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# The prognostic value of free triiodothyronine/free thyroxine ratio in short-term outcomes after left ventricular assist device implantation

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## Abstract

**Background:** Despite advancement in technology adverse events after left ventricular assist device(LVAD) implantation continue to be the main barrier to more widespread use of it. Therefore, it is vital to identify prognostic factors to reduce adverse cardiac events after LVAD implatation. Thyroid dysfunction is associated with a poor prognosis in individuals with heart failure. The objective of this study is to examine the correlation between thyroid hormones and adverse cardiovascular events following LVAD implantation.

**Method and Results:** The study included a total of 36 patients, with an average age of 60 ± 9 years, of which 77.7% were male. Although there was no significant relationship between TSH and FT3 levels and post-operative adverse events($p>0.05$ for both), there was a significant association between FT3/FT4 and all-cause and cardiovascular mortality($p<0.001$ for both). ROC analysis revealed that FT3/FT4 values lower than 1 were significantly associated with adverse events(all $p < 0.05$). There was no significant difference between the two groups in terms of age, gender, BMI, etiology of heart failure, EF, sPAP, smoking status and the presence of comorbid diseases, BNP, TSH and FT3 levels($p>0.05$ for all). All-cause mortality, cardiac mortality, arrhythmia prevelance, vasopressor need(day) and duration of ICU stay were significantly higher in FT3/FT4 < 1 group(all $p < 0.05$).

**Conclusion:** Our findings suggest that FT3/FT4 ratio might be useful as a biomarker of short-term adverse clinical outcomes in patients who underwent LVAD implantation.

**Keywords:** Left ventricular assist device; Heart failure; Thyroid disfunction; FT3/FT4 ratio; Cardiac mortality

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# Sol ventrikül destek cihazı implante edilen hastalarda serbest triiyodotironin/serbest tiroksin oranının kısa vadeli olumsuz klinik sonuçlar açısından prognostik değeri

**Öz**

**Giriş ve Amaç:** Teknolojideki ilerlemelere rağmen, sol ventrikül destek cihazı(LVAD) implantasyonu sonrası gelişen olumsuz olayların sıklığı, bu teknolojinin daha geniş çapta kullanımının önünde engel olmaya devam etmektedir. Bu nedenle, LVAD implantasyonu sonrası olumsuz kardiyak olayları azaltmak için prognostik faktörleri belirlemek hayati önem taşımaktadır. Tiroiddisfonksiyonu, kalp yetmezliği hastalarında kötü prognozla ilişkilidir. Bu çalışmanın amacı, LVAD implantasyonu sonrası olumsuz kardiyovasküler olaylar ile tiroid fonksiyonu arasındaki ilişkiyi incelemektir.

**Yöntem ve Bulgular:** Toplam 36 hasta (ortalama yaş 60 ± 9, %77,7 erkek) çalışmaya dahil edildi. Cerrahi sonrası olumsuz olaylar ile TSH ve FT3 düzeyleri arasında anlamlı bir ilişki olmamasına rağmen (her ikisi için de $p>0.05$), FT3/FT4 oranı ile tüm nedenlere bağlı ve kardiyovaskülermortalite arasında anlamlı bir ilişki bulundu (her ikisi için de $p<0.001$). ROC analizi, FT3/FT4 değerlerinin 1'in altında olması ile kötü prognoz arasında anlamlı ilişki olduğunu ortaya koydu (tümü için $p < 0.05$). İki grup arasında yaş, cinsiyet, BMI, kalp yetmezliği etiyolojisi, EF, sPAP, sigara içme durumu, eşlik eden hastalıkların varlığı, BNP, TSH ve FT3 düzeyleri açısından anlamlı fark yoktu (tümü için $p>0.05$). Tüm nedenlere bağlı mortalite, kardiyak mortalite, aritmi prevalansı, vazopressör gereksinimi (gün) ve yoğun bakım yatış süresi FT3/FT4 < 1 grubunda anlamlı derecede yüksekti (tümü için $p < 0.05$).

**Sonuç:** Bulgularımız, FT3/FT4 oranının, LVAD implante edilen hastalarda kısa vadeli olumsuz klinik sonuçların bir biyobelirteci olarak kullanışlı olabileceğini göstermektedir.

**Anahtar kelimeler:** Sol ventrikül destek cihazı; Kalp yetmezliği; Tiroid bozukluğu; serbestT3/serbestT4 oranı; Kardiyak mortalite.

## INTRODUCTION

Thyroid hormone (TH) plays a vital role in regulating cardiovascular homeostasis by influencing heart rate (HR), cardiac contractility, myocardial relaxation and systemic vascular resistance(SVR)[1]. These hormones mainly triiodothyronine (T3) and thyroxine (T4), circulate in the bloodstream, with T3 primarily deriving from the conversion of T4 through the action of deiodinase iodothyronine enzymes in peripheral tissues.While both hormones exert biological effects, T3 is considered asthe more potent of the two[2]. Research findings indicate that reduced free T3 levels and elevated levels of thyroid-stimulating hormone (TSH) are linked to a poorer prognosis in heart failure patients, even in the absence of clinically apparent thyroid disorders[3,4].

Heart failure (HF) is a significant cardiac condition that continues to pose a substantial public health challenge, persisting as a major concern despite advancements in medical therapy. Its prevalence in developed countries typically falls within the range of 1.5 to 2.0[5,6]. A substantial number of individuals with heart failure (HF) progress to an advanced HF stage, marked by persistent symptoms despite receiving the most intensive therapy available. While heart transplantation remains the gold standard therapy for end-stage HF, LVAD therapy has emerged as a valuable alternative for individuals who are not eligible for transplantation, serving as a destination treatment option.

With an aging population and a limited supply of donor organs for transplantation, it is increasingly probable that a greater number of patients will undergo LVAD treatment in the future. The ongoing advancements in LVAD technology have led to improved clinical outcomes[7]. Notwithstanding these encouraging outcomes, post-implantation complications remain the primary impediment to broader adoption of this technology in LVAD use[8].

Hence, the identification of prognostic factors is crucial in mitigating adverse cardiac events following LVAD implantation.

This study was conducted to investigate the potential correlation between thyroid hormones and the occurrence of both all-cause mortality and adverse cardiovascular events following LVAD implantation. Thus, the aim was to identify high-risk patients during the preoperative process in order to enable early intervention.

## METHODS

### Patient population

In this retrospective cohort study, we included 36 patients who received Heart Mate II LVAD and Heart Mate III LVAD at our institution between December 2018 and October 2022. We collected baseline demographic characteristics, intensive care unit (ICU) duration, arrhythmia occurrences (ventricular tachycardia or ventricular fibrillation), and data on all-cause and cardiac mortality from hospital medical records. Demographics, preoperative echocardiographic findings, and pre-existing comorbid conditions were manually documented. Thyroid function parameters that masured on admission were recorded. Patients who had not undergone thyroid function tests during the preoperative process were excluded.

### LVAD implantataion procedure

LVAD implantation is performed under general anesthesia in a sterile operating room environment. The surgical approach involves median sternotomy or minimally invasive techniques, depending on patient characteristics and surgeon preference. Following exposure of the heart, the left ventricle is accessed, and the LVAD pump is implanted. Careful attention is paid to cannulation of the left ventricular apex and connection of inflow and outflow cannulas to the heart chambers. The driveline is tunneled subcutaneously and exits the abdomen for connection to an external power source. Intraoperative transesophageal echocardiography was used in assessing device positioning and function. Hemodynamic monitoring guides optimal pump speed adjustment to achieve adequate cardiac output while minimizing complications such as suction events and thrombosis.

### Ethics

This study received approval from the institutional ethics committee of the University(E-10840098-772.02-5426, 01.09.2023). In compliance with the Declaration of Helsinki, informed consent was obtained from all patients for their participation in the study.

### Clinical outcomes

The primary endpoint of this study was cardiac mortality. Cardiac mortality was defined as death resulting from myocardial infarction, ischemia, heart failure, or cardiac arrest due to other or unknown causes. Secondary endpoints encompassed the length of ICU stay, occurrences of arrhythmias (ventricular tachycardia or ventricular fibrillation), and all-cause mortality. The survival status of the patients was determined by a comprehensive review of their medical records.

### Statistical Analyses

Statistical analysis was carried out using SPSS software (version 25.0, SPSS Inc., Chicago, IL, USA). Continuous variables were presented as mean ± standard deviation or median (interquartile range, IQR), while categorical variables were expressed as percentages. A p-value $< 0.05$ was considered statistically significant for all comparisons. Normal distribution was assessed using the Shapiro-Wilk test. Independent samples were compared using Student's t-test for normally distributed data, and the Mann-Whitney U test was employed for non-normally distributed data. Associations between categorical variables

among groups were analyzed using the Chi-square test. The relationship between the FT3/FT4 and both cardiac and all-cause mortality was demonstrated with separate box plot graphics. Receiver Operating Characteristic (ROC) analysis was performed to determine the cutoff FT3/FT4 value for predicting mortality.

## RESULTS

The study comprised a total of 36 patients. Table 1 provides an overview of the patients' baseline characteristics. The average age of the patients was 60 years (SD 9), with 77.7% of them being male. The mean left ventricular ejection fraction (LV EF) was 19.4% (SD 3.3). Among the participants, 66.6% had coronary artery disease, 61.1% had hypertension, and 69.4% had diabetes. The median TSH levels were 1.24 µIU/mL (interquartile range: 0.46–3.32), and the mean FT3 levels in the study were 3.02 ng/dL (SD 0.24).

**Table I:** Baseline demographic, clinical, echocardiographic and laboratory features of patients (n=36)

| | OverallPopulation (n = 36) |
|---|---|
| **Age (years) mean** | 60 ± 9 |
| **Gender (male), n (%)** | 28 (77.7%) |
| **BMI, kg/m2, mean** | 27.6 ± 3.2 |
| **HT, n (%)** | 22(61.1%) |
| **CAD, n(%)** | 24(66.6%) |
| **DM, n (%)** | 25(69.4%) |
| **CVA, n (%)** | 4(11.1%) |
| **CRF, n (%)** | 13(36.1%) |
| **Arrhythmias, n (%)** | 8 (22.2%) |
| **Smoking, n (%)** | 22(61.1%) |
| **Etiology; Non-İschemic, n (%)** | 12 (33.3%) |
| **Heart mate II, n(%)** | 14 (38.8%) |
| **NYHA 4, n(%)** | 18 (50%) |
| **LVEF, %, mean** | 19.4 ± 3.3 |
| **sPAP, mmHg, mean** | 48.6 ± 9.6 |
| **BNP, pg/mL,median** | 11449,6 ± 9540 |
| **TSH, µIU/mL, median** | 1.24 (0.46–3.32) |
| **Free T3, ng/dL, mean** | 3.02 ± 0.24 |

*BMI: Body Mass Index, HT: Hypertension, CAD: Coronary Artery Disease, DM: Diabetes Mellitus, CVA: Cerebrovascular Accident, CRF: Chronic Renal Failure, NYHA: New York Heart Association, LVEF: Left Ventricular Ejection Fraction, sPAP: Systolic Pulmonary Artery Pressure, BNP: Brain Natriuretic Peptide, TSH: Thyroid-Stimulating Hormone, T3: Triiodothyronine*

Association of thyroid status with postoperative adverse events investigated. Even though there was no significant link between TSH and FT3 levels and post-operative adverse events, ($p>0.05$ for both), a substantial association was identified between FT3/FT4 and cardiovascular and all-cause mortality($p<0.001$ for both)(figure 1 and 2).

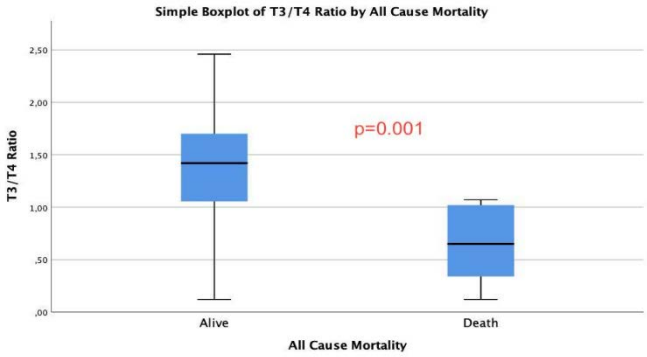


**Figure 1.** The box-plot graph shows association of FT3/FT4 ratio with all-cause mortality. There is a negative and significant correlation between FT3/FT4 ratio and all-cause mortality p<0.001)

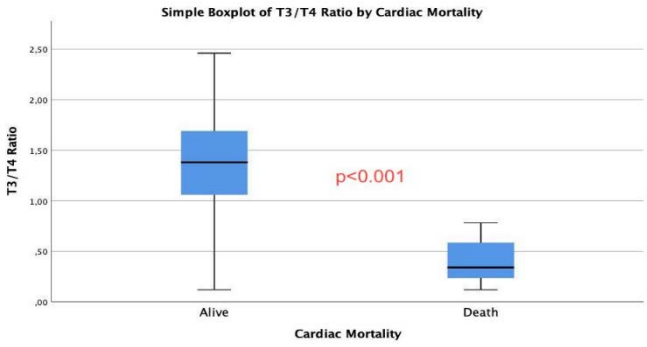


**Figure 2.** The box-plot graph shows association between FT3/FT4 ratio and cardiac mortality. There is a significant relationship between FT3/FT4 ratio and cardiac mortality (p<0.001)

To establish a cut-off value for FT3/FT4 to determine post-operative adverse events, we performed ROC analysis that revealed FT3/FT4 values lower than 1 were significantly associated with post-operative adverse events. According to the cut-off FT3/FT4 value, we

devided patients into 2 groups as 1) FT3/FT4 < 1 and 2) FT3/FT4 ≥ 1. Comparison of the baseline demographic, clinical and echocardiographic features between the groups defined in accordance with the specified cut-off value for FT3/FT4 are shown in Table 2. There was no substantial difference between the two groups concerning gender, age, BMI, etiology of heart failure, EF, sPAP, smoking status and the presence of comorbid diseases (coronary artery disease, diabetes mellitus, hypertension, arrhythmia, cerebrovascular disease, renal disease, peripheral artery disease), BNP, TSH and FT3 levels (all p>0.05).

**Table II:** Comparison of the baseline demographic, clinical, echocardiographic and laboratoryfeatures between the groups defined according to the cut-off value for FT3/FT4 ratio (n=36)

| | FT3/FT4 ratio<1 (n= 12) | FT3/FT4 ratio≥1 (n= 24) | p value |
|---|---|---|---|
| **Age (years) mean** | 57.9 ± 7.3 | 60.2 ± 8.2 | 0.230 |
| **Gender (male), n (%)** | 9 (75%) | 19(79.1%) | 0.282 |
| **BMI, kg/m2, mean** | 28.1 ± 3.3 | 27.4 ± 3.3 | 0.440 |
| **HT, n (%)** | 8 (66.6%) | 14 (58.3%) | 0.808 |
| **CAD, n(%)** | 7(58.3%) | 17(70.8%) | 0.343 |
| **DM, n (%)** | 6 (50%) | 19 (79.1%) | 0,157 |
| **CVA, n (%)** | 2 (16.7%) | 2 (8.3%) | 0.453 |
| **CRF, n (%)** | 4 (33.3%) | 9 (37.5%) | 0.326 |
| **Arrhythmias, n (%)** | 3 (25%) | 5 (20.8%)) | 0.313 |
| **Smoking, n (%)** | 8 (66.6%) | 14 (58.3%) | 0.369 |
| **Etiology; Non-İschemic, n (%)** | 5 (41.6%) | 7 (29.1%) | 0.414 |
| **Heart mate II, n(%)** | 6 (50%) | 8 (33.3%) | 0,156 |
| **NYHA calss 4, n(%)** | 7 (58.3%) | 11 (45.8%) | 0.480 |
| **LVEF, %, mean** | 59.4 ± 3.9 | 60.1 ± 4.3 | 0.577 |
| **sPAP, mmHg, mean** | 45± 8.7 | 50.4 ± 9.7 | 0.099 |
| **BNP, pg/mL,median** | 6562(28871 6902) | 7265(4375-9173) | 0.591 |
| **TSH, µIU/mL, median** | 1.36 (0.68–3.71) | 1.18 (0.62–3.44) | 0.376 |
| **Free T3, ng/dL, mean** | 2.77 ± 0.38 | 3.09 ± 0.42 | 0.462 |

*BMI: Body Mass Index, HT: Hypertension, CAD: Coronary Artery Disease, DM: Diabetes Mellitus, CVA: Cerebrovascular Accident, CRF: Chronic Renal Failure, NYHA: New York Heart Association, LVEF: Left Ventricular Ejection Fraction, sPAP: Systolic Pulmonary Artery Pressure, BNP: Brain Natriuretic Peptide, TSH: Thyroid-Stimulating Hormone, T3: Triiodothyronine*

Table 3 presents a comparison of post-operative outcome variables between the groups categorized based on the FT3/FT4 cutoff value. In the FT3/FT4 < 1 group, all-cause mortality, cardiac mortality, arrhythmia prevalence, vasopressor requirement (days), and duration of ICU stay were significantly higher (all p < 0.05).

**Table III:** Comparison of the post-operative outcome variables between the groups defined according to the cut-off value for FT3/FT4 ratio

| Outcome Variable | FT3/FT4 ratio<1 (n= 12) | FT3/FT4 ratio≥1 (n= 24) | p value |
|---|---|---|---|
| **ICU Stay (days, median)** | 8(4-13.7) | 4(3.2-6) | < 0.040 |
| **Cardiac Mortality, n (%)** | 7 (58.3%) | 0 (0%) | < 0.001 |
| **All-cause Mortality, n (%)** | 6 (50%) | 3 (12.5%) | 0.014 |
| **Arrhythmias(VT/VF), n (%)** | 7 (58.3%) | 2 (8.3%) | 0.001 |
| **Vasopressorneed (Day, median)** | 5.5(3-13.5) | 2.5(1-5.5) | 0.019 |

*ICU:Intensive Care Unit, VT/VF: Ventricular Tachycardia/Ventricular Fibrillation*

## DISCUSSION

In this study, association between thyroid function and short-term outcomes after LVAD implantation was investigated. The results indicate that FT3/FT4 was significantly associated with cardiac mortality during hospitalization after the LVAD implantation. We found a consistent negative association between FT3/FT4 and cardiac mortality, all-cause mortality, ventricular arrythmia, duration of ICU stay and need of postoperative vasopressor. On the other hand, neither TSH nor FT3 levels had shown to be associated with these end points.

In previosus studies it has been shown that cardiovascular system is an important target for TH activity. The major effects of TH on the heart are mediated by free triiodothyronine (FT3). T3 is mainly converted from T4 by deiodinase iodothyronine in peripheral tissues. It exerts influence on the vascular system as well as the heart[9]. FT3 modulates systolic contraction and

diastolic relaxation[10]. In addition to maintaining normal arteriolar remodeling, FT3 directly influences vascular smooth muscle cells, resulting in promotion of relaxation[11,12].

There are numerous cardiac conditions shown to be related to thyroid dysfunction like atherosclerosis, arrythmias, pericardial diseases, dyslipidemia and hypertension. Also there is increasing evidence suggesting that reduced thyroid function could be a contributing factor to heart failure[13,14]. Among individuals with heart failure, decreased T3 levels have been linked to myocardial scarring and abnormalities in myocardial perfusion[15]. Research has shown a connection between subclinical hypothyroidism and increased mortality rates in individuals with heart failure[16].

In research examining the link between thyroid dysfunction and heart failure, greater emphasis has been placed on evaluating FT3 and TSH levels[17,18]. However, in our study, we also prefered to examine the FT3/FT4. The FT3/FT4 represents the degree of transformation from T4 to T3, which might correlate with cardiovascular function. Therefore, there could be a significant connection between heart failure and thyroid hormone, which could be represented by the FT3/FT4 for the activity of extrathyroidal transformation of T4 to T3. Unlike prior studies, we were unable to establish a link between T3 and TSH levels and cardiovascular events. However, we demonstrated a remarkable correlation between the FT3/FT4 and prognostic outcomes following LVAD implantation. This finding might suggest that the FT3/FT4 could serve as a more effective predictor of thyroid function for end-stage heart failure patients implanted with LVAD.

Bielka at al retrospectively investigated impact of thyroid status at consecutive 147 patients who underwent LVAD implantation and they showed that there is an connection between TSH and FT3 levels and survival after LVAD implantation[19]. Nonetheless, number of studies examining the link between thyroid function and outcomes in individuals who have undergone LVAD implantation is insufficient. Our study holds significance as being the first investigation to investigate the connection between the FT3/FT4 and post-LVAD cardiovascular events.

## CONCLUSION

In conclusion, our study revealed that preoperatively measured FT3/FT4 ratio has an association with unfavorable outcomes in LVAD implanted patients. Our findings suggest that FT3/FT4 ratio might be a valuable biomarker of short-term adverse clinical outcomes. Close follow-up of the patients who have lower FT3/FT4, for the risk of developing postoperative adverse events can provide a significant benefit in reducing cardiovascular events by ensuring early diagnosis and treatment.

### Limitations

The primary drawback of our study was the limited sample size, thus warranting the validation of these results in a larger population. Another drawbacks are the absence of a control group and lack of assesment of postoperative thyroid function.

**Ethics Committee Approval:**This study received approval from the institutional ethics committee of the University(E-10840098-772.02-5426, 01.09.2023). In compliance with the Declaration of Helsinki, informed consent was obtained from all patients for their participation in the study.

**Conflict of Interest:** The authors declared no conflicts of interest.

**Financial Disclosure:** The authors declared that this study has received no financial support.

## REFERENCES

1. Razvi S, Jabbar A, Pingitore A, et al. Thyroid hormones and cardiovascular function and diseases.

Journal of the American College of Cardiology. 2018;71(16):1781-96.

2. PR L. Thyroid-pituitary interaction: feedback regulation of thyrotropin secretion by thyroid hormone. N Engl J Med. 1982;306:23-32.

3. Suzuki Y, Nanno M, Gemma R, Yoshimi T. Plasma free fatty acids, inhibitor of extrathyroidal conversion of T4 to T3 and thyroid hormone binding inhibitor in patients with various nonthyroidal illnesses. Endocrinologia japonica. 1992;39(5):445-53.

4. Mitchell JE, Hellkamp AS, Mark DB, et al. Thyroid function in heart failure and impact on mortality. JACC: Heart Failure. 2013;1(1):48-55.

5. Conrad N, Judge A, Tran J, et al. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. The Lancet. 2018;391(10120):572-80.

6. Murphy SP, Ibrahim NE, Januzzi JL. Heart failure with reduced ejection fraction: a review. Jama. 2020;324(5):488-504.

7. Mehra MR, Goldstein DJ, Cleveland JC, Cowger JA, Hall S, Salerno CT, et al. Five-year outcomes in patients with fully magnetically levitated vs axial-flow left ventricular assist devices in the MOMENTUM 3 randomized trial. JAMA. 2022;328(12):1233-42.

8. Kilic A, Macickova J, Duan L, et al. Machine learning approaches to analyzing adverse events following durable LVAD implantation. The Annals of Thoracic Surgery. 2021;112(3):770-7.

9. Grais IM, Sowers JR. Thyroid and the heart. The American journal of medicine. 2014;127(8):691-8.

10. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. New England Journal of Medicine. 2001;344(7):501-9.

11. Fukuyama K, Ichiki T, Takeda K, et al. Downregulation of vascular angiotensin II type 1 receptor by thyroid hormone. Hypertension. 2003;41(3):598-603.

12. Carrillo-Sepúlveda MA, Ceravolo GS, Fortes ZB, et al. Thyroid hormone stimulates NO production via activation of the PI3K/Akt pathway in vascular myocytes. Cardiovascular research. 2010;85(3):560-70.

13. Tang Y-D, Kuzman JA, Said S, et al. Low thyroid function leads to cardiac atrophy with chamber dilatation, impaired myocardial blood flow, loss of arterioles, and severe systolic dysfunction. Circulation. 2005;112(20):3122-30.

14. Pantos C, Dritsas A, Mourouzis I, et al. Thyroid hormone is a critical determinant of myocardial performance in patients with heart failure: potential therapeutic implications. European Journal of Endocrinology. 2007;157(4):515-20.

15. Wang W, Guan H, Fang W, et al. Free triiodothyronine level correlates with myocardial injury and prognosis in idiopathic dilated cardiomyopathy: evidence from cardiac MRI and SPECT/PET imaging. Scientific reports. 2016;6(1):39811.

16. Rhee CM, Curhan GC, Alexander EK, Bhan I, Brunelli SM. Subclinical hypothyroidism and survival: the effects of heart failure and race. The Journal of Clinical Endocrinology & Metabolism. 2013;98(6):2326-36.

17. Cappola AR, Fried LP, Arnold AM, et al. Thyroid status, cardiovascular risk, and mortality in older adults. Jama. 2006;295(9):1033-41.

18. Gencer B, Collet T-H, Virgini V, et al. Subclinical thyroid dysfunction and the risk of heart failure events: an individual participant data analysis from 6 prospective cohorts. Circulation. 2012;126(9):1040-9.

19. Bielka A, Kalinowski M, Gawlikowski M, et al. Thyroid Function at Left Ventricular Assist Device (LVAD) Implantation Predicts Prognosis During LVAD Support. The Journal of Heart and Lung Transplantation. 2022;41(4):S121-S2.