A report on treatment options in Graves' disease

for

Universitätsklinikum Schleswig-Holstein/Campus Kiel

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28 October 2020

(Revised 11 November 2020)

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LIST OF ABBREVIATIONS

AE	adverse event
ATD	anti-thyroid drug
CI	confidence interval
CPG	clinical practice guideline
CRD	Centre for Reviews and Dissemination
DARE	Database of Abstracts of Reviews of Effects
GO	Graves' orbitopathy
GIN	Guidelines International Network
HRQoL	health-related quality of life
hrs	hours
HTA	Health technology assessment
KSR	Kleijnen Systematic Reviews
mths	months
N/A	not applicable
NHS	National Health Service
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Care Excellence (UK)
NR	not reported
RAI	radioiodine therapy
RCT	randomised controlled trial
SR	systematic review
TT	total thyroidectomy
TSH	thyroid-stimulating hormone
UK	United Kingdom
wks	weeks
yrs	years

1. PROJECT OBJECTIVES

A key aim of the research project “Making SDM a reality” is to inform patients as part of shared decision making (SDM).

Kleijnen Systematic Reviews (KSR) Ltd has prepared an evidence report with a synthesis of the evidence of the relevant treatment options for Graves’ disease.

2. METHODS

2.1 INCLUSION CRITERIA

The research question underpinning the literature searches was developed jointly with clinical departments at Universitätsklinikum Schleswig-Holstein/Campus Kiel. The question reflects the relevant characteristics of participants, interventions, comparators, outcomes, and study designs (PICOS), see Table 1. Systematic reviews (SR), health technology assessments (HTA) and clinical practice guidelines (CPG) evaluated herein aim to inform clinicians, patients, researchers, and health policy makers on published evidence relating to the aetiology, epidemiology, diagnosis and management of Graves' disease- the most common cause of hyperthyroidism. However, these sources of evidence also cover toxic nodular goiter, thyroid nodules and differentiated thyroid cancer.

Table 1: Inclusion and exclusion criteria

	Included	Excluded
Population	Adult patients with hyperthyroidism caused by Graves' disease, where medication is not effective any more or not well tolerated	Men who want to father a child; Pregnant women and breastfeeding mothers; Patients with other contraindications to either treatment, e.g. patient with active severe orbitopathy
Intervention	• Surgery, i.e. total thyroidectomy • Radioiodine therapy	• Bilateral subtotal thyroidectomy • Unilateral total and contralateral subtotal thyroidectomy • The Dunhill procedure
Comparator	Any (including unilateral or bilateral subtotal thyroidectomy or antithyroid drugs)	Nil
Outcomes	• Rate of resolution of hyperthyroidism • Recurrence of hyperthyroidism (relapse of Graves') • Worsening of Graves' ophthalmopathy • Time to resolution • Quality of life • Risks of acute thyroiditis, secondary malignancy, hypocalcemia and laryngeal nerve injury • Adverse effects i.e., anesthesia-related complications, bleeding, infections, and wound healing	Nil

	Included	Excluded
	problems	
Study design	Systematic reviews, health technology assessments and clinical practice guidelines	Narrative reviews; expert opinions; primary research; letters

2.2 FREQUENTLY ASKED QUESTIONS

The following frequently asked questions (FAQs) were identified:

1. What does the treatment involve?
   a. How is the radioactive iodine administered?
   b. Is the intervention radioactive and are there any associated precautions or contraindications?
   c. How does the treatment option choice might impact daily life?
   d. What is the length of hospital stay?
   e. How long does it take for a patient to return to work and usual activities?
2. Will I have to take lifelong thyroid replacement therapy?
3. Will my high thyroid state go away?
   a. How long it takes for hyperthyroidism to resolve?
   b. What is the success rate?
4. Will my high thyroid state come back?
   a. What is recurrence/relapse rate of hyperthyroidism after radioiodine therapy or thyroidectomy surgery?
5. Will I develop (or worsen) Graves' ophthalmopathy?
6. Will my quality of life change?
   a. How will the two treatment options affect my quality of life?
7. What are the risks?
   a. Will I develop acute thyroiditis and secondary malignancy following radioiodine therapy?
   b. What are the risks of hypocalcaemia or laryngeal nerve injury following surgical treatment?

2.3 LITERATURE SEARCHES

Literature searches were carried out to identify relevant systematic reviews (SRs) and evidence-based guidelines on the treatment options in Graves' disease.

The search strategies were developed specifically for each database and the keywords adapted according to the configuration of each database. Searches were not limited by date range for systematic reviews and guidelines. Searches were not limited by language or publication status. In addition, the team at Universitätsklinikum Schleswig-Holstein/Campus Kiel provided 4 additional references including two German CPGs,[1, 2] one American CPG,[3] and one European CPG.[4] One additional SR was identified via web-search. [5]

2.4 SEARCH SOURCES

Systematic reviews and guidelines

The following systematic review specific databases were searched from inception to present:

- Cochrane Database of Systematic Reviews (CDSR) (Wiley): up to 2020/08/Iss9
- Database of Abstracts of Reviews of Effects (DARE) (www.crd.york.ac.uk): up to 2015/03
- Health Technology Assessment (HTA) database (www.crd.york.ac.uk): up to 2018/03
- KSR Evidence (www.ksrevidence.com) (KSR): up to 2020/09/10
- Epistemonikos (www.epistemonikos.org): up to 2020/09/10

The following guidelines resources were searched from inception to present:

- Guidelines International Network (G-I-N) (www.g-i-n.net): up to 2020/09/10
- NHS Evidence (www.evidence.nhs.uk): up to 2020/09/10
- ECRI Guidelines Trust (https://guidelines.ecri.org/): up to 2020/09/10
- NICE (www.nice.org.uk): up to 2020/09/10

Full details of all search strategies are presented in Appendix 1.

2.5 HANDLING OF CITATIONS

Identified references from the bibliographic database searches were downloaded into EndNote bibliographic management software for further assessment and handling.

2.6 METHODS OF STUDY SELECTION AND DATA EXTRACTION

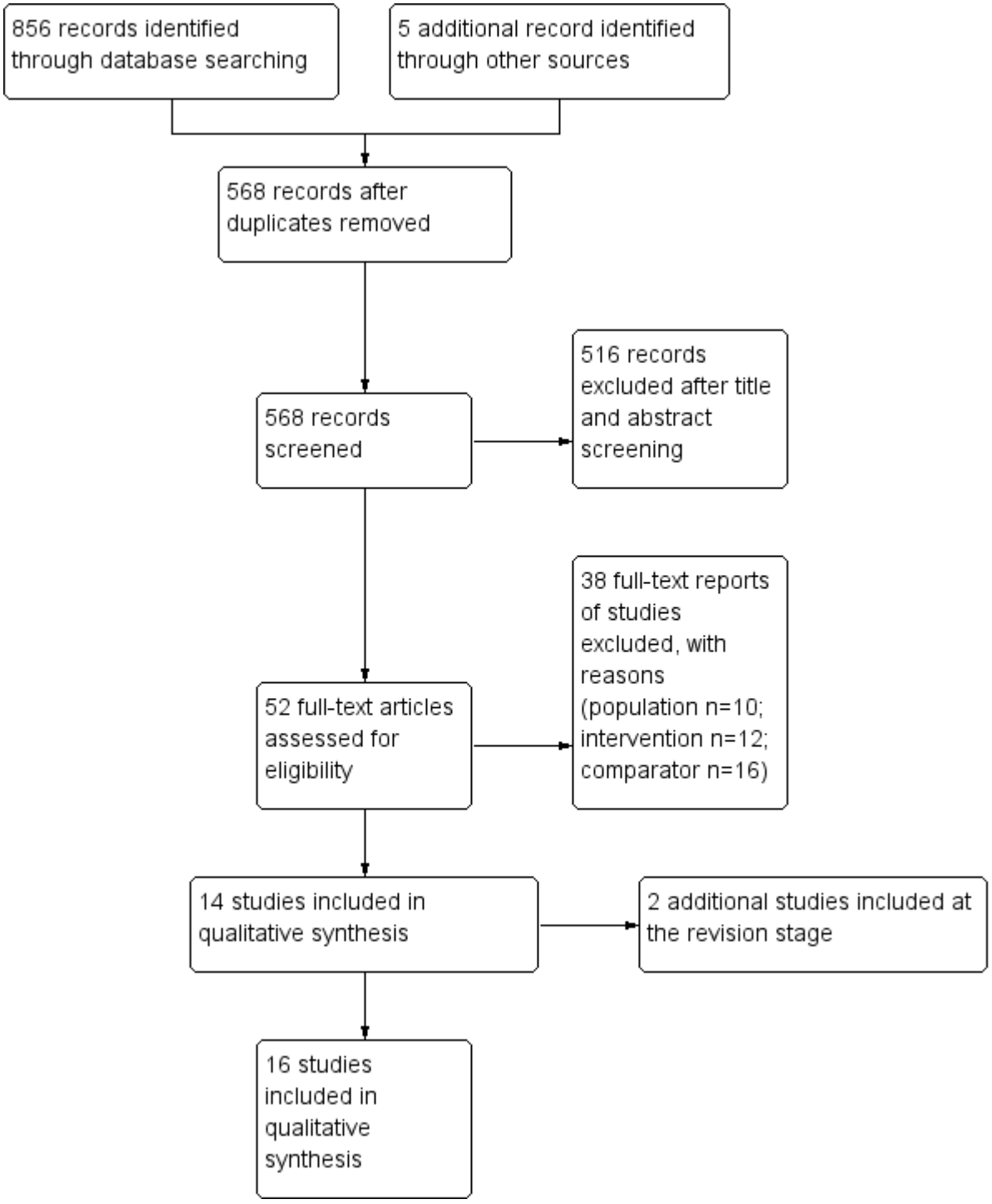
Two reviewers independently of each other screened titles and abstracts of all records identified by the searches. Any disagreements were settled through discussion. For potentially relevant SRs, Health Technology Assessments (HTAs) or Clinical Practice Guidelines (CPG), full-text versions were obtained, and screened against eligibility criteria by these same two reviewers. For each study, data were extracted by one reviewer and validated by another. Any disagreements were resolved through a consensus. When evaluating the quality of the evidence, sometimes we relied on ratings of the authors of secondary studies and sometimes we rated studies ourselves depending on availability of such gradings/judgments.

3. RESULTS

3.1 LITERATURE SEARCHES AND INCLUSION ASSESSMENT

Searches were conducted in September 2020 to identify all relevant SRs, HTAs, or CPGs. A total of 856 records were retrieved from the electronic literature searches. Five additional publications were identified from the targeted web search. After the removal of duplicate records 568 titles and abstracts were screened by two reviewers. After screening of 52 full-text papers, 38 records were selected for further assessment and 14 met the inclusion criteria.[4-17] Two additional CPGs were utilised at the revision stage.[2, 18, 19] A summary of the study selection process according to modified PRISMA reporting guidelines is reported in Figure 1.

Figure 1: Study selection process



3.2 Overview of included studies

Overall, 11 systematic reviews and five CPGs were eligible for inclusion.[2, 4-17] Table 2 summarises the sources of evidence used to answer the five FAQs. These systematic reviews and three clinical practice guidelines included both observational evidence, mainly from cohort and case control studies (range 9 to 62) and experimental, RCTs (range 1 to 4) and non-RCTs (range 2 to 19). Evidence from direct evidence comparing RAI and total thyroidectomy was limited, hence we also included indirect comparisons whereby RAI was

compared with antithyroid drugs or/and total thyroidectomy was compared with subtotal thyroidectomy to answer the respective FAQs. However, the target populations from these indirect comparisons are likely to differ from a population of patients that are eligible for definitive treatment with RAI or total thyroid resection.

Table 2: Evidence sources

Study/year	Evidence type	Intervention	FAQ1: What does the treatment involve?	FAQ2: Will I have to take lifelong thyroid replacement therapy?	FAQ3: Will my high thyroid state go away?	FAQ4: Will my high thyroid state come back?	FAQ5: Will I develop (or worsen) Graves' ophthalmopathy?	FAQ6: Will my quality of life change?	FAQ7: What are the risks?
Acharya 2008[6]	SR	RAI				✓	✓		
		thyroidectomy				✓			
American Thyroid Association[18, 19]	CPG	RAI		✓					
		thyroidectomy		✓					
Deutsche Gesellchaft für Allgemein- und Viszeralchirurgie[2]	CPG	thyroidectomy							✓
Fan 2019[7]	SR	thyroidectomy	✓						
Feroci 2014[8]	SR	thyroidectomy				✓	✓		✓
Genovese 2013[5]	SR	RAI			✓	✓			✓
		thyroidectomy			✓	✓			✓
Guo 2013[9]	SR	thyroidectomy				✓	✓		✓
Kahaly 2018[4]	CPG	RAI	✓						
		thyroidectomy	✓						
Li 2016[10]	SR	RAI				✓	✓		
Liu 2017[11]	SR	thyroidectomy							✓
Liu 2015[12]	SR	thyroidectomy			✓	✓	✓		✓
Ma 2016[13]	SR	RAI			✓	✓	✓	✓	✓
Maia 2013[14]	CPG	thyroidectomy							✓
NICE CG 145[15]	CPG	RAI			✓	✓			✓
		thyroidectomy			✓	✓	✓		✓

Study/year	Evidence type	Intervention	FAQ1: What does the treatment involve?	FAQ2: Will I have to take lifelong thyroid replacement therapy?	FAQ3: Will my high thyroid state go away?	FAQ4: Will my high thyroid state come back?	FAQ5: Will I develop (or worsen) Graves' ophthalmopathy?	FAQ6: Will my quality of life change?	FAQ7: What are the risks?
Sundaresh 2013[16]*	SR/NMA	RAI	✓			✓			
Wang 2016[17]	SR	RAI				✓	✓		

* = 4 out of 4 studies compared RAI to subtotal thyroidectomy and the type of surgery was not reported in 4 studies. CPG = clinical practice guideline; NMA = network meta-analysis; RAI = radioiodine therapy; SR = systematic review

3.3 FAQ 1: WHAT DOES THE TREATMENT INVOLVE?

This section covers the two treatment options of Graves' disease, i.e. radioiodine therapy and surgery (total thyroidectomy). These two options and a description of the condition are given in Table 3.

Table 3: Description of treatments for Graves' disease

Graves' disease
Graves' disease is an autoimmune thyroid condition (misguided response of the immune system against the thyroid gland) affecting children, adolescents and adults of both sexes.[7, 20] Graves' disease is the most common cause of hyperthyroidism i.e., overactivity of the thyroid gland;[21] and it is characterised by the infiltration of certain type of cells i.e., thyroid antigen-specific T cells into certain type of tissues i.e., thyroid-stimulating hormone receptor-expressing tissues.[4] The condition may affect multiple other organs including skin and eyes, i.e. Graves' orbitopathy (GO); symptoms of hyperthyroidism typically include tachycardia (rapid heartbeat), systolic hypertension, abnormally rapid breathing, warm and moist skin, hair and weight loss, diarrhoea, muscle weakness, sleeping disturbances, diffuse palpable goiter (abnormal enlargement of the thyroid gland) and altered mental status.[22] Diagnosis of the disease involves a thorough family history and physical examination including pulse rate, blood pressure, respiratory rate, body weight, thyroid size, tenderness, symmetry, and nodularity; and biochemical evaluation i.e., the thyroid-stimulating hormone (TSH) test.[20]
Radioiodine therapy (RAI)
Radioiodine therapy (RAI) uses radioactive iodine (^{131}I) leading to a targeted and controlled damage and death of thyroid cells causing the disease. It is typically ingested (taken orally) in the form of capsules, pills, or liquid.[4,18] RAI emits radiation so patients should avoid radiation exposure to others, particularly to pregnant women and young children. Depending on regulations in different countries, patients may have to stay isolated in the hospital for approximately 24 hours post-treatment for quality control and radiation protection, i.e. an outpatient treatment should be avoided. Also, patients should consult their physician if they intend to travel following RAI as it might trigger airport scanners detecting radioactivity; and patients need medical certificates.[1,2,18] Treatment effectiveness of RAI is related to the radiation dose, thyroid follicle size, iodine-concentrating ability of the thyroid gland, dietary iodine restriction, (^{131}I) biokinetics as well as individual radiosensitivity (i.e., sensitivity of an individual to the effect of ionising radiation; which is highly variable, influenced by age, smoking status, diabetes, collagen vascular disease and genotype).[23] Indications for RAI include side effects to or recurrence after a course of anti-thyroid drugs (ATD), cardiac arrhythmias, and thyrotoxic periodic paralysis.[4] If definite treatment is the treatment objective, RAI will result in hypothyroidism (underactive thyroid) and a requirement for life-long thyroid hormone replacement also affecting quality of life.[15]
Total thyroidectomy
Total thyroidectomy (TT) is a surgical procedure involving a complete removal of the thyroid gland.[4] It should be performed by a highly skilled surgeon typically under general or local anaesthesia.[24] There are several indications for thyroid surgery in Graves' disease including uncontrollable hyperthyroidism, coincident primary hyperparathyroidism, large goiter, coexisting malignant tumours, retrosternal or substernal extension, Graves' ophthalmopathy and females planning pregnancy, reluctance to take antithyroid drugs or

radioiodine therapy.[4, 7] Too, TT can potentially result in hypothyroidism and a need for life-long thyroid hormone replacement also affecting quality of life.[15]

3.4 FAQ 2. Will I have to take lifelong thyroid replacement therapy?

This section explains the transition from hyperthyroidism to hypothyroidism and the need for taking lifelong hormonal replacement therapy following both TT and RAI.

Anyone with Graves' disease who is interested in a rapid resolution of their symptoms and wishes to avoid a prolonged transition from hyperthyroidism (overactive thyroid) to hypothyroidism (underactive thyroid) would benefit from TT. In contrast, RAI treatment may take up to several months to have its effect. It is worth mentioning that hypothyroidism (underactive thyroid) is a common side-effect of both RAI and TT. Regardless of the treatment option, underactive thyroid is being treated by thyroid hormone replacement (THR). It is usually given in pill form and its goal is to closely replicate normal thyroid functioning (necessary for the whole body's functioning). A managing physician will determine whether you should start your THR immediately after surgery or RAI or you should wait a few days before starting it.[19] That depends whether or not your thyroid hormone levels were poorly controlled prior to surgery, or you experienced an additional hormone release during treatment.

3.5. FAQ 3. Will my high thyroid state go away?

Total thyroidectomy vs. radioiodine therapy

Four studies reported quantitative data pertaining to this outcome – see Table 4 below. Genovese 2013 pooled data from 62 observational studies originating from multiple countries.[5] In that study, 1,388 patients had total thyroidectomy (reported in 8 observational studies of quality that had not been critically evaluated) and 9,699 had radioactive Iodine (52 observational studies of quality that had not been critically evaluated). That study found that total thyroidectomy was associated with a higher success rate defined as 'post-procedure euthyroidism or hypothyroidism' in 1,272 per 1,388 (92%) patients compared with 7,619 per 9,699 (78%) in RAI (OR 94.46, 95 % confidence interval (CI) 35.36–252.34) at the follow-ups ranging from 2 to 240 months and 4 to 111 months respectively. It is worth noting that the definition of this outcome provided by the authors was somehow vague and included both success (euthyroidism) and failure (hypothyroidism).[5] While this outcome is a needed effect of treatment stopping hyperthyroid function it is at the same time putting the patient into a hypothyroid state requiring consequential thyroid hormone replacement therapy. The certainty of the evidence is very low due to low quality data and indirectness.

Radioiodine therapy vs. anti-thyroid drug

Although many patients with Graves' thyrotoxicosis are initially managed with ATD (carbimazole or propylthiouracil), a majority of them will relapse when the drugs are stopped.[15] Based on evidence from Wang 2016, when compared with ATD, RAI was

associated with improvements in hyperthyroid cure rate (relative risk (RR) 1.66, 95% CI 1.49 to 1.86) at follow-ups ranging from 1 to 10 years.[17] The certainty of the evidence is very low. However, no differences were shown in euthyroidism between RAI and ATD based on three RCTs (RR 0.78, 95% CI 0.37-1.62) at 2.5 to 9 years follow-up based on very low certainty evidence in NICE CG 145.[15] Of note, the Cochrane authors Ma 2016 did not activate the "switch events and non-events" function when running the meta-analysis.[13] This can make a substantial difference for risk ratios, affecting the (direction of) effect estimate, its statistical significance, and the consistency of intervention effects across studies. Based on re-calculated analyses, compared with RAI, ATD was associated with improvements in euthyroid state (RR 15.14, 95% CI 6.19- 37.02, low certainty evidence) following at least four years follow-up.

Table 4: FAQ 2 – Evidence synthesis

Outcome	Author	No. of studies (type of study)	Average follow up time	Intervention events/total (proportion)	Comparator events/total (proportion)	Effect estimate with 95% CIs e.g., mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
Success defined as postoperative euthyroidism or hypothyroidism	Genovese 2013[5]	62 (cohort and case control studies)	RAI (range = 4-111 months) SUR (range = 2-240 months)	1,272/1,388 SUR (92%)	7,619/9,699* RAI (78%)	OR 94.46, 95 % CI 35.36–252.34	Very low (data of low quality and indirectness)	Difference in favour of SUR but data of very low quality ⇗
Euthyroidism	Ma 2016[13]	1 RCT	At least 4 years	0/39 RAI (0%)	64/68 ATD (94%)	RR 15.14, 95% CI 6.19- 37.02^^	Low (high risk of bias and imprecision)	
Euthyroidism	NICE CG 145[15]	3 RCTs**	2.5- 9 years	278/387 RAI (72%)	240/354 ATD (68%)	RR 0.78, 95% CI 0.37-1.62	Very low (risk of bias and inconsistency)	
Hyperthyroid cure rate	Wang 2016[17]	9 cohort studies	Range = 1-10 years	77.8% RAI	45.6% ATD	RR 1.66, 95% CI 1.49-1.86^	Very low (data of very low quality, inconsistency)	

* = all doses combined; ** between 15-25% of patients had toxic nodular goitre; ^ = estimates inclusive of a trial which involved paediatric patients and got an RR of 1.63, 95% CI 1.63,1.86 – also difference in favour of RAI); however the authors do not provide percentage data for this RR. ^^ original estimate from Ma 2016 was 0.01, 95% CI 0-0.21- however, the authors did not activate the "switch events and non-events" function when running the meta-analysis. ATD = antithyroid drug; CI = confidence interval; OR = odds ratio; RAI = radioiodine therapy; RCT = randomised controlled trial; RR = relative risk; SD = standard deviation; SUR = surgery i.e., total thyroidectomy.

3.6 FAQ 4. WILL MY HIGH THYROID STATE COME BACK?

Ten studies reported quantitative data pertaining to this outcome – see Table 5 below. The outcome was measured in several ways including recurrence of hyperthyroidism, relapse rate.

Recurrence/relapse

This subsection provides evidence for the following question: What is recurrence/relapse rate of hyperthyroidism after radioiodine therapy or thyroidectomy surgery?

Total thyroidectomy vs. radioiodine therapy

Based on very low quality evidence, Genovese 2013 found lower persistent or recurrent hyperthyroidism (therein defined as 'treatment failure') in total thyroidectomy compared with RAI (four per 1,388 (0.2%) versus 2,080/9,699 (21%)) at follow-ups ranging from 2-240 months and 4-111 months respectively.[5]

Total or subtotal thyroidectomy vs. radioiodine therapy

There was no difference between bilateral subtotal thyroidectomy compared with RAI in reducing hyperthyroidism at 21 years follow-up (three per 37 (8.1%) versus eight per 39 (20.5%); RR 2.53, 95% CI 0.73 to 8.82).[15] Also, there were no differences between RAI and surgery (subtotal thyroidectomy and unreported in four studies) (37 per 314 (12%) versus 28 per 386 (7%); OR 1.53; 95% CI 0.64- 3.65) in the outcome based on low quality of the evidence.[16]

Total thyroidectomy vs. subtotal thyroidectomy

Feroci 2014 found that compared with bilateral subtotal thyroidectomy, total thyroidectomy reduces recurrent hyperthyroidism 128/1,577 (8.1%) versus seven per 1,665 (0.4%) (OR 0.10, 95% CI 0.06 to 0.18) based on low certainty evidence.[8] Similarly, based on moderate certainty evidence Guo 2013 found reduced risk of recurrent hyperthyroidism following total thyroidectomy compared with bilateral subtotal thyroidectomy at follow-ups ranging from 26.4 to 60 months (three per 342 (0.8%) versus 26 per 332 (7.8%); RR 0.14, 95% CI 0.05 to 0.41).[9] Also, Liu 2015 reported lower odds of recurrent hyperthyroidism after total thyroidectomy compared with subtotal thyroidectomy at follow-ups ranging from six months to six years (0 per 150 (0%) versus 11 per 200 (5.5%); OR 0.14, 95% CI 0.04 to 0.46) based on low quality evidence.[12]

Radioiodine therapy vs. antithyroid drugs

Ma 2016 found there was no difference between RAI versus ATD in recurrent hyperthyroidism at four years follow-up based on very low quality evidence (10 per 202 (4.9%) versus 55 per 215 (25.5%); RR 0.20, 95% CI 0.01 to 2.66).[13] Relapse rate was lower in RAI compared with ATD (6.3% versus 35%; RR 0.16, 95% CI 0.08 to 0.33) at follow-ups ranging from one to 10 years in Wang 2016[17] based on very low quality evidence.

Table 5: FAQ 3 – Evidence synthesis

Outcome	Author	No. of studies (type of study)	Average follow up time	Intervention events/total (proportion)	Comparator events/total (proportion)	Effect estimate with 95% CIs e.g., mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
Recurrence/relapse								
Relapse rate	Sundaresh 2013[16]	7 (cohort studies and randomised trial)	Range (36-75 months)	37/314* RAI (12%)	28/386 SUR** (7%)	OR 1.53; 95% CI 0.64 to 3.65***	Low (data of low quality)	No difference shown ⇔
Recurrent hyperthyroidism	Feroci 2014[8]	4 RCTs; 19 non-RCTs	N/A	7/1,665 SUR (0.4%)	128/1,577 BST (8.1%)	OR 0.10, 95% CI 0.06 to 0.18	Low (high risk of bias)	
Recurrent hyperthyroidism	Guo 2013[9]	4 RCTs	Range= 26.4-60 months	3/342 SUR (0.8%)	26/332 BST (7.8%)	RR 0.14, 95% CI 0.05 to 0.41	Moderate (unclear or high risk of bias)	
Rate of recurrent hyperthyroidism	Liu 2015[12]	2 RCTs	Range = 6 months to 6 years	0/150 SUR (0%)	11/200 ST (5.5%)	OR 0.14, 95% CI 0.04 to 0.46	Low (risk of bias and imprecision)	
Recurrence of hyperthyroidism	Ma 2016[13]	2 RCTs	At least 4 years	10/202 RAI (4.9%)	55/215 ATD (25.5%)	RR 0.20, 95% CI 0.01 to 2.66	Very low (risk of bias and imprecision and inconsistency)	
Hyperthyroidism	NICE CG 145[15]	1 RCT	21 years	8/39 RAI (20.5%)	3/37 BST (8.1)	RR 2.53, 95% CI 0.73 to 8.82	Low (imprecision)	

Outcome	Author	No. of studies (type of study)	Average follow up time	Intervention events/total (proportion)	Comparator events/total (proportion)	Effect estimate with 95% CIs e.g., mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
Relapse rate	Wang 2016[17]	10 cohort studies	Range = 1-10 years	6.3% RAI	35% ATD	RR 0.16, 95% CI 0.08 to 0.33	Very low (data of very low quality)	
Other measures								
Failure defined as postoperative persistent or recurrent hyperthyroidism	Genovese 2013[5]	62 (cohort and case control studies)^^^	RAI (range = 4-111 months) SUR (range = 2-240 months)	2,080/9,699* RAI (21%)	4/1,388 SUR (0.2%)	N/A	Very low (data of low quality and indirectness)	Difference in favour of SUR but data of very low quality⇗

* = all doses combined; ** = 4 out of 8 studies compared RAI to subtotal thyroidectomy and the type of surgery was not reported in 4 studies; *** = estimates from direct comparisons; BST = bilateral subtotal thyroidectomy; ST = subtotal thyroidectomy; ^^^ there were 11 studies on subtotal thyroidectomy. ATD = antithyroid drug; CI = confidence intervals; N/A = not available; OR = odds ratio; RAI = radioiodine therapy; SD = standard deviation; SUR = surgery, i.e., total thyroidectomy.

3.7 FAQ 5: Will I develop or worsen Graves Ophthalmopathy

This subsection provides evidence for the following question: Will I develop or worsen Graves' ophthalmopathy? Eight studies reported quantitative data pertaining to this outcome – see Table 6 below.

Total thyroidectomy vs. radioiodine therapy

In terms of the risk of developing new ophthalmopathy or worsening of pre-existing ophthalmopathy, there were no differences between RAI and total thyroidectomy (22 per 59 (37%) versus 13 per 57 (23%); RR 1.59; 95% CI 0.89 to 2.81) in Acharya 2008.[6] However, there was an indication of a clinically important harm of RAI compared with total thyroidectomy in NICE CG 145[15] (13 per 39 (33%) versus six per 37 (16%); RR 2.06, 95% CI 0.87 to 4.84) at maximum of 21 years follow-up based on moderate quality evidence.

Total versus subtotal thyroidectomy

There were no differences between total and bilateral subtotal thyroidectomy (33 per 386 (8.5%) versus 23 per 220 (10%); OR 0.90, 95% CI 0.48 to 1.71) in Feroci 2014[8] and in Guo 2013[9] (16 per 151 (10%) versus 17 per 148 (11%); RR 0.92, 95% CI 0.50 to 1.71). One study also measured regression of Graves' ophthalmopathy and reported no differences between total and subtotal thyroidectomy at follow-ups ranging from six months to six years (107 per 131 (82%) versus 122 per 156 (78%); OR 1.15, 95% CI 0.64 to 2.08) based on low quality evidence.[12]

Radioiodine therapy vs. antithyroid drugs

Li 2016 reported fewer cases of worsening of ophthalmopathy following ATD compared with RAI (66 per 469 (14%) versus 135 per 507 (27%); OR 2.25, 95% CI 1.61 to 3.14) at follow-ups ranging from 18 to 108 months based on moderate quality evidence.[10] Based on low quality evidence similar findings were reported in Ma 2016[13] (40 per 215 (19%) versus 76 per 202 (38%); RR 1.94, 95% CI 1.4 to 2.7); and based on very low quality evidence in Wang 2016[17] (187 per 1,158 (16%) versus 266 per 1,138 (23%); RR 1.36, 95% CI 1.04 to 1.77) at follow-ups ranging from one to 11.1 years.

Table 6: FAQ 5 – Evidence synthesis

Outcome	Author	No. of studies (type of study)	Average follow up time	Intervention events/total (proportion)	Comparator events/total (proportion)	Effect estimate with 95% CIs e.g., mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
Ophthalmopathy								
Risk of ophthalmopathy	Acharya 2008[6]	2 RCTs	N/A	22/59 RAI (37%)	13/57 SUR (23%)	RR 1.59; 95% CI 0.89 to 2.81	Low (imprecision)	No difference shown ⇔
New/worsening cases of ophthalmopathy	NICE CG 145[15]	1 RCT	21 years	13/39 RAI (33%)	6/37 SUR (16%)	RR 2.06, 95% CI 0.87 to 4.84	Moderate (imprecision)	No indication of difference ⇔
Progression of ophthalmopathy	Feroci 2014[8]	3 RCTs; 2 non-RCTs	N/A	33/386 SUR (8.5%)	23/220 BST (10%)	OR 0.90, 95% CI 0.48 to 1.71	Low (high risk of bias)	
Progression of ophthalmopathy	Guo 2013[9]	3 RCTs	Range= 36-60 months	16/151 SUR (10%)	17/148 BST (11%)	RR 0.92, 95% CI 0.50 to 1.71	Moderate (unclear or high risk of bias)	
Worsening of ophthalmopathy	Li 2016[10]	4 RCTs	18-108 months	135/507 RAI (27%)	66/469 ATD (14%)	OR 2.25, 95% CI 1.61 to 3.14	Moderate (inconsistency)	
Regression of Graves' ophthalmopathy	Liu 2015[12]	2 RCTs	Range = 6 months to 6 years	107/131 SUR (82%)	122/156 ST (78%)	OR 1.15, 95% CI 0.64 to 2.08	Low (risk of bias and imprecision)	
Development and worsening of	Ma 2016[13]	2 RCTs	Range = 2 to 4 years	76/202 RAI (38%)	40/215 ATD (19%)	RR 1.94, 95% CI 1.4 to 2.7	Low (risk of bias and imprecision)	

Outcome	Author	No. of studies (type of study)	Average follow up time	Intervention events/total (proportion)	Comparator events/total (proportion)	Effect estimate with 95% CIs e.g., mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
ophthalmopathy								
Development of ophthalmopathy (new cases)	Wang 2016[17]	12 cohort studies	Range = 1-11.1 years	266/1,138 RAI (23%)	187/1,158 ATD (16%)	RR 1.36, 95% CI 1.04 to 1.77	Very low (data of very low quality)	

ATD = antithyroid drug; BST = bilateral subtotal thyroidectomy; CI = confidence intervals; N/A = not available; OR = odds ratio; RAI = radioiodine therapy; SD = standard deviation; ST = subtotal thyroidectomy; SUR = surgery, i.e., total thyroidectomy.

3.8 FAQ 6. WILL MY QUALITY OF LIFE CHANGE?

One study reported qualitative data pertaining to this outcome – see Table 6 below. Based on low certainty evidence, Ma 2016 found no differences in health-related quality of life between RAI and ATD at follow-ups ranging from four to 21 years.[13] However, the symptoms of hypothyroidism (such as tiredness, constipation, slow heart rate, depression, or weight gain) that might initially not be managed well by thyroid hormone replacement and the need for lifelong THR might have an impact on your quality of life.

Table 7: FAQ 4 – Evidence synthesis

Outcome	Author	No. of studies (type of study)	Average follow up time	Intervention events/total (proportion)	Comparator events/total (proportion)	Effect estimate with 95% CIs e.g., mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
Health-related quality of life	Ma 2016[13]	2 RCTs	Range = 4 to 21 years	No data for RAI	No data for ATD	One trial reported no differences between RAI and ATD	Low (high risk of bias)	

ATD = antithyroid drug; RAI = radioiodine therapy; RCT = randomised controlled trial; SD = standard deviation

3.9 FAQ 7. WHAT ARE THE RISKS?

Although RAI is generally safe, the therapy produces radiation so patients must do their best to avoid exposure to others. RAI should never be used in pregnant or breastfeeding women.[18] Seven studies reported quantitative data pertaining to this outcome – see Table 7 below. For surgery, the outcome was measured in several ways including laryngeal nerve palsy (permanent or transient), postoperative bleeding, permanent hypocalcaemia/hypoparathyroidism. The incidence of cancer diagnoses was measured for both interventions, total thyroidectomy and RAI. In addition, the German CPG on RAI reports the following AEs for RAI as definitive treatment: hypothyroidism (lifelong hormone replacement needed), inflammation of salivary glands (very rare), radiation-induced thyroiditis (rare).[2] The American Thyroid Association also reports temporary loss of taste or dry mouth due to salivary gland damage as potential side effects.[18]

Incidence of cancer diagnosis

Total thyroidectomy vs. radioiodine therapy

There was no difference between RAI and total thyroidectomy in the incidence of cancer diagnoses at 15 and 21 years follow-ups, respectively (0 per 1,005 (0%) versus 0 per 2,141 (0%); RR 1.00, 95% CI 0.70 to 1.43) based on very low certainty evidence.[15]

Risk of laryngeal nerve palsy

Total vs. subtotal thyroidectomy

Based on low quality of the evidence, the risk of permanent laryngeal nerve palsy was ranged 0–0.2 %, and the rate of transient nerve palsy was 1.3–7 % following total thyroidectomy.[5] Based on very low and low certainty evidence, four studies found no differences in permanent laryngeal nerve palsy between total thyroidectomy and bilateral subtotal thyroidectomy or subtotal thyroidectomy at follow-ups ranging from six months to six years. Specifically, rates were 15 per 1,526 (0.9%) versus 12 per 1,279 (0.9%) (OR 0.91, 95% CI 0.41 to 2.02) in Feroci 2014,[8] five per 342 (1.4%) versus three per 332 (0.9%) (RR 1.54, 95% CI 0.41 to 5.73) in Guo 2013,[9] five per 172 (2.9%) versus four per 221 (1.8%) (OR 1.45, 95% CI 0.38 to 5.59) in Liu 2015,[12] and 0.9% versus 0.7% in Maia 2013.[14]

Postoperative bleeding

Findings were less consistent for postoperative bleeding/haemorrhage. Based on low certainty evidence, Guo 2013 found no difference between total and bilateral subtotal thyroidectomy at follow-up ranging from 26.4 to 36 months (one per 196 (0.5%) versus four per 187 (2.1%); RR 0.32, 95% CI 0.05 to 1.96).[9] However, there was a higher risk of postoperative haemorrhage in total compared with bilateral subtotal thyroidectomy (720 per 35,640 (2%) versus 411 per 28,692 (1.4%); OR 1.71, 95% CI 1.50 to 1.96) based on low certainty evidence.[11]

Wound infection

A German CPG reports a frequency of wound infections after thyroid surgery to be between 0.3% and 2.9%.[2] These are described to be typically subcutaneous low-risk complications that are easily treatable.[2]

Hypocalcaemia/hypoparathyroidism

In Liu 2015,[12] there was a higher risk of permanent hypocalcaemia/hypoparathyroidism in total compared with subtotal thyroidectomy at six months to six years follow-up (eight per 172 (4.6%) versus three per 221 (1.3%); OR 4.79, 95% CI 1.36 to 16.83) based on low certainty evidence.

Table 8: FAQ 5 – Evidence synthesis

Outcome	Author	No. of studies (type of study)	Average follow up time	Intervention events/total (proportion)	Comparator events/total (proportion)	Effect estimate with 95% CIs e.g., mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
Laryngeal Nerve Palsy								
Permanent Laryngeal Nerve Palsy	Feroci 2014[8]	4 RCTs; 16 non-RCTs	N/A	15/1,526 SUR (0.9%)	12/1,279 BST (0.9%)	OR 0.91, 95% CI 0.41 to 2.02	Low (high risk of bias)	
Permanent Laryngeal Nerve Palsy	Genovese 2013[5]	8 cohort/case control studies	range = 2-240 months	% range 0-0.2%/1,388	N/A	N/A	Very low (data of low quality and indirectness)	
Transient Laryngeal Nerve Palsy	Genovese 2013[5]	8 cohort/case control studies	range = 2-240 months	% range 1.3-7/1,388	N/A	N/A	Very low (data of low quality and indirectness)	
Temporary Laryngeal Nerve Palsy	Guo 2013[9]	3 RCTs	Range= 26.4-60 months	11/320 SUR (3.4%)	10/311 ST (3.2%)	RR 1.08, 95% CI 0.47 to 2.48	Low (high risk of bias, and imprecision)	
Permanent Laryngeal Nerve Palsy	Guo 2013[9]	4 RCTs	Range= 26.4-60 months	5/342 SUR (1.4%)	3/332 BST (0.9%)	RR 1.54, 95% CI 0.41 to 5.73	Low (high risk of bias, and imprecision)	
Permanent recurrent laryngeal nerve palsy	Liu 2015[12]	3 RCTs	Range = 6 months to 6	5/172 SUR (2.9%)	4/221 ST (1.8%)	OR 1.45, 95% CI 0.38 to 5.59	Low (high risk of bias, and imprecision)	

Outcome	Author	No. of studies (type of study)	Average follow up time	Intervention events/total (proportion)	Comparator events/total (proportion)	Effect estimate with 95% CIs e.g., mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			years					
Permanent Laryngeal Nerve Palsy	Maia 2013[14]	N/M	N/A	0.9% SUR	0.7% ST	N/A	Very low (data of very low quality)	
Bleeding/ infections								
Postoperative bleeding	Guo 2013[9]	2 RCTs	Range= 26.4-36 months	1/196 SUR (0.5%)	4/187 BST (2.1%)	RR 0.32, 95% CI 0.05 to 1.96	Low (high risk of bias, and imprecision)	
Wound infection	Dt. Ges. f. Allg.- u. Viszeral-chir.[2]	CPG	NR	Frequency of wound infections after thyroid surgery: 0.3% to 2.9%		N/A	Moderate (imprecision)	
Postoperative haemorrhage	Liu 2017[11]	9 cohort studies	N/A	720/35,640 SUR (2%)	411/28,692BST (1.4%)	OR 1.71, 95% CI 1.50 to 1.96	Low (high risk of bias, and indirectness)	
Other measures								
Total cancer diagnoses	NICE CG 145[15]	1 non-RCT	RAI = 15 years SUR =21 years	0/1005 RAI (0%)	0/2141 SUR (0%)	RR 1.00, 95% CI 0.70 to 1.43	Very low (high risk of bias and imprecision)	No difference shown among groups ⇔

Outcome	Author	No. of studies (type of study)	Average follow up time	Intervention events/total (proportion)	Comparator events/total (proportion)	Effect estimate with 95% CIs e.g., mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
Permanent hypocalcaemia/hypoparathyroidism	Liu 2015[12]	3 RCTs	Range = 6 months to 6 years	8/172 SUR (4.6%)	3/221 ST (1.3%)	OR 4.79, 95% CI 1.36 to 16.83	Low (high risk of bias, and imprecision)	
Temporary hypoparathyroidism	Guo 2013[9]	3 RCTs	Range= 26.4-36 months	104/320 SUR (32.5%)	38/311 ST (12%)	RR 2.66, 95% CI 1.89 to 3.73	Low (high risk of bias, and imprecision)	
Permanent hypoparathyroidism	Guo 2013[9]	3 RCTs	Range= 26.4-36 months	9/342 SUR (2.6%)	3/332 ST (0.9%)	RR 2.30, 95% CI 0.78 to 6.76	Low (high risk of bias, and imprecision)	

^ = Graves versus non-Graves'; BST = bilateral subtotal thyroidectomy; ST = subtotal thyroidectomy
ATD = antithyroid drugs; CI = confidence intervals; N/A = not applicable; NR = not reported; RAI = radioiodine therapy; RCT = randomised controlled trial; RR = risk ratio; SUR = surgery

4. DISCUSSION

4.1 SUMMARY OF FINDINGS

In general terms, low certainty evidence suggests that total thyroidectomy has a clinically important benefit over RAI in terms of the likelihood of relapse or persistence of hyperthyroidism; however this is based on small studies and the certainty of the evidence is low. On the other hand, moving from a state of hyperthyroidism to hypothyroidism sooner (surgery) or later (radioiodine) involves important changes for the patient. The patient will transfer to a hypothyroid state involving the typical symptoms such as tiredness, constipation, slow heart rate, depression, or weight gain. [25] To avoid occurrence of these symptoms the patient will have to take thyroid hormone replacement therapy, which will take a while to get the patient on the right dosage. Potential complications of total thyroidectomy include hypoparathyroidism, recurrent laryngeal nerve injury, postoperative bleeding when compared with subtotal (unilateral or bilateral) thyroidectomy. While treatment with RAI is generally safe, certain risks include loss of taste and dry mouth due to salivary gland damage.[18] Certain safety precautions have to be taken which involve avoiding radiation exposure to others; pregnant or nursing females should never use RAI. Furthermore, patients who need to travel following RAI treatment are advised to carry a letter of explanation from their physician.[18]

4.2 STRENGTHS, LIMITATIONS, AND UNCERTAINTIES

This report was developed using evidence from systematic reviews and clinical practice guidelines. Strengths of this report include robust literature searches without date restrictions, inclusion of the best quality evidence as well as coverage of a wide range of outcomes of interest.

Nevertheless, some limitations need to be noted. First and foremost, there was an unequal distribution of data/outcomes under respective FAQs. Recurrence of hyperthyroidism, or relapse rate, or risk of ophthalmopathy were the clinical areas where some evidence was found. Slightly less evidence was found in regard to the risks of the interventions; seven studies reported quantitative data on laryngeal nerve palsy, postoperative bleeding, permanent hypocalcaemia/hypoparathyroidism, incidence of cancer diagnoses or hypothyroidism. In contrast, only one study reported qualitative data on health-related quality of life. Also, some CPGs dating back to 2015 are now considered outdated. [2]

There was limited evidence to answer FAQ 6: Will my quality of life change with only one study reporting no between group differences. [13] With that in mind, it will be important to consider primary studies and expert opinion.

It is worth mentioning that for RAI, most SRs and CPGs reported on combined doses and in some studies between 15-25% of patients had toxic nodular goitre. The number and quality of primary studies ranged from one RCT to 62 observational studies; follow-ups ranged from two months to 21 years. Only four outcomes were based on moderate certainty evidence,

whereas 25 outcomes were based on low certainty evidence, and four on very low certainty evidence. The main reasons for downgrading were high risk of bias in the primary studies, imprecision (small samples, wide confidence intervals), imprecision (heterogeneity of the pooled analyses) and indirectness.

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APPENDIX 1: SEARCH STRATEGY

Database	Dates	Results
CDSR	Iss 9, Sept 2020	11
DARE	up to 31 Mar 2015	47
HTA	up to 31 Mar 2018	12
NICE Evidence	up to 2020/09/17	490
NICE Guidance	up to 2020/09/17	15
KSR Evidence	up to 2020/09/10	163
Epistemonikos	up to 2020/09/17	64
GIN	up to 2020/09/10	23
ECRI	up to 2020/09/17	29
Total		**854**
Total after deduplication		**568**
Duplicates removed		**288**

Search strategies

Cochrane Database of Systematic Reviews (CDSR): Issue 9/12 Sept 2020: All years Searched 8.9.20

#1 MeSH descriptor: [Graves Disease] this term only 335
#2 ((graves* or basedow) near/3 (disease or syndrome or disorder)):ti,ab,kw 624
#3 ((graves* or basedow) near/3 hyperthyroid*):ti,ab,kw 28
#4 (exophthalmic near/3 (goiter* or goitre* or hyperthyroid*)):ti,ab,kw 2
#5 ((Autoimmun* or Auto-immun*) near/2 hyperthyroid*):ti,ab,kw 10
#6 thyrotoxic*:ti,ab,kw 0
#7 MeSH descriptor: [Hyperthyroidism] this term only 296
#8 hyperthyroid*:ti,ab 1043
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 in Cochrane Reviews, Cochrane Protocols 18

Database of Abstracts of Reviews of Effects (DARE) (Internet): up to 2015/03/Searched 8.9.20
Health technology Assessment Database (HTA) (Internet): up to 2015/03/Searched 8.9.20
https://www.crd.york.ac.uk/CRDWeb/HomePage.asp

1 MeSH DESCRIPTOR Graves Disease IN DARE,HTA 15
2 (((graves* or basedow) near3 (disease or syndrome or disorder))) 29
3 (((graves* or basedow) near3 hyperthyroid*)) 4
4 ((exophthalmic near3 (goiter* or goitre* or hyperthyroid*))) 0
5 (((Autoimmun* or Auto-immun*) near2 hyperthyroid*)) 0
6 (Thyrotoxic* or hyperthyroid*) 58
7 MeSH DESCRIPTOR Hyperthyroidism IN DARE,HTA 11
8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 79
9 (#8) IN DARE 47
10 (#8) IN HTA 12

KSR Evidence (Internet): up to 2020/09/10
https://ksrevidence.com/
1 "graves disease" or "graves disorder" or "graves syndrome" or " basedow disease" or " basedow disorder" or " basedow syndrome" in All text 55 results
2 "graves hyperthyroidism" or "basedow hyperthyroidism" in All text 3 results
3 "exophthalmic goiter" or "exophthalmic goiters" or "exophthalmic goitre" or "exophthalmic goitres" or "exophthalmic hyperthyroidism" in All text 0 results
4 "Autoimmune hyperthyroidism" or "Auto-immune hyperthyroidism" in All text 0 results
5 Thyrotoxic* or hyperthyroid* in All text 134 results
6 #5 or #4 or #3 or #2 or #1 in All text 163 results

Search run Thu Sep 10 2020
Guidelines International Network (GIN) Library (Internet): up to 2020/09/10
http://www.g-i-n.net

Search terms	**Results**
graves	1
basedow	0
Hyperthyroidism	2
Thyroid	20
Thyrotoxicosis	0
exophthalmic	0
Total	**23 (21 after deduplication)**

National Institute of Health and Care Excellence (NICE) Guidance (Internet): up to 2020/09/17
Searched 17.9.20
https://www.nice.org.uk/guidance

Search terms	**Results**
graves	0
basedow	0
Hyperthyroidism	0
Thyroid	15
Thyrotoxicosis	0
Exophthalmic	0
Total	**15**

NICE Evidence (Internet): up to 2020/09/17
Searched 17.9.20
https://www.evidence.nhs.uk/
Limited to Guidance, Systematic reviews and Health Technology Assessments

Search terms	Results
"Graves disease"	107
basedow	3
Hyperthyroidism	289
Thyrotoxicosis	90
Exophthalmic	1
Total	**490**

ECRI Guidelines (Internet): up to 2020/09/17
Searched 17.9.20
https://guidelines.ecri.org/

Search terms	Results
"Graves disease"	2
Basedow OR Hyperthyroidism	2
Thyroid	23
Thyrotoxicosis OR Exophthalmic	2
Total	**29**

Epistemonikos (Internet): up to 2020/09/17
Searched 17.9.20
https://www.epistemonikos.org/

Limited to Systematic reviews, not Cochrane reviews.

Search terms: Title or abstract	Results
"graves disease" or "graves disorder" or "graves syndrome" or " basedow disease" or " basedow disorder" or " basedow syndrome"	23
"graves hyperthyroidism" or "basedow hyperthyroidism"	0
"exophthalmic goiter" or "exophthalmic goiters" or "exophthalmic goitre" or "exophthalmic goitres" or "exophthalmic hyperthyroidism"	0
Thyrotoxic*	39
"Autoimmune hyperthyroidism" or "Auto-immune hyperthyroidism"	2
Total	**64**