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Efficacy and safety of Triiodothyronine (T3) treatment in Cardiac Surgery or Cardiovascular Diseases – a Systematic Review and Meta-analysis of Randomized Controlled Trials

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Short title: T3 in cardiac conditions

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Abstract

Background: Low levels of the active thyroid hormone triiodothyronine (T3) in cardiac patients are associated with worse outcomes. The aim of this analysis was to assess if T3 treatment is beneficial and safe in patients undergoing cardiac surgery or those with cardiovascular diseases in whom there is observed or expected reduction in serum T3 levels.

Methods: A systematic review and meta-analysis of randomized controlled trials (RCTs) was performed as per the PRISMA guidelines. Pubmed, Embase and Web of Science databases were searched for RCTs published between 1st January 1960 and 30th March 2022 that evaluated the effects of T3 therapy in patients undergoing cardiac surgery or with cardiovascular diseases. The primary outcomes were measures of cardiac function. Weighted mean difference (MD) or relative risk were calculated using a random effects model. PROSPERO registration no. CRD42020211966

Results: Of the 3181 full-text articles screened, 34 studies with 2547 participants (number ranging between 13 to 223, mean ages between 0.5 to 73 years, mean percentage of women between 7 to 64%) were included. In 12 RCTs with 1093 adults undergoing cardiac surgery T3 therapy was associated with improvement in cardiac index (MD [95% CI], 0.24 [0.08 to 0.40] L/min/m^2, I^2=74%). The quality of evidence was high to moderate. In 3 RCTs with 188 children undergoing cardiac surgery, 3 RCTs with 131 adult cardiac donors, 3 RCTs with 83 adult patients with heart failure, and 2 RCTs with 89 adults with acute myocardial infarction, T3 therapy did not improve cardiac index or left ventricular function; the quality of evidence ranged from high (paediatric cardiac surgery) to low (other groups). No detrimental effect of T3 therapy was observed on heart rate, risk of in-hospital atrial fibrillation or mortality.

Conclusions: Short-term T3 therapy is safe and trials in adults undergoing cardiac surgical procedures to evaluate longer term clinical endpoints are required. Current data does not support the routine use of T3 therapy in children undergoing cardiac surgery or in cardiac donors. Adequately designed trials are required to determine if T3 therapy improves

cardiac function and clinical outcomes in patients with heart failure or acute myocardial infarction.

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Introduction

The cardiovascular system in general and the myocardium in particular is a major target of thyroid hormone action (1). The active thyroid hormone triiodothyronine (T3) has a strong influence on several structural and regulatory proteins of the cardiac myocyte and is important for myocardial contractility, acts as a vasodilator and has a direct positive action on myocardial mitochondrial function (2). Furthermore, myocardial injury, caused by either disease or surgical intervention, leads to reduced intra- and extra-cellular T3 levels due to the effects on thyroid hormone-modulating enzymes (3). Epidemiological studies have consistently demonstrated that low serum T3 levels are a strong prognostic marker of higher mortality in patients with cardiac disease or those undergoing cardiac surgical procedures (4, 5).

Trials of T3 in a small number of patients either undergoing cardiac surgery or with cardiovascular disease have shown conflicting results (6). This uncertainty regarding the utility and safety of T3 in high-risk patients has led to variations in clinical practice, which is best observed by its use in cardiac donor procedures. Some cardiac centres in the United States routinely use T3 and/or thyroxine (T4) in brain dead cardiac donors prior to organ retrieval although this practice isn't universally shared (7), despite a meta-analysis of randomized controlled trials (RCTs) showing no benefit (8). Similarly, experience from routine clinical practice has suggested that therapy with T3 may be useful in weaning patients from cardiopulmonary bypass who are on maximal inotropic support (9). Previous systematic reviews have evaluated the use of thyroid hormones in specific patient groups such as organ donors, post-operative non-thyroidal illness in adults or children after surgery for congenital heart defects (8, 51, 52). However, systematically synthesising and analysing the literature pertaining to T3 supplementation in the various cardiac conditions including cardiovascular diseases could clarify its role and guide clinical practice.

We performed a systematic review and meta-analysis of RCTs with the primary aim to identify the effects of T3 therapy or control on cardiac function in patients undergoing cardiac surgery or with cardiovascular disease. Our secondary aims were to investigate the impact of T3 treatment on hospital length of stay (LOS), post-operative inotrope use, thyroid function parameters and to assess any adverse effects. The results of this analysis

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could provide clinicians with evidence to guide clinical practice regarding the potential efficacy and safety of T3 treatment in patients with cardiac conditions.

Materials and Methods

This systematic review was conducted as per the PRISMA guidelines for evidence-based reporting of randomized trials. The protocol was published on PROSPERO (CRD42020211966), available at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=211966.

Data sources and search strategy

We searched three electronic databases (PubMed, Embase and Web-of-Science) for articles written in English from 1960 to 30th March 2022, with the help of expert librarians. The searches were a combined result of the terms thyroid hormone (T3, Triiodothyronine, Liothyronine) and cardiovascular disease (cardiovascular, heart, cardiac, cardiology, heart failure, congestive heart failure, CHF, cardiac arrest, MI, myocardial infarction, coronary heart bypass, coronary artery bypass graft, heart bypass, valvular, paediatric cardiac surgery and adult cardiac surgery). References of the full text articles identified by the search were reviewed to identify any additional studies that could be eligible for inclusion. In addition, global database of clinical trials was also interrogated (ClinicalTrials.gov) for relevant studies (details in **Supplementary Methods)**. Authors of studies that were potentially eligible for inclusion but had not provided the required data in a suitable manner were contacted.

Study selection and data extraction

RCTs that evaluated the effects of T3 therapy in patients with cardiac disorders were eligible to be included in the systematic review. Low serum T3 levels at recruitment were not a criteria for inclusion in the cardiac surgical studies as T3 levels are known to decrease in these patients (3). Two independent reviewers (MT and SR) reviewed the titles and abstracts of each citation and differences were resolved through discussion. A semi-automated app was utilised for the initial screening of titles and abstracts identified from

the various sources to expedite the initial screening of titles and abstracts and to help identify duplicates (10). Duplicates between each database were then individually removed and the full texts of relevant articles were independently reviewed. Studies that reported any cardiac procedures including cardiopulmonary bypass grafting, valvular surgery or repair of heart defects were classed as cardiac surgeries. And, studies that included patients with cardiac conditions such as heart failure, ischemic heart disease or acute myocardial infarction were classed as cardiovascular diseases. For studies that utilised more than one dose of T3 the results for the highest dose were included. If studies reported results for an outcome at multiple time points during or after the intervention, only the latest measurement was used in the statistical analyses. Using a predesigned data collection format, one of the authors (MT) gathered information from the studies and a second author (SR) checked the information for accuracy (**Supplementary Methods**).

Quality assessment

Risk of bias assessment tool version 2 (ROB2) was utilised to assess for potential bias for each RCT (11). The Grading of Recommendations Assessment, Development and Evaluation (GRADE) was used to evaluate the quality of evidence for each outcome being evaluated based on five domains including risk of bias, inconsistency, indirectness, imprecision and publication bias. The quality of evidence was then summarised to range from high, moderate, low to very low (12).

Data synthesis and analysis

The main outcome for assessment were measures of cardiac function. Other secondary outcomes included parameters of safety of T3, resource utilisation and thyroid function parameters. For continuous variables, mean difference in changes for each treatment arm (T3 or placebo) and its standard deviation were calculated for each trial. Weighted mean differences (MD) and their 95% confidence intervals using the random effects model of Hartung-Knapp-Sidik-Jonkman method, which is considered more robust than the commonly reported DerSimonian-Laird method when the number of included studies is less than twenty, were calculated (13). For binary outcomes pooled risk ratios (RR) and

their 95% confidence intervals using random effects model were estimated. For outcomes that were measured differently across trials (such as reporting the measured thyroid hormone as either the total or the free fraction, measure of systemic vascular resistance as the direct value or its derived index, or infarct size as either the late gadolinium enhancement extent as percentage of mass or the absolute volume), standardised mean differences (SMD) were calculated (**Supplementary Methods**). Studies that reported zero events in both the arms were included and 0.5 events were added to both arms (14). Heterogeneity was assessed by the I^2 method and tau (τ^2) (15). I^2 levels between 0% to 40%, 41% to 60%, and >60% were classed as being indicative of low, moderate and substantial heterogeneity, respectively (16). To assess the underlying causes of the observed variation and to test the robustness of our findings, metaregression of outcomes that included 10 or more studies was performed. The influence of mean daily dose of T3, route of T3 administration (IV or oral), duration of T3 therapy and baseline left ventricular function (LVEF < or > 40%) was analysed in the metaregression. In addition, prediction intervals were calculated for outcomes that included 10 or more studies to help in the clinical interpretation of the heterogeneity by estimating the range of true effects to be expected in future settings (17). Contour enhanced funnel plots were utilised to assess for evidence of publication bias and small study effects (18). Various sensitivity analyses were performed *post hoc* for outcomes that included 10 or more studies. Further details of statistical techniques are provided in **Supplementary Methods**. The statistical package R (*meta, metasens, metareg*) was used for all analyses.

Results

The PRISMA checklist is provided in **Supplementary Results.**

Literature search

The systematic literature search retrieved 3900 studies from databases, 127 studies from trial registry and an additional three articles from the full text studies reviewed **(Figure 1)**. From the studies identified from databases, duplicates (n=721) were removed, and, subsequently, 2 reviewers (MT and AT) independently screened 3182 unique articles for potential eligibility based on title and abstract. Among these, 3129 studies did not meet

the inclusion criteria. None of the studies identified from the trial registry were eligible for inclusion. Of the remaining 53 studies, 19 articles did not meet the study criteria and were therefore excluded (**eTable 1**). To obtain additional data an attempt was made to contact authors of eligible studies; 5 authors indicated that data were no longer available, 3 authors did not respond, and one refused to share data.

Thirty four studies with 2547 participants met the inclusion criteria (19–52) **(Table 1)**. Study sizes ranged from 13 to 223 participants; mean ages ranged from 0.1 to 73 years; percentages of women ranged from 7% to 64%; and the mean daily dose of administered T3 ranged from 4 to 246 mcg, administered as a single dose, repeated boluses or continuous infusion.

Quality of evidence

Overall, the quality of evidence ranged from high for outcomes such as risk of atrial fibrillation and LOS in cardiac surgery to very low in the two studies evaluating the effects of T3 on LVEF in patients with acute myocardial infarction **(Table 2)**.

Triiodothyronine in Cardiac surgery

Triiodothyronine treatment in adult cardiac surgery

Cardiac index: In 12 studies including 1093 adults undergoing cardiac surgery T3 therapy was associated with increased cardiac index (MD of 0.24 L/min/m^2; 95% CI, 0.08 to 0.40, I^2=74%) **(Figure 2)** (19, 21–31). Prediction interval ranged from -0.29 to 0.77 L/min/m^2. Meta-regression demonstrated that duration of treatment with T3 (ranging from 6 hours to a few days post-operatively) was positively associated with increased cardiac index (p=0.04), whereas the mean daily dose of T3 (p=0.11), route of administration (IV or oral) (p=0.10) or baseline left ventricular function (LVEF < or >40%) (p=0.69) were not significant predictors.

Systemic vascular resistance: In 11 studies including 1069 adult patients undergoing cardiac surgery T3 therapy was not associated with any significant reduction in SVR (SMD of -0.18; 95%CI, -0.43 to 0.08, I^2=74%) **(eFigure 1)** (21–31). Prediction interval ranged from -1.04 to 0.69. The mean daily dose of T3 (p=0.82), route of T3 administration (IV or oral)

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(p=0.43), baseline LVEF (p=0.49) or duration of treatment (p=0.16) were not associated with variation in SVR in adults undergoing cardiac surgery on meta-regression.

Triiodothyronine treatment in paediatric cardiac surgery

Cardiac index: In three studies including 188 children undergoing cardiac surgery therapy with T3 was associated with no significant change in the cardiac index (MD of 0.0 L/min/m^2; 95% CI, -0.01 to 0.01, I^2=0%) **(eFigure 2)** (34, 36, 41).

Triiodothyronine treatment in cardiac donors

Cardiac index and systemic vascular resistance: In three studies including 131 cardiac donors T3 therapy did not significantly alter cardiac index (MD of -0.15 L/min/m^2; 95% CI, -0.64 to 0.33, I^2=0%) **(Figure 3)** (43, 45, 46). Similarly, in two studies including 79 cardiac donors T3 therapy was not associated with significant reduction in SVR (MD of -93.6 dyn.sec.cm^{-5}; 95%CI, -423 to 236, I^2=0%) **(eFigure 3)** (43, 46).

Triiodothyronine in Cardiovascular diseases

Triiodothyronine treatment in heart failure

In three studies including 83 adults with stable heart failure with reduced ejection fraction and low serum T3 levels, T3 therapy did not significantly improve LVEF (MD of 2.95%; 95%CI, -1.54 to 7.44%, I^2=0%) **(Figure 4)** (48–50). Similarly, in these three studies, there was no significant association of T3 therapy with change in NT-proBNP levels (MD of -1050.9 ng/L; 95%CI, -2345.0 to 243.2, I^2=86%) **(eFigure 4)** (48–50).

Triiodothyronine treatment in acute myocardial infarction

Two studies including 89 participants assessed the utility of T3 supplementation in adult patients with acute myocardial infarction and low or low normal serum T3 levels (51, 52). There was no evidence of significant improvement in LVEF over 6 months in these patients (MD of 1.78%; 95%CI, -1.91 to 5.47%, I^2=0%) **(eFigure 5)**. Likewise, there was no significant reduction in infarct volume over 6 months in the T3 group compared to the placebo group (SMD of -0.19; 95%CI, -0.65 to 0.27, I^2=0%) **(eFigure 6)**.

Effect of triiodothyronine treatment on safety parameters

Heart rate: In 18 studies including 1063 participants (11 studies in adult cardiac surgery, 1 study in children undergoing cardiac surgery, 2 studies in cadiac donors, 3 studies in adults with heart failure and 1 study in adults with acute myocardial infarction), T3 therapy had no significant effect on heart rate (MD of 2.21 bpm; 95% CI, -0.96 to 5.39, I^2=68%) overall nor in any of the subgroups included **(eFigure 7)** (20–27, 29–31, 33, 43, 44, 48-50, 52). The prediction interval ranged from -9.45 to 13.87 bpm. The mean daily T3 dose (p=0.002), duration of treatment (p=0.04) and studies with LVEF>40% (p=0.03) were positively associated with heart rate on metaregression.

Atrial fibrillation: In 7 studies in adults (n=793) and 5 studies in children (n=599) undergoing cardiac surgical procedures T3 therapy was not associated with a higher risk of incident AF with RR of 1.03; 95%CI, 0.84 to 1.27, I^2=0% and RR of 0.77; 95%CI, 0.47 to 1.26, I^2=0%, respectively **(Figure 5)** (22, 24–28, 31, 33, 34, 39, 41, 42). The mean duration of follow-up in the studies that were included in the analysis for incident atrial fibrillation ranged from 2.3 to 21 days. In a pilot study that utilised an intravenous infusion of T3 at relatively high doses (median of 500 mcg T3 over 48 hours) in patients with acute anterior myocardial infarction the incidence of atrial fibrillation was non-significantly higher in the T3 group (5/26) compared to the placebo group (1/22) (52).

Mortality: In 9 studies including 839 adults undergoing cardiac surgery T3 therapy was not associated with higher risk of in-hospital mortality (RR of 1.22; 95%CI, 0.57 to 2.62, I^2=0%) **(eFigure 8)** (19, 22, 24–28, 31). The mean duration of follow-up in the studies that were included in the analysis for mortality ranged from 2.3 to 21 days. In 8 studies including 816 children undergoing cardiac surgery T3 therapy was associated with lower risk of mortality (RR of 0.52; 95%CI, 0.31 to 0.87, I^2=0%) **(eFigure 9)** (32, 33, 36-39, 41, 42). However, the beneficial effect of T3 on mortality outcome in children was mainly influenced by a single trial with high event rates which contributed 61.5% weight to the pooled analysis (41). The pooled RR did not show evidence of benefit of T3 once this trial was removed from the analysis (RR of 0.67; 95%CI, 0.29 to 1.54, I^2=0%). The mean duration of follow-up ranged between 3 days to 24 months.

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Effect of triiodothyronine treatment on LOS in hospital including intensive care

In 6 studies including 593 adults undergoing cardiac surgery T3 therapy had no association with LOS in hospital (MD of -0.35 days; 95%CI, -0.78 to 0.07, I^2=0%) **(Figure 6)** (22, 25, 27, 28, 30, 31). In 7 studies including 475 children undergoing cardiac surgery T3 therapy was not associated with any significant changes in hospital LOS (MD of -0.15 days; 95%CI, -1.26 to 0.95, I^2=0%) (32, 34-36, 38, 39, 41) **(Figure 6)**. LOS in intensive care post cardiac surgery was no different in the T3 or control groups in both adults and children **(eFigure 10)**.

Effect of triiodothyronine treatment on post-operative inotrope, mechanical assist devices and ventilation time

In 10 studies including 950 adults and 5 studies with 549 adults post cardiac surgery T3 treatment was not associated with reduced use of inotropic support or circulatory assist devices **(eFigure 11, eFigure 12, Table 2)**. On metaregression, neither the dose, route or duration of T3 therapy nor underlying left ventricular function predicted inotrope requirements. In 8 studies assessing post-surgical ventilation duration in 595 children, there was no difference in the T3 versus the placebo groups **(eFigure 13)**.

Effect of triiodothyronine treatment on thyroid function parameters

Overall, serum T3 levels increased, serum TSH levels were lower, and T4 levels remained unchanged in the T3 therapy group **(eFigure 14, eFigure 15, eFigure 16)**. Serum reverese T3 levels were measured in 3 studies and did not change with T3 therapy **(eFigure 17)**.

Bias assessment

Risk of bias assessment for each included study is provided in **eTable 2**. Overall, no evidence of small study or publication bias was observed **(eFigure 18, eFigure 19)**.

Sensitivity analysis

Several sensitivity analyses were performed. The main findings was that the risk of using inotropic support post cardiac surgery in adults was lower when fixed effects model was used due to low heterogeneity between studies **(Supplementary Results)**.

Discussion

This systematic review and meta-analysis evaluated RCTs of T3 therapy in patients with acute and chronic cardiac conditions. We observed an association between T3 therapy and an improvement in cardiac index in adults undergoing cardiac surgery. However, the quality of the evidence was moderate. In other cardiac conditions including paediatric cardiac surgical procedures, cardiac donor procedures, heart failure, or acute myocardial infarction, T3 therapy was not associated with any evidence of benefit or harm, although this finding was limited by the small number of trials of low to moderate quality included in the meta-analysis.

Compared with previous systematic reviews and meta-analyses of thyroid hormone therapy for post-operative nonthyroidal illness (8, 53, 54), this systematic review and meta-analysis has included more studies, has assessed other patient groups such as paediatric cardiac surgery, cardiac donors, heart failure, and acute myocardial infarction, and evaluated the economically-vital parameter of LOS in hospital in the cardiac surgical procedure groups. Overall, the quality of evidence varied from high to moderate across most outcomes except for the effect of T3 in acute myocardial infarction patients, where the quality was deemed to be poor due to the inclusion of two pilot RCTs with small number of participants (51, 52).

Most experts do not advocate T3 therapy in hospitalised patients with low serum T3 levels as, in their view, the reduced T3 is an adaptive physiological phenomenon (55, 56). However, some others argue that non-thyroidal illness and the resultant low T3 level is a manifestation of hypothalamic-pituitary dysfunction and should be corrected (57). Such conflicting views probably explain, at least in part, the variation in thyroid hormone use in cardiac conditions with 31% of intensive care physicians in Canada (58) and 72% of organ procurement organisations in the USA reporting use of thyroid hormone (including T4) for all cardiac donors (59). Data on the routine use of thyroid hormones in cardiac surgical procedures is not available. Guidelines formulated by the American Thyroid Association recommend against the use of T3 therapy in hospitalised patients with critical illness or heart failure with low T3 levels (60). The results of this meta-analysis suggest that there may be short-term benefits of T3 therapy in adult patients undergoing cardiac surgery but

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more research is required to assess long-term safety and efficacy as well as patient reported outcomes.

Our systematic review and meta-analysis suggests that T3 use in adult cardiac surgery improves short-term cardiac function with no apparent immediate safety concerns. However, the quality of the evidence is moderate and longer term effects of T3 therapy on important clinical outcomes has not been evaluated. Furthermore, there is no accepted minimal clinically important difference for cardiac index or systemic vascular resistance. Thus, it is unclear whether the observed improvement in cardiac index in adults undergoing cardiac surgery is of clinical value. The benefit of improved cardiac performance that is most likely to be observed in a clinical setiing is in the reduced requirement for inotropic support in the immediate post-surgical period and a consequent reduction in the length of intensive care and hospital stay. Our results sugest that the short-term improvement in cardiac performance may be associated with the trend observed in reduced inotrope use and hospital LOS in adults treated with T3 post cardiac surgery. However, larger adequate designed trials are required to confirm this finding. The other important finding of our analysis is the ressuring short-term safety profile of T3 in high-risk individuals and/or situations. In one study, the occurrence of atrial fibrillation in adults undergoing cardiac surgery was not significantly different in the T3 group during the period of drug infusion and up to 18 hours post-surgery (22). However, the T3 treated group had a lower incidence of atrial fibrillation and fewer required cardioversion when they were followed up to 5 postoperative days (61). Conversely, there was a worrying trend of a 4-fold higher risk of incident atrial fibrillation in the first 48 hours in a study that utilised high-dose T3 infusion in patients with acute myocardial infarction (52). This finding highlights that close monitoring of high-risk patients is essential, especially when high dose T3 is used. Moreover, the possible benefits of short-term T3 use in high risk adults on cardiac function has to be balanced with cost of using and monitoring T3, particularly if an infusion is utilised. Our analysis also suggests that the duration of treatment with T3 may have a direct effect on the improvement in cardiac index and increased heart rate and that the dose of T3 may also influence heart rate. Thus, adequately designed trials are required to assess the safest, most effective dose and duration of therapy as well as evaluate the

long-term benefits and risks of T3 in this group. In children followed for 10 years after cardiac surgery, no effect of T3 therapy was observed on neurocognitive, growth and cardiac parameters (62). Due to the limited number of low quality studies analysed in paediatric cardiac surgery, cardiac donor operations, heart failure and acute myocardial infarction patients with low T3 levels, more well-designed trials are required in these groups. Based on the evidence obtained so far the routine clinical use of T3 in these groups of patients do not appear to be justified, outside of a clinical trial.

This systematic review and meta-analysis collected data from RCTs and hence the results obtained are robust. Other strengths of this analysis include the broad clinical outcomes analysed, multiple sensitivity analyses were performed, and the utilization of GRADE assessment to evaluate quality. However, most studies included relatively small number of participants and long-term outcome data are lacking. Assessment of bias including bias related to small study did not suggest that this could have influenced the results. Another limitation is the high heterogeneity observed for certain outcomes that may be due, at least in part, to differences in dose, route and duration of T3 therapy and variations in populations and outcomes being assessed. For example, some studies (adults with heart failure or acute myocardial infarction) only recruited participants with low serum T3 levels whereas this was not the case with studies in cardiac surgery (where reduction in serum T3 levels is expected but wasn't a prerequisite for inclusion). In addition, our literature search did not include the grey literature or studies that were published in languages other than English and therefore may have missed some relevant studies.

Conclusions

Based on moderate quality evidence, T3 therapy improves cardiac index in adult patients undergoing cardiac surgery. Trials evaluating longer-term clinical outcomes are needed to assess the utility and safety of T3 treatment. There is no improvement in short-term cardiovascular parameters in paediatric patients undergoing cardiac surgery or cardiac donors and, therefore, routine use of T3 is not justified unless used as part of research. Evidence for efficacy and safety for the use of T3 therapy in patients with heart failure or acute myocardial infarction and low circulating T3 levels is inconclusive and potential for benefit or harm cannot be excluded due to the small number of participants studied and

the low quality of evidence. Appropriately designed trials are needed in this group to clarify the role of T3 supplementation.

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Authorship confirmation statement

MT and AT performed literature search and collated data. RPWK, AB and SR did the statistical analyses. MT wrote the first draft of the report with input from AT, AB and SR. MT, AT, RPWK, AP, GI, JD, AB and SR provided critical input for the final version of the report. MT and SR accessed and verified the data. All authors had full access to all the data in the study and have final responsibility for the decision to submit for publication.

Conflict of interest statement

We declare no competing interests.

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Data sharing

The data utilised in this meta-analysis was obtained from published literature. Data for 2 studies was obtained from the authors directly and can be obtained from the corresponding author on request.

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Table1. Details of RCTs of T3 therapy in cardiac conditions

Author, year (Ref)	Country	Population	Main outcomes	Secondary outcomes	Number of participants T3 P	Female (%)	Mean age (yrs)	Route	Mean daily dose (mcg)	Treatment duration
Adult cardiac surgery										
Novitzky, 1989 (19)	USA	CABG (LVEF <30%)	ns	ns	12 12	ns	ns	IV	19.3[a]	8 hours (in boluses)
Novitzky, 1989 (19)	USA	CABG (LVEF >40%)	ns	ns	13 11	ns	ns	IV	38.5[a]	20 hours (in boluses)
Teiger, 1993 (20)	France	Cardiac surgery for various cardiac	Thyroid function Haemodynamic data	ns	10 10	25	56 (T3) 51 (P)	IV	38.5[a]	20 hours (in boluses)

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		procedures								
Vavouranakis, 1994 (21)	Greece	CABG (LVEF >40%)	ns	ns	15 15	7	63 (T3) 59 (P)	IV	38.5[a]	14 hours (in boluses)
Klemperer, 1995 (22)	USA	CABG (LVEF ≤40%)	ns	ns	71 71	15	66 (T3) 68 (P)	IV	110.5[a]	9 hours (in boluses)
Bennett-Guerrero, 1996 (23)	USA	CABG (LVEF ≤40%)	Haemodynamic data Inotrope use Serum T3 levels	Morbidity Mortality	66 71	37	66 (T3) 67 (P)	IV	114.4[a]	11 hours (in boluses)
Mullis-Jansson, 1999 (24)	USA	CABG	Haemodynamic data Inotrope use Morbidity Mortality	ns	81 89	19	64	IV	140[a]	Bolus and infusion for 6 hours
Guden, 2002	Turkey	CABG	Haemodynamic data	Morbidity	30 30	38	64 (T3	IV	10 3.5	Bolus and 6

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(25)				Mortality			) 66 (P)		[a]	hour infusion
Sirlak, 2004 (26)	Turkey	CABG (LVEF <30%)	Haemodynamic data Inotrope use Morbidity Mortality	ns	40 40	28	65 (T3) 66 (P)	Oral	125	7 days pre-operatively till discharge
Magalhaes, 2006 (27)	Brazil	Cardiac valvular surgery (LVEF <40%)	Serum T3 levels	Haemodynamic data Morbidity	8 10	44	50 (T3) 59 (P)	Oral	75	3 days
Ranasinghe, 2006 (28)	UK	CABG	Cardiac index	Haemodynamic data Morbidity Myocardial injury	63 160	17	63 (T3) 64 (P)	IV	10 3.5 [a]	Bolus and 6 hour infusion
Spratt, 2007	USA	CABG (LVEF	Thyroid	Haemodynamic	30	12	64 (T3	IV	70[a]	Bolus and 24

(29)		≥40%)	function	data Morbidity	29		) 59 (P)			hour infusion
Choi, 2009 (30)	Korea	Cardiac valvular surgery (NYHA class III or IV)	Thyroid function	Haemodynamic data Morbidity	25 25	64	54 (T3) 55 (P)	Oral	40	2 days
Choi, 2013 (31)	Korea	CABG (LVEF ≥35%)	Thyroid function	Haemodynamic data Morbidity Mortality	50 50	25	63 (T3) 65 (P)	Oral	40	2 days
Paediatric cardiac surgery										
Mainwaring, 2000 (32)[b]	USA	Cardiac surgery (modified Fonta	Pharmacokinetics of T3	Duration of mechanical ventilation	21 7	50	2.2 5	IV	4, 6 or 8[c]	Single bolus

		n proce dure)		LOS						
Portman , 2000 (33)	USA	Cardia c surger y	Haemodyn amic data	Thyroid function Morbidi ty	7 7	ns	0.5 (T3) 0.5 (P)	IV	8[b]	2 bolus doses
Bettend orf, 2000 (34)	Ger man y	Cardia c surger y	Haemodyn amic data Thyroid function	Morbidi ty	20 20	40	0.7 (T3) 0.6 (P)	IV	13 0[c]	Up to 12 days
Chowdh ury, 2001 (35)	USA	Cardia c surger y	TISS score	Morbidi ty LOS	14 14	ns	1.3 (T3) 3.2 (P)	IV	12	Infusio n up to 7 days
Mackie, 2005 (36)	USA	Cardia c surger y	Composite clinical outcome score Cardiac index	Morbidi ty	22 20	36	0.8	IV	12	3 days
Portman , 2010 (37)	USA	Cardia c surger	TTE	Morbidi ty	98 95	44	0.4 (T3)	IV	14[c]	9 hours (in

		y					0.5 (P)			boluses)
Marwali, 2013 (38)[b]	Indonesia	Cardiac surgery	Thyroid function	Morbidity Mortality LOS	15 28	53	0.8	Oral	15[c] 30[c]	60 hours in either 3 or 6 doses
Marwali, 2017 (39)	Indonesia	Cardiac surgery	TTE	Haemodynamic data Morbidity Mortality	104 101	41	0.9 (T3) 0.8 (P)	Oral	110[c]	60 hours in 11 doses
Tehrani, 2020 (40)	Iran	Cardiac surgery	LOS in ICU Inotrope requirement LVEF	Thyroid function	60 60	51	2.0 (T3) 1.9 (P)	Oral	40[c]	3 doses (6 hours pre-surgery, post-anaesthesia and 24 hours post-surger

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Marwali, 2021 (41)	Indonesia	Cardiac surgery	TTE Safety	Thyroid function LOS Morbidity Mortality	61 59	ns	0.3 (T3) 0.3 (P)	Oral	50[c]	11 doses (from anaesthesia, every 6 hours till 60 hours)
Portman, 2022 (42)	USA	Cardiac surgery	TTE	Safety	110 110	38	0.1	IV	18.4[c]	Loading dose followed by infusion up to 48 hours
Cardiac donor surgery										
Randell, 1992 (43)	Finland	Brain-dead organ donors	Haemodynamic data	Temperature maintenance Organ function	13 12	34	46	IV	6	Continuous infusion
Goarin, 1996	France	Brain-dead	Haemodynamic data	Thyroid function	19 18	35	35	IV	14[a]	Single bolus

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(44)		organ donors								
Jeevanandam, 1997 (45)	USA	Brain-dead organ donors	Donor stabilisation parameters	ns	15 15	ns	21 (T3) 27 (P)	IV	42[a]	Single bolus
Perez-Blanco, 2005 (46)	Spain	Brain-dead organ donors	Haemodynamic data	Thyroid hormones	29 23	ns	38 (T3) 41 (P)	IV	89[a]	Bolus and 4.5 hour infusion
Venkateswaran, 2009 (47)	UK	Brain-dead organ donors	Cardiac index	Haemodynamic data	20 21	48	54 (T3) 51 (P)	IV	47[a]	Bolus and 6 hour infusion
Heart failure										
Pingitore, 2008 (48)	Italy	Dilated cardiomyo-pathy (NYHA class I-II;	Clinical status Cardiac function Neuroendocrine/pro-inflammato	ns	10 10	30	72 (T) 68 (P)	IV	24.2	36 hours

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		LVEF< 40%) and low serum T3 levels	ry profile							
Amin, 2015 (49)	Iran	Systolic HF (NYHA class I-III; LVEF< 40%) and low serum T3 levels	6MWD	NYHA NT-proBNP hsCRP LVEF	25 25	22	60	Oral	25	6 weeks
Holmager, 2015 (50)	Denmark	Systolic HF (LVEF <45%) and low serum T3 levels	Cardiac function	ns	6 7	15	73	Oral	20	3 months
Acute myocardial infarction										

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Pingitore, 2018 (51)	Italy	STEMI and low serum T3 levels	Feasibility trial	Cardiac parameters	19 18	16	65	Oral	12-22	6 months
Pantos, 2022 (52)	Greece	STEMI and low serum T3 levels	Pilot trial	Cardiac parameters Safety	28 24	8	56	IV	24 6[a]	Bolus and 48 hour infusion

[a]Assuming 70 kg body weight, [b]Number of participants in the analyses may differ than stated in the manuscript or this table as this study compared varying doses of T3 and the group receiving the highest dose was utilised for analyses, [c]Assuming 10 kg body weight

T3 – triiodothyronine, P – placebo, CABG – coronary artery bypass grafting, LVEF – left ventricular ejection fraction, ns- not stated, IV – intravenous, NYHA – New York Heart Association, LOS – length of stay, TISS – therapeutic intervention scoring system, TTE – time to extubation, ICU – intensive care unit, HF – heart failure, NT-proBNP – N terminal pro-brain natriuretic peptide, hsCRP – high sensitivity C reactive protein, STEMI – ST-elevation myocardial infarction.

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Table 2. Summary of findings of T3 treatment in various cardiac conditions.

Patients: cardiac conditions with low T3 levels **Setting: hospital (in- or out-patient settings)** **Intervention: T3** **Comparison: Placebo**				
Outcomes	**Pooled effect (95% CI), I^2, p value**	**No. of participants (studies)**	**Quality of evidence (GRADE)**	**Comments**
Adult cardiac surgery				
Cardiac index ($L/min/m^2$)	MD of 0.24 (0.08 to 0.40), I^2=74%, p<0.01	1091 (12)	⊕⊕⊕◯ Moderate[a]	Positive values indicate benefit of T3 - ROB ⊕ (overall low risk; some concerns) - Inconsistency ◯ (CI do not overlap and high I^2) - Indirectness ⊕ (no concerns) - Imprecision ⊕ (no concerns) - Publication bias ⊕ (no concerns)
Systemic vascular resistance ($dyn.sec.cm^{-5}$)	SMD of -0.18 (-0.43 to 0.08), I^2=74%, p<0.01	1069 (11)	⊕⊕⊕◯ Moderate[a]	Negative values indicate benefit of T3 - ROB ⊕ (overall low risk; some concerns) - Inconsistency ◯ (CI do not overlap and high I^2)

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				- Indirectness ⊕ (no concerns) - Imprecision ⊕ (no concerns) - Publication bias ⊕ (no concerns)
Heart rate (beats/min)	MD of 2.50 (-0.97 to 5.97), I^2=69%, p<0.01	866 (11)	⊕⊕⊕◯ Moderate[a]	Negative values indicate benefit of T3 - ROB ⊕ (overall low risk) - Inconsistency ◯ (high I^2) - Indirectness ⊕ (no concerns) - Imprecision ⊕ (no concerns) - Publication bias ⊕ (no concerns)
Risk of AF	RR of 1.03 (0.84 to 1.27), I^2=0%, p=0.99	793 (7)	⊕⊕⊕⊕ High	Values less than 1.0 indicate benefit of T3 - ROB ⊕ (overall low risk) - Inconsistency ⊕ (no concerns) - Indirectness ⊕ (no concerns) - Imprecision ⊕ (no concerns) - Publication bias ⊕ (no concerns)
In-hospital mortality	RR of 1.22 (0.57 to 2.62), I^2=0%, p=0.90	839 (9)	⊕⊕⊕◯ Moderate	Values less than 1.0 indicate benefit of T3 - ROB ⊕ (overall low risk)

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				- Inconsistency ⊕ (no concerns) - Indirectness ⊕ (no concerns) - Imprecision ◯ (small number of events, n=25) - Publication bias ⊕ (no concerns)
Length of stay in hospital (days)	MD of -0.35 (-0.78 to 0.07), I^2=0%, p=0.74	593 (6)	⊕⊕⊕⊕ High	Negative values indicate benefit of T3 - ROB ⊕ (overall low risk) - Inconsistency ⊕ (no concerns) - Indirectness ⊕ (no concerns) - Imprecision ⊕ (no concerns) - Publication bias ⊕ (no concerns)
Length of stay in ICU (days)	MD of -0.19 (-0.54 to 0.16), I^2=83%, p<0.01	673 (7)	⊕⊕⊕⊕ High	Negative values indicate benefit of T3 - ROB ⊕ (overall low risk) - Inconsistency ⊕ (no concerns) - Indirectness ⊕ (no concerns) - Imprecision ⊕ (no concerns) - Publication bias ⊕ (no

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				concerns)
Post-operative inotrope use	RR of 0.83 (0.64 to 1.07), I^2=23%, p=0.23	950 (10)	⊕⊕⊕⊕ High	Values less than 1.0 indicate benefit of T3 - ROB ⊕ (overall low risk) - Inconsistency ⊕ (no concerns) - Indirectness ⊕ (no concerns) - Imprecision ⊕ (no concerns) - Publication bias ⊕ (no concerns)
Post-operative intra-aortic balloon pump use	RR of 0.80 (0.32 to 1.97), I^2=47%, p=0.11	359 (3)	⊕⊕⊕◯ Moderate	Values less than 1.0 indicate benefit of T3 - ROB ⊕ (overall low risk) - Inconsistency ⊕ (no concerns) - Indirectness ⊕ (no concerns) - Imprecision ◯ (small number of events, n=48) - Publication bias ⊕ (no concerns)
Paediatric cardiac surgery				
Cardiac index (L/min/m^2)	MD of 0.00 (-0.01 to 0.01), I^2=0%, p=0.95	188 (3)	⊕⊕⊕⊕ High[b]	Positive values indicate benefit of T3 - ROB ⊕ (overall low risk)

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				- Inconsistency ⊕ (no concerns) - Indirectness ⊕ (no concerns) - Imprecision ⊕ (no concerns) - Publication bias ⊕ (comprehensive search)
Heart rate (beats/min)	MD of -13.00 (-37.72 to 11.72)	14 (1)	⊕⊕◯◯ Low[b]	Negative values indicate benefit of T3 - ROB ⊕ (some concerns) - Inconsistency ◯ (one trial with 14 participants) - Indirectness ◯ (one trial with 14 participants) - Imprecision ◯ (one trial with 14 participants) - Publication bias ⊕ (comprehensive search)
Risk of AF or SVT	RR of 0.77 (0.47 to 1.26), I^2=0%, p=0.62	599 (5)	⊕⊕⊕⊕ High	Values less than 1.0 indicate benefit of T3 - ROB ⊕ (overall low risk) - Inconsistency ⊕ (no concerns) - Indirectness ⊕ (no concerns) - Imprecision ⊕ (no concerns) - Publication bias ⊕ (no

				concerns)
In-hospital mortality	RR of 0.52 (0.31 to 0.87), I^2=0%, p=0.94	816 (8)	⊕⊕⊕◯ Moderate	Values less than 1.0 indicate benefit of T3 - ROB ⊕ (overall low risk) - Inconsistency ⊕ (no concerns) - Indirectness ⊕ (no concerns) - Imprecision ◯ (49 events, of which 28 occurred in one trial) - Publication bias ⊕ (no concerns)
Length of stay in hospital (days)	MD of -0.15 (-1.26 to 0.95), I^2=0%, p=0.49	475 (7)	⊕⊕⊕⊕ High	Negative values indicate benefit of T3 - ROB ⊕ (overall low risk) - Inconsistency ⊕ (no concerns) - Indirectness ⊕ (no concerns) - Imprecision ⊕ (no concerns) - Publication bias ⊕ (no concerns)
Length of stay in ICU (days)	MD of -0.13 (-0.73 to 0.47), I^2=65%, p<0.01	695 (8)	⊕⊕⊕⊕ High	Negative values indicate benefit of T3 - ROB ⊕ (overall low risk)

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				- Inconsistency ⊕ (no concerns) - Indirectness ⊕ (no concerns) - Imprecision ⊕ (no concerns) - Publication bias ⊕ (no concerns)
Ventilation time (days)	MD of -0.06 (-0.59 to 0.47), I^2=60%, p=0.01	595 (8)	⊕⊕⊕⊕ High	Negative values indicate benefit of T3 - ROB ⊕ (overall low risk) - Inconsistency ⊕ (no concerns) - Indirectness ⊕ (no concerns) - Imprecision ⊕ (no concerns) - Publication bias ⊕ (no concerns)
Cardiac donor surgery				
Cardiac index (L/min/m^2)	MD of -0.15 (-0.64 to 0.33), I^2=0%, p=0.94	131 (3)	⊕⊕◯◯ Low[c]	Positive values indicate benefit of T3 - ROB ◯ (2/3 studies had some concerns) - Inconsistency ⊕ (no concerns) - Indirectness ⊕ (no concerns) - Imprecision ◯ (small number assessed)

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				- Publication bias ⊕ (no concerns)
Systemic vascular resistance (dyn.sec.cm^{-5})	MD of -93.6 (-423 to 236), I^2=0%, p=0.93	79 (2)	⊕⊕◯◯ Low[c]	Negative values indicate benefit of T3 - ROB ◯(1/2 studies had some concerns) - Inconsistency ⊕ (no concerns) - Indirectness ⊕ (no concerns) - Imprecision ◯ (small number assessed) - Publication bias ⊕ (no concerns)
Heart failure				
LVEF (%)	MD of 2.95 (-1.54 to 7.44), I^2=0%, p=0.81	83 (3)	⊕⊕◯◯ Low[c]	Positive values indicate benefit of T3 - ROB ◯(One study contributing 51% weight has high concerns) - Inconsistency ⊕ (no concerns) - Indirectness ⊕ (no concerns) - Imprecision ◯ (small number of participants) - Publication bias ⊕ (no concerns)

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Heart rate (beats/min)	MD of -1.44 (-11.24 to 8.36), I^2=67%, p=0.05	83 (3)	⊕⊕◯◯ Low[c]	Negative values indicate benefit of T3 - ROB ⊕ (overall low risk) - Inconsistency ◯ (high heterogeneity) - Indirectness ⊕ (no concerns) - Imprecision ◯ (small number of participants) - Publication bias ⊕ (no concerns)
NT-pro BNP (ng/L)	MD of -1048.8 (-2477.7 to 380.2), I^2=86%, p<0.01	83 (3)	⊕⊕◯◯ Low[c]	Negative values indicate benefit of T3 - ROB ⊕ (overall low risk) - Inconsistency ◯ (high heterogeneity) - Indirectness ⊕ (no concerns) - Imprecision ◯ (small number of participants) - Publication bias ⊕ (no concerns)
Acute myocardial infarction				
LVEF (%)	MD of 1.78 (-1.91 to 5.47), I^2=0%, p=0.59	74 (2)	⊕◯◯◯ Very low[d]	Positive values indicate benefit of T3 - ROB ⊕ (one trial not blinded) - Inconsistency ◯ (two pilot

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				trials) - Indirectness ◯ (small number of participants) - Imprecision ◯ (small number of participants) - Publication bias not able to be assessed.
Infarct size (% or ml)	SMD of -0.19 (-0.65 to 0.27), I^2=0%, p=0.98	74 (2)	⊕◯◯◯ Very low[d]	Negative values indicate benefit of T3 - ROB ⊕ (one trial not blinded) - Inconsistency ◯ (two pilot trials) - Indirectness ◯ (small number of participants) - Imprecision ◯ (small number of participants) - Publication bias not able to be assessed.

[a] Serious inconsistency (high I-squared value with some trials not overlapping with each other).

[b] Some concern for ROB (due to no pre-specified analysis plan and selection of the outcome) and serious concern regarding small sample sizes in the trials.

[c] Serious concern regarding imprecision due to very small number of participants in each trial.

[d] Serious ROB and only one trial with small number, no details of blinding or pre-specified analysis plan.

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MD – weighted mean difference, SMD – standardized mean difference, RR- risk ratio, CI – confidence intervals, ROB – risk of bias, AF – atrial fibrillation, ICU – intensive care unit, LVEF – left ventricular ejection fraction, NT-proBNP = N terminal pro-brain natriuretic peptide.

Risk of bias was assessed based on 7 domains (random sequence generation, allocation concealment, blinding of participants and study personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias.

Inconsistency was assessed by degree of heterogeneity or if point estimates and confidence intervals varied considerably.

Indirectness was assessed based on variations in populations, intervention, comparator or outcomes.

Imprecision was based on number of participants and/or events included.

Publication bias was assessed by visual inspection and also quantitatively analysing funnel plots.

GRADE (Grading of Recommendations, Assessment, Development and Evaluations) is a transparent framework for developing and presenting summaries of evidence and provides a systematic approach for making clinical practice recommendations. GRADE has four levels of evidence:

Very low (◯◯◯◯ or ⊕◯◯◯) – The true effect is probably markedly different from the estimated effect.

Low (⊕⊕◯◯) – The true effect might be markedly different from the estimated effect.

Moderate (⊕⊕⊕◯) – The authors believe that the true effect is probably close to the estimated effect.

High (⊕⊕⊕⊕) - The authors have a lot of confidence that the true effect is similar to the estimated effect.

Evidence from randomised controlled trials starts at high quality. The certainty in the evidence may be decreased for several reasons such as risk of bias, imprecision, inconsistency, indirectness, and publication bias; authors have the option of decreasing their level of certainty one or two levels (e.g., from high to moderate).

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Figure legends

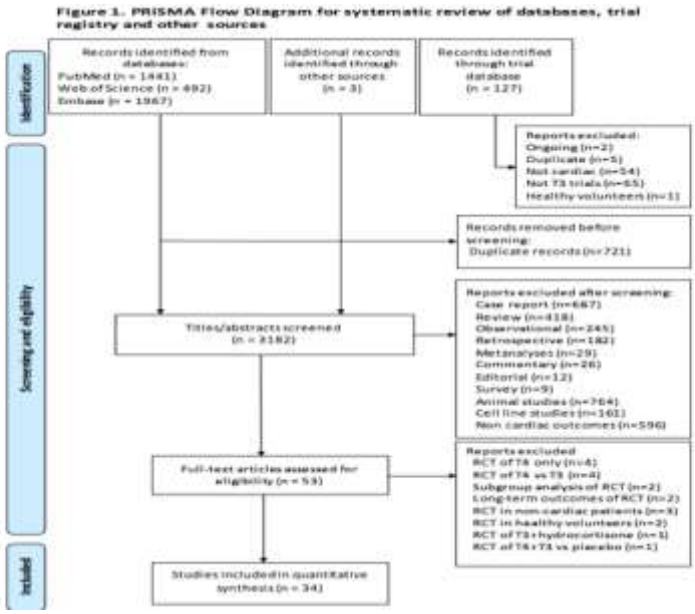

Figure 1. PRISMA Flow Diagram for systematic review of databases, trial registry and other sources

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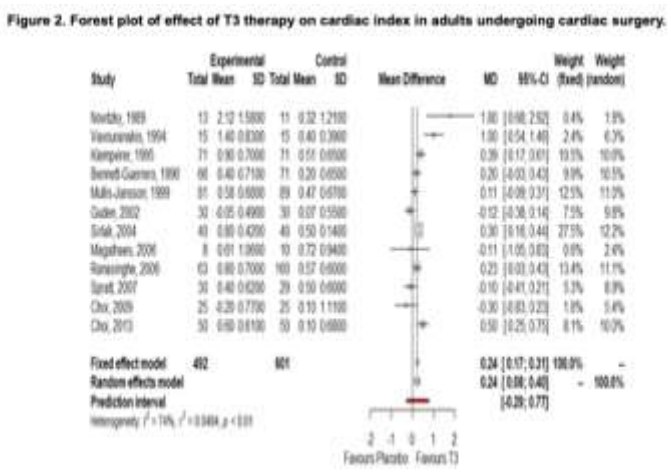

Figure 2. Forest plot of effect of T3 therapy on cardiac index in adults undergoing cardiac surgery.

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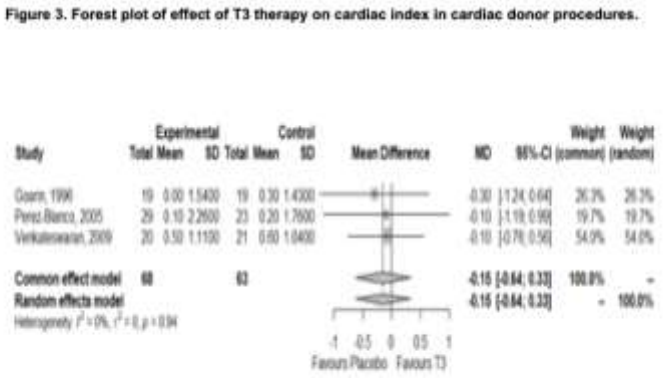

Figure 3. Forest plot of effect of T3 therapy on cardiac index in cardiac donor procedures.

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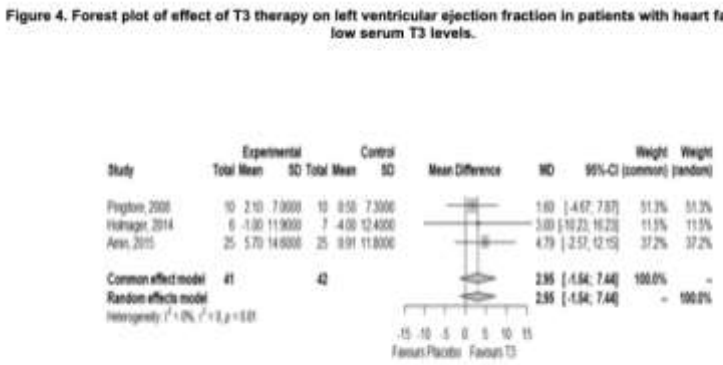

Figure 4. Forest plot of effect of T3 therapy on left ventricular ejection fraction in patients with heart failure and low serum T3 levels.

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Figure 5. Forest plot of effect of T3 therapy on risk of developing atrial fibrillation in adults and children undergoing cardiac surgical procedures.

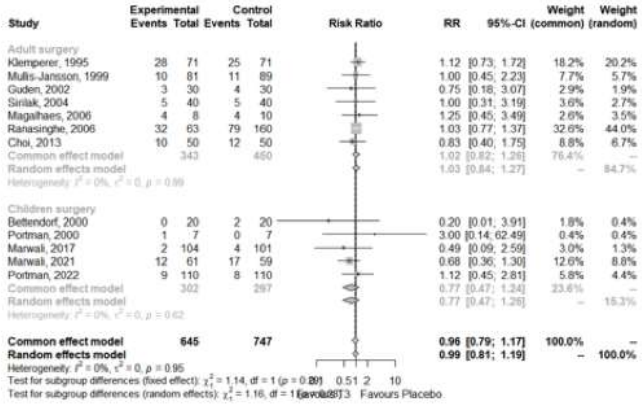

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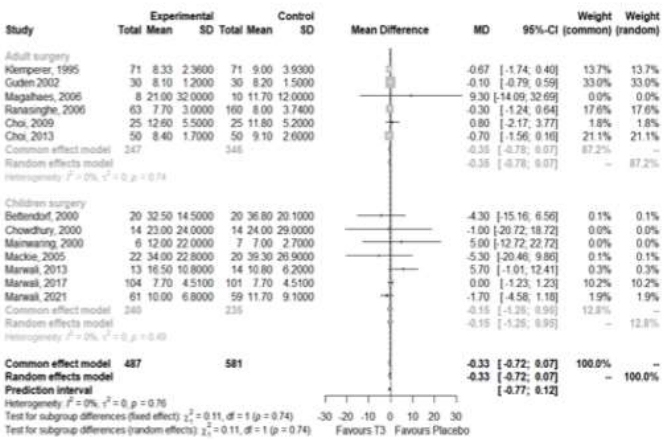
Figure 6. Forest plot of effect of T3 therapy on length of stay in hospital



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