Risk of death and adverse effects in patients on Liothyronine: a multi-source systematic review and meta-analysis

Authors:

Suhani Bahl[1], Peter N Taylor[1], Lakdasa D Premawardhana[1], Mike Stedman[2], Adrian Heald[3], Colin M Dayan[1], Onyebuchi E Okosieme[1,4]

Authors institution:

1. Thyroid Research Group, Systems Immunity Research Institute, Cardiff University School of Medicine, Cardiff, Wales, UK.

2. Res Consortium, Andover, UK.

3. The School of Medicine and Manchester Academic Health Sciences Centre, University of Manchester, Manchester, UK.

4. Diabetes Department, Prince Charles Hospital, Cwm Taf Morgannwg University Health Board, Merthyr Tydfil, Wales, UK

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Correspondence:

Dr Suhani Bahl, Thyroid Research Group, Systems Immunity Research Institute, Cardiff University School of Medicine, Cardiff, Wales, UK.
Email: bahls2@cardiff.ac.uk
ORCID ID: https://orcid.org/0009-0002-3216-896X

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ABSTRACT (250)

Context: Although some patients with hypothyroidism prefer combination therapy with Liothyronine (LT3) and Levothyroxine (LT4), the safety of LT3 remains unresolved.

Objective: We undertook a multi-source systematic-review and meta-analysis of LT3 safety.

Data sources: We searched PubMed for articles relating to death, adverse events (AEs), and cardiovascular outcomes in LT3 users. We also searched AEs data in the UK yellow-card scheme and US Food and Drug Administration Adverse Reporting System (FAERS).

Data extraction: Data was extracted independently by two reviewers. Out of 1814 articles identified, 52 studies were selected, comprising 21 randomised controlled trials (RCTs), 4 cohort-studies, and 27 case-reports. Meta-analyses were conducted for adverse outcomes in RCTs and cohort studies of combination vs. monotherapy.

Data synthesis: LT3-related AEs were only reported with unregulated LT3 use or pharmacy compounding errors. LT3 and LT4 showed similar adverse severity profiles in the yellow-card scheme. Disproportionality analysis in FAERS database showed no increased LT3 safety signals. Meta-analysis of RCTs (n=2128) showed similar AEs risk for combination vs. monotherapy (Relative risk [RR] 1.22, 95% Confidence Interval [95%CI] 0.66–2.25). Cohort study meta-analysis (LT3 vs. LT4-only users, n=630,254) showed no increased risk of atrial fibrillation (RR 1.10 95%CI, 0.74–1.63), heart failure (RR 1.54, 95%CI 0.95–2.47), or strokes (RR 0.86, 95%CI 0.11–6.75), but reduced mortality risk was observed for LT3 (RR 0.70, 95%CI 0.62–0.78).

Conclusions: Our findings are reassuring that regulated LT3 use is not associated with risk of death or serious adverse outcomes. More studies are needed to supplement existing data.

INTRODUCTION

Thyroid hormones have been used in the treatment of hypothyroidism for over a century (1). Hypothyroidism affects about 2–5% of the global population, with increasing prevalence in women and older adults (2). Untreated hypothyroidism is characterised by symptoms such as lethargy, memory problems, depression, and weight gain (3,4). Furthermore, hypothyroidism carries an increased risk of cardiovascular disease, abnormal lipid metabolism, and neurocognitive problems (3,4). Early therapy for hypothyroidism relied on desiccated thyroid extracts (DTE), which was eventually replaced by synthetic preparations in the 1960s (5). Levothyroxine (LT4), a synthetic form of thyroxine (T4), subsequently became the treatment of choice due to its biochemical stability and peripheral conversion to the active hormone, triiodothyronine (T3) (2,5,6). LT4 is now the third most prescribed medication in the UK and is likely to become even more widely used in future (7).

Most patients with hypothyroidism respond well to LT4 and report improvement in well-being, with TSH returning to normal within weeks of initiating treatment. However, observational studies suggest that a proportion of patients on LT4 alone continue to display impairment of psychological wellbeing compared with controls of similar age and sex (8,9). For some patients, combination treatment with LT4 and Liothyronine (LT3) offers an alternative treatment approach (10). Although the superiority of combination therapy over LT4 alone remains unproven in randomised controlled trials (RCTs) (11-13), meta-analyses have shown that patients with hypothyroidism prefer combination therapy over LT4 monotherapy (14). However, due to the unproven efficacy data, major international guidelines continue to recommend LT4 as the standard of care, with

combination therapy only reserved for patients who have not equivocally derived symptomatic benefit from LT4 monotherapy (15-18).

A potential hindrance to the use of LT3 however is the perception that it has a less favourable safety profile than LT4 and that it exerts adverse effects on cardiovascular and bone health (19). This perceived risk of harm has contributed to a reluctance to prescribe LT3 and DTE amongst clinicians (8). These concerns do not however appear to be based on substantial evidence. Systematic reviews on LT3 safety are limited and have been confined to the analyses of short-term adverse outcomes in treatment efficacy trials (11,12). A recent industry-funded review evaluated LT3 safety including market safety information pertaining to an LT3-LT4 combination tablet (20). However, the review was non-systematic, and the safety reports were limited to the authors' own branded product (20). A comprehensive evaluation of short and long-term safety outcomes of LT3 using validated systematic review and pharmacovigilance methods is therefore lacking.

We recently reported on a case of sudden death in a patient who was suspected to have ingested self-procured LT3 (21). This case thus prompted us to undertake a systematic review on the risk of death and severe adverse reactions in patients taking LT3, using a variety of sources from the published literature and pharmacovigilance databases. Our aim was to systematically summarise the available safety data on LT3 in the treatment of hypothyroidism using a multi-source approach.

METHODS

We conducted a systematic review of published case reports, cohort studies, randomised controlled trials, and reports in drug monitoring databases to determine the risk of death and major adverse reactions in patient on treatment with LT3.

Search Criteria

We searched PubMed from database inception to October 2024, without language restrictions, using a combination of the search terms Liothyronine, triiodothyronine, T3, Desiccated thyroid extracts, combination therapy, AND death, mortality, fatality, major adverse reactions, major adverse events, cardiovascular disease, strokes, heart failure, atrial fibrillation, myocardial infarction, AND hypothyroidism, Hashimoto's thyroiditis, autoimmune thyroiditis. We selected relevant articles based on information from their titles and abstracts with full texts accessed if the abstract information was insufficient to exclude the study. Additional papers were obtained from within references cited in relevant articles or from adverse case reports cited in pharmacovigilance databases. We also searched online research databases namely ClinicalTrials.gov (www.clinicaltrials.gov) and the UK Clinical Study registry (www.isrctn.com/). Two reviewers (SB, OO) reviewed the abstracts, and discrepancies were resolved by consensus or referral to a third reviewer (CMD).

Study inclusion

Studies were included in the review if they were: (1) case reports or case series that reported on death or serious adverse reactions in patients on LT3, (2) observational studies that addressed the risk of death, cardiovascular outcomes, or severe adverse events in LT3 vs. LT4 treated patients, and (3) RCTs of combination therapy vs. LT4 monotherapy that provided information on adverse effects (AEs).

Pharmacovigilance databases

The FAERS database: Drug safety data was obtained from the United States Food and Drug Administration Adverse Reporting System (FAERS) (22). FAERS is a publicly

accessible database of drug adverse reports submitted by members of the public, healthcare professionals, and pharmaceutical companies https://fis.fda.gov (22). We ran a search in FAERS for all adverse events from 1968-2024 that were reported in association with LT3 and LT4 comprising all the different preparations of these drugs (e.g. Levothyroxine sulphate, levothyroxine sodium etc) including generic and brand names. Results were further searched for in-text references of published case reports pertaining to LT3, to supplement the case report literature search.

Yellow-card scheme: we also searched the UK Medicines and Healthcare Regulatory Agency (MHRA) Yellow-Card Scheme. The Yellow-Card scheme is run by the UK MHRA, through which it collects and monitors information on suspected safety concerns involving medicines and healthcare products. Adverse event reports are held online in MHRA's publicly available Interactive Drug Analysis Profiles (iDAP) reports https://yellowcard.mhra.gov.uk/idaps. In the iDAP database, we searched for adverse events reported in association with LT4 and LT3 for the period 1967 – 2024 (23). Reports were grouped by severity and adverse reactions were classified by the primary system organ class as defined by the Medical Dictionary for Regulatory Activities (MedDRA) terminology (MedDRA version 27.0) (24).

Data analysis

Case reports and case series were summarised according to patient demographics (age, sex), indication for Liothyronine use, dose and duration of treatment, and adverse event outcome. For cohort studies we assessed the methodological quality of studies using the Newcastle Ottawa Scale (NOS) for the assessment of observational studies (25). Effect estimates are presented for individual studies as reported by the authors. Where feasible,

meta-analysis of cohort studies was undertaken with effect estimates summarised as risk ratios and 95% confidence intervals (CIs) using a random effects model with the restricted maximum likelihood ratio method. Heterogeneity was assessed using I2 statistics.

For RCTs of combination LT4/LT3 vs. LT4, the occurrence of adverse effects was summarised as counts. For each study, we counted numbers of participants in each study arm who discontinued medications or withdrew from the trial after recruitment due to the development of side effects or adverse effects that were judged by the trial authors to be related to the study drugs. These included participants who discontinued medications or withdrew from the trial after developing features of thyrotoxicosis, palpitations, cardiac arrhythmias, strokes, gastrointestinal side effects, headaches, etc. We did not count individuals who withdrew for personal or administrative reasons, protocol violation, lack of treatment effect, or following the development of unrelated diseases such as cancer. Studies that provided inadequate information to determine withdrawals in each study arm were excluded from meta-analysis in contrast to studies that reported zero withdrawals which were included. Pooled relative risks were derived using a random effects model with the restricted maximum likelihood ratio method. Relative risks were calculated first for all eligible studies and then for studies without zero counts. Adjustment for zero counts was undertaken using a continuity correction method as described by Sweeting (26).

Disproportionality analysis

We used disproportionality analysis to evaluate potential associations between LT3 and LT4 and severe adverse events including fatal events. Disproportionality analyses is a validated pharmacovigilance tool for evaluating associations between drug and adverse event. This analysis was conducted in the FAERS database but was not feasible in the

Yellow-card scheme or other pharmacovigilance databases, as total number of all reactions to all drugs was not readily accessible as in FAERS. For each drug, we derived reporting odds ratios (RORs) and proportional reporting ratios (PRRs). These ratios are based on the observed counts of adverse effects reported for a drug with respect to the expected count based on all other drugs in the database (27,28). The ratios were calculated from 2x2 contingency tables as shown in supplementary table S1 (29). Signals were considered significant for both measures if the ratios were >1.0 with 95% confidence interval >1.0. In confirmatory analyses, we calculated the information component (IC) with 95% confidence interval (95%CI) (supplementary table S1) (29). This was considered significant if the IC was >0.

RESULTS:

Study selection

The original search identified 1814 articles including published reports in drug monitoring databases. We excluded 418 articles comprising 86 duplicates and 332 articles with non-human subjects. A further 1321 articles were excluded after title or abstract screening, and 23 papers excluded after full text review, resulting in a total number of 52 papers in the review. The selected studies comprised 27 case reports, 4 cohort studies, and 21 RCTs. Study flow chart and reasons for exclusions on full text review are shown in figure 1.

Case reports

We identified 28 cases of serious adverse effects linked to LT3, in 25 reports published between 1979 and 2024 (21,30-53). We excluded one report of sagittal sinus thrombosis in a patient on Liothyronine and Armour thyroid due to the presence of other more

plausible aetiological factors, including a positive screen for prothrombin gene deficiency (32). Of the remaining 27 cases, 59% were female with age-range 20–71 years (table 1). Adverse effects were mostly due to pharmacy compounding errors (10 cases) or the unlicensed use of LT3 for body building, weight loss, or fatigue in individuals without hypothyroidism (14 cases). Compounding errors involved the ingestion of LT3 doses that were 10–1000 times the intended doses equivalent to the ingestion of LT3 at dose ranges of 1000-50,000 mcg daily. Thyrotoxicosis, thyroid storm, or thyrotoxic periodic paralysis were the most frequently reported adverse effects and these usually resolved on discontinuing the offending preparation. Two fatalities were reported, one in a 29-year-old male without a history of hypothyroidism who had self-administered 100 mcg of LT3 daily for six months for weight loss purposes (47), and the other in a 42-year-old lady who ingested an unspecified amount of LT3 that had been procured over the internet presumably for fatigue (21). No adverse effect was reported for patients with hypothyroidism who received supervised treatment with standard LT3 doses under licensed indications. (table 1).

Randomised Control Trials:

We initially reviewed 23 RCTs of LT3 efficacy (54-76). We excluded trials that did not provide information on adverse effects (72,74), or did not distinguish adverse effect events between the trial arms (71), or trials which only addressed LT3 monotherapy vs. LT4 monotherapy (75,76). Details of RCTs of combination LT3/LT4 versus LT4 monotherapy with adverse effect reports are shown in table 2 (54-70,73). Reported AEs mostly included symptoms of hyperthyroidism or hypothyroidism. Only one study reported significantly increased AEs in the combination group. This study, conducted by Smith *et*

al in the 1960s (69), administered relatively high LT3 doses of 40-60 mcg daily, in combination with LT4 doses of 200-300mcg. No statistically significant differences were noted in any of the other studies between AEs recorded in treatment or control arms and none of the RCTs reported any sudden deaths (table 2).

Of the included studies, 18 trials contained information on the number of trial participants in each study arm who discontinued treatment or withdrew from trials due to adverse effects (54-70,73). The numbers of adverse effect withdrawals or treatment discontinuation for trials of combination LT3/LT4 versus LT4 monotherapy were pooled in meta-analysis and grouped by administered dose (figure 2). LT3 was administered in combination with LT4 at average daily doses of 5-25 mcg daily with the exception of the high-dose study by Smith *et al*, which administered 40-60 mcg daily in combination with LT4 doses of 200-300mcg and showed increased risk of adverse effects (69) (figure 2). However, despite inclusion of this study in the meta-analysis, there was no overall increased risk of adverse effect withdrawals in the combination vs LT4 monotherapy groups (figure 2). The lack of association persisted after excluding trials with zero adverse effect withdrawals (supplementary figure 1) (29).

Cohort Studies

We identified four cohort studies, from Scotland (77), Sweden (78), Korea (79) and USA (80), that reported morbidity and mortality data in LT3 vs. LT4 users (table 3). Studies were all retrospective observational studies using national or health expenditure datasets with mean follow-up periods ranging from over 90 days to 9 years (77-80). Studies were of moderate to good quality (supplementary table 2) (29). Patients were grouped into LT3 users (either alone or in combination with LT4, n=13,060) vs. users of LT4 alone

(n=616,942). One study also included patients on DTE (n=252) in their LT3 group (80). Cohorts included varying proportions of thyroid cancer patients (table 3). The study by Leese comprised 0.4% thyroid cancer patients in the LT4 group and 22% in the LT3 group (77). The other two studies contained <5% of patients with thyroid cancer in either group (78,80). In contrast, the study by Yi *et al* comprised higher rates of thyroid cancer patients (40% in the LT3 group, and 35% in the LT4 group) (79). Outcomes reported in at least two studies are summarised in figure 3 and include all-cause mortality (2 studies), atrial fibrillation (3 studies), strokes (2 studies), heart failure (2 studies), and breast cancer (2 studies). Event rates were summarised as hazard ratios and 95% confidence intervals (HR, 95%CI).

In the meta-analysis, LT3 use was not associated with a significantly increased risk of any of the reported outcomes (figure 3). There was a non-significant increased risk of heart failure with combination therapy (HR 1.54, 95%CI 0.95, 2.47), driven by the large Korean study by Yi *et al (79)*. Further subgroup analyses of this cohort showed that increased heart failure risk was only seen in patients with a history of thyroid cancer, raising the possibility of unaccounted risk factors such as targeted thyroid hormone suppression in this cohort. In contrast, pooled analysis of the two studies that reported on all-cause mortality showed a reduction in mortality (HR 0.70, 95%CI 0.62–0.78) in LT3 users, driven by the large Swedish study by Planck et al (figure 3).

Yellow-card reports

Data from yellow-card reports were generated for LT3 and LT4 from 1967–2024. In the period, 3226 adverse reports were linked to LT4, comprising 14,663 reactions while 292 reports and 1,687 reactions, were linked to LT3. The breakdown of reactions according

to the MedDRA System Organ Class is presented in supplementary figure 2 (29) which summarises reactions reported in each system as a percentage of the total reactions for each drug. Both drugs showed similar AE profiles, with most reactions being general disorder events, nervous system, or psychiatric illness disorders (supplementary figure S2) (29). For LT3, 22% of all reactions were general disorder events compared to 17% of LT4 reactions. In contrast, gastric and skin reactions accounted for 11% and 10% of LT4 reactions compared to 7% and 7% of LT3 reactions, respectively. The breakdown of reports according to severity is shown in supplementary figure 3 (29). Similar rates of serious and non-serious adverse effects were reported for LT4 and LT3, with one death reported in association with LT4 and no reported deaths for LT3.

FAERS database:

Disproportionality analysis using the FAERS database did not show any signal for LT3 either for serious adverse events or deaths (table 4). These results were consistent for the reporting odds ratio (ROR), proportional reporting ratio (PRR), and information components (IC), which are drug safety signal measures derived from 2x2 contingency tables in disproportionality analyses (supplementary table S1) (29). Increased signal in the ROR and IC was seen for LT4 for serious adverse effects but not for deaths (table 4).

DISCUSSION

We conducted a systematic review and meta-analysis on the safety of LT3, using a variety of sources comprising case reports, cohort studies, randomised controlled trials, and pharmacovigilance databases. Our findings suggest that LT3, when used within medically recommended doses and under appropriate supervision, is not associated with an increased risk of serious adverse effects (AEs), cardiovascular events, or death. Case

reports revealed that serious AEs were almost exclusively linked to supratherapeutic LT3 exposure, either through compounding errors, unregulated online procurement, or misuse for weight loss and bodybuilding. These cases often involved doses 10–1000 times above therapeutic levels. Importantly, no adverse outcomes were reported when LT3 was prescribed and monitored in line with clinical guidelines.

Meta-analysis of RCTs showed no increase in AE-related treatment discontinuation in combination LT4/LT3 therapy compared to LT4 monotherapy, even when trials using higher LT3 doses were included. Similarly, cohort studies involving over 13,000 LT3 users found no excess risk of atrial fibrillation, heart failure, or stroke. Notably, pooled mortality data from two large studies showed a statistically significant reduction in all-cause mortality among LT3 users compared with LT4 users. Pharmacovigilance data provided further reassurance on LT3 safety. Yellow Card reports from the UK and FAERS data from the US revealed similar AE profiles for LT3 and LT4. Disproportionality analysis did not identify a safety signal for LT3 but did show an increased reporting signal for serious AEs with LT4, albeit not for mortality.

Ours is the first comprehensive systematic review of its kind to collate evidence from multiple sources on the safety of LT3. Also, we have presented the first meta-analysis of cohort studies on cardiovascular and mortality outcomes associated with LT3 use. Adverse effect risks in RCTs were only specifically addressed in a few previous systematic reviews (11,12). One study by Millan-Alanis et al, which described adverse effects in RCTs without a formal meta-analysis, concluded that overall incidence of adverse effects in the two arms did not differ (11). A meta-analysis of RCTs by Grozinsky-Glasberg et al showed

similar results to ours with no significant increase in adverse effect risk for LT3 compared to LT4 (12). However, these meta-analyses were limited to trials that met criteria for efficacy analysis. In contrast our study included more RCTs regardless of the primary study outcome as the key interest of our analysis was drug safety. Our findings are also broadly consistent with a recent narrative review which reported a low number of spontaneous adverse events for a branded LT3-LT4 product based on market safety information in the Merck global pharmacovigilance database (20). In contrast to this study, however, our study was systematic, evaluated all available LT3 products in independent national datasets, and employed validated pharmacovigilance and meta-analyses methods to establish short and long-term safety outcomes.

Our findings have implications for the treatment of hypothyroidism. Although LT4 remains the recommended treatment in hypothyroidism, a proportion of patients appear best served with combination LT3/LT4 therapy. A limitation to the use of combination therapy is the paucity of safety data. Earlier studies in the 1960s suggested that LT3 was associated with excess risk of thyrotoxicosis and its cardiovascular complications (69). However, as our review shows, such reported risks are inconsistent with data from more recent studies and is likely to have been a function of excessive LT3 dosing. A large cohort study from Korea reported an increased risk of heart failure and strokes amongst LT3 users compared to LT4 users (79). This study however comprised a high proportion of patients who had been treated for thyroid cancer and would conceivably have been on TSH suppressive treatment doses. Furthermore, this effect was lost when pooled in meta-analysis with another study from the United States (80). Interestingly, pooled analysis of two studies from the UK (77) and Sweden (78) which addressed all-cause mortality

showed reduced mortality risk for LT3 compared to LT4. However, this finding should be interpreted with caution as it may point to unexplored factors in the selection of patients for LT3 treatment. Nonetheless, our data show that LT3 is at least as safe as LT4 and should inform treatment choices in patients with hypothyroidism.

Our study has several limitations. The drug databases rely on reports submitted by patients, pharmacists, health care workers, and medical professionals, and under-reporting is a well-known limitation of such datasets. In addition, the nature of symptoms associated with LT3 treatment may be subjective, with a lack of objective proof linking LT3 to adverse effects. Furthermore, LT3 reporting may be subject to notoriety bias due to publicised safety concerns. Lastly, the disproportionality analyses are only measures of drug safety signals and cannot be considered as indicators of association or causality (27). The randomised controlled trials also suffer from limitations in terms of inadequate power for adverse effect analysis, short follow-up durations, and possible bias by association with underlying diagnoses and cardiovascular risk. Furthermore, several RCTs could not be included in our meta-analysis as these studies did not report on the incidence of adverse effects. Lastly, the cohort studies were heterogeneous in study design, patient characteristics, and outcomes, and due to the small number of published studies, the meta-analysis was limited to 2-3 studies per individual outcome.

The above limitations therefore underscore the need for further studies to establish the safety of LT3. Further large cohort studies will be particularly insightful as they will reflect practice in real world cohorts with longer follow-up durations which is challenging to capture within the limited time-frame of controlled trials. Such studies should ideally include an evaluation of treatment dose and duration as well as thyroid hormone status

to better understand the role of treatment dose and TSH suppression in mitigating outcome risks. Assessments of exposure to other alternative therapies apart from combination therapy including LT3 monotherapy and desiccated thyroid extracts should also be undertaken and will provide valuable insights to these increasingly used treatment approaches. Future trials on combination therapy addressing the limitations of existing trials are likely to be undertaken given that the evidence surrounding the benefits of combination therapy remains unproven (18). It is important that future RCTs report specifically on adverse effects and treatment withdrawals according to established clinical trials procedures.

In conclusion, our systematic review addresses a critical gap in the growing need for safety assurance around the use of LT3, given the strong patient preference, hesitancy of clinicians to prescribe LT3, and potential for abuse by patients self-medicating from unregulated sources. Our report highlights the real risks of LT3 misuse outside medical supervision, together with the surprising frequency of pharmacy compounding errors. On the other hand, when used and monitored appropriately by registered physicians, LT3 is safe and well tolerated, and is not associated with increased adverse effect risks, emphasizing that the frequency of LT3-associated harm appears to reflect misuse rather than pharmacologic toxicity. Thus, in view of the analysis conducted above, where doses are not excessive, the occurrence of a sudden death in an LT3 user may be just as likely to be coincidental, as in an LT4 user, especially when considering similar risks reported with LT4. Thus, while clinicians should remain vigilant regarding unregulated LT3 use and compounding practices, these risks should not preclude its use in medically supervised settings.

Data availability statement

Original data was generated for this study from data in the published literature. These data are included in this article and in the data repository listed in the reference.

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TABLES AND FIGURES

LEGENDS FOR TABLES AND FIGURES

Table 1: Case reports of serious adverse effects associated with Liothyronine (LT3)

Legend: LT3, Liothyronine, mcg, microgram, NS, not stated, *MMI, Methimazole

Table 2: Adverse events (AEs) in RCTs of combination LT3/LT4 vs. LT4 monotherapy

Legend: Randomised controlled trials (RCTs), LT4, Levothyroxine, LT3, Liothyronine, DTE, desiccated thyroid extracts, mcg, micrograms.

Table 3: Cohort Studies on mortality and cardiovascular outcomes for Levothyroxine (LT4) vs. Liothyronine (LT3) users

Legend: LT4, Levothyroxine only users, LT3, Liothyronine users, TC, Thyroid cancer, TSH, thyroid stimulating hormone, DTE, Desiccated thyroid extracts

Table 4: Disproportionality analysis

Legend: Table shows Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), and Information Components (IC) for Liothyronine (LT3) and Levothyroxine (LT4) using the FAERS database. AEs, adverse effects, A/C, adverse effect of interest reported with target drug/adverse effect of interest reported with other drugs, B/D, other adverse effects reported with target drug/other adverse effects reported with other drugs. ** Significant signals

Figure 1: Flow chart for study inclusions

Figure 2: Meta-analysis of withdrawals from RCTs due to adverse effects

Legend: REML, Restricted Maximum Likelihood

Figure 3: Meta-analysis of cohort studies

Legend: REML, Restricted Maximum Likelihood

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Table 1: Case reports of serious adverse effects associated with Liothyronine (LT3)

Author, year (ref)	Age, sex	Treatment, dose, duration	Adverse outcome
Pharmacy compounding errors			
Sola, 2002 (41)	44, F	LT3 ~ 50,000 mcg daily, 8 days	Thyroid storm
Shah, 2017 (42)	53, F	LT3 in thyroid extracts, dose NS	Thyrotoxicosis
Khan, 2019 (40)	30, F	LT3 ~ 30,000 mcg daily, 2 weeks	Thyroid storm
Bains, 2015 (45)	71, F	LT3, dose NS	Myocardial infarction
Bains, 2015 (45)	59, F	LT3, dose NS	Thyrotoxicosis
He, 2020 (48)	20, M	LT3, 10,794 mcg	Thyrotoxicosis
He, 2020 (48)	30, F	LT3, 30,000 mcg daily, 16 days	Thyroid storm
He, 2020 (48)	44, F	LT3, 10 x usual dose	Thyrotoxicosis

DL Calzada, 2011 (49)	43, F	LT3, 1300 mcg daily	Thyrotoxicosis
Jha, 2012 (50)	62, F	LT3 in thyroid extracts, dose NS	Thyroid storm
Pharmacy dispensing error			
Manasra, 2023 (31)	53, M	LT3 15 mcg daily, erroneously dispensed instead of MMI*	Atrial fibrillation
Unlicensed use for weight loss			
Cheema 2018 (38)	33, M	LT3 containing supplements	Thyrotoxic periodic paralysis
Regina, 2016 (43)	30, F	LT3 diet pills, 625 mcg, 2 weeks	Thyrotoxicosis
Chou, 2009 (46)	23, M	LT3, 64 mcg daily, 4 weeks	Thyrotoxic periodic paralysis
Hartung, 2010 (47)	29, M	LT3, 100 mcg, 6 months	Fatal thyroid storm
Akinyemi, 2011 (51)	35, F	LT3 in diet pills, dose NS	Thyrotoxic periodic paralysis
Panikkath, 2014 (52)	24, M	LT3 in diet pills, dose NS	Thyrotoxic periodic paralysis
Daniels, 2013 (53)	49, F	LT3 in diet pills	Thyrotoxicosis
Unlicensed use for fatigue			
Shaw, 2021 (30)	58, F	LT3, 5–40 mcg daily, 6 weeks	Stress cardiomyopathy
Parimi, 2021 (35)	52, F	LT3, 250 mcg daily, 18 months	Thyrotoxicosis
Bahl, 2024 (21)	42, F	LT3, dose NS	Sudden death
Unlicensed use for body building			
Miklin, 2023 (33)	31, M	LT3, dose NS	Cardiomyopathy
Warner, 2020 (34)	25, M	LT3, 25 mcg daily, 4 weeks	Persistent tachycardia,
Kwak, 2016 (44)	25, M	LT3, 75 mcg daily, 3 weeks	Thyrotoxicosis
Van Bokhorst, 2021 (36)	29, M	LT3, 50–100 mcg daily, 8 years	Thyrotoxic periodic paralysis
Intentional overdose			
Quan, 2016 (39)	50, M	LT3, 180 tablets, dose NS	Thyroid storm
Dahlberg, 1979 (37)	30, F	LT3, 1600 mcg	Thyrotoxicosis

LT3, Liothyronine, mcg, microgram, NS, not stated, *MMI, Methimazole

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Table 2: Adverse events (AEs) in RCTs of combination LT3/LT4 vs. LT4 monotherapy

First Author, Year	RCT design	AEs reported*	N	Duration	LT4 dose	LT4/LT3 dose
Appelhof, 2005 (54)	Parallel	No difference	141	15 weeks	LT4 usual dose	LT4/LT3 in 10:1 ratio or 5:1 ratio
Biondi, 2023 (55)	Parallel	No difference	28	1 year	Usual LT4 dose	Usual LT4 dose/LT3 in 17:1 ratio
Brigante, 2024 (56)	Parallel	No difference	141	6 months	Usual LT4 dose	Usual LT4 dose/LT3 in 13-20:1 ratio
Bunevicius, 1999 (73)	Cross over	No difference	31	5 weeks	Usual LT4 dose	Usual LT4 dose minus 50 mcg /LT3 12.5 mcg
Clyde, 2003 (57)	Parallel	No AEs reported	46	4 months	Usual LT4 dose	50% usual LT4 dose/ LT3 7.5 mcg
E-Morreale, 2005 (58)	Cross over	No difference	28	8 weeks	LT4 100 mcg	LT4 75-87.5 mcg/ LT3 5-7.5 mcg
Hoang, 2013 (59)	Cross over	No difference	70	16 weeks	LT4 75-225 mcg	DTE 43-172 mg
Kaminski, 2016 (60)	Cross over	No AEs reported	32	8 weeks	LT4 125-150 mcg	LT4 125-150 mcg/LT3 7.5-15 mcg
Krysiak, 2018 (61)	Quasi-randomised	No difference	39	6 months	Usual LT4 dose	50% LT4 dose/ LT3 in 5:1 ratio
Nygaard, 2009 (62)	Cross over	No difference	59	12 weeks	Usual LT4 dose	Usual LT4 dose/ LT3 20 mcg
Rodriguez, 2006 (63)	Cross over	No difference	30	6 weeks	Usual LT4 dose	Usual LT4 dose minus 50 mcg/LT3 10 mcg
Saravanan, 2005 (64)	Parallel	No difference	697	1 year	Usual LT4 dose	Usual LT4 dose minus 50 mcg/ LT3 10 mcg
Sawka, 2003 (65)	Parallel	No difference	40	15 weeks	Usual LT4 dose	50% LT4 dose/LT3 12.5 mcg
Shakir, 2021 (66)	Cross over	No AEs reported	75	22 weeks	LT4 88-250 mcg	LT4 63-175 mcg/LT3 7.5-20 mcg
Siegmund, 2004 (67)	Cross over	No AEs reported	23	12 weeks	LT4 100-175 mcg	LT4 100-175 mcg/LT3 5-10 mcg
Slawik, 2007 (68)	Cross over	No difference	29	5 weeks	LT4 1.6 mcg/kg	LT4 1.4 mcg/kg/LT3 0.16 mcg/kg
Smith, 1970 (69)	Cross-over	More AEs in LT3/LT4 arm	87	2 months	LT4 200-300 mcg	LT4 200-300 mcg/LT3 40-60 mcg
Valizadeh, 2009 (70)	Parallel	No AEs reported	71	4 months	LT4 100 mcg	LT4 50 mcg/LT3 6.25 mcg

Randomised controlled trials (RCTs), LT4, Levothyroxine, LT3, Liothyronine, DTE, desiccated thyroid extracts, mcg, micrograms.

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Table 3: Cohort studies on mortality and cardiovascular events for Levothyroxine vs. Liothyronine users

Author, year, country	Study Design	Mean age, sex	Variables adjusted for	Mean follow-up	Numbers, exposures, indications	Outcomes
Leese, 2016, Scotland (77)	Retrospective cohort population study of national registries	LT3 47 yrs, 84% female LT4 60 yrs, 81% female	Age, sex, thyroid cancer, past hyperthyroidism, baseline TSH	9.3 yrs	LT3, 400 (22% thyroid cancer), LT4 only, 34,000 (0.3% thyroid cancer)	Mortality, cardiovascular disease, atrial fibrillation, fractures, breast cancer & mental disorders
Planck, 2021 Sweden (78)	Retrospective cohort population study of national registries	LT3 46 yrs, 91% female LT4 59 yrs, 82% female	Age, dose, sex, thyroid cancer & other cancers, antithyroid drug & sex hormone use	8.1 yrs	LT3, 11,147 (1.2% thyroid cancer), LT4 only, 573,928 (0.8% thyroid cancer)	Mortality, breast cancer, any cancer
Yi, 2022, Korea (79)	Retrospective, cohort study of hospital databases	Median age 40-50 yrs LT3 84% female LT4 82% female	Propensity scores matched for age, sex, & comorbidity	Over 90 days	LT3, 1434 (40% thyroid cancer), LT4 only, 3908 (35% thyroid cancer)	Atrial fibrillation, heart failure, ischaemic heart disease, stroke, cancer, anxiety & mood disorders, osteoporosis
Penna, 2024 USA (80)	Retrospective cohort study of medical expenditure database	LT3 61 yrs, 97% female LT4 61 yrs, 76% female, DTE 56 yrs, 92% female	Age, gender, race, ethnicity, family income, survey year, comorbidities	Median 6 yrs (LT4), 3 yrs (LT3/LT4 & DTE)	LT4, 5106, (3.6% thyroid cancer), DTE, 252 (3.0% thyroid cancer), LT3, 79 (1.3% thyroid cancer)	Atrial fibrillation, heart failure, myocardial infarction, stroke, osteoporosis, fracture

LT4, Levothyroxine only users, LT3, Liothyronine users, TC, Thyroid cancer, TSH, thyroid stimulating hormone, DTE, Desiccated thyroid extracts

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Table 4: Disproportionality analysis

	Cases, N	Non-cases, N	Disproportionality measures		
Adverse Effects	**Target drug/ Other drugs (A/C)**	**Target drug/ Other drugs (B/D)**	**ROR (95%CI)**	**PRR (95%CI)**	**IC (95%CI)**
LT3, serious AEs	1,212/10,974,443	2085/9,840,513	0.52 (0.49, 0.56)	0.70 (0.25, 1.98)	-0.61 (-0.52, -0.45)
LT4, serious AEs	44,545/10,931,110	27,667/9,814,930	1.45 (1.42, 1.47)**	1.17 (0.42, 3.30)	0.21 (0.23, 0.24)**
LT3, deaths	56/1,777,557	3,241/19,037,400	0.19 (0.14, 0.24)	0.20 (0.17, 0.24)	-2.75 (-2.32, -2.00)
LT4, deaths	4,917/1,772,696	67,295/18,973,344	0.78 (0.76, 0.81)	0.80 (0.67, 0.94)	-0.37 (-0.33, -0.29)

Table shows Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), and Information Components (IC) for Liothyronine (LT3) and Levothyroxine (LT4) using the FAERS database. AEs, adverse effects, A/C, adverse effect of interest reported with target drug/adverse effect of interest reported with other drugs, B/D, other adverse effects reported with target drug/other adverse effects reported with other drugs. ** Significant signals

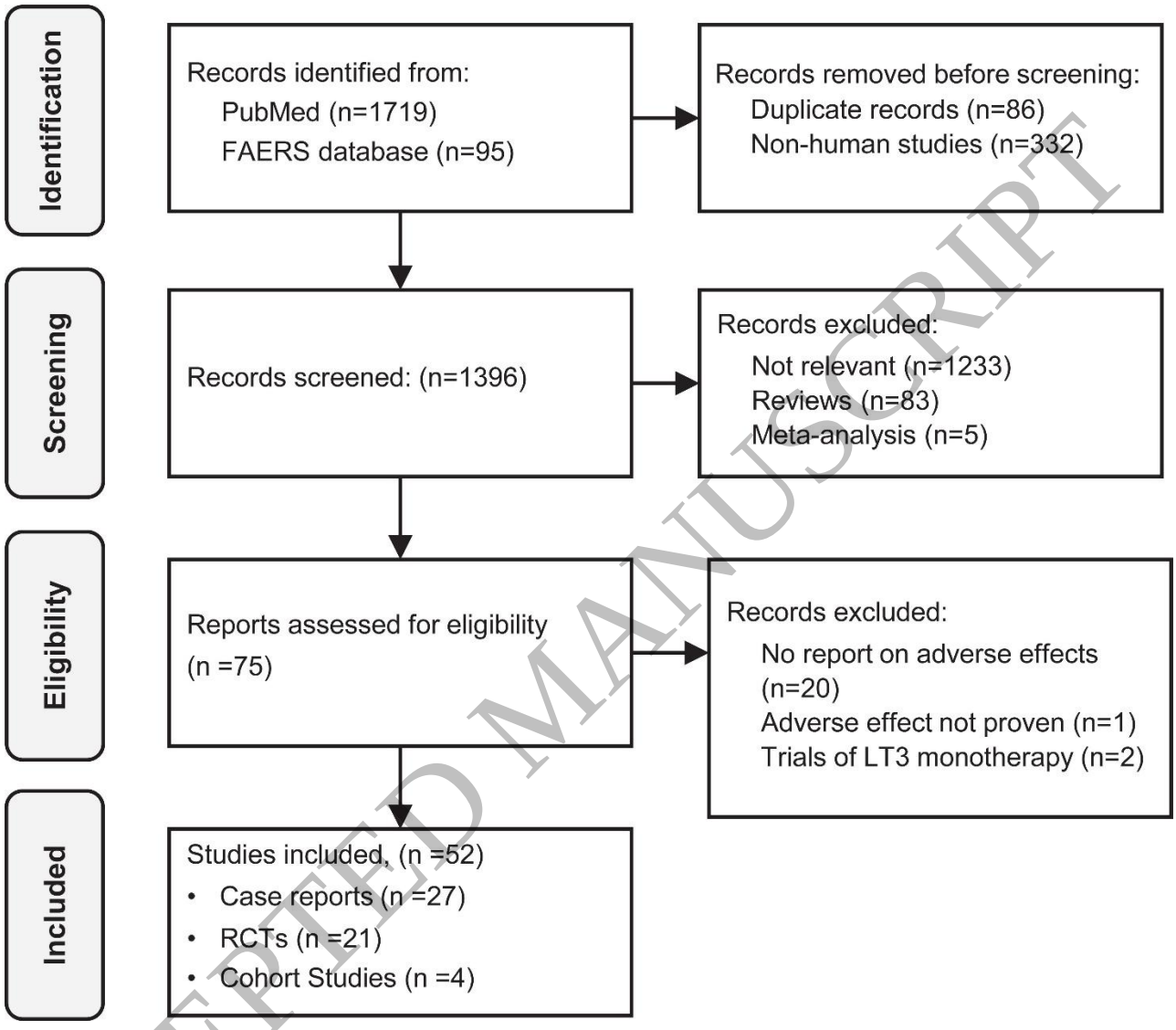

Figure 1
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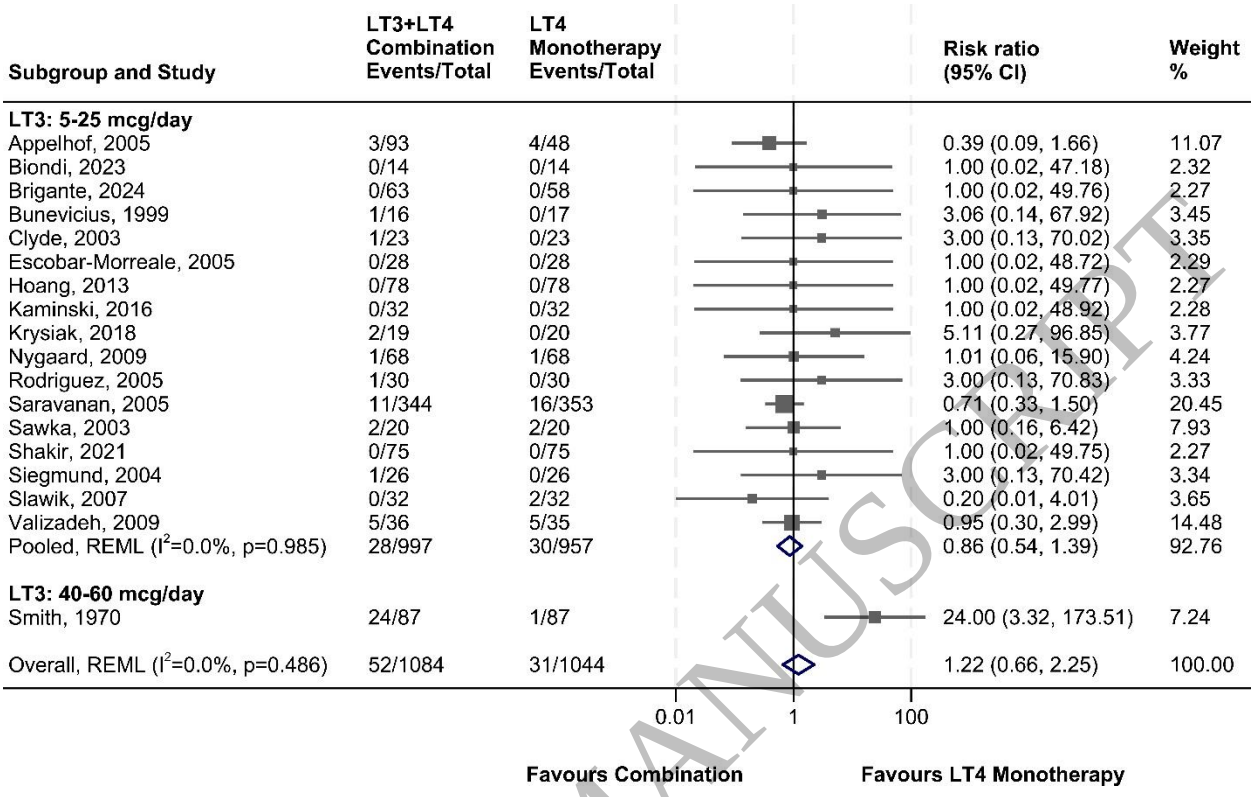

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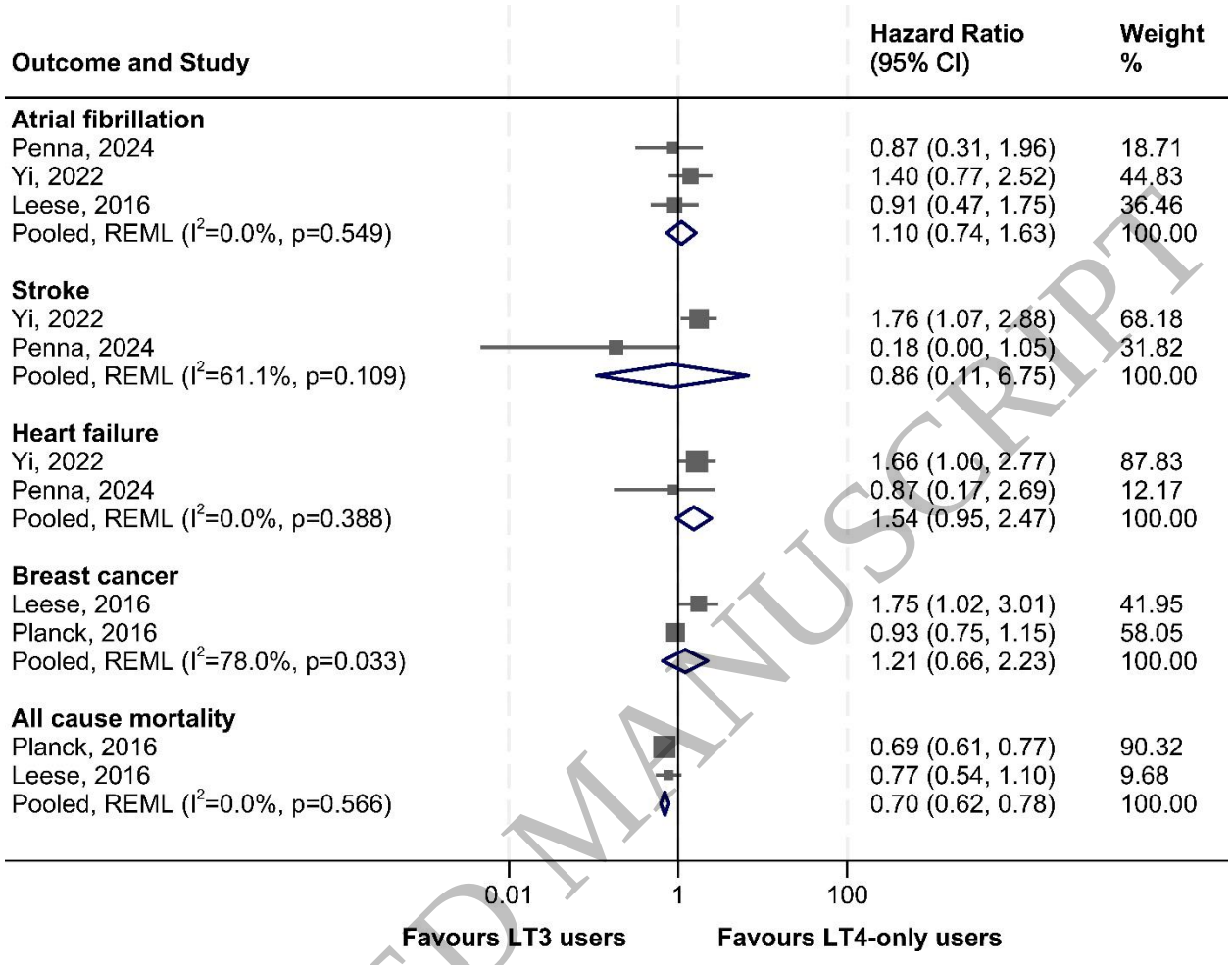

Figure 3
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