Cardiovascular effects of overt and subclinical hyperthyroidism

Links, Thera P; van der Boom, Trynke; Zandee, Wouter T; Lefrandt, Joop D

Published in:
Endocrine Connections

DOI:
10.1530/EC-20-0539

Publication date:
2020

 Accepted Manuscript published as EC-20-0539. Accepted for publication: 14-Dec-2020

Cardiovascular effects of overt and subclinical hyperthyroidism: focus on differentiated thyroid cancer

Thera P. Links, MD PhD[1], Trynke van der Boom, MD[1], Wouter T. Zandee, MD PhD[1], Joop. D. Lefrandt, MD PhD[2]

University of Groningen, University Medical Center Groningen, department of Internal medicine division of [1]Endocrinology and [2]Vascular Medicine

Corresponding author:
Prof. dr. Thera P. Links
University Medical Center Groningen
Department of Endocrinology, HPC AA31
P.O. Box 30.001
9700 RB Groningen
The Netherlands
Telephone number: +3150 3616161
Email: t.p.links@umcg.nl
Fax: +3150 3619392

Short title

Key words:	cardiovascular risk, thyroid carcinoma, hyperthyroidism,
Number of tables/figures:	1/1 (1 supplemental)
Disclosure:	None
Word count	3509

Abstract

Thyroid hormone stimulates cardiac inotropy and chronotropy via direct genomic and non-genomic mechanisms. Hyperthyroidism magnifies these effects, resulting in an increase in heart rate, ejection fraction and blood volume. Hyperthyroidism also affects thrombogenesis and this may be linked to a probable tendency towards thrombosis in patients with hyperthyroidism. Patients with hyperthyroidism are therefore at higher risk for atrial fibrillation, heart failure and cardiovascular mortality. Similarly, TSH suppressive therapy for differentiated thyroid cancer is associated with increased cardiovascular risk.

In this review, we present the latest insights on the cardiac effects of thyroid suppression therapy for the treatment of thyroid cancer. Finally, we will show new clinical data on how to implement this knowledge into the clinical practice of preventive medicine.

 Accepted Manuscript published as EC-20-0539. Accepted for publication: 14-Dec-2020

Introduction

Thyroid hormones and the cardiac system are closely related. This is illustrated by the fact that most characteristics and common symptoms of hyperthyroidism - such as palpitations, excitability, and perspiration - are the result of the effects of thyroid hormones on the cardiovascular and nervous system. In this review we will explain these effects, first describing some general aspects of the relation between the thyroid and the cardiovascular system, and then clarifying the impact of overt and subclinical hyperthyroidism on the cardiovascular system. We will thereafter present the latest insights on the cardiac effects of thyroid suppression therapy for the treatment of thyroid cancer. Finally, we will show new clinical data on how to implement this knowledge into the clinical practice of preventive medicine.

Effects of thyroid hormones

Thyroid hormones influence the cardiovascular system via direct and indirect mechanisms. The most direct mechanism is the presence of thyroid hormone receptors on the myocardium and vascular endothelial cells (1). Indirect mechanisms include the cardiovascular effects of thyroid hormones via inflammatory cytokines and lipid metabolism.

Vascular effects

Triiodothyronine (T3) is the physiologically active thyroid hormone produced by de-iodination of the inactive hormone thyroxine (T4). T3 increases cardiac output by reducing systemic vascular resistance. First, T3 stimulates the endothelium of the vascular smooth muscle cells to synthesize and secrete nitric oxide (2).This results in relaxation of the smooth muscles, which reduces systemic vascular resistance, thereby diminishing the volume of effective arterial filling. This results in a release of renin and activation of the angiotensin-aldosterone axis, leading to an increase in plasma volume by renal sodium reabsorption. Finally, this increased plasma volume increases the cardiac output by an increase in preload (3).

The pathological state of hyperthyroidism magnifies the above-mentioned effects, resulting in an increase in heart rate, ejection fraction, and blood volume, and in a decrease in systemic vascular resistance and isovolumic relaxation time (4).

Cardiac effects

T3 influences cardiac inotropy and chronotropy via direct genomic and non-genomic mechanisms. A direct genomic effect of T3, mediated by thyroid hormone nuclear receptors, is modulation of the transcription rate of multiple cardiac genes involved in - among others - the kinetics of the influx and efflux of the calcium ions in the sarcoplasmatic reticulum. This is an essential contribution to optimal contraction and relaxation of the cardiomyocyte. Non-genomic effects of T3 are not receptor dependent and may influence the performance characteristics of various sodium potassium and calcium channels. This changes the intracellular levels of calcium and potassium, thereby influencing inotropy and chronotropy (1).

Haemostatic system

For the thyrotoxic state, an extensive meta-analysis has illustrated a relation between thyroid hormone levels and the haemostatic system. Analysis revealed in thyrotoxicosis evidence of a hypercoagulable and hypofibrinolytic state, in both endogenous and exogenous thyrotoxicosis, and also in clinical and subclinical hyperthyroidism (5).

Overt hyperthyroidism

The cardiovascular effects of overt hyperthyroidism have been observed for decades. In fact, some examples of pioneering publications were published > 25 years ago. One example is a paper by Sawin and colleagues, which showed a low serum thyrotropin (thyroid-stimulating hormone [TSH]) concentration in people aged 60 or older to be associated with a three times higher incidence of atrial fibrillation in the subsequent decade (6). The group of Franklyn showed that a low serum TSH is associated with increased mortality from all causes, and in particular mortality due to cardiovascular diseases (7). In the studies by both Sawin and Franklyn, low TSH was considered to be the best marker of thyroid hormone excess. However, neither researcher could show an association between serum free T3 and T4

 Accepted Manuscript published as EC-20-0539. Accepted for publication: 14-Dec-2020

concentrations, and they suggested a greater specificity of serum TSH as tissue marker of thyroid hormone status. A more recent meta-analysis showed a 20% increase in all-cause mortality in patients diagnosed with hyperthyroidism (8). Moreover, a later study by the same authors showed a significant increase particularly in cardiovascular mortality, especially in Graves patients (9).

The increased mortality in overt hyperthyroidism can be explained by both heart failure and atrial fibrillation. In overt hyperthyroidism, congestive circulation results in high output failure. In addition, the associated atrial fibrillation may increase the risk of heart failure and stroke. Clinical data have already confirmed the relation between hyperthyroidism and heart failure. Thirteen percent of patients with new onset atrial fibrillation were found to have biochemical hyperthyroidism, and conversely, 10-15 % of patients with hyperthyroidism are known to develop atrial fibrillation – a rate much higher than the 1% atrial fibrillation present in the general population (10).

Hyperthyroidism also affects thrombogenesis with a rise in factors VIII and IX, fibrinogen, von Willebrand factor, and plasminogen activator inhibitor-1 factor, whereas these factors are not increased in euthyroid patients. This may be linked to a probable tendency towards thrombosis in patients with hyperthyroidism. Increasing levels of T4 have been shown to be a risk factor for venous thrombosis (11). Although a specific mechanism remains to be elucidated (12), the procoagulant effects observed in hyperthyroidism have been shown to be mediated via the TRβ (13).

Subclinical hyperthyroidism

Subclinical hyperthyroidism is defined as a subnormal serum TSH level while serum levels of T3 and T4 remain within the normal range. The prevalence of subclinical hyperthyroidism ranges from 0.6-1.8 % in adults, depending on age, sex and iodine status (14). Although patients with subclinical hyperthyroidism often do not experience symptoms of hyperthyroidism, they are nevertheless at increased risk of cardiovascular disease, osteoporosis, and dementia (14). A landmark study with pooled data from 10 large prospective cohorts showed subclinical hyperthyroidism to be associated with an increased

risk of atrial fibrillation (HR 1.68; 95% CI: 1.16-2.43). The strength of this meta-analysis was that it included only prospective studies, and selected cohorts using second- and third-generation TSH assays (15). Especially TSH levels lower than 0.10 mIU/L were associated with an increase in cardiovascular events and atrial fibrillation. The risk of atrial fibrillation had already been illustrated in the earlier mentioned study of Sawin, who also included patients with subclinical hyperthyroidism in his study (6).

In general, subclinical hyperthyroidism is associated with a higher incidence of major adverse cardiovascular events. This could be the result of a hypercoagulable state, because increased factor X activity has been measured in patients with subclinical hyperthyroidism(16). Moreover, in subclinical hyperthyroidism an increased carotid intima-media thickness has also been reported (17). Altogether, subclinical hyperthyroidism results in an increased risk of death from cardiovascular disease (HR 1.29; 95% CI: 1.02-1.62), as well as leading to other effects, such as an increased left ventricular mass, sinus tachycardia, and diastolic dysfunction (15).

TSH suppression in differentiated thyroid cancer.

Adults

Differentiated thyroid cancer, consisting of papillary and follicular thyroid cancer, is common at a relatively young age, with a peak incidence at ages 35 to 50 years. DTC has a relatively good prognosis (18). Thyroid cancer is the fifth most common type of cancer in women (19). For all patients the standard initial treatment for DTC has consisted of thyroidectomy, radio-active iodine (RAI) adjuvant therapy, and TSH suppression therapy. Nowadays, this treatment is given mainly to patients with high risk of recurrence. In the past, TSH suppression was standard follow-up therapy for all patients with thyroid cancer, regardless of the cancer stage. This has provided insight regarding long-term effects of this suppression therapy, including the increased risk of cardiovascular disease and mortality. As a result, moderate and complete suppression is currently recommended for patients with biochemically or structurally incomplete disease, whereas the other stages are treated with mild or no suppression (20).

 Accepted Manuscript published as EC-20-0539. Accepted for publication: 14-Dec-2020

In the early nineties, adult patients on TSH suppression therapy for thyroid cancer or multi-nodular goiter were already shown to have diastolic dysfunction and an increased left ventricular mass (21). A significantly lower left ventricular ejection fraction (within reference range) was found in 25 thyroid cancer patients after more than 10 years of TSH suppressive therapy, compared to controls. A randomized study in these 25 patients showed the diastolic dysfunction, also reported in this study, to be partly reversible after 6-month restoration of euthyroidism (22). Patients on TSH suppression therapy also are at risk of overt cardiovascular disease, according to increasing evidence presented from several points of view. Table 1 summarizes the most important studies on the cardiovascular effects of exogeneous TSH suppression since 2010. Our group showed in more than 500 DTC patients, compared to 1500 controls, a 2.5- fold increase in AF that was independent from the well-known AF risk factors (23). Other studies also showed a higher prevalence of AF in thyroid cancer patients (24,25). One study also showed a higher risk of stroke (26). However, none of these studies could find an association between TSH level and AF.

Children

Although thyroid cancer during childhood is rare, it is nevertheless the most common endocrine malignancy in children and its incidence is increasing (19). At the time of diagnosis children often have a larger tumors and higher prevalence of cervical lymph nodes and distant (mostly pulmonary) metastases, and show a higher recurrence rate compared to adults (27,28). Nevertheless, their prognosis is even better than that of adults, with 15-year survival rates above 95% (29,30). In the last decade more attention has also been given to late effects in survivors of pediatric differentiated thyroid cancer. This underscores the need for data to evaluate in children the effects of cancer treatment consisting of a total thyroidectomy and, if necessary, extensive lymph node dissection, radio-active iodine (RAI) adjuvant therapy, and TSH suppression comparable to the treatment in adults.

A nationwide study was performed to evaluate the outcome, surgical complications and late effects of 131-I treatment and TSH suppressive therapy as well as quality of life in survivors of pediatric DTC in The Netherlands treated between 1970 and 2013 (30). The outcomes of more than 100 survivors were studied, and the majority showed no evidence of disease; 8 had recurrent and 9 persistent disease. In 66 subjects, all of them long-term adult survivors of pediatric DTC with a median follow up of 17 years, the prevalence of cardiac dysfunction

was studied in relation to treatment variables, and compared with reference data for echocardiography based on the recommendations of the American Society of Echocardiography, and using retrospective data of 66 unaffected sex- and age-matched Dutch controls. The most striking observation was diastolic dysfunction in 14 out of these 66 asymptomatic survivors (21.2%) without an association with the available TSH levels during their medical history (31). Higher attained age and larger waist circumference were associated with decreased diastolic function, whereas TSH levels and cumulative administered radioiodine dose were not. The biomarkers (N-Terminal pro-brain natriuretic peptide, high-sensitive Troponin-T, galectin-3), were also not associated with diastolic dysfunction. Atrial fibrillation was not observed during a 24-hour Holter electrocardiography. Recently, 47 of these 66 survivors were re-evaluated with echocardiography, and this assessment of cardiac function established a further worsening, after five years, of the earlier found impaired diastolic function. The main finding was a further deterioration of the diastolic function, illustrated in the early diastolic lateral tissue velocity, the e' lateral and e' septal, as a hemodynamic determinant of left ventricle relaxation, restoring forces, and filling pressure. Diastolic dysfunction was present in the e' septal in 23.9% of the survivors, and in the e' lateral in 40.4%. However, in these data an association with TSH level could not be confirmed, possibly because of insufficient lab data to cover the entire follow-up period adequately (Reichert, submitted data). However, these data may have a clinical impact, because diastolic dysfunction has been considered as a possible primary manifestation of more overt heart failure (32).

So far, these data support the presence of cardiovascular damage and risk of cardiovascular disease, although the pathophysiological background is not yet clear; evidence of an obvious relation with TSH suppression is still lacking.

Relation TSH suppression

However, other data have shown a relationship between the risk of cardiovascular mortality and TSH level. In a cohort of 524 adult patients with DTC, a 3.3 fold increase in cardiovascular mortality, independent of cardiovascular risk factors, was shown when they were compared with more than 1500 age- and sex-matched controls (33). This study reported an association between lower TSH levels and higher risk. Moreover, after adjustment for cardiovascular risk factors, DTC risk (based on the TNM classification),

Accepted Manuscript published as EC-20-0539. Accepted for publication: 14-Dec-2020

histology, cumulative radioiodine dose and neck radiotherapy, TSH level remains predictive of cardiovascular mortality. The specific mechanism of the effects of suppressed TSH levels, thereby accompanied by increased free thyroxin levels, is still unknown. After all, the effect of altered thyroid hormone status may also have thus far unknown results on cellular level, as circulating free T3 and free T4 concentrations do not reflect intracellular concentration. This was illustrated more than 20 years ago in a study on thyroidectomized rats treated with T4; the study showed that euthyroidism could not be restored in the rat tissues (34). Thus, intracellular thyroid metabolism in patients on thyroxine replacement therapy may also differ from that in subjects with normal thyroid function. These pathophysiological gaps do not eliminate the clinical relevance of the risk of cardiovascular disease in patients treated with a suppressive dosage of thyroxine for thyroid cancer. Cardiovascular disease is a significant challenge for thyroid cancer survivors, and a long existing problem, as already shown in the study by MD Anderson among adult thyroid cancer survivors. Of patients reporting by questionnaires, 9.7%, 6.9% and 19.1% developed cardiovascular disease after respectively <10 years, 10-20 years, and >20 years of follow-up. Especially considering the excellent prognosis of this disease, this is a large group of patients (35). Furthermore, other cohort studies also indicate that administration of TSH suppression therapy is associated with increased cardiovascular risk (36,37).

Prevention of cardiovascular events in differentiated thyroid carcinoma

The question arises which DTC patients are at risk of developing cardiovascular events, and whether screening and primary prevention are useful in this patient category. The use of TSH suppressive therapy is currently tempered in both adult and pediatric patients who have long term disease-free survival. However, especially in high and intermediate risk groups, TSH suppression is still being applied during the first five years of follow-up and for long term follow-up during persistent disease. Also, for children, long term suppression therapy is still being recommended (38). As has been suggested in one small study, cardiac remodeling may be triggered by chronic hemodynamic overload, caused by the subclinical hyperthyroidism, and may recover after euthyroidism (22). However, it is unclear whether this recovery occurs in all patients. In patients with longstanding TSH suppression cardiac damage may be more permanent.

The question is, how can we find the patients at risk of a cardiovascular event? A more stringent approach and treatment of cardiovascular risk factors may prevent cardiovascular events and improve the survival and quality of life of patients with thyroid cancer.
In this context the biomarker N-terminal pro Brain Natriuretic Peptide (NT-proBNP) has been studied in DTC patients. Elevated levels of circulating concentrations of NT-proBNP in DTC patients were associated with an increased risk of cardiovascular events and all-cause mortality. This was shown in 266 DTC patients without a history of cardiovascular events, comparing each patient with 3 age- and sex-matched selected controls (39). The median age of patients and controls was 54 years, and one of the inclusion criteria was DTC survival of at least 1 year. NT-proBNP levels were evaluated median 10 years (IQR: 4.1-18.8) after DTC diagnosis. Median NT-proBNP level was significantly higher, with 70 (IQR: 40-119) ng/l for DTC patients and 49 (IQR: 25-89) ng/l for controls. DTC patients in quartile 4 (NT-proBNP > 119 ng/ml) had the worst prognosis for all-cause mortality and cardiovascular events during median follow-up of 8.6 years (IQR: 6.6-9.0) after serum sample collection. However, this finding remains to be translated into clinical practice.

Recently, the European Society of Cardiology (ESC) provided recommendations regarding cardiovascular monitoring and decision-making regarding cancer therapies with potential cardiovascular side effects (40). However, these recommendations were limited to patients diagnosed with cancer types that are treated with chemotherapy and radiation therapy. Those therapies are not usually involved in the treatment of DTC. For DTC specific guidelines for monitoring and treatment of cardiovascular risk are lacking.

Furthermore, the available risk estimations for non-cancer patients are not appropriate for DTC patients. Ten-year cardiovascular risk estimates, like SCORE and the Framingham risk score, are used to identify patients at high risk of cardiovascular events (41,42). However, these estimates have not been validated in cancer patients. Furthermore, when using 10-year risk estimates, only patients above the age of 50-55 years (50 in men, 55 in women) are eligible for primary cardiovascular prevention (41). Thus, especially for cancer types with peak incidence at ages <50 years, these cardiovascular risk estimates are not appropriate to assess the cardiovascular risk.

Accepted Manuscript published as EC-20-0539. Accepted for publication: 14-Dec-2020

An example of a cancer type with peak incidence at young age and increased cardiovascular mortality is testicular cancer. Lubberts and colleagues developed a tool called the vascular fingerprint to identify patients at high cardiovascular risk in a primary prevention setting. This tool involves assessing five risk factors: high body mass index (BMI), smoking, hypertension, dyslipidemia and impaired fasting glucose. A high-risk vascular fingerprint (≥3 risk factors) before the start of chemotherapy identified patients at highest risk of arterial cardiovascular events. Although not externally validated, these factors promised to be useful for selection of patients who might benefit from preventive strategies (43). In line with this approach we re-analyzed the results of the earlier mentioned cohort of DTC patients (33), and developed a cardiovascular fingerprint specifically for survivors of DTC. For this thyroid cancer cardiovascular fingerprint, we added 2 risk factors that were not relevant to the series of young male patients with testicular cancer: sex and age. The components of this thyroid cancer cardiovascular fingerprint are shown in table 2.

The following cut-off values or definitions were used: BMI >25 kg/m2, current smoking, blood pressure >140/90 mm Hg (or use of antihypertensive drugs), dyslipidemia (total cholesterol >5.1 mmol/L, HDL <1.04 mmol/L, LDL >2.5 mmol/L or use of lipid lowering drugs), and use of blood glucose lowering drugs. We defined high risk as ≥4 points after testing with a receiver operating characteristic (ROC) curve. A cut-off score for the cardiovascular fingerprint was determined to differentiate between patients with a high or a low risk of developing cardiovascular events. We tested cut-off values of 3 to 5 with a receiver operating characteristic (ROC) curve (see supplemental figure 1). The cut-off score of 4 was found to have the optimal discriminative power to identify DTC patients with high cardiovascular risk (sensitivity of 65.0% and specificity 72.5%).

We applied this simple tool to 619 consecutive DTC patients, diagnosed between 1980 and 2010. As we aimed to identify patients for primary cardiovascular prevention, we excluded patients who had experienced a cardiovascular event before the DTC diagnosis. A cardiovascular event was defined as a stroke (CVA or TIA), myocardial infarction, heart failure (NYHA 2-4), or revascularization procedure. After the diagnosis of DTC, 60 of the 619 DTC patients (9.7%) developed a first cardiovascular event within the follow-up time

(median 12.6 years). The cardiovascular fingerprint identified 39 of those 60 patients (65.0%) as high risk.

Of 426 patients with a low score on the cardiovascular fingerprint, 21 (4.9%) developed a cardiovascular event. Of the other 193 patients with a high score, 39 (20.2%) developed a cardiovascular event. The cardiovascular fingerprint was compared to the traditional cardiovascular risk estimation of the European Society of Cardiology for non-cancer patients (41). Of the 60 patients with a cardiovascular event, 22 (36.7%) were classified as high risk by this traditional estimation. The cardiovascular fingerprint had a higher diagnostic odds ratio (4.8, 95% CI 2.7 – 8.4) compared to the traditional risk estimation (3.0, 95% CI 1.70 – 5.34). The cardiovascular fingerprint was more effective, particularly in identifying younger patients at risk of cardiovascular disease. Twenty patients with a cardiovascular event, classified as low-risk by the traditional risk estimation, had a positive cardiovascular fingerprint. Those patients were younger than the patients identified by the traditional risk estimation (mean 52.9 ± SD 10.5 vs. mean 70.7 ± SD 7.5 years, p =<0.001). Although preliminary, the cardiovascular fingerprint may be a simple and effective tool to identify DTC patients at increased risk of a first cardiovascular event. Nevertheless, this tool must be validated in another cohort of DTC patients.

Conclusion

This overview has illustrated that the cardiovascular risks of clinical and subclinical hyperthyroidism also apply to long term survivors of DTC, in both adult and pediatric survivors. Therefore, for all DTC patients cardiovascular risk management should be considered in line with their elevated risk factors. For example, lifestyle advice regarding smoking cessation, healthy dietary habits, and regular physical activity (44), could be offered to all DTC patients with high cardiovascular fingerprints. Furthermore, initiation of antihypertensive drugs could be considered for DTC patients found to have a blood pressure >140/90 mmHg upon several visits (45). In patients with dyslipidaemia, lipid-lowering drugs should be considered (46). However, further research is needed to establish the beneficial effect of cardiovascular prevention specifically in DTC patients. Moreover, the mechanisms of cardiovascular toxicity in DTC patients should be elucidated.

 Accepted Manuscript published as EC-20-0539. Accepted for publication: 14-Dec-2020

Declaration of interest

All authors have no conflicts of interest to declare.

Funding

This research did not receive any specific grant from any agency in the public, commercial or non-profit sector.

Figure 1. Scores on the cardiovascular fingerprint at the time of DTC diagnosis for patients who did/did not develop a cardiovascular event.

Supplemental figure 1

The cut-off score of 4 shows the optimal discriminative power to identify DTC patients with high cardiovascular risk (sensitivity of 65.0% and specificity 72.5%). Cut-off scores of 3 and 5 had a sensitivity of 50.6% and 88.4%, and a specificity of 90.0% and 33.3%, respectively (data not shown).

References

1. Razvi S, Jabbar A, Pingitore A, Danzi S, Biondi B, Klein I, Peeters R, Zaman A, Iervasi G. Thyroid Hormones and Cardiovascular Function and Diseases. *J Am Coll Cardiol*. 2018;71(16):1781-1796.
2. Park KW, Dai HB, Ojamaa K, Lowenstein E, Klein I, Sellke FW. The direct vasomotor effect of thyroid hormones on rat skeletal muscle resistance arteries. *Anesth Analg*. 1997;85(4):734-738.
3. Klein I, Danzi S. Thyroid Disease and the Heart. *Curr Probl Cardiol*. 2016;41(2):65-92.
4. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. *N Engl J Med*. 2001;344(7):501-509.
5. Stuijver DJ, van Zaane B, Romualdi E, Brandjes DP, Gerdes VE, Squizzato A. The effect of hyperthyroidism on procoagulant, anticoagulant and fibrinolytic factors: a systematic review and meta-analysis. *Thromb Haemost*. 2012;108(6):1077-1088.
6. Sawin CT, Geller A, Wolf PA, Belanger AJ, Baker E, Bacharach P, Wilson PW, Benjamin EJ, D'Agostino RB. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. *N Engl J Med*. 1994;331(19):1249-1252.
7. Parle JV, Maisonneuve P, Sheppard MC, Boyle P, Franklyn JA. Prediction of all-cause and cardiovascular mortality in elderly people from one low serum thyrotropin result: a 10-year cohort study. *Lancet*. 2001;358(9285):861-865.
8. Brandt F, Green A, Hegedus L, Brix TH. A critical review and meta-analysis of the association between overt hyperthyroidism and mortality. *Eur J Endocrinol*. 2011;165(4):491-497.
9. Brandt F, Thvilum M, Almind D, Christensen K, Green A, Hegedus L, Brix TH. Graves' disease and toxic nodular goiter are both associated with increased mortality but differ with respect to the cause of death: a Danish population-based register study. *Thyroid*. 2013;23(4):408-413.
10. Frost L, Vestergaard P, Mosekilde L. Hyperthyroidism and risk of atrial fibrillation or flutter: a population-based study. *Arch Intern Med*. 2004;164(15):1675-1678.
11. van Zaane B, Squizzato A, Huijgen R, van Zanten AP, Fliers E, Cannegieter SC, Buller HR, Gerdes VE, Brandjes DP. Increasing levels of free thyroxine as a risk factor for a first venous thrombosis: a case-control study. *Blood*. 2010;115(22):4344-4349.
12. Franchini M, Lippi G, Targher G. Hyperthyroidism and venous thrombosis: a casual or causal association? A systematic literature review. *Clin Appl Thromb Hemost*. 2011;17(4):387-392.
13. Elbers LP, Moran C, Gerdes VE, van Zaane B, Meijers J, Endert E, Lyons G, Chatterjee VK, Bisschop PH, Fliers E. The Hypercoagulable state in Hyperthyroidism is mediated via the Thyroid Hormone beta Receptor pathway. *Eur J Endocrinol*. 2016.
14. Biondi B, Cooper DS. Subclinical Hyperthyroidism. *N Engl J Med*. 2018;379(15):1485-1486.
15. Collet TH, Gussekloo J, Bauer DC, den Elzen WP, Cappola AR, Balmer P, Iervasi G, Asvold BO, Sgarbi JA, Volzke H, et al. Thyroid Studies C. Subclinical hyperthyroidism and the risk of coronary heart disease and mortality. *Arch Intern Med*. 2012;172(10):799-809.
16. Erem C. Blood coagulation, fibrinolytic activity and lipid profile in subclinical thyroid disease: subclinical hyperthyroidism increases plasma factor X activity. *Clin Endocrinol (Oxf)*. 2006;64(3):323-329.

Accepted Manuscript published as EC-20-0539. Accepted for publication: 14-Dec-2020

17. Volzke H, Robinson DM, Schminke U, Ludemann J, Rettig R, Felix SB, Kessler C, John U, Meng W. Thyroid function and carotid wall thickness. *J Clin Endocrinol Metab*. 2004;89(5):2145-2149.
18. Cabanillas ME, McFadden DG, Durante C. Thyroid cancer. *Lancet*. 2016;388(10061):2783-2795.
19. Siegel DA, King J, Tai E, Buchanan N, Ajani UA, Li J. Cancer incidence rates and trends among children and adolescents in the United States, 2001-2009. *Pediatrics*. 2014;134(4):e945-955.
20. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*. 2016;26(1):1-133.
21. Biondi B, Fazio S, Carella C, Amato G, Cittadini A, Lupoli G, Sacca L, Bellastella A, Lombardi G. Cardiac effects of long term thyrotropin-suppressive therapy with levothyroxine. *J Clin Endocrinol Metab*. 1993;77(2):334-338.
22. Smit JW, Eustatia-Rutten CF, Corssmit EP, Pereira AM, Frolich M, Bleeker GB, Holman ER, van der Wall EE, Romijn JA, Bax JJ. Reversible diastolic dysfunction after long-term exogenous subclinical hyperthyroidism: a randomized, placebo-controlled study. *J Clin Endocrinol Metab*. 2005;90(11):6041-6047.
23. Klein Hesselink EN, Lefrandt JD, Schuurmans EP, Burgerhof JG, Groen B, Gansevoort RT, van der Horst-Schrivers AN, Dullaart RP, Van Gelder IC, Brouwers AH, Rienstra M et al. Increased Risk of Atrial Fibrillation After Treatment for Differentiated Thyroid Carcinoma. *J Clin Endocrinol Metab*. 2015;100(12):4563-4569.
24. Abonowara A, Quraishi A, Sapp JL, Alqambar MH, Saric A, O'Connell CM, Rajaraman MM, Hart RD, Imran SA. Prevalence of atrial fibrillation in patients taking TSH suppression therapy for management of thyroid cancer. *Clin Invest Med*. 2012;35(3):E152-156.
25. Wang LY, Smith AW, Palmer FL, Tuttle RM, Mahrous A, Nixon IJ, Patel SG, Ganly I, Fagin JA, Boucai L. Thyrotropin suppression increases the risk of osteoporosis without decreasing recurrence in ATA low- and intermediate-risk patients with differentiated thyroid carcinoma. *Thyroid*. 2015;25(3):300-307.
26. Toulis KA, Viola D, Gkoutos G, Keerthy D, Boelaert K, Nirantharakumar K. Risk of incident circulatory disease in patients treated for differentiated thyroid carcinoma with no history of cardiovascular disease. *Clin Endocrinol (Oxf)*. 2019;91(2):323-330.
27. Hay ID, Gonzalez-Losada T, Reinalda MS, Honetschlager JA, Richards ML, Thompson GB. Long-term outcome in 215 children and adolescents with papillary thyroid cancer treated during 1940 through 2008. *World J Surg*. 2010;34(6):1192-1202.
28. Jarzab B, Handkiewicz-Junak D, Wloch J. Juvenile differentiated thyroid carcinoma and the role of radioiodine in its treatment: a qualitative review. *Endocr Relat Cancer*. 2005;12(4):773-803.
29. Hogan AR, Zhuge Y, Perez EA, Koniaris LG, Lew JI, Sola JE. Pediatric thyroid carcinoma: incidence and outcomes in 1753 patients. *J Surg Res*. 2009;156(1):167-172.
30. Klein Hesselink MS, Nies M, Bocca G, Brouwers AH, Burgerhof JG, van Dam EW, Havekes B, van den Heuvel-Eibrink MM, Corssmit EP, Kremer LC, et al. Pediatric

Differentiated Thyroid Carcinoma in The Netherlands: A Nationwide Follow-Up Study. *J Clin Endocrinol Metab*. 2016;101(5):2031-2039.
31. Klein Hesselink MS, Bocca G, Hummel YM, Brouwers AH, Burgerhof JGM, van Dam E, Gietema JA, Havekes B, van den Heuvel-Eibrink MM, Corssmit EPM, Kremer LCM, et al. Diastolic Dysfunction is Common in Survivors of Pediatric Differentiated Thyroid Carcinoma. *Thyroid*. 2017;27(12):1481-1489.
32. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;37(27):2129-2200.
33. Klein Hesselink EN, Klein Hesselink MS, de Bock GH, Gansevoort RT, Bakker SJ, Vredeveld EJ, van der Horst-Schrivers AN, van der Horst IC, Kamphuisen PW, Plukker JT, et al. Long-term cardiovascular mortality in patients with differentiated thyroid carcinoma: an observational study. *J Clin Oncol*. 2013;31(32):4046-4053.
34. Escobar-Morreale HF, Obregon MJ, Escobar del Rey F, Morreale de Escobar G. Replacement therapy for hypothyroidism with thyroxine alone does not ensure euthyroidism in all tissues, as studied in thyroidectomized rats. *J Clin Invest*. 1995;96(6):2828-2838.
35. Schultz PN, Stava C, Vassilopoulou-Sellin R. Health profiles and quality of life of 518 survivors of thyroid cancer. *Head Neck*. 2003;25(5):349-356.
36. Pajamaki N, Metso S, Hakala T, Ebeling T, Huhtala H, Ryodi E, Sand J, Jukkola-Vuorinen A, Kellokumpu-Lehtinen PL, Jaatinen P. Long-term cardiovascular morbidity and mortality in patients treated for differentiated thyroid cancer. *Clin Endocrinol (Oxf)*. 2018;88(2):303-310.
37. Park J, Blackburn BE, Ganz PA, Rowe K, Snyder J, Wan Y, Deshmukh V, Newman M, Fraser A, Smith K, et al. Risk Factors for Cardiovascular Disease Among Thyroid Cancer Survivors: Findings From the Utah Cancer Survivors Study. *J Clin Endocrinol Metab*. 2018;103(7):2468-2477.
38. Lebbink CA, Dekker BL, Bocca G, Braat A, Derikx JPM, Dierselhuis MP, de Keizer B, Kruijff S, Kwast ABG, van Nederveen FH, et al. New national recommendations for the treatment of pediatric differentiated thyroid carcinoma in the Netherlands. *Eur J Endocrinol*. 2020;183(4):P11-P18.
39. Klein Hesselink EN, van der Horst-Schrivers ANA, van der Horst ICC, Bakker SJL, Muller Kobold AC, Brouwers AH, de Bock GH, Gietema JA, Dullaart RPF, Links TP, et al. NT-proBNP is increased in differentiated thyroid carcinoma patients and may predict cardiovascular risk. *Clin Biochem*. 2017;50(12):696-702.
40. Zamorano JL, Lancellotti P, Rodriguez Munoz D, Aboyans V, Asteggiano R, Galderisi M, Habib G, Lenihan DJ, Lip GYH, Lyon AR, et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;37(36):2768-2801.
41. Conroy RM, Pyorala K, Fitzgerald AP, Sans S, Menotti A, De Backer G, De Bacquer D, Ducimetiere P, Jousilahti P, Keil U, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J*. 2003;24(11):987-1003.

Accepted Manuscript published as EC-20-0539. Accepted for publication: 14-Dec-2020

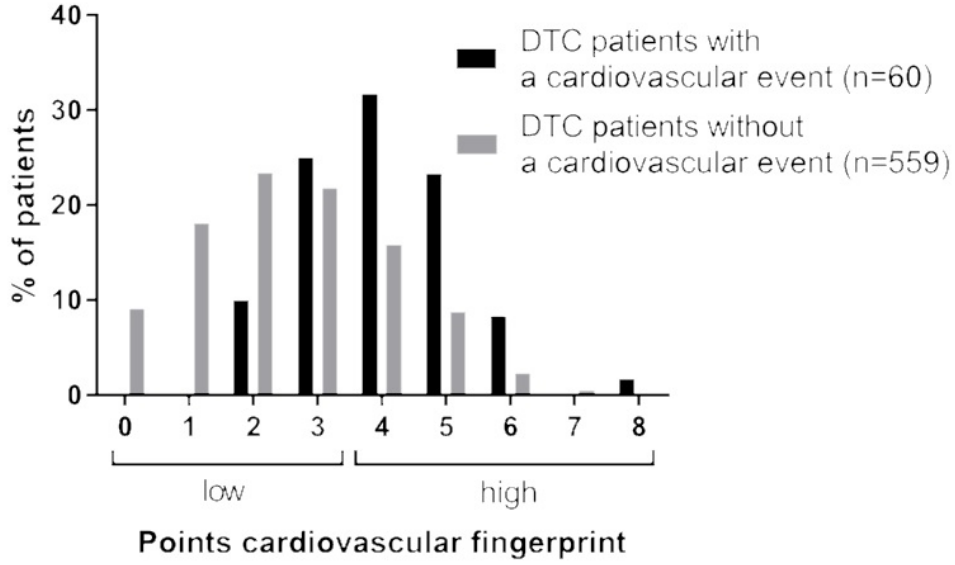
42. D'Agostino RB, Sr., Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*. 2008;117(6):743-753.
43. Lubberts S, Boer H, Altena R, Meijer C, van Roon AM, Zwart N, Oosting SF, Kamphuisen PW, Nuver J, Smit AJ, et al. Vascular fingerprint and vascular damage markers associated with vascular events in testicular cancer patients during and after chemotherapy. *Eur J Cancer*. 2016;63:180-188.
44. Tonstad S, Sundfor T, Seljeflot I. Effect of lifestyle changes on atherogenic lipids and endothelial cell adhesion molecules in young adults with familial premature coronary heart disease. *Am J Cardiol*. 2005;95(10):1187-1191.
45. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corra U, Cosyns B, Deaton C, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J*. 2016;37(29):2315-2381.
46. Cholesterol Treatment Trialists C, Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, Barnes EH, Voysey M, Gray A, Collins R, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet*. 2012;380(9841):581-590.
47. Abdulrahman RM, Delgado V, Ng AC, Ewe SH, Bertini M, Holman ER, Hovens GC, Pereira AM, Romijn JA, et al. Abnormal cardiac contractility in long-term exogenous subclinical hyperthyroid patients as demonstrated by two-dimensional echocardiography speckle tracking imaging. *Eur J Endocrinol*. 2010;163(3):435-441.
48. Wang R, Yang L, Jin S, Han X, Liu B. Thyroid stimulating hormone suppression time on cardiac function of patients with differentiated thyroid carcinoma. *Cancer Cell Int*. 2018;18:189.

Figure legends

Figure 1. Scores on the cardiovascular fingerprint at the time of DTC diagnosis for patients who did/did not develop a cardiovascular event.

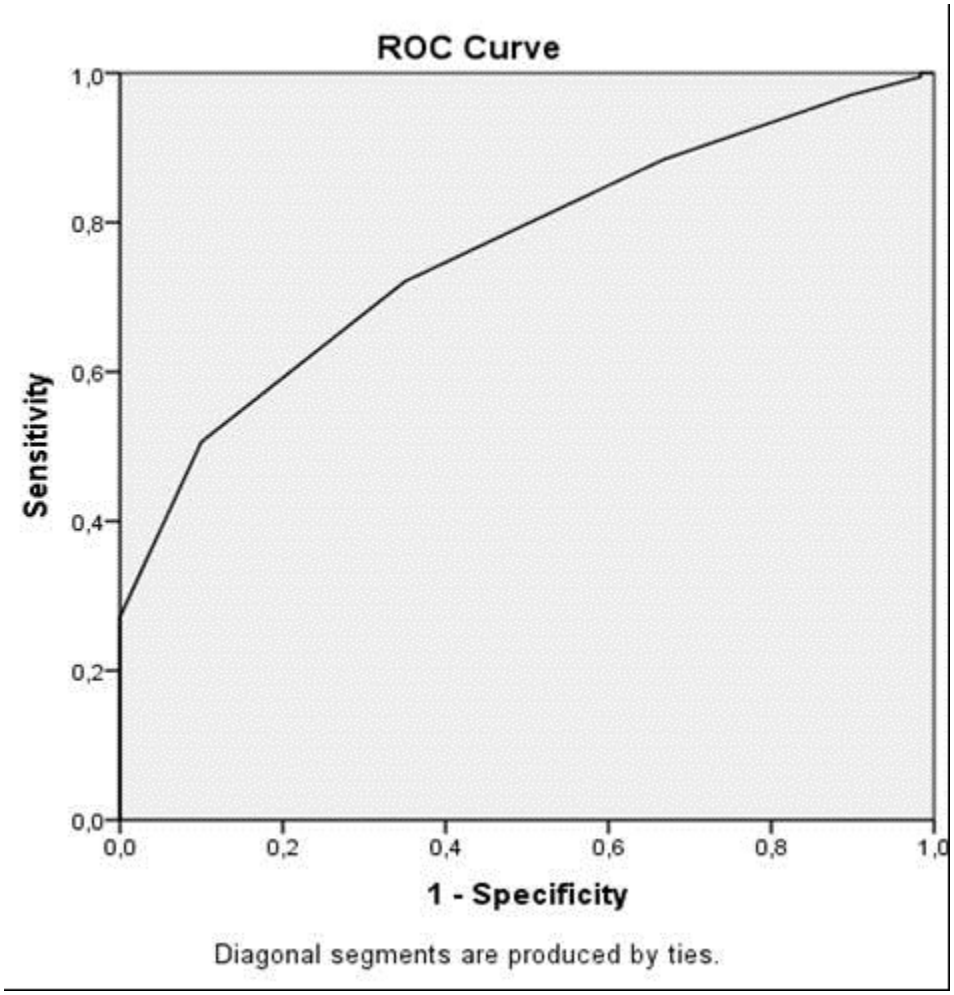
Supplemental figure 1

The cut-off score of 4 shows the optimal discriminative power to identify DTC patients with high cardiovascular risk (sensitivity of 65.0% and specificity 72.5%). Cut-off scores of 3 and 5 had a sensitivity of 50.6% and 88.4%, and a specificity of 90.0% and 33.3%, respectively (data not shown).



208x130mm (96 x 96 DPI)

Accepted Manuscript published as EC-20-0539. Accepted for publication: 14-Dec-2020



Supplemental figure 1

The cut-off score of 4 shows the optimal discriminative power to identify DTC patients with high cardiovascular risk (sensitivity of 65.0% and specificity 72.5%). Cut-off scores of 3 and 5 had a sensitivity of 50.6% and 88.4%, and a specificity of 90.0% and 33.3%, respectively (data not shown).

125x130mm (96 x 96 DPI)

Tabel 1 Studies on cardiovascular endpoints in DTC patients on TSH suppression therapy

Author /year of publication	Patients	Outcome parameters	Type of study
Abdulrahman (2010)(47)	25 DTC patients, 40 controls	systolic and diastolic dysfunction after prolonged subclinical hyperthyroidism reversible after euthyroidism.	Prospective, single-blinded, placebo-controlled randomized trial
Abonowara (2012)(24)	136 DTC patients	TSH suppression associated with high AF prevalence	Cross-sectional
Klein Hesselink (2013)(33)	524 DTC patients 1572 controls	Increased cardiovascular and all-cause mortality, independent from established risk factors, relation lower TSH	retrospective
Klein Hesselink (2015)(23)	518 DTC patients 1563 controls	Increased risk atrial fibrillation, independent from established AF risk factors	retrospective
Klein Hesselink (2017)(39)	266 DTC patients 798 controls	NT-proBNP levels associated with increased risk cardiovascular events and all-cause mortality	prospective
Klein Hesselink 2017 (31)	66 adult pediatric DTC survivors	21% diastolic dysfunction (e' septal and e' lateral)	Cross-sectional
Pajamaki (2018) (36)	901 DTC patients 4485 controls	Increased cardiovascular morbidity, accountable to atrial fibrillation and TSH < 0.1	retrospective
Toulis (2018) (26)	3009 DTC patients 11303 controls	Significantly higher risk of atrial fibrillation and stroke	prospective
Park (2018)(37)	3822 DTC patients	Year and age at cancer diagnosis, sex, cancer stage, TSH suppression therapy, baseline BMI, and baseline comorbidity were risk factors for CVD	cohort
Wang (2018) (48)	105 DTC patients (subdivided in TSH ≤0.1 and > 0.1 and duration of TSH suppression 0.5;1;> 1yr)	Prolonged suppression time associated with decrease left ventricular diastolic function, systolic synchrony and myocardial perfusion	observational

Accepted Manuscript published as EC-20-0539. Accepted for publication: 14-Dec-2020

Table 2 **The cardiovascular fingerprint**

Risk factor	**Score**
Sex	Male = 1
Age	>45 years = 1, >60 years = 2
Body mass index	>25 kg/m^2= 1
Hypertension	Blood pressure >140/90 mmHg OR usage of antihypertensive drugs = 1
Dyslipidemia	total cholesterol >5.1 mmol/L OR HDL <1.04 mmol/L OR LDL >2.5 mmol/L OR usage of lipid lowering drugs = 1
Smoking	Current smoking = 1
Diabetes	Usage of blood glucose lowering drugs = 1
Total	8 points, ≥ 4 points = 'high cardiovascular fingerprint'