

Treatment Preferences in Patients With Hypothyroidism

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Abstract

Context: Levothyroxine (L-T4) monotherapy is the standard of care for the treatment of hypothyroidism. A minority of L-T4-treated patients remain symptomatic and report better outcomes with combination therapy that contains liothyronine (L-T3) or with desiccated thyroid extract (DTE).

Objective: This work aimed to assess patient preferences in the treatment of hypothyroidism.

Methods: A systematic review, meta-analysis, meta-regression, and network meta-analysis of randomized controlled trials (RCTs) comparing treatments for adults with hypothyroidism (L-T4 vs L-T4 + L-T3 or DTE). Searches were conducted in PubMed, Embase, and Cochrane databases up to April 10, 2024. Data extraction and quality assessment were independently performed by 4 researchers.

Results: Eleven RCTs (8 cross-over studies) with a total of 1135 patients were considered. Overall, 24% of patients preferred L-T4 vs 52% who preferred L-T4 + L-T3 or DTE; 24% had no preference. The meta-analysis confirmed the preference for combination therapy over L-T4 monotherapy (relative risk [RR]: 2.20; 95% CI, 1.38–3.52; $P = .0009$). Excluding 4 studies reduced the high heterogeneity ($I^2 = 81\%$) without affecting the results (RR: 1.97; 95% CI, 1.52–2.54; $P < .00001$; $I^2 = 24\%$). This preference profile remained when only crossover studies were considered (RR: 2.84; 95% CI, 1.50–5.39; $P < .00001$). Network meta-analysis confirmed the preference for DTE and L-T3 + L-T4 vs L-T4 alone.

Conclusion: Patients with hypothyroidism prefer combination therapy (L-T3 + L-T4 or DTE) over L-T4 monotherapy. The strength of these findings justifies considering patient preferences in the setting of shared decision-making in the treatment of hypothyroidism.

Key Words: L-T4, L-T3, DTE, hypothyroidism, patient preference, combination therapy

Abbreviations: D2, type 2 iodothyronine-deiodinase; DTE, desiccated thyroid extract; L-T3, liothyronine; L-T4, levothyroxine; FDA, US Food and Drug Administration; fT3, free 3,5,3'-triiodothyronine; fT4, free thyroxine; NAc, nucleus accumbens; NMA, network meta-analysis; OR, odds ratio; PRO, patient-reported outcome; QoL, quality of life; RCT, randomized clinical trial; RR, relative risk; SUCRA, surface under the cumulative ranking; TH, thyroid hormone; TSH, thyrotropin.

The treatment of hypothyroidism has evolved over the past 140 years (1, 2). Initially, attempts were made to treat hypothyroidism by transplanting one-half of a sheep's thyroid gland under the skin of the inframammary region on each side in a 36-year-old woman—but the heterologous transplant attempts proved ineffective, even with more advanced techniques in the early 20th century. Transplant attempts were followed by daily subcutaneous injections of a glycerin-based thyroid extract from sheep but the prospect of lifelong treatment with these injections was daunting (1, 2).

Subsequent improvements came with the recognition that ingestion of raw or cooked thyroid glands was as effective as injections of thyroid extract, but the taste was reportedly unpleasant. Despite efforts to mask the taste (1, 2), physicians increasingly turned to oral administration of thyroid gland extract, preferably from a standardized source for more consistent potency (1, 2). This extract, prepared from a pool of sheep thyroids, was conveniently administered orally as a solution known officially as liquor thyroidei. In cases where oral administration was not feasible, the body was

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rubbed with a mixture of thyroid extract, ether, and lanolin (1, 2).

These treatments were largely effective but not always practical and were soon replaced by daily tablets containing a desiccated thyroid extract (DTE), and eventually, some 80 years later, by tablets of synthetic levothyroxine (L-T4). In its various forms, thyroid replacement therapy has substantially improved the management of a debilitating (often fatal) disease, primarily affecting women. The transition from one treatment form to the next was generally logical and successful, improving effectiveness, safety, and convenience. Patients and physicians recognized the necessity of each subsequent form of treatment, leading to their widespread acceptance (1, 2).

The last transition from DTE to L-T4 was also largely successful, but not without challenges (1, 2). It is true that while DTE potency varied due to inconsistent calibration methods before 1985 (3, 4), L-T4 offered physicians a more reliable and convenient alternative with color-coded, accurately dosed tablets (5). However, anecdotal reports emerged that some patients felt worse on L-T4 and preferred to return to DTE or avoid switching altogether (1, 2). This prompted investigations into the possibility that combination therapy with synthetic thyroxine (T4) and 3,5,3'-triiodothyronine (T3), or with the naturally occurring porcine thyroglobulin (contained in DTE), might be more effective than L-T4 alone (6). Approximately 20 randomized, double-blinded clinical trials (RCTs) were conducted to explore this hypothesis.

The RCTs, which spanned up to several months, consistently demonstrated that L-T4 and L-T4 + L-T3 treatments were both equally effective based on patient-reported outcomes (PROs), such as questionnaires evaluating quality of life (QoL), mood, and cognition. Moreover, the incidence of adverse effects/reactions indicated that both treatments were equally safe for patients with hypothyroidism (7, 8).

Consequently, expert groups tasked with drafting clinical guidelines reasoned that the inconvenience of taking 2 daily tablets, along with the associated costs and effort required for implementing and monitoring combination therapy, outweighed any potential benefits to patients (9). Additionally, theoretical concerns regarding the long-term safety of combination therapy were raised (9) based on the rapid absorption and clearance of T3 from plasma, leading to a transient peak (~3 hours) with a magnitude that varied with L-T3 dosage (10). Nonetheless, evidence for worse adverse effects is lacking to this day.

Despite consistent findings from patient preference outcomes in RCTs, including those confirmed in recent meta-analyses (7, 8), the 2014 American Thyroid Association guidelines for hypothyroidism treatment did not consider patient preference for L-T4 + L-T3 therapy (9). For instance, preference for DTE was interpreted as indicative of a lack of understanding or appreciation of L-T4's pharmacological properties, or as potentially exposing patients to risks such as elevated serum T3 levels. Moreover, the task forces considered that preference without substantiation through PROs may not truly represent a health outcome and had not traditionally been considered as such (9). The absence of endorsement from clinical guidelines resulted in many physicians declining treatment with L-T4 + L-T3, and in a considerable number of patients feeling deeply dissatisfied (11).

The US Food and Drug Administration (FDA) has substantial expertise in evaluating patient preferences during the approval and clearance of FDA-regulated medical products.

The FDA holds a distinct perspective on the relationship between PROs and patient preference (12). PROs are reports on a patient's health condition that come directly from the patient, without any interpretation by a clinician or other individual. While they assess a patient's perceptions of their health status before, during, and after therapy, they do not indicate how much the patient values a particular outcome or therapy compared to other options (12). This is assessed through patient preference after the patient is asked to decide on different treatments, which requires weighing the pros and cons of each treatment (12).

Here we performed a systematic review of the literature and identified RCTs that considered patient preference as an outcome in the treatment of hypothyroidism. The data were analyzed through traditional meta-analysis as well as network meta-analysis (NMA) and meta-regression. The purpose of this study was to determine which treatment (L-T4 vs L-T4 + L-T3 vs DTE) was most likely to be preferred when considering all participants for the eligible RCTs.

Materials and Methods

Three previous meta-analyses evaluated patient preference as reported in those RCTs comparing L-T4 vs L-T4 + L-T3, with conflicting results. Therefore, in this study, we included new RCTs (completed recently) and reexamined patient preference in the treatment of hypothyroidism, in an effort to clarify the inconsistent results. We conducted a comprehensive literature review and performed a meta-analysis, a meta-regression analysis, and a network meta-analysis of all eligible RCTs comparing L-T4 vs L-T4 + L-T3 or DTE. This study was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (13) and the protocol was registered in PROSPERO (CRD42024540978). We included RCTs comparing patient preferences for combination therapy (synthetic L-T3 + L-T4 or DTE) vs L-T4 monotherapy in adult patients treated for overt hypothyroidism.

Eligibility Criteria

The inclusion criteria were predefined as follows: (1) RCTs of parallel or crossover designs comparing the efficacy of combination therapy vs L-T4 monotherapy; (2) investigation of adults (age ≥ 18 years) with overt primary hypothyroidism (autoimmune, postsurgical, or radioactive iodine-induced hypothyroidism). Exclusion criteria were as follows: (1) case reports, retrospective studies, observational studies, or post hoc analyses of RCTs; (2) studies that did not evaluate patient preference or acceptability; (3) simultaneous use of other drugs; (4) studies that had overlapping populations; and (5) studies that included patients with subclinical hypothyroidism or central hypothyroidism.

Search Strategy and Screening

Two authors (F.E.L.B. and G.C.) performed, independently, an electronic search of the PubMed, Embase, and Cochrane databases for relevant studies. Disagreements between the reviewers were solved through discussion with a third independent reviewer (A.B.). We reviewed publications up to April 10, 2024, without language restrictions. The search strategies included: (levothyroxine OR L-T4 OR LT-4 OR thyroxine OR L-Thyroxine) AND (L-Triiodothyronine OR L-T3 OR L-T3 OR liothyronine OR Thyroid Extract) AND (hypothyroidism

OR hypothyroid). Rayyan was used to perform primary screening. Duplicate trials were handled by including the publication with the largest case number or complete cohort.

Data Extraction and Quality Assessment

Four researchers (F.E.L.B., G.C., D.C.A.B., and F.E.L.B.) independently extracted data from eligible studies, including the name of the author, year of publication, country of research, study design, number of patients, follow-up time (weeks), sex female (n, %), age (years), dose of L-T3, etiology of hypothyroidism, outcome of the study, evaluated questionnaires, patient preference for treatment, minimum sample size (n), power (%), variables assessed, main results, and study limitations.

Bias was assessed by 2 authors (F.E.L.B. and G.C.) independently using the Cochrane Risk of Bias tool (RoB V.2.0) (14). The ROB 2.0 assesses 5 domains: D1, randomization process; D2, deviations from intended interventions; D3, missing outcome data; D4, measurement of the outcome; and D5, selection of the reported result. Bias levels were categorized as low risk, some concerns, and high risk based on Cochrane Handbook guidelines. Discrepancies were resolved by a third researcher (A.B.).

Statistical Analysis

In this study, we used Review Manager 5.4 (The Cochrane Collaboration) for meta-analysis. The chi-square-based Q test was used to assess the between-study heterogeneity ($P < .1$ indicating statistically significant heterogeneity). I^2 statistic and Cochran Q test were applied to examine the heterogeneity and the pooled risk ratio estimation of each study was calculated by the fixed and random-effects model (the Mantel-Haenszel method). The I^2 statistic was specifically documented for the percentage of study variability observed due to heterogeneity rather than chance ($I^2 = 0\%-25\%$, no heterogeneity; $I^2 = 25\%-50\%$, moderate heterogeneity; $I^2 = 50\%-75\%$, high heterogeneity; $I^2 = 75\%-100\%$, extreme heterogeneity). The random-effects model was used for I^2 greater than 50%; otherwise, the fixed-effects model was used. P less than .05 was considered statistically significant. Several RCTs allowed participants to express their treatment preferences, including no preference, combination therapy (L-T3 + synthetic L-T4 or DTE), or L-T4 monotherapy.

Funnel plot asymmetry, involving 5 or more studies, was visually assessed due to biased results in statistical tests for prevalence outcomes in single-group studies (15, 16). Meta-regression analyses were conducted using the meta package in RStudio (version 2023.12.1 + 402) to investigate potential associations between treatment effect estimates and predefined clinical characteristics, such as the daily dose of L-T3 (μg), duration of follow-up (weeks), age (years), weight difference (kg), and thyrotropin (TSH) difference ($\mu\text{IU/mL}$). Specifically, we analyzed the difference in final body weight (kg) and TSH ($\mu\text{IU/mL}$) between patients on combination therapy vs monotherapy with L-T4 for all studies and for crossover studies only.

A power analysis was calculated using the R “metapower” package (17), which calculates power using the summary effect size, the average number of participants per study, the number of effect sizes, and the I^2 value to calculate power.

Considering the present meta-analysis encompasses 3 treatments (combination therapy [L-T3 + L-T4 or DTE] and L-T4 monotherapy), NMA integrates both direct and indirect

evidence for all relative treatment effects. Consequently, it can produce estimates with maximum statistical power and enhanced precision. The NMA employed the R statistical package (RStudio version 2023.12.1 + 402) for both frequentist statistical analysis (using the netmeta package) and Bayesian methods (employing the BUGSnet package) (18).

Specifically, 2 forest plots were generated, one encompassing all aggregated studies and another focusing solely on crossover designs, for dichotomous data. These plots were created using random-effects models, with point estimates of relative risk (RR) and a 95% CI calculated.

Network consistency was evaluated through node-split models. Treatments were prioritized using the P score for frequentist methods and the surface under the cumulative ranking (SUCRA) for Bayesian methods, with scores ranging from 0 (indicating poorer performance) to 1 (reflecting superior performance) (19). Patient preferences were considered a beneficial factor for treatment, simplifying comparative analysis through the subtraction of 1 from both the P score and the SUCRA (20). Consequently, the intervention hierarchy in NMA was determined by $1 - (P\text{-score})$ and $1 - (\text{SUCRA})$.

We assessed the general within-network inconsistency between direct effects and indirect comparisons for each outcome using χ^2 tests. If no general inconsistency was detected, the inconsistency between each of 2 agents was tested by calculating the differences in direct effects and indirect comparisons using their SEs. We considered evidence of inconsistency if P values were less than .05.

Results

Literature Search

The process of conducting a systematic literature search and selecting relevant studies is outlined in Fig. 1. In the initial literature search, we identified 19 385 articles. After removing duplicates (8413 articles), 10 914 records underwent primary screening based on title and abstract analysis. Of these, 8011 studies were irrelevant to our study question, 1391 were review papers, and 1512 articles involved animal studies and were excluded, leaving 58 for full-text review. Following a thorough examination of these studies, 47 articles were excluded based on predetermined criteria (see Fig. 1). In total, 11 studies met the inclusion criteria and were eligible for the meta-analysis (21-31).

Characteristics of Studies

The key characteristics of the 11 studies included in the present analyses are summarized in Table 1. These studies involved 592 patients receiving combination therapy (L-T3 + L-T4 or DTE) and 543 receiving L-T4 monotherapy. Three studies were conducted in the United States, 2 in Lithuania, 2 in the United Kingdom, and 1 in Australia, Denmark, Italy, the Netherlands, Russia, and Spain. Four studies presented a low risk of bias across the 5 domains (21-24). Six other studies were classified as exhibiting some concerns (25-30), and one was deemed to have a high risk (21) (Fig. 2). Nonetheless, Egger's test of the intercept identified no evidence of funnel plot asymmetry and potential publication bias (all $P > .05$).

Meta-Analysis

Among the 11 RCTs (3 parallel) (22-24) and 8 crossover studies (21, 25-30, 47), 5 (263 participants) identified a statistically

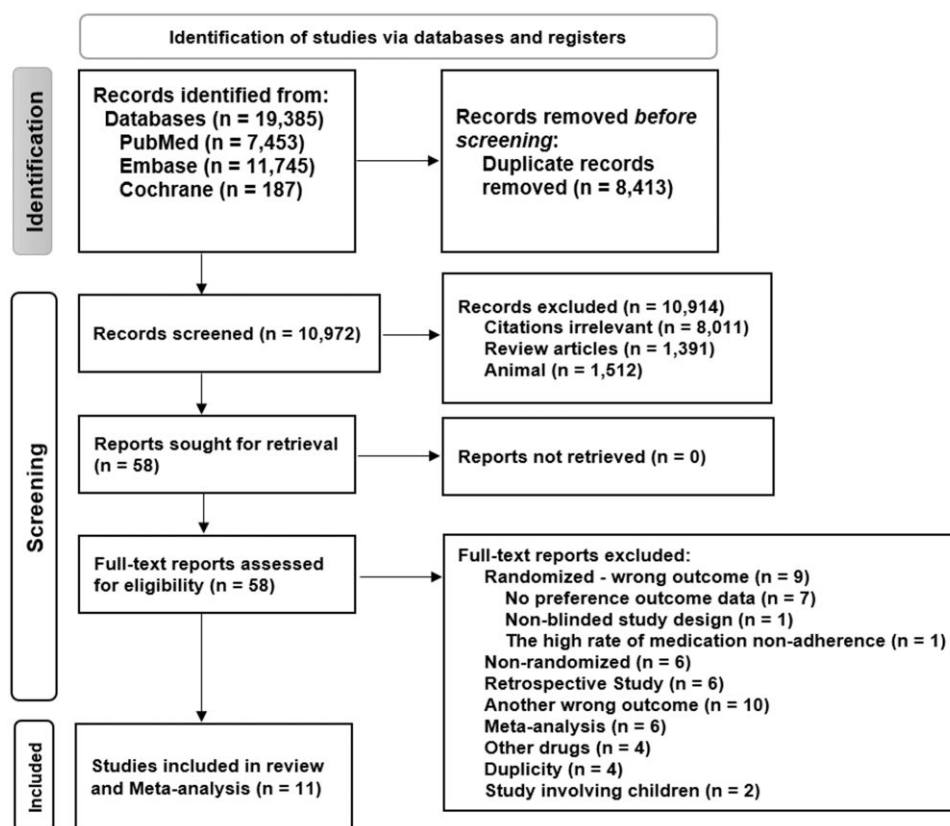


Figure 1. PRISMA flowchart depicting literature search and screening process (n indicates number of studies).

significant preference for combination therapy (25-29), none identified a preference for L-T4 monotherapy, and 6 (21-24, 28, 30) (435 participants) did not identify a difference in preference.

The present meta-analysis of these 11 RCTs indicates that patients preferred combination therapy to L-T4 monotherapy (RR: 2.20; 95% CI, 1.38-3.52; $P = .0009$). However, we observed a large heterogeneity in the study outcomes ($\chi^2 = 52.8$, $I^2 = 81\%$; $P < .00001$), potentially affecting the validity of an overall pooled estimate (Fig. 3). Therefore, we used visual assessment of the funnel plot to identify and eliminate 4 studies contributing to the high heterogeneity as measured by I^2 (26-28, 30) (Fig. 4). As a result, the heterogeneity of the pooled estimate dropped markedly (Fig. 5), without affecting the pooled effect of the primary outcome (RR: 1.97; 95% CI, 1.52-2.54; $P < .00001$; $I^2 = 24\%$).

Combination therapy was consistently preferred vs L-T4 monotherapy (RR: 2.84; 95% CI, 1.50-5.39; $P < .00001$; $I^2 = 86\%$) or vs the absence of preference (RR: 2.09; 95% CI, 1.47-2.98; $P < .00001$; $I^2 = 65\%$), even when restricting the meta-analysis to crossover studies (Fig. 6). Here we also used the funnel plot to mitigate heterogeneity (Fig. 7), which resulted in the exclusion of 3 studies (26, 27, 30). Preference for combination therapy remained superior vs L-T4 monotherapy (RR: 3.00; 95% CI, 2.13-4.22; $P < .00001$; $I^2 = 18\%$) and vs no preference (RR: 1.65; 95% CI, 1.28-2.12; $P < .00001$; $I^2 = 5\%$) (Figs. 8 and 9). Two additional forest plots (Supplemental Figs. 1 and 2 (31)) illustrate patient preferences in crossover studies in which the differences in the final TSH values (combination therapy vs monotherapy) were less than 0.1 $\mu\text{IU/mL}$ or greater than 0.1 $\mu\text{IU/mL}$,

respectively. When the difference in TSH was less than 0.1 $\mu\text{IU/mL}$, the preference was for combination therapy (RR 4.87 [2.95-8.03]; $P < .00001$). However, no statistically significant preference was observed with TSH differences greater than 0.1 $\mu\text{IU/mL}$ (RR 1.85 [0.83-4.13]; $P = .13$). The forest plot of patient preferences (combination therapy vs monotherapy) across parallel trials did not show a statistically significant difference (Supplemental Fig. 3 (31)).

Power Analysis

Power measurements for patient preferences across all 11 selected studies ranged from 74% to 98%, indicating significant capability to detect the primary outcome (Fig. 10 and Supplemental Figs. 4-7 (31)).

Meta-Regression Analysis

Meta-regression analyses were conducted to examine the effect of a daily dose of L-T3 (μg), duration of follow-up (weeks), age (years), difference in final body weight (kg), and difference in TSH values ($\mu\text{IU/mL}$) on the overall results. The difference in the final TSH values in crossover studies was statistically significantly associated with the results ($P = .01$), but none of the other variables were ($P = .527$ for dose of L-T3; $P = .117$ for duration of follow-up; $P = .399$ for age; and $P = .956$ for body weight difference) (Table 2 and Supplemental Figs. 8-12 (31)).

Network Meta-Analysis

The pooled estimates from the frequentist and NMA showed that DTE (RR: 2.34; 95% CI, 1.07-5.11) and L-T3 + L-T4

Table 1. Study and participant characteristics in the included randomized controlled trials

Study, y, country	Design	Follow-up, wk	Hypothyroidism etiology	Patients, No.	Age, y Female, %	Patient preference treatment		
						L-T4	L-T4 + L-T3L-T3	No preference
Appelhof et al 2005 (23), Netherlands	Parallel	15	Primary autoimmune hypothyroidism	140	48.5 85.1	14/48 (29%)	L-T4 + L-T3L-T3 (10:1) 2×/d: 19/46 (41%); L-T4 + L-T3L-T3 (5:1) 2×/d: 24/46 (52%)	—
Brigante et al 2023 (22), Italy	Parallel	24	Totally thyroidectomized (benign or malignant disease)	121	56 71.4	7/63 (11%)	L-T4 + L-T3L-T3 (20:1) 2×/d: 7/58 (12%)	—
Bunevicius et al 1999 (27), Lithuania	Crossover	5	Autoimmune and thyroid cancer (post thyroidectomy)	33	46 94	2/33 (6%)	L-T4 + L-T3L-T3 12.5 µg 1×/d: 20/33 (60.6%)	11/33 (33.4%)
Bunevicius et al 2002 (21), Lithuania	Crossover	5	Thyroidectomy for Graves	10	34 100	2/10 (20%)	L-T4 + L-T3L-T3 10 µg 1×/d: 6/10 (60%)	2/10 (20%)
Escobar-Morreale et al 2005 (28), Spain	Crossover	8	Autoimmune and thyroid ablation for hyperthyroidism	26	48 100	18/26 (69.2%)	L-T4 + L-T3L-T3 5 µg or 7.5 µg QD: 2/26 (7.7%)	6/26 (23%)
Fadeyev et al 2010 (24), Russia	Parallel	24	Primary hypothyroidism (autoimmune, surgery, radioiodine)	36	41.5 100	8/36 (22.2%)	L-T4 + L-T3 12.5 µg 1×/d: 10/36 (27.8%)	18/36 (50%)
Hoang et al 2013 (25), USA	Crossover	16	Primary hypothyroidism	70	50.6 75.7	13/70 (18.5%)	DTE: 34/70 (48.5%)	23/70 (33%)
Nygaard et al 2009 (29), Denmark	Crossover	12	Primary autoimmune hypothyroidism	59	46 93.2	9/59 (15.3%)	L-T4 + L-T3 20 µg 1×/d: 29/59 (49.1%)	21/59 (35.6%)
Rodriguez et al 2005 (47), USA	Crossover	6	Primary hypothyroidism	27	47.5 83	7/27 (26%)	L-T4 + L-T3 10 µg 1×/d: 12/27 (44.4%)	8/27 (29.6%)
Shakir et al 2021 (26), USA	Crossover	22	Primary hypothyroidism	75	50 77.3	15/75 (20%)	L-T4 100 µg + L-T3 10 µg 1×/d: 23/75 (30.7%); DTE: 29/75 (38.6%)	8/75 (10.7%)
Walsh et al 2003 (30), Australia	Crossover	10	Primary hypothyroidism	101	47.7 92	46/101 (46%)	L-T4 + L-T3 10 µg 1×/d: 36/101 (36%)	18/101 (18%)

Abbreviations: DTE, desiccated thyroid extract; L-T3, liothyronine; L-T4, levothyroxine.



Figure 2. Risk-of-bias assessment using the Cochrane Risk of Bias tool (RoB V.2.0).

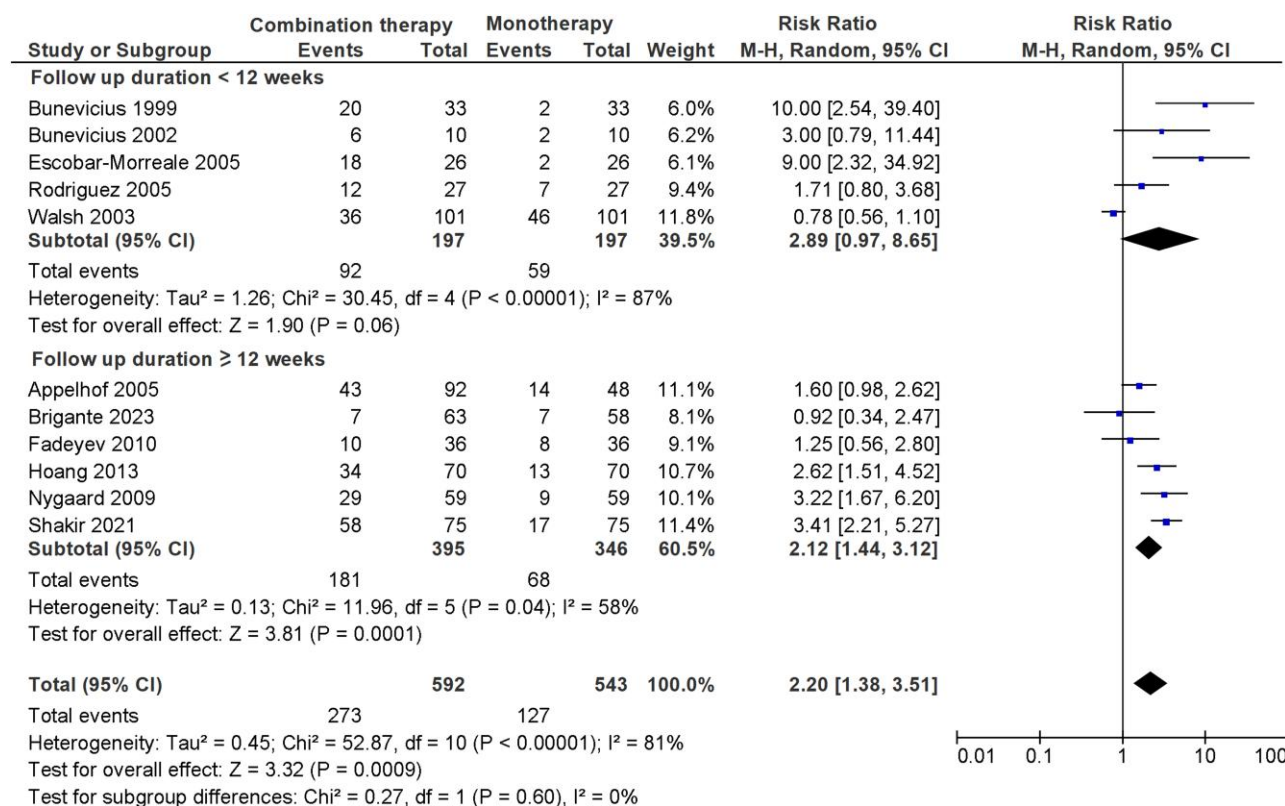


Figure 3. Forest plot of patient preferences (combination therapy vs monotherapy) across all 11 selected studies.

(RR: 1.90; 95% CI, 1.24-2.89) were favored interventions by patients over L-T4 monotherapy across all selected studies (Fig. 11A). Only L-T3 + L-T4 demonstrated statistical superiority to monotherapy (RR: 2.41; 95% CI, 1.33-4.39) (Fig. 11B) when only crossover studies were considered (8 studies). The network plots in Fig. 12 depict the NMA outcomes. Based on the data presented in Supplemental Table 2 (31), comparisons between L-T4 vs L-T4 + L-T3, L-T4 vs DTE, and L-T4 + L-T3

vs DTE revealed no statistically significant discrepancies between direct and indirect comparisons. The P values, ranging from .54 to .95, indicate a consistent evaluation of treatment effects across all comparisons, including both the overall and crossover studies.

Based on the $(1 - P)$ scores and $(1 - \text{SUCRA score})$, which had identical values, L-T3 + L-T4 and DTE showed superiority in patient-preferred intervention outcomes. Rank probability

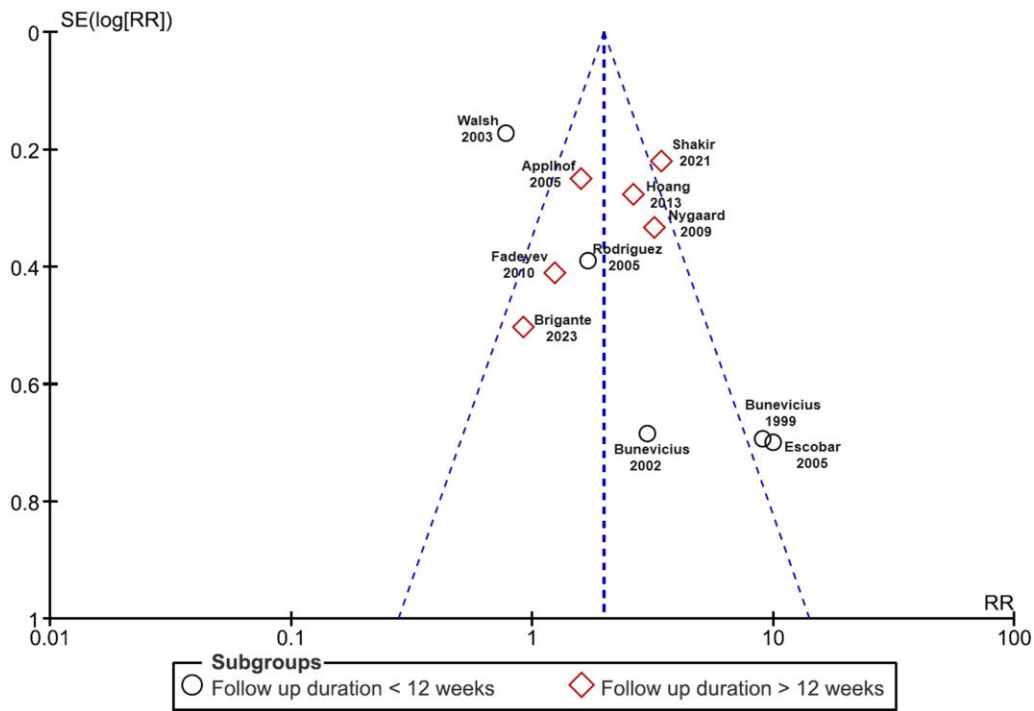


Figure 4. Funnel plots of patient preferences (combination therapy vs monotherapy) across all 11 selected studies.

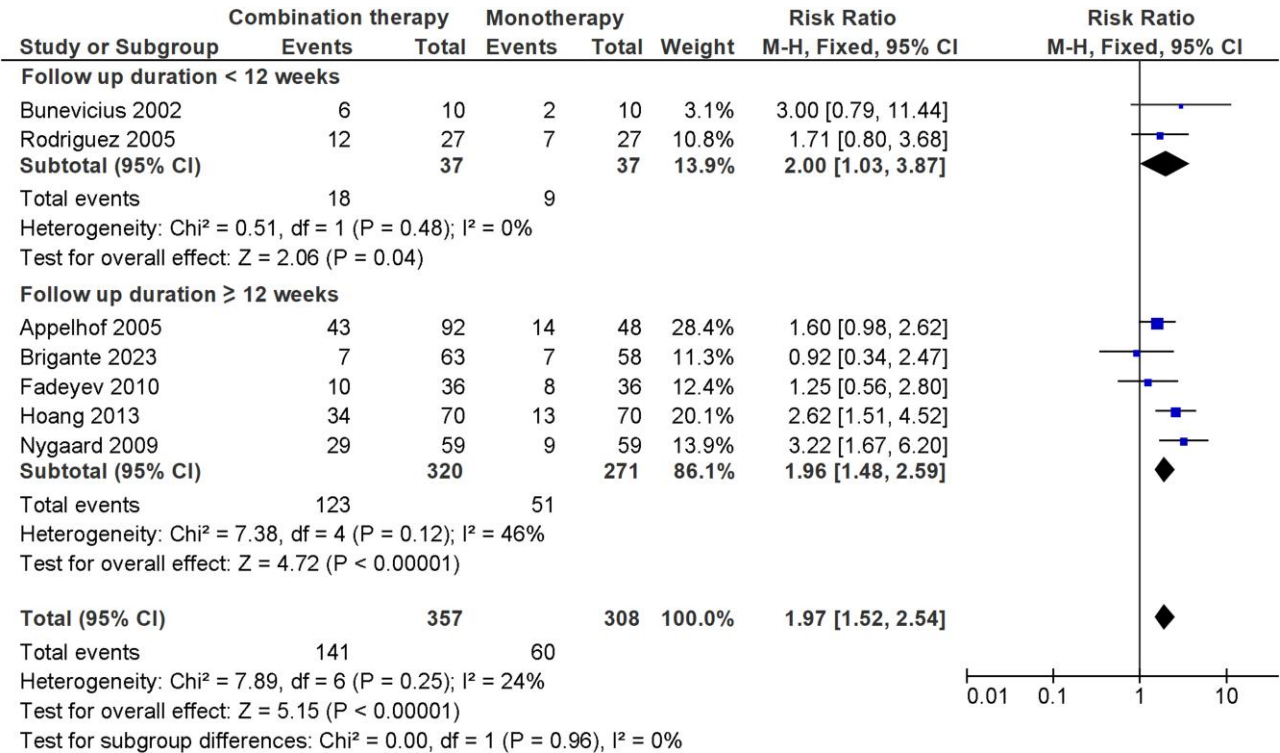


Figure 5. Forest plot depicting patient preferences (combination therapy vs monotherapy) following the exclusion of four studies (26-28, 30) after funnel plot analysis.

analysis indicated that DTE had an 84% probability of being the preferred therapy, followed by L-T3 + L-T4 (65%) and L-T4 (1%) (see Fig. 11A). In crossover studies, only L-T3 + L-T4 (73%) exhibited a higher probability of preference (see Fig. 11B).

Discussion

Therapeutic preference for thyroid hormone (TH) replacement therapy in adult patients with overt hypothyroidism remains unresolved given the conflicting findings in 3 recent meta-analyses (7, 8, 32). Here we addressed this question

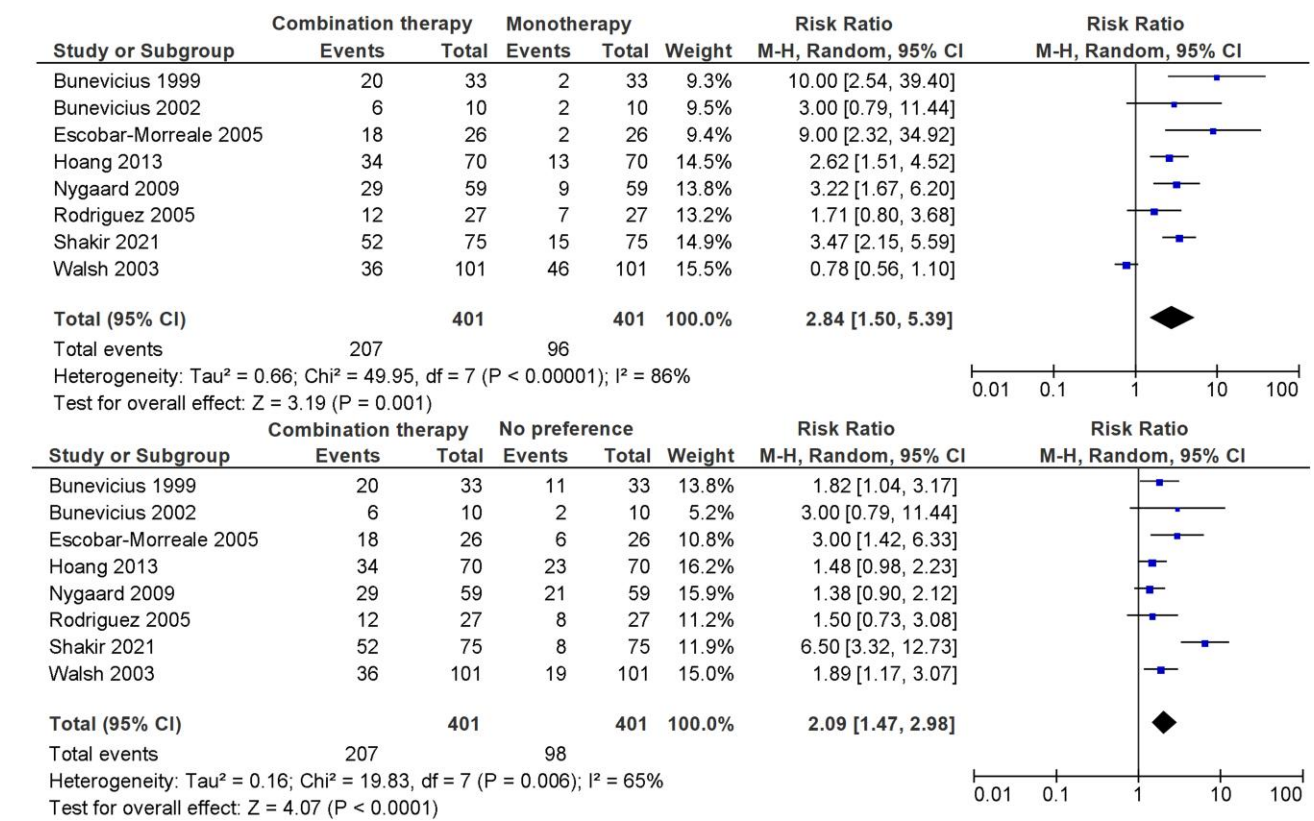


Figure 6. Forest plot of patient preferences (combination therapy vs monotherapy and combination therapy vs no preference) across crossover trials.

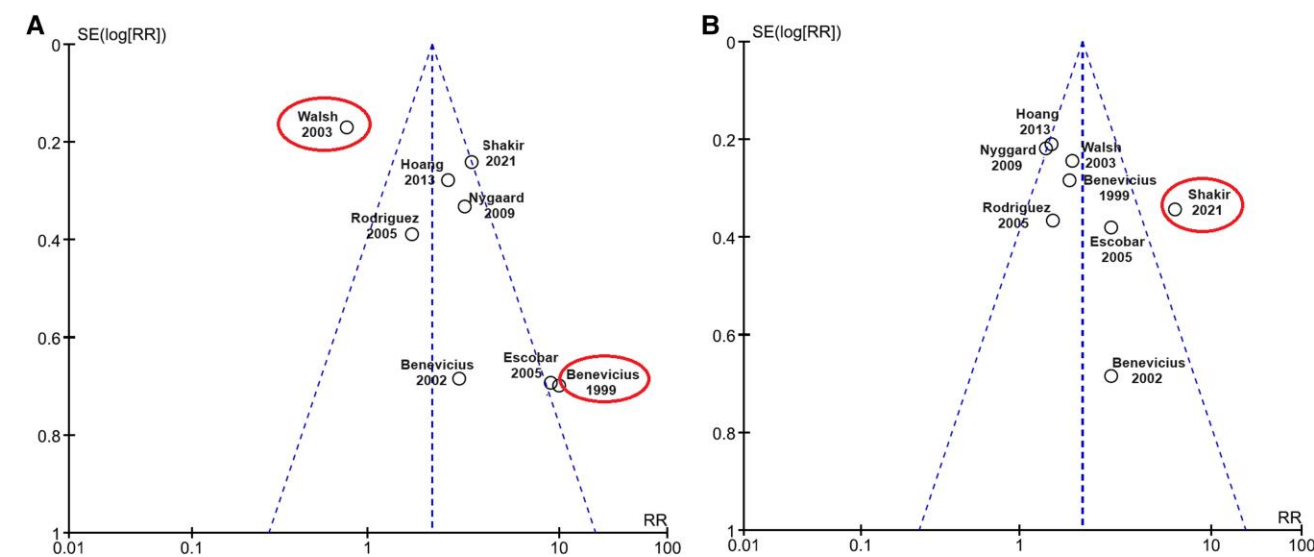


Figure 7. Funnel plots of patient preferences across crossover trial: A (combination therapy vs monotherapy) and B (combination therapy vs no preference).

using more stringent criteria and expanded statistical tools (NMA, and meta-regression) while considering 11 RCTs that enrolled 1135 patients (21-30, 47). We considered 5 additional RCTs not considered by Akirov et al (32), 5 additional RCTs not considered by the Millan-Alanis meta-analysis (8), and 4 additional RCTs not considered by Lan (7). The results indicate a clear preference for combination therapy (L-T3 + L-T4 or DTE) over L-T4 monotherapy, which was unrelated

to age, the dose of L-T3, the duration of the trial, or the final body weight. The preference for combination therapy was held even as we dropped some RCTs to reduce heterogeneity, limited the analyses to crossover RCTs, or both.

In the present analysis, we assessed the robustness of the 11 RCTs, which were categorized into crossover (8 studies) and parallel (3 studies). While only 5 out of 11 studies assessed both the minimum sample size and statistical power

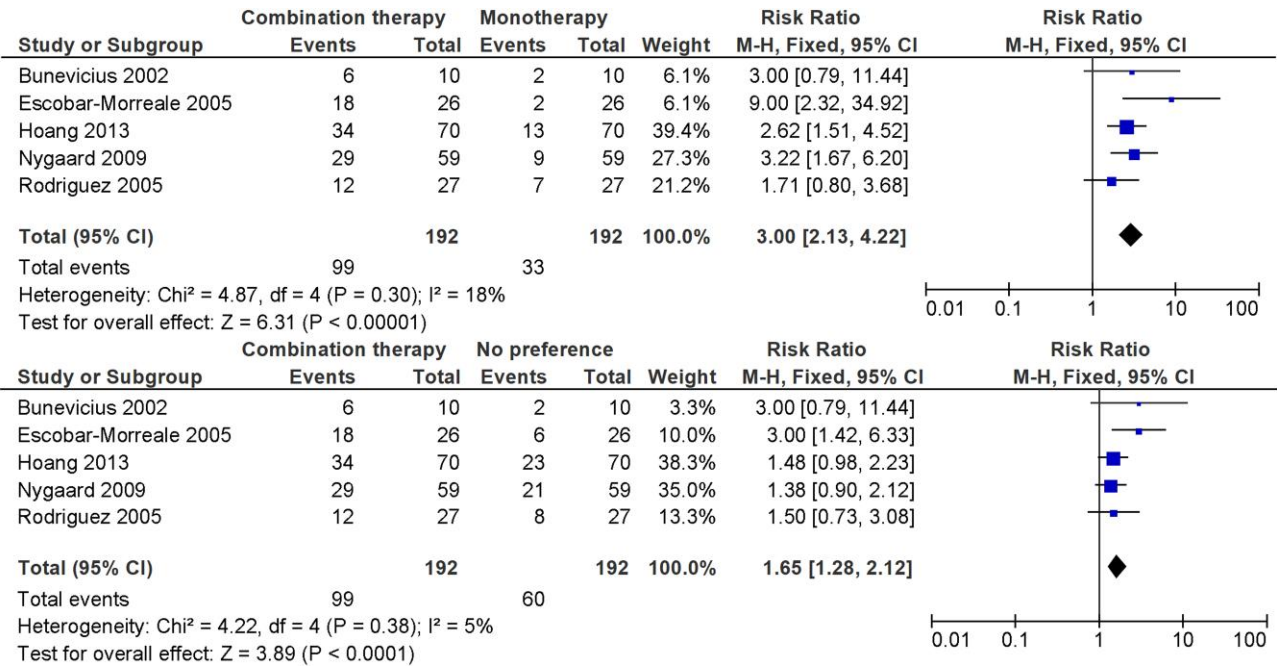


Figure 8. Forest plot of patient preferences (combination therapy vs monotherapy and combination therapy vs no preference) across crossover trials following the exclusion of 3 studies (26, 27, 30) after funnel plot analysis.

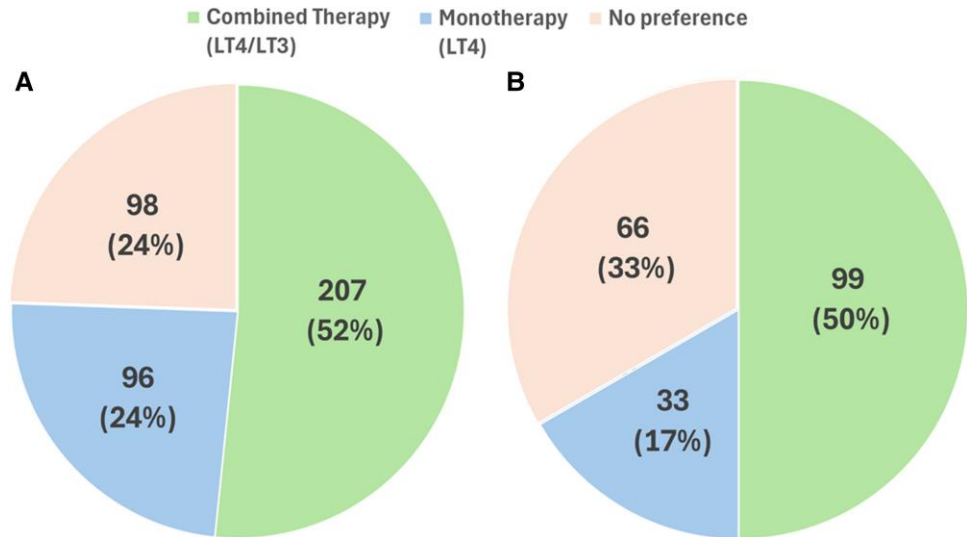


Figure 9. Pie chart depicting patients' preferences at the end of the crossover study periods: A) including all crossover studies and B) after the exclusion of three studies (26, 27, 30), following funnel plot analysis.

(22, 25, 26, 29, 30), the overall analytical power of the 11 studies combined was 0.985, despite considerable heterogeneity ($I^2 = 81\%$) (see Fig. 10). Notably, the crossover RCTs (estimated power [random-effects model] = 0.74) (Supplemental Fig. 5 (31)) demonstrated greater statistical power than the parallel RCTs (estimated power [fixed-effects model] = 0.30) (Supplemental Fig. 7 (31)). Moreover, 2 previous meta-analyses (7, 8) included nonrandomized trials (quasi-experimental), potentially compromising the quality of the assessment. Throughout the present analyses, we performed a sensitivity analysis with the funnel plot to identify and eliminate RCTs that contributed to an elevated heterogeneity (without affecting the robust preference for L-T4 +

L-T3 and DTE), an approach that was not followed in the previous meta-analyses (7, 8, 32). To date, only 3 meta-analyses evaluated patient preferences (Supplemental Table 3 (31)). Akirov et al (32) considered 7 RCTs and asked whether combination therapy is the preferred treatment for hypothyroidism. Their conclusion was negative given their binomial categorization of individuals into only 2 groups: those who had no preference or preferred L-T4 vs those who preferred combination therapy (L-T4 and L-T3). They did not compare L-T4 monotherapy vs L-T4 + L-T3, an approach that likely underestimated the preference for the combination therapy group. They also used a meta-regression analysis to assess the effect of potential confounding variables,

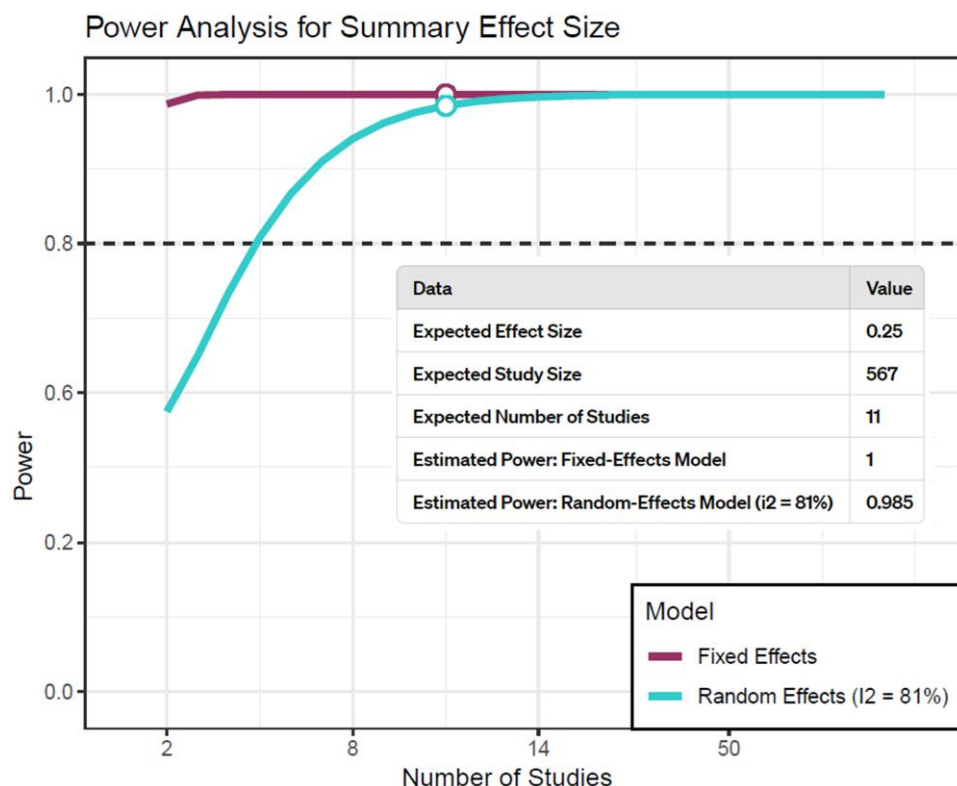


Figure 10. Power analysis of patient preferences (combination therapy vs monotherapy) across all 11 selected studies.

Table 2. Meta-regression analysis of study variables: daily dose of liothyronine (L-T3) (μg), follow-up duration (weeks), and age (years), comparing monotherapy with levothyroxine (L-T4) vs combination therapy (L-T4 + L-T3)

Variables	Coefficient	Z	95% CI	P	I^2
All studies					
Dose of L-T3 per day, μg	0.0172	0.632	−0.0362 to 0.0707	.527	69.7%
Follow-up duration, wk	−0.0478	−1.566	−0.1076 to 0.0120	.117	70.7%
Age, y	−0.0372	−0.841	−0.1237 to 0.0494	.399	72.7%
Difference in weight, kg	−0.0218	−0.0548	−0.8016 to 0.7580	.956	78.8%
Difference in TSH, $\mu\text{IU/mL}$	−0.1769	−0.9074	−0.5589 to 0.2052	.364	76.7%
Crossover studies					
Dose of L-T3 per d, μg	−0.0038	−0.092	−0.0833 to 0.0758	.926	82.4%
Follow-up duration, wk	−0.0062	−0.113	−0.1129 to 0.1006	.910	82.8%
Age, y	−0.0117	−0.169	−0.1480 to 0.1245	.866	84.3%
Difference in weight, kg	−0.1051	−0.225	−1.0188 to 0.8087	.821	80.4%
Difference in TSH, $\mu\text{UI/mL}$	−0.4935	−2.571	−0.8696 to 0.1174	.010	64.4%

Abbreviations: L-T3, liothyronine; TSH, thyrotropin.

specifically the total daily dose of L-T3 (μg) and the L-T3:L-T4 ratio in the dose administered. They found a positive association between the dose of L-T3 (0–20 $\mu\text{g/day}$) and treatment preference (regression slope 0.043; 95% CI, 0.007–0.078; $P = .020$), a finding that was not reproduced in the present analyses. However, there was no association between treatment preference and the L-T4:L-T3 ratio (1:0.4:1) (slope 0.124; 95% CI, −0.489 to 0.738; $P = .691$) (32).

The other 2 meta-analyses by Millan-Alanis et al (8) and Lan et al (7) did not consider patient preference as a primary objective, and neither focused on randomized RCTs.

Millan-Alanis et al and Lan et al included one quasi-randomized study, and the latter also included 3 non-randomized studies. Neither used funnel plots to reduce heterogeneity when treatment preference was evaluated. Despite these limitations, Lan et al (7) found a significantly greater preference for combination treatment, with an RR of 2.47 (95% CI, 1.31–4.67), I^2 of 86%, and a P value of less than .05. Similarly, Millan-Alanis et al (8) identified a higher preference for combination therapy, with 43% of participants favoring it compared to 23% for monotherapy and 30% showing no preference.

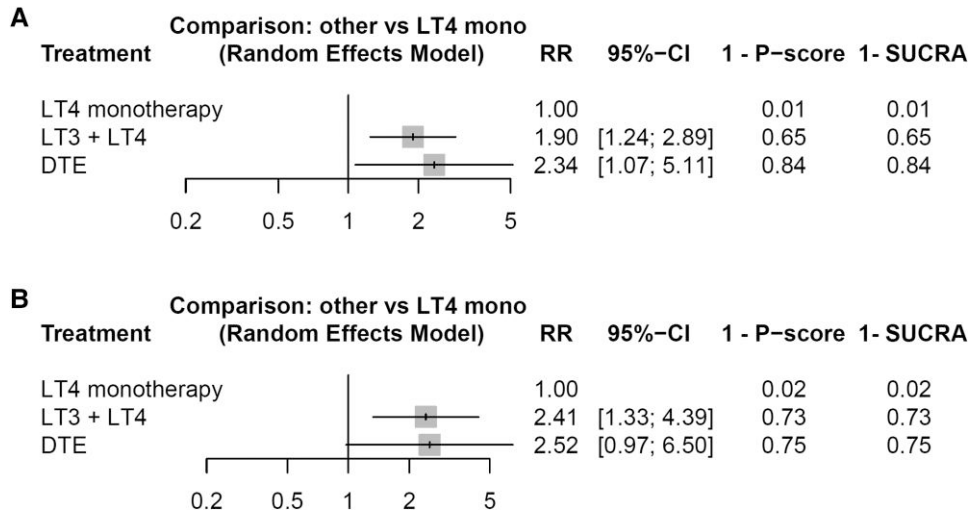


Figure 11. Network meta-analysis (Forest plot [random-effects model]) results of patient preferences for monotherapy (L-T4) vs combination therapy (L-T3 + L-T4) vs DTE: A, Across all selected studies (11 studies) and B, across crossover trials (8 studies); forest plot of the efficacy outcomes. Abbreviations: DTE, desiccated thyroid extract; L-T3, liothyronine; L-T4, levothyroxine; RR, relative risk; SUCRA, surface under the cumulative ranking.

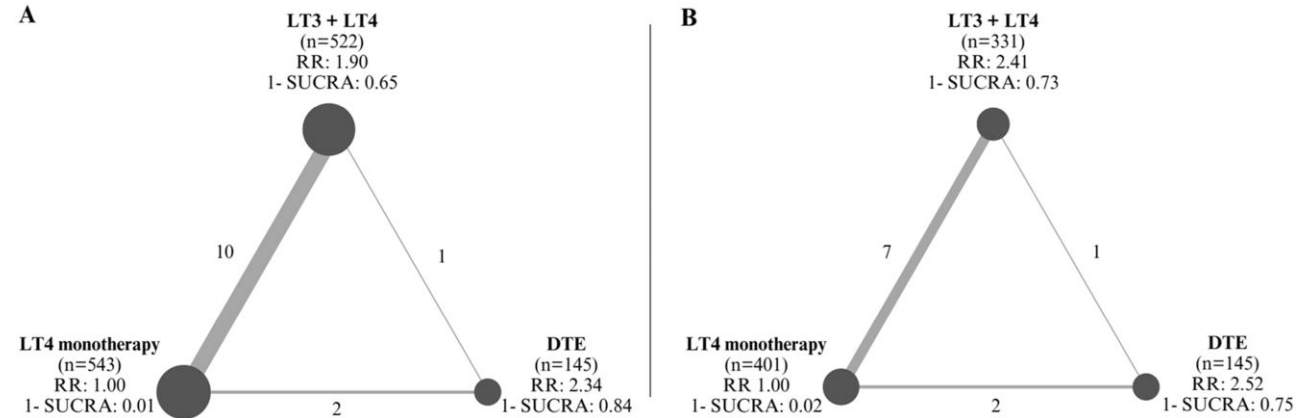


Figure 12. Schematic of the treatments used in the network meta-analysis (monotherapy [L-T4] vs combination therapy [L-T3 + L-T4] vs DTE): A, Across all 11 selected studies and B, across crossover trials (8 studies); geometry of the treatment network. The nodes in the graph layout correspond to the treatments, and the edges display the observed treatment comparisons. The thickness of the edges is proportional to the number of participants in trials, directly comparing the 3 connected treatments. Abbreviations: DTE, desiccated thyroid extract; L-T3, liothyronine; L-T4, levothyroxine; RR, relative risk; SUCRA, surface under the cumulative ranking.

The patient preference for DTE alone has not been considered in previous meta-analyses. Here we considered 2 RCTs in which DTE was used but could not apply traditional meta-analysis to assess L-T4 vs L-T4 + L-T3, or DTE at the same time. Instead, we used NMA, which was developed to compare more than 2 interventions at the same time. Our analysis revealed that patients exhibited a greater preference for DTE (RR: 2.34; CI, 1.07-5.11; 1-SUCRA: 0.84) than L-T3 + L-T4 (RR: 1.90; CI, 1.24-2.89; 1-SUCRA: 0.65) across all selected RCTs. However, when only crossover studies were considered (8 studies), no differences between DTE and L-T3 + L-T4 were observed, with 1-SUCRA ranging between 0.73 and 0.75 (Figs. 11 and 12).

In health care, preference is the result of a subjective evaluation based on the level of overall satisfaction and the patient's perceived efficacy of each treatment. It is the expression of individual likes and dislikes. Intuitively, preference could be inferred through reports of PROs that assess QoL, mood, and cognition. However, PROs overlap with each

other and do not allow patients to identify and rank what is most important to them in the choice of treatment. In addition, it is unlikely that all patients attribute similar importance to the different PROs. We also do not know if all the elements that influence patient preference for specific treatment are identified and addressed in the PRO questionnaires and tests applied in the RCTs. For example, the textual analysis of open-ended questions in a survey of 5170 participants self-reporting brain fog while being treated for hypothyroidism identified areas of concern that are not often included in thyroid-specific QoL questionnaires. These include a focus on the diagnosis of hypothyroidism, the types and doses of medications, and the patient-doctor relationship (33).

Patient preferences for treatments are multifaceted and influenced by a combination of personal, health-related, treatment-related, psychosocial, and informational factors. However, in blinded studies, these factors are unlikely to play a major role. Thus, the finding of preference for therapy with L-T4 + L-T3 or DTE in the RCTs could be linked to

neural mechanisms such as reward processing. The reward system in the brain is a network of structures that process reward, motivation, pleasure, and reinforcement. Key structures include the ventral tegmental area, nucleus accumbens (NAc), prefrontal cortex, and amygdala. While neurons in general respond to TH, the NAc, in particular, is a bona fide target of TH (34). The NAc receives dopaminergic inputs from the ventral tegmental area, and the dopamine release is associated with the experience of pleasure and reward, influencing preferences toward stimuli that produce these feelings. Whereas dopamine turnover rates are reduced in the NAc of $TR\beta^{-/-}$ mice (35) and in mice with perinatal hypothyroidism (36), chronic treatment of hypothyroid rats with T3 or T4 selectively increases dopamine utilization within the NAc (37). This is critically important because there is evidence that TH signaling is not restored in L-T4-treated rats (38) and L-T4-treated patients exhibit residual mood and cognitive symptoms of hypothyroidism (39).

TH homeostasis in the brain is unique, with approximately 50% of its T3 content coming from the plasma and the other 50% being locally generated through the deiodination of T4 to T3 via type 2 iodothyronine-deiodinase (D2) (40). Notably, treatment with L-T4 that normalizes TSH levels also results in an upshift in the serum free T4 (FT4) levels and a downshift in the serum T3 levels. This is so dramatic that approximately 47% of patients had at least 1 serum FT4 levels above the control reference range (>1.52 ng/dL) and 15.6% had at least 1 serum FT3 below the reference range (<0.23 ng/dL) (41). Logically, the reduction in plasma T3 compromises its contribution to brain T3 (42).

Neurons take up and package T3 into endosomes, which are subsequently retrogradely transported to the cell nucleus, where it regulates gene transcription (43). A reduction in plasma T3 could in theory be compensated for by a homeostatic acceleration of the D2 pathway, increasing locally produced T3 (44). However, this mechanism is unlikely to be activated in L-T4-treated patients given the elevated FT4 levels. T4 induces ubiquitination and proteasomal degradation of D2, limiting T3 production via this pathway (45). In human skeletal muscle, for example, D2-mediated T3 production drops by approximately 50% with the increase in FT4 from 10 to 20 pM, reaching nearly zero at 30 pM FT4 (46).

These alterations in TH homeostasis associated with L-T4 treatment set the stage for an incomplete restoration of TH signaling in the brain, potentially affecting the reward and motivation circuitry (and the NAc). The preference for L-T4 + L-T3 could then be influenced by the increased T3 and lowered FT4 in the plasma, and the subsequent normalization of TH signaling in the NAc and associated structures.

The present analyses emphasize the importance of considering individual patient preferences when selecting treatment for hypothyroidism. However, the study is not without limitations. First, the number of included studies and patients was relatively small. The power analysis of the crossover studies, as depicted in Supplemental Fig. 5 (31), indicated a power of 0.748 due to study heterogeneity. Ideally, at least 14 studies on the topic would be needed to achieve optimal reliability. Second, in the NMA, only 1 study evaluated all 3 treatments simultaneously (direct evidence), and indirect comparisons could introduce heterogeneity. Third, the influence of ethnic diversity and polymorphisms on patient preferences was not considered, as all studies were conducted in Europe, the United States, and Australia, and only one study evaluated

the effect of gene polymorphisms. Fourth, comorbidities were considered in only 3 RCTs (were excluded or randomized; Supplemental Table 1 (31)), but possible differences in intestinal absorption of iodothyronines were not considered. Further RCTs are necessary to confirm these observations. Finally, patient preference for one therapy over another remains a subjective and possibly mutable outcome. It is often measured as a binary choice, although strength of preference may vary between individuals. However, patient preference should be an important consideration in the shared decision-making process and provides insight into the overall response to a given therapy.

In conclusion, our comprehensive analysis found a consistent preference for combination therapy over L-T4 monotherapy. Although we do not understand fully the mechanistic basis for such preference, it could reflect a suboptimal normalization of TH signaling in the brain. Given that the effectiveness (normalization of TSH and resolution of most symptoms of hypothyroidism) and safety of L-T4 + L-T3 and L-T4 therapies are similar, physicians should consider using a model of shared decision-making that respects patient preference when treating patients with hypothyroidism. Patients are more likely to adhere to treatments that align with their preferences, even when the rationale behind those preferences is not clear, which can lead to better health outcomes.

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Author Contributions

Fabyan E.L.B., A.B., and G.C. contributed to the study concept and design. All authors contributed to data acquisition and analysis. Fabyan E.L.B., A.B., D.C.A.B., Fabricia E.L.B., and G.C. contributed to drafting the manuscript and figures. M.O.R. and M.D.E. contributed to interpreting the results and editing the manuscript.

Disclosures

A.C.B. is a consultant for AbbVie, Acella, Aligos, and Synthonics. The other authors have no disclosures to declare.

Data Availability

The data sets generated and/or analyzed during this study are publicly available in their original publications. Supplementary figures and tables are available as listed in "References."

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