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Clinical Research Article

A Cross-Sectional Analysis of Cardiovascular and Bone Health Care Utilization During Treatment With Thyroid Hormone

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Abstract

Context: Combination therapy with levothyroxine and liothyronine (LT4 + LT3) and desiccated thyroid extract (DTE) make up >10% of new thyroid hormone (TH) prescriptions in the United States.

Objective: To assess health care utilization related to cardiovascular disease (CVD) and bone health (BH) events (atrial fibrillation [AF], heart failure [HF], myocardial infarction [MI], stroke, and osteoporosis/fractures [FX]) in participants taking LT4+LT3 or DTE surveyed in the Medical Expenditure Panel Survey database.

Materials and Methods: Multi-year cross-sectional analysis examining 5437 participants (≥18 years old) treated with LT4, LT4+LT3, or DTE between 2016 and 2020. Health care utilization was assessed through outpatient, emergency, and hospital visits for AF, HF, MI, stroke, FX, and a composite index. A weighted analysis provided national estimates of health care utilization parameters. Utilization was re-analyzed following propensity score–based matching to balance sociodemographic and clinical covariates between treatment groups. Additionally, provider type and specialty data were obtained from visits associated with TH prescriptions.

Results: 5106 participants were treated with LT4 monotherapy, 252 with DTE, and 79 with LT4 + LT3. Prevalence of combined outpatient CVD and BH-related care utilization was lower among DTE/LT4+LT3 vs LT4 users (3.5% vs 7.7%; $P = .008$). There were no differences in emergency/hospital events. After covariate balancing, CVD and BH-related care utilization was similar between groups in outpatient and emergency/hospital settings. LT3 and DTE made up 7.6% of all TH prescriptions. For visits associated with DTE prescriptions, nurse practitioners and alternative medicine professionals were more likely to be identified as the primary provider type.

Conclusion: No significant differences in CVD- and BH-related health care utilization were identified between LT4 and DTE/LT4+LT3 users after covariate balancing. Non-MD providers were more likely to prescribe DTE.

Key Words: hypothyroidism, levothyroxine, desiccated thyroid extract, health care utilization, healthcare utilization

Abbreviations: AF, atrial fibrillation; BH, bone health; CVD, cardiovascular disease; DTE, desiccated thyroid extract; ED, emergency department; FX, osteoporosis/fracture; HF, heart failure; ICD-10, International Classification of Disease, Tenth Revision; LT3, liothyronine; LT4, levothyroxine; MEPS, Medical Expenditure Panel Survey; MI, myocardial infarction; T3, triiodothyronine; T4, thyroxine; TH, thyroid hormone; TSH, thyrotropin (thyroid-stimulating hormone); USP, United States Pharmacopoeia.

The treatment of hypothyroidism was developed during the late 19th century (1, 2) when a woman with hypothyroidism received a heterologous thyroid transplant. Oral administration of thyroid extract was first used in 1892. Since that time, desiccated thyroid extract (DTE) has been prepared and sold under different brand names and remained the standard of care to treat participants with hypothyroidism into the 1970s (1, 2). This continued even after thyroxine (T4) was isolated in 1914 (3) and triiodothyronine (T3) was synthesized in 1952 (4-6).

Despite being the standard of hypothyroidism care for decades, DTE potency could be inconsistent because the potency was standardized based on iodine content per grain (65 mg), which does not accurately reflect the content of T4 and T3 (7). Thus, the discovery that humans convert T4 to T3 via deiodinase activity (8), and that T3 is the biologically active thyroid hormone (TH) (9), provided the scientific rationale to change the therapeutic approach to patients with hypothyroidism. Daily tablets of synthetic levothyroxine (LT4) at doses that normalized serum thyroid stimulating hormone (TSH) became the new standard of care (10).

While LT4 remains the current standard of care, a subset of patients treated with LT4 have emerged who continue to experience symptoms of hypothyroidism despite the normalization of serum TSH (11-14). Meanwhile, the use of DTE for the treatment of patients with hypothyroidism is increasing. It is estimated that about 10% of the patients diagnosed with hypothyroidism are treated with DTE, a number that has doubled in the last 10 years (15).

Clinical experts authoring guidelines from professional societies remain concerned with the use of DTE given the paucity of long-term safety data (10). Based on the T3 content of DTE, it is estimated that the daily DTE dose required to normalize

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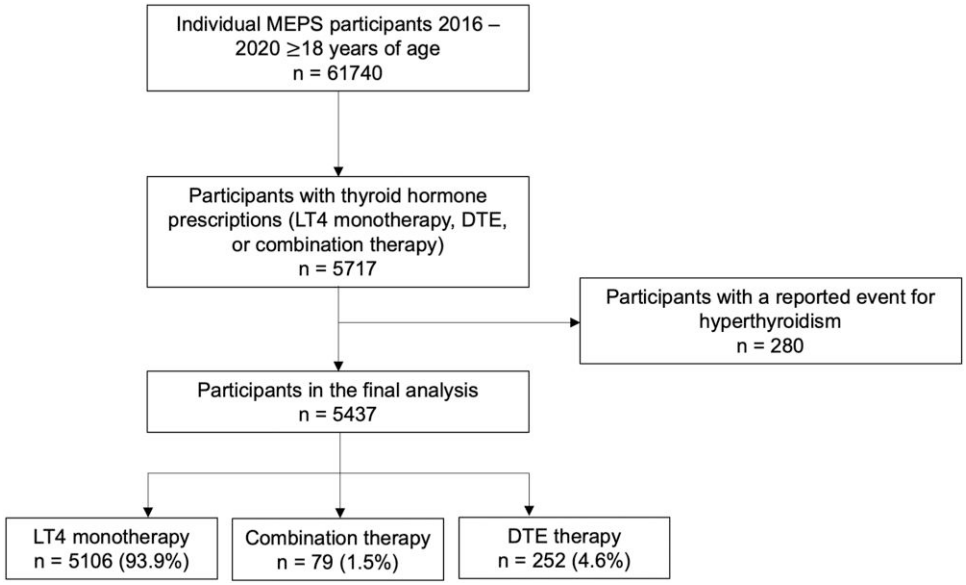

Figure 1. Study flowchart. Combination therapy refers to LT4 + LT3. Abbreviations: DTE, desiccated thyroid extract; LT3, liothyronine; LT4, levothyroxine; MEPS, Medical Expenditure Panel Survey.

serum TSH levels in adults (~80 mg) contains approximately 11 mcg of T3 (16, 17), an amount that can elevate serum T3 levels by ~45% (18). Three recent studies in which the dose of DTE was adjusted using serum TSH, failed to show excess adverse events. Two studies involving nearly 150 patients with hypothyroidism compared treatment with DTE vs LT4 for 16 weeks (16, 17). While serum TSH remained within the normal range in all patients, serum T3 was about 55% higher and FT4 was 40% lower in patients taking DTE. In addition, treatment with LT4 or DTE resulted in a similar frequency of adverse events (16, 17). An observational retrospective study examining 57 patients prescribed DTE compared with LT4 (2010 to 2016; mean follow-up 27 months) indicated that 97% of patients had therapeutic TSH levels, with <5% exhibiting supra-therapeutic levels of FT3 (19).

The ARCH study is the most recent to assess the effectiveness and safety of DTE (vs LT4) in the treatment of patients with hypothyroidism (20). This was a phase 2, multicenter, double-blind, randomized, dose-conversion study. Participants were randomized to receive LT4 or a matching dose of DTE calculated using the United States Pharmacopoeia (USP) dose-conversion chart for 30 to 48 weeks. In the end, 95% of DTE participants achieved an in-range TSH compared with 98% of LT4 participants. When compared to LT4, DTE was safe and well tolerated, and no excess adverse effects were observed (20).

Given that DTE and LT4 + liothyronine (LT3) continue to be prescribed regularly in the United States (15), it is important to assess the safety of these therapies. This study aims to evaluate health care utilization related to cardiovascular disease (CVD) and bone health (BH) in patients taking LT4 + LT3 and DTE using data from the Medical Expenditure Panel Survey (MEPS) database. It also aims to investigate the basic characteristics of the health care professionals who prescribe LT4, LT4 + LT3, and DTE in the United States.

Materials and Methods

In this multi-year cross-sectional study, we analyzed medical expenditure and prescription data related to CVD and BH events (atrial fibrillation [AF], heart failure [HF], myocardial infarction [MI], stroke, and osteoporosis/fractures [FX]) in participants using DTE or LT4 + LT3. These data were obtained from the MEPS database, a multi-year survey of a nationally representative sample of the noninstitutionalized US population collecting medical data from households, medical providers, and employers. The survey follows a panel design, enabling tracking of changes over multiple rounds of interviews spanning 2 calendar years. For each participant, the number of health care visits during the survey period is assessed, including hospitalizations, emergency care events, and outpatient and office visits. Medical conditions associated with health care events and prescriptions are recorded as International Classification of Disease (ICD) codes and linkage files are provided to pair event and prescription data (where available). This study received exempt status from the University of Chicago Institutional Review Board (IRB).

Study Population

In this study, we included all adult participants (≥18 years of age) in the MEPS database from 2016 to 2020 (Fig. 1). To be included, participants had to receive at least one prescription for LT4 monotherapy, LT4 + LT3 (as individual prescriptions for both LT4 and LT3), or DTE. To capture as completely as possible the US population prescribed TH, an associated diagnosis of hypothyroidism (ICD-10: E03) was recorded but not required for study inclusion. However, participants with events or prescriptions related to thyrotoxicosis (ICD-10: E05) were excluded to avoid measuring care utilization outcomes that may be primarily related to hyperthyroidism (and for which TH was initiated following definitive treatment). For the primary analysis, the study population was then divided into 2 groups based on class of TH: (i) those treated with LT4 monotherapy, and (ii) those treated with LT4 + LT3 or DTE. These groups were combined due to the relatively small number of participants treated with LT4 + LT3. A secondary analysis was completed with the LT4 + LT3 and DTE groups separated.

Study Outcomes and Covariates

To evaluate health care utilization among TH users, the proportion of the study population with at least one hospital, emergency department (ED), outpatient, and office-based visit associated with AF (ICD-10: I48), HF (ICD-10: I50), MI (ICD-10: I21), cerebral infarction or transient ischemic attack (stroke/TIA) (ICD-10: I63, G45), and osteoporosis or hip/spine/femur fracture [FX] (ICD-10: M81, S32, S72) was estimated. Additionally, a composite outcome was generated to determine the prevalence of care related to any of the medical conditions of interest. Given the difference in acuity between the types of events, hospitalizations and emergency visits were grouped and outpatient and office-based visits were grouped. Data were collected on sociodemographic covariates, including participant age, gender, race, ethnicity, and family income. Due to the presence of additional CVD risk factors impacting the primary study outcomes, additional clinical covariates were collected from the medical conditions database on each study participant, including hypertension (ICD-10: I10), hyperlipidemia (ICD-10: E78), and type 2 diabetes (ICD-10: E11), as well as hypothyroidism (ICD-10: E03).

Visits Associated With Thyroid Hormone Prescriptions

Prescriber and encounter data were collected from outpatient and office-based health care visits associated with TH prescriptions. The type of health care provider (eg, medical doctor, alternative medicine practitioner, physician's assistant, nurse practitioner), medical doctor specialty (eg, endocrinology, family medicine, general practice, internal medicine, Ob/Gyn, psychiatry), and visit reason (eg, check-up, diagnosis/treatment, postoperative/follow-up) were recorded. Linking these data to the medical conditions database, we determined the proportion of prescriptions that were provided to participants who had a diagnosis of thyroid disease (ICD-10: E03, E04, E07) or thyroid cancer (ICD-10: C73).

Statistical Analysis

The primary statistical approach consisted of 2 components: (i) weighted bivariate analysis comparing those of the 2 study groups and (ii) covariate balancing via a propensity score–matched approach in which the LT4 monotherapy group served as a matched control group. In the weighted analysis, each study participant was ascribed a corresponding sample weight to approximate the total number of TH users in the United States. Because the analysis spanned multiple years, sample weights assigned within the MEPS database (PERWT**F) were averaged across the study period (2016-2020) using the pooled linkage file per MEPS analytical guidelines (21). Weighted bivariate analyses of sociodemographic and clinical covariates and utilization outcomes were performed using the "survey" R package for complex survey analysis. Weighted statistical testing was performed using the Student *t* test (continuous variables) and Chi-square test (categorical variables). In the matched analysis, covariates to be balanced included age, gender, race, ethnicity, family income, survey year, and the presence of medication conditions (hypothyroidism, hypertension, hyperlipidemia, and type 2 diabetes). A propensity score–based fine stratification matching strategy with 20 subclasses was employed to generate the covariate-balanced LT4 control group using the "MatchIt" package. A bivariate analysis was then completed similar to that of the weighted analysis. As mentioned above, a secondary analysis was completed in which the LT4 + LT3 and DTE groups were separated. Covariate balancing was completed for both groups independently.

Finally, visit and provider data from events associated with TH prescriptions were compared similarly to the weighted bivariate analysis. Because this analysis examined events associated with prescriptions, prescriptions for LT4, LT3, and DTE were separated to distinguish provider characteristics between the 3 therapies. Data collection, manipulation, and statistical testing were completed using R statistical software (version 4.1.2).

Results

A total of 5437 adult participants were included in the study, of which 5106 (94%) were taking LT4 monotherapy, 252 (4.6%) were taking DTE, and 79 (1.5%) were taking LT4 + LT3 (Fig. 1). Median treatment time was 6 years [interquartile range [IQR]: 1, 16], 3 years [IQR: 1, 9], and 3 years [IQR: 1, 9.5], respectively. Baseline characteristics showed that the LT4 monotherapy group had a lower proportion of White individuals (88.4% vs 95.7% vs 91.9%; $P = .042$), female individuals (76.2% vs 97.1% vs 92.2%; $P < .001$), and older age (mean 61.4 vs 60.7 vs 56.0 years; $P < .001$) compared with the LT4 + LT3 and DTE therapy groups, respectively (Table 1). Participants on LT4 + LT3 and DTE therapy had significantly fewer cardiovascular risk factors, including hypertension, hyperlipidemia, and type 2 diabetes mellitus.

CVD and BH Health Care Utilization

In the weighted bivariate analysis, the prevalence of CVD and BH visits among TH users showed significant differences between the LT4 monotherapy group and the LT4 + LT3/DTE therapy group (Table 2). The proportion of LT4 + LT3/DTE users with at least one CVD or BH outpatient visit was significantly lower than that of the LT4 monotherapy group (3.5% vs 7.7%; $P = .008$). Visits related to stroke were very rare among LT4 + LT3/DTE users (0.1% vs 1.6%; $P < .001$). No significant differences were observed for emergency/hospital events. After propensity score–based covariate matching, sociodemographic and clinical characteristics were similar between the groups (Table 3). With the matched LT4 monotherapy users serving as a control group, the proportion of TH users with CVD and BH visits was reexamined (Table 4). The proportion of LT4 monotherapy and LT4 + LT3/DTE users with visits during the study period was not significantly different. The proportion of LT4 + LT3/DTE users with a composite outpatient visit was 4.5% (vs 5.5%; $P = .447$) and 1.8% for emergency/hospital visits (vs 1.7%; $P = .902$).

Secondary Analysis Separating the LT4 + LT3 and DTE Treatment Groups

Secondary weighted and covariate-balanced analyses were completed in which LT4 + LT3 and DTE-treated participants were separated in an effort to identify any CVD and BH outcome differences associated with the 2 T3-containing therapies. The results were largely similar to the primary analysis; however, due to the relatively small population sizes and the small number of outcomes, these findings should be interpreted cautiously. In the weighted analysis, the proportion of participants with at least one CVD or BH outpatient visit

Table 1. Sociodemographics and cardiovascular risk factors among users of thyroid hormone (weighted)

Participant characteristics	LT4 monotherapy N = 11 695 001	LT4 + LT3 therapy N = 178 255	DTE therapy N = 617 083	*P* value
Age, mean years (SD)	61.4 (16.0)	60.7 (12.5)	56.0 (14.0)	<.001
Gender female, n (%)	8 914 723 (76.2)	173 038 (97.1)	569 124 (92.2)	<.001
Race, n (%)				.042
White	10 332 736 (88.4)	170 657 (95.7)	567 145 (91.9)	
Black	624 545 (5.3)	5158 (2.9)	18 632 (3.0)	
Native American/Alaskan	65 952 (0.6)	0 (0.0)	3672 (0.6)	
Asian/Pacific Islander	484 163 (4.1)	1206 (0.7)	4755 (0.8)	
Multiple races	188 605 (1.6)	1234 (0.7)	22 880 (3.7)	
Hispanic ethnicity, n (%)	1 031 815 (8.8)	1376 (0.8)	47 634 (7.7)	.043
Family income, mean $ (SD)	84 069 (72 747)	102 132 (71 878)	97 508 (76 741)	.014
Cardiovascular risk factors, n (%)				
Hypertension	5 272 620 (45.1)	69 665 (39.1)	152 525 (24.7)	<.001
Hyperlipidemia	4 669 732 (39.9)	53 302 (29.9)	94 829 (15.4)	<.001
Type 2 diabetes mellitus	2 186 691 (18.7)	27 745 (15.6)	48 078 (7.8)	<.001
Medical therapies, n (%)				
Antihyperlipidemic	4 647 528 (39.7)	53 748 (30.2)	89 808 (14.6)	<.001
Antiplatelet	395 397 (3.4)	7573 (4.2)	5934 (1.0)	.223

Abbreviations: DTE, desiccated thyroid extract; LT3, liothyronine; LT4, levothyroxine; N, estimated population number based on participant weights.

Table 2. Proportion of population treated with thyroid hormone with CVD and BH visits events (weighted)

Health care utilization	LT4 monotherapy N = 11 695 001	DTE and LT4 + LT3 therapy N = 795 338	*P* value
Outpatient/office-based event, n (%)			
AF	288 974 (2.5)	9671 (1.2)	.146
HF	120 007 (1.0)	3960 (0.5)	.309
MI	220 240 (1.9)	5934 (0.7)	.178
Stroke	190 346 (1.6)	590 (0.1)	<.001
FX	229 903 (2.0)	7443 (0.9)	.265
Composite	904 121.2 (7.7)	27 599 (3.5)	.008
ED/Hospital event, n (%)			
AF	61 610 (0.5)	2066 (0.3)	.480
HF	30 164 (0.3)	1910 (0.2)	.945
MI	42 810 (0.4)	3248 (0.4)	.916
Stroke	97 769 (0.8)	0 (0.0)	.142
FX	46 354 (0.4)	4123 (0.5)	.728
Composite	272 203 (2.3)	11 346 (1.4)	.293

Stroke includes cerebrovascular ischemia and transient ischemic attack.
Only fractures of lumbar spine, pelvis, or femur included.
Abbreviations: AF, atrial fibrillation; BH, bone health; CVD, cardiovascular disease; DTE, desiccated thyroid extract; ED, emergency department; FX, osteoporosis/fracture; HF, heart failure; LT3, liothyronine; LT4, levothyroxine; MI, myocardial infarction; N, estimated population number based on participant weights.

was lower in the LT4 + LT3 (5.8%) and DTE (2.8%) groups vs the LT4 monotherapy group (7.7%; $P = .023$) (Supplementary Table S1) (22). The covariate-balanced analyses are summarized in Supplementary Tables S2 and S3 (22).

Visits Associated With Thyroid Hormone Prescriptions

A total of 2924 TH prescriptions were identified that were associated with a health care visit during the study period. Of those, 2703 (92.4%) were for LT4, 67 (2.3%) were for LT3, and 154 (5.3%) were for DTE (Table 5). Several differences in provider and visit characteristics were identified between the different TH classes. While a medical doctor was the primary health care professional for a majority of all visits, the proportion was greater for visits where LT4 or LT3 were prescribed (87.1% and 84.6%, respectively) compared with visits in which DTE was prescribed (69.9%; $P < .001$). In visits where DTE was prescribed, the primary provider was more often a nurse practitioner (10.5%) or alternative medicine professional (9.8%). Of note, endocrinologists were responsible for 23.1% of LT3 prescriptions, 12.8% of LT4 prescriptions, and just 9.8% of DTE prescriptions. Of those participants receiving TH prescriptions, a similar proportion from each TH class reported having thyroid disease (range, 76.1%-81.2%) and thyroid cancer (range, 1.3%-3.6%).

Discussion

In the past, clinicians were hesitant to offer combination therapy (LT4 + LT3 or DTE) for patients with hypothyroidism (including those that remain symptomatic while on LT4) due to perceived potency inconsistency of DTE, potential adverse reactions to T3, and the majority of data showing that LT4 was not inferior to LT4 + LT3 (10, 23, 24). While the potency issue has been resolved with the new USP standardization (7), only short-duration prospective and observational studies report on the safety outcomes of LT4 + LT3; there are few long-term studies (>1 year) available for DTE-treated patients. In this study, we examined CVD and

Table 3. Comparison of sociodemographic and clinical characteristics after propensity score–based matching

Matched characteristics	LT4 monotherapy N = 5106 (ESS = 2992.4)	DTE and LT4 + LT3 therapy N = 331 (ESS = 331)	*P* value
Age, mean years (SD)	56.8 (16.0)	56.9 (14.0)	.900
Gender female, n (%)	4673 (91.5)	305.0 (92.1)	.685
Race, n (%)			.998
White	4560 (89.3)	295 (89.1)	
Black	239 (4.7)	16 (4.8)	
Native American/ Alaskan	32 (0.6)	2 (0.6)	
Asian/Pacific Islander	86 (1.7)	5 (1.5)	
Multiple races	189 (3.7)	13 (3.9)	
Hispanic ethnicity, n (%)	4694 (91.9)	304 (91.8)	.950
Family income, mean $ (SD)	92 278 (79 060)	94 863 (76 242)	.563
Survey year, n (%)			1.000
2016	1205 (23.6)	77 (23.3)	
2017	838 (16.4)	54 (16.3)	
2018	1830 (35.8)	119 (36.0)	
2019	702 (13.8)	46 (13.9)	
2020	531 (10.4)	35 (10.6)	
Hypothyroidism, n (%)	4840 (94.8)	314 (94.9)	.953
Hypertension, n (%)	1484 (29.1)	98 (29.6)	.834
Hyperlipidemia, n (%)	986 (19.3)	65 (19.6)	.881
Type 2 diabetes mellitus, n (%)	588 (11.5)	38 (11.5)	.989

Matching via fine stratification process in which control population was separated into 10 weighted subclasses.
Abbreviations: DTE, desiccated thyroid extract; ESS, effective sample size; LT3, liothyronine; LT4, levothyroxine; N, actual number of participants.

Table 4. Proportion of population treated with thyroid hormone with CVD and BH visits after covariate balancing

Health care utilization	LT4 monotherapy N = 5106 (ESS = 2992.4)	DTE and LT4 + LT3 therapy N = 331 (ESS = 331)	*P* value
Outpatient/office-based event, n (%)			
AF	88 (1.7)	5 (1.5)	.770
HF	42 (0.8)	2 (0.6)	.681
MI	49 (1.0)	3 (0.9)	.926
Stroke	51 (1.0)	1 (0.3)	.206
FX	87 (1.7)	4 (1.2)	.497
Composite	282 (5.5)	15 (4.5)	.447
ED/Hospital event, n (%)			
AF	18 (0.4)	1 (0.3)	.883
HF	11 (0.2)	1 (0.3)	.760
MI	12 (0.2)	2 (0.6)	.212
Stroke	33 (0.6)	0 (0.0)	.254
FX	15 (0.3)	2 (0.6)	.348
Composite	88 (1.7)	6 (1.8)	.902

Stroke includes cerebrovascular ischemia and transient ischemic attack.
Only fractures of lumbar spine, pelvis, or femur included.
Abbreviations: AF, atrial fibrillation; BH, bone health; CVD, cardiovascular disease; DTE, desiccated thyroid extract; ED, emergency department; ESS, effective sample size; FX, osteoporosis/fracture; HF, heart failure; LT3, liothyronine; LT4, levothyroxine; MI, myocardial infarction; N, actual number of participants.

BH health care utilization among DTE and LT4 + LT3 users in an effort to uncover whether these participants required more care relative to LT4-treated participants. We found that the use of LT4 + LT3/DTE was not associated with an increased utilization of care related to AF, MI, stroke, HF, or fractures, and that there was a tendency for non-MD providers to prescribe DTE, including alternative medicine health professionals.

Given the rapid plasma kinetics of T3, it is a logical concern that T3 treatment may be associated with excess adverse reactions. After all, it has been well documented that patients with thyrotoxicosis do exhibit poor CVD and BH outcomes (25-27). However, the stability of serum TSH levels in patients with hypothyroidism treated with LT4 + LT3 or DTE has also been well documented (28). Furthermore, 2 recent meta-analyses of 18 prospective clinical trials did not find differences in quality of life, cognitive parameters, adverse events, or reactions between therapy with LT4 vs LT4 + LT3 but concluded that the patients preferred LT4 + LT3 (23, 24). Of note, one study reported higher anxiety scores in patients taking LT4 + LT3 (29). Whereas prospective long-term studies are scarce (30), similar safety reports were made after retrospective analyses of 2 European populations on LT3 for a median follow-up time of 8 years (31, 32). In contrast, a Korean study reported an increased risk of heart failure and stroke in LT3 users, particularly in those with a longer duration of LT3 use (33), but unfortunately, no serum TSH or T3 levels were reported, making it difficult to assess overtreatment in this population. The data available about the safety of DTE utilization is short-term (6-12 months) but supports the findings in the present study (16, 17, 34).

Notably, in the present investigation participants on DTE/LT4 + LT3 were on average nearly 4 years younger and exhibited fewer CVD risk factors when compared to the LT4-treated participants. These findings suggest that individuals treated with LT4 + LT3/DTE are healthier at baseline than LT4-treated participants, and thus would be less likely to experience adverse outcomes. This observation may reflect that clinicians are more hesitant to prescribe T3-containing treatments to patients they perceive as higher risk. Furthermore, younger, healthier patients may be more likely to show a preference for DTE as a more "natural option," given our recent findings in the National Health and Nutrition Examination Survey (NHANES) database that DTE-treated participants reported higher utilization of dietary supplements (thiamin, riboflavin, Vitamin B12, magnesium, and selenium) vs LT4-treated participants (15). While it is difficult to speculate the reasons for these observations, the fact that concurring data were obtained in 2 distinct national databases suggests that DTE-treated participants are less likely to have CVD risk factors at baseline and may have a healthier lifestyle.

DTE is included in the Beers criteria for potentially inappropriate medication use in older adults (35) and is not supported

Table 5. Characteristics of health care visits linked with thyroid hormone prescriptions (unweighted)

Visit characteristics	LT4 N = 2703	LT3 N = 67	DTE N = 154	*P* value
Event type, n (%)				.507
Office-based	2543 (94.1)	62 (92.5)	150 (97.4)	
Outpatient	100 (3.7)	3 (4.5)	3 (1.9)	
Emergency	16 (0.6)	0 (0.0)	1 (0.6)	
Hospitalization	44 (1.6)	2 (3.0)	0 (0.0)	
Provider type, n (%)				<.001
Medical Doctor	2302 (87.1)	55 (84.6)	107 (69.9)	
Physician Assistant	69 (2.6)	4 (6.2)	5 (3.3)	
Nurse Practitioner	132 (5.0)	3 (4.6)	16 (10.5)	
Alternative Medicine	73 (2.8)	1 (1.5)	15 (9.8)	
Other	67 (2.5)	2 (3.1)	10 (6.5)	
MD Specialty, n (%)				<.001
General practice	723 (27.4)	11 (16.9)	27 (17.6)	
Family medicine	650 (24.6)	16 (24.6)	37 (24.2)	
Internal medicine	335 (12.7)	3 (4.6)	9 (5.9)	
Endocrinology	338 (12.8)	15 (23.1)	15 (9.8)	
Ob/Gyn	38 (1.4)	0 (0.0)	5 (3.3)	
Psychiatry	17 (0.6)	5 (7.7)	2 (1.3)	
Other/non-MD	542 (20.5)	15 (23.1)	58 (37.9)	
Visit type, n (%)				.030
Check-up	1696 (63.8)	29 (44.6)	90 (58.4)	
Diagnosis/treatment	523 (19.7)	18 (27.7)	35 (22.7)	
Postop/follow-up	337 (12.7)	14 (21.5)	19 (12.3)	
Other	103 (3.9)	4 (6.2)	10 (6.5)	
Reported diagnoses, n (%)				
Thyroid disease	2184 (80.8)	51 (76.1)	125 (81.2)	.625
Thyroid cancer	97 (3.6)	2 (3.0)	2 (1.3)	.311

Because national estimates with weighting are less reliable with small samples, these data are presented unweighted. Thyroid disease includes ICD-10 codes E03 (other hypothyroidism), E04 (goiter), and E07 (other thyroid disease).
Abbreviations: DTE, desiccation thyroid extract; LT3, liothyronine; LT4, levothyroxine.

in the most recent American Thyroid Association guidelines for the treatment of hypothyroidism (10). However, we recently observed that the proportion of participants with hypothyroidism receiving DTE therapy increased from 5.4% in 2010 to 10.2% in 2020, reflecting a recent survey showing a marked increase in the willingness of physicians to prescribe DTE in specific circumstances (36). Notably, here we found that MDs staffed about 85% of the visits where LT4 and LT3 were prescribed, but only under 70% of DTE visits, in which case the primary provider was more often a nurse practitioner or an alternative medicine professional. With these findings, it is important to recognize that even for those clinicians that adhere to professional guidelines, the likelihood that they encounter patients treated with LT4 + LT3 or DTE is increasing. When examining and treating patients, especially for conditions related to CVD and BH, physicians must have the data available to understand the potential risks (if any) of LT4 + LT3/DTE. Our study did not identify any apparent increased risk, but long-term prospective studies are needed.

Our study is not without limitations. Due to the cross-sectional nature of the study design, we are not able to establish a cause-effect relationship between the different forms of TH treatment and the CVD or BH events. It is likely that, in the case of some outpatient visits, the initial CVD or bone diagnosis was made prior to the initiation of TH. However, it was our intention to compare care utilization in a cross-sectional fashion in an effort to uncover a potential excess of visits among users of a certain TH type. We believe the use of a covariate balancing approach helped to minimize differences in baseline event risk between the 2 groups and isolate the potential effect of TH treatment. It is also important to note that national estimates from weighted data can be less reliable with small samples. This should be considered when interpreting national utilization estimates among LT4 + LT3 and DTE-treated participants. The rates of individual and composite outcomes were lower than anticipated, with the study population's relatively younger average age likely contributing. A post hoc analysis revealed that the size of the present study would be powered to detect an approximate difference of ~2.0 to 2.5 (odds ratio) among the composite outcome between the LT4 monotherapy group and the combined DTE/LT4 + LT3 group. While no outcome rates in the DTE/LT4 + LT3 group approached this level (perhaps with the exception of ED/hospital FX events in the covariate-balanced analysis), the possibility of a false-negative outcome

should be considered when interpreting the data. Finally, we were unable to determine the extent of control of hypothyroidism due to the lack of thyroid function tests available in the MEPS database.

In conclusion, in the analyses of the MEPS database, we found that participants treated with LT4 + LT3/DTE were relatively younger and had fewer CVD risk factors, but after covariate balancing there were no differences in CVD or BH care utilization. When examining TH prescription data, DTE was more frequently associated with visits with non-MD providers. While we did not identify excess health care visits among LT4 + LT3 and DTE-treated participants, long-term safety data are still needed. Future real-world studies of clinical outcomes of DTE and LT4 + LT3 may need to account for a healthier study population at baseline.

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Disclosures

A.C.B. is a consultant for Abbvie, Acella, Sention, Synthonics, and Thyron. G.P. is a consultant for Knight, Ipsen, and Bayer. The other authors have no relevant disclosures.

Data Availability

Original data generated and analyzed during this study are included in this published article or in the data repositories (including Medical Expenditure Panel Survey data) listed in References.

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