COMMENTARY

How could we improve the increased cardiovascular mortality in patients with overt and subclinical hyperthyroidism?

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Abstract

Over the past five years several meta-analyses have evaluated the cardiovascular mortality in patients with hyperthyroidism. They assessed various studies in which different inclusion criteria were used for the analysis of the cardiovascular mortality. More selective criteria have been used in recent meta-analyses. Only prospective cohort studies were included and only cohorts using second and third generation TSH assays were chosen. In addition, only the studies where the TSH evaluation was repeated during the follow-up were selected. The results of these recent meta-analyses provide evidence that overt and subclinical hyperthyroidism, particularly in patients with undetectable serum TSH, may increase the cardiovascular mortality. However, still today, the results remain inconclusive and not sufficient enough to recommend treatment for patients with low-detectable serum TSH. The high cardiovascular risk and mortality in presence of thyroid hormone excess suggest that this dysfunction is an important health problem and requires guidelines for the treatment of patients at high cardiovascular risk. Rigorous studies are necessary to evaluate the effects of the various causes of hyperthyroidism on the clinical outcomes. Randomized controlled clinical trials are needed to assess the benefits of treatment to improve the cardiovascular mortality and morbidity of mild and overt hyperthyroidism.

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Introduction

Parry (1) and Graves (2) reported the first descriptions of the cardiovascular (CV) manifestations of hyperthyroidism in 1800. However, only in the last 5 years have several meta-analyses recognized that hyperthyroidism, in both overt and subclinical conditions, is associated with an increased CV mortality (3, 4, 5, 6, 7, 8, 9). Three of these meta-analyses have been published in the *European Journal of Endocrinology* (4, 7, 8).

CV mortality in overt hyperthyroidism

Only two meta-analyses have assessed the CV mortality in overt hyperthyroidism (3, 4) (Table 1). The first meta-analysis was published in 2007 and evaluated the results of seven cohort studies (3); a 1.7-fold elevated risk for CV mortality rate was detected in the presence of overt thyroid hormone excess (3). In particular, an increased circulatory mortality was observed in three studies (10, 11, 12).

A critical review and meta-analysis published in 2011 reported a 20% increased mortality in patients with overt hyperthyroidism and six studies assessing CV mortality were included (4). When the authors pooled them together, they were associated with a higher CV

mortality in overt hyperthyroidism compared with the control population (relative risk (RR) 1.13; 95% confidence interval (CI) 1.00 to 1.28) (4). Particularly, in this last meta-analysis, four studies (10, 13, 14, 15) found a significantly raised CV mortality in hyperthyroid patients compared with the control population. The majority of epidemiological studies assessing CV mortality in overt hyperthyroidism only adjusted their results for age, sex, and race as relevant confounders; moreover, in some studies, the gender-matched control group was inhomogeneous (3, 4).

Some of the studies included in these two meta-analyses were performed in Europe where iodine deficiency determines the increased risk of hyperthyroidism due to thyroid autonomy (toxic multinodular goiter (TMNG) and toxic adenoma (TA)) (16). Other studies came from the United States, where Graves disease (GD) is the main form of hyperthyroidism because iodine sufficiency is present in this country (16).

It is important to identify the potential cardiac events responsible for the increased CV mortality in the presence of thyroid hormone excess. The etiology of hyperthyroidism, the severity, duration, and age of this dysfunction, the association with smoking, genetic, and environmental factors, underlying heart conditions, or comorbidities may influence the CV risk (16, 17). In the majority of the epidemiological studies, these

Table 1 Summary of meta-analyses assessing the cardiovascular mortality in the presence of thyroid hormone excess.

References	Studies included
Meta-analyses on cardiovascular mortality in patients with overt hyperthyroidism	
Völzke <i>et al.</i> (3)	7
Brandt <i>et al.</i> (4)	6
Meta-analyses on cardiovascular mortality in patients with subclinical hyperthyroidism	
Völzke <i>et al.</i> (1)	2
Singh <i>et al.</i> (5)	3
Ochs <i>et al.</i> (6)	5
Haentjens <i>et al.</i> (7)	7
Yang <i>et al.</i> (8)	17
Collet <i>et al.</i> (9)	10

confounders were not considered, and this could have severely limited the recognition of the potential causes responsible for the increased CV mortality in overt hyperthyroidism.

Thyroid autonomy usually develops in elderly patients who may have underlying heart disease or comorbidity and it is preceded by prolonged subclinical hyperthyroidism (SHyper) (16, 17). Persistent atrial fibrillation with left atrial enlargement, embolic events, systolic hypertension with a wide pulse pressure, heart failure (HF), and coronary heart disease (CHD) represent the most frequent adverse cardiac events observed in elderly patients with hyperthyroidism, especially in patients with associated heart disease (16, 17). GD usually develops in young and middle-aged patients with severe hyperthyroidism; moreover, it may be associated with autoimmune CV involvement with the potential onset of pulmonary arterial hypertension, cardiac valve involvement, and dilated cardiomyopathy (16). Therefore, different CV risk factors might be associated with different etiologies of hyperthyroidism, although this assumption remains to be demonstrated after the evaluation of large clinical studies, comparing the CV risk in patients with different causes of hyperthyroidism.

CV risk during treatment with antithyroid drugs

It is essential to improve the CV mortality with an appropriate treatment of overt hyperthyroidism. The persistence of some CV risk factors has been reported in some studies during the treatment of overt thyroid dysfunction (13, 18). Supraventricular dysrhythmias, CV symptoms, and negative hemodynamic changes persisted after treatment with antithyroid drugs in the prospective study performed by Osman *et al.* (13). These data suggest a delay in restoring the tissue euthyroidism during medical therapy of hyperthyroidism, despite the normalization of thyroid hormone levels. In fact, TSH levels may be persistently low to undetectable during treatment with antithyroid drugs and do not allow

restoration of sinus rhythm in patients with atrial fibrillation and improvement of cardiac function in the presence of heart disease (19, 20).

Atrial fibrillation is an important cause of stroke and pulmonary embolism (21, 22) and may be reversible after treatment of hyperthyroidism (23). Spontaneous reversion occurs in up to 50% of adequately treated patients (23). However, the reversion of atrial fibrillation rarely happens in patients with advanced age, history of cardiac failure, and the presence of associated CV risk factors such as diabetes, left ventricular hypertrophy, elevated systolic and/or diastolic blood pressure, and atrial enlargement (13, 23). These considerations could suggest the importance of rapidly normalizing serum TSH levels during treatment with antithyroid drugs in elderly patients and in those with associated CV risk factors. Moreover, special attention should be given to an adequate and prompt treatment of atrial fibrillation to avoid its persistence, mainly in patients with new onset atrial fibrillation with the appearance of hyperthyroidism.

CV mortality after radioiodine treatment

An increased mortality, although statistically nonsignificant, was reported in the meta-analysis by Brandt *et al.* (4) after pooling all studies assessing the risk of hyperthyroidism after radio active iodine (RAI) treatment. An overall increased all cause mortality and CV mortality was reported in four studies after radioiodine treatment (14, 15, 24, 25). Interestingly, the majority of these studies adjusted their analyses for sex, age, CV disease (CVD), and comorbidities.

Total CVD and fractures were the major significant factors contributing to the increased mortality in the study by Franklyn *et al.* (15). The excess mortality was associated with cerebrovascular disease and ischemic heart disease, especially in subjects older than 60 years (15).

Some studies differentiated the CV risk after RAI in patients with GD and TMNG (14, 25). An increased rate of hospitalization for arrhythmias, atrial fibrillation, cerebrovascular disease, and HF was reported after RAI, particularly in patients with TMNG (14, 25). Cerebrovascular diseases were the most important causes of mortality in patients with TMNG aged over 65 years, whereas RAI was not associated with an increased CV mortality in GD (14).

It is not clear whether the increased CV mortality after radioiodine is due to the severity of hyperthyroidism itself or to the negative effects in hyperthyroid patients inadequately prepared for RAI. In some studies, a strong link was observed between mortality and the dose of radioiodine as an indirect marker for the severity of hyperthyroidism. RAI may lead to a worsening of hyperthyroidism and of its CV implications because it induces thyroiditis due to radiation. This effect is

particularly dangerous in older patients and in subjects with severe hyperthyroidism. McDermott *et al.* (26) reported some cases of thyroid storm after RAI.

The recent American Thyroid Association guidelines on the treatment of hyperthyroidism have suggested that treatment with beta-blocking drugs may be sufficient to control severe hyperthyroidism before RAI. However, they have reported conflicting opinions on pretreatment with antithyroid drugs (Recommendation 33) (27). Previous considerations could suggest that hyperthyroidism should be treated before RAI especially in severe disease, elderly patients, and in those with atrial fibrillation (AF) and CVD.

A meta-analysis on the effects of antithyroid drugs before RAI treatment suggests that adjunctive antithyroid drugs may reduce biochemical and chemical hyperthyroidism in the weeks after treatment; it may lower cardiac morbidity and mortality (28). Nonetheless, antithyroid drugs may increase the rate of RAI failure: propylthiouracil induces more radioresistance and lower rates of hypothyroidism than methimazole, especially when administered in the week before RAI (28). Accordingly, methimazole should be the preferred option (27, 28). The withdrawal of antithyroid drugs could be performed when RAI becomes effective (28). The use of higher doses of RAI can compensate the risk of treatment failure after pretreatment with antithyroid drugs (27, 28). A lower mortality after RAI has been reported in two studies in subjects who developed hypothyroidism (14, 15). High doses of RAI, which may induce hypothyroidism, could be useful to improve the prognosis of elderly patients avoiding the development of an unrecognized thyroid failure during the follow-up (29).

It has been reported that radioiodine-treated patients may have an increased risk of atrial fibrillation compared with controls (14). Hypercoagulability and hypofibrinolysis may contribute to the increased risk of thromboembolism in hyperthyroid patients with AF. For this reason, anticoagulation should be considered in patients with atrial fibrillation; its beneficial effect should be balanced with the risk of bleeding and other complications of this treatment (16, 27). Anticoagulation treatment should be personalized after analyzing the age of the patients, the presence of comorbidities, and the CV risk factors for stroke.

A careful, long-term follow-up with a strict surveillance for the risk of CVD and fractures should be performed in patients with hyperthyroidism treated with RAI. Drugs to improve bone mineral density should be administered in patients with osteoporosis to rapidly improve the risk of fracture.

Randomized controlled trials are necessary to assess the best treatment to improve CV mortality in hyperthyroid patients and to evaluate the best approach considering the cause of this dysfunction, the age of the patients, and comorbidities.

CV mortality in SHyper

Conflicting results have been reported in the large cross-sectional and prospective studies assessing the CV morbidity and mortality in patients with endogenous SHyper, reflecting the heterogeneity of the different populations studied (30). Therefore, five meta-analyses have evaluated the CV mortality in patients with SHyper during the last years (3, 5, 6, 7, 8, 9) (Table 1).

The first meta-analysis performed by Völzke *et al.* (3) did not report a significant association between SHyper, circulatory mortality, and all-cause mortality. Similarly, the pooled relative risk revealed a nonsignificant difference in CV mortality in SHyper in the meta-analysis by Singh *et al.* (5), both at baseline and during the follow-up. However, these two meta-analyses only included the small number of studies (respectively two and three studies) available at that time and, therefore, they had a lower power to detect a potential association between SHyper and CV mortality.

The meta-analysis by Ochs published in 2008 included five population-based studies and showed a modestly increased risk for CHD, CV mortality, and total mortality in patients with SHyper (the RR was 1.21 (CI, 0.88 to 1.68) for CHD, 1.19 (CI, 0.81 to 1.76) for CV mortality, and 1.12 (CI, 0.89 to 1.42) for total mortality (6)). A significantly increased risk of CV disease was found in the general population with SHyper. On the contrary, the risk of CV and all-cause mortality was particularly increased in individuals with other morbidities. Heterogeneity was observed when pooling all the studies on SHyper and CV mortality, and a lower risk was estimated when pooling higher quality studies (6).

In 2008, another meta-analysis by Haentjens *et al.* (7) was published. This meta-analysis was performed on seven cohorts, including 290 participants with SHyper. It showed that elderly patients with SHyper and patients with comorbidities had an increased probability of death (7). This risk progressively increased during 10 years after the diagnosis of SHyper: the HR for all-cause mortality was 1.03 (95% CI, 0.78 to 1.35; $P=0.83$) in cohorts from the community and 1.76 (95% CI, 1.36 to 2.30; $P<0.001$) in cohorts of patients with comorbidities (7). Some limitations of the epidemiological studies included in these last two meta-analyses (6, 8) (one TSH evaluation at baseline and no information on treatment of SHyper during the follow-up) may have affected the results on CV mortality in the presence of mild thyroid hormone excess.

Recently, more selective criteria have been used in two recent meta-analyses, assessing the CV mortality in patients with SHyper (8, 9). Only prospective cohort studies were included, and only cohorts using second- and third-generation TSH assays were selected for the analysis. In fact, the diagnosis of SHyper can be limited using the first-generation TSH assays. Moreover, the authors considered the use of drugs for treatment of SHyper and selected the studies in which the TSH

evaluation was repeated during the follow-up. Furthermore, these two meta-analyses stratified their analysis according to the degree of TSH suppression.

Yang *et al.* (8) selected 17 prospective cohort studies in their meta-analysis. They included papers published between 2001 and 2011, which had a duration of follow-up ranging from 2 to 20 years; the majority of these studies were performed in Europe. Only seven of the included studies repeated the TSH evaluation during the follow-up. Moreover, subjects receiving thyroid medications (users of thyroxine and antithyroid drugs) were excluded in ten studies. The results of this meta-analysis showed that SHyper increased the risk of CV disease in the general population. Moreover, the subgroup analysis showed an increased risk of CV and all-cause mortality in patients with additional comorbidities, confirming previous results (6, 7). The overall combined relative risks of CVD for individuals with SHyper compared with the reference group were 1.19 (95% CI, 1.10 to 1.28) for CVD, 1.52 (95% CI, 1.08 to 2.13) for CV mortality, and 1.25 (95% CI, 1.00 to 1.55) for all-cause mortality. The omission of each individual study did not significantly change the pooled effects. Moreover, the exclusion of the studies defining SHyper as a suppressed TSH (<0.1 mU/l) did not significantly influence the results. All the included studies adjusted their results for conventional CV risk factors (age, BMI, blood pressure, diabetes, cholesterol, and smoking), suggesting that SHyper could be an independent risk factor of CVD. No sufficient data were available in these meta-analyses to perform a sub-analysis for the risk of atrial fibrillation and stroke.

Another meta-analysis assessing the individual data from ten prospective cohort studies on the association between SHyper and CV outcome has been recently published in the *Archives of Internal Medicine* (9). Total mortality and CHD mortality were assessed from all cohorts. CHD event data were analyzed from six cohorts and the data for incident atrial fibrillation events were available from five cohorts. The median follow-up was 8.8 years. Patients receiving thyroid medication or drugs potentially altering thyroid function were excluded. A stratified analysis by age, sex, race, TSH categories, and preexisting CVD was performed.

In age- and sex-adjusted analyses, SHyper was associated with increased total mortality (hazard ratio (HR), 1.24, 95% CI, 1.06 to 1.46), CHD mortality (HR, 1.29; 95% CI, 1.02 to 1.62), CHD events (HR, 1.21; 95% CI, 0.99 to 1.46), and AF (HR, 1.68; 95% CI, 1.16 to 2.43). When the risk was stratified according to the TSH levels, the results showed that endogenous SHyper was associated with an increased risk of total, CHD mortality, and incident atrial fibrillation, especially in the presence of a TSH level lower than 0.10 mU/l. The risk of stroke did not increase in SHyper.

Therefore, these two recent meta-analyses provide evidence that SHyper may increase CV mortality, particularly in patients with undetectable serum TSH

levels. However, still today, the results remain inconclusive and insufficient to recommend treating young patients with SHyper and low-detectable serum TSH levels. In both these recent meta-analyses, all included studies have not provided detailed information on the cause of primary SHyper and, therefore, a sub-analysis for CV complications related to the etiology of this condition is not available.

The mechanism by which SHyper may be associated with an increased CV risk may be linked to the risk of atrial arrhythmias, especially atrial fibrillation, and the negative changes in CV function, which have been reported in long-term, untreated, mild thyroid hormone excess (19, 30, 31, 32, 33). Few studies have evaluated the effects of medical and RAI treatment to improve CV parameters in SHyper (34, 35, 36).

Endogenous SHyper is prevalent in areas of iodine deficiency and may be persistent, unrecognized, and untreated mainly in elderly patients. Thus, the evidence of the high CV risk and mortality associated with SHyper suggests that this dysfunction is an important health problem in areas of iodine deficiency and requires guidelines for the best treatment, above all in patients at high CV risk. Further rigorous, randomized controlled studies are necessary to evaluate the effects of the various causes of hyperthyroidism on the clinical outcomes. Randomized, controlled clinical trials are also necessary to assess the benefits of treatment to improve the CV mortality and morbidity of mild thyroid hormone excess.

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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