade and potassium iodide alone should be undertaken.

- If surgery is contemplated in a patient whose compliance with these medications is likely to be suboptimal, consideration should be given to supervised medication in the period leading up to surgery. The mechanism by which this is achieved will be decided on an individual basis, but consideration may be given to the use of the day case unit for this purpose in consultation with the thyroid surgical team.

4. TREATMENT OF MULTINODULAR GOITRE (MNG)/ TOXIC NODULE

The treatment options for multinodular goitre and solitary toxic nodule are the same as for Graves' disease, but there is an emphasis on definitive treatment as first line in view of the fact that ATD treatment will not be curative.

Radioiodine treatment for toxic MNG/solitary toxic nodule

- 1st line treatment
- Contraindicated if pregnant or planning pregnancy within 6 months or problems with vomiting. Discuss with medical physics if urinary incontinence is an issue.
- Ultrasound or CT imaging may be considered before giving radioiodine if a multinodular goitre is large and there is concern regarding shortness of breath or high uptake around the tracheal ring on technecium scanning (due to risk, albeit very small, of tracheal compression with radioiodine).
- Rate of hypothyroidism is lower than in Graves' disease, but ongoing risk over time so ongoing monitoring is required. Rate of hypothyroidism is quoted as 3% at one year and 64% at 24 years for toxic MNG and, in a different observational study of both overt and subclinical hypothyroidism, 7.6% at one year and 60% at 20 years for solitary toxic nodule.
- It is suggested that radioiodine treatment is avoided if TSH is normal or high to prevent uptake by normal thyroid tissue (there are therefore implications for pre-treatment of patients with ATDs).
- Beta-blockers ± ATD treatment should be considered pre-radioiodine in patients that are at high risk for thyrotoxic complications – e.g. elderly, known cardiac disease, T4 > 2x ULN
- TFTs should be monitored at 6 weeks, 3 months, 6 months and 1 year post treatment, then patient discharged to GP for annual TFTs

ATDs for MNG/solitary toxic nodule

- Can be considered if patient unwilling or unable to have radioiodine therapy
- Longterm treatment would be the aim, not a "course" as thyrotoxicosis will inevitably recur after stopping treatment
- Starting dose will depend on the severity of thyrotoxicosis, and dose titrated on the basis of TFTs
- Risks of treatment similar to Graves' disease

Surgery for MNG/solitary toxic nodule

- Near total thyroidectomy would be procedure of choice in MNG; hypothyroidism expected
- Lobectomy or isthmusectomy would be procedure of choice in solitary toxic nodule; low risk of hypothyroidism (around 2%)
- Risk of hypoparathyroidism < 2% following surgery for MNG, minimal following surgery for toxic nodule. Small risks of recurrent laryngeal nerve injury.
- Patients should be rendered euthyroid prior to surgery with or without beta-blockade. Potassium iodide is **not** recommended.
- If there is recurrence of hyperthyroidism following surgery then radioiodine should be first line treatment due to increased risks of re-operation.

5. TREATMENT OF THYROIDITIS

Subacute/viral thyroiditis

- Presenting features include systemic symptoms (fever, malaise), painful, tender thyroid gland in addition to symptoms of thyrotoxicosis. ESR is high and activity on technetium scan low. In some patients, however, the inflammatory phase is much less pronounced.
- Treatment of mildly symptomatic subacute thyroiditis is with NSAIDs and beta-blockers
- Patients with moderate-to-severe subacute thyroiditis or those who fail to settle with the above treatment should be treated with glucocorticoids (prednisolone 40 mg daily for 1-2 weeks then taper over 2-4 weeks or longer depending on the response).
- TFTs should be performed at 6 weeks, 3months, 6 months and 12 months.
- If symptomatic hypothyroidism occurs then levothyroxine 100 microgams daily should be commenced. At 6 months the dose should be halved and TFTs repeated 6 weeks later to determine if ongoing treatment is required. If patient remains hypothyroid, consideration should be given to repeating this manoeuvre at 12 months.
- If patient is euthyroid at 12 months, anti-TPO antibodies should be checked. If anti-TPO antibodies are positive then the patient should have lifelong annual TFTs. If negative, consider 5-10 years of annual TFTs then stop if euthyroid .

Silent thyroiditis

- Painless thyroiditis often associated with autoimmunity (positive anti-TPO antibodies); can be associated with certain drugs e.g. lithium, interferon-α, interleukin-2
- Treat with beta-blockers if symptomatic thyrotoxicosis
- Monitor and treat for hypothyroidism as for subacute thyroiditis

6. AREAS OUTWITH THE REMIT OF THESE GUIDELINES

The following areas are not dealt with in the current guideline:

- Thyrotoxicosis in pregnancy and post-partum period
- Thyroid emergencies (including thyroid storm, “emergency” (thyroid) surgery; protocol in progress)
- Amiodarone-induced thyroid disease (see separate protocol)
- Thyroid eye disease (see separate protocol)

7. BACKGROUND TO RECOMMENDATIONS

A number of national and international guidelines have been examined in the drawing up of the above recommendations. In particular the guidelines of the Royal College of Physicians (Radioiodine in the Management of Benign Thyroid Disease), Association of Clinical Biochemistry/British Thyroid Association (BTA; UK Guidelines for the use of thyroid function tests), American Thyroid Association (ATA) and American Association of Clinical Endocrinologists (AACE)[1] have been utilised. Many of the recommendations are accepted practice, but the evidence that has informed decision making on some of the more controversial areas is summarised below.

7.1 Initial therapy in the treatment of Graves' Disease

The recommendation that patients be offered the choice of ATD, radioiodine and surgery as initial treatment in Graves' Disease is in line with ATA and AACE Guidelines. In contrast the BTA Guidelines recommend initial ATD treatment in all but those with mild thyrotoxicosis who are going on to have prompt definitive treatment with radioiodine.

In a study of 179 adults with Graves' Disease, 60 adults aged 20-34 were randomised to 18 month ATD or subtotal thyroidectomy, and a further 119 adults aged 35-55 years were randomised to ATD, subtotal thyroidectomy or radioiodine treatment[2]. The risk of relapse was highest in the medical treatment group (42% in the younger adults, 34% in the older adults over at least a 48 month period), compared with 21% in the radioiodine group, 3% in the younger adult surgery group and 8% in the older adult surgery group. There was no treatment-related difference in sick leave and 90% of participants in each group were happy with the treatment received.

The current guideline recommends that the three treatment options be discussed with the patient and choice tailored to them.

7.2 Initial dose of carbimazole in the treatment of Graves' Disease; titration vs block and replace regimen

In a study of 63 patients with hyperthyroidism (TRABs positive in 86%) and tT4 > 200 nmol/l (normal range 60 – 160), participants were randomised to 40mg vs 20mg carbimazole[3]. At 6 weeks, carbimazole dose was halved if tT4 had fallen by >50% and reduced to 10 mg daily if euthyroid. At 4

weeks T4 and T3 were significantly lower in the 40 mg group (fT4 19 pmol/l in 40mg group, 35 pmol/l in 20 mg group; tT3 2.6 nmol/l in 40 mg group, 4.3 nmol/l in 20 mg group). A higher proportion remained hyperthyroid in the 20 mg group (16 out of 34 participants) compared to the 40 mg group (4 out of 29 participants) at 4 weeks. Similarly, mean fT4 remained elevated at 10 weeks in the 20 mg group but not in the 40 mg group. Conversely, there was a higher rate of hypothyroidism in the 40 mg group (8 of 29 at 4 weeks in the 40mg group, vs 1 of 34 in the 20 mg group).

In another study, 509 patients with Graves' disease were randomised to methimazole 40 mg vs methimazole 10 mg (12 month course in both groups)[4]. 26% of 40 mg group had an adverse reaction compared with 15.5% of the 10 mg group ($p < 0.01$). There was no difference in relapse rate (37.2% in the 40 mg group, 35.9% in the 10 mg group).

A Cochrane review found no gain in terms of treatment outcomes when a block and replace regimen was used, compared to a titration regimen[5]. There was an increased incidence of side-effects in the block and replace group including a higher incidence of rash (9.85, vs 5.8% in the titration group).

The current guideline recommends that carbimazole 40 mg is the standard starting dose, with the option of using a lower dose if hyperthyroidism is mild, in order to reduce risk of hypothyroidism. It does not routinely recommend a block and replace regimen, but this can be considered in certain patient groups (poor attenders, eye disease, those non-tolerant of hypothyroidism).

7.3 Duration of ATD treatment in the initial treatment of Graves' Disease

The ATA and AACE Guidelines suggest 12-18 months treatment with ATD during first line treatment for Graves' Disease.

In a Cochrane review, four studies that considered duration of ATD therapy were identified involving 445 participants in total[5]:

- Allannic et al (1990)[6]: 6 vs 18 months. Significantly fewer relapses in the 12 month group (37% vs 58% in the 6 month group, odds ratio 0.42 (0.18 – 0.96))

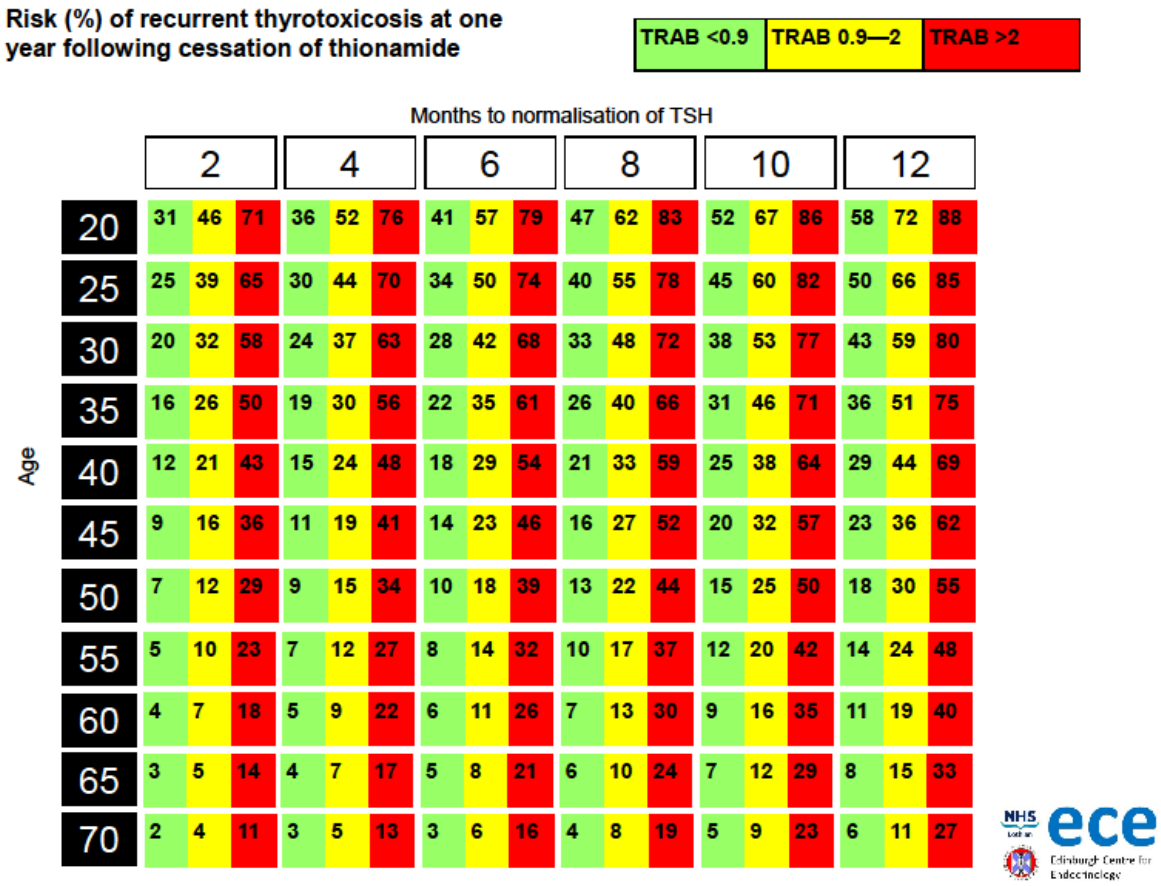
- Weetman et al (1994)[7]: 6 vs 12 months (using block and replace regimen). No significant differences between the groups (relapse rate 35% for 12 month group, 41% for 6 month group).
- Garcia-Mayor (1992)[8]: 12 vs 24 months. No significant difference in relapse rate. At two years post-treatment, relapse had occurred in 46.4% of the 12 month group and 54.1% of 24 month group. At 5 years relapse had occurred in 85.7% and 83.3% respectively.
- Maugendre et al (1999)[9]: 18 vs 42 months. No significant difference in relapse rate two years after discontinuation of treatment (36% in the 18 month group, 29% in the 42 month group).

The Cochrane review combined data from these latter two papers to show no statistically significant difference in relapse rate for > 18 month ATD therapy (44%) and < 18 month therapy (50%).

Audit data from Edinburgh[10], where the standard time on ATD therapy was 18 months, showed relapse rates of 27% at one year post-treatment cessation and 46.6% at two years post-cessation. Predictors of relapse on univariate analysis were initial TRAB level, anti-TPO antibody level, final (pre-ATD cessation) TRAB (< 0.9 in remission group; 1.3 in relapse group), time to normal TSH (4 months in remission group; 6 months in relapse group) and age (44.5 years in remission group, 39.5 years in relapse group). There was a two-fold risk of relapse if TRAB > 2 vs < 2). Independent predictors of relapse on multivariate analysis were age, final TRAB and time to TSH normalisation. These data have been combined into a table (Figure 4) which shows rate of relapse in groups defined on the basis of these independent risk factors.

Figure 4

Rate of relapse of Graves' disease dependent on age, time to TSH normalisation and TRAB at time of ATD cessation.



In an earlier study of 93 patients with Graves' disease, the utility of TRAB measurements in predicting relapse was examined[11]. Unfortunately only the abstract has been obtainable and it is not clear what the treatment was or for how long. In this group, 33 patients went into remission and did not relapse within median 22 months of follow-up, while 60 patients did not go into remission or developed relapse over the following 24 months. A TRAB level of > 10 mU/l had a positive predictive value of relapse of 96.4%. In contrast, a TRAB level of < 10 mU/l had no impact on the prediction of remission.

The current guideline recommends routinely a 12-18 month course of carbimazole depending on the presence or absence of good prognostic indicators, with the option of prolonging the course if TRABs remain positive at 18 months.

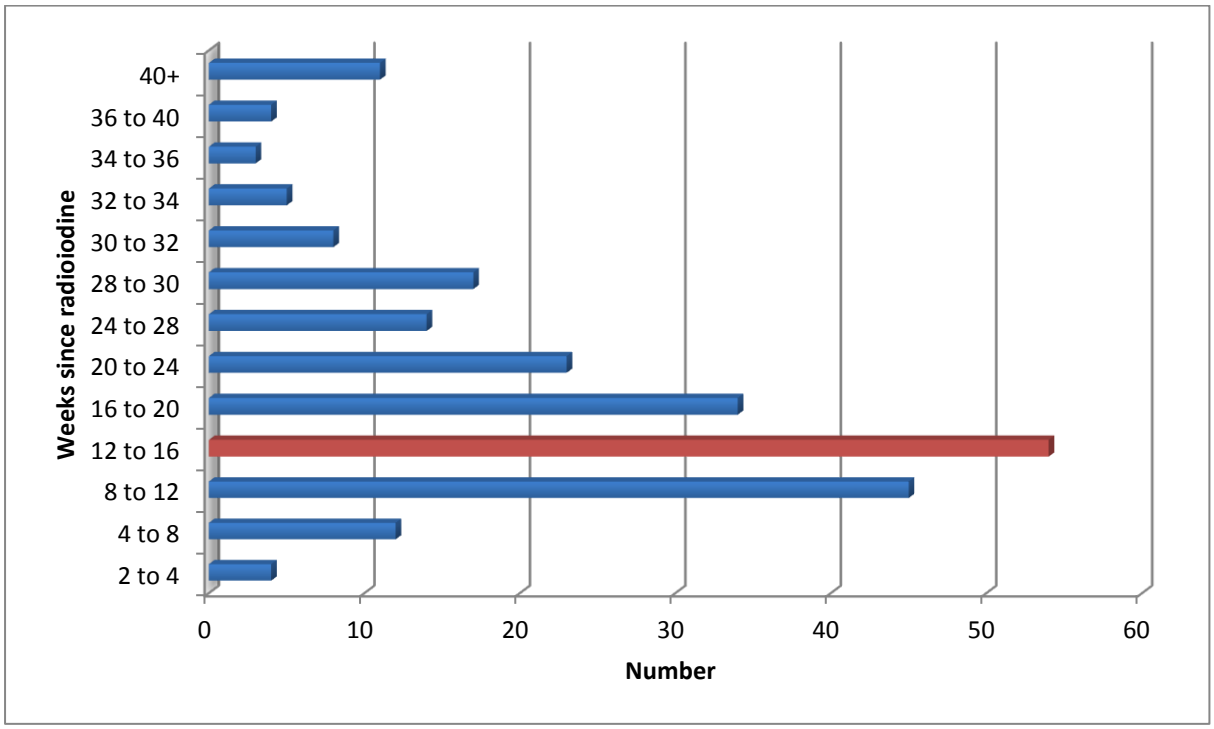
7.4 Monitoring of TFTs and treatment of hypothyroidism post-radioiodine for Graves' disease

The ATA recommends TFTs within the first 8 weeks after radioiodine treatment and thereafter 4-6 weekly if not hypothyroid. The Royal College of Physicians Guidelines recommend TFTs at 6 and 12 weeks after radioiodine and thereafter 3 monthly until 1 year.

Audit data from Edinburgh[10] showed that the first patients became hypothyroid by the end of the 4th week post-radioiodine. The peak incidence of hypothyroidism was at 12-16 weeks, as shown below in Figure 5.

Figure 5.

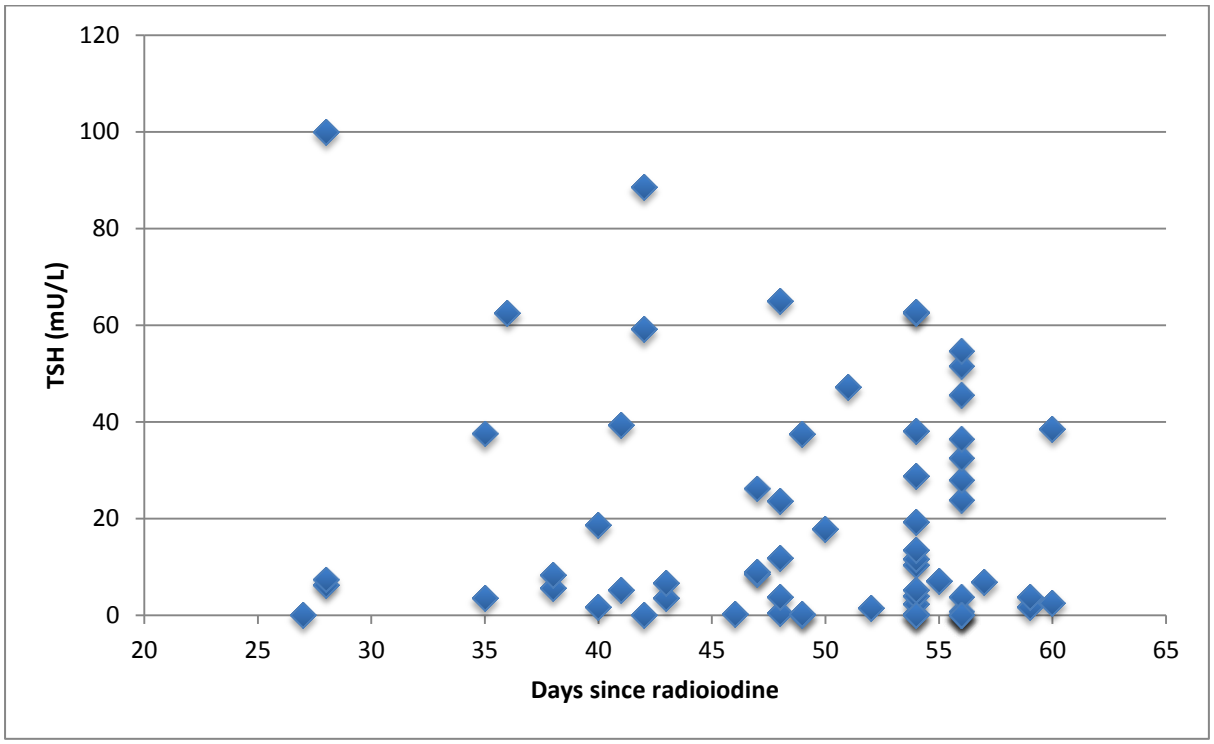
Incidence of hypothyroidism post-radioiodine



A total of 28.2% (66 of 234) of all post-radioiodine was diagnosed in the first 60 days following radioiodine, and 23 of 66 in this category had TSH levels > 20 mU/l at diagnosis of hypothyroidism, as is seen in Figure 6.

Figure 6

TSH levels at time of diagnosis of hypothyroidism post-radioiodine



In the same cohort of Edinburgh patients, TFTs at 4-8 weeks were broadly predictive of outcome. In particular, a detectable TSH or T4 within the normal range was predictive of hypothyroidism. No patient with a detectable TSH or fT4 < 15 had autonomous thyroid function at 1 year post-radioiodine. It was therefore conjectured that pre-emptive commencement of levothyroxine was unlikely to result in thyrotoxicosis if these threshholds were implemented.

There is a randomised placebo-controlled study of early levothyroxine treatment post-radioiodine underway, based at the Mayo clinic, which has an estimated completion date of July 2015 (www.clinicaltrials.gov).

The current guideline recommends checking TFTs at 4, 8 and 12 weeks post-radioiodine, and commencing levothyroxine 100 μg daily if hypothyroid at any time. There may be consideration of pre-emptive levothyroxine if T4 levels are in the normal range and falling, on the basis of the Edinburgh audit data. The use of pre-emptive levothyroxine shall be further considered in future review of these guidelines as more evidence becomes available.

7.5 Use of ATDs pre- and /or post-treatment with radioiodine in Graves' Disease

In a systematic review and meta-analysis of 14 trials, the risk of radioiodine treatment failure with any adjunctive ATD treatment was 1.28 (1.07 – 1.52, p = 0.006)[12]. There was some non-randomised data to suggest higher rates of treatment failure with PTU than carbimazole. The risk of new AF was 0.2% with adjunctive ATD treatment, 0.5% without adjunctive ATD treatment.

Local audit data[10] revealed the following rates of treatment failure:

- 18.9% of those receiving ATDs before RI
- 27.8% of those receiving ATDs after RI
- 23.3% of those receiving ATDs before and after RI
- 6.3% of those not on ATDs

One study of 42 patients randomised to pre-treatment vs no pre-treatment with methimazole, found an overall rate of late exacerbation of thyrotoxicosis after radioiodine therapy of 11.9% (5 patients)[13]. Of these, 3 were in the pre-treatment arm and 2 in the no pre-treatment arm. Pre-treatment did not therefore protect against a continual rise in T4 levels, but the rise and peak T4 levels were considerably higher in the 2 participants in the no pre-treatment group. 90% (19 of 21) of non-pre-treated patients experienced a continuous decline in T4 levels after radioiodine.

The current guideline recommends pre-treatment with ATD in those at high risk of complications of worsening hyperthyroidism, but otherwise considering avoiding pre-treatment due to the higher risk of treatment failure.

7.6 Medium/longterm use of ATDs instead of definitive therapy in Graves' Disease

One study has examined the outcomes of patients given ATD treatment in the long term[14]. Patients with Graves' disease, who had relapsed after a course of methimazole, were randomised to longterm methimazole (maintenance dose by the third month was 2.4 – 10 mg daily; n = 51) or radioiodine treatment (dose calculated according to thyroid weight and radioiodine uptake; n = 41). Over 10 years in the ATD group there were minor adverse reactions but no serious complications; 5.9% of TSH measurements over this time were > 5.0; 7.6% were < 0.3. In the radioiodine group, over the same follow-up period, 25 participants became hypothyroid; 12.8% of TSH measurements in the whole group were > 5.0; 9.1% were < 0.3. There were no differences between groups in quality of life scores, bone mineral density or financial cost.

The current guideline considers the use of longterm ATD therapy if more definitive therapy is not possible or desired.

7.7 Monitoring TFTs following an episode of subacute or painless thyroiditis

There are few studies that have examined the incidence of late-onset hypothyroidism after an episode of thyroiditis. One study focused exclusively on patients with subacute thyroiditis within Olmsted County. In this cohort of over 90 patients, 9 patients (9.5%) developed permanent hypothyroidism of whom 4 patients were diagnosed before one year, and 5 patients were diagnosed after one year (range 2 – 24 years). In a separate study of 105 cases of "subacute" thyroiditis (which included patients with painful thyroiditis but also painless thyroiditis including postpartum thyroiditis), 11% had longterm hypothyroidism. It is not clear from the obtainable abstract how many of these were early vs late presentations of hypothyroidism. The only clinical predictor of longterm hypothyroidism in this cohort was the presence of anti-TPO antibodies in women with postpartum thyroiditis.

The ATA/AACE guidelines do not give guidance on duration of TFT testing after an episode of viral or painless thyroiditis.

The current guideline recommends anti-TPO antibodies in patients who are euthyroid off treatment at 6-12 months after the thyrotoxic phase. If anti-TPO antibodies are positive then annual TFTs are recommended; if negative then consideration of annual TFTs for 5-10 years is recommended.

Reference List

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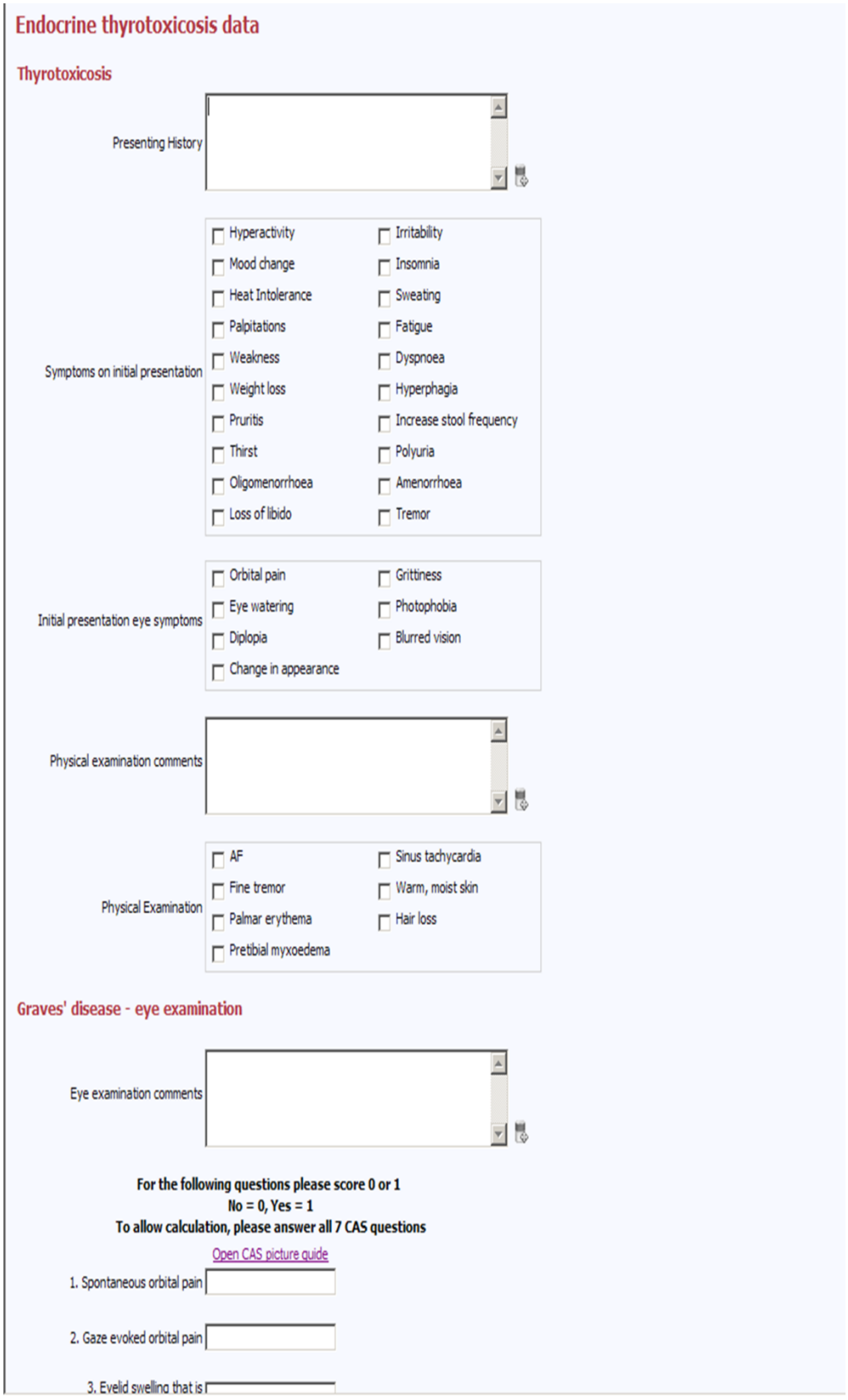
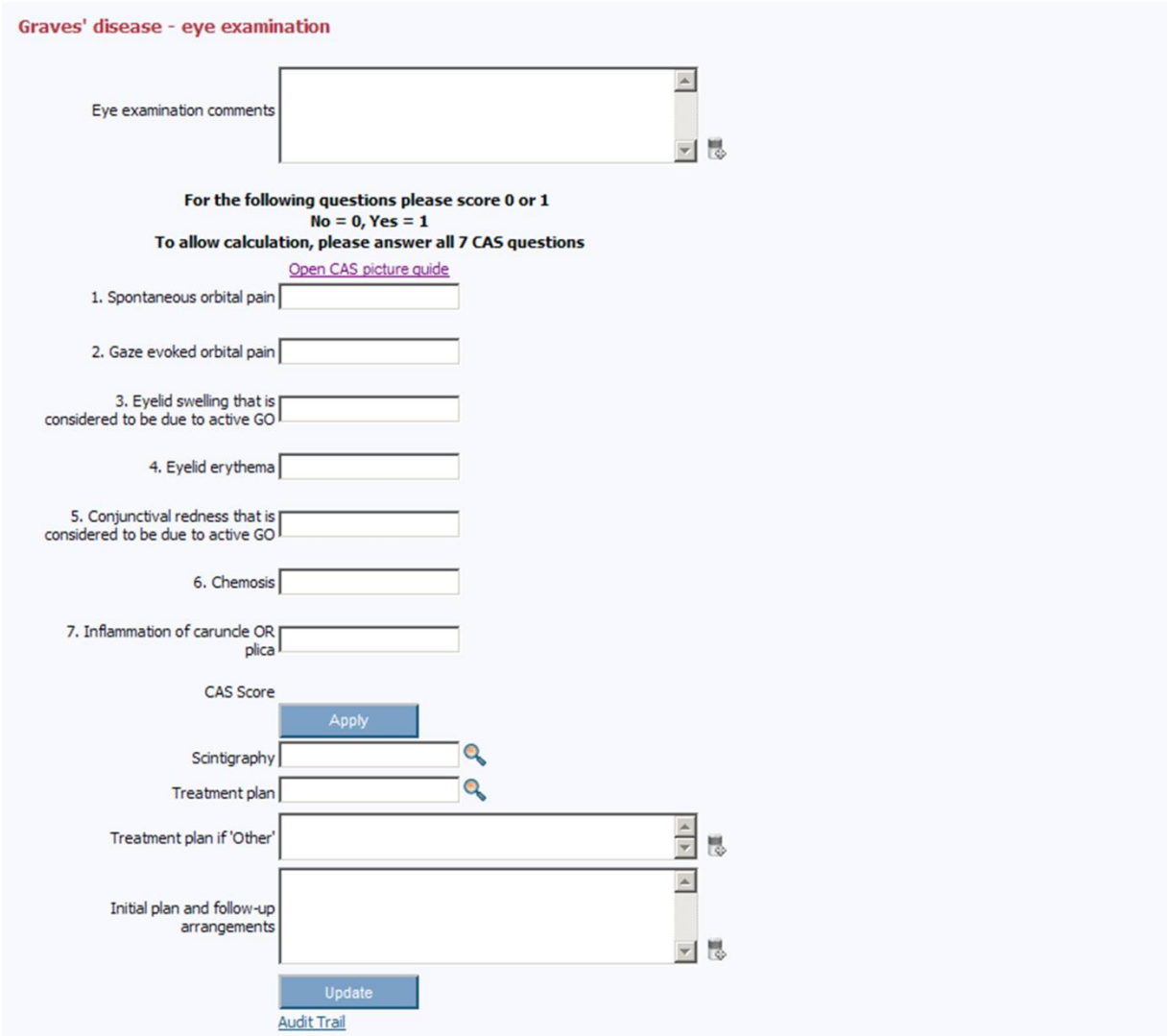
Appendix 1

TRAK screenshots for documenting initial thyroid assessment




Graves' disease - eye examination
Eye examination comments
For the following questions please score 0 or 1
No = 0, Yes = 1
To allow calculation, please answer all 7 CAS questions
Open CAS picture guide
1. Spontaneous orbital pain
2. Gaze evoked orbital pain
3. Eyelid swelling that is considered to be due to active GO
4. Eyelid erythema
5. Conjunctival redness that is considered to be due to active GO
6. Chemosis
7. Inflammation of caruncle OR plica
CAS Score
Apply
Scintigraphy
Treatment plan
Treatment plan if 'Other'
Initial plan and follow-up arrangements
Update
Audit Trail

Appendix 2

Advice sheets for patients.

Advice for patients

Finishing a course of antithyroid medications (carbimazole or propylthiouracil) treatment for Graves' Disease

You have been given this leaflet because you are coming to the end of a course of carbimazole or propylthiouracil (PTU) treatment for Graves' Disease. After a course of treatment for a first episode of Graves' Disease the thyroid blood tests stay normal in around 6 out of 10 people. However, in around 4 out of 10 people the thyroid gland becomes overactive again – it is not possible to know when this will happen or who it will happen to. We hope that by monitoring the thyroid blood tests it will be picked up early if the thyroid does become overactive again, and we will then discuss treatment with you.

After stopping the treatment you will usually be seen back in clinic 6 weeks later for a check-up, and if you are well at that time you will be seen again 6 months after that. **It is helpful if you have your thyroid blood tests done at your family doctor (GP) around one week before your hospital appointments so that the results can be discussed with you.** You will also be given a blood test form for you to have a blood test at the GP surgery 3 months after you stop your treatment. Sometimes your doctor may advise that you are seen more or less frequently. If your blood tests are normal then your family doctor (GP) might be asked to take over the monitoring of the thyroid blood tests.

Often the first sign that the thyroid gland is becoming overactive again is that you begin to notice symptoms. **If you notice any of the following symptoms persisting over several days then do not wait until the next blood tests are due – instead see your family doctor (GP) early for a thyroid blood test:**

- Weight loss
- Heart racing (palpitations)
- Feeling hot and sweaty when others are not
- Tremour or shakiness
- Periods becoming lighter or stopping (in women)
- Diarrhoea, loose stools or having to move your bowels more frequently than usual

Advice for patients

Monitoring the thyroid gland after radioiodine treatment for Graves' disease

You have been given this leaflet because you have decided to have radioiodine treatment for Graves' Disease. After your treatment the thyroid gland can become underactive. It is therefore important that we monitor your thyroid blood tests closely, so that any signs that the gland is becoming underactive can be picked up early and treatment (a replacement thyroid hormone called Levothyroxine) can be started.

We need to see you back in clinic around **4 weeks** after your radioiodine treatment. **It is helpful if you have thyroid blood tests done at your family doctor (GP) in the week before we see you so that we can discuss your results.** Sometimes levothyroxine treatment is started at that clinic visit, if there are signs that the thyroid gland is becoming underactive. If levothyroxine is not started then the thyroid blood tests will be monitored. The doctor at the hospital clinic will fill in the arrangements for checking your thyroid blood tests below:

1st blood test: e.g. To be seen at clinic 4 weeks after radioiodine treatment. Please have thyroid blood tests done at your family doctor (GP) in the week before you are seen.

2nd blood test: e.g. Please have blood tests done 8 weeks after treatment at your family doctor (GP) using the attached form. You will not be routinely seen in the hospital clinic after this test, but the results will come back to the hospital and they will contact you by 'phone if any change to treatment

3rd blood test: e.g. To be seen at the hospital clinic around 12 weeks after radioiodine treatment. Please have thyroid blood tests done at your family doctor (GP) in the week before you are seen.

Sometimes the first sign that the thyroid gland is becoming underactive is that you notice symptoms of this. **If you notice any of the following symptoms then do not wait until your next scheduled blood test, but instead see your family doctor (GP) for an early blood test – weight gain, tiredness, feeling the cold more than other people, constipation.**