

## THE PRESENT AND FUTURE

### STATE-OF-THE-ART REVIEWS

# Thyroid Hormones and Cardiovascular Function and Diseases



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#### ABSTRACT

Thyroid hormone (TH) receptors are present in the myocardium and vascular tissue, and minor alterations in TH concentration can affect cardiovascular (CV) physiology. The potential mechanisms that link CV disease with thyroid dysfunction are endothelial dysfunction, changes in blood pressure, myocardial systolic and diastolic dysfunction, and dyslipidemia. In addition, cardiac disease itself may lead to alterations in TH concentrations (notably, low triiodothyronine syndrome) that are associated with higher morbidity and mortality. Experimental data and small clinical trials have suggested a beneficial role of TH in ameliorating CV disease. The aim of this review is to provide clinicians dealing with CV conditions with an overview of the current knowledge of TH perturbations in CV disease. (J Am Coll Cardiol 2018;71:1781-96) © 2018 by the American College of Cardiology Foundation.

Despite major advances in their prevention and treatment, cardiovascular (CV) diseases remain the single largest cause of death globally (1). Recurrent ischemia resulting in adverse CV events following optimal treatment for an acute coronary syndrome occurs in approximately 10% of subjects in randomized controlled trials (RCTs) (2), and this number nearly doubles in real-world registries (3). The inexorable progress of CV disease, despite optimal guideline-based primary and secondary prevention, suggests a multifactorial etiology and the need to assess other precipitants that may exacerbate existing CV disease.

Thyroid hormone (TH) receptors (TRs) are present in myocardium and vascular endothelial tissues, thereby allowing changes in circulating TH concentration to modulate end-organ activity (Central

Illustration). Patients who are overtly hypo- or hyperthyroid show CV and hematologic manifestations that are well-documented, and both can, if left untreated, accelerate the onset of symptomatic CV disease. However, the clinical significance of mild thyroid dysfunction (subclinical thyroid disease) is uncertain. Minor changes in TH concentration may have an adverse impact on the CV system, and subclinical thyroid dysfunction has been associated with a 20% to 80% increase in vascular morbidity and mortality risk (4-6). Observational studies report increased adverse CV biomarkers and myocardial strain in patients with subclinical thyroid disease, but, in the absence of mechanistic studies and large RCTs, no cause and effect has been proven. Nevertheless, thyroid disease, both overt and subclinical, is a global burden and associated with increased CV



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## ABBREVIATIONS AND ACRONYMS

<b>AF</b>	= atrial fibrillation
<b>AIT</b>	= amiodarone-induced thyrotoxicosis
<b>AMI</b>	= acute myocardial infarction
<b>CV</b>	= cardiovascular
<b>CHD</b>	= coronary heart disease
<b>D (1-3)</b>	= deiodinase enzymes (1-3)
<b>HF</b>	= heart failure
<b>LDL</b>	= low density lipoprotein
<b>MHC</b>	= myosin heavy chain
<b>PLB</b>	= phospholamban
<b>rT<sub>3</sub></b>	= reverse T <sub>3</sub>
<b>SCH</b>	= subclinical hypothyroidism
<b>SERCA</b>	= sarcoplasmic reticulum adenosine triphosphatase
<b>SHyper</b>	= subclinical hyperthyroidism
<b>SVR</b>	= systemic vascular resistance
<b>T<sub>3</sub></b>	= triiodothyronine
<b>T<sub>4</sub></b>	= thyroxine
<b>TH</b>	= thyroid hormones
<b>TR</b>	= thyroid hormone receptor
<b>TRH</b>	= thyrotropin releasing hormone
<b>TSH</b>	= thyrotropin

disease. The wide availability and affordability of treatments for correcting TH dysfunction has led to increased interest in exploring the role of TH in CV disease. This review summarizes the role of TH in CV function and diseases.

## MOLECULAR AND CELLULAR MECHANISMS OF TH ACTION

**PHYSIOLOGY OF THYROID FUNCTION.** Thyroid function is regulated by the hypothalamic-pituitary-thyroid axis via a classic endocrine feedback loop mechanism. Thyrotropin-releasing hormone (TRH) is secreted at the level of the hypothalamus and stimulates the anterior pituitary to produce thyroid-stimulating hormone (TSH), which, in turn, drives the thyroid gland to release TH. TH levels regulate TRH and TSH production and release (7). TSH has a log-linear relationship with thyroxine (T<sub>4</sub>) levels; therefore, even mild changes in TH concentrations lead to large changes in TSH. Thus, serum TSH is a robust marker of systemic TH status. The 2 main iodinated THs are T<sub>4</sub> and triiodothyronine (T<sub>3</sub>). Both have biological effects; however, T<sub>3</sub> is considered the active and more potent hormone. The normal negative feedback regulation of thyroid function is disrupted by illness, including conditions such as acute myocardial infarction (AMI) or heart failure (HF), and is characterized by a reduction

in serum TH without a concomitant rise in circulating TSH levels (termed nonthyroidal illness and further discussed later). With the recognition that TSH is extremely sensitive to subtle changes in circulating TH concentrations, and with the advent of high-sensitivity TSH assays, clinicians are able to detect subtle changes in thyroid function, leading to the concept of subclinical thyroid disease.

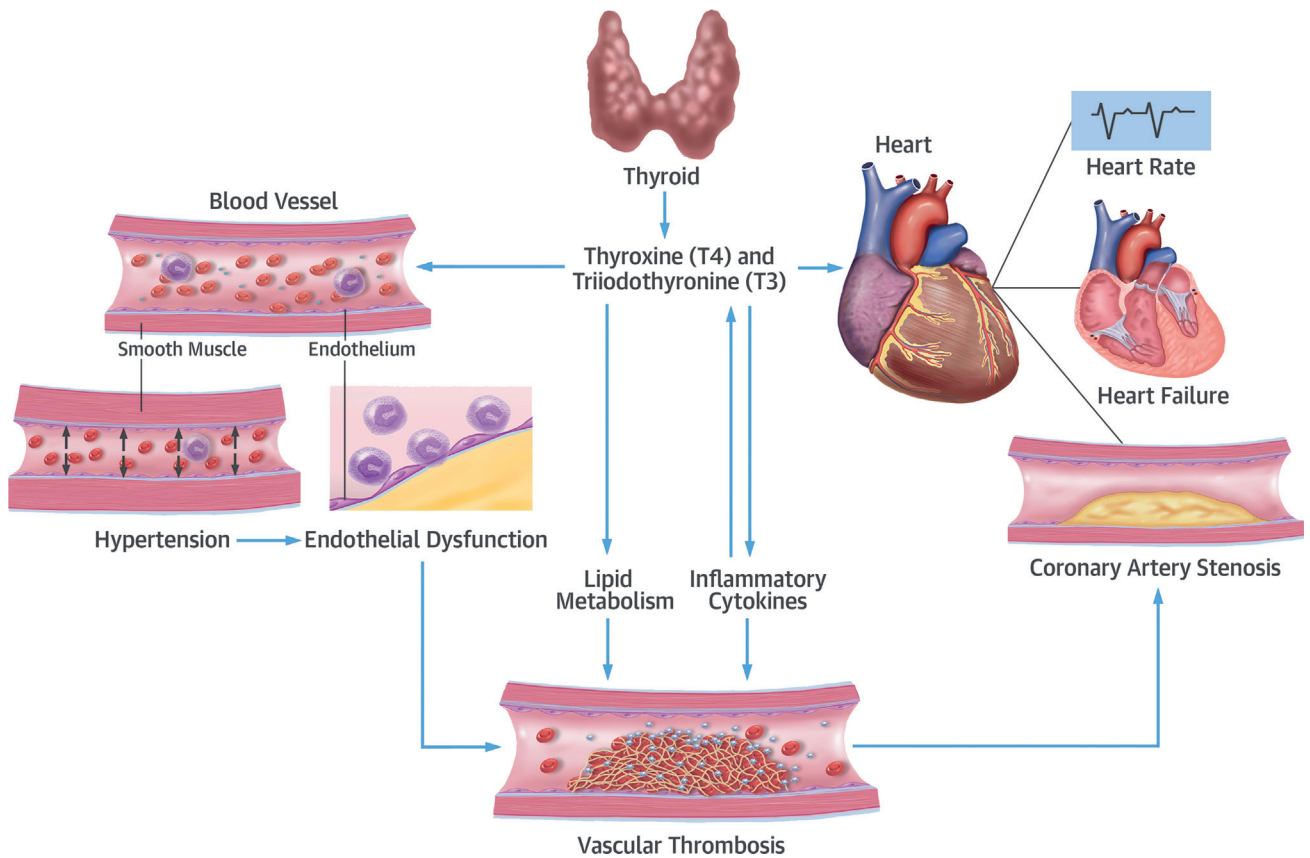
**TH ACTION ON CARDIAC MYOCYTES.** Genomic effects of TH are mediated by TH nuclear receptors located in the intracellular compartment. The protein receptors bind T<sub>3</sub> with greater (>10×) affinity than T<sub>4</sub> (8). In mammals, these receptor proteins exist in 2 isoforms, α and β (TRα and TRβ), and bind to TH response elements in the promoter regions of TH-responsive genes. TRα and TRβ activate expression of positively regulated genes in the presence of T<sub>3</sub> and repress expression in its absence. The TRα1 isoform has been shown to play an important role in the regulation of cardiac genes (Figure 1). A list of cardiac genes regulated by TH can be found in Table 1.

The contractile apparatus of the cardiac myocyte contains the myosin heavy chains (MHCs), α and β (α-MHC and β-MHC). α-MHC, the fast myosin, and β-MHC, the slow myosin, are positively and negatively regulated by T<sub>3</sub>, respectively. Cardiac contractility is further regulated by several important cardiac proteins, including the sarcoplasmic reticulum calcium adenosine triphosphatase (SERCA2) and its inhibiting counterpart phospholamban (PLB). SERCA2 functions to pump calcium ions (Ca<sup>2+</sup>) back into the sarcoplasmic reticulum in the relaxation phase of myofilament contraction. SERCA2 is positively regulated by T<sub>3</sub>, whereas PLB is negatively regulated. Together, they are responsible for the kinetics of calcium ion influx into (and subsequent efflux from) the sarcoplasmic reticulum. Efficient calcium sequestration and release is essential for energetically optimal cardiac myocyte relaxation and contraction. This lusitropic effect of TH is a characteristic of T<sub>3</sub> regulation of myocyte contractility (9). Decreased calcium cycling in the cardiac myocyte has been reported in the impaired diastolic function of hypothyroidism, with aging in humans, and in experimental models of HF. Other important cardiac genes regulated by TH include those encoding the TR proteins themselves, the voltage-gated potassium ion (K<sup>+</sup>) channels (Kv1.5 and Kv4.2), and the sodium/calcium ion (Na<sup>+</sup>/Ca<sup>2+</sup>) exchanger (NCX1).

In addition to the genomic effects of T<sub>3</sub> described previously, TH (both T<sub>4</sub> and T<sub>3</sub>) exert nongenomic effects on the cardiac myocyte and, as discussed later, on the vasculature. Nongenomic effects are usually receptor-independent and largely occur at the plasma membrane, regulating ion transporter activity (10). Nongenomic mechanisms are identified by their rapid rate of action. Several ion channels that are transcriptionally regulated by TH are also post-translationally regulated by nongenomic mechanisms. These combined mechanisms at the level of the atrial myocyte are responsible, in part, for the ability of T<sub>3</sub> to increase the heart rate. The other pathway mediating the chronotropic effect of thyrotoxicosis relates to the decrease in vagal tone and enhanced adrenergic tone characteristic of hyperthyroidism (11).

Unlike steroid hormones, T<sub>3</sub> is not lipid-soluble and must be transported into the cytoplasm of TH-responsive cells. Several families of TH transporters have been identified, including the Na<sup>+</sup>-taurocholate cotransporting polypeptides, the Na<sup>+</sup>-independent organic anion transporting polypeptides, the heterodimeric L-type amino acid transporters, and, perhaps most importantly, the monocarboxylate transporters (MCTs) 8 and 10, which are highly specific for

**CENTRAL ILLUSTRATION** The Interactions Between Thyroid Hormones and the Cardiovascular System



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Thyroid hormones (TH) have a complex relationship with the cardiovascular system through multiple mechanisms. The main effects of thyroid hormones are observed on the heart (by influencing rate, rhythm, myocardial contraction, and risk of coronary artery disease), the vascular tree (through regulating blood pressure via smooth muscle tone and endothelial function), and by direct effects on cardiovascular risk factors (via lipid metabolism and modulation of inflammatory pathways).

iodothyronines. MCT8 and 10 are expressed in the rodent heart, but it is unclear whether they have a role in the human heart. In humans, MCT8 mutations are the cause of Allan-Herndon-Dudley syndrome, an X-linked syndrome with specific thyroid and neurological defects, and heart rate abnormalities, thus suggesting a role for MCT8 in TH transport in human cardiac tissues. MCT10 has a greater affinity for  $T_3$  than  $T_4$ , and an even greater capacity to transport  $T_3$  than MCT8 (12). The cardiac myocyte TH-responsive genes are expressed as a function of serum  $T_3$ , and not  $T_4$ , implying that  $T_4$  is neither transported across the myocyte sarcolemma nor deiodinated into  $T_3$ . Therefore, optimal myocyte gene expression remains dependent on serum  $T_3$  levels, and if they fall, despite the fact that TSH and  $T_4$  levels may be normal, the heart will express a hypothyroid phenotype.

**TH ACTION ON THE VASCULATURE.** TH effects on the vasculature include genomic and nongenomic mechanisms that occur at both the vascular smooth muscle and endothelial cell levels. Nongenomic, indirect effects of TH include ion channel activation ( $Na^+$ ,  $K^+$ ,  $Ca^{2+}$ ) and regulation of specific signal transduction pathways. Activation of phosphatidylinositol 3-kinase and serine/threonine protein kinase pathways cause the production of endothelial nitric oxide, leading to a reduction in systemic vascular resistance through its effects on vascular smooth muscle cells (6,13). Several studies have shown that TH regulates endothelial nitric oxide production and vascular tone, and that patients with hypothyroidism (both overt and subclinical) exhibit impaired endothelial function, which improves with TH replacement therapy (14-16). In addition,  $T_3$  can produce a vasodilatory effect within

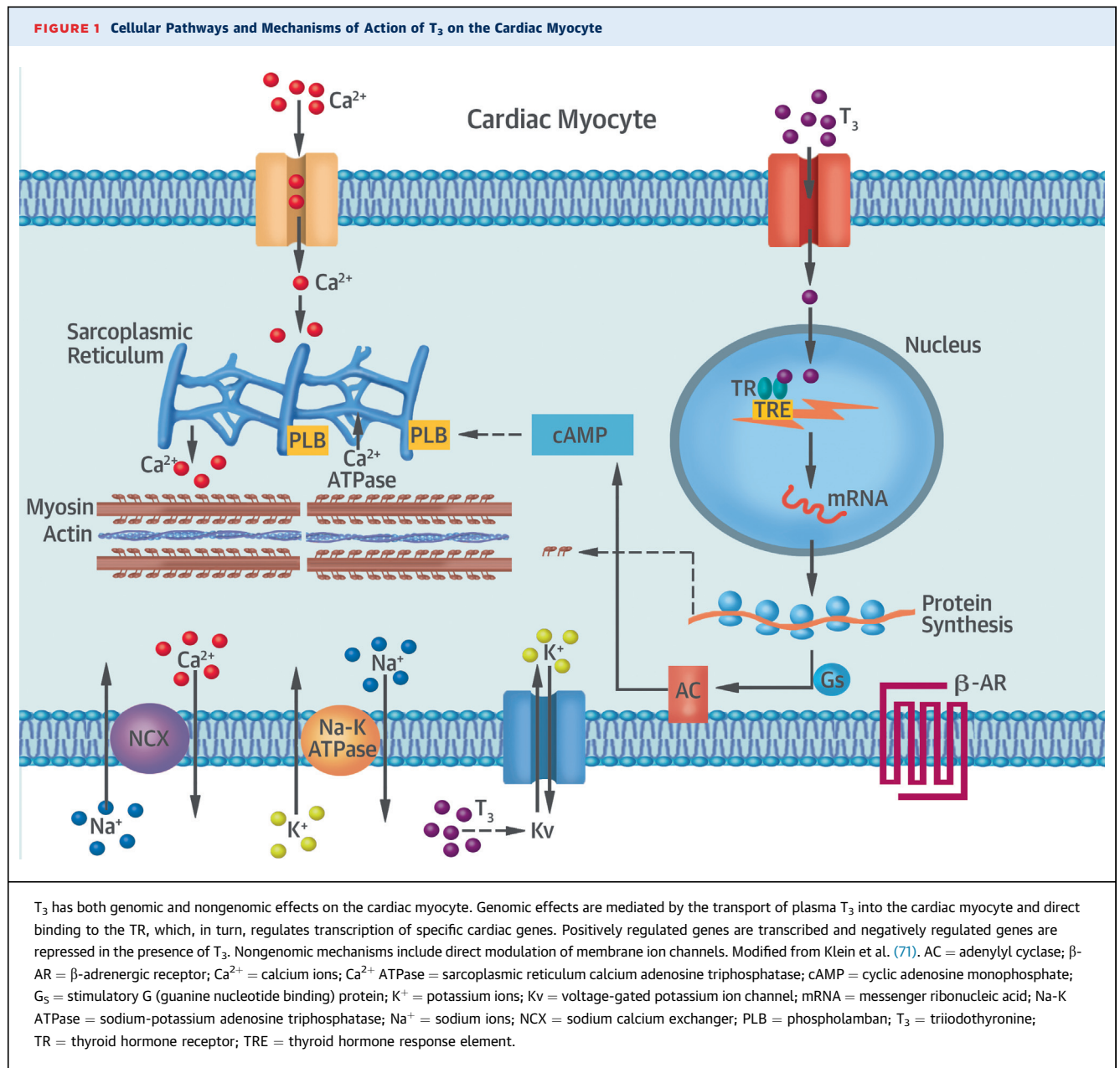
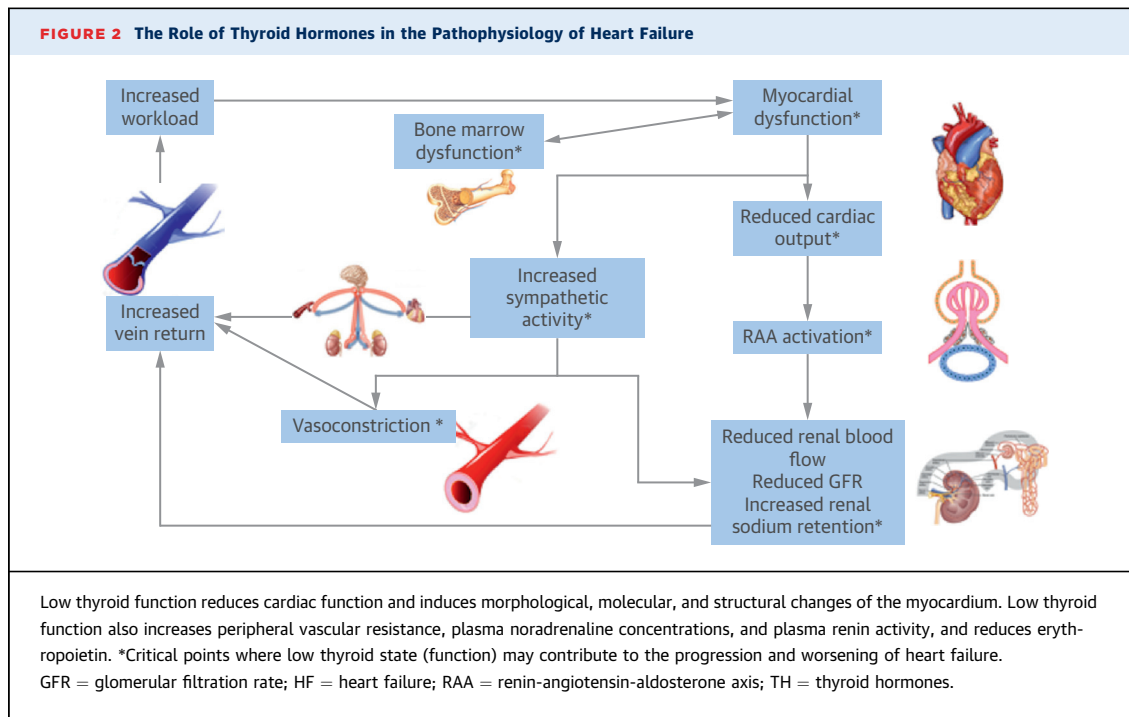


TABLE 1 T <sub>3</sub> -Regulated Cardiac Genes	
Positively Regulated	Negatively Regulated
α-MHC	β-MHC
Voltage-gated K <sup>+</sup> channels (Kv1.5, Kv4.2)	Na <sup>+</sup> /Ca <sup>2+</sup> exchanger (NCX1)
SERCA2	Phospholamban
Na <sup>+</sup> /K <sup>+</sup> ATPase	Adenylyl cyclase types V, VI
β1-adrenergic receptor	Thyroid hormone receptor α1
Adenine nucleotide translocase (ANT1)	Thyroid hormone transporters (MCT8, 10)

ATPase = adenosine triphosphatase; Ca<sup>2+</sup> = calcium; K<sup>+</sup> = potassium; Na<sup>+</sup> = sodium; MHC = myosin heavy chain; SERCA = sarcoplasmic reticulum adenosine triphosphatase; T<sub>3</sub> = triiodothyronine.

hours after administration to patients undergoing coronary artery bypass grafting (17). Similar effects are observed when patients with chronic HF are treated with intravenous T<sub>3</sub> (18). Thus, T<sub>3</sub> has the unique pharmacological properties of an inodilator acting primarily on diastolic dysfunction.

The pulmonary vasculature is not as responsive to the vasodilatory effects TH as is the systemic vasculature (19). Pulmonary artery hypertension that resolves after return to the euthyroid state has been reported in patients with thyrotoxicosis mainly due to a fall in cardiac output.



**TH AND CARDIOPROTECTION.** Cardioprotection is an emerging target of therapeutic intervention in AMI to minimize irreversible ischemic damage and favor functional recovery of the ischemic-damaged myocardium (20). THs have a role in cardioprotection due to activation of cytoprotective mechanisms, stimulation of cell growth, neo-angiogenesis, and metabolic adaptation. The net result, as documented by histological and functional parameters, is a reduction in myocardial damage and positive reverse left ventricular (LV) remodeling, resulting in a delay, or even absence, of evolution toward post-ischemic irreversible HF. Recent experimental studies using the ischemia/reperfusion rat model showed multiple protective effects of TH, particularly on mitochondria. TH is a regulator of the tumor suppressor p53, which is activated during AMI, enhancing the mitochondrial apoptosis pathway (21). p53 expression, in turn, is blunted by microRNA 30a (miR-30a), which is down-regulated in the post-ischemic setting. This favors p53 accumulation, and therefore enhances mitochondrial dysfunction and bcl-2-like protein 4 activation, resulting in extended myocardial cell loss (22). T<sub>3</sub> treatment counteracts the decrease in miR-30a levels, thus limiting the activation of p53 and the cascade leading to mitochondrial injury and cell death in the AMI border zone (23). This finding is relevant because, in patients with post-ischemic HF, p53-responsive microRNA (miR-192, miR-194, and

miR-34a) levels are elevated in the early phase of AMI and are positively correlated with LV diastolic dimension (24). Moreover, T<sub>3</sub> mitochondrial protection is also exerted through other pathways, including mitochondrial adenosine triphosphate-dependent potassium pathway, peroxisome proliferator-activated receptor gamma coactivator 1-alpha, and the mitochondrial transcription factor A (25). These are key intracellular signals controlling mitochondrial activity and biogenesis, and their overexpression limits post-ischemic LV remodeling and impairment of cardiac performance. Furthermore, T<sub>3</sub> treatment preserves the expression of hypoxia-inducible factor 1-alpha, whose protective effect against reperfusion injury is mediated by inhibiting the mitochondrial opening of the permeability transition pore (26).

In the context of HF, THs have a cardioprotective role through multifaceted direct or indirect actions at the level of the myocytes, the interstitium, and the vasculature (Figure 2) (6). THs have an antiapoptotic effect on myocytes via activation of the phosphatidylinositol 3-kinase/serine/threonine protein kinase and protein kinase C signaling cascades, the expression, phosphorylation, and translocation of heat shock proteins 70 and 27, and the suppression of p38 mitogen-activated protein kinase signaling (27). In addition, TH treatment reduces interstitial fibrosis in animal models of ischemic and nonischemic HF, and this effect can be partially related to the influence of



**TABLE 2** Effect of Thyroid Dysfunction on CV Disease Risk Factors

	Overt Hyperthyroidism and Subclinical Hyperthyroidism	Overt Hypothyroidism and Subclinical Hypothyroidism
Lipid parameters	Mild reduction	Increased total cholesterol and LDL cholesterol
Hypertension	Systolic hypertension Wide pulse pressure	Diastolic hypertension
Endothelial dysfunction	Excessive endothelial NO production and exaggerated vascular reactivity Increased arterial stiffness and carotid intima-media thickness in longstanding untreated disease	Impaired endothelial dependent vasodilation Increased arterial stiffness
Thrombogenicity	Increased fibrinogen and vWF in overt disease	Unclear
Cardiac function	Increased risk of atrial arrhythmias Increased atrial size, LV mass, and impaired diastolic function in longstanding untreated disease	LV systolic and diastolic dysfunction at rest and during exercise

CV = cardiovascular; LDL = low-density lipoprotein; LV = left ventricular; NO = nitric oxide; vWF = von Willebrand factor.

TH on the activity of metalloproteinases and their inhibitors (28). Furthermore, the antifibrotic effect of TH is also linked to the T<sub>3</sub>-induced inhibition of profibrotic pathways, (29), and is supported by the association of low serum T<sub>3</sub> levels with the presence of cardiac fibrosis in patients with idiopathic dilated cardiomyopathy (30).

### THYROID DISEASE AND CV RISK FACTORS

**TH AND HYPERLIPIDEMIA.** Hyperthyroidism reduces cholesterol levels, which are reversed when euthyroidism is achieved. Hypothyroidism is associated with a small but significant increase in lipid parameters (31), in particular, an elevation of low-density lipoproteins (LDLs) (32). Hypothyroidism is associated with increased oxidation of LDL, which promotes atherogenesis and reverses with treatment (33,34). Lipoprotein(a), a more potent marker of atherogenesis, also increases in overt hypothyroidism and decreases with TH replacement (35,36).

The effect of subclinical hypothyroidism (SCH) on hyperlipidemia is less clear (37-39). Hyperlipidemia in hypothyroidism is due to a decrease in LDL receptors, resulting in reduced cholesterol clearance from the liver and decreased activity of cholesterol 7 $\alpha$ -hydroxylase, which is activated by TH, in breaking down cholesterol (32). A Cochrane review of 6 RCTs concluded that levothyroxine treatment of SCH had no overall effect in reducing total cholesterol, but suggested a trend toward reducing LDL cholesterol (LDL-C) levels >155 mg/dl in a subgroup analysis (40). Two subsequent trials suggested that the reduction of LDL-C was approximately 0.3 mmol/l (11.6 mg/dl)

(16,41). Thus, an association, if present, is likely to be weak, with SCH contributing to a small increase in serum LDL-C, ranging between 3 and 15 mg/dl (0.1 to 0.4 mmol/l) (42). This could, in theory, contribute to the high risk of CV disease observed in this population (Table 2).

### TH, VASCULATURE, AND BLOOD PRESSURE.

Hyperthyroidism causes a hyperdynamic circulation, characterized by increased cardiac contractility and heart rate, increased preload, and decreased systemic vascular resistance (SVR), resulting in significantly increased cardiac output. Although hyperthyroidism can increase systolic blood pressure, the net effect is dependent on the balance between increased cardiac output and decreased SVR (43,44). The relationship between subclinical hyperthyroidism (SHyper) and blood pressure is less clear, with most published studies showing no association (45-47). Furthermore, some studies have shown SHyper patients to have increased carotid intima-media thickness and carotid artery plaques (48,49), although this was not confirmed in a recent large, population-based study (50).

Overt and SCH are associated with diastolic hypertension, impaired vascular function, and increased carotid intima hyperplasia (45,47). Endothelial-dependent vasodilation is lower in overtly hypothyroid and SCH patients (51), and improves with levothyroxine treatment (15,16), as does pulse wave velocity, a surrogate measure of arterial stiffness (52,53).

Several factors could likely contribute to arterial stiffness and endothelial dysfunction in SCH and hypothyroidism, including hyperlipidemia and a proinflammatory state (54-56). Thus, in the Rotterdam Study, aortic calcification and the prevalence of myocardial infarction was higher in patients with SCH who were positive for thyroid autoantibodies than in those with SCH alone (57). Both hyperlipidemia and thyroid antibodies are thought to reduce expression of endothelial nitric oxide synthase, thereby impairing vasodilation (15). In addition, increased arterial stiffness and a low renin state are contributory factors leading to blood pressure and vascular dysregulation due to the lack of the normal vasodilatory effects of T<sub>3</sub> (4,43) (Table 2).

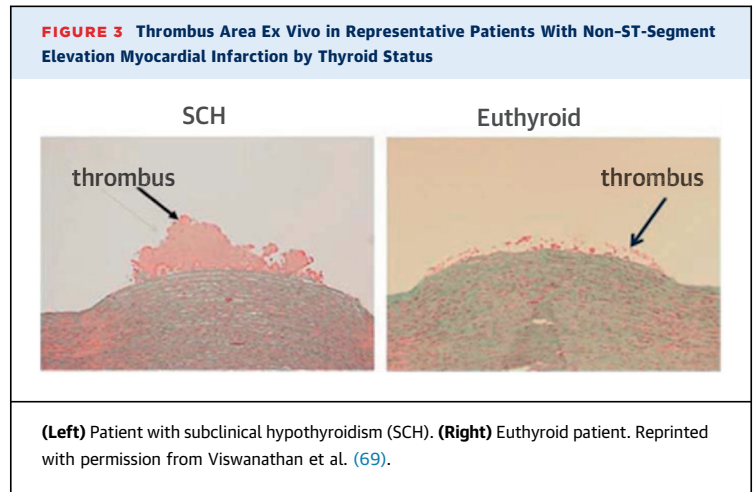
**TH AND THROMBOGENESIS.** Overt and SHyper have been associated with increased markers of thrombogenesis (fibrinogen and factor X levels) (58,59). Hyperthyroid patients may also have higher von Willebrand antigen levels compared with euthyroid patients, leading to enhanced platelet plug formation, which decreases after treatment (60). The relevance of these findings is uncertain, although a

review of published case reports in hyperthyroidism suggests a tendency toward increased overall thrombosis (61). The increased cerebral thrombosis and cerebrovascular events in overt hyperthyroidism warrant further scrutiny to investigate if such events are due to increased thrombosis, related to alterations in the vascular tree (increased carotid intima-media thickness), or due to a higher risk of atrial fibrillation (AF) (49).

Studies investigating coagulation in overt hyperthyroidism have yielded conflicting results, with 2 studies showing hypercoagulability (62,63) and 1 study showing increased fibrinolysis (64). Interestingly, a study comparing moderate and severely hypothyroid patients with euthyroid controls found that patients with moderate hypothyroidism had decreased fibrinolytic activity and were more susceptible to clot formation, whereas patients with severe hypothyroidism had increased fibrinolysis and lower tissue plasminogen activator antigen (65). In SCH, factor VII activity and the factor VII activity-to-factor VII antigen ratio were significantly increased in women with SCH compared with controls (66). Another study showed decreased antithrombin III activity and increased levels of fibrinogen, factor VII, and plasminogen activator inhibitor antigen in SCH patients to explain a potential hypercoagulable state (67). This is further supported by a study that found lower global fibrinolytic activity, such as tissue plasminogen activator, in SCH patients than in euthyroid controls (68). The effects of TH on platelet function are unclear (60). A study using the Badimon chamber, a surrogate ex vivo model of plaque rupture in a moderately stenosed coronary artery, showed increased thrombus in patients with SCH 7 to 10 days post-non-ST-segment elevation myocardial infarction compared with euthyroid patients, despite dual antiplatelet therapy (69) (Figure 3). This heightened thrombogenic state may, in part, explain the higher CV risk seen in patients with SCH. In summary, both TH deficiency and excess can alter the coagulation pathway, although the precise clinical relevance of this finding is unclear (Table 2).

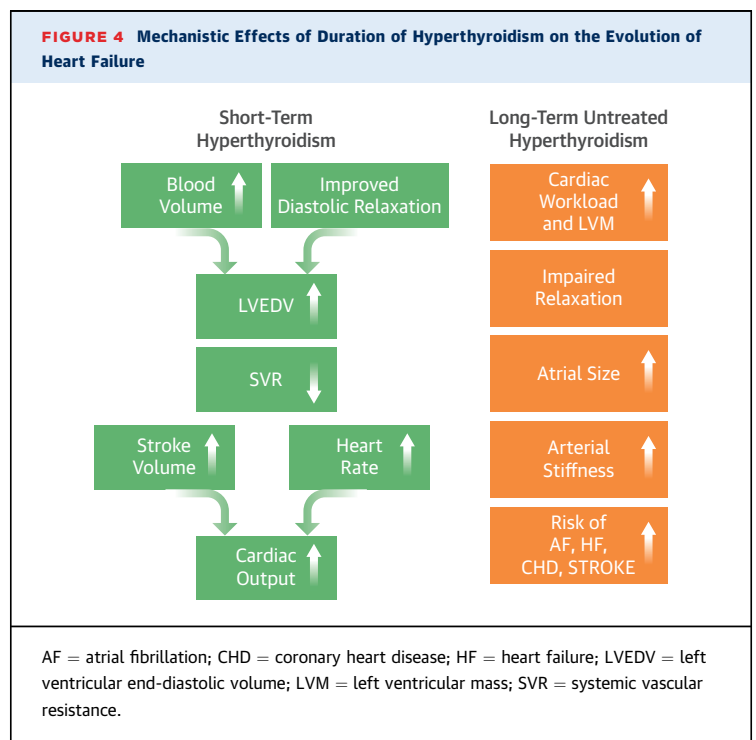
### CARDIOVASCULAR CONSEQUENCES OF OVERT HYPERTHYROIDISM AND SHYPER

Hyperthyroidism is a clinical condition characterized by TH excess, commonly due to Graves' disease, toxic adenoma, and toxic multinodular goiter (70). TH excess increases cardiac output by affecting stroke volume and heart rate (6,71). Echocardiographic data indicate that short-term hyperthyroidism induces positive CV changes by improving LV systolic



function and enhancing LV relaxation (diastolic flow velocities and isovolumic relaxation time) (72). However, despite the high cardiac output state, hyperthyroid patients have impaired cardiopulmonary function during effort, reflecting their reduced CV and respiratory reserve during exercise (70).

Untreated hyperthyroidism is associated with increased CV morbidity and mortality (73). Overt hyperthyroidism has been associated with 16% increased risk of major CV events, mainly due to higher incidence of HF events (74). Severe hyperthyroidism may induce so-called high-output HF, even in patients without underlying heart disease.



This congestive circulation results from the increases in blood volume and heart rate, and the associated pulmonary arterial hypertension (Figure 4). Clinical features of this condition are pleural effusion, hepatic congestion, and fluid retention, which can improve with diuretic agents and beta-blockers (75).

Hyperthyroidism is linked to increased supraventricular ectopic activity (76). The onset of AF may increase CV morbidity and mortality, resulting from severe HF and stroke (75). T<sub>3</sub> increases systolic depolarization and diastolic repolarization, and decreases the action potential duration, the refractory period of the atrial myocardium, and the atrial/ventricular nodal refractory period. The reduced interatrial action potential duration facilitates the occurrence of AF by enhancing the spreading of ectopic activity from the left atrium (76). Experimental studies have shown that TH excess can provoke the occurrence of paroxysmal AF by increasing triggered activity in pulmonary veins (76). Approximately 13% of patients with new-onset AF have biochemical evidence of hyperthyroidism, whereas AF is noted in 10% to 15% of patients with hyperthyroidism (compared with 0.5% of the general population). The main risk factors for the development of AF in hyperthyroid patients are increasing age, ischemic heart disease, congestive HF, or heart valve disease (77). The risk of ischemic stroke is enhanced by 44% in adults with hyperthyroidism compared with euthyroid controls (78). Advanced age and the presence of associated CV risk factors (history of HF, hypertension, or diabetes mellitus, previous thromboembolism, left atrial enlargement, and LV dysfunction) can further elevate the embolic risk (70). Despite the evidence of the increased rate of stroke, no trials have been performed to assess the risk-benefit ratio of the efficacy of anticoagulation treatment in patients with AF and hyperthyroidism. Patients with severe hyperthyroidism may have coronary vasospasm leading to chest pain at rest or myocardial ischemia (6,70,71,79). Mild and usually asymptomatic pulmonary arterial hypertension has been reported, especially in autoimmune hyperthyroidism, with an incidence ranging from 36% to 65% in echocardiographic studies (80).

Prompt recognition and effective treatment of hyperthyroidism is crucial to improve the prognosis of hyperthyroid patients (81-83). Antithyroid drugs and beta-blockers represent the first-line therapy to control CV involvement of overt hyperthyroidism by restoring euthyroidism and controlling the heart rate (82).

SHyper, affecting up to 1% of the iodine-replete and up to 10% of the iodine-deficient adult

population, is diagnosed when the serum TSH level is persistently subnormal with concomitant free TH levels at the upper limits of their respective reference intervals (4). It can be further classified as grade 1 (low, but detectable serum TSH levels [e.g., TSH 0.1 to 0.39 mU/l]) or grade 2 (suppressed serum TSH levels < 0.1 mU/l) (4). Similar to overt hyperthyroidism, patients with SHyper may have an increased risk of AF, HF, and CV disease. The Thyroid Studies Collaboration, an international consortium, assessed individual participant data from prospective cohort studies to estimate the risk of HF and coronary heart disease (CHD) during median follow-ups of 10.4 and 7 years, respectively (84,85). In age- and sex-adjusted analyses, these risks were significantly higher in participants with grade 2 SHyper (hazard ratio [HR]: 1.94; 95% confidence interval [CI]: 1.01 to 3.72 for HF; HR: 1.21; 95% CI: 0.99 to 1.46 for CHD events; and HR: 1.29; 95% CI: 1.02 to 1.62 for CHD mortality) than in those with grade 1 SHyper. Moreover, grade 2 SHyper was associated with a higher risk of developing AF (HR: 2.54; 95% CI: 1.08 to 5.99) than grade 1 SHyper (HR: 1.63; 95% CI: 1.10 to 2.41) (85). The attributable risk for AF was 41.5% in these patients, and it was not altered by the presence of existing CV disease or other CV risk factors (85). Interestingly, the risk of AF, sudden cardiac death, and reduced life expectancy have been noted to be related to higher free T<sub>4</sub> levels, even within the euthyroid range, in 1 prospective study of middle-aged and older people from Rotterdam (86). Conflicting results have been reported on the association between SHyper and stroke. A meta-analysis of 6 studies did not find any evidence supporting an increased risk of stroke in participants with SHyper (87). Similarly, a Danish population study did not find any link between the risk of stroke and overt, mild, and severe hyperthyroidism after stratifying the analysis according to TSH levels (74).

Management of SHyper should include control of thyroid function and prevention of CV complications. International guidelines strongly recommend treatment of grade 2 SHyper (TSH < 0.1 mU/l) in patients older than 65 years of age and in younger patients with comorbidities (81,82). They also recommend treatment of grade 1 SHyper in patients older than 65 years of age in the presence of CV risk factors or complications, although this recommendation is weak because of low-quality evidence (81,82). Treatment of grade 1 SHyper is not recommended in young adults.

#### CV CONSEQUENCES OF OVERT AND SCH

Overt hypothyroidism is diagnosed when serum TSH is elevated and circulating THs are low and is



**TABLE 3 Causes of Hypothyroidism, Including Subclinical Hypothyroidism**

Autoimmune disease	Hashimoto's autoimmune thyroiditis, TSH receptor-blocking antibodies
Structural	Thyroid damage due to thyroidectomy or radiation (radioactive iodine therapy or external radiotherapy of head and neck)
Release of preformed TH	Post-thyroiditis state
Pituitary disease	Secondary hypothyroidism due to TSH deficiency
Drugs	Antithyroid drugs, lithium, amiodarone, tyrosine kinase inhibitors, interferon therapy, radiographic contrast agents, sulfonamides
Thyroid infiltration	Amyloidosis, hemochromatosis, acquired immunodeficiency syndrome, sarcoidosis, Riedel's thyroiditis
Other	Inadequate TH replacement or noncompliance for overt hypothyroidism, industrial and environmental agents.

TH = thyroid hormone; TSH = thyrotropin.

prevalent in 0.2% to 2% of nonpregnant adults (31,37). The causes of hypothyroidism are described in Table 3. Overt hypothyroidism has several cardiac manifestations, including a reduction in cardiac output, a decrease in heart rate, and an increase in peripheral vascular resistance and diastolic dysfunction (71). There are also significant changes in modifiable atherosclerotic risk factors, including hypercholesterolemia, diastolic hypertension, increased carotid intimal-media thickness, and reduced endothelial nitric oxide, which accompany overt hypothyroidism. All these clinical features are reversible with TH replacement (88).

SCH is diagnosed when serum THs are within their reference range in the presence of raised serum TSH concentrations. SCH can be classified as grade 1 (TSH >4.0 or 4.5, but <10 mU/l) or grade 2 (TSH >10 mU/l). In fact, most (at least 80%) patients with hypothyroidism have SCH (31). However, there is a lack of consensus on what constitutes the “normal” upper limit of TSH leading to controversy on definition, prevalence and clinical significance of SCH (89). The stated prevalence of SCH in published reports ranges from 4% to 10% of the adult population, being more common in women and older individuals (31,37). This wide range reflects that a variety of factors can influence serum TSH levels such as age, sex, body mass index, race, smoking habits, iodine intake, time of sampling, concomitant medical conditions and treatments, plus the cutoff concentrations of serum TSH used to define the condition.

The most frequent cardiac abnormality observed in SCH is diastolic dysfunction due to impaired

ventricular filling and relaxation (90,91). SCH can also impair relaxation of vascular smooth muscle cells, inducing increases in systemic vascular resistance and arterial stiffness, as well as changes in endothelial function by reduction of nitric oxide availability, without apparent clinical significance (92). Population studies support these findings, with the Whickham Survey cohort revealing higher systolic and diastolic blood pressures and total cholesterol concentrations in SCH individuals than in euthyroid controls (93), and the EPIC-Norfolk (European Prospective Investigation of Cancer, Norfolk) study reporting a worse CV risk factor profile (94).

There is conflicting evidence from population studies about the association of SCH with CV disease and mortality. A number of observational studies of community-dwelling individuals have shown an increased risk for CV disease (56,95-97). In addition, SCH after admission for an acute cardiac problem has been associated with an up to 3.6-fold increase in cardiac mortality and a 2.3-fold increase in overall death (98). However, this relationship has not been confirmed in all studies (94,99,100). This discrepancy in results between the various cohorts is likely due to differences in the underlying populations studied and the study design. One of the major factors that influences CV risk in SCH populations is age, and several observations have concluded that older individuals with SCH may have a lower risk of CV disease than younger ones (101). Furthermore, a retrospective observational study showed that treatment of SCH with levothyroxine was associated with fewer ischemic heart disease events in younger individuals, but this was not evident in older people (102). In addition, several studies of older patients have shown SCH to have either a protective or no impact on CV disease risk (103-105). A patient-level meta-analysis of several prospective cohort studies, providing 542,494 person-years of follow-up, showed that SCH is associated with a higher risk of CV events and mortality in people with higher serum TSH levels, particularly in those with TSH levels >10 mU/l, irrespective of age (21).

Despite the known CV risks associated with SCH, high-quality evidence for treatment is lacking, mainly as current data is derived from observational studies or small interventional trials with cardiac risk factor changes as outcomes. Trials of levothyroxine in SCH using surrogate markers have shown improvement in LV function, vascular endothelial function, atherogenic lipid particles, or cardiac mitochondrial function (4,91,105-108).

RCTs are needed to evaluate the clinical benefits and safety of treatment of SCH in reducing CV risk. Meanwhile, international guidelines suggest that

treatment should only be considered in those with more severe disease (serum TSH >10 mU/l), symptoms of hypothyroidism, or younger than 70 years of age, particularly if they also have other CV risk factors (109).

### INTERPLAY BETWEEN NONTHYROIDAL ILLNESS AND CV DISEASE

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A few hours after the onset of acute illness, marked changes in serum TH levels occur. This is referred to as nonthyroidal illness (NTI). A decrease in  $T_3$  and increase in reverse  $T_3$  ( $rT_3$ ) are the most characteristic and persistent abnormalities of NTI. In severely ill patients,  $T_4$  levels drop as well. Both low  $T_4$  and  $T_3$  levels, as well as high  $rT_3$  levels are associated with a worse prognosis. TSH levels may rise briefly after the onset of disease, but despite the drop in serum  $T_3$  (and in severe illness also  $T_4$ ) levels, circulating TSH usually remains within the low to normal range. Decreased activation and increased inactivation of TH are the major causes of these changes in the acute phase of NTI, whereas an altered feedback setting at the hypothalamus-pituitary level is more important in the chronic phase of severe illness. As low levels of TH are associated with a decreased metabolic rate, the changes in TH homeostasis during the acute phase of NTI have been interpreted as an attempt to save energy expenditure, which does not require any intervention. However, this remains controversial, has been a debate for many years, and may be different in the acute and chronic phases of illness (110,111).

Similar changes occur in patients with CV disease (CVD). NTI occurs in 15% to 20% of patients with AMI (112,113). A rapid but transient decrease in serum TH concentrations occurs immediately after AMI (114), with maximal changes between 24 h and 36 h after the onset of pain. These changes are due to increased inactivation of TH by the inactivating enzyme deiodinase 3 (D3) and decreased activation by D1 and D2 activity (115,116) (Figure 5). Although a reduction in oxygen consumption by lowering TH levels during acute ischemia could be considered beneficial, the net effect of lower TH levels in the heart may still be detrimental because of its important role in post-ischemic LV remodeling, maintaining CV function and mitochondrial integrity (6). As in patients with other chronic illnesses, NTI is also very common in patients with HF, with a prevalence of approximately 20% to 30% (117). Although these changes may, in part, be due to the illness in general, animal studies provide convincing evidence for additional, specific down-regulation of local TH action in CV disease. This

was first shown in a rat model of right ventricular (RV) hypertrophy and failure, where D3 activity increased in the chronically overloaded RV, with no change of activity in the LVs of the same hearts (116). D3 activity in the RV of rats with HF was significantly higher than that in the RV of rats with hypertrophy alone. Follow-up studies in a post-AMI model in mice showed a strong and stable induction of D3 activity in the remodeling ventricle from 1 week to at least 8 weeks after AMI (118), and studies in rats have shown that the acute decrease in serum  $T_4$  and  $T_3$  after AMI is mediated by the induction of D3 activity in the heart (115). The induction of D3 is localized in cardiomyocytes only and is associated with a substantial decrease in tissue  $T_3$  concentrations and  $T_3$ -dependent gene expression (118). This change in  $T_3$ -dependent gene expression was independent of the circulating  $T_3$  concentration in mice, showing that pathological ventricular remodeling after AMI leads to high and stable induction of D3 activity in cardiomyocytes, resulting in a subsequent local hypothyroid condition. Whether this local hypothyroidism inside the myocardium in patients with HF is beneficial or harmful is unclear.

Similar to critical illness in general, lower circulating levels of  $T_3$  in patients with AMI are associated with a more severe clinical condition and with poorer clinical outcome (119,120), particularly in patients with LV dysfunction, large AMI, and intense proinflammatory and stress responses (121,122). This is not only the case in the acute setting, but also in the longer term after recovery from AMI. Low  $T_3$  and high  $rT_3$  levels at the time of AMI are an independent predictor of both short-term and long-term mortality (120), and lower  $T_3$  levels after AMI are an independent predictor of late recovery of LV function after 6 months (123). Also, in patients with chronic HF, NTI has been associated with a worse prognosis (96,124,125). However, considering the strong effects of disease in general on thyroid function, it is impossible to distinguish between cause and consequence in these clinical observational studies. Interestingly, ameliorating oxidative stress with antioxidants prevents the acute reduction of serum  $T_3$  levels in patients with AMI, although it is unknown if this has any effect on cardiac function or outcomes (126).

### TH IN AMI AND ISCHEMIA REPERFUSION INJURY

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Low  $T_3$  syndrome (an isolated reduction of serum  $T_3$  levels with normal  $T_4$  and TSH concentrations) after AMI is observed in up to 1 in 5 patients (114), whereas SCH is observed in almost 12% (127).  $T_3$  down-

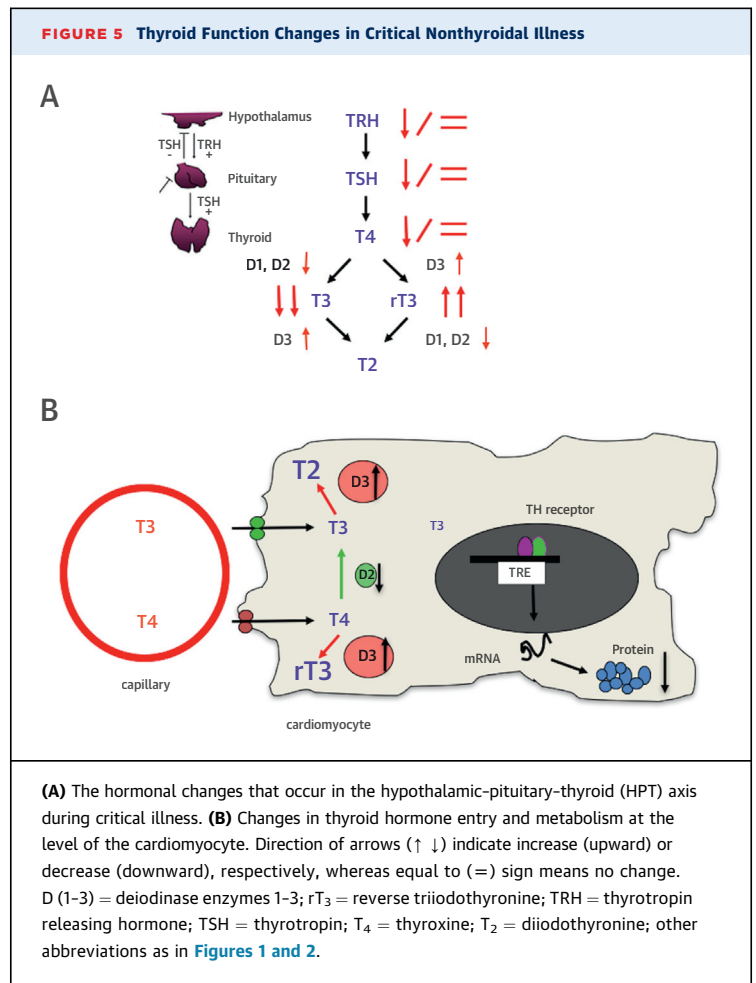
regulation is consistent with experimental data showing that changes in circulating TH parameters after AMI are a result of increased D3 activity and reduced D1 and D2 activity (115). Convincing data show that TH metabolism abnormalities occurring during early stage of AMI are associated with increased incidence of cardiac events. The degree of TH down-regulation is associated with higher impairment of cardiac function and higher inflammatory response (114,121).

The increase in rT<sub>3</sub>, the inactive TH metabolite, is a predictor of both short- and long-term mortality independent of other traditional parameters (120). Similarly, in 501 patients with AMI (of whom 34% had low T<sub>3</sub> syndrome), the rate of major cardiac events at follow-up was higher in those with low free triiodothyronine (FT<sub>3</sub>) levels than in those with preserved FT<sub>3</sub> circulating levels, and, importantly, FT<sub>3</sub> was the most important predictor of subsequent cardiac events (119). In another study of 457 AMI patients, thyroid dysfunction including SCH, SHyper, and low T<sub>3</sub> syndrome was associated with higher incidence of major cardiac events (112). Furthermore, in patients with AMI and early reperfusion therapy, T<sub>3</sub> circulating levels correlated with LV ejection fraction both at the early, in-hospital phase and at the 6-month follow-up visit. Interestingly, T<sub>3</sub> at 6 months was an independent predictor of LV ejection fraction changes between the early and follow-up periods (123). However, pathophysiological and therapeutic relevance of the thyroid dysregulation after AMI are far from elucidated. No interventional studies of TH replacement in AMI patients have been published to date, therefore making a causal relationship between thyroid dysfunction and outcomes difficult to ascertain.

Overall, the experimental and observational findings mentioned previously are in contrast to the common interpretation that TH down-regulation after AMI is an adaptive, favorable process that helps in reducing catabolism and energy expenditure (128), and suggests the potential critical role of the thyroid system in cardioprotection in AMI. Future research to better understand the interaction between acute TH changes and cardiac ischemia, particularly ischemia-reperfusion injury, and whether normalizing thyroid function parameters may have a role, is required.

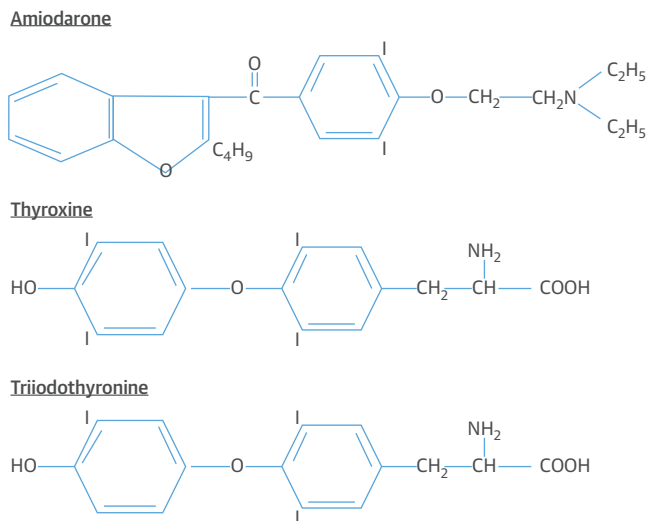
### TH IN HF

In the clinical setting, the most frequent alteration of TH metabolism is the low T<sub>3</sub> syndrome that occurs in 15% to 30% of patients with HF, with the incidence changing in relation to the clinical severity of the disease. SCH and SHyper, in contrast, occur in 6% and 3%



of HF patients, respectively (129). Serum T<sub>3</sub> levels may be an independent predictor of LV dysfunction and New York Heart Association functional class (130). Furthermore, in addition to conventional risk factors, TH metabolism alterations have been associated with a worse prognosis in patients with both ischemic and nonischemic LV dysfunction in both acute decompensated and chronic stable HF (131-133). In particular, patients with reduced LV ejection fraction and low T<sub>3</sub> have higher mortality than patients with similar LV ejection fractions, but normal T<sub>3</sub> (134). This result was also confirmed in a large multicenter cohort of patients with ischemic and nonischemic HF with severe LV dysfunction (LV ejection fraction ≤35%), in which abnormal TH function was associated with significantly increased risk for death (135).

There are a few clinical studies that used disparate methodologies to study the effects of TH replacement therapy in HF patients. However, the overall results showed an improvement in CV performance, induced by both direct and indirect actions. Moreover, there was also evidence of neuroendocrine system

**FIGURE 6** Structural Resemblance of Amiodarone to Thyroid Hormones T<sub>4</sub> and T<sub>3</sub>

There is a structural similarity between amiodarone and thyroid hormones, with each molecule of the drug containing 2 iodine atoms, whereas T<sub>4</sub> has 4 and T<sub>3</sub> has 3 iodine atoms. This structural likeness contributes, in part, to the effects of the drug on thyroid hormones and function.

inactivation, resulting from the significant reduction in vasoconstrictor/sodium-retaining noradrenaline, aldosterone, and N-terminal pro-B-type natriuretic peptide plasma levels (18). These positive results contrast with those of another study, which showed that oral T<sub>3</sub> treatment is not beneficial in patients with HF and moderate LV dysfunction (mean ejection fraction of 43%) (136). Therefore, these discordant results suggest that T<sub>3</sub> therapy may benefit only a subgroup of patients, and that the dose and modality of administration may influence its effectiveness. None of the interventional studies of TH in patients with HF revealed any major or minor side effects, and it was well-tolerated. In contrast, a trial of 3,5-diiodothyropropionic acid (DITPA), a TH analog, was stopped prematurely due to the occurrence of thyrotoxic side effects and a trend toward increased mortality, suggesting excess DITPA administration (137). These results underscore an important endpoint of TH treatment, which is to restore and maintain levels of circulating TH and TSH to within their respective reference ranges. Large multicenter trials documenting a definite role of TH treatment in HF are lacking. Considering that HF affects millions of individuals in the United States, and that TH therapy in a selected group may be safe and effective, TH could offer a clinically useful and cost-effective treatment if confirmed in large-scale trials.

## MODULATION OF TH LEVELS BY DRUGS AND ITS IMPACT ON CV SYSTEM

**AMIODARONE.** Amiodarone is a potent class III antiarrhythmic drug that also possesses beta-blocking properties. It is an iodinated derivative of benzofuran and is structurally similar to TH (Figure 6). Amiodarone contains iodine, and a 200-mg tablet contains 500 times more iodine than the average daily requirement (138). Both hyper- and hypothyroidism can occur with amiodarone therapy. Amiodarone-induced thyroid dysfunction occurs because of both its iodine content and its direct toxic effects on thyroid parenchyma. However, the majority of patients commenced on amiodarone (nearly 90%) remain euthyroid, at least in the short to medium term. The prevalence of amiodarone-induced hypothyroidism is between 5% and 22%, depending on iodine status, being more common in iodine-sufficient regions and in those with existing thyroid autoimmunity, and thus is more frequently observed in women. The management of amiodarone-induced hypothyroidism is similar to that for all other forms of the condition: levothyroxine replacement. If amiodarone therapy is discontinued, then levothyroxine treatment can be stopped after 2 to 4 months in individuals without pre-existing thyroid autoimmunity. Patients with underlying autoimmune thyroid disease may remain hypothyroid, and thus require lifelong levothyroxine treatment, even after amiodarone cessation. However, amiodarone-induced thyrotoxicosis (AIT) is seen in 2% to 12% of those treated with the drug and is more frequently observed in iodine-deficient areas. AIT is classified into 2 different categories based on the presence of underlying thyroid disease. Type 1 AIT occurs in those with pre-existing multinodular goiter or latent Graves' disease and is due to increased synthesis and release of TH. Type 2 AIT, conversely, is observed in those without any thyroid abnormalities and is due to destructive thyroiditis, leading to the release of pre-formed TH into the circulation. It is, however, common to have patients with a combination of both types of AIT coexisting. AIT can be a difficult condition to diagnose and treat. Management of AIT includes cessation of amiodarone, if possible (although its long half-life means that the effects could last for months after cessation), with further treatment depending on the underlying etiology. Type 1 AIT is usually treated with high doses of antithyroid drugs, whereas type 2 AIT is treated with corticosteroids.

**PROPRANOLOL.** Propranolol decreases circulating serum T<sub>3</sub> levels in a dose-dependent manner due to inhibition of the deiodinase enzymes (139). This effect is observed in hyperthyroid, euthyroid, and

levothyroxine-treated hypothyroid patients. Serum free T<sub>4</sub> and TSH levels remain unchanged. In a clinical context, propranolol is favored over other beta-blockers in the management of hyperthyroidism due to its nonselective β-blocking activity (to reduce systemic symptoms such as tremor and anxiety), membrane-stabilizing action, and reduction in serum T<sub>3</sub> levels (20% to 30%, depending on the dose).

**IODINE-CONTAINING CONTRAST DYES USED IN ANGIOGRAPHY.** As observed with amiodarone, excess amounts of iodine in any form can result in thyroid dysfunction, particularly in susceptible individuals. Iodinated contrast media, as used in coronary angiograms, contain at least 2,000 times more iodine (depending on the amount of contrast used) than the recommended daily allowance in the United States (140). This supraphysiological dose of iodine exposure has no major effects on thyroid function in most euthyroid individuals but may cause thyroid dysfunction (both hyper- and hypothyroidism) in susceptible groups. Data on the prevalence of thyroid dysfunction after coronary angiogram contrast exposure is sparse, and no guidelines exist. However, case-control studies suggest that iodinated contrast media exposure at least doubles the risk of subsequent overt hyperthyroidism and triples the risk of overt hypothyroidism (141).

## CONCLUSIONS

The CV system is a major target of TH action, and even subtle changes in thyroid function can lead to cardiac dysfunction. A number of experimental studies and observational clinical data in both hypo- and hyperthyroidism suggest that modulation of TH may be beneficial in reducing CV disease. However, high-quality evidence is required before this can be translated into clinical practice. Similarly, there is increasing evidence that changes in TH levels in otherwise euthyroid patients with CV disease (such as AMI or HF) may be a marker of poor prognosis, and clinical trials are required to see if TH therapy may be efficacious and safe. Clinical trials of TH therapy in AMI patients are underway and could provide evidence for or against their use in routine clinical care (142,143). These therapies, if proven, could provide cost-effective and widely available treatments to millions of patients worldwide.

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**KEY WORDS** acute myocardial infarction, amiodarone, heart failure, thyroxine, triiodothyronine