Hypertension, Atrial Fibrillation and Aldosteronism

A Study of Interplay, Predictors and Outcome

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To my parents

ABSTRACT

Background: Atrial fibrillation (AF) is the most common significant arrhythmia, affecting almost 3% of the adult population in Sweden. Although AF is associated with increased risk of lower quality of life, heart failure, stroke and mortality, the therapeutically options are still limited. Hypertension is a common cardiovascular disease affecting approximately one third of the adult population, and is the underlying cause for more AF cases than any other disease. Almost 10% of the hypertension cases may be due to primary aldosteronism, a condition that can be treated by a specific therapy. Little is known regarding the prevalence of primary aldosteronism in the general population and in the AF population. Moreover, current data suggest that AF is overrepresented among hypertensive patients with primary aldosteronism.

Major research question: The present thesis aims to evaluate the possibility of screening for primary aldosteronism in the AF population, and to estimate the prevalence of primary aldosteronism in the AF population. Furthermore, this thesis aims to assess the role of blood pressure levels and lipid profile in preventing new-onset AF in the hypertensive population.

Methods: In Study I, 149 AF patients < 65 years were screened for primary aldosteronism by using the aldosterone to renin ratio. In the case-control Study III, all AF cases in Sweden between 1987 and 2013 (N=713,569) were identified by using the Swedish Patient Register. An age, sex and place of birth matched control-cohort without AF was randomly selected from the Swedish Total Population Register with a case to control ratio of 1:2 (N=1,393,953). The prevalence of primary aldosteronism for the individuals alive on 31 December, 2013 in both cohorts was calculated through linkage to the Swedish Patient Register. Studies II and IV utilized the primary care hypertensive population in the Swedish Primary Care Cardiovascular Database (SPCCD). Approximately 50,000 hypertensive patients without AF were followed-up between 2002 and 2008, and dichotomized according to AF development or not. The in-treatment blood pressure and lipid profile were compared between the new-onset AF group and the no-AF group.

Results: Four individuals (2.6%) of the screened AF population were found to have undiagnosed primary aldosteronism. The prevalence of primary aldosteronism in December 2013 was 0.056% in the AF cohort and 0.024% in controls. Besides, lower in-treatment systolic blood pressure was found to be associated with lower risk of new-onset AF. Paradoxically, total cholesterol and low-density lipoprotein cholesterol were found to have an inverse association with new-onset AF.

Conclusions: Assessment of aldosterone to renin ratio can be useful for identification of underlying primary aldosteronism in patients with diagnosed AF and hypertension. This recommendation is strengthened by the finding of a doubled risk for primary aldosteronism in the AF population compared to matched controls without AF. Moreover, successful blood pressure control in hypertensive patients may reduce the risk of new-onset AF. Finally, the underlying mechanism regarding the dyslipidemia paradox in AF development is unclear.

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LIST OF PAPERS

This thesis is based on the following papers.

I Mourtzinis G, Ebrahimi A, Gustafsson H, Johannsson G, Manhem K. Aldosterone to renin ratio as a screening instrument for primary aldosteronism in a middle-aged population with atrial fibrillation.
Horm Metab Res 2017; 49: 831–837.

II Mourtzinis G, Schiöler L, Kahan T, Bengtsson Boström K, Hjerpe P, Hasselström J, Manhem K. Antihypertensive control and new-onset atrial fibrillation: Results from the Swedish Primary Care Cardiovascular Database (SPCCD).
Eur J Prev Cardiol. 2017;24(11):1206-1211.

III Mourtzinis G, Adamsson Eryd S, Rosengren A, Björck L, Adiels M, Johannsson G, Manhem K. Primary aldosteronism and thyroid disorders in atrial fibrillation: A Swedish nationwide case-control study.
Eur J Prev Cardiol. 2018. doi: 10.1177/2047487318759853.

IV Mourtzinis G, Kahan T, Bengtsson Boström K, Schiöler L, Cedstrand Wallin L, Hjerpe P, Hasselström J, Manhem K. Relation Between Lipid Profile and New-Onset Atrial Fibrillation in Patients with Systemic Hypertension (From the Swedish Primary Care Cardiovascular Database [SPCCD])
Submitted.

CONTENTS

ABBREVIATIONS

ACTH	adrenocorticotropin
AF	atrial fibrillation
ARR	aldosterone to renin ratio
CI	confidence interval
DBP	diastolic blood pressure
HDL-C	high-density lipoprotein cholesterol
ICD	International Classification of Disease
LDL-C	low-density lipoprotein cholesterol
NADPH	nicotinamide adenine dinucleotide phosphate
NO	nitric oxide
OR	odds ratio
P	probability value
PP	brachial pulse pressure
RR	risk ratio
SBP	systolic blood pressure
SD	standard deviation
SPCCD	Swedish Primary Care Cardiovascular Database

INTRODUCTION

Cardiovascular diseases account for the majority of global premature deaths [1]. A common cardiac disease is atrial fibrillation (AF), an arrhythmia affecting almost 3% of the adult population in Sweden [2]. AF is a condition associated with increased risk of lower life quality, heart failure, stroke, and mortality [3,4]. During recent decades the incidence of AF has increased and this renders us with an upward trend in hospitalization and medical costs due to AF [5,6]. Thus, AF has become a major public health issue. But at the same time the therapeutic options for the majority of AF patients have not been substantially increased, still characterized as modest effective and potentially harmful [7]. Therefore, in the absence of effective AF treatment AF prevention should be a priority matter in our health care system. This thesis deals with the opportunity for AF prevention by investigating two conditions promoting AF, namely hypertension and primary aldosteronism. Understanding in depth of the association between hypertension and primary aldosteronism, and further the connection to AF, can provide us useful tools in AF prevention.

Atrial fibrillation

First of all it is important to understand how AF arises. AF is characterized by disorganized atrial depolarizations that result in the absence of effective atrial contraction and a rapid chaotic rhythm. Common symptoms of AF are palpitations, asthenia, dyspnea, and angina. However, up to 25% of the patients with AF experiencing no symptoms [8]. The AF diagnosis is based on standard electrocardiogram showing irregular ventricular rhythm without consistent P-waves (Figure 1). Initially, AF is often presented as self-terminating episodes. Over time though, those episodes last longer and end up in sustained forms of AF [9]. The progressive nature of AF depends partly on the progression of underlying structural heart diseases, and partly on the AF itself.

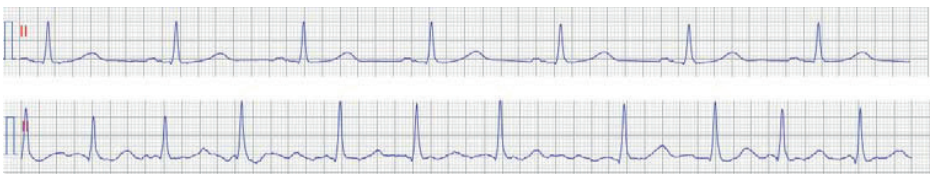

Figure 1. Electrocardiogram of a patient in sinus rhythm (above) and in atrial fibrillation (below).

Electropathophysiology in atrial fibrillation

The pathophysiology of AF has a complex multifactorial mechanism that is still not fully understood. In general, AF requires both a trigger and a susceptible substrate in the human atria. The trigger for the AF initiation is often, but not exclusively, enhanced electrical activity in the myocardial sleeves of the pulmonary veins [10]. As AF progresses to persistent and permanent forms ectopic activity outside the pulmo-

nary veins seems to play a more important role, explaining partly the lower efficacy of treatment with pulmonary vein isolation in those populations [11]. Thereafter, AF is maintained in the vulnerable atrial substrate by a driver mechanism (a sustained rapid ectopic activity or a rapid local re-entry) [12]. Ectopic activity can be attributable to delayed or early afterdepolarizations [13,14]. Re-entrant activity has been described in various theoretical and experimental models. The main concepts of re-entry mechanism are the circular or spiral wavefronts (rotors), and the multiple wavelets. Circus movement re-entry was first demonstrated in cardiac tissue in 1914 [15]. It is characterized by an activation wave that can travel around an anatomical obstacle and reactivate previously excited tissue when tissue refractoriness is short or wave-conduction is slow [16]. If tissue refractoriness is prolonged or conduction is accelerated the re-entry terminates. In 1924, Garrey proposed a theory of re-entry without anatomical structure in the middle of the circuit [17]. This circular re-entry without anatomical obstacle, so-called leading circle concept, demonstrated experimentally by Allessie et al in 1973 [18].

Another re-entry mechanism, the spiral wave re-entry is a rapidly circulating rotor with a wavefront rotating around a central core [19]. Critical for the maintenance of the spiral wave re-entry is the collision of the wavefront with an excitable wavetail of another wave. Furthermore, in the late 1950s Moe proposed the hypothesis that AF was sustained by multiple wavelets [20]. The multiple wavelet hypothesis is supported by numerous experimental and clinical observations, as for example the Maze procedure [21]. According to this hypothesis, continuous wavefront–wavetail interactions lead to wavebreak and generation of new wavefronts. On the other hand, block, collision, and fusion of wavefronts tend to reduce their number. As long as the number of wavefronts is above a critical level, multiple wavelets will be capable to sustain the arrhythmia. However, many remaining gaps between experimental models and clinical observations delay the understanding of AF mechanism, and subsequently the development of effective treatment alternatives.

Atrial remodeling in atrial fibrillation

Atrial remodeling is the essential substrate for the rise of AF. Of importance is that AF itself can promote electrophysiological atrial remodeling, creating also an AF substrate that begets AF [22]. Sustained AF leads to various changes in currents resulting in shortening of the action potential and effective refractory period, and therefore establishment of AF. Increased atrial rate during AF increases Ca^{2+} loading. Myocytes respond by reducing inward L-type Ca^{2+} current to prevent cytotoxic Ca^{2+} overload. This action, though, decreases action potential duration, and promotes AF perpetuation [23]. Besides, increased inward-rectifier K^+ current affects the resting membrane potential that becomes more negative in AF, and may contribute to AF prolongation [24]. The transient outward K^+ current is also affected and consistently decreased in AF, but the effects of this downregulation are unclear but it may indirectly increase the action potential amplitude [25]. Electrical remodeling in AF seems to engage even Na^+ current, although findings regarding effect on Na^+ current are discrepant. Moreover, AF causes cardiomyocyte contractile dysfunction due to impaired Ca^{2+} handling and decreased systolic Ca^{2+} transient [26]. Whether AF can produce additional forms of remodeling, particularly when in sustained forms, remains uncertain.

Structural atrial remodeling plays a crucial role in AF establishment. AF is associated with atrial dilatation, which increases the amount of atrial tissue that can accommodate re-entry circuits [27,28]. The most prominent atrial cardiomyocyte remodeling in AF includes increase in atrial cell size with myolysis and perinuclear accumulation of glycogen [29]. These alternations resemble the hibernation state of ventricular myocytes due to chronic low flow ischemia.

Atrial fibrosis

One of the most important factors in the formation of AF substrate is atrial fibrosis. Atrial fibrosis is the cardiac remodeling process that involves cellular components and the extra-cellular matrix leading to the accumulation of fibrotic tissue in the myocardium. There are four major cell types in the normal heart; cardiomyocytes, endothelial cells, smooth muscle cells in the vessels, and fibroblasts. Fibroblasts account for up to 60% of the cells in the heart, although cardiomyocytes determine the total myocardial mass [30]. Fibroblasts' pivotal role is to maintain the extra-cellular matrix homeostasis, and provide structural and mechanical support to the cardiomyocytes. The extra-cellular matrix consists of a dynamic network of fibers (mainly collagen), and is important in maintaining tissue architecture. The extra-cellular matrix is in a constant state of collagen turnover, which is regulated by mechanisms that are incompletely understood. It is, however, known that matrix metalloproteinases are responsible for collagen degradation. Whereas interleukin-1, prostaglandin, Tumor Necrosis Factor α, and Brain Natriuretic Peptide upregulate matrix metalloproteinases production [31].

Atrial fibrosis occurs when fibroproliferative signaling pathways get activated. Angiotensin II is a well-established profibrotic molecule. Angiotensin II mediates profibrotic effect through binding to angiotensin type-1 receptor that stimulates fibroblast proliferation, cardiomyocyte hypertrophy, and apoptosis. Other known profibrotic pathways act through Transforming Growth Factor β1, Platelet-Derived Growth Factor, and Connective Tissue Growth Factor. Reparative fibrosis replaces degenerating myocardial cells, whereas reactive fibrosis causes interstitial expansion between bundles of myocytes. Atrial fibrosis can be the result of a variety of pathological conditions including cardiac dysfunction, valvular heart disease, and myocardial ischemia. Pathologically produced collagen differs from that in normal myocardium [32]. In the healthy heart the number of the fibroblasts is maintained at a relatively low level, but increases dramatically under pathological conditions. During the fibrotic pathway, cardiac fibroblasts differentiate into myofibroblasts, a cell type that is normally not found in the heart. Myofibroblasts have a higher capacity to produce collagen than "normal" cardiac fibroblasts. Besides, myofibroblasts are more responsive to proinflammatory and profibrotic stimuli, and produce a variety of cytokines [30,33]. Thus, myofibroblasts enhance the atrial fibrosis and the inflammatory response in the atria.

Whether structural atrial remodeling is the cause or the consequence of AF remains unclear. Patients with history of any AF had tree- to five-fold greater extend of fibrosis compared with patients without AF, in a post-mortem investigation of patients with and without AF [34]. Another study reported similar degree of collagen expression in paroxysmal and permanent AF [35]. Thus, there are patients with paroxysmal AF having massive fibrosis, while there are patients with permanent AF having only mild

degree of fibrosis. These data do not support the theory that fibrotic alterations are a result of AF. In contrary, AF seems to be a consequence of the underlying fibrotic disease. There is, however, low level of evidence that could provide us an answer to this question.

The golden standard for evaluation of cardiac fibrosis has been the histological quantification through a cardiac biopsy. This method has of course the inherent limitation of the invasive nature. Nowadays, cardiac magnetic resonance imaging has been validated to provide accurate non-invasive assessment of regional myocardial fibrosis using late gadolinium enhancement, while diffuse interstitial myocardial fibrosis is accurately assessed with post-contrast T1 mapping [36]. Magnetic resonance imaging is though expensive and has a limited availability. A new, non-invasive, echocardiographic modality for assessment of the cardiac fibrosis is the integrated backscatter signal analysis by acoustic densitometry [37]. This low-cost technique is widely available and might be useful in assessment of atrial fibrosis.

Comorbidity in atrial fibrillation

In at least up to 90% of the AF cases the disease can be attributable to an associated comorbidity, while remaining use to be defined as lone AF [38]. The exactly proportion of lone AF among AF patients depends on our ability to diagnose concomitant conditions. Most probably, "untrue" lone AF patients with underdetected AF substrate are present in many more situations than we believe [39]. It is suggested that lone AF, i.e., without apparent heart disease, is the arrhythmic manifestation of a structural atrial disease that has been described as fibrotic atrial cardiomyopathy [40]. Over the past years, conditions that promote AF substrate have been identified by numerous studies. The most important conditions related to AF development are ageing, male sex, hypertension, heart failure, valvular heart disease, myocardial infarction, diabetes mellitus, hyperthyroidism, obesity, and obstructive sleep apnea [41-44]. Because of its high prevalence in the general population, hypertension is the underlying modifiable cause for more AF than any other risk factor [38,45]. Hence, hypertension is an obvious target in AF prevention.

Hypertension

Hypertension is defined as systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg. Those levels have been validated for office blood pressure in numerous studies, while for ambulatory blood pressure and home blood pressure the hypertension cut-off limit has been set slightly lower [46]. It is general agreement that the golden standard for the clinical blood pressure measurement is the indirect auscultatoric cuff/stethoscope method, based on the occluding arm cuff invented by Riva-Rocci and the blood flow sounds observed by Korotkoff [47]. However the auscultatoric cuff/stethoscope method presents inaccuracy and wide range of pressure difference compared to intra-arterial measurement [48]. In general, the auscultator method underestimates SBP and overestimates DBP. The direct intra-arterial measurement, however, is not possible to use in the clinical practice because of the invasive nature. Thus the method of choice is the auscultatoric method, but it should be performed with caution in order to avoid errors like digit preference, too rapid cuff

deflation, inappropriate cuff size, and beat selection during pulse variation. The newer oscillometric method is not better than the auscultatoric method, but it gains acceptance in every day practice because it offers greater convenience [49].

Globally, hypertension is prevalent in almost one out of three adults, without significant differences between developed and developing countries [50]. Only in communities isolated from the modern civilization hypertension has been shown to be absent or present in few individuals [51,52]. Hypertension is not only associated with AF, but is a strong independent risk factor of stroke, heart failure, myocardial infarction, peripheral artery disease, and cardiovascular death [53]. The vast majority of hypertension cases are idiopathic so called essential hypertension, while only about 10% are due to secondary hypertension forms depending on an identifiable cause [54]. Typically, essential hypertension arises in the middle or old ages after an interaction between genetic and environmental factors.

Secondary hypertension forms may be rare, but their diagnosis offers different therapeutically options. The most common causes of secondary hypertension in adults are obstructive sleep apnea, renal parenchymal disease, renal artery stenosis, and primary aldosteronism. While Cushing's syndrome, pheochromocytoma, hypo- and hyperthyroidism, acromegaly, primary hyperparathyroidism, and coarctatio aortae are far more uncommon [55]. Secondary hypertension has, in general, an earlier age at onset. Screening for secondary hypertension is expensive, time-consuming, and in many cases difficult to perform. Therefore, clinical suspicion should guide the screening investigation.

Pathophysiology in hypertension

Hypertension is a disease of vascular regulation resulting from malfunction of arterial pressure control mechanisms. The pathophysiological mechanisms of essential hypertension are complex and not fully understood. Blood pressure is described as the product of cardiac output and peripheral vascular resistance (blood pressure = cardiac output x peripheral arterial resistance). A cornerstone of the essential hypertension is the increased peripheral arterial resistance. But also increase of cardiac output through fluid retention plays an important role. The blood pressure regulation is a complex mechanism of interaction between the vasculature, the heart, the kidney, and the nervous system. The mechanisms that control the arterial blood pressure include baroreceptors that sense acute changes in blood pressure, and thereby affect the autonomous nervous system activity; activation of the renin-angiotensin system through fall in renal perfusion; adrenergic receptors that increase heart rate; endothelium-derived factors that cause vasodilation or vasoconstriction; natriuretic-peptides secretion in response to elevated blood pressure. Malfunction in those mechanisms plays a crucial role in development of essential hypertension.

Autonomous nervous system

All arteries are connected to the network of the autonomous nervous system [56]. The arterial tone is determined by the balance between vasoconstrictory and vasodilatory stimuli. Increased sympathetic tone activates the vascular smooth muscu-

lar and increases the vascular resistance. This process is suppressed by inhibitory feedback from the carotid baroreceptors [57]. The human organs differ in the density of α- and β-adrenoreceptors. Activation of α_1-adrenoreceptors leads to vasoconstriction, whereas stimulation of α_2-adrenoreceptors leads to vasodilation. Both β_1- and β_2-adrenoreceptors increase cardiac output through heart rate raise, but have less effect on the vascular resistance. Moreover, sympathetic innervation has direct effect on the kidneys. Sympathetic activation of the juxtaglomerular cells increases renin release, while sympathetic action on the tubular sodium reabsorption has anti-natriuretic effect. Both those actions result in increase blood pressure. In hypertension the autonomous cardiovascular control is impaired. Already in early hypertensive stages the parasympathetic action is reduced and the sympathetic increased. As hypertension progresses the sympathetic overdrive progress to further potentiation. However, what drives this adrenergic activation to cause blood pressure elevation is unclear [58].

Endothelium-derived factors

The human arteries have a three-coat construction: the inner endothelial coat (tunica intima), the middle smooth muscular coat (tunica media), and the external connective tissue coat (tunica adventitia). The large arteries are supplied with nutrient blood vessels (vasa vasorum), which reach the tunica adventitia [59]. The inner surface of the blood vessels consists of a cellular monolayer that comprises the endothelium. The endothelium plays an important role in the regulation of the vascular tone, and thereby the regulation of the vascular resistance. This regulation occurs through endothelium-produced mediators that affect the surrounding vascular smooth muscle cells. Endothelium-derived constricting factors (e.g., angiotensin II and endothelin) have vasoconstriction effect. On the contrary, endothelium-derived relaxing factors, mainly nitic oxide (NO), cause vasodilation [60]. Of importance is the endothelium-produced kinins (e.g., bradykinin), which both increase concentration of NO and reduce the noradrenergic vasoconstriction effect [61]. Imbalance between those factors leads to excessive vasoconstriction and endothelial dysfunction, which is a major characteristic of hypertension. NO has in addition an anti-inflammatory role by suppressing thrombosis and leukocyte adhesion to the vascular wall [62]. Hypertension has been associated with reduced levels of NO, which leads to impaired endothelial function and structural alterations of the vessel wall [63]. The microvasculature, (i.e., the network of arterioles, venules, and capillaries) is particularly vulnerable because it is the major site of systemic resistance. Especially the vascular beds are susceptible for blood pressure elevation. This process results to microvascular damage, which is the earliest organ damage in hypertension. The structural alterations of the vessel wall in hypertension are described as vascular remodeling. This vascular remodeling has been shown to be predominant for the small vessels, where the lumen is reduced and the media-to-lumen ratio increased [64].

Renin-angiotensin system

It is well established that dysregulation of the renin-angiotensin system contributes to the development and maintenance of hypertension. The renin-angiotensin system produces the active metabolite angiotensin II that has direct actions on the blood vessels, the kidneys, the adrenal glands, and the brain (Figure 2). Angiotensin II action is

typically directly vasoconstrictive through activation of the angiotensin type 1 receptor on the vascular endothelium. However, angiotensin II causes hypertension even through other pathways, as for instance through activation of interleukin-6 release that causes vasoconstriction and inflammation [65]. Moreover, angiotensin II plays a pivotal role in blood pressure regulation and sodium homeostasis in the kidneys. Angiotensin II has a direct effect on the proximal tubules to increase sodium reabsorption, and it has a complex and variable effect on glomerular filtration and renal blood flow [66]. Furthermore, angiotensin II acts on the adrenal cortex to stimulate the synthesis and secretion of aldosterone, which in turn promotes sodium reabsorption, water retention and potassium loss, and thus raise of blood pressure [67]. Angiotensin II receptors have also been found in the brain, and current data suggest that renin-angiotensin system contributes to hypertension even by direct affect on the central nervous system. Angiotensin II is thought to avoid the blood brain barrier at the sensory circumventricular organs, and through dysregulation of the sympathetic outflow affects key central pathways in blood pressure regulation and blood fluid homeostasis [68]. Moreover, angiotensin II induces vascular remodeling by promoting vascular inflammation. Angiotensin II stimulates nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and enhances production of reactive oxygen species, which in turn inactivate NO, leading to endothelial dysfunction, and to vascular inflammation by upregulating adhesion molecules, cytokines, and chemokines [69].

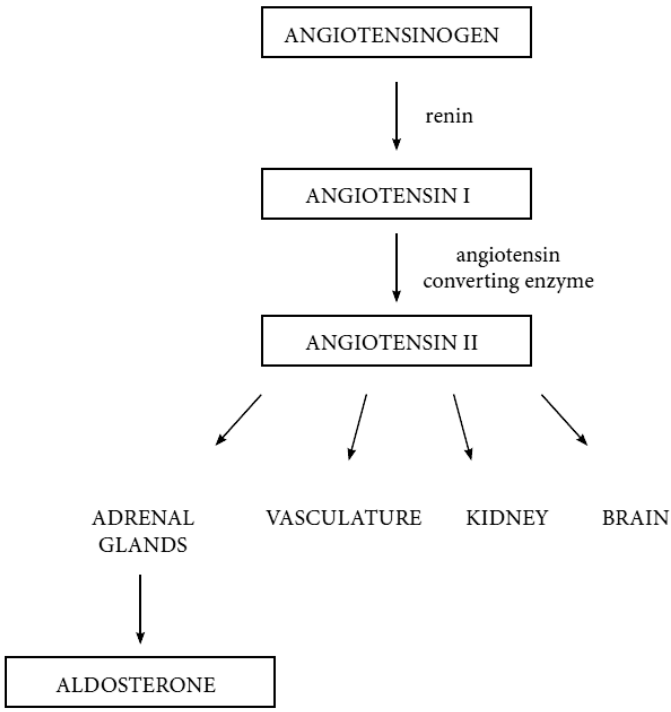

Figure 2. The renin-angiotensin system.

Hypertensive heart disease

Hypertensive heart disease is characterized by left ventricular hypertrophy. Elevated arterial blood pressure (i.e., increased afterload) induces cardiomyocyte hypertrophy, and stimulates fibroblasts and collagen deposit. This fibrotic remodeling process creates a concentric cardiac hypertrophy with increase in cardiac mass at the expense of the chamber volume [70]. When pressure overload is sustained, the diastolic function progressively fails after a point that the left ventricle decompensates and hypertensive heart failure with preserved ejection fraction appears. In contrast, when the volume overload is sustained, the left ventricle undergo an eccentric remodeling that leads to increase in both cardiac mass and chamber volume. Decompensation of the eccentric remodeled left ventricle results to heart failure with reduced ejection fraction [71]. Moreover, hypertension promotes coronary artery atherosclerosis, a major risk of ischemic systolic heart failure. Hence, hypertension plays a pivotal role in heart failure progression.

There is a strong association between hypertension and atrial remodeling, i.e., the susceptible AF substrate. Hypertensive patients with left ventricular hypertrophy have been found to have an association with slower conduction velocity and sustained AF inducibility [72]. Hypertension in an ovine-model, resulted in biatrial hypertrophy, left atrial dysfunction, greater AF inducibility, and increased interstitial fibrosis [73]. Whereas elevated afterload, i.e., hypertension, in a rat-model resulted to atrial remodeling that includes atrial fibrosis, altered gap-junction protein expression, conduction abnormalities, and increased inducibility of AF [74]. Consequently, hypertension creates substrate needed for AF development.

In general, SBP rises throughout life, while DBP rises until the age of 50-60 and thereafter progressively falls due to progressive arterial stiffness. Increased arterial stiffness can be measured as higher pulse pressure velocity. Aortic pulse pressure velocity is an independent strong predictor of cardiovascular mortality [75]. Besides, hypertension is linked to impaired vascular elasticity that also indicates substantially increased stiffness of the large artery wall [76]. Hypertensive patients who progressively develop heart failure usually develop normal or low blood pressure as heart failure becomes more severe. This phenomenon of low blood pressure despite increased peripheral vascular resistance depends on fall in cardiac output [71].

Primary aldosteronism

Dr. Jerome W. Conn was Professor of Medicine at the University of Michigan when he introduced the term primary aldosteronism in 1954 [77]. Dr. Conn had previously, for more than six months, examined a 34-years-old woman with hypertension, hypokalemia, alkalosis, and history of muscle spasm, tetany and weakness. Thereafter he explained the clinical picture through possible excess secretion of the adrenal salt-retaining corticoid, and he planned for bilateral adrenalectomy. During the operation, a huge right adrenal tumor was found and expired, while contralateral gland left intact. The patient´s clinical condition were reversed, and Dr. Conn established the relationship between aldosterone-producing adenoma, hypertension, and hypokalemia [78]. Later, although, it has been found that half of the primary aldosteronism cases

depend on idiopathic adrenal hyperplasia (unilateral or bilateral) and half of them on aldosterone-producing adenoma [79,80]. Other subtypes of primary aldosteronism as familial hyperaldosteronism, aldosterone-producing adrenocortical carcinoma, and ectopic aldosterone-producing tumor are extremely rare [78]. Furthermore, it is now recognized that only 9-37% of patients with primary aldosteronism has hypokalemia [81,82].

Aldosterone is the main mineralocorticoid hormone, responsible for the regulation of extracellular volume, blood pressure, and control of potassium homeostasis [83]. The main action of aldosterone is to regulate the transport of Na+, K+, and water over the epithelial cells, particularly in the renal collecting duct and distal convoluted tubule, but also in the parotid gland and colon. The aldosterone effect is mediated by the mineralocorticoid receptor, leading to Na+ and water retention, and K+ excretion [84].

The synthesis of aldosterone takes place in the zona glomerulosa, the outer layer of the adrenal cortex [85]. The major stimulators of aldosterone synthesis are angiotensin II, potassium, and adrenocorticotropin (ACTH). Renin, produced in the juxtaglomerular cells of the kidney, upregulates the aldosterone synthesis by enzymatic cleavage of inactive angiotensinogen to angiotensin I, which then converts to active angiotensin II by the angiotensin converting enzyme (Figure 2). Situations associated with enhanced renin production are reduced sodium chloride delivery to the macula densa of the juxtaglomerular apparatus, reduced perfusion pressure within the afferent arteriole of the glomerulus and sympathetic activation of the juxtaglomerular cells via beta-adrenergic signals. On the contrary, renin production is inhibited in situations of excessive sodium retention and volume expansion. Renin is also under negative feedback regulation via angiotensin II [83].

In primary aldosteronism, aldosterone excess leads to excessive sodium retention, volume expansion, and eventually hypertension. The increase in sodium chloride delivery to macula densa and the rise in the systemic blood pressure in the juxtaglomerular apparatus result in a remarkable renin suppression. But, aldosterone synthesis is not inhibited because it occurs autonomously of the renin-angiotensin II system. The sodium resorption is accompanied by an increase in potassium and hydrogen ions excretion, leading to hypokalemia and alkalosis. Hence, primary aldosteronism presents the classical clinical picture with hypertension, hypokalemia, alkalosis, elevated aldosterone, and suppressed renin.

Diagnosis of primary aldosteronism

The approach of primary aldosteronism diagnosis includes three phases: screening, confirmatory testing, and subtype classification.

Screening

Taken into account that hypokalemia is present in only a minority of the primary aldosteronism patients, measurement of serum potassium in order to demonstrate hypokalemia lacks sensitivity for primary aldosteronism. Demonstration of elevated plasma aldosterone levels also lack sensitivity for primary aldosteronism, since many

patients with primary aldosteronism do have plasma aldosterone concentration within the normal range [86]. Besides, elevated plasma aldosterone levels may be observed due to raised renin and angiotensin II in secondary aldosteronism (e.g., heart failure, liver failure, renovascular disease) or under treatment with diuretics. Measurement of plasma renin is more sensitive for primary aldosteronism than measurement of potassium or aldosterone levels, since renin should always be suppressed in primary aldosteronism. However, plasma renin may be suppressed because of: 1) Treatment with beta-adrenoreceptor blockers [87,88]. 2) Treatment with agents promoting salt retention (e.g., nonsteroidal anti-inflammatory drugs). 3) Diet with high sodium intake [89]. 4) Lower renin production due to reduced renal function in advancing age [90]. 5) Renal impairment [89]. 6) Other low-renin forms of hypertension (e.g., Liddle syndrome [91], deficiency of 11β-hydroxysteroid dehydrogenase type 2 [92], primary glucocorticoid resistance [93]). The aldosterone to renin ratio (ARR) addresses many of the above limitations, and is now the recommended screening test for primary aldosteronism.

ARR is based on the paired measurement of plasma aldosterone and renin concentrations, where typically primary aldosteronism results in elevated aldosterone and suppressed renin, and therefore a between them elevated ratio. Plasma aldosterone circulates in picomolar concentrations, creating a challenge for high sensitive and accurate assays. A concern in plasma aldosterone measurement is that different, although well established, assays demonstrate variability in reported performance [94]. The most modern way to measure renin is the direct renin concentration, which offers a less labor and time-consuming procedure comparing with the previously used plasma renin activity [95]. ARR seems to be more sensitive for variations in renin rather than aldosterone, especially in the lower renin concentrations, small absolute changes in renin result in large ARR changes [96]. Of importance is also that ARR has demonstrates a high within-patient reproducibility after withdrawal of interfering medication [97]. There is however a substantial variability in the ARR cut-off values, mainly due to the lack of uniformity in diagnostic protocols and assay methods for measuring the ARR [89]. The sensitivity and specificity of ARR varies depending on the choice of cut-off value. Several studies have present a wide span of sensitivity (66% to 100%) and specificity (61% to 100%), depending also on the tested population and the test performance [98,99].

A key issue for the interpretation of the ARR is the interfering conditions during the test. Necessary conditions for ARR testing are normokalemia (aim plasma K+ of 4.0 mmol/l), liberal sodium-intake diet, and withdrawal of mineralocorticoid-receptor antagonists, amiloride, potassium-wasting diuretics, and licorice root products for at least four weeks. It has to be taken into consideration that renal failure can lead to false-positive ARR, patients >65 years may have lowered renin production, ovulating females have higher ARR especially during the luteal phase of the menstrual cycle, ARR is more sensitive if blood collected midmorning after the patient has been up for at least two hours and seated for 5–15 minutes, estrogen-containing medications may lower renin and cause false-positive ARR. Besides, beta-adrenergic blockers, central agonists (e.g., clonidine, alpha-methyldopa), and nonsteroidal anti-inflammatory drugs reduce renin more than aldosterone and may cause false-positive ARR. On the contrary, angiotensin-converting enzyme inhibitors and angiotensin-receptor block-

ers cause rise in renin, and therefore false-negative ARR. If the results of ARR are not diagnostic withdrawal of interfering medication for at least two weeks should be considered [89].

Confirmatory testing

ARR is only a screening test. Thus, patients with positive ARR result should undergo further examination in order to confirm or exclude the primary aldosteronism suspicion. The Endocrine Society recommends the use of one of the four confirmatory testing procedures; oral sodium loading, saline infusion, fludrocortisone suppression, and captopril challenge [89].

Oral sodium loading consists of administration of salt supplementation for three days, high 24h urinary aldosterone excretion level the third day makes primary aldosteronism highly likely. Saline infusion test requires intravenous infusion of two liters of 0.9% saline over four hours, thereafter high postinfusion plasma aldosterone level makes primary aldosteronism very probable. Fludrocortisone suppression test requires four days hospitalization and the consumption of fludrocortisone tablets together with potassium and salt supplementation, high plasma aldosterone on the fourth day confirms primary aldosteronism. In captopril challenge test, patients receive 25–50 mg of captopril orally, and primary aldosteronism is likely if plasma aldosterone remains elevated and renin remains suppressed one to two hours after the challenge. Besides, those tests comprise a risk of hypertension-worsening and should be performed under standardized monitor conditions. It is important to point out, however, that the above described confirmatory tests do not have perfect sensitivity and specificity [100,101]. Further investigation may be needed, if the clinical suspicion still exists although negative confirmatory test result.

Subtype classification

Subtype classification is of importance because it guides the choice of primary aldosteronism treatment. In case of unilateral disease (aldosterone producing adenoma or unilateral adrenal hyperplasia), unilateral adrenalectomy results in normalization of hypokalemia, while hypertension is always improved and in up to half of the cases cured [102,103]. In bilateral disease (bilateral adrenal hyperplasia) the treatment of choice is medical therapy with mineralocorticoid receptor antagonists (spironolactone or eplerenone) [104].

Performance of adrenal computed tomography is recommended in order to assess the presence of large tumors with image phenotype suspicious for carcinoma. Besides, compute tomography is useful for localizing the adrenal veins. But adrenal computed tomography is not appropriate examination to identify lateralization of the source of the excessive aldosterone. Computed tomography seems to be accurate only in half of the examined cases, while a quarter of the patients may incorrectly be excluded from adrenalectomy and a quarter of them may be led to a unnecessary surgery [105]. Further, magnetic resonance imaging has no advantage over computer tomography in subtype evaluation, likely due to less spatial resolution than computed tomography. A systematic review has shown that magnetic resonance imaging and computed tomography misdiagnosed the cause of primary aldosteronism in 37% of patients [106]. The

most accurate, and only reliable, way to differentiate unilateral from bilateral forms of primary aldosteronism is to perform adrenal venous sampling [89]. Blood from both adrenal veins and a peripheral vein is taken, and assayed for aldosterone and cortisol concentrations. However, the criteria for lateralization vary widely, but a so-called lateralization-index is required. Furthermore, young adults with severe hypertension and family history of early-onset hypertension or premature hemorrhagic stroke may have a rare familial form of primary aldosteronism, and should be considered for genetic examination [107].

Primary aldosteronism and cardiovascular disease

Accumulating evidence since the 2000s suggests that cardiovascular diseases are overrepresented among patients with primary aldosteronism compared with patients with essential hypertension. Primary aldosteronism seems to have three to six times higher risk of myocardial infarction and almost three times higher risk of heart failure, compared with essential hypertension matched for age, sex, and blood pressure. Furthermore, the risk of AF seems to be four to twelve times higher in primary aldosteronism than in essential hypertension [108,109].

Experimental data suggest that aldosterone induces direct cardiovascular effect regardless hemodynamic alternations. The classical mineralocorticoid receptor was cloned and characterized in 1987 [110]. Expression of the mineralocorticoid receptor has, not unexpected, been located in the distal tubule and the collecting duct of the kidney. But, mineralocorticoid receptor has even been identified in endothelial cells, vascular smooth muscle, macrophages, adipocytes, cardiomyocytes ,and the hippocampus of the brain [111,112]. These findings extend the aldosteronism effects beyond the sodium and water retention mechanism, and suggest a direct aldosterone action on these sites. Indeed, aldosterone excess can induce endothelial dysfunction and vascular remodeling in endothelial and vascular smooth muscle cells, and can also increase vascular resistance [113]. In addition to causing hypertension, aldosterone excess seems to induce cardiovascular remodeling, causing fibrosis and increasing the left ventricular mass [114,115]. In animal model aldosterone promotes atrial fibrosis, myocyte hypertrophy, and conduction disturbances leading to higher incidence of AF [116]. Whereas mineralocorticoid receptor antagonist, eplerenone, has been found able to attenuate aldosterone induced cardiac fibrosis in mice-models [117]. Moreover, in animal models, aldosterone induces cardiac electrical remodeling by increasing the Ca^{2+} currents density [117], and by causing alternations in the K^{+} currents leading to shortening of action potential [118]. Consequently, there is evidence of direct aldosterone effect on the cardiovascular system, outside the aldosteronism-hypertension pathway.

Atrial fibrillation and lipid profile

Cholesterol is a strong risk factor of cardiovascular disease [119,120]. There is, also, evidence that cholesterol lowering treatment reduce both cardiovascular events and mortality in both men and women [121-123]. On the contrary, the relationship between dyslipidemia and AF is still controversial. Studies from the United States of America, Japan, and Europe have shown that lower total cholesterol and low-density

lipoprotein cholesterol (LDL-C) levels were associated with higher new-onset AF [124-126]. But this inverse association of total cholesterol and LDL-C with the risk of new-onset AF could not be reproduced in the composite of two large studies in North America [127]. In contrast, this composite-study demonstrated an inverse association only between high-density lipoprotein cholesterol (HDL-C) and new-onset AF. While an association between higher triglycerides levels and new-onset AF was also reported. Consequently, we face a paradoxical phenomenon where elevated cholesterol levels seem to be associated with a reduced risk of new-onset AF. Most important, there in no satisfactory rationale to support the connection of lower blood cholesterol levels with lower risk of new-onset AF.

AIMS

The overall aim of this thesis is to study factors associated with the prevention of AF. This objective is achieved by evaluating knowledge gaps and controversies regarding AF development in the hypertensive population.

Study I

The aim of this study was to determine the usefulness of ARR as a screening instrument for primary aldosteronism in an AF population with relatively low cardiovascular risk profile.

Study II

The aim of this study was to evaluate the importance of blood pressure level for the development of new-onset AF in real-life treated hypertensive patients.

Study III

This study aimed to assess the prevalence of primary aldosteronism in the AF population. A secondary aim in this study was to compare the prevalence of primary aldosteronism with the prevalence of hypothyroidism and hyperthyroidism in the same population.

Study IV

The aim of this study was to evaluate the association between the lipid profile and the development of AF in a hypertensive population. Moreover this study aimed to investigate this effect in relation to gender.

METHODS

Study I

All consecutive patients under 65 years of age, with at least one electrocardiogram-documented AF episode at the Department of Medicine and Emergencies at Sahlgrenska University Hospital in Mölndal Sweden between January 2006 and December 2008, were offered to participate in this study. A total of 356 eligible patients with AF were invited to participate and 149 of them (73% male) accepted to take part in the study, and underwent screening for primary aldosteronism using the ARR. The screening procedure was done under concomitant antihypertensive medication. Aldosterone was measured using the Aldosterone Coat-A-Count, kit insert, Siemens, PITKAL-5, 20061229 (reference range for supine position 30-444 pmol/L and for standing position 110-860 pmol/l). The Direct Renin (310470) was measured using the Liaison, DiaSorin S.p.A. (reference range for supine position 2.8-40 mIU/l and for standing position 4.4-46 mIU/l), lower detection limit 2.8 mIU/l. The blood samples were taken in the sitting position after 15 minutes of rest and were sent to the laboratory for direct analysis.

Baseline characteristics including medical history, medication, serum-potassium, serum-creatinine and blood pressure were retrieved at the time of enrollment. In all participants with increased ARR (>65 pmol/mIU) beta-blockade was withdrawn for 3 weeks and ARR was measured again in order to unmask false positive results before confirmatory tests. All participants without beta-blockade and positive ARR were referred for confirmatory test.

Mann-Whitney U-test was used to compare mean difference. Fisher's exact test was used for comparison of proportions. Pearson's chi-squared test was used to compare proportions of elevated ARR in hypertensive and non-hypertensive patients. Statistical significance was considered with a two-sided probability (P) <0.05. IBM® SPSS® Statistics Version 20 was used in the analysis.

Study II

This study is based on the hypertensive population of the Swedish Primary Care Cardiovascular Database (SPCCD). SPCCD is a large primary health care cohort of 74,751 patients ≥30 years old attending primary health care with a recorded diagnosis of hypertension during 2001-2008. The SPCCD includes 48 primary health care centers with an almost total regional coverage of patients in a rural (Skaraborg) and an urban (south-west Stockholm) region in Sweden. A purpose-built software was used to extract information from the digital medical records, including diagnoses codes according to the International Classification of Disease 10th revision (ICD-10), clinical chemistry, and blood pressure values. The unique personal identity number assigned to each Swedish resident was used to link data from the National Patient Register. The National Patient Register includes diagnose codes according to the ICD-10 for all hospital inpatient and outpatient care in Sweden from 2001.

The current study population consists of all patients in SPCCD (i.e., with diagnosed hypertension), but no documented diagnosis of AF or atrial flutter. In order to exclude patients with long standing hypertension we included only patients with hypertension diagnosed within the last year before inclusion (i.e., from January 1, 2002). All participants were followed until December 31, 2008, or until diagnosed with AF or death. The participants received antihypertensive treatment according to national guidelines and clinical practice, at the discretion of the treating physician. Baseline blood pressure was defined as the blood pressure recorded at the inclusion or the last previously recorded in the SPCCD. In-treatment blood pressure was defined as the most recent blood pressure in SPCCD at the end of the follow-up. Brachial pulse pressure was defined as the difference between SBP and DBP. A blood pressure recording from a single visit in the SPCCD has been shown to give a valid reflection of the average of the three most recent measurements during same year [128]. We evaluated SBP, DBP, and pulse pressure at baseline and at the end of follow-up with respect to AF development.

Comparisons were made by using Student's t-test, and general linear models after multivariable adjustment. Multiple logistic regression was used to calculate odds ratios (OR) and 95% confidence interval (CI) for the relationship between in-treatment achieved blood pressure and new-onset AF. The analyses included adjustment for age, sex, diabetes mellitus, heart failure, ischemic heart disease, cerebrovascular disease, and number of visits. A 2-tailed probability value (P) of <0.05 was considered statistically significant. Data management and analyses were performed using SAS version 9.3 (SAS Institute, Cary, North Carolina, USA).

Study III

This original research utilized two national registers in Sweden in order to perform a nationwide case–control study. The case-cohort consists of all patients diagnosed with AF in the National Patient Register during 1987-2013. The National Patient Register includes all hospital in-patient care in Sweden from 1987, and contains also all hospital outpatient visits data from 2001. AF diagnosis was defined according to the codes, ICD-10: I48, ICD-9: 427.31and ICD-8: 427.92. The control-cohort consists of randomly selected individuals without AF diagnosis from the Swedish Total Population Register, selected with case to control ratio 1:2 and matched for age, sex, and place of birth. The selection of the cases and the controls performed computerized.

Diagnoses data for each individual from the National Patient Register starting seven years prior to the AF diagnosis time until the end of the follow up December 31, 2013 was extracted in order to assess the prevalence of primary aldosteronism, hypothyroidism, and hyperthyroidism among the cases and the controls. Primary aldosteronism was defined as the ICD-10 codes E26.0, E26.8, and E26.9, the ICD-9 code 255.B, and the ICD-8 code 255.00. Hypothyroidism was defined as the ICD-10 codes E03.4, E03.5, E03.8, and E03.9, the ICD-9 codes 244.W and 244.X, and the ICD-8 codes 244.00 and 244.09. The prevalence was reported as the proportion of cases of primary aldosteronism, hypothyroidism, and hyperthyroidism in the population alive December 31, 2013.

Logistic regression models were used to estimate ORs for the prevalence of primary aldosteronism, hypothyroidism, and hyperthyroidism. The logistic regression models were adjusted for age, sex, hypertension, ischemic heart disease, heart failure, diabetes mellitus, cerebrovascular disease, and cancer. A two-tailed P value of 0.05 was considered significant. Data management and analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Study IV

This study also utilizes the SPCCD, forming a cohort of hypertensive patients without AF or atrial flutter at baseline that had been included in SPCCD earliest January 1, 2002. This cohort of patients was followed in SPCCD from January 1, 2002 until December 31, 2008 or until diagnosed with AF or death. Besides, data retrieved from the digital medical records. Data upon the participants were also collected through linkage to the Swedish National Patient Register, the Swedish Census Register, the Swedish Register of Education and the Prescribed Drug Register. Patients with new-onset AF at the end of the follow-up were compared to patients without AF with respect to their lipid profile. Lipid profile included total cholesterol, LDL-C, HDL-C, and triglycerides, defined as the most recent collected in SPCCD at the end of the follow-up. Poisson regression models were used to calculate risk ratios (RRs) and 95% CI for the relationship between different blood lipid measurements and new-onset AF. The analyses were adjusted for age, sex, diabetes mellitus, heart failure, ischemic heart disease, cerebrovascular disease, heart valvular disease, chronic kidney disease, thyroid disorder, chronic obstructive pulmonary disease, obstructive sleep apnea syndrome, alcohol abuse, antihypertensive medication, lipid-lowering medication, antidiabetic medication, smoking habits, place of birth, education level, and body mass index. A two-tailed probability value (P) of 0.05 was considered significant. Data management and analyses were performed using SAS version 9.3 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Study I

Pathologically increased ARR (> 65 pmol/mIU) was found in 15 participants (10.1%). Six patients (4.0%) were found to have elevated ARR even after beta-blockade had been withdrawn. Further investigation with saline infusion test resulted in a diagnosis of primary aldosteronism in four individuals out of 149 (2.6%) (Figure 3). Three out of the four individuals with primary aldosteronism had previously been diagnosed with hypertension, but only one out of the four had uncontrolled blood pressure (i.e., >140/90 mmHg). Besides, two of those patients were treated with two or more anti-hypertensive agents. All participants had normal potassium levels. Individuals with increased ARR had significantly higher mean systolic and diastolic blood pressure in comparison to participants with normal ARR (136 vs. 126 mmHg, p=0.02 and 84 vs. 78 mmHg, p=0.02). Furthermore, an increased ARR above the cut-off value of 65 pmol/mIU was almost twice as often found in patients with both AF and a history of hypertension compared to patients with AF but without hypertension, 13.6% and 7.8%, respectively (p=0.25).

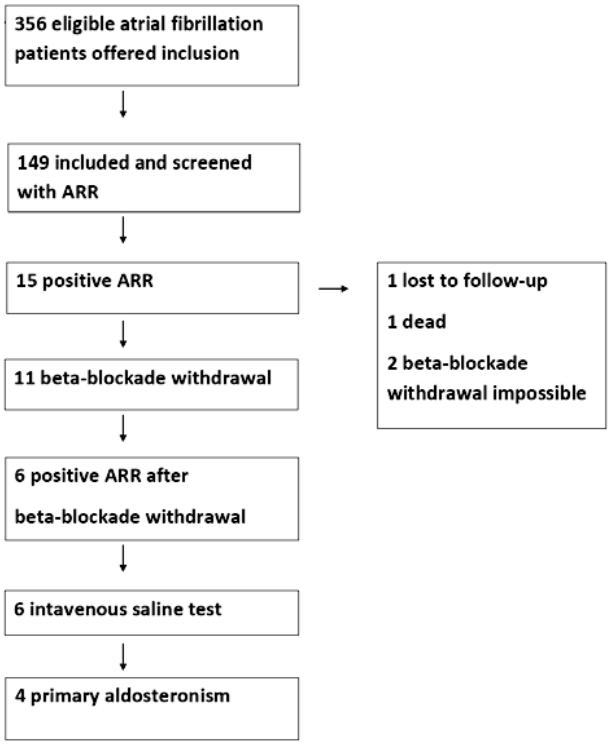

Figure 3. Screening procedure for primary aldosteronism in an atrial fibrillation population.

Study II

We followed 45,530 hypertensive patients with no previously documented AF. After a mean follow-up of 3.5 years and a total of 158,222 person-years, 2057 patients (4.5%) developed AF. Compared to patients with no AF, the new-onset AF group had 4.0 mmHg higher multivariable-adjusted mean in-treatment SBP (95% CI: 3.4 to 5.0; p<0.0001), and 1.7 mmHg DBP (95% CI: 1.3 to 2.2; p<0.0001). Similarly, multivariable-adjusted mean in-treatment pulse pressure in the new-onset AF group was 2.5 mmHg higher (95% CI: 1.8 to 3.2; p <0.001) (Table 1). In a multivariable-adjusted logistic regression analysis (Figure 4), achieved SBP ≥140 mmHg was associated with a higher risk of new-onset AF, as compared to SBP 130-139 mmHg (OR 1.5; 95% CI: 1.3 to 1.7) and to SBP <130 mmHg (OR 1.3; 95% CI 1.2 to 1.6). There was no difference in risk of new-onset AF between SBP 130-139 mmHg and SBP >130 mmHg.

Table 1. Comparison of mean blood pressure and brachial pulse pressure levels of 45,530 hypertensive patients with respect to new-onset atrial fibrillation. AF, atrial fibrillation; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, brachial pulse pressure; CI, confidence interval; *unadjusted. Data are mean ±SD unless otherwise indicated.

	No AF (n=43473)			New-onset AF (n=2057)		
	SBP, mmHg	**DBP, mmHg**	**PP, mmHg**	**SBP, mmHg**	**DBP, mmHg**	**PP, mmHg**
At baseline*	159 ±22	89 ±12	70 ±19	163 ±22	86 ±12	77 ±20
Δ baseline and in-treatment*	-14.2 ±21.4	-7.0 ±11.4	-7.3 ±16	-12.8 ±21.9	-4.8 ±10.8	-8.1 ±18
In-treatment* (95% CI)	145 (145, 145)	82 (81, 82)	64 (63, 64)	151 (150, 151)	81 (80, 81)	70 (69, 70)
In-treatment, adjusted for age (95% CI)	145 (145, 145)	81 (81, 82)	64 (64, 64)	149 (149, 148)	83 (83, 84)	66 (65, 67)
In-treatment, adjusted for age, sex and comorbidity (95% CI)	145 (145, 145)	81 (81, 82)	64 (64, 64)	149 (149, 150)	83 (83, 84)	66 (66, 67)

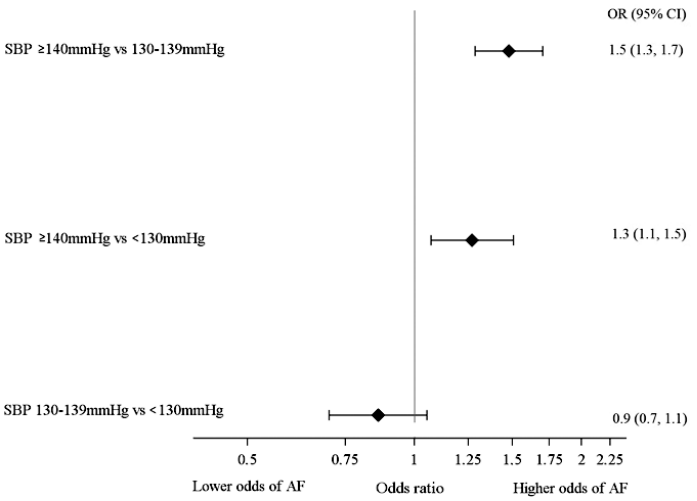

Figure 4. Adjusted odds ratios for new-onset atrial fibrillation according to in-treatment systolic blood pressure. Adjusted for age, sex, diabetes mellitus, heart failure, ischemic heart disease, and cerebrovascular disease. SBP, systolic blood pressure; AF, atrial fibrillation; OR, odds ratio CI, confidence interval.

Study III

A total of 713,569 patients (53% men, mean age 74 years) received a first hospital diagnostic code of AF between 1987 and 2013. The matched controls constituted a cohort of 1,393,953 individuals. The prevalence of primary aldosteronism in December 31, 2013, was 0.056% in the AF population, and 0.024% in the control population. At the same time, the prevalence of hypothyroidism was 5.9% in the AF population and 3.7% in the control population. Whereas the prevalence of hyperthyroidism was 2.3% in AF population and 0.8% in controls. In a multiple-adjusted logistic regression analysis the AF population had a significantly higher risk of being diagnosed with primary aldosteronism compared with controls (OR 1.65; 95% CI: 1.40 to 1.94) (Table 2). Increased risk of AF found also for hypothyroidism (OR 1.42; 95% CI: 1.39 to 1.44) and hyperthyroidism (OR 2.79; 95% CI: 2.71 to 2.86).

Table 2. Adjusted associations between atrial fibrillation and primary aldosteronism, hypothyroidism, and hyperthyroidism compared to controls. Adjusted for age, sex, hypertension, ischemic heart disease, heart failure, diabetes mellitus, and cerebrovascular disease.

	Odds ratio (95% confidence interval)	**P value**
Primary aldosteronism	1.65 (1.40, 1.94)	<0.0001
Hypothyroidism	1.42 (1.39, 1.44)	<0.0001
Hyperthyroidism	2.79 (2.71, 2.86)	<0.0001

Study IV

A total of 51,020 patients (45% men) were included in the current study. During a mean follow-up time of 3.5 years (178,304 person-years) new-onset AF occurred in 2389 participants (4.7%). In the fully adjusted Poisson regression model, 1.0 mmol/l increase in total cholesterol was found to be associated with 19% lower risk of new-onset AF (95% CI: 9% to 28%), and 1.0 mmol/l increase in LDL-C was associated with 16% lower risk of new-onset AF (95% CI: 3% to 27%). Gender-specific Poisson regression analyses shown that increase in total cholesterol by 1.0 mmol/l was found to be associated with lower risk of new-onset AF with 21% in men (95% CI: 8% to 32%), and 18% in women (95% CI: 1% to 31%). Moreover, a significant inverse association found between LDL-C and new-onset AF in men [relative risk 0.84 (95% CI: 0.70 to 0.99)], but not in women. In contrast there was no significant association between HDL-C or triglycerides and new-onset AF, neither in the whole population nor in respect to separate gender (Figures 5 and 6).

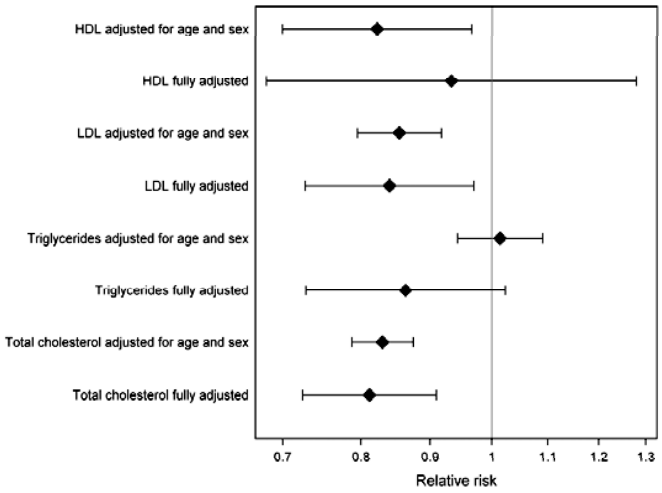

Figure 5. Relative risk of atrial fibrillation in relation to blood lipids among 51,020 hypertensive patients. LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; Fully adjusted, adjusted for: age, sex, systolic blood pressure, diabetes mellitus, heart failure, ischemic heart disease, cerebrovascular disease, heart valvular disease, chronic kidney disease, thyroid disorder, chronic obstructive pulmonary disease, obstructive sleep apnea syndrome, alcohol abuse, antihypertensive medication, lipid-lowering medication, antidiabetic medication, smoking habits, place of birth, education level, and body mass index.

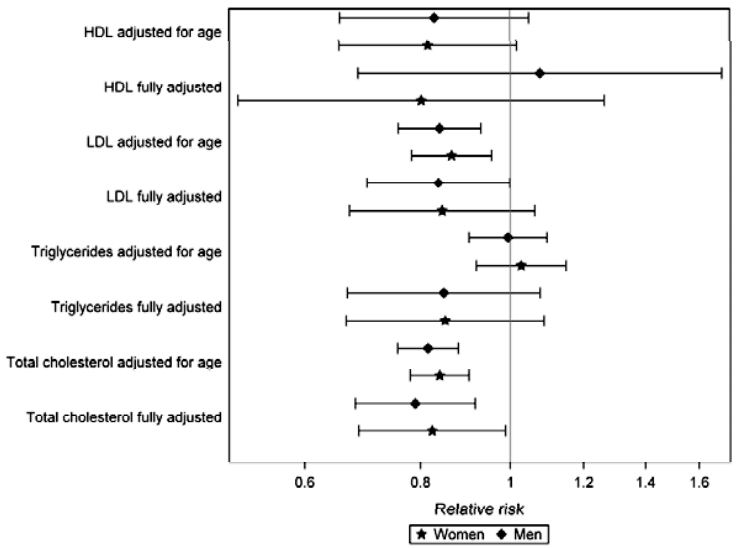

Figure 6. Relative risk of atrial fibrillation in relation to blood lipids among 51,020 hypertensive patients with respect to the gender. LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; Fully adjusted, adjusted for age, sex, systolic blood pressure, diabetes mellitus, heart failure, ischemic heart disease, cerebrovascular disease, heart valvular disease, chronic kidney disease, thyroid disorder, chronic obstructive pulmonary disease, obstructive sleep apnea syndrome, alcohol abuse, antihypertensive medication, lipid-lowering medication, antidiabetic medication, place of birth, education level, and body mass index.

DISCUSSION

How common is primary aldosteronism?

The prevalence of primary aldosteronism is still uncertain; partly because of the inconvenient diagnostic approach, and partly because of the different populations studied. It is important to clarify in which population the prevalence is studied. Primary aldosteronism prevalence has been estimated to be 5%, among newly diagnosed hypertension cases in the primary health care setting [129]. While, it reaches 11%, among patients with newly diagnosed hypertension who have been referred from primary care to specialized centers [81]. In Study III, the prevalence of primary aldosteronism in the Swedish AF population was 0.056%. Whereas in a screened AF population <65 years, in Study I, the primary aldosteronism prevalence was as high as 2.6%. In the general population, though, the primary aldosteronism prevalence is unknown. However, the control-group in Study III consists of the general population without AF, indicating a very low prevalence of primary aldosteronism in the general population. Thus, in selected and in screened populations the primary aldosteronism prevalence is distinctly higher. Not unexpected, it is more likely for primary aldosteronism to be found in the hypertensive population. Furthermore, this thesis points out that AF is associated with a 65% higher risk of primary aldosteronism independently of hypertension.

Where should we search for primary aldosteronism?

The Endocrine Society recommends case detection of primary aldosteronism in patients with sustained blood pressure above 150/100mmHg resistant to three conventional antihypertensive drugs; controlled hypertension on four or more antihypertensive drugs; hypertension and hypokalemia; hypertension and adrenal-incidentaloma; hypertension and sleep apnea; hypertension and a family history of early onset hypertension or cerebrovascular accident at a young age (<40 years); and all hypertensive first-degree relatives of patients with primary aldosteronism [89]. Those guidelines do not mention AF as a group with high prevalence of primary aldosteronism. The results of Study III support those guidelines, presenting primary aldosteronism prevalence in the general AF population of 0.056%. Further, the European Society of Cardiology proposes the detection and management of concomitant conditions in AF [130]. However, primary aldosteronism is not proposed as a modifiable concomitant factor. Nevertheless, Study I identified a relatively young AF population of whom 42% had lone AF and 40% hypertension. In this particular population primary aldosteronism was astonishing high. This finding suggests that AF in younger ages, without concomitant diseases except hypertension, may depend on aldosterone excess. Hence, screening for primary aldosteronism in this context may be of clinical useful, since AF patients with proven primary aldosteronism should have a special therapy approach.

Blood pressure treatment goal and atrial fibrillation

In the past decades, numerous investigations have addressed the issue of drug therapy in hypertension, and the main focus has been on the choice of antihypertensive agent. The first-line agents used in the treatment of hypertension include thiazide diuretics,

angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers. The choice between those agents depends on patients' comorbidity. In recent years, special focus has been on the blood pressure goal for patients with hypertension. There is now enough evidence, and is general agreement, that blood pressure should be ≤140/90 mmHg. How much lower than 140/90 mmHg the blood pressure should reach is still under debate. In Europe it is recommended to treat the blood pressure to ≤ 140/90 mmHg, whereas the latest guideline in the United States of America suggests a blood pressure target <130/80 mmHg [55].

Furthermore, for the primary prevention of AF in the hypertensive population, the European Heart Rhythm Association and the European Association of Cardiovascular Prevention and Rehabilitation, propose an in-treatment SBP goal of <130 mmHg [131]. This recommendation is based on one post hoc retrospective analysis of the Losartan Intervention For Endpoint reduction in hypertension study, among hypertensive patients with left ventricular hypertrophy signs on electrocardiogram and without AF at baseline [132]. In this post hoc analysis, every 10 mmHg decrease in SBP as a continuous variable was associated with 13% lower risk of new-onset AF until SBP reached 126 mmHg. Further SBP reduction was no longer associated with lower risk of new-onset AF. In Study II, achieved SBP 130-139 mmHg and <130 mmHg were associated with lower risk of new-onset AF compared with SBP ≥140 mmHg. However, there was no significant difference in risk of new-onset AF between in-treatment SBP 130-139 mmHg and <130 mmHg. Hence, Study II confirms the benefit of targeting SBP <140 mmHg. Whereas an additional AF preventing effect of lowering SBP <130 mmHg remains controversial.

The cholesterol effect on atrial fibrillation development

The metabolic syndrome includes dyslipidemia, insulin resistance, abdominal obesity, and hypertension, and affects 10-20% of the adult population [133]. Moreover, the metabolic syndrome has been associated with higher risk of new-onset AF [134]. Of the metabolic syndrome components, hypertension and obesity are independent risk factors of new-onset AF [135,136]. Insulin resistance was not significantly associated with new-onset AF in the Framingham study [137], whereas higher levels of glycated hemoglobin and diagnosed diabetes mellitus have been associated with AF [138,139]. Paradoxically, an inverse association between dyslipidemia and new-onset AF has been reported. Study IV, reproduced previous findings of inverse association between cholesterol and new-onset AF in a hypertensive population. Why, although, higher cholesterol levels would have a protective effect on new-onset AF is difficult to explain. Previous studies have proposed a possible explanation by an interaction with hyperthyroidism, which can result in both increase in AF and a lowered cholesterol levels.

In Study IV, however, the analyses were adjusted for diagnoses of thyroid disorders. Moreover, it has been suggested that cholesterol has membrane stabilizing characteristics that can prevent AF [140]. Mice models, however, have shown that mice with high serum cholesterol and mice with low serum cholesterol had similar cellular cholesterol levels. In addition, both mouse strains demonstrated an equally increased

QT-interval, suggesting the higher importance of the sarcolemmal cholesterol content than the circulating cholesterol. Increased sarcolemmal cholesterol content causes action potential prolongation [141]. Moreover, lipid rafts constitute dynamic platforms that include ion channels, and float in cardiomyocyte membranes [142]. The exact role of these membrane structures is not known. Theoretically, alternations in the consistency of these lipid structures may lead to arrhythmia. It is obvious that the pathophysiology that connects cholesterol and AF is unclear, and further research is needed to clarify cholesterols' impact on AF development.

In the gender-specific analyses in Study IV, the inverse association between total cholesterol and new-onset AF was demonstrated for both men and women. On the contrary, an inverse association between LDL-C and new-onset AF was found only in men. Besides, no gender-specific association could be found between HDL-C or triglycerides and new-onset AF. However, a statistical interaction analysis did not show any significant difference between the genders, suggesting parallel that the study became underpowered when it was dichotomized to men and women. Previous studies, though, have demonstrated inverse association between cholesterol and new-onset AF both in men and women [126,143]. Actually, the gender differences in lipid profile and its effects is complex. Many genes, related to the lipid metabolism, are expressed in a sexual dimorphic pattern that can lead to gender differences [144]. An important issue is of course the action of sex hormones, and particular the hormonal alternations that accompany menopause. Premenopausal women have lower LDL-C and triglycerides compared to men and postmenopausal women, which maybe is mediated through an estrogen facilitated increase in LDL-receptor activity and decrease in abdominal lipoprotein lipase activity [145,146]. In Study IV, however, 86% of the women were >50 years old and probably postmenopausal, which might have attenuated the hormonal gender difference.

Limitations

Study I included only 149 AF patients, but had the power to detect primary aldosteronism in 2.6% of them. The group with elevated ARR consists of only 15 individuals, while the group with normal ARR of 134. That rendered us two unequal sized groups to compare, and further conclusions of the statistical analysis of those groups should be done with caution. A limitation with the screening procedure in Study I is that some of the participants were on treatment with angiotensin converting enzyme inhibitors or angiotensin receptor blockers. Those treatments cause elevation of renin levels, and therefore the possibility of false negative ARR. The screening procedure was designed also to avoid false positive results. Hence, the possibility of still unmasked primary aldosteronism cases in the studied population is obvious. Overall, withdrawal of concomitant medication in that kind of population is difficult to perform.

Study II and Study IV, as most of the register-studies, were vulnerable to misclassification or missed diagnoses. The studied population is, however, large enough to minimize that problem. Besides, the outcome of new-onset AF may have been missed in cases of asymptomatic paroxysmal AF. The AF-unawareness is, however, a global and not study-specific issue. Moreover, patients were treated according to standard clinical practice and not according to a study protocol, leading to possible treatment-bias.

Study III is also vulnerable to misclassification or missed diagnoses. An important limitation to point out is the failure to register hypertension diagnosis in the hospitals [147], and hereby in the National Patient Register. But it is believed that those diagnosis-misses would have affected case- and control-group equal. Furthermore, active screening for primary aldosteronism has not been performed, and was not possible because of the nature of this register-based retrospective study. The magnitude of missed primary aldosteronism diagnoses is though difficult to estimate.

SUMMARY AND FUTURE PERSPECTIVES

The aim of this thesis was to investigate knowledge gaps and controversies regarding AF development in the hypertensive population. Study I proposes a relatively simply screening procedure for primary aldosteronism in the younger AF population. This screening procedure seems to be able to reveal unknown primary aldosteronism cases, where specific treatment could prevent both hypertension and AF development. Those data extend the current primary aldosteronism screening recommendations of the Endocrine Society to a new target group. The weak link in this screening procedure is, of course, the complex performance and interpretation of the ARR. Future and easier to use screening tools could establish a wide use of the primary aldosteronism screening in the younger AF population.

Study II emphasizes the importance of SBP control <140 mmHg in order to prevent new-onset AF in the hypertensive population. In particular, Study II demonstrates the beneficial effect of blood pressure control regardless of type of antihypertensive drug. Whereas a specific antihypertensive agent is more effective in preventing new-onset AF in the general hypertensive population without heart failure is still controversial [148], and an obvious field of future studies.

Study III is the first to demonstrate the primary aldosteronism prevalence in the AF population. Although primary aldosteronism prevalence in the AF population is two-fold higher compared to controls it reaches only 0.056%. However, those results point out that it may be reasonable to screen for primary aldosteronism in case of AF and coincident hypertension concurrence. In the future, more feasible screening tests with high sensitivity and specificity for primary aldosteronism will increase our ability to diagnose and treat this disease.

Study IV assessed the association of blood lipid profile and new-onset AF in the hypertensive population. Lower cholesterol levels were found to be associated with higher incidence of AF as in some, but not all, previous studies. These paradoxical results are in line with the fact that statin-treatment has not been shown to have beneficial effect on AF prevention [149]. Furthermore, the design of this study does not allow us to assess eventual causality between the blood lipid profile and new-onset AF. Given the current known data, AF prevention through lipid profile modification is not a possible option by the moment.

CONCLUSIONS

Assessment of ARR can be useful for identification of underlying primary aldosteronism in young patients with diagnosed AF and hypertension. This recommendation is strengthened by the finding of a doubled risk of primary aldosteronism in the AF population compared to matched controls without AF. Moreover, successful blood pressure control in hypertensive patients may reduce the risk of new-onset AF, but lower cholesterol levels were not associated with lower risk of new-onset AF in hypertensive patients. The underlying mechanism regarding the dyslipidemia paradox in AF development is still unclear and further research is needed. Our task is to be aware of common causes of secondary hypertension, to use the effective antihypertensive drugs available, to treat blood pressure to target goals and hereby prevent cardiovascular disease burden.

POPULÄRVETENSKAPLIG SAMMANFATTNING PÅ SVENSKA

Bakgrund: Förmaksflimmer är den vanligaste betydelsefulla hjärtrytmrubbingen och den drabbar ungefär 3 % av den vuxna befolkningen i Sverige. Behandlingsmöjligheterna för förmaksflimmer är begränsade, trots att förmaksflimmerdiagnosen är förknippad med sänkt livskvalitet, hjärtsvikt, stroke och för tidig dödlighet. Hypertoni (högt blodtryck), en kärlsjukdom som drabbar ungefär en tredjedel av den vuxna befolkningen, är den vanligaste bakomliggande orsaken till förmaksflimmer. Uppskattningsvis 10% av all hypertoni orsakas av primär aldosteronism. Primär aldosteronism verkar vara överrepresenterad bland patienter med förmaksflimmer, men prevalensen av primär aldosteronism i förmaksflimmerpopulationen och i befolkningen generellt är inte helt klarlagd.

Syfte: Målet med denna avhandling är att värdera screening för primär aldosteronism i förmaksflimmerpopulationen och att skatta prevalensen av primär aldosteronism i förmaksflimmerpopulationen. Dessutom syftar denna avhandling till att kartlägga blodtryckets och lipidprofilens betydelse för utvecklingen av förmaksflimmer.

Resultat: Studie I visade att screening för primär aldosteronism bland 149 patienter <65 år med förmaksflimmer avslöjade primär aldosteronism i 2,6% av undersökt population. Studie II demonstrerade att lägre blodtrycksnivå var förknippat med lägre incidens av förmaksflimmer i en stor primärvårdspopulation med hypertoni. Studie III visade att prevalensen av primär aldosteronism i förmaksflimmerpopulationen i Sverige år 2013 var 0,056 %, vilket är dubbelt så högt som bland matchade kontroller utan förmaksflimmer. Studie IV beskrev en omvänd association mellan kolesterolnivå i blodet och incidens av förmaksflimmer i en stor primärvårdspopulation med hypertoni.

Slutsats: Screening för primär aldosteronism kan vara värdefullt för patienter <65 år med förmaksflimmer, särskilt vid samsjuklighet med hypertoni. Bättre blodtryckskontroll hos patienter med hypertoni kan sannolikt förebygga utveckling av förmaksflimmer. Primär aldosteronism är dubbelt så vanligt bland patienter med förmaksflimmer, jämfört med en kontrollpopulation utan förmaksflimmer. Den omvända associationen mellan kolesterolnivå och förmaksflimmerincidens förblir paradoxal eftersom en förklarande bakomliggande mekanism fortfarande saknas.

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