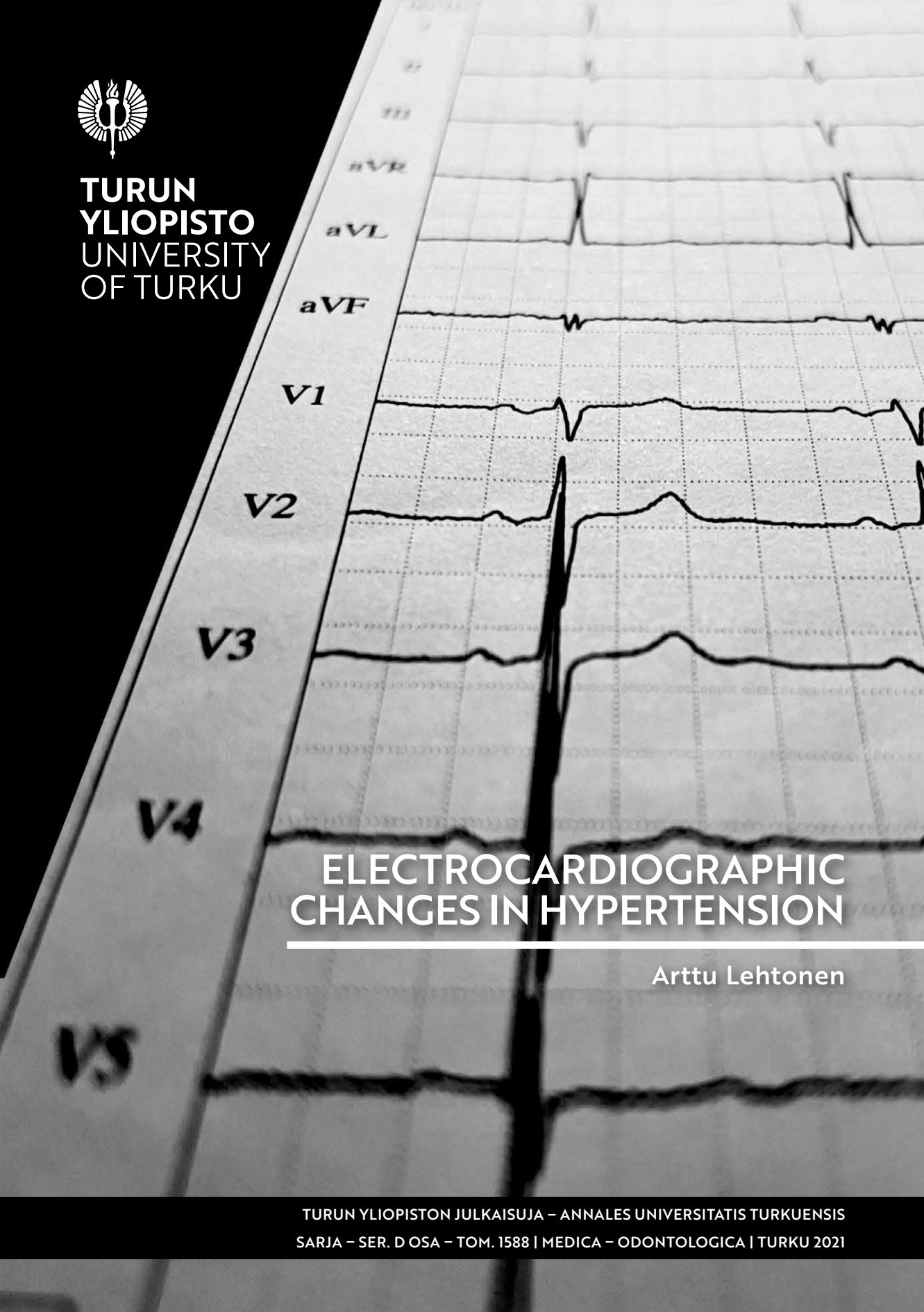

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ELECTROCARDIOGRAPHIC CHANGES IN HYPERTENSION

Arttu Lehtonen

TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
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ABSTRACT

The resting electrocardiogram (ECG) is a recommended procedure for the routine assessment of every hypertensive patient to detect electrocardiographic left ventricular hypertrophy (ECG-LVH), a potent cardiovascular risk factor. Previously several other ECG abnormalities have been shown to associate with incident cardiovascular disease (CVD) and atrial fibrillation (AF) in the general population. However, less is known about the prevalence and prognosis of these ECG abnormalities in hypertensive individuals.

The aim of this thesis was to investigate the prevalence, incidence, and cardiovascular prognosis of ECG abnormalities in relation to blood pressure (BP) in a large, population-based sample of Finnish adults (n=8028).

The prevalence of ECG abnormalities was higher in hypertensive than in nonhypertensive individuals and it increased with the severity of hypertension. Several ECG abnormalities were associated with incident CVD and AF not only in hypertensive subjects but also in the whole study sample. However, the incremental value of the studied ECG abnormalities in the prediction of an individual's cardiovascular risk was marginal.

P-wave abnormalities were frequent in the general population. Modifiable risk factors, such as obesity and hypertension, seemed to be associated with the incidence of these P-wave abnormalities. Of all the studied P-wave abnormalities, only a prolonged P-wave duration was predictive of AF.

The self-reported hypertension onset age did not offer any incremental value over the simple presence of hypertension when assessing the odds of ECG-LVH.

In conclusion, several ECG abnormalities are associated with incident CVD and AF in hypertensive individuals. However, the incremental value of single ECG abnormalities beyond traditional risk factors in cardiovascular risk prediction seems to be rather limited.

KEYWORDS: electrocardiography, epidemiology, blood pressure, risk marker, cardiovascular disease, atrial fibrillation

TURUN YLIOPISTO
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TIIVISTELMÄ

Sydänfilmi (EKG) suositellaan otettavan rutiinisti verenpainetautia sairastavilta vasemman kammion liikakasvun havaitsemiseksi. Useiden muiden EKG-muutosten on osoitettu ennustavan sydän- ja verisuonisairauksia sekä eteisvärinää väestössä. Tutkimuksia näiden EKG-poikkeavuuksien esiintyvyydestä ja ennusteesta verenpainetautia sairastavilla on kuitenkin rajoitetusti.

Tämän väitöskirjan tavoitteena oli tutkia EKG-poikkeavuuksien esiintyvyyttä, ilmaantuvuutta ja ennustetta suhteessa verenpaineeseen suuressa väestöpohjaisessa, suomalaisista aikuisista koostuvassa Terveys 2000 aineistossa (n=8028).

EKG-poikkeavuuksien esiintyvyys oli suurempi verenpainetautia sairastavilla, kuin niillä, joilla oli normaali verenpaine, ja esiintyvyys suureni, mitä korkeampi verenpainetaso oli. Useat EKG-poikkeavuudet ennustivat sydän- ja verisuonitapahtumia ja eteisvärinää sekä koko tutkimusväestössä että verenpainetautia sairastavissa. Näiden muutosten lisäarvo sydän- ja verisuonitautitapahtumien ennustamisessa perinteisten riskitekijöiden lisäksi oli kuitenkin vähäinen.

P-aallon muutokset olivat yleisiä löydöksiä väestössä. Muunneltavissa olevat riskitekijät, kuten kohonnut verenpaine ja ylipaino, näyttivät liittyvän P-aallon muutosten ilmaantuvuuteen. Tutkituista P-aallon muutoksista ainoastaan pidentynyt P-aallon kesto ennusti eteisvärinää.

Itse ilmoitettu verenpainetaudin alkamisikä ei vaikuttanut sydänfilmillä arvioitavan vasemman kammion liikakasvun todennäköisyyteen suhteessa pelkkään itse ilmoitetun verenpainetaudin olemassaoloon.

Näin ollen useat EKG-poikkeavuudet ovat yhteydessä sydän- ja verisuonitapahtumiin ja eteisvärinään verenpainetautia sairastavilla. Yksittäisten EKG-poikkeavuuksien lisäarvo sydän- ja verisuonitautitapahtumien ennustamisessa suhteessa jo vakiintuneisiin riskitekijöihin näyttää kuitenkin olevan vähäinen

AVAINSANAT: sydänfilmi, epidemiologia, verenpaine, riskitekijä, sydän- ja verisuonitaudit, eteisvärinä

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Abbreviations

AF	Atrial fibrillation
ARIC	Atherosclerosis Risk in Communities study
AUC	Area under the receiver-operating-characteristic curve
AVRT+	Positive T-wave in lead aVR
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
CVD	Cardiovascular disease
DCA	Decision curve analysis
ECG	Electrocardiogram
FHS	Framingham Heart Study
HDL	High-density lipoprotein
HMOD	Hypertension-mediated target organ damage
HR	Hazard ratio
IDI	Integrated discrimination index
LVH	Left ventricular hypertrophy
MRI	Magnetic resonance imaging
NRI	Net reclassification improvement
QTc	Heart rate corrected QT interval
SD	Standard deviation

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Lehtonen AO, Puukka P, Varis J, Porthan K, Tikkanen JT, Nieminen MS, Huikuri HV, Anttila I, Nikus K, Kähönen M, Jula A, Niiranen TJ. Prevalence and prognosis of ECG abnormalities in normotensive and hypertensive individuals. *Journal of Hypertension*, 2016; 34(5): 959-66.

II Lehtonen AO, Langén VL, Puukka PJ, Kähönen M, Nieminen MS, Jula AM, Niiranen TJ. Incidence rates, correlates, and prognosis of electrocardiographic P-wave abnormalities - a nationwide population-based study. *Journal of Electrocardiology*, 2017; 50(6): 925-932.

III Lehtonen AO, Langén VL, Porthan K, Kähönen M, Nieminen MS, Jula AM, Niiranen TJ. Electrocardiographic predictors of atrial fibrillation in nonhypertensive and hypertensive individuals. *Journal of Hypertension*, 2018; 36(9): 1874-1881.

IV Lehtonen AO*, Suvila K*, Jula A, Niiranen TJ. Association between self-reported hypertension onset age and electrocardiographic left ventricular hypertrophy. *Journal of Human Hypertension*, 2020; 35(5):479-482.

*Equal contribution

1 Introduction

Hypertension continues to be a leading risk factor for morbidity and mortality worldwide (1). In 2019, high blood pressure (BP) was estimated to account for 10.8 million deaths – nearly one fifth of all deaths in that year (1). In Finland, BP at a population level has decreased significantly from the 1970s until the beginning of the 21st century (2). However, the decreasing trend in population BP has since flattened, so that still today, over 50% of the Finnish adult population is hypertensive (3,4). Therefore, the prevention and management of hypertension are important challenges in Finland, as they are in the rest of the world.

Atrial fibrillation (AF) is a common arrhythmia with a prevalence that increases significantly with advancing age (5), i.e. from below 1% in middle-aged adults to nearly 10% in older population (6,7). AF is associated with a 3-5-fold increased risk of stroke and a nearly doubled risk of death (6,8). Because of its high prevalence, hypertension is the most important modifiable risk factor for AF (9,10). The coexistence of AF and hypertension greatly increases the risk of cardiovascular morbidity (11).

Hypertension is associated with the cardiovascular risk, independent of its onset age. However, recent studies have shown that when compared with late onset hypertension, early onset hypertension is a stronger risk factor for cardiovascular mortality (12,13). Early onset hypertension, and not late-onset hypertension, is also associated with hypertension-mediated target organ damage (HMOD), especially anatomic left ventricular hypertrophy (LVH) (14).

Taking an electrocardiogram (ECG) is recommended for the routine assessment of every hypertensive patient in order to detect electrocardiographic LVH (ECG-LVH) (15,16). Several other ECG abnormalities, such as P-wave abnormalities, ventricular depolarization abnormalities, and repolarization abnormalities, have been previously shown to associate with incident cardiovascular disease (CVD) or atrial fibrillation (AF) in the general population (17-24). However, there is only sketchy data on the prevalence, incidence, and prognosis of these ECG abnormalities in hypertensive individuals. In addition, even less is known about the extent to which early onset hypertension is associated with ECG-LVH. These data would aid physicians in the treatment and evaluation of hypertensive patients.

2 Review of the Literature

2.1 The hypertensive heart

The progression of hypertension to heart failure has been recognized for a long time (25,26). Over the past decades, a plethora of studies have demonstrated that longstanding hypertension induces a wide spectrum of pathological structural and functional disturbances in the heart (27-29) (**Figure 1**.). The definition of hypertensive heart disease encompasses all these changes that progress gradually to manifest clinically as symptomatic heart failure.

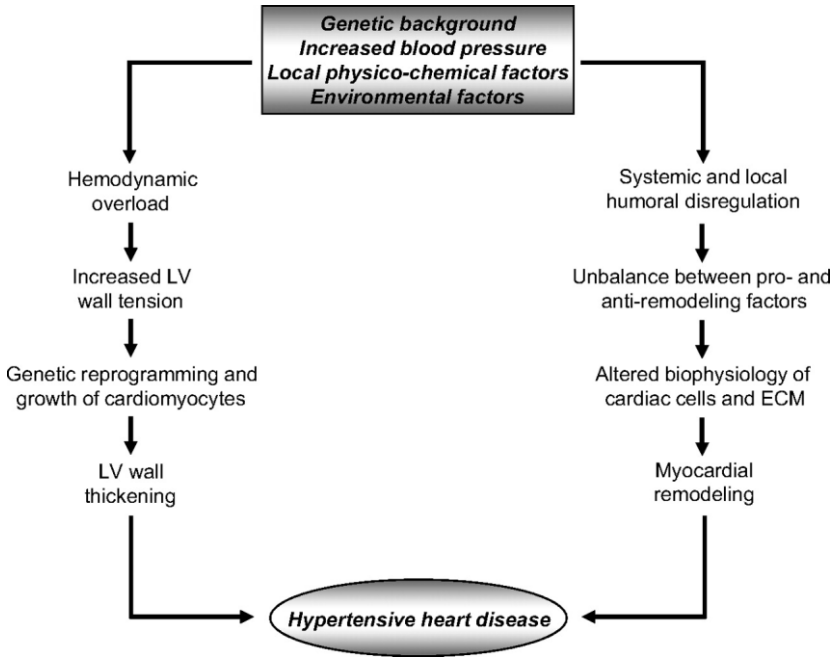

Figure 1. Mechanisms involved in the development of hypertensive heart disease. ECM, extracellular matrix. LV, left ventricular. Reproduced with permission from Díez J, Frohlich ED. A translational approach to hypertensive heart disease. Hypertension. 2010;55(1):1-8. American Heart Association https://doi.org/10.1161/HYPERTENSIONAHA.109.141887.

Persistently elevated BP levels cause a hemodynamic overload that imposes stress upon the left ventricular wall. As an adaptive response to maintain cardiac output and in an attempt to normalize left ventricular wall stress, the left ventricular wall thickens or dilates (30) and as a result, left ventricular mass increases and LVH develops (28). The prevalence of LVH varies according to the population being studied, ranging from nearly 20% in individuals with uncomplicated hypertension (31) to over 70% in hypertensive patients with chronic kidney disease and the metabolic syndrome (32). In addition to the severity and duration of hypertension, recognized risk factors for increased left ventricular mass include advancing age, obesity, salt intake, diabetes mellitus, current smoking, valvular diseases, and genetic factors (33-36). The mechanisms behind each risk factor are complex and may be intertwined. For example, obesity increases left ventricular mass via increases in systemic blood volume, activation of the sympathetic, renin-angiotensin-aldosterone, and aldosterone-mineralocorticoid receptor systems and via abnormal production of growth factors resulting in a typical salt-sensitive hypertension with increases in arterial stiffness and peripheral vascular resistance (37). However, the influence of obesity on left ventricular mass is partly mediated by sodium balance as obesity is associated not only with increased salt intake but also with hyperinsulinemia and activation of the aldosterone-mineralocorticoid receptor system, which in turn lead to impaired pressure natriuresis and sodium retention (38). LVH is one of the best recognized features of hypertensive heart disease and is an established risk factor for adverse cardiovascular outcomes in hypertension (39-43).

Beyond left ventricular mass alone, left ventricular geometry is also an important aspect regarding the heart's response to hypertension. The classical view is that the growth of the left ventricular mass in hypertension displays two morphological patterns: LVH occurring from ventricular wall thickening is defined as concentric whereas LVH resulting from chamber dilatation is described as eccentric (44) (**Figure 2**). Historically, hypertension has been associated with concentric LVH, which over time evolves into dilated cardiac failure (increased left ventricular volume with reduced ejection fraction) (30). However, data on the prevalence of left ventricular geometric patterns have revealed the absence of a uniform left ventricular geometric response to hypertension (44). Nonetheless, as individuals with concentric hypertrophy have been shown to have significantly higher BP than those with eccentric hypertrophy, the duration of exposure and intensity of the elevated BP appear to be important factors in determining the impact of hypertension on left ventricular geometry (44,45). In addition to hemodynamic factors, also non-hemodynamic factors are known to contribute to the progression of hypertensive heart disease and cardiac remodeling. Demographic factors such as age, sex, and race have been shown to modulate the left ventricle's response to an elevation in BP.

Advancing age, black ethnicity, and female sex seem to predispose more often to concentric hypertrophy (46-48). Concomitant conditions such as coronary heart disease (CHD) (49), diabetes mellitus (50), obesity (51), and chronic kidney disease (32) also affect the left ventricular geometry. In addition, there is also evidence that genetic factors may influence the heart's response to pressure overload (52). Left ventricular geometry has been shown to possess incremental prognostic value beyond left ventricular mass (53,54) and it may be a determinant of subsequent functional impairment and heart failure phenotype (55).

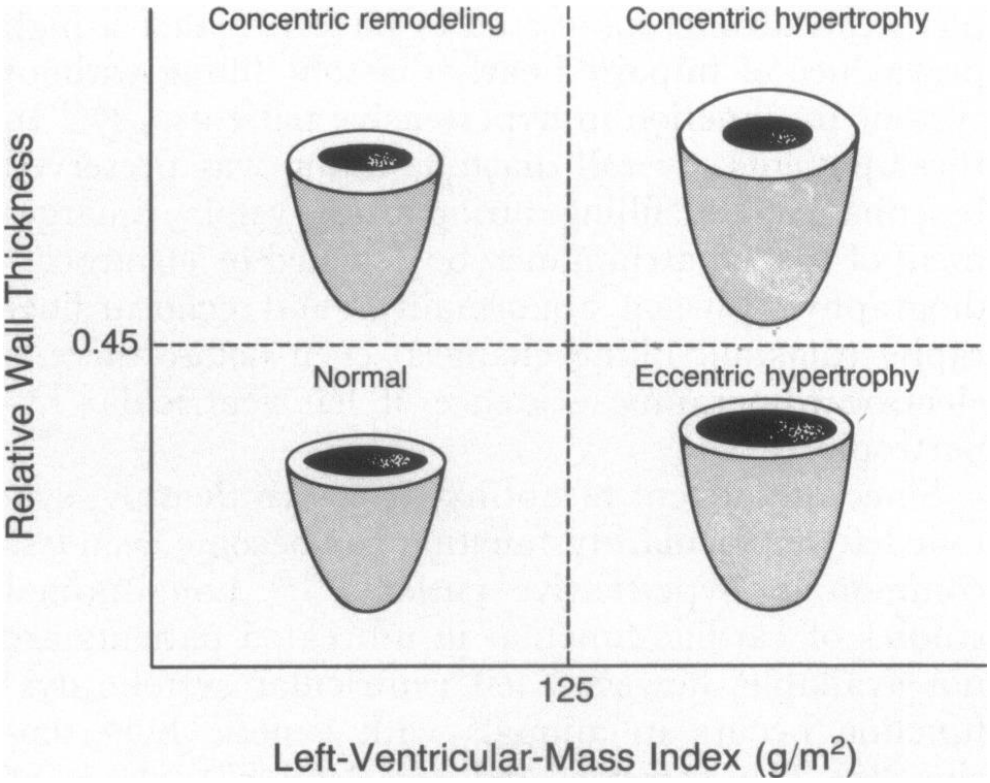

Figure 2. Left ventricular geometry and the relation between left ventricular mass and relative wall thickness. Reproduced with permission from Frohlich et al. The heart in hypertension. N Engl J Med. 1992; 327(14):998-1008, Copyright Massachusetts Medical Society.

Structural and functional alterations in the left atrium are also an important feature of hypertensive heart disease. As an adaptation to persistently elevated BP levels, the left atrium increases in size (56,57). Initially, the output of the left atrium may improve, but with the progression of hypertensive heart disease, the left atrium dilates and a decline in function is observed (58-60). The structural and functional

changes in the left atrium seem to carry prognostic information for a variety of clinical outcomes, such as incident AF, heart failure, and CVD (61-63).

At the microscopic level, the main changes evident in the hypertensive myocardium are cardiomyocyte hypertrophy, cardiomyocyte apoptosis, interstitial fibrosis, a reduced lumen/wall ratio in intramyocardial arteries, and a relative decrease in the vascular density (64). The cardiac myocytes increase in size, which results from the stimulation of intracellular signaling cascades that activate gene expression and promote contractile protein synthesis (65,66). In addition to cardiomyocyte hypertrophy, apoptosis of cardiomyocytes resulting from an imbalance between factors that induce or block apoptosis is a key feature in the hypertensive myocardium (67). Apoptosis of cardiomyocytes is suggested to contribute to the development of hypertensive heart disease through the loss of contractile mass and function, interfering with the function of viable cardiomyocytes, and geometric remodeling of the left ventricle (64).

In addition to the changes in the cardiomyocytes, changes in the myocardial extracellular matrix are also part of the structural remodeling of the myocardium in the hypertensive heart (29,64). Myocardial fibrosis, i.e. an exaggerated accumulation of myocardial collagen, is considered as the initial response to myocardial stressors or the injury associated with persistent hypertension (68). Experimental studies in rats have demonstrated that the myocardial fibrosis in hypertension was also linked to a high salt-intake (69). Myocardial fibrosis not only disrupts the myocardial architecture but also affects the physical properties of the myocardium, thereby contributing to impaired diastolic and systolic function (70,71). In addition, myocardial perivascular fibrosis may decrease the coronary blood flow (72). Furthermore, the increased deposition of fibrous tissue is thought to be an arrhythmogenic substrate as fibrosis has been linked to conduction abnormalities (73,74).

Hypertension also affects the microvasculature of the myocardium (64). The small vessel structure changes with increases in the thickness of vascular wall and a relative reduction in the size of the lumen (75). In addition, there is a relative decline in the vascular density (76). These microvascular changes, along with perivascular fibrosis, increased oxygen demand of the hypertrophied left ventricle, and increased intramyocardial pressure, impair the coronary flow reserve in the hypertensive heart and predispose to ischemia (77,78).

At the molecular level, mechanical stress evokes changes in neurohormonal activation, including but not limited to altered plasma renin, angiotensin II, aldosterone, endothelin, and bradykinin activity, that affect the hemodynamics of the circulatory system and act also as direct growth factors in the myocardium (79). Subsequently, other cell growth mediators, such as cytokines, growth hormone, and insulin-like growth factor 1, influence myocardial growth and composition (28,80)

and the sympathetic nervous system is also activated (81). These triggers induce complex intracellular signaling cascades that increase the size of the cardiomyocytes (82).

In addition to subclinical changes in cardiac structure, hypertension is related to subclinical left ventricular systolic and diastolic dysfunction (29). Commonly, chronic hypertension induces left ventricular chamber stiffness, which leads to impaired left ventricular relaxation, elevated left ventricle filling pressures, and a deterioration in diastolic function, while ejection fraction is preserved (83,84). It is noteworthy that a high salt-intake has been shown to associate with impaired diastolic filling even in early essential hypertension (85). More rarely, longstanding hypertension may eventually lead to systolic dysfunction, where the heart loses its ability to contract normally and ejection fraction is reduced (86). Systolic dysfunction is usually accompanied with concomitant CHD and myocardial infarction (87,88).

Finally, arrhythmogenicity is also a feature of the hypertensive heart disease. Hypertensive individuals are susceptible to both supraventricular and ventricular arrhythmias, especially in the presence of associated LVH (6,89,90). The hemodynamic changes, neuroendocrine factors, and cardiac remodelling discussed above have been shown to associate with the generation of arrhythmias (91). Especially, the accumulation of fibrosis appears to increase the vulnerability to arrhythmia (92). In addition, hypertension seems to induce structural remodelling in cellular gap-junctions and abnormal expression of ion channels or junctional complexes which may affect the propagation of electrical impulses and predispose to arrhythmia (93,94).

The pathways linking myocardial remodelling with clinical manifestations in hypertensive heart disease are summarized in **Figure 3**.

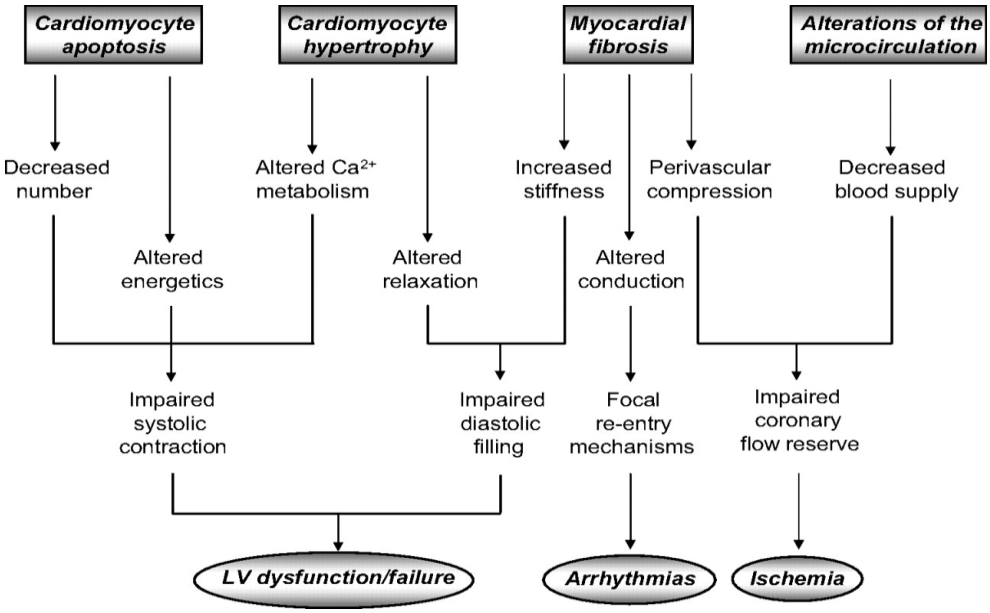

Figure 3. Pathways linking myocardial remodeling with clinical manifestations in hypertensive heart disease. Reproduced with permission from Díez J, Frohlich ED. A translational approach to hypertensive heart disease. Hypertension. 2010;55(1):1-8. American Heart Association https://doi.org/10.1161/HYPERTENSIONAHA.109.141887.

2.2 Definition and clinical significance of hypertensive electrocardiographic changes

2.2.1 Electrocardiographic left ventricular hypertrophy

Prior to the development of noninvasive methods, capable of accurately estimating the dimensions, mass, and wall motion of cardiac chambers, electrocardiography in association with chest radiography and physical examination played an important role in assessing the size and mass of the cardiac chambers (95).

The established ECG changes associated with LVH are increases in the amplitude and duration of the QRS complex, changes in the QRS vector, abnormalities in the ST segment and T wave, and abnormalities in the P wave. More specifically, increases in the R-wave amplitude in the lateral ECG leads (I, aVL, V4-V6) are accompanied by a deepening of the S-wave in the right-sided leads (III, aVR,

V1-V3). As a result, the QRS axis tends to shift leftward. The presence of a thickened and remodeled left ventricular wall leads to prolonged depolarization and delayed repolarization (QRS- and QT-prolongation and ST- and T-wave abnormalities). These changes have been correlated with direct and indirect assessments of ventricular size or mass to establish electrocardiographic criteria for the diagnosis of hypertrophy (96-98).

There are numerous criteria for diagnosing electrocardiographic LVH (ECG-LVH). **Table 1**. Summarizes the different clinically relevant ECG-LVH criteria. The most commonly used diagnostic ECG-LVH criteria are based on QRS-voltage measurements either in the limb or in the precordial leads. In addition to mere QRS voltage assessment, point scores incorporating different ECG changes associated with anatomic LVH (e.g. changes in QRS voltage, P wave, and repolarization) and products of QRS voltage and duration have also been used for diagnosing ECG-LVH. In 2009, American recommendations for standardization and interpretation of ECG listed 36 criteria for LVH diagnosis but emphasized that none is superior to the others (98).

The prevalence of ECG-LVH in hypertensive individuals varies according to the criteria used and the population being studied. One analysis of 26 studies published in the time period 2000-2010 reported an average ECG-LVH prevalence of 18% ranging from 1 to 40% in over 40,000 hypertensive individuals (99). According to the literature, ECG-LVH, similar to hypertension (100), seems to be more frequent in men than in women.

Table 1. Clinically relevant ECG criteria of left ventricular hypertrophy (LVH).

Criterion	Description
Cornell voltage	SV3 + RaVL > 2.8 mV for men and > 2.0 mV for women
Cornell product	(SV3 + RaVL, with 0.8 mV added for women) × QRS duration ≥ 244 mV × ms
Framingham criterion	RaVL > 1.1 mV, RI + SIII ≥ 2.5 mV, SV1/V2 + RV5/V6 ≥ 3.5 mV, SV1/V2 ≥ 2.5 mV, or RV5/V6 ≥ 2.5 mV
Gubner–Ungerleider voltage	RI + SIII ≥ 2.5 mV
Left ventricular strain	ST-segment depression + asymmetric T-wave inversion in lateral leads
Lewis voltage	RI + SIII − SI − RIII ≥ 1.7 mV
Minnesota code	Codes 3.1 or 3.3
Peguero–Lo Presti	Deepest S-wave in any lead + SV4 ≥ 2.8 mV for men and ≥ 2.3 mV for women
Perugia criterion	SV3 + RaVL > 2.4 mV for men and > 2.0 mV for women, left ventricular strain, or Romhilt–Estes score ≥ 5
RaVL	RaVL > 1.1 mV
Romhilt–Estes score	≥ 5 points (LVH); ≥ 4 points (probable LVH)
Sokolow–Lyon voltage	SV1 + RV5/V6 ≥ 3.5 mV

ECG-LVH is not only an independent risk factor for cardiovascular mortality but it carries a significant risk of non-fatal cardiovascular events including arrhythmias, CHD, myocardial infarction, stroke, and congestive heart failure (101-107). Different ECG-LVH criteria differ in terms how well they predict the cardiovascular risk, ranging from a 2- to 4-fold increase in cardiovascular morbidity and mortality (106). More importantly, serial changes in the QRS voltage and the repolarization pattern have been shown to be associated with the cardiovascular prognosis (108). Indeed, evidence from cohorts consisting of hypertensive patients suggests that independent of BP and other risk factors, a regression of ECG-LVH changes confers, an improvement in the risk for CVD, whereas a worsening imposes an increased risk (109-112). It is noteworthy that the LIFE study investigators have shown that ECG-

LVH regression is associated with a favorable impact on multiple adverse outcomes, such as cardiovascular death, myocardial infarction, stroke, sudden cardiac death, AF, heart failure, and even new-onset diabetes mellitus (110,113-116). Based on these findings, serial changes in ECG-LVH during antihypertensive treatment could aid in the evaluation of treatment success and risk stratification.

Despite its prognostic value, the diagnostic accuracy of ECG-LVH is hampered by its poor sensitivity to detect anatomic LVH as compared with other noninvasive modalities such as echocardiography or magnetic resonance imaging (MRI). However, ECG-LVH has been shown to provide unique prognostic information independent of anatomic LVH, and thus it complements information derived from echocardiography and MRI. This feature is discussed in detail in chapter 2.3. Even though more accurate modalities to detect LVH exist, ECG, due to its simplicity, wide availability and established prognostic value, remains the first line method to detect LVH. Therefore, European guidelines for the management and treatment of hypertension recommend the routine assessment of ECG-LVH in all hypertensive patients (16).

2.2.2 Cardiac rhythm

Hypertension predisposes to cardiac arrhythmias, including ventricular arrhythmias, but most commonly AF, which may be considered as a manifestation of hypertensive heart disease (91). AF is defined as a tachyarrhythmia with uncoordinated atrial activation and consequently ineffective atrial contraction. On the ECG, AF is characterized by irregular R-R intervals, the absence of distinct repeating P waves, and irregular atrial activity (117).

The estimated global prevalence of AF is currently 2-4 % (5). Aging of the population along with the increasing burden of other comorbidities predisposing to AF such as hypertension, diabetes, CHD, and obesity, is expected to result in doubling in the prevalence of AF in the up-coming decades. The estimated lifetime odds that an individual 55 years or older will experience AF is 1 in 3.

Due to its high prevalence, hypertension is the most important risk factor for incident AF and these two conditions frequently co-exist (91). As discussed above, factors that contribute to arrhythmogenesis include hemodynamic changes, neuroendocrine factors, atrial and ventricular structural remodeling (i.e. myocardial fibrosis), and a hypertrophied left ventricle that by itself is considered to be arrhythmogenic.

Both hypertension and AF contribute to a markedly increased risk of stroke and heart failure, with the risk being further accentuated when both are present (91).

In addition to AF, supraventricular and ventricular premature beats are frequently encountered in hypertensive individuals (91).

2.2.3 P-wave abnormalities

The P-wave reflects the electrical activity of the atria. Atrial depolarization originates from the sinus node in the right atrium. As the wave of depolarization spreads from the right to the left atrium, the ECG normally records a monophasic positive P-wave in lateral leads and a biphasic (positive-negative) P-wave in the precordial lead V1 that is oriented perpendicularly to the direction of current flow. Consequently, in lead V1, the initial positive deflection corresponds with right atrial activation and the subsequent negative deflection denotes left atrial activation.

P-wave abnormalities that are known to be associated with left atrial dilatation, hypertrophy, conduction delay, or elevated pressure (118-122), are frequently associated with LVH, and have been used as diagnostic criteria for LVH (97). P-wave changes occur frequently in patients with hypertension, and they may be the earliest electrocardiographic sign of hypertensive heart disease. However, similar P-wave abnormalities also often occur in the absence of LVH (98).

P-wave duration is usually defined as the maximum P-wave duration (ms) across all 12 leads measured from the P-wave onset (conclusion of the T-P segment) to its offset (return to baseline for the remaining PR interval) (123). The P-wave duration in lead II has also been used in studies (17). In both cohorts of the Framingham Heart Study (FHS) and the Atherosclerosis Risk in Communities (ARIC) study, the mean P-wave duration was 109±12 ms in (123). The criteria for an abnormally long P-wave duration varies, as there are studies examining the prevalence of P-wave duration exceeding various cut-points. For example, the prevalence of P-wave duration ≥ 110 ms was 59% in a community based sample of 678 individuals aged ≥65 years (124), whereas the prevalence of P-wave duration ≥120 ms was 47% in hospitalized patients (125). Furthermore, in a Danish patient cohort of over 285,000 individuals, 20% of the participants had a P-wave duration ≥120 ms (126). Moreover, advancing age, male sex, hypertension, and obesity seem to be associated with prolonged P-wave duration (127-129). More importantly, a prolonged P-wave duration has been shown to predict incident AF, sudden cardiac death, and cardiovascular mortality in prospective patient and population cohorts (17,126,130,131). Especially a prolonged P-wave duration concomitantly with ± biphasic P-wave in inferior leads, i.e. third degree interatrial block, is strongly associated with incident AF (132).

Another well-known P-wave abnormality, P-terminal force (PTF) is defined as the product of the duration and the amplitude of the terminal portion of the P-wave in lead V1. Abnormal PTF has long been considered as ≤ -4mVms (121). Originally

derived to separate patients with left-sided valvular lesions from normal subjects, abnormal PTF has subsequently been proven to be a specific indicator of left atrial enlargement (133). Supporting the ubiquitousness of an abnormal PTF in hypertension, the prevalence of abnormal PTF was 37% in 7,778 hypertensive patients with ECG-LVH aged 55-80 years (134). For comparison, in a Finnish general population sample of 10,600 middle aged subjects, the prevalence of an abnormal PTF was 7.5% (18), while the ARIC study reported a prevalence of 10.1% (135). Individuals with an abnormal PTF compared to those without this abnormality seem to be older, have a higher BMI and more elevated BP values (127,128). Similar to a prolonged P-wave duration, an abnormal PTF has been shown to predict incident AF in prospective cohorts (18,136,137).

Because of consistent evidence linking P-wave abnormalities and AF, P-wave abnormalities have been suggested as markers of an electroanatomic substrate that predisposes to arrhythmia (138,139). However, the mechanisms underlying this observation remain unclear. Despite adjustment for conventional cardiovascular risk factors, the association between P-wave abnormalities and AF may be partially explained by the development of CHD or heart failure. However, one potential mechanism for arrhythmogenesis could be the accumulation of fibrosis as the degree of interstitial left ventricular fibrosis on cardiac MRI has been shown to be linearly associated with increasing P-wave duration and negative P-terminal force in V1 (140).

In addition to the AF risk, PTF (as a dichotomized or continuous variable) has been linked to incident ischemic stroke even after adjustment for clinically apparent AF (134,135,137,141). This association between PTF and incident stroke is suggested to have two potential explanations. First, PTF, a marker of left atrial cardiomyopathy, may serve as a surrogate for subclinical AF, which has been associated with stroke (142). Second, cardiac thromboembolism does not necessarily require AF and may occur in the setting of atrial cardiomyopathy (143). However, the latter explanation is considered controversial (144), though it would help to explain why many cryptogenic strokes appear radiologically to have resulted from an embolism (145) and also the lack of any strong temporal linkage between AF and stroke (146).

While the prevalence of P-wave abnormalities has been extensively studied in different populations, limited data exist on the incidence of P-wave abnormalities, whether P-wave abnormalities change during longer follow-up, and what are the clinical determinants of change. In addition, studies on the predictive value of P-wave abnormalities have been somewhat conflicting (147,148) Furthermore, in contrast to the usefulness of ECG-LVH changes to evaluate risk and treatment success, there are no studies addressing how changes in P-wave abnormalities affect the risk of cardiovascular outcomes.

2.2.4 Prolonged QT-interval

QT interval is the time from the beginning of ventricular depolarization to the end of ventricular repolarization. From the standpoint of time, the QT interval reflects ventricular repolarization more than depolarization (95). The duration of the QT interval is proportionate to the heart rate (i.e. the faster the heart beats, the shorter the QT interval and vice versa), and the QT interval must therefore be corrected for heart rate (95). The QT interval is also longer in women than in men (149). Though there has been some variation in the cut-points used, a prolonged heart rate corrected QT (QTc) interval has been suggested to be defined as ≥460 ms in women and ≥450 ms in men (149). A variety of cardiac and non-cardiac causes (such as cardiomyopathies, myocardial ischemia, congenital and neurogenic causes, hypothermia, hypokalemia, hypocalcemia, drugs) can result in a prolongation of the QTc interval (95). The QTc interval is also used to evaluate drug safety (149).

In individuals with hypertension, the QTc interval prolongation represents a non-specific marker of cardiac pathology. It is well known that increased left ventricular mass is associated with a prolongation of the QTc interval (150,151). The mechanisms underlying the association between LVH and QTc interval prolongation are attributable to the cardiac remodeling and neurohumoral changes discussed above. In contrast, some population-based studies have proposed that there may be a significant positive relationship between BP and the QTc interval (152). However, these studies have not examined the extent to which this association is mediated by left ventricular mass. Only one recent study has shown that increasing BP levels and hypertension, independent of left ventricular mass, seem to be associated with a prolongation of the QTc interval (153), which emphasizes that not only left ventricular mass, but also systemic BP and/or neurohumoral factors may be important for the manifestation of the prolongation of the QTc interval. It is noteworthy that antihypertensive medication may also affect the QTc interval, usually by reducing it (154).

The distribution of QTc interval varies depending on the heart-rate correction formula, the measurement technique (i.e. manual, computer software), and the population studied. For example, the mean QTc interval using Bazett's formula ($QTc = QT/\sqrt{RR/1s}$, where RR is the cardiac cycle in seconds) and digital caliper measurements in the FHS cohorts ranged from 405.4 ±22.1 ms to 410.5 ±20.4 ms (155), whereas in the ARIC study, the manually measured mean QTc interval using Bazett's formula ranged from 421 ms to 436 ms depending on sex and ethnicity (156). One study examining 3 different large population-based cohorts reported a mean QTc interval using 4 different formulas and manual or computerized

Table 2. Uncorrected and heart rate corrected QT intervals stratified by cohort with different measurement technique in the study of Mandyam et. al (157).

Variable	ARIC (n=14,538) computer	CHS (n=4,745) computer	Health ABC (n=2,396) manual
QT uncorrected, ms	399 ± 30	409 ± 34	412 ± 33
QTc Framingham, ms	410 ± 16	416 ± 18	420 ± 21
QTc Fridericia, ms	410 ± 17	416 ± 19	421 ± 22
QTc Bazett, ms	416 ± 17	420 ± 19	426 ± 23
QTc Hodge, ms	410 ± 18	417 ± 21	421 ± 22

measurements (157). The mean QTc intervals calculated in the study of Mandyam et al. are shown in **Table 2**. In the population-based REGARDS study, 2.7% of the participants had prolonged QTc (158). For comparison, the prevalence of prolonged QTc interval was 10% and 29% in patients with uncomplicated and resistant hypertension, respectively (159,160).

A prolonged QTc interval has been shown to predict cardiovascular events, AF, cardiovascular mortality, and sudden cardiac death in large prospective studies (155,157,158,161-164). While the risks associated with prolonged QT interval especially in the general population have been somewhat controversial (165), the effect of QTc prolongation on the absolute risk of CVD appears to be most pronounced in older adults and in those individuals with prior CVD (166). The association between adverse cardiovascular outcomes and QTc prolongation seems to hold true also in hypertension. Thus, QTc prolongation has been shown to predict cardiovascular death in patients with resistant hypertension and in hypertensive subjects with ECG-LVH (160,167). Furthermore, even in subjects with uncomplicated hypertension, a prolonged QTc interval has been shown to double the risk of cardiovascular events and cardiovascular mortality (159).

2.3 Differences between electrocardiographic and anatomic left ventricular hypertrophy

Originally, the measurement of ventricular mass at autopsy was the reference standard used to establish ECG criteria, and the 12-lead ECG was the only available method to diagnose LVH in living subjects. Later, the echocardiographic assessment

of LVH replaced the ECG-LVH criteria as the gold standard. The main reason for this shift in clinical practice has been the reported low sensitivity (usually less than 25%) of different ECG-LVH criteria for the diagnosis of LVH with echocardiography, MRI, or during autopsy (168,169). More recently, MRI has evolved as the new golden standard (170).

The diagnosis of LVH based on QRS voltage is susceptible to considerable challenges as QRS voltages are influenced by a variety of factors including age, gender, race, and body size (98). Day-to-day variability and electrode placement also affect QRS voltages limiting the diagnostic accuracy of detecting LVH based on QRS voltages. Therefore, some ECG-LVH criteria also take QRS duration or other ECG abnormalities into account (170). Regardless of the ECG-LVH criteria used, the sensitivity of the various criteria is generally quite low, although specificity is high (98,170). The sensitivity of ECG-LVH in detecting anatomic LVH may be enhanced by using ECG amplitudes and products as continuous variables and interpreting them together with other determinants of anatomic LVH such as BP and BMI (171). However, no single criterion is recommended for use i.e. none is superior to any of the other criteria (98). It has been long established that ECG-LVH is a harbinger of cardiovascular morbidity and mortality, and this association has been thought to be mediated by increases in left ventricular mass. Recent studies suggest, however, that ECG-LVH can occur in the absence of LVH observed by echo or MRI, and, independent of left ventricular mass it confers an increased risk of overall mortality, sudden cardiac death, and AF (172).

Anatomic LVH can be assessed by echocardiography, computerized tomography, and MRI. Echocardiography has permitted a reliable, noninvasive estimation of left ventricular mass and has proved to be a more sensitive method than ECG for the detection of LVH (41). It follows that the prevalence of anatomic LVH is greater than that of ECG-LVH. In hypertension, the prevalence of echo LVH ranges from <30% in recently diagnosed untreated individuals to >75% in patients with resistant hypertension (173). However, there is also significant variation in the echocardiographic measurement and definition of LVH, which affects the prevalence rates. In most studies, left ventricular diameters and wall thickness have been measured by the M-mode technique (173). Left ventricular mass is then calculated using necropsy-validated equations and indexed to body size or height (173). Some investigators have defined echo LVH using a cut-off associated either with an increased risk of cardiovascular events or above the reference limits or percentile values in apparently healthy individuals (173).

Anatomic LVH, regardless of the imagining modality, is associated with an increased risk of cardiovascular mortality and morbidity, and as with ECG-LVH, its regression has been shown to improve the patient's prognosis (41,90,169,174-177).

It is noteworthy that the relationship between left ventricular mass and cardiovascular events has been shown to be continuous (43).

The fundamental difference between electrical and anatomic LVH is that they quantify different aspects of the heart's physiology. ECG provides information on the electrophysiological properties of the myocardium while echocardiography and MRI estimate left ventricular mass or dimensions. The development of hypertensive heart disease involves structural, bioelectrical, and biochemical changes, which can all affect the ECG, and therefore ECG-LVH seems to be more than just a mere surrogate for left ventricular mass or anatomic LVH (172,178). While a large proportion of hypertensive individuals will have both electrical and anatomic LVH, there are individuals that will have either isolated anatomic or electrical LVH. The absence of ECG-LVH in individuals with anatomic LVH might contribute to the poor sensitivity of ECG, whereas in individuals without anatomic LVH, the presence of ECG-LVH suggests a clinically distinct entity (172). Indeed, simulation studies have shown that a diffuse and regionally slowed conduction velocity and reduced intracellular coupling in the left ventricle result in QRS patterns consistent with the ECG findings in LVH, being present even without any increase in the size of the left ventricle (178). As a proof of concept, ECG-LVH has been shown to predict AF independent of left ventricular mass (177,179).

2.4 Early onset hypertension

2.4.1 Definition and epidemiology

The appearance of elevated BP is dependent upon age; in general, both systolic BP (SBP) and diastolic BP (DBP) steadily increase from childhood to middle age until the person is 50 to 60 years old when the upward trend flattens or BP begins to decline (180,181). However, an individual's long-term patterns of change in BP are known to vary and seem to involve different cardiovascular risks (182-184). Given that the cumulative BP load plays an important role in determining the cardiovascular risk, younger hypertensive individuals in particular have a high risk of lifetime CVD (185). In addition, as compared to older hypertensive individuals, younger hypertensive individuals are also more likely to be undiagnosed and undertreated (186,187).

Despite this information, however, there is very limited evidence on the clinical relevance and prognosis of hypertension that begins in early versus late life. Long-term BP exposure rather than single BP measurements has been shown to associate more strongly with adverse outcomes (83,188,189). However, long-term exposure has been reported using several indices, such as time-averaged BP, cumulative BP,

and BP trajectory pattern that are complex and require many BP measurements, limiting their use in everyday clinical practice. Recent evidence suggests that a simple assessment of the hypertension onset age could prove to be a good alternative for quantifying the individual's lifetime BP exposure (190).

There are many different methods that have been exploited in the determination of the hypertension onset age. Some previous studies have defined hypertension onset age using objective serial BP measurements, medical records, or self-report. In epidemiological studies using serial BP measurements for the definition of hypertension onset age, hypertension has usually been defined as SBP/DBP ≥ 140/90 mmHg or the use of antihypertensive medication at two or more consecutive examinations (12,14,183,191). While some cross-sectional cohort studies have also used documented BP reports or medical reports to define hypertension onset age (192,193), others have defined hypertension onset using self-reported age when the patient was first diagnosed or treated for hypertension (194).

The precise definition of early onset hypertension is also lacking. Previous studies have used varying thresholds for the definition of early onset hypertension. For example, in some studies, early onset hypertension has been defined as an onset age ≤ 55 years (12,183,191,193), which is based on British hypertension treatment strategy guidelines and these differ for patients over and under 55 years of age (195). Some studies have divided participants into several 10-year age of onset categories depending on the age range of the study sample for the definition of hypertension onset (13,14). There are no studies which would have examined the association between adverse outcomes and hypertension onset age as a continuous variable.

Male sex, higher body mass index and parental hypertension seem to be associated with early onset hypertension (12,13,193). Furthermore, a family history of early onset hypertension seems to cross over generations, as early onset hypertension in grandparents has been demonstrated to predict hypertension also in the grandchildren (191).

Because no exact definition for early onset hypertension exists, there is limited information on its prevalence and incidence. If early onset hypertension is defined as hypertension onset age ≤55 years, then the cumulative incidence of early onset hypertension has been reported to be 34-42% in the decedents of FHS cohorts (12,183) and 18 % in 1160 white male former medical students of the Johns Hopkins precursor study (193). In a study with 2680 nonhypertensive participants aged 18-30 years and 25 years of follow-up, 17.9% developed (early-onset) hypertension (14). One study investigating hypertension onset age and the risk of dementia reported that 34.7% of the study population developed hypertension before the age of 56 years (192). A recent Chinese large-scale epidemiological study reported that of 71,245 individuals without hypertension at baseline, 19,887 (27.9%) individuals developed

hypertension after 9 years of follow-up, and of the hypertensive participants, 13.6% and 43.9% had a hypertension onset at age <45 and ≤54 years, respectively (13).

2.4.2 Association with target organ damage

Only two studies have examined the association of hypertension onset age and HMOD in the same study population using either objective serial BP measurements or self-report for the definition of hypertension onset age (14,194). The samples of these studies consisted of nearly 2700 middle-aged participants of the CARDIA study, who underwent up to 8 serial BP measurements between 1985 and 2011 in addition to assessments of various types of HMOD. The age range at baseline was 18-30 years and the presence of HMOD was assessed at the mean age of 50±4 years. These investigators reported that early onset hypertension, defined as hypertension onset <35 years, was strongly associated with echocardiographic LVH, left ventricular diastolic dysfunction, and coronary calcification whereas if the hypertension onset was ≥45 years, then this was only associated with left ventricular diastolic dysfunction when the hypertension onset was defined by self-report.

2.4.3 Prognostic significance

Early onset hypertension has been shown to be associated with CVD and death in three studies. Already in 1987, Buck et al. showed that the risk of cardiovascular complications for hypertensive subjects, compared with nonhypertensive subjects of similar age, decreased significantly as the age of hypertension onset increased from 40 to 69 years (196). Since then, similar findings have emerged from the FHS (n=3,614) and Kailuan study (n=71,245) (12,13). The former used a retrospective case-control design while the latter was the first time-to-event cohort study on this topic. In the study conducted by Niiranen et al., participants with hypertension onset age ≤45 years carried the highest, an approximately 2.2-fold, risk for cardiovascular mortality compared to nonhypertensive participants, and the risk gradually declined with each decade's increase in the hypertension onset age (12). Wang et al. reported similar risk estimates for cardiovascular events and all-cause mortality (13).

In addition to cardiovascular risk, one study has examined the association between hypertension onset age and incident dementia (192). In this study, mid-adulthood (age range 40.0-55.9 years) hypertension was associated with a 65% increase in risk of dementia in women whereas early adulthood (age range 30.0-36.0 years) hypertension was not related to dementia. However, women who were hypertensive in both measurements, had a 63% higher risk of dementia compared to

women who were not hypertensive at either of these time points. All these associations were null for men.

2.5 Summary

Hypertension induces a wide spectrum of pathological structural and functional disturbances in the heart; these can be partly quantified in the ECG. ECG changes specific to LVH are common, increase the risk of adverse cardiovascular outcomes, and can be used to evaluate treatment success in hypertensive patients (197). Therefore, hypertension guidelines recommend the routine assessment of ECG-LVH (15,16).

In addition to ECG-LVH, several other ECG abnormalities, such as P-wave abnormalities, depolarization abnormalities, and repolarization abnormalities, have been associated with cardiovascular events and AF in the general population (17-24). Given that hypertension alters the electrophysiological properties of the heart, it could be hypothesized that these ECG abnormalities would be more common in hypertensive individuals and might involve a higher risk for adverse cardiovascular outcomes in these patients. However, there is no conclusive data about the prevalence and the predictive value of these ECG abnormalities in cardiovascular and AF risk prediction in a hypertensive population.

The P-wave abnormalities, such as prolonged P-wave duration and abnormal P-terminal force, are considered to reflect the electroanatomical remodelling of the atria that acts as a substrate for AF and other arrhythmias. Although there are many studies which have addressed the prevalence of P-wave abnormalities, studies examining the incidence of P-wave abnormalities are fewer in number and furthermore, the clinical correlates of incident P-wave abnormalities are unknown. In addition, P-wave abnormalities have been shown in some cases to associate with AF, although the results have been controversial.

Objectively defined early onset hypertension is associated with cardiovascular mortality and HMOD, such as echocardiographic LVH, albuminuria, and diastolic dysfunction (12-14). These associations seem to hold true also when hypertension onset is defined by self-report (194). However, so far there are no studies which would have investigated the association between self-reported hypertension onset age and ECG-LVH, a feasible and widely available marker of HMOD.

3 Aims

This thesis was designed to provide contemporary knowledge regarding certain ECG abnormalities in a general Finnish population aged ≥ 30 years.

The specific aims were:

1. To investigate whether ECG abnormalities improve the cardiovascular risk prediction in hypertensive vs nonhypertensive individuals (I)
2. To study the prevalence, incidence, and prognosis of P-wave abnormalities in the general population (II)
3. To determine whether ECG abnormalities improve the AF risk prediction in hypertensive vs nonhypertensive individuals (III)
4. To examine the association between self-reported hypertension onset age and ECG-LVH (IV)

4 Participants and Methods

4.1 Study sample

The study sample is based on the Health 2000 Survey and its follow-up, the Health 2011 Survey. These studies using similar methods were conducted in Finland in the time periods 2000–2001 and 2011–2012. In the Health 2000 Survey, a total of 8028 persons was drawn randomly from the national population register to represent the Finnish adult population aged ≥ 30 years. Subjects were re-invited 11 years later to a follow-up examination in the Health 2011 Survey. The sampling and selection of participants have been previously reported in detail (198,199). The Health 2000 and 2011 Survey study protocols were approved by the ethical committee of the hospital district of Helsinki and Uusimaa and carried out according to the Declaration of Helsinki. A total of 79% (6354, 2876 men and 3478 women) participated in a health examination and a health interview in the baseline survey. All participants signed informed consent. Studies I-IV were based on this study population after relevant exclusions (**Figure 4).**

In Study I, participants with missing ECG (n=55), previous CHD event (n=200), digitalis use (n=127), or incomplete covariate data (n=60) were excluded. In addition, participants with one or more of the following ECG-abnormalities were excluded: Wolff-Parkinson-White pattern (Minnesota code 6.4, n=1), paced rhythm (Minnesota code 6.8, n=4), complete branch block (Minnesota codes 7.1 and 7.2, n=143) and AF/flutter (Minnesota code 8.3, n=94). After exclusions, 5800 participants were included in the analyses. In the analyses concerning incident CVD, also participants with prevalent stroke (n=78) were excluded and 5722 participants were included in the analyses.

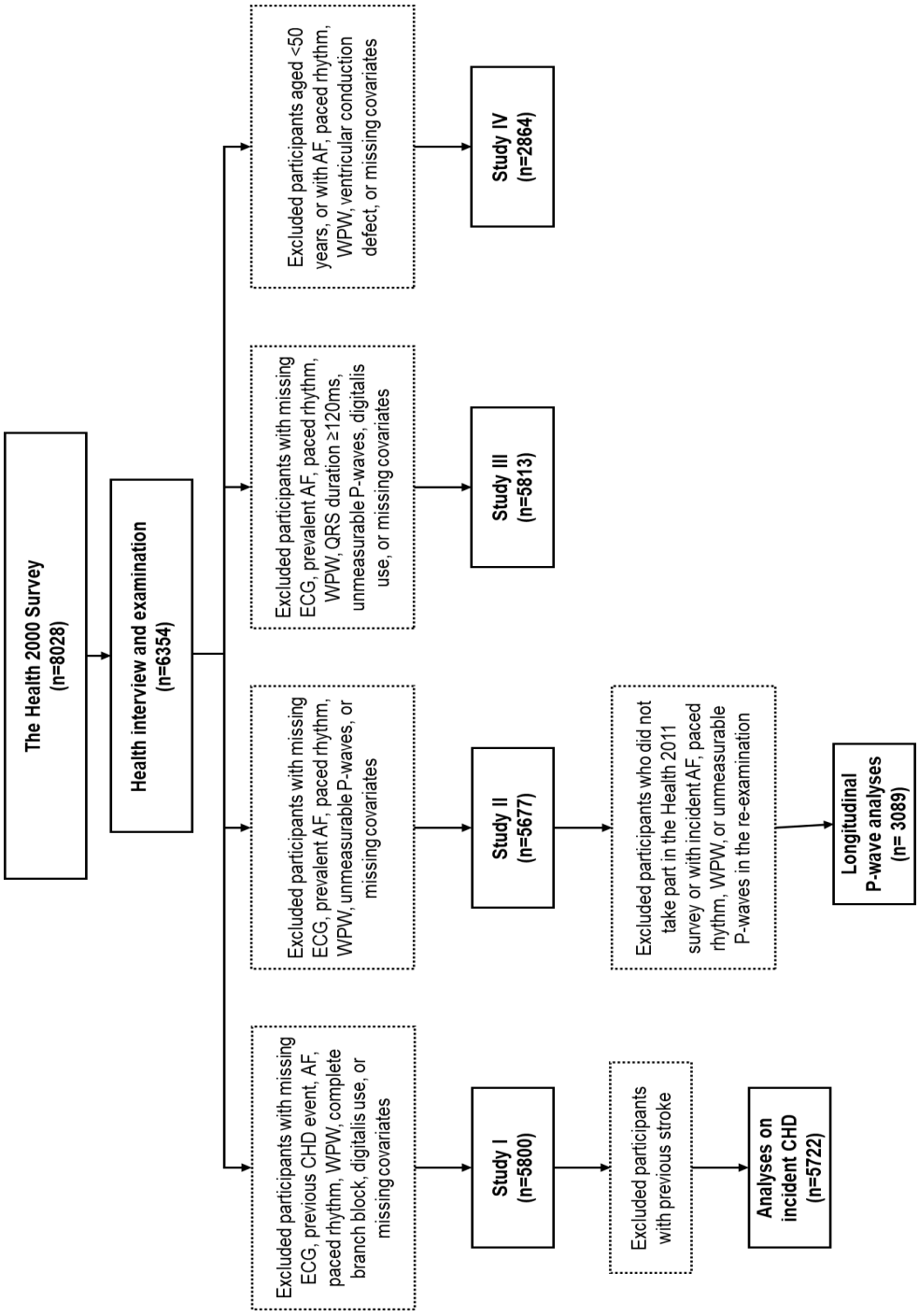

Figure 4. A flow chart illustrating the exclusion criteria of participants in studies I-IV. Detailed exclusion criteria for each study are presented in the text.

In Study II, the correlates of prevalent P-wave abnormalities and the association between P-wave abnormalities and incident AF were assessed in the baseline population. Participants with missing ECG (n=55), previous diagnosis of AF/atrial flutter or AF/atrial flutter on the study ECG (n=208), Wolff-Parkinson-White ECG pattern (n=2), paced rhythm (n=12), unmeasurable P waves (n=110), or missing baseline covariates (n=440) were excluded. As a result, 5667 participants were included in the baseline analyses. The longitudinal changes and determinants of change were assessed in 3242 of 5667 individuals included in the baseline analyses who participated in the re-examination. At the re-examination, participants with incident AF/atrial flutter (n=140), Wolff-Parkinson-White ECG pattern (n=0), paced rhythm (n=12), or unmeasurable P waves (n=89) were excluded, resulting in 3089 (55%) participants. In this study, the AF/atrial fibrillation, Wolff-Parkinson-White ECG pattern, and paced rhythm on study ECGs were acquired by computer-generated automatic interpretation (and not manually by Minnesota coding), see section 4.4. Electrocardiography.

In Study III, participants with missing ECG (n=55), previous register-based diagnosis of AF or atrial flutter (n=180), AF or atrial flutter on baseline ECG (Minnesota code 8.3, n=94), QRS duration at least 120 ms (n=210), Wolff-Parkinson-White ECG pattern (Minnesota code 6.4, n=1), paced rhythm (Minnesota code 6.8, n=4), unmeasurable P waves (n=110), digitalis use (n=127), or missing baseline covariates (n=67) were excluded. As a result, the study population consisted of 5813 participants.

In Study IV, participants younger than 50 years (n=2950) or with paced rhythm (Minnesota code 6.8, n=4), Wolff-Parkinson-White ECG pattern (Minnesota code 6.4, n=1), AF (Minnesota code 8.3, n=94), ventricular conduction defect (Minnesota code 7, n=566), or missing covariates (n=130) were excluded resulting in a final study sample of 2864 participants.

4.2 Study flow

Each participant's examination consisted of 1) an interview and 2) a health examination, which took place a few weeks after the interview. In the interview, information covering different aspects of health, illnesses, use of health care services, medications, and functional capacity were collected by centrally trained interviewers of Statistics Finland. The interviews were carried out in the participants' homes during the baseline survey and in a local facility during the follow-up survey. The health examination was performed on each participant in a local health centre by centrally trained physicians and nurses.

4.3 Blood pressure classification, measurement, and hypertension onset age

BP was measured after the participants had been seated quietly in the measurement room for at least five minutes. Measurements were taken with a standard mercury manometer (Mercuro 300; Speidel & Keller, Jungingen, Germany) using standard procedures from the right arm if possible. A second set of readings was taken two minutes after the first measurement. The means of two measurements were used to determine BP. Hypertension was defined as baseline systolic BP (SBP) at least 140mmHg or diastolic BP (DBP) at least 90mmHg or use of antihypertensive medication.

In study I, participants were further divided into three categories based on their BP and the use of antihypertensive medication according to then-current European guidelines. Category I (normotension) included normotensive participants with baseline SBP <140 mmHg and DBP <90 mmHg. Category II (Grade 1 hypertension) included participants with baseline SBP 140–159 mmHg or DBP 90–99 mmHg. Category III (Grade 2 hypertension) included participants with SBP ≥160 mmHg or DBP ≥100 mmHg or daily use of antihypertensive medication.

Hypertension onset age was self-reported in the health interview. In study IV, participants were divided into categories according to their hypertension onset age (<40 years, 40–49 years, ≥50 years, or no hypertension). Early onset hypertension was determined as hypertension onset at age <40 years; late onset hypertension was designated as hypertension onset at age ≥50 years.

4.4 Electrocardiography

A standard 12-lead ECG was recorded from each subject in the resting supine position using standard procedures with Marquette Hellige MAC 500 electrocardiographs in 2000–2001 (Freiburg, Germany and Milwaukee, WI, USA) and MAC5000 or MAC5500 electrocardiographs (GE Healthcare, Freiburg, Germany) in 2011–2012. The ECGs were processed using the Marquette 12SL analysis program (Marquette Electronics Inc., Milwaukee, WI, USA) embedded in the electrocardiographs. The Marquette 12SL algorithm analyses all 12 leads simultaneously and forms a median wave complex of every single lead for the measurement of intervals and voltages either across all leads or lead-specifically. The ECG data including 10 second tracings of 12-lead ECG waveforms, automated interval and voltage measurements, and computer-generated diagnostic interpretations were stored digitally.

The electronic recordings stored on diskettes or memory cards were sent for further analysis to the Social Insurance Institution’s research center in Turku,

Finland. The technically most valid recording of the often several recordings of the same subject was chosen and stored electronically. The ECGs were then analyzed with the Magellan software (Marquette Electronics Inc., Milwaukee, WI, USA). The measurement points were checked, and if necessary, corrected by centrally trained nurses supervised by an experienced clinical physiologist.

All ECG strips were read and coded in accordance with the Minnesota coding scheme (200) separately by two investigators blinded to clinical status in the Institute of Cardiology, Kaunas Medical Academy, Lithuania. In the case of disagreement (28% of cases), final coding was resolved through consensus between the two investigators.

In study I, early repolarization measurements were obtained manually with a custom-made software by two experienced readers in a blinded fashion (201).

4.5 Definitions of ECG abnormalities

In studies I and III, the studied ECG abnormalities were chosen primarily because of 1) their established role as ECG risk markers or 2) recent publications demonstrating their association with the studied outcome in the general population.

In studies I-III, computerized measurements were used for the measurement of P-wave duration, PTF, P-wave axis, PR interval, QRS voltages (to define ECG-LVH), QRS duration (to define non-specific IVCD), R-wave amplitudes (to define poor R-wave progression), QT interval, and T-wave amplitudes (in leads AVR, I and V6), whereas ST-depression with negative T-wave (ST/T changes), prolonged PR-interval, and left axis deviation were obtained manually through Minnesota coding.

The definitions of the ECG abnormalities in studies I-IV are presented in **Table 3** and the Minnesota codes used in the definitions of ECG abnormalities are presented in **Table 4**.

Table 3. The definitions of ECG abnormalities in studies I-IV

ECG abnormality	Definition
Prolonged P-wave duration	P-wave duration > 120 ms in lead II (study I)
	P-wave duration > 120 ms in any lead (studies II-III)
Abnormal PTF	Amplitude x duration of the terminal portion of P wave in lead V1 ≤ -4 mV·ms (studies I-III)
	Amplitude x duration of the terminal portion of P wave in lead V1 ≤ -6 mV·ms (studies I-II)
Abnormal P-wave axis	P-wave axis < 0° or > 75° (study I)
Left P-wave axis deviation	P-wave axis < 0° (study II)
Right P-wave axis deviation	P-wave axis > 75° (study II)
Prolonged PR interval	Minnesota code 6.3 (studies I and III)
LVH Sokolow-Lyon	SV1+RV5/V6 ≥ 3.5 mV (studies I, III, IV)
LVH Cornell	SV3+RaVL > 2.8 mV for men and > 2.0 mV for women (studies I, III, IV)
LVH Minnesota code	Minnesota codes 3.1 or 3.3 (study IV)
Non-specific IVCD	QRS duration > 110 ms without Minnesota codes 7.1, 7.2, 7.3, 7.5 and 7.6 (study I)
Poor R-wave progression	RV3 ≤ 0.3 mV and RV2 ≤ RV3 without Minnesota code 7 or Minnesota code 1 (studies I and III)
Left axis deviation	Minnesota code 2.1 or 2.4 (studies I and III)
ST/T changes	Minnesota code 4.1 or 4.2 concomitantly with Minnesota code 5.1 or 5.2 (study I)
Early repolarization pattern	J-point amplitude ≥ 0.1 mV in inferior (II, III, aVF) or lateral (I, aVL, V4-V6) leads (study I)
Negative T-wave (I, V6)	T-wave amplitude < 0 mV in leads I and V6 (study III)
Positive T-wave (aVR)	T-wave amplitude ≥ 0 mV in lead aVR (studies I and III)
Prolonged QT interval	Heart rate corrected QT interval ≥ 450 ms in men and ≥ 460 ms in women
LVH with ST/T changes	LVH Sokolow-Lyon and ST/T changes (study I)

IVCD, intraventricular conduction delay; LVH, left ventricular hypertrophy; PTF, P terminal force; ST/T changes, ST depression and negative T-wave.

Table 4. Minnesota codes used in the studies I-IV

Minnesota codes	Definition
Q and QS patterns	
1	Q waves and QS patterns
QRS axis deviation	
2.1	QRS axis -30° - (-90)°
2.4	QRS axis -90° - (-149)°
High amplitude R waves	
3.1	RV5/RV6 > 2.6 mV, or RI/RII/RIII/RaVF > 2.0 mV, or RaVL > 1.2 mV
3.3	1.5 mV < RI ≤ 2.0 mV, or SV1+RV5/RV6 > 3.5 mV
ST-depression	
4.1	J-point amplitude ≤ -0.1mV and ST segment horizontal or downward sloping
4.2	-0.1 mV < J-point amplitude ≤ -0.05mV and ST segment horizontal or downward sloping
T-wave items	
5.1	T-wave amplitude ≤ -0.5 mV
5.2	-0.5 mV < T-wave amplitude ≤ -0.1 mV
AV conduction defect	
6.4	WPW pattern
6.8	Artificial pacemaker
Ventricular conduction defect	
7.1	Complete left bundle branch block
7.2	Complete right bundle branch block
7.3	Incomplete right bundle branch block
7.4	Intraventricular block
7.5	R-R' pattern in leads V1/V2 with R' amplitude ≤ R
7.6	Incomplete left bundle branch block
7.7	Left anterior hemiblock
7.8	Combination of 7.7 and 7.2
Arrhythmias	
8.3	Atrial fibrillation or atrial flutter

AV, atrioventricular; WPW, Wolff-Parkinson-White.

4.6 Other measurements and definitions

Weight and height were measured. Body mass index (BMI) was calculated as body mass (kg) divided by height (m) squared. Serum concentrations of total cholesterol, high-density lipoprotein (HDL) cholesterol, and glucose were determined enzymatically from venous blood samples. The serum non-HDL cholesterol concentration was calculated as total cholesterol minus HDL-cholesterol. Diabetes mellitus was defined as a serum glucose level of 7.0 mmol/l or greater or a history of the use of oral hypoglycemic agents or insulin therapy. Current smoking was defined as self-reported daily use of cigars, cigarettes, or pipe tobacco. Heart rate was obtained from the ECGs. Spirometry was performed on each participant.

In study II, chronic obstructive pulmonary disease (COPD) was defined as having been diagnosed with COPD by a physician and receiving medication for COPD; or having a spirometry result indicative of COPD according to the Global Initiative for Chronic Obstructive Lung Disease criteria (202).

In studies II and III, use of chronotropic medication (beta-blockers, digitalis, calcium-channel blockers, and antiarrhythmic agents) was determined based on the participant's self-reported use of medication prescriptions in the health interview.

4.7 Definitions of cardiovascular disease and follow-up for outcomes

Information on prevalent and incident CVD was retrieved from the National Hospital Discharge and Causes of Death registers. These registers are nationwide and contain information on all periods of care in all Finnish secondary- and tertiary-care hospitals. Diagnoses are listed in these registers with codes defined in the 10th revision of the International Classification of Diseases (ICD-10). In addition, data on drug purchases, and entitlements to special reimbursements due to chronic diseases were gathered from the Drug Reimbursement register.

Prevalent CHD was defined as a previous hospitalization with ICD-10 codes I20-I22 and/or percutaneous coronary intervention or coronary artery bypass surgery. Heart failure was determined if a participant used furosemide, had received reimbursement of costs for heart failure medication, or had been previously hospitalized with ICD-10 codes I50, I11.0, I13.0, and I13.2.

In study I, two outcomes were used: 1) CHD events, and 2) CVD events that were a composite endpoint consisting of CHD and stroke events. CHD events were defined as ICD-10 codes I20-I22 and/or percutaneous coronary intervention or

coronary artery bypass surgery in the Hospital Discharge Register or ICD-10 codes I20-I25, I46, R96 and R98 in the Causes of Death Register. Stroke events were defined as ICD-10 codes I60-I61 and I63-I64, excluding I63.6, in the Hospital Discharge and Causes of Death Registers. Only the first event was included in the analyses. The participants were followed-up for cardiovascular events until December 31, 2011.

In studies II and III, the outcome was incident AF. Incident AF was defined as the ICD-10 code I48 in the National Hospital Discharge or Causes of Death registers during follow-up. In addition, in study II, incident AF was also defined as AF in the Health 2011 Survey follow-up ECG. All subjects were followed-up for incident AF until death or December 31, 2013.

The CHD, stroke, and heart failure definitions used in these studies have been previously validated. (203-206).

4.8 Statistical analyses

In study I, ECG abnormalities were analyzed as dichotomous variables. The differences in the prevalence of ECG abnormalities according to hypertension status were compared with the X^2 test. The general linear regression model was used to calculate and compare age- and sex-adjusted prevalence rates. Cox proportional hazards regression models were used to evaluate the associations between ECG abnormalities and incident CVD and CHD events in the whole study population and in BP categories. Participants in grades 1 and 2 hypertension were combined to increase the number of events in the categories. The models were adjusted for age, sex, BMI, current smoking, non-HDL-cholesterol, and diabetes mellitus. In addition, the BP category was added as a covariate in the analyses of the whole study population. These covariates were chosen because of their importance as CVD risk factors. The interaction between the BP category and ECG abnormalities was tested by introducing their product as an interaction term in the models. Because body size impacts on the sensitivity of ECG criteria in detecting anatomical LVH, the interaction between the BMI category (over and under a median of 26.2 kg/m2) and LVH by Sokolow-Lyon criteria was tested similarly. Direct adjusted Kaplan-Meier survival curves for the different categories based on unstratified Cox models were computed (207). The area under the receiver-operating-characteristic curve (AUC) and the integrated discrimination index (IDI) analyses were used to assess the incremental prognostic information of the ECG abnormalities (208). The AUC and IDI analyses were performed in the whole study population and in the different BP categories by comparing two logistic regression models with and without ECG

abnormalities CHD event as the outcome. These models were adjusted for age, sex, SBP, BMI, current smoking, non-HDL-cholesterol, and diabetes mellitus.

In study II, the differences in baseline characteristics between individuals with and without P-wave abnormalities using the X^2, the Wilcoxon rank sum, and the Kruskal-Wallis tests. In addition, the baseline characteristics of participants who were re-examined were compared to those who did not attend the re-examination to assess the possibility of a selection bias in the longitudinal analyses. The cross-sectional and longitudinal associations between baseline characteristics and P-wave abnormalities were examined using logistic regression. Models were adjusted for baseline age, sex, systolic BP, BMI, non-HDL-cholesterol, smoking, diabetes, use of chronotropic medication, COPD, heart failure, and CHD. These variables were included in the models due to their significance as cardiovascular risk factors, or due to their potential impact on the P-wave abnormalities. Cox proportional hazards regression models were used to evaluate the association of P-wave abnormalities with incident AF. These models were adjusted for important AF risk factors including baseline age, sex, systolic BP, BMI, non-HDL-cholesterol, smoking, diabetes, CHD, heart failure, and heart rate. The proportional hazards assumption was confirmed with the Kolmogorov-type supremum test. A sensitivity analysis with an abnormal PTF defined as ≤ -6 mVms was performed as in a previous publication (18). Kaplan–Meier curves were computed to illustrate the incidence of AF in participants with and without prolonged P-wave duration.

In study III, ECG abnormalities were analyzed primarily as dichotomous variables. However, PR interval, P-wave duration, QTc interval, Sokolow-Lyon voltage (SV1+RV5/V6), Cornell voltage (SV3+RaVL), and T-wave amplitude in lead aVR were also analyzed as continuous variables. The X^2 test was used to compare the difference in the prevalence of ECG abnormality between non-hypertensive and hypertensive participants. Fine-Gray proportional subdistribution hazards models treating death as a competing risk were used to evaluate the association of ECG abnormalities with incident AF. Models were adjusted for baseline age, sex, BMI, current smoking, use of chronotropic medication, diabetes mellitus, CHD, heart failure, and heart rate. In addition, hypertension was included as a covariate in the analyses covering the whole study population. The interaction between the BP category and ECG abnormalities on AF incidence was tested by introducing their product as an interaction term in the models. In addition, the effect of the ECG abnormality x age (dichotomized at 65 years) interaction on AF incidence in hypertensive individuals was tested. In individuals aged 65 and over, we also assessed the effect of the ECG abnormality x hypertension interaction on the AF incidence. Cumulative incidence function curves were used to illustrate the AF incidence in participants stratified according to PR interval and BP category. The AUC, net reclassification improvement (NRI) with risk categories of <5%, 5% to

10%, and >10%, and IDI analyses were used to evaluate the incremental prognostic information of the ECG abnormalities that were significantly associated with AF (208). The AUC, NRI, and IDI were computed in two logistic regression models i.e. with and without ECG abnormalities with an AF event as the outcome. These models were adjusted for the same covariates used in the Fine-Gray models except for hypertension, which was replaced with SBP. The clinical usefulness and net benefit of a prolonged PR interval and a negative T wave in lateral leads for AF prediction were assessed using logistic regression modeling and decision curve analysis (DCA) (209).

In study IV, the prevalence of ECG-LVH across groups was compared using a X^2 test. Univariable and multivariable logistic regression models were used to evaluate the association between hypertension onset age groups and ECG-LVH. The differences in odds ratios for ECG-LVH between hypertension onset at <40 years and ≥50 years were compared using a z test with those participants who did not report having hypertension as the referent category. The models were adjusted for age, sex, body mass index (BMI), smoking, diabetes, non-HDL-cholesterol, heart rate, heart failure, CHD, use of antihypertensive medication, and SBP. To explore the possible effect of medications on the associations, the multivariable adjusted odds-ratios of ECG-LVH were also assessed in participants not using renin-angiotensin-aldosterone system inhibitors (n=2514).

All statistical analyses were performed using SAS 9.4 (SAS institute Inc., Cary, NC). Two-tailed $P < 0.05$ was considered statistically significant in all analyses.

5 Results

5.1 Prevalence and prognosis of ECG abnormalities according to hypertension status (I and III)

5.1.1 Prevalence of ECG abnormalities (I)

Study I included 5800 participants. The characteristics of the participants are presented in Article I, Table 1. The prevalence of 15 ECG abnormalities was assessed. The unadjusted prevalence of ECG abnormalities differed by BP category ($P \leq 0.003$ for all) except for an abnormal P-wave axis ($P=0.95$) (**Figure 5**). The prevalence of ECG abnormalities increased with the severity of hypertension except for the prevalence of non-specific IVCD and an early repolarization pattern (Article I, Table 2). Similarly, the age- and sex-adjusted prevalence of 12 ECG abnormalities differed according to BP category ($P \leq 0.047$ for all). However, the adjusted prevalence of LVH with ST/T changes, left axis deviation, and non-specific IVCD did not differ by BP category ($P \geq 0.073$ for all). Again, the prevalence of ECG abnormalities increased with the severity of hypertension with only a few exceptions as the adjusted prevalence of abnormal P-wave axis and early repolarization pattern was the highest in normotensive subjects and decreased with the increasing severity of hypertension.

The unadjusted prevalence of 5 out of 15 ECG abnormalities exceeded 5% in hypertensive participants. The most common ECG abnormality in hypertensive participants was an abnormal PTF as its unadjusted prevalence ranged from 16.9% in grade 1 hypertension up to 23.1% in grade 2 hypertension. For comparison, the unadjusted prevalences of LVH by Sokolow-Lyon criteria were 11.7% and 13.3% in grade 1 and grade 2 hypertension, respectively.

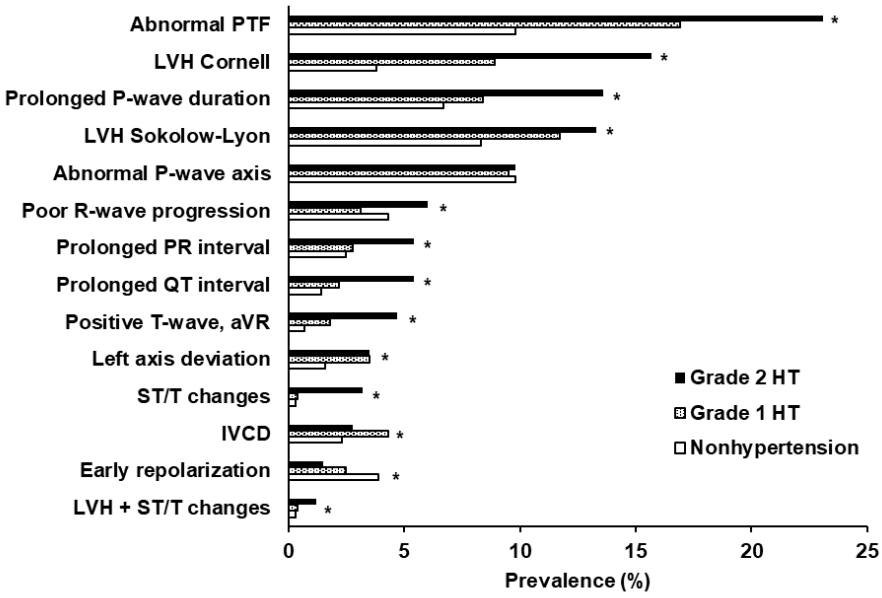

Figure 5. The unadjusted prevalence of ECG abnormalities according to BP category. Grade 1 HT was defined as BP 140-159/90-99 mmHg; Grade 2 HT was defined as BP ≥ 160/100 mmHg or use of antihypertensive medication. HT, hypertension; IVCD, nonspecific intraventricular conduction delay; LVH, left ventricular hypertrophy; PTF, P terminal force.

* *P* for difference between categories <0.05

5.1.2 Association of ECG abnormalities with incident cardiovascular disease (I)

The multivariable-adjusted hazard ratios (HRs) and their 95% confidence intervals (95% CIs) for CHD and CVD events among participants with ECG abnormalities are presented in Article I, table 3. The median follow-up for CHD and CVD events was 11.2 years. A total of 359 CHD and 493 CVD events occurred during follow-up.

Five out of 15 ECG abnormalities were associated with future CHD and CVD events in hypertensive participants and in the whole study sample in the multivariable-adjusted Cox models (P≤0.03 for all); these were LVH as assessed by Sokolow-Lyon criteria, LVH with ST/T changes, ST/T changes, AVRT+, and poor R-wave progression. The risk of a CHD event in hypertensive participants with one of these ECG abnormalities ranged from 1.5-fold to 2.3-fold. These main findings are summarized in **Figure 6.** and in adjusted Kaplan-Meier curves in Figure 1,

Article I. Non-specific IVCD was associated with a 1.5-fold risk of suffering a CVD event in the whole study population (P=0.02).

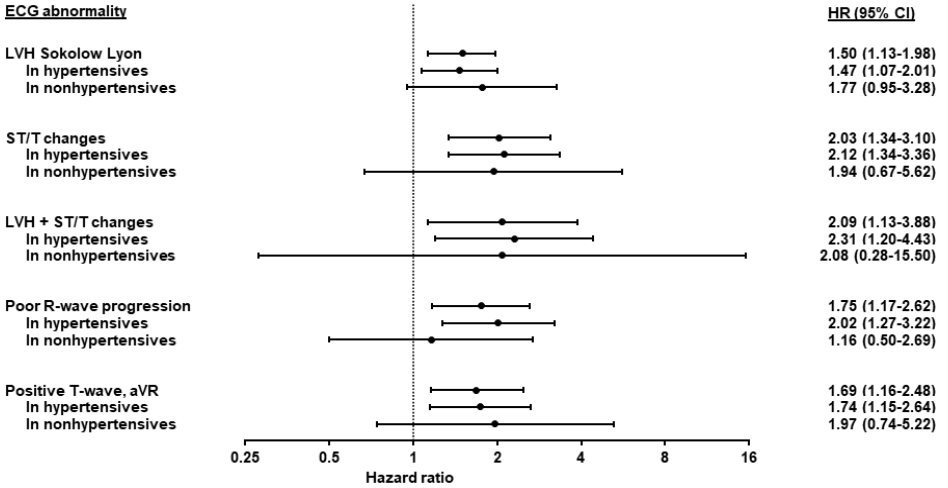

Figure 6. ECG abnormalities and risk of coronary heart disease in the whole study population and in blood pressure categories. CI, confidence interval; HR, hazard ratio; LVH, left ventricular hypertrophy. Models were adjusted for age, sex, BMI, current smoking, non-HDL-cholesterol, and diabetes mellitus. Blood pressure category was used as a covariate in the models of the whole study population.

The other ECG abnormalities, including LVH by Cornell criteria, prolonged QT-interval, P-wave abnormalities, early repolarization pattern, and left axis deviation, were not associated with future CHD or CVD events (P≥0.07 for all).

Only an abnormal P-wave axis and early repolarization in the inferior leads revealed a statistically significant interaction with the cardiovascular risk between the BP category and the ECG abnormality. (P=0.04 for both). For hypertensive participants with an abnormal P-wave axis, the cardiovascular risk was decreased compared to nonhypertensives and vice versa for hypertensive participants with an early repolarization pattern in inferior leads. LVH assessed by Sokolow-Lyon criteria did not display an interaction with the BMI category on CHD and CVD events (P≥0.36 for both).

5.1.3 Association of ECG abnormalities with incident atrial fibrillation (III)

The characteristics of the participants are presented in Article III, Table 1. The mean values of the continuous ECG characteristics in the whole study population and in BP categories are presented in **Table 5**.

Table 5. Continuous ECG variables in the whole study population and in blood pressure categories

Characteristic	Total	BP Category		
		Nonhypertension	Grade 1 HT	Grade 2 HT
n	5813	3148	1146	1519
Heart rate, /min	63.3 (10.7)	61.8 (9.9)	65.1 (11.0)	65.1 (11.4)
P-wave duration ms	103.9 (15.8)	102.6 (14.6)	104.4 (15.2)	106.3 (18.0)
PR interval, ms	161.6 (25.0)	158.2 (24.3)	161.2 (22.4)	168.8 (26.8)
QRS duration, ms	90.0 (10.0)	89.5 (9.8)	90.7 (10.4)	90.3 (9.9)
QTc, ms	416.6 (16.4)	413.7 (15.4)	417.0 (15.6)	422.3 (17.7)

Variables are presented as mean (SD). Nonhypertension was defined as blood pressure <140/90 mmHg, grade 1 hypertension was defined as blood pressure 140-159/90-99 mmHg and grade 2 hypertension was defined as blood pressure ≥160/100 mmHg or use of antihypertensive medication. P-wave duration was defined as maximum P-wave duration in any lead. BP, blood pressure; HT, hypertension; QTc, corrected QT interval.

The multivariable-adjusted subdistribution hazard ratios (HR) and their 95% confidence intervals (CI) for incident AF in participants with versus those without ECG abnormalities are presented in Table 3, article III. In addition, the association between continuous ECG variables and incident AF is presented in Table 4, article III. The mean follow-up for AF events was 11.9 years. A total of 412 AF events occurred during follow-up.

In hypertensive participants, negative T-wave in lateral leads, LVH assessed by Sokolow-Lyon criteria, a poor R-wave progression, a prolonged PR interval, and a prolonged P-wave duration were associated with incident AF ($P \leq 0.04$ for all). The HRs for AF in hypertensive participants with these ECG abnormalities were of a similar magnitude, ranging from 1.43 to 1.81. A negative T-wave in lateral leads was also associated with incident AF in nonhypertensive participants (HR, 4.59; $P=0.001$). These findings are illustrated in **Figure 7**. Of the continuous ECG variables, Sokolow-Lyon voltage and PR interval were associated with incident AF in hypertensive participants ($P<0.02$ for both), whereas corrected QT interval and T-

wave amplitude in lead aVR were related to AF in nonhypertensive participants (P≤0.007 for both). All of the above-mentioned ECG abnormalities predicted AF in the whole study population (P≤0.04 for all).

The rest of the ECG abnormalities including abnormal PTF, abnormal P-wave axis, left axis deviation, ST/T changes, and LVH by Cornell criteria were not associated with incident AF in the multivariable-adjusted models (P≥0.06 for all).

A longer corrected QT interval and a higher T-wave amplitude in lead aVR predicted AF in non-hypertensive but not in hypertensive participants (P for interaction ≤0.047 for both). Similarly, the corrected QT interval was a stronger predictor of AF in non-hypertensive than in hypertensive participants aged 65 years and over (1-SD increment in corrected QT interval: HR, 1.75; 95% CI, 1.27-2.41 versus HR, 1.13; 95% CI, 0.98-1.29; P for interaction 0.005). A prolonged PR interval (HR, 3.52; 95% CI, 1.90-6.52 versus HR, 1.32; 95% CI, 0.79-2.22) and left axis deviation (HR, 5.06; 95% CI, 2.58-9.95 versus HR, 0.95; 95% CI 0.51-1.75) were stronger predictors of AF in younger than in older hypertensive individuals (P for interaction 0.01 and <0.001, respectively).

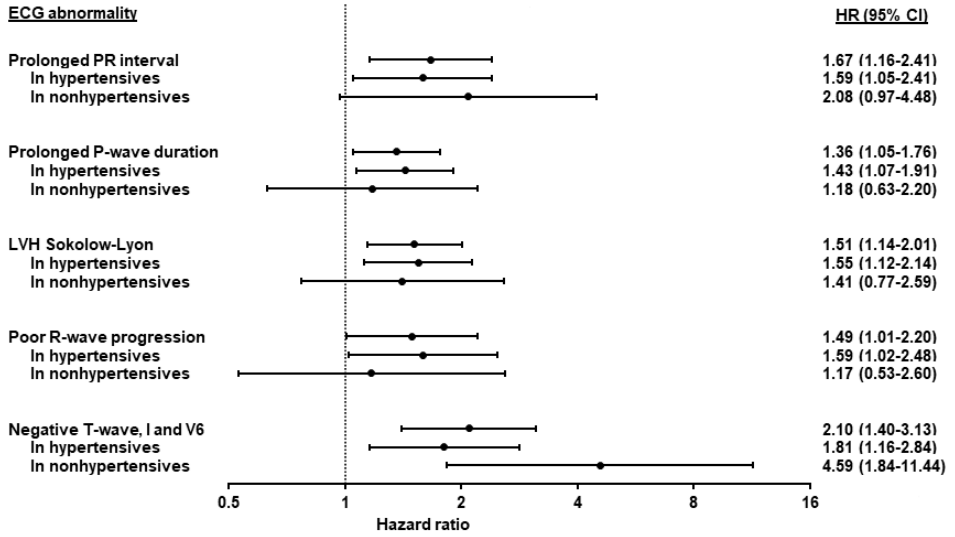

Figure 7. ECG abnormalities and risk of atrial fibrillation in the whole study population and in blood pressure categories. CI, confidence interval; HR, hazard ratio; LVH, left ventricular hypertrophy. Models were adjusted for age, sex, BMI, current smoking, diabetes, use of chronotropic medication, heart failure, coronary heart disease, and heart failure. Hypertension was used as a covariate in the models of the whole study population.

5.1.4 The incremental value of ECG abnormalities in cardiovascular risk prediction (I and III)

In study I, the use of ECG abnormalities did not improve risk prediction in terms of AUC. The addition of LVH as assessed by Sokolow-Lyon criteria (absolute IDI, 0.004; relative IDI 3.3%; P=0.046) and ST/T changes (absolute IDI, 0.006; relative IDI 5.3%; P=0.03) in the models was associated with an increase in IDI in hypertensive participants. The use of ST/T changes was also associated with an increase in IDI in the whole study population (absolute IDI, 0.004; relative IDI 3.3%; P=0.03).

In study III, the results of the AUC, IDI, and NRI analyses in the whole study population and in hypertensive participants are presented in Table 5, article III. The addition of a prolonged PR interval in the models improved the risk prediction in terms of AUC in the whole study population (0.806 versus 0.809; P=0.032) and in hypertensive participants (0.753 versus 0.758; P=0.049). The addition of other ECG abnormalities in the models did not result in increases of AUC ($P \geq 0.08$ for all). In hypertensive participants, the addition of continuous PR interval (absolute IDI, 0.004; P=0.01) and negative T wave in lateral leads (absolute IDI, 0.004; P=0.045) in the models resulted in increases in IDI. In non-hypertensive participants, the addition of continuous corrected QT interval in the model improved IDI (absolute IDI, 0.011; P=0.005, data not shown). These ECG variables improved IDI in the models of the whole study population (absolute IDI 0.002-0.005; $P \leq 0.048$ for all). The addition of ECG abnormalities in the models did not result in increases of NRI ($P \geq 0.09$ for all).

The unadjusted cumulative incidence of AF in participants stratified according to PR interval and BP category is illustrated in Figure 1 article III.

In hypertensive participants, the use of prolonged PR interval in the models did not confer any net clinical benefit in the DCA as illustrated in Figure 2, Article III. The DCA performed in the whole study sample and with a negative T wave in the lateral leads included in the models instead of a prolonged PR interval yielded similar results. (data not shown).

5.2 Incidence, correlates, and prognosis of P-wave abnormalities (II)

5.2.1 Prevalence, incidence, and clinical correlates of P-wave abnormalities

The baseline characteristics of participants are presented in Table 1, Article II. A prolonged P-wave duration, abnormal PTF, left P-wave axis deviation, and right P-wave axis deviation were present in 9.9%, 15.2%, 5.1%, and 4.6% of the participants in the whole study sample at baseline, respectively. Participants with P-wave abnormalities were older, had more heart failure and CHD, and used more often chronotropic medications than those with normal P-waves. Participants with a prolonged P-wave duration and an abnormal PTF had higher values of SBP, DBP, BMI, non-HDL-cholesterol, and more diabetes, whem compared to participants without these ECG abnormalities ($P<0.007$ for all).

Cross-sectional determinants of the P-wave abnormalities derived from the multivariable-adjusted logistic regression analyses are shown in Table 2, Article II. Older age was associated with P-wave abnormalities ($P<0.001$ for all); male sex, higher BMI, and use of chronotropic medication were associated with prolonged P-wave duration ($P<0.001$ for all). Higher SBP and smoking were positively, and COPD inversely associated with abnormal PTF ($P\leq0.03$ for all). Male sex, smoking, COPD, lower BMI, lower non-HDL-cholesterol, and heart failure were associated with right P-wave axis deviation ($P\leq0.02$ for all).

The longitudinal changes in P-wave abnormality statuses between baseline and follow-up examination are illustrated in Figure 1, Article II. The incidences of prolonged P-wave duration, abnormal PTF, left P-wave axis deviation, and right P-wave axis deviation in the follow-up examination were 16.0%, 7.4%, 3.4%, and 2.2%, respectively. Over half of the baseline P-wave abnormalities had reversed to normal in the re-examination. The determinants of incident P-wave abnormalities are shown in Table 3, Article II. The incident prolonged P-wave duration was associated with older age, male sex, higher SBP, and higher BMI ($P\leq0.001$ for all). The incident abnormal PTF was associated with older age, higher BMI, and prevalent CHD ($P\leq0.01$ for all). An incident right P-wave axis deviation was associated with higher SBP, lower BMI, smoking, prevalent heart failure, and prevalent COPD ($P\leq0.02$ for all).

Participants, who did not attend re-examination, were older, more likely to be male, and had a higher BP, a higher BMI, a higher non-HDL-cholesterol level, a higher heart rate, more diabetes, more CHD, more COPD, more heart failure, and more chronotropic medication use than those who attended the re-examination ($P<0.001$ for all, data not shown). The baseline values of the P-wave duration

(104.7ms vs 103.9ms; P=0.03) and PTF (-2.3 mVms vs. -2.0 mVms; P<0.001) were greater in participants who were not re-examined as compared to those who were re-examined.

5.2.2 Association of P-wave abnormalities with incident atrial fibrillation

During a mean follow-up of 11.9 years, a total of 423 participants had an AF event. The multivariable-adjusted hazard ratios (HR) and 95% confidence intervals (CI) for incident AF are presented in **Figure 8**.

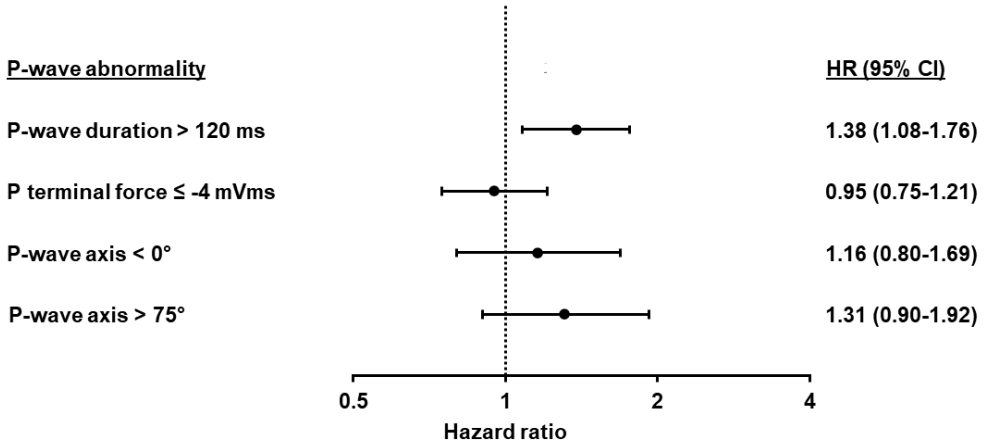

Figure 8. P-wave abnormalities and risk of atrial fibrillation. HR, hazard ratio; CI, confidence interval. Models were adjusted for baseline age, sex, systolic BP, BMI, non-HDL-cholesterol, smoking, diabetes, coronary heart disease, heart failure, and heart rate. In the models of abnormal P-wave axis, P-wave axis 0-75° was considered as the reference.

In the multivariable-adjusted models, only a prolonged P-wave duration was associated with incident AF: (HR, 1.38; 95% CI, 1.08-1.76; P=0.001). This association was stronger in participants not on chronotropic medication (n=4858) (HR, 1.75; 95% CI, 1.27-2.41) (data not shown). Figure 2, Article II illustrates the cumulative risk of AF in individuals with and without a prolonged P-wave duration. No association was observed between abnormal PTF or abnormal P-wave axis and incident AF in the multivariable-adjusted models (P≥0.16 for all). Abnormal PTF defined as ≤ -6 mVms was not associated with incident AF (P=0.23). However, an abnormal PTF, defined as ≤ -6mVms, predicted AF in those participants not consuming chronotropic medication (HR, 1.79; 95% CI, 1.14-2.82; P=0.01).

5.3 Association between self-reported hypertension onset age and ECG-LVH (IV)

The characteristics of the study sample in groups according to self-reported hypertension onset age are shown in Table 1, Article IV. A total of 1158 participants (40%) had self-reported hypertension and 801 individuals (28 %) used antihypertensive medication. The prevalence of early onset hypertension was 6%, whereas 23 % of the participants had late onset hypertension. Participants with self-reported hypertension had more ECG-LVH as assessed by Sokolow-Lyon voltage, Cornell voltage, and Minnesota code criteria than those without self-reported hypertension. (P<0.001). No difference was observed in the prevalence of ECG-LVH between hypertension onset age groups (P≥0.47 for all).

Figure 9. illustrates the odds of ECG-LVH by age group of hypertension onset in the multivariable adjusted models. Hypertension onset at any age was associated with ECG-LVH based on the Sokolow-Lyon and Minnesota criteria (P<0.001 for both). No difference was observed in the odds of LVH with any criteria when examining the different hypertension onset age groups (P≥0.60 for all).

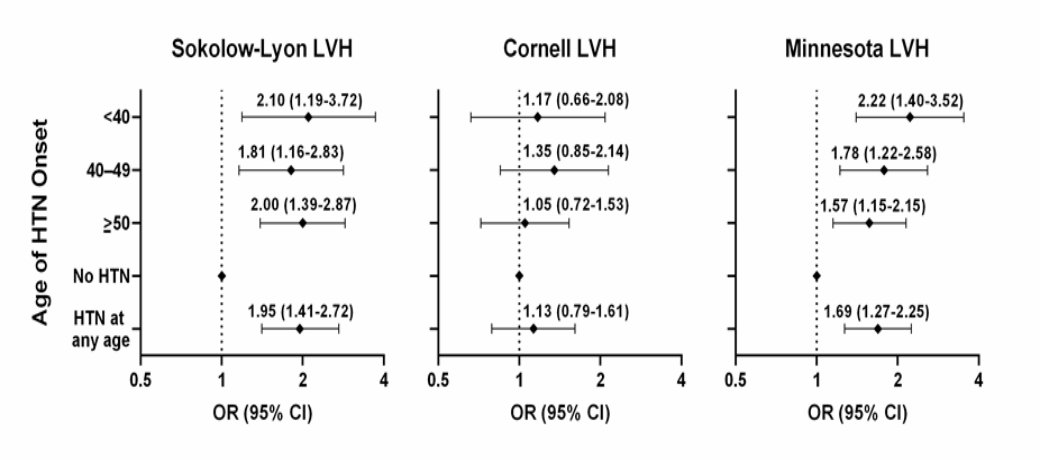

Figure 9. Odds of ECG-LVH according to self-reported hypertension onset age. Model is adjusted for age, sex, body mass index, smoking, diabetes, non-HDL-cholesterol, heart rate, heart failure, coronary heart disease, use of antihypertensive medication and systolic blood pressure. HTN, hypertension; OR, odds ratio; CI, confidence interval; LVH, left ventricular hypertrophy. Original image made by Karri Suvila,

6 Discussion

6.1 Prevalence and prognosis of ECG abnormalities according to hypertension status (I and III)

6.1.1 Prevalence of ECG abnormalities (I)

Study I revealed that ECG abnormalities are common in a general Finnish population sample, and their prevalence mainly increases in relation to the severity of hypertension.

The prevalence of established ECG risk markers in hypertension, such as ECG-LVH, ST/T changes, and a prolonged QT-interval, was somewhat lower than previously reported. In hypertensive participants, the prevalence of ECG-LVH as assessed by Sokolow-Lyon criteria increased from 11.7% in grade 1 hypertension to 13.3% in grade 2 hypertension. The corresponding values for LVH by the Cornell criteria were 8.9% and 15.7%. As reported earlier in this dissertation, an average ECG-LVH prevalence of 18% was observed in an analysis of 26 studies investigating over 40,000 hypertensive individuals (99). The prevalence of ST/T changes in hypertensive participants, 2.3%, was also lower than the value stated in the study of Schillaci et al. who reported a prevalence of ST/T changes of 5.7% in 1970 patients with essential hypertension who had no clinically overt CVD (210). Furthermore, the prevalence of prolonged QT-interval in the whole study sample (2.6%) was similar to previously reported values (158). However, its prevalence among hypertensive participants (4.0%) was markedly lower than in previous studies (153,159,160). These differences in prevalence rates between studies can be explained by the differences in study samples and measurement techniques. Nonetheless, these ECG abnormalities were common, and their prevalence was highest in participants with grade 2 hypertension underlining their ubiquitousness in hypertension.

All P-wave abnormalities except an abnormal P-wave axis were more common at higher BP levels. According to earlier reports (127-129), it is known that P-wave abnormalities are associated with higher BP and hypertension. The prevalences of prolonged P-wave duration and abnormal PTF were high in participants with grade

2 hypertension (13.6% and 23.1%, respectively). For comparison, a similar prevalence (9.5%) of a prolonged P-wave duration was reported in hypertensive subjects in a Chinese general population sample (211). However, the prevalence of abnormal PTF was even higher (37%) in hypertensive individuals with ECG-LVH aged 55-80 years (134). In this study by Okin et al., the high prevalence of abnormal PTF can be explained by the older study sample already with signs of HMOD, although abnormal PTF was acquired manually. In addition to measurement technique and differences in study samples, methodological and racial factors can also explain differences in the prevalence of P-wave abnormalities, as P-wave morphology may vary significantly due to variables such as the placement of the ECG leads, the position of the heart, and ethnicity (95,136,138).

A prolonged PR interval was less common than a prolonged P-wave duration and abnormal PTF, but its prevalence was also highest in participants with grade 2 hypertension. The PR interval is the time from the onset of the P-wave to the start of the QRS complex and it reflects conduction through the atria and AV node. As the PR interval partly consists of the P-wave duration, a high correlation exists between PR-interval and P-wave duration (129). Similar to a prolonged P-wave duration, a prolonged PR interval has been associated with older age, obesity, and hypertension (127-129), which is in line with our study results.

Similarly, a poor R-wave progression, was a common finding in hypertensive participants (4.7%). This is not surprising as a poor R-wave progression has been associated with a previous myocardial infarction, LVH, and branch blocks, (22,212,213) that are relatively common in hypertensive individuals.

AVRT+ was also a relatively prevalent ECG abnormality (3.4%) in hypertensives and the prevalence increased with the severity of hypertension. Lead aVR displays reciprocal information covered by lateral leads, and thus AVRT+ reflects the repolarization abnormalities of the ventricles similarly to depressed T waves in the lateral leads (214). These T-wave abnormalities are often seen in ischemia and LVH, both of which are associated with hypertension, supporting our study results.

The prevalence of non-specific IVCD, early repolarization pattern, and left axis deviation was low in hypertensive participants and it did not increase with the severity of hypertension. On the contrary, the prevalence of an early repolarization pattern decreased with the severity of hypertension, supporting the previously reported association between a lower BP and an early repolarization pattern in the Health 2000 Survey and FHS (201).

6.1.2 Association of ECG abnormalities with incident cardiovascular disease (I)

Study I confirmed the findings of several previous studies (101-105,108,111,112), that established ECG risk markers such as LVH and ST/T changes are significant predictors of cardiovascular events not only in hypertensive individuals but also in the general population. As discussed earlier in this dissertation, LVH is a sign of hypertensive heart disease and a harbinger of cardiovascular morbidity and mortality. Anatomic LVH often manifests as high QRS voltages or as repolarization abnormalities (ST depression and flat or negative T-waves in the lateral leads, also known as the strain pattern). The co-existence of ECG-LVH by voltage criteria and repolarization abnormalities has been shown to worsen the patient's prognosis (215). The results of Study I are in line with the previous literature as ECG-LVH defined by the Sokolow-Lyon criteria and ST/T changes were significant predictors of CHD and CVD events in hypertensive participants. Furthermore, the presence of ECG-LVH with ST/T changes was even more markedly associated with adverse outcomes, especially in the hypertensive participants. In addition, ECG-LVH as designated by Sokolow-Lyon criteria and ST/T changes were the only ECG abnormalities that could improve model discrimination in hypertensives, albeit marginally.

Interestingly, ECG-LVH as assessed by Cornell voltage was not associated with cardiovascular events even though its prevalence was similar to that of ECG-LVH assessed by Sokolow-Lyon criteria. This could at least partly be because of our study sample's relatively low number of events, younger age, and lower prevalence of ECG-LVH when evaluated by Cornell voltage as compared with previous studies. Another explanation for this observed lack of association could be that different ECG-LVH criteria identify hypertensive patients with differing demographic and clinical characteristics associated with increased risk (216). In a previous Health 2000 Survey study examining the effect of sex on the prognostic value of several ECG-LVH criteria, ECG-LVH assessed by Sokolow-Lyon voltage performed the best after adjustments in both sexes, while ECG-LVH assessed by Cornell voltage was not associated with CVD events (217). The authors observed that covariate adjustments attenuated the associations between ECG-LVH criteria and CVD markedly, but, compared to other criteria including Cornell voltage, the effect on Sokolow-Lyon voltage was weaker. The authors concluded that the covariates used in their study may have had less effect on the Sokolow-Lyon voltage than on the other criteria because of the potential different risk factor profiles for Sokolow-Lyon voltage compared to other ECG-LVH criteria, which could also help to explain the results of our study using similar covariate adjustments.

Poor R-wave progression and AVRT+ also predicted CHD and CVD events in hypertensive participants. Both of these ECG abnormalities have been shown to be associated with cardiovascular mortality in the Health 2000 survey (22,23). While

AVRT+ reflects repolarization abnormalities in the lateral leads and the association between it and adverse outcomes is therefore supported by previous studies, the ability of poor R-wave progression to predict cardiovascular outcomes is a more novel finding. As discussed earlier, poor R wave progression may reflect the impact of LVH or a previous myocardial infarction on the ECG, which supports the observed risk associated a with poor R-wave progression. However, apart from the study conducted by Anttila et al (22), there are no prospective studies examining the prognostic value of a poor R-wave progression. A poor R-wave progression may sometimes accompany the leftward shift of the QRS transition zone, a finding associated with increased risk of overall mortality and sudden cardiac death (218). Our results suggest that a poor R-wave progression could aid in the screening for subclinical CVD especially in hypertensive individuals. Further research in other prospective cohorts will be needed to confirm these results.

In our study, non-specific IVCD was a predictor of cardiovascular events in the whole study population. These results support studies that demonstrate non-specific IVCD as a sign of adverse future outcome in the general population (21,219). However, this ECG abnormality may not be a particularly good risk marker in hypertensives as it was a relatively rare finding and the association between it and cardiovascular events failed to reach significance in hypertensive participants.

A prolonged QT interval was not associated with adverse outcomes in hypertensive participants in contrast to previous publications (159,160). A potential explanation for our results could be the use of a prolonged QT interval as a dichotomous variable. An approach treating QT interval as continuous or categorical variable could have improved our understanding of the associations. For example, in a large Danish study with 173,529 primary care patients, a robust association between QT interval prolongation and cardiovascular death was observed when participants were divided into nine categories based on QT interval distributions (166).

None of the P-wave abnormalities were associated with cardiovascular events in Study I, although several previous large-scale epidemiological studies have claimed that P-wave abnormalities are potential cardiovascular risk markers (17,19,130,136,137). Neither an early repolarization pattern nor left axis deviation was associated with cardiovascular events. Left axis deviation has been considered as a benign abnormality (220,221), whereas an early repolarization pattern in the lateral or inferior leads has been previously shown to associate with cardiac mortality and especially sudden cardiac death (20,222). Though the relatively low number of events in our study could at least partly explain these discrepancies between our observations and previous reports, our results suggest that the predictive value of these ECG abnormalities is rather limited.

6.1.3 Association of ECG abnormalities with incident atrial fibrillation (III)

Apart from the known association between ECG-LVH and incident AF in hypertension (90,114), there is very limited information addressing the value of other ECG abnormalities in AF risk prediction in hypertension. Study III confirmed that several ECG abnormalities predict AF independently of other risk markers in the general non-hypertensive and hypertensive population (24). In addition, the results of the study were similar in individuals aged 65 years and over, although it is evident that AF significantly increases with age (9).

In agreement with previous studies, participants with ECG-LVH defined by the Sokolow-Lyon criteria had an increased risk of AF. A composite of ECG-LVH evaluated by either the Sokolow-Lyon or Cornell criteria was also associated with incident AF. These results support ECG-LVH as a marker of arrhythmogenicity. Interestingly, ECG-LVH has been shown to associate with incident AF independently of left ventricular mass (177,179). ECG-LVH and anatomic LVH could therefore be considered as two clinically distinct entities providing different prognostic information (172).

A prolonged PR interval, a poor R-wave progression, and repolarization abnormalities (negative T-wave in lateral leads, positive T-wave in lead aVR) were also associated with incident AF in the whole study sample. A prolonged PR interval was also a particularly strong predictor of AF in younger hypertensive participants in the additional analyses. While the PR interval and repolarization abnormalities have been previously shown to predict AF (223-226), this finding is novel with respect to a poor R-wave progression. Based on the results of study I, a poor R-wave progression could be a marker of subclinical CVD in hypertensive individuals, which could explain the detected association between a poor R-wave progression and AF in hypertensive participants. In contrast, repolarization abnormalities were associated with incident AF especially in the nonhypertensive participants. In theory, the repolarization abnormalities in this study could partly represent subclinical ischemia, masked hypertension, or some other conditions (e.g. changes in the autonomic tone or electrolyte disturbances) possibly affecting repolarization, and thus associated with an increased risk for AF (227-229).

The corrected QT interval (only as a continuous variable) was associated with incident AF in the whole study sample and in nonhypertensive participants, which is in line with the current knowledge (157,163). A significant interaction was observed between the QT interval and the BP category, indicating that the QT interval may not be a useful marker in AF risk prediction in hypertensive individuals. Similar results have been described previously i.e. in a Danish study conducted by Nielsen et al. (163), the association of QT interval with incident AF was the strongest in participants who developed lone AF and the weakest in participants with

cardiovascular comorbidities. These results indicate that QT interval is a marker of increased susceptibility to arrhythmias in individuals without evident clinical heart disease.

A prolonged P-wave duration was associated with incident AF in the whole study sample as well as in the hypertensives. This association is covered in the chapter 6.2.2.

6.1.4 The incremental value of ECG abnormalities in cardiovascular risk prediction

According to a scientific statement issued by the American Heart Association, the evaluation of novel markers of cardiovascular risk should involve not only ways to detect a statistical association between a risk marker and an outcome but also tests to measure the degree to which markers add to the prognostic information provided by standard risk markers (230). Furthermore, the statement emphasizes that a novel risk marker should also have clinical utility to change recommended therapy, its use should improve clinical outcomes, and it should improve outcomes sufficiently to justify the additional costs of testing and treatment. Our study results on the incremental value of ECG abnormalities need to be interpreted in this context.

Although we found several associations between ECG abnormalities and incident CVD and AF, the studied ECG abnormalities had only minor or no incremental value over conventional risk factors in CVD or AF risk prediction. However, we analysed the incremental value of ECG abnormalities separately, which differs from the everyday clinical practice where multiple ECG abnormalities can be assessed from the same ECG recording. Therefore, the observed associations between ECG abnormalities and incident CVD or AF might still be important in clinical practice although the measures of incremental value were not significant. An approach examining the effect of clustering of ECG abnormalities in hypertensives (231), might have shown more relevant and convincing results in the measures of incremental value.

In addition, the modifiability of ECG abnormalities as risk markers merits some consideration. Of all the studied ECG abnormalities, only changes in ECG-LVH have been shown to affect prognosis. In other words, serial changes in ECG-LVH can be used to evaluate risk and treatment success, whereas in the presence of the other studied ECG abnormalities, clinicians would have to settle for optimizing other known risk factors or perhaps consider other tests (e.g. Holter monitoring in the case of AF). Therefore, further studies are needed to clarify whether the changes in these other ECG abnormalities truly relate to changes in the outcome risk.

6.2 Incidence, correlates, and prognosis of P-wave abnormalities (II)

6.2.1 Prevalence, incidence, and clinical correlates of P-wave abnormalities

Study II revealed that prolonged P-wave duration is a common phenomenon in the general population with a prevalence of 9.9%. Furthermore, 16.0% of participants without a prolonged P-wave at baseline displayed this phenomenon in the follow-up examination. At baseline, older age, male sex, higher BMI, and use of chronotropic medication were associated with a prolonged P-wave duration. At baseline, we observed associations between a prolonged P-wave duration and aging, male sex, obesity, and chronotropic medication use, results which are in line with previous studies (95,127-129). However, in this study, due to the broad definition of the covariate, the use of chronotropic medication might partly reflect diseases, such as hypertension or arrhythmia, that might have been treated with such medications at the time of the study and these are associated with atrial remodelling and a prolongation of P-wave duration. In addition, we were able to show that aging, male sex, higher BMI, and higher systolic BP were also associated with the incidence of a prolonged P-wave duration. This finding highlights the contribution of aging, obesity, and hypertension in the incidence of P-wave abnormalities, and thus in the development of the electroanatomical remodelling of the atria.

Similar to the prolonged P-wave duration, an abnormal PTF was also highly prevalent in the general population; 15.2% of the study population displayed an abnormal PTF, which is a slightly higher prevalence than previously reported (18,135). Advancing age, BMI, and hypertension have been shown to associate with abnormal PTF in cross-sectional studies (127,128). We observed that participants with an abnormal PTF at baseline were not only more likely to be older and have higher BP, but also to smoke but not to show any evidence of COPD, which stresses the effect of lung diseases on the electrocardiographic atrial measures. The incidence of abnormal PTF was associated with older age, higher BMI, and CHD. The observed associations between higher BMI, and both abnormal PTF and prolonged P-wave duration highlight the central role of obesity in the development of atrial cardiomyopathy.

The prevalence of an abnormal P-wave axis in our study was nearly 10% (5.1% and 4.6% for the left and right P-wave axis deviations, respectively), which is a markedly lower value than that reported previously (19,232). In addition, the incidence of left and right P-wave axis deviations was low (3.4% and 2.2%, respectively) when compared to other P-wave abnormalities. Given that an abnormal P-wave axis is associated with older age, the most likely explanation for the lower

prevalence is the younger age of our study sample as compared to previous studies. In addition to older age, an abnormal P-wave axis has been shown to be associated with lower BMI and COPD in previous studies (19,232). Our study results revealed that these associations are mainly driven by right P-wave axis deviation, as participants with right P-wave axis deviation at baseline were more likely to be older, male, smoke, and have COPD, heart failure, lower BMI, and lower non-HDL cholesterol. Furthermore, higher systolic BP, lower BMI, heart failure, smoking, and COPD, were associated with the incidence of right P-wave axis. Lung diseases and central obesity affect the orientation of the heart in the thoracic cavity, which explains the association of right P-wave axis with COPD and lower BMI (95,233). However, it is more difficult to find an explanation for the detected association between heart failure and right P-wave axis deviation. It is possible that pleural oedema, often seen in heart failure, might affect the orientation of the heart similarly to the hyperinflated lungs encountered in COPD. Interestingly, an abnormal P-wave axis (defined as values outside the range of 0-75°) was recently shown to predict heart failure with preserved ejection fraction (234). Although the authors did not specify the direction of P-wave axis deviation (left or right), their results underpin the relationship observed here between the P-wave axis and heart failure.

Although P-wave abnormalities were common, over half of the baseline P-wave abnormalities had reversed to normal at re-examination. While this finding may reflect regression to the mean, one potential explanation for this could be that individuals with the most severe forms of P-wave abnormalities were less likely to attend the re-examination, leading to an overestimation of reversal rates. Another cause for this could be the modest reproducibility of P-wave abnormalities attributable to biological variation in cardiac electrophysiology, measurement error, technical factors, electrode positioning, and environmental factors (235). Interestingly, it could be speculated that an improvement in the correlates associated with incident P-wave abnormalities during follow-up may have led to reversal of P-wave abnormalities. However, the low number of individuals with prevalent P-wave abnormalities that reversed to normal during follow-up prevented us from forming formal analyses on the possible correlates of this phenomenon. Whatever is the case, our findings will require confirmation and further investigation in larger populations and, meanwhile, suggest that a cautious approach should be adopted when interpreting studies on P-wave abnormalities measured at a single time-point.

6.2.2 Association of P-wave abnormalities with incident atrial fibrillation

A prolonged P-wave duration was associated with incident AF as previously reported (123,126). In addition, a prolonged P-wave duration was even more strongly

associated with incident AF in participants not being prescribed chronotropic medication as stated in a previous publication (123). These findings support the hypothesis that P-wave abnormalities reflect the electroanatomical remodeling of the atria that predisposes to AF.

However, an abnormal PTF was not predictive of AF in contrast to previous large-scale epidemiological studies (136,137). The association between abnormal PTF and incident AF was apparent only in those participants not consuming chronotropic medication, when abnormal PTF was defined as ≤ -6mVms instead of ≤-4mVms as in a previous Finnish large-scale study (18). These discrepancies in results from previous studies might result from differences in study samples and methods. Interestingly, a recent meta-analysis of 12 studies (including this study) examining the association between abnormal PTF and incident AF observed that studies conducted in Europe showed weaker associations than those conducted in Asia or United States (148). The authors also concluded that an abnormal PTF was predictive of AF (148). However, based on our results, the association between abnormal PTF and incident AF seems to be limited in the general population, at least when defined as ≤-4mVms.

Similar to an abnormal PTF, a P-wave axis deviation was not associated with incident AF. Shifts in the P-wave axis have been associated with atrial enlargement, a potent AF risk factor (236). An abnormal P-wave axis, defined as any value outside 0 to 75°, has been shown to predict AF in two large prospective general population cohorts (232,237) and in one cohort consisting of patients with type 2 diabetes (238). In addition, these studies have demonstrated that both left and right P-wave axis deviations seem to confer an excess AF risk. The observed lack of association between abnormal P-wave axis and incident AF noted here could result from the differences in study samples and the relatively low number of events. For example, our study population was significantly younger than the samples in the above-mentioned reports. Furthermore, in the study of Rangel et al., 30% of the participants developed AF over a median follow-up of 12.1 years (232), whereas Maheshwari et al., stated that 17% of their participants experienced an AF event over a mean follow-up of 20.3 years (237). For comparison, 7% of our study sample was diagnosed with AF over a mean follow-up of 11.9 years. It is noteworthy that in the two general population samples, there was a higher prevalence of smoking in their participants with an abnormal P-wave axis, even although smoking was defined as “ever smoker” in the study of Rangel et al. Smoking is a strong risk factor for COPD that is also associated with incident AF (239). We observed that a P-wave axis deviation was strongly linked to the presence of COPD. An abnormal P-wave axis could therefore at least partly represent an association between COPD and AF. However, none of these studies (including ours) have examined whether an abnormal P-wave axis predicts AF independent of the presence of COPD.

The differences in reversal rates of P-wave abnormalities during follow-up may be considered in the context of the observed AF risk. A prolonged P-wave duration had lower reversal rates than either an abnormal PTF or a deviated P-wave axis. It could be speculated that the more pronounced reversal of an abnormal PTF and P-wave axis could at least partly explain the lack of association, whereas in the case of a prolonged P-wave duration, the lower reversal rates could reflect the increased AF risk. However, the limited follow-up data on AF events prevented us from examining this phenomenon. So far, it is unknown whether changes in P-wave affect the risk of AF and other outcomes. Further research is needed to clarify whether P-wave abnormalities could be used as markers to evaluate treatment success similarly to ECG-LVH.

6.3 Association between self-reported hypertension onset age and ECG-LVH (IV)

Study IV revealed that the odds of ECG-LVH were similar in individuals with self-reported early onset hypertension as in individuals with late-onset hypertension. This is in contrast with previous findings on the associations between hypertension onset age and HMOD (14,194). As reported earlier in this dissertation, early onset hypertension, defined either objectively by precise and carefully documented measurements (14) or by self-report (194), has been shown to associate more strongly with echocardiographic LVH and other types of HMOD than late-onset hypertension.

A potential explanation for our study results could be the known poor sensitivity of ECG-LVH to detect anatomic LVH (98). Another explanation for our discrepant results could be the exclusion of participants younger than 50 years so that all participants could be classified into all age-of-onset categories. It is known that the QRS voltages often decrease with aging, which could affect the prevalence of ECG-LVH observed in this study (95). Indeed, the prevalence of ECG-LVH as assessed by Cornell voltage and Sokolow-Lyon voltage criteria in this study (12.5% and 10.8%, respectively) was slightly lower than the prevalence of the same ECG-LVH criteria in hypertensive participants in article III (12.8% and 12.5%, respectively). The exclusion of younger participants might also affect the reliability of self-report, as younger individuals may have a better ability to recall a previous hypertension diagnosis than older individuals. In addition, the use of self-reported hypertension diagnosis may not be reliable enough in a Finnish study population from the beginning of 21st century, as the awareness of hypertension at the time of the study in Finland was 71% in women but only 57% in men (240). It is noteworthy that in the study of Suvila et al. (194), the agreement between self-reported and objectively

defined hypertension onset age ranged from moderate to substantial as the sensitivity and specificity of self-reported hypertension for the diagnosis of objective hypertension were 95 % and 83%, respectively. However, unlike in our study, the participants of CARDIA study were examined on several occasions before they were asked to recall the time when they had a prior hypertension diagnosis, which is likely to lead to more accurate estimation of hypertension onset age in the CARDIA study.

The identification of those hypertensive patients at the highest risk for HMOD could provide opportunities for the prevention and early intervention of cardiovascular outcomes. Based on earlier studies, the assessment of hypertension onset age could be a feasible method to refine the cardiovascular risk of hypertensive patients (12-14,190). It must be noted that the majority of the recent studies have defined early onset hypertension objectively by precise serial BP measurements. However, in primary care, hypertension onset age based on serial BP measurements is often difficult to obtain and physicians must rely on the patient's memory. In addition, the diagnosis of HMOD according to hypertension guidelines (15,16) in primary care is often confined to ECG-LVH and urinary albumin excretion. For these reasons, further research on whether the self-reported hypertension onset age is associated with HMOD (especially ECG-LVH and urinary albumin excretion) and cardiovascular outcomes is needed, although in our study, self-reported early-onset hypertension was not superior to mere self-reported hypertension when assessing the odds of ECG-LVH.

6.4 Study limitations

Despite the large study sample and the good quality data on mortality and inpatient events, there are several limitations which need to be considered.

Studies I-III shared several limitations. First, the number of CVD, CHD, and AF events was relatively low in studies I-III. A greater number of events could have resulted in improved statistical power. In study I, inclusion of hospitalization with heart failure as an outcome could have provided not only events but also important information on the prognosis of hypertensive individuals with electrocardiographic abnormalities. However, at the planning stage of the study, we did not have information on reliability of the heart failure diagnoses and therefore chose not to use heart failure hospitalization as an outcome. Second, we did not use the Bonferroni correction although the study designs especially in studies I and III led to multiple regression analyses increasing the possibility of a type I error. However, given the *a priori* information of the risks associated with the ECG abnormalities studied, it is unlikely that our observations are false positives. Third, apart from study II, the ECG measurements were performed at only one single time point. This

prevented us from assessing the natural history of ECG abnormalities or how changes in ECG abnormalities affected the risk of cardiovascular outcomes. Fourth, although we used a validated CHD definition in study I, the exclusion of participants with prevalent CHD included only participants with previous hospitalization with ICD-10 codes of CHD. Therefore, the sample of study I may have included some participants who had experienced a previous silent myocardial infarction (e.g. participants with Q-waves), which may have attenuated the observed associations to some extent. Fifth, we used mostly dichotomized variables in the definition of ECG abnormalities. An examination of continuous variables could have improved our understanding of the cardiovascular risk of the detected ECG abnormalities. Sixth, we used only Cornell and Sokolow-Lyon voltage criteria in the analyses because of their widespread use in clinical practice and in previous studies. It is therefore possible that other ECG-LVH criteria could have performed better in the risk assessment of hypertensive participants.

In study II, one of the major limitations was that approximately half of the participants did not attend the re-examination, which affects the results examining the incidence and reversal of P-wave abnormalities. Another limitation was that P-wave measurements were performed on only two visits spaced 11 years apart. More frequent measurements could have depicted the natural history of P-wave abnormalities more precisely. In studies II and III, given the asymptomatic nature of AF, it is possible that the number of AF events was underestimated. In addition, the data on incident AF was primarily based on register information from secondary and tertiary care. Thus, AF events diagnosed only in primary care were not accounted for in our analyses, possibly leading to some underestimation of AF events.

In study IV, the most important limitation was the cross-sectional nature of the study, which is not ideal in establishing causation. In addition, we could not assess the duration or the intensity of antihypertensive treatment, a factor known to affect the prevalence of ECG-LVH.

In studies I-IV, echocardiographic data was not available. A comparison of electrocardiographic findings with echocardiographic data would have helped us in the interpretation of the detected associations.

7 Conclusions

The aims of this thesis were to investigate certain ECG abnormalities in a general Finnish population stratified according to BP in order to identify ECG abnormalities that could be particularly useful in the cardiovascular risk assessment of hypertensive individuals. In addition, we studied the incidence and the clinical correlates of P-wave abnormalities. Finally, we assessed whether self-reported early onset hypertension would be associated with ECG-LVH, a marker of HMOD.

Based on the results of studies I and III, ECG abnormalities are common in patients with hypertension and their prevalence seems to increase with the severity of hypertension. Our results confirmed that the well-known ECG risk markers such as ECG-LVH and repolarization abnormalities do predict future cardiovascular events and AF in hypertension. In addition, a poor R wave progression seemed to carry important predictive information for future cardiovascular events and AF in hypertensive individuals. However, the incremental value of single ECG abnormalities to supplement the established markers in cardiovascular risk prediction was marginal, at best.

Study II demonstrated that P-wave abnormalities are frequent in the general population. We found that obesity and hypertension seemed to be associated with the incidence of prolonged P-wave duration and abnormal PTF. We also observed high reversal rates of P-wave abnormalities in an 11 years' follow-up indicating that there is considerable variation in the P-wave's morphology. A prolonged P-wave duration was associated with incident AF highlighting the importance of P-wave abnormalities as markers of atrial remodeling predisposing to AF. However, further research is needed to clarify how serial changes in the P-wave abnormalities affect the risk of adverse outcomes.

According to study IV, self-reported early onset hypertension does not seem to associate with ECG-LVH more strongly than the simple presence of self-reported hypertension. However, given the strong association between objectively defined early onset hypertension and HMOD, further research in populations more aware of their hypertension status and with different outcomes (e.g. albuminuria) might help to determine the clinical value of self-reported hypertension onset age.

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