Tero Pääkkö

PREDICTORS OF LEFT VENTRICULAR HYPERTROPHY, DIASTOLIC DYSFUNCTION AND ATRIAL FIBRILLATION

THE ROLES OF ADIPOnectin, Ambulatory BLOOD PRESSURE AND DIETARY SODIUM INTAKE
TERO PÄÄKKÖ

PREDICTORS OF LEFT VENTRICULAR HYPERTROPHY, DIASTOLIC DYSFUNCTION AND ATRIAL FIBRILLATION
The roles of adiponectin, ambulatory blood pressure and dietary sodium intake

Academic dissertation to be presented with the assent of the Doctoral Training Committee of Health and Biosciences of the University of Oulu for public defence in Auditorium 8 of Oulu University Hospital (Kajaanintie 50), on 7 December 2018, at 12 noon

UNIVERSITY OF OULU, OULU 2018
Pääkkö, Tero, Predictors of left ventricular hypertrophy, diastolic dysfunction and atrial fibrillation. The roles of adiponectin, ambulatory blood pressure and dietary sodium intake
University of Oulu Graduate School; University of Oulu, Faculty of Medicine; Medical Research Center; Clinical Research Center; Oulu University Hospital
Acta Univ. Oul. D 1495, 2018
University of Oulu, P.O. Box 8000, FI-90014 University of Oulu, Finland

Abstract
Left ventricular hypertrophy (LVH), a common complication of elevated blood pressure (BP), is a risk factor for cardiovascular (CV) morbidity and mortality. Adiponectin has been shown to have cardioprotective effects and is inversely associated with LVH. BP can be measured at a clinical visit, as a momentary value. Ambulatory blood pressure (APB) measurement (ABPM) is a method of repeated BP measurements through a defined period, targeted to evaluate the circadian BP profile. High BP and ABPM have been shown to be associated with LVH and left ventricular diastolic dysfunction (LVDD). A high sodium intake has been associated with elevated BP and adverse CV outcome. The aim of this study was to investigate the associations between adiponectin and left ventricular mass index (LVMI), a measure of LVH, ABPM and the development of LVDD during long-term follow-up, ABPM and the change in LVMI during long-term follow-up, and the role of dietary sodium intake in the incidence of AF.

Adiponectin has been shown to have vasoprotective, anti-inflammatory and cardioprotective effects. Hypoadiponectinemia has been associated with hypertension, coronary artery disease (CAD) and LVH. In this study, adiponectin levels were inversely associated with LVMI, even after adjustment with conventional risk factors of LVH, in a fairly large sample of middle-aged subjects.

Elevated BP and pulse pressure (PP) have been associated with echocardiographic measures of LVDD. In this study, the association between APBM and the development of LVDD during a 20-year follow-up was evaluated. Ambulatory PP (APP) was shown to independently associate with the development of LVDD, even after adjustment with conventional risk factors of LVDD.

APBM has been associated with LVH in cross-sectional assessments and has also been shown to have predictive value in future LVMI or LVH. In a few studies the predictive value of APP in future LVMI was observed. In the present study, an increase in APP was shown to predict the change in LVMI during long-term follow-up.

In this study, the association between dietary sodium intake and the incidence of AF was evaluated. A high sodium intake predicted the occurrence of AF, which is a novel finding.

In conclusion, this study offers novel findings about predictive factors in the entity of cardiac remodelling.

Keywords: adiponectin, ambulatory blood pressure, ambulatory pulse pressure, atrial fibrillation, diastolic dysfunction, dietary sodium intake, left ventricular hypertrophy, left ventricular mass index
Pääkkö, Tero, Vasemman kammion hypertrofian, diastolisen vajaatoiminnan ja eteisvärinän riskitekijät. Adiponektiinin, ambulatorisen verenpaineen, sekä natriumia saannin merkitykset

Oulun yliopistollinen sairaala; Medical Research Center; Kliinisen tutkimuksen keskus; Oulun yliopistollinen sairaala

Acta Univ. Oul. D 1495, 2018

Oulun yliopisto, PL 8000, 90014 Oulun yliopisto

Tiivistelmä


Adiponektiini on osoitettu olevan suotuisia vaikutuksia verisuonistoon, tulehdusreaktion hiljentämiseen sekä sydänmuistikseen. Matalan adiponektiinitason on osoitettu olevan yhteydessä verenpainetautiin, sevelvaltimotautiin sekä vasemman kammion hypertrofiaan. Tässä tutkimuksessa adiponektiiniä on osoitettu olevan käänteisesti vasemman kammion massaindeksiin, vaikka perinteiset riskitekijät otettiin huomioon.

Kohonneella verenpaineella on osoitettu olevan yhteys vasemman kammion hypertrofiaan. Tässä tutkimuksessa adiponektiiniä on osoitettu olevan käänteisesti vasemman kammion massaindeksiin, vaikka perinteiset riskitekijät otettiin huomioon.

Ambulatorisella verenpaineella ja pulssipaineella on osoitettu olevan yhteys vasemman kammion hypertrofiaan poikkeavuustutkimuksissa ja seurantatutkimuksissa. Tässä tutkimuksessa adiquoteen verenpaineen pulssipaineen kasvu tuotti natriumin massaindeksin kasvua pitkäaikaiseurannassa.

Tässä tutkimuksessa korkean natriumin saannin todettiin olevan yhteydessä lisääntyneeseen eteisvärinän ilmamaataan, vaikka perinteiset riskitekijät otettiin huomioon.

Asiakirjat: adiponektiini, ambulatorinen pulssipaine, ambulatorinen verenpaine, diastolinen vajaatoiminta, eteisvärinä, suolan käyttö, vasemman kammion hypertrofia, vasemman kammion massaindeksi
Acknowledgements

This study was carried out at the Department of Internal Medicine, Institute of Clinical Medicine, Medical Research Center, University of Oulu, and Clinical Research Center, Oulu University Hospital.

I wish to express my sincerest gratitude to my principal supervisor, Professor and leader of the Research Unit of Internal Medicine, Olavi Ukkola, MD, PhD, for the collaboration during these years. His guidance and support have kept me moving towards my goal, the PhD degree. I would like to thank my second supervisor, Professor Juha Perkiömäki, MD, PhD, for his superior know-how in the field of research. I wish to express my highest respect and thankfulness for their experienced guidance, scientific and practical help during this process. The role of my supervisors has been essential.

I would also like to thank Professor Emeritus Antero Kesäniemi, MD, PhD, for his support, guidance and professional views during my career in research.

I want to acknowledge all the co-authors of the original publications: Professor Emeritus Markku Ikäheimo, MD, PhD; Reko Renko, MD; Antti Ylitalo, MD, PhD; Jarmo Lumme, MD, PhD; Professor Heikki Huikuri, MD, PhD; Professor Heikki Ruskoaho, MD, PhD; Professor Olli Vuolteenaho, MD, PhD; Marja-Leena Silaste, PhD and Risto Bloigu, MSc, for their help, support and practical comments on my original publications.

I wish to express my sincere gratitude and warmest thanks to:

The official referees of this thesis, Professor Risto Kaaja, MD, PhD and Professor Ilkka Pörsti, MD, PhD. My follow-up group: Professor Juhani Junttila, MD, PhD; Docent Antti Kiviniemi, PhD and Minna Koivikko, MD, PhD. Ms Marita Koistinen, Ms Sajja Kortetjärvi and Ms Leena Ukkola for help in practical and especially impractical questions. Ms Seija Leskelä for her help with the illustrations related to this thesis. Anna Vuolteenaho, MA, for revising the English language of the thesis. My talented and cheerful colleagues at Oulu University Hospital, for all the support during these years. My dearest friends and colleagues of SKLTYS: Juha Karhu, MD; Arto Korkiakoski, MD; Jukka Juntunen, MD; Lauri Laru, MD; Taneli Lehto, MD; Taneli Mattila, MD and Riku Renko, MD, for your existence and all the fun times we share in our annual meetings. My dearest friends: Aino, Joona, Heta, Toni, Mika, Eetu, Juha, Vesa and Jukka-Pekka, for their support and friendship throughout my life. Aapo Läspä, MD, for providing the excellent two-dimensional echocardiographic images.
I want to thank Minna’s family: Aaro, Pirjo, Matti, Suvi, Mari and Ville for their love, support and interest in my research.

I owe my dearest gratitude to my family: my mother, Eija, my father, Paavo, my brother, Aki and my sister, Heli, for your unconditional love and support. In particular, I am thankful to my parents for the effort they have put into raising me into a decent citizen. Also, I owe gratitude to Aki’s wife Eeva and Heli’s husband Ilkka, for their support.

Last, I wish to express my deepest gratitude to my beloved wife, Minna, for your presence, without which I’m incomplete. The couples that are meant to be are the ones who go through everything that is meant to tear them apart, and come out even stronger. I love you from the bottom of my heart.

This work was financially supported by Research Grants from the Medical Research Center Oulu Doctoral Program, the Ida Montin Foundation, Juhani Aho Foundation and Aarne Koskelo Foundation.

Oulu, September 2018

Tero Pääkkö
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABP</td>
<td>ambulatory blood pressure</td>
</tr>
<tr>
<td>ABPM</td>
<td>ambulatory blood pressure measurement</td>
</tr>
<tr>
<td>AF</td>
<td>atrial fibrillation</td>
</tr>
<tr>
<td>APP</td>
<td>ambulatory pulse pressure</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
</tr>
<tr>
<td>BP</td>
<td>blood pressure</td>
</tr>
<tr>
<td>BPM</td>
<td>blood pressure measurement</td>
</tr>
<tr>
<td>BPV</td>
<td>blood pressure variability</td>
</tr>
<tr>
<td>BSA</td>
<td>body surface area</td>
</tr>
<tr>
<td>C</td>
<td>compliance</td>
</tr>
<tr>
<td>CAD</td>
<td>coronary artery disease</td>
</tr>
<tr>
<td>CHD</td>
<td>coronary heart disease</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CV</td>
<td>cardiovascular</td>
</tr>
<tr>
<td>CVD</td>
<td>cardiovascular disease</td>
</tr>
<tr>
<td>DBP</td>
<td>diastolic blood pressure</td>
</tr>
<tr>
<td>DR</td>
<td>dietary recall</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>eGFR</td>
<td>estimated glomerular filtration rate</td>
</tr>
<tr>
<td>ELISA</td>
<td>enzyme linked immunosorbent assay</td>
</tr>
<tr>
<td>ESI</td>
<td>estimation of sodium intake</td>
</tr>
<tr>
<td>FFD</td>
<td>food follow-up diary</td>
</tr>
<tr>
<td>HDL</td>
<td>high-density lipoprotein</td>
</tr>
<tr>
<td>HF</td>
<td>heart failure</td>
</tr>
<tr>
<td>HFP EF</td>
<td>heart failure with preserved ejection fraction</td>
</tr>
<tr>
<td>HR</td>
<td>hazard ratio</td>
</tr>
<tr>
<td>hs-CRP</td>
<td>high-sensitivity C-reactive protein</td>
</tr>
<tr>
<td>kcal</td>
<td>kilocalories</td>
</tr>
<tr>
<td>LAD</td>
<td>left atrial diameter</td>
</tr>
<tr>
<td>LAE</td>
<td>left atrial enlargement</td>
</tr>
<tr>
<td>LDL</td>
<td>low-density lipoprotein</td>
</tr>
<tr>
<td>LV</td>
<td>left ventricle</td>
</tr>
<tr>
<td>LVEF</td>
<td>left ventricular ejection fraction</td>
</tr>
<tr>
<td>LVH</td>
<td>left ventricular hypertrophy</td>
</tr>
<tr>
<td>LVDD</td>
<td>left ventricular diastolic dysfunction</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>LVM</td>
<td>left ventricular mass</td>
</tr>
<tr>
<td>LVMI</td>
<td>left ventricular mass index</td>
</tr>
<tr>
<td>MAP</td>
<td>mean arterial pressure</td>
</tr>
<tr>
<td>MI</td>
<td>myocardial infarction</td>
</tr>
<tr>
<td>NF</td>
<td>night-time fall</td>
</tr>
<tr>
<td>NT-proANP</td>
<td>N-terminal pro-atrial natriuretic peptide</td>
</tr>
<tr>
<td>OPERA</td>
<td>Oulu Project Elucidating Risk of Atherosclerosis</td>
</tr>
<tr>
<td>PP</td>
<td>pulse pressure</td>
</tr>
<tr>
<td>R</td>
<td>resistance</td>
</tr>
<tr>
<td>RAAS</td>
<td>renin-angiotensin-aldosterone system</td>
</tr>
<tr>
<td>RR</td>
<td>risk ratio</td>
</tr>
<tr>
<td>SBP</td>
<td>systolic blood pressure</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
</tr>
<tr>
<td>SV</td>
<td>stroke volume</td>
</tr>
<tr>
<td>TOD</td>
<td>target organ damage</td>
</tr>
<tr>
<td>UNaV</td>
<td>twenty-four-hour urine collection for sodium excretion</td>
</tr>
<tr>
<td>VLDL</td>
<td>very low-density lipoprotein</td>
</tr>
<tr>
<td>y</td>
<td>years</td>
</tr>
</tbody>
</table>
List of original publications

This thesis is based on the following publications, which are referred to throughout the text by their Roman numerals:


Contents

Abstract  
Tiivistelmä  
Acknowledgements  
Abbreviations  
List of original publications  
Contents  
1 Introduction  
2 Review of the literature  

2.1 Hypertension  19
2.2 Blood pressure measurement  20
2.2.1 The bias of office blood pressure measurement  21
2.2.2 Diurnal variability of blood pressure  23
2.3 Ambulatory blood pressure measurement  24
2.3.1 Ambulatory blood pressure measurement and left ventricular hypertrophy  24
2.3.2 Ambulatory blood pressure measurement and left ventricular diastolic dysfunction  28
2.4 Pulse pressure  29
2.5 Pulse pressure and cardiovascular risk  30
2.6 Dipping pattern  32
2.6.1 Dipping pattern and cardiovascular risk  32
2.7 Adiponectin from the adipokine family  33
2.7.1 Adiponectin and cardiovascular risk  33
2.7.2 Adiponectin and left ventricular hypertrophy  34
2.8 Dietary sodium intake  35
2.8.1 Salt sensitivity  35
2.8.2 Dietary sodium intake and cardiovascular risk  36
2.8.3 Dietary sodium intake and cardiac remodelling  42
2.8.4 Dietary sodium intake and cardiac arrhythmias  44

3 Aims of the study  45

4 Subjects and methods  47
4.1 Subjects  47
4.2 Methods  48
4.2.1 Clinical methods  48
4.2.2 Blood pressure measurements  48
4.2.3  Echocardiographic measurements ................................................ 49
4.2.4  Initial laboratory analyses ............................................................ 52
4.2.5  Follow-up laboratory analyses ..................................................... 53
4.2.6  Nutritional follow-up diary ........................................................... 53
4.2.7  Atrial fibrillation outcome classification ..................................... 54
4.2.8  Statistical methods ................................................................. 54

5  Results

5.1  Study subjects (Studies I-IV) ............................................................ 57
   5.1.1  Main characteristics ............................................................... 57
   5.1.2  Blood pressure measurements ............................................... 63
   5.1.3  Echocardiographic measurements .......................................... 64

5.2  Adiponectin and left ventricular mass index (Study I) ....................... 65
5.3  Ambulatory blood pressure measurement and the development
    of left ventricular diastolic dysfunction (Study II) ............................ 66
5.4  Ambulatory blood pressure measurement and the change in left
    ventricular mass index (Study III) ................................................... 67
5.5  Dietary sodium intake and the incidence of atrial fibrillation
    (Study IV) .................................................................................. 68

6  Discussion

6.1  Study population and design .......................................................... 71
6.2  Adiponectin and left ventricular mass index .................................... 73
6.3  Ambulatory pulse pressure and cardiac remodelling ....................... 75
6.4  Dipping pattern and cardiac remodelling ....................................... 76
6.5  Dietary sodium intake and atrial fibrillation .................................... 77

7  Conclusions

References ................................................................. 83
Original publications .............................................. 113
1 Introduction

Cardiovascular disease (CVD) is the number one cause of death worldwide (GBD 2013 Mortality and Causes of Death Collaborators 2015). CVD covers a wide range of disorders, including diseases of the heart and of the vascular system supplying the heart and other vital organs (Gaziano et al. 2006). Hypertension is the leading global risk factor for the burden of CVD, concerning a significant proportion of population (Catala-Lopez et al. 2012). Despite hypertension being the most common treatable cardiovascular (CV) risk factor, the mechanisms of how it causes end-organ damage and vascular events are not completely understood (Rothwell 2010).

Within-individual standard deviation (SD) of office systolic blood pressure (SBP) at the time of separate clinic visits has ranged from 10 to 20 mmHg (Hebel et al. 1980), which elucidates the fact that office blood pressure (BP) measurement (BPM) is prone to several artefacts. Diagnosis and follow-up of high BP relied traditionally on office BPM; however, out-of-office (home) measurements are more commonly used. A single BPM only offers a momentary, cross-sectional view of diurnal BP. The normal circadian rhythm among normotensive subjects is characterized by higher pressure at daytime, a night-time decrease, called dipping, and an early morning surge.

Ambulatory blood pressure measurement (ABPM) is a method in which repeated BPMs take place, allowing the evaluation of circadian BP profile during normal daily activities and during sleep. It provides more accurate and specific BPMs in patients with suspected or documented high BP (Hansen et al. 2011, Sorof et al. 2000). ABPM has shown to be superior to clinic BPM in predicting CV mortality and outcome (Banegas et al. 2018, Bjorklund et al. 2004, Clement et al. 2003, Staessen et al. 1999). Especially night-time BP has been shown to predict adverse CV outcome (Clement et al. 2003, Dolan et al. 2005, Ingelsson et al. 2006, Staessen et al. 1999). ABPM is the only method to evaluate circadian blood pressure variability (BPV) and non-dipping (nocturnal BP fall less than 10% of daytime mean BP), which are of clinical significance. BPV is directly related to the severity of hypertensive target organ damage (TOD) (Frattola et al. 1993, Palatini et al. 1992, Parati et al. 1987) and the association between non-dipping status and unfavourable CV outcome has been shown in several studies (O'Brien et al. 1988, Ohkubo et al. 2002, Staessen et al. 1999, Verdecchia et al. 1999b, Verdecchia et al. 1994, Verdecchia 2000a).
Pulse pressure (PP) is calculated by subtracting diastolic blood pressure (DBP) from SBP. Normally, the resting PP in healthy adults, in sitting position, is about 30-40 mmHg. PP arises from the interaction of stroke volume and the properties of the arterial circulation. An increased stiffness of the large arteries leads to an increase in PP through a reduction in arterial compliance and effects on wave enhanced reflection. A number of factors are known to influence arterial wall properties, including aerobic exercise training (Dart & Kingwell 2001). PP is known to increase during aging, mainly due to stiffening of the large arteries. Elevated PP has been shown to be a significant risk factor for CV events (Benetos et al. 1997, Darne et al. 1989, Kannel et al. 1981).

Adiponectin is a peptide hormone secreted by the adipose tissue and its concentrations are negatively correlated with the amount of adipose tissue (Ouchi et al. 1999). Adiponectin has been shown to have crucial effects in regulation of glucose and lipid metabolism (Hada et al. 2007). In addition, adiponectin improves lipid and simple carbohydrate profiles, which has protective effects against inflammation and insulin resistance (Berg et al. 2001). Adiponectin has been shown to modulate vascular remodelling and suppress endothelial cell migration and adhesion (Ouchi et al. 2000). Hypoadiponectinemia has been discovered to be a risk factor for hypertension independent of insulin resistance and diabetes (Iwashima et al. 2004), and it has been suggested to be involved in the pathogenesis of hypertension (Chow et al. 2007). Low adiponectin levels have been associated with left ventricular hypertrophy (LVH). Adiponectin has been shown to have antihypertrophic (Shibata et al. 2004, Shibata et al. 2005) and antifibrotic (Fujita et al. 2008) effects in the cardiomyocyte cell.

The association between dietary salt and elevated BP has been well documented. However, scepticism remains since it has been observed that not all individuals have demonstrable changes in BP after ingestion of increased or decreased amounts of sodium. Salt contains 40% of sodium, which is considered the active metabolite in dietary salt, and therefore can be seen as a measure of the dietary exposure to salt. The recommendations of sodium intake are <1.5 g/d for hypertensives, middle-aged and older adults and <2.3 g/d for all other adults. In 2005, only 9.6% of adults met the recommendations for salt consumption. Mainly because of the use of salt as food seasoning and in highly salted processed food, dietary sodium intake remains high (Chobanian et al. 2003). The relationship between salt intake and BP seems to be direct and progressive, and it has been suggested that there is a consistent dose-related response of salt in the range of 3-12 g/d (He & MacGregor 2002). There is increasing evidence suggesting that high
salt intake, independently of BP, increases the risk of stroke, LVH, heart failure (HF) and albuminuria (Frisoli et al. 2012). A conservative estimation has been made that reducing salt intake by 3 g/d would reduce strokes by approximately 13% and ischemic heart disease by 10%; with a 6 g/d reduction, the effects would be almost doubled (He & MacGregor 2003).

LVH is growth in left ventricular mass (LVM) caused by increased cardiomyocyte size, but it is not considered a disease in itself, but rather a consequence of disease when pathological. Physiological LVH is usually benign, caused by physical activity. Pathological LVH is a compensatory phenomenon and may evolve towards progressive left ventricular (LV) dysfunction and HF (Lazzeroni et al. 2016). Pathological LVH is a common complication of hypertension and is a strong, independent risk factor for CV morbidity, such as coronary heart disease (CHD), heart failure, cardiac arrhythmias and stroke, and all-cause mortality (Casale et al. 1986, Koren et al. 1991, Manyari 1990).

Abnormalities of LV diastolic filling are often seen in patients with hypertension (Schillaci et al. 2002). Left ventricular diastolic dysfunction (LVDD), also referred to as HF with preserved ejection fraction (HFP EF), in hypertensive patients is characterized primarily by impaired isovolumic relaxation (de Simone et al. 2000, Mureddu et al. 1997). As a consequence, a decrease in the velocity of early diastolic filling and an increase in the late atrioventricular gradient is seen, yielding a decreased early/atrial (E/A) velocity ratio (Appleton et al. 1988). The ratio of E to E’ (E/E’), where the E’ in the tissue Doppler registration measures the mitral longitudinal motion during early diastole, is considered to be an even better echocardiographic measurement of diastolic dysfunction (Okura et al. 2009). LVDD is associated with significant morbidity and mortality (Shah et al. 2016) and since the incidence of LVDD increases with aging, it is predicted to become the most common type of HF (Irizarry Pagan et al. 2016).

Atrial fibrillation (AF) is the most common sustained arrhythmia worldwide (Feinberg et al. 1995). The prevalence of AF has been estimated to be 1.5–6.2% and calculated from four population-based studies, nearly 6% of those over 65 years of age have been diagnosed with AF (Ryder & Benjamin 1999). It has been widely recognized that AF is an independent predictor of morbidity and mortality (Benjamin et al. 1998, Gajewski & Singer 1981, Krahn et al. 1995). Several prospective and retrospective studies have reported that AF increases the risk for stroke (Flegel et al. 1987, Hill et al. 1987, Kannel et al. 1982, Kitchin & Milne 1977, Lake et al. 1989, Omundarson et al. 1987).
Although sodium intake has been associated with elevated BP and increased risk of CVD, it has not yet been associated with the incidence of AF. Atrial fibrosis (Frustaci et al. 1997, Ih & Saitoh 1982) and inflammation (Frustaci et al. 1997) are thought to be involved in the pathophysiological mechanisms behind AF. Sodium intake has been shown to activate the renin-angiotensin-aldosterone system (RAAS) (Cappuccio et al. 1985, MacGregor 1987), which has been shown to cause myocardial fibrosis (Ferreira et al. 2010, Hayakawa et al. 2015). Aldosterone has also been shown to directly cause inflammation and fibrosis of the heart (Brown 2013). It is therefore possible that sodium intake increases the risk for AF incidence by causing myocardial fibrosis and inflammation.

The purpose of the present study is to investigate the risk factors for LVH, LVDD and AF, the focus being on ambulatory blood pressure (ABP), adiponectin and dietary sodium intake.
2 Review of the literature

2.1 Hypertension

Several causes of hypertension have been identified, such as genetic factors, obesity, dietary factors and lack of physical exercise. Hypertension has been identified as a complex polygenetic disorder, and several genes or gene combinations influence BP (Padmanabhan et al. 2015). Several dietary factors have been associated with elevated BP, e.g. high sodium intake and low intakes of potassium, calcium, magnesium, fibre and protein (Chan et al. 2016, Savica et al. 2010). In addition, alcohol consumption has been observed to have a direct and positive association with BP (Klatsky 2010). An inverse relationship between physical activity and BP has been observed in several epidemiological studies (Lesniak & Dubbert 2001) and even modest levels of physical activity have shown to decrease the risk of hypertension (Hayashi et al. 1999).

As early as the 1920s, a direct and strong relationship was noted between elevated BP and the risk of clinical complications and death. Observational studies have reported the association between elevated SBP and DBP and CVD risk, including stroke, coronary and peripheral atherosclerosis, myocardial infarction (MI) and HF (Lewington et al. 2002, Rapsomaniki et al. 2014). Numerous studies since have shown the benefits of reducing elevated BP to decrease the risk of CVD morbidity and mortality.

In recent years, hypertension has been defined as office BP of 140/90 mmHg or more, and the threshold BP for the diagnosis of hypertension has declined over time based on trials showing the benefits of treatment to lower BP to reduce CVD morbidity and mortality (Chobanian et al. 2003). In 2010, as part of the INVEST (the International Verapamil SR – Trandolapril Study) trial, 6,400 subjects over 50 years of age who had diabetes and CAD were randomized into three groups based on the SBP target: SBP<130 mmHg, SBP 130-140 mmHg or SBP>140 mmHg (Cooper-DeHoff et al. 2010). Tight SBP control (SBP<130 mmHg) in this study did not improve CV outcomes compared to subjects with SBP 130-140 mmHg; however, the risk of all-cause mortality was slightly higher in the SBP<130 mmHg group compared to the SBP 130-140 mmHg group (22.8% vs. 21.8%, HR 1.15; 95% confidence interval (CI), 1.01–1.32, p=0.04). In the recent SPRINT (Systolic Blood Pressure Intervention Trial) study, 9,361 subjects whose BP was measured at visit, with SBP of 130-180 mmHg and high CV risk, were randomly assigned to a SBP
target of either less than 120 mmHg or less than 140 mmHg (SPRINT Research Group et al. 2015). The more intense BP target group demonstrated a significant benefit of CV event reduction (Hazard ratio 0.75; 95% CI, 0.64 to 0.89) compared to the less intense BP target group and the study was discontinued after 3.3 years. In addition, total mortality was observed to be lower in the more intense BP group compared to the less intense BP group. In another recent study, the ACCORD (Action to Control Risk in Diabetes) trial, involving 4,733 subjects with type 2 diabetes, in which subjects were randomized into two groups: SBP<120 mmHg or SBP<140 mmHg at visit (ACCORD Study Group et al. 2010). A significant difference in the incidence of stroke was observed favouring the lower BP target.

Mainly because of the results from SPRINT and ACCORD, the multi-institutional U.S. group lowered the threshold of stage 1 hypertension to 130/80 mmHg in the new 2017 guideline (Whelton et al. 2017). The new guideline defines normal BP as below 120/80 mmHg, elevated BP as 120-129 mmHg systolic with a diastolic BP below 80 mmHg, stage 1 hypertension as 130-139/80-89 mmHg and stage 2 hypertension as 140/90 mmHg or higher. The newest ESH/ESC (European Society of Hypertension/European Society of Cardiology) guideline for the management of arterial hypertension is from 2018, in which hypertension is defined as office values SBP ≥140 mmHg and/or DBP ≥90 mmHg (Williams et al. 2018).

It has been estimated that among U.S. adults, the overall prevalence of hypertension was 31.9% according to the previous definition of hypertension and is 45.6% according to the new 2017 guideline definition (Muntner et al. 2018).

### 2.2 Blood pressure measurement

Since the end of the 19th century, BP has been measured using a mercury sphygmomanometer and a stethoscope. Automatic devices have since replaced the traditional BP measurement and are nowadays widely used in office and at home (out-of-office). The reasons for routinely measuring BP in adults are evident. Raised BP is a common condition that does not have specific clinical manifestations until TOD develops. A single BPM only offers a momentary, cross-sectional view of diurnal BP. BP is affected by the physiological state and environmental circumstances and in all people, it is a continuum that varies throughout the day. BPM is prone to several artefacts which can affect the reliability of the measurement, e.g. talking during measurement, exposure to cold, ingestion of alcohol, wrong position or wrong size of the cuff, wrong position of the patient’s arm and rounding of BP values by the measurer (McAlister & Straus 2001). ABP
is used to detect hypertension and it has been reported to be more accurate than office BPM in detecting hypertension and in CV risk determination (Redon et al. 1998, Verdecchia 2000a).

### 2.2.1 The bias of office blood pressure measurement

Combined office and out-of-office BPM provide a more accurate evaluation of the BP status of a given individual and have for this reason gained an increasing application for clinical purpose (Mancia & Verdecchia 2015). Combined office and out-of-office BPM enables to identify four BP phenotypes: 1) true normotensives (normal office and out-of-office BP), 2) sustained hypertensives (elevated office and out-of-office BP), 3) white coat hypertensives (elevated office and normal out-of-office BP), and 4) masked hypertensives (normal office and elevated out-of-office BP).

White coat hypertension was described for the first time by measuring the intra-arterial BP of hospitalized patients in Italy (Mancia et al. 1983a). In almost all the 48 subjects tested, the doctor’s arrival at the bedside induced immediate rises in SBP and DBP (mean 26.7±2.3 mmHg and 14.9±1.6 mmHg above pre-visit values). Later, in 2005 Verdecchia et al. defined white coat hypertension as raised office BPM (BP ≥ 140/90 mmHg) in subjects whose daytime ABPM is lower than 135/85 mmHg (Verdecchia et al. 2005). In 2013, the European Society of Hypertension suggested that white coat hypertension diagnosis should be based on office BP>140/90 mmHg and mean 24-h BP<130/80 mmHg, thereby adding nocturnal BP values in the definition (O'Brien et al. 2013). The phenomenon has been considered to be a rise in BP seen only when measured in medical care environment (White 2003) and it is more pronounced when BP is measured by a physician than a technician (Pickering et al. 1988).

The majority of clinical studies have reported that white coat hypertension accounts for up to 25-30% of subjects attending outpatient hypertension centres. In an epidemiological study performed in Italy among 1,657 untreated subjects the prevalence of white coat hypertension ranged from 9 to 12%, depending on whether out-of-office normotension was defined by home BP (<132/83 mmHg) or 24-h ABP (<125/79 mmHg) (Sega et al. 2001). In a community-based study organized in Taiwan, among 1,257 untreated subjects the prevalence of white coat hypertension was 12% when defined as office BP ≥ 140/90 mmHg and normal ABPM (Sung et al. 2013). The white coat hypertensives were older and had a higher body mass index (BMI) than the normotensives (office BP<120/80 mmHg
and day-time ABPM<135/85 mmHg) or pre-hypertensives (office BP ≥120/80 mmHg but <140/90 mmHg, and normal day-time ABPM). In a sub-analysis conducted in Spain among 869 untreated subjects, white coat hypertension was present in 24% of the subjects (de la Sierra et al. 2016). In 2016 an international registry (the Ambulatory blood pressure Registry TElleMonitoring of hypertension and cardiovascular rIsk (ARTEMIS) project) in patients attending hypertension clinics in all five continents provided updated information on the different hypertension subtypes resulting from the combination of office and ambulatory BPMs (Omboni et al. 2016). A total of 14,143 patients from 27 countries were analysed. Sustained hypertension (elevated office BP and ABPM) was detected in 49% of the subjects. White coat hypertension (elevated office BP and normal ABPM) was detected in 23% and masked hypertension (normal office BP and elevated ABPM) in 10% of the subjects. White coat hypertension was less common in Australia, America and Africa, and more common in elderly and obese women. In an 11-country report with 9,691 subjects, the prevalence of masked hypertension in untreated normotensive participants was higher among diabetics (29.3%) than nondiabetics (18.8%) (Franklin et al. 2013).

White coat and masked hypertension are states that are not of clinical insignificance. Subjects who were considered white coat hypertensives or masked hypertensives had an increased risk for developing sustained hypertension in the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study (Mancia et al. 2009). The subjects were followed for 10 years, and 43% of the white coat hypertensives and 47% of the masked hypertensives developed sustained hypertension. As compared to normotensives, the white coat hypertensives had a 2.5-fold risk of developing sustained hypertension. White coat hypertension has been related to adverse cardiac remodelling and atherosclerosis. In a meta-analysis which included 25 studies in different clinical settings, white coat hypertensives showed a significant increase in left ventricular mass index (LVMI), a reduced E/A ratio and greater left atrial diameter (LAD) compared to normotensives (Cuspidi et al. 2015a). In a second meta-analysis of 3,478 untreated subjects, common carotid intima-media thickness was greater among white coat hypertensives compared to normotensives (Cuspidi et al. 2015b). Masked hypertension has been shown to increase the risk of stroke (Kario et al. 2003) and is closely related to total CV morbidity (Bjorklund et al. 2004, Ohkubo et al. 2005). In a recent Spanish follow-up study with 63,910 adults who were followed for a median of 4.7 years, white-coat hypertension and masked hypertension were associated with increased all-cause mortality compared to sustained hypertension (Banegas et al. 2018).
2.2.2 Diurnal variability of blood pressure

In normotensive subjects, the diurnal BP rhythm is designated by a decline in BP during sleep and an early morning surge. The diurnal variation has been verified by ABPM and intra-arterial methods (Dimsdale & Heeren 1998).

The diurnal variation of BP is the sum of responses to extrinsic pressor stimuli, spontaneous and regulatory fluctuations consequential to influences of the central nervous system (Narkiewicz et al. 2002, Nishi et al. 2015), mechanical forces caused by respiration (Elghozi et al. 1991), and the effects of humoral and local vasomotor phenomena (Mancia et al. 1999, Parati et al. 1995). The diurnal variability of BP is mainly mediated by baroreflex mechanisms (Conway et al. 1984, Mancia et al. 1986, Mancia et al. 1997). Reduced efficacy of baroreflex sensitivity can result in significant increases in BP oscillations. No difference was found in baroreflex sensitivity between dipper and non-dipper untreated hypertensives (Vaile et al. 1996). While it is well known that regular physical exercise has a moderate beneficial effect on BP, Pagonas et al. found that regular physical exercise had no effect on 24-h BPV (Pagonas et al. 2014). Within-subject intra-arterially recorded BPV has been shown to increase with elevated mean BP and age (Mancia et al. 1980, Mancia et al. 1983b). Most cross-sectional studies indicate that SBP increases continuously during aging, whereas DBP tends to level off or decline in persons older than 50 years (Franklin et al. 1997a, Izzo et al. 2000). Consequently, PP increases progressively as a function of chronological age.

BPV has traditionally been assessed by calculation of the SD of 24-hour BP, SBP, DBP and mean arterial pressure (MAP) (Mancia & Grassi 2000). 24-h MAP varies approximately 10% among subjects, but interindividual differences are large. Based on SD, SBP seems to vary more than DBP. The variations in SBP over 24-h may be as much as 50-60 mmHg (Mancia et al. 1983b, Mancia et al. 1993).

Twenty-four-hour BPV has been shown to have clinical significance. Several studies have shown that increased BPV is directly related to the severity of TOD (Frattola et al. 1993, Palatini et al. 1992, Parati et al. 1987). In the Ohasama study, an increase in daytime systolic ABP variability was associated with a significant increase in CV mortality (Kikuya et al. 2000). Hansen et al. and Mena et al. discovered that BPV is associated with CV events and mortality (Hansen et al. 2010, Mena et al. 2014), whereas Hsu et al. found the association among untreated hypertensives but not normotensives (Hsu et al. 2016). Clement et al. discovered the value of higher ambulatory SBP and DBP in treated hypertensives, as high ABPM predicted CV events even after adjustments with traditional risk factors,
including office BPM (Clement et al. 2003). In the PAMELA study, SBP had a more predictive value than DBP (Sega et al. 2005), although in later studies a higher risk was associated with DBP rather than SBP (Hansen et al. 2010, Mena et al. 2014, Sundström et al. 2011).

2.3 Ambulatory blood pressure measurement

ABPM is a method in which repeated BP readings are recorded while the patient undergoes normal daily activities. The measurement was developed to determine BP during work, physical activity, rest and sleep. It was initially intra-arterial. ABPM has been available for more than four decades. Since the early 1980s, non-invasive, fully automated methods have been available (O'Brien 2011, White 2003). ABPM is used to detect 24-h BP profile for diagnosing hypertension. ABPM is recommended if white coat hypertension is suspected and before initiating antihypertensive therapy, often as a lifelong treatment (O'Brien et al. 2000, O'Brien et al. 2001, O'Brien 2011, Pickering et al. 2006). ABPM has proven to be a more accurate method in controlling BP among treated hypertensives (Head et al. 2010, O'Brien 2011). In addition, ABPM has been observed to reduce misdiagnosis, is cost-effective in diagnosing hypertension (Lovibond et al. 2011), and is the only commonly used practical method to examine nocturnal BP dipping (Staessen et al. 1997).

Evidence from numerous of studies recommend that the ABPM mean is $\leq 135/85$ at daytime, $\leq 120/70-75$ at night-time and $\leq 130/80$ during 24-h period. ABPM should consist of >14 SBP and DBP measurements by day and >7 measurements by night (Head et al. 2010, O'Brien 2011). ABPM is prone to several artefacts; for example, poor technique, unsuitable cuff, insufficient instructions to the patient, arrhythmias, small pulse volume and inability for the device to measure BP can cause inaccuracy in registrations (O'Brien et al. 1993, O'Brien et al. 2000, O'Brien 2011).

2.3.1 Ambulatory blood pressure measurement and left ventricular hypertrophy

It is generally believed that the heart has three compensatory mechanisms when faced with a hemodynamic burden: (1) the Frank-Starling mechanism increases crossbridge formation; (2) increase in muscle mass to bear the extra burden; (3) increase in contractility by recruiting neurohumoral mechanisms. The increase in
mass is due to hypertrophy of myocytes (Lorell & Carabello 2000). Cardiac hypertrophy is most often a consequence of either pressure or volume overload. In response to pressure overload wall thickness is increased by an increase in myocyte width, resulting in an increase in ratio of wall thickness/chamber dimension called concentric hypertrophy. LV pressure increases with states that increase systolic stress, also called afterload of the heart, including systemic hypertension. LV wall stress is the force acting against the myocardial cells which can be determined by the law of LaPlace: LV wall stress = (LV pressure \times radius) / 2 \times \text{wall thickness}. The law of LaPlace indicates that wall stress is directly proportional to the LV pressure and radius, and indirectly proportional to two times the wall thickness. Therefore, an increase in pressure can be offset by an increase in wall thickness leading to LVH (Gunther & Grossman 1979).

\[ \text{Law of LaPlace: LV wall stress} = \frac{(\text{LV pressure} \times \text{radius})}{2 \times \text{wall thickness}} \]

The weak relation of casual BP to echocardiographic LVH (Savage et al. 1979) aroused interest in ABPM as a correlate to LVH. The association between ABPM and LVM has been studied since the early 1980s. In 1981, Rowlands et al. recorded intra-arterial ABPM in 46 patients with mild to moderate hypertension (Rowlands et al. 1981). They discovered that mean 24-h SBP was significantly correlated with LVMI (r=0.534, p<0.001). Later, Drayer et al. discovered that casual BP did not correlate with LVM in 12 hypertensive subjects, but LVM correlated significantly with the averages of whole-day, daytime, night-time and two-hour morning systolic pressures (Drayer et al. 1983). Devereux et al. were interested in the effects of regularly recurring stress on LVH (Devereux et al. 1983). They recorded 24-h BP in 19 normotensive subjects and 81 patients with mild hypertension. A weak correlation between systolic and diastolic pressures and LVMI was observed (r=0.24, p<0.02 and r=0.20, p<0.05), but higher correlations existed when BP was measured by a portable recorder at work in 60 subjects (r=0.50, p<0.001 and r=0.39, p<0.01). In two later studies, LVMI or LVM were also correlated with 24-h, daytime and night-time SBP, but not with DBP (Den Hond et al. 2003, Feola et al. 1998).

In prior studies, mainly systolic parameters of ABPM correlated with LVM or LVMI. The association between diastolic ABPM parameters and LVMI has also been observed. In 1,648 participants in the PAMELA-study, LVMI was significantly related to mean 24-h systolic and diastolic BP (Sega et al. 2002). In a
later study among 111 Japanese patients by Ozawa et al., 24-h, daytime and nighttime SBP and DBP were associated with LVH in a multivariate analysis adjusted with confounding factors (Ozawa et al. 2009). Verdecchia et al. performed ABPM on 98 normotensive subjects and 137 untreated, hypertensive subjects (Verdecchia et al. 1990b). Mean 24-h SBP (r=0.48, p<0.01) and DBP (r=0.36, p<0.01) correlated with LVMI, whereas among hypertensive subjects, LVMI correlated more closely with night-time SBP (r=0.51, p<0.01) and DBP (r=0.35, p<0.01) than daytime SBP (r=0.38, p<0.01) and DBP (r=0.20, p<0.01), suggesting that night-time BP could be a better correlate than daytime BP to LVMI.

The role of PP in cardiovascular remodelling was studied in 61 never-treated hypertensives (Baguet et al. 2000). LVMI was related to ambulatory (r=0.41 over 24 h, r=0.38 daytime and r=0.42 night-time) PP. Twenty-four-hour PP was also shown to be an independent predictor of LVMI (p=0.009) in a study of 110 patients with known coronary artery disease (CAD) (Zakopoulos et al. 2001). Rizzo et al. found among 108 subjects (mean age 54.2 years) that those whose clinic and ambulatory PP was >60 mmHg had higher LVMI compared to those with clinic and ambulatory PP was <60 mmHg (Rizzo et al. 2004). The ABP measurements associated with the measures of LVH of these studies are presented in Table 1.

Table 1. The ambulatory measured blood pressure parameters associated with measures of left ventricular hypertrophy in eleven cross-sectional studies

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>ABP parameters</th>
<th>Target of outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rowlands et al. 1981</td>
<td>46</td>
<td>24-h SBP</td>
<td>LVMI ↑</td>
</tr>
<tr>
<td>Drayer et al. 1983</td>
<td>12</td>
<td>24-h, daytime and night-time SBP</td>
<td>LVMI ↑</td>
</tr>
<tr>
<td>Devereux et al. 1983</td>
<td>60</td>
<td>Daytime BP</td>
<td>LVMI ↑</td>
</tr>
<tr>
<td>Verdecchia et al. 1990</td>
<td>235</td>
<td>24-h SBP and DBP</td>
<td>LVMI ↑</td>
</tr>
<tr>
<td>Feola et al. 1998</td>
<td>80</td>
<td>24-h, daytime and night-time SBP</td>
<td>LVMI ↑</td>
</tr>
<tr>
<td>Baguet et al. 2000</td>
<td>61</td>
<td>24-h, daytime and night-time PP</td>
<td>LVMI ↑</td>
</tr>
<tr>
<td>Zakopoulos et al. 2001</td>
<td>110</td>
<td>24-h PP</td>
<td>LVMI ↑</td>
</tr>
<tr>
<td>Sega et al. 2002</td>
<td>1,648</td>
<td>24-h SBP and DBP</td>
<td>LVMI ↑</td>
</tr>
<tr>
<td>Den Hond et al. 2003</td>
<td>784</td>
<td>24-h, daytime and night-time SBP</td>
<td>LVMI ↑</td>
</tr>
<tr>
<td>Rizzo et al. 2004</td>
<td>108</td>
<td>Clinic and ambulatory PP &gt; 60 mmHg</td>
<td>LVMI ↑</td>
</tr>
<tr>
<td>Ozawa et al. 2009</td>
<td>111</td>
<td>24-h, daytime and night-time SBP and DBP</td>
<td>LVH ↑</td>
</tr>
</tbody>
</table>

↑, positive correlation with studied parameter. ABP, ambulatory blood pressure; DBP, diastolic blood pressure; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; PP, pulse pressure; SBP, systolic blood pressure.

The studies previously mentioned were based on cross-sectional assessments. Some follow-up studies also exist. In 1997, Khattar et al. performed a 24-h ambulatory intra-arterial BPM on 140 subjects who were then followed for a mean period of 9.4 years (Khattar et al. 1997). The mean PP and SBP correlated
positively with follow-up LVMI ($r=0.46$, $p<0.001$ and $r=0.36$, $p<0.001$). In a later study by Khattar et al. among 295 subjects who were followed for 10.2 years, 24-h mean SBP and PP correlated with LVMI and 24-h mean SBP was an independent correlate of LVH (Khattar et al. 1999). In a study conducted by Jokiniitty et al., intra-arterial ABP was initially performed on 97 healthy, untreated 35- to 45-year-old men whose baseline LVMI showed no difference (Jokiniitty et al. 2001). A follow-up after 10 years was arranged. Sixty-six subjects, who were untreated for hypertension, were analysed for predictors of future LVMI. 24-h ($p=0.008$), daytime (0.016) and night-time PP ($p=0.020$) were independent predictors of future LVMI. Andrikou et al. followed 305 hypertensive subjects whose mean age was 51.5 years at baseline for 42 months (Andrikou et al. 2013). Night-time SBP was a predictor for the development of LVH whereas daytime SBP was not. Cuspidi et al. followed 1,682 subjects (mean age 50.2 years) for 10 years in the PAMELA study (Cuspidi et al. 2013). Multiple regression analyses, including daytime SBP, age, sex, and BMI, showed that the lowest SBP level during night-time and the extent of nocturnal SBP decline were independently related to baseline LVM. After adjustment for several confounders, both mean night-time SBP and the lowest SBP level were independent predictors of new-onset LVH. This was not the case for the magnitude of night-time SBP fall. In a study by Veloudi et al., in 267 subjects (mean age 64 years) with uncomplicated hypertension who were followed for one year the increase in 24-h, daytime and night-time SBP were predictors of the increase in LVM even after adjustments for baseline age, sex and BMI (Veloudi et al. 2016). The ABP measurements associated with the measures of LVH of these follow-up studies are presented in Table 2.

The results from studies assessing the association between BPV and LVH are controversial. Among 33 untreated hypertensive subjects, night-time SBP and daytime DBP variability correlated with LVMI (Veerman et al. 1996), whereas in 180 untreated subjects, awake SBP variability was associated with LVMI (Tatasciore et al. 2007). In a Japanese study among 111 patients, night-time DBP variability was associated with LVH (Ozawa et al. 2009). In two recent studies, central BPV was associated with LVM or LVH and was considered superior to brachial BPV (Chi et al. 2017, Weber et al. 2017). Controversially, the association between BPV and LVM or LVMI was not observed in several other studies (Kristensen et al. 2001, Roman et al. 2001, Schillaci et al. 1998, Veloudi et al. 2016).
Table 2. The ambulatory measured blood pressure parameters associated with measures of left ventricular hypertrophy in six follow-up studies

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Follow-up (y)</th>
<th>ABP parameters</th>
<th>Target of outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khattar et al. 1997</td>
<td>140</td>
<td>9.4</td>
<td>24-h SBP and PP</td>
<td>Follow-up LVMI ↑</td>
</tr>
<tr>
<td>Khattar et al. 1999</td>
<td>295</td>
<td>10.2</td>
<td>24-h SBP and PP</td>
<td>Follow-up LVMI ↑</td>
</tr>
<tr>
<td>Jokinility et al. 2001</td>
<td>66</td>
<td>10.0</td>
<td>24-h, daytime and night-time PP</td>
<td>Follow-up LVMI ↑</td>
</tr>
<tr>
<td>Andrikou et al. 2013</td>
<td>305</td>
<td>3.5</td>
<td>Night-time SBP</td>
<td>Follow-up LVH ↑</td>
</tr>
<tr>
<td>Cuspidi et al. 2013</td>
<td>1,632</td>
<td>10.0</td>
<td>Night-time SBP</td>
<td>New on-set LVH ↑</td>
</tr>
<tr>
<td>Veloudi et al. 2016</td>
<td>267</td>
<td>1.0</td>
<td>Increase in 24-h, daytime and night-time SBP</td>
<td>Increase in LVMI ↑</td>
</tr>
</tbody>
</table>

↑, positive correlation with studied parameter. ABP, ambulatory blood pressure; DBP, diastolic blood pressure; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; PP, pulse pressure; SBP, systolic blood pressure.

2.3.2 Ambulatory blood pressure measurement and left ventricular diastolic dysfunction

Impaired LV diastolic function is a common finding in essential hypertension. The association between ABPM and LVDD has been studied since the late 1980s. The studies so far have been conducted as cross-sectional assessments and no longitudinal studies exist.

In 1989, White et al. demonstrated among 47 subjects that 24-h systolic and diastolic BP showed negative correlations with LV filling rate (r=-0.59 and r=-0.57, and p<0.001 for both) (White et al. 1989). A year later when Verdecchia et al. measured late and early diastolic transmitral peak flow velocities and their ratio, the rate of deceleration of early diastolic mitral flow and the time of deceleration of early diastolic mitral flow in 250 subjects, mean daytime or night-time ABP showed a significant independent relationship with each of these Doppler indexes of LV diastolic filling (Verdecchia et al. 1990a). Bongiovi et al. observed among 66 hypertensives that 24-h BP correlated inversely with the ratio of E/A peak filling velocity (r=-0.307, p<0.05) (Bongiovi et al. 1992). In a study among 125 untreated subjects whose mean age was 46 years, 62 had E/A<1 (impaired diastolic function) (Galdersi et al. 1996). Negative correlations of E/A were found with mean 24-h and mean night-time systolic and diastolic BP. In a multivariate model, night-time DBP (beta=-0.28, p=0.0001) was the only ABP parameter to predict E/A. Trika et al. studied the possible relationships between E/A and 24-h BP among 198 patients divided into two groups: 1 (n=88, age 40-54 years) and 2 (n=110, age 55-79 years).
In group 1 the mean night-time SBP \((\beta=-0.33, \ p<0.041)\) and in group 2 the mean night-time PP \((\beta=-0.60, \ p<0.0007)\) independently predicted E/A (Trika et al. 2004). In a more recent study of 230 participants, septal and lateral E/Ea (Ea meaning early diastolic annular velocity) were associated with 24-h brachial and aortic SBP and PP \((p<0.04)\) (Zhang et al. 2015).

2.4 Pulse pressure

PP arises as a consequence of the episodic disposition of cardiac contraction and the features of the arterial circulation. Thus, while MAP is described by cardiac output and total peripheral resistance, the origins of PP are more complex. The best-known model system to explain PP is the simple, two-element form known as the Windkessel model. In 1733, Stephen Hales presented a basic and conceptual model of the arterial tree based on the observation that the blood flow is relatively smooth in the peripheral arteries despite the pulsatile action of the heart. In his model, the interaction between the heart and the arteries has similarities with the working principle of a fire hose, in which the pulsatile action of the pump is damped by an air chamber (Windkessel in German). In the CV system, large arteries play the role of the air chamber. In 1899, Otto Frank formulated these ideas mathematically and introduced the two-element Windkessel, which consists of two building blocks: peripheral resistance, \(R\), (representing the peripheral arterioles and capillaries) and total arterial compliance, \(C\), accounting for the compliance of the larger conduit vessels.

In the Windkessel model, compliance is simply a measure of the capacity of a volume-containing structure (arterial structure) to accommodate further increases in volume. While compliance is distributed throughout the arterial tree, total systemic compliance is predominantly determined by the aorta (Kelly et al. 1992) and its major branches. Arterial compliance may be estimated from the decline in diastolic pressure (Liu et al. 1986) as well as by another approach: \(C=\text{stroke volume (SV)/PP}\).

\[
PP = \frac{SV}{C}(2)
\]

Studies have suggested appropriate correspondence between these methods (Chemla et al. 1998, Stergiopulos et al. 1999). It is obvious from the approximation \(C=\text{SV/PP}\) that elevation in PP can be secondary to a rise in SV or a fall in C. The rise in PP with age in healthy subjects (Franklin et al. 1997a) relates to falls in C,
whereas an increase in PP in the young appears to be related to increases in SV (Alfie et al. 1999).

Stergiopulos & Westerhof constructed a canine study in which aortic pressures were measured under controlled conditions and under obstruction of the aorta and carotids (Stergiopulos & Westerhof 1998). They concluded that peripheral resistance and total compliance are the only two arterial parameters that determine PP virtually completely.

Aging causes a loss of elasticity in the aorta and major conduits. The increase in large artery stiffness resulting from fragmentation and disruption of elastic lamellae and alteration in the collagen-to-elastin ratio is found to be important in the genesis of increased PP during aging (Avolio et al. 1998, Franklin et al. 1997a). There is evidence for a relation between central pressure augmentation due to enhanced wave reflection, thus, central PP and short stature, and such a relation is expected to produce male-female differences (Cameron et al. 1998, London et al. 1995, Smulyan et al. 1998). A lower heart rate also seems to amplify central PP (Cameron et al. 1998). The somewhat faster heart rate found in women will therefore counteract the effects of shorter stature.

A number of pathophysiological states have also been shown to affect large artery features. In a 2009 review, Cecelja and Chowienczyk presented that diabetes mellitus was a risk factor for arterial stiffness in 12 of 23 (52%) of the studies, whereas total and LDL cholesterol were risk factors in only 2 of 41 (5%) and 1 of 21 (5%) of the studies (Cecelja & Chowienczyk 2009). The results from the review indicate that diabetes certainly affects arterial stiffness, whereas circulating total or LDL cholesterol levels do not.

2.5 Pulse pressure and cardiovascular risk

Since the early 1970s, the Framingham group has pointed to a more powerful association between systolic, rather than diastolic, BP and CV events (Kannel et al. 1971, Kannel et al. 1981). In 1985, Fisher challenged the theorem with diastolic rather than systolic BP (Fisher 1985), and soon after, in 1989, Dustan referred to an alteration in hypertensive disease, with problems shifting from the young and middle-aged subjects with diastolic hypertension to older subjects with systolic hypertension (Dustan 1989). Also, in 1989, Darne et al. pointed out that PP added further risk to subjects with elevated diastolic or mean BP, at least with respect to cerebral events (Darne et al. 1989).
In a French study by Benetos et al., 19,083 men aged 40-69 years underwent routine systematic health examinations and were followed for a medium of 19.5 years (Benetos et al. 1997b). A high PP was an independent and significant predictor of total CV, especially coronary, mortality. In a later French cohort study consisting of two cohorts of 15,561 and 6,246 men, elevated PP increased the risk for CV mortality 2-fold compared to those with no changes in either systolic or diastolic BP (Benetos et al. 2000). In the Boston Veteran’s Administration Study of healthy male volunteers aged 21-80 years, CV mortality was related to baseline SBP in subjects <60 years of age, whereas in older (>59 years) subjects PP was observed to be a more accurate predictor of death than SBP or DBP (Lee et al. 1999). In a non-invasive 24-h ambulatory study among untreated 2,010 subjects with essential hypertension, baseline ambulatory PP (APP) was a marginally superior risk factor than clinic PP or 24-h ambulatory SBP for CV events and mortality over a mean follow-up of 3.8 years (Verdecchia et al. 1998).

In a study by Madhavan et al., a wide PP was identified as a predictor for MI among 2,207 pre-treated hypertensives (Madhavan et al. 1994). In the Framingham study, 1,924 men and women were followed for 20 years and a high PP predicted the development of CHD (Franklin et al. 1999). PP was observed to be a higher risk factor than SBP.

In a study of 36 hypertensive subjects, those with PP ≥ 60 mmHg had significantly higher values of LVM than those with PP<60 mmHg (Pannier et al. 1989). In the East Boston senior health project, 1,621 men and women at a mean age of 77.9 years were followed for an average of 3.8 years (Chae et al. 1999). Baseline brachial PP was an independent predictor of congestive heart failure in subjects >65 years who were free of congestive heart failure at baseline.

In a cross-sectional study of 43 normotensive and 124 hypertensive subjects, carotid intima-media thickness was related to carotid, but not radial PP (Boutouyrie et al. 1999). In the Framingham study, PP was a better predictor than SBP for carotid artery stenosis among 374 subjects (Franklin et al. 1997b).

Among 460 middle-aged subjects, in-office PP was a predictor for the development of LVDD during a 20-year follow-up (Perkiömäki et al. 2015). Among 512 patients with HFpEF, both PP lower than 45 mmHg or higher than 75 mmHg were closely associated with HFpEF prognosis (Tokitsu et al. 2016).
2.6 Dipping pattern

Dipping is recognized as a categorical variable grouping the population based on day- and night-time BP values (Dimsdale & Heeren 1998). A normal dipping pattern is considered a reduction of BP during night-time of $\geq 10\%$. A non-dipping pattern is defined as a $<10\%$ reduction in night-time BP compared to daytime BP. A clear standard time frame for separating daytime and night-time BP is absent, but most studies consider the period from 6 AM to 10 PM as daytime and from 10 PM to 6 AM as night-time. In some studies, the dipping pattern is based on SBP (Bankir et al. 2008, Kario et al. 2000, Verdecchia et al. 2007), whereas some regard DBP values as more reliable because of their smaller variability (Mancia & Grassi 2000), and in some studies both SBP and DBP values are used (Cuspidi et al. 2006, Grassi et al. 2008, Perk et al. 2001).

The mechanisms resulting in non-dipping are not clear. The mechanisms are supposed to have multiple causes, e.g. the effects of physical activity, nocturnal urination (Perk et al. 2001), sodium intake and natriuresis (Fujii et al. 1999, Uzu et al. 1997), sympathetic activity (Lombardi & Parati 2000, Sherwood et al. 2002) and race (Harshfield et al. 2002, Hyman et al. 2000, Ohkubo et al. 2002).

2.6.1 Dipping pattern and cardiovascular risk


In studies evaluating the association between LVH and dipping pattern, the dipping pattern was based more often on both SBP and DBP values, but in a single study the dipping pattern was based only on SBP. In hypertensive subjects, when the dipping pattern is based on both SBP and DBP values, non-dippers have been shown to have significantly higher LVMI values compared to dippers (Cuspidi et al. 2004a, Hoshide et al. 2003, Verdecchia et al. 1990b). Similar results were also seen in black normotensives (Mezue et al. 2016). Ivanovic et al. showed that non-dippers had significantly higher LVM values compared to dippers (Ivanovic et al. 2013). Non-dippers have been shown to have a higher prevalence of LVH (Cuspidi et al. 2001), and concentric (Mozdzan et al. 2013) and eccentric (BaIc et al. 2004) hypertrophy compared to dippers. Zakopoulos et al. showed that non-dippers had
higher LVM values compared to dippers when the dipping pattern was based on SBP values (Zakopoulos et al. 1997).

Soylu et al. performed ABPM and echocardiography among 62 normotensives and discovered that the E/A ratio was lower in non-dipper compared to dipper individuals (p<0.001) (Soylu et al. 2009). Whereas, Ivanovic et al. showed among 376 hypertensive patients that non-dippers had significantly higher E/E’ ratios compared to dippers (8.2±2.1 vs. 8.8±2.4, p<0.001) (Ivanovic et al. 2013).

2.7 Adiponectin from the adipokine family

Adipose tissue has been recognized as being hormonally active, secreting several proteins called adipokines. Adipokines are peptides which have several effects in the brain, liver, pancreas, immune system, vasculature, muscle and other tissues. Secretion of adipokines is altered in adipose tissue dysfunction and may contribute to obesity-related diseases including CVD. Numerous different adipokines have been identified including leptin, adiponectin, resistin, vaspin, apelin and fibroblast growth factor 21. (Fasshauer & Bluher 2015)

Adiponectin was first identified in 1996 (Maeda et al. 1996, Nakano et al. 1996). Adiponectin is involved in lipid and glucose metabolism and has been one of the most extensively studied adipokines (Toussirot et al. 2007). Adiponectin is present in the serum mainly as three isoforms: a low molecular trimer, medium molecular hexamer or high-molecular weight form, which has a better predictive value for the prediction of insulin resistance and metabolic syndrome than plasma total adiponectin level (Hara et al. 2006). Plasma adiponectin levels are negatively correlated with body adiposity and weight (Arita et al. 1999, Li et al. 2011) and are reduced in insulin resistance (Kadowaki et al. 2006).

2.7.1 Adiponectin and cardiovascular risk

Adiponectin has been shown to have a wide range of beneficial effects on the CV system, having anti-inflammatory, anti-apoptotic, antioxidant and vasorelaxant properties (Kadowaki & Yamauchi 2005). However, a wide range of clinical studies has produced controversial results as to the usefulness of adiponectin as a biomarker of CV risk and CAD progression. Laughlin et al. produced the first long-term study, demonstrating that higher adiponectin concentrations were associated with a favourable CV risk profile in both genders from the same population (Laughlin et al. 2007). In a study by Kumada et al., male patients with
hypoadiponectinemia had a significant increase in CAD prevalence, independently of well-known CAD risk factors (Kumada et al. 2003), whereas Hotta et al. discovered among diabetic subjects that low adiponectin concentrations were associated with the prevalence of CAD (Hotta et al. 2000). Low adiponectin levels have been shown to increase the risk for MI (Nakamura et al. 2004, Otsuka et al. 2007), whereas Pischon et al. found that high plasma adiponectin concentrations decreased the risk of MI in men independently of common CVD risk factors (Pischon et al. 2004). Low adiponectin levels have also been suggested to increase the risk of ischemic stroke (Baranowska et al. 2011, Bienek et al. 2012, Kizer et al. 2013). In addition, low adiponectin levels are associated with endothelial dysfunction (Tan et al. 2004) and vascular hypertrophy (Matsuo et al. 2007). On the contrary, in a study by Lawlor et al., the association between low adiponectin concentrations and CAD among women was not observed (Lawlor et al. 2005). In addition, two meta-analyses found no association between low adiponectin concentrations and higher CVD risk and contrary to expectations, these studies associated higher adiponectin levels with increased CVD risk and total mortality (Sook Lee et al. 2013), and with higher risk of stroke (Hao et al. 2013).

2.7.2 Adiponectin and left ventricular hypertrophy

Low adiponectin levels have been shown to correlate with LVH in cross-sectional studies. In 2004, Shibata et al. demonstrated that pressure overload in adiponectin-deficient mice resulted in enhanced concentric cardiac hypertrophy (Shibata et al. 2004). Also, in 2004, Hong et al. showed that plasma adiponectin concentrations correlated inversely with LVMI ($r = -0.525; p<0.001$) among 275 subjects (Hong et al. 2004). The negative association between adiponectin and LVMI was also observed in three later studies consisting of 70 type II diabetics (Top et al. 2007), 231 obese patients (Ybarra et al. 2007) and 117 lean and obese patients (Ebinet et al. 2008). In the Framingham Offspring Study, including 2,615 participants, adiponectin concentrations were also inversely related to LVM in multivariable linear regression models adjusting for key clinical correlates, including BMI; this is the largest study to date (McManus et al. 2012). Mitsuhashi et al. studied electrocardiogram (ECG) based LVH in 2,839 Japanese males and showed that adiponectin concentrations were inversely and independently associated with LVH (Mitsuhashi et al. 2007).

In some other studies the results have been contrary. In the Jackson Heart Study among 2,649 black middle-aged subjects, adiponectin levels were positively
associated with LVMI after multivariate adjustments in subjects with hypertension and insulin resistance (Bidulescu et al. 2011). Positive relationships between adiponectin levels and LVMI have also been observed in patients on dialysis (Ayerden Ebinc et al. 2009, Komaba et al. 2007). A just recent South-Korean community-based, cross-sectional study performed on 1,414 subjects suggested that serum adiponectin levels have a biphasic distribution with increasing LVMI (Lee et al. 2013). They concluded that adiponectin levels show an inverse relation with LVMI at low risk of LVH and a positive relation at high risk of LVH.

2.8 Dietary sodium intake

2.8.1 Salt sensitivity

Based on the observation that dietary exposure to sodium does not affect BP in all individuals, it is apparent that salt sensitivity varies between individuals. The observation was first made in 1978 (Kawasaki et al. 1978). In the study, 19 hypertensive subjects were followed after three different diets containing different amounts of sodium. The normal-sodium diet contained 109 mmol/d, the low-sodium diet 9 mmol/d and the high-sodium diet 249 mmol/d. BP fell significantly (p<0.05) in the entire population with dietary sodium restriction and increased significantly (p<0.05) after the high-sodium diet. In a single individual, BP increase was not observed during the high-sodium diet. The investigators then separated the population into two different groups based on whether at least a 10% increase in MAP was observed after the high-sodium diet. Nine subjects were considered salt sensitives and 10 subjects non-salt sensitives. The observations in hypertensive subjects were then extended to normotensive population in two later studies. In 1979, Luft et al. arranged a study in which 16 normotensive young men were on a sodium restricted (10 mmol/d) diet for 7 days, followed by successive 3-day periods of 300, 600 or 800, and 1,200 or 1,500 mmol/d (Luft et al. 1979). BP rose significantly (p<0.001) from the lowest to the highest sodium intake. None of the subjects demonstrated a decrease in BP; however, individual responses were variable and ranged from an increase of 1.5% to 34%. In a longer 12-week study conducted in 82 normotensive subjects, a modest sodium restriction (≤75 mmol/d) was observed to significantly decrease mean BP (p<0.01) (Miller et al. 1987). However, individual BP responses varied from decreases of 20 mmHg in SBP and DBP to increases exceeding 10 mmHg in SBP and 6 mmHg in DBP.
Salt sensitivity has been suggested to be influenced by several different factors. In a few studies, black hypertensives were observed to have a greater frequency of salt sensitivity than whites, although the salt sensitivity among normotensive blacks seems to be similar to that seen among whites (Falkner & Kushner 1991, Sullivan 1991, Weinberger et al. 1986). Increasing salt sensitivity has been noted with increasing age (Overlack et al. 1993, Weinberger et al. 1986, Weinberger & Fineberg 1991). It has been suggested that females are more salt sensitive compared to males (Kojima et al. 1992), although this was not confirmed in other studies (Ishibashi et al. 1994, Weinberger et al. 1986). High body weight has also been suggested to correlate with salt sensitivity (Overlack et al. 1993), although other studies of salt sensitivity have failed to identify a relationship with body weight (Overlack et al. 1995, Weinberger et al. 1986). In addition, it has been discovered that salt sensitivity of BP alters after weight loss in obese subjects (Rocchini et al. 1989, Tuck 1991).

It has been suggested that a family history of hypertension is related to salt sensitivity of BP, implying that this phenomenon might be of genetic origin. In a Japanese study among salt sensitive subjects a positive family history was more frequently reported (Murakami et al. 1992). In a study by Weinberger et al. among both normotensive and hypertensive populations salt sensitivity varied individually with different haptoglobin genotypes (Weinberger et al. 1987).

Although the pathophysiology of salt-sensitive hypertension is complex, it is mainly attributable to the abnormal sodium excretion in the kidney (Guyton 1992). During high salt intake, salt-sensitive subjects require higher BP to excrete sodium sufficiently. Aldosterone is the mediator of sodium retention by stimulation of epithelial sodium channel absorption in the distal nephron and presumably in the proximal tubules (Drumm et al. 2006, Pinto et al. 2008, Xu et al. 2008). It has also been suggested that salt-sensitive hypertension might be mediated by activation of the sympathetic nervous system (Campese et al. 1982) and adrenergic receptors (Feldman et al. 1987).

### 2.8.2 Dietary sodium intake and cardiovascular risk

A significant number of epidemiologic, evolutionary and clinical studies have stated that salt intake is an important factor in elevated BP in humans. MacGregor et al. performed the first double-blind controlled study of modest salt restriction in 1982 among 19 mild to moderate hypertensives (MacGregor et al. 1982). The study confirmed that moderate sodium restriction affects BP and should become part of
the management of essential hypertension. The INTERSALT study was one of the first large international epidemiological studies on sodium intake and hypertension (1988). The relations between 24-h urinary sodium excretion and BP were studied in 10,079 men and women aged 20-59 from 52 centres across the world. In individual subjects, sodium intake was significantly related to BP.

The results from studies aiming to find a relationship between sodium intake and CVD morbidity or mortality have been controversial. The estimation of sodium intake varies between studies. In some studies, the estimation is based on 24-h dietary recall or food follow-up diaries, whereas in some studies the estimation is based either on urine spot samples or 24-h urine samples. There are at least four epidemiological and population-based studies in which the association between sodium intake and total CVD morbidity or mortality was observed (Äijälä et al. 2015, He et al. 1999, Tuomilehto et al. 2001, Umesawa et al. 2008). The details of these studies are presented in Table 3. The relation was observed only in men in the study by Tuomilehto et al. (Tuomilehto et al. 2001) and in overweight subjects in the study by He et al. (He et al. 1999). In addition, in a study by Cook et al., a risk reduction of 30% for CVD events with sodium restriction among 744 participants was observed (Cook et al. 2007).
<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Events</th>
<th>Follow-up (y)</th>
<th>Outcome</th>
<th>ESI</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>He et al. 1999</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal-weight</td>
<td>6,797</td>
<td>566</td>
<td>19.0</td>
<td>CVD death</td>
<td>24-h DR</td>
<td>1.02 (0.85 to 1.22) (A 100 mmol/7,452 kJ increase in sodium-to-energy ratio)</td>
</tr>
<tr>
<td>Overweight</td>
<td>2,688</td>
<td>329</td>
<td></td>
<td></td>
<td></td>
<td>1.61 (1.32 to 1.96)</td>
</tr>
<tr>
<td>Tuomilehto et al. 2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1,173</td>
<td>72</td>
<td>13.0</td>
<td>CVD event</td>
<td>24-h urine</td>
<td>1.38 (1.04 to 1.82) (A 100 mmol increase in 24-h sodium intake)</td>
</tr>
<tr>
<td>Women</td>
<td>1,263</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td>1.43 (0.73 to 2.78)</td>
</tr>
<tr>
<td>Umesawa et al. 2008</td>
<td>58,730</td>
<td>2,087</td>
<td>12.7</td>
<td>CVD death</td>
<td>FFD</td>
<td>1.42 (1.20 to 1.69) (Highest vs. lowest quintile of sodium intake)</td>
</tr>
<tr>
<td>Āijālā et al. 2015</td>
<td>716</td>
<td>112</td>
<td>19.0</td>
<td>CVD event</td>
<td>FFD</td>
<td>1.66 (1.05 to 2.64) (A 1 g/1,000 kcal increase in sodium-to-energy ratio)</td>
</tr>
</tbody>
</table>

CVD, cardiovascular disease; DR, dietary recall; ESI, estimation of sodium intake; FFD, food follow-up diary; HR, hazard ratio; kcal, kilocalorie; kJ, kilojoule; y, year.
One of the aims of the National Health and Nutrition Examination Survey (NHANES) follow-up studies was to assess the association between sodium intake and CVD mortality. The sodium intake was estimated from a single 24-h dietary recall. In NHANES I, 11,346 US adults were followed for 17-21 years and 1,970 CVD deaths occurred (Alderman et al. 1998). A statistically significant association between sodium intake and CVD mortality was not observed (p=0.086), but sodium intake proportioned to calorie intake was directly associated with CVD mortality (p=0.0056). In NHANES II, 7,154 US adults were followed for an average of 13.7 years and 541 CVD deaths occurred (Cohen et al. 2006). Sodium intake showed an inverse association with CVD mortality. Adjusted HR for CVD mortality for sodium intake <2300 mg/d was 1.37 (95% CI; 1.03 to 1.81, p=0.033) compared to sodium intake >2300 mg/d. The results from the NHANES III study were observed to be contrary (Cohen et al. 2008). Eight thousand six hundred and ninety-nine adults were followed an average of 8.7 years and 436 CVD deaths occurred. Sodium intake as a continuous variable was not associated with CVD mortality (p=0.07). O’Donnell et al. followed 28,880 subjects for an average of 56 months and observed that the association between estimated sodium excretion, from a single urine spot sample and CV events was J-shaped (O’Donnell et al. 2011). Compared with sodium excretion of 4-5.99 g/d, sodium excretion greater than 7 g/d was associated with an increased risk of CV events, while a sodium excretion <3 g/d was associated with increased risk of CV mortality. In addition, in The Rotterdam study, 7,983 subjects were followed for an average of 5 years and no association between sodium intake, estimated from an overnight urine sample and CVD mortality was observed (Geleijnse et al. 2007).

The association between sodium intake and stroke (He et al. 1999, Nagata et al. 2004, Umesawa et al. 2008), and CHD morbidity or mortality (Äijälä et al. 2015, Tunstall-Pedoe et al. 1997, Tuomilehto et al. 2001) has also been observed. The details of these studies are presented in Table 4. A high sodium intake was observed to increase stroke mortality among overweight subjects in the study by He et al. (He et al. 1999) and only among men in the study by Nagata et al. (Nagata et al. 2004). In addition, a high sodium intake was associated with CHD events only in men in the study by Tuomilehto et al. (Tuomilehto et al. 2001) and only in women in the study by Tunstall-Pedoe et al. (Tunstall-Pedoe et al. 1997). In contradiction, in a study by Alderman et al. a low sodium intake, estimated from a 24-h urine sample was associated with an increased risk for MI (HR 4.3, 95% CI; 1.7 to 10.6) (Alderman et al. 1995). In two additional studies the association between sodium
intake, estimated from food questionnaires and stroke incidence was not observed to be significant (Kagan et al. 1985, Larsson et al. 2008).

In addition, high sodium intake is associated with proteinuric renal disease (du Cailar et al. 2002, Han et al. 2014, Huang et al. 2016). There seems to be a direct association between salt intake and urinary albumin excretion, independently of BP (Verhave et al. 2004). Overweight and obese subjects had higher urinary albumin excretion than lean subjects in this study. Interestingly, dietary sodium restriction has been shown to decrease BP and reduce proteinuria more effectively than the addition of angiotensin receptor blockade to angiotensin-converting enzyme inhibitor (Slagman et al. 2011).
Table 4. The association between sodium intake and stroke or coronary heart disease events in six studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Events</th>
<th>Follow-up (y)</th>
<th>Outcome</th>
<th>ESI</th>
<th>HR (95% CI)</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>He et al. 1999</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normalweight</td>
<td>6,797</td>
<td>430</td>
<td>19.0</td>
<td>Stroke death</td>
<td>24-h DR</td>
<td>0.98 (0.83 to 1.16)</td>
<td>A 100 mmol/7,452 kJ increase in sodium-to-energy ratio</td>
</tr>
<tr>
<td>Overweight</td>
<td>2,688</td>
<td>250</td>
<td>19.0</td>
<td>Stroke death</td>
<td>24-h DR</td>
<td>1.37 (1.07 to 1.64)</td>
<td></td>
</tr>
<tr>
<td>Tunstall-Pedoe et al. 1997</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>5,754</td>
<td>404</td>
<td>7.6</td>
<td>CHD event</td>
<td>24-h urine</td>
<td>1.05 (0.96 to 1.14)</td>
<td>Highest vs. lowest quintile of sodium intake</td>
</tr>
<tr>
<td>Women</td>
<td>5,675</td>
<td>177</td>
<td>7.6</td>
<td>CHD event</td>
<td>24-h urine</td>
<td>1.16 (1.00 to 1.33)</td>
<td></td>
</tr>
<tr>
<td>Ulomilehto et al. 2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1,173</td>
<td>98</td>
<td>13.0</td>
<td>CHD event</td>
<td>24-h urine</td>
<td>1.34 (1.06 to 1.70)</td>
<td>A 100 mmol increase in 24-h sodium intake</td>
</tr>
<tr>
<td>Women</td>
<td>1,263</td>
<td>30</td>
<td>13.0</td>
<td>CHD event</td>
<td>24-h urine</td>
<td>1.35 (0.77 to 2.35)</td>
<td></td>
</tr>
<tr>
<td>Nagata et al. 2004</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>13,355</td>
<td>137</td>
<td>7.0</td>
<td>Stroke death</td>
<td>FFD</td>
<td>2.33 (1.23 to 4.45)</td>
<td>Highest vs. lowest tertile of sodium intake</td>
</tr>
<tr>
<td>Women</td>
<td>15,724</td>
<td>132</td>
<td>7.0</td>
<td>Stroke death</td>
<td>FFD</td>
<td>1.70 (0.96 to 3.02)</td>
<td></td>
</tr>
<tr>
<td>Umesawa et al. 2008</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>58,730</td>
<td>986</td>
<td>12.7</td>
<td>Stroke event</td>
<td>FFD</td>
<td>1.55 (1.21 to 2.00)</td>
<td>Highest vs. lowest quintile of sodium intake</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Äijälä et al. 2015</td>
<td>716</td>
<td>81</td>
<td>19.0</td>
<td>CHD event</td>
<td>FFD</td>
<td>1.87 (1.13 to 3.08)</td>
<td>A 1 g/1,000 kcal increase in sodium-to-energy ratio</td>
</tr>
</tbody>
</table>

CHD, coronary heart disease; DR, dietary recall; ESI, estimation of sodium intake; FFD, food follow-up diary; HR, hazard ratio; kcal, kilocalorie; kJ, kilojoule; y, year.
2.8.3 Dietary sodium intake and cardiac remodelling

Several studies have shown the association between sodium intake and adverse cardiac remodelling, and the association seems to be independent of BP. Sodium intake estimated either from urine samples or from food follow-up diaries has been shown to correlate with LVM (du Cailar et al. 1992, du Cailar et al. 2002, Kupari et al. 1994, Liebson et al. 1993, Schmieder et al. 1988). The details of the studies are presented in Table 5. In addition, a high sodium/potassium ratio has been shown to correlate with LVMI in young adults (Rodriguez et al. 2011) and in hypertensives (Haring et al. 2015). There is also evidence that a modest dietary sodium restriction decreases LVM (Jula & Karanko 1994).

There is evidence suggesting that sodium intake is associated with HF. In 1998, Langenfeld et al. observed that in early hypertension, among 44 young subjects, sodium excretion was correlated with impaired LV diastolic filling independent of LVM (Langenfeld et al. 1998). He et al. found that dietary sodium intake evaluated from a food follow-up diary was a strong independent risk factor for congestive HF in overweight subjects (He et al. 2002). They followed 5,233 lean and 5,129 overweight subjects for a mean of 19 years. Those whose sodium intake exceeded 113.6 mmol/d had a greater risk for congestive heart failure (risk ratio (RR) 1.43 (95% CI, 1.07-1.91)) than those whose sodium intake was less than 50.2 mmol/d, even after adjustment for known risk factors of congestive HF. In addition, Kagiyama et al. observed that among 46 patients with type 2 diabetes, increased sodium excretion was associated with impaired cardiac diastolic function (Kagiyama et al. 2009).

In a recent analysis as part of the HyperGEN (Hypertension Genetic Epidemiologic Network) study, among 2,996 participants (mean age 49, SD 14), high sodium intake was associated with adverse atrial remodelling (Selvaraj et al. 2017). Sodium intake was estimated from overnight urinary samples, and a positive correlation with LAD and a negative correlation with E/A-ratio were also observed.
Table 5. The association between sodium intake and left ventricular mass in five studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Age</th>
<th>Men / Women</th>
<th>Hypertensives/normotensives</th>
<th>ESI</th>
<th>Association between sodium intake and LVM</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schmieder et al. 1988</td>
<td>42</td>
<td>48.2</td>
<td>32 / 10</td>
<td>42 / 0</td>
<td>24-h urine</td>
<td>+</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>du Cailar et al. 1992</td>
<td>141</td>
<td>37.0</td>
<td>91 / 50</td>
<td>91 / 50</td>
<td>24-h urine</td>
<td>+</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Liebson et al. 1993</td>
<td>844</td>
<td>54.8</td>
<td>511 / 333</td>
<td>844 / 0</td>
<td>Urine spot</td>
<td>+</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Kupari et al. 1994</td>
<td>93</td>
<td>36-37</td>
<td>42 / 49</td>
<td>ND</td>
<td>FFD</td>
<td>+</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>du Cailar et al. 2002</td>
<td>839</td>
<td>15-70</td>
<td>471 / 368</td>
<td>ND</td>
<td>24-h urine</td>
<td>+</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

ESI, estimation of sodium intake; FFD, food follow-up diary; LVM, left ventricular mass; ND, not determined.
2.8.4 Dietary sodium intake and cardiac arrhythmias

While the association between sodium intake and CVD in general has been investigated in numerous studies, the association between sodium intake and cardiac arrhythmias has been investigated in only a few studies so far. In a 2013 study, Marketou et al. discovered among 255 patients, whose mean age was 60 (7 SD) years, that sodium intake estimated from a 24-h urine collection correlated positively with the percentage of premature ventricular contractions measured from 24-h ambulatory electrocardiograph (r=0.2, p=0.02) (Marketou et al. 2013).

Prolongation of the electrocardiographically measured QT-interval has been associated with ventricular arrhythmias (Yap & Camm 2003) and with increased CV morbidity and mortality (Algra et al. 1991, Elming et al. 1998, Straus et al. 2006). In two studies, the association between sodium intake and corrected QT-interval (QTc) was evaluated. Michishita et al. found out that among 41 elderly patients with high BMI, QTc correlated positively with sodium-to-energy ratio (mg/1,000 kcal) estimated from a brief diet history questionnaire among both sexes (r=0.531, p<0.05 for males and r=0.453, p<0.05 for females) (Michishita et al. 2015). In a study by He et al., 64 normotensive men and women, ranging from 28 to 60 years of age, were first on a seven-day low-salt (3 g/d of salt) diet followed by a seven-day salt loading (18 g/d of salt) diet (He et al. 2015). A significant prolongation of QTc was seen during the salt loading period compared to the low-salt period (406.2, SD 22.6 vs. 396.0, SD 23.2, p<0.001).

The association between sodium intake and the incidence of AF has not been previously reported.
3 Aims of the study

To evaluate the potential risk factors for the development of left ventricular hypertrophy, left ventricular diastolic dysfunction and atrial fibrillation. The specific aims of each paper were:

1. To study the association between adiponectin concentrations and LVMI, a measure of LVH in a middle-aged population-based cohort (I).
2. To study the role of ABPM in the development of LVDD during a long-term follow-up of 20 years in a population-based cohort representing initially middle-aged subjects (II).
3. To assess the role of ABPM in the development of LVH measuring the change in LVMI during a long-term follow-up of 20 years in a population-based cohort representing initially middle-aged subjects (III).
4. To evaluate the association between dietary sodium intake and the incidence of atrial fibrillation during a long-term follow-up of 20 years in a population-based cohort representing initially middle-aged subjects (IV).
4 Subjects and methods

4.1 Subjects

The Oulu Project Elucidating Risk of Atherosclerosis (OPERA) is a population-based, epidemiological study designed to designate the risk factors and disease endpoints of atherosclerotic CVD. The study population consists of a hypertensive cohort and a control cohort, both consisting of 300 men and 300 women, recruited from the city of Oulu, Finland. The subjects were 40-59 years old (middle-aged) at the time of recruitment. The hypertensive cohort was randomly selected by age stratification (15 men and 15 women per year) from the Social Insurance Institute register for reimbursement for antihypertensive medication. They were entitled to a special refund (higher reimbursement class) of antihypertensive medication. For each hypertensive subject, an age- and sex-matched control was randomly selected from the national health register. Any subject entitled to a higher reimbursement for antihypertensive medication was excluded from the control cohort. The participants were recruited from December 1990 to May 1993 by an invitation letter. The study population consisted of altogether 1,200 subjects, 1,045 of whom participated in the study. The overall participation rate was 87.1% (86.5% in the hypertensive and 87.7% in the control cohort). The whole study population and design have been previously described in detail (Rantala et al. 1999). The participating study subjects visited the research laboratory of the Department of Internal Medicine, University of Oulu, between January 1991 and March 1993, first the men during 1991 to 1992 and the women approximately a year later.

All the blood samples were collected after an overnight fast. At the visit, anthropometric measurements (weight, height, waist, hip) and BPM were performed. During the same visit, a standardized health questionnaire covering past medical history, current and former medication use, smoking habits and alcohol consumption was presented by two specially trained study nurses, and the subjects received food records and instructions on how to fill them. The details of the questionnaire were checked by a physician later during the same visit. All study subjects were interviewed and examined by three trained physicians with special competence in internal medicine. All subjects were invited on a separate occasion to 24-h ABPM and echocardiography, which were performed 6-12 months after the primary visit. After a 20-year follow-up period the subjects were recruited for
revisit. During the follow-up period 232 participants died. Of the 813 survivors, majority (N=600 (281 males and 319 females)) were available for re-examinations. The study was approved by the Oulu University Ethical committee. Informed consent was received from all study participants.

4.2 Methods

4.2.1 Clinical methods

All the subjects participating in the study visited the research laboratory. They filled a questionnaire about their past medical history, current and former medication use, smoking history, alcohol consumption, family history of CVD and physical activity. Alcohol consumption was determined in an interview with a trained physician using questions from the Khavari alcohol test (Khavari & Farber 1978). Alcohol consumption was calculated by summing the average amount of absolute alcohol in the different beverages and reporting the result in grams of absolute alcohol per week. Cumulative smoking amount was reported in pack-years (1 pack-year = 20 cigarettes smoked/d in one year). Height was measured without shoes to the nearest centimetre. Weight was measured in light underwear without shoes to the nearest 0.1 kilogram. BMI was calculated as weight (kg) divided by height squared (m²). Body surface area (BSA) was determined by the Dubois equation (Du Bois & Du Bois 1989). Waist and hip circumferences were measured with a tape measure to the nearest 0.5 cm. All measurements were performed by the same trained nurse.

4.2.2 Blood pressure measurements

All office BP values were recorded with an automatic oscillometric BP recorder (Dinamap® model 18465X, Criticon Ltd., Ascot, UK) according to the recommendations of the American Society of Hypertension. The resting BP was measured a total of three times at 1-minute intervals on the right arm in sitting position after at least 5 minutes of rest. The BP values used in the analyses are the mean value of the second and third measurements. PP was calculated by subtracting DBP from SBP.

At baseline, ABPM was recorded with the automatic SpaceLabs 90207 oscillometric unit (SpaceLabs Inc., Redmond, Washington, USA). It was set to measure BP every 15 min between 04:00 AM to 12:00 PM (daytime) and every 20
min between 12:00 PM to 04:00 AM (night-time). The accuracy and reproducibility of the BP readings obtained with this device has been previously settled by the British Hypertension Society and the US Association for the Advancement of Medical Instrumentation (O'Brien et al. 1993). The proper positioning of the cuff was ensured by means of the similarity (difference < 5 mmHg) between four SpaceLabs BPMs and four auscultatory readings (Y-connector). The subjects were instructed to relax their arm during the measurements. Based on accuracy, values of SBP less than 70 or more than 250 mmHg, DBP less than 40 or more than 150 mmHg, and heart rate less than 40 or more than 150 bpm were automatically excluded from the analyses. On the basis of these criteria, less than 3% of the BP readings were rejected as artefacts. At the follow-up visit, the ABPM was recorded with Oscar 2 oscillometric ambulatory blood pressure monitor (SunTech Medical), which has been approved by the British Hypertension Society (Goodwin et al. 2007). AccuWin Pro™ V3 software was used in the analysis of the ABPM data.

The subjects were categorized into two groups based on the size of night-time (systolic and/or diastolic) BP fall (NF): dippers (NF at least 10%) and non-dippers (NF by less than 10%). Combined dippers had a NF of at least 10% in both SBP and DBP.

4.2.3 Echocardiographic measurements

At baseline, an experienced cardiologist performed the echocardiographic measurements blinded to the patients’ clinical data using Hewlett-Packard ultrasound colour system Sonos 500 (Hewlett-Packard Company, Massachusetts, USA). M-Mode, 2-dimensional and Doppler examinations were performed according to the recommendations of the American Society of Echocardiography (Lang et al. 2015). LVM was calculated using the formula of Devereux et al. (Devereux et al. 1986) in (studies I, II and IV) or the formula of Troy et al. (Troy et al. 1972) in (study III), and LVMI was calculated by dividing the difference between LVM values by BSA.

\[
LVM \text{ (Devereux)} = 0.81(1.04((LVEDD + IVSd + PWD)^3 - LVEDD^3)) + 0.6(3)
\]

\[
LVM \text{ (Troy)} = 1.05((LVEDD + PWD + IVSd)^3 - LVEDD^3)(4)
\]

An echocardiographic view of the LV dimensions that are used to calculate LVM are shown in Figure 1.
Fig. 1. An echocardiographic view of the left ventricular dimensions that are used to calculate left ventricular mass. IVSd, intraventricular septum in diastole; LVEDD, left ventricular end-diastolic diameter, PVWd, posterior ventricular wall in diastole.

The LV dimensions are echocardiographically measured in M-mode and a view of the M-mode is shown in Figure 2.
Fig. 2. A view of the M-mode in echocardiography that is used to measure the dimensions of the left ventricle. IVSd, intraventricular septum in diastole; LVEDD, left ventricular end-diastolic diameter; PVWd, posterior ventricular wall in diastole.

At the follow-up visit, the study subjects underwent an echocardiographic examination in a core laboratory using GE Healthcare Vivid E 9 version 110. x.x ultrasound device (General Electric Company, Fairfield, Connecticut, USA). Standard and modern parameters including tissue Doppler based measurements were defined according to the recommendations of the American Society of Echocardiography (Lang et al. 2015). In the pulsed Doppler registration, E wave describes the early mitral inflow in diastole, and in the tissue Doppler registration, E’ measures the mitral annular longitudinal motion in early diastole (Paulus et al. 2007). The ratio of E to E’ (E/E’) is considered to be one of the best echocardiographic measurements of LVDD (Okura et al. 2009). LVDD was defined as E/E’ ≥15 based on previous experience (Perkiömäki et al. 2015). LAD was measured in M-mode. An M-mode view in the echocardiography of the LAD is shown in Figure 3.
4.2.4 Initial laboratory analyses

A wide spectrum of routine clinical laboratory analyses was carried out in the Central Laboratory of Oulu University Hospital. All the laboratory analyses were drawn after an overnight fast. Venous blood was drawn into EDTA sample tubes. Plasma was separated by centrifugation at 2000-2600 rounds/min for 10 min and kept at 4°C until further analyses, which were done, if possible, within two days after the blood samples had been drawn. Otherwise plasma was stored at -20°C--70°C for further analyses. The glucose concentrations were measured using the glucose dehydrogenase method (Diagnostica, Merck, Darmstadt, Germany). Very low-density lipoprotein (VLDL) was isolated from plasma by ultracentrifugation. High-density lipoprotein (HDL) was determined from the VLDL-free fraction. Low-density lipoprotein (LDL) was calculated by subtracting the cholesterol concentration in HDL from that in the VLDL-free fraction (Kervinen et al. 1994).
The concentrations of total cholesterol and triglycerides were defined in the plasma and lipoprotein fractions by enzymatic colorimetric methods (Boehringer diagnostic, Mannheim GmbH, Germany) using a Kone Specific analyser (Kone Specific, Selective Chemistry Analyser, Kone Instruments, Espoo, Finland). High sensitivity C-reactive protein (hs-CRP) was measured by commercially available enzyme-linked immunosorbent assay (ELISA) kits with a detection limit of 0.31 ng/mL (Diagnostic Systems Laboratories, Texas, USA). The plasma adiponectin concentrations were measured with an ELISA technique constructed in our laboratory (Santaniemi et al. 2006). Concentrations of N-terminal pro-atrial natriuretic peptide (NT-proANP) were measured as described earlier (Ala-Kopsala et al. 2004). Serum creatinine was determined with a method based on the Jaffe reaction. The Modification of Diet in Renal Disease (MDRD) formula was acquired to determine an approximation of renal function (estimated glomerular filtration rate, eGFR).

\[
\text{eGFR (mL/min/1.73m}^2) = 186 \times \left(\frac{\text{serum creatinine in mg/dL}}{\text{Age}}\right)^{(-0.203)} \times (0.742 \text{ if female})^5
\]

### 4.2.5 Follow-up laboratory analyses

The laboratory analyses at follow-up were carried out in the Joint Municipal Service Provider of Northern Finland Laboratory Centre, NordLab Oulu (since 2013; previously Laboratory of the Oulu University Hospital) using Siemens Advia 1800 chemistry and Siemens Advia Centaur XP immunochemistry analysers (Siemens Healthcare Diagnostics Oy). Cholesterol, LDL cholesterol, HDL cholesterol and triglycerides were analysed using enzymatic methods.

### 4.2.6 Nutritional follow-up diary

During the baseline visit to the laboratory, the subjects received food records and were instructed by a nutritionist on how to fill them. A 7-day record of food consumption was requested and the subjects were instructed to use household measures to evaluate portion sizes. Of the 1,045 subjects, 857 (82%) returned the completed food records to the laboratory. Of the food records, 141 (16%) were incomplete or inaccurately fulfilled and were thus not accepted; 716 (84%) of the returned food records were accepted as material for the study. The NUTRICA
computer program (Social Insurance Institution, Helsinki) was used to calculate nutrient intakes from the 7-day food records using the Finnish nutrient database (Rastas et al. 1993). The daily sodium intake was proportioned to the daily calorie intake and reported as mg/1,000 kcal or g/1,000 kcal.

4.2.7 Atrial fibrillation outcome classification

The diagnosis of AF (atrial flutter included) was made if ICD-10 code I48 was listed in the National Death Registry and/or hospital discharge registry (HILMO) during the follow-up period. The validity of this method has been shown to be adequate (Alonso et al. 2009). Diagnosis of AF was defined on standard 12-lead resting ECG. The follow-up period lasted until December 31, 2009, or until the first AF event was occurred.

4.2.8 Statistical methods

The data were analysed with SPSS version 15.0 – 24.0 software (SPSS, Inc.). The data are presented as mean (SD) for continuous variables and as N (percentages) or 95% CI for categorical variables. P-values <0.05 were considered statistically significant.

In study I, adiponectin concentrations were divided into quartiles. Analysis of variance was used to test the differences in variable means between the groups. The adjustment for confounding factors was performed using the analysis of covariance in the general linear model.

In study II, the analysis of variance was used to assess whether continuous variables differed statistically between the subjects divided into three subgroups based on E/E’. A χ²-test was carried out to examine the independence between categorical variables. The power of different factors to predict E/E’ after adjusting with other relevant univariate predictors was assessed in the logistic regression analysis multivariate model. An E/E’ value ≥15 was used as a criterion for LVDD in the logistic regression analysis.

In study III, LVMI change was divided into quartiles. The analysis of variance was used to assess whether continuous variables differed statistically between the LVMI change quartiles. The power of different factors to predict LVMI change quartiles and dipping status after adjusting with other univariate predictors was assessed in the general linear model.
In study IV, the subjects were divided into quartiles based on dietary sodium intake. The analysis of variance was used to assess whether continuous variables differed statistically between the subjects divided into the four subgroups of dietary sodium intake or the incidence of AF during follow-up. A $\chi^2$-test was carried out to examine the independence between categorical variables. Pearson's coefficient of correlation was used to determine correlations between dietary sodium intake and the risk factors of AF. A Kaplan-Meier curve was used to calculate the cumulative event-full curves of AF for the quartiles of dietary sodium intake. A Cox regression analysis was used to determine the predictive value of sodium intake as a continuous variable in the risk of AF incidence.
5 Results

5.1 Study subjects (Studies I-IV)

5.1.1 Main characteristics

Of the whole 1,045 participants in the study 520 (49.8%) were males and 525 (50.2%) were females. The general characteristics of the subjects at baseline according to gender are presented in Table 6. Women were approximately a year older because they visited the laboratory approximately a year later than men. Men had larger waist circumference, higher SBP and DBP, higher cumulative smoking amount, consumed more alcohol and sodium, had higher levels of creatinine, eGFR, fasting glucose, total cholesterol, LDL cholesterol and triglycerides and lower levels of adiponectin and HDL cholesterol compared to women.
Table 6. The general characteristics of the study population at baseline according to gender

<table>
<thead>
<tr>
<th>Variable</th>
<th>Males</th>
<th>Females</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>520</td>
<td>525</td>
<td>-</td>
</tr>
<tr>
<td>Cohort (hypertensive / control)</td>
<td>261 / 259</td>
<td>258 / 267</td>
<td>0.734</td>
</tr>
<tr>
<td>Diabetics, n(%)</td>
<td>58 (11.2%)</td>
<td>48 (9.1%)</td>
<td>0.282</td>
</tr>
<tr>
<td>Age (y)</td>
<td>50.7 (6.0)</td>
<td>51.8 (5.9)</td>
<td>0.003</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>27.9 (4.2)</td>
<td>27.4 (5.0)</td>
<td>0.083</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>97.5 (10.9)</td>
<td>93.8 (11.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Office SBP (mmHg)</td>
<td>152.0 (21.4)</td>
<td>144.6 (22.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Office DBP (mmHg)</td>
<td>92.5 (11.2)</td>
<td>85.7 (12.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking (pack-years)</td>
<td>14.9 (16.0)</td>
<td>4.9 (10.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcohol consumption (g/week)</td>
<td>95.4 (110.1)</td>
<td>27.0 (42.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sodium intake (mg/1000 kcal)</td>
<td>1955.1 (420.7)</td>
<td>1821.5 (353.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum creatinine (µmol/L)</td>
<td>87.2 (13.9)</td>
<td>78.0 (42.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m2)</td>
<td>88.0 (16.9)</td>
<td>76.0 (14.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting blood glucose (mmol/L)</td>
<td>4.9 (1.6)</td>
<td>4.6 (1.4)</td>
<td>0.011</td>
</tr>
<tr>
<td>hs-CRP (mg/L)</td>
<td>3.9 (7.6)</td>
<td>3.7 (7.3)</td>
<td>0.567</td>
</tr>
<tr>
<td>NT-proANP (pmol/L)</td>
<td>271.4 (137.0)</td>
<td>290.3 (192.5)</td>
<td>0.069</td>
</tr>
<tr>
<td>Plasma adiponectin (mg/L)</td>
<td>13.9 (6.1)</td>
<td>17.8 (7.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plasma total cholesterol (mmol/L)</td>
<td>5.6 (1.1)</td>
<td>5.6 (1.1)</td>
<td>0.023</td>
</tr>
<tr>
<td>Plasma LDL cholesterol (mmol/L)</td>
<td>3.7 (0.9)</td>
<td>3.4 (0.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plasma HDL cholesterol (mmol/L)</td>
<td>1.2 (0.3)</td>
<td>1.5 (0.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plasma triglycerides (mmol/L)</td>
<td>1.8 (1.1)</td>
<td>1.4 (0.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antihypertensive therapy n(%)</td>
<td>265 (51.0%)</td>
<td>277 (52.8%)</td>
<td>0.560</td>
</tr>
</tbody>
</table>

Values are means or number of subjects, standard deviation (SD) or percentages in parentheses. BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; NT-proANP, N-terminal pro-atrial natriuretic peptide; SBP, systolic blood pressure.

Echocardiographic measurements were major factors in all of the four studies, and the baseline characteristics of the participants based on whether echocardiography was performed or not are presented in Table 7. There was a significant difference in the participation rate in the echocardiographic measurements based on the cohort group, hypertensives participating less frequently. Also, the frequency of diabetes was significantly higher among those who did not participate in echocardiographic measurements. The participants who did not participate in echocardiographic measurements had higher BMI, waist circumference, in-office SBP, consumed more sodium, had higher fasting glucose, hs-CRP and triglycerides, had lower adiponectin concentrations, eGFR and HDL cholesterol and were more frequently
on antihypertensive therapy than the participants who underwent echocardiographic measurements.

Table 7. The general characteristics of the study population at baseline according to participation in echocardiography

<table>
<thead>
<tr>
<th>Variable</th>
<th>ECHO</th>
<th>No ECHO</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>896</td>
<td>149</td>
<td>-</td>
</tr>
<tr>
<td>Cohort (hypertensive / control)</td>
<td>419 / 477</td>
<td>100 / 49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex (males / females)</td>
<td>440 / 456</td>
<td>80 / 69</td>
<td>0.300</td>
</tr>
<tr>
<td>Diabetics, n(%)</td>
<td>8 (0.9%)</td>
<td>98 (65.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (y)</td>
<td>51.1 (6.0)</td>
<td>52.4 (5.9)</td>
<td>0.013</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>27.3 (4.4)</td>
<td>29.8 (5.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>89.5 (12.8)</td>
<td>97.1 (14.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Office SBP (mmHg)</td>
<td>147.2 (21.7)</td>
<td>155.1 (23.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Office DBP (mmHg)</td>
<td>88.7 (12.2)</td>
<td>91.7 (11.7)</td>
<td>0.004</td>
</tr>
<tr>
<td>Smoking (pack-years)</td>
<td>9.7 (13.7)</td>
<td>11.2 (17.3)</td>
<td>0.222</td>
</tr>
<tr>
<td>Alcohol consumption (g/week)</td>
<td>60.5 (89.9)</td>
<td>63.9 (91.1)</td>
<td>0.672</td>
</tr>
<tr>
<td>Sodium intake (mg/1000 kcal)</td>
<td>1865.3 (366.1)</td>
<td>2029.1 (525.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum creatinine (µmol/L)</td>
<td>82.7 (33.6)</td>
<td>81.7 (16.6)</td>
<td>0.703</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m2)</td>
<td>88.0 (16.9)</td>
<td>76.0 (14.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting blood glucose (mmol/L)</td>
<td>4.4 (0.5)</td>
<td>6.6 (3.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>hs-CRP (mg/L)</td>
<td>3.4 (6.8)</td>
<td>6.2 (10.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NT-proANP (pmol/L)</td>
<td>278.0 (162.3)</td>
<td>298.4 (194.6)</td>
<td>0.169</td>
</tr>
<tr>
<td>Plasma adiponectin (mg/L)</td>
<td>16.1 (6.9)</td>
<td>14.1 (6.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Plasma total cholesterol (mmol/L)</td>
<td>5.7 (1.0)</td>
<td>5.8 (1.4)</td>
<td>0.239</td>
</tr>
<tr>
<td>Plasma LDL cholesterol (mmol/L)</td>
<td>3.5 (0.9)</td>
<td>3.5 (1.1)</td>
<td>0.879</td>
</tr>
<tr>
<td>Plasma HDL cholesterol (mmol/L)</td>
<td>1.4 (0.4)</td>
<td>1.2 (0.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plasma triglycerides (mmol/L)</td>
<td>1.5 (0.8)</td>
<td>2.1 (1.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antihypertensive therapy n(%)</td>
<td>437 (48.8%)</td>
<td>105 (70.5%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are means or number of subjects, standard deviation (SD) or percentages in parentheses. BMI, body mass index; DBP, diastolic blood pressure; ECHO, echocardiography; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; NT-proANP, N-terminal pro-atrial natriuretic peptide; SBP, systolic blood pressure.

Nine hundred subjects (86.4%) participated in the 24-h ABPM at baseline. The general characteristics of ABP-measured subjects are presented in Table 8. Only triglyceride concentrations were observed to be higher among those who did not participate in ABPM compared to those who did participate in ABPM.
Table 8. The general characteristics of the study population at baseline according to participation in ambulatory blood pressure measurement

<table>
<thead>
<tr>
<th>Variable</th>
<th>ABPM</th>
<th>No ABPM</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>900</td>
<td>145</td>
<td>-</td>
</tr>
<tr>
<td>Cohort (hypertensive / control)</td>
<td>438 / 462</td>
<td>81 / 64</td>
<td>0.108</td>
</tr>
<tr>
<td>Sex (males / females)</td>
<td>446 / 454</td>
<td>74 / 71</td>
<td>0.741</td>
</tr>
<tr>
<td>Diabetics n(%)</td>
<td>91 (10.1%)</td>
<td>15 (10.3%)</td>
<td>0.931</td>
</tr>
<tr>
<td>Age (y)</td>
<td>51.4 (5.9)</td>
<td>50.4 (6.2)</td>
<td>0.055</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>27.6 (4.6)</td>
<td>28.2 (5.1)</td>
<td>0.131</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>90.3 (13.0)</td>
<td>92.4 (14.4)</td>
<td>0.085</td>
</tr>
<tr>
<td>Office SBP (mmHg)</td>
<td>148.2 (22.1)</td>
<td>148.8 (21.8)</td>
<td>0.749</td>
</tr>
<tr>
<td>Office DBP (mmHg)</td>
<td>89.1 (12.2)</td>
<td>89.4 (12.1)</td>
<td>0.747</td>
</tr>
<tr>
<td>Smoking (pack-years)</td>
<td>9.9 (14.1)</td>
<td>10.0 (15.0)</td>
<td>0.919</td>
</tr>
<tr>
<td>Alcohol consumption (g/week)</td>
<td>60.9 (90.9)</td>
<td>61.7 (84.8)</td>
<td>0.920</td>
</tr>
<tr>
<td>Sodium intake (mg/1000 kcal)</td>
<td>1888.6 (393.9)</td>
<td>1863.9 (386.8)</td>
<td>0.602</td>
</tr>
<tr>
<td>Serum creatinine (µmol/L)</td>
<td>81.8 (14.6)</td>
<td>87.3 (76.9)</td>
<td>0.055</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m2)</td>
<td>81.7 (16.5)</td>
<td>83.6 (19.6)</td>
<td>0.216</td>
</tr>
<tr>
<td>Fasting blood glucose (mmol/L)</td>
<td>4.7 (1.4)</td>
<td>4.9 (1.8)</td>
<td>0.180</td>
</tr>
<tr>
<td>hs-CRP (mg/L)</td>
<td>3.6 (7.5)</td>
<td>4.9 (6.9)</td>
<td>0.065</td>
</tr>
<tr>
<td>NT-proANP (pmol/L)</td>
<td>277.3 (152.5)</td>
<td>303.1 (234.0)</td>
<td>0.086</td>
</tr>
<tr>
<td>Plasma adiponectin (mg/L)</td>
<td>15.9 (6.8)</td>
<td>15.7 (6.9)</td>
<td>0.746</td>
</tr>
<tr>
<td>Plasma total cholesterol (mmol/L)</td>
<td>5.7 (1.0)</td>
<td>5.7 (1.2)</td>
<td>0.920</td>
</tr>
<tr>
<td>Plasma LDL cholesterol (mmol/L)</td>
<td>3.5 (0.9)</td>
<td>3.5 (1.0)</td>
<td>0.301</td>
</tr>
<tr>
<td>Plasma HDL cholesterol (mmol/L)</td>
<td>1.3 (0.4)</td>
<td>1.4 (0.4)</td>
<td>0.786</td>
</tr>
<tr>
<td>Plasma triglycerides (mmol/L)</td>
<td>1.5 (0.9)</td>
<td>1.8 (1.5)</td>
<td>0.002</td>
</tr>
<tr>
<td>Antihypertensive therapy n(%)</td>
<td>460 (51.1%)</td>
<td>82 (56.6%)</td>
<td>0.224</td>
</tr>
</tbody>
</table>

Values are means or number of subjects, standard deviation (SD) or percentages in parentheses. ABPM, ambulatory blood pressure measurement; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; NT-proANP, N-terminal pro-atrial natriuretic peptide; SBP, systolic blood pressure.

Dietary sodium intake could be estimated in 716 subjects at baseline. The general characteristics of the population according to whether sodium intake was estimated or not are presented in Table 9. Those whose sodium intake was not estimated were observed to have a higher prevalence of diabetes, were younger, had higher BMI and waist circumference, higher cumulative smoking amount, higher eGFR, higher fasting glucose, hs-CRP and triglycerides, and lower NT-proANP and HDL cholesterol levels compared to those whose sodium intake was estimated.
Table 9. The general characteristics of the study population at baseline according to whether sodium intake was estimated or not

<table>
<thead>
<tr>
<th>Variable</th>
<th>ESI</th>
<th>No ESI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>716</td>
<td>329</td>
<td>-</td>
</tr>
<tr>
<td>Cohort (hypertensive / control)</td>
<td>342 / 374</td>
<td>177 / 152</td>
<td>0.070</td>
</tr>
<tr>
<td>Sex (males / females)</td>
<td>345 / 371</td>
<td>175 / 154</td>
<td>0.133</td>
</tr>
<tr>
<td>Diabetics n(%)</td>
<td>63 (8.8%)</td>
<td>43 (13.1%)</td>
<td>0.034</td>
</tr>
<tr>
<td>Atrial fibrillation n(%)</td>
<td>74 (10.3%)</td>
<td>31 (9.4%)</td>
<td>0.649</td>
</tr>
<tr>
<td>Age (y)</td>
<td>51.5 (6.1)</td>
<td>50.6 (5.7)</td>
<td>0.022</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>27.3 (4.4)</td>
<td>28.6 (5.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>89.2 (12.4)</td>
<td>93.6 (14.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Office SBP (mmHg)</td>
<td>148.9 (22.4)</td>
<td>147.0 (21.3)</td>
<td>0.203</td>
</tr>
<tr>
<td>Office DBP (mmHg)</td>
<td>88.7 (12.0)</td>
<td>90.1 (12.5)</td>
<td>0.089</td>
</tr>
<tr>
<td>Smoking (pack-years)</td>
<td>8.9 (13.8)</td>
<td>11.9 (15.1)</td>
<td>0.002</td>
</tr>
<tr>
<td>Alcohol consumption (g/week)</td>
<td>56.2 (87.5)</td>
<td>71.5 (94.7)</td>
<td>0.010</td>
</tr>
<tr>
<td>Serum creatinine (µmol/L)</td>
<td>83.5 (37.2)</td>
<td>80.6 (13.5)</td>
<td>0.172</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m2)</td>
<td>81.0 (17.0)</td>
<td>84.2 (16.8)</td>
<td>0.005</td>
</tr>
<tr>
<td>Fasting blood glucose (mmol/L)</td>
<td>4.6 (1.8)</td>
<td>4.9 (1.8)</td>
<td>0.002</td>
</tr>
<tr>
<td>hs-CRP (µg/L)</td>
<td>3.5 (0.9)</td>
<td>5.0 (1.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NT-proANP (pmol/L)</td>
<td>288.7 (182.7)</td>
<td>263.8 (126.3)</td>
<td>0.025</td>
</tr>
<tr>
<td>Plasma adiponectin (mg/L)</td>
<td>15.9 (7.0)</td>
<td>15.7 (6.8)</td>
<td>0.629</td>
</tr>
<tr>
<td>Plasma total cholesterol (mmol/L)</td>
<td>5.7 (1.0)</td>
<td>5.7 (1.1)</td>
<td>0.535</td>
</tr>
<tr>
<td>Plasma LDL cholesterol (mmol/L)</td>
<td>3.5 (0.9)</td>
<td>3.5 (1.0)</td>
<td>0.345</td>
</tr>
<tr>
<td>Plasma HDL cholesterol (mmol/L)</td>
<td>1.4 (0.4)</td>
<td>1.3 (0.4)</td>
<td>0.007</td>
</tr>
<tr>
<td>Plasma triglycerides (mmol/L)</td>
<td>1.5 (0.8)</td>
<td>1.8 (1.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antihypertensive therapy n(%)</td>
<td>362 (50.6%)</td>
<td>180 (54.7%)</td>
<td>0.212</td>
</tr>
</tbody>
</table>

Values are means or number of subjects, standard deviation (SD) or percentages in parentheses. BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ESI, estimation of sodium intake; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; NT-proANP, N-terminal pro-atrial natriuretic peptide; SBP, systolic blood pressure.

After the follow-up period, 600 participants were available for re-examinations. The general characteristics of the subjects at baseline according to attendance in the follow-up study are presented in Table 10. The subjects who did not participate in the follow-up study were more often males, had higher prevalence of diabetes, were older, had higher BMI, waist circumference, office SBP and DBP, fasting glucose, hs-CRP, NT-proANP, total cholesterol, LDL cholesterol and triglycerides and higher cumulative smoking amount and consumed more alcohol.
Table 10. The general characteristics of the study population at baseline according to attendance in the follow-up study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Attendance</th>
<th>No attendance</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>600</td>
<td>445</td>
<td>-</td>
</tr>
<tr>
<td>Cohort (hypertensive / control)</td>
<td>290 / 310</td>
<td>229 / 216</td>
<td>0.317</td>
</tr>
<tr>
<td>Sex (males / females)</td>
<td>281 / 319</td>
<td>239 / 206</td>
<td>0.028</td>
</tr>
<tr>
<td>Diabetics n(%)</td>
<td>40 (6.7%)</td>
<td>66 (14.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>50.1 (5.7)</td>
<td>52.8 (6.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.4 (4.5)</td>
<td>28.1 (4.8)</td>
<td>0.023</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>89.3 (12.8)</td>
<td>92.3 (13.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Office SBP (mmHg)</td>
<td>145.4 (20.5)</td>
<td>152.2 (23.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Office DBP (mmHg)</td>
<td>87.9 (11.8)</td>
<td>90.8 (12.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking (pack-years)</td>
<td>7.5 (12.3)</td>
<td>13.1 (16.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcohol consumption (g/week)</td>
<td>51.8 (68.3)</td>
<td>73.5 (111.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum creatinine (µmol/L)</td>
<td>81.2 (13.8)</td>
<td>84.4 (43.8)</td>
<td>0.109</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>82.0 (15.8)</td>
<td>82.0 (18.5)</td>
<td>0.945</td>
</tr>
<tr>
<td>Fasting blood glucose (mmol/L)</td>
<td>4.6 (1.2)</td>
<td>5.0 (1.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>hs-CRP (mg/L)</td>
<td>3.3 (7.8)</td>
<td>4.5 (6.9)</td>
<td>0.007</td>
</tr>
<tr>
<td>NT-proANP (pmol/L)</td>
<td>263.2 (135.7)</td>
<td>304.7 (200.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plasma adiponectin (mg/L)</td>
<td>15.6 (6.4)</td>
<td>16.1 (7.4)</td>
<td>0.243</td>
</tr>
<tr>
<td>Plasma total cholesterol (mmol/L)</td>
<td>5.6 (1.0)</td>
<td>5.8 (1.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Plasma LDL cholesterol (mmol/L)</td>
<td>3.5 (0.9)</td>
<td>3.6 (1.0)</td>
<td>0.007</td>
</tr>
<tr>
<td>Plasma HDL cholesterol (mmol/L)</td>
<td>1.4 (0.4)</td>
<td>1.3 (0.4)</td>
<td>0.115</td>
</tr>
<tr>
<td>Plasma triglycerides (mmol/L)</td>
<td>1.5 (0.8)</td>
<td>1.7 (1.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antihypertensive therapy n(%)</td>
<td>299 (49.8%)</td>
<td>243 (54.6%)</td>
<td>0.127</td>
</tr>
</tbody>
</table>

Values are means or number of subjects, standard deviation (SD) or percentages in parentheses. BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; NT-proANP, N-terminal pro-atrial natriuretic peptide; SBP, systolic blood pressure.

The general characteristics at follow-up according to gender are presented in Table 11. At follow-up, sodium intake was not evaluated and NT-proANP or hs-CRP were not measured. Men had higher waist circumference, higher DBP and cumulative smoking amount and consumed more alcohol, had higher creatinine levels and lower levels of adiponectin, total cholesterol and HDL cholesterol compared to women.
Table 11. The general characteristics of the study group at follow-up according to gender

<table>
<thead>
<tr>
<th>Variable</th>
<th>Males</th>
<th>Females</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>281</td>
<td>319</td>
<td>-</td>
</tr>
<tr>
<td>Cohort (hypertensive / control)</td>
<td>145 / 136</td>
<td>145 / 174</td>
<td>0.133</td>
</tr>
<tr>
<td>Diabetics n(%)</td>
<td>108 (38.4%)</td>
<td>108 (33.9%)</td>
<td>0.244</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.0 (4.9)</td>
<td>29.2 (5.2)</td>
<td>0.680</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>102.3 (13.3)</td>
<td>92.4 (12.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Office SBP (mmHg)</td>
<td>137.4 (21.6)</td>
<td>139.0 (22.6)</td>
<td>0.363</td>
</tr>
<tr>
<td>Office DBP (mmHg)</td>
<td>74.9 (10.6)</td>
<td>69.9 (9.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking (pack-years)</td>
<td>16.5 (19.9)</td>
<td>5.1 (12.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcohol consumption (g/week)</td>
<td>56.6 (87.0)</td>
<td>23.9 (42.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum creatinine (µmol/L)</td>
<td>82.3 (29.8)</td>
<td>65.5 (26.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting blood glucose (mmol/L)</td>
<td>5.8 (0.6)</td>
<td>5.7 (0.6)</td>
<td>0.087</td>
</tr>
<tr>
<td>Plasma adiponectin (mg/L)</td>
<td>13.0 (6.4)</td>
<td>17.4 (8.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plasma total cholesterol (mmol/L)</td>
<td>4.5 (1.0)</td>
<td>4.9 (1.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plasma LDL cholesterol (mmol/L)</td>
<td>2.8 (1.0)</td>
<td>2.8 (1.0)</td>
<td>0.886</td>
</tr>
<tr>
<td>Plasma HDL cholesterol (mmol/L)</td>
<td>1.3 (0.3)</td>
<td>1.6 (0.4)</td>
<td>0.007</td>
</tr>
<tr>
<td>Plasma triglycerides (mmol/L)</td>
<td>1.5 (0.8)</td>
<td>1.8 (1.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antihypertensive therapy n(%)</td>
<td>362 (50.6%)</td>
<td>180 (54.7%)</td>
<td>0.212</td>
</tr>
</tbody>
</table>

Values are means or number of subjects, standard deviation (SD) or percentages in parentheses. BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

5.1.2 Blood pressure measurements

ABP was measured in 900 (86.1%) participants at baseline and 537 (89.5%) participants at follow-up. The BP values of the ABP-measured participants are presented in Table 12. As expected, ABP-measured mean SBP and PP show an increase with aging whereas DBP shows a decrease (Safar et al. 2003).
### Table 12. Blood pressure measurements of the ambulatory blood pressure measured subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>900</td>
<td>537</td>
</tr>
<tr>
<td>Office SBP</td>
<td>148.2 (22.1)</td>
<td>137.9 (21.8)</td>
</tr>
<tr>
<td>Office DBP</td>
<td>89.1 (12.2)</td>
<td>72.4 (10.5)</td>
</tr>
<tr>
<td>Office PP</td>
<td>59.2 (15.0)</td>
<td>65.5 (17.0)</td>
</tr>
<tr>
<td>ABPM, 24-h SBP</td>
<td>130.0 (13.6)</td>
<td>132.8 (14.5)</td>
</tr>
<tr>
<td>ABPM, 24-h DBP</td>
<td>81.1 (8.4)</td>
<td>72.5 (8.0)</td>
</tr>
<tr>
<td>ABPM, 24-h PP</td>
<td>48.8 (9.0)</td>
<td>60.4 (11.7)</td>
</tr>
<tr>
<td>ABPM, daytime SBP</td>
<td>134.7 (14.2)</td>
<td>134.4 (14.5)</td>
</tr>
<tr>
<td>ABPM, daytime DBP</td>
<td>85.2 (8.8)</td>
<td>73.8 (8.1)</td>
</tr>
<tr>
<td>ABPM, daytime PP</td>
<td>49.5 (9.7)</td>
<td>60.6 (11.8)</td>
</tr>
<tr>
<td>ABPM, night-time SBP</td>
<td>116.8 (14.3)</td>
<td>124.6 (18.1)</td>
</tr>
<tr>
<td>ABPM, night-time DBP</td>
<td>70.2 (9.4)</td>
<td>65.4 (10.0)</td>
</tr>
<tr>
<td>ABPM, night-time PP</td>
<td>46.6 (9.1)</td>
<td>59.1 (13.2)</td>
</tr>
</tbody>
</table>

Values are means, standard deviation (SD) in parentheses. ABPM, ambulatory blood pressure measurement; DBP, diastolic blood pressure; PP, pulse pressure; SBP, systolic blood pressure.

### 5.1.3 Echocardiographic measurements

Echocardiographic measurements were performed on 949 (90.8%) participants at baseline and on 599 (99.8%) participants at follow-up. The echocardiographic measurements are presented in Table 13.

### Table 13. Echocardiographic measurements of the subjects attending echocardiography

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>900</td>
<td>537</td>
</tr>
<tr>
<td>Intraventricular septum (mm)</td>
<td>10.8 (2.2)</td>
<td>10.7 (2.3)</td>
</tr>
<tr>
<td>Posterior ventricular wall (mm)</td>
<td>10.1 (1.8)</td>
<td>10.7 (1.7)</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>51.6 (5.4)</td>
<td>52.0 (6.4)</td>
</tr>
<tr>
<td>Left atrium diameter (mm)</td>
<td>39.1 (5.3)</td>
<td>39.8 (6.9)</td>
</tr>
<tr>
<td>LVMI (g/m²) (Devereux)</td>
<td>131.2 (38.8)</td>
<td>-</td>
</tr>
<tr>
<td>LVMI (g/m²) (Troy)</td>
<td>107.9 (28.5)</td>
<td>115.2 (28.9)</td>
</tr>
<tr>
<td>E/A integral</td>
<td>1.7 (0.6)</td>
<td>1.3 (0.5)</td>
</tr>
<tr>
<td>E/E´</td>
<td>-</td>
<td>11.1 (3.6)</td>
</tr>
</tbody>
</table>

Values are means, standard deviation (SD) in parentheses. E wave describes the ejection phase of mitral flow in early diastole, E´ measures the mitral annulus movement in early diastole and A wave describes the atrial booster in mitral flow in late diastole. LVEDD, left ventricular end-diastolic diameter; LVMI, left ventricular mass index.
5.2 Adiponectin and left ventricular mass index (Study I)

Study I was aimed to investigate the relationship between adiponectin concentrations and echocardiographic parameters including LVMI in a population of 933 (453 hypertensives and 480 controls) middle-aged subjects from the OPERA cohort. Adiponectin concentrations were divided into quartiles. The hypertensive and control cohorts were studied separately. In the univariate analysis adiponectin showed an inverse association with intraventricular septum, posterior ventricular wall, LVM, LVMI and LV internal diameter in both cohorts. Even after adjustments for traditional risk factors of LVH (sex, age, smoking and office SBP) the inverse association between adiponectin and LVMI remained statistically significant in both the hypertensive and the control cohort. The association between plasma adiponectin quartiles and LVMI is shown in Figure 4.

![Figure 4](image_url)

**Fig. 4.** Left ventricular mass index in plasma adiponectin quartiles. Values are means (±standard error of mean). *P*<0.001 before and *P*=0.028 after adjustment for age, sex, pack-years (smoking) and systolic blood pressure.
5.3 **Ambulatory blood pressure measurement and the development of left ventricular diastolic dysfunction (Study II)**

Study II was aimed at studying the predictive value of ABPM in the development of LVDD during a 20-year follow-up of 414 participants from the OPERA cohort. The study population was divided into three subgroups based on follow-up E/E’ (1st subgroup: E/E’ ≤ 8, 2nd subgroup: 8 < E/E’ < 15 and the 3rd subgroup: E/E’ ≥ 15), which is considered one of the best echocardiographic measurements indicating LVDD (Okura et al. 2009). E/E’ ≥ 15 indicates significant LVDD. Several baseline characteristics were associated with future E/E’, such as higher age, female gender, diabetic status, shorter stature, higher BMI, higher office SBP and PP, higher NT-proANP and fasting glucose and the use of antihypertensive therapy. Twenty-four-hour, daytime and night-time APP were all significant predictors of LVDD in the univariate analysis and the predictive value remained significant after adjustment for the significant baseline factors in the multivariate analysis. The association between the three E/E’ subgroups and 24-h APP is shown in Figure 5. Three hundred and eighty-one subjects also underwent APBM at follow-up. A significant increase in all of the PP measurements was observed in all of the subjects, but the increase in PP was observed to be higher among those whose E/E’ ≥ 15 compared to those whose E/E’ < 15. Therefore, a high APP predicts the development of LVDD in over 20 years of follow-up.
5.4 Ambulatory blood pressure measurement and the change in left ventricular mass index (Study III)

Study III was designed to address the predictive value of APBM in the change of LVMI during a follow-up of 20 years in 420 participants from the OPERA cohort. LVMI change was calculated by subtracting baseline LVMI from follow-up LVMI and then divided into quartiles. Baseline LVMI was a strong predictor of LVMI change. No other baseline characteristic predicted LVMI change. Of the BPMs, in-office DBP was a predictor of LVMI change, but none of the baseline ABPM predicted LVMI change. A greater increase in daytime and night-time SBP and 24-h, daytime and night-time PP predicted LVMI change when baseline LVMI was used as a covariate. In addition, diastolic non-dipping status seemed to be a predictor of LVMI change when in-office DBP and baseline LVMI were used as covariates. The results of this study are presented in Figure 6.
Fig. 6. The association between 24-h, daytime and night-time pulse pressure changes to left ventricular mass index change quartiles in three figures. Adjusted with baseline left ventricular mass index. The association between diastolic dipping status and left ventricular mass index change. Adjusted with baseline left ventricular mass index and in-office diastolic blood pressure. Values are means (±standard error of mean).

5.5 Dietary sodium intake and the incidence of atrial fibrillation (Study IV)

Study IV was aimed to investigate the association between dietary sodium intake and the incidence of AF during a mean 19-year follow-up among 713 subjects from the OPERA cohort. Sodium intake correlated positively with baseline age,
cumulative smoking amount, in-office SBP, BMI, waist circumference and LDL cholesterol, which are considered CVD risk factors. Sodium intake also correlated positively with LAD. Several baseline characteristics were associated with the incidence of AF, such as age, BMI, waist circumference, cumulative smoking amount, in-office SBP, LAD, LVMI and sodium consumption. The incidence of AF events was positively associated with sodium intake quartiles. The Kaplan-Meier curve of the cumulative hazard of AF events in sodium intake quartiles is shown in Figure 7. When age, BMI, smoking, LAD, LVMI and the use of antihypertensive therapy were added as covariates, sodium consumption as a continuous variable predicted the incidence of AF events.

![Fig. 7. Kaplan-Meier curve of the cumulative hazard of atrial fibrillation events in the quartiles of sodium intake based on 7-day food diary. The number of subjects in the sodium intake quartiles are as follows: 1st: 178, 2nd: 179, 3rd: 179 and 4th: 179.](image-url)
6 Discussion

6.1 Study population and design

The OPERA study was determined to represent middle-aged Finnish hypertensive subjects and their age- and sex-matched control counterparts. At the time of recruitment, 31 December 1990, the Social Insurance Institute criteria for special reimbursement for antihypertensive therapy were set at SBP>180 mmHg and DBP>95 mmHg with the presence of hypertensive TOD or SBP>200 mmHg and DBP>105 mmHg without the presence of hypertensive TOD, which were also the inclusion criteria for the hypertensive cohort. Any subjects entitled to special reimbursement for antihypertensive therapy were excluded from the control cohort; however, the control cohort does not represent the “hypertension-free” part of the population. Subjects suffering from mild (SBP ≤ 180 mmHg and DBP ≤ 105 mmHg), uncomplicated hypertension are included in the control cohort because they were not entitled to special reimbursement for antihypertensive therapy at the time. Furthermore, 7 men and 14 women of the control cohort were using antihypertensive therapy. The control cohort included a large proportion of subjects with high BP previously undetected and untreated. More than one third of the male control subjects and one fourth of the female control subjects had hypertensive BP values. Therefore, these factors may potentially dilute the differences between the hypertensive and control group and make it further more challenging to draw actual conclusions from the differences between hypertensives and “normotensives”. Furthermore, the main characteristics of the control cohort are similar and comparable to those previously reported for the Finnish population (Vartiainen et al. 1994).

The overall participation rate at baseline was 86.4%, which can be considered excellent, and the participation rate at follow-up was 73.8%, which was sufficient. A large number of subjects were lost during follow-up, mainly due to death (N=232), but 216 subjects were not available for re-examinations for various reasons, e.g. migration. The somewhat lower participation rate at follow-up most likely affected the data at follow-up, but the effects remain unknown. Since a large number of subjects who did not attend the follow-up study were deceased and CVD are the number one cause of death, it seems only natural that the study subjects who did not participate in the follow-up study had a significantly greater risk of CVD compared to the subjects who did take part in the follow-up study.
Comparing the study subjects based on whether echocardiographic measurements were performed at baseline or not, it is evident that the subjects who did not attend the baseline echocardiographic measurements were at higher CV risk. The subjects who did not attend echocardiography were more often in the hypertensive cohort, had a significantly higher prevalence of diabetes, were older, had a higher BMI and waist circumference, higher SBP and DBP, higher concentrations of fasting glucose, hs-CRP and triglycerides, lower concentrations of adiponectin and HDL cholesterol and used antihypertensive therapy more frequently than the subjects who attended echocardiography. Especially the frequency of diabetics differed significantly between the two groups. This raises an issue concerning the results of studies I and III. The non-echocardiographically measured subjects were at significantly higher CV risk at baseline, and it could be estimated that if all subjects had attended echocardiographic measurements the inverse association between adiponectin concentrations and LVMI could have been even more significant and could have had a favourable effect on the results. Concerning study III, the effects may have been unfavourable. If all the non-echocardiographically measured subjects had attended baseline echocardiographic measurements, the mean baseline LVMI could have been higher in the whole study group. Therefore, it is possible that the mean increase in LVMI over 20 years could have been smaller and could thus affect the results.

LVM was calculated with two methods, using the formulas of Devereux et al. (Devereux et al. 1986) (in studies I, II and IV) and Troy et al. (Troy et al. 1972) (in study III). Even though LVM calculations from these formulas may alter by more than 20% they are linearly correlated (Foppa et al. 2005), indicating that the formula chosen for calculating LVM does not affect the results.

The non-ABP measured subjects had only slightly higher triglycerides compared to the APB measured subjects. It is safe to say that while no significant differences were observed in the demographic and other laboratory findings, the CV risk profiles are quite identical and there is no effect on the results.

Comparing the study subjects based on whether dietary sodium intake could be estimated or not at baseline, it seems that the CV risk between these groups is different. Those whose sodium intake was not estimated were more often diabetics, had higher BMI and waist circumference, higher cumulative smoking amount, consumed more alcohol, had higher fasting glucose and triglycerides, and lower HDL cholesterol compared to those whose sodium intake was estimated. In study IV sodium consumption correlated positively with CV risk factors, therefore it is possible that mean sodium intake of the whole study group could have been higher.
if sodium intake could have been estimated in all participants. Since there was no difference in AF incidence between the sodium intake estimated and non-estimated groups, the results of study IV could have been less favourable. The association between sodium intake quartiles and the incidence of AF could have been diluted or could even be insignificant.

In the present study, the ABP recordings were performed over a single 24-h period. The reproducibility of circadian BP and dipping phenomenon cannot thus be analysed. It has been observed that the circadian BP variable pattern is non-reproducible in about one fourth of subjects (Cuspidi et al. 2004b). In our study the day- and night-times were fixed to certain hours and no data about subjects’ sleeping habits were acquired; it can therefore be considered a major limitation as asleep-awake BP analysis is not possible. Furthermore, the classification of non-dipping/dipping status may be uncertain because of the fixed margins and the lack of subjects’ sleeping habits. Another major concern is the lacking data on sleep apnoea, as sleep apnoea may affect the night-time BP values. A separate second 24-h APBM and a diary of actimetric recording would provide reliability to the circadian pattern.

6.2 Adiponectin and left ventricular mass index

In this study, only total adiponectin levels were measured. It has been suggested that different isoforms of adiponectin have different biological activities (Pajvani et al. 2003, Tsao et al. 2003, Waki et al. 2003). In particular, the ratio of high-molecular weight to total adiponectin may be a sensitive marker of the biological activity of adiponectin (Pajvani et al. 2004, Tonelli et al. 2004). Aso et al. suggested that the measurement of high-molecular weight form or its ratio to total adiponectin is preferred to total adiponectin in CV risk determination (Aso et al. 2006). Further, the ratio was observed to be significantly lower in patients with CAD than in healthy subjects (Kobayashi et al. 2004). In a study by Kozakova et al., total and high-molecular weight adiponectin were inversely associated with relative LV wall thickness, but not with LVM (Kozakova et al. 2008). None of the other prior studies have assessed the possible association between high-molecular weight adiponectin or its ratio to total adiponectin and measures of LVM. In several studies, total adiponectin has been negatively associated with the measures of LVM. However, whether the cardioprotective effects originate from high-molecular weight adiponectin or not remains unknown.
Low adiponectin concentrations have been described in conditions associated with insulin resistance, such as hypertension, overweight and diabetes (Adamczak et al. 2003, Hotta et al. 2000), which are also associated with LVH and cardiac remodelling. In the present study, the hypertensive cohort had higher BMI, higher BP and lower adiponectin concentrations compared to the control cohort. Blood glucose or the prevalence of diabetes were not considered in the present study. Adiponectin was an independent predictor of LVMI in the whole study group and in the hypertensive cohort when traditional risk factors of LVH were considered. Hypertension and obesity increase LVM, but the negative association between adiponectin and LVM seems to be partly independent of these factors. Adiponectin has been proven to have several beneficial CV effects in animal models (Smith & Yellon 2011). Adiponectin has also been shown to have athero-protective properties and to exert anti-inflammatory effects both on the vascular wall and directly on the myocardium in both in vitro and in vivo studies (Hajer et al. 2008, Maury & Brichard 2010, Smith & Yellon 2011). In addition, adiponectin has been shown to exert antihypertrophic effects in the cardiomyocyte in adiponectin-deficient mice (Shibata et al. 2004, Shibata et al. 2005), and Fujita et al. demonstrated that adiponectin protects against angiotensin II-induced cardiac fibrosis in mice, possibly by adenosine-monophosphate-activated protein kinase-dependent peroxisome proliferator-activated receptor-alpha activation (Fujita et al. 2008).

In the present study, the negative association between adiponectin concentrations and LVMI was observed only in the hypertensive cohort, indicating that adiponectin levels are downregulated in a state characterized by more advanced LVH. The results are quite opposite to the findings of two other studies. In a study among South Korean participants, adiponectin was negatively associated with LVMI in subjects with a low risk of LVH and positively associated with LVMI in subjects with a high risk of LVH (Lee et al. 2013). In the Jackson Heart Study conducted among African American participants, normotensive subjects exhibited an inverse association between adiponectin and LVMI, whereas participants with hypertension and insulin resistance had a direct association (Bidulescu et al. 2011). It is possible that the contradictory results could be explained by demographic or ethnic factors. Furthermore, it seems evident that the factors behind the regulation of adiponectin are not well understood and further studies are needed.
6.3 Ambulatory pulse pressure and cardiac remodelling

PP describes the oscillation around the MAP and it is influenced by three major factors: 1) the velocity of ventricular ejection, 2) the elastic properties of the arterial wall and 3) the timing of the reflected waves. As mentioned, PP increases during aging and is a predictor of CV morbidity and mortality. ABPM has proven to be a more accurate method in CV risk determination than clinical BP (Verdecchia 2000b). In the present study, APP and the increase in APP were found to predict the development of LVDD. The increase in APP was also found to be a predictor in the development of LVH. These findings are supported by previous research. The association between PP and LVDD (Perkiömäki et al. 2015, Trika et al. 2004, Zhang et al. 2015) and the association between PP and the measures of LVH (Baguet et al. 2000, Jokiniitty et al. 2001, Khattar et al. 1997, Khattar et al. 1999, Pannier et al. 1989, Rizzo et al. 2004, Zakopoulos et al. 2001) have been shown in prior studies.

In the present study, baseline higher age, female gender, the prevalence of diabetes, shorter stature, higher weight, higher in-office SBP and PP, and higher levels of NT-proANP were all risk factors for the development of LVDD. These risk factors are consistent with the ones observed in prior studies. Compared to subjects with heart failure with reduced ejection fraction (HFrEF), subjects with HfPfEF are older, have higher BMI, are more likely to be female, have higher BP (Owan et al. 2006, Steinberg et al. 2012), tend to be shorter (Moon et al. 2014, Perkiömäki et al. 2015) and have higher levels of atrial natriuretic peptide (Grandi et al. 2004).

The ratio of E/E’ was chosen in the present study, because it is considered one of the best measurements of diastolic dysfunction. Patients with present HfPfEF and E/E’ ≥ 15 after medical therapy are in increased risk of death and hospitalization due to HF (Okura et al. 2009).

In the present study, of the baseline characteristics, only in-office DBP and LVMI were observed to predict the change in LVMI during follow-up. Numerous studies have shown the association between BP and LVM. Other factors that have been associated with increased LVM are obesity (de Simone et al. 1994, Hammond et al. 1988, Levy et al. 1988), high salt diets (Schmieder et al. 1988) and diabetes (Devereux et al. 2000, Galderisi et al. 1991). The present study is the first to evaluate the risk factors concerning the change in LVMI during long-term follow-up, a matter to be taken into consideration when comparing to other studies.
One of the major determinants of PP is the elasticity of the aorta and major conduits. Stiffening of the aorta increases pulse wave velocity (O'Rourke et al. 2002), leading to earlier return of wave reflection from the periphery to the proximal part of the aorta, an increase in aortic systolic pressure and a decrease in aortic pressure during diastole (O'Rourke 2001). During LV systole the resulting increase in afterload and during LV diastole the relative reduction in coronary artery perfusion may endorse concentric LV remodelling and hypertrophy (Palmieri et al. 2003, Roman et al. 2000) and inhibit LV relaxation (Leite-Moreira et al. 1999). In addition, the onset of subendocardial hypoperfusion may lead to a further impaired myocardial relaxation and interstitial fibrosis with later reduction in LV compliance (Weber & Brilla 1991). Furthermore, even in the absence of CV risk factors, pulse wave velocity has been shown to rise at a constant rate up to the age of 40 years (McEniery et al. 2005), after which it increases at an accelerating rate (Reference Values for Arterial Stiffness' Collaboration 2010).

Furthermore, in the present study the increase in PP during the 20-year follow-up was associated with adverse cardiac remodelling. Elevated BP is a major cause of LVM increase (Ather et al. 2012, Payne et al. 2007), which favours the development of LVDD. In prior studies, a high baseline LVM has been a predictor for the development of hypertension, independently of standard risk factors (de Simone et al. 1991, Iso et al. 1994, Post et al. 1994). The increase in PP seen in the present study is highly likely a cause for compromised cardiac function.

6.4 Dipping pattern and cardiac remodelling

In the present study, the lack of at least 10% NF in BP was not associated with the development of LVDD. Instead, among those who presented a lack of at least 10% NF in DBP were observed to have greater increase in LVMI compared to those whose DBP NF was at least 10%. The phenomenon was observed to be independent of DBP, indicating that diastolic non-dipping status may be a predictor for the development of LVH. Large vessels are elastic and expand when the blood is pushed during heartbeats and contract again during heart rest. It is possible that the increased stiffness and loss of elasticity that reduce compliance of the large arteries (Ozawa et al. 2009) during night-time result in a rise in DBP, causing increasing load to the LV tissue in the long term. The present study is the first to suggest such an association. The present study has limitations, since the circadian BP profile was determined from a single 24-h ABPM. It has been shown that the circadian variable pattern is reproducible in only about three fourths of subjects (Cuspidi et al. 2004b).
6.5 Dietary sodium intake and atrial fibrillation

The present study was addressed to evaluate the potential effects of dietary sodium intake on the incidence of AF events. The results indicate that a high sodium intake is an independent risk factor for AF events in an initially middle-aged population of hypertensive and control subjects. Older age, higher BMI, smoking and higher SBP, LAD and LVMI were all considered as risk factors for the incidence of AF. The risk factors are similar to those shown in previous studies (Benjamin et al. 1994, Feinberg et al. 1995, Omae & Inada 2018, Psaty et al. 1997, Wang et al. 2004).

In previous studies, sodium intake has been associated with several CV morbidities, which are also closely related to AF. Numerous epidemiological and clinical studies have shown the association between sodium intake and elevated BP. A high sodium intake has been related to stroke, independently of BP (He et al. 1999, Tuomilehto et al. 2001). A high sodium intake has also been shown to be an independent predictor of LVM (Messerli et al. 1997). A sodium-restricted diet with other lifestyle changes has been shown to reduce LVM (Jula & Karanko 1994). In addition, compared to a sodium-restricted diet, a high sodium diet was shown to increase the relative risk of HF (He et al. 2002).

LVH has been shown to be an important risk factor for AF (Omae & Inada 2018, Psaty et al. 1997) and subjects with ECG-determined LVH were shown to have a 3-3.8 fold risk for new-onset AF (Kannel et al. 1998). There is evidence suggesting that left atrial enlargement (LAE) may develop in early hypertension and may develop before any signs of LVM increase (Ferrara et al. 1998, Miller et al. 1988, Tsioufis et al. 2006). LAE has been shown to increase the occurrence of AF (Kannel et al. 1998, Pritchett et al. 2005, Tsang et al. 2001, Vaziri et al. 1994). In the present study sodium intake correlated positively with LAD. Since a high sodium intake has been shown to increase LVM, it is possible that the mechanisms of sodium-dependent increase in LAD and LVM are the same. Sodium has been shown to have direct effects on myocardial cell protein synthesis, which may lead to myocardial hypertrophy (Gu et al. 1998, Popov et al. 2012). Atrial fibrosis (Frustaci et al. 1997, Ih & Saitoh 1982) and inflammation (Frustaci et al. 1997) have been suggested to be involved in the pathophysiology behind AF. Sodium intake is known to activate the renin-angiotensin-aldosterone system (RAAS) (Cappuccio et al. 1985, MacGregor 1987), which was observed to cause myocardial alterations, including interstitial fibrosis in Wistar rat studies (Ferreira et al. 2010, Hayakawa et al. 2015). Furthermore, in a more recent Wistar rat study,
it was suggested that the cardiac effects of high sodium diet were due to the activation of the myocardial tissue RAAS, instead of the circulating RAAS, which was rather suppressed than up-regulated (Katayama et al. 2014). Also, aldosterone has been shown to directly cause inflammation and fibrosis of the heart (Brown 2013). In addition, aldosterone excess acts synergistically with high sodium diets, which was associated with the increase of LAD (Selvaraj et al. 2017). In four different trials, the use of angiotensin receptor blockers was shown to reduce the risk of new-onset AF by 20-35% (Ducharme et al. 2006, Maggioni et al. 2005, Schmieder et al. 2008, Wachtell et al. 2005), strengthening the hypothesis that the activation of the RAAS is a mediator in the pathophysiology of AF. The possible sodium-mediated effects in the development of AF are presented in Figure 8.

Fig. 8. The possible mechanisms by which sodium intake may cause atrial fibrillation. Sodium has been shown to directly activate protein synthesis of myocardial cells, which may lead to left ventricular wall thickening, which may precede left atrial enlargement. Left atrial enlargement is a risk factor for atrial fibrillation. Sodium has also been shown to activate the renin-angiotensin-aldosterone system. Aldosterone has been observed to cause interstitial fibrosis and inflammation in the heart, which are suggested to be involved in the pathophysiology of atrial fibrillation.

The present study design has several limitations. The number of subjects in the study and the number AF events was fairly small. The determination of sodium intake was based on 7-day food records. It has been stated that dietary surveys underestimate dietary sodium intake by 30–50% due to difficulty in measuring
discretionary sodium use at the table and in cooking, underreporting, and incomplete food composition databases (Cobb et al. 2014, Ekinci et al. 2010). In addition, the sodium consumption was estimated only once at the beginning of the study, and it is highly possible that individuals change their sodium consumption during the long-term follow-up.

A different approach to estimating individual sodium intake is from urine samples, since it has been reported that typically, >90% of the consumed sodium by healthy individuals is recovered in urine (Liu & Stamler 1984, Luft et al. 1986). Overnight or spot urine samples are easier for participants but estimating sodium intake from these samples has been shown to be inaccurate compared to 24-h urine samples (Liu et al. 1979, Mann & Gerber 2010). Traditionally, the analytic gold standard to determine sodium intake has been a 24-h urine collection for sodium excretion (UNaV) (1988, Land et al. 2014). Quite recently, the accuracy of UNaV was challenged in 2 ultra-long sodium balance studies lasting 105 (4 men) and 205 (6 men) days (Lerchl et al. 2015). Dietary salt intakes of 12, 9 and 6 g/d were controlled for months and all urine was collected. Even at fixed salt intake, UNaV showed infradian rhythmicity indicating that single 24-h urinary collections at intakes ranging from 6 to 12 g of salt per day are not suitable for detecting a 3-g difference in individual salt intake. Seven repeated measurements of UNaV improved classification accuracy, but they concluded that weeks or even months are required before sodium output is similar to intake. In addition, the accuracy of UNaV was also challenged in a prior meta-analysis (Hooper et al. 2004). Hooper et al. indicated that the goals of sodium intake in salt trials were reduction of sodium intake below the range of <80 mmol/d to <100 mmol/d. However, such magnitudes of dietary sodium intake reduction in these salt studies reduced 24-h urinary sodium excretion by no more than 35 to 50 mmol/d, even though it has been estimated that the average sodium intake ranges from 150 to 200 mmol/d in Western societies (Titze & Ritz 2009). Furthermore, collection of 24-h urine causes a huge burden to participants and it has been shown that the samples are often incomplete (Stamler et al. 2003).

All of the studies addressing sodium intake and CVD face the same methodological issues as the present study. Estimating sodium intake has two approaches: 1) urine collections or 2) dietary surveys. Based on the studies by Lerchl et al. and Hooper et al., it seems that estimating sodium intake based on 24-h urine collections may not provide accurate information about actual sodium intake. Repeated UNaV may improve the accuracy, but further studies are required. Estimating sodium intake by dietary methods includes use of food records, 24-h
recalls and food frequency questionnaires. The reliability of these methods is based on how many days are assessed. As mentioned before, a significant underestimation in sodium intake has been reported in association with the use of dietary surveys. Furthermore, underreporting is often influenced by key variables (Prentice et al. 1986, Rennie et al. 2007), e.g. overweight subjects tend to underestimate their food intake compared to their lean counterparts.
7 Conclusions

The OPERA study began in the early 1990s and a follow-up visit was arranged 20 years after the study had begun. The initial data with a follow-up of 20-years is almost unique in the scientific world. The data still have several aspects that can be explored in the field of hard CV endpoints.

The present study was designed to assess novel points of view in the entity of cardiac remodelling. In this study the roles of adiponectin hormone, ABPM and dietary sodium intake were evaluated as predictors of cardiac remodelling. Adiponectin was shown to have a role in predicting LVMI, APP was shown to predict the development of LVDD, and increase in LVMI and dietary sodium intake was shown to increase the occurrence of AF events. All of these cardiac alterations share a common nominator, the LV. LV is the most important part of the CV system. As discussed earlier, several factors are involved in the remodelling of the LV. High BP, hypoadiponectinemia, high sodium intake etc. increase LVM, which is involved in the development of LVDD and LAE, which in addition, is associated with AF. What are the actual causes and consequences remains to be elucidated in further studies.

1. Adiponectin concentrations were measured at baseline and at follow-up. The predictive value of adiponectin and future CVD morbidity can and should be evaluated from the data. In this study, no measures of different adiponectin isoforms were available. It would be of particular importance to evaluate the predictive value of high-molecular weight adiponectin and its ratio to total adiponectin and future CVD morbidity. Adiponectin has been shown to associate with BP, endothelial function and CVD. The results from studies addressing the association between adiponectin and LVM in different ethnic groups have been controversial. In the present study, adiponectin levels were independent and inversely associated with LVMI in a middle-aged Caucasian population. Because adiponectin concentrations are inversely correlated with body adiposity, this finding indicates that low body adiposity may protect from the development of LVH. Further studies are needed to completely understand the factors behind the regulation of adiponectin and its impact on CVD. So far, adiponectin has been used for research purposes only; further studies are needed to assess its possible role in clinical use in detecting patients with elevated risk of CVD.
2. ABPM has shown its advantages over clinical BP in analysing 24-h BPV and in CVD risk determination. In the present study, 24-h, daytime and night-time PP predicted the development of LVDD. Also, the increase in these PP measures was associated with the development of LVDD and increase in LVMI during long-term follow-up. The advantages of ABPM-detected PP over clinical PP cannot be evaluated from the present study. Furthermore, the rise in PP is caused by large arterial stiffness and is most likely the cause for increasing LVM and the development of LVDD. Further studies addressing these issues are needed, and it remains to be seen whether patients with an increased PP would benefit from treatment targeting to lower PP.

3. The non-dipping phenomenon has been associated with LVH in prior studies. In the present study, diastolic non-dippers were observed to have a greater increase in LVMI compared to diastolic dippers during long-term follow-up. To rule out the possibility of chance in these results, further studies are needed to show whether the results are reproducible or not. Further studies are needed to evaluate whether treatment to target nocturnal DBP decline will have beneficial CVD outcomes.

4. Results from studies addressing the association between sodium intake and CVD have been controversial. The studies share methodological issues in estimating sodium intake regardless of whether sodium intake is estimated from urine samples or dietary surveys. Reliable sodium intake estimations cause a huge burden to participants in long food follow-up surveys and frequent 24-h urine collections. Novel methods to estimate sodium intake accurately are desperately needed. The present study offered a novel finding that a high sodium intake may increase the incidence of AF events, perhaps due to increased fibrosis and inflammation of the heart. This finding indicates that subjects with paroxysmal AF or who are at high risk of AF incidence may benefit from sodium restricted diet. Further studies are needed to verify this finding.
References


Koren MJ, Devereux RB, Casale PN, Savage DD & Laragh JH (1991) Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. Ann Intern Med 114(5): 345-352.


Clinical relevance of nighttime blood pressure and of daytime blood pressure variability. 
Arch Intern Med 152(9): 1855-1860.

Palmieri V, Bella JN, Roman MJ, Gerds E, Papademetriou V, Wachtell K, Nieminen MS, 
Dahlof B & Devereux RB (2003) Pulse pressure/stroke index and left ventricular 

Pannier B, Brunel P, el Aroussy W, Lacolley P & Safar ME (1989) Pulse pressure and 

blood pressure mean and variability to severity of target-organ damage in hypertension. 

heart rate variability in evaluating cardiovascular regulation. A critical appraisal. 

Paulus WJ, Tschope C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, Marino 
to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart 
failure with normal left ventricular ejection fraction by the Heart Failure and 
Echocardiography Associations of the European Society of Cardiology. Eur Heart J 
28(20): 2539-2550.

Payne JR, James LE, Eleftheriou KI, Hawe E, Mann J, Stronge A, Banham K, World M, 
Humphries SE, Pennell DJ & Montgomery HE (2007) The association of left 
ventricular mass with blood pressure, cigarette smoking and alcohol consumption; data 
from the LARGE Heart study. Int J Cardiol 120(1): 52-58.


Predictors of Development of Echocardiographic Left Ventricular Diastolic 
Dysfunction in the Subjects Aged 40 to 59 Years (from the Oulu Project Elucidating 

common is white coat hypertension? JAMA 259(2): 225-228.


genomic regulation of aldosterone-stimulated NHE1 activity in SHR renal proximal 


Original publications


Original publications are not included in the electronic version of the thesis.
1481. Kelloniemi, Annina (2018) Novel factors regulating cardiac remodeling in experimental models of cardiac hypertrophy and failure
1492. Karhula, Sakari (2018) Quantification of osteochondral tissue modifications during osteoarthritis using micro-computed tomography
1493. Kyönsöja, Elina (2018) Osteoclastogenesis from bone marrow and peripheral blood monocytes: The role of gap junctional communication and mesenchymal stromal cells in the differentiation

Book orders:
Granum: Virtual book store
http://granum.uta.fi/granum/
Tero Pääkkö

PREDICTORS OF LEFT VENTRICULAR HYPERTROPHY, DIASTOLIC DYSFUNCTION AND ATRIAL FIBRILLATION

THE ROLES OF ADIPONECTIN, AMBULATORY BLOOD PRESSURE AND DIETARY SODIUM INTAKE