Relation of Low T3 to One-Year Mortality in Non–ST-Elevation Acute Coronary Syndrome Patients

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Background: Low T3 which is defined as decreased triiodothyronine (T3) and normal thyroid-stimulating hormone (TSH) and thyroxine (T4) levels is present in many acute diseases and is related to increased mortality. We studied low T3 level's relation to long-term mortality in non–ST-elevation acute coronary syndrome (NSTEMI-ACS) patients. **Methods:** T3, T4, and TSH levels of consecutive NSTEMI-ACS patients were measured. Patients with normal T4 and TSH levels, but low T3 level were defined as low T3 group. Patients with normal T3, T4, and TSH levels were defined as normal group. Clinical and laboratory findings in these two groups were compared. In addition, we examined low T3 level's relation to early and long-term mortality. **Results:** Mean patient age was 61 ± 13 (67% male) and 31 (11%) patients had low T3 level. Free T3 values were negatively correlated

with age, serum creatinine, and brain type natriuretic peptide values at the time of admission ($r = -0.452$, $P < 0.0001$; $r = -0.255$, $P < 0.0001$; $r = -0.544$, $P < 0.0001$, respectively). Mortality at 1 month and 1 year was higher in low T3 group (3% vs. 16%, $P = 0.002$; 6.4% vs. 23%, $P = 0.003$, respectively). In multivariate analysis, low T3 was found to be related to mortality at 1 year (OR: 2.6, 95% CI: 1.1–6.5, $P = 0.02$). In ROC analysis, free T3 had a good area under the curve (AUC) value for mortality at 1 year [AUC: 0.709 (95% CI: 0.619–0.799, SE: 0.0459)]. **Conclusion:** Low T3 is related to increased early and late mortality in NSTEMI-ACS patients. Free T3 levels may be used to identify NSTEMI-ACS patients with high mortality risk. J. Clin. Lab. Anal. 31:e22036, 2017. © 2016 Wiley Periodicals, Inc.

Key words: acute coronary syndrome; free T3; prognosis

INTRODUCTION

Homeostasis of thyroid hormones plays a pivotal role for cardiovascular system (1). Thyroid hormone (TH) increases cardiac output by lowering systemic vascular resistance and by increasing contractility of the heart (2). Thyroid hormone regulates sarcoplasmic reticulum calcium-activated ATPase (SERCA) synthesis; thus, they have lusitropic effects by increasing cellular calcium turnover (3). They lower total cholesterol and LDL-cholesterol levels (4). In experimental studies they have been shown to have positive effects on post-infarct left ventricular functions by blocking apoptosis in cardiac myocytes, increasing angiogenesis, and decreasing reperfusion injury after myocardial infarction (5, 6). In many acute diseases, “euthyroid sick syndrome” or low T3 which is defined as decreased triiodothyronine (T3) and normal thyroid-stimulating

hormone (TSH) and thyroxine (T4) levels is present and acute myocardial infarction is one of these diseases (7, 8). Because low T3 in early stages of an acute disease decrease body oxygen consumption, it is considered to be an adaptive state (9). However, previous studies show that low T3 is associated with increased mortality (10, 11). Studies on low T3 level's effect on mortality in myocardial infarction have patient population formed of myocardial infarction patients with ST elevation (12–14). Data on prevalence and long-term effects of low T3 in non–ST-elevation acute

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coronary syndrome (NSTEMI-ACS) patients are limited. In this study we investigated the prevalence, correlation between clinical laboratory parameters, and early and late mortality rates of low T3 in NSTEMI-ACS patients.

METHODS

In our study, we prospectively collected thyroid test data of NSTEMI-ACS patients who were hospitalized between May 2012 and January 2013. This study was approved by the Institutional Review Board, and complied with the Declaration of Helsinki.

The inclusion criteria were a history of chest pain at rest or other symptoms suggestive of an ACS, with the most recent episode occurring within 24 h of admission. This could be associated with ST or T-wave changes on the electrocardiogram suggestive of myocardial ischemia or elevated levels of cardiac troponin-I (cTn-I). Patients excluded from this study were those with a history of thyroid disease (history of thyroiditis, underwent thyroid surgery, radioactive thyroid ablation, and antithyroid or thyroid hormone usage), abnormal serum levels of TSH or free T4, treated with drugs that affected the thyroid system (amiodarone, heparin, oral anticoagulants, corticosteroids), and the presence of any predominant severe systemic diseases (sepsis, end-stage liver insufficiency, metastatic cancer). The remaining 274 patients were included in this study.

Serum free T3, free T4, and TSH levels were determined by the ADVIA system after overnight fasting, utilizing chemiluminescent technology (Siemens Healthcare Diagnostic Inc., Tarrytown, NY). The most of thyroid tests were performed before coronary angiographic procedure. Only nine (3%) patient's thyroid tests were performed after the procedure. Normal values are for free T3 2.3–4.5 pg/ml; free T4, 0.74–2 ng/dl; and TSH, 0.55–4.78 μ IU/ml. Patients with decreased serum free T3 but with normal free T4 and TSH levels were defined as low T3 group. Patients with normal free T3, T4, and TSH levels were defined as normal group.

Echocardiography was performed with a commercially available ultrasound machine (Vivid 3; GE Healthcare, Horten, Norway) and 3.5 MHz probe. All images were obtained from standard parasternal and apical position using 2D, M-mode, and Doppler echocardiographic techniques. All examinations were performed by an experienced cardiologist. Left ventricular ejection fraction (LVEF) was determined by visual estimation and confirmed by Simpson's rule. Left ventricular diastolic filling pattern was graded on a scale from I to IV based on transmitral inflow patterns. Moderate-to-severe diastolic dysfunction was defined as grade 2 or more (15).

Myocardial infarction was established by an elevation in serum cTnI level in addition to characteristic chest pain or typical electrocardiographic changes. Percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) surgery was defined as coronary revascularization. Cerebrovascular attack was defined as global or focal neurologic deficit that was diagnosed by a neurologist and confirmed by a brain computed tomographic scan.

The primary endpoint was the 1-year total mortality. Recurrent myocardial infarction, coronary revascularization, and cerebrovascular event during 1 year follow-up were defined as major adverse cardiovascular events (MACE). For follow-up death and MACE data collection, hospital records, patients and/or patients' relatives, and national identity database were used. Mean follow-up period was 65 ± 19 weeks.

Statistical analysis

Numeric data were checked for the normal distribution assumption using the Kolmogorov–Smirnov test. Continuous variables showing normal distribution were given standard deviation and independent *t*-test was used to compare the data between groups. Continuous variables showing non-normal distribution were given median and quartiles and these data were compared between groups using Mann–Whitney U test. Categorical variables were given ratios and numbers and compared with chi-square test. Continuous variable correlation analysis was performed via Pearson or Spearman tests. Receiver operating characteristics curve was performed to assess discriminative power of free T3 to predict 1-year mortality and area under the curve (AUC) was calculated. Kaplan–Meier survival analysis was performed to compare the difference in survival between low T3 and normal group. To determine independent predictors of primary end point, variables with $P < 0.1$ in univariate analysis were included in Cox regression analysis was performed. A $P < 0.05$ (two-tailed) was considered as statistically significant. All statistical studies were carried out using the Statistical Package for Social Sciences software (SPSS 16.0 for Windows; SPSS Inc., Chicago, IL).

RESULTS

Mean patient age was 61 ± 13 (67% male) and 31 (11%) of the patients had low T3 level. Patients with low T3 level were older and predominantly women. Ratio of patients with a history of congestive heart failure and cerebrovascular disease was higher in low T3 group than normal T3 group. Clinical characteristics and laboratory findings of both group are presented in

Table 1. Most reported symptom at the time of admission was chest pain, whereas number of patients with dyspnea was significantly higher in low T3 group (10% vs. 2%, $P = 0.008$).

In low T3 group number of patients who underwent coronary angiography was less than normal T3 group (39% vs. 81%, $P < 0.001$), but the ratio of PCI and CABG was similar. Medical and interventional treatment ratios are presented in Table 2. LVEF of low T3 patients was lower than normal T3 patients (Table 1). Furthermore, ratio of patients with more than moderate diastolic dysfunction was significantly higher in low T3 group (respectively, 27% vs. 7%, $P = 0.008$).

Free T3 values were negatively correlated with age, serum creatinine, and brain type natriuretic peptide (BNP) values at the time of admission ($r = -0.452$, $P < 0.0001$; $r = -0.255$, $P < 0.0001$; $r = -0.544$,

$P < 0.0001$, respectively), whereas there was a strong positive correlation with hemoglobin values ($r = 0.525$, $P < 0.0001$). GRACE2 score has a significant negative correlation as well ($r = -0.488$, $P < 0.0001$). ROC analysis was performed to predict mortality at 1 year and AUC value was 0.709 (95% CI: 0.619–0.799, SE: 0.0459, Fig. 1).

Patients who died in the first month and first year had lower mean free T3 values than survivors (respectively, 2.22 ± 0.7 vs. 2.78 ± 0.5 pg/ml, $P = 0.01$; and 2.52 ± 0.39 vs. 2.81 ± 0.50 pg/ml, $P = 0.002$). TSH and free T4 values were similar in two groups (Table 3). MACE frequency rates were higher in low T3 group at 1 month and 1 year, but it was statistically insignificant. Mortality at 1 month and 1 year was significantly higher in low T3 group (Table 1 and Fig. 2). Multivariate analysis showed low T3 is

TABLE 1. Baseline Characteristics

Variable	Normal T3 ($n = 243$)	Low T3 ($n = 31$)	P value
Age, years (mean $\pm$ SD)	61 $\pm$ 13	70 $\pm$ 14	<0.0001
Female, n (%)	73 (30)	17 (55)	0.006
History of diabetes mellitus, n (%)	84 (35)	16 (52)	0.06
History of hypertension, n (%)	165 (68)	25 (81)	0.1
History of CHF, n (%)	15 (6)	6 (19)	0.009
History of CAD, n (%)	106 (44)	18 (58)	0.1
History of CVD, n (%)	17 (7)	6 (19)	0.019
History of PAD, n (%)	10 (4)	1 (3)	0.8
Systolic blood pressure, mmHg (mean $\pm$ SD)	137 $\pm$ 22	131 $\pm$ 29	0.2
Heart rate, beat/min. (mean $\pm$ SD)	77 $\pm$ 16	81 $\pm$ 14	0.09
ST-segment depression >0.5 mm on ECG, n (%)	71 (29)	11 (37)	0.4
Left ventricular EF, % (mean $\pm$ SD)	52 (11)	43 (11)	0.001
LA diameter, mm (mean $\pm$ SD)	3.8 $\pm$ 0.5	4.4 $\pm$ 0.6	0.001
Left ventricular ESD, mm (mean $\pm$ SD)	3.2 $\pm$ 0.7	3.5 $\pm$ 0.6	0.01
Left ventricular EDD, mm (mean $\pm$ SD)	4.9 $\pm$ 0.5	5.1 $\pm$ 0.5	0.02
Hemoglobin, g/dl (mean $\pm$ SD)	13.6 $\pm$ 1.8	11.5 $\pm$ 1.8	<0.0001
Serum glucose, mg/dl (mean $\pm$ SD)	146 $\pm$ 68	163 $\pm$ 82	0.2
Serum creatinine, mg/dl (mean $\pm$ SD)	0.9 $\pm$ 0.3	1.5 $\pm$ 1	<0.0001
Troponin-I ^a , pg/dl	1.3 (0.18–4.9)	1.8 (0.84–9.2)	0.049
Free T4, ng/dl (mean $\pm$ SD)	1.09 $\pm$ 0.1	1.12 $\pm$ 0.2	0.7
TSH, μ IU/ml (mean $\pm$ SD)	1.6 $\pm$ 0.9	1.6 $\pm$ 0.8	0.8
Free T3, pg/ml (mean $\pm$ SD)	2.89 $\pm$ 0.3	1.7 $\pm$ 0.5	<0.0001
CRP ^a , mg/dl	0.6 (0.2–1.5)	1.8 (0.4–7.7)	0.006
BNP ^a , pg/dl	68.5 (23–225)	445 (137–1428)	0.001
Total cholesterol, mg/dl (mean $\pm$ SD)	180 $\pm$ 46	167 $\pm$ 82	0.3
LDL cholesterol, mg/dl (mean $\pm$ SD)	107 $\pm$ 36	100 $\pm$ 32	0.3
HDL cholesterol, mg/dl (mean $\pm$ SD)	38 $\pm$ 10	36 $\pm$ 13	0.1
Triglycerides, mg/dl (mean $\pm$ SD)	167 $\pm$ 80	161 $\pm$ 90	0.2
GRACE 1 year mortality risk ^a , %	3.6 (2.3–7.3)	10 (4.3–35)	<0.0001
First month MACE rate, n (%)	11 (5%)	3 (10%)	0.2
First month mortality rate, n (%)	8/243 (3%)	5/31 (16%)	0.002
1 year MACE rate, n (%)	26 (11%)	4 (13%)	0.7
1 year mortality rate, n (%)	15/235(6%)	6/26 (23%)	0.003

BNP, brain type natriuretic peptide; CAD, coronary artery disease; CHF, congestive heart failure; CVD, cerebrovascular disease; CRP, C-reactive protein; ECG, electrocardiography; EF, ejection fraction; EDD, end-diastolic diameter; ESD, end-systolic diameter; GRACE, global registry acute coronary event; IQR, interquartile range; LA, left atrium; MACE, major adverse cardiac event; PAD, peripheral artery disease; SD, standard deviation.

^aThese values were described by median with interquartile range (25th and 75th percentile).

TABLE 2. In-hospital Interventional and Medical Treatments Rates

Treatment and intervention	Normal T3 group (n = 243)	Low T3 group (n = 31)	P value
PCI, n (%)	71 (29)	5 (16)	0.1
CABG, n (%)	40 (17)	3 (10)	0.3
Asetilsalisilik asit, n (%)	234 (97)	28 (93)	0.2
Klopidogrel, n (%)	226 (94)	26 (88)	0.1
Statin, n (%)	209 (87)	27 (90)	0.8
Beta-blocker, n (%)	206 (86)	27 (90)	0.5
ACE-inhibitor, n (%)	180 (75)	15 (50)	0.005
ARB, n (%)	20 (8)	2 (7)	0.7

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery by-pass grafting; PCI, percutaneous coronary intervention.

Fig. 1. Receiver operating characteristics curve of free T3 to predict 1 year mortality.

significantly related to mortality at 1 year [HR: 2.6 (CI 95%: 1.1–6.5, $P = 0.02$), Table 4].

As iodinated contrast medium used during coronary angiography could have altered thyroid functions, we repeated our statistical analyses excluding nine patients whose thyroid functions were investigated after coronary angiography. In these new analyses, we found that our findings did not change (Table 5).

DISCUSSION

Major findings of our study are as follows: (a) low T3 is related to early and late mortality in NSTEMI-ACS patients, (b) free T3 value is correlated with age, serum

creatinine, hemoglobin, and BNP values at admission, (c) discriminative power of free T3 to predict death at 1 year is good.

Low T3 rates in acute myocardial infarction are reported to be 5.8–18.6% (14, 16). In this study this rate was 11%. Difference in rates probably is caused by different patient populations. Studies about long-term effects of TH on acute myocardial infarction had ST-elevation MI patients as their population (11–14, 16). NSTEMI-ACS and ST-elevation MI patient populations have distinct features. We think this study is valuable because it focuses on low T3 prevalence and its relation to mortality in NSTEMI-ACS patients.

T3 have an important role in maintaining intracellular calcium homeostasis in cardiac myocytes (17). T3 boosts sarcoplasmic reticulum Ca²⁺-ATPase (SERCA) synthesis in cardiac myocytes while decreasing phospholamban synthesis which is a SERCA inhibitor (3, 18). Clinical importance of these cellular mechanisms is shown in clinical studies. In overt and subclinical hypothyroidism cardiac diastolic functions have been shown to deteriorate (17, 19). In our study we found grade 2 or more severe diastolic dysfunction rates were significantly higher in low T3 group. Increase in diastolic dysfunction in hypothyroidism had been shown using echocardiography in previous studies, but diastolic function deterioration in low T3 was not documented.

We found, in accordance with previous studies, mean patient age is higher in low T3 group (13, 20). Decrease in T3 caused by acute illness may be more pronounced in the elderly patients. Most of the T3 which is an active thyroid hormone is produced from T4 by type 1 iodothyronine deiodinase (17). Deiodinase activity decreases with increasing age (21). Also, the deiodinase is induced at the transcriptional level by T3, but inflammatory cytokines block this induction and decline in deiodinase expression (22). Elderly patients who have ACS have high levels of inflammatory markers (23). These factors may explain why low T3 is more commonly observed in the elderly patients.

There are conflicting results in earlier studies about the relation between myocardial damage and T3 levels (8, 24). In this study, we found higher cardiac troponin levels in low T3 group predicting larger myocardial damage.

Coronary artery disease (CAD) prevalence and mortality were reported to be higher in subclinical hypothyroidism (25). Free T3 levels and CAD have been shown to be related even in the absence of thyroid dysfunction (26). CAD was found to be more frequent and severe in low T3 levels (27). Zang et al.'s study pointed out that three-vessel disease was more common in ST-elevation MI patients with low T3 levels (12). In low T3 group, number of patients who underwent coronary

TABLE 3. Comparison of TSH, T3, and T4 Levels between Survivor and Nonsurvivor Groups

	One month			One year		
	Survivor	Nonsurvivor	<i>P</i> value	Survivor	Nonsurvivor	<i>P</i> value
Free T3 (mean $\pm$ SD), pg/ml	2.78 $\pm$ 0.50	2.22 $\pm$ 0.77	0.01	2.81 $\pm$ 0.50	2.52 $\pm$ 0.39	0.002
Free T4 (mean $\pm$ SD), ng/ml	1.09 $\pm$ 0.17	1.23 $\pm$ 0.32	0.1	1.09 $\pm$ 0.16	1.11 $\pm$ 0.21	0.4
TSH (mean $\pm$ SD), μ U/ml	1.68 $\pm$ 0.90	1.51 $\pm$ 0.79	0.5	1.68 $\pm$ 0.91	1.66 $\pm$ 0.85	0.9

T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone.

Fig. 2. Kaplan-Meier plot for 1 year mortality.

angiography was less than normal T3 group, but the ratio of PCI and CABG was similar in this study. This is because patients in low T3 group had severe coronary lesions that needed intervention.

In our study mortality rates at 1 year was higher in low T3 group and this is consistent with previous studies (12–14). Low T3 patients were older, had higher rates of renal dysfunction, more extensive myocardial damage, and atherosclerosis. All these factors are known to increase mortality in CAD (28, 29). It remains unclear if low T3 is directly linked to increased mortality or it is a sign of more diffuse and active atherosclerosis which is the underlying cause of mortality. There are data supporting both hypothesis. In hypothyroidism characterized by low T3 levels, diastolic hypertension and impaired lipid metabolism explain increased atherosclerosis rates (30). But in low T3, the situation is different because TSH and T3 levels are most likely normal before acute onset of the disease. Therefore, it is not possible to mention

increased atherosclerosis due to hypertension or impaired lipid metabolism in low T3 like we did for hypothyroidism or subclinical hypothyroidism. Our findings support this hypothesis. Neither hypertension prevalence nor LDL levels were higher in low T3 group than normal T3 group.

Furthermore, T3 decreases systemic vascular resistance and after load (2). In animal models, thyroid hormones have been shown to promote angiogenesis (31). Ioannis et al. have found strong correlation between T3 levels and LVEF recovery at 6 months after MI (32). In experimental studies, thyroid hormones were found to decrease myocardial infarction damage (6). These findings suggest T3 has a role in cardiovascular recovery and in decreasing myocardial damage after MI. Thus, higher myocardial injury and slow cardiovascular recovery in low T3 group may be the cause of increased mortality.

In this study, we found that discriminative power of free T3 to predict death at 1 year is good. This is

TABLE 4. Univariate and Multivariate Analysis of Predictors One Year Mortality

Variable	Univariate HR (95% CI)	P value	Multivariate HR (95% CI)	P value
Low T3	4.2 (2.06–8.70)	<0.0001	2.6 (1.10–6.50)	0.029
Age >75 years	3.4 (1.74–6.84)	<0.0001	1.0 (0.35–2.88)	0.9
PCI	0.23 (0.07–0.75)	0.015	0.3 (0.10–1.27)	0.1
ST-segment depression >0.5 mm	2.4 (1.25–4.82)	0.009	2.1 (1.04–4.62)	0.038
eGFR<60 ml/min/1.73 m ²	2.9 (1.50–5.82)	0.002	1.5 (0.58–3.94)	0.3
Hemoglobin ^a g/dl	0.8 (0.74–1.01)	0.08	1.0 (0.83–1.29)	0.7
Killip class ^b	2.0 (1.14–3.63)	0.016	1.1 (0.60–2.29)	0.6
History of DM	1.6 (0.84–3.23)	0.14		
History of CAD	1.7 (0.88–3.48)	0.105		
History of CHF	2.1 (0.83–5.59)	0.11		
cTn-I > 0.06 pg/ml	2.6 (0.63–11.1)	0.17		
LVEF <40%	2.1 (1.03–4.32)	0.04	1.1 (0.49–2.72)	0.7

CAD, coronary artery disease; CHF, congestive heart failure; cTn-I, cardiac troponin-I; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.

^aIncrement per g/dl.

^bIncrement per class.

TABLE 5. Univariate and Multivariate Analysis of Predictors One Year Mortality^a

Variable	Univariate HR (95% CI)	P value	Multivariate HR (95% CI)	P value
Low T3	4.1 (1.94–8.66)	<0.0001	2.5 (1.10–5.89)	0.029
Age >75 years	3.6 (1.82–7.38)	<0.0001	1.7 (0.73–4.25)	0.2
PCI	0.16 (0.03–0.68)	0.013	0.2 (0.58–1.08)	0.6
ST-segment depression >0.5 mm	2.5 (1.27–5.08)	0.008	2.1 (1.05–4.37)	0.036
eGFR <60 ml/min/1.73 m ²	3.1 (1.57–6.29)	0.001	1.4 (0.59–3.42)	0.3
Hemoglobin ^b gr/dl	0.8 (0.72–1.00)	0.06	1.0 (0.84–1.31)	0.6
Killip class ^c	2.0 (1.17–3.72)	0.012	1.3 (0.71–2.40)	0.3
History of DM	1.8 (0.91–3.64)	0.09	1.8 (0.89–3.88)	0.9
History of CAD	1.7 (0.88–3.61)	0.108		
History of CHF	2.2 (0.85–5.74)	0.103		
cTn-I > 0.06 pg/ml	2.6 (0.62–11.0)	0.18		
LVEF <40%	1.9 (0.94–4.16)	0.07	1.2 (0.57–2.88)	0.5

CAD, coronary artery disease; CHF, congestive heart failure; cTn-I, cardiac troponin-I; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.

^aThis table shows patients who have thyroid sampling before coronary angiography (265 patients).

^bIncrement per g/dl.

^cIncrement per class.

noteworthy because free T3 may be used for risk classification of NSTEMI-ACS patients. There was a good correlation of age, serum creatinine, and BNP with free T3 levels. These factors are linked to increased mortality in ACS patients (28, 29, 33). Hemoglobin levels at the time of admission and free T3 levels were strongly correlated in our study and low hemoglobin levels at admission have been shown to increase mortality in ACS patients (34). Free T3 levels and atherosclerosis severity are also related (27). All the above-mentioned factors' correlation with T3 may explain why it has good discriminative power.

There were limitations to our study. First of all, BNP levels were not measured for all of the patients. This was why we could not investigate if free T3 predicts mortality independently of BNP levels. Secondly, as the

only measurement of thyroid hormones was at admission, we might have missed some patients who might have developed into low T3 during follow-up. Thirdly, we did not measure anti-TPO, therefore we could not accurately excluded patients who have thyroiditis.

CONCLUSION

Low T3 is related to increased early and late mortality in NSTEMI-ACS patients. Thyroid hormones and TSH levels are easy and cheap to measure parameters which do not need expertise for interpretation. Free T3 levels may help to identify NSTEMI-ACS patients with high mortality risk. Further studies are needed to assess if thyroid replacement therapy lowers mortality in low T3 patients.

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