

Effects of antithyroid drugs on radioiodine treatment: systematic review and meta-analysis of randomised controlled trials

Martin A Walter, research associate,¹ Matthias Briel, research associate,² Mirjam Christ-Crain, research associate,³ Steen J Bonnema, professor of medicine,⁴ John Connell, professor of endocrinology,⁵ David S Cooper, professor of medicine,⁶ Heiner C Bucher, professor of medicine,² Jan Müller-Brand, professor of nuclear medicine,⁷ Beat Müller, professor of endocrinology³

¹Institute of Nuclear Medicine, University Hospital Basel, Switzerland, and Department of Endocrinology, Diabetology and Clinical Nutrition, University Hospital Basel

²Basel Institute for Clinical Epidemiology, University Hospital Basel

³Department of Endocrinology, Diabetology and Clinical Nutrition, University Hospital Basel

⁴Department of Endocrinology and Metabolism, University Hospital Odense, Denmark

⁵Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow

⁶Division of Endocrinology, Johns Hopkins University School of Medicine, Baltimore, USA

⁷Institute of Nuclear Medicine, University Hospital Basel, Switzerland

Correspondence to: MA Walter, m.a.walter@gmx.net

doi: 10.1136/bmj.39114.670150.BE

ABSTRACT

Objective To determine the effect of adjunctive antithyroid drugs on the risk of treatment failure, hypothyroidism, and adverse events after radioiodine treatment.

Design Meta-analysis.

Data sources Electronic databases (Cochrane central register of controlled trials, Medline, Embase) searched to August 2006 and contact with experts.

Review methods Three reviewers independently assessed trial eligibility and quality. Pooled relative risks for treatment failure and hypothyroidism after radioiodine treatment with and without adjunctive antithyroid drugs were calculated with a random effects model.

Results We identified 14 relevant randomised controlled trials with a total of 1306 participants. Adjunctive antithyroid medication was associated with an increased risk of treatment failure (relative risk 1.28, 95% confidence interval 1.07 to 1.52; $P=0.006$) and a reduced risk for hypothyroidism (0.68, 0.53 to 0.87; $P=0.006$) after radioiodine treatment. We found no difference in summary estimates for the different antithyroid drugs or for whether antithyroid drugs were given before or after radioiodine treatment.

Conclusions Antithyroid drugs potentially increase rates of failure and reduce rates of hypothyroidism if they are given in the week before or after radioiodine treatment, respectively.

INTRODUCTION

Hyperthyroidism is a common condition¹ that is associated with increased morbidity and mortality, especially because of cardiovascular complications.²⁻⁴ Radioiodine treatment was introduced in 1941⁵ and has become a cornerstone in the treatment of hyperthyroidism,⁶ although short and long term side effects are common. Short term side effects include an acute rise in thyroid hormone concentrations with potential clinical exacerbation and increased cardiovascular risk.⁷ Long term side effects include hypothyroidism,⁸ which requires permanent thyroid hormone substitution.

The antithyroid drugs propylthiouracil and methimazole and its precursor carbimazole are commonly used to alleviate symptoms of hyperthyroidism and to diminish the short and long term side effects of radioiodine treatment.^{9,10} There is disagreement, however, about the beneficial and detrimental effects and the optimal sequencing of the different antithyroid drugs before or after radioiodine treatment. So far, these controversies remain unsolved, although they have been subject to numerous clinical studies. Current recommendations and guidelines are solely based on single trials and narrative reviews.

We conducted a systematic review and meta-analysis of randomised controlled trials to compare the rates of treatment failure and the short and long term side effects in people with hyperthyroidism receiving radioiodine treatment with or without adjunctive antithyroid drugs.

METHODS

Search strategy

We searched the electronic libraries Medline, Embase (from their inception to August 2006), and the Cochrane central register of controlled trials (Cochrane Library 2006, issue 1) for randomised and non-randomised studies comparing adjunctive antithyroid drugs with control on the outcome of radioiodine treatment. We used the terms “antithyroid agents”, “thioamides”, “propylthiouracil”, “methylthiouracil”, “methimazole”, “carbimazole” and “iodine radioisotopes” as medical subject headings and “thioamides”, “propylthiouracil”, “methylthiouracil”, “methimazole”, “carbimazole”, “thyrostatic”, “anti-thyroid”, “131I”, “131-iodine”, “radioactive” and “radioiodine” as text words. There were no language restrictions. We also searched relevant websites (www.controlled-trials.com and www.update-software.com/nationalin August 2006) and reference lists of all identified articles, narrative reviews, and recently published editorials and contacted experts for unpublished trials and authors of included primary trials to obtain additional data where needed.

Study selection

For inclusion into the meta-analysis, studies had to be randomised controlled trials in adults with hyperthyroidism that examined the outcome of radioiodine treatment with adjunctive antithyroid drugs. Studies had to have a minimum follow-up of six months. We excluded studies that intended to deliver different target doses of radioiodine to compensate for a potential effect of the antithyroid drug. Table A on [bmj.com](#) gives characteristics of and data from identified studies that were not randomised but otherwise fulfilled our inclusion criteria.

Quality assessment

Three investigators (MC-C, MB, MAW) independently assessed study eligibility and quality blinded to each other's rating and resolved any disagreement by consensus. We assessed the quality of trials according to concealment of treatment allocation (to protect from selection bias), completeness of follow-up (to protect from attrition bias), blinding of patients and caregivers (to protect from performance bias), blinding of outcome assessors (to protect from detection bias), and performance of a sample size calculation. We

considered allocation of treatment to be concealed if studies mentioned a central independent randomisation facility, the use of numbered sealed opaque envelopes, or a central pharmacy that prepared and distributed containers.

Outcomes and data extraction

Main outcome measures were rates of treatment failure (persistent hyperthyroidism, recurrent hyperthyroidism, or need for further treatment), hypothyroidism, and adverse effects 6-12 months after radioiodine treatment. We defined thyroid status according to the criteria in the single primary trials (table 1). Radioiodine treatment was considered as successful if hyperthyroidism was eliminated according to the definition used in the corresponding trials. Three investigators (MC-C, MB, MAW) extracted information on baseline characteristics of included trials and patients, reported on methodological quality, and independently extracted clinical outcome.

Quantitative data synthesis

We pooled treatment effects and calculated risk ratios and corresponding 95% confidence intervals for the

Table 1 | Characteristics of trial included in systematic review of effect of antithyroid drugs on radioiodine treatment

Trial	Origin	Mean dose of antithyroid drug (mg/day)	Interval between stopping antithyroid drug and radioiodine therapy	Radioiodine dose regimen (target dose)	Criteria for thyroid status	Follow-up (months)	Sample size calculation/concealed allocation	Blinding	Complete follow-up (%)	No of participants: intervention/control/total
Hamilton (1952) ^{w1}	USA	Propylthiouracil (300) Methimazole (30)*	7 days after	Uptake adapted (ND)	SPI, BMR, ¹³¹ I uptake, clinic	7	No	None	100	33/22/55
Steinbach (1979) ^{w2}	USA	Propylthiouracil (ND)	7 days after/ simultaneous*	Uptake adapted (50 gray)	T4, T3, TSH	12	No	None	80.0	13/11/24
Bazzi (1993) ^{w3}	USA	Propylthiouracil (300)	5 days after	Uptake adapted (3.7 MBq/g)	T4, TSH, ¹³¹ I uptake	12	No	None	100	36/34/70
Tian (2001) ^{w4}	China	Propylthiouracil (50)	3 days after	Uptake adapted (3.7 MBq/g)	T4, T3, TSH	6	No	None	97.4	94/93/187
Bonnema (2004) ^{w5}	Denmark	Propylthiouracil (100)	4 days before	Uptake adapted (3.7 MBq/g)	T4, T3, TSH	12	Sample size only	None	98.8	39/41/80
Goolden (1969) ^{w6}	UK	Carbimazole (ND)	2 days before	Uptake adapted (5.6 MBq/g)	ND	12	No	None	100	83/98/181
Aro (1981) ^{w7}	Finland	Carbimazole (30)	2 days before/2 days after	Uptake adapted (3†/6‡ MBq/g)	Free T4 index, clinical score	6	No	Caregivers only	100	36/34/70
Connell (1986) ^{w8}	Scotland	Carbimazole (20-30)	3 days before	Uptake adapted (3.7 MBq/g)	T4, T3, TSH	12	No	None	87.8	45/45/90
Gamstedt (1986) ^{w9}	Sweden	Methimazole (30)	7 days before/1 day after	Fixed	T4, T3, ¹³¹ I uptake	12	Sample size only	None	97.5	17/22/39
Kung (1995) ^{w10}	Hong Kong	Methimazole (30)	4 days after	Uptake adapted (70-80 gray)	TSH, ¹³¹ I scan, clinic	12	No	None	97.0	80/79/159
Andrade (2001) ^{w11}	Brazil	Methimazole (30)	4 days before	Uptake adapted (7.4 MBq/g)	Antibodies, ¹³¹ I uptake, T4, T3, TSH	12	No	Assessors only	91.0	29/32/61
Braga (2002) ^{w12}	USA	Methimazole (30)	6 days before	Fixed	TSH, antibodies, ¹³¹ I uptake	12	Sample size only	None	90.5	18/20/38
Bonnema (2003) ^{w13}	Denmark	Methimazole (5)	7 days after	Fixed	T4, T3, TSH	12	No		94.1	73/76/149
Bonnema (2006) ^{w14}	Denmark	Methimazole (7.5)	Simultaneous	Uptake adapted (100 gray)	T4, T3, TSH	12	Sample size only	None	94.9	39/36/75

ND=not described, SPI=serum precipitable iodine (Chaney method); BMR=basal metabolic rate (Benedict-Roth method); T4=levothyroxine, T3=tri-iodothyronine; TSH=thyroid stimulating hormone.

*Two separate intervention arms.

†Graves' disease.

‡Toxic nodular goiter.

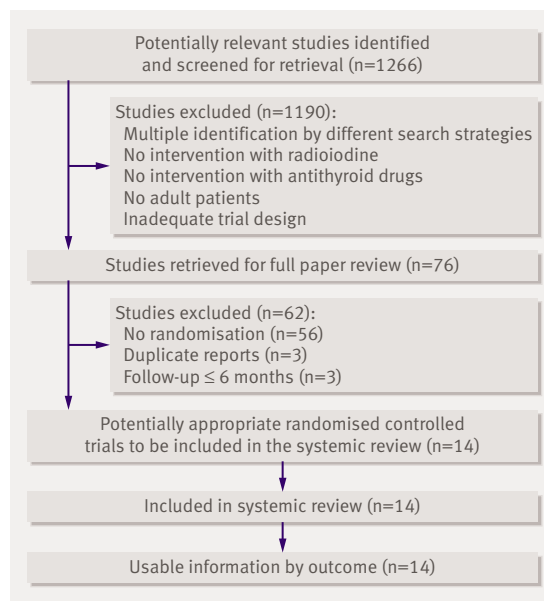


Fig 1 | Flowchart of search results

main outcomes in the treatment and control groups using a random effects model.¹¹ All comparisons were based on an intention to treat analysis. Loss of follow-up was regarded as unsuccessful treatment. We also performed a per protocol analysis restricted to patients with complete follow-up for treatment failure and hypothyroidism. We tested for heterogeneity with the Cochran Q test and measured inconsistency (I^2 ; the percentage of total variance across studies attributable to heterogeneity rather than chance) of treatment effects across trials.¹² We regarded an I^2 value up to 25% as low, up to 50% as moderate, and more than 50% as high

inconsistency. We examined the presence of a small study effect by means of funnel plots and Egger's test.^{13,14}

Sensitivity analyses were performed according to the use of fixed versus uptake adapted regimens of radioiodine dose, high versus low dose of antithyroid drugs, the discontinuation interval for the antithyroid drug before and after radioiodine treatment (within 3 v 4-7 days), the use of a thyroid stimulating hormone (TSH) assay for definition of thyroid status versus other criteria, and the inclusion of patients with Graves' disease only versus additionally including patients with toxic nodular goitre. We used logistic regression to examine the association of administered radioiodine and resulting hypothyroidism and success rates in the control arms of all included trials. We used Stata 9.2 (StataCorp, College Station, TX) and RevMan 4.2 (Nordic Cochrane Centre) for data analysis.

RESULTS

Fourteen randomised controlled trials met the inclusion criteria^{w1-w14} (fig 1), including one unpublished trial.^{w8} Four trials used propylthiouracil,^{w2-w5} three used carbimazole,^{w6-w8} six used methimazole,^{w9-w14} and one trial with two treatment arms used propylthiouracil and methimazole.^{w1} Two trials had additional treatment arms with betamethasone^{w9} or potassium iodide.^{w3} These arms were not considered for our analysis. The included trials randomly assigned 1306 patients receiving radioiodine treatment to adjunctive antithyroid drugs (n=660) or control (n=646).

Study characteristics

The included trials were conducted in different countries on four continents and were published over a period of 54 years (1952-2006). Except for one report in

Table 2 | Characteristics of participant's at time of randomisation. Figures shown are intervention/control

Trial	Women (%)	Mean age (years)	Graves' disease (%)	Thyroid size (ml)	T4 (nmol/l)	T3 (nmol/l)	TSH (mU/l)	¹³¹ I uptake (%)	¹³¹ I activity (MBq)
Hamilton ^{w1}	70/68	46/46	100/100	ND	ND	ND	ND	46/46	158/148
Steinbach ^{w2}	0/0	44/42	100/100	ND	ND	ND	ND	34/46	585/370
Bazzi ^{w3}	95/89	44/42	100/100	ND	ND	ND	ND	ND	ND
Tian ^{w4}	83/82	37/36	100/100	55/56*	217/206	6.2/6.5	<0.03/<0.03	72/67	281/306
Bonnema ^{w5}	90/85	58/53	26/32	21/24	331/348†	7.6/8.3‡	0.01/0.01	58/49	283/332
Goolden ^{w6}	ND	ND	100/100	ND	ND	ND	ND	ND	ND
Aro ^{w7§}	75/85	55/56	61/59	45/43*	298/310†	ND	ND	67/56	296/311
Connell ^{w8}	89/93	55/53	86/81	35/43*	ND	ND	ND	76/68	227/216
Gamstedt ^{w9}	94/78	59/60	100/100	ND	276/246	5.8/5.2	ND	64/65	370/370
Kung ^{w10}	74/75	46/48	100/100	42/41*	251/241	5.6/4.5	0.05/0.05	75/75	202/208
Andrade ^{w11}	93/88	37/35	100/100	31/38	59.2/57.9¶	7.1/7.3	0.03/0.03	70/73	329/392
Braga ^{w12}	63/100	45/35	100/100	ND	44.3/66.8¶	13.1/22.7**	ND	46/57	580/580
Bonnema ^{w13}	79/87	61/57	23/38	45/41	96.7/90.6†	1.8/1.8‡	0.05/0.09	65/65	400/400
Bonnema ^{w14}	95/89	55/58	31/49	34/41	83/82†	1.6/1.8‡	0.43/0.02	44/62	267/277

ND=not described; T4=levothyroxine, T3=tri-iodothyronine; TSH=thyroid stimulating hormone.

*Thyroid size in grams.

†Free T4 index.

‡FreeT3 index.

§Patients' characteristics at time of radioiodine therapy.

¶Free T4 (pmol/l).

**FreeT3 (pmol/l).

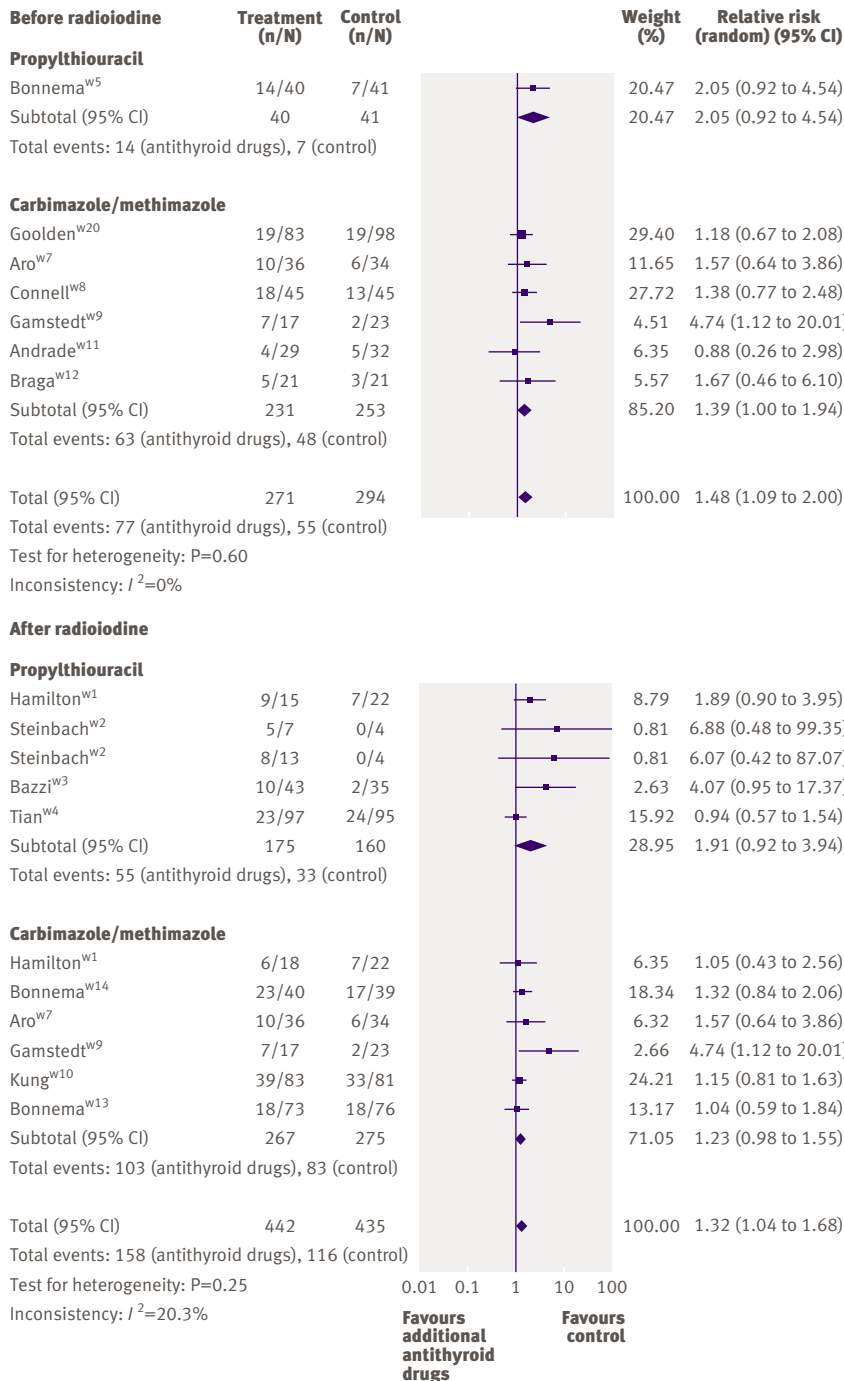


Fig 2 | Risk of treatment failure with antithyroid drugs given before or after radioiodine treatment

Chinese,^{w4} all publications were reported in English, and, with the exception of three trials,^{w1 w4 w7} the follow-up period was one year. The quality of methods of included trials was generally poor; few studies reported adequate methods for randomisation and blinding. Over the 54 years, different criteria were used to assess the thyroid status (table 1). Overall, 1269/1306 (97%) participants completed follow-up. The participants' mean age ranged from 37 years to 60 years, and the applied median dose of radioiodine varied between 158 and 585 MBq. Apart from one trial,^{w2} all reports included men and

women and, with the exception of five trials,^{w5 w7 w8 w13 w14} included only patients with Graves' disease (table 2). Several studies administered additional β adrenergic blocking agents to all patients,^{w12} to the controls only,^{w7} or solely to patients with severe hyperthyroidism.^{w3 w5 w10 w11 w13 w14} Five trials gave antithyroid drugs before radioiodine treatment,^{w5 w6 w8 w11 w12} seven trials gave them at the same time or after,^{w1-w4 w10 w13 w14} and two trials gave them before and after.^{w7 w9}

Treatment failure

The summary risk ratio for treatment failure with adjunctive antithyroid drugs compared with control was 1.28 (95% confidence interval 1.07 to 1.52; P=0.006). There was no difference in summary estimates for different antithyroid drugs. A similar risk ratio was obtained on the basis of a per protocol analysis (1.34, 0.96 to 1.88; P=0.09). Subgroup analysis revealed a risk ratio of 1.48 (1.09 to 2.00; P=0.01) when antithyroid drugs were given before radioiodine treatment and 1.32 (1.04 to 1.68; P=0.03) when they were given simultaneously or after radioiodine treatment (fig 2). Heterogeneity among treatment effects was low. The funnel plot indicated an asymmetric distribution (Egger's test P=0.002) with a larger effect size in smaller studies. When we excluded the three smallest studies we found a significantly increased risk of treatment failure (1.21, 1.00 to 1.45; P=0.04) and lower evidence for funnel plot asymmetry (Egger's test P=0.15).

Hypothyroidism

The summary risk ratio for hypothyroidism with adjunctive antithyroid drugs compared with control was 0.68 (0.53 to 0.87; P=0.006). Again, there was no difference in summary estimates for the different antithyroid drugs. A per protocol analysis revealed a similar risk ratio (0.77, 0.54 to 1.10; P=0.15). The risk ratio was 0.76 (0.57 to 1.01; P=0.06) when antithyroid drugs were given before radioiodine treatment and 0.57 (0.41 to 0.78; P<0.001) when they were given simultaneously or after radioiodine treatment (fig 3). Heterogeneity among treatment effects was low to moderate. The funnel plot indicated an asymmetric distribution (Egger's test P=0.022) with a larger effect size in smaller studies. When we excluded the three smallest studies sensitivity analysis showed a significant reduction in risk of hypothyroidism (0.80, 0.68 to 0.95; P=0.01) and lower evidence for funnel plot asymmetry (Egger's test P=0.13).

Sensitivity analyses

We found a trend towards a higher risk of treatment failure in the two trials using fixed radioiodine doses^{w9 w12} (2.68, 0.96 to 7.44) compared with the five trials that adapted dose calculation according to uptake^{w5-w8 w11} (1.38, 1.00 to 1.91) when antithyroid drugs were given before radioiodine. We found a trend towards larger effects on treatment failure (1.39, 1.00 to 1.94) and hypothyroidism (0.74, 0.54 to 1.02) in the six trials with high doses of antithyroid drug^{w1 w3 w7-w10} compared with

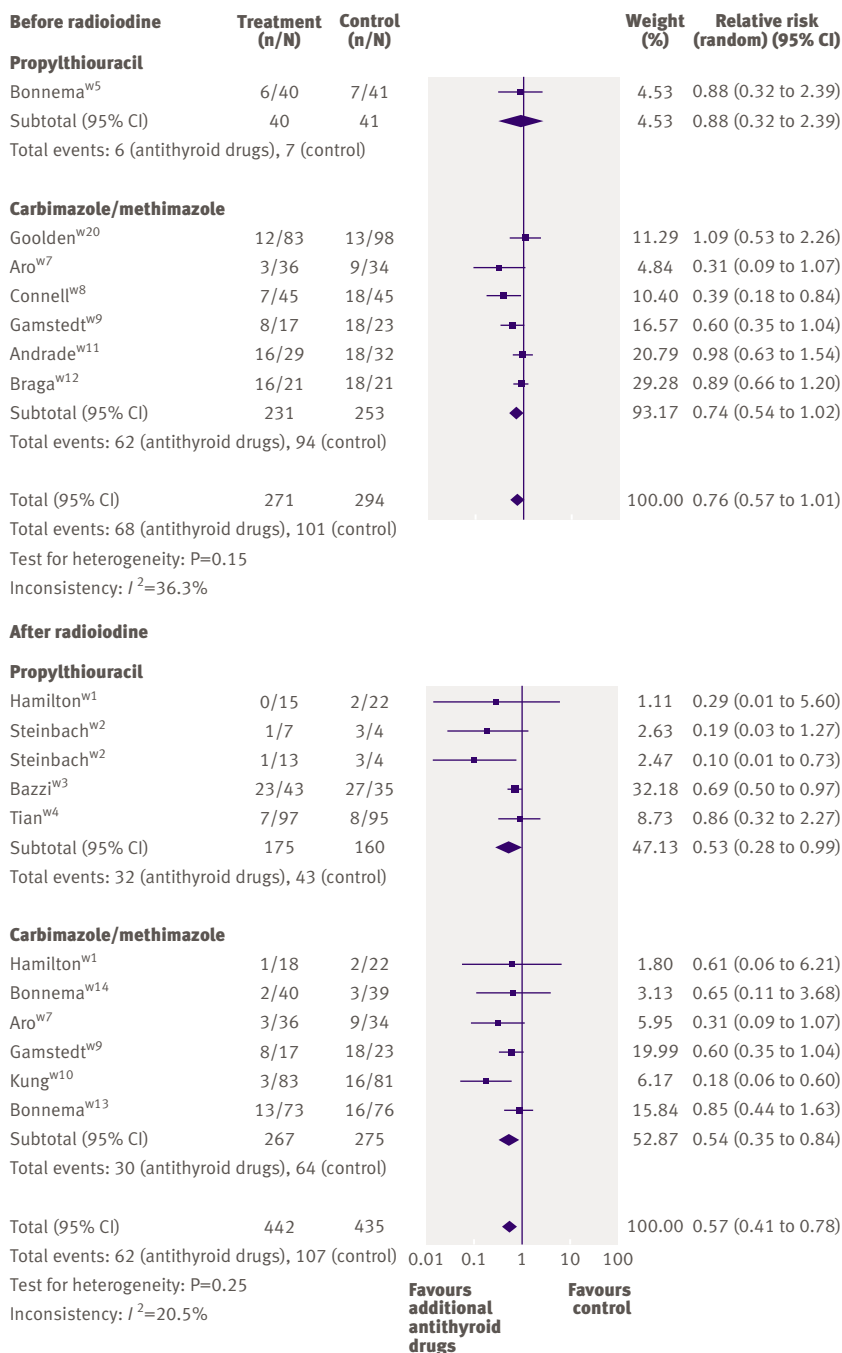


Fig 3 | Risk of hypothyroidism with antithyroid drugs given before or after radioiodine treatment

the three trials using lower doses^{w4 w13 w14} after radioiodine (1.11, 0.83 to 1.48, for treatment failure; 0.83, 0.49 to 1.39, for hypothyroidism). There was no difference in treatment effects for different discontinuation intervals of antithyroid drug, the use of a TSH assay for definition of thyroid status, or patients with Graves' disease or toxic nodular goitre, or both.

Correlation of radioiodine activity and outcome

Logistic regression showed a highly significant correlation between the administered radioiodine activity and the rates of hypothyroidism (P<0.001) and successful treatment (P<0.001) (fig 4).

Acute complications of antithyroid drugs and radioiodine

Adverse events with antithyroid drugs were reported in 12/660 participants (1.8%), including one non-specified allergic reaction in 233 patients (0.4%) taking propylthiouracil^{w5} and 10 allergic skin reactions and one transient neutropenia in 263 patients (4.2%) taking methimazole.^{w5 w10 w11} Seven trials systematically monitored thyroid hormone concentrations in the weeks before or after radioiodine treatment, or both. Pretreatment with antithyroid drugs reduced concentrations of serum thyroid hormones before radioiodine treatment (mean time to achieve euthyroidism 7-12 weeks) and until six weeks after radioiodine treatment.^{w5 w7 w9 w11 w12} Antithyroid drugs given with or after radioiodine treatment reduced thyroid hormone concentrations until eight weeks after radioiodine treatment.^{w7 w13 w14} One trial monitored the acute clinical course after radioiodine treatment using the Crooks-Wayne hyperthyroidism score and found significant improvement with adjunctive antithyroid drugs compared with the controls.^{w7} New onset atrial fibrillation after radioiodine treatment was reported in 1/660 (0.2%) patients with additional antithyroid drugs and in 3/646 (0.5%) patients without additional antithyroid drugs. Death after radioiodine treatment was reported for 1/660 (0.2%) patients with and 6/646 patients (0.9%) without adjunctive antithyroid drugs.

DISCUSSION

In patients undergoing radioiodine treatment for hyperthyroidism, antithyroid drugs affect the rates of treatment failure and hypothyroidism and may affect morbidity and mortality in the year after treatment.

Failures of radioiodine treatment include persistent and recurrent hyperthyroidism, which increases the cardiovascular risk and necessitates further treatment.¹⁻⁴ Conversely, hypothyroidism requires regular and life long follow-up and consumption of healthcare resources for titration of the optimal dose of levothyroxine. The influence of antithyroid drugs on rates of failure and hypothyroidism with radioiodine treatment has been debated for decades, and most randomised controlled trials have been underpowered to detect significant

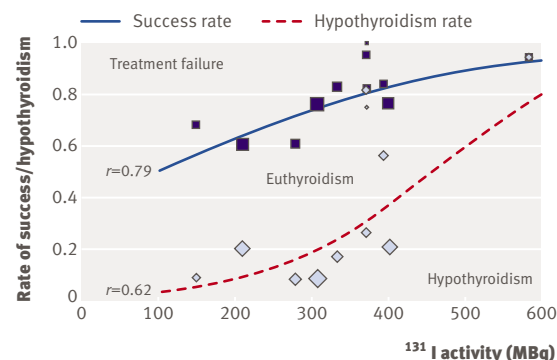


Fig 4 | Association between radioiodine activity and rates of success and hypothyroidism derived from logistic regression model. Size of squares and diamonds corresponds to number of participants in individual studies

WHAT IS ALREADY KNOWN ON THIS TOPIC

Antithyroid drugs are often used before, during, or after radioiodine treatment for hyperthyroidism

There is still disagreement about the overall beneficial and detrimental effects and the optimal sequencing of the different antithyroid drugs before or after radioiodine treatment

WHAT THIS STUDY ADDS

Adjunctive antithyroid drugs reduce the biochemical exacerbation of hyperthyroidism directly after radioiodine treatment

When given in the week before or after radioiodine, antithyroid drugs increase the failure rates and reduce the hypothyroidism rates

effects on either outcome. Importantly, our meta-analysis suggests increased treatment failures if antithyroid drugs are given before, with, or after radioiodine treatment and a reduced risk of hypothyroidism, especially if antithyroid drugs are given with or after radioiodine treatment. Considering the progressive nature of the yearly increasing incidence of hypothyroidism after radioiodine treatment,^{w1015} however, the extent of the protective effect of antithyroid drugs remains uncertain.

About 10% of patients experience an acute subclinical rise in concentrations of thyroid hormone after radioiodine treatment,⁷ and about 0.3% experience exaggerated hyperthyroidism including thyroid storm. The mortality from thyroid storm is about 25%, mainly from cardiac and cerebrovascular events, and use of adjunctive antithyroid drugs may prevent its occurrence.¹⁶ Yet the frequency of thyroid storm and the mortality associated with radioiodine treatment with and without antithyroid drugs have not been systematically investigated. Our systematic review suggests that adjunctive antithyroid drugs reduce biochemical and clinical hyperthyroidism in the weeks after radioiodine treatment; however, this was not systematically monitored in all trials. In accordance with these findings, we found lower cardiac morbidity and mortality with adjunctive antithyroid drugs, though this was not significant and neither events were primary outcomes. Furthermore, the small number of events precludes firm conclusions. Adverse events with antithyroid drugs were reported, even though the overall prevalence of 2% was lower than expected,¹⁰ probably because primary trials excluded patients with known allergies.

There is an ongoing controversy about potential differences in the influence of propylthiouracil and imidazoles on radioiodine treatment. Four studies have compared these drugs so far. Two non-randomised studies found greater effects with propylthiouracil than with methimazole,^{17 18} but one randomised controlled trial^{w1} and one non-randomised study did not support these findings.¹⁹ Our meta-analysis found no disparity; nevertheless, data from non-randomised studies suggest more distinct and protracted effects with propylthiouracil than with imidazoles (see fig A on [bmj.com](#)). According to the non-randomised studies, methimazole or carbimazole could be preferable to render euthyroidism when planning radioiodine therapy.

Pretreatment with antithyroid drugs potentially decreases the uptake of iodine.^{20 21} In a sensitivity

analysis we found some evidence that dose regimens that were adapted to uptake, rather than fixed dose regimens, possibly compensate for this effect. Although the effects of antithyroid drugs on the outcome of radioiodine treatment have been attributed to the decrease in uptake of iodine, we found that antithyroid drugs can influence the outcome when they are taken in the week after radioiodine treatment. Therefore, their effect is unlikely to be solely mediated by alteration of iodine kinetics. Rather, the inhibition of the thyroid peroxidase catalysed synthesis of oxygen free radicals,²² which mainly mediate cell damage in radioiodine treatment, seems to be more likely. Our meta-analysis indicates that antithyroid drugs reduce the effectiveness of radioiodine, and this could be over-ridden by increasing the radioiodine dose.

Strengths and limitations of study

Despite more than six decades of empiric combination treatment for hyperthyroidism, the quantity of evidence is limited. We cannot rule out publication bias, though we performed an extensive literature search, contacted experts, and identified eligible trials published in several languages as early as 1952. The reported methodological quality of most included trials was low, and we could not perform sensitivity analyses according to quality components. The different discontinuation intervals, the inclusion of patients with Graves' disease and toxic nodular goitre, the different criteria defining thyroid status, the different doses of antithyroid drug and radioiodine, and the use of adapted dose or fixed dose models were potential sources of heterogeneity. Nevertheless, the heterogeneity of all effects was generally low, and we performed additional sensitivity analyses to study sources of the remaining heterogeneity. Additionally, we found robust treatment effects after we excluded the smallest trials from the analyses. Yet, limited information on the size of goitre at baseline and lack of specification of the degree of iodine sufficiency in individual trials precluded a more extensive sensitivity analysis. We also collected data from non-randomised studies that support the results of the randomised trials and indicate an effect of antithyroid drugs on radioiodine treatment even after long term withdrawal. As antithyroid drugs are widely used as first line treatment and several patients in the control arms in some studies had antithyroid drugs withdrawn several weeks before radioiodine treatment, our risk estimates for hypothyroidism and treatment failure might even be underestimated.

This meta-analysis, in contrast with the conclusions of most single trials, suggests that antithyroid drugs increase rates of failure and reduce rates of hypothyroidism when they are given in the week before or after radioiodine treatment. Results from trials included into this review, however, do not allow us to draw firm conclusions regarding the optimal interruption period of antithyroid drugs for patients undergoing radioiodine treatment to avoid both relapse of hyperthyroidism and cardiovascular complications while keeping the long term risk of hypothyroidism at an acceptable level. In some patients long term monitoring for detection of

hypothyroidism may not be guaranteed and therefore withholding antithyroid drugs to allow for the early development and substitution of hypothyroidism may be considered an option. Adequately powered randomised long term follow-up trials are needed to examine a potential superiority of longer discontinuation intervals of different antithyroid drugs to avoid relapse of hyperthyroidism and to minimise the risk of hypothyroidism. Quality of life during and after radioiodine treatment under these different regimens and cardiovascular morbidity and mortality should also be monitored.

We thank Peter Wolf for assistance in electronic libraries search and Liu Kun, Sibylle Tschumi, and Martin Stoecklin for translations. We also thank Marcel Wolbers for statistical advice and Helmut Rasch and Anthony Toft for their valuable comments on the manuscript.

Contributors: MAW designed the study, collected and analysed the data, wrote the manuscript, and is guarantor. MB performed quality assessment, did all statistical analyses, and participated in the design of the study and writing of the manuscript. MC-C performed data extraction and quality assessment and contributed to the writing of the manuscript. SJB, DSC, JC, HCB, and JM-B participated in data collection, interpretation, and writing of the manuscript. BM directed study design, data analysis, and writing of the manuscript.

Funding: MB and HCB are supported by grants from santésuisse and the Gottfried and Julia Bangerter-Rhyner-Foundation.

Competing interests: None declared.

Ethical approval: Not needed.

- 1 Lazarus JH. Hyperthyroidism. *Lancet* 1997;349:339-43.
- 2 Parle JV, Maisonneuve P, Sheppard MC, Boyle P, Franklyn JA. Prediction of all-cause and cardiovascular mortality in elderly people from one low serum thyrotropin result: a 10-year cohort study. *Lancet* 2001;358:861-5.
- 3 Sawin CT, Geller A, Wolf PA, Belanger AJ, Baker E, Bacharach P, et al. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. *N Engl J Med* 1994;331:1249-52.
- 4 Cappola AR, Fried LP, Arnold AM, Danese MD, Kuller LH, Burke GL, et al. Thyroid status, cardiovascular risk, and mortality in older adults. *JAMA* 2006;295:1033-41.
- 5 Sawin CT, Becker DV. Radioiodine and the treatment of hyperthyroidism: the early history. *Thyroid* 1997;7:163-76.
- 6 Becker DV. Choice of therapy for Graves' hyperthyroidism. *N Engl J Med* 1984;311:464-6.
- 7 Cooper DS. Hyperthyroidism. *Lancet* 2003;362:459-68.
- 8 Franklyn JA. The management of hyperthyroidism. *N Engl J Med* 1994;330:1731-8.
- 9 Solomon B, Glinoe D, Lagasse R, Wartofsky L. Current trends in the management of Graves' disease. *J Clin Endocrinol Metab* 1990;70:1518-24.
- 10 Cooper DS. Antithyroid drugs. *N Engl J Med* 2005;352:905-17.
- 11 Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. *BMJ* 1997;315:1533-7.
- 12 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60.
- 13 Sterne JA, Egger M, Smith GD. Systematic reviews in health care: Investigating and dealing with publication and other biases in meta-analysis. *BMJ* 2001;323:101-5.
- 14 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-34.
- 15 Holm LE, Lundell G, Israelsson A, Dahlqvist I. Incidence of hypothyroidism occurring long after iodine-131 therapy for hyperthyroidism. *J Nucl Med* 1982;23:103-7.
- 16 McDermott MT, Kidd GS, Dodson LE Jr, Hofeldt FD. Radioiodine-induced thyroid storm. Case report and literature review. *Am J Med* 1983;75:353-9.
- 17 Santos RB, Romaldini JH, Ward LS. Propylthiouracil reduces the effectiveness of radioiodine treatment in hyperthyroid patients with Graves' disease. *Thyroid* 2004;14:525-30.
- 18 Imseis RE, Vanmiddlesworth L, Massie JD, Bush AJ, Vanmiddlesworth NR. Pretreatment with propylthiouracil but not methimazole reduces the therapeutic efficacy of iodine-131 in hyperthyroidism. *J Clin Endocrinol Metab* 1998;83:685-7.
- 19 Alexander EK, Larsen PR. High dose of (131)I therapy for the treatment of hyperthyroidism caused by Graves' disease. *J Clin Endocrinol Metab* 2002;87:1073-7.
- 20 Walter MA, Christ-Crain M, Muller B, Muller-Brand J. Radioiodine uptake and thyroid hormone levels on or off simultaneous carbimazole medication: a prospective paired comparison. *Nuklearmedizin* 2005;44:33-6.
- 21 Sabri O, Zimny M, Schulz G, Schreckenberger M, Reinartz P, Willmes K, et al. Success rate of radioiodine therapy in Graves' disease: the influence of thyrostatic medication. *J Clin Endocrinol Metab* 1999;84:1229-33.
- 22 Wilson R, McKillop JH, Buchanan LM, Bradley H, Smith WE, Thomson JA. The effect of carbimazole therapy on interleukin 2, interleukin 2 receptors and free radicals. *Autoimmunity* 1990;8:3-7.

Accepted: 4 January 2007