Tampere University

ESSI RYÖDI

Long-term Consequences of Previously Treated Hyperthyroidism

Tampere University Dissertations 107

Tampere University Dissertations 107

ESSI RYÖDI

Long-term Consequences of Previously Treated Hyperthyroidism

ACADEMIC DISSERTATION
To be presented, with the permission of
the Faculty Council of the Medicine and Health Technology
of Tampere University,
for public discussion in the Jarmo Visakorpi auditorium
of the Arvo building, Arvo Ylpön katu 34, Tampere,
on 20 September 2019, at 12 o'clock.

ACADEMIC DISSERTATION
Tampere University, Faculty of Medicine and Health technology, Finland
Tampere University Hospital, Department of Internal Medicine, Finland
Tampere University Hospital, Heart Hospital, Finland

Supervisor and Custos	Professor Pia Jaatinen University of Tampere Finland	
Supervisor	Docent Saara Metso University of Tampere Finland	
Pre-examiners	Docent Kari Kervinen University of Oulu Finland	Docent Ilkka Heiskanen University of Helsinki Finland
Opponent	Ulla Feldt-Rasmussen University of Copenhagen Denmark	

The originality of this thesis has been checked using the Turnitin OriginalityCheck service.

Cover design: Roihu Inc.

ISBN 978-952-03-1197-1 (print)
ISBN 978-952-03-1198-8 (pdf)
ISSN 2489-9860 (print)
ISSN 2490-0028 (pdf)
http://urn.fi/URN:ISBN:978-952-03-1198-8

PunaMusta Oy – Yliopistopaino

Tampere 2019

To patients with hyperthyroidism – treated or untreated

ABSTRACT

Hyperthyroidism is defined as excess secretion of thyroid hormones by a diseased thyroid gland. The most common diseases causing hyperthyroidism are Graves´ disease, multinodular goiter and toxic adenoma. There are three different treatment modalities of hyperthyroidism –antithyroid drugs (ATD), radioactive iodine (RAI) and thyroidectomy. All these treatments have been used for several decades. Hyperthyroidism causes several disadvantageous changes in the metabolism, due to excess amount of circulating thyroid hormones. Based on the previous studies, hyperthyroid patients have an increased risk of cardiovascular diseases, even after achieving euthyroidism. Furthermore, there are studies suggesting an increased risk of cancer in patients treated for hyperthyroidism with RAI. It is unclear, whether the excess risk is due to hyperthyroidism, its treatment, or the shared risk factors of these diseases.

The aim of this study was to assess cardiovascular and cancer morbidity and mortality in hyperthyroidism before and after the treatment, and to compare the long-term outcome of patients treated with RAI and those treated with thyroid surgery.

This comparative cohort study included all the patients treated for hyperthyroidism in Finland during 1986-2007 with subtotal or total thyroidectomy (n=4334) and all the patients treated with RAI in Tampere University Hospital during the same period of time (n=1819). Three age- and gender-matched controls were obtained for each patient from the National Population Registry. Cancer diagnoses of the patients and the controls were obtained from the Cancer Registry, and hospitalizations for cardiovascular diseases from the hospitalization database of National Institute for Health and Welfare (HILMO).

Firstly, hospitalizations due to CVDs and the incidence of cancer until the treatment of hyperthyroidism were analyzed. Secondly, the hazard ratios (HR) for any new hospitalization and mortality due to CVDs and for the incidence of cancer after the treatment were estimated among all the hyperthyroid patients compared to the age- and gender-matched controls, and also in the RAI-treated patients compared to the thyroidectomy-treated patients. The results were adjusted for prevalent CVDs and prevalent cancers at the time of treatment.

The main results of this study were that hyperthyroidism increased the risk of CVD-related hospitalizations, and the risk was sustained up to two decades after

treatment with RAI or surgery. Subtotal or total thyroidectomy was more effective in decreasing cardiovascular morbidity and mortality in hyperthyroid patients than treatment with RAI, and the patients treated with RAI had over twice as high CVD mortality rates compared to patients treated with thyroidectomy. Hypothyroidism after treatment with RAI, however, predicted better cardiovascular outcome. The overall risk of cancer in hyperthyroid patients was unchanged compared to age- and gender-matched reference subjects, but there was an increased risk of gastric and respiratory tract cancers. The effect of treatment modality on cancer incidence was neutral.

As a conclusion, the increased risk of CVDs and cancer in hyperthyroid patients is associated to hyperthyroidism and shared risk factors, not the treatment modality. This underlines the importance of efficient treatment of hyperthyroidism in the future. Furthermore, disregarding the treatment modality, the patients treated for hyperthyroidism should be regarded as high-risk patients for CVDs and to some cancers and long-term follow-up should be arranged.

TIIVISTELMÄ

Hypertyreoosilla tarkoitetaan sairastuneen kilpirauhasen liiallista kilpirauhashormonien tuotantoa. Tavallisimpia syitä ovat Basedowin tauti, monikyhmystruuma ja yksittäinen toksinen adenooma. Hypertyreoosia voidaan hoitaa kolmella tavalla: tyreostaattisilla lääkkeillä, radioaktiivisella jodilla (RAI) tai kilpirauhasen osa- tai kokopoistolla. Kaikki nämä hoitomuodot ovat olleet käytössä jo vuosikymmeniä. Kilpirauhashormonit säätelevät elimistön aineenvaihduntaa, solujen kasvua ja energian tuotantoa. Aiempiin tutkimuksiin perustuen hypertyreoosiin sairastuneilla potilailla on lisääntynyt sydän- ja verenkiertoelimistön sairauksien riski vielä pitkään hoidon jälkeenkin. Osassa seurantatutkimuksia on tullut esiin myös lisääntynyt syöpäriski RAI-hoidetuilla potilailla. Toistaiseksi on ollut epäselvää, johtuuko lisääntynyt sairastuvuus hypertyreoosin ja sydänsairauksien tai hypertyreoosin ja syövän yhteisistä riskitekijöistä, vai itse sairastetusta hypertyreoosista tai sen hoitomuodoista.

Tutkimuksen tarkoituksena oli selvittää hypertyreoosipotilaiden sairastuvuutta ja kuolleisuutta sydän- ja verenkiertoelimistön sairauksiin ja syöpään ennen ja jälkeen hypertyreoosin hoidon ja verrata näiden sairauksien riskiä kahden erilaisen hoitomuodon, RAI-hoidon ja kilpirauhasleikkauksen jälkeen.

Tähän vertailevaan kohorttitutkimukseen otettiin mukaan kaikki Suomessa vuosina 1986-2007 hypertyreoosin vuoksi kilpirauhasleikatut potilaat (n=4 334) ja kaikki samaan aikaan Tampereen yliopistollisen sairaalan alueella hypertyreoosin vuoksi RAI-hoidetut potilaat (n=1 819). Jokaiselle haettiin kolme ikä- ja sukupuolivakioitua verrokkia Väestörekisterikeskuksesta. Tiedot potilaiden ja verrokkien syöpäsairastuvuudesta ja kuolleisuudesta haettiin Syöpärekisteristä ja tiedot sydän- ja verenkiertoelimistön sairauksista johtuvista sairaalahoitojaksoista Terveyden ja Hyvinvoinnin laitoksen (THL) Hoito- ja poistoilmoitusrekisterin (HILMO) tietokannasta. Ensin analysoitiin potilaiden sydän- ja verisuonisairauksiin liittyvät sairaalahoitojaksot ja syövän ilmaantuvuus hypertyreoosin hoitoon saakka. Sen jälkeen analysoitiin sydän-ja verisuonisairauksista johtuvan uuden sairaalahoitojakson ja uuden syövän riski ja sekä kuolleisuus verrattuna ikä- ja sukupuolivakioituihin verrokkeihin. Lisäksi verrattiin hypertyreoosin vuoksi RAI-hoidon saaneiden sairastuvuutta ja kuolleisuutta hypertyreoosin vuoksi leikattuihin potilaisiin. Tulokset vakioitiin

aiemmalla syöpäsairastuvuudella syövän suhteen ja aiemmalla sydän- ja verisuonisairauksien sairastuvuudella sydänsairauksien suhteen.

Saatujen tulosten perusteella hypertyreoosi lisäsi riskiä joutua sairaalahoitoon sydän- ja verenkiertoelimistön sairauksien vuoksi ja riski oli koholla vielä kahden vuosikymmenen ajan RAI-hoidon tai kilpirauhasleikkauksen jälkeen ikä- ja sukupuolivakioituihin verrokkeihin verrattuna. Kilpirauhasleikkaus vähensi tehokkaammin sydänsairastuvuutta ja kuolleisuutta hypertyreoosipotilailla kuin RAI-hoito ja RAI-hoidetuilla potilailla oli yli kaksinkertainen kuolleisuus leikattuihin potilaisiin verrattuna. Hypotyreoosi RAI-hoidon jälkeen merkitsi parempaa ennustetta.

Syövän ilmaantuvuudessa ja syöpäkuolleisuudessa ei ollut eroa potilaiden ja verrokkien välillä, mutta hengitystiesyöpien ja mahasyövän riski oli potilailla korkeampi kuin verrokeilla. Hoitomuodolla ei ollut vaikutusta syövän ilmaantuvuuteen tai syöpäkuolleisuuteen.

Tämän tutkimuksen tuloksista voidaan päätellä, että hypertyreoosin sairastaneiden potilaiden lisääntynyt sydän- ja verisuonisairauksien ja maha- ja hengitystiesyöpien riski ei näyttäisi liittyvän hypertyreoosin hoitoon, vaan sairastettuun hypertyreoosiin sekä hypertyreoosin ja sydän- ja verisuonisairauksien ja hypertyreoosin ja tiettyjen syöpien yhteisiin riskitekijöihin. Saadut tulokset korostavat hypertyreoosin tehokkaan hoidon merkitystä tulevaisuudessa. Valitusta hypertyreoosin hoitomuodosta huolimatta, potilaita tulisi pitää sydän- ja verisuonisairauksien ja syövän suhteen korkean riskin potilaina hoidon jälkeenkin ja huolehtia pitkäaikaisseurannan toteutumisesta näiden sairauksien suhteen.

CONTENTS

ABSTRACT....5
TIIVISTELMÄ....8
ABBREVIATIONS....14
LIST OF ORIGINAL COMMUNICATIONS....15
1 INTRODUCTION....16
2 REVIEW OF THE LITERATURE....19
2.1 Hyperthyroidism....19
2.1.1 Definitions and epidemiology of hyperthyroidism and thyrotoxicosis....19
2.1.2 Causes of hyperthyroidism and thyrotoxicosis....19
2.1.3 Clinical presentations of hyperthyroidism....21
2.2 Treatment of hyperthyroidism....21
2.2.1 Antithyroid drug therapy....21
2.2.1.1 Indication and contraindications....21
2.2.1.2 Side-effects of ATDs....22
2.2.1.3 Efficacy of the treatment....22
2.2.2 Radioactive iodine (RAI)....22
2.2.2.1 Indications and contraindications....23
2.2.2.2 Efficacy and short-term side-effects of treatment with RAI....23
2.2.2.3 RAI and the risk of cancer....23
2.2.3 Surgery....25
2.2.3.1 Indications and contraindications....25
2.2.3.2 Complications....25
2.2.3.3 Efficacy of the treatment....27
2.2.4 Current treatment strategies for hyperthyroidism....27
2.3 Morbidity during thyrotoxicosis....28
2.3.1 The functions of the thyroid hormones in the cardiovascular system....28
2.3.2 The effect of thyrotoxicosis on the cardiovascular system....29
2.3.3 Cardiovascular morbidity in hyperthyroidism....30
2.3.4 Thyrotoxicosis and cancer....32
2.4 Morbidity and mortality after the treatment of hyperthyroidism....33
2.4.1 Mortality after the treatment of hyperthyroidism....33
2.4.2 Cardiovascular morbidity and mortality after the treatment of hyperthyroidism....34
3 AIMS OF THE STUDY....39

4 SUBJECTS AND METHODS 40
4.1 1. Subjects (I, II, III) 40
4.1.1 The patients treated with thyroidectomy 40
4.1.2 The patients treated with RAI 40
4.1.3 The reference subjects 41
4.2 Methods (I, II, III) 41
4.2.1 The etiology of hyperthyroidism 41
4.2.2 The thyroid status of the patients 41
4.2.3 Hospitalization rates for cardiovascular diseases (I, III) 42
4.2.4 The incidence of cancer (II) 43
4.2.5 Mortality (I, II, III) 44
4.2.6 Comparison between the patients treated either with RAI or thyroidectomy (II, III) 44
4.2.7 Statistical analysis 45
4.2.7.1 Statistical analysis of cardiovascular diseases (I, III) 45
4.2.7.2 Statistical analysis of cancer (II) 45
4.2.8 Ethical considerations 46
5 RESULTS 48
5.1 The clinical characteristics of the patients 48
5.1.1 The patients treated with thyroidectomy 48
5.1.2 The patients treated with RAI 50
5.2 Cardiovascular morbidity 51
5.2.1 The risk of cardiovascular diseases before the treatment of hyperthyroidism (I, III) 51
5.2.1.1 The patients treated with thyroidectomy 51
5.2.1.2 The patients treated with RAI 53
5.3 The risk of cardiovascular hospitalization after the treatment of hyperthyroidism 55
5.3.1 The patients treated with thyroidectomy (I) 55
5.3.2 The patients treated with RAI (III) 56
5.3.3 The effect of the treatment modality on CVD hospitalization (III) 58
5.4 The risk of cancer after treatment of hyperthyroidism (II) 60
5.4.1 Cancer morbidity 60
5.4.2 The impact of the etiology of hyperthyroidism on cancer incidence (II) 62
5.4.3 Patients treated with thyroidectomy and cancer 64
5.4.4 Patients treated with RAI and cancer 66
5.4.5 The impact of treatment modality (RAI or thyroidectomy) on cancer incidence (II) 68

5.5 Mortality in hyperthyroid patients 68
5.5.1 Overall and CVD mortality (III) 68
5.5.2 The comparison between the patients treated with thyroidectomy and RAI 71
5.5.3 Cancer mortality (II) 72
5.6 Geographical differences between the study groups 72
6 DISCUSSION 74
6.1 Major findings of this study 74
6.1.1 Cardiovascular morbidity and mortality in hyperthyroidism 74
6.1.2 The impact of treatment modality on cardiovascular morbidity and mortality 75
6.1.3 Cancer incidence and mortality 78
6.2 The strengths and limitations of the study and the validity of the data 80
6.2.1 Enrollment of the patients treated with thyroidectomy 80
6.2.2 The register of the patients treated with RAI 80
6.2.3 Cardiovascular diseases 81
6.2.4 Cancer incidence 82
6.2.5 Mortality 83
7 SUMMARY AND CONCLUSIONS 85
8 ACKNOWLEDGEMENTS 87
9 REFERENCES 89
10 ORIGINAL COMMUNICATIONS 100

ABBREVIATIONS

^{131}I	radioactive isotope 131 of iodine
AF	atrial fibrillation
CAD	coronary artery disease
CI	confidence interval
CO	cardiac output
CT	computed tomography
CVD	cardiovascular disease
Gy	Gray; unit for the absorbed dose of radiation
ICD	International Classification of Diseases
HILMO	Hoito – ja poistoilmoitusrekisteri
HR	hazard ratio
MBq	megabecquerel; unit for radioactivity (106 disintegrations per second)
mCi	millicurie; unit for radioactivity (13.7 x 107 disintegrations per second)
OR	odds ratio
RAI	radioactive iodine
RLN	recurrent laryngeal nerve
RR	rate ratio
SIR	standardized incidence ratio
SQRTPA	Scandinavian Quality Register for Thyroid, Parathyroid and Adrenal Surgery
STUK	Säteilyturvakeskus / Radiation and Nuclear Safety Authority
SV	stroke volume
THL	Terveyden ja hyvinvoinnin laitos / National Institute for Health and Welfare
TSHRAb	thyroid stimulating hormone receptor antibodies
TSH	thyrotropin
T3	triiodothyronine
T4	thyroxine

LIST OF ORIGINAL COMMUNICATIONS

This thesis is based on the following three original publications which are referred to in the text by their roman numerals **I-III**.

I Ryödi E, Salmi J, Jaatinen P, Huhtala H, Saaristo R, Välimäki M, Auvinen A, Metso S (2014): Cardiovascular morbidity and mortality in surgically treated hyperthyroidism - a nation-wide cohort study with a long-term follow-up. Clinical Endocrinology, 80(5), 743-750.

II Ryödi E, Metso S, Jaatinen P, Huhtala H, Saaristo R, Välimäki M, Auvinen A (2015): Cancer incidence and mortality in patients treated either with RAI or thyroidectomy for hyperthyroidism. The Journal of Clinical Endocrinology and Metabolism, 100(10), 3710-3717.

III Ryödi E, Metso S, Huhtala H, Saaristo R, Välimäki M, Auvinen A, Jaatinen P (2018): Cardiovascular morbidity and mortality after treatment of hyperthyroidism with either radioactive iodine or thyroidectomy. Thyroid: Official Journal of the American Thyroid Association, 28(9), 1111-1120.

INTRODUCTION

Hyperthyroidism, which refers to increased secretion of thyroid hormones by a diseased thyroid gland, is a common disease, with a prevalence of 2.5% in women and 0.6% in men (Bjoro et al., 2000). The most common causes for hyperthyroidism are Graves´ disease, multinodular goiter and toxic adenoma. Graves´ disease is responsible for 60-80% of cases (Weetman, 2000). The risk factors for Graves´ disease are smoking, stress, pregnancy and female sex (Kahaly et al., 2018). The proportion of toxic adenoma and toxic multinodular goiter as an etiology of hyperthyroidism increases with age and they are more common in iodine-deficient areas (Ross et al., 2016).

Thyroid hormones have direct and indirect effects on all parts of the cardiovascular system and affect growth and metabolism. Thyrotoxicosis causes several changes in the cardiovascular system and predisposes acutely to hypertension, heart failure and arrhythmias (Klein, Irwin & Danzi, 2016). The changes in cardiovascular system have been regarded as reversible, without persistent consequences after the treatment of hyperthyroidism. However, several long-term follow-up studies have reported increased cardiovascular morbidity and mortality even after the treatment (Franklyn et al.; 1991; Franklyn et al., 2005; Flynn et al., 2006; Metso, Auvinen et al., 2007; Metso et al., 2008). Hypothyroidism after the treatment has been associated with better prognosis (Boelaert et al., 2013). There are also a few reports on increased incidence of different cancers and cancer mortality in hyperthyroid patients (Goldman et al., 1988). However, conflicting results with decreased or unchanged total cancer incidence have also been reported (Franklyn et al., 1999).

There are three different options for the treatment of hyperthyroidism-antithyroid drugs (ATDs), thyroidectomy and RAI. All of these options have been used since 1940s and have their own advantages and disadvantages (Ross et al., 2016). The previous long-term follow-up studies on CVD and cancer morbidity and mortality in hyperthyroidism after the treatment have included mainly patients treated with RAI. Therefore, it is unclear whether the increased morbidity and mortality are an outcome associated with the treatment with RAI or caused by hyperthyroidism *per se*. For example, in a study published by Metso et al, there was an association between the cancer risk and the dose of RAI administered

(Metso, Auvinen et al., 2007), suggesting a long-term oncogenic effect of RAI. Previously, no long-term comparative studies on the outcome of the patients after different treatment modalities have been published. The aim of this thesis was to study the long-term outcome of the hyperthyroid patients and to compare the impact of two different treatment modalities, RAI and thyroidectomy, on the long-term outcome of the patients.

REVIEW OF THE LITERATURE

2.1 Hyperthyroidism

2.1.1 Definitions and epidemiology of hyperthyroidism and thyrotoxicosis

Hyperthyroidism is a significant disease affecting 2.5% of women and 0.6% of men (Bjoro et al., 2000). In the United States, the prevalence of hyperthyroidism is 1.2% (Singer et al., 1995) and in Finland about 1% (Sane, 2010). Hyperthyroidism refers to increased synthesis and secretion of thyroid hormones by the thyroid gland. Overt hyperthyroidism is defined as a subnormal or undetectable level of thyrotropin stimulating hormone (TSH) and increased level of T4 and/or T3. Overt hyperthyroidism may be preceded by subclinical hyperthyroidism, in which the level of TSH is decreased while the levels T4 and T3 are still within the normal range. Thyrotoxicosis is defined as an increased concentration of circulating thyroid hormones, i.e thyroxine (T4) and/or triiodothyronine (T3) and can also be caused by other reasons than hyperthyroidism (Ross et al., 2016).

2.1.2 Causes of hyperthyroidism and thyrotoxicosis

Thyrotoxicosis is usually caused by diseases affecting the thyroid gland, but may also be caused by other, non-thyroidal diseases or conditions. Graves´ disease, toxic multinodular goiter, toxic adenoma and destructive thyroiditis are the most common diseases causing hyperthyroidism.

Graves´ disease is responsible for 80% of cases in Europe in iodine-rich areas, but in iodine-deficient areas 50% of hyperthyroidism is caused by nodular goiter (Ross et al., 2016). It is an autoimmune disease in which thyroid stimulating autoantibodies (TSHRab) bind to thyroid-stimulating hormone receptors causing thyroid hyperplasia and excess production and secretion of thyroid hormones by the thyroid gland (Kahaly et al., 2018). The etiology of Graves' disease is not totally clear, but it is known to be multifactorial. Several associated genes have been recognized (De Leo et al., 2016). According to a Danish twin study, 79% Graves´

disease is due to genetic factors and the rest is caused by environmental factors (Brix et al., 2001). The prevalence and concordance rate of hyperthyroidism in twin pairs has been studied in a cohort from Denmark (Brix et al., 2001) and a cohort from California, USA (Ringold et al., 2002). In the Danish study, 35% concordance was reported between monozygotic twins while in the Californian cohort, concordance rate for hyperthyroidism between monozygotic twins was 17% (Ringold et al., 2002). Other risk factors for Graves´ disease include stress, smoking, pregnancy and female sex, and factors influencing the immune system have been suspected, for example infections and some drugs (Kahaly et al., 2018). Furthermore, thyroid damage or a deficiency of vitamin D or selenium may predispose to Graves´ disease (Marinò et al., 2015).

Toxic multinodular goiter and toxic adenoma are more common in iodine-deficient areas and in older people (Carlé et al., 2011; Ross et al., 2016). In nodular thyrotoxicosis, thyroid nodule or nodules become autonomous and begin to produce excess of thyroid hormones despite the feedback from TSH or TSH-receptor antibodies (Ross et al., 2016). The progression of thyroid nodules may be accelerated by an excessive iodine intake for example due to amiodarone therapy. Almost 40% of the amiodarone molecule consists of iodine which may promote hyperthyroidism either by enhancing excessive production and secretion of thyroid hormones in a thyroid gland with a latent disease, or by causing a destructive thyroiditis with an accelerated release of previously produced, stored thyroid hormones (Capel et al., 2017). Other drugs that may induce hyperthyroidism include lithium and interferone α.

The conditions that can result in thyrotoxicosis without hyperthyroidism are thyrotropin-producing pituitary tumours, struma ovarii, metastatic follicular thyroid cancer, thyrotoxicosis caused by HCG secreted during pregnancy or by a chorioncarcinoma (De Leo et al., 2016).

Iatrogenic thyrotoxicosis may be caused by excessive or unnecessary use of levothyroxine (LT4) or liothyronine (LT3), either as a treatment of subclinical or clinical hypothyroidism or of other conditions misdiagnosed as hypothyroidism (i.e. fatigue, depression, weight gain). Normal thyroid gland produces mainly T4 which converts to the active form T3 intracellularly by deiodinases. The standard therapy for hypothyroidism is LT4, and a vast majority of the patients respond to LT4 with relief of hypothyroid symptoms, and normalized levels of TSH, T4 and T3. However, some patients continue having symptoms of hypothyroidism

despite normalized laboratory values. A few studies have been published comparing the effects of LT4 and LT3 with conflicting results (Grozinsky-Glasberg et al., 2006; Joffe et al., 2007), but the current guidelines recommend LT4 as the first line therapy for hypothyroidism, due to its efficacy and favourable safety profile (Jonklaas et al., 2014; Kraut & Farahani, 2015).

2.1.3 Clinical presentations of hyperthyroidism

Thyroid hormones regulate energy and heat production and synthesis of several proteins affecting the metabolism of almost every organ in human body. They are essential to hepatic, cardiac, neurological and muscular functions. Classical symptoms caused by excess load of thyroid hormones are anxiety, fatigue, decreased weight, increased sweating, heat intolerance, palpitations, osteoporosis, mental disorders and tachycardia (Davies Terry F., Laurberg Peter, Bahn Rebecca S, 2016). The severity of symptoms depends on the level of thyrotoxicosis, but the symptoms may be misleading or lacking, especially in the elderly (Boelaert et al., 2010). Orbitopathy is associated with Graves´ disease and involves ca. 25% of the patients. The main symptoms of orbitopathy are exophthalmos (proptosis), periorbital edema and diplopia (Bartalena & Fatourechi, 2014).

2.2 Treatment of hyperthyroidism

2.2.1 Antithyroid drug therapy

2.2.1.1 Indication and contraindications

Antithyroid drugs (ATDs) are thionamide derivative drugs that inhibit the synthesis of thyroid hormones. ATDs (carbimatzole, methimatzole and propylthiouracil) are used as a medical therapy for hyperthyroidism, usually as a short-term treatment before RAI-therapy or surgery. As a primary treatment of hyperthyroidism, ATDs are used in children, young adults, seniors and in persons, who do not wish any

other treatment (Ross et al., 2016). They can also be used as a long-term treatment in pregnant or breast-feeding women and with significant eye symptoms in Graves´ disease (Cooper, 2005). ATDs, especially methimatzole and carbimatzole, are not recommended during the first trimester of pregnancy, due to the teratogenic effects occurring in 2-4% of pregnancies with ATDs (Alexander et al., 2017).

2.2.1.2 Side-effects of ATDs

ATDs may cause cutaneous reactions, gastrointestinal symptoms and arthralgia as mild side effects in 5-25% of the patients. More serious side effects are rare, agranulocytosis occurring in 0.2-0.5% and hepatitis in 0.1-0.2% of the patients (Cooper, 2005). Although the ATDs are known to be safe in continued use up to 10 years (Azizi et al., 2005), even the long-term ATD therapy is usually used only for 12-18 months.

2.2.1.3 Efficacy of the treatment

Since ATDs are not ablative therapies for hyperthyroidism, they have a high relapse rate compared to RAI or thyroidectomy. In a recent comparative study of 720 patients with Graves´ disease, patients treated with ATDs had a relapse rate of 48% while those treated with RAI had a relapse rate of 8% and those with thyroidectomy 0% (Sundaresh et al., 2017). Similar relapse rate for ATDs (53%) was reported previously in a meta-analysis with 1402 patients with Graves´ disease (Sundaresh et al., 2013).

2.2.2 Radioactive iodine (RAI)

The administration of RAI has been used since the 1940s as a treatment modality for hyperthyroidism. Treatment with RAI (^{131}I) is based on the iodine uptake of thyroid gland and the aim of the treatment is to achieve euthyroidism or hypothyroidism by destroying a part of the functional tissue of the thyroid gland. RAI is given in liquid or as a capsule form of ^{131}I-labeled sodium iodide. RAI is actively transported into the thyroid follicular cells in which its beta emissions result in tissue necrosis. Tissue ablation is caused during the next 6-18 weeks or longer

and meanwhile hyperthyroidism may even worsen (Ross, 2011). The dose may be fixed or calculated individually based on the size of a thyroid gland (Ross, 2011).

2.2.2.1 Indications and contraindications

Treatment with RAI is used in all three major causes of hyperthyroidism as a permanent cure of the disease. It can also be used in relapses after ATDs or subtotal surgery. RAI is one of the first line treatment choices for most of the patients with hyperthyroidism (Ross et al., 2016). The main contraindications are pregnancy and lactation. As primary safety regulations, the patient has to avoid the company of children for five days and of pregnant women for 10 days, and minimize the contact time with other adults for five days after the administration of RAI (STUK, 2013). The regulations and instructions vary between countries, but inability to follow the radiation safety precautions is a contraindication for the treatment (Ross, 2011).

2.2.2.2 Efficacy and short-term side-effects of treatment with RAI

After the administration of RAI, euthyroidism develops for 50-95% of patients during 2-6 months (Franklyn et al., 1991). The most common side-effect is hypothyroidism, which develops for 6-15% of patients during the first year and for 70-78% of patients after a longer period of time (Franklyn et al., 1991; Metso et al., 2004). However, hypothyroidism may also be considered as a favourable outcome since it is easier to manage than a relapse of hyperthyroidism. RAI is cleared by the kidneys and renal failure may thus lead to a longer exposition of the body organs to radiation (Holst et al., 2005).

Other possible side-effects are thyroiditis, a painful condition harming about 1% of the patients and an evolving Graves´ disease after the treatment of multinodular goiter (Ross, 2011). Furthermore, the incidence of orbitopathy has been reported to increase after the treatment with RAI (Tallstedt et al., 1992).

2.2.2.3 RAI and the risk of cancer

As a long-term consequence of RAI-therapy, there is a suspicion of increased cancer incidence after the treatment. During the past 40 years, several studies with large

cohorts on cancer incidence and mortality after treatment of hyperthyroidism have been published. The first study included patients treated either with thyroidectomy or RAI (Hoffman et al., 1982), but other studies have mainly included patients treated with RAI for hyperthyroidism. Hoffman et al found no difference in the incidence of breast cancer, leukemia or all cancers between the two treatment groups, but a higher incidence of cancers in organs that concentrate RAI, ie. salivary glands, digestive tract, kidneys and bladder, was reported. Another American study with 1 762 hyperthyroid women treated mostly with RAI reported a small increase in the incidence of breast cancer in patients treated with RAI and an increase in pancreatic cancer (Goldman et al., 1988). A Swedish study with 10 552 patients reported no increase in cancer incidence overall, but an increased incidence of lung (SIR 1.32), kidney (SIR 1.39) and stomach cancers (SIR 1.33) and a decreased incidence of malignant lymphoma (SIR 0.53) (Holm et al., 1991).

Conflicting results, however, with a decreased or unchanged total cancer incidence were reported from Birmingham, England by Franklyn et al in 1999. The study of 7 417 patients treated with RAI found decreased cancer incidence and mortality in patients. A decreased risk of pancreas, bronchus, trachea and bladder cancers, and cancers of lymphatic and haemopoietic systems was reported, but there was an increased incidence of small bowel and thyroid cancers and increased mortality for these cancers (Franklyn et al., 1999).

Metso et al. published several articles during 2004-2008 on morbidity and mortality after treatment of hyperthyroidism with RAI. In these studies, there were 2 793 patients treated with RAI for hyperthyroidism during 1965-2002 in Tampere University Hospital, Finland. One of the main results was an increased cancer incidence and mortality during 20 years of follow-up after treatment of hyperthyroidism with RAI. The overall cancer incidence was 25% higher in the patients treated with RAI compared to age- and gender-matched controls. Furthermore, the incidences of kidney cancer (RR 2.32), stomach cancer (RR 1.75) and breast cancer (RR 1.53) were increased. The cancer incidence was higher in patients with higher doses of RAI, and there was a latency period of five years before the increase in cancer incidence (Metso, Auvinen et al., 2007). A paper reporting increased risk of cancer mortality with the same study cohort was also published in 2007 (Metso, Jaatinen et al., 2007).

The results of the previous studies led to a discussion in Finland on whether it is safe to treat patients with RAI for hyperthyroidism (Metso, 2009) (Sane, 2010).

Later on, Hieu et al from Australia published a meta-analysis including all the studies mentioned above. In this large meta-analysis, there was no increase in the overall cancer risk, but the risk at some sites, such as the kidneys and the thyroid gland was significantly increased, with a statistically insignificant tendency to stomach cancer (RR 1.11, 95% CI 0.92-1.33). The increased risk was explained as a side-effect of ablative doses of RAI (Hieu et al., 2012).

2.2.3 Surgery

2.2.3.1 Indications and contraindications

In Finland, approximately 200 procedures are performed each year due to hyperthyroidism (HILMO database). The main reason for thyroid surgery is malignancy or a suspicion of malignancy, but thyroidectomy is also used as a treatment option for hyperthyroidism or as a treatment of goiter for compressive symptoms. A large goiter may compress the respiratory tract, esophagus or the recurrent laryngeal nerve. The main reasons for the surgical treatment of hyperthyroidism are an inadequate response to treatment with antithyroid medication or RAI, contraindications for RAI (e.g., severe Graves´ orbitopathy or pregnancy), and patient preference (Cooper, 2003; Ross et al., 2016).

2.2.3.2 Complications

The four main complications of thyroid surgery are hemorrhage, recurrent laryngeal nerve palsy, hypocalcemia and infections. During the first procedures, bleeding was the most fatal complication of thyroid surgery with 40% mortality rate. Afterwards, the techniques were developed first by Jaques-Louis Reverdin and then by Theodor Kocher, who received a Nobel Prize of Medicine for the understanding of the physiology and the surgical treatment of the thyroid gland (Fortuny et al., 2015). Nowadays, severe intraoperative hemorrhage is rare due to new techniques and devices (Boger & Perrier, 2004). Re-bleeding after thyroidectomy occurred in 2.1% of cases in a large follow-up study with 3 660 thyroid operations in 26 Scandinavian hospitals. The risk was associated with older age and male gender. In the same study, infection was detected in 1.6% of cases and unilateral recurrent

laryngeal nerve (RLN) palsy in 3.9% with recovering in most of the cases after six months of follow-up. The risk of nerve palsy was associated again with older age, but also with intrathoracic goiter, thyrotoxicosis and routine laryngoscopy (Bergenfelz et al., 2008). In a report from 2009, the complication rate for nerve palsy was 6.7% immediately after operation. After 12 months of follow-up, however, most of the nerve palsies had been recovered. The authors concluded that the recovery of RLN palsy is possible in 90% of cases (Dionigi et al., 2010).

The complication rate of uni- or bilateral RLN palsy may be decreased by new techniques, like neuromonitoring of the RLN during the operation (Fortuny et al., 2015). According to a report by Bergenfeltz et al including 5 252 patients registered to Scandinavian Quality Register for Thyroid, Parathyroid and adrenal Surgery (SQRTPA), the intraoperative nerve monitoring (IONM) did not decrease the risk of early nerve palsy, but was associated with a decreased risk of permanent nerve palsy during the follow-up (Bergenfelz et al., 2016).

Hypocalcemia is a major complication of thyroid surgery and most often caused by injury to parathyroid glands during operation. The positions of the parathyroid glands vary and it is essential to keep them in their original positions during the operation, to preserve their terminal vascularization (Duclos et al., 2012). In a large study with 3 574 operations and 28 different surgeons, the risk of hypoparathyroidism was 2.7% and its prevalence depended on surgeons experience and age: the surgeons aged 35-50 years had smaller complication rates than older or younger surgeons (Duclos et al., 2012)**.** The main risk factors for hypoparathyroidism are recurrent operations, central neck dissection and goiter size, as well as thyroiditis and Graves´ disease due to their inflammatory nature (Erbil et al., 2007; Bergenfelz et al., 2008).

The complication rate in thyroidectomy is associated with the number of procedures the surgeon performs yearly. In a recently published study of 16 954 patients with thyroidectomy for either thyroid cancer (47%) or a benign thyroid disease (53%), the cut-off threshold for the lowest complication rate was achieved, if the surgeon performed over 25 procedures yearly. In the study, 51% of the surgeons performed only one thyroidectomy per year, and the overall complication rate was 6% (Adam et al., 2017).

2.2.3.3 Efficacy of the treatment

Thyroidectomy as a treatment of hyperthyroidism has many advantages. The most important advantage is an almost immediate effect; the half-life of T4 is 7-8 days. Nowadays, thyroidectomy is preferred to a subtotal thyroidectomy to avoid a relapse in the remnant (Palit et al., 2000) (Wilhelm & McHenry, 2010). The other advantages of thyroidectomy as a treatment of hyperthyroidism are the availability of a tissue sample for histologic examination, removing target tissue for the TSHRAbs, avoiding radiation and its possible long-term effects, and a neutral or positive effect on Graves' orbitopathy (Boger & Perrier, 2004; Fortuny et al., 2015). The risk of recurring hyperthyroidism is negligible after thyroidectomy, and surgery does not prohibit immediate pregnancy and lactation, contrary to RAI therapy (Boger & Perrier, 2004).

In a meta-analysis of 35 studies and 7 241 patients with Graves´ disease treated with subtotal or total thyroidectomy, all the patients treated with total thyroidectomy became hypothyroid. Of the patients treated with subtotal thyroidectomy, 60% achieved euthyroidism and 26% became hypothyroid. Persistent or recurrent hyperthyroidism occurred in 8% of the patients during a mean follow-up of 5.6 years (range 32 months to 32 years) (Palit et al., 2000). The conclusion of the meta-analysis was that total thyroidectomy is safe and recommended particularly for severe Graves´ disease and large goiters. The studies with patients with hyperthyroidism caused by toxic adenoma or multinodular goiter were excluded from the meta-analysis (Palit et al., 2000).

2.2.4 Current treatment strategies for hyperthyroidism

The treatment modalities of hyperthyroidism have not evolved over a half century. They are targeted to inhibit, destroy or remove the thyroid gland. Research on the etiology and pathogenesis of the disease is essential for the development of a targeted treatment that would cure the disease, without toxicity and without sustained damage to the thyroid gland. None of the current treatment modalities – RAI, antithyroid medication, or thyroidectomy - meets the criteria. However, they are the treatment options currently available and widely used. Some of the patients are even treated with all three modalities before achieving remission (Ross et al.,

2016). ATDs are used before RAI or surgery and are the main treatment option for children or for people with comorbidities and relatively short life expectancy for other reasons than hyperthyroidism.

An important factor affecting the treatment modality chosen is the correct diagnosis of the etiology of hyperthyroidism. Without an accurate diagnosis the treatment modality chosen might be disadvantageous to a patient (Ross et al., 2016). Nevertheless, even the right diagnosis and the best possible treatment modality do not protect from the side-effects, discomfort or restrictions during and after the treatment. Therefore, the patient has to be given sufficient information on the possible side-effects, costs, length of the recovery phase and other disadvantages as well as on the advantages of the possible treatment options available. After that the treatment modality or modalities are chosen in collaboration with the patient and the physician (Ross et al., 2016).

2.3 Morbidity during thyrotoxicosis

2.3.1 The functions of the thyroid hormones in the cardiovascular system

Thyroid gland and heart have a connection through migration during embryology and thyroid hormones have direct and indirect effects in all parts of the cardiovascular system (Klein, I., 2012). The human thyroid gland synthesizes and secretes thyroid hormones, of which 85% is T4 and 15% T3. T4 is converted mainly in the liver to T3, which is the active form of thyroid hormone (Salvatore et al., 2016). Cardiac myocytes cannot metabolize T4 to T3, and all the changes in the cardiovascular system are dependent on the level of T3 in blood (Everts et al., 1996).

There are specific transport proteins for T3 in the cell membranes. In the myocytes, T3 enters the nucleus and binds to nuclear receptors, which then bind to specific elements of the target genes. There are several T3-responsive genes in the heart, which encode several structural and regulatory proteins. The most important gene transcription-mediated reaction regulated by T3 in the heart is the production of sarcoplasmic proteins, calcium-activated ATPase (Ca^{2+}-ATPase) and phospholamban. The flux of Ca^{2+} in and out sarcoplasmic reticulum determines systolic contractility and diastolic relaxation of the heart. The active transportation of Ca2+ by Ca2+

-ATPase is regulated by phospholamban, and the activity of phospholamban is modified by its phosphorylation. Thyroid hormone inhibits the genetic expression of phospholamban and increases its phosphorylation, modulating the systolic contractility and the force of diastolic relaxation (Grais & Sowers, 2014). Thyroid hormone has also other functions in cardiac myocytes. T3 regulates the performance characteristics of various sodium, potassium and calcium channels, which may have inotropic and chronotropic effects on the heart (Klein, I. & Ojamaa, 1998).

2.3.2 The effect of thyrotoxicosis on the cardiovascular system

Cardiac output (CO) is a term describing the volume of blood pumped by the heart per unit of time. It is calculated with the equation CO=Heart Rate x Stroke Volume (SV). Thus, the factors that modulate CO are the factors affecting heart rate and SV. CO is controlled by the oxygen demands of the tissues in the body. The primary factors influencing heart rate are autonomic innervation and hormonal actions. SV is modulated by heart size and contractility, gender, duration of the contractions, preload and afterload (vascular resistance) (Guyton and Hall, 2016). For example, CO increases during exercise mainly due to increased heart rate. Furthermore, in systolic heart failure CO decreases due to decreased contractility.

In hyperthyroidism, CO increases remarkably as a result of increased heart rate and contractility, together with decreased peripheral resistance and diastolic blood pressure, and with increased venous return and preload (Klein, 2012). The systolic contraction and the force of diastolic relaxation are enhanced mainly by direct effects of T3 on the regulation of intracellular Ca^{2+} transport. The decrease in peripheral resistance leading to decreased diastolic blood pressure and decreased afterload results from direct effects of T3 in smooth muscle cells.

Decreased diastolic blood pressure activates the renin-angiotensin-aldosterone system, leading to salt and fluid retention. Meanwhile, thyroid hormone also increases the production of erythropoietin leading to an increased red cell mass (Klein, 2012) (Grais & Sowers, 2014). As a combined effect of the latter two, the blood volume is increased, leading to increased preload of the heart and thus to increased stroke volume (the Frank-Starling law). Left ventricular hypertrophy may develop in the hyperthyroid heart as a compensatory mechanism to increased preload, heart rate and cardiac output (Dörr et al., 2005).

2.3.3 Cardiovascular morbidity in hyperthyroidism

Most changes in the cardiovascular system during a hyperthyroid state are meaningful reactions to meet the demands of increased energy metabolism and heat production in the body. As a result, however, the cardiovascular system uses its capacity already at rest, leading to exercise intolerance (Klein & Ojamaa, 1998; Klein, I. & Ojamaa, 2001). Atrial fibrillation (AF), tachycardia, elevated blood pressure, increased blood volume and increased oxygen demands of the heart predispose to heart failure and to worsening of the symptoms of a coexisting heart disease (Klein & Ojamaa, 1998; Klein & Ojamaa, 2001; Klein & Danzi, 2016). Left ventricular hypertrophy is a complication of long-term hypertension and was found to be an independent risk factor for cardiovascular morbidity and mortality in the Framingham Heart Study (Manyari, 1990; Kannel & Cobb, 1992).

Because thyroid hormones do not decrease pulmonary flow resistance, pulmonary pressure may increase. The pulmonary pressure may rise due to hypertension and left ventricular hypertrophy leading to diastolic dysfunction, or due to systolic dysfunction caused by high-output heart failure. These mechanisms have been present in heart failure and in rise of pulmonary pressure associated with both subclinical and overt hyperthyroidism (Biondi, 2012).

Hyperthyroidism, even subclinical, is a strong risk factor for AF. The excess of T3 shortens the atrial refractory period by altering cell membrane functions (Komiya et al., 2002) and also seems to increase supraventricular ectopic activity in hyperthyroid patients without previous heart disease (Wustmann et al., 2008). Both these factors are triggers for AF, and AF feeds itself by altering the electrical (Wijffels et al., 1995) and mechanical functions of the atria (Sparks et al., 1999) and also changes the atrial structure by causing fibrosis in the myocardium (Burstein & Nattel, 2008; Nattel et al., 2000). This remodeling of the atria prolongs arrhythmias and predisposes to relapses.

Patients with hyperthyroidism are thus susceptible to AF and an episode of AF predisposes to recurrent AF, which explains the persisted risk of AF among the patients with treated hyperthyroidism. A large Danish population-based study of 586 460 subjects showed that the risk of AF is associated with thyroid function across the spectrum of subclinical and clinical thyroid diseases, the incidence of AF increasing with a decreasing TSH level (Selmer et al., 2012). Likewise, another Danish study found an association between newly diagnosed AF and the risk of

future hyperthyroidism. In this study, euthyroid patients with new-onset AF during 1997-2009 were followed up to 13 years. Of the patients with new-onset AF, 3% developed hyperthyroidism during the follow-up time, while the prevalence of hyperthyroidism was 1% in the control group (Selmer et al., 2013).

In another recently published large Danish study, including 85 856 hyperthyroid patients and ten age- and gender-matched controls for each patient, reported a higher prevalence of many cardiovascular events after the diagnosis of hyperthyroidism. The risk of cardiovascular events peaked during the first three months after the diagnosis of hyperthyroidism. The risk of AF and arterial embolism was 6 to 7-fold, but also the risk of venous thromboembolism, ischemic or non-ischemic stroke, and percutaneous coronary intervention was increased up to 2-3 -fold. The risk of almost any subgroup of cardiovascular diseases persisted during the mean follow-up time of 9.2 years. The risk of percutaneous coronary intervention (PCI) was no longer statistically significant after the first year (Dekkers et al., 2017).

The significance of thyroid hormone excess in atherosclerosis and coronary artery disease (CAD) is uncertain. There are a few clinical studies evaluating the risk and prevalence of atherosclerotic changes in coronary arteries related to the spectrum of thyroid function. An association of low normal serum free T4 concentration and increased coronary artery calcium scores detected by multi-detector computed tomography was reported by Kim et al in 2012, in 1 849 euthyroid subjects without significant risk factors for CAD (Kim et al., 2012). In the Kangbuk Samsung health study (Park et al., 2016), 2 173 healthy subjects were followed for four years. Thyroid hormones and TSH levels were measured and coronary artery calcium score (CACS) was defined by multi-detector computed tomography (CT) at the beginning and at the end of the follow-up. Low normal baseline T4 level was reported to associate with increase in CACS during 4 years, but there was no association between FT3 or TSH levels on CACS progression. Furthermore, another study on prevalence of coronary artery stenosis in CT angiography showed an increased risk of coronary artery calcification in overt and subclinical hyperthyroidism. The study included 51 women with overt hyperthyroidism, 74 women with subclinical hyperthyroidism, and 619 euthyroid women. All the patients were evaluated with computed tomography angiography. More high-grade stenoses (39.2%, 37.8%, 24.2%; P=0.007), higher CACS (456.5, 199.5, 155.9; $P < 0.0001$), and higher plaque burden were detected among women with overt and subclinical hyperthyroidism, compared to women in euthyroidism.

The patients with overt hyperthyroidism had the highest scores, but also the patients with subclinical hyperthyroidism had higher scores than euthyroid women. In line with the CT findings, after a 168 months of mean follow-up hyperthyroid women had had significantly more revascularizations compared to euthyroid women (Beyer et al., 2017). The prevalence of other risk factors for atherosclerosis or the mechanisms of increased risk of atherosclerosis related to overt or subclinical hyperthyroidism were not discussed in this paper.

2.3.4 Thyrotoxicosis and cancer

Thyroid hormones are essential for normal growth and metabolism, but may also have a role in tumor progression (Moeller & Führer, 2013). Thyrotoxicosis and hyperthyroidism have been linked to increased risk of cancer in several recent studies. The Rotterdam study included 10 318 patients with free T4 and TSH measurements, and reported an association between higher free T4 levels and any solid cancer (HR 1.42), lung cancer (HR 2.33) and breast cancer (HR 1.77) (Khan et al., 2016). In a Taiwanese study including 17 033 patients with a new diagnosis of hyperthyroidism and twice as many matched euthyroid controls, the patients with hyperthyroidism had a higher risk of any cancer (HR 1.21) and thyroid cancer (HR 6.80) after adjustment for confounding factors during four years of follow-up (Yeh et al., 2013).

Hellevik et al studied the association between cancer incidence and low TSH in a large population-based study of 29 691 Norwegian patients (Hellevik et al., 2009). TSH was measured at the beginning of the study, and cancer incidence was followed during the follow-up of nine years. Low TSH levels (<0.05 mU/L) were associated with an increased cancer risk (HR 1.34), compared to the euthyroid reference group. Of specific cancer-sites, there was an increased risk of lung (HR 2.34), breast (HR 1.20), prostate (HR 1.97) and colon cancer (HR 1.23) in the hyperthyroid patients. The results of this Norwegian study were adjusted for age and gender, as well as for smoking.

Subclinical or overt hyperthyroidism have also been found to associate to increased risk of prostate cancer (Mondul et al., 2012) (Chan et al., 2017), breast cancer (Tosovic et al., 2012) (Søgaard et al., 2016), breast cancer mortality (Journy et al., 2017) and mortality for ovarian cancer (Minlikeeva et al., 2017).

The increased risk of cancer in hyperthyroidism might be due to an impact of hyperthyroidism per se, or due to shared risk factors for thyroid nodularity, hyperthyroidism and cancer. Smoking is a well-known risk factor for cancer and also

a risk factor for hyperthyroidism. A meta-analysis reported an increased prevalence of Graves' disease (OR 3.3) among current smokers compared to non-smokers, but no association was detected between smoking and multinodular goiter (Vestergaard, 2002). In a substudy of Nurse's Health Study II, current smoking (HR 1.93) and previous smoking (HR 1.23) were associated with Graves´ disease, with a dose-dependent increase in incidence (Holm et al., 2005).

In addition to smoking, atrophic gastritis and iodine deficiency are shared risk factors for cancer and hyperthyroidism. Atrophic gastritis associates with both autoimmune thyroid disease and gastric cancer (Centanni et al., 1999). Furthermore, hyperthyroidism itself might be a risk factor for gastric cancer, due to inhibition of gastric acid production and hypergastrinemia during thyrotoxicosis (Dahlberg et al., 1981; Centanni et al., 1999) , which is involved with carcinogenesis in the gastric mucosa (Watson et al., 2006). Venturi et al have published a short review on studies on iodine intake and gastric cancer and shown a correlation between iodine deficiency, goiter, and atrophic gastritis (Venturi et al., 2000). Gastric carcinoma is more prevalent in areas of iodine deficiency and also high in countries with excess iodine intake, such as Japan, China, and Korea (Song et al., 2018). Furthermore, iodine deficiency has been suggested to associate with the development of breast cancer (Venturi, 2001), and an excess iodine intake might inhibit or delay the development of breast cancer (Smyth, 2003).

2.4 Morbidity and mortality after the treatment of hyperthyroidism

Both overt and subclinical hyperthyroidism are a significant burden to the human body and cause several acute and subacute changes affecting morbidity during hyperthyroidism. Most changes are regarded as reversible. However, several long-term follow-up studies have reported a persisting cardiovascular and cancer morbidity and/or increased all-cause, cardiovascular or cancer mortality after the treatment of hyperthyroidism.

2.4.1 Mortality after the treatment of hyperthyroidism

There are a few studies offering data on all-cause mortality after treatment of hyperthyroidism (Hoffman et al., 1982; Goldman, 1990; Hall et al., 1993; Franklyn

et al., 2005; Flynn et al., 2006; Metso, Jaatinen et al., 2007; Bauer et al 2007) and a few on CVD or cancer mortality (Hall et al., 1993; Franklyn et al., 1998; Franklyn et al., 2005; Metso, Jaatinen et al., 2007). Most of the studies report increased all-cause, CVD or cancer mortality, but there are also results of unchanged risk of mortality in hyperthyroidism (Hoffman, McConahey, Diamond, & Kurland, 1982; Flynn et al., 2006). Most of the studies have included mainly patients treated with RAI. The oldest of the reports, a study by Hoffman et al (1982) included patients treated either with RAI or with thyroidectomy, and found no increased risk of mortality in patients treated with RAI (Hoffman, McConahey, Diamond, & Kurland., 1982). Increased CVD mortality has been reported after treatment with RAI (Goldman, 1990; Hall et al., 1993; Franklyn et al., 1998; Franklyn et al., 2005), but also after treatment with antithyroid drugs (Boelaert et al., 2013).

2.4.2 Cardiovascular morbidity and mortality after the treatment of hyperthyroidism

There are a few large studies with rather similar results on CVD morbidity and mortality in patients with hyperthyroidism (Table 1). Nyirenda et al included 3 346 patients with either Hashimoto´s thyroiditis, Graves´ disease or multinodular goiter in Edinburgh between 1981-2001. They reported an increased hospitalization rate for CVDs in all the diagnostic subgroups after treatment of hyperthyroidism compared to patients hospitalized for other reasons than hyperthyroidism (Nyirenda et al., 2005). The patients treated for Graves´ disease had 42% higher risk of hospitalization and the patients treated with multinodular goiter 50% higher risk. There was no increase in CVD mortality in this study. Flynn et al included 3 888 hyperthyroid patients treated either with RAI, thyroidectomy or ATDs in Scotland during 1994-2001, and reported no increase in CVD mortality among hyperthyroid patients during 21 190 patient-years of follow-up. However, there was almost three-fold (SIR 2.71) risk of arrhythmias in treated hyperthyroidism in this study (Flynn et al., 2006). The outcomes between different treatment groups were not compared.

In a Finnish case-control cohort study including 2 611 hyperthyroid patients treated with RAI during 1969-2002, a 12% increase in the risk of CVD hospitalization was detected compared to age- and gender-matched control group (Metso et al., 2008). In the subgroup analyses of this study, the risk of hospitalization for AF (RR 1.35), cerebrovascular disease (RR 1.31), diseases of

other arteries and veins (RR 1.22), hypertension (RR 1.20) and heart failure (1.48) were also significantly increased, but the risk of CAD was unchanged. In a mortality study for the same cohort of patients, there was a 40% higher risk cerebrovascular mortality among hyperthyroid patients (Metso, Jaatinen et al., 2007).

In most studies, patients have been treated mainly with RAI and only smaller studies have been published with other treatment modalities. In 2007 Osman et al reported the outcome of 393 patients treated with ATDs for hyperthyroidism, compared to a euthyroid age- and gender-matched control group. All the patients and controls were studied with 24-hour ECG monitoring, resting ECG, and measurement of blood pressure and pulse rate at the time diagnosis of hyperthyroidism, and these studies were repeated during the follow-up. Serial measurements of TSH, T4 and T3 were performed. The hyperthyroid patients had a higher prevalence of cardiovascular symptoms and findings – namely a higher blood pressure and pulse rate, and a higher prevalence of arrhythmia – during hyperthyroidism, but also after achieving euthyroidism compared to the control group (Osman et al., 2007). Muthukumar et al published in 2016 a rare prospective study on reversal of cardiovascular dysfunction after surgical treatment of hyperthyroidism (Muthukumar et al., 2016). They included 41 hyperthyroid patients selected to total thyroidectomy. The patients were examined with echocardiography and natriuretic peptide (NT-proBNP) before treatment, after achieving euthyroidism with antithyroid drugs before the surgery and three months after total thyroidectomy. Before any treatment, 63% of the patients had either pulmonary hypertension, dilated cardiomyopathy, heart failure or elevated NT-proBNP. After achieving euthyroidism with antithyroid drugs, 73% of the patients had recovered and three months after surgery 92% of patients had a complete recovery of cardiovascular function.

There are few studies including patients treated with thyroidectomy for hyperthyroidism. A recent Swedish paper from Giesecke et al included 12 239 hyperthyroid patients treated either with RAI or thyroidectomy during 1976-2000 in Stockholm area (Giesecke et al., 2017). Patients treated with thyroidectomy for a non-toxic thyroid disease were used as a control group (n= 3 685), as well as the general Stockholm population. Most of the hyperthyroid patients were women (85%), over a half were treated for Graves´ disease (n =6 248) and the rest for a toxic nodular goiter. Cardiovascular morbidity and mortality were compared between the controls and the study groups but not between different treatment modalities. Overall cardiovascular morbidity consisting mostly of heart failure and ischemic

stroke was 12% higher and CVD mortality was 27% higher among hyperthyroid patients compared to both control groups. The patients treated for a toxic nodular goiter had the highest cardiovascular risk.

Two previous studies have compared mortality rates after different treatment modalities of hyperthyroidism. Boelaert et al compared studied patients treated with antithyroid medication or RAI (Boelaert et al., 2013). The all-cause mortality rates were increased during the periods of thionamide treatment for hyperthyroidism and after less intensive treatment with RAI (not resulting in hypothyroidism and treatment with thyroxine replacement therapy). The existence of AF was an independent risk factor for increased mortality rate. However, after intensive treatment with RAI (resulting in hypothyroidism and thyroxin replacement therapy), the all-cause mortality rates did not differ between the patients and the controls. Similar results of the advantages of more aggressive treatment (resulting in hypothyroidism) have been reported also in other studies (Franklyn et al., 2005) (Metso et al., 2008). Giesecke et al published recently a comparative study on mortality rates after treatment of hyperthyroidism either with RAI or thyroidectomy. They included 10250 patients treated with RAI and 742 patients treated with thyroidectomy and reported significantly lower all-cause mortality rates on the patients treated with thyroidectomy compared to patients treated with RAI during a mean of 16-22 years of follow-up (Giesecke et al., 2018).

Table 1. Characteristics of the long-term studies evaluating cardiovascular morbidity or mortality after the treatment of hyperthyroidism

Study	Country	Design	Study years	Number of patients	Control group	Treatment modality	Follow-up time	risk of all CVD	risk of CVD mortality
Hall et al 1993	Sweden	Cohort	1950-1975	10 552	Swedish Cause of Death Register	RAI	average 15 years	-	SMR 1.65
Franklyn et al 1998	Birmingham, UK	Cohort	1950-1989	7 209	Death Register England and Wales (Age-specific mortality)	RAI	105 028 person-years	-	SMR 1.20
Nyirenda et al 2005	Scotland	Cohort	1981-2001	3 346	Morbidity register of Scotland	RAI	not specified	HR 1.42 for GDτ HR 1.50 for MNG*	-
Flynn et al 2006	Scotland	Cohort	1994-2001	3 888	Population Tayside, Scotland	RAI, thyroidectomy or ATDs	21 190 person-years	SIR 2.71 for arrhythmias	No increased risk
Metso et al 2007	Tampere, Finland	Cohort	1965-2002	2 793	Age-and gender matched controls	RAI	median 9 years	-	RR 1.40
Osman et 2007	Edinburgh, UK	Case-control	1999-2002	393	Age-and gender matched controls	RAI or ATDs	not specified	increased, not specified	-
Metso et al 2008	Tampere, Finland	Cohort	1969-2002	2 611	Age-and gender matched controls	RAI	median 9 years	RR 1.12	-
Boelaert et al 2013	Birmingham, UK	Cohort	1989-2003	12	Death Register England and Wales (Age-specific mortality)	RAI or ATDs	12 868 person-years	-	SMR 1.20
Giesecke et al 2017	Stockholm, Sweden	Cohort	1976-2000	12 239	Stockholm residents treated for euthyroid goiter	RAI or thyroidectomy	median 18,4 years	HR 1.12	HR 1.29

τGD = Grave`s disease
*MNG = Multinodular goiter

AIMS OF THE STUDY

The aim of this study was to clarify the long-term prognosis of hyperthyroid patients treated with thyroidectomy for hyperthyroidism and to compare the results to hyperthyroid patients treated with RAI.

The specific questions were:

1. Does hyperthyroidism and/or its treatment affect CVD morbidity and mortality?

2. Is there a difference in CVD morbidity or mortality between the patients treated for hyperthyroidism with thyroidectomy and those treated with RAI?

3. Does hyperthyroidism and/or its treatment affect cancer morbidity and mortality?

4. Is there a difference in cancer morbidity or mortality between the patients treated for hyperthyroidism with thyroidectomy and those treated with RAI?

SUBJECTS AND METHODS

4.1 1. Subjects (I, II, III)

4.1.1 The patients treated with thyroidectomy

The present study is based on two different groups of patients treated for hyperthyroidism. The first group of 4 334 patients (3 719 women and 615 men) includes all the patients treated surgically for hyperthyroidism between January 1986 and December 2007 in Finland. The patients were identified from the Finnish Hospital Discharge Registry (HILMO) maintained by the National Institute for Health and Welfare (THL). The nationwide register covering all surgically treated patients was computerized in 1986. The search for surgically treated patients was based on both the diagnosis of hyperthyroidism (International Classification of Diseases, 8th, 9th and 10th revisions, codes 242 and E05) and the procedure codes for total or subtotal thyroidectomy (based on NCSP, Nordic Classification of Surgical Procedure codes) 2504, 2505 and 2506 BAA25, BAA40, BAA50 and BAA60 for total or subtotal thyroidectomy depending on the year of the procedure). The etiological diagnoses of hyperthyroidism were obtained from HILMO database. The follow-up data for thyroid status was not available for operated patients.

4.1.2 The patients treated with RAI

The second group of patients consist of 1 819 (1 485 women and 329 men) patients treated with RAI between January 1986 and December 2007 in Tampere, Finland. These patients were identified from the database of Tampere University Hospital. Patients treated with RAI have been systematically registered in Finland only in Tampere University Hospital with a catchment population of 500 000 (10% of the Finnish population). Information on the etiology of hyperthyroidism, previous surgical treatment, the dates and doses of RAI treatments and the follow-up of thyroid function were recorded in the computerized register kept in Tampere

University Hospital since 1965. Following the RAI treatment, the thyroid status of the patients was monitored by blood samples every 1-3 months during the first year and subsequently at a 1-3 years interval.

4.1.3 The reference subjects

The reference population was formed by choosing randomly three age- (+/- 6 months) and gender-matched control subjects (n=18 432) for each patient from the comprehensive national Population Register. The control subject had to be alive at the time the patient was treated and reside in the same county. There were no other inclusion or exclusion criteria.

4.2 Methods (I, II, III)

4.2.1 The etiology of hyperthyroidism

The etiology of hyperthyroidism for the patients treated with thyroidectomy was available from the HILMO database. For the patients treated with RAI the etiology of hyperthyroidism was obtained from the database of Tampere University Hospital. The classification to different etiological subgroups of hyperthyroidism was made according to the ICD-codes. The ICD-8 codes 2400A, 2410A 2420a, ICD-9 codes 2420A, 2420X, 4240A and ICD-10 codes E05 and E05.0 were classified as Graves´ disease, ICD-8 codes 2421a, 2421A, ICD-9 codes 2422a, 2422A, 2422X and ICD-10 codes E05.1 and E05.2 as Nodular goiter and the rest of the diagnoses or patients without a specific diagnosis were classified as “Other”.

4.2.2 The thyroid status of the patients

The thyroid status after the treatment was available only for the patients treated with RAI. Patients were classified as hypothyroid if biochemical evidence (low total T4 or free T4 and an elevated TSH) was associated with symptoms of

hypothyroidism and treatment with levothyroxine was started. Hyperthyroidism and a relapse after the treatment was recorded if biochemical evidence (high total or free T4 and TSH below 0.4mU/l) was associated with symptoms, if antithyroid medication was still needed one year after RAI or if a repeated RAI therapy was necessary. The remission was recorded if the patient was euthyroid or hypothyroid during the follow-up.

4.2.3 Hospitalization rates for cardiovascular diseases (I, III)

The lifetime causes of hospitalization, as well as the dates of hospital admissions were obtained from HILMO database maintained by THL, with deterministic record linkage based on the unique personal identification number assigned to all the residents of Finland. The HILMO database includes the hospitalizations (hospital admission requiring at least one overnight stay) and causes of hospitalization of the Finnish residents since January 1969, and the procedure codes since 1986. Recording diagnoses to the HILMO database is obligatory in Finland.

Both the primary and secondary diagnoses recorded at discharge from the hospital were used in the analysis. The diagnoses have been coded according to the Finnish version of the 8th revision of the International Classification of Diseases (ICD-8) in 1986, ICD-9 up to 1995, and the Finnish version of ICD-10 thereafter. The equivalent codes were identified between the different version of ICDs and the causes of hospitalization were classified into ten major cardiovascular groups, which were analyzed separately: any cardiovascular disease (any CVD); hypertension; CAD; diseases of the pulmonary circulation; arrhythmias; heart failure; cerebrovascular diseases; diseases of arteries and veins (including for example arteriosclerosis obliterans, aortic aneurysms and dissections and thrombosis of arteries and veins), and valvular diseases and cardiomyopathies. Of the arrhythmias, AF was studied separately.

The rates of hospitalizations among the patients and the controls were illustrated with Kaplan-Meier curves beginning 10 years before the treatment of hyperthyroidism. In addition, the odds ratios (OR) of hospitalization due to different CVDs until the treatment were analyzed (prevalent CVDs).

Secondly, the effect of the treatment on the hospitalizations and mortality due to CVDs was estimated by analyzing the new hospitalizations and deaths due to

CVDs after the treatment of hyperthyroidism, with the follow-up starting on the date of RAI administration or the date of thyroidectomy for the patients, and on the same date for the matched controls. The follow-up ended on the date of the first hospitalization due to different CVDs, the date of death, emigration, or the common closing date (May 31st, 2009), whichever occurred first. The results were adjusted for the prevalent CVDs at entry.

4.2.4 The incidence of cancer (II)

The lifetime cancer cases occurring among the patients and the controls were identified from the Finnish Cancer Registry using computerized record linkage, with the unique personal identification number as the key. In the cancer registry, cancers are classified according to the latest International Classification of Diseases for Oncology, ICD-O-3. We excluded benign and *in situ* tumors, as well as those with uncertain or borderline malignancy, and included only malignant primary tumors. Cancer diagnoses were classified into 18 topographic groups: mouth and pharynx, salivary gland, esophagus, gastric, intestinal, thyroid gland, liver and pancreas, respiratory tract, bladder and urinary tract, kidney, skin, nervous system, hematopoietic, breast, gynecological, and prostate cancers, and cancers of unspecified site.

The follow-up of the patients for cancer incidence started three months after the treatment, *i.e.,* thyroidectomy or the first dose of RAI, and on the same day for the corresponding controls. The latency period of three months after the treatment was chosen to exclude cancers incidentally found in the thyroid gland after thyroidectomy (= occult thyroid cancers). The follow-up ended on the day of the cancer diagnosis, death, emigration from Finland, or the common closing date (December 31st 2009), whichever occurred first.

Prevalent cancers at baseline, i.e., those diagnosed before the beginning of the follow-up, were excluded. Site-specific cancer incidence was calculated with follow-up until the diagnosis of site-specific cancer, regardless of any other cancer diagnosed. Regarding breast and gynecological cancers, the person-years at risk were counted only for women, and regarding prostate cancer, for men only.

4.2.5 Mortality (I, II, III)

The dates and causes of death among the patients and the controls were obtained from Statistics Finland, using a computerized record linkage. The dates and causes of death of all Finnish citizens certified by a physician have been included in this register since 1971. The causes of death have been coded according to the International Classification of Diseases (ICD, versions 8-10). A translation between the different versions was made and the underlying causes of death were classified into nine groups: infectious diseases, malignant tumors, endocrine diseases, cardiovascular diseases, dementia, respiratory diseases, trauma, other causes of death and unknown causes of death. The underlying cause of death was used for the for the analysis of cause-specific mortality rates. The mortality for AF was analyzed by using both the underlying cause of death and in addition, the contributory cause of death. The follow-up for all-cause mortality and cardiovascular mortality continued until 31st May 2009 (I, III) and for cancer mortality until 31st of December 2009 (II).

4.2.6 Comparison between the patients treated either with RAI or thyroidectomy (II, III)

Secondly, the effect of the treatment on the hospitalizations and mortality due to CVDs was estimated by analyzing the new hospitalizations and deaths due to CVDs after the treatment of hyperthyroidism, with the follow-up starting on the date of RAI administration or the date of thyroidectomy for the patients, and on the same date for the matched controls. The follow-up ended on the date of the first hospitalization due to different CVDs, the date of death, emigration, or the common closing date (May 31st, 2009), whichever occurred first. The results were adjusted for the prevalent CVDs at entry.

The comparison of hospitalization rates and mortality between patients treated with thyroidectomy or RAI was made by Cox regression analyses. Clinical differences between these study groups -age, gender, prevalent CVDs and the etiology of hyperthyroidism- were used as covariates to adjust for the differences between the groups.

4.2.7 Statistical analysis

Statistical software Stata for Windows version 13 (StataCorp, College Station, Texas, USA) was used to calculate the hospitalization rates for various diseases. Cox regression analyses were performed using IBM SPSS Statistics for Windows, Version 19.0 (IBM Corp. Released 2010. Armonk, NY: IBM Corp.). A two-sided p-value of less than 0.05 was considered statistically significant. The differences in clinical characteristics (age, gender, etiology of hyperthyroidism) between patients treated with either RAI or thyroidectomy were estimated with a Mann-Whitney U and with a $\chi 2$ -tests when appropriate.

4.2.7.1 Statistical analysis of cardiovascular diseases (I, III)

The Kaplan-Meier analysis was used to illustrate the hospitalization rates before and after the treatment and for mortality rates after the treatment. Conditional logistic regression model was fitted to assess the odds ratios (OR) of hospitalization due to different CVDs until the treatment (prevalent CVDs) and the Cox regression analyses for the hazard ratios (HR) and 95% confidence intervals (95% CI) for CVD hospitalization and mortality rates after the treatment. The comparison of hospitalization rates and mortality between patients treated with thyroidectomy or RAI was made by Cox regression analyses using age, gender, prevalent CVDs and the etiology of hyperthyroidism as covariates to adjust for the differences between the groups.

4.2.7.2 Statistical analysis of cancer (II)

Cancer rates were calculated from the number of cancers divided by the corresponding person-years for both study groups. The ratio of the cancer incidence and mortality rates in the patients and the age- and sex-matched control group was estimated by the Mantel-Haenszel method. Adjustment for confounding factors was performed with Cox regression multivariate analyses. Cox regression analyses were done both with and without prevalent cancer diagnosis as a covariate to exclude the possibility of the prevalent cancer diagnosis affecting the results.

In order to analyze the impact of the treatment modality of hyperthyroidism (RAI or thyroidectomy) on cancer incidence and mortality among the hyperthyroid patients, the etiology of hyperthyroidism (Graves´ disease, nodular disease or unspecified), age and gender of the patients were used as covariates in Cox regression multivariate analyses. In these analyses, no controls were included. Cox regression analyses were done both with and without prevalent cancer diagnosis as a covariate to exclude the possibility of the prevalent cancer diagnosis affecting the results.

4.2.8 Ethical considerations

The study was undertaken in accordance with the Declaration of Helsinki. No informed consent could be obtained from the study subjects, because of the large number of participants and because many of them died before the data collection for the study. The ethics committee of the Tampere University Hospital District_ reviewed the study protocol. The National Institute of Health and Welfare (THL) gave a permission to use the data from the Hospital Discharge Registry, The Statistics Finland for the dates and causes of death derived from the data of Statistics Finland and the Population Registration Centre for choosing the control population from the data of the Population Registration Centre.

RESULTS

5.1 The clinical characteristics of the patients

5.1.1 The patients treated with thyroidectomy

A total of 4 334 patients were treated for hyperthyroidism with total or subtotal thyroidectomy between January 1986 and December 2007 in Finland. Eighty-six per cent (n=3 719) of the patients were women and 14% (n= 615) were men. The median age of the patients and the reference group at the time of surgery was 46 years in the whole group, 48 (interquartile range 33-61) years in men and 46 (IQR 34-59) years in women (Table 2). Four per cent of the patients (179 patients) were under 20 years of age at the time of the operation. Twelve per cent (n =497) of the patients and 11% (n=1 421) of the controls deceased during the follow-up time for CVD (common closing day 31st May 2009) and a total of 146 subjects emigrated from Finland. Until the end of the follow-up period (common closing day 31st Dec 2009), there were 523 deaths among the patients and 1 496 deaths among the controls. The mean follow-up was 11.7 years for the patients and the controls for cancer morbidity and mortality; 10.3 years for the patients (IQR 5.9-17.2 years) and 11.6 years for the controls (IQR 5.9-17.2 years). The mean follow-up period for CVD morbidity and mortality was 11.5 years (IQR 5.6-17.1) for the patients and 11.5 years (IQR 5.6-17.2) for the controls.

The most common cause of hyperthyroidism among the operated patients was Graves´ disease. Hyperthyroidism was caused by a toxic nodular goiter (including toxic adenoma and multinodular goiter) in 39% of the patients and the rest of the patients were classified as "Other". The most common etiological diagnosis in patients under 40 years of age was Graves´ disease and in patients older than 40 years toxic nodular goiter ($p < 0.001$). The distribution of the etiological diagnoses was similar between men and women (Table 2).

There was a total of 4 454 thyroidectomies performed during 1986-2007, of which 69% (n=3 063) were subtotal and 31% (n= 1 391) total. Three patients had three subtotal thyroidectomies and 114 patients were operated twice during the follow-up time. Forty-four of the patients with two operations had first a subtotal

and then a total thyroidectomy, and 70 patients had only subtotal operations. Thus 68% of the patients (n=2 943) had only subtotal operations and 31% (n=1 347) only total operations. Subtotal operations were more common in all age groups and etiological groups (III), but the proportion of total operations from all the operations performed increased during the follow-up time (Fig 1).

Table 2. Clinical characteristics of the hyperthyroid patients treated with thyroidectomy or radioactive iodine (RAI).

	Thyroidectomy n = 4 334		RAI[1] n = 1 814		
	n	**%**	**n**	**%**	**p value**
Median age, years (Q_2-Q_3)[2]	46 (33-59)		59 (44-71)		p< 0.001*
Sex					p<0.001**
Male patients	615	14	329	18	
Female patients	3 719	86	1 485	82	
Etiology of hyperthyroidism					p< 0.001**
Graves´ disease	2 070	48	1 022	56	
Nodular disease	1 697	39	319	18	
Unspecified	567	13	473	26	

[1] The patients treated with radioactive iodine
[2] interquartile range
*Mann-Whitney U test
**X^2-test

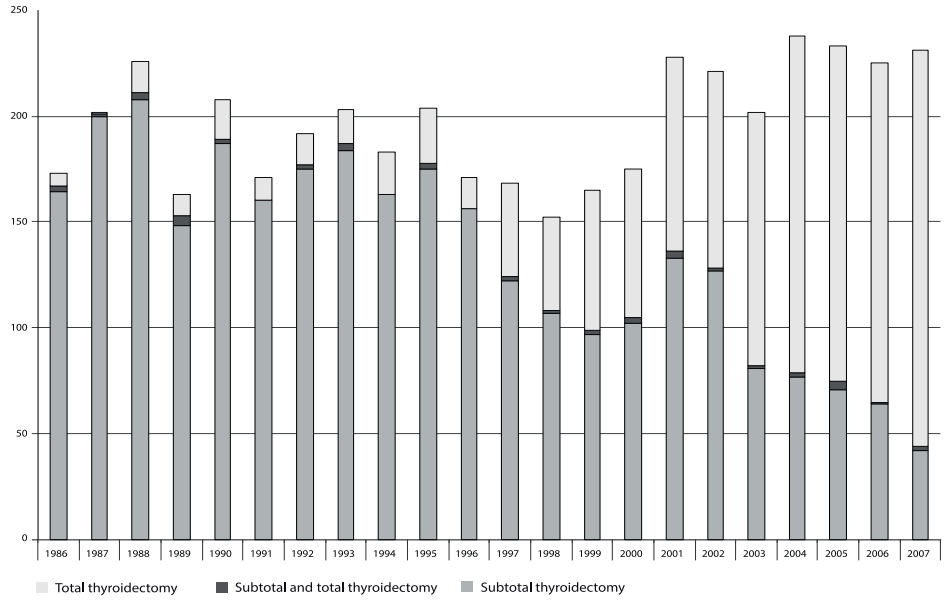

Fig. 1. The amount of thyroidectomies due to hyperthyroidism during 1986-2007 in Finland and the proportions of total and subtotal operations.

5.1.2 The patients treated with RAI

A total of 1 814 patients were treated for hyperthyroidism with RAI between January 1986 and December 2007 in Tampere University Hospital. Eighty-two per cent (n=1 480) of the patients were women and 18% (n= 329) were men. The median age of the patients and the reference group at the time of treatment was 59 years in the whole group, 54 (interquartile range 39-68) years in men and 60 (interquartile range 45-72) years in women (Table 2). Twenty-eight per cent (n=491) of the patients and 24% (n=1 254) of the controls deceased during the follow-up time for CVD (common closing day 31st May 2009) and a total of 30 subjects emigrated from Finland until 31st of May 2009. Until the end of the follow-up period for cancer morbidity and mortality (common closing day 31st Dec 2009), there were 512 death among the patients and 1 292 deaths among the controls.

The mean follow-up period for cancer incidence and mortality were 10.3 years for the patients (IQR 5.5-14.5 years) and 10.6 years for the controls (IQR 5.7-14.9 years). The mean follow-up period for CVD morbidity and mortality was 9.5 years for the patients (IQR 5.3-14.4 years) and 9.8 years for the controls (IQR 4.9-13.9 years).

Most of the patients treated with RAI had Graves´ disease, every fifth of the patients had nodular goiter (including toxic adenoma and multinodular goiter) and the rest of the patients (26%) were classified as "Other" (Table 2).

The total dose of RAI administered varied between 78MBq and 2264MBq, the mean dose was 323MBq and the median dose 259MBq. Most patients (n=1 442, 79%) had only one treatment, 15% two treatments, 3.4% three treatments and the rest of the patients had four or more repetitive doses of RAI. In Tampere University Hospital, there were 38 patients treated first with RAI and then operated on (2% of the RAI-treated patients), and 145 patients treated surgically prior to treatment with RAI (8%). The information on overlapping of two treatment modalities was not available from other Finnish hospitals.

5.2 Cardiovascular morbidity

5.2.1 The risk of cardiovascular diseases before the treatment of hyperthyroidism (I, III)

5.2.1.1 The patients treated with thyroidectomy

The risk of hospital admission due to any CVD increased among both the patients and the controls during the whole follow-up. The difference between the two groups increased until the treatment of hyperthyroidism with thyroidectomy, becoming statistically significant five years before the thyroidectomy as illustrated by modified Kaplan-Meier analysis (Fig 2, Panel A). Until the thyroidectomy the patients had a 50% increase in the risk of hospitalization due to any CVD, compared to the controls (Table 3). The risk of hospitalization due to CVDs was increased in most of the subgroups of CVDs studied expect for ischemic heart disease (including acute myocardial infarctions), diseases of other arteries and veins, cerebrovascular diseases or diseases of pulmonary circulation compared to the control group.

The most frequent subgroup of CVD associated with the increased hospitalization before the treatment of hyperthyroidism was hypertension.

The difference in hospitalizations with hypertension between the patients and the controls increased prior to the thyroidectomy (Fig 2, Panel B) and the hospitalization rate was twice as high in the patients as among the controls by the time of the operation (Table 3). The second most frequent indication for hospitalization was arrhythmias, of which AF was the most common diagnosis (81% of arrhythmias). The difference in the rates of hospitalizations due to AF increased towards the time of thyroidectomy (Fig 2, Panel C), the rate being almost five times higher in the patients at the time of thyroidectomy. The risk of hospitalization due to heart failure by the time of thyroidectomy was increased twofold and the risk of valvular diseases or cardiomyopathies was 57% higher among the patients compared to the reference group (Table 3).

Table 3. The odds ratios for cumulative hospitalization rates prior to the treatment due to different cardiovascular diseases in patients treated with RAI and in patients treated with thyroidectomy, compared with the age- and sex-matched controls.

	RAI-treated patients (n=1 814) vs. controls (n=5 441)		Thyroidectomy-treated patients (n=4 334) vs. controls (n=12 991)	
Cardiovascular disease	Odds Ratio (95% CI)	p value	Odds Ratio (95% CI)	p value
Any cardiovascular disease	**1.81 (1.61-2.01)**	**< 0.001**	**1.50 (1.37-1.64)**	**< 0.001**
Hypertension	**1.50 (1.23-1.84)**	**< 0.001**	**2.05 (1.67-2.51)**	**< 0.001**
All arrhythmias	**4.31 (3.52-5.27)**	**< 0.001**	**3.93 (3.20-4.81)**	**< 0.001**
Atrial fibrillation	**5.86 (4.64-7.40)**	**< 0.001**	**4.60 (3.72-5.67)**	**< 0.001**
Diseases of arteries and veins	1.15 (0.99-1.33)	0.068	1.10 (0.95-1.28)	0.212
Coronary artery disease	**1.67 (1.36-2.05)**	< 0.001	0.80 (0.56-1.15)	0.412
Cerebrovascular diseases	**1.60 (1.23-2.07)**	< 0.001	1.12 (0.95-1.32)	0.231
Heart failure	**2.86 (2.19-3.72)**	< 0.001	**1.92 (1.22-3.00)**	**0.050**
Valvular diseases and cardiomyopathies[1]	**3.52 (2.14-5.77)**	< 0.001	1.57 (0.98-2.51)	0.056
Diseases of pulmonary arteries	1.63 (0.85-3.14)	0.145	1.56 (0.80-3.04)	0.213

[1]Non-bacterial endo-, peri- and myocardial diseases, including valvular diseases and cardiomyopathy
Bolded values are statistically significant

5.2.1.2 The patients treated with RAI

The risk of hospitalization due to CVDs increased among the patients and the controls during the follow-up time. The difference between the patients and the controls due to all cardiovascular indications started to increase years before the RAI treatment and by the time of the first treatment it was 1.81-fold in the patients compared to the controls (Fig. 2, Panel D and Table 3).

The most frequent subgroup of CVD associated with hospitalization was hypertension. The difference between the patients treated with RAI and their controls increased prior to the treatment and the hospitalization rate was 50% higher until it (Fig. 2, Panel E). The second most frequent indication for hospitalization was arrhythmias, of which AF was the most common. The difference in the risk of hospitalization due to AF increased years before the treatment with RAI (Fig. 2, Panel F) and by the time of it was almost six-fold (Table 3).

There was no difference in the hospitalization rates in diseases of arteries and veins or the diseases of pulmonary circulation between the patients and the controls prior to the treatment of hyperthyroidism. The risk of hospitalization due to CAD, cerebrovascular diseases, heart failure and valvular diseases and cardiomyopathy was substantially higher by the time of treatment among the patients (Table 3).

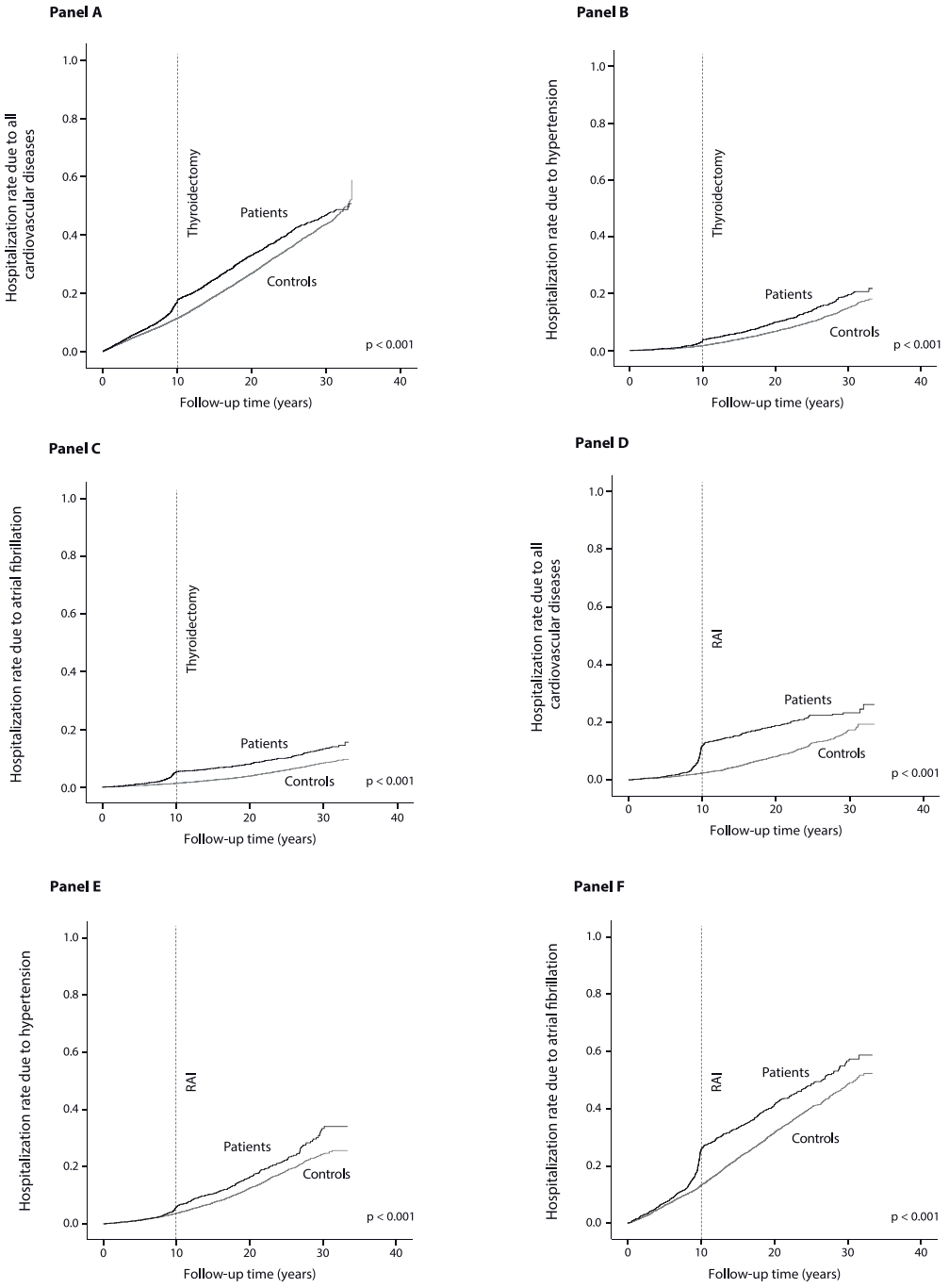

Fig. 2. Cumulative hospitalization rate due to different cardiovascular diseases by time 10 years before and about 23 years after thyroidectomy (Panels A-C) or after RAI (Panels D-F) in patients treated for hyperthyroidism compared with the age and sex-matched control group (Log rank test).

5.3 The risk of cardiovascular hospitalization after the treatment of hyperthyroidism

5.3.1 The patients treated with thyroidectomy (I)

The risk of new hospitalization due to any CVD remained significantly higher among the patients after thyroidectomy, when adjusted for hospitalization preceding thyroidectomy (HR 1.15, 95% CI 1.06-1.24). The incidence of new hospitalization due to hypertension (HR 1.23, 95% CI 1.08-1.41), all arrhythmias (HR 1.25, 95% CI 1.07-1.47), heart failure (HR 1.17, 95% CI 1.01-1.50) and valvular diseases and cardiomyopathies (HR 1.55, 95% CI 1.17-2.04) was significantly higher in the patients, when adjusted for prevalent CVDs due to the given disease prior to the surgical treatment. There was no significant difference in hospitalization rates between the patients and the controls due to new-onset AF (HR 1.15, 95% CI 0.96-1.39), CAD (1.03, 95% CI 0.87-1.19), cerebrovascular diseases (HR 1.19, 95% CI 0.99-1.41), diseases of other arteries or veins (HR 1.09, 95% CI 0.96-1.25) nor due to diseases of pulmonary circulation (HR 0.78, 95% CI 0.53-1.15).

In subgroup analyses including only the patients treated either with subtotal or total thyroidectomies and their own age- and gender-matched controls, the patients treated with total thyroidectomy did not have statistical difference in the risk of any CVD hospitalization compared to their controls after treatment of hyperthyroidism (RR 1.16, 95% CI 0.98-1.37). Nevertheless, the patients treated with subtotal thyroidectomy had a higher risk of any CVD hospitalization (HR 1.09, 95% CI 1.00-1.08, p=0.043) compared to their controls.

In a Cox regression analysis including only the patients with hyperthyroidism, male gender (HR 1.23, 95% CI 1.05-1.46), age at the time of surgery (HR 1.06, 95% CI 1.06-1.07/year) and prevalent CVD (RR 2.19, 95% CI 1.91-2.50) predicted hospitalization due to any CVD after thyroidectomy, but the surgical technique (subtotal or total thyroidectomy) or the etiology of hyperthyroidism did not have a statistically significant impact on the risk of CVD hospitalization.

5.3.2 The patients treated with RAI (III)

After the treatment of hyperthyroidism with RAI, the risk of new hospitalization due to any CVD remained significantly higher among the patients up to two decades, when adjusted for hospitalization preceding RAI (HR 1.23, 95% CI 1.13-1.34). The incidence of new hospitalizations due to CAD or the diseases of pulmonary circulation was not significantly increased, but new hospitalization due to hypertension, arrhythmias, heart failure, cerebrovascular diseases, diseases of other arteries and veins and valvular diseases and cardiomyopathies were significantly higher in the patients compared to age- and gender-matched controls, when adjusted for prevalent CVD due the given disease (Table 4).

The patients treated with RAI were divided in two groups based on the outcome of treatment with RAI. A total of 856 patients became hypothyroid during the follow-up time and started a treatment with levothyroxine. The rest of the patients (n=935) became euthyroid or had a relapse of hyperthyroidism during the follow-up period. The risk of hospitalization due to any CVD was significantly increased in both of the groups.

In the subgroup analyses of different CVDs, the risk of hypertension, cerebrovascular diseases, heart failure, valvular diseases or cardiomyopathies were not significantly increased in the patients treated more effectively with RAI (resulting in hypothyroidism), and the CAD was decreased (HR 0.70, 95% CI 0.52-0.94), but the risk of diseases of other arteries and veins was increased. Among the patients treated less effectively with RAI (not resulting in hypothyroidism), the risk of CAD, hypertension, all arrhythmias, cerebrovascular diseases, heart failure and valvular diseases or cardiomyopathies were increased (Table 4).

Table 4. The hazard ratios (HR) for hospitalizations due to different cardiovascular diseases after the treatment of hyperthyroidism with RAI compared with the age- and sex-matched control group, adjusted for the CVDs prior to the treatment.

	RAI vs controls		**RAI NOT resulting in hypothyroidism vs controls**		**RAI resulting in hypothyroidism vs controls**	
Cardiovascular disease	Hazard Ratio	p value	Hazard Ratio	p value	Hazard Ratio	p value
All cardiovascular diseases	**1.23 (1.13-1.34)**	**< 0.001**	**1.30 (1.17-1.46)**	**< 0.001**	**1.17 (1.00-1.37)**	**0.044**
Hypertension	**1.26 (1.09-1.44)**	**< 0.001**	**1.37 (1.15-1.62)**	**< 0.001**	1.16 (0.91-1.48)	0.226
All arrhythmias	**1.18 (1.03-1.36)**	**0.020**	**1.26 (1.06-1.49)**	**0.008**	1.15 (0.88-1.51)	0.317
Atrial fibrillation	1.08 (0.92-1.27)	0.360	1.16 (0.96-1.41)	0.128	0.99 (0.71-1.37)	0.950
Diseases of arteries and veins	**1.22 (1.02-1.45)**	**0.030**	1.05 (0.83-1.33)	0.665	**1.54 (1.18-2.01)**	**0.002**
Coronary disease	1.11 (0.97-1.28)	0.136	**1.21 (1.03-1.42)**	**0.023**	0.91 (0.68-1.22)	0.527
Cerebrovascular diseases	**1.34 (1.12-1.62)**	**< 0.001**	**1.49 (1.20-1.84)**	**< 0.001**	1.13 (0.78-1.64)	0.523
Heart failure	**1.25 (1.05-1.48)**	**0.010**	**1.32 (1.09-1.61)**	**0.005**	1.14 (0.77-1.69)	0.522
Valvular diseases and cardiomyopathies[1]	**1.69 (1.23-2.32)**	**< 0.001**	**2.19 (1.48-3.25)**	**< 0.001**	0.99 (0.55-1.79)	0.972
Diseases of pulmonary arteries	0.96 (0.64-1.45)	0.846	0.72 (0.41-1.27)	0.260	1.73 (0.92-3.2)	0.090

[1]Non-bacterial endo-, peri- and myocardial diseases, including valvular diseases and cardiomyopathy
Bolded values are statistically significant

5.3.3 The effect of the treatment modality on CVD hospitalization (III)

The risk of CVD hospitalization after the treatment of hyperthyroidism was higher among the RAI-treated patients compared to the patients treated with thyroidectomy, adjusted for age, gender and prevalent CVDs (HR 1.14, 95% CI 1.03-1.26). Additional adjustment for the etiology of hyperthyroidism did not change the result (HR 1.17, 95% CI 1.05-1.30) (Table 5). The risk of hospitalization due to arrhythmias (HR 1.32, 95% CI 1.12-1.57) and new-onset AF (HR 1.40, 95% CI 1.16-1.68) was also increased in the RAI-treated patients compared to the surgically-treated ones, but there were no significant differences in the other subgroups of CVDs (Table 5).

The patients treated more effectively with RAI (resulting in hypothyroidism) and the patients treated less effectively with RAI (not resulting in hypothyroidism) were compared with the patients treated with thyroidectomy in a Cox regression analysis, and adjusted with age, gender, prevalent CVDs and the etiology of hyperthyroidism. The patients treated effectively with RAI had no difference in the risk of any CVD hospitalizations compared to the patients treated with thyroidectomy (RR 0.95, 95% CI 0.82-1.09) (Table 5). In the analyses of subgroups of CVDs, the risk of CAD was even lower (HR 0.70, 95% CI 0.52-0.94) in the patients treated effectively with RAI compared to the patients treated with thyroidectomy, but the risk of diseases of the pulmonary circulation was higher. The number of the hospitalizations in the latter analysis was small. The patients treated ineffectively with RAI, however, had a higher risk of any CVD hospitalizations compared to the patients treated with thyroidectomy, similarly to the main analyses, but also an increased risk of hospitalization due to heart failure (Table 5).

Table 5. The hazard ratios for hospitalizations due to different cardiovascular diseases after the treatment of hyperthyroidism with RAI compared with the patients treated with thyroidectomy, and adjusted for the age at the time of treatment, sex, prevalent CVDs, and the etiology of hyperthyroidism.

	RAI (n=1 814) vs thyroidectomy (n=4 334)		**RAI resulting in hypothyroidism (n=855) vs thyroidectomy (n=4 334)**		**RAI not resulting in hypothyroidism (n=959) vs thyroidectomy (n=4 334)**	
Cardiovascular disease	Hazard Ratio	p value	Hazard Ratio	p value	Hazard Ratio	p value
All cardiovascular diseases	**1.17 (1.05-1.30)**	**0.005**	0.95 (0.81-1.11)	0.534	**1.28 (1.13-1.43)**	**< 0.001**
Hypertension	1.02 (0.86-1.21)	0.802	1.00 (0.78-1.27)	0.968	1.08 (0.89-1.30)	0.436
All arrhythmias	**1.32 (1.12-1.57)**	**0.001**	1.12 (0.86-1.46)	0.389	**1.35 (1.13-1.62)**	**< 0.001**
Atrial fibrillation	**1.40 (1.16-1.68)**	**< 0.001**	1.23 (0.90-1.66)	0.191	**1.44 (1.18-1.75)**	**< 0.001**
Diseases of arteries and veins	0.94 (0.76-1.16)	0.561	1.02 (0.78-1.33)	0.882	0.84 (0.65-1.08)	0.178
Coronary artery disease	0.99 (0.83-1.19)	0.935	**0.70 (0.52-0.94)**	**0.019**	1.13 (0.93-1.37)	0.227
Cerebrovascular diseases	1.05 (0.83-1.32)	0.718	0.74 (0.51-1.07)	0.112	1.20 (0.93-1.54)	0.161
Heart failure	1.14 (0.89-1.44)	0.299	0.78 (0.53-1.15)	0.201	**1.30 (1.01-1.68)**	**0.039**
Valvular diseases and cardiomyopathies[1]	1.15 (0.79-1.67)	0.466	0.80 (0.45-1.45)	0.467	1.25 (0.84-1.85)	0.272
Diseases of pulmonary arteries	1.67 (0.95-2.94)	0.074	**2.34 (1.16-4.71)**	**0.017**	1.03 (0.53-1.99)	0.941

Bolded values are statistically significant

5.4 The risk of cancer after treatment of hyperthyroidism (II)

5.4.1 Cancer morbidity

There were 469 (7.3%) hyperthyroid patients and 883 (4.7%) persons among their controls, who had at least one cancer diagnosis before the beginning of the follow-up, *i.e.* before thyroidectomy or the first RAI treatment, or up to three months afterwards. Among the patients, 32% (n=151) of the prevalent cancers and among the control subjects 1% (n=26) were thyroid carcinomas (ICD-O-3 code C73.9), most of them occult thyroid carcinomas found incidentally in the thyroidectomy for a benign disease without prevalent cancer suspicion. After excluding these diagnoses, 318 (5.2%) patients had prevalent cancer diagnosis, 187 (4.3%) in the surgical group and 478 (3.7%) among their control subjects and 131 patients (7.2%) in the RAI group and 379 (7.0%) among their controls at the beginning of the follow-up.

A total of 651 (10.2%) new cancers were diagnosed in the patients and 1 882 (10.4%) among the controls during the average of 10 years of follow-up. There was no significant difference in cancer incidence between the patients and the controls (RR 1.05, 95% CI 0.96-1.15) (Table 6). The figures were similar in women (RR 1.05, 95% CI 0.95-1.16) and in men (RR 1.04, 95% CI 0.85-1.28). In the analysis of specific cancer sites, the risk of respiratory tract cancers (RR 1.46, 95% CI 1.05-2.02), and stomach cancer (RR 1.64, 95% CI 1.01-2.68) were increased among the patients with hyperthyroidism compared to the control group (Table 6).

Table 6. Cancer incidence per 10,000 person-years at risk in treated hyperthyroidism, and in the age- and sex-matched control group.

	PATIENTS			CONTROLS			PATIENTS VS. CONTROLS	
Cancer	**Cases**	**Person-years**	**Hospitalization rate**	**Cases**	**Person-years**	**Hospitalization rate**	**Rate ratio**	**p value**
All cancer sites	651	66 628	97.1	1882	201 895	93.2	1.05 (0.96-1.15)	0.30
Skin***	153	68 340	22.4	440	206 799	21.3	1.05 (0.88-1.27)	0.59
Breast	140	58 334	24.0	362	177 040	20.5	1.17 (0.97-1.43)	0.11
Intestinal*	57	69 028	8.25	166	208 592	8.0	1.90 (0.77-1.40)	0.81
Respiratory tract	54	69 106	7.8	112	209 092	5.4	**1.46 (1.05-2.02)**	**0.02**
Gynecological	42	58 996	7.1	163	178 367	9.1	0.78 (0.56-1.09)	0.15
Hematopoietic	36	69 091	5.2	105	208 896	5.0	1.04 (0.71-1.51)	0.85
Liver and pancreas	35	69 197	5.1	104	209 161	5.0	1.02 (0.69-1.49)	0.93
Prostate	33	9 940	33.2	110	59 632	37.1	0.89 (0.61-1.32)	0.57
Stomach	25	69 134	3.6	46	209 095	2.2	**1.64 (1.01-2.68)**	**0.04**
Kidney	23	69 169	3.3	52	209 012	2.5	1.34 (0.82-2.18)	0.25
Unspecified site	17	69 212	2.5	55	209 188	2.6	0.93 (0.54-1.61)	0.81
Bladder and urinary tract**	9	69 198	1.3	37	209 042	1.8	0.74 (0.36-1.52)	0.41
Mouth and pharynx	8	69 198	1.2	23	109 992	20.9	1.05 (0.47-2.35)	0.90
Salivary glands	0	69 225	0	2	209 200	0.1	0.00 (0.00-16.1)	0.55
Thyroid gland	9	69 183	1.3	21	209 070	1.0	1.30 (0.59-2.83)	0.52
Nervous system	5	69 223	0.7	26	209 182	1.2	0.58 (0.22-1.51)	0.26
Esophagus	1	69 225	0.1	13	209 206	0.6	0.23 (0.03-1.78)	0.13

*Cancers of the small intestine, colon and rectum
**Cancers of the urinary bladder, ureters and urethra
***Malignant skin tumours (melanoma, squamous cell carcinoma and basal cell carcinoma)
Bolded values are statistically significant

5.4.2 The impact of the etiology of hyperthyroidism on cancer incidence (II)

All the patients treated for hyperthyroidism (ignoring the treatment modality) were analyzed together by the etiological subgroups. There was a tendency towards an increased cancer risk in the patients with a nodular thyroid disease, but it did not reach statistical significance (RR 1.13, 95% CI 0.99-1.28, p=0.0792). However, increased risk of breast cancer (RR 1.36, 95% CI 1.02-1.81, p=0.0387), respiratory tract cancer (RR 1.79, 95% CI 1.13-2.84, p=0.0114) and kidney cancer (2.62, 95% CI 1.25-5.11, p=0.0083) were associated with a nodular disease, but not with Graves´ disease or with hyperthyroidism of unspecified etiology (Table 7).

Table 7. Rate ratios (RR) for cancer incidence in specific cancer sites in etiological subgroups of treated hyperthyroidism compared to the age- and sex-matched control groups.

	Graves´ disease		Nodular disease		Other	
Cancer sites (with statistically significant incidences)	RR (95% CI)	p value	RR (95% CI)	p value	RR (95% CI)	p valu
Breast cancer	1.16 (0.86-1.55)	0.3392	**1.36 (1.02-1.81)**	**0.0387**	0.74 (0.40-1.35)	0.318
Respiratory tract cancers	1.43 (0.84-2.43)	0.1888	**1.79 (1.13-2.84)**	**0.0114**	0.74 (0.28-1.97)	0.551
Gastric cancer	1.50 (0.61-3.71)	0.3784	1.97 (0.98-3.95)	0.0530	1.30 (0.46-3.69)	0.620
Kidney cancer	0.78 (0.32-1.92)	0.5889	**2.62 (1.25-5.11)**	**0.0083**	0.89 (0.29-2.71)	0.841
Thyroid cancer	1.20 (0.23-6.18)	0.8286	0.86 (0.28-2.62)	0.7951	4.69 (0.78-28.05)	0.062

Bolded values are statistically significant

5.4.3 Patients treated with thyroidectomy and cancer

In separate analyses of cancer morbidity on patients treated with thyroidectomy compared to their respective controls, there was an increased risk of respiratory tract cancer, skin cancer and stomach cancer, but the overall risk of cancer was not increased. The risk of gynecological cancers was reduced (Table 8).

Table 8. Cancer incidence per 10,000 person-years at risk in the surgically treated hyperthyroidism, and in the age- and sex-matched control group.

	PATIENTS			CONTROLS			PATIENTS VS CONTROLS	
Cancer	**Cases**	**Person years**	**Hospitalization rate**	**Cases**	**Person years**	**Hospitalization rate**	**Rate ratio**	**p value**
All cancer sites	419	48 839	85.8	1178	146 912	80.2	1.07 (0.96-1.20)	0.235
Mouth and pharynx	6	50 621	1.19	14	151 621	0.9	1.28 (0.49-3.34)	0.608
Salivary glands	0	50 631	0	1	151 707	0.1	-	-
Esophagus	1	50 631	0.2	6	141 839	0.4	0.50 (0.06-4.15)	0.512
Stomach	16	50 550	3.2	24	151 649	1.6	**2.00 (1.06-3.77)**	**0.029**
Intestinal*	31	50 499	6.1	103	151 299	6.8	0.92 (0.60-1.35)	0.948
Liver and pancreas	22	50 616	4.3	67	151 677	4.4	0.98 (0.61-1.59)	0.948
Respiratory tract	35	50 560	6.9	67	151 629	4.4	**1.57 (1.04-2.36)**	**0.030**
Thyroid gland	6	50 590	1.2	17	151 586	1.1	1.06 (0.42-2.68)	0.906
Bladder and urinary tract**	6	50 614	1.2	29	151 569	1.9	0.62 (0.26-1.49)	0.281
Kidney	13	50 592	2.6	26	151 599	1.7	1.50 (0.58-2.92)	0.231
Skin***	105	49 987	21.0	252	150 253	16.8	**1.25 (1.00-1.57)**	**0.052**
Brain and nervous system	3	50 630	0.6	13	151 692	0.9	0.69 (0.20-2.42)	0.562
Hematopoietic	20	50 540	4.0	67	151 461	4.4	0.90 (0.54-1.47)	0.662
Breast	101	43 193	23.3	249	130 080	19.1	1.22 (0.97-1.54)	0.090
Gynecological	24	43 671	5.5	112	131 020	8.5	**0.64 (0.41-1.00)**	**0.050**
Prostate	19	6 786	28.0	61	19 928	30.6	0.92 (0.55-1.53)	0.734
Unspecified site	11	50 621	2.17	24	151 697	1.6	1.37 (0.67-2.80)	0.381

*Cancers of small intestine, colon and rectum
**Cancers of urinary bladder, ureters and urethra
***Malignant skin tumors (cutaneous melanoma, squamous cell carcinoma and basal cell carcinoma)
Bolded values are statistically significant

5.4.4 Patients treated with RAI and cancer

Among the patients treated with RAI, there were 131 (7.2%) persons who already had at least one cancer diagnosis before the beginning of the follow-up *ie.* before the first treatment with RAI or up to three months afterwards. During the follow-up time there were 232 new cancers among the patients. The total dose of RAI administered for one patient varied between 8MBq and 2 264MBq, and the median dose was 259MBq. Most of the patients (n=1 442, 79%) had only one treatment.

In an analysis including only the patients treated with RAI and their respective controls, there was no increased risk of cancer (RR 1.02, 95% CI 0.88-1.18, p=0.808) or any specific cancer sites (Table 9). The rate ratios for specific cancer sites, however, were similar to the risk ratios of patients treated with thyroidectomy but the number of cancers was smaller due to a smaller number of patients. There was no correlation between cancer incidence and the dose of RAI administered. In a Cox regression analysis performed only on the patients treated with RAI, the age at the time of first treatment with RAI (HR 1.05, 95% CI 1.04-1.06/year) and male gender (HR 1.74, 95% CI 1.27-2.38) predicted cancer diagnosis. However, the prevalent cancer diagnosis (HR 1.28, 95% CI 0.82-1.99) or the dose of RAI (HR 1.00, 95% CI 1.00-1.00) did not have a statistically significant effect on cancer incidence.

Table 9. Cancer incidence per 10,000 person-years at risk in the patients treated with RAI for hyperthyroidism, and in the age- and sex-matched control group.

	PATIENTS			CONTROLS			PATIENTS VS CONTROLS	
Cancer	**Cases**	**Person years**	**Hospitalization rate**	**Cases**	**Person years**	**Hospitalization rate**	**Rate ratio**	**p value**
All cancer sites	232	17 788	130.4	704	54 983	128.0	1.02 (0.88-1.18)	0.808
Mouth and pharynx	2	18 577	1.08	9	57 452	0.8	0.69 (0.15-3.18)	0.629
Salivary glands	0	18 594	0	1	57 494	0.0	0.0 (0.00-120.6)	0.775
Esophagus	0	18 594	0	7	57 496	0.6	0.0 (0.00-2.15)	0.141
Stomach	9	18 583	4.8	22	57 446	3.8	1.27 (0.58-2.75)	0.552
Intestinal*	1	18 529	14	63	57 293	11.0	1.28 (0.81-2.02)	0.294
Liver and pancreas	13	18 581	7.0	37	57 484	6.4	1.09 (0.58-2.05)	0.796
Respiratory tract	19	18 546	10.2	45	57 463	7.8	1.31 (0.77-2.24)	0.325
Thyroid gland	3	18 593	1.6	4	57 484	0.7	2.32 (0.52-10.36)	0.257
Bladder and urinary tract**	3	18 584	1.6	8	57 473	1.4	1.16 (0.31-4.37)	0.827
Kidney	10	18 577	5.4	26	57 413	4.5	1.19 (0.57-2.47)	0.642
Skin***	148	18 353	26.2	188	56 546	33.2	0.79 (0.57-1.08)	0.137
Brain and nervous system	2	18 593	1.1	13	57 491	2.26	0.48 (0.11-2.11)	0.317
Hematopoietic	16	18 551	8.6	38	57 435	6.6	1.30 (0.73-2.34)	0.372
Breast	39	15 140	25.8	113	46 960	24.1	1.07 (0.74-1.54)	0.714
Gynecological	18	15 326	11.7	51	47 347	10.8	1.09 (0.464-1.87)	0.752
Prostate	14	3 154	44.4	49	9 704	50.5	0.88 (0.49-1.59)	0.671
Unspecified site	6	18 591	3.23	31	57 491	5.39	0.60 (0.25-1.44)	0.245

*Cancers of small intestine, colon and rectum
**Cancers of urinary bladder, ureters and uretha
***Malignant skin tumors (cutaneuos melanoma, squamous cell carcinoma and basal cell carcinoma)

5.4.5 The impact of treatment modality (RAI or thyroidectomy) on cancer incidence (II)

The evaluation of the impact of treated hyperthyroidism and its treatment modality on cancer incidence was done by Cox regression analyses. The first analysis included all the patients treated for hyperthyroidism either with RAI or thyroidectomy and all the controls. Age, gender, hyperthyroidism, and prevalent cancer were used as covariates. A previous cancer diagnosis (RR 1.29, 95% CI 1.12-1.49), male gender (RR 1.55, 95% CI 1.41-1.72) and increasing age (RR 1.06/year, 95% CI 1.06-1.06) predicted the risk of cancer, but treated hyperthyroidism did not (RR 1.06, 95% CI 0.97-1.16). The second analysis assessed the effect of the treatment modality and the etiological subgroup of hyperthyroidism on cancer incidence. The age at the time of treatment (HR 1.06/year, 95% CI 1.05-1.06) and male gender (HR 1.49, 95% CI 1.22-1.81) predicted the risk of cancer and there was also a tendency towards an increased risk in patients with a nodular thyroid disease (HR 1.19, 95% CI 0.99-1.43). The type of treatment (HR 0.86, 95% CI 0.86-1.20 for RAI compared to thyroidectomy), however, was not associated with the risk of cancer.

5.5 Mortality in hyperthyroid patients

5.5.1 Overall and CVD mortality (III)

A total of 11.4% (n=497) of the patients and 10.9% (n=1 421) of the controls deceased during the follow-up. Overall mortality (RR 1.05, 95% CI 0.95-1.16) or mortality for CVDs (RR 0.91, 95% CI 0.77-1.07) was not increased among the patients compared to the controls. The mortality for CVDs was unaffected when adjusted for prevalent CVDs in a Cox regression analysis. The result was similar in Kaplan-Meier analysis (Fig. 3, Panel C, p=0.228). The mortality rates did not differ between the patients and the controls, when analyzed separately in men and women or in different subgroups of CVDs (data not shown).

Overall mortality (HR 1.22, 95% CI 1.08-1.43, p=0.003) and CVD mortality (HR 1.24, 95% CI 1.08-1.43), were higher among the patients treated with RAI

for hyperthyroidism compared to the age- and gender -matched control group (Fig. 3 Panel B, p=0.004). However, adjustment for prevalent CVDs in Cox regression analysis attenuated the CVD mortality to insignificant (HR 1.07, 95% CI 0.92-1.23).

In the subgroup analyses of mortality, the risk of overall mortality (HR 1.42, 95% CI 1.27-1.60, p < 0.001) and CVD mortality (HR 1.23, 95% CI 1.05-1.44, p=0.011) (Fig 3, Panel E, p > 0.001) were increased in the patients treated ineffectively with RAI (not resulting in hypothyroidism) compared to age- and gender-matched control group. CVD mortality was adjusted to prevalent CVDs in the Cox regression analysis. On the contrary, the risk of both, overall mortality (HR 0.74, 95% CI 0.57-0.96, p=0.026) and CVD mortality (RR 0.62, 95% CI 0.42-0.92, p < 0.001) were significantly lower in the patients treated with RAI leading to hypothyroidism compared to the age- and gender-matched control group in a Cox regression analysis with prevalent CVDs as a covariate. In a Kaplan-Meier analysis (without adjustment for prevalent CVDs) on patients treated effectively with RAI, the mortality for CVDs was comparable to the controls group (Figure 3, Panel D, p=0.053).

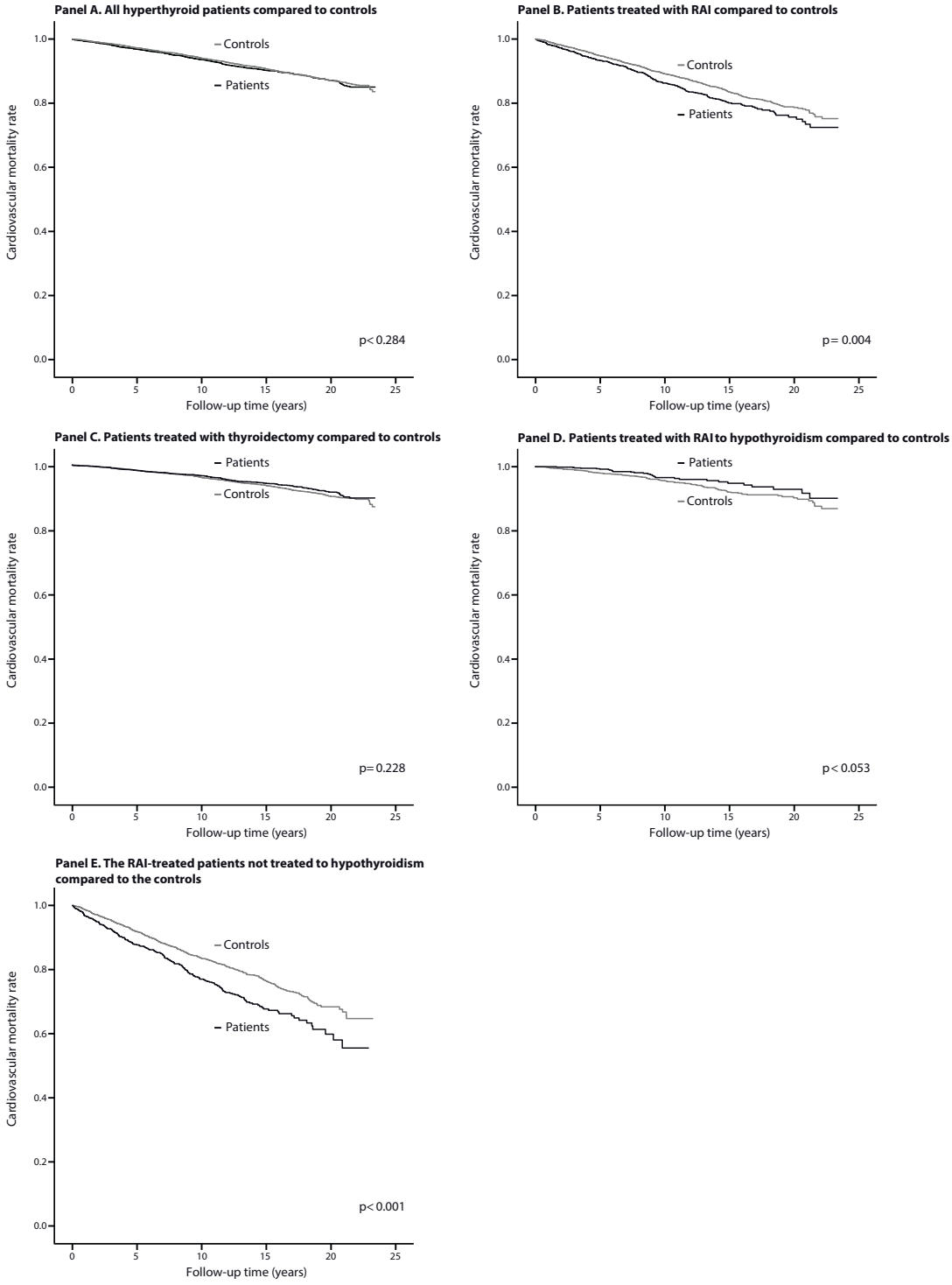

Fig. 3. Cumulative cardiovascular mortality rate by time since the treatment of hyperthyroidism in the different groups of patients compared with the age and sex-matched control group (Log rank test).

5.5.2 The comparison between the patients treated with thyroidectomy and RAI

In a Cox regression analysis, cardiovascular mortality was significantly higher in the patients treated with RAI compared to the patients treated with thyroidectomy, when adjusted for age, gender and prevalent CVDs (HR 2.05, 95% CI 1.69-2.48). The result was unaffected when analyzed separately in different subgroups of etiologies; Graves´ disease (HR 1.86, 95% CI 1.22-2.84, p=0.004), nodular disease (HR 2.83, 95% CI 2.11-3.80, p < 0.001) and other etiologies (HR 2.96, 95% CI 1.95-4.51, p < 0.001), or by including only the patients treated with subtotal (HR 2.05, 95% CI 1.67-2.52) or total thyroidectomy (HR 3.17, 95% CI 2.16-4.65).

CVD mortality was also analyzed in subgroups of CVD although the number of deaths in the subgroups was small leading to wide confidence intervals. The patients treated with RAI had a higher risk of CVD mortality for CAD (HR 2.47, 95% CI 1.88-3.24, p < 0.001), AF (HR 3.68, 95% CI 1.11-12.18, p =0.033), cerebrovascular diseases (HR 2.55, 95% CI 1.69-3.84, p < 0.001) and valvular diseases and cardiomyopathies (HR 3.47, 95% CI 1.86-6.48, p < 0.001) compared to the patients treated with thyroidectomy, but not for hypertension (HR 1.23, 95% CI 0.30-5.12, p=0.77) or heart failure (HR 1.99, 95% CI 0.60-6.60, p =0.259). All the results were adjusted for age, gender, prevalent CVDs and the etiology of hyperthyroidism.

In an analysis including only the patients treated effectively with RAI (resulting in levothyroxine-treated hypothyroidism) and the patients treated surgically, the risk of death due to any CVD was significantly lower in the RAI-treated patients compared to those treated surgically, adjusted for age, gender and prevalent CVDs (RR 0.29, 95% CI 0.20-0.43). The mortality for CVD was not analyzed in subgroups of CVDs due to the small number of deaths. However, when these patients were compared only to the patients treated with total thyroidectomy, there were no difference in the risk of CVD mortality (HR 0.58, 95% CI 0.34-1.00). In this analysis, there was no statistically significant difference either in the subgroup of patients with nodular disease compared to the patients with Graves´ disease (HR 1.48, 95% CI 0.75-2.92). Furthermore, in an analysis including only the patients with Graves´ disease treated effectively with RAI (resulting in levothyroxine-treated hypothyroidism) and the Graves´ disease patients treated surgically with total thyroidectomy, the risk of death due to any CVD was statistically insignificant in the RAI-treated patients, adjusted for age, gender and prevalent CVDs (1.37, 95% CI 0.51-3.70).

5.5.3 Cancer mortality (II)

There was no difference in cancer mortality in an analysis including all the patients treated for hyperthyroidism (either with thyroidectomy or RAI) compared to the control group (RR 1.09, 95% CI 0.95-1.26). There was no difference in cancer mortality in male (RR 1.04, 95% CI 0.76-1.42) or female patients (RR 1.11, 95% CI 0.95-1.30), patients treated with thyroidectomy (RR 1.19, 95% CI 0.99-1.42, p=0.0565) or patients treated with RAI (RR 0.96, 95% CI 0.78-1.22, p =0.8824) compared to their respective controls.

In a Cox regression analysis of cancer mortality including the patients and controls, treated hyperthyroidism was not significantly associated with death from cancer (RR 1.04, 95% CI 0.91-1.20), but older age at the time of treatment (RR 1.08, 95% CI 1.07-1.08/year), male gender (RR 1.77, 95% CI 1.52-2.07) and a previous cancer diagnosis (RR 4.29, 95% CI 3.71-4.97) increased the risk of cancer death.

In the analysis comparing the two treatment groups (excluding the controls), the age at the time of treatment (RR 1.08 /year, 95% CI 1.07-1.09) and a previous cancer diagnosis (RR 3.45, 95% CI 2.60-4.56) predicted cancer mortality, but the treatment modality RR 0.99, 95% CI 0.75-1.30 for RAI compared to thyroidectomy) or any of the etiological subgroups of hyperthyroidism did not.

5.6 Geographical differences between the study groups

Due to geographical differences between the two study groups, additional analyses were made to evaluate the possible effect of regional differences in the treatment of CVDs in Finland. Among the group treated with thyroidectomy, there were 241 patients treated in Tampere University Hospital with 723 controls. When the Cox regression analyses on CVD hospitalizations among the thyroidectomized patients were performed including only these patients, the risk of any CVD hospitalization was comparable to the main result (HR 1.13, 95% CI 0.85-1.46, p=0.370).

To test further whether the differences in CVD hospitalizations could be due to the geographical differences, some of the analyses were performed including only the control groups. There was no difference in the risk of hospital admission due to CVDs when the controls of the RAI-treated patients were compared to the

controls of the thyroidectomized patients, adjusted for age, gender and prevalent CVDs (HR 0.97, 95% CI 0.91-1.03), excluding any significant effect of the geographical difference on the results. Similarly, there was no difference in the risk of CVD mortality, when the controls of the RAI-treated patients were compared to the controls of the thyroidectomy-treated patients, adjusted for age, gender and prevalent CVDs (HR 0.98, 95% CI 0.89-1.12).

DISCUSSION

6.1 Major findings of this study

6.1.1 Cardiovascular morbidity and mortality in hyperthyroidism

Considering the CVD morbidity and mortality, there are two main results in this study. The first main result is that the patients treated with thyroidectomy had an increased risk of CVD morbidity compared to their age- and gender-matched control group. The second main result is that the patients treated with RAI remained at a markedly increased risk after the treatment, compared to the patients treated with thyroidectomy. The first main result strengthens the hypothesis that the increased cardiovascular morbidity is not caused by the treatment, but by the disease, hyperthyroidism per se. The second main result may help in understanding the mechanisms behind the increased CVD risk.

In this study, the risk of CVDs already increased several years before the treatment of hyperthyroidism in both treatment groups. The risk was attenuated by both treatment modalities. The increased CVD morbidity, still sustained up to two decades after the treatment of hyperthyroidism in both treatment groups, highlighting the significant effect of hyperthyroidism *per se*.

A hyperthyroid state causes stress to the cardiovascular system. Most changes in the cardiovascular system during hyperthyroidism are adaptive responses to increased energy metabolism and heat production in the body. Nevertheless, as a result of this adaptation, the cardiovascular system is strained already in the resting conditions, leading to exercise intolerance even in otherwise healthy persons (Klein & Ojamaa, 1998; Klein & Ojamaa, 1998). AF, tachycardia, elevated blood pressure, increased blood volume and increased oxygen demands of the heart predispose to heart failure and to worsening of the symptoms of a coexisting heart disease (Klein & Ojamaa, 2001; Klein, 2012; Klein & Danzi, 2016).

Similar results of an increased CVD morbidity even before the diagnosis of hyperthyroidism have been reported in a recent Danish study, emphasizing the importance of a timely diagnosis of hyperthyroidism (Brandt et al., 2013b). This study included 2 631 hyperthyroid patients, 375 twin pairs with one hyperthyroid

and one euthyroid twin and a three-fold group of age- and gender-matched controls. An increased risk of CVDs (OR 1.65), lung diseases (OR 1.53) and diabetes (OR 1.43) was detected before the diagnosis of hyperthyroidism in this large study with a six years` follow-up time. The risk remained increased even after the diagnosis of hyperthyroidism, but this study did not report on the treatments the patients received for hyperthyroidism. The overall morbidity was also increased in hyperthyroid twins compared to euthyroid twins (OR 1.16).

The genetic exposition for CVDs or other diseases could not be studied because of the insufficient power for the subgroup analyses of morbidity. The impact of genetics on mortality was studied in a larger twin pair study of 926 hyperthyroid patients with a euthyroid or a hyperthyroid twin sibling (Brandt et al., 2012). In this study, there was an increased risk of overall mortality in hyperthyroid patients compared to their dizygotic twin siblings. The monozygotic twin pairs, however, had a similar risk of overall mortality despite the other sibling being hyperthyroid (Brandt et al., 2012). The authors suggest that genetic factors may have an impact on mortality in hyperthyroidism, as previously reported on obesity and mortality (Carlsson et al., 2011), although they state that this matter needs to be studied further.

6.1.2 The impact of treatment modality on cardiovascular morbidity and mortality

One of the most important findings in this study was an impact of treatment modality on CVD morbidity and mortality. The increased CVD morbidity and mortality in patients treated with RAI compared to patients treated with subtotal or total thyroidectomy in this study helps in understanding the mechanisms behind the association between hyperthyroidism and CVDs. In the present study, CVD morbidity was 14% higher and CVD mortality twice as high in RAI-treated patients compared to the patients treated with thyroidectomy, adjusted for the clinical features (age, gender, the etiology of hyperthyroidism and prevalent CVDs prior to the treatment). The excess risk was eliminated by an effective treatment with RAI, resulting in hypothyroidism. A similar result with a better prognosis after treatment with thyroidectomy compared to treatment with RAI has been published by Giesecke et al in 2018. They reported recently higher all-cause mortality rates

in patients treated with RAI compared to patients treated with thyroidectomy in a comparative study including 10250 patients treated with RAI and 742 patients treated with thyroidectomy (Giesecke et al., 2018).

There are several possible reasons for increased CVD morbidity and mortality in the RAI-treated patients compared to those treated with thyroidectomy. After the treatment with RAI, thyroid function usually returns to normal within 2-6 months and hypothyroidism develops within 4-12 months, or even later (Cooper, 2003). In a meta-analysis of 35 studies and 7 241 patients with Graves´ disease treated with subtotal or total thyroidectomy, all the patients treated with total thyroidectomy became hypothyroid. Of the patients treated with subtotal thyroidectomy, 59.7% achieved euthyroidism and 25.6% hypothyroidism (Palit et al., 2000). The patients treated with RAI may remain hypo- or hyperthyroid for longer periods of time after the treatment compared to the thyroidectomized patients. Thyroidectomy offers almost an immediate cure of hyperthyroidism and the treatment with levothyroxine is started without delay. This hypothesis is supported by the results of a recent comparative study on the time lag to euthyroidism after the treatment of hyperthyroidism either with RAI or thyroidectomy (Davis et al., 2018). There were 96 patients treated with thyroidectomy and 121 patients treated with RAI in this study. The patients treated with thyroidectomy became euthyroid within three months after surgery compared to nine months after RAI, and the RAI-treated patients needed twice as often adjustments in medication during this time as the thyroidectomized patients. The difference in the restoration of euthyroidism may partly explain the better prognosis of the patients treated surgically. This is supported by the better outcome of the patients treated more effectively with RAI (resulting in levothyroxine-treated hypothyroidism) compared to the patients treated surgically in this study.

The results indicate that an effective treatment of hyperthyroidism is likely to have a major impact on the cardiovascular prognosis of the patients. Similar results with a decreased CVD morbidity and mortality of patients developing hypothyroidism after treatment with RAI have been reported previously (Flynn et al., 2006; Metso, Jaatinen et al., 2007; Boelaert et al., 2013). Furthermore, the duration of dysthyroidism, i.e overt or subclinical hyperthyroidism or hypothyroidism, was reported to increase overall mortality in a large Danish register-based study of TSH measurements in 239 678 individuals. A 9% excess overall mortality was detected for each six-month period with low TSH levels. An

excess mortality, however, was also associated with elevated TSH, highlighting the importance of euthyroidism for the prognosis (Laulund et al., 2014).

Likewise, a recent paper based on the same Danish register data reported an increased risk of mortality in both treated and untreated hyperthyroidism. There was an association between the number of periods of low TSH and mortality (Lillevang-Johansen et al., 2017). According to the results of this study and the previous studies with a long-term follow-up (Franklyn et al., 1991; Hall et al., 1993; Franklyn et al., 2005; Metso, Jaatinen et al., 2007; Metso et al., 2008) changes in the cardiovascular system during the hyperthyroid phase result in increased CVD morbidity and also mortality even after restoring euthyroidism. The mechanisms of the persistent risk still remain unclear. Based on the current literature represented, it seems that the excess morbidity and mortality associated with hyperthyroidism seem not to be caused by a specific treatment modality, but rather an inability to keep the patients euthyroid. Giesecke et al. presented a similar interpretation of the effect of hyperthyroidism *per se* and not the treatment modality on CVD morbidity and mortality, based on their study including hyperthyroid patients treated either with RAI or thyroidectomy. They did not, however, report the impact of the treatment modality on the cardiovascular outcomes in this study (Giesecke et al., 2017).

The patients treated surgically for hyperthyroidism differ from the patients treated with RAI in several aspects. The underlying thyroid disease, patient preferences, as well as the age and the operative risks of the patient are considered when choosing the treatment modality. Most of the hyperthyroid patients have been treated with RAI during the past few decades in Finland. Thyroidectomy may have been chosen, if the patient had a large goiter with compressive symptoms, a suspicion of malignancy, severe eye symptoms of Graves´ disease, or hyperthyroidism resistant to antithyroid medication during pregnancy. Due to the different patient selection for the different treatment modalities, the treatment groups are not totally comparable in a non-randomized, register-based study, and there is a possibility of confounding by indication.

6.1.3 Cancer incidence and mortality

One of the main results in this study is that the overall cancer incidence was not increased in a large cohort of hyperthyroid patients treated either with thyroidectomy or with RAI, compared to age- and gender-matched populations, and that the treatment modality of hyperthyroidism did not have an effect on cancer morbidity or mortality. The result of unchanged cancer incidence contradicts with some previous studies (Goldman et al., 1988; Metso, Auvinen et al., 2007; Metso, Jaatinen et al., 2007; Hoffman et al., 1982), but is in line with others (Holm et al., 1991; Ron et al., 1998). Furthermore, some of our study population treated with RAI overlaps with a study population of a study by Metso et al with a result of increased cancer incidence (Metso, Auvinen et al., 2007) and mortality (Metso, Jaatinen et al., 2007). The study population of Metso et al consisted of patients treated with RAI for hyperthyroidism in Tampere University Hospital between January 1965 and June 2002. The patients in this more recent study were treated between 1986 and 2007 with an overlap of 4,5 years in these cohorts. The possible explanations for the differences in cancer incidence in these partly overlapping study cohorts are the higher number of patients included in the first cohort (2 793 patients compared to 1809 patients) and the higher median age of the patients (62 years compared to 59 years). Furthermore, the first cohort included patients since 1965 with fewer diagnostic and treatment resources available for cancer, compared to the later cohort during the follow-up time. The mean dose of RAI administered, however, was comparable in these cohorts (305MBq and 323MBq).

There has been a significant increase in cancers of some specific sites, even in studies reporting unchanged overall outcome to cancer incidence or mortality in hyperthyroid patients. An increased incidence of stomach cancer (Hoffman et al., 1982; Holm et al., 1991; Metso, Auvinen et al., 2007), breast cancer (Goldman et al., 1988; Metso, Auvinen et al., 2007), kidney cancer (Metso, Auvinen et al., 2007; Hieu et al., 2012) and lung cancer (Holm et al., 1991) has been reported. These previous studies have mainly included patients treated with RAI for hyperthyroidism. Previously, the increased incidence of cancer has been assumed to be associated with the oncogenic effects of radiation. Nevertheless, in this present study with 70% of patients treated with thyroidectomy, an increase in respiratory tract and stomach cancer incidence was detected without association with treatment modality. In addition, the median age of the patients was lower (49 vs

56–62 y, respectively) compared to previous studies indicating a lower baseline risk of cancer and the exposure to RAI (median 259MBq) was lower in the RAI-treated group than in most of the previous studies (300–500MBq).

In our study, there was an association between kidney, breast, and respiratory tract cancer incidence and nodular thyroid disease. Hyperthyroidism caused by nodular disease develops slowly and thus a longer period of subclinical or undiagnosed and untreated hyperthyroidism may be more common in nodular disease than in Graves´ disease prolonging the exposure to an excess of thyroid hormones. There could also be an association between breast cancer and thyroid nodularity. Turken et al studied 150 patients with breast cancer and 100 healthy controls and found an increased incidence of nodular goiter and higher level of thyroid peroxidase autoantibodies (TPO-Ab) in patients with breast cancer compared to healthy controls (Turken et al., 2003). In a recent Danish study on the etiological subgroups of hyperthyroidism, the patients with a multinodular goiter were older compared to patients with Graves' disease (Brandt et al., 2013a). To some extent the association between cancer incidence and nodular goiter could be explained by the advanced age of the patients with a nodular goiter as increasing age is a known risk factor for cancer. In our study, the patients with a nodular thyroid disease were older compared to the patients with Graves´ disease, and age increased the risk of cancer by 8% / year. Similarly, breast cancer and thyroid disorders are both more prevalent in postmenopausal women, which could be a confounding factor.

An increased risk of specific cancer types, however, was detected compared to age- and gender-matched controls, indicating that toxic nodular goiter may be an independent risk factor for these cancers or may have some shared risk factors with them. There are also shared risk factors for thyroid nodularity and cancer. Thyroid nodularity has been associated with iodine deficiency (Laurberg et al., 2006) and, interestingly, with the metabolic syndrome (Kir et al., 2018). In a large register-based study on 94 555 women, there was a 13% higher risk of breast cancer in women with the metabolic syndrome compared to women without the syndrome (Dibaba et al., 2018). In another study on postmenopausal women aged 50-79, the risk of invasive estrogen- or progesterone-receptor positive breast cancer and breast cancer mortality had a strong association with BMI over 35.0 (Neuhouser et al., 2015).

6.2 The strengths and limitations of the study and the validity of the data

6.2.1 Enrollment of the patients treated with thyroidectomy

The patients treated with thyroidectomy for hyperthyroidism were identified from the HILMO database maintained by the THL. The search for the patients was based on the combination of the diagnosis of hyperthyroidism (ICD-codes) and the procedure codes for total or subtotal thyroidectomy. The database includes the hospitalizations with overnight stay since January 1969 and the procedure codes since 1986. The selection of the starting date of this study (1st Jan 1986) was based on the availability of the procedure codes. Due to the nationwide registration and the specific codes, it was possible to obtain data on all the patients treated for thyroidectomy during the study period in Finland.

The validity of the procedure codes has been addressed in some Finnish studies. The procedure codes in HILMO database for CAD between 2007-2014 covered 84,6% of the procedure codes of PCI and 97,1% for coronary artery bypass grafting (CABG) compared to the local register of Kuopio University Hospital Heart Center (Heiskanen et al., 2016). However, about one-third of the elective procedures were misclassified as non-elective procedures although the procedure codes were correct. The procedure codes for multiple trauma patients were found to be quite good compared to patient files and the trauma registry of Helsinki University Hospital trauma unit (Heinänen et al., 2017). The validity of procedure codes for thyroidectomies has not been evaluated. Since thyroidectomy is a demanding surgery performed by a few surgeons in Finland, it is quite likely that the enrolling of the diagnoses and procedure codes are accurate.

6.2.2 The register of the patients treated with RAI

Information on the patients treated with RAI has been systematically registered since 1965 into a computerized register in collaboration with the department of nuclear medicine and the department of internal medicine at Tampere University Hospital. There is no similar register-based data available from other hospitals in Finland. Tampere University Hospital has a catchment population of 500 000

(10% of the Finnish population) and it is the only provider on RAI treatment in the area ensuring that all the patients treated with RAI are included in the study. Information on the etiology of hyperthyroidism, previous surgical treatment, the dates and doses of RAI treatments, and the follow-up data on thyroid function after the treatment were obtained from the register. Following the RAI treatment, the thyroid status of the patients has been monitored by blood samples every 1-3 months during the first year, and subsequently every 1-3 years.

6.2.3 Cardiovascular diseases

The enrolling of diagnoses to the HILMO database is obligatory in Finland and the register has been used since 1969. The variables gathered in the register include date of birth, gender, county, hospital ID, dates of admissions and discharges and all the diagnoses given. The accuracy of the register was found to vary from satisfactory to good in a large study of 32 articles using information from this database and comparing it to an external data. Over 95% of the hospital discharges were found in the register with positive predictive value varying between 75-99% (Sund, 2012).

In separate studies evaluating the validity of this database during the follow-up time of this study, the validity has been found to be fairly good for stroke morbidity and mortality (coverage 95% and sensitivity 85-86%) compared to the population-based FINSTROKE register (Tolonen et al., 2007) and reasonable for CAD compared to the FINMONICA/FINAMI data (positive predictive value 90%, sensitivity 82% (Pajunen et al., 2005).

Since no data on out-patient visits was available, our study lacks information on diseases treated mainly on out-patient visits. Since significant cardiovascular and cancer diseases usually require a hospital admission at least for one night at some point, the information was evaluated to be sufficient for this study. Furthermore, we included the first three ICD-codes for each hospitalization, which increases the probability of accessing also for the diseases treated mainly on out-patient visits, like hypertension and a stable CAD.

A randomized study comparing the treatment modalities of hyperthyroidism is not possible, since the indications for the treatment modalities differ and many of the patients are not eligible for thyroidectomy due to comorbidities affecting surgical and anesthetic risk. In this study, however, it was possible to narrow the

gap between study groups by adjusting the results for the main clinical variables, including age, gender, prior CVDs, and the etiology of hyperthyroidism. Because of the register-based nature of this study, the results could not be adjusted for the common risk factors of CVDs, including smoking, family history, diabetes, hyperlipidemia or medication. Furthermore, the possible relapses of hyperthyroidism after thyroid surgery could not be verified due to a lack of data on thyroid function tests after thyroidectomy. Neither did we have information on the treatment response of the levothyroxine treatment after thyroid surgery, which could be a confounding factor in evaluating of the risk of CVDs.

6.2.4 Cancer incidence

The information on cancer diagnoses and mortality was obtained from the Finnish Cancer registry, which is a nation-wide, population-based registry. The registry was established in 1952 and contains information on most of the cancer diagnoses and deaths in Finland since then. The accuracy of the database has been evaluated to be excellent (Teppo, Pukkala, & Lehtonen, 1994). Reporting of new cancer diagnoses has been obligatory in Finland since 1961 for all physicians, hospitals and diagnostic laboratories involved in cancer diagnostics. The aim of the Finnish Cancer Registry is to obtain at least three different notifications from one cancer: from a physician with the clinical information, from a laboratory with the diagnostic data, and finally from Statistics Finland, in case of death caused by the cancer. Information is derived from laboratories twice a year digitally and the information on cancer deaths is updated yearly by Statistics Finland. The accuracy of the information in the Finnish Cancer Registry is dependent on the accuracy of the information in announcements received. However, the accuracy is improved due to several notifications regarding the same cancer diagnosis. In case of conflicting information, the information of the clinical announcement by a physician is regarded as the most reliable (Finnish cancer registry, description of statistics and their quality.).

Due to the register-based nature of this study, we were not able to adjust the risk of cancer for the other common risk factors i.e smoking, obesity, medications, family history or for diseases treated mainly in outpatient clinics, such as atrophic gastritis. Furthermore, it is unclear, how many of our patients treated with

thyroidectomy had a previous treatment with RAI due to the lack of nationwide registering of RAI treatments in Finland.

All of the controls were matched with the patients for age, gender, and county of residence at the beginning of the follow-up. Matching for the county adjusted for any geographical differences in the analyses comparing the patients and the controls. Geographical differences, however, could not be adjusted in the analyses comparing the patients treated with thyroidectomy and those treated with RAI. Nevertheless, the regional variation in cancer incidence is known to be minor in Finland; the ratio of the lowest to the highest age-standardized cancer incidence rate among the five university hospital districts is 0.83; SD, 13% (Institute for Statistical and Epidemiological Cancer Research. Finnish Cancer Registry). In support of no notable bias by geographical differences in the present study, the results did not change when only the patients treated in Tampere University Hospital were included in the analyses.

6.2.5 Mortality

The information on the deceased and the causes of death were derived from Statistics Finland and the dates of deaths from the Population Register Centre via a computerized link between the HILMO database and the other two institutions. The information on deaths for cancer was also derived from the Finnish Cancer Registry. Statistics Finland has kept the archive of causes of death since 1936. The database is updated from the death certificates written by Finnish physicians. The information obtained from death certificates is checked and completed by information on dates of deaths derived from the Finnish Population Centre which ensures that the database covers almost 100% of deaths in Finland (Statistic Finland. Quality Description: Causes of death 2017. 2018).

In this study, the underlying cause of death was used. The underlying cause of death is derived from the death certificate based on the ICD-code and the written diagnosis. If the underlying cause of death is unclear based on this information, the underlying cause of death is decided by the verbal clinical information given on the death certificate or the physician is asked for additional information, which makes the enrolling of the causes of death very accurate (Statistic Finland. Quality Description: Causes of death 2017. 2018). Furthermore, when the mortality of

the controls of the patients treated with thyroidectomy and was compared to the controls of the RAI-treated patients in this study, the ratio of the mortality rates in this analysis was close to 1.00 indicating no difference in mortality between these two control groups, which both represent the general Finnish population.

SUMMARY AND CONCLUSIONS

Several studies on cardiovascular and cancer outcomes after treated hyperthyroidism have been published during the past 40 years. The general outcome in these studies has been an increased cardiovascular and cancer morbidity associated with treated hyperthyroidism. There are also results indicating an increased CVD and cancer mortality.

The primary aim of this study was to clarify the possible reasons for the increased CVD and cancer morbidity and mortality associated with previously treated hyperthyroidism. The hypothesis at the beginning of the study was that the increased risk of CVDs and cancer is not due to the treatment of hyperthyroidism, but to the disease itself. By studying patients treated either with RAI or with thyroidectomy, it was possible to analyze the possible effect of the treatment modality on the increased morbidity.

Prior to the present study, no studies comparing the long-term effects of different treatment modalities for hyperthyroidism had been published. In this large-scale, comparative cohort study of hyperthyroid patients, the long-term consequences of hyperthyroidism and its treatment modalities were studied. A significant increase in cardiovascular morbidity and mortality was detected in patients with hyperthyroidism. The increased risk for CVDs was attenuated by both the treatment modalities studied. Thyroidectomy was more beneficial in decreasing the risk of cardiovascular morbidity and mortality in hyperthyroid patients than treatment with RAI, and the patients treated with RAI had twice as high CVD mortality rates as the patients treated with thyroidectomy. The patients who developed hypothyroidism after the treatment with RAI, however, had a similar CVD morbidity and an even lower CVD mortality than the patients treated with thyroidectomy. After the treatment of hyperthyroidism, there was no significant increase in cancer incidence overall in hyperthyroid patients, compared to the general population. Nevertheless, an increased risk of gastric and respiratory tract cancers in all the hyperthyroid patients and an increased risk of kidney, breast, and respiratory tract cancers in the patients with a nodular thyroid disease was detected. The treatment modality (RAI or thyroidectomy), however, did not affect the risk of cancer.

In conclusion, hyperthyroidism *per se* seems to increase cardiovascular morbidity, regardless of the treatment modality used. The incidence of some types of cancer is associated with hyperthyroidism, probably due to shared risk factors. Most importantly, the risk of CVDs can be decreased by a timely diagnosis and effective treatment of hyperthyroidism. Despite the treatment modality, all the patients with previous hyperthyroidism should be considered as high-risk patients regarding future CVDs and some cancer types. An active follow-up for other risk factors and for new cardiovascular symptoms of previously hyperthyroid patients is warranted. Furthermore, the results underline the importance of an immediate and efficient management of hyperthyroidism, to improve the long-term prognosis of hyperthyroid patients.

ACKNOWLEDGEMENTS

This thesis was carried out at the Department of Internal Medicine in Tampere University Hospital, In Tampere Heart Hospital and in Tampere University, Faculty of Medicine and Health Technology.

This project which I started several years ago, has sometimes been a real handful. Nevertheless, I have enjoyed the process and especially the privilege to learn from the best. My deepest gratitude goes to my marvelous thesis supervisors. Docent **Saara Metso**, M.D has been like a big sister to me in this project and guided me with an amazing pedagogic attitude. In the beginning she gave me very detailed and concrete instructions and in the end, she allowed me to make my own decisions and showed her admiration for my work. Professor **Pia Jaatinen**, M.D has taught me to always aim at my best. I am grateful for her uncompromising attitude to scientific writing and reporting and for her detailed guidance. Docent **Jorma Salmi**, M.D has been a great inspirer for me since my fourth day at medical school and taught me the power of logical advancing in diagnostics. I am grateful for his ideas and belief in me.

I am most thankful to **Heini Huhtala**, M. Sc. for her everlasting compassion and for her creative understanding of statistics. She has had enough patience to repeatedly explain me the basics of statistics. Nevertheless, she has always treated me with respect and listened to my ideas – no matter how peculiar they must sometimes have seemed to her. I am grateful to professor **Anssi Auvinen**, M.D for his constructive instructions and all the corrections he has made to my manuscripts. I admire his knowledge of epidemiology and scientific writing. I am also thankful to my other co-authors, docent **Matti Välimäki**, M.D. and docent **Rauni Saaristo**, M.D and for the reviewers of this thesis, docent **Kari Kervinen**, M.D and docent **Ilkka Heiskanen**, M.D. for helping me to improve my work. My humble gratitude goes to **Esko J. Väyrynen**, M.A., for the revision of the English language in the original communications and this thesis.

I wish to express my deepest gratitude to docent **Kari Niemelä**, M.D., CEO of the Heart Hospital, **Pasi Lehto**, MD, Ph.D, the Head of the Tampere Heart Hospital, professor **Kjell Nikus**, M.D and docent **Saila Vikman**, M.D. from the Tampere Heart Hospital and to docent **Jaakko Antonen**, M.D, the Head of the Department of Internal Medicine and docent **Kari Pietilä**, M.D, the previous

Head of the Department of Internal Medicine of Tampere University Hospital for providing me the facilities to perform this study and for their valuable advice, guidance and encouragement.

My most heartfelt thanks belong to **all my friends and colleagues** in Tampere Heart Hospital and in the Department of Internal Medicine. I have a privilege to enjoy their pleasant company, humor, fresh insights and sound advice every day. They have made this project so much easier for me to handle. Especially I am grateful to my friend **Minna Tahvanainen**. You are my most valuable protection against frustration and exhaustion.

Above all, I am grateful to my beloved husband and friend **Joona Ryödi**. His endless love, belief in equality between spouses and professional level coffee making skills are my daily life savers. This project would have never been possible without his supportive attitude, creativity, knowledge of technical issues and concrete help.

My precious children, **Vilma** and **Aapo**, I simply thank them for their love. They are the purpose and the light of my life. I embrace the idea of showing an example for them. They are, however, free to decide themselves later on, whether the example was a good or a bad one. I have benefited from their ability to take me instantly back to the ground, if I have for a moment thought too much of myself. My big brothers, **Riku** and **Jyri Ryödi**, I want to thank for the same lovable ability.

Finally, I wish to thank my parents, **Anita** and **Seppo Ryödi**, for their endless pride and support. The most valuable thing they have given me, is that they raised me as a person I was, instead of raising me according to some prejudice of me. During these busy years of mine, they have showed me their concrete support by taking care of me, my family and our home, whenever needed.

This thesis was financially supported by the Jalmari and Rauha Ahokas Foundation, Tampere Heart Hospital, the Hospital District of South Ostrobothnia, the Medical Research Fund of Tampere University Hospital and the Competitive State Research Financing of the Expert Responsibility Area of Tampere University Hospital.

REFERENCES

Adam, M. A., Thomas, S., Youngwirth, L., Hyslop, T., Reed, S. D., Scheri, R. P., . . . Sosa, J. A. (2017). Is there a minimum number of thyroidectomies a surgeon should perform to optimize patient outcomes? Annals of Surgery, 265(2), 402-407. doi:10.1097

Alexander, E. K., Pearce, E. N., Brent, G. A., Brown, R. S., Chen, H., Dosiou, C., . . . Sullivan, S. (2017). 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid: Official Journal of the American Thyroid Association, 27(3), 315-389. doi:10.1089/thy.2016.0457

Azizi, F., Ataie, L., Hedayati, M., Mehrabi, Y., & Sheikholeslami, F. (2005). Effect of long-term continuous methimazole treatment of hyperthyroidism: Comparison with radioiodine. European Journal of Endocrinology, 152(5), 695-701. doi:10.1530/eje.1.01904

Bartalena, L., & Fatourechi, V. (2014). Extrathyroidal manifestations of Graves' disease: A 2014 update. Journal of Endocrinological Investigation, 37(8), 691-700. doi:10.1007/s40618-014-0097-2

Bauer, D. C., Rodondi, N., Stone, K. L., & Hillier, T. A. (2007). Thyroid hormone use, hyperthyroidism and mortality in older women. The American Journal of Medicine, 120(4), 343-349. doi:10.1016/j.amjmed.2006.04.034

Bergenfelz, A., Jansson, S., Kristoffersson, A., Mårtensson, H., Reihnér, E., Wallin, G., & Lausen, I. (2008). Complications to thyroid surgery: Results as reported in a database from a multicenter audit comprising 3,660 patients. Langenbeck's Archives of Surgery, 393(5), 667-673. doi:10.1007/s00423-008-0366-7

Bergenfelz, A., Salem, A. F., Jacobsson, H., Nordenström, E., & Almquist, M. (2016). Risk of recurrent laryngeal nerve palsy in patients undergoing thyroidectomy with and without intraoperative nerve monitoring. The British Journal of Surgery, 103(13), 1828-1838. doi:10.1002/bjs.10276

Beyer, C., Plank, F., Friedrich, G., Wildauer, M., & Feuchtner, G. (2017). Effects of hyperthyroidism on coronary artery disease: A Computed tomography angiography study. The Canadian Journal of Cardiology, 33(10), 1327-1334. doi:10.1016/j.cjca.2017.07.002

Biondi, B. (2012). Mechanisms in Endocrinology: Heart failure and thyroid dysfunction. European Journal of Endocrinology, 167(5), 609-618. doi:10.1530/EJE-12-0627

Bjoro, T., Holmen, J., Krüger, O., Midthjell, K., Hunstad, K., Schreiner, T., . . . Brochmann, H. (2000). Prevalence of thyroid disease, thyroid dysfunction and thyroid peroxidase antibodies in a large, unselected population. the Health Study of Nord-Trondelag (HUNT). European Journal of Endocrinology, 143(5), 639-647.

Boelaert, K., Torlinska, B., Holder, R. L., & Franklyn, J. A. (2010). Older subjects with hyperthyroidism present with a paucity of symptoms and signs: A large cross-sectional study. The Journal of Clinical Endocrinology and Metabolism, 95(6), 2715-2726. doi:10.1210/jc.2009-2495

Boelaert, K., Maisonneuve, P., Torlinska, B., & Franklyn, J. A. (2013). Comparison of mortality in hyperthyroidism during periods of treatment with thionamides and after radioiodine. The Journal of Clinical Endocrinology and Metabolism, 98(5), 1869-1882. doi:10.1210/jc.2012-3459

Boger, M. S., & Perrier, N. D. (2004). Advantages and disadvantages of surgical therapy and optimal extent of thyroidectomy for the treatment of hyperthyroidism. The Surgical Clinics of North America, 84(3), 849-874. doi:10.1016/j.suc.2004.01.006

Brandt, F., Almind, D., Christensen, K., Green, A., Brix, T. H., & Hegedüs, L. (2012). Excess mortality in hyperthyroidism: The influence of preexisting comorbidity and genetic confounding: A Danish nationwide register-based cohort study of twins and singletons. The Journal of Clinical Endocrinology and Metabolism, 97(11), 4123-4129. doi:10.1210/jc.2012-2268

Brandt, F., Thvilum, M., Almind, D., Christensen, K., Green, A., Hegedüs, L., & Brix, T. H. (2013a). 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: Official Journal of the American Thyroid Association, 23(4), 408-413. doi:10.1089/thy.2012.0500

Brandt, F., Thvilum, M., Almind, D., Christensen, K., Green, A., Hegedüs, L., & Brix, T. H. (2013b). Morbidity before and after the diagnosis of hyperthyroidism: A nationwide register-based study. PloS One, 8(6), e66711. doi:10.1371/journal.pone.0066711

Brix, T. H., Kyvik, K. O., Christensen, K., & Hegedüs, L. (2001). Evidence for a major role of heredity in Graves' disease: A population-based study of two Danish twin cohorts. The Journal of Clinical Endocrinology and Metabolism, 86(2), 930-934. doi:10.1210/jcem.86.2.7242

Burstein, B., & Nattel, S. (2008). Atrial fibrosis: Mechanisms and clinical relevance in atrial fibrillation. Journal of the American College of Cardiology, 51(8), 802-809. doi:10.1016/j.jacc.2007.09.064

Capel, I., Tasa-Vinyals, E., Cano-Palomares, A., Bergés-Raso, I., Albert, L., Rigla, M., & Caixàs, A. (2017). Takotsubo cardiomyopathy in amiodarone-induced hyperthyroidism. Endocrinology, Diabetes & Metabolism Case Reports, 2017 doi:10.1530/EDM-16-0116

Carlé, A., Pedersen, I. B., Knudsen, N., Perrild, H., Ovesen, L., Rasmussen, L. B., & Laurberg, P. (2011). Epidemiology of subtypes of hyperthyroidism in Denmark: A population-based study. European Journal of Endocrinology, 164(5), 801-809. doi:10.1530/EJE-10-1155

Carlsson, S., Andersson, T., de Faire, U., Lichtenstein, P., Michaëlsson, K., & Ahlbom, A. (2011). Body mass index and mortality: Is the association explained by genetic factors? Epidemiology (Cambridge, Mass.), 22(1), 98-103. doi:10.1097/EDE.0b013e3181fce2a2

Centanni, M., Marignani, M., Gargano, L., Corleto, V. D., Casini, A., Delle Fave, G., . . . Annibale, B. (1999). Atrophic body gastritis in patients with autoimmune thyroid disease: An underdiagnosed association. Archives of Internal Medicine, 159(15), 1726-1730.

Chan, Y. X., Knuiman, M. W., Divitini, M. L., Brown, S. J., Walsh, J., & Yeap, B. B. (2017). Lower TSH and higher free thyroxine predict incidence of prostate but not breast, colorectal or lung cancer. European Journal of Endocrinology, 177(4), 297-308. doi:10.1530/EJE-17-0197

Cooper, D. S. (2003). Hyperthyroidism. Lancet (London, England), 362(9382), 459-468. doi:10.1016/S0140-6736(03)14073-1

Cooper, D. S. (2005). Antithyroid drugs. The New England Journal of Medicine, 352(9), 905-917. doi:10.1056/NEJMra042972

Dahlberg, P. A., Karlsson, F. A., & Lundqvist, G. (1981). High serum gastrin levels in thyrotoxic patients. Clinical Endocrinology, 14(2), 125-131.

Davies Terry F., Laurberg Peter, Bahn Rebecca S. (2016). Hyperthyroid disorders. In: Williams Textbook of Endocrinology. (13TH ed.). Philadelphia: Elsevier.

Davis, J. R., Dackiw, A. P., Holt, S. A., Nwariaku, F. E., & Oltmann, S. C. (2018). Rapid relief: Thyroidectomy is a quicker cure than radioactive iodine ablation (RAI) in patients with hyperthyroidism. World Journal of Surgery, doi:10.1007/s00268-018-4864-7

De Leo, S., Lee, S. Y., & Braverman, L. E. (2016). Hyperthyroidism. Lancet (London, England), 388(10047), 906-918. doi:10.1016/S0140-6736(16)00278-6

Dekkers, O. M., Horváth-Puhó, E., Cannegieter, S. C., Vandenbroucke, J. P., Sørensen, H. T., & Jørgensen, J. O. L. (2017). Acute cardiovascular events and all-cause mortality in patients with hyperthyroidism: A population-based cohort study. European Journal of Endocrinology, 176(1), 1-9. doi:10.1530/EJE-16-0576

Dibaba, D. T., Braithwaite, D., & Akinyemiju, T. (2018). Metabolic syndrome and the risk of breast cancer and subtypes by race, menopause and BMI. Cancers, 10(9) doi:10.3390/cancers10090299

Dionigi, G., Boni, L., Rovera, F., Rausei, S., Castelnuovo, P., & Dionigi, R. (2010). Postoperative laryngoscopy in thyroid surgery: Proper timing to detect recurrent laryngeal nerve injury. Langenbeck's Archives of Surgery, 395(4), 327-331. doi:10.1007/s00423-009-0581-x

Dörr, M., Wolff, B., Robinson, D. M., John, U., Lüdemann, J., Meng, W., . . . Völzke, H. (2005). The association of thyroid function with cardiac mass and left ventricular hypertrophy. The Journal of Clinical Endocrinology and Metabolism, 90(2), 673-677. doi:10.1210/jc.2004-1554

Duclos, A., Peix, J., Colin, C., Kraimps, J., Menegaux, F., Pattou, F., . . . Lifante, J. (2012). Influence of experience on performance of individual surgeons in thyroid surgery: Prospective cross sectional multicentre study. BMJ (Clinical Research Ed.), 344, d8041.

Erbil, Y., Barbaros, U., Işsever, H., Borucu, I., Salmaslioğlu, A., Mete, O., . . . Ozarmağan, S. (2007). Predictive factors for recurrent laryngeal nerve palsy and hypoparathyroidism after thyroid surgery. Clinical Otolaryngology: Official Journal of ENT-UK ; Official Journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery, 32(1), 32-37. doi:10.1111/j.1365-2273.2007.01383.x

Everts, M. E., Verhoeven, F. A., Bezstarosti, K., Moerings, E. P., Hennemann, G., Visser, T. J., & Lamers, J. M. (1996). Uptake of thyroid hormones in neonatal rat cardiac myocytes. Endocrinology, 137(10), 4235-4242. doi:10.1210/endo.137.10.8828482

Finnish Cancer Registry, Description of Statistics and Their Quality. Retrieved from https://syoparekisteri.fi/tilastot/tilastokuvaus-ja-laatuselosteet/

Flynn, R. W. V., Macdonald, T. M., Jung, R. T., Morris, A. D., & Leese, G. P. (2006). Mortality and vascular outcomes in patients treated for thyroid dysfunction. The Journal of Clinical Endocrinology and Metabolism, 91(6), 2159-2164. doi:10.1210/jc.2005-1833

Fortuny, J. V., Guigard, S., Karenovics, W., & Triponez, F. (2015). Surgery of the thyroid: Recent developments and perspective. Swiss Medical Weekly, 145, w14144. doi:10.4414/smw.2015.14144

Franklyn, J. A., Daykin, J., Drolc, Z., Farmer, M., & Sheppard, M. C. (1991). Long-term follow-up of treatment of thyrotoxicosis by three different methods. Clinical Endocrinology, 34(1), 71-76.

Franklyn, J. A., Maisonneuve, P., Sheppard, M. C., Betteridge, J., & Boyle, P. (1998). Mortality after the treatment of hyperthyroidism with radioactive iodine. The New England Journal of Medicine, 338(11), 712-718. doi:10.1056/NEJM199803123381103

Franklyn, J. A., Maisonneuve, P., Sheppard, M., Betteridge, J., & Boyle, P. (1999). Cancer incidence and mortality after radioiodine treatment for hyperthyroidism: A population-based cohort study. Lancet (London, England), 353(9170), 2111-2115. doi:10.1016/S0140-6736(98)12295-X

Franklyn, J. A., Sheppard, M. C., & Maisonneuve, P. (2005). Thyroid function and mortality in patients treated for hyperthyroidism. Jama, 294(1), 71-80. doi:10.1001/jama.294.1.71

Giesecke, P., Frykman, V., Wallin, G., Lönn, S., Discacciati, A., Törring, O., & Rosenqvist, M. (2018). All-cause and cardiovascular mortality risk after surgery versus radioiodine treatment for hyperthyroidism. The British Journal of Surgery, 105(3), 279-286. doi:10.1002/bjs.10665

Giesecke, P., Rosenqvist, M., Frykman, V., Friberg, L., Wallin, G., Höijer, J., . . . Törring, O. (2017). Increased cardiovascular mortality and morbidity in patients treated for toxic nodular goiter compared to Graves' disease and nontoxic goiter. Thyroid: Official Journal of the American Thyroid Association, 27(7), 878-885. doi:10.1089/thy.2017.0029

Goldman, M. B. (1990). Thyroid diseases and breast cancer. Epidemiologic Reviews, 12, 16-28.

Goldman, M. B., Maloof, F., Monson, R. R., Aschengrau, A., Cooper, D. S., & Ridgway, E. C. (1988). Radioactive iodine therapy and breast cancer. A follow-up study of hyperthyroid women. American Journal of Epidemiology, 127(5), 969-980.

Grais, I. M., & Sowers, J. R. (2014). Thyroid and the heart. The American Journal of Medicine, 127(8), 691-698. doi:10.1016/j.amjmed.2014.03.009

Grozinsky-Glasberg, S., Fraser, A., Nahshoni, E., Weizman, A., & Leibovici, L. (2006). Thyroxine-triiodothyronine combination therapy versus thyroxine monotherapy for clinical hypothyroidism: Meta-analysis of randomized controlled trials. The Journal of Clinical Endocrinology and Metabolism, 91(7), 2592-2599. doi:10.1210/jc.2006-0448

Guyton and Hall. (2016). Cardiac muscle; the heart as a pump and function of the heart valves. In: Textbook of medical physiology (13th ed.). Philadelphia: Elsevier.

Hall, P., Lundell, G., & Holm, L. E. (1993). Mortality in patients treated for hyperthyroidism with iodine-131. Acta Endocrinologica, 128(3), 230-234.

Heinänen, M., Brinck, T., Handolin, L., Mattila, V. M., & Söderlund, T. (2017). Accuracy and coverage of diagnosis and procedural coding of severely injured patients in the Finnish hospital discharge register: Comparison to patient files and the Helsinki trauma registry. Scandinavian Journal of Surgery: SJS: Official Organ for the Finnish Surgical Society and the Scandinavian Surgical Society, 106(3), 269-277. doi:10.1177/1457496916685236

Heiskanen, J., Martikainen, J., Miettinen, H., Hippeläinen, M., Roine, R. P., Hartikainen, J., & Tolppanen, A. (2016). The coverage of elective revascularisation procedure codes in the national Finnish hospital discharge register. Annals of Medicine, 48(7), 552-558. doi:10.1080/07853890.2016.1211733

Hellevik, A. I., Asvold, B. O., Bjøro, T., Romundstad, P. R., Nilsen, T. I. L., & Vatten, L. J. (2009). Thyroid function and cancer risk: A prospective population study. Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology, 18(2), 570-574. doi:10.1158/1055-9965.EPI-08-0911

Hieu, T. T., Russell, A. W., Cuneo, R., Clark, J., Kron, T., Hall, P., & Doi, S. A. R. (2012). Cancer risk after medical exposure to radioactive iodine in benign thyroid diseases: A meta-analysis. Endocrine-Related Cancer, 19(5), 645-655. doi:10.1530/ERC-12-0176

Hoffman, D. A., McConahey, W. M., Diamond, E. L., & Kurland, L. T. (1982). Mortality in women treated for hyperthyroidism. American Journal of Epidemiology, 115(2), 243-254.

Hoffman, D. A., McConahey, W. M., Fraumeni, J. F., & Kurland, L. T. (1982). Cancer incidence following treatment of hyperthyroidism. International Journal of Epidemiology, 11(3), 218-224.

Holm, I. A., Manson, J. E., Michels, K. B., Alexander, E. K., Willett, W. C., & Utiger, R. D. (2005). Smoking and other lifestyle factors and the risk of Graves' hyperthyroidism. Archives of Internal Medicine, 165(14), 1606-1611. doi:10.1001/archinte.165.14.1606

Holm, L. E., Hall, P., Wiklund, K., Lundell, G., Berg, G., Bjelkengren, G., . . . Larsson, L. G. (1991). Cancer risk after iodine-131 therapy for hyperthyroidism. Journal of the National Cancer Institute, 83(15), 1072-1077.

Holst, J. P., Burman, K. D., Atkins, F., Umans, J. G., & Jonklaas, J. (2005). Radioiodine therapy for thyroid cancer and hyperthyroidism in patients with end-stage renal disease on hemodialysis. Thyroid: Official Journal of the American Thyroid Association, 15(12), 1321-1331. doi:10.1089/thy.2005.15.1321

Institute for Statistical and Epidemiological Cancer Research. Finnish Cancer Registry. Retrieved from http://www.cancer.fi/syoparekisteri/en/statistics/cancer-statistics/

Joffe, R. T., Brimacombe, M., Levitt, A. J., & Stagnaro-Green, A. (2007). Treatment of clinical hypothyroidism with thyroxine and triiodothyronine: A literature review and meta-analysis. Psychosomatics, 48(5), 379-384. doi:10.1176/appi.psy.48.5.379

Jonklaas, J., Bianco, A. C., Bauer, A. J., Burman, K. D., Cappola, A. R., Celi, F. S., . . . Sawka, A. M. (2014). Guidelines for the treatment of hypothyroidism: Prepared by the American Thyroid Association task force on thyroid hormone replacement. Thyroid: Official Journal of the American Thyroid Association, 24(12), 1670-1751. doi:10.1089/thy.2014.0028

Journy, N. M. Y., Bernier, M., Doody, M. M., Alexander, B. H., Linet, M. S., & Kitahara, C. M. (2017). Hyperthyroidism, hypothyroidism, and cause-specific mortality in a large cohort of women. Thyroid: Official Journal of the American Thyroid Association, 27(8), 1001-1010. doi:10.1089/thy.2017.0063

Kahaly, G. J., Bartalena, L., Hegedüs, L., Leenhardt, L., Poppe, K., & Pearce, S. H. (2018). 2018 european thyroid association guideline for the management of Graves' hyperthyroidism. European Thyroid Journal, 7(4), 167-186. doi:10.1159/000490384

Kannel, W. B., & Cobb, J. (1992). Left ventricular hypertrophy and mortality--results from the Framingham study. Cardiology, 81(4-5), 291-298. doi:10.1159/000175819

Khan, S. R., Chaker, L., Ruiter, R., Aerts, Joachim G. J. V., Hofman, A., Dehghan, A., . . . Peeters, R. P. (2016). Thyroid function and cancer risk: The Rotterdam Study. The Journal of Clinical Endocrinology and Metabolism, 101(12), 5030-5036. doi:10.1210/jc.2016-2104

Kim, E. S., Shin, J. A., Shin, J. Y., Lim, D. J., Moon, S. D., Son, H. Y., & Han, J. H. (2012). Association between low serum free thyroxine concentrations and coronary artery calcification in healthy euthyroid subjects. Thyroid: Official Journal of the American Thyroid Association, 22(9), 870-876. doi:10.1089/thy.2011.0366

Kir, S., Aydin, Y., & Coskun, H. (2018). Relationship between metabolic syndrome and nodular thyroid diseases. Scandinavian Journal of Clinical and Laboratory Investigation, 78(1-2), 6-10. doi:10.1080/00365513.2017.1402363

Klein, I. (2012). Endocrine disorders and cardiovascular disease. In: Braunwald´s Heart Disease; 9th edition volume 2 ed. Philadephia: Elsevier (Saunders).

Klein, I., & Ojamaa, K. (1998). Thyrotoxicosis and the heart. Endocrinology and Metabolism Clinics of North America, 27(1), 51-62.

Klein, I., & Ojamaa, K. (2001). Thyroid hormone and the cardiovascular system. The New England Journal of Medicine, 344(7), 501-509. doi:10.1056/NEJM200102153440707

Klein, I., & Danzi, S. (2016). Thyroid disease and the heart. Current Problems in Cardiology, 41(2), 65-92. doi:10.1016/j.cpcardiol.2015.04.002

Komiya, N., Isomoto, S., Nakao, K., Hayano, M., & Yano, K. (2002). Electrophysiological abnormalities of the atrial muscle in patients with paroxysmal atrial fibrillation associated with hyperthyroidism. Clinical Endocrinology, 56(1), 39-44.

Kraut, E., & Farahani, P. (2015). A systematic review of clinical practice guidelines' recommendations on levothyroxine therapy alone versus combination therapy (LT4 plus LT3) for hypothyroidism. Clinical and Investigative Medicine. Medecine Clinique Et Experimentale, 38(6), 305.

Laulund, A. S., Nybo, M., Brix, T. H., Abrahamsen, B., Jørgensen, H. L., & Hegedüs, L. (2014). Duration of thyroid dysfunction correlates with all-cause mortality. the OPENTHYRO register cohort. PloS One, 9(10), e110437. doi:10.1371/journal.pone.0110437

Laurberg, P., Jørgensen, T., Perrild, H., Ovesen, L., Knudsen, N., Pedersen, I. B., . . . Vejbjerg, P. (2006). The Danish investigation on iodine intake and thyroid disease, DanThyr: Status and perspectives. European Journal of Endocrinology, 155(2), 219-228. doi:10.1530/eje.1.02210

Lillevang-Johansen, M., Abrahamsen, B., Jørgensen, H. L., Brix, T. H., & Hegedüs, L. (2017). Excess mortality in treated and untreated hyperthyroidism is related to cumulative periods of low serum TSH. The Journal of Clinical Endocrinology and Metabolism, 102(7), 2301-2309. doi:10.1210/jc.2017-00166

Manyari, D. E. (1990). Prognostic implications of echocardiographically determined left ventricular mass in the Framingham heart study. The New England Journal of Medicine, 323(24), 1706-1707. doi:10.1056/NEJM199012133232413

Marinò, M., Latrofa, F., Menconi, F., Chiovato, L., & Vitti, P. (2015). Role of genetic and non-genetic factors in the etiology of Graves' disease. Journal of Endocrinological Investigation, 38(3), 283-294. doi:10.1007/s40618-014-0214-2

Metso, S. (2009). Onko hypertyreoosin radiojodihoito turvallista? Suomen Lääkärilehti, 64(10), 901-907.

Metso, S., Auvinen, A., Huhtala, H., Salmi, J., Oksala, H., & Jaatinen, P. (2007). Increased cancer incidence after radioiodine treatment for hyperthyroidism. Cancer, 109(10), 1972-1979. doi:10.1002/cncr.22635

Metso, S., Auvinen, A., Huhtala, H., Salmi, J., Oksala, H., & Jaatinen, P. (2007). Increased cancer incidence after radioiodine treatment for hyperthyroidism. Cancer, 109(10), 1972-1979. doi:10.1002/cncr.22635

Metso, S., Auvinen, A., Salmi, J., Huhtala, H., & Jaatinen, P. (2008). Increased long-term cardiovascular morbidity among patients treated with radioactive iodine for hyperthyroidism. Clinical Endocrinology, 68(3), 450-457. doi:10.1111/j.1365-2265.2007.03064.x

Metso, S., Jaatinen, P., Huhtala, H., Auvinen, A., Oksala, H., & Salmi, J. (2007). Increased cardiovascular and cancer mortality after radioiodine treatment for hyperthyroidism. The Journal of Clinical Endocrinology and Metabolism, 92(6), 2190-2196. doi:10.1210/jc.2006-2321

Metso, S., Jaatinen, P., Huhtala, H., Luukkaala, T., Oksala, H., & Salmi, J. (2004). Long-term follow-up study of radioiodine treatment of hyperthyroidism. Clinical Endocrinology, 61(5), 641-648. doi:10.1111/j.1365-2265.2004.02152.x

Minlikeeva, A. N., Freudenheim, J. L., Cannioto, R. A., Eng, K. H., Szender, J. B., Mayor, P., . . . Moysich, K. B. (2017). History of thyroid disease and survival of ovarian cancer patients: Results from the ovarian cancer association consortium, a brief report. British Journal of Cancer, 117(7), 1063-1069. doi:10.1038/bjc.2017.267

Moeller, L. C., & Führer, D. (2013). Thyroid hormone, thyroid hormone receptors, and cancer: A clinical perspective. Endocrine-Related Cancer, 20(2), 19. doi:10.1530/ERC-12-0219

Mondul, A. M., Weinstein, S. J., Bosworth, T., Remaley, A. T., Virtamo, J., & Albanes, D. (2012). Circulating thyroxine, thyroid-stimulating hormone, and hypothyroid status and the risk of prostate cancer. PloS One, 7(10), e47730. doi:10.1371/journal.pone.0047730

Muthukumar, S., Sadacharan, D., Ravikumar, K., Mohanapriya, G., Hussain, Z., & Suresh, R. V. (2016). A prospective study on cardiovascular dysfunction in patients with hyperthyroidism and its reversal after surgical cure. World Journal of Surgery, 40(3), 622-628. doi:10.1007/s00268-015-3352-6

Nattel, S., Li, D., & Yue, L. (2000). Basic mechanisms of atrial fibrillation--very new insights into very old ideas. Annual Review of Physiology, 62, 51-77. doi:10.1146/annurev.physiol.62.1.51

Neuhouser, M. L., Aragaki, A. K., Prentice, R. L., Manson, J. E., Chlebowski, R., Carty, C. L., . . . Anderson, G. L. (2015). Overweight, obesity, and postmenopausal invasive breast cancer risk: A secondary analysis of the women's health initiative randomized clinical trials. JAMA Oncology, 1(5), 611-621. doi:10.1001/jamaoncol.2015.1546

Nyirenda, M. J., Clark, D. N., Finlayson, A. R., Read, J., Elders, A., Bain, M., . . . Toft, A. D. (2005). Thyroid disease and increased cardiovascular risk. Thyroid: Official Journal of the American Thyroid Association, 15(7), 718-724. doi:10.1089/thy.2005.15.718

Osman, F., Franklyn, J. A., Holder, R. L., Sheppard, M. C., & Gammage, M. D. (2007). Cardiovascular manifestations of hyperthyroidism before and after antithyroid therapy: A matched case-control study. Journal of the American College of Cardiology, 49(1), 71-81. doi:10.1016/j.jacc.2006.08.042

Pajunen, P., Koukkunen, H., Ketonen, M., Jerkkola, T., Immonen-Räihä, P., Kärjä-Koskenkari, P., . . . Salomaa, V. (2005). The validity of the Finnish hospital discharge register and causes of death register data on coronary heart disease. European Journal of Cardiovascular Prevention and Rehabilitation: Official Journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology, 12(2), 132-137.

Palit, T. K., Miller, C. C., & Miltenburg, D. M. (2000). The efficacy of thyroidectomy for Graves' disease: A meta-analysis. The Journal of Surgical Research, 90(2), 161-165. doi:10.1006/jsre.2000.5875

Park, H., Kim, J., Han, E. J., Park, S. E., Park, C., Lee, W., . . . Rhee, E. (2016). Association of low baseline free thyroxin levels with progression of coronary artery calcification over 4 years in euthyroid subjects: The Kangbuk Samsung Health Study. Clinical Endocrinology, 84(6), 889-895. doi:10.1111/cen.12946

Ringold, D. A., Nicoloff, J. T., Kesler, M., Davis, H., Hamilton, A., & Mack, T. (2002). Further evidence for a strong genetic influence on the development of autoimmune thyroid disease: The California twin study. Thyroid: Official Journal of the American Thyroid Association, 12(8), 647-653. doi:10.1089/105072502760258613

Ron, E., Doody, M. M., Becker, D. V., Brill, A. B., Curtis, R. E., Goldman, M. B., . . . Boice, J. D. (1998). Cancer mortality following treatment for adult hyperthyroidism. Cooperative thyrotoxicosis therapy follow-up study group. Jama, 280(4), 347-355.

Ross, D. S. (2011). Radioiodine therapy for hyperthyroidism. The New England Journal of Medicine, 364(6), 542-550. doi:10.1056/NEJMct1007101

Ross, D. S., Burch, H. B., Cooper, D. S., Greenlee, M. C., Laurberg, P., Maia, A. L., . . . Walter, M. A. (2016). 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. Thyroid: Official Journal of the American Thyroid Association, 26(10), 1343-1421. doi:10.1089/thy.2016.0229

Salvatore Domenico, Davies Terry F., Schlumberger Martin-Jean, Hay Ian D., Larsen Reed P. (2016). Thyroid physiology and diagnostic evaluation of patients with thyroid disorders. In: Williams textbook of Endocrinology (13th ed.). Philadelphia: Elsevier.

Sane, T. (2010). Aikuisten hypertyreoosin hoidon vaikea valinta. Duodecim, 126(20), 2419-20.

Selmer, C., Olesen, J. B., Hansen, M. L., Lindhardsen, J., Olsen, A. S., Madsen, J. C., . . . Gislason, G. H. (2012). The spectrum of thyroid disease and risk of new onset atrial fibrillation: A large population cohort study. BMJ (Clinical Research Ed.), 345, e7895.

Selmer, C., Hansen, M. L., Olesen, J. B., Mérie, C., Lindhardsen, J., Olsen, A. S., . . . Gislason, G. H. (2013). New-onset atrial fibrillation is a predictor of subsequent hyperthyroidism: A nationwide cohort study. PloS One, 8(2), e57893. doi:10.1371/journal.pone.0057893

Singer, P. A., Cooper, D. S., Levy, E. G., Ladenson, P. W., Braverman, L. E., Daniels, G., . . . Nikolai, T. F. (1995). Treatment guidelines for patients with hyperthyroidism and hypothyroidism. Standards of Care Committee, American Thyroid Association. Jama, 273(10), 808-812.

Smyth, P. P. A. (2003). The thyroid, iodine and breast cancer. Breast Cancer Research: BCR, 5(5), 235-238. doi:10.1186/bcr638

Søgaard, M., Farkas, D. K., Ehrenstein, V., Jørgensen, J. O. L., Dekkers, O. M., & Sørensen, H. T. (2016). Hypothyroidism and hyperthyroidism and breast cancer risk: A nationwide cohort study. European Journal of Endocrinology, 174(4), 409-414. doi:10.1530/EJE-15-0989

Song, M., Rabkin, C. S., & Camargo, M. C. (2018). Gastric cancer: An evolving disease. Current Treatment Options in Gastroenterology, doi:10.1007/s11938-018-0203-1

Sparks, P. B., Mond, H. G., Vohra, J. K., Yapanis, A. G., Grigg, L. E., & Kalman, J. M. (1999). Mechanical remodeling of the left atrium after loss of atrioventricular synchrony. A long-term study in humans. Circulation, 100(16), 1714-1721.

Statistic Finland; Quality Description: Causes of death 2017. (2018). Retrieved from http://tilastokeskus.fi/til/ksyyt/2017/ksyyt_2017_2018-12-17_laa_001_en.html

STUK. (2013). Radiation safety in nuclear medicine. Guide ST 6.3. Retrieved from http://www.finlex.fi/data/normit/21736/ST6-3e.pdf

Sund, R. (2012). Quality of the Finnish hospital discharge register: A systematic review. Scandinavian Journal of Public Health, 40(6), 505-515. doi:10.1177/1403494812456637

Sundaresh, V., Brito, J. P., Thapa, P., Bahn, R. S., & Stan, M. N. (2017). Comparative effectiveness of treatment choices for Graves' hyperthyroidism: A historical cohort study. Thyroid: Official Journal of the American Thyroid Association, 27(4), 497-505. doi:10.1089/thy.2016.0343

Sundaresh, V., Brito, J. P., Wang, Z., Prokop, L. J., Stan, M. N., Murad, M. H., & Bahn, R. S. (2013). Comparative effectiveness of therapies for Graves' hyperthyroidism: A systematic review and network meta-analysis. The Journal of Clinical Endocrinology and Metabolism, 98(9), 3671-3677. doi:10.1210/jc.2013-1954

Tallstedt, L., Lundell, G., Tørring, O., Wallin, G., Ljunggren, J. G., Blomgren, H., & Taube, A. (1992). Occurrence of ophthalmopathy after treatment for Graves' hyperthyroidism. the Thyroid Study Group. The New England Journal of Medicine, 326(26), 1733-1738. doi:10.1056/NEJM199206253262603

Teppo, L., Pukkala, E., & Lehtonen, M. (1994). Data quality and quality control of a population-based cancer registry. Experience in Finland. Acta Oncologica (Stockholm, Sweden), 33(4), 365-369.

Tolonen, H., Salomaa, V., Torppa, J., Sivenius, J., Immonen-Räihä, P., & Lehtonen, A. (2007). The validation of the Finnish hospital discharge register and causes of death register data on stroke diagnoses. European Journal of Cardiovascular Prevention and Rehabilitation: Official Journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology, 14(3), 380-385. doi:10.1097/01.hjr.0000239466.26132.f2

Tosovic, A., Becker, C., Bondeson, A., Bondeson, L., Ericsson, U., Malm, J., & Manjer, J. (2012). Prospectively measured thyroid hormones and thyroid peroxidase antibodies in relation to breast cancer risk. International Journal of Cancer, 131(9), 2126-2133. doi:10.1002/ijc.27470

Turken, O., NarIn, Y., DemIrbas, S., Onde, M. E., Sayan, O., KandemIr, E. G., . . . Ozturk, A. (2003). Breast cancer in association with thyroid disorders. Breast Cancer Research: BCR, 5(5), 110. doi:10.1186/bcr609

Venturi, S. (2001). Is there a role for iodine in breast diseases? Breast (Edinburgh, Scotland), 10(5), 379-382. doi:10.1054/brst.2000.0267

Venturi, S., Donati, F. M., Venturi, A., Venturi, M., Grossi, L., & Guidi, A. (2000). Role of iodine in evolution and carcinogenesis of thyroid, breast and stomach. Advances in Clinical Pathology: The Official Journal of Adriatic Society of Pathology, 4(1), 11-17.

Vestergaard, P. (2002). Smoking and thyroid disorders -a meta-analysis. European Journal of Endocrinology, 146(2), 153-161.

Watson, S. A., Grabowska, A. M., El-Zaatari, M., & Takhar, A. (2006). Gastrin - active participant or bystander in gastric carcinogenesis? Nature Reviews. Cancer, 6(12), 936-946. doi:10.1038/nrc2014

Weetman, A. P. (2000). Graves' disease. The New England Journal of Medicine, 343(17), 1236-1248. doi:10.1056/NEJM200010263431707

Wijffels, M. C., Kirchhof, C. J., Dorland, R., & Allessie, M. A. (1995). Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation, 92(7), 1954-1968.

Wilhelm, S. M., & McHenry, C. R. (2010). Total thyroidectomy is superior to subtotal thyroidectomy for management of Graves' disease in the United States. World Journal of Surgery, 34(6), 1261-1264. doi:10.1007/s00268-009-0337-3

Wustmann, K., Kucera, J. P., Zanchi, A., Burow, A., Stuber, T., Chappuis, B., . . . Delacrétaz, E. (2008). Activation of electrical triggers of atrial fibrillation in hyperthyroidism. The Journal of Clinical Endocrinology and Metabolism, 93(6), 2104-2108. doi:10.1210/jc.2008-0092

Yeh, N. -., Chou, C. -., Weng, S. -., Yang, C. -., Yen, F. -., Lee, S. -., . . . Tien, K. -. (2013). Hyperthyroidism and thyroid cancer risk: A population-based cohort study. Experimental and Clinical Endocrinology & Diabetes: Official Journal, German Society of Endocrinology [and] German Diabetes Association, 121(7), 402-406. doi:10.1055/s-0033-1341474

ORIGINAL COMMUNICATIONS

Clinical Endocrinology (Oxf), 80(5):743-750 © 2014 John Wiley & Sons Ltd, reprinted with the permission from the John Wiley & Sons (I)

The Journal of Clinical Endocrinology and Metabolism, 100(10):3710-3717 © 2015 Oxford University Press, reprinted with the permission from the Oxford University Press (II)

Thyroid: Official Journal of the American Thyroid Association, 28(9):1111-1120 © 2018 Mary Ann Liebert, Inc.; New Rochelle, NY, reprinted with the permission from Mary Ann Liebert (III)

Clinical Endocrinology (2014) **80**, 743–750 doi: 10.1111/cen.12359

ORIGINAL ARTICLE

Cardiovascular morbidity and mortality in surgically treated hyperthyroidism – a nation-wide cohort study with a long-term follow-up

Essi Ryödi*,†, Jorma Salmi‡, Pia Jaatinen†,‡, Heini Huhtala§, Rauni Saaristo¶, Matti Välimäki**, Anssi Auvinen§ and Saara Metso†,‡

*Heart Center Co., Tampere University Hospital, †School of Medicine, University of Tampere, ‡Department of Internal Medicine, Tampere University Hospital, §School of Health Sciences, Tampere University, ¶Department of Surgery, Tampere University Hospital, Tampere, and **Division of Endocrinology, Department of Medicine, Helsinki University Central Hospital, Helsinki, Finland

Summary

Objective Previous studies suggest that patients with hyperthyroidism remain at an increased risk of cardiovascular morbidity even after restoring euthyroidism. The mechanisms of the increased risk and its dependency on the different treatment modalities of hyperthyroidism remain unclear. The aim of this long-term follow-up study was to compare the rate of hospitalizations for cardiovascular causes and the mortality in hyperthyroid patients treated surgically with an age- and gender-matched reference population.

Patients and Measurements A population-based cohort study was conducted among 4334 hyperthyroid patients (median age 46 years) treated with thyroidectomy in 1986–2007 in Finland and among 12 991 reference subjects. Firstly, the hospitalizations due to cardiovascular diseases (CVD) were analysed until thyroidectomy. Secondly, the hazard ratios for any new hospitalization due to CVDs after the thyroidectomy were calculated in Cox regression analysis adjusted with the prevalent CVDs at the time of thyroidectomy.

Results The risk of hospitalization due to all CVDs started to increase already 5 years before the thyroidectomy, and by the time of the operation, it was 50% higher in the hyperthyroid patients compared to the controls ($P < 0{\cdot}001$). After the thyroidectomy, the hospitalizations due to all CVDs (HR 1·15), hypertension (HR 1·23), heart failure (HR 1·17) and valvular diseases or cardiomyopathies (HR 1·55) remained more frequent among the patients than among the controls for 20 years after thyroidectomy. The increased morbidity was not clearly related to the aetiology of hyperthyroidism. Despite the increased CVD morbidity among the patients, there was no difference in cardiovascular mortality.

Conclusions The present study shows that hyperthyroidism increases the risk of hospitalization due to CVDs and the risk is sustained up to two decades after effective surgical treatment. However, there was no excess CVD mortality in the middle-aged patient cohort studied.

(Received 9 June 2013; returned for revision 3 July 2013; finally revised 30 September 2013; accepted 27 October 2013)

Correspondence: Essi Ryödi, Heart Center Co., Tampere University Hospital, 33521 Tampere, PL 2000, Finland. Tel.: +358 3 31167993; Fax: +358 3 311 64157; E-mail: essi.ryodi@sydankeskus.fi

Introduction

Hyperthyroidism is a common disease, with a prevalence of approximately 2·5% among women and 0·6% in men.[1] Surgical treatment of hyperthyroidism is considered if a patient has a large goitre with compressive symptoms, a suspicion of malignancy or hyperthyroidism with severe eye symptoms of Graves' disease and during pregnancy in severe hyperthyroidism resistant to antithyroid medication.[2] Subtotal thyroidectomy was the standard treatment for hyperthyroidism in the early part of the twentieth century,[3] but nowadays total thyroidectomy is increasingly recommended to reduce thyroid autoimmunity and the risk of relapsing hyperthyroidism, especially in patients with Graves' ophthalmopathy.[4,5] Other forms of treatment, that is, long-term antithyroid medication and radioiodine (RAI) therapy, are commonly used for the treatment of hyperthyroidism. An immediate relief of hyperthyroidism is an advantage of surgery over other treatment modalities. Low complication rates have been reported, but their incidence depends largely on the skills and the experience of the surgeon.[6] The most important complications are permanent hypoparathyroidism and recurrent laryngeal nerve damage in 0·7–3% of the patients.[6] Transient hypocalcaemia, bleeding and infection are also potential complications of thyroid surgery.[7]

Hyperthyroidism has previously been regarded as a reversible disorder without persistent consequences, when treated effectively. However, a long-term follow-up study revealed an

increased cardiovascular morbidity persisting for decades after RAI treatment of hyperthyroidism, compared with the general population.[8] Cardiovascular mortality has also been found to increase after treatment with RAI for hyperthyroidism.[9–12] Likewise, increased long-term cardiovascular morbidity has been reported in patients treated with antithyroid therapy for hyperthyroidism, despite normalized thyroid hormone levels.[13] In a recently published study comparing antithyroid medication and RAI, the mortality rates were higher than expected during the periods of thionamide treatment for hyperthyroidism and after less intensive treatment with RAI (not resulting in hypothyroidism), but not after intensive treatment with RAI, resulting in hypothyroidism and T_4 replacement therapy.[14]

To date, no long-term studies have been published on the incidence of cardiovascular diseases (CVD) in relation to total or subtotal thyroidectomy for hyperthyroidism. Thus, the purpose of the present study was to assess the rate of hospitalization and mortality due to CVD among hyperthyroid patients treated with thyroid surgery in comparison with a matched reference population.

Subjects and methods

The patients operated for hyperthyroidism were identified from the nationwide Hospital Discharge Registry (HILMO) maintained by the National Institute of Health and Welfare (THL) based on both the diagnosis for hyperthyroidism (International Classification of Diseases, 8th, 9th and 10th revisions, codes 242 and E05) and the procedure codes for total or subtotal thyroidectomy (NCSP, Nordic Classification of Surgical Procedure codes 2504, 2505 and 2506 or BAA25, BAA40, BAA50 and BAA60 for total or subtotal thyroidectomy). The enrolling of diagnoses to the HILMO database is obligatory in Finland, and its completeness and accuracy has been found to vary from satisfactory to very good.[15] The database includes the hospitalizations and causes of hospitalization (hospital admission requiring an overnight stay) of the Finnish residents since January 1969, and the procedure codes since 1986. Our follow-up covers patients treated with total or subtotal thyroidectomy for hyperthyroidism between the years 1986 and 2007. Due to the nationwide registration and the specific codes, the case series represents all incident cases of hyperthyroidism treated with total or subtotal thyroidectomy in Finland during the follow-up period.

A reference group was formed by randomly choosing three age- ($\pm$6 months) and gender-matched control subjects for each patient from the comprehensive national Population Register Centre. Three controls were chosen to optimize the sample size and the statistical power of the study. The control subject had to be alive at the time the patient was operated and reside in the same county. The persons were excluded if they were already in the group of patients.

The lifetime causes of hospitalization, as well as the date of hospital admission were obtained from the HILMO, with deterministic record linkage based on the unique personal identification number assigned to all the residents of Finland. Both the primary and secondary diagnoses recorded at discharge from the hospital were used in the analysis. The diagnoses have been coded according to the Finnish version of the 8th revision of the International Classification of Diseases (ICD-8) in 1986, ICD-9 between 1986 and 1995, and the Finnish version of ICD-10 thereafter. A conversion between the different versions was made, and the causes of hospitalization were classified into eight major cardiovascular groups, which were analysed separately: hypertension; coronary artery disease; diseases of the pulmonary circulation; arrhythmias; heart failure; cerebrovascular diseases; diseases of arteries and veins (including for example arteriosclerosis obliterans, aortic aneurysms and dissections and thrombosis of both arteries and veins), and valvular diseases and cardiomyopathies. Within the group of arrhythmias, atrial fibrillation (AF) was studied separately.

The causes of death of the patients and controls were obtained from the Statistics Finland using a computerized record linkage. The dates and causes of death of all deceased citizens certified by a physician are included in this register since 1971. The causes of death have been coded according to the International Classification of Diseases (ICD). For mortality analysis, we used the underlying cause of death. The dates of death and emigration of the patients and the controls were obtained from the Population Registration Centre using computerized record linkage.

Firstly, the difference in the rate of hospitalizations between the patients and the controls was illustrated by Kaplan–Meier curve beginning 10 years before the thyroidectomy in the whole study population. Furthermore, Kaplan–Meier curves were estimated separately in different aetiological subgroups of patients and by age group (under 20, 20–40, 40–60 and over 60 years) using only the corresponding controls. The incidence of first hospitalization due to different CVDs preceding thyroidectomy was analysed until the date of thyroidectomy.

Secondly, the effect of thyroidectomy on the hospitalizations due to CVD was analysed by counting the new hospitalizations due to CVDs after the treatment of hyperthyroidism with follow-up starting at the date of the surgery for the patients and for the same date for the matched controls. The follow-up ended on the date of the first hospitalization due to CVD, the date of death, emigration or the common closing date (31 May, 2009), whichever occurred first (Fig. 1).

The study was undertaken in accordance with the Declaration of Helsinki. No informed consent could be obtained from the patients, because of the large number of participants. The ethics committee of the Pirkanmaa Hospital District reviewed the study protocol. The National Institute of Health and Welfare (THL) gave a permission to use data from the Hospital Discharge Registry.

Statistical analysis

We used the statistical software Stata for Windows version 8.2 (StataCorp, College Station, TX, USA) to calculate the hospitalization rates for various diseases. Cox regression analyses were

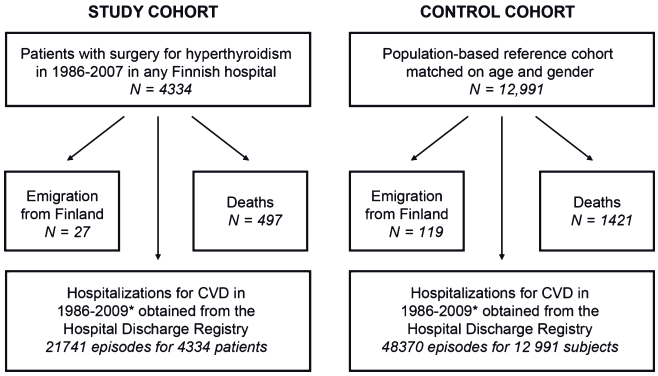

Fig. 1 Number of the patients treated with thyroidectomy for hyperthyroidism and the age- and gender-specific control group.

performed using IBM SPSS Statistics for Windows, version 19.0 (IBM Corp. Released 2010. Armonk, NY, USA). A two-sided *P*-value of less than 0·05 was considered statistically significant.

Hospitalization rates due to CVDs beginning 10 years before thyroidectomy were illustrated with Kaplan–Meier curves in the patients and the controls. Conditional logistic regression model was fitted to assess the cumulative risk of hospitalization due to different CVDs until the date of thyroidectomy. The distribution of the aetiological diagnoses between men and women or between different age groups was analysed using chi-square test.

To estimate the CVD morbidity after the thyroidectomy, two different kinds of Cox regression analyses were performed. The first analysis included all the patients and the controls and was used to estimate the hazard ratios (patients vs. controls) for CVD hospitalizations after the thyroidectomy. Previous hospitalization due to the given CVD was used as a covariate in this analysis to adjust for differences in CVD morbidity between the groups prior to the time of thyroidectomy.

Another Cox regression analysis was performed only on the patients to evaluate the effect of age, gender, the type of surgery and the aetiology of hyperthyroidism on CVD morbidity after the thyroidectomy. The covariates used were age at the time of thyroidectomy, gender, the type of surgery (total or subtotal) and the aetiology of hyperthyroidism (Graves′ disease, multinodular goitre, toxic adenoma, other). To adjust for any differences in prevalent CVD morbidity, previous CVD hospitalization (prior to the thyroidectomy) was used as a covariate, as well.

In addition to the analyses of the whole study population, we analysed the time varying component of CVD morbidity by dividing the study cohort in two subgroups, based on the year of thyroidectomy (1986–1995, coded by ICD-8 and ICD-9, or 1996–2007, coded by ICD-10).

Mortality rates were calculated by dividing the number of the deceased subjects with the corresponding person-years. The ratio of the death rates after the thyroidectomy in the patients treated surgically for hyperthyroidism and in the age- and sex-matched control group was estimated by the Mantel–Haenszel method.

Results

A total of 4334 patients were treated for hyperthyroidism with total or subtotal thyroidectomy between January 1986 and December 2007 in Finland. Eighty-six per cent (n = 3719) of the patients were women and 14% (n = 615) were men. The median age of the patients and the reference group at the time of surgery was 46 (interquartile range 33–59) years in the whole group, 48 (interquartile range 33–61) years in men and 46 (interquartile range 33·9–59) years in women. Four per cent of the patients (179 patients) were under 20 years of age at the time of the operation. Twelve per cent (n = 497) of the patients and 11% (n = 1421) of the controls deceased during the follow-up time and a total of 146 subjects emigrated from Finland (Fig. 1). There were no statistically significant differences in total mortality or emigration rates between the groups.

The risk of hospital admission due to any CVD increased among both the patients and the controls during the whole follow-up, and the difference between the two groups increased up to the time of thyroidectomy, becoming statistically significant already 5 years before the thyroidectomy (OR 1·15, 95% CI 1·04–1·28) [Figs 2 (panel a) and 3]. Until the thyroidectomy, the patients had a 50% increase in the risk of hospitalization due to any CVD, compared to the controls (OR 1·50, 95% CI 1·37–1·64) (Table 1). The most frequent subgroup of CVD associated with the increased hospitalization was hypertension. The difference in hospitalizations with hypertension between the patients and the controls increased prior to the thyroidectomy (Fig 2, Panel b), and the hospitalization rate was twice as high in the patients as among the controls by the time of the operation (OR 2·05, 95% CI 1·67–2·51) (Table 1). The second most frequent indication for hospitalization was arrhythmias, of which AF was the most common diagnosis (81% of arrhythmias). The difference in the rates of hospitalization due to AF increased towards the time of thyroidectomy (Fig 2, Panel c), the rate being almost five times higher in the patients at the time of thyroidectomy (OR 4·60, 95% CI 3·72–5·67). There were no substantial differences in the hospitalization rates due to ischaemic heart disease (including acute myocardial infarctions), diseases of other

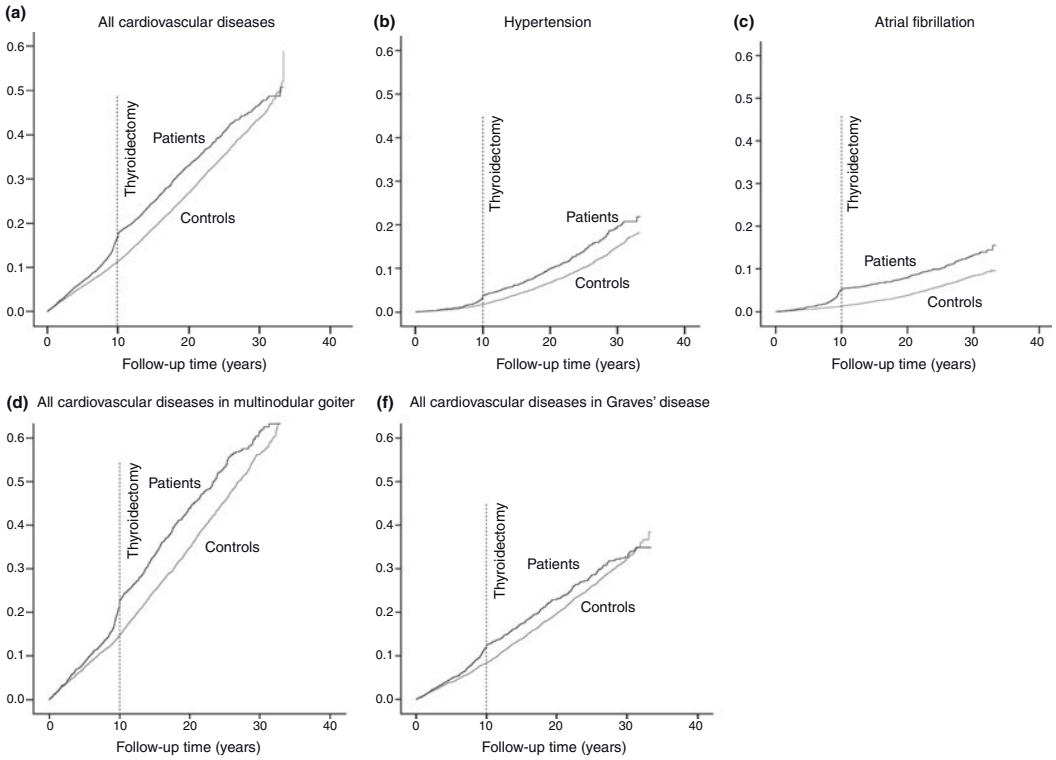

Fig. 2 Cumulative hospitalization rates due to different cardiovascular diseases (a-c) 10 years before and more than 20 years after thyroidectomy in all patients treated surgically for hyperthyroidism (a-c) and in different ethiologies of hyperthyroidism (d-e), compared with the age- and sex-matched control group.

arteries and veins, cerebrovascular diseases or diseases of pulmonary circulation between the patients and the controls before the thyroidectomy. However, the risk of hospitalization due to heart failure by the time of thyroidectomy was almost twofold (OR 1·92, 95% CI 1·22–3·00), and the risk of valvular diseases or cardiomyopathies was 57% higher (OR 1·57, 95% CI 0·98–2·51) among the patients compared to the reference group (Table 1).

After the thyroidectomy, the risk of new hospitalization due to any CVD was still significantly higher among the patients, when adjusted for hospitalization preceding thyroidectomy (HR 1·15, 95% CI 1·06–1·24). The incidence of new hospitalizations due to hypertension (HR 1·23, 95% CI 1·08–1·41), arrhythmias (HR 1·25, 95% CI 1·07–1·47), heart failure (HR 1·17, 95% CI 1·01–1·50) and valvular diseases and cardiomyopathies (HR 1·55, 95% CI 1·17–2·04) was significantly higher in the patients, when adjusted for hospitalization due to the given disease prior to the operation. Furthermore, the risk of new hospitalization due to AF tended to remain higher in the patients than in the controls, although the difference was not statistically significant (HR 1·15, 95% CI 0·96–1·39) (Table 2).

The most common cause of hyperthyroidism among the operated patients was Graves′ disease (48% of the patients). Hyperthyroidism was caused by a multinodular goitre in 33% of the patients, and 6% had a toxic adenoma. Thirteen per cent of the patients had a diagnosis of nonspecified hyperthyroidism and was classified as 'Other'. Twenty-six patients (0·6%) had subclinical hyperthyroidism, and they were analysed as a separate group. The most common aetiological diagnosis in patients under 40 years of age was Graves′ disease and in patients older than 40 years multinodular goitre ($P < 0·001$). The distribution of the aetiological diagnoses was similar between men and women.

The risk of hospitalization due to any CVD among the patients was not yet increased 10 years before the surgery, compared with the corresponding controls, but the risk began to increase several years before the thyroidectomy, regardless of the aetiology of hyperthyroidism (Fig. 2, Panels d-e). In patients with multinodular goitre, the cumulative risk up to the thyroidectomy was 56% higher compared with their controls (OR 1·56, 95% CI 1·36–1·80) and in patients with Graves′ disease 32% higher (OR 1·32, 95% 1·13–1·54).

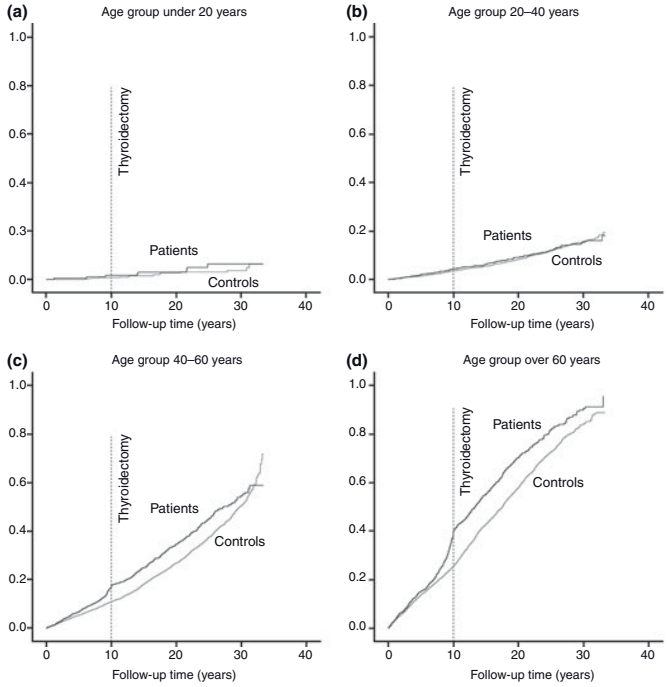

Fig. 3 Cumulative hospitalization rates due to all cardiovascular diseases 10 years before and more than 20 years after thyroidectomy in the different age groups of patients (a-d) treated surgically for hyperthyroidism, compared with the age- and sex-matched control group.

Table 1. The odds ratios for cumulative hospitalization rates prior to the thyroidectomy due to different cardiovascular diseases in patients treated with thyroidectomy for hyperthyroidism, compared with the age- and sex-matched controls

	Patients *vs* Controls	
Cardiovascular disease	Odds ratio (95% CI)	*P* value
All cardiovascular diseases	1·50 (1·37–1·64)	<0·001
Hypertension	2·05 (1·67–2·51)	<0·001
All arrhythmias	3·93 (3·20–4·81)	<0·001
Atrial fibrillation	4·60 (3·72–5·67)	<0·001
Diseases of arteries and veins	1·10 (0·95–1·28)	0·209
Coronary disease	0·80 (0·56–1·15)	0·413
Cerebrovascular diseases	1·12 (0·95–1·32)	0·227
Heart failure	1·92 (1·22–3·00)	0·005
Valvular diseases and cardiomyopathies*	1·57 (0·98–2·51)	0·060
Diseases of pulmonary arteries	1·56 (0·80–3·04)	0·211

*Nonbacterial endo-, peri- and myocardial diseases, including valvular diseases and cardiomyopathy.

However, in a Cox regression analysis on hospitalizations after the thyroidectomy including only the patients, male gender (HR 1·23, 95% CI 1·05–1·46), age at the time of surgery (HR 1·06, 95% CI 1·06–1·07/year) and hospitalization due to CVD before surgery (HR 2·19, 95% CI 1·91–2·50) predicted hospitalization due to CVD after surgery, while the surgical technique (subtotal or total thyroidectomy) or the aetiology of hyperthyroidism did not).

When the time varying component of CVD morbidity was analysed by dividing the study cohort in two subgroups by the year of thyroidectomy (1986–1995 and 1996–2007), hospitalization due to any CVD after the thyroidectomy was increased in both patient groups *vs* the respective controls. The risk of CVD hospitalization was 12% higher in the patients operated during 1986–1995 compared with their controls (RR 1·12, 95% CI 1·01–1·24), and the patients treated during 1996–2007 had a 20% higher risk than their controls (RR 1·20, 95% CI 1·04–1·40).

A total of 11·4% ($n = 497$) of the patients and 10·9% ($n = 1421$) of the controls deceased during the follow-up. Mortality from CVDs was not increased among the patients compared to the controls (RR 0·91, 95% CI 0·77–1·07). The mortality rates did not differ between the patients and the controls, when analysed separately in men and women, in different subgroups of CVDs, or in the aetiological subgroups of hyperthyroidism (data not shown).

Discussion

The present study is the first one to show that patients treated with total or subtotal thyroidectomy for hyperthyroidism have an increased risk of hospitalizations due to CVDs already before the treatment and the risk is sustained after thyroidectomy. The

Table 2. The number of hospitalizations and hazard ratios (HR) for hospitalization rates due to different cardiovascular diseases after the thyroidectomy in patients treated with thyroidectomy for hyperthyroidism, compared with the age- and sex-matched control group, and adjusted for the prevalent CVDs prior to the thyroidectomy

	Hospitalizations		Patients *vs* controls	
Cardiovascular disease	Patients	Controls	Hazard ratio	*P* value
All cardiovascular diseases	1000	2658	1·15 (1·06–1·24)	0·001
Hypertension	386	924	1·23 (1·08–1·41)	0·002
All arrhythmias	335	678	1·25 (1·07–1·47)	0·005
Atrial fibrillation	262	527	1·15 (0·96–1·39)	0·139
Diseases of arteries and veins	330	893	1·09 (0·96–1·25)	0·185
Coronary disease	304	878	1·03 (0·87–1·19)	0·727
Cerebrovascular diseases	194	521	1·19 (0·99–1·41)	0·057
Heart failure	169	432	1·17 (1·01–1·50)	0·039
Valvular diseases and cardiomyopathies*	87	170	1·55 (1·17–2·04)	0·002
Diseases of pulmonary arteries	33	126	0·78 (0·53–1·15)	0·211

*Nonbacterial endo-, peri- and myocardial diseases, including valvular diseases and cardiomyopathy.

increased risk of hospitalization due to CVD is mostly related to hypertension, AF, heart failure, and valvular diseases and cardiomyopathies. However, the risk of hospitalization due to diseases affecting coronary arteries, other arteries or veins, or pulmonary circulation is not increased. The results are in line with the previous findings regarding patients treated with RAI for hyperthyroidism, although the patients selected for surgery were younger (median age 46 years in the present study) than those treated with RAI. In our previous study on patients treated with RAI for hyperthyroidism, the median age at the time of treatment was 62 years[8] and in other similar studies on RAI-treated patients the median ages have been between 57 and 62 years.[9,10,16] Thyroid surgery is an effective treatment for hyperthyroidism with a high and predictable cure rate.[17,18] Our results indicate that hyperthyroidism increases cardiovascular morbidity even in relatively young patients. Importantly, the cardiovascular changes caused by hyperthyroidism are not totally and immediately reversed by thyroidectomy, neither a total nor a subtotal one.

Despite the increased risk of hospital admission due to CVD before thyroidectomy and the sustained risk afterwards, there was no difference in CVD mortality between the patients and their controls. A recent meta-analysis on mortality after treated hyperthyroidism, including seven studies with 31 138 patients, showed a 20% increase in all-cause mortality.[19] In these studies, the patients were treated mainly with RAI. In our study, the statistical power and the length of the follow-up may be insufficient for detecting a slightly increased mortality in the relatively young group of patients (median age at thyroidectomy 46 years), but the equal mortality may also be due to the effective treatment of hyperthyroidism with thyroidectomy. Based on a recent study from Boelaert *et al.*, an effective treatment with RAI (resulting in hypothyroidism) reduces mortality compared to an ineffective RAI treatment or treatment with thionamides.[15]

In our study, the patients with hyperthyroidism had an increased risk of hospitalization related to hypertension already years before thyroidectomy, and the risk was sustained afterwards. In hyperthyroidism, increased preload, heart rate and cardiac output may lead to hypertension and left ventricular hypertrophy.[20] Left ventricular hypertrophy was a complication of long-term hypertension and an independent risk factor for cardiovascular morbidity and mortality in the Framingham Heart Study.[21] However, hyperthyroidism reduces peripheral vascular resistance,[22] and in previous studies, the association between elevated blood pressure and hyperthyroidism has been less convincing**.** Elevated blood pressure has been more prevalent in subclinical hypothyroidism than in subclinical hyperthyroidism.[23] Hypertension is rarely the only reason for hospitalization, but it is probably associated with other cardiovascular diagnoses, which may have been the primary reason for hospitalization in our study, where both the primary and the secondary diagnoses were analysed. The present results suggest that hyperthyroidism may predispose to a permanent rise in blood pressure, with associated cardiovascular morbidity. On the other hand, elevated blood pressure may also reflect inadequate L-Thyroxine treatment after the thyroidectomy.

The hyperthyroid patients in our study had a remarkably high risk of arrhythmias, especially AF, before thyroidectomy, but the thyroidectomy seemed to slow down the rapid increase in the incidence of new arrhythmias. However, the risk of new arrhythmias remained higher after treatment of hyperthyroidism with thyroidectomy, when adjusted for the prior arrhythmias at the time of thyroidectomy. This is in line with previous studies.[24] The increased risk of hospitalization due to CVDs seen already years before the thyroidectomy might be caused by undiagnosed or ineffectively treated hyperthyroidism before the surgery. In fact, a recently published Danish study showed that the risk of AF is associated with thyroid function, with a low risk in hypothyroidism and a high risk in hyperthyroidism. There was also an association between the TSH level and the risk of AF across the spectrum of subclinical thyroid disease.[25] Hyperthyroidism shortens the atrial refractory period by altering cell membrane functions[26] and also seems to increase supraventricular ectopic activity in hyperthyroid patients without previous heart disease.[27] Both these factors are triggers for AF, and AF feeds itself by altering the electrical[28] and mechanical functions of the atria[29] and also changes the atrial structure by causing fibrosis in the heart muscle.[30,31] This remodelling of the atria prolongs arrhythmias and predisposes to relapses. Patients with hyperthyroidism are susceptible to AF and an episode of AF predisposes to recurrent AF. This combined effect of AF and hyperthyroidism on the heart muscle may explain the persisted risk of AF among the patients with treated hyperthyroidism. Based on our results, treatment of hyperthyroidism with thyroidectomy seems to decrease the incidence of AF significantly, but the risk still remains higher in the patients than in the controls.

The risk of hospitalization due to heart failure and valvular diseases or cardiomyopathies after surgically treated hyperthyroidism was increased before the thyroidectomy and remained increased after surgical treatment of hyperthyroidism. Hyperthyroidism increases cardiac preload, body fluid volume and heart rate and affects both the systolic and the diastolic function of the heart.[22] Overt hyperthyroidism may thereby worsen the symptoms of an underlying, undiagnosed heart disease, leading to an earlier hospitalization and diagnosis of the heart disease, compared to an euthyroid person with the same undiagnosed heart disease.

When analysed separately, the cumulative risk ratio of hospitalization due to CVDs seemed to be slightly higher in the patients with a toxic nodular goitre than in those with Graves' disease before the thyroidectomy (OR 1·56 *vs* 1·32). After the thyroidectomy, the different aetiological subgroups did not have an impact on the CVD hospitalization risk in a multivariate analysis. Hyperthyroidism caused by multinodular goitre develops slowly and a prolonged period of subclinical or undiagnosed and untreated hyperthyroidism may be more common in patients with a multinodular goitre than in those with Graves' disease. However, thyroidectomy seemed to reduce the incidence of CVD in both aetiological subgroups, and their long-term prognosis did not differ.

Subtotal thyroidectomy was the standard surgical treatment for hyperthyroidism in Finland until the end of the 20th century, but later on total thyroidectomy has been the preferred technique. In 1986, only three per cent of the thyroidectomies were total, but the proportion of total thyroidectomies out of all operations increased up to 80% by the end of the study period in 2007. The proportion of subtotal operations was higher in all the age groups and aetiological groups in our study. In the multivariate analysis, the type of thyroidectomy did not have an effect on the risk of hospitalization due to any CVD.

The risk of CVD hospitalization was slightly higher in the patients thyroidectomized during 1996–2007 than in those treated during 1986–1995. The diagnostic and treatment strategies of CVDs have developed remarkably during the follow-up time, and the slightly higher risk of CVD hospitalization in the patients of the latter time period is probably explained by improved diagnostic methods and more intensive treatment strategies.

The strengths of our study are the relatively long follow-up and a large cohort of patients, representing all the incident cases of hyperthyroidism treated with thyroidectomy in Finland during the follow-up period, due to the nationwide registration and the specific diagnosis and procedure codes. Furthermore, we were able to analyse the cardiovascular morbidity in the different aetiological subgroups of hyperthyroidism. However, there are some limitations to this study. The results are based on register data and dependent on the correct recording of the diagnoses. However, several assessments consistently indicate high completeness and reliability of the Finnish Hospital Discharge Register for CVDs.[32,33] Owing to the nature of our study, we were not able to adjust the results for the common risk factors of CVD, such as smoking, hypercholesterolaemia, diabetes or family history. Smoking is a common confounding factor in epidemiological studies and may also be a common risk factor underlying both hyperthyroidism and CVD.[34] Hence, its effect may result in overestimation of the CVD risk caused by hyperthyroidism.

The lack of information on the time of the beginning of hyperthyroidism based on TSH and T4 values is a major limitation of our study. The increased risk of hospitalization due to CVD seen already years before the thyroidectomy might be caused by undiagnosed or ineffectively treated hyperthyroidism before the surgery. Furthermore, in the absence of data on thyroid function tests, we could not assess the severity of hyperthyroidism. On the other hand, hyperthyroidism may be caused by iodine-containing drugs used in CVD, like amiodarone or radiological contrast media. Interestingly, a recent twin study showed that patients with hyperthyroidism may have shared genetic susceptibility to both cardiovascular morbidity and hyperthyroidism, and their cardiovascular system might be affected already before the emergence of hyperthyroidism.[35] Due to the registry-based setting of the study, we do not have information on the duration of hyperthyroidism before the thyroidectomy, on the rate of relapses of hyperthyroidism, or on the success or failure of the L-thyroxine treatment after thyroid surgery. Both under- and overtreatment of hypothyroidism could increase the risk of CVD after thyroid surgery. However, there is a strict follow-up of the thyroid function after thyroidectomy in Finland, and any relapses of hyperthyroidism are treated with RAI, medical treatment or reoperation without delay.

In conclusion, hyperthyroidism seems to have deleterious effects on the cardiovascular system even years before the diagnosis and the effects persist still after definitive treatment with surgery. Further prospective, controlled studies are warranted to resolve, whether the long-term effects of hyperthyroidism differ depending on its treatment modality.

Acknowledgements

This work was supported by grants from the Competitive Research Funding of the Pirkanmaa Hospital District. We thank Esko Väyrynen, M.A. for the revision of the language of this manuscript.

Disclosures

Nothing to declare.

References

1 Bjoro, T., Holmen, J., Kruger, O. *et al.* (2000) Prevalence of thyroid disease, thyroid dysfunction and thyroid peroxidase antibodies in a large, unselected population. The Health Study of Nord-Trondelag (HUNT). *European Journal of Endocrinology*, **143**, 639–647.

2 Cooper, D.S. (2003) Hyperthyroidism. *Lancet*, **362**, 459–468.

3 Klementschitsch, P., Shen, K.L. & Kaplan, E.L. (1979) Reemergence of thyroidectomy as treatment for Graves' disease. *Surgical Clinics of North America*, **59**, 35–44.

4 Weber, K.J., Solorzano, C.C., Lee, J.K. *et al.* (2006) Thyroidectomy remains an effective treatment option for Graves' disease. *The American Journal of Surgery*, **191**, 400–405.

5 Winsa, B., Rastad, J., Akerstrom, G. *et al.* (1995) Retrospective evaluation of subtotal and total thyroidectomy in Graves' disease with and without endocrine ophthalmopathy. *European Journal of Endocrinology*, **132**, 406–412.

6 Sosa, J.A., Bowman, H.M., Tielsch, J.M. *et al.* (1998) The importance of surgeon experience for clinical and economic outcomes from thyroidectomy. *Annals of Surgery*, **228**, 320–330.

7 Gaujoux, S., Leenhardt, L., Tresallet, C. *et al.* (2006) Extensive thyroidectomy in Graves' disease. *Journal of the American Collegues of Surgeons*, **202**, 868–873.

8 Metso, S., Auvinen, A., Salmi, J. *et al.* (2008) Increased long-term cardiovascular morbidity among patients treated with radioactive iodine for hyperthyroidism. *Clinical Endocrinology*, **68**, 450–457.

9 Franklyn, J.A., Maisonneuve, P., Sheppard, M.C. *et al.* (1998) Mortality after the treatment of hyperthyroidism with radioactive iodine. *The New England Journal of Medicine*, **338**, 712–718.

10 Franklyn, J.A., Sheppard, M.C. & Maisonneuve, P. (2005) Thyroid function and mortality in patients treated for hyperthyroidism. *The Journal of American Medical Association*, **294**, 71–80.

11 Hall, P., Lundell, G. & Holm, L.E. (1993) Mortality in patients treated for hyperthyroidism with iodine-131. *Acta Endocrinologica*, **128**, 230–234.

12 Metso, S., Jaatinen, P., Huhtala, H. *et al.* (2007) Increased cardiovascular and cancer mortality after radioiodine treatment for hyperthyroidism. *The Journal of Clinical Endocrinology and Metabolism*, **92**, 2190–2196.

13 Osman, F., Franklyn, J.A., Holder, R.L. *et al.* (2007) Cardiovascular manifestations of hyperthyroidism before and after antithyroid therapy: a matched case-control study. *Journal of the American College of Cardiology*, **49**, 71–81.

14 Boelaert, K., Maisonneuve, P., Torlinska, B. *et al.* (2013) Comparison of mortality in hyperthyroidism during periods of treatment with thionamides and after radioiodine. *The Journal of Clinical Endocrinology & Metabolism*, **98**, 1869–1882.

15 Sund, R. (2012) Quality of the Finnish Hospital Discharge Register: a systematic review. *Scandinavian Journal of Public Health*, **40**, 505–515.

16 Holm, L.E., Hall, P., Wiklund, K.l., *et al.* (1991) Cancer risk after iodine-131 therapy for hyperthyroidism. *Journal of National Cancer Institute*, **83**, 1072–1077.

17 Franklyn, J.A., Daykin, J., Drolc, Z. *et al.* (1991) Long-term follow-up of treatment of thyrotoxicosis by three different methods. *Clinical Endocrinology*, **34**, 71–76.

18 Palit, T.K., Miller, C.C. 3rd & Miltenburg, D.M. (2000) The efficacy of thyroidectomy for Graves' disease: a meta-analysis. *Journal of Surgical Research*, **90**, 161–165.

19 Brandt, F., Green, A., Hegedus, L. *et al.* (2011) A critical review and meta-analysis of the association between overt hyperthyroidism and mortality. *European Journal of Endocrinology*, **165**, 491–497.

20 Klein, I. (1988) Thyroxine-induced cardiac hypertrophy: time course of development and inhibition by propranolol. *Endocrinology*, **123**, 203–210.

21 Levy, D., Garrison, R.J., Savage, D.D. *et al.* (1990) Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *The New England Journal of Medicine*, **322**, 1561–1566.

22 Klein, I. & Ojamaa, K. (2001) Thyroid hormone and the cardiovascular system. *The New England Journal of Medicine*, **344**, 501–509.

23 Cai, Y., Ren, Y. & Shi, J. (2011) Blood pressure levels in patients with subclinical thyroid dysfunction: a meta-analysis of cross-sectional data. *Hypertension Research*, **34**, 1098–1105.

24 Flynn, R.W., Macdonald, T.M., Jung, R.T. *et al.* (2006) Mortality and vascular outcomes in patients treated for thyroid dysfunction. *The Journal of Clinical Endocrinology and Metabolism*, **91**, 2159–2164.

25 Selmer, C., Olesen, J.B., Hansen, M.L. *et al.* (2012) The spectrum of thyroid disease and risk of new onset atrial fibrillation: a large population cohort study. *British Medical Journal*, **345**, e7895.

26 Komiya, N., Isomoto, S., Nakao, K. *et al.* (2002) Electrophysiological abnormalities of the atrial muscle in patients with paroxysmal atrial fibrillation associated with hyperthyroidism. *Clinical Endocrinology*, **56**, 39–44.

27 Wustmann, K., Kucera, J.P., Zanchi, A. *et al.* (2008) Activation of electrical triggers of atrial fibrillation in hyperthyroidism. *The Journal of Clinical Endocrinology and Metabolism*, **93**, 2104–2108.

28 Wijffels, M.C., Kirchhof, C.J., Dorland, R. *et al.* (1995) Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. *Circulation*, **92**, 1954–1968.

29 Sparks, P.B., Mond, H.G., Vohra, J.K. *et al.* (1999) Mechanical remodeling of the left atrium after loss of atrioventricular synchrony. A long-term study in humans. *Circulation*, **100**, 1714–1721.

30 Burstein, B. & Nattel, S. (2008) Atrial fibrosis: mechanisms and clinical relevance in atrial fibrillation. *Journal of the American College of Cardiology*, **51**, 802–809.

31 Nattel, S., Li, D. & Yue, L. (2000) Basic mechanisms of atrial fibrillation–very new insights into very old ideas. *Annual Review of Physiology*, **62**, 51–77.

32 Heliovaara, M., Reunanen, A., Aromaa, A. *et al.* (1984) Validity of hospital discharge data in a prospective epidemiological study on stroke and myocardial infarction. *Acta Medica Scandinavica*, **216**, 309–315.

33 Rapola, J.M., Virtamo, J., Korhonen, P. *et al.* (1997) Validity of diagnoses of major coronary events in national registers of hospital diagnoses and deaths in Finland. *European Journal of Epidemiology*, **13**, 133–138.

34 Vestergaard, P. (2002) Smoking and thyroid disorders -a meta-analysis. *European Journal of Endocrinology*, **146**, 153–161.

35 Brandt, F., Almind, D., Christensen, K. *et al.* (2012) Excess mortality in hyperthyroidism: the influence of preexisting comorbidity and genetic confounding: a danish nationwide register-based cohort study of twins and singletons. *The Journal of Clinical Endocrinology and Metabolism*, **97**, 4123–4129.

THYROID
Volume 28, Number 9, 2018

DOI: 10.1089/thy.2017.0461

Cardiovascular Morbidity and Mortality After Treatment of Hyperthyroidism with Either Radioactive Iodine or Thyroidectomy

Essi Ryödi,[1,2] Saara Metso,[2,3] Heini Huhtala,[4] Matti Välimäki,[5] Anssi Auvinen,[4] and Pia Jaatinen[2,3,6]

Background: Hyperthyroid patients remain at an increased risk of cardiovascular diseases (CVDs) after restoring euthyroidism. The impact of the different treatment modalities of hyperthyroidism on future CVD risk remains unclear. The aims of this study were to assess cardiovascular morbidity and mortality in hyperthyroidism before and after treatment, and to compare the effects of two different treatment modalities: radioactive iodine (RAI) and thyroid surgery.

Methods: A comparative cohort study was conducted among 6148 hyperthyroid patients treated with either RAI or thyroidectomy and 18,432 age- and sex-matched controls. First, hospitalizations due to CVDs prior to the treatment were analyzed. Second, the hazard ratios (HR) for any new hospitalization and mortality due to CVDs after treatment were estimated among all the hyperthyroid patients compared to the age- and sex-matched controls and also in the RAI-treated patients compared to the thyroidectomy-treated patients. The results were adjusted for prevalent CVDs at the time of treatment.

Results: Before treatment for hyperthyroidism, hospitalizations due to all CVDs were more common in the hyperthyroid patients compared to the controls (odds ratio = 1.61 [confidence interval (CI) 1.49–1.73]). During the post-treatment follow-up, hospitalizations due to CVDs remained more frequent among the patients (HR = 1.15 [CI 1.09–1.21]), but there was no difference in CVD mortality (HR = 0.93 [CI 0.84–1.03]). Compared to the patients treated with thyroidectomy, the RAI-treated patients had a higher risk of hospitalization due to all CVDs (HR = 1.17), atrial fibrillation (HR = 1.28), as well as a higher CVD mortality rate (HR = 2.56). Yet, treatment with RAI resulting in hypothyroidism was not associated with increased CVD morbidity compared to thyroidectomy.

Conclusions: Hyperthyroidism increases the risk of CVD-related hospitalization, and the risk is sustained for up to two decades after treatment with RAI or surgery. Hyperthyroid patients treated with RAI remain at a higher CVD risk compared to patients treated with thyroidectomy. Hypothyroidism during follow-up, however, predicts better cardiovascular outcomes.

Keywords: hyperthyroidism, morbidity, mortality, thyroidectomy, RAI therapy

Introduction

Hyperthyroidism is associated with increased cardiovascular morbidity and mortality, which are not completely reversed by the common treatment modalities (1–5). Increased cardiovascular morbidity after treatment of hyperthyroidism with radioactive iodine (RAI) has been reported in several previous long-term follow-up studies (2,6,7). In a previous study of 4334 hyperthyroid patients treated with thyroidectomy, the risk of hospitalization due to cardiovascular diseases (CVDs) remained higher among the patients than among the controls for 20 years after thyroidectomy (1). Increased long-term cardiovascular morbidity has also been reported in patients treated with antithyroid therapy for hyperthyroidism, despite normalized thyroid hormone levels (8).

Previous studies have also shown increased cardiovascular mortality after treatment with RAI for hyperthyroidism

[1]Heart Center Co.; [2]Department of Internal Medicine; [3]Faculty of Medicine and Life Sciences; [4]Faculty of Social Sciences; Tampere University Hospital, Tampere, Finland.
[5]Division of Endocrinology, Department of Medicine, Helsinki University Central Hospital, Helsinki, Finland.
[6]Division of Internal Medicine, Seinäjoki Central Hospital, Seinäjoki, Finland.

(3–5,8) but not after thyroidectomy (1). In a recently published study comparing antithyroid medication and RAI, the mortality rates were increased during the periods of thionamide treatment for hyperthyroidism and after less intensive treatment with RAI (not resulting in hypothyroidism). However, after intensive treatment with RAI (resulting in hypothyroidism and thyroxine replacement therapy), the mortality rates did not differ between the patients and the controls (9).

Cardiovascular and cancer morbidity and mortality of patients treated with thyroidectomy and patients treated with RAI for hyperthyroidism have been reported previously (1,2,5,10). In the present work, those analyses are extended by comparing cardiovascular morbidity before and after the treatment of hyperthyroidism either with RAI or with thyroidectomy, and the impact of the treatment modalities and of the treatment outcomes (hypothyroidism or not) on cardiovascular mortality is studied after hyperthyroidism has been treated.

Methods

For this retrospective, register-based study, two groups of patients treated previously for hyperthyroidism were identified. The first group consisted of all the patients treated with thyroidectomy for hyperthyroidism in Finland in 1986–2007 ($n = 4334$). The patients were identified based on the procedure codes and International Classification of Diseases (ICD) codes from the nationwide Hospital Discharge Registry (HILMO) maintained by the National Institute for Health and Welfare, as previously reported (1). For thyroidectomized patients, the etiology of hyperthyroidism was obtained from the HILMO database. Follow-up data on thyroid status after the treatment were not available for the patients treated with thyroidectomy.

The second group consisted of the patients treated with RAI for hyperthyroidism during 1986–2007 at Tampere University Hospital ($n = 1814$). It was only possible to study the patients treated at Tampere University Hospital, where patients treated with RAI have been systematically registered since 1969. There were no register-based data available from other hospitals in Finland. Tampere University Hospital has a catchment population of 500,000 (10% of the Finnish population). The information on the etiology of hyperthyroidism, previous surgical treatment, the dates and doses of RAI treatments, and the follow-up data of thyroid function after treatment have been collected in the register since 1969. Following RAI treatment, the thyroid status of the patients has been monitored by blood samples every one to three months during the first year and subsequently every one to three years.

A control population was formed by randomly choosing three age- (±6 months) and sex-matched control subjects for each patient (treated with either RAI or thyroidectomy) from the comprehensive national Population Register Centre. The control subject had to reside in the same county as the patient and to be alive at the time the patient was treated. The total number of controls chosen was 18,432, with 12,991 controls for the patients treated with thyroidectomy and 5441 controls for the patients treated with RAI (Fig. 1).

The discharge diagnoses, as well as the dates of hospital admissions before and after the treatment, were obtained

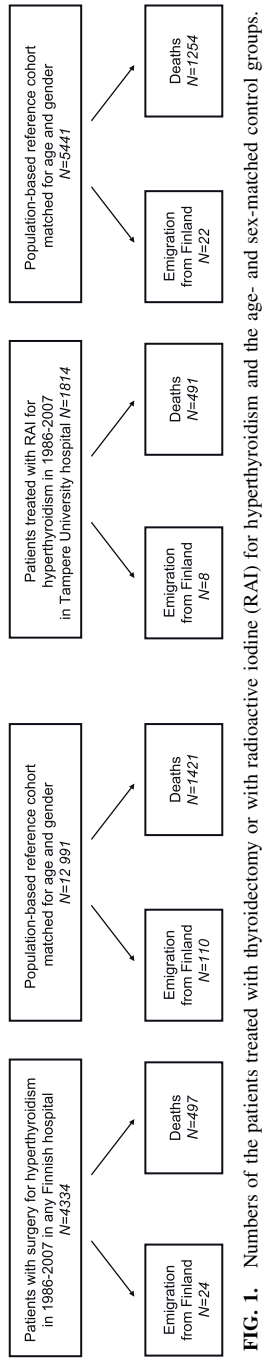

FIG. 1. Numbers of the patients treated with thyroidectomy or with radioactive iodine (RAI) for hyperthyroidism and the age- and sex-matched control groups.

from the nationwide HILMO database, with deterministic record linkage based on the unique personal identification number assigned to all the residents of Finland. The HILMO database includes hospitalizations (hospital admission requiring an overnight stay) and causes of hospitalization of the Finnish residents since January 1969 and the procedure codes since 1986. Recording diagnoses to the HILMO database is compulsory in Finland, and its completeness and accuracy has been found to vary from satisfactory to very good (11).

Both the primary and secondary diagnoses recorded at discharge from the hospital were used in the analysis. The diagnoses have been coded according to the Finnish version of the eighth revision of the ICD (ICD-8) in 1986, the ninth revision (ICD-9) up to 1995, and the 10^{th} revision (ICD-10) thereafter. A conversion between the different versions was made, and the cardiovascular diagnostic codes were classified into 10 major subgroups, which were analyzed separately: any CVD, hypertension, coronary artery disease, diseases of the pulmonary circulation, arrhythmias, heart failure, cerebrovascular diseases, diseases of other arteries and veins (including, for example, arteriosclerosis obliterans, aortic aneurysms and dissections, and thrombosis of both arteries and veins), and valvular diseases and cardiomyopathies. Of the arrhythmias, atrial fibrillation (AF) was also studied separately. The follow-up ended on the date of the first hospitalization due to each CVD, the date of death, emigration, or the common closing date (May 31, 2009), whichever occurred first.

The dates of death and emigration of the study subjects were obtained from the Population Registration Centre using computerized record linkage. The causes of death of the patients and the controls were obtained from Statistics Finland through record linkage. The dates and causes of death of all deceased citizens certified by a physician have been included in this register since 1971. The causes of death have been coded according to the ICD. For the mortality analysis, the underlying cause of death was used.

The study was undertaken in accordance with the Declaration of Helsinki. No informed consent could be obtained from the study subjects because of the large number of participants and because many of them died before data collection for the study. The ethics committee of the Pirkanmaa Hospital District reviewed the study protocol. The National Institute of Health and Welfare (THL) gave a permission to use the data from the Hospital Discharge Registry.

Statistical analysis

Stata for Windows v13 (StataCorp, College Station, TX) was used to calculate the hospitalization and mortality rates for various CVDs. Cox regression analyses were performed using IBM SPSS Statistics for Windows v23.0 (IBM Corp., Armonk, NY). A two-sided p-value of <0.05 was considered statistically significant. The differences in clinical characteristics between the patients treated with RAI and the thyroidectomized ones were estimated with a Mann–Whitney U-test or chi-square test, as appropriate. Kaplan–Meier curves were plotted to illustrate the hospitalization rates before and after the treatment of hyperthyroidism, and mortality after the treatment. Conditional logistic regression models were fitted to estimate the odds ratios (OR) of pretreatment hospitalization due to different CVDs (i.e., prevalent CVDs at the time of treatment). Cox regression analysis was used to estimate the hazard ratios (HR) and confidence intervals (CI) for CVD hospitalizations, and mortality after the treatment for hyperthyroidism, adjusted for prevalent CVDs.

Results

A total of 6148 patients treated for hyperthyroidism between January 1986 and December 2007 were included in the study. Of these, 4334 patients (5204 [85%] female) were treated surgically in the whole of Finland, and 1814 patients were treated with RAI at Tampere University Hospital. The median age of the patients at the time of treatment and of the corresponding controls was 49 years (interquartile range [IQR] 35–63 years). The median age was 50 years (IQR 35–64 years) in men and 49 years (IQR 35–64 years) in women. Sixteen percent ($n=988$) of the patients and 15% ($n=2675$) of the controls died during the follow-up, and a total of 177 subjects emigrated from Finland (Fig. 1). The median follow-up time after the treatment for hyperthyroidism was 10.6 years for the patients and 10.4 years for the controls.

The clinical characteristics of the RAI-treated and thyroidectomized patient groups are described in Table 1. The patients treated surgically were younger than the RAI-treated ones (median age at the time of the treatment 46 vs. 59 years). The sex distribution was quite similar, but the proportion of nodular disease was higher in the surgically treated patients (Table 1).

In Tampere University Hospital, 38 patients were treated first with RAI and then underwent surgery (2% of the RAI-treated patients), and 145 patients were treated surgically prior to RAI treatment (8% of the RAI-treated patients). No information on RAI treatment among the surgically treated patients was available from other Finnish hospitals. The patients treated first with RAI and then surgically were analyzed in the thyroidectomy group, and the patients treated first with thyroidectomy and then with RAI were analyzed in the RAI group.

CVD hospitalizations before the treatment of hyperthyroidism

The difference in hospitalization rates between the patients (treated with either thyroidectomy or RAI) and the controls due to any CVD started to increase several years before the treatment of hyperthyroidism (Fig. 2). The risk of CVD hospitalization was increased by the time of the treatment in most of the subgroups of CVDs in the hyperthyroid patients compared to the controls (Table 2). The subgroup of CVDs most frequently associated with hospitalization before the treatment was hypertension. The hypertension-associated hospitalizations were 75% higher in the hyperthyroid patients compared to the controls at the time of the treatment. The second most frequent subgroup of CVDs consisted of arrhythmias, of which AF was the most common one. By the time of the treatment of hyperthyroidism, the OR for hospitalization due to AF was fivefold (OR = 5.13 [CI 4.39–6.00]) in the patients compared to the controls (Table 2). When the treatment groups (RAI or thyroidectomy) were separately compared to their own age- and sex -matched controls, a similar increase was seen in both treatment groups in hospitalizations due to any CVD,

Table 1. Clinical Characteristics of the Hyperthyroid Patients Treated with Thyroidectomy or RAI

	Thyroidectomy, n = *4334*		*RAI,* n = *1814*		
	n	%	n	%	p-*Value*
Median age, years (Q_1–Q_3)	46 (33–59)		59 (44–71)		<0.001*
Sex					<0.001**
Male	615	14	329	18	
Female	3719	86	1485	82	
Etiology of hyperthyroidism					<0.001**
Graves' disease	2070	48	1022	56	
Nodular disease	1697	39	319	18	
Unspecified	567	13	473	26	
Type of surgery					
Near-total	1347	31			
Total	2943	68			
Both	44	1			

*Mann–Whitney *U*-test.
**Chi-square test.
RAI, radioactive iodine.

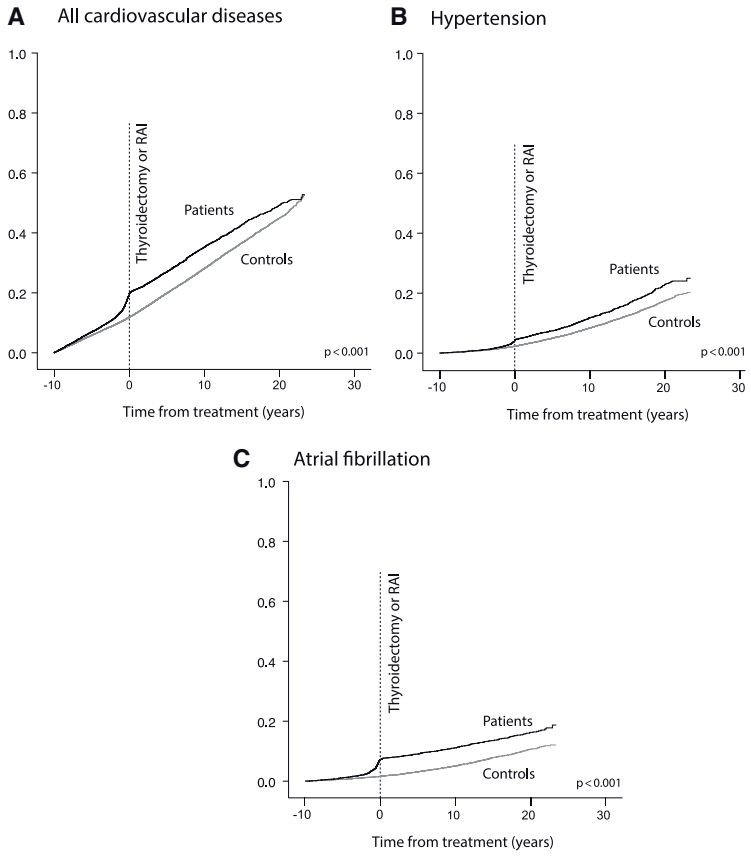

FIG. 2. **(A–C)** Cumulative hospitalization rate due to different cardiovascular diseases 10 years before and >20 years after the treatment of hyperthyroidism compared to the age- and sex-matched control group (log-rank test).

Table 2. Odds Ratios for Cumulative Hospitalization Rates Prior to Treatment due to Different CVDs in Patients Treated for Hyperthyroidism Compared to Age- and Sex-Matched Controls

	RAI-treated patients (n = *1814*) *vs. controls* (n = *5441*)		*Thyroidectomy-treated patients* (n = *4334*) *vs. controls* (n = *12,991*)		*All patients* (n = *6148*) *vs. all controls* (n = *18,432*)	
CVD	*OR [CI]*	p-*Value*	*OR [CI]*	p-*Value*	*OR [CI]*	p-*Value*
Any CVD	1.81 [1.61–2.01]	<0.001	1.50 [1.37–1.64]	<0.001	1.61 [1.49–1.73]	<0.001
Hypertension	1.50 [1.23–1.84]	<0.001	2.05 [1.67–2.51]	<0.001	1.75 [1.52–2.02]	<0.001
All arrhythmias	4.31 [3.52–5.27]	<0.001	3.93 [3.20–4.81]	<0.001	4.12 [3.57–4.75]	<0.001
Atrial fibrillation	5.86 [4.64–7.40]	<0.001	4.60 [3.72–5.67]	<0.001	5.13 [4.39–6.00]	<0.001
Diseases of arteries and veins	1.15 [0.99–1.33]	0.068	1.10 [0.95–1.28]	0.212	1.13 [1.01–1.25]	0.026
Coronary artery disease	1.67 [1.36–2.05]	<0.001	0.80 [0.56–1.15]	0.412	1.37 [1.18–1.60]	<0.001
Cerebrovascular diseases	1.60 [1.23–2.07]	<0.001	1.12 [0.95–1.32]	0.231	1.23 [1.00–1.52]	0.045
Heart failure	2.86 [2.19–3.72]	<0.001	1.92 [1.22–3.00]	0.050	2.59 [2.06–3.25]	<0.001
Valvular diseases and cardiomyopathies[a]	3.52 [2.14–5.77]	<0.001	1.57 [0.98–2.51]	0.056	2.28 [1.63–3.19]	<0.001
Diseases of pulmonary arteries	1.63 [0.85–3.14]	0.145	1.56 [0.80–3.04]	0.213	1.60 [1.00–2.55]	0.051

[a]Nonbacterial endo-, peri and myocardial diseases, including valvular diseases and cardiomyopathy.
CVD, cardiovascular disease; OR, odds ratio; CI, confidence interval.

hypertension, or arrhythmias before the treatment of hyperthyroidism. The risk of hospitalization due to most other CVDs was also increased in the RAI-treated patients, but not in the thyroidectomized patients, compared to the respective control group (Table 2).

CVD hospitalizations after the treatment of hyperthyroidism

There were a total of 1719 hospitalizations due to any new CVD among the patients after the treatment of hyperthyroidism and 4408 hospitalizations among the controls. The risk of hospitalization due to any CVD was slightly but significantly higher among the patients compared to the controls during the follow-up when adjusted for prevalent CVDs at the time of treatment (HR = 1.15 [CI 1.09–1.21]). However, the risk clearly decreased when compared to the pretreatment risk of hospitalization due to CVDs (HR = 1.61 [CI 1.49–1.79]).

The most common subgroup of CVDs leading to hospitalization after treated hyperthyroidism among all the patients was arrhythmias (680 hospitalizations in the patients and 1275 in the controls), and the next most common was hypertension (668 hospitalizations in the patients and 1590 in the controls). The risk of hospitalization due to hypertension, arrhythmias, heart failure, cerebrovascular diseases, diseases of other arteries and veins, and valvular diseases and cardiomyopathies was slightly higher in the patients when adjusted for the prevalent hospitalizations due to the same disease prior to the treatment of hyperthyroidism. However, the risk of hospitalization for AF, coronary artery disease, or the diseases of pulmonary circulation was no longer increased after treated hyperthyroidism (Table 3).

In separate analyses of the two treatment groups, the patients treated with RAI remained at an increased risk of CVD hospitalization due to any CVD, hypertension, arrhythmias, heart failure, cerebrovascular diseases, diseases of other arteries and veins, and valvular diseases and cardiomyopathies

Table 3. Hazard Ratios and *p*-Values for Hospitalization Rates due to Different CVDs After Treatment of Hyperthyroidism in Patients Compared to Age- and Sex-Matched Controls and Adjusted for Prevalent CVDs

	RAI-treated patients (n = *1814*) *vs. controls* (n = *5441*)		*Thyroidectomy-treated patients* (n = *4334*) *vs. controls* (n = *12,991*)		*All patients* (n = *6148*) *vs. all controls* (n = *18,432*)	
CVD	*HR [CI]*	p-*Value*	*HR [CI]*	p-*Value*	*HR [CI]*	p-*Value*
Any CVD	**1.23 [1.13–1.34]**	**<0.001**	**1.11 [1.03–1.19)]**	**0.006**	**1.15 [1.09–1.21]**	**<0.001**
Hypertension	**1.26 [1.09–1.44]**	**<0.001**	**1.18 [1.05–1.33]**	**0.005**	**1.21 [1.10–1.32]**	**<0.001**
All arrhythmias	**1.19 [1.03–1.37]**	**0.019**	1.14 [0.99–1.30]	0.064	**1.14 [1.04–1.26]**	**0.007**
Atrial fibrillation	1.08 [0.92–1.28]	0.350	0.98 [0.84–1.15]	0.820	1.02 [0.91–1.15]	0.700
Diseases of arteries and veins	**1.22 [1.02–1.45]**	**0.027**	1.11 [0.98–1.26]	0.100	**1.15 [1.04–1.27]**	**0.009**
Coronary artery disease	1.11 [0.97–1.28]	0.135	1.03 [0.91–1.18]	0.610	1.07 [0.97–1.17]	0.193
Cerebrovascular diseases	**1.35 [1.12–1.62]**	**0.002**	1.19 [0.99–1.41]	0.064	**1.22 [1.08–1.38]**	**0.001**
Heart failure	**1.25 [1.05–1.48]**	**0.012**	1.14 [0.97–1.34]	0.121	**1.16 [1.03–1.32]**	**0.019**
Valvular diseases and cardiomyopathies[a]	**1.69 [1.23–2.32]**	**0.001**	**1.51 [1.16–1.95]**	**0.002**	**1.57 [1.29–1.92]**	**<0.001**
Diseases of pulmonary arteries	0.96 [0.64–1.45]	0.857	0.77 [0.52–1.13]	0.176	0.85 [0.64–1.12]	0.242

Statistically significant values are shown in bold.
[a]Nonbacterial endo-, peri and myocardial diseases, including valvular diseases and cardiomyopathy.

Table 4. Hazard Ratios for Hospitalizations due to Different CVDs After Treatment of Hyperthyroidism with RAI Compared to Patients Treated with Thyroidectomy and Adjusted for the Age at Time of Treatment, Sex, Prevalent CVDs, and Etiology of Hyperthyroidism

	RAI (n = 1814) vs. thyroidectomy (n = 4334)		*RAI resulting in hypothyroidism (n = 855) vs. thyroidectomy (n = 4334)*		*RAI not resulting in hypothyroidism (n = 959) vs. thyroidectomy (n = 4334)*	
CVD	*HR*	p-*Value*	*HR*	p-*Value*	*HR*	p-*Value*
All CVDs	**1.17 [1.05–1.30]**	**0.005**	0.95 [0.81–1.11]	0.534	**1.28 [1.13–1.43]**	**<0.001**
Hypertension	1.02 [0.86–1.21]	0.802	1.00 [0.78–1.27]	0.968	1.08 [0.89–1.30]	0.436
All arrhythmias	**1.32 [1.12–1.57]**	**0.001**	1.12 [0.86–1.46]	0.389	**1.35 [1.13–1.62]**	**<0.001**
Atrial fibrillation	**1.40 [1.16–1.68]**	**<0.001**	1.23 [0.90–1.66]	0.191	**1.44 [1.18–1.75]**	**<0.001**
Diseases of arteries and veins	0.94 [0.76–1.16]	0.561	1.02 [0.78–1.33]	0.882	0.84 [0.65–1.08]	0.178
Coronary artery disease	0.99 [0.83–1.19]	0.935	**0.70 [0.52–0.94]**	**0.019**	1.13 [0.93–1.37]	0.227
Cerebrovascular diseases	1.05 [0.83–1.32]	0.718	0.74 [0.51–1.07]	0.112	1.20 [0.93–1.54]	0.161
Heart failure	1.14 [0.89–1.44]	0.299	0.78 [0.53–1.15]	0.201	**1.30 [1.01–1.68]**	**0.039**
Valvular diseases and cardiomyopathies	1.15 [0.79–1.67]	0.466	0.80 [0.45–1.45]	0.467	1.25 [0.84–1.85]	0.272
Diseases of pulmonary arteries	1.67 [0.95–2.94]	0.074	**2.34 [1.16–4.71]**	**0.017**	1.03 [0.53–1.99]	0.941

Statistically significant values are shown in bold.

compared to their age- and sex-matched controls. The thyroidectomized patients had an increased risk of CVD hospitalization due to any CVD, hypertension, and valvular diseases and cardiomyopathies, but not due to any other subgroup of CVDs (Table 3).

Comparison of CVD hospitalizations between the RAI-treated and the thyroidectomized group

The risk of hospital admission due to CVDs after the treatment of hyperthyroidism was somewhat higher among the RAI-treated patients compared to the patients treated with thyroidectomy when adjusted for age, sex, and prevalent CVDs (HR = 1.14 [CI 1.03–1.26]; Table 4). Additional adjustment for the etiology of hyperthyroidism did not change the result (HR = 1.17 [CI 1.05–1.30]; Table 4). The risk of hospitalization due to arrhythmias (HR = 1.21 [CI 1.03–1.42]) and new-onset AF (HR = 1.29 [CI 1.08–1.54]) was also increased in the RAI-treated patients compared to the surgically treated ones, but there were no significant differences in the other CVD subgroups (Table 4).

To test whether the differences in CVD hospitalizations could be due to the geographical differences between the RAI-treated and the thyroidectomized group, the same analyses were performed in the control groups. There was no difference in the risk of hospital admission due to CVDs when the controls of the RAI-treated patients were compared to the controls of the thyroidectomized patients when adjusted for age, sex, and prevalent CVDs (HR = 0.97 [CI 0.91–1.03]), excluding any significant effect of the geographical difference on the results.

Forty-seven percent ($n = 855$) of the RAI-treated patients started levothyroxine replacement therapy during the follow-up, indicating that RAI treatment had resulted in hypothyroidism. The rest of the patients ($n = 959$) either had a relapse of hyperthyroidism or became euthyroid without thyroid hormone replacement therapy. In a subgroup analysis including only the patients with RAI-induced hypothyroidism and all the surgically treated patients, there was no difference in the risk of CVD hospitalizations between the treatment groups (relative risk [RR] = 0.95 [CI 0.82–1.09]; Table 4). The result did not change in an analysis including only the patients treated with total (RR = 0.98 [CI 0.79–1.21]) or near-total (HR = 0.96 [CI 0.81–1.13]) thyroidectomy. The patients treated first with near-total and then with total thyroidectomy ($n = 44$ patients; 1% of all thyroidectomized patients) were not included in these analyses.

CVD mortality

Despite the increased CVD morbidity, there was no difference in the overall CVD mortality between all the hyperthyroid patients and the age- and sex-matched controls (HR = 1.06 [CI 0.96–1.18]; Fig. 3A; $p = 0.284$). The result remained similar when adjusted for the prevalent CVDs (HR = 0.93 [CI 0.84–1.03]) at the time of treatment, and in subgroup analyses by age and etiology (data not shown). In the analyses of different treatment groups compared to their controls, the patients treated with RAI had a higher CVD mortality rate compared to their respective controls (Fig. 3B; $p = 0.004$). However, CVD mortality among the patients treated with thyroidectomy (Fig. 3C; $p = 0.228$) and the patients treated with RAI to hypothyroidism (Fig. 3D; $p = 0.053$) was comparable to their control groups.

In a Cox regression analysis, cardiovascular mortality was significantly higher in the patients treated with RAI compared to the patients treated with thyroidectomy when adjusted for age, sex, and prevalent CVD (HR = 2.05 [CI 1.69–2.48]). The result was unaffected by adjustment for the etiology of hyperthyroidism (HR = 2.56 [CI 2.08–3.15]) or by including only the patients treated with near-total (HR = 2.05 [CI 1.67–2.52]) or total thyroidectomy (HR = 3.17 [CI 2.16–4.65]).

There was no difference, however, in the mortality rate between the patients treated effectively with RAI (resulting in levothyroxine-treated hypothyroidism) and those treated with total thyroidectomy (HR = 0.58 [CI 0.34–1.00]). In this analysis, there was no statistically significant difference in

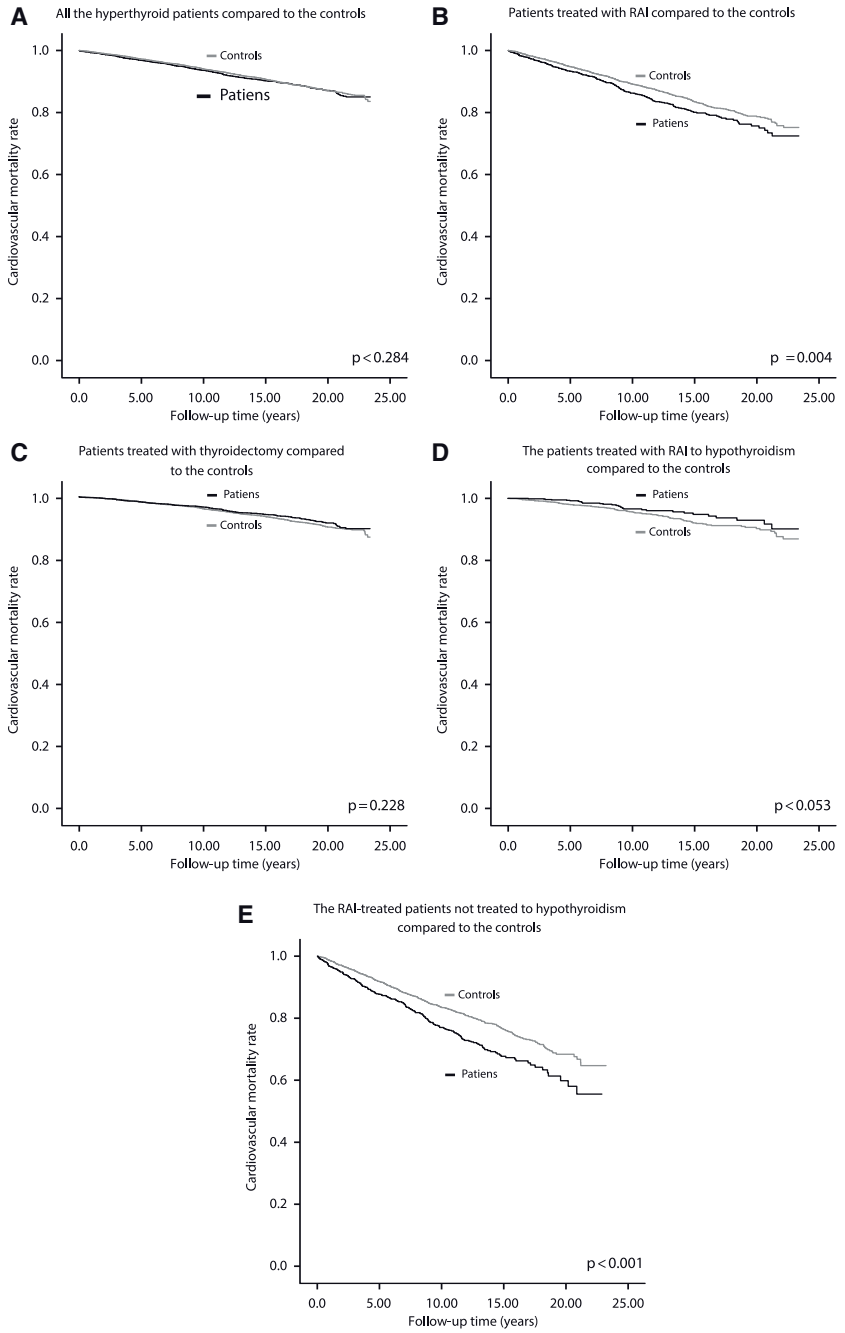

FIG. 3. **(A–E)** Cumulative cardiovascular mortality rate by time since the treatment of hyperthyroidism in the different groups of patients compared to the age and sex-matched control group (log-rank test).

the subgroup of patients with nodular disease compared to the patients with Graves' disease (HR = 1.48 [CI 0.75–2.92]).

In an additional analysis including only the patients with Graves' disease treated effectively with RAI (resulting in levothyroxine-treated hypothyroidism) and the Graves' disease patients treated surgically, the risk of death due to any CVD was significantly lower in the RAI-treated patients when adjusted for age, sex, and prevalent CVDs (RR = 0.43 [CI 0.23–0.78]). However, by including only the Graves' disease patients treated with total thyroidectomy (resulting in levothyroxine-treated hypothyroidism), there was no difference in mortality rate compared to the Graves' disease patients treated with RAI (HR = 1.37 [CI 0.51–3.70]).

To test for the geographical differences between the two groups of patients, the risk of CVD mortality of the controls of the RAI-treated patients was compared to the CVD mortality of the controls of the thyroidectomized patients and adjusted for age, sex, and prevalent CVDs. There was no significant difference in this analysis (HR = 0.98 [CI 0.89–1.12]), excluding any significant effect of the geographical difference on the results.

Discussion

There are a few previous studies on long-term CVD morbidity and mortality in hyperthyroid patients treated with RAI, but only two of them included patients treated with thyroidectomy for hyperthyroidism (12,13). In the present study study, cardiovascular morbidity already increased several years before the treatment of hyperthyroidism in both groups of patients. The risk was attenuated by both treatment modalities, but the increased CVD morbidity still lasted for two decades after the treatment of hyperthyroidism. The main finding in this study is that of increased CVD morbidity and mortality in the RAI-treated patients compared to those treated with thyroidectomy. Cardiovascular morbidity or mortality did not differ between the treatment modalities if the treatment with RAI resulted in (levothyroxine-treated) hypothyroidism.

After the treatment of hyperthyroidism, the RAI-treated patients had a significantly higher risk of CVD hospitalization and mortality compared to the surgically treated patients. The patients treated with thyroidectomy were younger than those receiving RAI, but the results were adjusted for age and other clinical differences between the groups. Thyroid surgery is an effective treatment modality for hyperthyroidism, offering a predictable, high cure rate (13,14). The onset of euthyroidism is immediate after surgery, and levothyroxine therapy is started without delay if needed. After RAI treatment, thyroid function usually returns to normal within two to six months, and hypothyroidism develops within 4–12 months or even later (15). Thus, the RAI-treated patients may be either hypo- or hyperthyroid for longer time periods, allowing the stress in the cardiovascular system to last longer, compared to the thyroidectomized patients. This might explain the better prognosis of the patients treated surgically for hyperthyroidism. This explanation is supported by the better prognosis of the patients treated effectively with RAI (resulting in levothyroxine-treated hypothyroidism) compared to the patients treated surgically in this study.

Both treatment modalities are widely used, but the patients treated surgically for hyperthyroidism differ from the patients treated with RAI in several aspects. The underlying thyroid disease, patient preferences, as well as the age and the operative risks of the patient are taken into account when choosing the treatment modality. In Finland, most hyperthyroid patients have been treated with RAI over the past few decades. Thyroidectomy may have been chosen if the patient had a large goiter with compressive symptoms, a suspicion of malignancy, severe eye symptoms of Graves' disease, or hyperthyroidism resistant to antithyroid medication during pregnancy. Due to different patient selection for the different treatment modalities, the treatment groups are not totally comparable in a nonrandomized, register-based study, and there is a possibility for confounding by indication. In this study, however, the results were adjusted for the main clinical variables, including age, sex, prior CVDs, and the etiology of hyperthyroidism.

In hyperthyroidism, cardiac output increases substantially as a result of increased heart rate and contractility, together with decreased peripheral resistance and increased venous return and preload (16). Most changes in the cardiovascular system during hyperthyroidism are adaptive responses to increased energy metabolism and heat production in the body. Nevertheless, as a result of this adaptation, the cardiovascular system is strained already in resting conditions, leading to exercise intolerance, even in otherwise healthy persons (17). AF, tachycardia, elevated blood pressure, increased blood volume, and increased oxygen demands of the heart predispose to heart failure and to worsening of the symptoms of a coexisting heart disease (16,18,19). Based on this and previous studies on hyperthyroid patients (1,2,4,7,8), changes in the cardiovascular system during the hyperthyroid phase result in increased CVD morbidity and also mortality, even after restoring euthyroidism, although the mechanisms of the persistent risk remain unclear. In the present study, CVD morbidity was already increased years before the treatment. Similar results have been reported in a Danish study on hyperthyroid patients (20), which emphasizes the importance of a timely diagnosis of hyperthyroidism, especially among patients with cardiovascular symptoms, to prevent permanent impairment. Likewise, these patients should be considered at high risk for future CVDs, despite the treatment of hyperthyroidism. An active follow-up for other risk factors and for new cardiovascular symptoms of previously hyperthyroid patients are warranted.

The risk of new-onset AF remained higher in patients treated with RAI compared to patients treated with thyroidectomy. There was, however, no difference in the risk of new-onset AF between the patients treated with RAI to permanent hypothyroidism and those who underwent thyroidectomy. The risk of AF is increased in hyperthyroidism, and the prevalence also increases with age (21). After thyroidectomy, eu- or hypothyroidism is achieved faster than after RAI treatment, leading to a shorter exposure to the pro-arrhythmic effects of hyperthyroidism. A Danish study showed that the risk of AF is associated with thyroid function across the spectrum of subclinical and clinical thyroid diseases, the incidence of AF increasing with a decreasing thyrotropin (TSH) level (22). The risk of recurrent clinical or subclinical hyperthyroidism is lower after thyroidectomy than after RAI treatment, probably explaining the lower risk of new-onset AF among patients treated with thyroidectomy.

CVD mortality was similar between the hyperthyroid patients and their age- and sex-matched controls. This contradicts previous studies reporting increased CVD mortality in hyperthyroid patients (3–5,8). The previous studies, however, were conducted mainly on patients treated with RAI. The majority of the patients in this study were treated with thyroidectomy, which may have affected the result. In a previous study on patients treated with thyroidectomy, there was no significant difference in CVD mortality between the patients and their age- and sex-matched controls (1). In the present study, CVD mortality was twice as high in RAI-treated patients compared to the patients treated with thyroidectomy, adjusted for the clinical features (age, sex, the etiology of hyperthyroidism, and prevalent CVDs prior to treatment). The excess risk was eliminated by effective treatment with RAI, resulting in hypothyroidism. The increased CVD mortality among the RAI-treated patients may thus reflect an ineffective or too slow restoration of the normal cardiovascular function after treatment with RAI in many hyperthyroid patients. Nevertheless, levothyroxine-treated hypothyroidism after treatment with RAI seemed to protect against the risk of CVD death. Similarly, decreased cardiovascular morbidity associated with the development of hypothyroidism in RAI-treated patients has been reported previously (5,7,9). This indicates that effective treatment of hyperthyroidism has a major impact on the cardiovascular prognosis of patients. In a large Danish register-based study of TSH measurements in 239,678 individuals, a 9% excess overall mortality was detected for each six-month period with low TSH levels. An excess mortality was also associated with elevated TSH measurements, highlighting the importance of euthyroidism for prognosis (23). Likewise, a recent study based on the same Danish register data reported an increased risk of mortality in both treated and untreated hyperthyroidism. There was an association between cumulative periods of low TSH and mortality. As the authors state, the excess mortality associated with hyperthyroidism may not be due to a lack of therapy, but rather to an inability to keep the patients euthyroid (24). Giesecke *et al*. (12) presented a similar interpretation of the effect of hyperthyroidism *per se* and not the treatment modality on CVD morbidity and mortality in a recently published study of 12,239 hyperthyroid patients. They found a 12% increase in CVD morbidity, but also a 27% increase in CVD mortality in hyperthyroid patients treated with either RAI or thyroidectomy compared to patients treated with thyroidectomy for nontoxic goiter.

The strengths of this study are the complete and relatively long follow-up and a large patient cohort. There are, however, some limitations to this study. The results are based on register data. Because of the nature of the study, it was not possible to adjust the results for the common risk factors of CVDs, including smoking, family history, diabetes, or medication. Smoking is a common confounding factor, and it is also a shared risk factor for CVD and hyperthyroidism, mainly Graves' disease (25,26). This may have resulted in overestimation of the risk of CVDs in the patients with hyperthyroidism compared to the age- and sex-matched controls, but is unlikely to have confounded the comparisons between the two treatment modalities because the results were adjusted for the etiology of hyperthyroidism. Information on the results of any laboratory tests after thyroidectomy or RAI was not available. Therefore, it was not possible to identify relapses of hyperthyroidism after thyroid surgery. Information on the treatment response of the levothyroxine treatment after thyroid surgery was also lacking. Both under- and overtreatment of hypothyroidism could increase the risk of CVDs. Finally, the thyroidectomy group consisted of patients treated in the whole of Finland, but the RAI group included only patients treated at Tampere University Hospital. The geographical difference is, however, unlikely to have affected the results due to broad adherence to the national guidelines on the treatment of hyperthyroidism and CVDs in Finland. In line with this view, there was no difference in the risk of CVD hospitalization or CVD mortality between the controls from the Tampere University Hospital catchment area and those from the whole of Finland. Furthermore, virtually all the patients are treated with antithyroid medication before the definitive treatment for hyperthyroidism, regardless of the treatment modality chosen.

In conclusion, hyperthyroidism increases cardiovascular morbidity compared to age- and sex-matched controls. The risk can be decreased by effective treatment of hyperthyroidism. The results underline the importance of an immediate and efficient management of hyperthyroidism and an active follow-up for cardiovascular risks after the treatment for hyperthyroidism.

Acknowledgments

This work was supported by grants from the Competitive Research Funding of the Pirkanmaa Hospital District and Heart Center Co., Tampere University Hospital. We thank Jorma Salmi, MD, and Rauni Saaristo, MD, for the support and enthusiasm, and Esko Väyrynen, MA, for the revision of the language of this manuscript.

Author Disclosure Statement

The authors have nothing to disclose.

References

1. Ryodi E, Salmi J, Jaatinen P, Huhtala H, Saaristo R, Valimaki M, Auvinen A, Metso S 2014 Cardiovascular morbidity and mortality in surgically treated hyperthyroidism—a nationwide cohort study with a long-term follow-up. Clin Endocrinol **80:**743–750.
2. Metso S, Auvinen A, Salmi J, Huhtala H, Jaatinen P 2008 Increased long-term cardiovascular morbidity among patients treated with radioactive iodine for hyperthyroidism. Clin Endocrinol **68:**450–457.
3. Franklyn JA, Sheppard MC, Maisonneuve P 2005 Thyroid function and mortality in patients treated for hyperthyroidism. JAMA **294:**71–80.
4. Hall P, Lundell G, Holm LE 1993 Mortality in patients treated for hyperthyroidism with iodine-131. Acta Endocrinol (Copenh) **128:**230–234.
5. Metso S, Jaatinen P, Huhtala H, Auvinen A, Oksala H, Salmi J 2007 Increased cardiovascular and cancer mortality after radioiodine treatment for hyperthyroidism. J Clin Endocrinol Metab **92:**2190–2196.
6. Nyirenda MJ, Clark DN, Finlayson AR, Read J, Elders A, Bain M, Fox KA, Toft AD 2005 Thyroid disease and increased cardiovascular risk. Thyroid **15:**718–724.
7. Flynn RW, Macdonald TM, Jung RT, Morris AD, Leese GP 2006 Mortality and vascular outcomes in patients

treated for thyroid dysfunction. J Clin Endocrinol Metab **91:**2159–2164.
8. Franklyn JA, Maisonneuve P, Sheppard MC, Betteridge J, Boyle P 1998 Mortality after the treatment of hyperthyroidism with radioactive iodine. New Engl J Med **338:**712–718.
9. Boelaert K, Maisonneuve P, Torlinska B, Franklyn JA 2013 Comparison of mortality in hyperthyroidism during periods of treatment with thionamides and after radioiodine. J Clin Endocrinol Metab **98:**1869–1882.
10. Ryodi E, Metso S, Jaatinen P, Huhtala H, Saaristo R, Valimaki M, Auvinen A 2015 Cancer incidence and mortality in patients treated either with RAI or thyroidectomy for hyperthyroidism. J Clin Endocrinol Metab **100:**3710–3717.
11. Sund R 2012 Quality of the Finnish Hospital Discharge Register: a systematic review. Scand J Public Health **40:** 505–515.
12. Giesecke P, Rosenqvist M, Frykman V, Friberg L, Wallin G, Hoijer J, Lonn S, Torring O 2017 Increased cardiovascular mortality and morbidity in patients treated for toxic nodular goiter compared to Graves' disease and nontoxic goiter. Thyroid **27:**878–885.
13. Franklyn JA, Daykin J, Drolc Z, Farmer M, Sheppard MC 1991 Long-term follow-up of treatment of thyrotoxicosis by three different methods. Clin Endocrinol **34:**71–76.
14. Palit TK, Miller CC 3rd, Miltenburg DM 2000 The efficacy of thyroidectomy for Graves' disease: a meta-analysis. J Surg Res **90:**161–165.
15. Cooper DS 2003 Hyperthyroidism. Lancet **362:**459–468.
16. Klein I 2012 Endocrine disorders and cardiovascular disease. In: Bonow RO, Mann DL, Zipes DP, Libby P (eds) Braunwald's Heart Disease. Ninth edition, volume 2. Elsevier (Saunders), Philadelphia, PA, pp 1833–1841.
17. Klein I, Ojamaa K 1998 Thyrotoxicosis and the heart. Endocrinol Metab Clin North Am **27:**51–62.
18. Klein I, Ojamaa K 2001 Thyroid hormone and the cardiovascular system. New Engl J Med **344:**501–509.
19. Klein I, Danzi S 2007 Thyroid disease and the heart. Circulation **116:**1725–1735.
20. Brandt F, Thvilum M, Almind D, Christensen K, Green A, Hegedus L, Brix TH 2013 Morbidity before and after the diagnosis of hyperthyroidism: a nationwide register-based study. PLoS One **8:**e66711.
21. Grais IM, Sowers JR 2014 Thyroid and the heart. Am J Med **127:**691–698.
22. Selmer C, Olesen JB, Hansen ML, Lindhardsen J, Olsen AM, Madsen JC, Faber J, Hansen PR, Pedersen OD, Torp-Pedersen C, Gislason GH 2012 The spectrum of thyroid disease and risk of new onset atrial fibrillation: a large population cohort study. BMJ **345:**e7895.
23. Laulund AS, Nybo M, Brix TH, Abrahamsen B, Jorgensen HL, Hegedus L 2014 Duration of thyroid dysfunction correlates with all-cause mortality. The OPENTHYRO Register Cohort. PLoS One **9:**e110437.
24. Lillevang-Johansen M, Abrahamsen B, Jorgensen HL, Brix TH, Hegedus L 2017 Excess mortality in treated and untreated hyperthyroidism is related to cumulative periods of low serum TSH. J Clin Endocrinol Metab **102:**2301–2309.
25. Brent GA 2010 Environmental exposures and autoimmune thyroid disease. Thyroid **20:**755–761.
26. Vestergaard P 2002 Smoking and thyroid disorders–a meta-analysis. Eur J Endocrinol **146:**153–161.

Address correspondence to:
Essi Ryödi, MD
Heart Center Co., Tampere University Hospital
P.O. Box 2000
FIN-33521 Tampere
Finland

E-mail: essi.ryodi@sydansairaala.fi