Department of Clinical Sciences, Danderyd Hospital
Division of Cardiovascular Medicine
Karolinska Institutet, Stockholm, Sweden

HYPERTHYROIDISM AND ITS IMPACT ON CARDIOVASCULAR DISEASE - WITH SPECIAL EMPHASIS ON ATRIAL FIBRILLATION

Peter Giesecke, M.D.

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HYPERTHYROIDISM AND ITS IMPACT ON CARDIOVASCULAR DISEASE - with special emphasis on atrial fibrillation

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Peter Giesecke

Principal Supervisor:
Professor Mårten Rosenqvist
Karolinska Institutet
Department of Clinical Sciences, Danderyd Hospital
Division of Cardiovascular Medicine

Co-supervisors:
Dr Viveka Frykman, Ph.D.
Karolinska Institutet
Department of Clinical Sciences, Danderyd Hospital
Division of Cardiovascular Medicine

Associate Professor Ove Törring
Karolinska Institutet
Department of Clinical Science and Education, Södersjukhuset
Division of Internal Medicine

Opponent:
Professor Isabelle van Gelder
University of Groningen
Department of Cardiology,
University Medical Center Groningen,
The Netherlands

Examination Board:
Associate Professor Jonas Schwieler
Karolinska Institutet
Department of Cardiology, Karolinska University Hospital

Associate Professor Stefan Sjöberg
Karolinska Institutet
Department of Medicine, Halland County Hospital

Associate Professor Marie Eriksson
Umeå University
Department of Statistics
Umeå School of Business and Economics

“All models are wrong. Some are useful.”

George Box

“Il faut imaginer Sisyphe heureux.”

Albert Camus

To Jasna, Adrian, Sasha and Alma

ABSTRACT

Background

Hyperthyroidism is a common disease throughout the world, affecting 0.5%-2% of women and one-tenth as many men at some time. Graves' disease and toxic nodular goitre are the two most common etiologies. Cardiovascular symptoms are often prominent, and atrial fibrillation (AF) is a well-known complication.

Several large register studies have indicated that patients treated for hyperthyroidism may be at increased risk of death compared to the general population; it appears that this difference in mortality is chiefly attributable to cardiovascular and endocrine diseases. However, these previous studies are quite heterogenous with sometimes contradictory results.

Subclinical hyperthyroidism (SH) is a condition afflicting approximately 1% of the population, defined as serum levels of thyroid-stimulating hormone (TSH) below the normal range while levels of triiodothyroxine (T3) and thyroxine (T4) are within the reference range. Symptoms are similar to, but milder than those seen in regular hyperthyroidism. AF, in particular, appears to occur more often when SH is present.

Aims

The aim of this thesis is to further investigate the correlation between hyperthyroidism and cardiovascular disease. Using a very large cohort based on register data, long-term cardiovascular mortality and morbidity (Paper I) were assessed in patients treated for hyperthyroidism. Another study addressed differences in long-term effects between treatments for hyperthyroidism (Paper II). In the last article, we attempted to find out whether subclinical hyperthyroidism might be a common cause of AF (Paper III).

Methods

Papers I-II were both based on essentially the same data on individuals with thyroid disease: Information on patients who had undergone thyroidectomy (complete or partial removal of the thyroid gland) was gathered from the Swedish National Patient Register, and information on patients treated with radioactive iodine was based on a material consisting of local hospital records. Data on cardiovascular outcomes and death was collected from the Patient Register, the Causes of Death Register, and Statistics Sweden. The Swedish Prescription Register was also used for assessment of levothyroxine treatment. Study subjects had undergone either surgery or radioiodine treatment between the years 1976-2000, and the cohort was followed until 2012.

In Paper I, patients treated for nontoxic nodular goitre were used as a control group, but comparisons were also made to the general population of Stockholm. Outcomes were assessed in terms of all-cause mortality, cardiovascular mortality, and cardiovascular morbidity.

In Paper II, which included only patients with hyperthyroidism, thyroidectomy was compared to radioiodine treatment in terms of all-cause and cause-specific mortality. Three different

statistical methods were applied: Cox regression, propensity score matching, and inverse probability matching.
Paper III was a cross-sectional observational study in which thyroid status was assessed among patients who underwent electrophysiological ablation for cardiac arrhythmias. Cases of AF were compared to controls with AV-nodal re-entry tachycardia with regard to thyroid hormone levels. The hypothesis was that AF would correlate to a higher prevalence of subclinical hyperthyroidism, defined as a suppression of TSH levels and normal free T4 levels, compared to controls.

Results

In Paper I, an increased risk of all-cause mortality (hazard ratio (HR) 1.27 with a 95% confidence interval (CI) of 1.20-1.35) was found among the 12,239 patients treated for either Graves' disease or toxic nodular goitre, compared to the 3,685 patients treated for nontoxic goitre. Increased cardiovascular mortality (HR 1.29, CI 1.17-1.42) and cardiovascular morbidity (HR 1.12, CI 1.06-1.18) was also seen, with AF being by far the most common finding at early follow-up. Furthermore, all of these outcomes were significantly more common in comparisons with the general population. The risk of death and cardiovascular disease was most evident in patients treated for toxic nodular goitre while only a weak association was seen among Graves' disease patients. No decrease in risk was found among subjects included later (after 1990) compared to those included earlier.
Paper II included 10,992 subjects with hyperthyroidism; 10,250 had been treated with radioiodine and 742 with thyroidectomy. Surgically treated subjects had lower all-cause mortality as assessed by cox regression (HR 0.82, CI 0.71-0.96), propensity score matching (HR 0.80, CI 0.68-0.94), and inverse probability weighting (0.85, CI 0.72-1.00, p = 0.044) compared to subjects who received radioiodine. Significantly lower cardiovascular mortality was also found among thyroidectomised individuals in all three analyses while no clear differences were found regarding cancer mortality or other causes of death.
In Paper III, 312 patients were included. Of these, 212 had AF, and 100 had AV-nodal re-entry tachycardia. Analyses showed that subclinical hyperthyroidism was not more common among subjects with AF than among control subjects. However, it was found that levels of free T4 were significantly higher in the AF group (CI of difference 0.03-1-35, p = 0.039).

Conclusions

Hyperthyroidism is associated with an increased risk of cardiovascular disease and death. The mechanisms behind this observation remain unknown, but some factors – notably hyperthyroidism due to toxic nodular goitre and treatment with radioiodine – seem to represent a stronger association. As for the specific diagnosis of AF, we found no clear evidence to support that subclinical hyperthyroidism might be one of the predominant underlying causes, although we did make the interesting observation that levels of free T4 were significantly elevated among AF patients.

LIST OF SCIENTIFIC PAPERS

I. Giesecke P, Rosenqvist M, Frykman V, Friberg L, Wallin G, Höijer J, Lönn S, Törring O. Increased cardiovascular mortality and morbidity in patients treated for toxic nodular goiter compared to Graves' disease and nontoxic goiter. Thyroid. 2017;27(7):878-885.

II. Giesecke P, Frykman V, Wallin G, Lönn S, Discacciati A, Törring O, Rosenqvist M. All-cause and cardiovascular mortality risk after surgery *versus* radioiodine treatment for hyperthyroidism. Br J Surg. 2017 Nov 8. doi: 10.1002/bjs.10665. [Epub ahead of print]

III. Giesecke P, Allahyari A, Törring O, Tabrizi F, Englund A, Jensen-Urstad M, Frykman V, Rosenqvist M. Prospective study on the prevalence of subclinical hyperthyroidism in patients undergoing atrial fibrillation ablation. *Manuscript.*

INNEHÅLL

LIST OF ABBREVIATIONS

AVNRT	AV-Nodal Re-entry Tachycardia
AF	Atrial Fibrillation
CI	Confidence Interval
HR	Hazard Ratio
ICD	International Classification of Diseases
KS	*Karolinska Sjukhuset* (Karolinska University Hospital)
SAC	Stockholm Arrhythmia Centre
SIC	Stockholm Iodine Cohort
SMR	Standardised Mortality Ratio
TSH	Thyroid Stimulating Hormone
T3	Triiodothyronine
T4	Thyroxine

1 INTRODUCTION

1.1 A TALE OF TWO DISEASES

1.1.1 The history of cardiovascular disorders

Diseases arising from the heart and vessels have most likely afflicted humankind since prehistoric times. Coronary calcification, the substrate for angina pectoris and myocardial infarction, has been demonstrated in mummies from ancient Egypt[1]. There are, however, no known historical records to prove that these conditions were acknowledged by the physicians of that era. It was not until 1772 that William Heberden, a British medical doctor, first gave an account of the symptoms typical for ischemic heart disease[2]. By contrast the clinical signs of cerebrovascular disease may have been noted as early as the 4th century B.C. by Hippocrates, the father of medicine, who coined the term "apoplexy" to signify a sudden loss of both speech and motor function. The expression means "struck down by force" – an analogy that still remains with us today as the word "stroke"[3]. As for cardiac arrhythmias, the measurement of a patient's pulse is arguably one of the oldest known diagnostic tools. The ancient Greeks appear to have been almost obsessed by sphygmology (as the discipline was called), as were the Romans, Chinese and Indians; Ayurvedic teachings, for instance, mention some 600 different types of pulse[4]. The association between a slow pulse and fainting – both cardinal symptoms of atrioventricular block – was later described by Giovanni Batista Morgagni (in 1761), Robert Adams (1827), and William Stokes (1846), although only Adams and Stokes are credited with naming the syndrome[2].

The most common form of non-physiological tachycardia was probably described as early as 1628 by William Harvey who documented "auricular fibrillation" in animals. The term was adequate and has not changed much since; it is known today as atrial fibrillation[5]. To be fair, it is possible that Harvey's Chinese or Greek colleagues beat him to the post by a couple of millennia, at least in terms of describing atrial fibrillation symptoms; we will never know for certain. There is, however, little doubt that the first electrocardiographic recording of atrial fibrillation was made in 1909 by Sir Thomas Lewis, a British physician, who also noted that this arrhythmia was frequently found in patients with mitral stenosis[6].

1.1.2 The history of thyroid disorders

An enlarged thyroid gland is called a goitre. If allowed to progress without treatment it becomes visible as a conspicuous swelling on the front of the neck. This probably contributed to goitres being mentioned in the oldest known medical text, "Emperor Shen Nung's prescriptions", written in China around 2700 B.C. Astoundingly, the author declared seaweed to be the cure. This was actually correct; seaweeds are rich in iodine, and iodine deficiency is a very common cause of goitre[7]. The same remedy was later suggested in records from other

cultures of the ancient world. In the 10th century A.D., Abul Kasim, renowned personal physician of the Andalusian caliph, removed the thyroid gland of a living subject - the first known account of such a procedure[8]. It took the medical community centuries to come up with an alternative cure for hyperthyroidism. In 1905 the American surgeon Robert Abbé treated Graves' disease by implanting radium into a patient's goitre[9]. This paved the way for radioiodine treatment which followed a few decades later, in the mid-1940s.

1.1.3 The connection

Caleb Hillier Parry (1755-1822) was a distinguished British physician and keen observer whose early reports of a number of medical conditions spanned several medical disciplines[10]. Not only did he describe angina pectoris and mitral stenosis, but he also gave a vivid account of "exophthalmic goitre" decades before his eponymic colleagues Robert Graves and Karl Adolph von Basedow defined the disease in 1834 and 1840, respectively. Parry wrote of a 37-year-old woman with goitre whose eyes "protruded from their sockets… each systole of the heart shook the whole trunk of the body." Although his notes were made in 1786, they were published posthumously. The first account of an association between the thyroid gland and the heart must therefore be credited to Guiseppe Flajani, physician to the Pope, who in 1802 wrote about two patients with large thyroid glands, bulging eyes, and palpitations. The Italian, however, did not delve further into his discovery. He left it to Parry , Graves and von Basedow to ponder the strange triad of symptoms. They concluded that the aetiology was probably to be found in the heart and that the other findings were secondary manifestations. It took until the end of the 19th century for the medical community to realise that the thyroid gland was the site of the disease[11]. The first reports on the connection between thyrotoxicosis and specific cardiovascular diagnoses – in this case atrial fibrillation and heart failure, often in combination – were presented around 1920[12]. At almost the same time, it was recognized that thyroidectomy could improve symptoms[13]. Some doctors named these patients "thyrocardiacs"; the most prominent thyrocardiac to this date might be former U.S. President George Bush Sr., who developed atrial fibrillation as a consequence of Graves' disease.

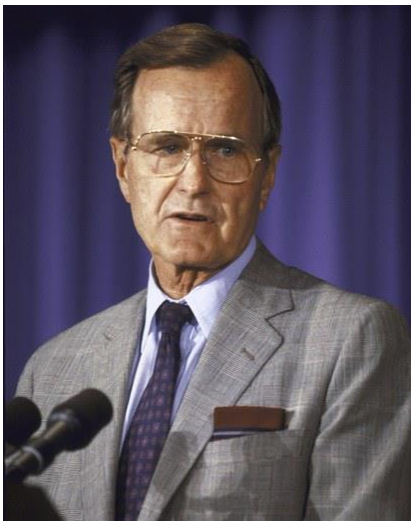

Figure 1. *George Bush, U.S. president from 1989 to 1993, was diagnosed with atrial fibrillation deemed to be caused by Graves' disease in 1991.*

1.2 CARDIOVASCULAR DISEASE

1.2.1 Overview

Cardiovascular disease is one of the leading causes of disability and death in the Western world, accounting for between 30-45% of all mortality[14,15]. Within the cardiovascular spectrum, diagnoses such as myocardial infarction, stroke, and heart failure are the main culprits. However, recent decades have seen a dramatic reduction in cardiovascular deaths. To some extent this is due to improved treatment methods. To give a few examples, the first studies on the effect of reperfusion therapy to treat acute myocardial infarction were published in the early 1980s[16]. As for heart failure, the modern era of treatment has been said to have originated around 1990 when ACE-inhibitors and beta blockers were seen to reduce both mortality and morbidity[17]. Although these breakthroughs have profoundly affected the prognosis for many patients, efforts to prevent the occurrence of disease in the first place have also played – and continue to play – a very important role. To this end, the notion of *primary prevention* has been developed. It is based on two concepts: 1) to discover factors that are associated with future development of cardiovascular disease on the general population level, and 2) to find and, when possible, modify these risk factors in the individual patient. Primary prevention does not always have to take place in a healthcare setting. Public policy measures to reduce smoking, for example, have very likely had large effects on the incidence of coronary heart disease. Within the sphere of medicine, the recognition that hypertension causes harm to the heart and vessels has led to the development of a number of blood pressure lowering medications, which in turn has led to significant reductions in both mortality and morbidity[18]. The role of oral anticoagulants to prevent stroke in AF patients, or the importance of cholesterol lowering drugs in coronary heart disease, are two further discoveries from the last decades that deserve mentioning[19]. However, it is possible that not all risk factors in the cardiovascular field are yet known.

1.2.2 Atrial fibrillation

The most common cardiac arrhythmia is atrial fibrillation, a condition associated with symptoms such as palpitations, dyspnoea and exercise intolerance. Lifetime incidence in the Western world is high, at about one in four individuals[20,21]. Risk factors that predispose for atrial fibrillation are similar to those involved in other types of cardiovascular disease such as age, hypertension, diabetes and male gender. Overt cardiovascular conditions such as valvular disease and heart failure are also strong risk factors[22]. The issues with atrial fibrillation are several, with the most obvious one – from the patients' perspective – being the symptoms caused by rapid and/or irregular pulse. These often appear unexpectedly and may be severe enough to prompt hospitalisation. Great efforts have been made to reduce symptoms related to atrial fibrillation, including a number of drugs developed in recent decades[23]. It is possible, however, that a rather new type of procedure called percutaneous ablation may emerge as the first line of treatment in patients with very pronounced

symptoms. The purpose of ablation therapy is to electrically isolate those segments of atrial tissue that most often initiate the arrhythmia, with the aim of permanently preventing new episodes[24]. Immediate symptoms aside, it has been increasingly recognised that atrial fibrillation is also associated with both increased mortality and morbidity in the longer term[25]. The risk of ischaemic stroke in particular is markedly elevated in many patients with atrial fibrillation. This is particularly true among the elderly[26]. In the late 1980s to the early 1990s, treatment with the oral anticoagulant warfarin was shown to drastically reduce this risk[27]. Over the last few years, a number of new drugs for stroke prevention have also emerged that may offer even further benefits compared to warfarin [28].

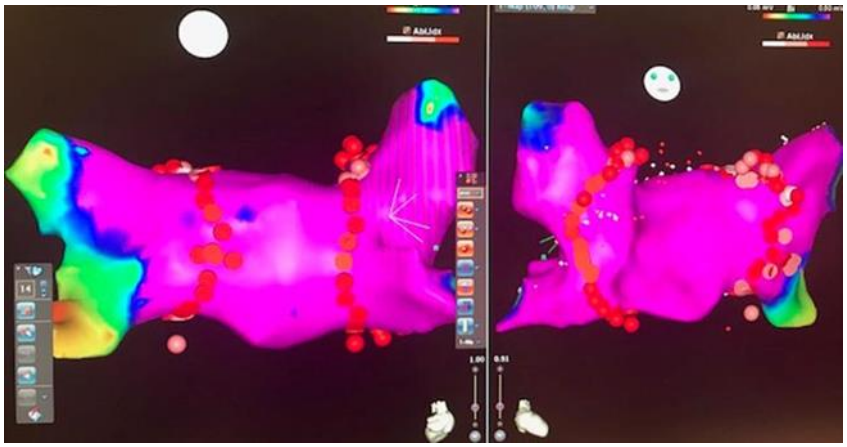

Figure 2. *Three-dimensional map of the left atrium of the heart obtained at the end of an atrial fibrillation ablation procedure.Image courtesy of Stockholm Arrhythmia Centre.*

1.3 THYROID HORMONES

1.3.1 General effects

Thyroid hormones, first isolated and described just over one century ago, affect most tissues in the human body[29]. Their main function is to regulate basal metabolic rate. The thyroid gland is regulated by the hypothalamic-pituitary axis through the influence of thyroid stimulating hormone (TSH), as part of a sensitive feedback system in which the pituitary gland adapts TSH production in response to circulating thyroid hormone levels. The major form of thyroid hormone produced is thyroxine (T4), which is converted to triiodothyronine (T3) peripherally. T3 is the biologically active form, but it has a shorter half-life than T4 and is therefore found in lesser quantities in the body[30].

1.3.2 Actions on the cardiovascular system

Thyroid hormones have several different effects on the heart through both long-term transcriptional and short-acting non-genomic mechanisms. Myosin expression, intracellular calcium cycling and beta-adrenergic receptor expression represent a few of the intranuclear effects while direct changes to membrane ion transporters stand for some of the direct effects.

Peripheral vasculature is also affected through multiple signalling pathways, including membrane ion channels and endothelial nitric oxide synthase. Furthermore, the thyroid gland influences other organ systems in ways that indirectly affect hemodynamics, such as haematopoiesis in the bone marrow and renin production in the kidney. Tissue thermogenesis is also enhanced by thyroid hormones. In hyperthyroidism, this typically results in an increased heart rate, enhanced cardiac contractile function and diastolic relaxation, reduced peripheral vascular resistance, and an increased blood volume (illustrated in figure 3). All of these mechanisms act in combination to cause an increase in resting cardiac output of as much as 300% compared to euthyroid subjects. The subject has been most comprehensively reviewed by Klein et. al. in several reports[31].

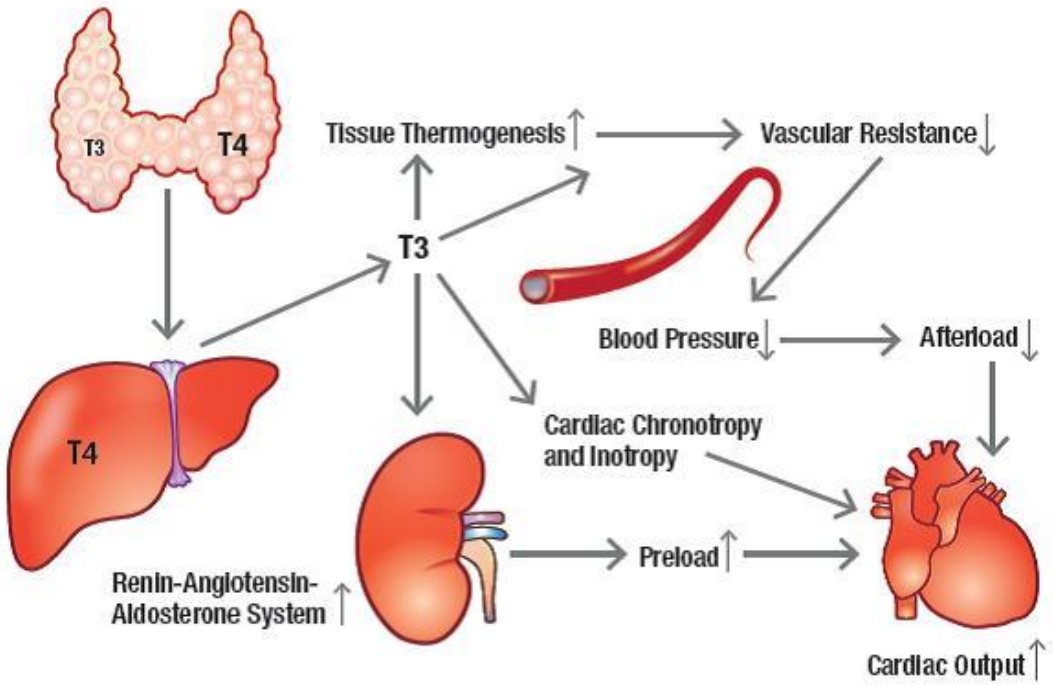

Figure 3. *Overview of the short-term effects of thyroid hormones on the cardiovascular system. The direct influence from triiodothyronine (T3) och cardiac chronotropy is the cause of palpitations experienced by many hyperthyroid patients. This, along with actions mediated through the kidneys and the vascular bed, may result in an three-fold increase of resting cardiac output.*

1.4 HYPERTHYROIDISM

1.4.1 Prevalence, causes and treatments

Most studies on the prevalence of hyperthyroidism have been conducted in developed countries. Estimates range from around 0.5%-2.0% in women, and about a tenth as much in men. Age influences these numbers, as does the level of iodine deficiency in the general population[32]. The most common causes of hyperthyroidism are Graves' disease, toxic nodular

goitre, and toxic adenoma. Graves' disease has an autoimmune aetiology, while the other two diagnoses (which share many common features and are henceforth referred to only as toxic nodular goitre) are caused by an autonomously overfunctioning thyroid gland. A recent survey from Sweden showed that the typical Graves' disease patient is between 40 and 60 years old while toxic nodular goitre has a peak incidence between 70 and 90 years of age[33].

Regardless of aetiology, hyperthyroidism can be cured through:

1) Radioiodine treatment – Iodine is one of the main substrates of thyroid hormone and by administering radioactive iodine to patients, an accumulation of radiation to the thyroid gland is achieved, thus killing most or all of the tissue.

2) Surgery, through which part (or the whole) of the thyroid gland is removed – In some cases both radioiodine and surgery are used in one and the same patient.

3) Antithyroid drugs – These act by inhibition of thyroid hormone synthesis and are not curative *per se*, but they may give time to allow a transient hyperthyroidism to heal.

Much research – including several randomised controlled trials[34-38] – has been performed to compare efficacy and short-term complications between treatments, mostly in terms of relapse into hyperthyroidism and/or progression of ophthalmopathy. A recent meta-analysis concluded that in patients with Graves' disease, radioiodine and surgery were equally effective in terms of relapse prevention, while antithyroid drugs were less effective[39].

However, only five previous studies have to our knowledge compared long-term adverse effects between different treatments for hyperthyroidism. The first one, performed in 1982, found no difference in mortality between 3,146 women treated with either radioiodine or surgery[40]. A few years later, other researchers found a slightly increased risk of cardiovascular death in 1,932 women treated with radioiodine compared to thyroidectomy or antithyroid drugs[41]. More recently two studies focused on cancer incidence and cancer mortality in both men and women with regard to treatment modality but found no differences[42,43]. In 2013, one further study compared all-cause mortality between patients treated with either radioiodine or antithyroid drugs and found no clear differences[44]. No studies have explored all-cause and

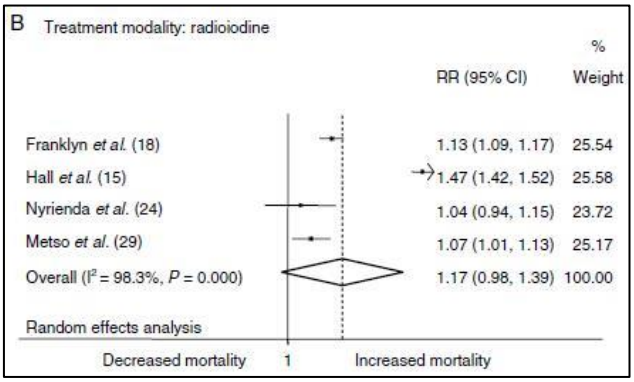

Figure 4. *Forrest plot showing the relative risk (RR) of mortality in patients diagnosed with hyperthyroidism, stratified for treatment modality.*

Brandt et al, A critical review and meta-analysis of the association between overt hyperthyroidism and mortality, European journal of endocrinology / European Federation of Endocrine Societies 2011; 165(4): 491-7. Reprinted with permission by Bioscientifica Ltd.

cause specific mortality in both men and women; the only attempt at such an assesment was made in a meta-analysis by Brandt et al. in 2011, where pooled data from four cohort studies showed 17% higher all-cause mortality in hyperthyroid patients treated with radioiodine (figure 4). However, this finding did not reach statistical significance.

1.4.2 Subclinical hyperthyroidism

As thyroid hormone assays have improved and become more accessible over time, the concept of subclinical hyperthyroidism has attracted increasing attention. Because TSH production depends on a sensitive feedback loop, even slight changes of T3/T4 levels in an individual may cause large alterations in TSH levels. When TSH is suppressed below the reference range but T3 and T4 levels are normal, subclinical hyperthyroidism is considered to be present. The treatment guidelines of the American Thyroid Association state a subclinical hyperthyroidism prevalence of around 0.7%[45]. However, other researchers have suggested somewhat higher prevalences at roughly 2%. By and large, treatment options are the same as for overt hyperthyroidism.

1.5 HYPERTHYROIDISM AS A RISK FACTOR

1.5.1 General

When the complications of hyperthyroidism are discussed, it must be remembered that this is a condition that follows a rather particular course over time. At the time of first diagnosis, the patient is in a so-called thyrotoxic state during which classic symptoms like palpitations, tremor, weight loss and nervousness may be present. After treatment the patient is generally rendered either euthyroid or hypothyroid on thyroxine substitution with few or no residual symptoms[46]. If hypothyroidism occurs, lifelong substitution with exogenous thyroxine is necessary. Most previous researchers have dealt with either ongoing or treated hyperthyroidism. These situations will, therefore, be addressed separately below.

1.5.2 Cardiovascular conditions associated with ongoing thyrotoxicosis

Arguably, the complication most commonly associated with hyperthyroidism is atrial fibrillation. Several researchers have confirmed an increased incidence of this arrhythmia in patients with thyrotoxicosis[47,48]. In the late 1970s and early 1980s, a number of studies were published that indicated an increased risk of thromboembolic events in thyrotoxicosis with AF[49-51]. There were, however, severe methodological weaknesses to these analyses with no possibility of discerning the thyroid disorder as an independent risk factor. In 1988, Petersen et. al. published results showing that when appropriate adjustments for baseline status were made, age was the only independent risk factor for stroke in thyrotoxicosis with concomitant

AF [52]. The topic has been reviewed by Traube et. al. in 2011, who stated that current evidence might warrant the use of anticoagulation in this patient group unless contraindications to such treatment exist[53]. Support for this conclusion comes from another small but well-designed study by Siu et. al. from 2009 in which an increased risk of ischemic stroke was seen in subjects with thyrotoxicosis and AF compared to patients with AF alone, after adjustment for CHADS2- factors.

The risk of heart failure has been mentioned above; the most comprehensive study to date was made by Siu et. al. (2007), who found clinical signs and symptoms of heart failure in 5.8% of hyperthyroid patients admitted to a hospital clinic. However, only about half of these had impaired left ventricular function. After treatment of hyperthyroidism, persistent systolic heart failure remained in roughly 1% of the cohort[54].

1.5.3 Long-term complications after hyperthyroidism

Several large register studies (here defined as those with more than 500 subjects included) have shown an increased risk of all-cause death in patients treated for hyperthyroidism[41,55-60]. (table 1). This observation was first made by Goldman et. al. in 1988 as part of the Thyrotoxicosis Follow-up Study in the U.S.A. The researchers' primary aims were to assess mortality from all causes and cancer incidence, but specific causes of death were also reported. Comparisons were made to the general population. Within the cardiovascular spectrum, an increased risk of death due to atherosclerotic heart disease and rheumatic heart disease was found[41].

In 1993, Hall et. al. conducted a register study in Sweden to investigate the safety of radioiodine treatment that compared cases to the general population. The researchers found an increased risk of all-cause mortality with a standardised mortality ratio (SMR) of 1.47, largely due to cardiovascular and endocrine diseases[55].

Using a cohort of radioiodine treated subjects from the UK, Franklyn et. al. (1998) published their findings of increased all-cause mortality in subjects compared to the general population (SMR 1.13). The major underlying causes appeared to be cardiovascular and endocrine diseases[61]. The same research group refined their study method in another investigation from 2005, in which it was demonstrated that this risk increase was no longer evident in patients rendered hypothyroid by treatment[56].

Two large register studies from Finland have approached this topic in a slightly different way, by using randomly selected sex- and age-matched control subjects from the general population for comparisons:

Metso et. al. (2007) showed an increased all-cause mortality in 2,793 radioiodine treated subjects (HR 1.12) due to cardiovascular and endocrine diseases[57]. In 2008 these same researchers also demonstrated excess cardiovascular morbidity in the same cohort (HR

1.12)[62]. Ryödi et. al. (2013) could find no increased risk of death in 4,334 hyperthyroid patients treated with thyroid surgery; although the risk of cardiovascular morbidity was elevated (HR 1.15)[63]

	No. of patients	Time period	Follow-up time, y	Graves vs TNG, %	RAI treated only	Reference group	Risk of all-cause death	Risk of CV death	Risk of CVD
Goldman 1988	1 762	1946-1978	17	_	no	Background population	1,3	1,4	_
Hall 1993	10 646	1950-1985	15	51/42	yes	Background population	1,47	1,65	_
Franklyn 1998	7 209	1950-1996	15	_	yes	Background population	1,13	1,2	_
Franklyn 2005	2 668	1984-2003	6	_	yes	Background population	1,14	1,19	_
Nyirenda 2005	2 230	1981-2001	_	70/18	yes	Sex- and age matched	_	_	1.42/1.5†
Flynn 2006	3 888	1994-2001	8	_	no	Background population	1.00*	0.89*	1.03*
Metso 2007	2 793	1965-2003	9	57/43	yes	Sex- and age matched	1,12	1,19	_
Metso 2008	2 611	1969-2003	9	60/40	yes	Sex- and age matched	_	_	1,12
Ryödi 2013	4 334	1986-2009	_	54/33	none	Sex- and age matched	_	0.91*	1,15
Brandt 2013	3 006	1977-2008	6	_	_	Sex- and age matched	_	_	1,34
Brandt 2013	2 152	1977-2008	11	60/40	_	Sex- and age matched	1,42/1,22†	1.49/0.94*	_
Boelaert 2013	1 063	1989-2012	12	_	no	Background population and internal comparisons	1,15	1,2	_
Selmer 2014	3 902	2000-2009	6	_	_	Internal comparisons to euthyroid patients	1,25	_	1,16
Laulund 2014	4 857	1995-2011	8	_	_	Internal comparisons to euthyroid patients	1,12	_	_
Dekkers 2017	85 856	1980-2012	9	_	no	Sex- and age matched	1,35	_	_**

Table 1. *Compilation of previous large (> 1000 patients) studies on long-term effects of hyperthyroidism where at least one of the following outcomes were assessed: All-cause mortality, cardiovascular mortality, or cardiovascular morbidity. TNG = Toxic Nodular Goitre. RAI = Radioactive Iodine. CV = Cardiovascular. CVD = Cardiovascular disease. Dash signifies that no information exists. * not statistically significant, ** only specific cardiovascular diagnoses stated, † Graves' disease / TNG*

Two other studies from the UK likewise did not demonstrate any increased mortality in previously hyperthyroid subjects. Nyirenda et. al. (2005) examined 3,346 cases while the study by Flynn et. al. from 2006 was conducted on 3,888 patients of which only the 772 that were incident cases were analysed[64,65]. Nyirenda et. al. gathered a control group from patients hospitalised for reasons other than thyroid disease while Flynn et. al. used general population data for comparisons. However, Nyirenda et. al. demonstrated an increased risk of cardiovascular morbidity after treatment for both Graves' disease (HR 1.42) and toxic nodular goitre (HR 1.50), while Flynn et. al. found an increased risk only for AF specifically (HR 2.7).

During the last few years, results from several large register studies have been reported by Danish researchers. In most of these, patients have been included not on the basis of treatment for hyperthyroidism but through collection of abnormal thyroid values gathered from laboratory databases. In 2013, Brandt et. al. found increased hazard ratios for all-cause death of 1.42 and 1.22 in patients with Graves' disease and toxic nodular goitre, respectively[58]. However, only patients from the Graves' disease group had any demonstrable increase in cardiovascular causes of death. Controls were age- and sex-matched individuals from the general population[58]. In a study from 2014, Selmer et. al. could reveal an increased all-cause mortality (HR 1.25) largely due to cardiovascular disease, using euthyroid individuals as controls[59]. Furthermore, Laulund et. al. (2014) reported increased mortality (HR 1.12) in a similar cohort, using euthyroid individuals as controls[60]. The most recent Danish study – and the largest one of its kind to date – was published by Dekkers et. al. in 2017, showing increased all-cause mortality (HR 1.35) as well as increased cardiovascular morbidity after hyperthyroidism[66].

Two large studies from Taiwan have examined a few specific cardiovascular diagnoses only; Sheu et. al. (2010) observed an increased risk for cerebrovascular morbidity while Lin et. al. (2010) reported an increased risk of pulmonary embolism[67,68].

Overall, an association between hyperthyroidism and cardiovascular disorders seems to exist. However, it is unclear whether this applies to all types of hyperthyroidism, and whether modern cardiovascular care have affected outcomes. The causal links behond the connection are also largely unknown.

Cardiovascular disease spans a range of specific diagnoses that deserve further mentioning: In thyrotoxicosis, the only cardiovascular disease that seemed to be definitely more prevalent was AF. As for treated hyperthyroidism, although only some of the above studies reported outcomes in detail, cerebrovascular disease was most frequently stated as a specific cause of death or hospitalisation (5 studies[57,61,62,66,67]) followed by arrhythmias (4 studies[62,63,65,66]), heart failure (2 studies[62,63]), and valvular disease (2 studies[57,61]). Ischaemic heart disease or pulmonary embolism were specifically mentioned in two studies respectively[61,66,68], and disorders of the pulmonary circulation in only one[61].

In a pooled meta-analysis on studies from before 2011, Brandt et. al. concluded that the risks of all-cause and cardiovascular mortality were both increased, with relative risks of 1.21 and 1.13 respectively, in patients treated for hyperthyroidism (figure 5)[69].

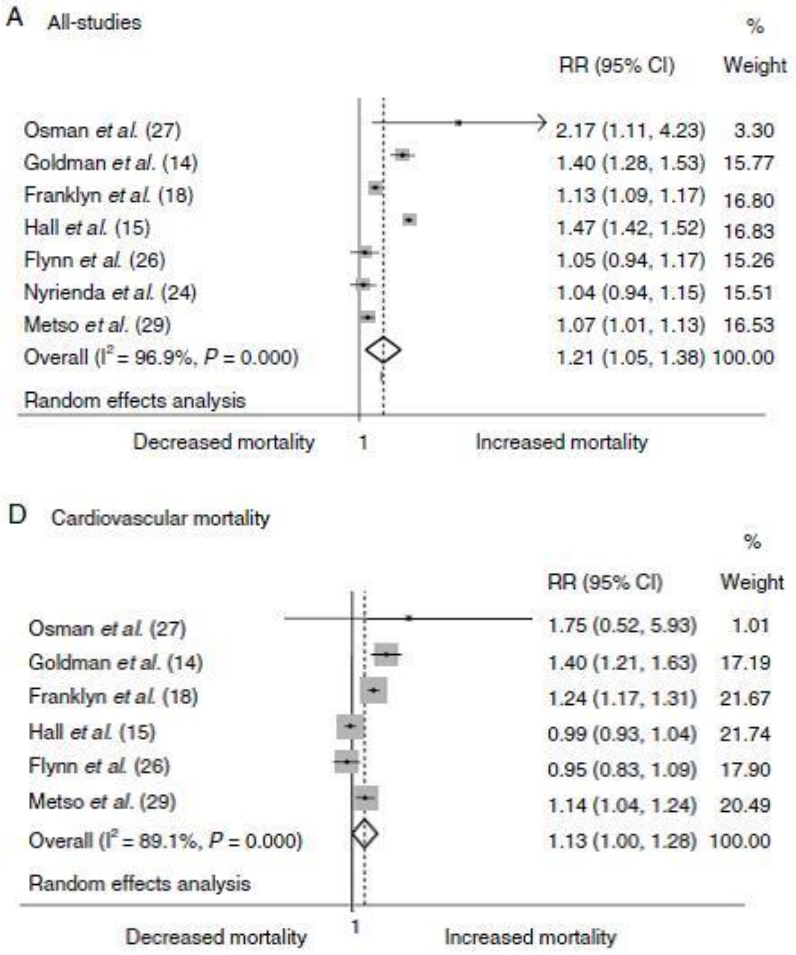

Figure 5. *Forrest plots showing the relative risk (RR) of mortality in patients diagnosed with hyperthyroidism. All studies (panel A), and mortality due to cardiovascular disease (panel D).*

Brandt et al, A critical review and meta-analysis of the association between overt hyperthyroidism and mortality, European journal of endocrinology / European Federation of Endocrine Societies 2011; 165(4): 491-7. Reprinted with permission by Bioscientifica Ltd.

1.5.4 Complications from subclinical hyperthyroidism

The association between subclinical hyperthyroidism and cardiovascular disease has attracted considerable attention in the last few decades. AF in particular has been the main point of interest. In a publication from 1979, Forfar et. al. presented data suggesting that subclinical hyperthyroidism – which was at the time defined by the response to an assay named TRH-test – might be a common cause of lone AF[70]. In a subsequent study, the same authors claimed that AF in such cases might be possible to treat with antithyroid drugs[71]. This finding was contested by Giladi et. al. in 1991 who found no increased prevalence of subclinical hyperthyroidism in a group of 25 subjects with lone AF[72] and who also pointed to methodological weaknesses in previous studies.

However, in a seminal paper from 1994 on subjects from the Framingham Cohort, Sawin et. al. demonstrated a 10-year cumulative AF incidence of 28% in persons with very suppressed TSH-levels, yielding a relative risk of 3.1 compared to euthyroid subjects even after adjustment for known risk factors for AF[73]. A similar observation was made by Auer et. al. in

2001 who in a large cross-sectional study at a hospital clinic found a relative risk for AF of 2.8 in patients with subclinical hyperthyroidism after adjustment for AF risk factors[74]. Cappola et. al. (2006) likewise found an increased relative AF risk of 1.9 after adjustments over a 12-year follow-up period among elderly participants in the Cardiovascular Health Study[75]. The reason for this lower number might have been due to counting of incident AF only, something which was not done in earlier studies. The risks of death from all causes, ischaemic heart disease or cerebrovascular disease were not increased.

In 2007, Gammage et. al. reported an odds ratio of 1.89 for AF in subjects with subclinical hyperthyroidism, using cross-sectional data from a primary care setting[76]. Data from the Rotterdam Study, a population based cohort of elderly people, also showed an increased relative risk of AF of 1.97 when the quartile with the lowest TSH values was compared to the quartile with the highest values[77]. Using pooled individual participant data from 10 cohorts Collet et. al. demonstrated increased risks of death from all causes (HR 1.24), death from ischaemic heart disease (HR 1.29), morbidity due to ischaemic heart disease (HR 1.21) and AF (HR 1.68). No increased risk of stroke was seen[78].

To conclude, subclinical hyperthyroidism may to some degree affect the risk of AF, overall cardiovascular disease and possibly even mortality, but the association is not entirely clear. This thyroid disorder is possible to cure using the same methods as for overt hyperthyroidism, something which has led to debate regarding possible indications for treatment. However controlled intervention studies are lacking. At present, guidelines from the American Thyroid Association strongly recommend treatment in patients with very suppressed TSH levels who are older than 65 years, postmenopausal women, individuals with cardiovascular risk factors or those with symptoms of hyperthyroidism. If TSH levels are only moderately suppressed, treatment "should be considered" using the same criteria, with an exception made for menopausal women.[45]

During the last few years, it has been debated whether free T4 levels close to the upper level of the normal range might also represent a clinically relevant form of excessive thyroid function, even in the absence of suppressed TSH levels. Researchers have shown that within groups of patients treated with atrial fibrillation ablation, individuals with the highest free T4 concentrations appear to relapse more frequently into AF[79,80]. A very recent meta-analysis by Baumgartner et al. (2017) actually concluded that free T4 levels, but not TSH levels, correlated to incident atrial fibrillation (figure 6, courtesy of Wolters Kluwer Health Inc)[81]. Also very recently, a study from the Rotterdam cohort showed that higher T4 levels were associated with coronary calcification, incident cardiovascular disease, and cardiovascular death; a similar negative correlation, albeit much weaker, was found for TSH[82].

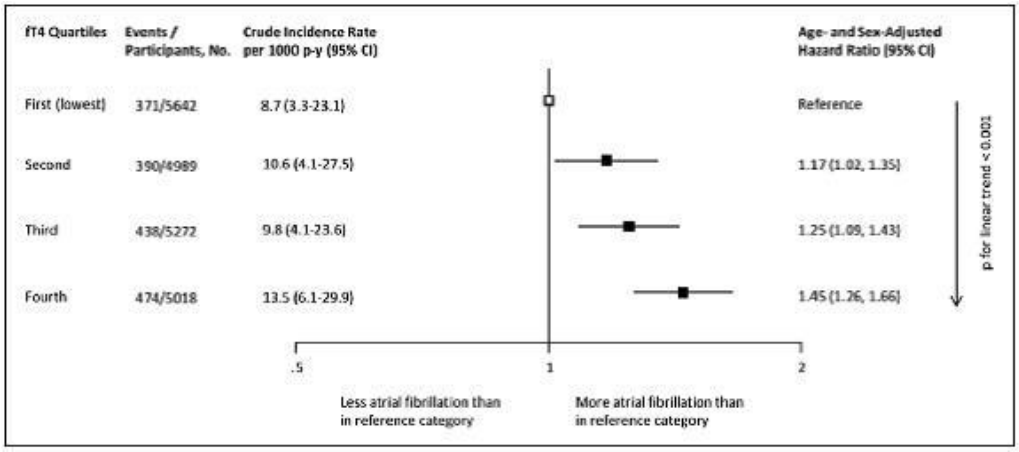

Figure 6. *Association between quartiles of free thyroxine within the reference range and the risk of atrial fibrillation.*

2 AIMS

The general purpose of this project was to study the relation between hyperthyroidism and cardiovascular disease. The specific aims and hypotheses of each study were as follows:

Study I: To analyse the association between hyperthyroidism and cardiovascular mortality and morbidity in the long term. Our hypothesis was that hyperthyroidism increases the risk of all-cause and cardiovascular death; this has been suggested from previous research by others but rarely in any cohort as large as the one available to us. Further aims were to investigate the impact of different causes of hyperthyroidism, and to examine changes over time.

Study II: To investigate the long-term impact of treatment with radioiodine *vs* surgey for hyperthyroidism in terms of both mortality and morbidity. Our hypothesis was that the choice of treatment significantly affects these outcomes.

Study III: To assess the prevalence of subclinical hyperthyroidism in patients admitted for ablation of AF. Our hypothesis was that AF patients would be more likely to suffer from subclinical hyperthyroidism than individuals without AF.

3 MATERIAL AND METHODS

In short, Papers I and II were both register studies largely based on the same group of patients: Stockholm residents treated for hyperthyroidism between the years 1976-2000. Paper III was a cross-sectional study that consecutively enrolled patients and controls from two arrhythmia ablation clinics in Stockholm between the years 2013-2015. For practical reasons, the word "thyroidectomy" – which usually implies complete resection of the thyroid gland – will henceforth be used as a catch-all term to describe all types of thyroid gland surgery, including partial resections.

3.1 PATIENTS

3.1.1 The Swedish national registers

Sweden has a very long history of population registration dating back to the 17th century[83]. Consequently, national authorities have had access to reliable data on the vital and migration status of each citizen for centuries. In 1947 personal identity numbers – unique 10-digit identifiers – became mandatory for all citizens and other permanent residents. This facilitated the development of various national healthcare registers, most of which were maintained by the Board of Health and Welfare. In 1952, construction began on the causes of death register which came into full effect in 1961. The patient register, which deals with hospital contacts, was first launched in 1964 and reached full coverage with regard to inpatient care (all diagnoses and all regions of the country) in 1987. From the year 2000, polyclinical hospital contacts were also added to this data base. Furthermore, a register on dispensed drugs was started in 2005[84]. Digitalisation had already begun in 1967, and large volumes of data have also been transferred to electronic records retrospectively. Aggregated data are posted online for the general public while individual-level data are made available to researchers upon approval by an ethics review board. The personal identity numbers enable cross-matching between healthcare registers which may then be matched again to census data. This makes possible the creation of very large healthcare cohorts that stretch back decades in time with little loss to follow-up[85-87].

In the present studies (numbers I and II), individuals who had undergone thyroidectomy were extracted from these national registers. That group was then merged with, or compared to, the group from the Stockholm Radioiodine Cohort (SIC, see below). Since the latter consisted solely of Stockholm residents treated between the years 1976-2000, similar exclusion criteria were applied to the thyroidectomy group so that only Stockholmers treated during that same period were included. This was done in order to avoid any potential bias due to geography or temporal variations.

3.1.2 The Stockholm Iodine Cohort

Radioiodine treatment has been used as a means of treating hyperthyroidism since the 1940s[88]. Since its discovery, the method rapidly became widespread and was implemented in most developed countries, including at various centres in Sweden. However, because treatment with radioiodine is usually performed in a polyclinical setting, no information about these treatments exists in the national patient register. Medical records from Sweden's nuclear medicine clinics have therefore been compiled by different researchers into a data base that has been updated on several occasions; at present, it consists of patients treated or examined with different radioactive substances (radioactive iodine or technetium) between the years 1950-2000. This material is commonly referred to as the Swedish Radioiodine Cohort, and it has previously been used in several research projects[55,89-91].

A subset of the Swedish Radioiodine Cohort is the Stockholm Radioiodine Cohort (SIC), a data base compiled from the hospital records of *Radiumhemmet* at Karolinska University Hospital (which has always been the sole provider of nuclear isotope therapy in the greater Stockholm area). The part of the SIC that covers the years 1976-2000 is considered to be the only portion that is essentially complete. For this reason, a choice was made to use only the SIC (as opposed to the entire Swedish Iodine Cohort) for the present studies and only for that time period. It contains detailed information on investigations and treatments where radioactive isotopes are used. For hyperthyroid patients, the probable etiology of hyperthyroidism is stated in over ninety per cent of cases as well as details about the treatment (doses of radioiodine, number of treatments etc.). Because radioiodine treatment is a form of outpatient care, it was not registered in national health data bases prior to the year 2000.

3.1.3 Electrophysiology centres in Stockholm

The greater Stockholm area comprises two units dedicated to invasive electrophysiological studies and catheter ablations. The first and largest of these is located at Karolinska University Hospital (*Karolinska sjukhuset* or KS), which is publically funded and treats mainly patients from the Stockholm region and adjacent regions. This centre treats patients with AF as well as other conditions, such as AV-nodal re-entry tachycardias (AVNRT:s) and ventricular arrhythmias. The second unit is the Stockholm Arrhythmia Centre (SAC), which is partly funded by private insurances and almost exclusively treats AF. The SAC receives patients from the whole of Sweden. Taken together, the two centres performed almost 800 AF ablations during 2016.

3.2 STUDY I

The national patient register and the SIC were used to collect data on all Stockholm residents treated for hyperthyroidism with either radioiodine or thyroidectomy between 1976-2000

(data on patients treated with anti-thyroid drugs were not obtained due to the fact that such information was not compiled in national registers during this time period). These were defined as an exposed population (i.e. exposed to hyperthyroidism). To obtain a reference group, data was also collected from the patient register on individuals that had been treated with surgery for non-toxic goitre. Because these patients had no hyperthyroidism, they were defined as an unexposed population (figure 7).

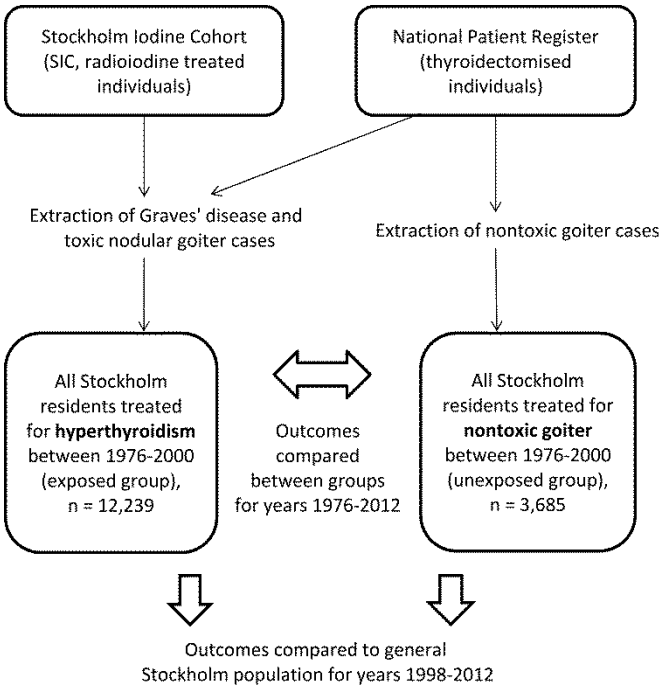

Figure 7 *Flowchart describing how the study cohort was assembled.*

The index date for all study patients was defined as the first date of treatment (with radioiodine or thyroid surgery). Only patients who had an index event between 1976-2000 were included, but diagnoses recorded in the patient register from between 1969-1975 were also taken into account as markers of baseline comorbidity. Patients younger than 18 or older than 90 years at the time of their index event were also excluded.

Subjects were followed until death, emigration or end of study (31 December, 2012). When all-cause mortality was analysed, census data from Statistics Sweden were used up until 11 December, 2013. Information about cause-specific mortality was gathered from the Swedish causes of death register. When these outcomes were assessed, only the underlying cause was taken into account for each deceased subject.

All individuals (both radioiodine treated and surgically treated) were then matched to the entire patient register for the period 1969-2000 in order to find other diagnoses related to any earlier hospitalisations that would constitute relevant baseline comorbidity. The main diagnosis and up to five secondary diagnoses were taken into account for each hospital

contact. For internal analyses within the cohort, adjustment was made for prevalent diabetes, hypertension, renal failure, rheumatoid arthritis, psoriasis and chronic obstructive pulmonary disease. For each outcome, adjustment was also made for whether that particular diagnosis was already present at baseline.

Diagnostic codes were categorized according to ICD8-ICD10, and a translation was made between the different classifications.

3.2.1 Statistical analyses

Mortality and morbidity outcomes were both assessed in two ways: exposed (hyperthyroid) subjects versus the general population and exposed subjects versus unexposed (nontoxic goitre) subjects.

In order to estimate the risk of death for exposed versus unexposed subjects, a Cox proportional hazard regression was fitted, adjusting for sex, age of inclusion (using restricted cubic spline), and year of inclusion (using restricted cubic spline). In order to assess potential differences in cause specific hazard ratios, a cause specific proportional hazards model was used, treating other deaths as censored[92]. Because mean age was known to vary considerably according to type of hyperthyroidism, outcomes were also stratified into quartiles according to age at index event.

The Patient Register was used to identify incident cardiovascular morbidity after inclusion, using the same procedure as for baseline comorbidity but with follow-up until 2012. Because death is a competing event, the notion of cause-specific hazard regression was used, treating death as censored. To assess the change in hazard ratio over time for all cardiovascular disease, a flexible parametric model was used[93]. Stratification according to age was done in the same manner as for mortality. Further stratification according to time of the index event was performed by assessing incident morbidity separately for patients included before or after the year 1990.

Comparisons were also made to the general population of Stockholm regarding both morbidity and mortality. All three etiologies of thyroid disorders – Graves' disease, toxic nodular goitre, or nontoxic goitre – were analysed separately. When mortality was assessed, Standardized Mortality Ratios (SMR) for death due to both all-cause mortality and any cardiovascular disease were used. The expected number of deaths was calculated by multiplying the mortality rates in the background Stockholm population (divided into strata of 5-year age groups, sex and for each of the years between 1976 and 2013) by the stratum-specific person-time in the cohort. Cause specific SMR was calculated between 1998-2012. When morbidity was assessed, standardised incidence rate ratios for the group of cardiovascular diseases as a whole were used. Standardisation was done for sex and age, and results were presented for each of the years between 1998 and 2012.

Adjustment for levothyroxine use as a variable that affected outcomes was not possible due to the fact that the last index event took place in the year 2000 while the first entry in the drug register was made in 2005. However, prescription data from 2005 were used to assess hypothyroidism in those study patients that were still alive at that time.

All analyses were performed in Stata 13.1 software (Stata Corp, College Station, TX 77845, USA).

3.3 STUDY II

Essentially the same cohort as in Study I was used in Study II. Thyroidectomised individuals were collected from the patient register, and radioiodine treated individuals were gathered from the SIC. However, a few further exclusion criteria were applied: First, patients with nontoxic goitre were not part of the analysis. Second, patients younger than 35 years at the index event were excluded because females (who make up the large majority of hyperthyroid patients) below that age are rarely recommended radioiodine as treatment for hyperthyroidism. The third and last group excluded was of those patients in whom the aetiology of hyperthyroidism was uncertain or those who had received both radioiodine and surgical treatment in order to reduce the risk of confounding. Outcomes were assessed in terms of all-cause and cause-specific mortality (figure 8).

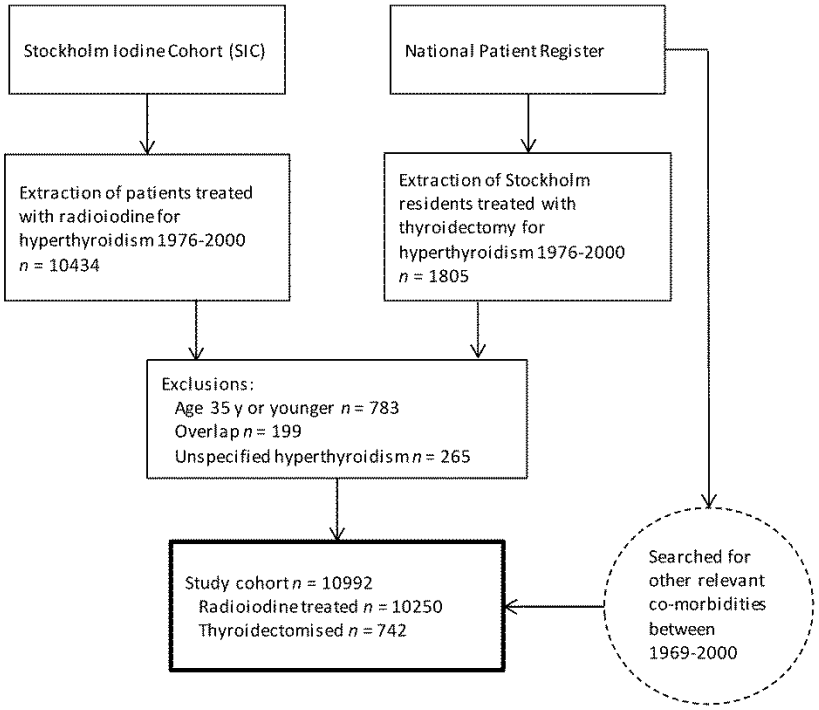

Figure 8 *Description of assembly of the study cohort.*

3.3.1 Statistical analyses

We applied three different statistical methods: regression adjustment, propensity score matching, and inverse probability weighting[94]. In the regression analyses, we used a Cox regression model that adjusted for all the potential confounders to estimate HRs and 95% Confidence Intervals (95% CIs). In the propensity score matching and inverse probability weighting analyses, we calculated propensity scores estimating the probability of receiving surgical treatment using a logistic regression model. For propensity score match analysis, a one-to-one nearest-neighbour matching algorithm without replacement was employed in order to pair each subject receiving surgical treatment with one subject receiving radioiodine treatment. Propensity score matching allows the estimation of the average treatment effect among the treated. This permits one to make inferences about the effects of surgical treatment in those patients that actually underwent surgery. In the inverse probability weighting analyses, we applied standardised mortality ratio weights[95]. In short, this means that surgery patients are given a weight of 1, while radioiodine patients are given a weight equal to the ratio of the estimated propensity score to one minus the propensity score. We chose to use standardised mortality ratio weights as their use results in an estimate of the average treatment effect among the treated, which is the same quantity estimated in the aforementioned propensity score analysis . After matching or weighting, we checked again for balance in the confounders using standardised differences. Finally, for both propensity score match and inverse probability weighting analyses, Cox regression models including treatment as the only covariate were used. To account for the matched nature of the sample (propensity score matching) or for the probability weights, we used a robust estimator of the variance-covariance matrix[94].

3.4 STUDY III

Study subjects were patients admitted at KS and SAC for catheter ablation of AF. Control subjects were patients admitted to those same clinics for catheter ablation of AVNRT. All individuals deemed eligible for inclusion were required to give written informed consent before participation. The exclusion criteria were as follows: AF patients who had not tried at least one anti-arrhythmic medication prior to ablation, subjects who had undergone ablation before, and subjects with a known thyroid disorder of any kind. Information about co-morbidity and continuous medication was collected using a clinical research form upon inclusion or, in some cases, retrospectively from medical records (figure 9). Blood samples for assessment of thyroid hormone levels (TSH, T3, and free T4) were drawn less than 7 days before the ablation procedure. Subclinical hyperthyroidism was defined as a TSH level below 0.3 mIU/L with T3 and free T4 levels within the reference range.

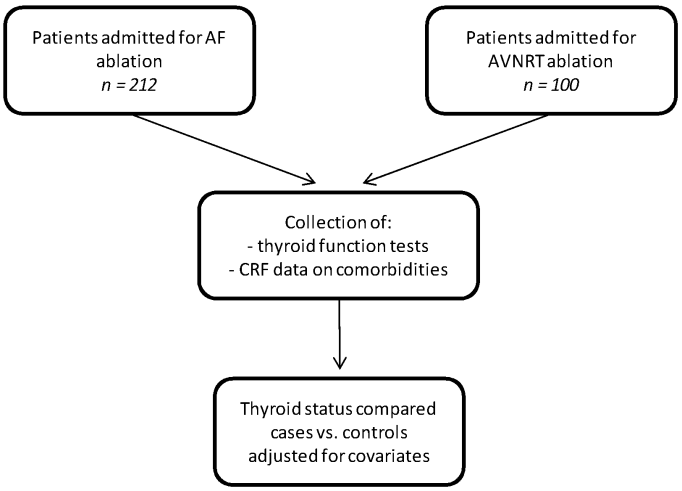

Figure 9. *Inclusion and analysis of study subjects from two electrophysiology clinics in Stockholm, Sweden.*

3.4.1 Statistical analyses

Given the uncertainty concerning the prevalence of subclinical hyperthyroidism in the general population and in particular among patients admitted for catheter ablation, an adaptive design was chosen. Assuming a prevalence of 7% in the AF group and of 1.4% in the control group, our power calculation showed that 412 patients would need to be included for a power of 80% and a 5% two-sided level of significance. An interim analysis was planned after inclusion of at least 50 patients in each group, using the Hwang-Shih-DeCani spending function and assuming that the trial stop for futility. Student's t-test was used for comparison of continuous variables, while the $\chi 2$ or Fisher's exact test were used to compare nominal variables. Adjustments of thyroid hormone levels were made using linear regression analysis for the following baseline variables: sex, age, body mass index, and amiodarone use.

3.5 ETHICAL CONSIDERATIONS

Studies I and II were approved by the Ethics Review Board of Stockholm, reference number 2013/638-31/3. Because this research was register based, a few particular ethical considerations had to be made. The most obvious drawback was that it was impossible – even in theory – to obtain individual consent from the tens of thousands of patients involved; a significant number of these had already died when our cohorts were compiled. Furthermore, the national data bases were never meant to be reserved strictly for research purposes; authorities also use them for administrative reasons and for statistics. In the Swedish healthcare system, patients are virtually never given the possibility to opt out of this kind of registration. Because research is clearly involved, one might ask whether this practice is fully in compliance with the Declaration of Helsinki. Another ethical issue is Sweden's use of personal identity numbers which, however practical they may be, introduce the risk of careless cross-linkage between registers. The resulting data sets may contain more (sensitive)

information about individual persons than what was originally intended. Sweden's national authorities address this problem by de-identifying all data before it is handed over to researchers, which was also the case in the present studies in which none of the authors had access to personal identity numbers. In addition, permission from an ethics review board is mandatory before data may be extracted.

Study III was approved by the Ethics Review Board of Stockholm, reference number 2012/1437-31/1. In this investigation the study subjects were recruited prospectively, and their written consent was required. Each patient was given information prior to enrolment. The study was purely observational and thus did not expose participants to any risk from potentially hazardous or ineffective treatments. An adaptive study design was used so that recruitment could be stopped before the inclusion goal was reached if the data suggested so.

4 RESULTS

4.1 STUDY I

4.1.1 Exposed *versus* unexposed patients

The selection procedure resulted in a study cohort consisting of 15,924 individuals. Among these were 12,239 patients treated for hyperthyroidism (exposed) and 3,685 patients treated for nontoxic goitre (unexposed). Within the hyperthyroid group there were 6,284 cases with Graves' disease and 5,702 with toxic nodular goitre; a further 289 cases had no defined aetiology of hyperthyroidism. The proportion of women was 84.7% with sex ratios roughly equivalent between groups (p = 0.46). Median ages differed considerably between patients with Graves' disease (54.4 years), toxic nodular goitre (68.6 years) and nontoxic goitre (49.1 years) (table 2).

	Exposed				Unexposed	
	All Hyperthyroid	Grave's Disease	Toxic Nodular Goiter	Unspecified Hyperthyroi-dism	Nontoxic Goiter	*p* value
Number of subjects (total = 15,924)	12,239	6,248	5,702	289	3,685	
Women, %	84.8	82.6	87.3	86.5	84.3	0.46 †
Mean age, years	61.3	54.4	68.6	34.9	49.1	< 0.001
Age quartiles, *n* (%)*						
1st quartile (18-45 years)	2,411 (19.6)	1,753 (28.1)	423 (7.4)	235 (81.3)	1,439 (39.1)	
2nd quartile (46-58 years)	2,899 (23.6)	1,870 (29.9)	987 (17.3)	42 (14.5)	1,212 (32.9)	< 0.001
3rd quartile (59-70 years)	3,096 (25,3)	1,395 (22.3)	1,692 (29.7)	9 (3.1)	747 (20.3)	
4th quartile (71-90 years)	3833 (31,3)	1,230 (19.7)	2,600 (45.6)	3 (1.0)	287 (7.8)	
Treatment, *n* (%)*						
Radioiodine	10,346 (84.5)	5,090 (81.5)	5,256 (92.2)	0	0	
Thyroidectomy	1,694 (13.8)	1,047 (16.8)	382 (6.7)	265 (91.7)	3,647 (99.0)	< 0.001
Both treatments	199 (1.6)	111 (1.8)	64 (1.1)	24 (8.3)	38 (1.0)	
Baseline comorbidities, *n* (%)*						
Cardiovascular disease	3,175 (25.9)	1,261 (20.2)	1,902 (33.4)	12 (4.2)	381 (10.3)	p < 0.001
Hypertension**	527 (4.3)	166 (2.7)	360 (6.3)	1 (0.3)	72 (2.0)	p < 0.001
Ischemic heart dis**	815 (6.7)	295 (4.7)	520 (9.1)	0	73 (2.0)	p < 0.001
Atrial fibrillation**	1,118 (9.1)	396 (6.3)	719 (12.6)	3 (1.0)	39 (1.1)	p < 0.001
Heart failure**	877 (7.2)	294 (4.7)	583 (10.2)	0	22 (0.6)	p < 0.001
Ischemic stroke**	266 (2.2)	81 (1.3)	184 (3.2)	1 (0.3)	9 (0.2)	p < 0.001
Renal failure	118 (1.0)	53 (0.8)	62 (1.1)	3 (1.0)	14 (0.4)	p = 0.001
COPD	216 (1.8)	75 (1.2)	140 (2.5)	1 (0.3)	25 (0.7)	p < 0.001
Rheumatoid arthritis	131 (1.1)	55 (0.9)	76 (1.3)	0	15 (0.4)	p < 0.001
Psoriasis	26 (0.2)	12 (0.2)	14 (0.2)	0	7 (0.2)	p = 0.793
Diabetes	471 (3.9)	168 (2.7)	302 (5.3)	1 (0.3)	60 (1.6)	p < 0.001
Cancer***	729 (6.0)	288 (4.6)	437 (7.7)	4 (1.4)	119 (3.2)	p < 0.001

Table 2. *Demographic characteristics, treatment modalities and baseline comorbidities of the participants treated with radioiodine or thyroidectomy between 1976-2000 in Stockholm, Sweden. *Percentages in relation to whole group with this thyroid disorder. Totals may not sum to 100 due to rounding. ** Also included in the overall category of cardiovascular diseases. ***Any previous malignancy diagnosis, not specified as ongoing or cured. † p values for comparisons between all hyperthyroid patients and nontoxic goiter group.*

Mean follow-up time was 18.5 years, ranging from one day to 37.9 years. Total time at risk was 295,246 person-years. Among the 9,650 patients still alive by the year 2005, 93% were prescribed levothyroxine in the Graves' disease group, 57% in the toxic nodular goitre group, and 63% in the nontoxic goitre group.

When all incident cardiovascular morbidity (as opposed to mortality) was assessed for the combined hyperthyroid group compared to the nontoxic goitre group, hazard ratios were found to be highest just after inclusion but remained elevated for a long time thereafter (figure 10).

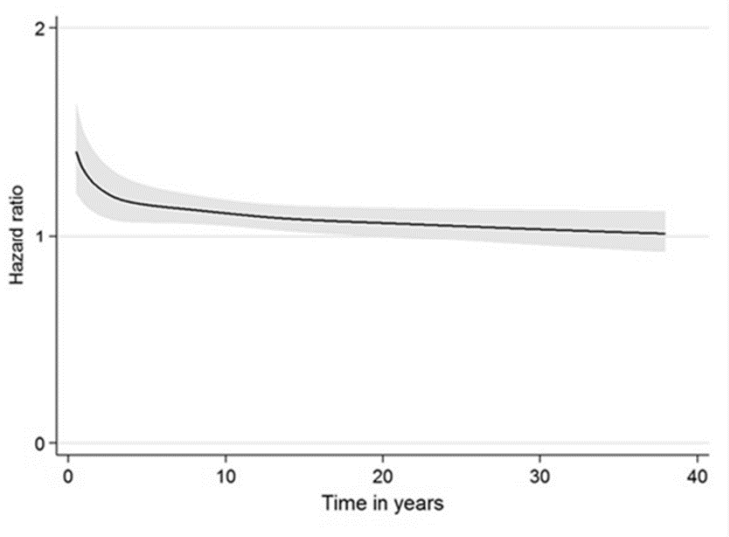

Figure 10. Hazard ratios for all cardiovascular morbidity over time during whole follow-up (mean 18,5 years); All hyperthyroid patients compared to reference group of nontoxic goiter patients. Shaded area represents the 95% confidence interval.

For both Graves' disease patients and toxic nodular goitre patients, atrial fibrillation was the diagnosis with the highest incidence at one year of follow-up with HR:s of 4.62 (CI 2.25-9.51) and 5.35 (CI 2.61-10.97), respectively. During the mean follow-up time of 18.5 years, increases in risk among Graves' disease patients lost statistical significance while toxic nodular goiter patients remained at increased risk (figure 11).

For the whole follow-up period, all-cause mortality was increased (HR 1.27, (CI 1.20-1.35) as was cardiovascular mortality (HR 1.29, (CI 1.17-1.42) for the hyperthyroid group compared to the nontoxic goitre group. Separate analyses according to aetiology of hyperthyroidism yielded an increased risk of all-cause mortality both for Graves' disease (HR 1.14, CI 1.03-1.27) and for toxic nodular goitre (HR 1.42, CI 1.28-1.57). Significant differences were also found for the shorter follow-up time of 10 years (figure 12). The risk of death from cardiovascular disease was likewise significantly increased regardless of aetiology of hyperthyroidism or length of follow-up.

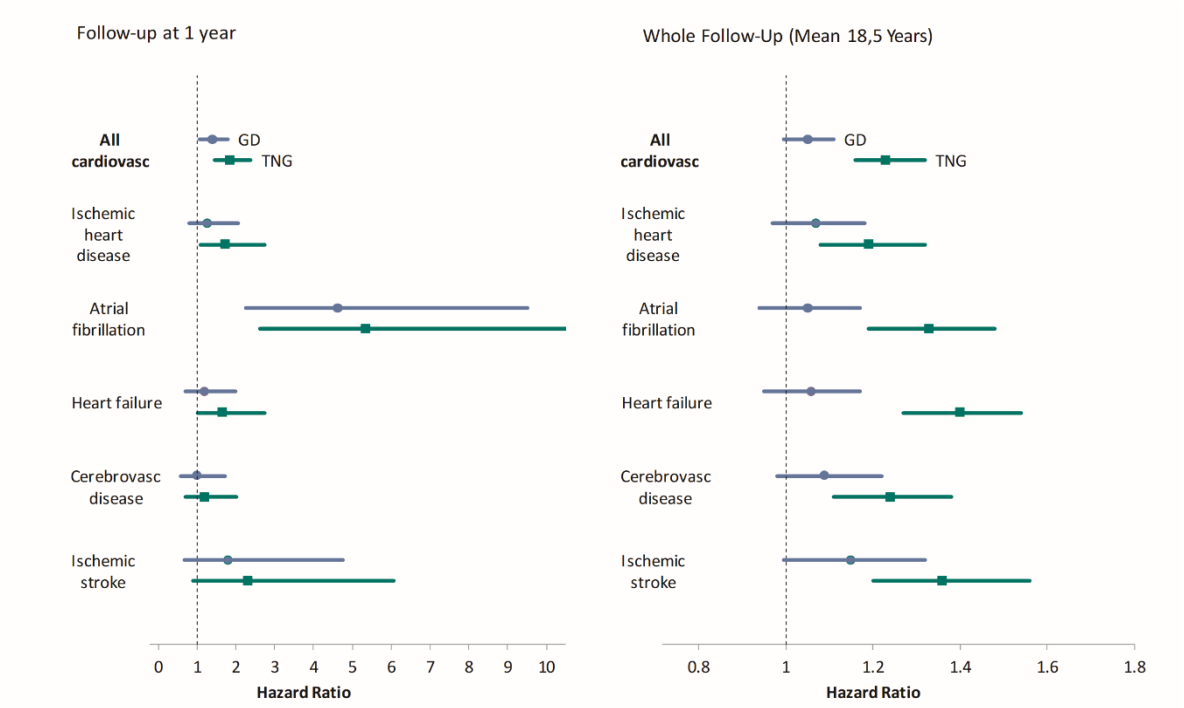

Figure 11. *Forest graphs depicting hazard ratios for different types of* ***incident cardiovascular*** *disease in hyperthyroid (Graves' disease (GD) or toxic nodular goitre (TNG)) patients at two separate time points during follow-up. The reference group (dashed vertical line) consisted of patients treated for nontoxic goitre. Adjusted for sex, age, prevalent diabetes, hypertension, renal failure, rheumatoid arthritis, psoriasis, and chronic obstructive pulmonary disease. Each incident diagnosis was also adjusted for its own baseline prevalence.*

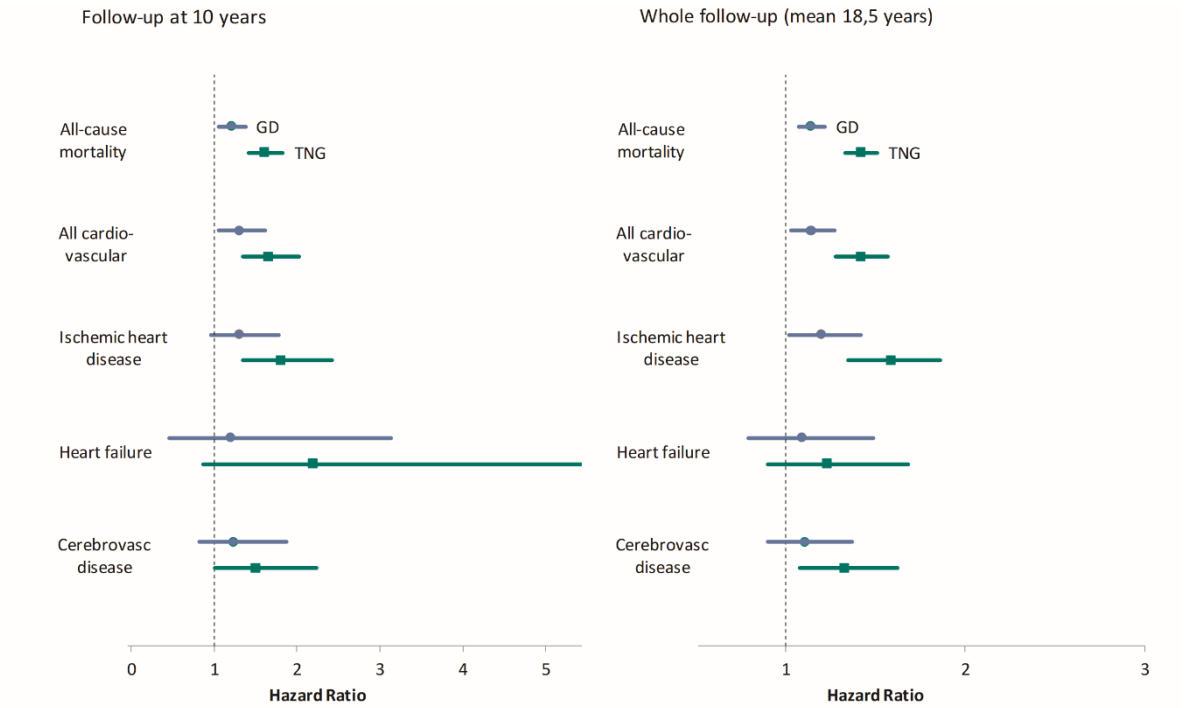

Figure 12. *Comparisons of* ***all-cause and cardiovascular mortality*** *for different lengths of follow-up; Horizontal bars denote hazard ratios and 95% confidence intervals for Graves' disease (GD) and toxic nodular goiter (TNG). Dashed vertical line denotes the reference group of nontoxic goiter patients. Adjustments for baseline factors were made as for figure 11.*

When the cohort was divided according to time of inclusion (before and after the year 1990), all-cause and cardiovascular mortality were increased in both types of hyperthyroidism for both time intervals. Cardiovascular morbidity was likewise increased among toxic nodular goitre patients included both before and after year 1990. For the Graves' disease patients, morbidity was higher only among those included after year 1990 (figure 13).

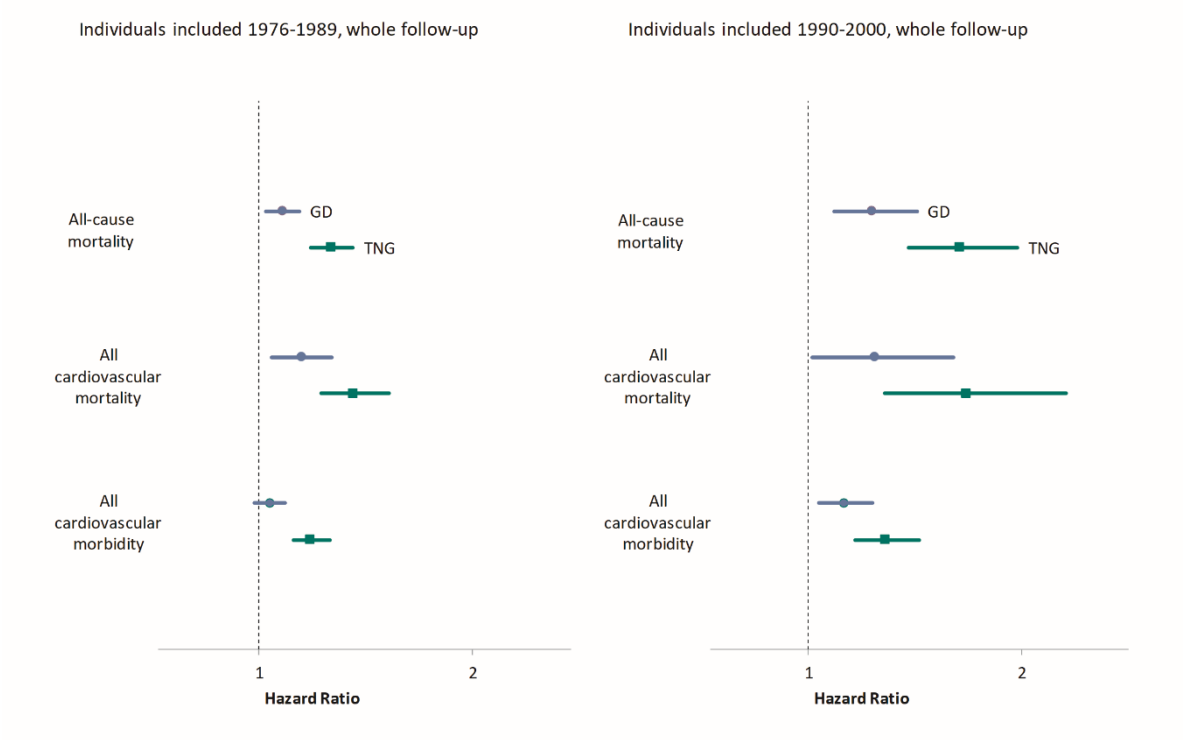

Figure 13. *Comparisons of all-cause and cardiovascular mortality, as well as cardiovascular morbidity, stratified according to inclusion time before or after 1990; Horizontal lines represent Graves' disease (GD) and toxic nodular goiter (TNG) with 95% confidence intervals compared to nontoxic goiter (vertical dashed lines). Adjusted for sex, age, prevalent diabetes, hypertension, renal failure, rheumatoid arthritis, psoriasis, and chronic obstructive pulmonary disease. Each incident diagnosis was also adjusted for its own baseline prevalence.*

4.1.2 Exposed and unexposed patients *versus* general population

In comparison to the general population, all-cause mortality was increased among hyperthyroid subjects with a standardised mortality ratio (SMR) of 1.22 (CI 1.20-1.25). The same was true for cardiovascular mortality (SMR 1.26, (CI 1.20-1.32). Both the Graves' disease group and the toxic nodular goitre group displayed increased all-cause and cardiovascular mortality by themselves. Nontoxic goitre patients showed no excess mortality compared to the general population (table 3).

	All Hyperthyroidism		Graves' Disease		Toxic Nodular Goiter		Nontoxic Goiter	
	SMR	95% CI	SMR	95% CI	SMR	95% CI	SMR	95% CI
Death from all causes*	1.22	1.20 - 1.25	1.07	1.05 - 1.15	1.35	1.31 - 1.39	0.95	0.90 - 1.00
Cardiovascular death**	1.26	1.20 - 1.32	1.12	1.04 - 1.20	1.38	1.30 - 1.47	0.96	0.86 - 1.06

Table 3. *Comparisons of mortality; Graves' disease, toxic nodular goitre and nontoxic goitre versus general population of Stockholm for 1998-2012. Adjusted for sex and 5-year age groups. * During the period of 1976 – 2013. ** During the period of 1998 – 2012.*

Cardiovascular morbidity as compared between the cohort and the general population are displayed as year-by-year standardised incidence-rate ratios in figure 14.

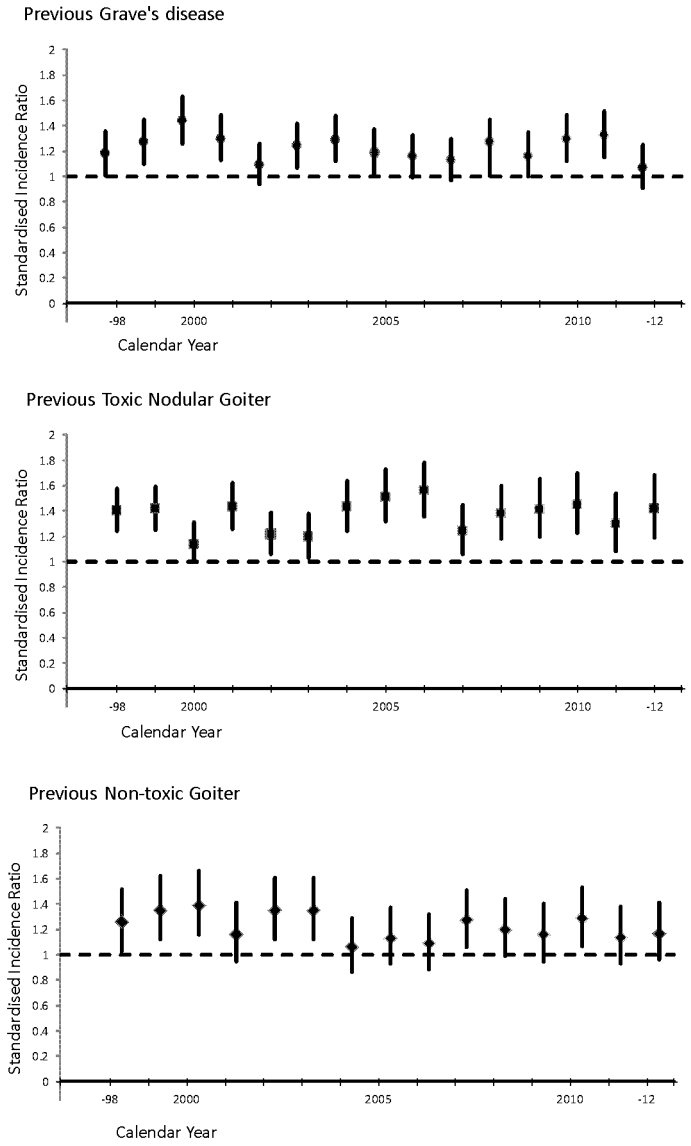

Figure 14. *Comparisons of cardiovascular morbidity; Graves' disease, toxic nodular goiter and nontoxic goiter versus general population during the years 1998-2012. Vertical lines denote standardized incidence ratios with 95% confidence intervals for each of these diagnoses year by year.*

Point estimates were higher than 1.0 for each of the three groups in all of the years, but these increases were not always statistically significant. The toxic nodular goitre group differed most clearly from the general population, showing significantly increased cardiovascular morbidity in 14 out of the 15 years observed.

4.2 STUDY II

After further exclusion criteria were applied to the cohort described in Study I, 10,992

	Radioiodine	Surgery	*p* value*	d #
	(n = 10250)	(n = 742)		
Age at treatment (years)				
35-45	915 (8.9)	394 (53.1)		1.086
45-55	1925 (18.8)	191 (25.7)		0.168
55-65	2270 (22.1)	101 (13.6)	<0.001	-0.224
65-75	2752 (26.9)	43 (5.8)		-0.594
75-90	2388 (23.3)	13 (1.8)		-0.688
Mean	64.0	47.0		-1.461
Women	8668 (84.8)	633 (85.3)	0.688	0.015
Year of treatment				
1976-1979	1557 (15.2)	136 (18.3)		0.084
1980-1984	1995 (19.5)	144 (19.4)		-0.001
1985-1989	2188 (21.4)	141 (19.0)	<0.001	-0.058
1990-1994	2295 (22.4)	123 (16.6)		-0.147
1995-2000	2215 (21.6)	198 (26.7)		0.119
Type of hyperthyroidism				
Graves' disease	5004 (48.8)	465 (62.7)		
Toxic nodular goiter	5246 (51.2)	277 (37.3)	<0.001	-0.281
Comorbidities at baseline				
Ischemic heart disease	812 (7.9)	3 (0.4)	<0.001	-0.383
Myocardial infarction	261 (2,6)	2 (0,3)	<0.001	-0.194
Atrial fibrillation	1090 (10.6)	20 (2.7)	<0.001	-0.322
Cerebrovascular disease	538 (5,3)	6 (0,8)	<0.001	-0.261
Stroke	260 (2.5)	5 (0.7)	0.001	-0.148
Heart failure	864 (8.4)	10 (1.4)	<0.001	-0.333
Cardiomyopathy	18 (0,2)	1 (0,1)	0.796	-0.01
COPD	208 (2.0)	5 (0.7)	0.010	-0.117
Renal failure	103 (1.0)	4 (0.5)	0.212	-0.053
TAO	867 (8.5)	98 (13.2)	<0.001	0.153
Hypertension	509 (5.0)	15 (2.0)	<0.001	-0.161
Diabetes	453 (4.4)	7 (0.9)	<0.001	-0.216
Cancer	693 (6.8)	25 (3.4)	<0.001	-0.155

Table 4. *Baseline characteristics of 10992 Stockholm residents treated for hyperthyroidism between 1976-2000. Treatment modalities were radioiodine and surgery. Percentages are stated within brackets and calculated separately for each treatment group. COPD, chronic obstructive pulmonary disease; TAO, thyroid associated ophthalmopathy. *p values from chi-squared test. d# standardized difference.*

individuals remained. Of these, 10,250 had received radioiodine treatment, and 742 had received surgical treatment for hyperthyroidism. The radioiodine group had a median age of 65.1 years and the thyroidectomy group of 44.1 years, and the sex ratios were 84.8% and 85.3% women respectively. Levels of baseline comorbidity were substantially higher among radioiodine treated subjects (table 4).

In the regression analysis, there were 7,007 deaths during whole follow-up, with a total number of person-years at risk of 179,409 equivalent to a mean follow-up time of 16.3 years. The propensity score match included 1,484 individuals of which 400 died; total observation time was 33,074 person years, and mean follow-up time was 22.3 years. In the inverse probability weighting, 1,476 subjects were included, 386 of which died. Total observation time was 32,911 years and mean follow-up 22.3 years (table 5).

	Regression analysis		Propensity score matching		Inverse probability weighting	
	(n = 10992)		(n = 1484)		(n = 1478)	
	Nr of deaths	Hazard ratio	Nr of deaths	Hazard ratio	Nr of deaths	Hazard ratio
All-cause*	7007	0.82 (0.71-0.96)	400	0.80 (0.68-0.94)	387	0.85 (0.72-1.00)**
Cancer	1378	1.04 (0.80-1.36)	122	1.05 (0.75-1.48)	121	1.07 (0.82-1.41)
Cardiovascular disease	3324	0.70 (0.53-0.91)	143	0.64 (0.48-0.86)	132	0.74 (0.56-0.97)
Other causes	2126	0.78 (0.59-1.04)	120	0.74 (0.53-1.05)	117	0.78 (0.58-1.04)

Table 5. *Comparisons of mortality in hyperthyroid patients treated with surgery versus radioiodine, during a period of follow-up between 1976-2013. Three different statistical methods were used. Mean follow-up time was 16,3 years when regression analysis was applied; in the propensity score match and the inverse probability weighting, mean follow-up time was 22,3 years. Numbers within brackets denote 95% confidence intervals. * Number of all-cause deaths exceeds the sum of deaths from specific causes, since no data on causes of death was available for the year 2013. ** p = 0.044 for this observation.*

Surgically treated subjects had lower all-cause mortality as assessed by cox regression (HR 0.82, CI 0.71-0.96), propensity score matching (HR 0.80, CI 0.68-0.94), and inverse probability weighting (0.85, CI 0.72-1.00, p = 0.044) compared to subjects who received radioiodine. (table 5 and figures 15 and 16). Significantly lower cardiovascular mortality was also found among thyroidectomised individuals in all three analyses; the HR by cox regression was 0.70 (CI 0.53-0.91), by propensity score matching 0.64 (CI 0.48-0.86), and by inverse probability weighting 0.74 (CI 0.56-0.97). No clear differences were found regarding

cancer mortality or other causes of death. One further unexpected finding was made in the regression analyses which showed that men in particular had a markedly lower risk of dying if treated with surgery as opposed to radioiodine (HR 0.45, CI 0.30-0.67).

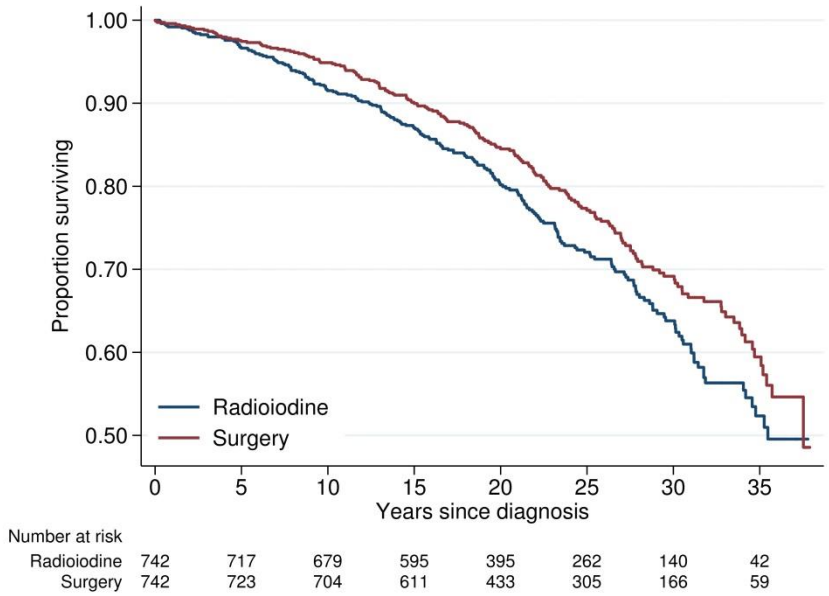

Figure 15. *Kaplan-Meier survival curves describing all-cause mortality in patients treated for hyperthyroidism with radioiodine versus surgery, according to the propensity score match analysis.*

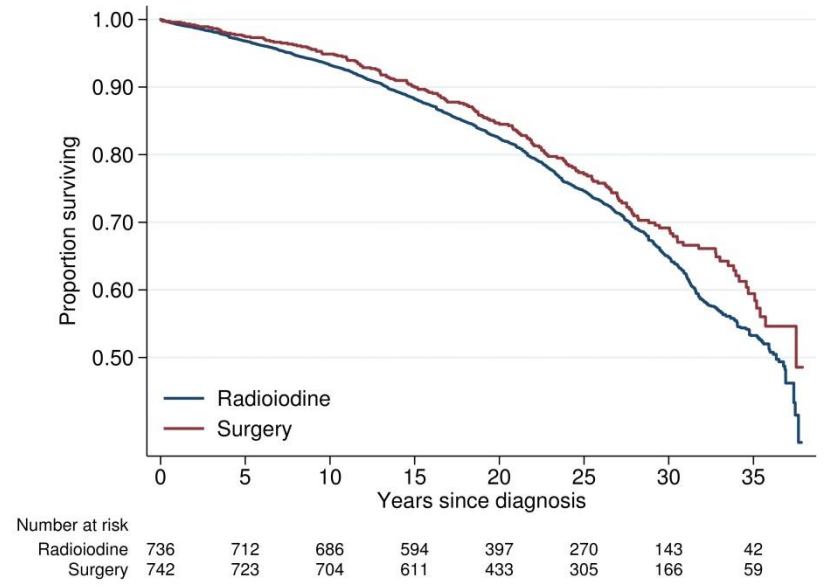

Figure 16. *Kaplan-Meier survival curves describing all-cause mortality in patients treated for hyperthyroidism with radioiodine versus surgery, according to the inverse probability weighting analysis.*

4.3 STUDY III

Three hundred twelve participants were recruited. Among these, 212 had a diagnosis of AF (cases), and 100 had an AVNRT diagnosis (controls). The AF group had a mean age of 59.4 years and consisted of 77.8% men. The AVNRT group had a mean age of 51.1 years and consisted of 40.0% men. Mean body mass index, age, and sex ratios differed significantly between groups (table 6).

	Overall (n=312)	AF (n=212)	AVNRT (n=100)	P
Age, years	56.7±11.0	59.4±8.9	51.1±12.8	<0.001
Female Gender, %	34.3 (107)	22.2 (47)	60.0 (60)	<0.001
BMI, Kg/m²	26.6±4.0	27.0±3.8	25.7±4.4	0.011
TSH, mU/L	2.0±1.1	2.0±1.1	1.9±1.2	0.393
FT4, pmol/L	16.4±2.2	16.7±2.2	15.9±2.2	0.002
FT3, pmol/L	4.7±0.6	4.7±0.6	4.6±0.6	0.746
FT3/FT4 ratio	0.3±0.05	0.3±0.05	0.3±0.04	0.022
Beta blocker, %	59.8 (186)	68.7 (145)	41.0 (41)	<0.001
Antiarrhythmic agent, %	32.4 (101)	42.9 (91)	10.0 (10)	<0.001
Amiodarone, %	4.2 (13)	6.1 (13)	0 (0)	0.011
Diabetes Mellitus, %	5.8 (18)	4.7 (10)	8.0 (8)	0.246
Hypertension, %	26.9 (84)	30.7 (65)	19.0 (19)	0.030
Heart Failure, %	2.2 (7)	3.3 (7)	0 (0)	0.101
Valvular Heart Disease, %	1.6 (5)	1.4 (3)	2.0 (2)	0.657
Stroke/TIA, %	3.8 (11)	5.8 (11)	0 (0)	0.018

Table 6. *Patient characteristics according to arrhythmia. BMI= Body mass index; TIA = Transient ischemic attack; TSH= Thyroid stimulating hormone. FT4 = Free thyroxine; FT3 = Free triiodothyronine. *Amiodarone: ongoing treatment, or discontinued less than 3 months ago.*

One (1) patient with subclinical hyperthyroidism was found in the AF group, while none were found in the AVNRT group. As a consequence further inclusion into the study was

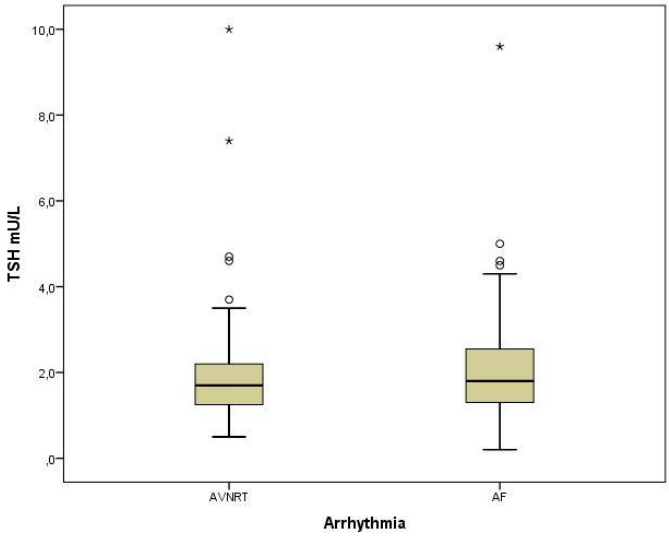

Figure 17. *Box plot showing the observed TSH levels in the two study groups.*

stopped for futility. When thyroid hormone concentrations were compared between cases and controls as continuous variables, no statistically significant differences in mean levels of TSH (figure 17) or T3 could be found. However, levels of free T4 differed significantly between groups, with a mean concentration that was 0.8 pmol/L higher among AF patients (95% CI for difference 0.31-1-35, p = 0.002) (figure 18).

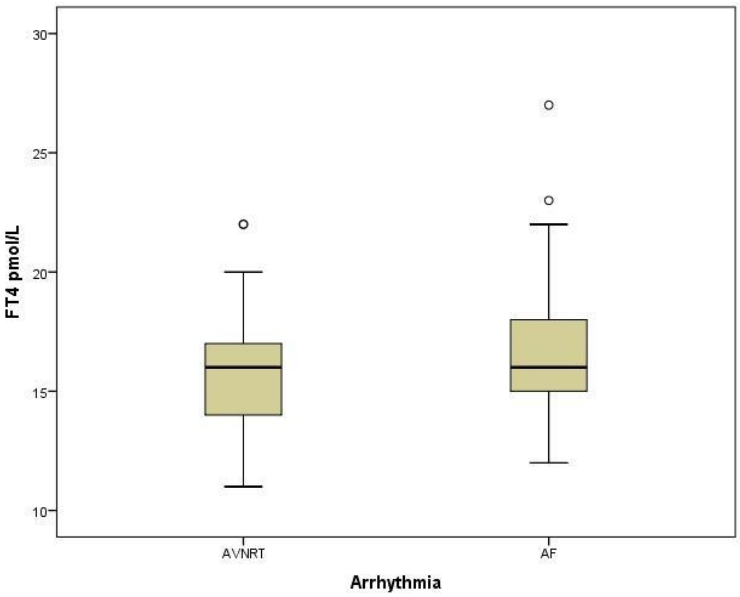

Figure 18. *Box plot showing the observed FT4 levels in the two study groups.*

After adjustments for sex, age, BMI, and amiodarone using multivariate linear regression, a significant difference in mean FT4 remained (95% CI, 0.03-1.23, p = 0.039) (figure 19). No significant differences in mean TSH or FT3 levels were observed after adjustments.

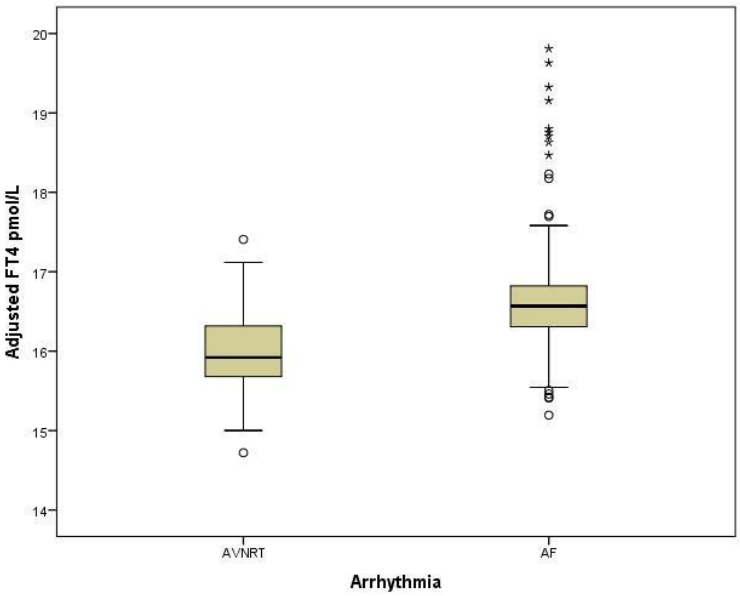

Figure 19. *Box plot showing FT4 levels adjusted for age, sex, BMI and amiodarone in the two study groups. All the extremes in the AF plot are patients with amiodarone treatment.*

AF patients on recent or ongoing amiodarone treatment (n=13) had higher mean FT4 concentrations (18.7 pmol/L) but lower mean FT3 concentrations (4.23 pmol/L) compared to 16.6 pmol/L and 4.69 pmol/L respectively in AF patients not on amiodarone (95% confidence interval of difference, 0.92 – 3.35, p = 0.001 for FT4; and -0.78 – -0.14, p = 0.006 for FT3). Patients on amiodarone treatment constitute the extremes illustrated in the AF box plot as seen in figure 19.

When patients with amiodarone treatment were excluded, AF patients still had significantly higher mean FT4 levels compared to the control group; both before (mean difference 0.7 pmol/L, 95% CI, 0.18 – 1.21, p = 0.008) and after adjustments for sex, age, and BMI (95% CI, 0.02 – 0.71, p = 0.038) (figure 20).

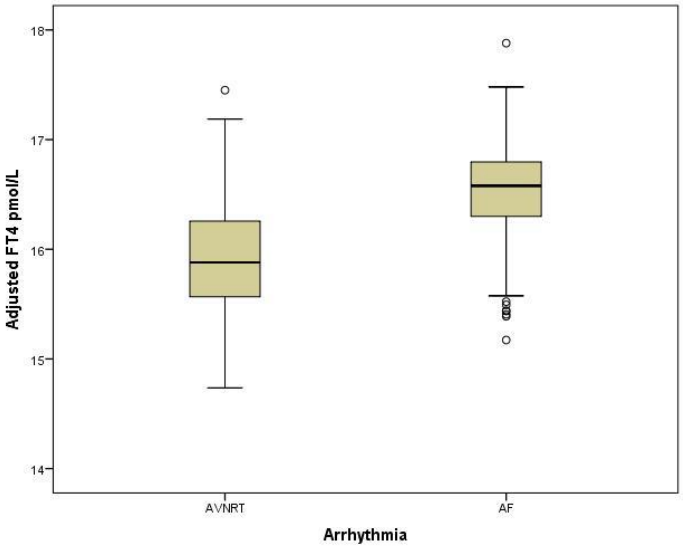

Figure 20. *Box plot, with amiodarone treated patients excluded, showing predicted FT4 values adjusted for sex, age, and BMI in the two study groups.*

5 DISCUSSION

The main conclusion from our first two studies is that patients treated for hyperthyroidism are at increased risk of hospitalisation and death in the long term. Individuals with toxic nodular goiter represent the group with the largest risk, and this finding has not changed over time. However, surgically treated patients - especially men – seem to fare better in the long term. In our third study, we did not find an increased prevalence of subclinical hyperthyroidism among AF ablation patients, although this group had significantly higher levels of free T4.

5.1 STUDY I

We found an increased risk of all-cause death as well as cardiovascular disease and death among patients treated for hyperthyroidism. The risk of all-cause mortality for the whole hyperthyroid group was elevated by 27%, a number that lies remarkably close to the 21% risk increase found in an earlier meta-analysis that was based on similar patients but older data[69]. One particular paper deserves further mentioning here because it has had a marked impact on the way that long-term risk is viewed on this topic: In 2005, a British research group showed that radioiodine treated subjects had increased all-cause and cardiovascular mortality (compared to the general population) only if they were still hyperthyroid or euthyroid after treatment[56]. In other words, iatrogenic hypothyroidism should perhaps be regarded as the preferred outcome. This conclusion is intuitively appealing to most physicians, and we attempted to address it in our study; however, since hypothyroidism is virtually never a cause for hospitalisation, it was not possible to use patient register data to this end. Instead we searched the drug register to find levothyroxine users among those patients still alive in 2005. We could thus demonstrate very high prevalences of hypothyroidism among all patients, both those treated for hyperthyroidism and for nontoxic goitre. This finding seems to contradict the earlier notion that hypothyroidism as such is beneficial, seeing as how the nontoxic group did not have a lower risk than the general population. However, we wish to emphasize that such a conclusion is only valid if one accepts the assumption that post-treatment hypothyroidism was roughly as prevalent among patients that died before 2005.

Stratification according to calendar year of inclusion did not indicate a lower risk in patients who were treated for hyperthyroidism after year 1990 than in those treated earlier, compared to nontoxic goitre patients. There were also no apparent differences over time when comparisons were made to the general population. Several previous studies have analysed the impact of different time periods as a continuous variable, but none of these have found the calendar year of inclusion to significantly affect outcomes.[41,42,44,55,59]. To our knowledge only one other study has divided patients into strata depending on year of inclusion. In 2014, Finnish researchers reported that among patients who had undergone surgery for hyperthyroidism between 1986-2007, those operated after 1996 had a 20% higher risk of cardiovascular hospitalization compared to those treated earlier.[63] Our study yielded similar results but also demonstrated higher ratios of all-cause and cardiovascular mortality over

time. Taken together we believe these findings signal a worrying trend that requires further investigation in the future.

When outcomes in terms of cardiovascular hospitalization were examined at different lengths of follow-up, a striking rise in the incidence of AF – considerably higher than for any other diagnosis - was observed one year after inclusion. This was likely an effect of the well-known correlation between hyperthyroidism and AF[47]. It was only through a much longer period of follow-up that clear increases in other cardiovascular diagnoses could be found. An interesting thought is whether residual AF from hyperthyroidism might lead to other types of cardiovascular morbidity over time.

We found that the highest cardiovascular risk was confined to toxic nodular goitre patients as opposed to patients with Graves' disease. There is no obvious explanation for this. The results from those previous register studies that have compared aetiologies have been conflicting [58,62-64]. It is possible that the duration of hyperthyroidism plays a role here. Graves' disease often has a rapid onset with explicit symptoms. By contrast, toxic nodular goitre can linger as subclinical hyperthyroidism for several years before it progresses to thyrotoxicosis[96]. It is possible that such prolonged exposure to high levels of thyroid hormone has lasting detrimental effects on the heart and vessels.

Although the overall connection between hyperthyroidism and cardiovascular disease has been demonstrated before by other research groups, many previous studies have only used the background population for reference, thereby excluding the possibility of adjusting for any comorbidities. In the light of decreasing cardiovascular mortality in the developed world during the last decades, the relevance of some of the earliest findings on this subject could also be brought into question. We have explored the association between hyperthyroidism and cardiovascular disease in particular. This was done both by using a very large cohort and by comparing our study subjects to different reference populations, using recently updated registers to assess outcomes.

5.2 STUDY II

In this study, our main finding was that thyroidectomy as treatment for hyperthyroidism was associated with a lower long-term risk of dying compared to radioiodine. The difference in cardiovascular mortality between groups was the main reason for this finding. Males in particular seemed to benefit most from surgical treatment. In general, our results did not vary significantly across the different statistical methods used.

To the best of our knowledge, these findings have not been described before; on the other hand, the topic does not seem to have ever been comprehensively studied, at least not in males and/or for other outcomes than cancer. As a rule, it is always difficult to separate any inherent effects of a disease from the side-effects of its treatment if randomised trials are lacking. Given the known association between hyperthyroidism and cardiovascular risk, any

conclusions about treatment effects become particularly treacherous. However, a recent study from Denmark found an elevated risk of cerebrovascular disease in both hyperthyroid and nontoxic goitre patients who were treated with radioiodine, something which might imply a negative effect from radioiodine as such[97]. This cannot explain the difference between men and women found in our study; however, it is possible that radioiodine represents a cardiovascular risk factor that has a greater impact in a male population, considering that the cardiovascular risk profile among men in general is higher. Another explanation might be found from a study which showed that men are less likely than women to become hypothyroid from treatment with radioiodine[98]. Although we were not able to investigate this possibility in our cohort, it can be hypothesised that mean time to remission was longer among males treated with radioiodine than among those who received surgery. As discussed in study I, this might increase cardiovascular risk in the long run.

5.3 STUDY III

Here, we found no increased prevalence of subclinical hyperthyroidism among patients admitted for AF ablation (cases) compared to those admitted for AVNRT ablation (controls). In fact, the overall prevalence of subclinical hyperthyroidism was rather low compared to the general population prevalence stated in the literature[99]. Our finding is at odds with a previous retrospective study performed by our research group in which we found subclinical hyperthyroidism in 10% of AF ablation patients when medical records were scrutinised retrospectively. This discrepancy might possibly be because amiodarone use has decreased over the last few years. Amiodarone is a potent agent for treating arrhythmias, but it is well known to increase the risk of thyroid dysfunction due to its very high iodine content.

This project was based on the hypothesis that subclinical hyperthyroidism might be a contributing factor behind some of the most therapy-refractory cases of AF. Because catheter ablation can be seen as the last line of treatment, the prevalence of subclinical hyperthyroidism should be particularly high among AF patients referred for this procedure.

Both overt and subclinical hyperthyroidism are associated with an increased risk of AF.[74-76,100] In patients with hyperthyroidism-induced AF, only about 60% spontaneously convert to sinus rhythm if euthyroidism is restored[101,102]. Among the remaining 40%, however, the arrhythmia persists. This might be explained by the promotion of substrates for AF in the heart by a process of remodeling (sometimes referred to as “AF begets AF”).[103] Thus, early detection and treatment of subclinical hyperthyroidism in individuals with AF may perhaps have an impact on the recurrence of AF after catheter ablation.

Although our primary hypothesis was not verified in this study, we found a mean level of free T4 that was significantly higher among AF patients, even after adjustments were made for baseline differences between groups. High normal FT4 levels have previously been associated with an increased prevalence[76] and incidence of AF [77]. It has also been suggested to predict recurrence of AF after catheter ablation[79,80].

5.4 STRENGTHS AND LIMITATIONS

Analyses in Studies I and II were largely based on information collected from healthcare registers. This method of research is almost invariably connected with both unquestionable strengths and clear limitations. The most obvious strengths of both these projects are the size of the cohort and the very long follow-up time. Another strength comes from the structure of the Swedish healthcare registers which enable cross-matching between data bases; along with the system of personal identity numbers and census data, few patients are ever lost to follow-up. In Study I we collected thousands of nontoxic goitre patients for use as a reference group to our hyperthyroid cases. We argued that these subjects were more suitable for comparison than the general population or randomly selected controls because they had also received treatment for a thyroid disorder. Furthermore, results from internal comparisons (hyperthyroidism versus nontoxic goiter) were cross-checked with population level data.

Potential confounding due to age differences between groups was addressed both by adjusting for age as a continuous variable, and by stratifying for age upon inclusion.

Limitations of these register studies include a lack of complete information on important parameters such as body weight, smoking, and several comorbidities; hypertension, for instance, has a much higher "true" prevalence than can be found from healthcare registers. Also, even though the Swedish patient register is considered to be reliable with regards to several cardiovascular diagnoses, the death register has not been as conclusively validated.

Another limitation is the fact that diagnostic methods, treatment guidelines, and definitions of disease have changed considerably over the last decades. For instance, ICD codes and codes for surgical procedures have been re-defined twice since the beginning of our inclusion period in 1976. Furthermore, important diagnostic methods such as assays for thyroid receptor antibodies and cardiac troponin markers were not widely available forty years ago. Another example is the gradual realisation among endocrinologists during the '80s and '90s that the choice of treatment for Graves' disease might affect the progression of ophthalmopathy. Taken together, all of these changes are likely to have affected both treatments and diagnostics in ways that we were unable to adjust for.

Furthermore, we did not have access to information about possible subclinical dysfunction prior to inclusion into the study, and we did not know how patients responded to treatment (although we did know that the proportion of levothyroxine treated individuals was high in each group in 2005). Also, patients treated with antithyroid drugs were not included because they were not registered in national databases during the time period studied. It should also be noted that there was no one in the unexposed group of nontoxic goitre patients that had received radioiodine treatment. Lastly, radioiodine treated patients were gathered from a different data base than were surgically treated patients. It is possible that this might have skewed our assessment of baseline co-morbidity.

A few further considerations apply to study II: The use of three different statistical methods lends increased reliability to the final results, since these were by and large consistent with each other. Co-variables were well balanced, with all absolute standardized differences lower than 0.1. However, no amount of statistical adjustment could ever circumvent the possibility of indication bias when different treatments are compared to each other in a non-randomised, non-blinded fashion.

Study III is, to the best of our knowledge, the first of its kind to use a control group to investigate the prevalence of subclinical hyperthyroidism among catheter ablation patients. Other strengths include the use of clinical research forms to assess baseline co-variates, and systematic prospective collection of data. The difference in gender distribution and mean age between groups constitute study limitations. Furthermore, it is plausible that the low prevalence of subclinical hyperthyroidism was affected by patients not being referred to catheter ablation due to subclinical thyroid dysfunction.

6 CONCLUSIONS

In summary, the following conclusions can be drawn:

- Although hyperthyroidism is considered curable, it is nevertheless a diagnosis associated with an increased risk of death and cardiovascular disease in the long term.
- AF is the cardiovascular diagnosis with the highest incidence in the short term after hyperthyroidism of any aetiology. In the longer term, patients with toxic nodular goitre appear to have a particularly unfavourable risk profile in general. Future research might clarify whether the increased incidence of other diagnoses – most notably stroke – is due to residual AF.
- Advances in cardiovascular care during the last decades do not seem to have diminished the risk.
- Surgery as treatment for hyperthyroidism is associated with a lower risk of all-cause and cardiovascular death compared to radioiodine treatment.
- Previously undiagnosed subclinical hyperthyroidism, defined as a suppressed TSH level, is not a common finding among AF patients referred for catheter ablation.
- The mean level of T4 is higher among AF patients than among controls. Future studies should investigate whether this finding has implications for relapse into AF after ablation.

7 CLINICAL IMPLICATIONS & FUTURE PERSPECTIVES

Risk stratification is key as regards primary prevention of cardiovascular disease. It is possible that a history of hyperthyroidism should be considered yet another risk factor, along with such conditions as hypertension or smoking. In that case, increased vigilance for cardiovascular disease might be beneficial for this group. One concrete example of this could be AF screening, a procedure that has attracted increasing attention during recent years[104]. As shown in Study I, AF incidence is increased at an early stage after hyperthyroidism, and one might speculate whether the increased findings of other cardiovascular diagnoses later on might be a sign of inadequate medication with anticoagulants and substances for rate control. It should also be remembered that paroxysmal AF without symptoms – so-called "silent" AF – is known to be quite common in the general population; whether this is also the case among formerly hyperthyroid patients is not known[105]. To explore this question, the author is currently conducting an AF screening study in patients undergoing treatment for hyperthyroidism.

As for other cardiovascular risk factors, it is of course impossible to retrospectively change the fact that a patient was once hyperthyroid. However, other actions may be taken in order to reduce his or her total risk. Examples include the use of lipid lowering or antihypertensive drugs or programmes for smoking cessation. There is also one public policy measure that may reduce the incidence of hyperthyroidism worldwide: Programmes that aim to increase the level of iodine intake in areas of iodine deficiency should, in the long run, lead to a lower incidence of hyperthyroidism (especially toxic nodular goitre).

In a wider perspective, it is worth noting that hyperthyroidism is not the only metabolic hormone disturbance associated with diseases of the hearts and vessels. The most notorious among the other endocrine disorders is of course diabetes, the cardiovascular consequences of which have been quite thoroughly studied. However, less is known about the reasons for the increased cardiovascular risk that seems to be connected with, for instance, Cushing's disease or hypertestosteronism[106-108]. Although theories on this topic abound for thyroid disorders as well as for each of these other conditions, further research might be warranted to look for any possible common denominators between them.

Regarding our findings on differences between treatments for hyperthyroidism, one might consider surgery to be recommended as first-line treatment. However, register studies are not the firmest of foundations upon which to construct treatment recommendations. It is a disturbing fact that large randomised controlled trials are missing in this field. Such studies are warranted in order to change practice guidelines. For now, however, the best way forward will most likely be to conduct further research on other registers or healthcare cohorts. Fortunately, many medical centres worldwide that treat hyperthyroidism – in particular those that deal with radioiodine – already have a tradition of long-term follow-up. Although this is mainly done for the purpose of finding patients with late-onset hypothyroidism, the data might also be used to estimate the incidence of cardiovascular disease in the long term. It

should not be impossible to include persons treated with surgery or antithyroid drugs in these cohorts.

As for our third study, we have found no evidence that intensified screening for subclinical hyperthyroidism in AF ablation patients would be useful. We did, however, find an elevated mean level of free T4 among individuals with AF. Although this was an unexpected finding and not the answer to our initial hypothesis, it seems to be in accordance with other studies. As intriguing as this observation may be, the truly important issue here is whether T4 levels affect ablation success rates. At present the aim of any new similar investigation would be to confirm a correlation between thyroid hormones and AF ablation outcomes. Should this be the case, interventional trials that use randomized allocation of treatments to lower hormone levels would likely be a logical next step. The percentages of patients with atrial flutter or AVNRT who experience recurrences post-ablation are presently down to single digits. One of the ultimate goals within electrophysiology is to reach similar results for AF patients.

8 SVENSK SAMMANFATTNING

Hjärtkärlsjukdom är fortfarande den ledande dödsorsaken i västvärlden, även om risken minskat under senare årtionden till följd av förbättrade levnadsvanor och nya möjligheter till diagnostik och behandling. En av hjärtkärlforskningens viktigare uppgifter är den så kallade kardiovaskulära preventionen; med detta menas att man försöker utröna vilka faktorer som statistiskt sett hänger samman med en ökad sannolikhet för insjuknande i allvarliga sjukdomar som exempelvis hjärtinfarkt och stroke. Den informationen kan bland annat användas för att urskilja individer som löper ökad risk att drabbas, och därigenom finns möjlighet att rikta utredningar och förebyggande åtgärder mot dessa – samt att undvika överbehandling av andra. Även om många så kallade riskfaktorer redan är kända – rökning och högt blodtryck är ett par välkända exempel – så finns det fortsatt ett behov av att försöka finna ytterligare bitar i det pussel som utgör kardiovaskulära risk.

Hypertyreos (i dagligt tal ofta kallat giftstruma) är en sedan länge känd åkomma som uppstår då sköldkörteln – som i vanliga fall styr kroppens ämnesomsättning – blir överaktiv och börjar producera för stora mängder sköldkörtelhormon. Den klassas som en botbar folksjukdom som drabbar cirka två procent av alla svenskar någon gång i livet, företrädesvis kvinnor. Inte sällan uppstår uttalade och typiska symtom som leder den kliniska utredningen rätt i tidigt skede. Diagnos ställs enkelt genom blodprovtagning, ofta via primärvården. Det händer dock att både laboratoriemässiga förändringar och symtom är mer diskreta; man talar då om *subklinisk* hypertyreos, ett tillstånd som blivit föremål för allt mer forskning på senare år. Tidigare studier talar för att personer som insjuknar i hypertyreos (av antingen den vanliga eller subkliniska sorten) löper ökad risk att dö i förtid trots att hormonrubbningen behandlats framgångsrikt. Detta tycks åtminstone delvis bero på en ökad risk för hjärtkärlsjukdom hos denna grupp på lång sikt. Slutsatserna baseras dock till viss del på äldre studier, från en tid då både utrednings- och behandlingsmöjligheterna vid hjärtkärlsjukdom var betydligt mindre utvecklade. Vad gäller de andra, nyare studierna så byggde ett flertal sina resultat på jämförelsegrupper som möjligen inte var de mest relevanta i sammanhanget.

Vårt syfte med detta projekt var att vidare undersöka kopplingen mellan sköldkörtelsjukdom och hjärtkärlsjukdom med hjälp av uppdaterade data och delvis nya metoder. De två första arbetena är så kallade registerstudier baserade på data från de svenska befolknings- och sjukvårdsregistren, som tillsammans med sina motsvarigheter i norden är unika vad gäller långtidsuppföljning och tillförlitlighet. Det tredje delarbetet är en klinisk studie där vi undersökt sambandet mellan svårbehandlat förmaksflimmer och subklinisk hypertyreos.

Metod och resultat

I **delarbete I** inhämtade vi information om patienter som genomgått tyreoidektomi (fullständigt eller partiellt avlägsnande av sköldkörteln medelst kirurgi) från det nationella patientregistret. Information om patienter som behandlats med radioaktivt jod inhämtades från en databas baserad på journaluppgifter. Data över kardiovaskulära utfall och död samlades från patientregistret, det nationella dödsorsaksregistret, samt Statistiska

centralbyrån. Det svenska läkemedelsregistret användes också för att utvärdera levaxinmedicinering. Studiepersonerna utgjordes av i princip samtliga invånare i Stockholms län som genomgått antingen tyreoidektomi eller radiojodbehandling under perioden 1976-2000. Kohorten följdes fram till år 2012. De som behandlats för hypertyreos betraktades som exponerade individer, medan de som behandlats för icke-toxisk struma definierades som en icke-exponerad kontrollgrupp. Jämförelser gjordes även mot Stockholms bakgrundsbefolkning. Resultaten visade en ökad risk för död oavsett orsak, samt ökad risk för både kardiovaskulär sjukdom och död, hos hypertyreosgruppen (12 239 individer) jämfört med gruppen med icke-toxisk struma (3 685 individer). Liknande skillnader sågs även vid jämförelser mot normalbefolkningen. Risken var större för patienter med toxisk knölstruma än för patienter med Graves' sjukdom (två vanliga orsaker till hypertyreos). Vi fann ingen antydan till minskad risk hos patienter som inkluderades efter 1990, jämför med dem som inkluderats tidigare.

Delarbete II baserades i huvudsak på hypertyreosgruppen från delarbete I. Vi använde tre olika statistiska metoder för att utröna om valet av behandling vid hypertyreos (kirurgi eller radiojod) har någon betydelse för framtida risk för död och sjukdom. 10 250 patienter som behandlats med radiojod jämfördes med 742 patienter som behandlats med tyreoidektomi. Resultaten visade en minskad risk för död oavsett orsak, samt för kardiovaskulär död, hos patienter som behandlats med kirurgi. Detta gällde oavsett analysmetod. Särskilt män verkade dra fördel av kirurgi.

Delarbete III var en så kallad tvärsnitsstudie, i vilken vi mätte halterna av sköldkörtelhormoner hos patienter som var på väg att genomgå ablationsbehandling av förmaksflimmer (ett kateterburet ingrepp i hjärtat som brukar reserveras för särskilt svårbehandlade rytmrubbningar). Vår hypotes var att just denna grupp borde ha en hög förekomst av subklinisk hypertyreos, vilket också var något vi sett vid en journalgenomgång som föregick detta arbete. Som jämförelsegrupp använde vi oss av patienter som genomgick ablationsbehandling av andra rytmrubbningar än förmaksflimmer. Våra resultat visade dock ingen statistiskt signifikant skillnad i förekomst av subklinisk hypertyreos; däremot så fann vi signifikant högre nivåer av fria sköldkörtelhormoner hos förmaksflimmerpatienterna.

Slutsatser

- Hypertyreos är en sjukdom som sammanhänger med ökad risk för kardiovaskulär sjukdom och död på lång sikt.
- Toxisk knölstruma är associerad med högre risk än Graves' sjukdom.
- I valet mellan radiojod och kirurgi som behandling av hypertyreos är den senare metoden att föredra, då den är förenad med lägre risk för kardiovaskulärt insjuknande och död på lång sikt.
- Patienter som remitteras för ablation av förmaksflimmer har inte någon ökad förekomst av subklinisk hypertyreos.

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