Received: 15 November 2016 | Revised: 13 January 2017 | Accepted: 25 January 2017

DOI: 10.1002/clc.22689

WILEY CLINICAL CARDIOLOGY

REVIEWS

The role of thyroid hormones in acute coronary syndromes: Prognostic value of alterations in thyroid hormones

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The prognosis of acute coronary syndromes (ACS) is affected by many factors. Normal thyroid homeostasis is known to alter during various critical illnesses, a condition that has been shown to correlate with the severity of the disease and increased mortality. The purpose of this article is to review literature to emphasize the considerable association of thyroid function with the cardiovascular system and summarize all existing evidence with regard to the role of thyroid hormones alterations during ACS. The electronic databases of PubMed, Medline, Scopus, and Cochrane were searched for relevant literature and studies. Alterations in thyroid hormone plasma concentrations, especially low triiodothyronine (T3) levels, represent a hormonal imbalance that is not uncommon among patients suffering an acute coronary event. Many studies have identified this abnormal thyroid hormonal status to be related to worse prognosis. Although further large-scale clinical trials are needed, the low T3 syndrome manifesting in patients during ACS might be useful in prognostic stratification.

KEYWORDS

Thyroid Hormones, Acute Coronary Syndromes, Myocardial Ischemia, Prognosis, Low T3 Syndrome

1 | INTRODUCTION

Despite all advances in pharmacotherapy and myocardial reperfusion strategies, short- and long-term mortality of patients suffering an acute coronary syndrome (ACS) remains substantial.[1,2] Although patients presenting with ST-segment elevation myocardial infarction (STEMI) or non–ST-segment elevation myocardial infarction (NSTEMI) have the same risk factors and both types of ACS share a similar long-term prognosis, STEMI patients have a worse short-term prognosis than do NSTEMI patients.[1,2] In addition to clinical markers of risk, such as advanced age, diabetes mellitus (DM), renal insufficiency, faster heart rate, and hypotension, the initial Killip class clinical presentation and electrocardiogram (ECG) findings are highly predictive of early prognosis.[1,2] Moreover, biomarkers such as high-sensitivity troponin, natriuretic peptides, and C-reactive protein (CRP) confer additive prognostic value.[1,2]

It has been long recognized that alterations in plasma concentrations of thyroid hormones (THs) may occur during acute illnesses.[3–5] Abnormal thyroid function tests have been shown to be correlated with the severity of the disease and mortality in critically ill patients.[3,4] The term "low T3 syndrome" refers to alterations of THs plasma concentrations, mainly decreased triiodothyronine (T3) and/or free T3 (fT3), during a variety of acute and chronic illnesses in patients with no known intrinsic thyroid disease.[3–5] It has been found to constitute an independent predictor of early and late mortality in such patients.[4,6] Considering the significant effects of THs on the cardiovascular system, accumulating evidence suggests a potential prognostic role of THs alteration in patients suffering an ACS.[7,8]

The aim of the present article is to review literature in order to illustrate the role of THs alterations during ACS and their potential prognostic value. The electronic databases of PubMed, Medline, Scopus, and Cochrane were comprehensively searched for relevant articles concerning THs alterations during all types of ACS and clinical studies addressing their correlation to prognosis. All relevant articles published in English were included after thorough examination. Due to heterogeneity of results, a nonsystematic approach was attempted.

2 | EFFECTS OF THYROID HORMONES ON THE CARDIOVASCULAR SYSTEM

The synthesis of thyroxine (T4) and T3 in the thyroid gland is activated by thyroid-stimulating hormone (TSH).[9] Almost 85% of T4 is primarily secreted by the thyroid gland and then converted in the liver, kidneys, and skeletal muscles to T3 by the enzyme 5′-monodeiodinase.[9] Reverse T3 (rT3) is a biologically inactive alternate product of T4 deiodination.[9] Only a small fraction of the THs is unbound and biologically active, because most of the circulating THs are bound to transport proteins.[9]

The precise cellular and molecular mechanisms of the THs in cardiac cells have been investigated and well characterized.[10] The thyroid hormone nuclear receptors (TRs) bind to thyroid hormone response elements (TREs) as homodimers or, more commonly, as heterodimers, and mediate the induction of transcription in the promoter regions of positively regulated genes.[10] Triiodothyronine is the only TH transported into the myocyte.[10] In the absence of T3, TRs lead to induction of negatively regulated genes, such as β-myosin heavy chain and phospholamban.[9,10] On the other hand, in the presence of T3, multiple key structural cardiac genes, such as α-myosin heavy chain, sarcoplasmatic reticulum Ca^{2+}-adenosine triphosphatase (SERCA 2), and Na^{+}/K^{+}-adenosine triphosphatase, are positively regulated.[10] The cycling process of intracellular calcium, which is regulated by genes expressed after the T3 and TRs binding, is responsible for the enhanced myocardial contractile function (inotropic effect) and diastolic relaxation (lusitropic activity).[10] On a vascular level, T3 participates in the maintenance and renewal of endothelial integrity, as well as on peripheral arterial resistance, as it can modulate the vascular response to the activation of the renin-angiotensin-aldosterone system.[11]

Furthermore, the extranuclear, nongenomic effects of THs on cardiac myocytes and on the systemic vasculature are important TRE-independent processes.[12] Thyroid hormones, and especially T3, can modify ion channels for sodium, potassium, and calcium, and affect a variety of intracellular pathways in cardiac and vascular smooth-muscle cells.[13] As a result, they can cause an immediate increase in resting heart rate, left ventricular contractility, and in venous tone, augmenting cardiac preload. In addition, THs cause a decrease in systematic vascular resistance by rapid relaxation of vascular smooth muscle cells, resulting in increased cardiac output (Table 1).[9,10] All these effects can occur rapidly, within seconds to minutes, in contrast to the T3 effects mediated by nuclear pathways, which take at least 30 minutes to 2 hours to demonstrate.[12,14]

TABLE 1 Main effects of THs on hemodynamics

Parameter	Effect of THs
SVR	↓
DBP	↓
Afterload	↓
Cardiac inotropy-chronotropy	↑
Basal CO	↑
Blood volume preload	↑

Abbreviations: CO, cardiac output; DBP, diastolic blood pressure; HR, heart rate; SVR, systematic vascular resistance; THs, thyroid hormones.

The close link between thyroid hormonal status and cardiovascular diseases is evident by the significant effects of thyroid dysfunction, both subclinical and overt, on the cardiovascular system. Hypothyroidism is correlated with diastolic hypertension, dyslipidemia, atherosclerotic plaque progression and instability, and endothelial dysfunction.[9,10] On the other hand, hyperthyroidism is associated with increased systolic blood pressure, pulmonary hypertension, and atrioventricular valve regurgitation, especially of the tricuspid valve.[9] In rare cases, patients with overt hyperthyroidism and thyrotoxicosis can present with chest pain and ECG abnormalities, due to increases in oxygen demands in response to augmented cardiac contractility and workload or due to coronary vasospasm.[9] Moreover, patients with hyperthyroidism can present with signs and symptoms of heart failure, characterized by enhanced cardiac output and contractility.[9,15]

Heart rhythm and rate may be significantly affected by even mildly altered thyroid status. The arrhythmogenic effects of THs include altered electrophysiological characteristics of atrial myocytes, enhanced automaticity, triggered activity in pulmonary vein cardiomyocytes, and shortened action potential duration.[16] Arrhythmias such as sinus tachycardia, atrial flutter, and atrial fibrillation, and to a lesser extent ventricular arrhythmias, are commonly found in patients with overt or mild/subclinical hyperthyroidism.[16] On the other hand, hypothyroidism is correlated with sinus bradyarrhythmias and various ECG abnormalities.[16] Moreover, various clinical and experimental studies have suggested potential anti- and proarrhythmic effects of the THs and a direct effect on electrogenesis in myocardial cells.[13,17]

3 | ABNORMAL THYROID HORMONAL STATUS DURING CRITICAL ILLNESSES

Alterations in TH plasma concentrations during a variety of acute and chronic illnesses in patients with no known intrinsic thyroid disease are described by various terms in literature, such as "euthyroid sick syndrome," "nonthyroidal illness syndrome," and "low T3 syndrome."[3,4] The most frequently observed hormonal profile is characterized by low T3 and/or fT3, elevated rT3 and normal T4 and TSH (Table 2).[3,4,15] The principal pathophysiological mechanism is supposed to be the reduced activity of the enzyme 5′-monodeiodinase, which converts T4 to T3.[3–5]

The euthyroid sick syndrome seems to be a timing-related organ-specific response to inflammation during various critical illnesses and constitute an adaptive, compensatory, and beneficial response, decreasing energy consumption.[3,4] However, it has been linked to worse prognosis and increased mortality in patients with septic shock or acute stroke.[6,18] Acute cardiac diseases also have been associated with low serum T3 levels.[19,20] It has been reported that THs alterations constitute a powerful independent marker of the severity of illness and mortality in patients after resuscitated cardiac arrest.[19] Furthermore, Iervasi et al reported that lower serum fT3 levels are a strong predictor of mortality in all cardiac patients, with both acute and chronic diseases, as stable coronary artery disease or congestive heart failure.[15]

TABLE 2 Summary of alterations in plasma concentrations of THs during critical illnesses

Condition	THs Alterations	Main Mechanisms
Acute illness	↑rT3, ↓T3, ↓fT3, normal T4, normal fT4, normal TSH	Inhibition of 5′-MDI, which deiodinates T4 to T3 and rT3 to T2
Severe chronic illness	↑rT3, ↓T3, ↓fT3, normal fT4, ↓T4, ↓/normal TSH	1. Inhibition of 5′-MDI 2. Low binding of THs to serum proteins (especially low TBG binding) 3. Reduction of TRH release by the hypothalamus, causing a decrease in TSH secretion

Abbreviations: 5′-MDI, type I iodothyronine 5′-monodeiodinase; fT3, free triiodothyronine; fT4, free thyroxine; rT3, reverse triiodothyronine; T2, diiodothyronine; T3, triiodothyronine; T4, thyroxine; TBG, thyroxine-binding globulin; THs, thyroid hormones; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

4 | THYROID HORMONAL ALTERATIONS DURING ACS

Acute coronary syndromes are high-risk manifestations of coronary atherosclerosis and acute myocardial ischemia. Disruption of a coronary atherosclerotic plaque with subsequent thrombus formation is the main pathophysiology of such an event, which triggers an immediate inflammatory cascade.[21] Inflammation seems to play a key role in plaque disruption, which stimulates thrombosis, coagulation, activation of the sympathetic system, and release of stress hormones.[21]

Normal thyroid homeostasis seems to alter in a subgroup of patients with ACS. Several studies have observed a fall in total T3 and/or fT3 concentration and rise in rT3 concentration after an acute coronary event.[22–31] The exact prevalence of the low T3 syndrome among patients suffering an ACS seems not to be clearly defined yet. A wide range from 5% to 35% has been reported in literature, and this could be attributed to differences in study populations between the conducted studies.[7,8,22–33] However, the syndrome seems to occur more frequently in STEMI compared with NSTEMI patients, possibly because of their poorer early prognosis and the pathophysiologic features of the occlusive thrombus resulting in more myocardium at stake.[22–24]

Furthermore, the exact time of occurrence of THs alterations after an ACS is not clearly determined. Franklyn et al observed that total T3 reached their minimum levels at day 4 and rT3 maximum levels at day 2, in patients with uncomplicated acute myocardial infarction (AMI).[22] On the other hand, Friberg et al noticed, in a sample of 47 patients with AMI, that both the nadir of total T3 and the peak of rT3 were observed 24 to 36 hours after symptoms' onset.[7] Pimentel et al found the highest rT3 levels at 4 days after admission. However, rT3 was measured only at days 1, 4, and 7.[8] Concerning the other THs, Pavlou et al noticed that mean fT3, T4, fT4, and TSH levels remain unchanged in all patients with an ACS during the first 5 days after admission, whereas minimum T3 and maximum rT3 levels occurred on days 3 and 4.[23] Although there seem to be significant differences in the reported data with regard to the precise onset of TH alterations, it is clear that changes in T3 and rT3 occur during the first 5 days of ACS.

The acute effects of cytokines seem to play a key role in the pathogenesis of the low T3 syndrome. It has been reported that administration of interferon-α in healthy volunteers can cause disturbances in TH metabolism, mimicking the syndrome.[34] During critical illness, various pro-inflammatory cytokines such as interleukin 6 (IL-6), tumor necrosis factor-α, and interferon-γ can directly affect the pituitary gland and impair TSH release.[5] Concerning patients with ACS, THs alterations are supposed to develop through the inflammatory response activation. Increases in IL-6, a pleiotropic, pro-inflammatory cytokine; soluble IL-6 receptor (sIL-6R); and CRP levels may exert an inhibitory effect on thyroid axis function.[7,15,27,35–37]

Occurrence of decreased THs levels during an ACS has been associated in various clinical studies with specific clinical and biochemical parameters. Worsening angina pectoris preceding the AMI, known chronic heart failure, or previous MI and DM have been linked to lower T3 levels during the acute coronary event.[7,26,29] In general, although available evidence is not strong, factors that seem to be associated with the development of the low T3 syndrome among patients with ACS include older age, lower body mass index, DM, and high plasma levels of N-terminal pro-brain natriuretic peptide and CRP.[8,15,26,27,29,31]

5 | PROGNOSTIC VALUE OF THYROID HORMONES IN ACS

Several clinical studies have investigated the possible prognostic value of THs alterations in patients suffering an ACS (Table 3). Friberg et al found a correlation of increased rT3 levels in patients with MI with higher 1-year mortality, independently of other risk factors.[29] In line with these results are the conclusions of another small-sized study by Pimentel et al, who found an association of abnormal THs alterations with worse prognosis.[8] Two further larger studies involving consecutive STEMI patients undergoing primary percutaneous coronary intervention also have related the low T3 syndrome to increased short- and long-term mortality.[30,31] Moreover, a recent study with patients attending a cardiac rehabilitation program after an ACS also has reported an association of lower fT3 levels with all-cause mortality.[38]

Alterations in THs are more evident in critically ill patients. Not surprisingly, a study comparing the thyroid function of patients with resuscitated cardiac arrest due to ACS and patients with uncomplicated AMI showed that the latter group was characterized by a milder form of the low T3 syndrome.[35] In another study, THs alterations were more evident in the STEMI group compared with the NSTEMI group, although this difference was not statistically significant.[8] Furthermore, Pavlou et al found that THs alterations can manifest in patients with unstable angina and also be linked to adverse prognosis.[23] Nevertheless, in the same study, lower T3 and higher rT3 levels were significantly more pronounced in patients

TABLE 3 Clinical studies investigating the correlation of THs alterations during ACS with prognosis

Study	Year	Design	Condition	Sample Size	Time of THs Measurements	Follow-up	Results/Conclusions
Friberg et al[29]	2001	Prospective	AMI	331	At admission	1 year	High rT3 levels are associated with an increased risk of 1-year mortality.
Pavlou et al[23]	2002	Prospective	ACS	114	During the first 5 days after admission and at 1 month	1 month	ESS can manifest both in AMI and UA; the rT3 increase and T3 decrease were significantly greater in complicated MIs compared with uncomplicated MIs and UA; low T3 levels may have prognostic value.
Friberg et al[7]	2002	Prospective	AMI	47	During the first 5 days after admission	1 year	THs alterations are associated with increased mortality.
Iervasi et al[15]	2003	Prospective	Various heart diseases	573	From 2 to 5 days after admission	1 year	Low T3 levels are strongly related with increased mortality.
Iltumur et al[35]	2005	Prospective	Cardiac arrest due to ACS	121	At 72 hours and 2 months	2 months	THs are significantly altered in cardiac arrest induced by ACS; T3 and fT3 levels were lower in nonsurvivors compared with survivors up to 2 months.
Pimentel et al[8]	2006	Prospective	STEMI and NSTEMI/UA	70	Days 1, 4, and 7 after admission	7 days	Greater THs alterations were found in STEMI compared with NSTEMI/UA patients; ESS is associated with poorer prognosis in patients with ACS.
Adawiyah et al[26]	2010	Prospective	STEMI and NSTEMI/UA	85	Days 1, 5, and 42	6 months	ESS can manifest in patients with STEMI, NSTEMI, and UA and is related with mortality.
Lymvaios et al[39]	2011	Prospective	AMI	47	At 24 hours, 48 hours, 5 days, and 6 months	6 months	Lower T3 levels are associated with poor early and late myocardial functional recovery.
Zhang et al[28]	2012	Retrospective	AMI	501	After admission	10 $\pm$ 2 months	Decreased fT3 levels are correlated with worse short- and long-term prognosis.
Lazzeri et al[31]	2012	Prospective	STEMI treated with PCI	641	After admission	Up to 44.9 months	ESS represents part of the response to acute stress; decreased fT3 levels are associated with lower survival rates in STEMI patients age <75 years.
Özcan et al[30]	2014	Prospective	STEMI treated with PCI	457	Within 12 hours after admission	14.4 $\pm$ 5.4 months	ESS is related to higher in-hospital and long-term mortality.
Kim et al[32]	2014	Retrospective	STEMI treated with PCI	40	At admission	1–2 months	Lower T3 levels are associated with larger myocardial area at risk and increased salvage index in STEMI patients.
Abdulaziz Qari F[25]	2015	Prospective	STEMI and NSTEMI/UA	400	Days 1 to 4	NR	Lower fT3 levels are associated with increased mortality.
Yazıcı et al[33]	2016	Prospective	NSTEMI/UA	274	Before angiography	1 month and 1 year	Low T3 and fT3 levels are related to increased early and late mortality.
Brozaitiene et al[38]	2016	Prospective	Rehabilitation program 2 weeks post-ACS	642	At day 2 after admission to the rehabilitation clinic	Maximum of 118 months	Low fT3 levels during the rehabilitation after ACS are associated with mortality.

Abbreviations: ACS: acute coronary syndrome; AMI, acute myocardial infarction; ESS, euthyroid sick syndrome; fT3, free triiodothyronine; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NR, not reported; NSTEMI, non–ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; rT3, reverse triiodothyronine; STEMI, ST-segment elevation myocardial infarction; T3, triiodothyronine; THs, thyroid hormones; UA, unstable angina.

with complicated compared vs uncomplicated infarctions or unstable angina.[23]

In summary, existing evidence supports the assumption of a prognostic role for the low T3 syndrome in patients with ACS. However, data are available from clinical studies (Table 3) that are in general not large-scale, high-quality trials, and which are characterized by significant limitations, relatively small sample sizes, and varying use of strict diagnostic criteria for the low T3 syndrome. More important, the possible change of thyroid function tests during follow-up has not been additionally considered in the analyses used. Thus, further investigation is required for the clarification of cause-effect relationships, as the low T3 state during ACS may not be a direct causal factor for adverse prognosis.

Experimental data suggest a critical role for THs in the response of myocardium to ischemic stress.[36,39] Few clinical studies involving patients with AMI have addressed the possible correlation of THs with the extent of myocardial injury. Lower fT3 levels have been associated with increased serum levels of cardiac biomarkers

(troponin T and N-terminal pro-brain natriuretic peptide) as indicators of myocardial injury, as well as with lower left ventricular ejection fraction.[27,28] Lymvaios et al also reported a strong association of low T3 with impaired ventricular function among AMI patients, concluding that T3 levels may represent a predictor of ventricular functional recovery.[39] Interestingly, the findings of another study exhibited that the extent of transmural involvement in patients with STEMI, assessed by cardiac magnetic resonance imaging 40 days after the event, is strongly associated with T3 levels.[32] In this retrospective and small-sized study, the group with high/normal T3 levels had a significantly greater extent of transmural involvement than the low-T3 group, which presented a significantly larger myocardial area at risk, thus a greater extent of ischemia and an increased myocardial salvage index.[32] The authors concluded that the transient low T3 state during AMI is associated with lower transmurality, suggesting a protective role of the low T3 syndrome. Putting it all together, the existing data indicate that the link of the low T3 syndrome to worse prognosis and mortality among patients suffering an AMI is not necessarily reflected in the possible correlation of the syndrome with the extent of myocardial necrosis. Large initial myocardial ischemia can result in worse short-term prognosis, whereas large transmurality can result in worse long-term prognosis.

Different interpretations of the low T3 syndrome in literature reflect our limited understanding of the pathophysiology of the syndrome. Although low TH plasma concentrations have been linked to adverse prognosis, it has been proposed that this transient low T3 status during an AMI may be actually cardioprotective, by reducing energy expenditure, heart rate, and oxygen consumption during the ischemic stress.[32] Moreover, it has been also suggested that down-regulation of the thyroid hormone system in patients suffering from myocardial ischemia, even prior to AMI manifestation, might be beneficial, in an attempt to reduce myocardial oxygen demands.[7] However, a persisting down-regulated thyroid system after AMI might become maladaptive, because of the loss of the positive effects of T3 on the cardiovascular system.[7] Consequently, the low T3 syndrome might represent a hormonal homeostatic escape response, meaning a beneficial and physiologically adaptive mechanism during the early stress phase of an acute ischemic event, by minimizing myocardial metabolic demands and protecting against arrhythmias; and it may become maladaptive in later stages, with detrimental long-term effects, predisposing to development of heart failure.[3,15]

In summary, although TH plasma alterations have been studied more extensively in STEMI patients, they can occur in all aspects of ACS. It is important, though, to emphasize that the low T3 syndrome is evident in a small group of ACS patients that seem to have the worse outcome. In the absence of robust data derived by large-scale clinical studies, it remains unclear whether the low T3 syndrome is directly linked to worse prognosis or it constitutes a marker of the severity of illness, which is the underlying factor for increased mortality. However, the syndrome should not be underestimated, as disturbances of T3, fT3, and rT3 levels seem to carry an additive prognostic value in ACS, independently of traditional risk factors. In this setting, although the exact timing of THs alterations seems not to be clearly defined yet, routine determination of plasma levels of THs among patients suffering an ACS might reveal an otherwise silent prognostic marker. Nevertheless, further high-quality studies need to confirm this and additional research is needed to clarify when and how this potentially powerful prognostic marker could be operationalized in the clinical setting.

6 | TREATMENT OF THE LOW T3 SYNDROME

Available data from experimental studies suggest that TH replacement therapy aiming to reverse the abnormal thyroid state occurring during AMI may improve hemodynamics, ventricular function, and cardiac remodeling.[36] Clinical experience regarding TH supplementation during critical illness is available only from studies with patients undergoing coronary artery bypass surgery or chronic heart failure, with some promising evidence.[36] Unfortunately, data supporting TH administration in patients suffering an ACS and manifesting the low T3 syndrome are not available yet. Moreover, the type of the synthetic hormone (T4 or T3) and dosage and timing of administration are unknown. However, ongoing randomized clinical trials may offer insights into whether patients with AMI benefit from TH therapy, in addition to the treatment of the primary coronary event, in the short term and during the chronic phase after the ACS.[36,40]

7 | CONCLUSION

All available data indicate that alterations in thyroid function tests are not uncommon in patients with ACS, especially in STEMI patients. The low T3 syndrome represents a hormonal imbalance that may significantly influence pathophysiological mechanisms and cardiovascular hemodynamics. This altered thyroid state, and, more specifically, the fall of T3 and/or fT3 and the rise of rT3, seems to be related with overall worse prognosis, and it could be useful in the prognostic stratification of patients suffering an ACS. Future clinical and experimental studies need to investigate the low T3 syndrome more deeply during an acute coronary event to completely understand its pathophysiology and recognize whether it has a potential prognostic role for a subgroup of ACS patients or it manifests as an "epiphenomenon" due to critical illness.

Conflicts of interest

The authors declare no potential conflicts of interest.

REFERENCES

1. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-Elevation Myocardial Infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines [published correction appears in *Circulation*. 2013;128:e481]. *Circulation*. 2013;127:e362–e425.
2. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC Guideline for the management of Patients with Non–ST-Elevation Acute Coronary Syndromes [published correction appears in *J Am Coll Cardiol*. 2014;64:2713–2714]. *J Am Coll Cardiol*. 2014;64:e139–e228.
3. Chopra IJ. Euthyroid sick syndrome: is it a misnomer? *J Clin Endocrinol Metab*. 1997;82:329–334.

4. Farwell AP. Nonthyroidal illness syndrome. *Curr Opin Endocrinol Diabetes Obes.* 2013;20:478–484.
5. Warner MH, Beckett GJ. Mechanisms behind the non-thyroidal illness syndrome: an update. *J Endocrinol.* 2010;205:1–13.
6. Alevizaki M, Synetou M, Xynos K, et al. Low triiodothyronine: a strong predictor of outcome in acute stroke patients. *Eur J Clin Invest.* 2007;37:651–657.
7. Friberg L, Werner S, Eggertsen G, et al. Rapid down-regulation of thyroid hormones in acute myocardial infarction: is it cardioprotective in patients with angina? *Arch Intern Med.* 2002;162:1388–1394.
8. Pimentel RC, Cardoso GP, Escosteguy CC, et al. Thyroid hormone profile in acute coronary syndromes [article in English, Portuguese]. *Arq Bras Cardiol.* 2006;87:688–694.
9. Klein I, Danzi S. Thyroid disease and the heart. *Circulation.* 2007;116:1725–1735.
10. Kahaly GJ, Dillmann WH. Thyroid hormone action in the heart. *Endocrinol Rev.* 2005;26:704–728.
11. Vargas F, Moreno JM, Rodríguez-Gómez I, et al. Vascular and renal function in experimental thyroid disorders. *Eur J Endocrinol.* 2006;154:197–212.
12. Davis PJ, Davis FB. Nongenomic actions of thyroid hormone on the heart. *Thyroid.* 2002;12:459–466.
13. Klemperer JD, Klein I, Gomez M, et al. Thyroid hormone treatment after coronary-artery bypass surgery. *N Engl J Med.* 1995;333:1522–1527.
14. Schmidt BM, Martin N, Georgens AC, et al. Nongenomic cardiovascular effects of triiodothyronine in euthyroid male volunteers. *J Clin Endocrinol Metab.* 2002;87:1681–1686.
15. Iervasi G, Pingitore A, Landi P, et al. Low-T3 syndrome: a strong prognostic predictor of death in patients with heart disease. *Circulation.* 2003;107:708–713.
16. Tribulova N, Knezl V, Shainberg A, et al. Thyroid hormones and cardiac arrhythmias. *Vascul Pharmacol.* 2010;52:102–112.
17. Knezl V, Soukup T, Okruhlicová L, et al. Thyroid hormones modulate occurrence and termination of ventricular fibrillation by both long-term and acute actions. *Physiol Res.* 2008;57(suppl 2):S91–S96.
18. Angelousi AG, Karageorgopoulos DE, Kapaskelis AM, et al. Association between thyroid function tests at baseline and the outcome of patients with sepsis or septic shock: a systematic review. *Eur J Endocrinol.* 2011;164:147–155.
19. Longstreth WT Jr, Manowitz NR, DeGroot LJ, et al. Plasma thyroid hormone profiles immediately following out-of-hospital cardiac arrest. *Thyroid.* 1996;6:649–653.
20. Ray DC, Macduff A, Drummond GB, et al. Endocrine measurements in survivors and non-survivors from critical illness. *Intensive Care Med.* 2002;28:1301–1308.
21. Bentzon JF, Otsuka F, Virmani R, Falk E. Mechanisms of plaque formation and rupture. *Circ Res.* 2014;114:1852–1866.
22. Franklyn JA, Gammage MD, Ramsden DB, et al. Thyroid status in patients after acute myocardial infarction. *Clin Sci (Lond).* 1984;67:585–590.
23. Pavlou HN, Kliridis PA, Panagiotopoulos AA, et al. Euthyroid sick syndrome in acute ischemic syndromes. *Angiology.* 2015;53:699–707.
24. Eber B, Schumacher M, Langsteger W, et al. Changes in thyroid hormone parameters after acute myocardial infarction. *Cardiology.* 1995;86:152–156.
25. Abdulaziz Qari F. Thyroid hormone profile in patients with acute coronary syndrome. *Iran Red Crescent Med J.* 2015;17:e26919.
26. Adawiyah J, Norasyikin AW, Mat NH, et al. The non-thyroidal illness syndrome in acute coronary syndrome is associated with increased cardiac morbidity and mortality. *Heart Asia.* 2010;2:11–14.
27. Wang WY, Tang YD, Yang M, et al. Free triiodothyronine level indicates the degree of myocardial injury in patients with acute ST-elevation myocardial infarction. *Chin Med J (Engl).* 2013;126:3926–3930.
28. Zhang B, Peng W, Wang C, et al. A low fT3 level as a prognostic marker in patients with acute myocardial infarctions. *Intern Med.* 2012;51:3009–3015.
29. Friberg L, Drvota V, Bjelak AH, et al. Association between increased levels of reverse triiodothyronine and mortality after acute myocardial infarction. *Am J Med.* 2001;111:699–703.
30. Özcan KS, Osmonov D, Toprak E, et al. Sick euthyroid syndrome is associated with poor prognosis in patients with ST segment elevation myocardial infarction undergoing primary percutaneous intervention. *Cardiol J.* 2014;21:238–244.
31. Lazzeri C, Sori A, Picariello C, et al. Nonthyroidal illness syndrome in ST-elevation myocardial infarction treated with mechanical revascularization. *Int J Cardiol.* 2012;158:103–104.
32. Kim DH, Choi DH, Kim HW, et al. Prediction of infarct severity from triiodothyronine levels in patients with ST-elevation myocardial infarction. *Korean J Intern Med.* 2014;29:454–465.
33. Yazıcı S, Kırış T, Ceylan US, et al. Relation of low T3 to one-year mortality in non–ST-elevation acute coronary syndrome patients. *J Clin Lab Anal.* 2016. doi: 10.1002/jcla.22036.
34. Corssmit EP, Heyligenberg R, Endert E, et al. Acute effects of interferon-alpha administration on thyroid hormone metabolism in healthy men. *J Clin Endocrinol Metab.* 1995;80:3140–3144.
35. Iltumur K, Olmez G, Ariturk Z, et al. Clinical investigation: thyroid function test abnormalities in cardiac arrest associated with acute coronary syndrome. *Crit Care.* 2005;9:R416–R424.
36. Pingitore A, Chen Y, Gerdes AM, et al. Acute myocardial infarction and thyroid function: new pathophysiological and therapeutic perspectives. *Ann Med.* 2012;44:745–757.
37. Kimura T, Kanda T, Kotajima N, et al. Involvement of circulating interleukin-6 and its receptor in the development of euthyroid sick syndrome in patients with acute myocardial infarction. *Eur J Endocrinol.* 2000;143:179–184.
38. Brozaitiene J, Mickuviene N, Podlipskyte A, et al. Relationship and prognostic importance of thyroid hormone and N-terminal pro-B-type natriuretic peptide for patients after acute coronary syndromes: a longitudinal observational study. *BMC Cardiovasc Disord.* 2016;16:45.
39. Lymvaios I, Mourouzis I, Cokkinos DV, et al. Thyroid hormone and recovery of cardiac function in patients with acute myocardial infarction: a strong association? *Eur J Endocrinol.* 2011;165:107–114.
40. Jabbar A, Ingoe L, Pearce S, et al. Thyroxine in acute myocardial infarction (ThyrAMI)—levothyroxine in subclinical hypothyroidism post-acute myocardial infarction: study protocol for a randomised controlled trial. *Trials.* 2015;16:115.

How to cite this article: Lamprou V, Varvarousis D, Polytarchou K, Varvarousi G, Xanthos T. The role of thyroid hormones in acute coronary syndromes: Prognostic value of alterations in thyroid hormones. *Clin Cardiol.* 2017;40:528–533. https://doi.org/10.1002/clc.22689