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Review

Relationship between thyroid dysfunction and heart failure in older people

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Heart failure (HF) is one of the most common chronic diseases, affecting around 8% of older people, with an incidence rate of 10 per 1000 person-years. Besides ageing and classical cardiovascular risk factors, it is well recognized that HF may be worsened by endocrine alterations. The prevalence of thyroid dysfunction, similarly to HF, increases with increasing age and, 5-15% of the entire older population, especially women, suffer from overt or subclinical thyroid dysfunction. Thyroid and heart share a common embryologic origin and an intimate and complex functional relationship and, cardiovascular effects are the most prominent features of thyroid dysfunction. Not only alterations of thyroid hormone synthesis and release are risk factors for cardiac disease, but a mutual relationship has been documented and dysregulation of thyroid hormones represents also a marker for chronic heart disease. Thus, even mild thyroid dysfunction (either in excess or defect) may lead to the development of HF and may increase the risk of cardiovascular events. Consequently, thyroid dysfunction should be ruled out not only in older HF patients with no other identifiable causes but also in those with known cardiovascular risk factors. Nonetheless, the lack of randomized clinical trials leaves us with several unresolved key issues as also stated in the latest guidelines for the treatment of thyroid dysfunction, .key issues regarding specific criteria and goals of treatment, as also stated. Future large randomized intervention studies, balancing the risk and benefits of thyroid therapy according to the degree of serum TSH and TH alteration, are clearly warranted.

Key words: Heart failure, Hypothyroidism, Hyperthyroidism, Thyroid hormone, Thyrotropin, Elderly, Atrial fibrillation

INTRODUCTION

In western countries, epidemiologic data show a continuous shift towards older ages of the demographic distribution. Thus, it has been observed a huge increase of the prevalence of chronic diseases and the need for chronic and acute care services. In this regard, heart failure (HF) is one of the most common chronic diseases, affecting around 8% of people older than 75 years with an incidence rate of 10 per 1000 person-year [1 2]. The five-year mortality rate of patients with HF is around 45-60%, with a high risk of hospitalization for acute decompensated HF. Several risk factors concur for the development and progression of HF, the most important being represented by coronary heart diseases followed by elevated systolic blood pressure, structural cardiac alteration (valvulopathy), myocardiopathy, arrhythmia etc. [3 4]. In addition, even if less frequently, HF may be caused by endocrine alterations [5 6] among which thyroid hormone (TH) excess, as observed in overt hyperthyroidism, is the most undeniable [7]. Given the thigh link, at biomolecular level, among cardiac function, endothelial function, intermediate metabolism and thyroid status, even slight serum TH changes (either in excess or defect) have been associated to clinical conditions that may lead to the development of HF, cardiac structural changes, arrhythmia, systemic hypertension (either

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systolic or diastolic) as well as an early atherosclerotic process [7-15]. The effects of the ageing process on heart and vasculature make older people more susceptible to TH variations and consequently more prone to develop cardiovascular alterations, including HF, even in presence of mild thyroid dysfunction [8 9].

The prevalence of thyroid disease, similarly to HF, increases with the increasing population age [14]. It is estimated that 5-15% of the entire older population (aged > 65 years), especially women, suffer from overt or subclinical thyroid dysfunction [16]. Hyperthyroidism is characterized by the presence of reduced or undetectable serum thyroid-stimulating hormone (TSH) levels and increased (overt disease) or high normal (subclinical disease) TH values and, involves 1% to 7% of the adult population according to age [14 17]. The most common causes of hyperthyroidism in the elderly are represented by nodular goitre (especially in iodine deficient areas) and iatrogenic conditions such as excess iodine (amiodarone, iodine containing drugs etc.) or inappropriate L-thyroxin replacement while, Graves' disease is seldom observed [14 18 19]. The prevalence of hypothyroidism (especially subclinical) is more frequent than hyperthyroidism (up to 10-12% in older women); it's featured by the presence of serum TSH level above normal reference values and reduced (overt disease) or low-normal (subclinical disease) TH levels [14 16 20]. In this setting, it should be outlined that the actual prevalence of subclinical hypothyroidism in older people (especially those older than 80 years) is not clearly defined giving the shift of serum TSH towards upper values in healthy elderly and the lack of epidemiological data obtained by using age specific normal reference ranges for serum TSH [20 21]. The most frequent cause of thyroid failure is represented by autoimmune thyroiditis followed by surgical thyroid removal, concomitant drugs interfering with thyroid function (corticosteroids, ß-blockers) etc. [14 21].

In the current study, we focused on the relationship between thyroid dysfunction (either hyperthyroidism or hypothyroidism) and heart failure in older people by reviewing English literature available up to September 2016 on Medline website®. We described the main findings on the topic as reported by preclinical to clinical studies, focusing on the combined effect of thyroid dysfunction and the ageing process.

EFFECT OF THYROID HORMONES ON CARDIAC STRUCTURE AND FUNCTION

It is widely recognized the dose-dependent effect of triiodothyronine (T3) on vasculature and heart function [7 22]. Accordingly, opposite functional thyroid conditions (*i.e.* hypo- and hyperthyroidism) provoke inverse cardiac function changes that, no matter what they are, lead to cardiovascular disease with consequent increased risk of HF events (Fig. 1) [22]. To clearly explain how thyroid status affects heart function, we should focus on the bio-molecular effects of TH, and what alterations they exert in myocytes, endothelium and vascular muscle cells. In this setting, the concurrent modifications linked to the physiopathology of the ageing process, which involve either the heart or the vasculature (myocardial structural alteration, endothelial dysfunction, coronary stiffness, atherosclerosis development and progression) should be not overlooked [23].

There are two main routes for thyroid hormone action: the transcriptional genomic effects and the non-genomic effects, the last targeting directly different cell structures. As shown in many experimental models, TH has several effects on heart, mainly exerted through the action of T3 on thyroid receptors alpha-1 and beta-1 [24]. TH play a role in cardiac function acting as pro-contractile, anti-apoptotic, anti-inflammatory and anti-fibrotic agents thus favoring angiogenesis and regeneration [24]. At biomolecular level, the modification of TH availability may alter cardiac function by reducing or increasing the binding of T3 to the nuclear receptor. In addition to these local actions thyroid hormones exert significant systemic hemodynamic actions, mainly mediated by T3, acting on the cardiovascular system as a whole. Through its action on thermogenesis T3 decreases vascular resistance and cardiac afterload, contributing to regulation of cardiac output and inotropic function. Thus, TH changes lead to myocardial dysfunction either directly through gene expression dysregulation or indirectly, by modifying the sympathetic system response [24-26]. In the presence of chronic excess of TH, the development and progression of HF may be due to tachycardia-mediated cardiomyopathy with high-output HF while in the hypothyroid state, TH deficit results in lower heart rate and weakening of myocardial contraction and relaxation, which firstly gives rise to diastolic, low-output HF [26].

Hypothyroidysm

The effects of chronic thyroid failure at cardiovascular level have been well documented in hypothyroid animal models, where maladaptive shape of myocytes along with loss of coronary arterioles and impaired blood flow were observed [27]. Accordingly, TH dose effect studies showed reduced expression of both myosin heavy chains (MHC) and sarcoplasmic reticulum Ca2-ATPase as well as increased expression of its inhibitor phospholamban at lower T3 levels [27 28]. In humans, a report on a hypothyroid patient with dilated cardiomyopathy who underwent endomyocardial biopsies, at baseline and during TH replacement therapy, documented changes in myocardial gene expression with a trend

towards β-to-α MHC shift, which in turn led to cardiac function recovery [29]. Interestingly, treatment with T3 for three days after acute myocardial infarction reduced myocyte apoptosis in the border area, in animal models via complex intracellular signaling [30].

Both overt and subclinical hypothyroidism, according to the extent and time of exposure to TH deficit, may induce bradycardia, decreased ventricular filling, decreased cardiac contractility and oxygen consumption, leading to reduced cardiac output [22 26 31]. Therefore, prolonged isovolumic relaxation time, early reversible diastolic impairment and reduced contractility have been described in subclinical hypothyroid (sHT) patients [32 37]. Systolic function is also altered in sHT subjects as firstly demonstrated by increased pre-ejection/ejection time ratio and subsequently by mean aortic acceleration analysis and video-densitometric evaluation [32 36]. Accordingly, decreased cardiac preload along with increased afterload with consequent reduction in stroke volume and cardiac output was observed in sHT patients by magnetic resonance study, confirming a total impairment of cardiac function that may be worsened by exercise, which further reduce whole cardiorespiratory performance [34 37]. Cardiac modifications associated with hypothyroidism even in the subclinical form, either at rest or during exercise, may be reversed by TH replacement therapy as documented by case-control and placebo-controlled, randomized clinical studies [32 33 37]. TH act at vascular levels as vasodilators through different mechanisms involving both genomic and non-genomic pathways, leading to reduced systemic vascular resistances [14 38 39]. *In vitro* and *in vivo* studies showed different results on TH induced vasodilatation, suggesting that early relaxation may be due to non-genomic effect on vascular smooth muscle cells while delayed vasodilatation mainly depend on nitric oxide increased synthesis and release [14 38]. Accordingly, TH deficit leads to augmented systemic vascular resistances and higher diastolic blood pressure [39-42]. Rarefaction of coronary microvasculature with consequent impaired vasodilation has been also observed in chronic hypothyroidism, reversible by T3 administration [41]. In this regard, a home dwelling population study of almost 30,000 individuals, without previous known thyroid diseases and serum TSH within the reference range, revealed a linear positive association between TSH level and systemic blood pressure value [42]. In this way, chronic TH deficit may result in aortic stiffness and early atherosclerosis [42 43]. Accordingly, several studies documented significant intermediate metabolism and blood vessel alterations in sHT patients, characteristic of a pro-atherogenic status [11 44 45]. In detail, vascular reactivity and NO release as well as the response to acetylcholine were significantly impaired in sHT patients as compared to euthyroid controls [13 38]. Besides, flow-mediated vasodilation, a well-known marker of endothelial function, was also significantly altered, thus suggesting abnormalities of the parasympathetic nervous system [46]. Finally, a pro-atherogenic lipid profile with elevation of both total and LDL cholesterol levels, directly related to circulating TSH values, has been described in patients with mild thyroid failure and even in those with high normal serum TSH [11 44-48].

Overall, these findings show that both overt and subclinical hypothyroidism impact on cardiac function via complex mechanisms, including direct effects on myocardium and cardiac vessel reactivity as well as through pro-atherogenic metabolic changes, that may lead to cardiac dysfunction and HF, especially in older people, in whom the ageing process *per se* concurs in determining such modifications (Fig. 1).

Hyperthyroidism

The long-term exposure to TH excess can exert adverse effects on cardiac structure and function, by increasing left ventricular mass, arterial stiffness and left atrial dimension, which leads to altered left ventricle performance and diastolic dysfunction (Fig. 1). Untreated overt hyperthyroidism is one of the main causes of HF and, also persistent subclinical hyperthyroidism has been associated with the development and progression of HF [14 49]. The mechanism by which TH excess can induce HF is an important issue for both the endocrinologist and the cardiologist. Patients with overt or subclinical hyperthyroidism are at increased risk for cardiac death and, even high normal serum TH levels have been associated with increased risk of sudden death, although the exact mechanism is still not completely defined [15 50]. The increased risk of cardiac mortality, especially in the elderly, may be due to the high prevalence of arrhythmias and HF events associated with hyperthyroidism [50 51].

Hyperthyroid patients complain of reduced exercise tolerance and exertional dyspnoea due to reduced cardiac output [50 51]. Older patients may develop dyspnoea even while performing minor daily activities and, reduced exercise tolerance may be one of the first signs of HF in hyperthyroid older patients [49]. Orthopnoea, paroxysmal nocturnal dyspnoea, peripheral oedema and jugular vein turgor are all signs indicating the progression of HF [49]. Nonetheless, the extent and number of clinical manifestations and the severity of HF depend on a variety of factors such as the patient's age, the cause and degree of hyperthyroidism and the presence of pre-existing cardiac disorders [49 51].

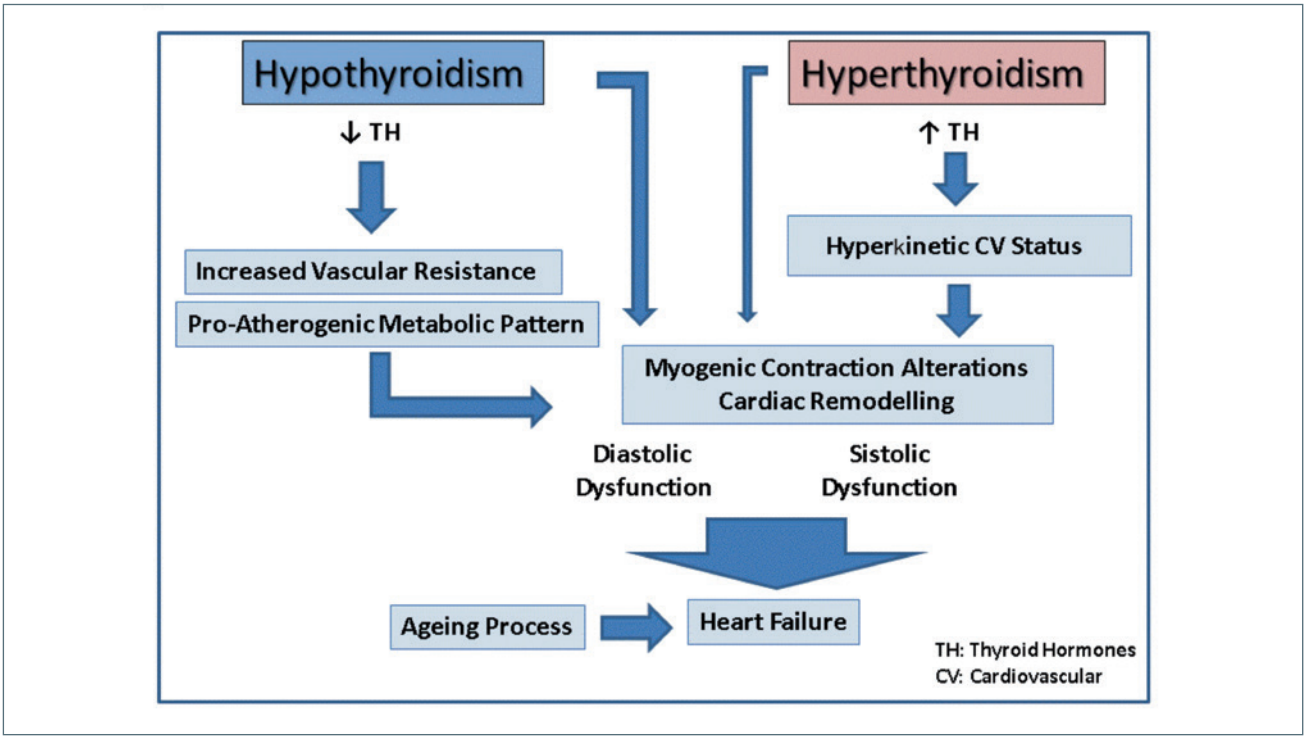

Figure 1. Relationship between thyroid dysfunction (hypo and hyperthyroidism) and heart failure (HF) development and progression.

CLINICAL EXPERIENCES

Hypothyroidism and heart failure

Several causes and risk factors of HF have been detected in large cohort studies, the most important being represented by cardiovascular (CV) diseases such as elevated systemic blood pressure, coronary heart disease (CHD), structural heart diseases and arrhythmia followed by endocrine disorders. In this regard, hypothyroidism (even the subclinical form) has been correlated with an increased risk of CHD events and some clinical conditions that lead to HF [12 52-55]. Several prospective studies were designed to evaluate the relationship between hypothyroidism and the risk of HF in different clinical settings, among which older population is one of most studied [12 54]. The common ageing modifications of cardiac structure, mainly represented by myocyte loss, interstitial fibrosis, remodeling and hypertrophy, favor the development of cardiac dysfunction, especially diastolic [32 36 56]. Moreover, when age related cardiac modifications are associated to organic disease such as CHD and valvulopathy, the risk of HF becomes highly significant especially in case of concomitant hypothyroidism [56]. In the Prospective Study of Pravastatin in the Elderly at Risk, the persistence of serum TSH values above 10 mIU/L over a 6-month period was associated with increased incident HF events in older people with previous cardiovascular risk [57]. Indeed, participants with TSH ≥ 10.0 mU/L had a greater incidence of HF events compared to euthyroid participants (41.7 *vs* 22.9/1000 person/year). An increased risk of HF was observed also in subclinical hypothyroid older patients without history of cardiac disease as shown in the Cardiovascular Health Study [58]. Moreover, mild thyroid failure of the elderly should be considered not only a worsening condition for patients already affected by HF, but also an independent risk factor for developing the disease. Thus, (mild) hypothyroidism is related not only to a greater likelihood of disease progression and hospitalization but also to a poorest prognosis and increased mortality [53 59].

Hypothyroidism, especially the subclinical form, has been shown to exert an age dependent, biphasic role in CHD development and progression: stronger in young adults (aged < 65 years) while vanishing in the last decade of life [53]. This trend seems not true for HF and, a meta-analysis on community-dwelling older subjects clearly showed that the rate of HF events increased in subclinical hypothyroid patients compared with euthyroid controls, with an incremental risk in those with circulating TSH above 10 mIU/L independently from ageing [54]. Surprisingly, a more recent meta-analysis on 13 longitudinal studies confirmed the association of hypothyroidism with cardiac and all-cause mortality and

hospitalization but, the association disappeared in patients aged < 65 years, suggesting a higher sensitivity of older heart to even mild TH deficit [60]. Moreover, as recently showed in a large naturalistic study of patients with mean age of 61 years, an important factor to be considered when evaluating the relationship between thyroid failure and CV disease or mortality is the duration of the exposure of tissues to TH deficit [61]. Overall, these findings clearly suggest that the potential detrimental effect of (mild) thyroid failure depends on several factors including ageing but also the specific organ or biological system which is analyzed. The concomitant presence of other diseases as well as the degree and duration of TH deficit should be also considered. Furthermore, while discussing on thyroid dysfunction and HF in older people the possible presence of the so called "non-thyroidal illness syndrome (NTIS)" or "low-T3 syndrome" should be not overlooked. Indeed, NTIS is a clinical condition frequently observed in the elderly, generally characterized by reduced circulating T3 and increased level of reverseT3 [62]. It is well described the association between NTIS and chronic diseases such as HF, especially during acute events and hospitalization, but it is still unclear whether it represents a protective condition to prevent excessive catabolism or an adjunctive negative illness. Holmager et al. carried out a randomized clinical trial and did not report any effect of T3 administration in older patients with chronic HF while, a previous study showed clinical benefits in terms of both neurondocrine parameters and systolic function in patients with dilated cardiomyopathy [30 63].

In conclusion, consistent data from large naturalistic studies exploring the relationship between either overt or subclinical hypothyroidism and HF are now available. However, given the lack of evidence of the impact of TH replacement therapy in preventing either the development or progression of HF, especially in older patients with mild thyroid failure, future large randomized studies are warranted to better delineate how to deal with (mild) hypothyroid older patients at risk for or with HF. Nonetheless, thyroid hormone status (not only serum TSH but also TH levels) should be assessed in older HF patients and, in case of certain thyroid failure, the possible usefulness of levothyroxine replacement should be taken into account.

Hyperthyroidism and heart failure

Several case control and naturalistic studies have evaluated the association between hyperthyroidism and HF [49]. In hyperthyroid patients systemic vascular resistances and diastolic blood pressure decrease while mean pulmonary arterial pressure is usually increased, nonetheless the development of right ventricle failure can be underestimated since it is usually reversible after recovery of euthyroidism [64]. The most frequent form of cardiac disease associated with hyperthyroidism is high output HF, which typically occurs in younger patients suffering from overt hyperthyroidism (Graves' disease) without pre-existing heart disease [56]. Patients suffering from high output HF may have symptoms of shortness of breath at rest and fatigue as well as water retention with peripheral oedema, pleural effusion, hepatic congestion and pulmonary arterial hypertension [56]. The low-output form of HF is seldom observed in hyperthyroid patients, its prevalence ranges from 6% to 15%, and usually affects older people with age related cardiac modifications and pre-existing CV diseases such as systemic arterial hypertension, CHD, valvular disorders and arrhytmia [56]. In these patients cardiac output is low, systemic vascular resistances are increased and left ventricular filling and contractility compromised. Approximately 7-8% of middle-aged hyperthyroid patients develop atrial fibrillation or flutter, the prevalence increases to 10-20% in older patients, up to 20-35% in those with pre-existing CHD or valvular disease [49].

In a study of 591 consecutive young adults (mean age 45 years) suffering from hyperthyroidism, HF was detected in 6% of the cases [65]. Few studies have assessed the risk of HF in older patients with (subclinical) hyperthyroidism. In the Cardiovascular Health Study, a naturalistic study that included 3044 adults older than 65 years without known heart disease, 46 HF patients (mean age 72.6 years) were affected by subclinical hyperthyroidism but, despite cardiac abnormalities at echocardiographic examination, no correlation was found between serum TH values and the risk of developing HF [58]. The authors found that during a 3.2-yr follow-up period, the incidence rate of hospitalization for HF was higher in older people with subclinical hyperthyroidism compared with the euthyroid group, with 31 *vs* 12 events per 1000 person/year ($p = 0.01$). However, other studies showed that the onset of subclinical hyperthyroidism might exacerbate cardiovascular risk in patients with pre-existing heart disease. Indeed, a recent longitudinal study showed a significant association between subclinical hyperthyroidism (TSH < 0.45 mIU/L) and the rate of HF in older patients (aged 72-82 years) with known CV risk factors or previous CV disease, over 3.2 years of follow-up [57]. Moreover, a large pooled analysis of individual participant data from six prospective cohorts, which included 25,390 participants with 216,248 person-years of follow-up, demonstrated an overall significantly increased risk of HF events in patients suffering from subclinical hyperthyroidism (n = 648, 2.6%), especially in case of suppressed serum TSH values [54]. Accordingly, a very recent nationwide cohort study, including 35% of subjects older than 70 years, documented increased

all-cause mortality in hyperthyroid patients as compared to euthyroid controls [66]. Also, an increased risk for all examined CV events was observed, with the highest probability in the first three months after diagnosis. The 3-month post-diagnosis risk was highest for atrial fibrillation and arterial embolism, but significantly increased risk was observed also for incident venous thromboembolism, ischemic and non-ischemic stroke and acute myocardial infarction as well as percutaneous coronary interventions [66]. In this setting, a large naturalist study showed that, beside the degree of hyperthyroidism, an important factor affecting patients' clinical outcome and survival is the duration of the exposure of tissues to thyroid hormone excess [61]. Accordingly, data from the Rotterdam Study, in which around 10,000 individuals older than 45 years were enrolled, showed that higher serum free thyroxine (FT4) levels, even in the normal range of thyroid function, were associated with an increased risk of sudden cardiac death, over 9.1 years of follow-up [15]. In this setting, another recent report from the same cohort showed that serum FT4 levels in the highest quartile of the normal range, were associated with higher rate of incident atrial fibrillation. In detail, absolute 10-year risk increased from 1% to 9% in younger participants and from 6% to 12% in those older than 65 years [67]. These two latter studies clearly demonstrate that even small variations of serum TH level, still in the normal range of thyroid function, may have significant impact at CV level, even in individuals younger than 65 years. Overall, these findings suggest that thyroid function tests should be performed not only in (older) patients with no other identifiable causes of HF but also in those with known CV risk factors or previous CV disease.

CONCLUSIONS

Overall, an increasing body of evidences documented a negative effect of overt thyroid dysfunction on heart function, increasing the risk of HF and mortality. Some experiences also suggested a negative effect of the subclinical form of either hypo- or hyperthyroidism. In detail, both overt and subclinical hypothyroidism impact on cardiac function via complex mechanisms, including direct effects on myocardium and cardiac vessel reactivity as well as through pro-atherogenic vascular changes, that may lead to cardiac dysfunction and HF, especially in the elderly in whom the ageing process *per se* concurs in determining such modifications. It is worth to mention that even subclinical hypothyroidism may increase the risk of hospitalization and death in older HF patients, indicating the extreme susceptibility of the ageing heart to slight TH deficit. Thus, it appears crucial to assess thyroid function in older patients suffering from HF, even if the lack of randomized clinical trials leaves us with several unresolved key issues regarding specific criteria and goal of treatment, as stated in latest guidelines [20 68]. For this reason, appropriately powered, randomized controlled trials of L-thyroxin replacement in older sHT patients, examining the effect in preventing HF progression and events as well as overall survival, are clearly warranted.

The association between hyperthyroidism and heart failure is well established in older population. Moreover, even small variations of serum TH level, still in the normal range of thyroid function, may have significant impact at cardiovascular level, not only in the elderly. Several mechanisms may directly contribute to HF in patients with hyperthyroidism, as vasculature changes and modification of myocardial contractility. Although high output HF is the most frequently observed in hyperthyroidism, older patients often suffer from low-output HF, especially in case of pre-existing cardiac disease. Approximately 10-20% of older hyperthyroid patients develop AF or flutter and, the prevalence increases up to 20-35% in those with pre-existing CHD or valvular disease. Thus, we should consider AF of the elderly as a possible condition that may worsen and precipitate early phase HF. Overall, these data suggest that hyperthyroidism should be ruled out not only in older patients with no other identifiable causes of HF but also in those with known CV risk factors or previous CV disease. It is important to early recognize (mild) hyperthyroidism in older patients [69] and, depending on the extent and the duration of such alteration, consider anti-thyroid medication [49]. However, future large randomized, intervention studies in elderly balancing the risk and benefits of anti-thyroid medication according to the degree of serum TSH reduction and TH elevation are warranted.

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