

Interplay between cardiovascular and thyroid dysfunctions: A review of clinical implications and management strategies

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Cardiovascular diseases (CVD) and thyroid dysfunction are two of the most prevailing disorders in the world that are closely interlinked. Actions of thyroid hormones are mediated via thyroid receptors present in the myocardium and the vascular tissue. Primary mechanism that links thyroid dysfunction with CVD is the modification of cardiovascular risk factors (dyslipidemia, blood pressure, coagulation parameters, etc.) resulting in endothelial and left ventricular systolic and diastolic dysfunction.

Both overt and subclinical hyperthyroidism and hypothyroidism may cause adverse alterations in cardiac function. Hyperthyroidism gives rise to palpitation, atrial fibrillation, systolic hypertension, and heart failure, whereas hypothyroidism increases diastolic hypertension, pericardial effusion, and the risk of ischemic heart disease via altering lipid and coagulation parameters. Early recognition and treatment of thyroid dysfunction may prevent adverse cardiovascular events in patients with or without pre-existing CVD.

Certain cardiac conditions and medications can cause alterations in thyroid function that may predispose an individual to higher morbidity and mortality. In certain situations, thyroid dysfunction treatment may have cardiovascular benefits. This study deals with the interplay between cardiovascular and thyroid dysfunctions associated with clinical implications and management strategies.

Key words: cardiovascular disease, heart failure, hyperthyroidism, hypothyroidism, subclinical thyroid dysfunction, thyroid hormones

Cardiovascular disease (CVD) is a worldwide leading morbidity and mortality disease, whereas only in India, approximately 25% of all death cases can be attributable to CVD (Institute for Health Metrics and Evaluation 2010; Prabhakaran et al. 2016). Global prevalence of hypothyroidism and hyperthyroidism is approximately 5% and 2%, respectively (Moini et al. 2020). Subclinical hypothyroidism (SHypo) and subclinical hyperthyroidism (SHyper) have been reported in 3–12% and 1–6% of people, respectively (Kim and Park 2014).

Thyroid dysfunction and CVD are closely associated and have an adverse impact on each other (Jabbar et al. 2017). Suboptimal management of either disease may further increase the burden of CVD. The objective of this work is to review an interplay between the cardiovascular and thyroid dysfunctions that predispose an individual to CVD or an increased risk of disease worsening. Recommendations for the optimal management of cardiovascular and thyroid dysfunctions are also reviewed (Mithal et al. 2014).

Effect of thyroid hormones on cardiovascular function

Thyroid hormones (THs) exert their action via TH receptors with TR α 1, which is the most common receptor subtype expressed in the myocardium regulating cardiac function. Circulating THs alter cardiac excitability and conduction via both genomic and non-genomic mechanisms (Figure 1).

Action on cardiac myocytes and vasculature

Triiodothyronine (T₃) modifies the activity of sodium, potassium, and calcium channels via multiple intracellular pathways in cardiac and vascular smooth muscle cells. Higher T₃ levels result in increased heart rate, cardiac contractility, and venous tone that eventually increases cardiac preload and output (Razvi et al. 2018; Razvi 2019). Moreover,

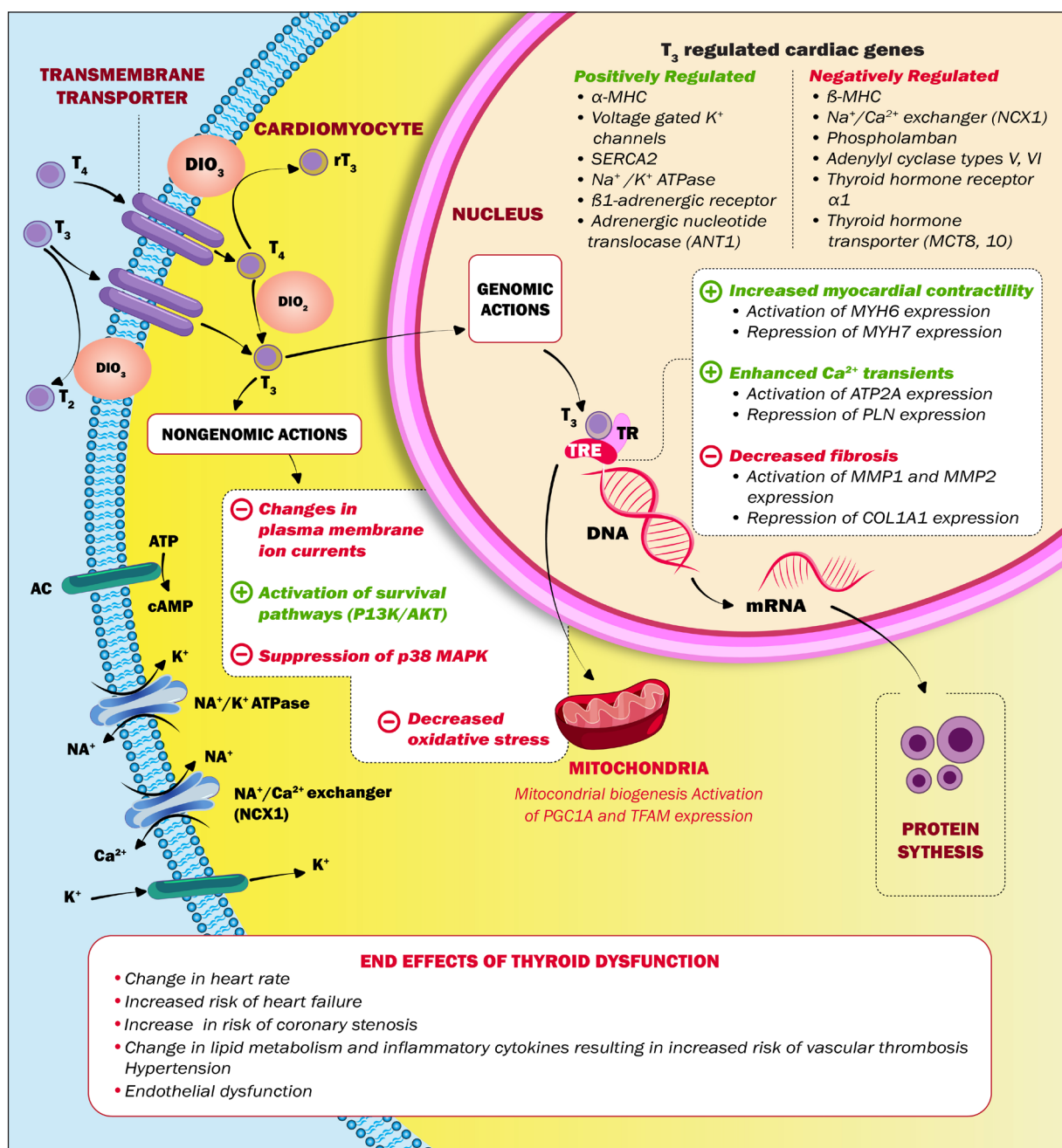


Figure 1. Mechanisms of thyroid hormones. Adapted from Razvi et al. 2018.

T₃ induces adrenergic membrane receptors, which increase myocardial sensitivity to the adrenergic system. T₃ induces vascular smooth muscle relaxation decreasing systemic vascular resistance that results in reduced renal perfusion causing activation of the renin-angiotensin-aldosterone system axis, which is a well-established feature of cardiovascular and renal dysfunction (Fukuyama et al. 2003; Davis et al. 2009). Thyroid dysfunction is an important cause of secondary hypertension that needs to be ruled out while treating resistant hypertension (Charles et al. 2017). Contrastingly, proangiogenic effect of THs is cardio-protective as it stimulates arteriolar growth in the normal heart and after myocardial infarction (Davis et al. 2009).

Role of thyroid hormones in mitochondrial regulation and lipid metabolism

Mitochondrial dysfunction plays a key role in cardiac dysfunction (Marin-Garcia and Goldenthal 2008). In patients with myocardial infarction, THs upregulate proteins that are essential for rescuing mitochondrial function, thereby reducing myocardial tissue loss in the peri-infarct zone. Therefore, euthyroid state is important for limiting the infarct scar size and preventing heart failure after myocardial infarction (Yoshida et al. 2001; Chen et al. 2008; Forini et al. 2011).

THs activate cholesterol 7 α -hydroxylase, which breaks down cholesterol and induces hepatic low-density lipoprotein (LDL) receptors (Duntas and Brenta 2018). Hypothyroidism frequently

induces secondary dyslipidemia; thus, its evaluation is important before commencing lipid-lowering therapy (Duntas and Brenta 2018).

Interplay between thyroid and cardiovascular dysfunction

Overt and subclinical hypo- and hyperthyroidism may cause adverse cardiovascular alterations as THs regulate various key components of the cardiovascular system (Tables 1 and 2) (Werner et al. 2005).

Cardiac dysfunction in hypothyroidism

In severe hypothyroidism, density of β -cell receptors is reduced and their coupling to adenylyl cyclase causes negative inotropic and chronotropic effects resulting in reduced stroke volume, bradycardia and reduced cardiac output leading to cardiogenic shock. Hypothyroidism elevates α -adrenergic responsiveness leading to peripheral vasoconstriction resulting in reduced body temperature a feeling of coldness and pale skin. Hypothyroidism causes abnormality in electrocardiogram readings like low voltage complex due to pericardial effusion, J wave for hypothermia, sinus bradycardia, prolonged QT interval, and inverted T waves. Rarely, severe hypothyroidism causes sustained ventricular tachycardia and torsades de pointes (Silva and Landsberg 2000; Schenck et al. 2006).

Patients with congestive heart failure (HF) and hypothyroidism have a higher risk of death than euthyroid patients (Moini et al. 2020). In a recent

Table 1
Effects of hypothyroidism and hyperthyroidism (Razvi et al. 2018)

	Overt hyperthyroidism	Subclinical hyperthyroidism	Overt hypothyroidism	Subclinical hypothyroidism
Definitions	Low TSH, high T ₃ and T ₄	Low TSH, normal T ₃ and T ₄	High TSH and low T ₃ and T ₄	High TSH and normal T ₃ and T ₄
Cardiac function	↑ Risk of atrial arrhythmias ↑ Atrial size, LV mass, and impaired diastolic function in longstanding untreated disease		LV systolic and diastolic dysfunction at rest and during exercise	
Hypertension	Systolic hypertension Wide pulse pressure		Diastolic hypertension	
Endothelial dysfunction	High endothelial nitric oxide production and exaggerated vascular reactivity ↑ Arterial stiffness and carotid intima-media thickness in longstanding untreated disease		Impaired endothelial dependent vasodilation ↑ Arterial stiffness	
Lipid parameter	Mild (↓)		↑ Total cholesterol and LDL cholesterol	
Thrombogenicity	↑ Fibrinogen and von Willebrand factor in overt disease		Unclear	

Abbreviations: LDL – low-density lipoprotein; LV – left ventricular; T₃ – triiodothyronine; T₄ – tetraiodothyronine; TSH – thyroid-stimulating hormone.

Table 2

Summary of systemic reviews and meta-analysis of studies evaluating subclinical thyroid dysfunction, NTIS and CV function.

Author Study type	Included studies, frequency, thyroid status, objective	Rated quality of outcomes	Results
Subclinical thyroid dysfunction and CV function			
Yang et al. (2019) Meta-analysis	n=14 SHypo: TSH >4.0–5.5 mIU/L SHyper: TSH <0.3–0.55 mIU/L Objective: To assess the association between subclinical thyroid dysfunction and the clinical outcomes of HF patients	The funnel plot or the Egger test showed no publication bias	Pooled HR of SHypo All-cause mortality: 1.45 (95% CI: 1.26–1.67; p=0.073) Cardiac death and/or hospitalization: 1.33 (95% CI: 1.17–1.50; p<0.001) Pooled HR of SHyper All-cause mortality: 1.31 (95% CI: 1.10–1.55; p=0.225) Cardiac death and/or hospitalization: 1.03 (95% CI: 0.87–1.23; p=0.958)
Gencer et al. (2012) Pooled analysis	n=6; prospective cohorts Euthyroidism: TSH 0.45–4.49 mIU/L SHypo: TSH 4.5–19.9 mIU/L, normal free thyroxine levels SHyper: TSH <0.45 mIU/L, normal free thyroxine levels Objective: To evaluate subclinical thyroid dysfunction and the risk of HF events	Limited evidence of publication bias with funnel plots; Egger test for SHypo (p=0.23) and SHyper (p=0.60)	HR for HF in SHypo: TSH 4.5–6.9 mIU/L: 1.01 (95% CI: 0.81–1.26) TSH 7.0–9.9 mIU/L: 1.65 (95% CI: 0.84–3.23) TSH 10.0–19.9 mIU/L: 1.86 (95% CI: 1.27–2.72) HR for HF in SHyper: TSH 0.10–0.44 mIU/L (p for trend <0.01): 1.31 (95% CI: 0.88–1.95) TSH <0.10 mIU/L (p for trend = 0.047): 1.94 (95% CI: 1.01–3.72)
Chaker et al. (2014) Systematic review and meta-analysis	n=6; cohort studies SHypo: TSH 4.5–20 mIU/L SHyper: TSH <0.45 mIU/L Objective: To evaluate the association between subclinical thyroid dysfunction and the risk of stroke in prospective cohort studies	No publication bias for SHypo and stroke; Significant publication bias for SHyper and stroke using funnel plots and the Egger test	SHypo Pooled HR: 1.08 (95% CI: 0.87–1.34) SHyper Pooled HR: 1.17 (95% CI: 0.54–2.56)
Rodondi et al. (2010) Meta-analysis	n=11; prospective cohorts Euthyroidism: TSH 0.50–4.49 mIU/L SHypo: TSH 4.5–19.9 mIU/L with normal thyroxine concentrations Objective: To assess the risks of CHD and total mortality for adults with SHypo	The funnel plot or the Egger test showed no publication bias	HR for CHD events (p<0.001): TSH 4.5–6.9 mIU/L: 1.00 (95% CI: 0.86–1.18) TSH 7.0–9.9 mIU/L: 1.17 (95% CI: 0.96–1.43) TSH 10–19.9 mIU/L: 1.89 (95% CI: 1.28–2.80) HR for CHD mortality (P < 0.005): TSH 4.5–6.9 mIU/L: 1.09 (95% CI: 0.91–1.30) TSH 7.0–9.9 mIU/L: 1.42 (95% CI: 1.03–1.95) TSH 10–19.9 mIU/L: 1.58 (95% CI: 1.10–2.27)
Rodondi et al. (2006) Meta-analysis	n=14; observational studies SHypo TSH cutoff: ≥ 4.5 mIU/L Objective: To determine whether SHypo is associated with CHD in adults	Publication bias using the funnel plot: little	Risk of CHD in SHypo: 1.65 (95% CI: 1.28–2.12)
Cai et al. (2011) Meta-analysis of cross-sectional data	n=7; cross-sectional studies Objective: To assess whether BP in patients with subclinical thyroid dysfunction differs from that of euthyroid subjects	No publication bias in the Egger's regression asymmetry test and the Begg's adjusted rank correlation test	SHypo Pooled WMD for SBP: 1.89 mmHg (95% CI: 0.98–2.80; p<0.05) Pooled WMD for DBP: 0.75 mmHg (95% CI: 0.24–1.27; p<0.05) SHyper No significant difference in SBP (WMD with 95% CI –0.75 mmHg [–1.81–0.31]) or DBP (WMD with 95% CI –0.64 mmHg [–2.36–1.08])
Liu et al. (2014) Meta-analysis	n=16; observational studies Objective: To investigate the association between subclinical hypothyroidism and lipid profiles	Egger and Begg tests showed no evidence of publication bias for studies on HDL-C and TG. For TC, only Egger test indicated a potential publication bias and for LDL-C, both tests indicated bias	SHypo compared with euthyroid patients TC: WMD = 12.17 (95% CI: 7.79–16.54; p<0.001) LDL-C: WMD = 7.01 (95% CI: 3.95–10.05; p<0.001) HDL-C: WMD = –0.50 (95% CI: –1.90–0.89; p=0.481) TG: WMD = 13.19 (95% CI: 4.92–21.46; p<0.001)

Table 2
Continued ...

Author Study type	Included studies, frequency, thyroid status, objective	Rated quality of outcomes	Results
Moon et al. (2018) Meta-analysis	n=35; prospective cohort studies Objective: To determine the impact of SHypo on the risk of CVD and all- cause mortality	The funnel plot showed no publication bias	Pooled RR for CVD 1.33 (95% CI: 1.14–1.54) Pooled RR for all-cause mortality 1.20 (95% CI: 1.07–1.34)
Ochs et al. (2008) Meta-analysis	n=10; population-based cohort studies Objective: To identify the relationship between subclinical thyroid dysfunction and CHD and mortality	The funnel plot or the Egger test showed no publication bias	SHypo RR for CHD 1.20 (95% CI: 0.97–1.49; p=0.14) RR for CV mortality 1.18 (95% CI: 0.98–1.42) RR for total mortality 1.12 (95% CI: 0.99–1.26) SHyper RR for CHD 1.21 (95% CI: 0.88–1.68) RR for CV mortality 1.19 (95% CI: 0.81–1.76) RR for total mortality 1.12 (95% CI: 0.89–1.42)
Ye et al. (2014) Meta-analysis	n=20; observational studies TSH cutoff points for SHypo: <4.5 mIU/L and ≥4.5 mIU/L Objective: To examine the relationship between SHypo and BP	The funnel plot or the Egger test showed no significant publication bias	WMD between SHypo and euthyroid: SBP: 1.47 mmHg (95% CI: 0.54–2.39 mmHg; p=0.002) DBP: 0.44 mmHg (95% CI: –0.15–1.02 mmHg; p=0.142)
Singh et al. (2008) Meta-analysis	n=6; cohort studies Objective: To estimate the impact of subclinical thyroid disorders on CHD, CV, and all-cause mortality		SHypo CHD: Pooled: RR 1.53 (95% CI: 1.31–1.79; p<0.05) CV mortality: Pooled: RR 1.28; (95% CI: 1.02–1.60; p=0.031) All-cause mortality: no significant difference SHyper CHD: RR 1.16 (95% CI: 0.709–1.883; no significant difference at baseline) CV mortality: RR 1.35 (95% CI: 0.949–1.923; no significant difference) All-cause mortality: no significant difference
NTIS and CV function			
Wang et al. (2017) A systematic review and meta- analysis	n=41 (Prevalence of NTIS); n=23 (Prognostic role of NTIS); cross-sectional, prospective, or retrospective cohort studies Objective: To evaluate the prevalence of NTIS in CV patients, and risks of all-cause mortality, cardiac mortality, and MACE in CV patients with NTIS compared with those without NTIS	All-cause mortality: $P_{\text{Egger's test}} = 0.02$; Cardiac mortality: $P_{\text{Egger's test}} = 0.15$; MACE: $P_{\text{Egger's test}} = 0.92$ in funnel plot	Prevalence of NTIS Pooled: 21.7% (95% CI: 18.4%–25.3%) In patients with HF: 24.5%; AMI: 18.9%; ACS: 17.1% Prognostic role of NTIS in CV patients All-cause mortality: HR 2.52 (95% CI: 1.87–3.40; p<0.001) Risk of cardiac mortality: HR 2.06 (95% CI: 1.58–2.69; p<0.001) Risk of MACE: HR 1.73 (95% CI: 1.32–2.26; p<0.001)

Abbreviations: ACS – acute coronary syndrome; AMI – acute myocardial infarction; BP – blood pressure; CHD – coronary heart disease; CI – confidence interval; CV – cardiovascular; CVD – cardiovascular disease; DBP – diastolic blood pressure; HDL-C – high-density lipoprotein cholesterol; HF – heart failure; HR – hazard ratio; LDL-C – low-density lipoprotein cholesterol; MACE – major adverse cardiovascular events; NTIS – non-thyroidal illness syndrome; RR – relative risk; SBP – systolic blood pressure; SHyper – subclinical hyperthyroidism; SHypo – subclinical hypothyroidism; TC – total cholesterol; TSH – thyroid-stimulating hormone; WMD – weighted mean difference.

meta-analysis of studies that enrolled patients with ischemic heart disease (IHD), hypothyroidism was associated with a higher risk of all-cause mortality [Hazard ratio (HR): 1.47; 95% confidence interval (CI): 1.10–1.97] and major adverse cardiac events (MACE) [HR: 1.53; 95% CI: 1.19–1.97] (Chang et al. 2020). Another meta-analysis has shown an increased risk of HF events for patients with

thyroid-stimulating hormone (TSH) >10 mIU/L and <0.10 mIU/L (Gencer et al. 2012). Hypothyroidism can result in skeletal muscle myopathy with cramps, stiffness, reduced muscle endurance, pseudohypertrophy, and pseudomyotonia (Mastropasqua et al. 2003). Patients on statins may develop statin-induced myopathy if they have hypothyroidism. Therefore, levothyroxine could be suggested for mild lipid

changes before initiating statin (Rush et al. 2006; Klein and Danzi 2016).

The SHypo is defined as high TSH (thyroid stimulating hormone) and normal T3 and T4 (tetraiodothyronine) levels. A meta-analysis of several prospective cohort studies (55,287 adults) has shown that SHypo is associated with an increased risk of coronary heart disease (CHD) and related mortality and this trend increased in patients with TSH levels >10 mIU/L (Rodondi et al. 2010). Another large meta-analysis has reported increased mortality and higher risk of IHD in SHypo patients younger than 65 years (Sun et al. 2017). It has been also shown that presence of serum TSH levels >10 mIU/L was associated with higher odds of prevalent metabolic syndrome (Waring et al. 2012). In summary, overt hypothyroidism exerts changes in endothelial function, vascular resistance and myocardial contractility, which are usually reversible with adequate treatment whereas SHypo causes similar but milder effects.

There are few studies that determine the clinical significance and two not significant impacts of SHypo in different phenotypes of HF. The comparison of the clinical outcomes demonstrated significantly increased levels of BNP (210.45 ± 52.42 vs. 188.75 ± 49.08 pg/mL; $p < 0.05$) and CRP (2.32 ± 0.89 vs. 1.26 ± 0.33 mg/L; $p < 0.05$) in HFpEF patients with SHypo as compared to HFpEF patients with euthyroidism indicating increased risk and severity of the cardiac dysfunction in the former cohort of the patients (Meng et al. 2020). Further, HFpEF patients with SHypo were found to have cardiac diastolic dysfunction as evident by increased E/E' and decreased E/A ratio.

Recently, Inciardi et al. (2020) have identified an association between the lower serum T3 level with the increased risk of incident HFpEF hospitalization (HR: 2.71; 95% CI: 1.08–6.82; $p = 0.035$) in a large cohort of patients without a pre-existing HF. However, such association could not be observed with incident HFrEF. In contrast, Saad et al. (2020) have reported higher readmission in 30 days and all-cause mortality in HFrEF patients with SHypo, but not in HFpEF with SHypo.

Cardiac dysfunction in hyperthyroidism

Palpitation is the most common cardiovascular symptom in the hyperthyroid patients and 2–20% of these patients have atrial fibrillation (Ertek and Cicero 2013). Threshold of TSH, in which the risk becomes clinically significant and its variability with age race/ethnicity, sex and underlying cardiac status,

is a subject of further research. Multiple studies have shown that TSH levels ≤ 0.1 – 0.44 mIU/L increase the risk of atrial fibrillation by 1.85- to 3.3-fold (Sawin et al. 1994; Cappola et al. 2006; Collet et al. 2012). Hyperthyroidism is associated with tachyarrhythmias, both QTc prolongations and short QTc intervals, and a heightened risk for torsades de pointes (Dorr et al. 2004; Schenck et al. 2006; Lee et al. 2015).

Overt hyperthyroidism increases the risk of major cardiovascular events by 16% and this could mostly be attributed to higher incidence of heart failure events (Selmer et al. 2014). Severe hyperthyroidism can induce high-output heart failure even in patients without any underlying heart disease due to increased heart rate and blood volume (Figure 2) (Biondi 2012). Prevalence of low-output heart failure in hyperthyroid patients is between 6–15% (Biondi 2012). Regression of heart failure occurs with euthyroidism, but it may be irreversible in some hyperthyroid patients and approximately one-third of the patients may develop hyperthyroid cardiomyopathy (Siu et al. 2007). Hyperthyroidism also triggers pulmonary hypertension that results in right ventricular failure (Biondi 2012).

Patients with SHyper exhibit an increased risk for atrial fibrillation, heart failure, and CVD (Razvi et al. 2018). The risk for atrial fibrillation was estimated to be 41.5% higher in SHyper patients than euthyroid patients, independent of the presence of existing CVD or other cardiovascular risk factors (Collet et al. 2012; Bano et al. 2017). Contrastingly, an association between SHyper and stroke is ambiguous. A meta-analysis and 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 (Chaker et al. 2014; Selmer et al. 2014). Both overt and SHyper reportedly increased thrombogenesis markers such as fibrinogen, factor X levels, or von Willebrand antigen levels showing a tendency towards increased incidence of thrombosis. However, it is not clear if increased numbers of cerebrovascular events were due to thrombosis-related alterations in the vascular tree (increase in carotid intima-media thickness) or due to heightened risk for atrial fibrillation (Erem et al. 2003; Squizzato et al. 2005; Dorr et al. 2006; Erem 2006; Homoncik et al. 2007; Franchini et al. 2011).

Onset of SHyper can aggravate cardiovascular risk in the presence of underlying heart disease (Biondi 2012). In a prospective study of pravastatin in the elderly at Risk (PROSPER) trial (Nanchen et al. 2012), incidence of heart failure was higher in elderly patients with SHyper and a history of CVD.

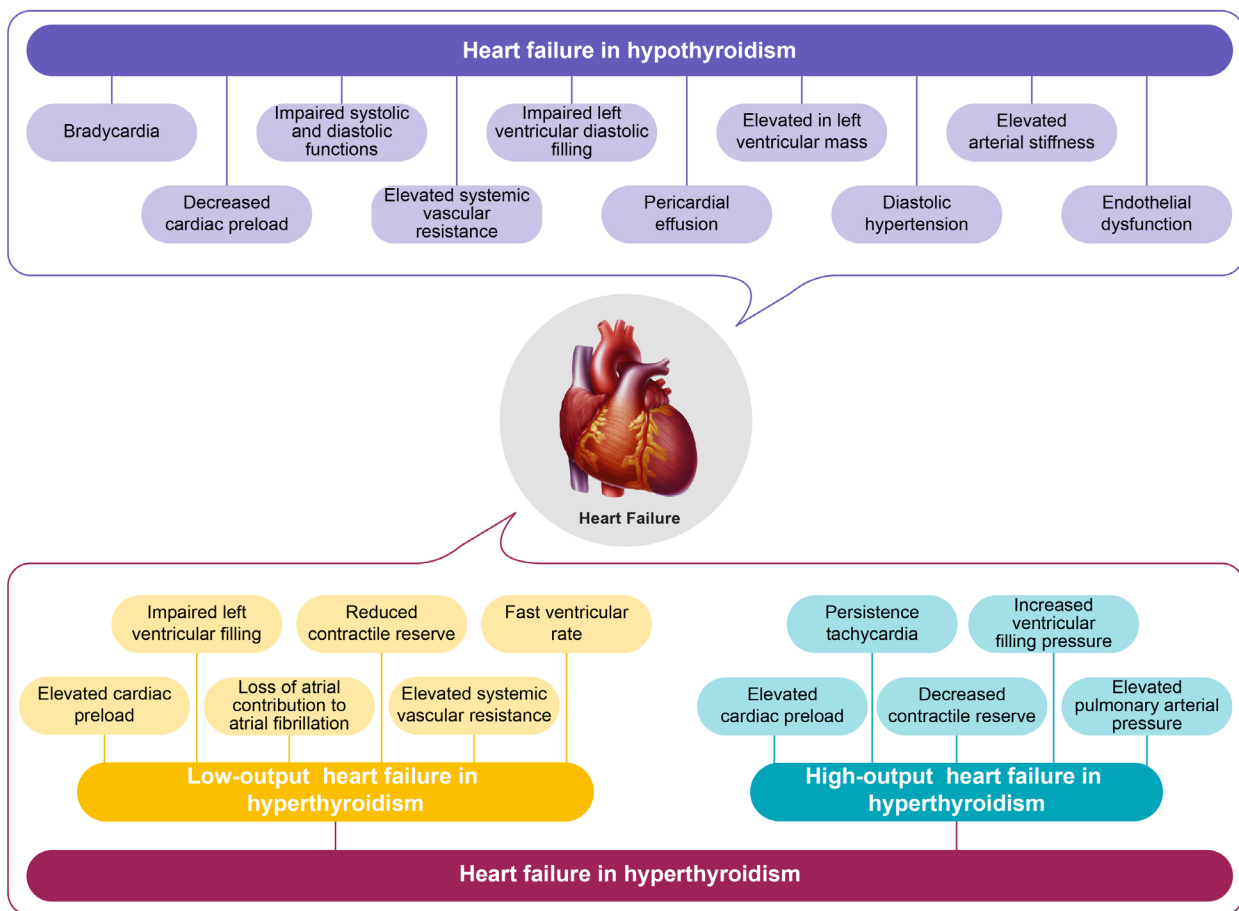


Figure 2. Mechanisms of heart failure in thyroid dysfunction. Adapted from Biondi 2012.

Thyrotoxicosis involves excess circulating TH produced either endogenously or exogenously causing increased sinoatrial node activity, weakened threshold for atrial activity, and reduced atrial repolarization phase resulting in sinus tachycardia. Thyrotoxicosis often leads to a pulmonary artery hypertension (PAH) producing right ventricular dysfunction (Dahl et al. 2008; Klein and Danzi 2016).

Thyroid hormone alterations in heart failure and acute myocardial infarction

Resetting of hypothalamic-pituitary-thyroid axis occurs immediately after an acute illness and is characterized by decreased serum T_3 , high reverse T_3 , normal TSH, and normal to low T_4 levels depending upon the disease severity. This is known as nonthyroidal illness syndrome (NTIS) or low T_3 syndrome, which is not a primary thyroid disorder (Adler and Wartofsky 2007; Klein and Danzi 2016).

A meta-analysis by Wang et al. (2017) has shown a pooled prevalence of NTIS in subjects with CVD to be up to 21.7% with higher prevalence in patients with heart failure (24.5%), acute myocardial infarction (AMI) (18.9%), and acute coronary syndrome (17.1%) (Wang et al. 2017). Lower circulating T_3 levels in patients with AMI are associated with poor clinical outcomes, increased short- and long-term mortality, and late recovery of left ventricular function after 6 months especially in the presence of large AMI, left ventricular dysfunction, and intense pro-inflammatory and stress responses (Lymvaivos et al. 2011). In a recent meta-analysis of 19,310 patients with IHD, NTIS was associated with a higher risk of all-cause mortality and MACE than in those without NTIS. Likewise, the risk of cardiovascular events was high with NTIS in patients with acute coronary syndrome (Chang et al. 2020).

Ischemic reperfusion of post-myocardial infarction is associated with adverse cardiac remodeling that

may culminate in heart failure. Mitochondrial dysfunction is an important feature of ischemic reperfusion injury. As THs favorably regulate mitochondrial function, thyroid pre-treatment may protect cardiomyocytes from ischemic reperfusion injury. Although protective role of thyroid treatment has been demonstrated in animal studies, its relevance in the clinical setting is not established yet (Pantos et al. 2003a, b; Yang et al. 2018). NTIS is associated with poor prognosis and increased risk of mortality in patients with chronic heart failure (Iervasi et al. 2003, 2007), particularly in those with reduced left ventricular ejection fraction. Possible benefits of thyroid replacement were evaluated in two studies but showed discordant results (Pingitore et al. 2008; Holmager et al. 2015). However, the results of these studies are suggesting that T_3 therapy may offer benefits only to a subgroup of patients and that these depend on the dose and route of administration. Taken together, it appears that TH could offer a

clinically useful and cost-effective treatment if their effects are confirmed in large-scale trials. At present, the thyroid function assay is recommended as class I indication in all patients with heart failure and IHD by most international guidelines (Table 3).

Thyroid hormone alterations in patients treated with amiodarone

Amiodarone, a potent anti-arrhythmic drug structurally similar to TH, is rich in iodine and can cause both amiodarone-induced hypothyroidism (AIH) and amiodarone-induced thyrotoxicosis (AIT). Prevalence of AIH ranges from 5–22% depending on the iodine status and is more frequent in iodine-sufficient regions whereas AIT is observed in 2–12% of patients treated with the drug and is more frequently observed in iodine-deficient areas (Razvi et al. 2018). Effects of amiodarone on the thyroid gland or TH metabolism are either due to iodine-induced direct

Table 3
Managing comorbid thyroid dysfunction and CVD interplay.

	Managing thyroid dysfunction	Managing cardiovascular symptoms
Heart failure, dilated cardiomyopathy	Thyroid testing at initial presentation (Ponikowski et al. 2016; Yancy et al. 2013) If subclinical thyroid dysfunction detected, manage as per Figure 3 Hyperthyroidism and hypothyroidism should be managed as per the standard guidelines Elderly patients with known cardiac disorders or severe hypothyroidism should be administered a low starting dose of levothyroxine, i.e., 25–50 µg/day, which should be adjusted every 10–12 weeks to bring TSH to normal limits (Garber et al. 2012; Vasileiou et al. 2020)	Diuretics for volume control β-blockers for controlling hyperadrenergic state (Ponikowski et al. 2016; Yancy et al. 2013)
Atrial fibrillation, supraventricular tachycardia	Thyroid testing at initial presentation (Kirchhof et al. 2016) Hyperthyroidism to be managed as per the guidelines using antithyroid drugs	β-blockers are used as the standard of care for rate control: if contraindicated, calcium channel antagonist (diltiazem or verapamil) (Fuster et al. 2006) Anticoagulation to prevent thromboembolism until achievement of euthyroid state (Fuster et al. 2006; Singer et al. 2008)
Amiodarone (Bartalena et al. 2018)	Thyroid testing before initiation of the drug, within 3 months of initiation, and every 3–6 months AIH: L-T ₄ treatment is recommended in all cases of overt AIH, whereas it may be avoided in some subclinical cases, particularly in the elderly, but with a frequent assessment of thyroid status to monitor possible progression to overt hypothyroidism AIT: AIT patients should be considered at risk of emergency treatment, particularly in the elderly, in patients with left ventricular dysfunction and should be managed as per the standard treatment guidelines	AIH does not require amiodarone withdrawal, if considered essential for the underlying cardiac disease (Bartalena et al. 2018) The decision to continue or to stop amiodarone in AIT should be individualized in relation to cardiovascular risk stratification and taken jointly by specialist cardiologists and endocrinologists

Abbreviation: AIH – amiodarone-induced hyperthyroidism; AIT – amiodarone-induced hypothyroidism; CVD – cardiovascular disease; TSH – thyroid-stimulating hormone.

effects leading to destructive thyroiditis – AIT type II or due to aggravation of intrinsic subclinical thyroid autonomy resulting from a toxic nodule or toxic multinodular goiter or subclinical Graves' disease (AIT type I) (Basaria and Cooper 2005). Amiodarone inhibits 5'-deiodinase and blocks conversion of T_4 into T_3 in the pituitary gland and in liver causing reduced serum T_3 levels and increased serum TSH and T_4 levels (Schmidt-Ott and Ascheim 2006).

Before starting amiodarone, the patients should be examined for pre-existing thyroid disorders, and after initiation, serum T_3 , T_4 , and TSH levels should be monitored biannually and then, annually (Toft and Menon 2000). Elevated TSH levels and low T_4 levels indicate AIH and patient can be treated with levothyroxine. Low TSH levels with elevated T_4 and T_3 suggests AIT. Ultrasound, Doppler, and nuclear imaging of the thyroid can be used to differentiate type I or type II AIT.

Considering significant impact on morbidity and mortality, AIT type I should be considered for an emergency situation, especially in older patients with impaired left ventricular function. The use of amiodarone should be stopped (if feasible) and an alternative antiarrhythmic drug should be prescribed. High doses of antithyroid drugs are used to treat this condition. Further, a sodium perchlorate addition increases the response of the thyroid gland towards antithyroid drugs, i.e., thioamides. Thyroidectomy could be considered if amiodarone cannot be stopped or rapid control of AIT is needed (Trohman et al. 2019). European Thyroid Association recommends thyroidectomy to treat AIT type I in patients with severe underlying cardiac disease or deteriorating cardiac function (Bartalena et al. 2018). However, it requires a multidisciplinary approach involving endocrinologist, cardiologist, anesthesiologist, and high-volume thyroid surgeon. While AIT type I is life-threatening condition, AIT type-II is usually a self-limiting disease. However, it may exacerbate the underlying cardiac disease. Hence, it needs to be treated with appropriate treatment. Oral glucocorticoids can be considered the drug of choice to treat moderate-to-severe thyrotoxicosis (AIT type II). Thyroidectomy can be considered in case of emergency to treat AIT type-II.

Diagnosis and management of patients with comorbid thyroid and cardiovascular dysfunction hypothyroidism

In patients with comorbid thyroid and cardiovascular dysfunction, CVD should be diagnosed and

managed immediately along with reversing hypothyroidism. Patients with newly-diagnosed heart failure should be screened for serum TSH levels (Ladenson 1990). Oral levothyroxine is the drug-of-choice for treating patients with hypothyroidism and its dose is based on disease severity, age, and history of CVD. In young and otherwise healthy patients without any known disorders, dose of levothyroxine should be $\sim 1.6 \mu\text{g/kg}$ once daily in an empty stomach. In patients with known cardiac diseases, levothyroxine should be administered 25–50 $\mu\text{g/day}$, and adjusted every 10–12 weeks to bring TSH within normal limits (Garber et al. 2012; Vasileiou et al. 2020). Levothyroxine is administered at 25–50 $\mu\text{g/kg}$ in the elderly, 2.0–2.4 $\mu\text{g/kg}$ body weight/day in pregnant women, and should be adjusted to 2.0 $\mu\text{g/kg}$ body weight/day in patients on enzyme-inducing drugs (Chakera et al. 2012). Levothyroxine improves cardiac function, ventricular remodeling, and decrease myocyte apoptosis in patients with hypothyroidism (Ladenson 1990; Biondi 2012; Chaudhary et al. 2015; Klein and Danzi 2016).

Hyperthyroidism

At initial presentation of supraventricular tachycardia, atrial fibrillation, dilated cardiomyopathy, and HF, thyroid function testing is recommended by most cardiology guidelines (Fuster et al. 2006; Yancy et al. 2013; Bozkurt et al. 2016; Ponikowski et al. 2016). Quick and effective management of cardiac symptoms in patients with hyperthyroidism is essential as cardiovascular complications account for most deaths in these patients (Biondi 2012).

Diuretics and β -blockers are used to control HR and adrenergic symptoms in hyperthyroidism and improve sustained tachycardia and heart failure. Hyperthyroidism increases the density of β -adrenergic receptors leading to a hyperadrenergic state characterized by increased sensitivity to circulating catecholamines. Propranolol (20–40 mg every 6 hours) or longer-acting β -blockers such as atenolol and bisoprolol are recommended for controlling adrenergic symptoms (Kahaly et al. 2018). High doses of propranolol (40 mg, 4 times daily) inhibits peripheral conversion of inactive T_4 to active T_3 . Beta1-selective adrenergic receptor antagonists such as landiolol (intravenous), esmolol (intravenous), bisoprolol (oral) should be selected as first choice of treatment for tachycardia in thyroid storm (Satoh et al. 2016). Cardio selective β -blockers also provide cardioprotection, prevent atrial

fibrillation, and are the preferred choice in patients with asthma. In patients with contraindications to β -blockers, a calcium channel antagonist (diltiazem or verapamil) should be used to control ventricular rate (Fuster et al. 2001).

The American College of Chest Physicians (ACCP) guideline for atrial fibrillation management recommends anticoagulation based on the CHA₂DS₂-VASC score irrespective of the presence or absence of hyperthyroidism (Singer et al. 2008). The American College of Cardiology (ACC) guidelines recommend oral anticoagulating agents (target INR: 2–3) for preventing thromboembolism that should be reconsidered when euthyroidism is achieved (Fuster et al. 2006).

Hyperthyroidism should be treated using antithyroid drugs, thyroid profile should be checked every 4–8 weeks post initiation of therapy and dosage should be adjusted as needed. Potassium iodide (oral) or sodium iodide (intravenous) should be given along

with antithyroid drugs to reduce the release of pre-existing intra glandular TH stores. Thyroidectomy is preferred in patients intolerant to antithyroid drugs or ¹³¹I ablation and in those with compressive symptoms caused by a nodule or goiter (Ladenson 1990; Kravets 2016).

Primary causes of various types of thyrotoxicosis can be differentiated using ¹³¹I-uptake scanning and these patients should be treated with antithyroid drugs, ¹³¹I and thyroidectomy (Pearce 2006; Dahl et al. 2008).

Subclinical thyroid dysfunction in cardiovascular disease

It is important to rule out the transient causes of abnormal serum TSH levels before considering the treatment in patients with subclinical thyroid dysfunction. The TSH threshold for considering treatment is described in Figure 3.

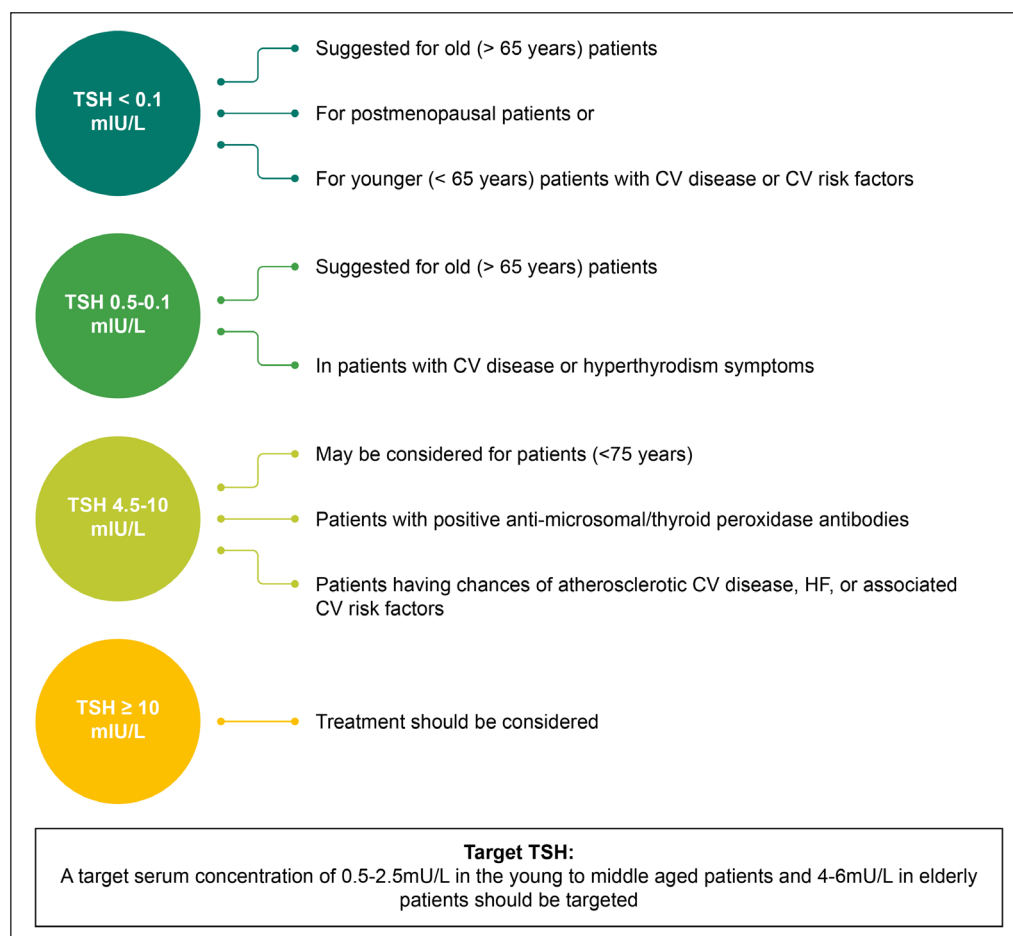


Figure 3. Management of subclinical thyroid function (Manolis et al. 2020).

Subclinical hypothyroidism

Despite knowing the potential long-term adverse consequences of SHypo, there are no consensus guidelines offering a treatment strategy. A Danish study of 1192 patients with cardiac disease and SHypo has reported that levothyroxine was not beneficial in reducing the risk of all-cause mortality, MACE, or hospitalization (Andersen et al. 2016). A recent randomized study has also found no apparent benefits, however, it was underpowered to assess effects on CVD (Stott et al. 2017). Conversely, levothyroxine treatment showed cardiovascular benefits in patients <65 years in a large cohort study of 12,212 patients (Andersen et al. 2015). A meta-analysis of three randomized controlled trials (RCTs) has shown that levothyroxine association with a significant reduction in progression of carotid intima-media thickness (Zhao et al. 2017). Few meta-analyses have shown significant reductions in total cholesterol and LDL-cholesterol levels with no significant effect on high-density lipoprotein (HDL) cholesterol or triglycerides with levothyroxine treatment (Abreu et al. 2017; Li et al. 2017). Evidence shows an increased risk for IHD and cardiovascular mortality in younger patients with TSH <10 mIU/L (Rodondi et al. 2010). Levothyroxine therapy in younger patients with SHypo resulted in a lower risk for CHD, MI, cardiovascular death and all-cause mortality (Razvi et al. 2012; Andersen et al. 2015). Moreover, given the evidence for risk of progression to overt hypothyroidism, elevated serum total cholesterol and LDL in patients with TSH >7.0 mIU/L, levothyroxine treatment may provide early cardiovascular risk reduction in these

patients (Baumgartner et al. 2014). Notably, current European Thyroid Association guidelines on SHypo recommend treatment for individuals aged <70 years at TSH levels >7.0 mIU/L rather than 10 mIU/L for risk of CVD. Overall, the effects and clinical significance of SHypo on CVD/coronary artery disease is recognized in young adults, but debated in the elderly. With no randomized clinical trials of levothyroxine therapy on cardiovascular outcomes in the elderly, there is no consensus for treating SHypo in the elderly (Pasqualetti et al. 2013).

Current guidelines for managing thyroid dysfunction recommend THs for adults with TSH levels >10 mIU/L. In patients with lower TSH levels, treatment is recommended for patients who are younger, symptomatic or have CVD or antibodies to thyroid peroxidase (Figure 4).

Subclinical hyperthyroidism

Although numerous non-randomized studies have shown improved cardiac function in patients with hyperthyroidism when treated, no RCTs have reported whether treatment of mild hyperthyroidism prevents new onset of atrial fibrillation or assists management of patients with pre-existing atrial fibrillation. Guidelines strongly recommend treating grade 2 SHyper (TSH <0.1 mIU/L) for patients >65 years of age and in younger patients with comorbidities. In grade 1 SHyper, treatment is not recommended in young adults and is recommended for patients >65 years of age presenting with cardiovascular risk factors or complications. However, this recommendation is weak due to low-quality evidence

	American Thyroid Association (ATA) 2012	European Thyroid Association (ETA) 2013	National Institute for health and Care Excellence (NICE) guideline
TSH >10 mIU/L	Start treatment	- Age <70 years: Start treatment - Age >70 years: Start treatment, if clear symptoms or high cardiovascular risk	- Age <70 years: Consider treatment - Age >70 years: Observe
TSH <10 mIU/L	Start treatment, if indications of hypothyroidism, positive thyroid peroxidase antibodies, or evidence of atherosclerotic cardiovascular disease, heart failure or relative risks of these diseases	- Age <70 years: if no clear symptoms - Observe if clear symptoms - start trial - Age >70 years: Observe	- Age <65 years: if clear symptoms - start trial - Age >65 years: Observe

Figure 4. Comparison of current treatment guidelines for subclinical hypothyroidism (Jonklaas et al. 2014; Persani et al. 2018; Vasileiou et al. 2020).

Table 4
Studies evaluating thyroid dysfunction and CV function in India.

Clinical conditions	Author, study type	Frequency and thyroid status	Outcomes
Subclinical thyroid dysfunction and CV function			
SHypo and HF	Kuchulakanti et al. (2019) Prospective	n=350 SHypo: serum TSH level >5.50 mIU/L, normal free T ₄	Prevalence of SHypo:18.5% SHypo in HF: LVD: severe 75.3%, moderate 23%, and mild 13.8% Mortality: 30% elevated TC (229.9±32.1 mg/dL), LDL-C (178.9±38.6 mg/dL), VLDL-C (25.1±3.9 mg/dL), TG (165.4±12.7 mg/dL), low levels of HDL-C (39.6±3.1 mg/dL) compared with euthyroid patients (p<0.0001)
SHypo and cardiac risk factors	Dey et al. (2019) Cross-sectional study	n=25 SHypo: raised TSH but normal T ₃ and T ₄	CV function in SHypo: Stage 1 hypertension: 16%; stage 2 hypertension: 4% Left ventricular diastolic dysfunction: 44% Dyslipidemia (92%), increased TC (36%), increased LDL (64%), increased TG (36%), increased hsCRP (44%), reduced HDL (68%)
Cardiac manifestations in SHypo	Ravishankar et al. (2018) Cross-sectional study	n=100 SHypo: serum TSH level >4.68 µIU/L, T ₄ within the reference range of 0.78–0.79 ng/dL	Prevalence of SHypo:18% CV function in SHypo: Bradycardia (33.3%), LVD (10%), abnormal LVC (22.2%), ST T changes (33.3%), prolonged PR (11.1%) Pericardial effusion (60%), LV hypokinesia (40%)
Hyper/Hypothyroidism and CV function			
Cardiac manifestation in hyperthyroidism	Kandan et al. (2016) Cross-sectional study	n=50 Based on clinical symptoms and signs	CV symptoms in hyperthyroidism: Tachycardia (82%), palpitations (78%), widened pulse pressure (50%), pedal edema (12%), sinus tachycardia (46%), atrial fibrillation (28%), systolic dysfunction and chamber enlargement (18%), dyspnea (26%), chest pain (4%)
Cardiac manifestation in hyper- and hypothyroidism	Bhatanagar (2018) Cross-sectional, observational, and descriptive study	n=56 Based on clinical symptoms and signs	CV symptoms in hyperthyroidism: Patients with CV symptoms 97% Palpitations (92.8%), fatigability (71.4%), chest pain (21%), dyspnea (71.4%) CV symptoms in hypothyroidism: Patients with CV symptoms 90% Fatigue (79%), dyspnoea (50%), chest pain (25%), palpitations (15%)
CV changes in hypothyroidism	Behera et al. (2017) Cross-sectional study	n=60 Thyroid hormone level by chemiluminescence immunoassay (CLIA) method; overt hypothyroid: TSH >10 mIU/L, low free T ₄ , SHypo: TSH 4.2–10 mIU/L, normal free T ₄	Patients with CV symptoms 20% Bradycardia (7%); diastolic hypertension (13.3%); diastolic dysfunction (26.6%); low voltage complexes in electrocardiogram (40%) Modified serum cholesterol level (16.7%), altered serum TG level (53.4%)

Table 4
Continued ...

Clinical conditions	Author, study type	Frequency and thyroid status	Outcomes
Cardiac manifestation in hypothyroidism	Selvamuthukumaran (2018) Cross-sectional study	n=41 Based on clinical symptoms and signs and thyroid function test; TSH range: >6–<10 mIU/L (25%), 10–20 mIU/L (41%), >20 mIU/L (24%)	Bradycardia (22%), diastolic dysfunction (51%), fatigue (88%), dyspnea (68%), chest pain (12%), palpitation (3%), pedal edema (10%), syncope (3%), ECG changes (50%)
CV changes in hypothyroidism	Shende et al. (2017) Cross-sectional study	n=45 Based on clinical symptoms and signs and thyroid function test; overt hypothyroidism: TSH >10 mIU/L, T ₃ level <60 ng/dL, T ₄ <4.5 µg/dL; SHypo: TSH level 4.3–10 mIU/L, normal T ₃ and T ₄	Bradycardia (6.6%), diastolic hypertension (17.8%), low voltage complexes in ECG (40%), pericardial effusion (16.6%), systolic dysfunction (4.5%), diastolic dysfunction (2.2%) Altered lipid profile Serum cholesterol (60%), TG (94.7%)

Abbreviation: CV – cardiovascular; ECG – electrocardiogram; HDL-C – high-density lipoprotein cholesterol; HF – heart failure; hsCRP – high sensitivity C-reactive protein; LDL-C – low-density lipoprotein cholesterol; LVD – left ventricular dysfunction; SHypo – subclinical hypothyroidism; T₃ – triiodothyronine; T₄ – tetraiodothyronine; TC – total cholesterol; TG – triglycerides; TSH – thyroid-stimulating hormone; VLDL-C – very low-density lipoprotein cholesterol.

(Biondi et al. 2015; Ross et al. 2016). The TH levels and antithyroid antibodies should be repeated within 2 weeks if TSH level is <0.1 mIU/L and within 1–3 months if TSH level is between 0.1–0.45 mIU/L.

Indian perspective

Approximately 42 million people in India have thyroid disorders (Unnikrishnan et al. 2011), with hypothyroidism being the most common disorder. Prevalence of CVD is increasing alarmingly in India. In 2016, approximately 54.5 million people in India suffered from CVD resulting in about 28.1% (i.e., 2.8 million) of total deaths (India State-Level Disease Burden Initiative CVD Collaborators 2018). Burden of CVD is mostly attributed to IHD and is mainly related to atherosclerotic coronary artery disease (Vaideeswar et al. 2018). Thyroid disease predisposes patients to CVD and is more relevant in those with hypothyroidism. Data regarding patients with CVD and thyroid dysfunction are scarce in India. Despite levothyroxine therapy for 2 months, TSH values were suboptimal in almost 54% of patients (Mithal et al. 2014). Overall, prevalence of cardiovascular symptoms in patients with thyroid dysfunction and the latter being reported in patients with CVD in India is similar to the global scenario (Table 4). Therefore, recommendations drawn from global studies are relevant in the Indian population.

Conclusion

Thyroid dysfunction and cardiovascular diseases are closely interlinked. Abnormal thyroid hormone levels negatively affect cardiovascular function and prompt diagnosis and management of both hypo- and hyperthyroidism in patients with cardiovascular risk may reduce associated complications and mortality. Whereas, cardiovascular illness and drugs used to treat cardiovascular diseases causes thyroid dysfunction by altering synthesis, secretion, metabolism, and transport of thyroid stimulating or thyroid hormones. Owing to high prevalence of thyroid dysfunction and cardiovascular diseases, especially in India, clinicians should suspect an interplay between them for effective management of this patient group.

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