

Efficiency of Thyroid Function Test in the Prediction of Atrial Fibrillation Following Open Heart Surgery

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ABSTRACT

Objective: To analyse the efficiency of thyroid function tests (thyroid stimulating hormone, thyroxine and tri-iodothyronine) on prediction of postoperative atrial fibrillation.

Study Design: Meta-analysis.

Place of Study: Siyami Ersek Chest and Cardiovascular Surgery Education and Research Hospital, Istanbul, Turkey.

Methodology: Literature review was carried out in *PubMed*, *Science Direct* and *Ovid Database*. No date limitations was applied. Trials, which evaluated the preoperative levels of thyroid stimulating hormone, thyroxine and tri-iodothyronine in cardiac surgery patients, were included. Only the articles in English language were reviewed. We evaluated the results with fix or random effect models according to the presence of heterogeneity ($I^2 > 25\%$).

Results: Five hundred and forty-seven articles were obtained after screening of databases. After checking over the titles and abstracts, five trials were included which covered 380 patients and complied with inclusion criteria. According to results of analysis, there was no significant relationship between postoperative atrial fibrillation and thyroid stimulating hormone (SMD: 0.38, 95%CI -0.46-1.23, $p=0.375$), and also thyroxine (SMD: 0.006, 95% CI -0.29-0.30, $p=0.966$). However, tri-iodothyronine (SMD: -1.06, 95% CI -2.08- -0.03, $p=0.04$) was correlated with development of atrial fibrillation. Heterogeneity was observed in three parameters (I^2 ; for TSH: 92.45%, for T3: 93.08% and for T4: 31.78%).

Conclusion: Preoperative levels of tri-iodothyronine was an effective parameter for predicting postoperative atrial fibrillation after cardiac surgery, but there was a need of larger trials for eliminating heterogeneity for all of the parameters of thyroid function tests.

Key Words: Cardiac surgery, Atrial fibrillation, Thyroid stimulating hormone, Thyroxine, Tri-iodothyronine.

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INTRODUCTION

Both hypothyroidism and hyperthyroidism may affect cardiac function and health. Hypothyroidism have many hemodynamic effects on cardiovascular system, such as, decreasing cardiac output and arterial compliance, increasing systemic vascular resistance, risk of coronary artery disease, risk of atherosclerosis and diastolic pressure, and also narrowing pulse pressure.¹ Hypothyroidism can decrease and thyroid hormones can increase heart rate due to various mechanisms, such as: endothelial dysfunction and decrease of nitric oxide production, vascular smooth muscle relaxation and cardiac contractility.²

On the other hand, hyperthyroidism affects cardiovascular hemodynamics. Heart failure and dilated cardiomyopathy may occur because of hyperthyroidism.³ Effective treatment of hyperthyroidism can prevent heart failure. Moreover, prevention of atrial fibrillation (AF) and thromboembolic events are very important during hyperthyroidism treatment.³

Atrial fibrillation is the most common arrhythmia that can cause heart failure and also stroke.⁴ Selmer *et al.* compared the euthyroid individuals with overt and subclinical hypothyroid/hyperthyroid patients in a large population cohort study.⁵ They found the incidence risk ratios for AF were 0.67 for overt hypothyroidism, 0.87 for subclinical hypothyroidism, 1.31 for subclinical hyperthyroidism, and 1.42 for overt hyperthyroidism. The authors concluded that the risk of AF was closely associated with thyroid activity: low risk with overt hypothyroidism and high risk with hyperthyroidism. They also found the AF risk was thyroid stimulating hormone (TSH) level dependent.

The aim of this study was to determine whether preoperative levels parameters (free thyroxine-FT4, free triiodothyronine-FT3 and TSH) of thyroid function tests can predict postoperative new onset AF (POAF) after cardiac surgery or not.

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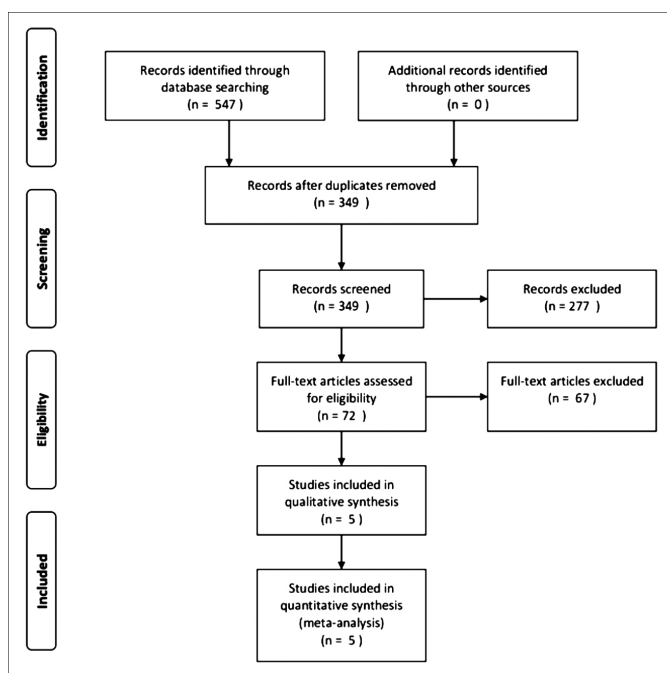
Table I: Summary of studies.

	Year	POAF n	Total n	Design	Type of surgery	Weights of studies in analysis (%)		
						TSH	FreeT3	FreeT4
Kokkonen <i>et al.</i>	2005	19	44	Prospective	CABG + valve surgery	19.79	25.27	18.50
Dietrich <i>et al.</i>	2015	17	39	Prospective	CABG + valve surgery	18.33	21.75	17.18
Cerillo <i>et al.</i>	2003	33	107	Prospective	Isolated CBABG	20.87	26.41	31.40
Gode <i>et al.</i>	2016	15	90	Prospective	Isolated CBABG	20.06	-	-
Özsin <i>et al.</i>	2018	50	100	Prospective*	Isolated CBABG	20.96	26.58	32.93

AF: Atrial Fibrillation, Randomised Controlled Study, CABG: Coronary Artery Bypass Grafting.

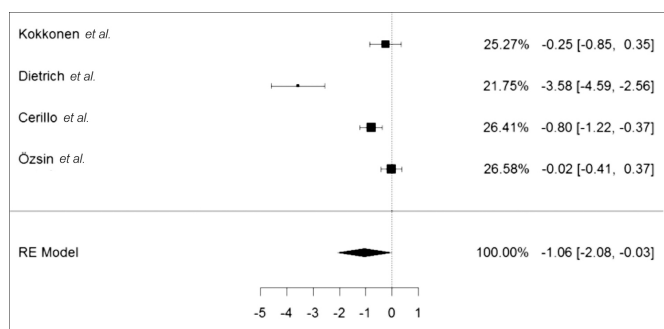
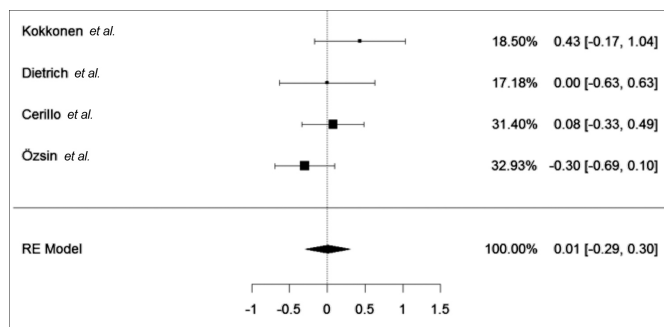
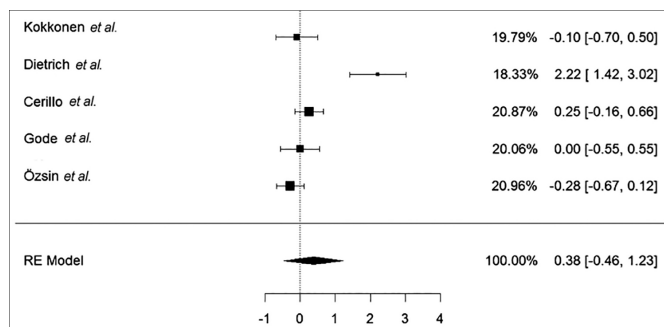
Table II: Results of analysis.

Variables	Results				Heterogeneity				Publication bias	Fail safe analysis	
	SMD	95%CI		p	Q	df	p	I ² (%)	Tau ²	n	p
Thyroid stimulating hormone	0.38	-0.46	1.23	0.375	31.30	4	<0.001	92.45	0.84	4	0.014
Tri-iodothyronine	-1.06	-2.08	-0.03	0.04*	43.36	3	<0.001	93.08	0.99	45	<0.001
Thyroxine	0.006	-0.29	0.30	0.966	4.28	3	0.23	31.78	0.029*	0	0.44

**Figure 1: Flow diagram of database searching.**

METHODOLOGY

Databases were searched according to the guidelines reported by Moher *et al.* to investigate whether preoperative thyroid function tests can predict the occurrence of atrial fibrillation after heart surgery or not.⁶ The database was searched until 20th December, 2019. There was no limitation for publication date. *PubMed*, *Science Direct* and *Ovid* was used as electronic database. Manual search was not employed. Keywords or combinations of them (*heart surgery, coronary artery bypass, cardiac surgery, atrial fibrillation, thyroid function test, thyroid stimulating hormone, thyroxine and tri-iodothyronine*) were used. Language was limited to English. The other languages were excluded. The study designs and patient numbers were not limiting factors.

**Figure 2: Forest plot for free T3.****Figure 3: Forest plot for free T4.****Figure 4: Forest plot for TSH.**

Inclusion criteria were (i) clinical trials, (ii) open heart surgery (iii) article in English, (iv) coronary artery or valve

surgery. Exclusion criteria were (i) case reports and case series (ii) non-English articles, (iii) experimental studies, and (iv) peripheral vascular surgery. The related articles not containing the knowledge about preoperative levels of thyroid stimulating hormone, thyroxine and tri-iodothyronine, were also excluded. Articles reporting data with figures were excluded.

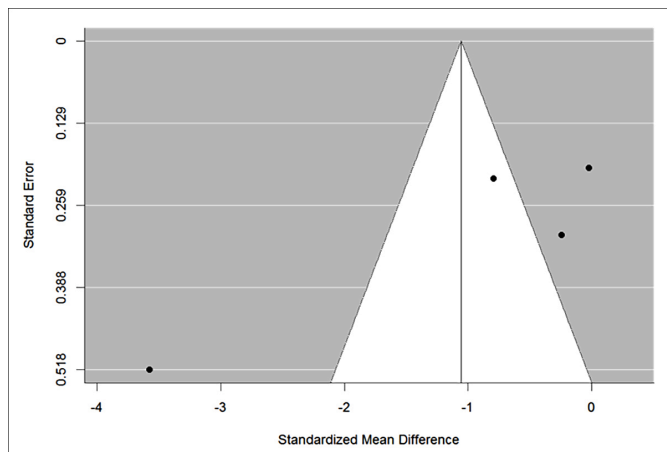


Figure 5: Funnel plot for free T3.

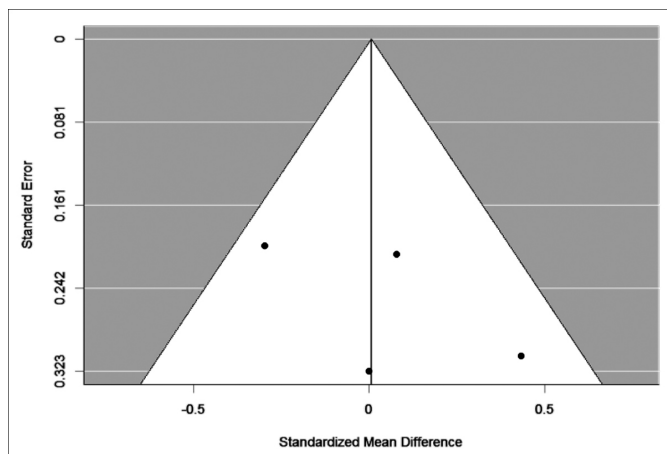


Figure 6: Funnel plot for free T4.

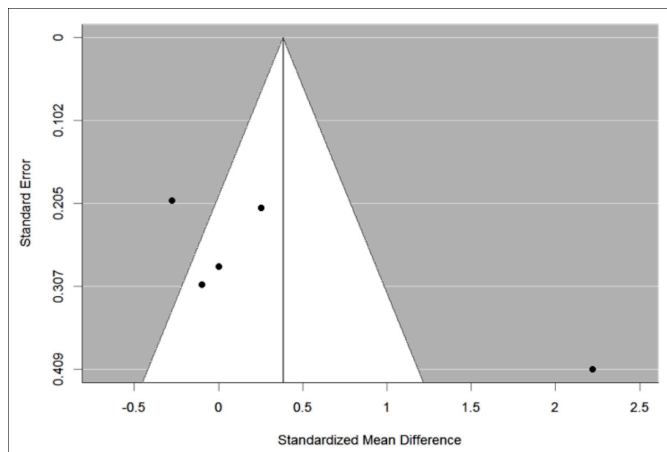


Figure 7: Funnel plot for TSH.

Three reviewers (S.Ö., Y.Ş. and İ.Ö.) extracted data from related trials. Publication information (first author's name, publication year, sample size, number of patients with POAF and also with no-POAF, in each group) were extracted. Disagreement was resolved by the other authors (İ.K. and K.Ö.). The mean, standard deviation and sample sizes were recorded as data.

Jamovi[®] software was used for statistical analysis. The standard mean difference (SMD) and 95% confidence interval (CI) was used for analysis. I^2 statistics was used for evaluation of heterogeneity. Presence of heterogeneity was agreed as significant if $I^2 \geq 25\%$. We evaluated the possible reasons of heterogeneity with the analysis of moderators. Meta-analysis was applied by using fixed or random effect models. Random effect model was performed for the presence of heterogeneity ($I^2 > 25\%$) and fixed effect model for the absence of heterogeneity ($I^2 < 25\%$). Begg test and funnel plot was used for publication bias.

RESULTS

Three hundred and fifty-eight articles were identified through database search. Three hundred and forty-nine records remained after removing the duplicated articles. Authors excluded 349 records after checking the titles and abstracts. The records were screened for relation; and 277 trials were excluded. Seventy-two full text articles were assessed for eligibility to the main question of our investigation. Sixty-seven trials without the detailed data were excluded. Five articles, summarised in Table I, were included to quantitative synthesis.⁷⁻¹¹ Flow diagram of database search strategy is shown in Figure 1; and demographical data of trials, weights of studies due to results of analysis for three parameters are summarised in Table I.

At the end of the analysis, only fT3 could predict POAF after cardiac surgery ($p=0.04$). Random effect model was used for evaluation because of the heterogeneity of studies (I^2 ; for TSH: 92.45%, for fT3: 93.08% and for fT4: 31.78%). Percentage of heterogeneity was smallest for fT4. Summary of analysis is shown in Table II; and forest plots of analysis were shown in Figures 2-4. We could determine the reason of heterogeneity as type of surgery, only for fT4. I^2 test was 0% in combined valve and CABG surgery.

For fT4, the publication bias was significant ($\tau^2=0.029$). For fT3 and TSH, τ^2 was not significant (>0.05). The funnel plots were shown in Figures 5-7.

The possible numbers of studies that we might missed out during database search (*fail-safe N*) were 45 for TSH, 4 for fT3 and 0 for fT4, according to Rosenthal approach.

DISCUSSION

It was found that preoperative levels of fT3 can predict POAF after cardiac surgery. Because of the limited numbers of articles in this issue, the rate of heterogeneity were very high for thyroid function test parameters. All the trials had a prospective design. However, only Ozsin *et al.* study was randomised controlled trial.¹⁰ We could not determine the main reason of heterogeneity, but we thought reason might be nonrandomisation of samples. The limited number of randomised controlled study (only one) prevented the analysis of heterogeneity during statistical analysis.

AF may occur after different types of surgeries, but the incidence of POAF is greatest in cardiac surgery. POAF is recorded up to 40% in coronary artery bypass grafting surgery, 63% in valve surgery and 11% in heart transplantation.^{12,13} On the other hand, many risk factors are defined for POAF after cardiac surgery. Age is the most reported and widely accepted risk factor.¹⁴ The possible mechanism of AF due to the aging process is leading to a loss of myocardial fibers, increasing fibrosis and collagen deposition in the atria.¹⁵ Except the age, one can classify the risk factors for POAF in two groups: cardiovascular and non-cardiovascular factors.¹⁶ Cardiovascular factors such as congestive heart failure, coronary artery disease, non-coronary vascular disease, prior history of AF/other arrhythmias, left atrial enlargement, hypertension, and left ventricular dysfunction; and non-cardiovascular factors such as chronic obstructive pulmonary disease, hyperthyroidism, chronic kidney disease, male gender, diabetes mellitus, Caucasian race, high cholesterol, and obesity can cause POAF.

Between the two opposite status of thyroidal function, hyperthyroidism is more agreed predisposing medical condition for POAF than hypothyroidism. Frost *et al.* diagnosed atrial fibrillation (8.3%) within 30 days from the diagnosis of hyperthyroidism, among 40,628 patients.¹⁷ On the other hand, contribution of hypothyroidism for POAF is controversial. In the earlier studies, possible correlation between AF and hypothyroidism has been suggested, but not proven.¹⁸ Barnes *et al.* found that 50% of patients received amiodarone and abnormal thyroid function tests due to amiodarone.¹⁸ Because of that they concluded routine screening for hypothyroidism has not seemed justifiable from their data.

Krahn *et al.* demonstrated that abnormal TSH level was common in new onset AF patients, but clinical thyroid disease was uncommon.¹⁹ Therefore, they suggested routine TSH screening of patients at higher risk of having undiagnosed clinical thyroid disease.

In two recent retrospective studies, hypothyroidism was associated with development of POAF after cardiac

surgery.^{20,21} Those studies were performed in 821 and 626 patients, respectively. Cerillo *et al.* have shown low fT3 concentration has been agreed as an univariate predictor of POAF development.⁹ Kokkonen *et al.* have performed an investigation in patients 65 years or older, and they had taken blood samples three times at preoperative, fourth postoperative hour and third postoperative month.⁷ Only the fourth postoperative hour fT3 values were different between POAF and non-POAF groups. No differences were observed for TSH or fT4. Authors demonstrated that fT3 at the fourth hour, age and number of grafts were independent predictors of POAF.

In an experimental trial, Zhang *et al.* concluded that both hypothyroidism and hyperthyroidism have led to increased AF vulnerability in a rat thyroidectomy model.²² According to this trial, normal thyroid hormone levels are required to prevent cardiac arrhythmias and AF.

The main limitation of this meta-analysis was the language restriction of articles. The second limitation was small sample sizes of studies, and inclusion of only a single trial.

CONCLUSION

According to the result of this analysis, preoperative lower levels of fT3 is an important predictor of POAF. However, that result depends on the smaller sample size trials. Therefore, there is a need for larger studies for a common outcome such as POAF.

CONFLICT OF INTEREST:

The authors declare no conflicts of interest with respect to the authorship and/or publication of this article.

AUTHORS' CONTRIBUTION:

SÖ, IK, YS, KÖ, İÖ: Concept, design, data collection, analysis, literature search, writing manuscript and critical review.

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