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Block-and-replace regimen versus titration of antithyroid drugs: a recent meta-analysis

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Abstract

Introduction: Drug therapy for Graves' disease (GD) is the first-line treatment in Europe. The use of a specific regimen for the administration of anti-thyroid drugs (ATDs) is still controversial. The objective was to compare block-and-replace therapy (BRT) with a titration (T) regimen in terms of incidence of overt hypothyroidism and development of Graves' orbitopathy (GO) over 18 months of treatment.
Material and methods: Two databases (PubMed, Cochrane Library) and reference lists were searched. Prospective and retrospective observational cohort studies were included. Data collection and analysis were performed independently by 2 authors.
Results: Two studies with 716 GD patients (40.36% treated with BRT, 59.64% with T regimen) were included. No statistically significant differences were observed between the ATDs regimens used in terms of incidence of overt hypothyroidism during 18 months of treatment [Mantel-Haenszel (M-H) odds ratio (OR): 1.54, 95% confidence interval (CI): 0.75–3.16, p-value = 0.24]. GD patients who followed BRT were less likely to achieve control of thyroid function than patients on T regimen (M-H OR: 0.55, 95% CI: 0.34–0.88, p = 0.01). One study reported fewer thyroid function tests (TFT) during BRT than during the T regimen. The other study included patients without GO at baseline and reported a lower incidence of GO during BRT than in the T regimen (9.1% versus 17.8%), with no statistical difference between the 2 regimens (M-H OR: 0.47, 95% CI: 0.19–1.14, p = 0.10).
Conclusion: BRT may be more useful than the T regimen for patients with complicated GD or for those who required fewer TFTs.
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Key words: *thyroid; Graves; block-replace; titration*

Introduction

Graves' disease (GD) is the most common cause of hyperthyroidism in iodine-replete regions, usually affecting women aged 40 to 60 years old [1]. It is an autoimmune disorder characterized by the presence of thyroid-stimulating hormone receptor antibodies (TRAb) that stimulate follicular thyroid cells to synthesize and secrete thyroxine (T_4) and triiodothyronine (T_3) [2]. Consequently, the thyroid gland increases its volume and vascularity. The main extra-thyroidal manifestation is Graves' orbitopathy (GO), which affects 20% of patients with Graves' hyperthyroidism (GH) [3]. GD is easily recognized by the triad: thyrotoxicosis, diffuse goiter, and ophthalmopathy [4].

Management of GD implies drug treatment using anti-thyroid drugs (ATDs) in different regimens, radioactive iodine (RAI), or thyroidectomy (Tx) [5]. The first-line treatment in Europe is anti-thyroid medication, while in the United States RAI is preferred [6]. The course of GO is not influenced by thionamides or surgery, but it is worsened by RAI treatment [7]. RAI and total thyroidectomy (TTx) have a low risk for hyperthyroidism recurrence, but patients require lifelong treatment with levothyroxine (LT_4) [8]. Using ATDs, the risk of GD recurrence is ~50% [9].

The main ATDs used are carbimazole (CBZ), with its active metabolite methimazole (MMI) and propylthiouracil (PTU). They control hyperthyroidism by inhibiting thyroid hormone synthesis and by their immunosuppressive effect. In addition, PTU inhibits the peripheral conversion of T_4 to T_3 [10]. The most common adverse reactions are skin rash, arthralgia, and transient mild leukopenia, which develop in 1% to 5% of patients. Very rarely (< 0.1% of cases) agranulocytosis may occur with MMI or CBZ therapy and liver failure during PTU therapy [11]. The optimal duration of ATDs administration is considered to be 12–18 months [12].

ATDs can be administrated in a titration (T) regimen or using a block-and-replace regimen, as first described by Hashizume [13]. No difference was observed be-

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tween the risk of GD relapse between the 2 treatment regimens or in the duration of therapy [12]. However, no systematic review has described the control of thyroid function during block and replace therapy (BRT) versus T of ATDs and how these therapies would influence the onset of GO.

We want to assess the control of GH during ATDs therapy. We compared ATDs used in a block-and-replace regimen versus a T regimen to evaluate the incidence of overt hypothyroidism during therapies, the number of euthyroid patients during 18 months of treatment, and the number of thyroid function tests (TFT) during therapies. Secondary outcomes are assessment of GO development, body weight changes, and lipid profile evolution in the BRT group versus the T group.

Material and methods

Criteria for considering studies for this review

Types of studies

Prospective and retrospective cohort studies that met the inclusion criteria were included in this systematic review and meta-analysis. The minimum duration of therapy should be 18 months, and thyroid function should be assessed during this period.

Types of participants

Patients with a first episode of GD following medical treatment were included. Diagnosis of GD was made on documentation of thyrotoxicosis [suppressed thyroid-stimulating hormone (TSH), increased free T_4 (fT_4) and/or free T_3 (fT_3)], positive TRAb, enlarged goiter, with increased vascularity or diffuse increased radioiodine uptake on thyroid scans. Patients aged < 18 years, pregnant women, or patients with a positive history of RAI or TTx were excluded.

Types of interventions

The intervention consists of using medical therapy with ATDs in patients with GD. We compared the number of patients with overt hypothyroidism during BRT versus T regimen. After 18 months of therapy, we compared the number of patients with stable thyroid function in each group. We defined stable thyroid function as: euthyroidism (TSH and fT_4 in reference range), subclinical hypothyroidism (TSH > 4.5 mIU/L, fT_4 in reference range), and subclinical hyperthyroidism (TSH < 0.4 mIU/L, fT_4 in reference range). The ATDs used were CBZ, MMI, or PTU. BRT consisted of the addition of LT_4 to a high dose of thionamide. In addition, we compared the number of GD patients who developed GO during BRT versus T and the number of TFT performed.

Types of outcome measures

Primary outcomes

Primary outcomes included:

— incidence of overt hypothyroidism during 18 months of treatment (the recommended duration of medical treatment for GD);
— prevalence of euthyroid patients over 18 months of ATDs treatment for GD;
— number of TFT during medical therapy of GD.

Secondary outcomes

Secondary outcomes included:

— incidence of GO development during ATDs treatment for GD;
— changes in weight during medical treatment for GD;
— lipid profile changes during GD drug therapy.

Search methods for identification of studies

Electronic searches

The following sources were used to identify cohort studies:

— PubMed database (MEDLINE) — until July 2023;
— Cochrane Library (CENTRAL) — until July 2023.

The terms used to identify potential articles were: "block replace", "thyroid", and "Graves". The search was restricted to articles written in English with full text available.

Searching other resources

The reference lists of retrieved papers were searched for additional cohort studies.

Data collection and analysis

Selection of studies

Two authors independently searched the literature and evaluated each record by the title and abstract of the article. Articles containing patients diagnosed with GD on ATD treatment for a period of 18 months were read in full text. Any queries regarding the criteria for inclusion of certain articles in the meta-analysis were discussed between the authors.

Data extraction and management

The extraction of data related to the first author, name of the journal, year of publication, title, and abstract of the article was done automatically in Reference Manager. Two authors independently extracted the data on sample size, age and sex of patients, accuracy of GD diagnosis, type of intervention, duration of treatment, and outcomes (number of euthyroid patients at the end of therapy, incidence of hypothyroidism during ther-

apy, presence of GO among the patients, and number of TFT during therapy). Statistical analysis was done in Review Manager 5.4.

Assessment of risk of bias in the included studies
Two authors independently assessed the risk of bias in the studies using the Newcastle-Ottawa scale (NOS). For each answer marked with asterisk one point is added. The maximum score for each section is as follows: 4 points for Selection, 2 points for Comparability, and 3 points for Outcomes. A score higher than 7 points indicates a high quality of the study. Any disagreements were discussed between the authors.

Measures of treatment effect
We expressed dichotomous data as Mantel-Haenszel (M-H) odds ratio (OR) with 95% confidence intervals (CI) using a random-effects model. We expressed continuous variables as mean difference or adjusted mean difference.

Dealing with missing data
To have complete data we chose the original studies of each author and avoided duplicate publications. We checked the guidelines for appropriate medical management of GD (doses of drugs used, addition to LT_4). We calculated the proportion of patients lost to follow-up. We estimated the number of patients with stable thyroid function during therapy using values at different treatment endpoints.

Assessment of heterogeneity
Heterogeneity was assessed by visual inspection of the forest plot and I^2 calculation. An I^2 value greater than 75% indicates high heterogeneity, while a value less than 25% indicates low heterogeneity. For this meta-analysis a random-effects model was used.

Assessment of reporting biases
Each publication was assessed for risk of bias. In addition, forest plots were inspected for their asymmetry.

Data synthesis
We used a random-effects model to statistically process data from heterogeneous studies. For each outcome the data were combined using dichotomous variables, expressed as OR, with 95% CI.

Quality of the evidence
Two authors independently assessed the quality of evidence on main outcomes according to Grading of Recommendation, Assessment, Development, and Evaluations (GRADE) [14]. Factors such as study design or the risk of bias of each study were taken into account.

Subgroup analysis and investigation of heterogeneity
Subgroup analysis was not performed.

Sensitivity analysis
We only included published articles written in English that met the inclusion criteria and that we assessed for risk of bias. For each outcome we statistically processed using both fixed-effect and random effect-models and expressed the results in risk ratio (RR), OR, and risk difference.

Results

Description of studies
The publication dates of the articles included in the meta-analysis are from 2014 to the present day. One study included patients from a single center [15], and the other study is a multicenter study, including 10 centers from Europe [16]. Both articles included observational cohort studies.

Results of the search
Two databases were searched, including a total of 115 studies: PubMed (MEDLINE) — 62 studies and Cochrane Library (CENTRAL) — 53 studies. An additional search was done using reference lists of retrieved articles. Three more studies were subsequently added. Duplicate papers and those without full-text available or not written in English were excluded. Also, articles that were not in accordance with the terms: "block replace", "thyroid", or "Graves" were excluded. Twenty-seven articles were sought for retrieval, and 17 of them were screened for eligibility (Fig. 1). Twelve articles [17–28], one conference paper [29], and 2 clinical trials were excluded.

Included studies
Only 2 articles were included in this meta-analysis and used for data abstraction (Tab. 1). Each study had 2 subgroups of patients: those who underwent BRT and those who underwent a T regimen of ATDs.

Overview of study population
The two studies included 794 GD patients who completed 18 months of treatment, but only 716 patients were included in the statistical analysis. We excluded 78 patients treated using both BRT and T [15]. In total, 289 (40.36%) GD patients were on BRT and 427 (59.64%) GD patients were on T. Approximately 8.75% (33/377) of patients were lost at follow-up [16].

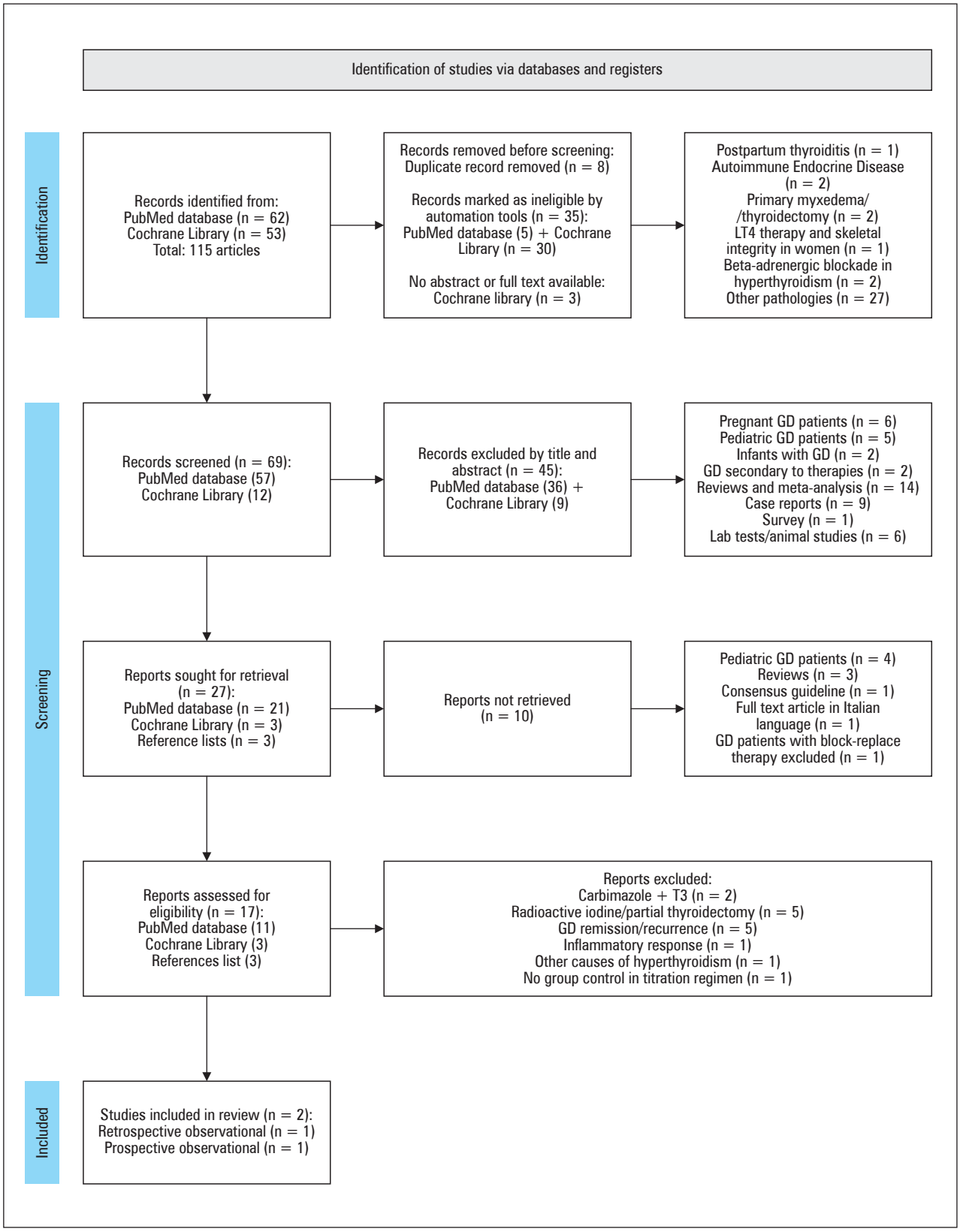

Figure 1. *PRISMA chart*

Study design and settings

The 2 cohort studies included were performed between 1997 and 2015. One was conducted in a retrospective design [15], while the other had a prospective design [16]. Consecutive hospitalized patients who followed ATD therapy for GD were included. Each main group

Table 1. *Characteristics of included studies*

Vaidya, 2014	
Study design	Retrospective observational cohort study
Patients	**Location:** single center, Royal Devon & Exeter Hospital, United Kingdom
	Period of study: 1 January 1997–31 January 2012
	Inclusion criteria: Patients with GD
	Diagnostic criteria: thyrotoxicosis with presence of a diffuse goiter, thyroid eye disease, positive TSH receptor antibodies (TRAb), thyroid peroxidase antibodies (TPO-Ab) or diffuse uptake on radionuclide uptake scan
	Exclusion criteria: Patients with thyrotoxicosis due to causes other than GD, GD treated with ATD < 6 months, GD treated with radioactive iodine or thyroidectomy and pregnancy
	Data collection: electronic database; data from the first episode of GD; data from the first 2 years of treatment with ATDs
	No. patients: Total: 450; BRT: 223; T: 149; Both regimens: 78
	Sex F/M: BRT: 178/45; T: 129/20
	Age [years] (mean (SD)): BRT: 49 (15); T:49 (18)
	Baseline characteristics: No statistically significant differences
Intervention	**BRT:** CBZ + LT_4
	T: CBZ/PTU
Outcome	**Main outcomes:**
	1. Stability of thyroid function during BRT versus T regimen
	2. Number of thyroid function test during BRT versus T regimen
	Secondary outcome:
	Changes in weight during medical treatment for GD
Study details	**Duration of therapy (months):** BRT: 20; T: 19
Publication details	**Language of publication:** English
Risk of bias	Newcastle-Ottawa Quality Assessment Scale (NOS): 7/9
Žarković, 2020	
Study design	Prospective observational cohort study
Patients	**Location:** multicenter [10 centers of the European Group of Graves' Orbitopathy (EUGOGO)]
	Period of study: May 2009–May 2015
	Inclusion criteria: Patients with untreated GH, absence of overt GO, and planned treatment with ATD for 18 months
	Diagnostic criteria: GH: (1) decreased TSH, elevated fT_4 and/or fT_3, and (2) a diffuse thyroid gland (either by palpation or ultrasonography) and/or homogeneous thyroid uptake at scintigraphy
	GO: (1) soft tissue changes (moderate or severe eyelid/conjunctival redness, moderate or severe eyelid/periorbital swelling); (2) proptosis above the upper normal limit (Asians 18 mm, Caucasian 20 mm, Black 22 mm); (3) diplopia (intermittent, inconstant, or constant), (4) decreased visual acuity attributable to GO
	Exclusion criteria: (A) previous or planned treatment with 131-I or thyroidectomy; (B) presence of GO; (C) drugs interfering with the natural course of GO (e.g., glucocorticoids, cytokines, anticytokines, thiazolidinediones, selenium); (D) drugs interfering with thyroid function (amiodarone, lithium, iodine supplements); (E) drug or alcohol abuse; (F) lack of informed consent
	Data collection: no description
	No. patients: Total: 344; BRT: 66; T:278
	Sex F/M: BRT: 53/13; T: 231/47
	Age [years] (mean (SD)): BRT: 41.6 (14.5); T: 43.1 (12.8)
	Baseline characteristics: No statistically significant differences except for overrepresentation of non-Caucasians in the BRT group
Intervention	**BRT:** ATD + LT_4
	T: ATD

→

Table 1. *Characteristics of included studies*

Outcome	Main outcome: Frequency of euthyroidism during BRT versus T regimen Secondary outcomes: Development of GO during BRT versus T regimen
Study details	**Duration of therapy (months):** BRT: 18; T: 18
	Allocated: BRT: 83; T: 305
	Completed: BRT: 66; T: 278
	Assessed: BRT: 66; T: 278
Publication details	**Language of publication:** English
Risk of bias	Newcastle-Ottawa Quality Assessment Scale (NOS): 7/9

GD — Graves' disease; TSH — thyroid-stimulating hormone; ATD — anti-thyroid drug; BRT — block-and-replace therapy; T — titration; SD — standard deviation; CBZ — carbimazole; LT4 — levothyroxine; PTU — propylthiouracil

was divided into 2 subgroups according to the ATD regimen used.

Participants

Patients included in both studies had a mean age of 40 years. Female patients were more prevalent in both studies: 82.52% (307/372) [15] and 82.55% (284/344) [16]. The number of current smokers was 29.36 % (101/344) in the first study and 21.5% (80/372) in the second one. Only one study [16] reported a higher prevalence of non-Caucasian patients in the block-and-replace subgroup.

Diagnosis

In both studies, the diagnosis of GD was based on the association of hyperthyroidism (suppressed TSH, increased fT_4 and/or fT_3), diffuse goiter (ultrasound/scintigraphy), and positive TRAb. The presence of extra-thyroidal manifestations of GD (e.g., GO, dermopathy) at baseline as a diagnostic criterion was included in only one study [15].

Intervention

All patients included in the 2 studies were at their first episode of GD and were treated with ATDs ± LT_4. Duration of treatment was 18 months regardless of the regimen used. One study [15] reported the use of CBZ and PTU as ATDs. None of the studies described the drug doses used or the method of administration. We assumed that the doses of drugs used were in line with current guidelines. Five centers used both ATDs regimens to treat GD patients and 6 centers used only the T regimen.

Outcomes

Both studies aimed to determine the maintenance of stable thyroid function during drug therapy and express the frequency of euthyroidism and overt hypothyroidism over 18 months of treatment. One study provided information on the number of thyroid function tests [15], and the other on the number of patients who developed GO during therapy [16].

Excluded studies

The main reasons for exclusion of studies initially considered as eligible were as follows: block-and-replace therapy consisting of the addition of T_3 to ATDs [27,28], absence of a control group [22], assessment of risk of relapse of GD (short duration of therapy or no assessment of thyroid function during therapy) [18, 19, 24, 26, 30], inclusion of patients with RAI and/or TTx [20, 21, 23], and hyperthyroidism of other causes or other primary outcomes [17, 29] (Tab. 2).

Risk of bias in the included studies

The risk of bias was assessed using the Newcastle-Ottawa scale (NOS). Both studies scored 7/9 points, indicating high study quality (Tab. 3).

Allocation

The allocation of GD patients to a particular type of ATDs regimen was not mentioned in any of the studies.

Blinding

This criterion was not applied for the type of studies included in the meta-analysis.

Incomplete outcome data

The percentage of patients lost to follow-up during therapy was low (8.75%) and was not taken into consideration in the statistical analysis. In one study, the percentage of euthyroid patients or patients with abnormal thyroid function during therapy was expressed at different endpoints of treatment. We used these values to calculate an average number of patients with normal or abnormal thyroid function tests.

Table 2. *Characteristics of excluded studies ordered by the name of the first author/identification name of the clinical trial*

Study	Reason for exclusion
Bonnema 2011	Other causes of hyperthyroidism (toxic nodular goiter)
Elbers 2011	Recurrence of GD
Grebe 1998	Recurrence of GD
Kung 1994	RAI
Kung 1995	RAI
Lantz 2016	No group control
Laurberg 2011	RAI + partial thyroidectomy
McIver 1996	Recurrence of GD
NCT02568085 (clinical trial), 2018	Thyroidectomy
Rittmaster 1996	Remission of GD
Stefanic 2014	Remission of GD
Rodionova 2015	Inflammatory response (level of cytokines)
UMIN000022261 (clinical trial), 2019	RAI
Wise 1973	CBZ + T_3
Wise 1979	CBZ + T_3

GD — Graves' disease; RAI — radioactive iodine; CBZ — carbimazole; T3 — triiodothyronine

Selective reporting

The 2 studies had a low risk of bias and reported data on thyroid function testing over 18 months of medical treatment of GD. However, outcomes such as development of GO during therapy were not reported in one study [15]. Weight gain during therapy was not reported in the other study [16]. None of the studies reported data on lipid profile changes during medical therapy of GD.

Other potential sources of bias

Other potential sources of bias could be estimating the number of patients with stable thyroid function by including subclinical hypothyroidism and/or hyperthyroidism. Also, the number of patients with stable thyroid function during therapy in one study was obtained by calculating an average of the number of patients at different treatment endpoints.

Effects of intervention

The main results of this meta-analysis are the proportion of patients with overt hypothyroidism and euthyroidism during 18 months of treatment with ATDs using a block-and-replace regimen versus a T regimen.

Baseline characteristics

No differences were observed between studies in terms of mean age of groups, proportion of female gender, current smokers, or duration of therapy. At baseline in both studies, the mean TSH was less than 0.03 mIU/L and fT_4 was 1.5 times the upper normal limit (UNL). Only one of the studies [16] included patients without GO at baseline.

Primary outcomes

Incidence of overt hypothyroidism

No statistically significant differences were observed between the ATD regimens used in terms of incidence of overt hypothyroidism during 18 months of treatment (M-H OR: 1.54, 95% CI: 0.75–3.16, p-value = 0.24) (Fig. 2**A**). Only 8.3% (24/289) of patients treated with a block-and-replace regimen had clinical hypothyroid-

Table 3. *Assessment of risk of bias. Newcastle-Ottawa scale (NOS) cohort studies used*

		Author, Year	
NOS		**Vaidya, 2014**	**Zarkovic, 2020**
Selection	Representativeness of the exposed cohort	*	*
	Selection of the non-exposed cohort	*	*
	Ascertainment of exposure	*	
	Demonstration that outcome of interest was not present at start of study	*	*
Comparability	Comparability of cohorts on the basis of the design or analysis	*	**
Outcome	Assessment of outcome	*	
	Was follow-up long enough for outcomes to occur	*	*
	Adequacy of follow up of cohorts		*
Total score		7/9	7/9

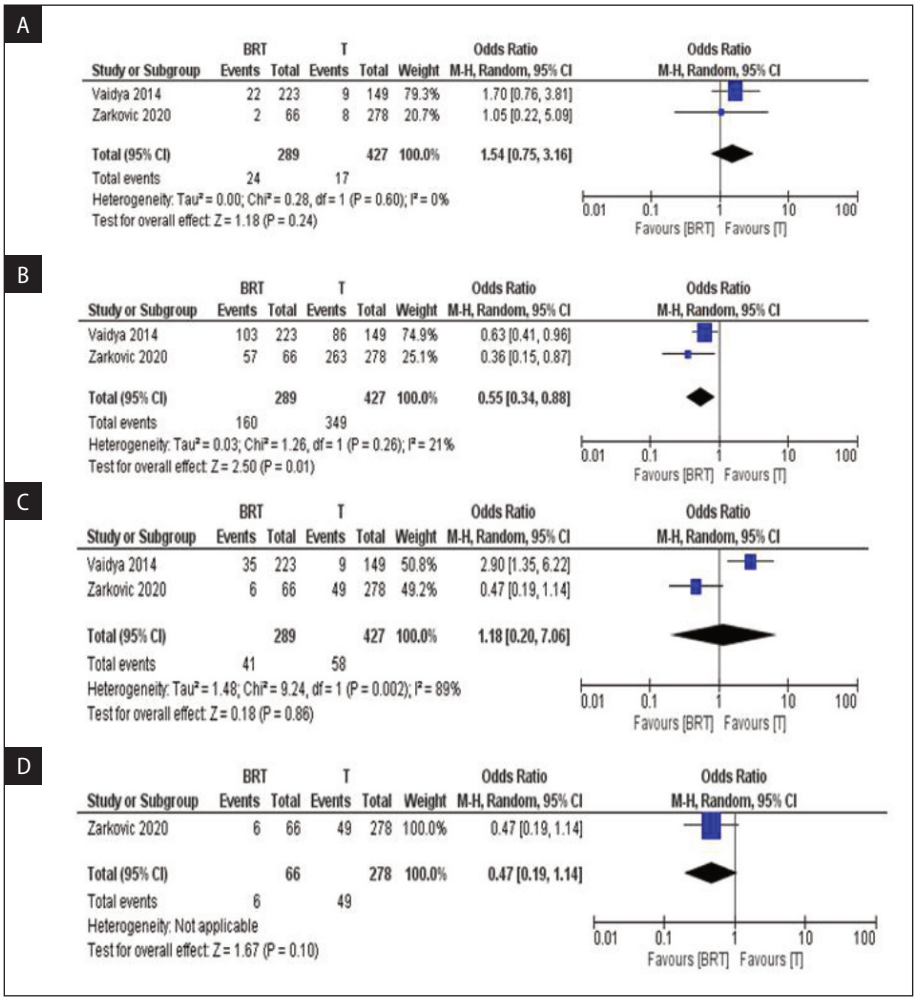

Figure 2. A. *Forest plot of comparison 1: Number of patients with overt hypothyroidism during 18 months of block-and-replace therapy (BRT) versus titration (T). Main outcome: 1. Incidence of overt hypothyroidism during 18 months of medical treatment of Graves' disease (GD).* **B**. *Forest plot of comparison 2: Prevalence of euthyroid patients over 18 months of BRT versus T. Main outcome: 2. Prevalence of euthyroid patients over 18 months of anti-thyroid drugs (ATDs) treatment for GD.* **C.** *Forest plot of comparison 3: Incidence of GO development during medical treatment. Secondary outcome: 1. Incidence of GO development during ATDs treatment for GD.* **D**. *Forest plot of comparison 4: Incidence of GO development during medical treatment. Secondary outcome: 1. Incidence of GO development during ATDs treatment for GD. BRT — block-and-replace therapy; CI — confidence interval; M-H — Mantel-Haenszel odds ratio*

ism, compared to 3.98% (17/427) of patients on the titration (T) regimen.

Prevalence of euthyroidism

GD patients who followed a block-and-replace therapy were less likely to achieve control of thyroid function than patients on a titration regimen (M-H OR: 0.55, 95% CI: 0.34–0.88, p = 0.01) (Fig. 2B). In this statistical analysis, all patients who achieved euthyroidism, or subclinical hypo- or hyperthyroidism were considered to have obtained control of overt hyperthyroidism due to GD.

Number of TFT during medical therapy

The number of TFT was assessed in one study during medical treatment of GD. Patients on BRT performed on average 3.2 ± 1.2 thyroid function tests per year, while patients on the T regimen required 3.4 ± 1.5 tests per year (adjusted mean difference –0.4, 95% CI: –0.7; –01, p = 0.008) [15].

Secondary outcomes

Incidence of GO development during ATD treatment

We assumed that both studies included at baseline GD patients without GO. No statistically significant difference in terms of incidence of GO development during BRT versus T regimen was observed (M-H OR: 1.18, 95% CI: 0.20–7.06, p = 0.86) (Fig. 2C).

If only the study that specified no GO at baseline is included in the analysis, then the incidence of GO

during BRT was lower than in the T regimen (9.1% versus 17.8%), with no statistically significant difference between the 2 regimens (M-H OR: 0.47, 95% CI: 0.19–1.14, p = 0.10) (Fig. 2D).

Changes in weight during medical treatment

Only one study assessed weight gain during BRT versus T regimen, which was greater in the former group, but not significantly. The adjusted mean difference between the groups was 1.6 kg (95% CI: –0.3–3.5, p = 0.09) [15].

Lipid profile changes during GD therapy

No data regarding the evolution of lipid profile during medical treatment of GD were included in the studies.

Subgroup analyses

Subgroup analysis was not performed.

Sensitivity analyses

Sensitivity analysis was performed only for one outcome (development of GO) by excluding articles not mentioning the absence of GO at baseline.

Assessment of reporting bias

Both studies were assessed as low risk of bias in terms of primary outcomes.

Discussion

Summary of outcomes and quality of evidence

Two observational cohort studies were included in this meta-analysis. Participants were following either a BRT or T regimen to treat GD hyperthyroidism. No differences in the incidence of overt hypothyroidism were observed between the 2 regimens. None of the studies mentioned the doses of drug used. In a systematic review by Abraham et al. CBZ was used in dose ranges between 30 and 60 mg per day and only in one study up to 100 mg per day [10]. Current guidelines recommend CBZ 40 mg/day, MMI 30 mg/day, or PTU 50–150 mg 3 times daily as the starting dose [6, 31].

There was a lower probability of achieving stable thyroid function using BRT compared to the T regimen. This result has low GRADE quality evidence, and further research is needed. One reason is that the number of patients considered to have stable thyroid function was estimated and included patients with euthyroidism and subclinical hypo- or hyperthyroidism. The second reason is that in the retrospective cohort study there were more patients at baseline with complicated GD in the BRT group than in the T-regimen group. This is consistent with studies in the literature, where BRT can be considered for patients with fluctuating thyroid disease [32]. Lewandowski et al. described an atypical onset of GD with myocardial infarction in a 31-year-old woman. She achieved control of hyperthyroidism using BRT [33]. It may also be suitable for patients with difficult access to healthcare due to the reduced number of thyroid function tests during therapy [15, 31].

GO development during BRT compared to T regimen was evaluated in a single study. The incidence of GO was lower in the group treated with BRT than in the T group, but the difference was not statistically significant [15]. No other studies were found to assess the occurrence of GO during different ATD regimens. The other study did not report on the proportion of patients with GO at baseline. However, more patients with extra-thyroidal manifestations were treated with BRT. In the BRT group, 15.5% of patients had GO and 2.8% of patients had dermopathy, compared to 6.3% and 1.4% in the T group [16]. The combined results of these studies have a very low quality of evidence. Further research is needed to assess whether BRT could be a protective factor in GO development.

We found no studies comparing the effects of different ATDs regimens used in GD on metabolism.

Summary of main results

BRT and T regimens have the same effectiveness in avoiding overt hypothyroidism during treatment.

BRT could offer a stable thyroid function with fewer thyroid function tests during therapy than the T regimen.

BRT could be more suitable for complicated GD than the T regimen.

This meta-analysis is assessed overall as having a low to very low quality of evidence.

Potential bias in the review process

One of the limitations of this study relates to the small number of articles included. Unpublished data were not included. Articles written in languages other than English were also not included.

Agreements and disagreements with other studies or reviews

To our knowledge there are no other publications comparing the incidence of overt hypothyroidism and GO development in GD patients using different ATD regimens.

Conclusion

Although initially controversial, block-and-replace therapy is now more and more accepted as being in-

dicated for selective categories of patients diagnosed with Graves' disease.

Conflict of interest
Authors declare no conflict of interest.

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Author contribution
A.M.S. and C.B. independently searched the literature and evaluated each article. A.M.S. performed the statistical analysis and wrote the article. C.B. supervised the writing of the article. Both authors reviewed and approved the final draft.

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Disclosures
None declared.

Data availability
Original data generated and analyzed during this study are available from the corresponding author on reasonable request.

References

1. Bartalena L, Chiovato L, Vitti P. Management of hyperthyroidism due to Graves' disease: frequently asked questions and answers (if any). J Endocrinol Invest. 2016; 39(10): 1105–1114, doi: 10.1007/s40618-016-0505-x, indexed in Pubmed: 27319009.
2. Menconi F, Marcocci C, Marinò M. Diagnosis and classification of Graves' disease. Autoimmun Rev. 2014; 13(4-5): 398–402, doi: 10.1016/j.autrev.2014.01.013, indexed in Pubmed: 24424182.
3. Bartalena L, Baldeschi L, Boboridis K, et al. European Group on Graves' Orbitopathy (EUGOGO). The 2016 European Thyroid Association/European Group on Graves' Orbitopathy Guidelines for the Management of Graves' Orbitopathy. Eur Thyroid J. 2016; 5(1): 9–26, doi: 10.1159/000443828, indexed in Pubmed: 27099835.
4. Subekti I, Pramono LA, Azizi F, et al. Management of hyperthyroidism during pregnancy in Asia. Endocr J. 2014; 61(8): 751–758, doi: 10.1507/endocrj.ej14-0145, indexed in Pubmed: 24849535.
5. Girgis CM, Champion BL, Wall JR. Current concepts in graves' disease. Ther Adv Endocrinol Metab. 2011; 2(3): 135–144, doi: 10.1177/2042018811408488, indexed in Pubmed: 23148179.
6. Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. Thyroid. 2016; 26(10): 1343–1421, doi: 10.1089/thy.2016.0229, indexed in Pubmed: 27521067.
7. Drui D, Du Pasquier Fediaevski L, Vignal Clermont C, et al. Graves' orbitopathy: Diagnosis and treatment. Ann Endocrinol (Paris). 2018; 79(6): 656–664, doi: 10.1016/j.ando.2018.08.005, indexed in Pubmed: 30177259.
8. Wiersinga WM. Graves' Disease: Can It Be Cured? Endocrinol Metab (Seoul). 2019; 34(1): 29–38, doi: 10.3803/EnM.2019.34.1.29, indexed in Pubmed: 30912336.
9. Struja T, Fehlberg H, Kutz A, et al. Can we predict relapse in Graves' disease? Results from a systematic review and meta-analysis. Eur J Endocrinol. 2017; 176(1): 87–97, doi: 10.1530/EJE-16-0725, indexed in Pubmed: 27780830.
10. Abraham P, Avenell A, McGeoch SC, et al. Antithyroid drug regimen for treating Graves' hyperthyroidism. Cochrane Database Syst Rev. 2003; 153(4): CD003420–498, doi: 10.1002/14651858.CD003420, indexed in Pubmed: 14583975.
11. Kahaly GJ, Bartalena L, Hegedüs L, et al. 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism. Eur Thyroid J. 2018; 7(4): 167–186, doi: 10.1159/000490384, indexed in Pubmed: 30283735.
12. Abraham P, Avenell A, McGeoch SC, et al. Antithyroid drug regimen for treating Graves' hyperthyroidism. Cochrane Database Syst Rev. 2003; 2010(4): CD003420, doi: 10.1002/14651858.CD003420, indexed in Pubmed: 14583975.
13. Hashizume K, Ichikawa K, Sakurai A, et al. Administration of thyroxine in treated Graves' disease. Effects on the level of antibodies to thyroid-stimulating hormone receptors and on the risk of recurrence of hyperthyroidism. N Engl J Med. 1991; 324(14): 947–953, doi: 10.1056/NEJM199104043241403, indexed in Pubmed: 1900575.
14. Morgan RL, Thayer KA, Bero L, et al. GRADE: Assessing the quality of evidence in environmental and occupational health. Environ Int. 2016; 92-93: 611–616, doi: 10.1016/j.envint.2016.01.004, indexed in Pubmed: 26827182.
15. Vaidya B, Wright A, Shuttleworth J, et al. Block & replace regime versus titration regime of antithyroid drugs for the treatment of Graves' disease: a retrospective observational study. Clin Endocrinol (Oxf). 2014; 81(4): 610–613, doi: 10.1111/cen.12478, indexed in Pubmed: 24801484.
16. Žarković M, Wiersinga W, Perros P, et al. EUGOGO (European Group on Graves' Orbitopathy). Antithyroid drugs in Graves' hyperthyroidism: differences between "block and replace" and "titration" regimes in frequency of euthyroidism and Graves' orbitopathy during treatment. J Endocrinol Invest. 2021; 44(2): 371–378, doi: 10.1007/s40618-020-01320-7, indexed in Pubmed: 32524368.
17. Bonnema SJ, Grupe P, Boel-Jørgensen H, et al. A randomized trial evaluating a block-replacement regimen during radioiodine therapy. Eur J Clin Invest. 2011; 41(7): 693–702, doi: 10.1111/j.1365-2362.2010.02452.x, indexed in Pubmed: 21175612.
18. Elbers L, Mourits M, Wiersinga W. Outcome of very long-term treatment with antithyroid drugs in Graves' hyperthyroidism associated with Graves' orbitopathy. Thyroid. 2011; 21(3): 279–283, doi: 10.1089/thy.2010.0181, indexed in Pubmed: 21190446.
19. Grebe SK, Feek CM, Ford HC, et al. A randomized trial of short-term treatment of Graves' disease with high-dose carbimazole plus thyroxine versus low-dose carbimazole. Clin Endocrinol (Oxf). 1998; 48(5): 585–592, doi: 10.1046/j.1365-2265.1998.00446.x, indexed in Pubmed: 9666870.
20. Kung AW, Yau CC, Cheng A. The incidence of ophthalmopathy after radioiodine therapy for Graves' disease: prognostic factors and the role of methimazole. J Clin Endocrinol Metab. 1994; 79(2): 542–546, doi: 10.1210/jcem.79.2.7913934, indexed in Pubmed: 7913934.
21. Kung AW, Yau CC, Cheng AC. The action of methimazole and L-thyroxine in radioiodine therapy: a prospective study on the incidence of hypothyroidism. Thyroid. 1995; 5(1): 7–12, doi: 10.1089/thy.1995.5.7, indexed in Pubmed: 7787438.
22. Lantz M, Calissendorff J, Träisk F, et al. Adjuvant Treatment of Graves' Disease with Diclofenac: Safety, Effects on Ophthalmopathy and Antibody Concentrations. Eur Thyroid J. 2016; 5(1): 50–56, doi: 10.1159/000443373, indexed in Pubmed: 27099839.
23. Laurberg P, Berman DC, Andersen S, et al. Sustained control of Graves' hyperthyroidism during long-term low-dose antithyroid drug therapy of patients with severe Graves' orbitopathy. Thyroid. 2011; 21(9): 951–956, doi: 10.1089/thy.2011.0039, indexed in Pubmed: 21834677.
24. McIver B, Rae P, Beckett G, et al. Lack of effect of thyroxine in patients with Graves' hyperthyroidism who are treated with an antithyroid drug. N Engl J Med. 1996; 334(4): 220–224, doi: 10.1056/NEJM199601253340403, indexed in Pubmed: 8531998.
25. Rittmaster RS, Zwicker H, Abbott EC, et al. Effect of methimazole with or without exogenous L-thyroxine on serum concentrations of thyrotropin (TSH) receptor antibodies in patients with Graves' disease. J Clin Endocrinol Metab. 1996; 81(9): 3283–3288, doi: 10.1210/jcem.81.9.8784084, indexed in Pubmed: 8784084.
26. Stefanic M, Karner I. Thyroid peroxidase autoantibodies are associated with a lesser likelihood of late reversion to hyperthyroidism after successful non-ablative treatment of Graves' disease in Croatian patients. J Endocrinol Invest. 2014; 37(1): 71–77, doi: 10.1007/s40618-013-0026-9, indexed in Pubmed: 24464453.
27. Wise PH, Marion M, Pain R. Mode of action of carbimazole in Graves' disease. Clin Endocrinol (Oxf). 1979; 10(6): 655–664, doi: 10.1111/j.1365-2265.1979.tb02124.x, indexed in Pubmed: 582580.
28. Wise PH, Marion M, Pain RW, et al. Single dose, "block-replace" drug therapy in hyperthyroidism. Br Med J. 1973; 4(5885): 143–145, doi: 10.1136/bmj.4.5885.143, indexed in Pubmed: 4752310.
29. Rodionova T, Frolova A. Clinical and Imunological Assesment of efficiency and safety of various schemes aplication for curing Graves' disease. Eur Thyroid J. 2014; 3(Suppl. 1): 73–226, doi: 10.1159/000365244.
30. McIver B, Morris JC. The pathogenesis of Graves' disease. Endocrinol Metab Clin North Am. 1998; 27(1): 73–89, doi: 10.1016/s0889-8529(05)70299-1, indexed in Pubmed: 9534029.
31. Boelaert K, Visser WE, Taylor PN, et al. Endocrinology in the time of COVID-19: Management of hyperthyroidism and hypothyroidism. Eur J Endocrinol. 2020; 183(1): G33–G39, doi: 10.1530/EJE-20-0445, indexed in Pubmed: 32438340.

32. Fan W, Tandon P, Krishnamurthy M. Oscillating hypothyroidism and hyperthyroidism - a case-based review. J Community Hosp Intern Med Perspect. 2014; 4(5): 25734, doi: 10.3402/jchimp.v4.25734, indexed in Pubmed: 25432652.

33. Lewandowski KC, Rechciński T, Krzemińska-Pakuła M, et al. Acute myocardial infarction as the first presentation of thyrotoxicosis in a 31-year old woman - case report. Thyroid Res. 2010; 3(1): 1, doi: 10.1186/1756-6614-3-1, indexed in Pubmed: 20181115.