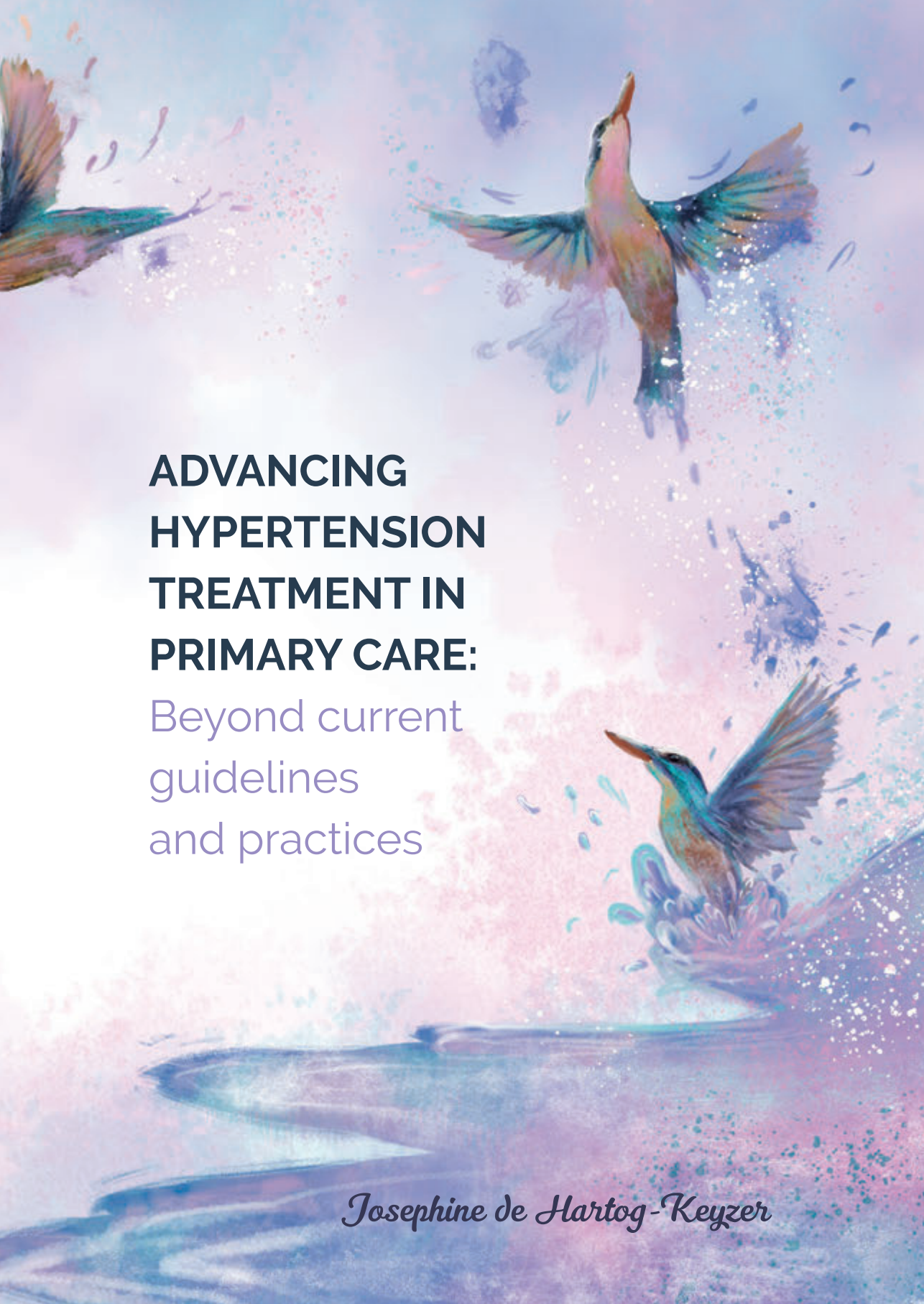

ADVANCING HYPERTENSION TREATMENT IN PRIMARY CARE:

Beyond current guidelines and practices

Josephine de Hartog-Keyzer

ADVANCING HYPERTENSION TREATMENT IN PRIMARY CARE

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Josephine Madeleine Louise de Hartog-Keyzer

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ADVANCING HYPERTENSION TREATMENT IN PRIMARY CARE

Beyond current guidelines and practices

Proefschrift ter verkrijging van de graad van doctor
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CHAPTER 1

General introduction
and outline of thesis

General introduction and outline of thesis

Epidemiological aspects of hypertension

Cardiovascular diseases (CVDs) are the leading cause of mortality worldwide, accounting for 32% of all global deaths[1]. In the Netherlands and Europe, CVDs hold the second position in mortality rates, surpassed only by cancer, accounting for 25% and 30% of all deaths, respectively[2]. Established risk factors for CVDs include hypertension, hypercholesterolemia, higher body mass index, smoking, and advancing age[3,4]. Worldwide, hypertension is a common and increasingly frequent condition in the general population[5], with a reported prevalence up to 62% in the adult population aged 60–70 years[6]. Hypertension is a complex multifactorial disorder involving the interplay of genetic, environmental, and lifestyle factors. The primary classifications of hypertension include essential (primary) hypertension and secondary hypertension, the first being the most prevalent form comprising about 90-95% of cases, while the latter is attributed to underlying medical conditions such as kidney disease, hormonal disorders, or medications[7]. Importantly, hypertension is often considered a "silent killer" as it is mostly asymptomatic in its early stages, making it challenging to diagnose without regular blood pressure measurements. Untreated or uncontrolled, hypertension can lead to serious complications such as coronary artery disease, heart failure, stroke, atrial fibrillation, peripheral artery disease and chronic kidney disease[8]. Moreover, hypertension's impact extends beyond the cardiovascular system, affecting cognitive function and increasing the risk of dementia and cognitive decline as well[8]. Clinical findings related to hypertensive heart disease include left ventricular hypertrophy (LVH), secondary left ventricular (LV) diastolic dysfunction and ultimately the development of heart failure, and increased mortality[9].

Effective management of hypertension involves lifestyle modifications, including adopting a balanced diet, reducing sodium intake, engaging in regular physical activity, and maintaining a healthy weight[10]. Pharmacological interventions, such as diuretics, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), calcium channel blockers, and other antihypertensive medications, are also commonly prescribed to control blood pressure and reduce the risk of associated cardiovascular events[11].

In conclusion, hypertension represents a significant global health challenge, contributing to the burden of cardiovascular diseases and related mortality rates. By understanding the underlying mechanisms, risk factors, and effective

management strategies for hypertension, healthcare professionals can improve early detection, prevention, and intervention efforts, leading to better patient outcomes and reduced morbidity and mortality associated with cardiovascular diseases.

Psychological distress in hypertension patients: an additional risk factor for future CVE

There is an increasing interest in the role of psychological distress as an additional risk factor for developing cardiovascular diseases, also in hypertension patients. Psychological distress can be defined as "a state of emotional suffering characterized by symptoms of depression and anxiety sometimes accompanied by somatic symptoms"[12]. Nowadays in the Netherlands, patients with (uncomplicated) hypertension are mainly managed in primary care according to the national guidelines[13]. However, these guidelines have limited focus on the psychological well-being and distress of patients with hypertension, despite their potential influence on future cardiovascular events (CVEs). In recent decades, research mainly focused on hospital patients regarding psychological distress as a potential risk factor for cardiovascular diseases (CVDs). However, the role of psychological distress in primary care remains unclear[14,15]. Primary care studies have primarily examined the association between psychological distress and the occurrence of a second event after an initial cardiovascular event[16-18]. Since 2012, the European Society of Cardiology has recognised psychosocial factors, including psychological distress, anxiety and depression, as potential risk factors for CVDs with Class IIa, Level B evidence[19,20]. Depression and anxiety in cardiovascular patients are associated with a higher incidence of CVDs and increased costs[21]. The coexistence of hypertension and psychological distress might have a negative synergistic effect on future CVEs. Affective disorders like depressive and anxiety disorders can be seen as stress disorders where key neural circuits that regulate stress reactivity are not functioning optimally[22]. An extensive review in the European Heart Journal listed the potential factors that could explain the relationship between cardiovascular disease and depression and anxiety[23], see **Figure 1.** While the guidelines recommend psychological screening in outpatient cardiology practice, its implementation remains limited in Europe, and its relevance in primary care cardiovascular risk management is not well understood.

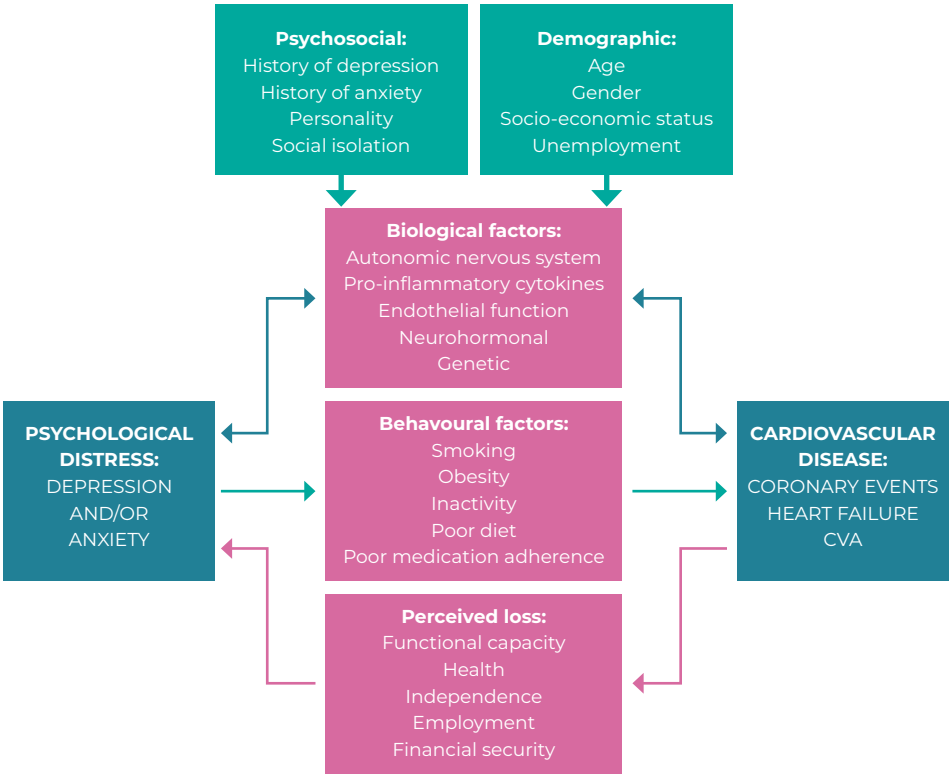

Figure 1. Potential factors that could explain the relationship between depression and/or anxiety and cardiovascular disease.

Adapted from Hare *et al.*[23].

More attention to additional diagnostics in asymptomatic patients with hypertension

Early detection of heart failure with Brain Natriuretic Peptide (BNP)

Hypertension, especially long-standing and inadequately managed hypertension, can lead to chronic heart failure (CHF). CHF is a condition in which the cardiac pump is unable to meet the demands for adequate circulation of the blood[24]. It is a common disorder with a prevalence of 1%–2% in developed countries[25]. In individuals aged 55 years, 30% will develop CHF during their remaining lifespan according to The Rotterdam Study[9]. Over the past decades, CHF prevalence has increased worldwide and due to ageing of the population, it is anticipated that the absolute number of patients with heart failure will increase by 46% in 2030[26].

Ideally, one would like to identify people at an early stage who are at high risk of developing heart failure in order to prevent fulminant (irreversible) heart failure by means of strict blood pressure regulation. One of the most important biomarkers used in the identification and follow-up of patients with heart failure is Brain Natriuretic Peptide (BNP). BNP is one member of the family of natriuretic peptides that were initially discovered by de Bold *et al.*[27]. BNP is synthesized and released into the blood in response to volume overload or conditions that cause ventricular stretch, in order to control fluid and electrolyte homeostasis by interaction with the renin- angiotensin-aldosterone system[28,29]. Plasma concentrations of BNP are consistently elevated in heart failure, but are not markedly elevated in other conditions that cause dyspnea and fatigue, such as chronic obstructive pulmonary disease[30,31], making it an ideal screening tool for cardiac dysfunction.

For the last three decades BNP is progressively used as a diagnostic tool for the identification and follow-up of patients with heart failure[32-35]. Nowadays, BNP is used in primary care in patients with signs and/or symptoms of heart failure. The guidelines for heart failure, both national and international, apply two single cut-off BNP levels for gradually and acute onset heart failure: 10 pmol/L (35 pg/mL) and 29 pmol/L (100 pg/mL), respectively[36,37]. No distinction is made for gender and age. For N-terminal proBNP (NT-proBNP), the closely related (inactive) peptide that remains after BNP is cleaved from the genuine precursor proBNP[38], it has clearly been demonstrated that the plasma levels vary according to gender, age, diabetic status and renal function[39-45]. As for BNP, only a few studies in the USA described the influence of age and gender on BNP, however both with a small study population[46,47].

According to the current heart failure guidelines[36,37], primary care patients with BNP above a specific cut-off should undergo further diagnostics, regardless of age and gender. However, using a single cut-off for BNP without considering age and gender might lack specificity in daily practice. The established cut-off aims to maximize sensitivity, potentially leading to numerous false positive cases at higher ages and unnecessary referrals to cardiologists for older patients. Consequently, there is a need to investigate whether there is added value in adjusting the reference values.

Left ventricular hypertrophy: ECG and echocardiography

Another clinical finding related to hypertensive heart disease is left ventricular hypertrophy (LVH), associated with a two- to fourfold increased risk of cardiovascular morbidity and mortality compared to patients with normal LV mass[48]. Achieving adequate blood pressure control is crucial to reduce

hypertension-mediated organ damage. In the Netherlands, general practitioners follow the national guidelines for CV risk management[13]. These guidelines are conservative in recommending additional testing to screen for LVH, such as standard ECG and/or echocardiography. Especially in cases of long-standing hypertension with known high morbidity and mortality, one may hypothesize that LVH should be recognised using the most reliable method available[49], in order to intensify the regulation of blood pressure so that LVH can be modified in time[50,51]. This will hopefully increase patient awareness and adherence to therapy. However, the value of ECG and/or echocardiography screening in primary care patients with hypertension has not been fully elucidated. Although ECG can detect an increase in myocardial wall thickness[51,52], its sensitivity to diagnose LVH in the general population is low compared to echocardiography[53,54]. It is also suggested that LVH detected using ECG and LVH detected using echocardiography are two distinct entities that only partially overlap and have different prognostic significance[55]. It remains unclear whether performing an electrocardiogram is sufficient to detect left ventricular hypertrophy, or if an echocardiogram would be required, or even if a combination of both would be the optimal choice. Given the current lack of knowledge and insufficient research in this area, this is a topic that needs to be addressed, especially in general practice.

Diagnostic tests to determine prognosis in asymptomatic patients with hypertension

Accurate risk stratification to identify those at high risk for future cardiovascular events in the primary care population with asymptomatic hypertension would be desirable. Screening for hypertensive-mediated organ damage is crucial, as highlighted by the World Health Organization. The presence of LVH on ECG has shown to be of prognostic value, but the sensitivity and specificity of ECG to detect LVH may be limited. Therefore, echocardiography has become the routine gold-standard to detect LVH[53,54]. Furthermore, there is growing interest in measuring BNP to stratify CV disease risk in patients with hypertension[57]. However, limited literature exists on the benefits of BNP assessment in elderly patients with hypertension without symptoms or signs of heart failure.

Primary care physicians play a critical role in the detection, risk stratification and treatment of patients with hypertension. The current European general practitioner guidelines for the management of hypertension, does recommend an ECG at the start of treatment but no other additional diagnostic tests, like echocardiography and/or the assessment of BNP[58,59]. The Dutch guidelines

do not recommend any routine investigation at diagnosis of hypertension[13]. It is conceivable that, even in patients with hypertension without symptoms, assessment of BNP, ECG and echocardiography may be valuable in predicting future cardiovascular disease (CVD).

Outline of this thesis

The general aim of the thesis focuses on cardiovascular risk assessment of asymptomatic elderly patients with (essential) hypertension in primary care. More specifically, we investigate several factors that may predict the development of cardiovascular events in patients with hypertension. These factors, such as psychological distress, BNP, ECG and echocardiography, are yet not well investigated or implemented in the current CVRM guidelines. With this thesis, we hope to shed a light on these factors beyond guidelines and current practices, contributing to advanced cardiovascular risk management in primary care (**Figure 2**).

In *the first part* we focus on the role of anxiety and depression symptoms as an additional risk factor in patients with hypertension for developing cardiovascular events and all-cause mortality.

Therefore, in **Chapter 2,** we determine the association between anxiety and/or depression symptoms in a sample of elderly patients with hypertension in the primary care setting and the subsequent development of new cardiovascular events at 8 years' follow-up. Additionally, we will assess the possible relation between anxiety and/or depression symptoms and all-cause mortality.

In *the second part,* we focus on additional diagnostic tools and their potential role in advancing cardiovascular risk management.

First, in **Chapter 3**, we present age- and gender-specific cut-off levels for BNP based on a large cohort of individuals referred to a primary care laboratory for BNP assessment.

Secondly, in **Chapter 4**, we investigate the prevalence of LVH in elderly primary-care patients with long-standing asymptomatic hypertension and the diagnostic value of ECG as a screening tool in the detection of LVH compared to echocardiography in this specific patient population.

Finally, in **Chapter 5**, we investigate, in the same cohort, the predictive value of LVH on ECG and/or on echocardiography and/or an elevated BNP for the development of future cardiovascular events (CVEs) and all-cause mortality in asymptomatic primary care patients with long-standing hypertension. The prospective design enables follow-up data up to nine years.

Finally, in the general discussion, **Chapter 6,** we review the results found and discuss their implications for practice and give recommendations for future research. **Chapter 7**, summarises the main results and conclusions of the studies presented in this thesis. Both an English and a Dutch summary are provided.

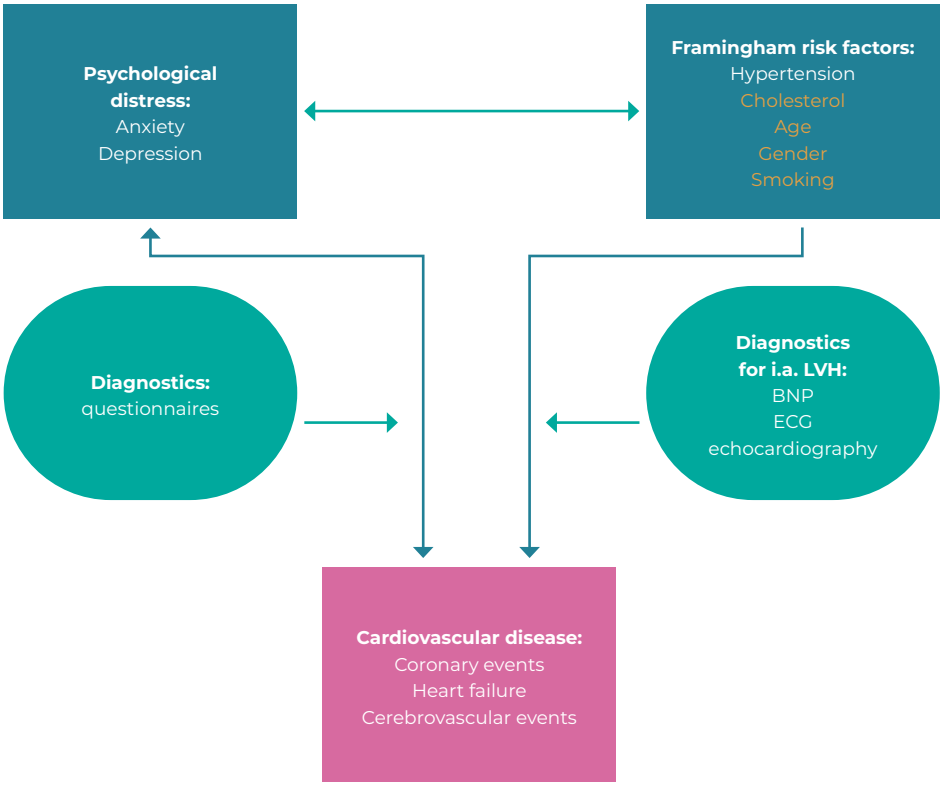

Figure 2. Several factors, such as psychological distress, BNP, ECG and echocardiography, that may predict the development of future cardiovascular diseases in hypertension patients.

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PART ONE:

Psychological distress in hypertension patients: an additional risk factor for future CVE



CHAPTER 2

Psychological distress is independently related to new coronary events at 8 years' follow-up in elderly primary care patients with hypertension

Journal of Psychosomatic Research, 2022

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Abstract

Objective

Occurrence of psychological distress in patients with hypertension could have a negative synergistic effect on future cardiovascular events (CVEs). The aim of this study was to determine the association between anxiety or depressive symptoms in elderly hypertensive primary care patients and the development of new CVEs and all-cause mortality.

Methods

A prospective cohort study was conducted in five Dutch general practices between June 2010 and January 2012. Patients with primary care managed hypertension, aged 60–85 years, were included and completed the GAD-7 and PHQ-9, measuring anxiety and depressive symptoms respectively. The incidence of new CVEs (coronary event, cerebrovascular disease, atrial fibrillation and heart failure) and all-cause mortality at 8 years' follow-up was recorded by data extraction of the digital information systems.

Results

Among the 555 included participants (mean age 70 ± 6.6 years; 56% female), 29 (5.2%) had a new coronary event, 42 (7.6%) a cerebrovascular disease, 57 (10.3%) atrial fibrillation, 22 (4%) heart failure and 68 (12.3%) died. Elevated anxiety and depression scores increased the risk of a coronary event independently and significantly by 12% (HR 1.12; 95% CI [1.04–1.22], $p = 0.005$) and 18% (HR 1.18; 95% CI [1.08–1.28], $p < 0.0001$), respectively, adjusted for relevant (Framingham) baseline covariates. No associations were found with regard to other CVEs and all-cause mortality.

Conclusion

In a random sample of elderly primary care hypertension patients there was a significant association between psychological distress and the occurrence of new coronary events after 8 years' follow-up but not with other CVEs and all-cause mortality.

Introduction

Cardiovascular diseases (CVDs) are the most common causes of death worldwide, representing 32% of all global deaths[1], and comprises the second cause of deaths in the Netherlands and Europe after cancer, respectively, representing 25% vs. 30% of all deaths in the Netherlands[2]. Well-known risk factors for CVDs are hypertension, hypercholesterolemia, higher body mass index, smoking and increasing age[3,4]. Hypertension is very common in the general population (22%)[5] and increases with age[6]. Hypertension is also an important facet of the Framingham risk profile of CVD[4]. Nowadays in the Netherlands, patients with (uncomplicated) hypertension are primarily treated in primary care within the context of the cardiovascular risk management program (CVRM). Within this primary care program, until now, there is little if any focus on psychological well-being and psychological distress of patients with hypertension as a risk factor for the development of future cardiovascular events (CVEs).

In recent decades, research has primarily focused on hospital (out)-patients with regard to psychological distress as a possible risk factor for CVDs. The possible role of psychological distress in primary care is still unclear[7,8], and primary care studies have mainly focused on the possible association between psychological distress and the occurrence of a second event after a first cardiovascular event[9-11]. Since 2012, the European Society of Cardiology included psychosocial factors – such as psychological distress, anxiety and depression – in their guidelines[12,13] as potential risk factors for CVD with a Class IIa, Level B evidence. Anxiety and depression in cardiovascular patients are related to a higher incidence of CVDs and increased costs[14]. The occurrence of both hypertension and psychological distress could have a negative synergistic effect on a future CVE. Although, the guidelines recommend psychological screening in the outpatient cardiology practice, this is far from implemented in cardiology practices in Europe, and its possible relevance in the primary care cardiovascular risk management program is even unknown.

Therefore, the aim of the current study was to determine the association between anxiety and/or depression symptoms in a sample of elderly patients with hypertension in the primary care setting and the subsequent development of new CVEs at 8 years' follow-up. The secondary aim was to determine the possible relation between anxiety and/or depression symptoms and all-cause mortality.

Methods

Participants

Patients in the current study were enrolled in the Chello cohort study (Chronic Heart Failure Prevention Program), of which the inclusion and exclusion criteria of participants have been described in detail elsewhere[15,16]. In short, primary care patients aged between 60-85 years diagnosed with essential hypertension were recruited for the Chello study from five general practices affiliated with the primary care organization PoZob[17], between June 2010 and January 2012. Exclusion criteria were previous diagnosis of heart failure, current treatment by a cardiologist and history of severe psychiatric illness other than mood or anxiety disorders. The study protocol was approved by the medical ethics committee of the Elisabeth Hospital in Tilburg, the Netherlands (NL38933.008.12).

Psychological assessments at baseline

Participants completed 2 standardized and validated questionnaires at study enrollment. Anxiety symptoms were assessed with the 7-item Generalized Anxiety Disorder scale (GAD-7)[18,19]. The 7 items are rated on a 4-point Likert scale, range 0-21, referring to the previous 2 weeks, with a higher score indicating more symptoms. A cut-off ≥ 8 is considered suitable for the detection of severe generalized anxiety disorder as well for the detection of any severe anxiety disorder for individuals, ≥ 18 years old, in primary care[18]. The GAD-7 has previously been validated in The Netherlands, showing adequate reliability (Cronbach's Alpha of 0.92)[20]. The Cronbach's Alpha of the GAD-7 questionnaire in the current study was 0.84.

Depression symptoms were assessed with the Patient Health Questionnaire 9 (PHQ-9)[21-24]. The PHQ-9 is a self-report questionnaire that consists of nine items that correspond to the DSM-V criteria for a depressive episode referring to the previous two weeks, with answers indicated on a 4-point Likert scale. The score range is from 0-27, with a higher score indicating more symptoms. The PHQ-9 has been validated in primary care populations (≥ 18 years old), with a cut-off of ≥ 5 and ≥ 10, indicative of mild and major depression, respectively[21,24,25] also in the Netherlands showing adequate reliability (Cronbach's Alpha of 0.88)[26]. The Cronbach's Alpha of the PHQ-9 questionnaire in the current study was 0.75.

The Incidence of new cardiovascular events and all-cause mortality

In order to evaluate the incidence of new CVEs and all-cause mortality, a data extraction of the digital general practitioner (GP) information system was performed at 8 years' follow-up. Every GP in the Netherlands uses standard

diagnosis codes for data entry into the electronic patient record form: international classification of primary care (ICPC). The specific codes for CVD were extracted from the digital systems at follow-up. After inclusion, the occurrence of the following CVDs and deaths has been registered: the development of coronary events (acute coronary syndrome; unstable angina pectoris or acute myocardial infarction), heart failure, atrial fibrillation, cerebrovascular diseases (transient ischemic attack and cerebrovascular accident (CVA)) and all-cause mortality with respectively ICPC codes: K74, K75, K77, K78, K89, K90 and A96.

Statistical analyses

When comparing differences between groups, the Chi-square test was used for dichotomous variables and a Student's t-test for continuous variables. In case a variable was not normally distributed, a non-parametric test Mann-Whitney U was applied[27]. Multivariable Cox regression analyses was used to analyze the predictive value (Hazard ratios and 95% confidence intervals) of elevated anxiety and depression scores on developing a coronary event. Baseline covariates used: previous coronary events, use of antihypertensive medication, Framingham risk variables[4] (age, gender, smoking, cholesterol, systolic blood pressure) and Body Mass Index. Single logistic regression analyses (odds ratio, 95% CI) and diagnostic parameters (sensitivity, specificity and positive predictive value (PPV)) were performed with new coronary events at follow-up as dependent variable and depressive and anxiety symptoms scores at baseline as independent variables. All data were analyzed with commercially available statistical software (IBM SPSS Statistics Version 26).

Results

Study Population

At baseline, a total of 592 participants provided written informed consent. For the current study, we excluded 3 patients with missing baseline information. At 8 years, of the remaining 589 participants, 34 patients were lost to follow-up. Baseline characteristics of patients who dropped out were similar to those who participated in the follow-up period. Therefore, data analyses in the current study include 555 patients.

Baseline characteristics

Baseline demographics of the patient cohort are displayed in Table 1. The mean age was 70 years (±6.6) and 56% of the study population was female, most participants (>75%) had a partner and 13% had a low (only primary) educational level. Regarding to lifestyle, 12% were active smokers and 32% regularly consumed alcohol. With regard to risk factors, 11% had diabetes, 5% had a previous myocardial infarction, 23% had a LDL cholesterol level on target (28) and 41% had a systolic blood pressure on target, according to the National Dutch guideline (28), see footnotes Table 1. A previous episode of depression or anxiety was found in 13% and 4% of the patients, respectively.

The scores on the GAD-7 and PHQ-9 were not normally distributed, with a skewness of respectively 2.7 and 2.2 and a Kurtosis of 8.8 and 6.3. The median scores for GAD-7 and PHQ-9 scores were respectively 1.0 [0-3.0] vs. 1.0 [0-3.0]. The correlation coefficient between GAD-7 and PHQ-9 scores was: r = 0.56 (Spearman, p < 0.001, large effect size). The cut-offs of the GAD-7 (≥8) and PHQ-9 (≥ 5) in the literature corresponded respectively to the 96th and the 84th percentile in this study cohort of elderly primary care patients. There was no significant difference in elevated anxiety scores (GAD-7 ≥8) between men (M=0.04, SD= 0.19) and women (M=0.06, SD=0.23 t (553) = 1.18, *P*=0.239). There was also no significant difference in elevated depression scores (PHQ-9 ≥ 5) between men (M=0.01, SD=0.11) and women (M=0.03, SD=0.18, t (553) = 1,56, *P*=0.119). The characteristics of the current sample did not differ from the original Chello cohort (15, 16) and patients who were lost to follow-up did not differ on age and gender.

CVEs and all-cause mortality during 8 years' follow-up

Table 2 shows the incidence of new CVEs and all-cause mortality during 8 years' follow-up. Of the participants, 29 (5.2%) had a new coronary event (unstable angina pectoris, acute myocardial infarction) during follow-up, 42 (7.6%) cerebrovascular disease (transient ischemic attack, cerebrovascular accident), 57 (10.3%) atrial fibrillation, 22 (4%) heart failure and 68 died (12.3%). For all CVEs and all-cause mortality no differences were found according to gender.

Psychological distress scores in relation to CVEs and all-cause mortality

Table 3 shows the median [IQR] scores on the GAD-7 and PHQ-9 at baseline, stratified by new CVEs and all-cause mortality. Patients who developed a coronary event had significantly higher median anxiety (Md=3.0, U=9763, z=2.69, *P*=0.007, r=0.11) and depression symptom scores (Md=2.0, U=9212, z=1.97, *P*=0.048, r=0.08) at baseline compared to those who did not develop a coronary event. No significant associations were found with regard to other CVEs and all-cause mortality.

Table 1. Baseline demographics of 555 hypertensive primary care patients with 8 years' follow-up

Characteristic	n (%)	mean (SD)	median [IQR]
Demographics			
Age, years		69.9 ± 6.5	
Female	309 (55.7)		
Male	246 (44.3)		
Socio-economics			
Having a partner	418 (75.3)		
Low education *	73 (13.2)		
Lifestyle			
Current smoker	69 (12.4)		
Regular alcohol use **	175 (31.5)		
Recommended physical exercise ***	81 (14.6)		
Clinical characteristics and risk factors			
Previous myocardial infarction	27 (4.9)		
Previous CVA (TIA / stroke)	50 (9.0)		
Diabetes	59 (10.6)		
BMI, kg/m^2		28.0 ± 4.4	
SBP, mmHg		150.1 ± 19.4	
DBP, mmHg		82.1 ± 10.4	
Blood pressure on target +	223 (40.5)		
Use of antihypertensive medication	427 (76.9)		
Total cholesterol, mmol/L		5.1 ± 1.0	
LDL, mmol/L		3.1 ± 0.9	
LDL on target ++	130 (23.4)		
Use of cholesterol lowering medication	239 (43.1)		
Anxiety/depression (with overlap)			
Previous diagnosis of anxiety	20 (3.6)		
Previous diagnosis of depression	73 (13.2)		
Anxiety / depressive symptoms score at baseline			
GAD-7 score			1.0 [0-3.0]
PHQ-9 score			1.0 [0-3.0]
Use of anxiolytic medication	35 (6.3)		
Use of antidepressant	28 (5.0)		

Table 1. Continued

Values for categorial variables are given as number (percentage); values for continuous variables are given as mean ± standard deviation. Scores on the GAD-7 and PHQ-9 were not normally distributed, with a skewness of respectively 2.7 and 2.2 and a Kurtosis of 8.8 and 6.3. Therefore, we used Mann-Whitney U test [median, inter quartile range].
** only primary elementary educated. ** defined as ≥ 2 glasses of alcohol per day on average. *** defined as ≥ 30 min exercise per day, at least 5 days per week.*
+ on-target systolic blood pressure defined as <140mmHg for persons aged less than 70 years and <150mmHg for persons aged 70 years or older, according to Dutch primary care guideline[28]. ++ on-target LDL defined as <1.8 mmol/L for persons aged less than 70 years and previous CVD, <2.6 mmol/L for persons aged less than 70 years without previous CVD and <2.6 mmol/L for persons aged 70 years or older, according to the Dutch primary care guideline[28].
Abbreviations: CVA, cerebrovascular accident; TIA, transient ischemic attack; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein; GAD-7, generalized anxiety disorder-7; PHQ-9, patient health questionnaire-9; CVD, cardiovascular disease.

Table 2. Incidence of new cardiovascular events and death at 8 years follow up

Cardiovascular event and death	**Total n=555**	**Men n=246**	**Women n=309**	***P*-value**
	n (%)	**n (%)**	**n (%)**	
Coronary event	29 (5.2%)	15 (6.1%)	14 (4.5%)	0.410
Myocardial infarction	8 (1.4%)	2 (0.8%)	6 (1.9%)	0.268
Unstable angina pectoris	21 (3.8%)	13 (5.3%)	8 (2.6%)	0.468
Cerebrovascular disease	42 (7.6%)	21 (8.5%)	21 (6.8%)	0.441
TIA	21 (3.8%)	10 (4.1%)	11 (3.6%)	0.913
Stroke	21(3.8%)	11 (4.5%)	10 (3.2%)	0.449
Atrial fibrillation	57 (10.3%)	28 (11.4%)	29 (9.4%)	0.441
Heart failure	22 (4.0%)	8 (3.3%)	14 (4.5%)	0.443
All-cause mortality	68 (12.3%)	34 (13.8%)	34 (11.0%)	0.315

Abbreviations: TIA, transient ischemic attack

Table 3. Median [IQR] anxiety and depression scores in relation to development of a CVE and all-cause mortality at 8 years follow-up

Cardiovascular event and all-cause mortality		Anxiety GAD-7 score			Depression PHQ-9 score		
		n	median [IQR]	*P*	n	median [IQR]	*P*
Coronary event	+	29	3.0 [0-6.5]	**0.007**	29	2.0 [0-7.0]	**0.048**
	-	526	1.0 [0-2.0]		526	1.0 [0-3.0]	
Cerebrovascular disease	+	42	1.0 [0-3.0]	0.706	42	1.0 [0-3.0]	0.977
	-	513	1.0 [0-3.0]		513	1.0 [0-3.0]	
Atrial fibrillation	+	57	1.0 [0-2.5]	0.861	57	1.0 [0-3.0]	0.973
	-	498	1.0 [0-3.0]		498	1.0 [0-3.0]	
Heart failure	+	22	1.0 [0-1.3]	0.530	22	1.0 [0-3.3]	0.514
	-	533	1.0 [0-3.0]		533	1.0 [0-3.0]	
All-cause mortality	+	68	0.5 [0-2.0]	0.207	68	1.0 [0-3.0]	0.754
	-	487	1.0 [0-3.0]		478	1.0 [0-3.0]	

Abbreviations: CVE, cardiovascular event; GAD-7, generalized anxiety disorder-7; PHQ-9, patient health questionnaire-9.

Anxiety and depression scores in relation to coronary events

We performed multivariable Cox regression analyses to analyze the association of elevated anxiety and depression scores on developing a coronary event, adjusting for relevant covariates like previous coronary events, use of antihypertensive medication, age, gender, smoking, cholesterol, systolic blood pressure and Body Mass Index. Elevated anxiety scores (GAD-7) increased the risk of a coronary event independently and significantly by 12 % (HR 1.12; 95% CI [1.04-1.22], *P*=0.005). Elevated depression scores (PHQ-9) increased the risk of a coronary event independently and significantly by 18% (HR 1.18; 95% CI [1.08-1.28], p<0.0001). To evaluate if all-cause mortality was not a competing risk we performed a sensitivity analysis, excluding all patients who had died during follow-up and we repeated the Cox regression analyses again, with similar results: elevated GAD-7 and PHQ-9 scores showed HR 1.12; 95% CI [1.03-1.22], *P*=0.006 and HR 1.15; 95% CI [1.06-1.26], *P*=0.001 respectively.

We subsequently defined subgroups of patients according to anxiety and depression scores using the cut-offs reported in the primary care literature. In single logistic regression analysis, patients with *both* GAD-7 (≥8) and PHQ-9 (≥5) scores above the cut-offs were 5.5 times more likely to develop new coronary

events compared to those without elevated scores (OR 5.5; 95% CI: 1.68-17.81). However, these cut-offs refer to general primary care patients over 18 years and it is well known that in elderly patients, psychological distress is much less prevalent[29] and the female / male ratio changes[30]. Also, GAD-7 cut-off of ≥8 refers to severe anxiety disorder while the PHQ-9 cut-off of ≥5 refers to minor depression. This is also reflected in the current sample: the GAD-7 cut-off of ≥8 reflects the 96th percentile, while the PHQ-9 cut-off of ≥5 reflects the 84th percentile. This suggests that especially the cut-off of the GAD-7 seems too high for this elderly primary care population. Therefore, we looked at the possible association of new coronary events at follow-up and sub-groups of patients with both high anxiety and depression symptom scores using several cut-offs, see Table 4. Already, GAD-7 scores ≥2 (reflecting the 63rd percentile) and PHQ-9 scores ≥3 (reflecting the 69th percentile) significantly increased the likelihood of new coronary events at follow-up. The higher the cut-off the higher the specificity and the lower the sensitivity – the PPV was overall rather low. The combination of diagnostic parameters was most optimal when we used the 75th percentile cut-off of the GAD-7 (≥3) and the PHQ-9 (≥4), reflecting anxiety / depression symptom scores in the highest quartiles, with a sensitivity of 52% and 41%, a specificity of 76% and 79% respectively. Though the PPV values were low with 11 and 10% respectively.

Table 4. Different cut-off scores of GAD-7 and PHQ-9 in relation to a new coronary event

	n (total = 555)	percentiles	OR (95% CI) for new coronary event	*P*-value	sensitivity	specificity	PPV
GAD-7 ≥ 1	295	47th	1.72 (0.79-3.77)	0.171	66%	48%	6%
GAD-7 ≥ 2	206	63rd	2.53 (1.17-5.40)	0.014	59%	64%	8%
GAD-7 ≥ 3	143	75th	3.33 (1.57-7.09)	0.001	52%	76%	11%
GAD-7 ≥ 4	100	83rd	4.10 (1.90-8.83)	<0.001	45%	83%	13%
GAD-7 ≥ 5	63	89th	3.93 (1.71-9.07)	0.001	31%	90%	14%
GAD-7 ≥ 6	45	92nd	5.04 (2.09-12.14)	<0.001	28%	93%	18%
GAD-7 ≥ 7	34	94th	5.88 (2.31-14.97)	<0.001	24%	95%	21%
GAD-7 ≥ 8	27	96th	3.50 (1.12-10.89)	0.022	14%	96%	15%
PHQ-9 ≥ 1	313	44th	1.50 (0.68-3.29)	0.309	66%	44%	6%
PHQ-9 ≥ 2	243	57th	1.62 (0.76-3.44)	0.204	55%	57%	7%
PHQ-9 ≥ 3	173	69th	2.15 (1.02-4.57)	0.041	48%	70%	8%
PHQ-9 ≥ 4	125	78th	2.58 (1.20-5.56)	0.013	41%	79%	10%
PHQ-9 ≥ 5	89	84th	2.98 (1.34-6.64)	0.005	35%	85%	11%
PHQ-9 ≥ 6	65	89th	3.78 (1.64-8.70)	0.001	31%	89%	14%
PHQ-9 ≥ 7	48	92nd	4.63 (1.93-11.11)	<0.001	28%	92%	17%
PHQ-9 ≥ 8	33	95th	3.71 (1.31-10.44)	0.008	17%	95%	15%
PHQ-9 ≥ 9	24	96th	2.78 (0.78-9.90)	0.102	10%	96%	13%
PHQ-9 ≥ 10	13	98th	5.95 (1.55-22.94)	0.003	10%	98%	23%

Abbreviations: GAD-7, generalized anxiety disorder-7; PHQ-9, patient health questionnaire-9; PPV, positive predictive value

Discussion

Summary

The current study indicates an association between psychological distress and the occurrence of new coronary events after 8 years' follow-up in a random sample of elderly (60-85 years) primary care patients with hypertension in the Netherlands. Patients with both anxiety and depression symptom scores above cut-offs are especially more likely to develop a new coronary event during 8 years of follow-up compared to those without elevated symptom scores at baseline. This association existed at much lower symptom cut-off scores on the general anxiety scale (GAD-7) as generally reported in primary care settings. No associations were found between baseline anxiety / depression symptoms and the development of other CVEs and all-cause mortality.

Strengths & Limitations

One strength of the current study is the relatively large primary care sample with carefully registered follow-up data up to 8 years of follow-up. This enabled us to evaluate possible associations between distress symptoms and the development of new coronary events at different cut-offs, lower as commonly reported in the literature.

A limitation of this study is that we measured anxiety and depression scores at a symptom level instead of syndromal level. However, the DSM-V advocates more focus now on intensity of distress symptoms rather than using syndromal diagnoses[31,32]. Furthermore, we only assessed the psychological symptoms scores at baseline and did not repeat the assessment during 8 years of follow-up. However, a study conducted by Denollet *et al.* showed that only one measurement of anxiety scores at baseline predicted premature all-cause and cardiovascular death in middle-aged women[33].

Another limitation is the fact that we only have data on all-cause mortality and not data on cardiac death. Therefore, we are unable to specify reasons for dropout due to cardiac death. This is mainly to be explained by ethical limitations considering privacy of centrally registered mortality causes in the Netherlands.

Furthermore, elevated GAD-7 and PHQ-9 scores significantly increased the likelihood of new coronary events at follow-up but the PPV values at different cut-off's were overall rather low. Although we had a large sample size, the number of new coronary events at eight years follow-up was not substantially high, probably

to be explained by the characteristics of the sample: an uncomplicated primary care hypertension population. Future research in a population at higher risk could elucidate on determining a more appropriate cut-off within a prediction model.

Comparison with the existing literature

In the current study, 22% of the patients had a new CVE during 8 years' follow-up and specifically 5.2% of the patients developed a new coronary event. These results are in line with a recent study on the incidence and prevalence of CVEs of primary care subjects in the UK[34]: the prevalence of CVEs increased with age up to 25% between 70-79 years old. Specifically, the latter study found a prevalence of 3.5% of coronary events in the whole population, but they did not stratify by age category.

The prevalence of anxiety and depressive symptoms found in the current study of elderly primary care participants is in line with other studies. A review by Roy-Byrne *et al.* indicates a prevalence of generalized anxiety disorder (GAD) in primary care between 3-9%[35]. In our study we found a GAD prevalence of 5%. Beekman *et al.* found a prevalence of 2% for major depressive disorder and 13% for minor depression in elderly primary care subjects[30], which is similar to our study; 2% and 16% with a score indicative of respectively, a major depressive disorder and minor depression. Interestingly, the patients reported more often a previous diagnosis of depression compared to a diagnosis of an anxiety disorder, while it is well-known that anxiety is more prevalent in the general population than depression[36]. However, it is also known that in primary care, both anxiety and depression are commonly overlooked problems, mostly to be explained by the aspecific presentation of these syndromes[35]. This 'under-diagnosis' prevalence is even much higher for anxiety than depression, comparable to the prevalence of the current study[18]. The prevalence of elevated psychological distress scores in our study may seem rather low, however, the prevalence of anxiety and depression decline with higher age[29] and our population was in the age range between 60-85 years. The classical finding of female / male ratio of 2 / 1 with regard to the prevalence of anxiety and depression in the age range of 18-65 years that disappears with increasing age was also demonstrated in the current study: there was no differences between the sexes[29,30,36].

There are hardly any data available on validation of cut-offs of GAD-7 and PHQ-9 in our specific population: primary care elderly subjects. We only found 4 reports of PHQ-9 cut-offs scores in elderly patients, three studies with a very

small population[24,37,38] and the only large sample study had a selected population of chronic ill patients with diabetes and chronic obstructive pulmonary disease[39]. The current study also showed that the association between psychological distress and new coronary event already exists at much lower cut-offs as commonly reported in the scarce primary care literature.

There is abundant literature on possible explanations of the association between psychological distress and CVD as summarized recently in the European Heart Journal[40]. Although the title of the paper (Depression and cardiovascular disease: a clinical review) suggests cardiovascular disease in general, the authors consistently quoted papers referring to an association between depression and *cardiac* disease. To explain the interplay between cardiac disease and distress several mechanism have been proposed: biological mechanism (including genetics, neuro-hormonal, inflammation pathways, e.g.), behavioral mechanisms (well-known association between depression / cardiac disease and poor life style habits such as smoking, obesity, inactivity, poor diet) and psycho-social mechanism (including financial problems, (un)employment, loss of capabilities resulting in loss of independency, sexual dysfunction e.g.)[40]. Interestingly, the particular association between anxiety / depression with cardiac disease is confirmed in the current study: we found a significant association with new coronary events and baseline distress but not with other future cardiovascular diseases such as CVA. In the same review, the authors mention the frequently and consistently found association between anxiety and cardiac disease[40]. Anxiety and depression are co-morbid disorders with an overlap up to 40-50%[41-44]. In the current study, the correlation at baseline between anxiety and depression symptoms was 0.56, suggesting that up to 36% of the variance of anxiety symptom scores is explained by depressive symptoms or vice versa. There is a growing consensus, also in the DSM-V, that anxiety and depression symptoms should conceptually be regarded together as distress symptoms[31,32]. In the current study, the highest association was found between the development of new coronary events and distress symptoms above a certain cut-off in line with previous reports[42].

Implications for practice

In the Netherlands, nowadays, there are large general health care management programs: diabetes care, COPD care and also CVRM[45]. Special trained nurses take care of patients with chronic diseases according to guidelines, developed by the Scientific Department of the Dutch College of General Practitioners[28]. In these guidelines, there is growing focus on mental health problems of patients with chronic diseases but in daily practice, there is no standardized instrument

implemented within, for example, CVRM. The current study underlines the relevance of implementing such an instrument to assess psychological distress. If implemented, patients with higher distress levels could be offered a simple intervention like for example mindfulness training. Using a randomized controlled design, cognitive based mindfulness interventions showed a benefit on emotional wellbeing in primary care elderly diabetes-II patients[46,47]. Nowadays, these mental health interventions are offered online: they are effective, easily accessible to the general population at minimal costs[48,49].

In psychiatry and psychology, most of the cut-offs on anxiety and depression scales are assessed using questionnaires as well as syndromal diagnostic interviews of anxiety and depression[50,51]. The established cut-offs are estimates with the highest positive predictive value at most optimal sensitivity and specificity predicting syndromal diagnosis of anxiety / depression. In the current study, we proposed an 'epidemiological' approach using percentiles or quartiles with regard to poor cardiac outcome. Using these substantially lower cut-offs compared to syndromal diagnostic research, we were able to show that elderly patients already at these lower cut-offs were significantly more likely to develop new coronary events during follow-up. This is comparable to large epidemiological follow-up studies of the last decades showing that lower levels of blood pressure, total cholesterol or LDL benefit health outcomes in patients at risk for cardiac disease[52]. In clinical practice, it could be beneficial for health outcomes to extrapolate symptom cut-off scores to poor cardiac outcomes[53].

In conclusion, the current study shows that elderly primary care hypertension patients with high levels of distress (anxiety / depression) are more likely to develop future coronary events.

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PART TWO:

Additional diagnostic factors and their possible role to advance cardiovascular risk management



CHAPTER 3

Age- and gender-specific brain natriuretic peptide (BNP) reference ranges in primary care

Clinical Chemistry and Laboratory Medicine, 2014

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Abstract

Background

Chronic heart failure is a common disease with a high morbidity and mortality. In primary care, brain natriuretic peptide (BNP) is used for excluding heart failure. The Dutch and European Society of Cardiology heart failure guidelines apply two BNP cut-off levels without making distinction for gender and age. The aim of our study was to establish BNP reference ranges for use in primary care.

Methods

We investigated BNP values of 9447 eligible participants in a primary care laboratory. For establishing the reference ranges in various age and gender classes we used the Bhattacharya method.

Results

Analysis of variance demonstrated that BNP data were significantly dependent on age and gender (respectively $P<0.001$ and $P=0.002$), with the age effect being the strongest. Further we found that the reference ranges were significantly higher than the cut-off values used in the heart failure guidelines, particularly in elderly participants. For example, the proportion of individuals with a BNP value higher than the 29 pmol/L cut-off increased from approximately 5% in the youngest group to no less than about 50% in the oldest participants.

Conclusions

BNP reference ranges need to be age- and gender-specific. When applying a single cut-off, many healthy participants, especially the elderly, would be falsely diagnosed as having elevated BNP, and referred for further unnecessary diagnostics.

Introduction

Chronic heart failure (CHF) is a chronic heart condition in which the cardiac pump is unable to meet the demands for adequate circulation of the blood[1]. CHF is a common disorder with a prevalence of 1-2% in developed countries. Depending on age, this figure increases to more than 10% among subjects of 70 years and older[2]. The overall incidence rate of CHF is 14.4/1000 person-years. In individuals aged 55 years, 30% will develop CHF during their remaining lifespan according to The Rotterdam Study[3]. Over the next three decades, CHF prevalence will increase dramatically. Due to the ageing of the population, it is anticipated that the absolute number of people with CHF will increase by 50% between now and 2025[4].

Only 30-40% of patients survive within 5 years of diagnosis[3,5-7]. Hospitalisation rates for CHF are approximately 103 per 100,000 which means that about 20% of all patients suffering from CHF annually experience a major event because of CHF (death or hospitalization)[7,8]. In 2007, the direct health costs in The Netherlands related to CHF were estimated on 455 million euro, which represents 0.6% of the total health care costs of the country and 6.6% of the total costs because of heart disease in general[9]. Brain natriuretic peptide (BNP) is one member of the family of natriuretic peptides that were initially discovered by de Bold *et al.*[10]. BNP is synthesized and released into the blood in response to volume overload or conditions that cause ventricular stretch, in order to control fluid and electrolyte homeostasis by interaction with the renin-angiotensin-aldosterone system[11,12]. Plasma concentrations of BNP are consistently elevated in heart failure, but are not markedly elevated in other conditions that cause dyspnea and fatigue such as chronic obstructive pulmonary disease[13,14]. For the last two decades BNP is progressively used as a diagnostic tool for heart failure[15-18]. From 2001, a BNP assay is part of the guidelines of the European Society of Cardiology (ESC)[19] which were also adopted by the Scientific Board of the Dutch College of General Practitioners (Nederlands Huisartsen Genootschap; NHG) in 2005[20]. Nowadays, BNP is widely used in Primary Care in the Netherlands for excluding or diagnosing heart failure. Both national and international guidelines apply two single cut-off BNP levels for gradually and acute onset heart failure: 10 pmol/L (35pg/ml) and 29 pmol/L (100pg/ml), respectively[19,20]. No distinction is made for gender and age. For NT-pro-BNP, the closely related peptide that remains after BNP is cleaved from the genuine precursor proBNP, it has clearly been demonstrated that the plasma levels vary according to gender, age, diabetic status and renal function[21-27]. As for BNP, only two studies in the USA described the influence of age and gender on

BNP, however both with a small study population[28,29]. According to the current guidelines, primary care patients with BNP above a certain cut-off (irrespective of sex or gender) should be referred for further diagnostics. One might question whether the use of one single cut-off level for BNP (not taking into account age and gender) is specific enough for daily practice. Since this cut-off was established for maximizing the sensitivity, it might be hypothesized that one rigorous, non-age-specific, cut-off of elevated BNP results in many false positive cases at higher ages and that too many older patients will undergo additional diagnostic tests or are referred to a cardiologist for further investigation. Therefore, there is a need for adjusting the reference values. To the best of our knowledge, the current paper is the first to report on age and gender specific cut-off points of BNP in primary care in Europe. Redfield *et al.* and Wang *et al.* examined age and gender impact on BNP, in relatively small groups of healthy US citizens, respectively 767 and 911 subjects[28,29]. Here we report on age and gender specific cut-off levels of BNP in a large cohort of individuals who were referred to a primary care laboratory for a BNP assessment.

Materials and methods

Participants

During a period of 39 months, from January 1, 2010 until March 31, 2013, all patients who were referred to the primary care laboratory "Diagnostics for you" for a BNP assessment were selected for data analysis. This laboratory is located in the southeastern part of the Netherlands and provides diagnostic services to approximately 500 general physicians (GP) and other primary healthcare professionals. We excluded all measurements of requesting physicians other than GPs (i.e., nursing home physicians), because the prevalence and incidence of CHF can be different from a GP practice. The aim was to focus on a primary care population in order to establish reference values for BNP measurement for primary care. In accordance with the guidelines, the majority of the GPs request a BNP measurement for excluding a diagnosis of CHF, as explained in the introduction. Therefore, participants with multiple BNP assessments were excluded as they were most likely requested for the follow-up of previously established CHF. As renal failure and diabetes are known to influence plasma BNP concentrations, we excluded all participants with a glomerular filtration rate < 60ml/min/1.73m^2 (calculated using the MDRD formula) and all participants with an HbA1c > 42 mmol/mol (equivalent to 6.0%) or fasting glucose > 7.0 mmol/L. Our study was conducted in accordance with local ethical and legal requirements. As we only used anonymised data that had been collected for routine diagnostic purposes, no permission from the Ethical Review Board was required. To verify that our population is representative of the primary care population in the Netherlands we compared our data with the data of another study performed by the same group of investigators. In summary, this second population consisted of a group of uncomplicated hypertension patients of six primary care offices in the same area as the large study population. The aim of this second study was to evaluate the adherence to cardiovascular risk management in primary care with regard to hypertension treatment[30]. Hypertension patients aged between 60 and 85 were selected in the central database of the GP with the International Classification of Primary Care (ICPC) code hypertension (n=650). In total 125 patients with the ICPC diagnosis heart failure or currently treated by a cardiologist or with a glomerular filtration rate < 60ml/min/1.73m^2 (calculated using the MDRD formula) or with an HbA1c > 42 mmol/mol (equivalent to 6.0 %) or fasting glucose > 7.0 mmol/L were excluded. In the remaining 425 patients BNP was evaluated according to age and gender. BNP analysis was done in the same laboratory using the same analytical methodology.

Assessments

Blood samples were taken in EDTA plasma and BNP was measured, within 6 h after blood sampling, using a chemiluminescent microparticle immunoassay (Architect BNP; Abbott Laboratories, Abbott Park, IL, USA). The between-run coefficients of variation are 5.8% and 3.4% at concentrations of 26 pmol/L and 145 pmol/L, respectively[31].

Statistical analysis

We used standard methods for statistical analyses, as indicated in the text, using the MedCalc software package (version 12; MedCalc, Oostende, Belgium).

Reference ranges were calculated separately for men and women, for age classes as indicated in the text. For establishing the reference ranges, we used the Bhattacharya method, after logarithmic data transformation[32] (courtesy of Dr. Graham Jones, Department of Chemical Pathology, St. Vincent ' s Hospital, Sydney, Australia).This deconvolution technique is able to identify an underlying normal distribution in a dataset containing abnormal results from patients[33].

Results

Recruitment assessments

In Figure 1 the flowchart of the data inclusion is shown. Initially, the database contained 18,066 BNP values. After exclusion of other requesters than GPs, multiple BNP measurements per patient, patients with renal impairment and with diabetic status there remained 9447 BNP assessments of individual eligible patients in this study. The mean age (± SD) of the study patients was 68.4 ± 13.5 years, the age range was 18-102 years and the majority was female (59.0%, n=5576).

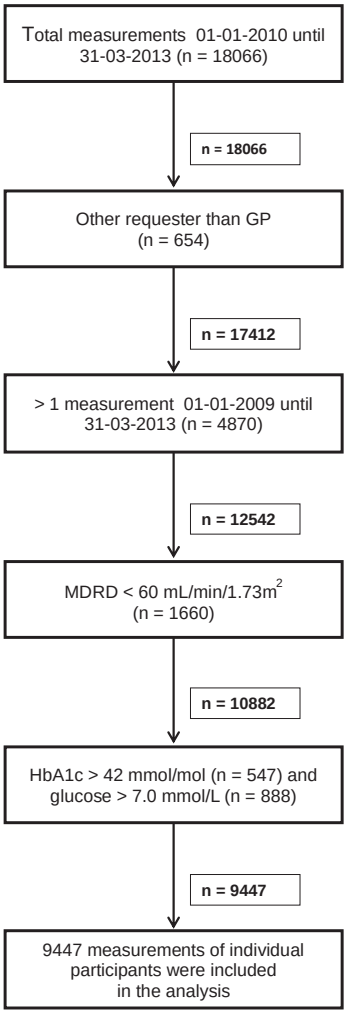

Figure 1. Flowchart of BNP data analysis in the study cohort.

Bhattacharya results

Analysis of variance demonstrated that BNP data were significantly dependent on age (F=140.67, *P*<0.001) as well as on gender (F=9.90, *P*=0.002), with the age effect being the strongest. Therefore, reference ranges were calculated separately for men and women, for four age classes: <60 years, 60-69 years, 70-79 years and ≥80 years. Furthermore, initial data analysis in each age class demonstrated that BNP data were not normally distributed (Kolmogorov-Smirnov test) and therefore we applied logarithmic transformation. For establishing the reference ranges of each age and gender class we used the Bhattacharya method, as shown in Table 1. Overall, the Bhattacharya method used 84% of the datapoints in males (range 76-98% in the different age classes) and 89% in females (range 83-99%).

The mean BNP values of males and females showed differences in the various age classes. In the youngest age class women had slightly higher values, whereas in the oldest classes men had higher BNP values; these differences were statistically significant, but too small to be clinical relevant. Most importantly, mean BNP increased with increasing age, both in men and in woman (Table 1).

In Figure 2 the age dependency is illustrated graphically, separately for men and women. These figures also show the current ESC guideline cut-off values, 10 pmol/L and 29 pmol/L, used for gradual and acute onset heart failure, respectively. As can be seen, both for men and women above approximately 60 years of age, the age group mean BNP value is higher than the 10 pmol/L cut-off and above approximately 80 years the group mean is even higher than the cut-off level 29 pmol/L (Figure 2). Moreover, the upper limit exceeds the 10 pmol/L cut-off level and the 29 pmol/L cut-off value already far under 60 years, irrespective of gender. Expressed numerically, the proportion of individuals with a BNP value higher than the 29 pmol/L cut-off increased from approximately 5% in the youngest group to no less than about 50% in the oldest participants (Table 2).

Comparison second population

As explained above, we compared our non-selected study cohort with a second, Primary Care study population in which heart failure was excluded by GP and all other conditions, which could possibly interfere with a BNP assessment, were excluded when they existed. Overall comparison of the two groups showed no significant differences in age, gender and plasma BNP

concentrations (*P*=0.155 by analysis of variance). For example, the control hypertension participants between 60 and 70 years had BNP concentrations ranging from 2.9-88 pmol/L (large study cohort 2.9-56 pmol/L; Table 1) and in those 70-80 years, BNP ranged from 2.9 to 150 pmol/L (large study cohort 2.9-127 pmol/L).

Table 1. BNP results in the different classes of age and gender

Age, years		**Male**		**Female**	**Significance**
	n	BNP, pmol/L	n	BNP, pmol/L	*P*-Value *
< 60	971	4.1 (0.4-41.2)	1308	4.6 (0.5-38.1)	*P*<0.0001
60-69	1076	10.6 (2.9-56.3)	1269	10.2 (2.1-48.8)	*P*=0.0005
70-79	1076	16.8 (2.2-127.5)	1648	13.2 (3.3-52.6)	*P*=0.4538
≥ 80	748	27.8 (3.8-201.6)	1351	25.7 (3.4-192.0)	*P*=0.0065
All ages	3871	6.8 (0.3-165.6)	5576	10.9 (1.0-122.7)	*P*<0.0001

Shown are mean values and 2 SD ranges (in parentheses) after logarithmic transformation and Bhattacharya analysis. The upper limit of the normal reference range of 2SD above mean is recommended as cut-off. * by Mann-Whitney U-test

Table 2. Consequences of applying a fixed BNP cut-off value (29 pmol/L) for the number of individuals with elevated BNP concentration, according to the ESC guideline

Age, years	**Males**			**Females**		
	n	**Elevated BNP if using cut-off 29 pmol/L**		n	**Elevated BNP if using cut-off 29 pmol/L**	
		n	%		n	%
< 60	971	48	4.9	1308	54	4.1
60-69	1076	155	14.4	1269	130	10.2
70-79	1076	341	31.7	1648	416	25.2
≥ 80	748	399	53.3	1351	622	46.0

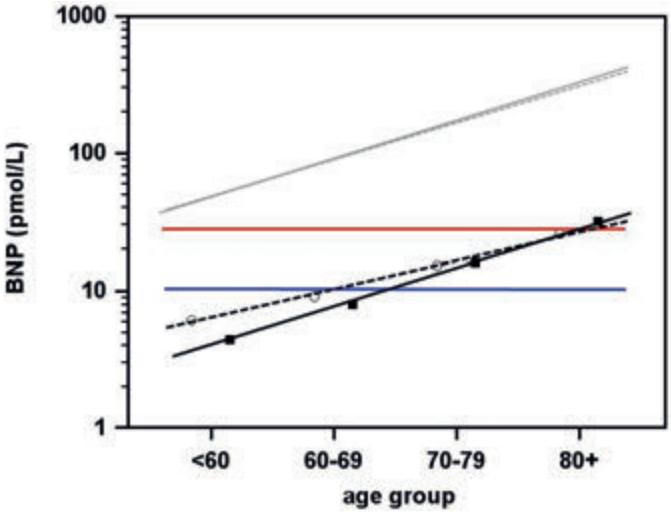

Figure 2. BNP concentrations as a function of age

Closed squares represent men and open circles represent women. The black solid line represents the regression of men, whereas the black dotted line represents the regression of women.

The regression equations are: log(BNP)=0.024(age) – 0.586 (r^2=0.994, *P*=0.003) for men and log(BNP)=0.020(age) – 0.329 (r^2=0.982, *P*=0.009) for women, respectively. The grey solid and dotted lines represent the upper 2SD range for men and women, respectively.

The cut-off values as recommended by the ESC for acute (29 pmol/L; red line) and gradually (10 pmol/L; blue line) onset heart failure are also shown.

Discussion

This study shows that age and gender have a significant influence on BNP levels. Age has more influence than gender. This was also found by Redfield *et al.* and by Wang *et al.*[28,29]. Other authors reported no significant age or gender influence[34]. However, all these studies had a much smaller study population than the present study, e.g., the study with the largest number is of Wang et al with 911 participants. As a consequence, their subgroups according to age and gender became rather small.

Some limitations of the present study need to be mentioned. First, we did not use a random sample of the general population, but a cohort of participants who were referred by their GP to the laboratory for BNP measurement. However, we compared the BNP assessment in our study group with that of a second study population of uncomplicated primary care hypertension patients, where heart failure was an exclusion criterion. No significant differences were found, so we assume that our population is well suited for using as a source of reference values. However, the fact that in the second study hypertension patients were included based on the ICPC and patients with ICPC of CHF were excluded, doesn't imply that there were no patients with CHF in this sample. It is well known in primary care that in early stages of CHF patients do not seek medical help and sometimes the diagnosis of CHF is overlooked by the GP during consultation. We believe that possibly inaccuracy in CHF diagnosis in this small study is representative for primary care and also applicable to our large study.

Moreover, we have corrected for two conditions which are known to be associated with abnormal BNP results: chronic renal failure and diabetes[22-28]. Also, it should be noticed that all participants of our study cohort visited the laboratory on their own without ambulance transport. This means that it is highly unlikely that these individuals suffer from acute or severe chronic heart failure.

Second, we used a statistical technique for establishing reference ranges[32], which identifies the underlying normal (or log-normal) data distribution in a dataset also containing abnormal results. This technique assumes that the majority of data is from "normal", healthy participants and our study cohort met this requirement. The Bhattacharya technique has been shown to be useful for estimating reference ranges in large cohorts of patients, even in a hospital setting referring to much more severely ill patients[33].

Currently both national and international guidelines use a single BNP cut-off for the Primary Care population without distinction for gender and age and this has definitely limitations. For example, in the sub-group of men between 70 and 80 years, a rigorous cut-off of 29 pmol/L would result in 31% of participants in this group diagnosed as having elevated BNP (Table 2). In the age group older than 80 years, this would even increase further to 53%. As a consequence, many participants would be falsely diagnosed as having elevated BNP (especially the elderly) and referred for unnecessary further diagnostics, such as cardiac echo which would substantially increase the costs. If the guidelines would apply age- and gender-dependent BNP cut-off values, a substantial lower number of patients will be referred by GPs for an echocardiogram, resulting in a considerable cost reduction.

Future research, however, should elaborate on the adjusted BNP cut-off findings of this study by assessing the specificity, sensitivity, positive and negative predictive value of an elevated BNP on an abnormal echocardiogram and clinical signs of heart failure.

In conclusion our present study shows that, in primary care, the definition of normal BNP reference ranges needs to be age-dependent when it is used to exclude the existence of possible heart failure.

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CHAPTER 4

Electrocardiography for the detection of left ventricular hypertrophy in an elderly population with long-standing hypertension in primary care: a secondary analysis of the CHELLO cohort study

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Abstract

Objectives

To investigate: (1) the prevalence of left ventricular hypertrophy (LVH) in elderly primary care patients with long-standing asymptomatic hypertension, and (2) the diagnostic value of ECG as a screening tool in the detection of LVH compared with echocardiography in this specific patient population.

Design and settings

A cross-sectional study in five general practices in the south-east of the Netherlands

Participants

Patients with primary care-managed hypertension, aged between 60 and 85 years, without known heart failure.

Primary and secondary outcome measures

Between June 2010 and January 2013, the patients underwent structured interviews, blood pressure assessment, laboratory testing, ECGs and echocardiograms. The primary outcome was to investigate the ability of ECG to detect LVH, compared with echocardiography as a reference test (gold standard).

Results

Four hundred and twenty-two patients (44% male; age 70 ± 7 years) who underwent ECG and echocardiographic assessment to determine LVH were included. The median duration of hypertension was 10 (4-15) years. The overall prevalence of LVH was 44%, which increased with age ($p<0.001$); up to 60% of patients were ≥75 years. ECG intimated LVH in 47 patients (11%) but in only 26 of those (55%) was LVH confirmed by echocardiography. The sensitivity of ECG for detecting LVH was poor (14%).

Conclusions

Asymptomatic primary care patients with long-standing hypertension have a high prevalence of previously undetected LVH, which increases with age. ECG is inadequate for detecting LVH in these patients. Early detection of LVH could potentially create more awareness for the optimal regulation of hypertension and compliance to therapy. Therefore, echocardiography should be considered a screening device for the detection of LVH in this population.

Introduction

Worldwide, hypertension is a common and increasingly frequent condition in the adult population[1]. A prevalence of up to 62% has been reported in the adult population of 60-70 years of age[2]. It is the most important (modifiable) risk factor for developing cardiovascular disease (CVD), including myocardial infarction (MI), stroke, atrial fibrillation and heart failure[3]. Clinical findings related to hypertensive heart disease include left ventricular hypertrophy (LVH), secondary left ventricular (LV) diastolic dysfunction and left atrial dilation. LV diastolic dysfunction is a well-known cause of heart failure, leading to high morbidity and mortality[4]. The detection of LVH is important because these patients' risk of cardiovascular (CV) morbidity and mortality is twofold to fourfold increased, compared to patients with normal LV mass[5].

Most patients with hypertension are diagnosed in primary care. The first choice of treatment is lifestyle and dietary interventions, followed by drug therapy. Achieving adequate blood pressure control is pivotal in reducing the risks of hypertension-mediated organ damage. In the Netherlands, general practitioners treat patients according to the latest nationwide guidelines for CV risk management[6]. However, these guidelines are conservative in their recommendations for additional testing after laboratory and blood pressure assessments. Standard ECG and echocardiography are not recommended in these guidelines to screen for, among other things, LVH. In particular, in long-standing hypertension with known high morbidity and mortality, LVH should be recognised using the most reliable method available[7], in order to intensify the regulation of blood pressure so that LVH can be modified in time[8,9]. This will hopefully increase patient awareness and adherence to therapy.

Moreover, the value of ECG screening in primary care patients with hypertension has not yet been fully explained. The increase in myocardial wall thickness is the most apparent finding with regard to end-organ damage due to uncontrolled hypertension and elevated pressure load[10]. This may first be noted by ECG, using specific criteria[11], however, the sensitivity to diagnose LVH in a general population is low, in comparison to echocardiography as the reference gold standard[12,13]. In primary care, though, ECG is still the preferred tool in patients with hypertension, since it is easy to obtain, fast and inexpensive. With the increasing accessibility of ultrasound machines to primary care physicians, it is important to decide whether ECG remains a viable tool as first choice for detecting LVH, or perhaps in selected patients only. It is conceivable that in patients with longer duration of hypertension, having a higher incidence and higher rates of severe LVH due to chronic pressure overload[14], ECG may still have a diagnostic role.

The aim of the current study was to investigate: (1) the prevalence of LVH in elderly primary care patients with long-standing asymptomatic hypertension, and (2) the diagnostic value of electrocardiography as a screening tool in the detection of LVH compared to echocardiography in this specific patient population.

Methods

Study design and patient population

This study was performed using data from the CHELLO (Chronic Heart Failure Prevention Program) study. The details of this study have been presented earlier[15-17]. In summary, between June 2010 and January 2013, a total of 913 primary care patients aged between 60 and 85 years with an International Classification of Primary Care for hypertension (K86/K87) were invited from five general practices affiliated with the primary care organization Praktijkondersteuning Zuidoost Brabant to participate in the CHELLO study.

Inclusion criteria were: elderly primary care patients (60-85 years) with asymptomatic hypertension. Patients with a history of CVD (e.g., MI) were included if they were no longer treated by a cardiologist. Exclusion criteria: patients with heart failure were excluded based on nature of the primary study (Chronic Heart Failure Prevention Program).

Other exclusion criteria included: severe psychiatric illness other than mood or anxiety disorders; serious cognitive impairment; terminal cancer; insufficient knowledge of the Dutch language; or illiteracy. This resulted in 595 eligible patients who gave written informed consent for participation. This study complies with the Declaration of Helsinki and was approved by the Medical Ethics Board of the Saint Elisabeth Hospital, Tilburg, the Netherlands.

Patient and public involvement

No patient involved.

Study procedure and data collection

Eligible patients received both verbal and written information on the study. After obtaining written informed consent, an interview was scheduled at the primary care practice. During this first visit, a healthcare nurse conducted a structured interview and performed a physical examination. Blood pressure was measured automatically after approximately 20 and 40 minutes, with the patient in a sitting position. The mean value of both blood pressure measurements was used for data analysis. In addition, demographic and clinical variables were obtained during the interview and after reviewing the patient's medical records. Following the first appointment, blood was drawn by venipuncture in order to measure brain natriuretic peptide (BNP), total cholesterol and low-density lipoprotein. BNP was measured since it is a known

indicator of heart failure, which could be the result of long-term LVH[3,18]. A follow-up visit was planned at the primary care practice in order to perform an ECG and echocardiogram.

Assessment of the electrocardiogram and echocardiogram

The primary outcome was to investigate the ability of ECG to detect LVH, compared to echocardiography as a reference test (gold standard).

ECG and echocardiogram were carried out by a trained, experienced echocardiographer at the local primary care laboratory 'Diagnostiek voor U' in Eindhoven, the Netherlands.

A standard resting 12-lead ECG was recorded (paper speed 25 mm/s, 10 mm/mV). We used the following eight well-known and often used criteria in order to evaluate LVH features during ECG:

- The Sokolow-Lyon index: the sum of the S wave in V1 and the R wave in V5 of V6 > 3.5mV[19]
- The sum of the S wave in V2 and the R wave in V5 or V6 > 4.5mV[20]
- The amplitude of the R wave in V5 or V6 > 2.6mV[19]
- A comparison of the amplitude of the R wave in V5 and V6; R V6 > R V5[21]
- The sum of the largest amplitude of the R wave and the largest amplitude of the S wave in precordial leads > 4.5mV[22]
- The Cornell Voltage: the sum of the R wave in aVL and the S wave in V3 > 2.0mV for females and > 2.8mV for males[23]
- The amplitude of the R wave in aVL > 1.1mV[19]
- The Gubner-Ungerleider voltage: the sum of the R wave in I and the S wave in the III lead > 2.5mV[24]

If one or more of these eight criteria were positive, ECG-LVH was diagnosed. An independent cardiologist who was blinded for outcomes of the echocardiogram gave a final review.

A transthoracic 2D echocardiographic examination was performed with an s5 transducer (Philips CX 50) in a standard position. All the echocardiograms were reviewed by a panel of cardiologists specialised in echocardiography, according to European recommendations and guidelines for evaluating chamber quantification, diastolic dysfunction and heart valve disease[25-27]. LVH was defined as any abnormal LV size measurement (septal or posterior wall thickness > 0.9 cm

in females or > 1.0 cm in males) and calculated LV mass index adjusted for body surface area > 95 g/m2 in females and > 115 g/m2 in males. We used Cube formula for LV mass = 0.8 x 1.04 x [(IVS+LVID+PWT)^3 – LVID^3] + 0.6g[26].

Statistical analyses

Statistical analyses were performed using the IBM Statistical Package for the Social Sciences, version 25.0. Data are presented as mean ± SD in the case of normally distributed data, median (interquartile interval) for non-normally distributed data and number (percentage) for nominal data. A *P*-value <0.05 (two-tailed) was considered to indicate statistical significance.

In order to examine the prevalence of LVH, we calculated the proportion of patients with echocardiography-diagnosed LVH. In addition, we computed the 95% CI for this estimate. In order to examine the diagnostic yield of ECG, we calculated sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) with a 95% CI. McNemar's test was used to compare LVH detection rates between ECG and echocardiography in 2x2 contingency tables. In addition, the kappa measure of agreement value was calculated.

To assess a potential effect of age on our result, we divided our population (n=422) in four groups: group 1 (n=116) less than 65 years old; group 2 (n=102) 65 - 69 years old; group 3 (n=102) 70 - 74 years old; group 4 (n=102) 75 years and older.

In order to assess the discriminative ability of ECG, we compared the demographic, lifestyle, and clinical characteristics of patients without LVH and patients with LVH. Characteristics were compared using an independent sample T-test for normally distributed continuous data, the Mann-Whitney U test for non-normally distributed continuous data and the x^2 test for categorical data. In the same way, the discriminative ability of echocardiograms was assessed.

Finally, in order to investigate whether the ECG, together with other demographic and clinical variables, can be used as a proxy for the echocardiogram when diagnosing LVH, we performed single and subsequent multiple logistic regression analyses with LVH (normal +/-abnormal) using the echocardiogram as the dependent variable. The multivariable logistic regression model was constructed using backward selection (P_{out} >0.1), including variables that were significantly associated with LVH on the echocardiogram in univariable analyses.

Results

Study population

A total of 427 patients from the CHELLO study cohort (595), with both an ECG and an echocardiogram, were included. Five patients were excluded due to the poor image quality of the echocardiogram, resulting in a total of 422 eligible patients[15-17].

Baseline characteristics

Table 1 presents the baseline characteristics of the study participants. The mean age of these patients was 69.7 ± 6.5 years, with the minority being male (44%, n=186). The median years of hypertension amounted to ten [4-15] years. Mean systolic blood pressure (SBP) was 149.2 ± 20.2 mmHg, and mean diastolic blood pressure (DBP) 81.8 ± 10.8 mmHg. In all the patients, 67% had an SBP >140 mmHg (n=281), and as much as 44% an SBP >150 mmHg (n=185). Therefore, in this population, 42% (n=175) had an SBP that was on target according to the Dutch guidelines for cardiovascular risk management. On-target systolic blood pressure was defined as <140 mmHg for those aged less than 70 years and <150 mmHg for those aged 70 years or older[6].

Prevalence and diagnostic yield of LVH using ECG compared to echocardiography

The overall prevalence of LVH using echocardiogram was 44% (n=184), while that of LVH using ECG was 11% (n=47). Of the 422 patients, 47 (11%) had LVH using ECG and, of these 47 patients, 26 (55%) had LVH confirmed using echocardiography. In other words, in almost half of those patients with LVH detected using ECG, this was not confirmed by echocardiography.

ECG had a sensitivity of 14% (95%CI, 9.44 to 20.02), a specificity of 91% (95%CI, 86.83 to 94.46), a PPV of 56% (95%CI, 41.86 to 68.04), and an NPV of 58% (95%CI, 56.13 to 59.58) for the detection of LVH using echocardiography.

Detection of LVH using ECG was not associated with LVH using echocardiography based on McNemar's Test (p<0.001). There was poor agreement between ECG and echocardiogram used for the detection of LVH (kappa 0.058, p = 0.086). A typical example of LVH mismatch is demonstrated in Figure 1.

Table 1. Baseline characteristics

Characteristic	Total patients n= 422
Demographics	
Age, years (mean, SD)	69.7 ± 6.5
Male (n, %)	186 (44.1)
Low education (n, %)	53 (12.6)
Having a partner (n, %)	327 (77.5)
Lifestyle	
Current smoker (n, %)	54 (12.8)
Regular alcohol use (n, %) +	135 (32.0)
Recommended physical exercise (n, %) ++	68 (16.1)
Clinical characteristics and risk factors	
Previous MI (n, %)	19 (4.5)
Peripheral artery disease (n, %)	18 (4.3)
Previous TIA/stroke (n, %)	36 (8.5)
Diabetes (n, %)	39 (9.2)
BMI, kg/m^2 (mean, SD) *	28 ± 4.6
BNP, pmol/l (median, IQR) **	10 [6-18]
Total cholesterol, mmol/L (mean, SD) ***	5.1 ± 1.0
LDL, mmol/L (mean, SD) ***	3.1 ± 0.9
SBP, mmHg (mean, SD)	149 ± 20.2
SBP>140 mmHg (n, %)	281 (66.6)
SBP>150 mmHg (n, %)	185 (43.8)
DBP, mmHg (mean, SD)	81.8 ± 10.8
DBP>90 mmHg (n, %)	86 (20.4)
Blood pressure on target (n, %) +++	175 (41.5)
Years of hypertension (median, IQR) ***	10 [4-15]

Values for categorial variables are given as number (percentage); values for continues variables are given as mean ± SD or median [IQR].
+ defined as ≥ 2 glasses of alcohol per day on average. ++ defined as ≥ 30 minutes exercise per day, at least 5 days/week. +++ on-target systolic blood pressure defined as <140mmHg for persons aged less than 70 years and <150mmHg for persons aged 70 years or more.
* n=418. ** n=400. ***n=407 due to missing data.
Abbreviations: MI, myocardial infarction; TIA, transient ischemic attack; BMI, body mass index; BNP, brain natriuretic peptide; LDL, low-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure

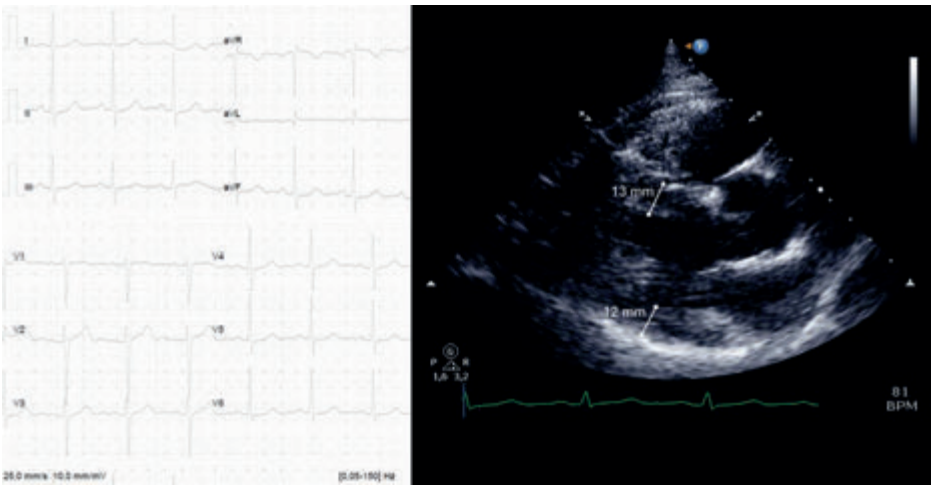

Figure 1. Normal ECG and abnormal echocardiogram of LVH in one patient

Abbreviations: aVF, augmented vector foot; aVL, augmented vector left; aVR, augmented vector right; LVH, left ventricular hypertrophy.

Prevalence of LVH in different age categories using ECG and echocardiogram

The prevalence of LVH using ECG increased with increasing age, however not significantly ($\chi^2(3) = 5.06$, $P=0.17$). The prevalence of LVH using echocardiography increased significantly with increasing age ($\chi^2(3) = 18.58$, $p<0.001$). Figure 2 shows the distribution of LVH using ECG and echocardiography in the four different age categories.

The prevalence of LVH confirmed by echocardiography increased from 33% in the youngest age group (<65 years) to 60% in the oldest age group (>74 years), while the prevalence of LVH using ECG only increased from 11% in the youngest age group to 18% in the oldest age group.

Study characteristics with regard to LVH status using ECG and echocardiogram

Table 2 presents patient characteristics with regard to LVH using ECG and echocardiogram. LVH was only significantly correlated with age using the echocardiogram; patients with LVH by echocardiography were older when compared to those without LVH (71 ± 6.9 vs. 69 ± 6.0, t(420)=-4.29, $P<0.001$). BNP was significantly higher in those with LVH on both ECG (17 [9.9-31] vs. 9.7 [5.8-16.3], U=5132, z=-4.08, $P<0.001$, r=0.20) and echocardiography (11 [6.9-18] vs. 9.8 [5.3-17], U=17220, z=-2.11, $P=0.035$, r=0.11) when compared to those without LVH. An elevated BNP was more strongly associated with LVH when using ECG than when using the echocardiogram.

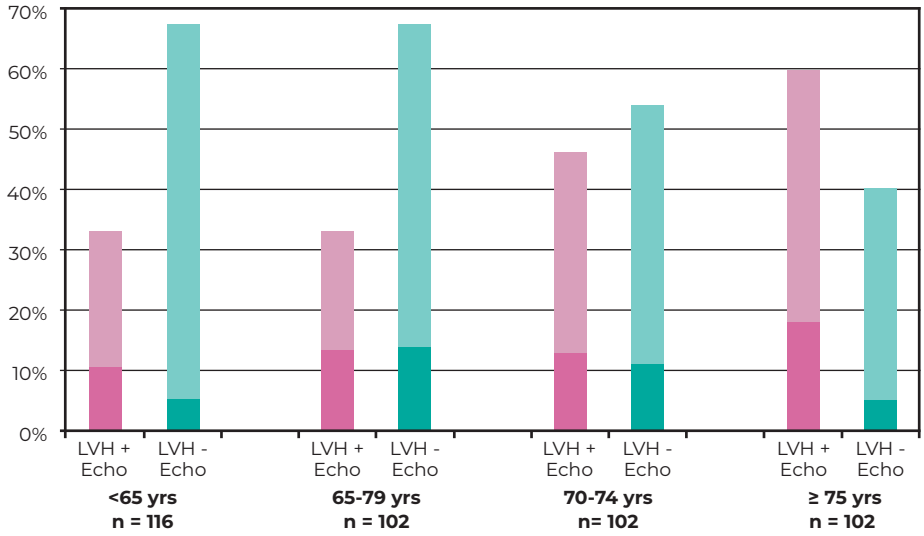

Figure 2. Prevalence of LVH using echocardiography and ECG (%) in different age categories

Light pink: LVH – ECG. Dark pink: LVH + ECG. Light turquoise: LVH – ECG. Dark turquoise: LVH + ECG.

Abbreviations: LVH, left ventricular hypertrophy.

Furthermore, only SBP was significantly higher in those with LVH using ECG compared to those without LVH (155 ± 23.1 vs. 149 ± 19.7, t(420)= -1.82, *P*=0.041). Moreover, an SBP > 150 mmHg was significantly higher in those with LVH compared to those without LVH using ECG (60% vs. 42%, $\chi^2(1) = 5.32$, *P*=0.021).

With regard to the echocardiogram, patients with LVH were more likely to have had a previous MI compared to those without LVH (7% vs. 3%, $\chi^2(1)= 4.98$, *P*=0.026). Moreover, the body mass index (BMI) was significantly higher in those with LVH using echocardiography compared with those without LVH (29 ± 4.3 vs. 28 ± 4.7, t(416)=-2.03 *P*= 0.043). Lastly, SBP was significantly higher in those with LVH on the echocardiogram, compared with those not suffering from LVH (152 ± 21.7 vs. 147 ± 18.7, (t(420)=-2.69 *P*=0.007).

Table 2. Characteristics according to LVH using electrocardiogram and echocardiogram

Characteristics	ECG n=422	
	LVH + **n=47**	**LVH -** **n=375**
Demographics		
Age, years (mean, SD)	70.9 ± 6.4	69.5 ± 6.5
Male (n, %)	23 (48.9)	163 (43.5)
Low education (n, %)	5 (10.6)	48 (12.8)
Having a partner (n, %)	37 (78.7)	290 (77.3)
Lifestyle		
Current smoker (n, %)	4 (8.5)	50 (13.3)
Regular alcohol use (n, %) +	14 (29.8)	121 (32.3)
Recommended physical exercise (n, %) ++	8 (17.0)	60 (16.0)
Clinical characteristics and risk factors		
Previous MI (n, %)	2 (4.3)	17 (4.5)
Peripheral artery disease (n, %)	1 (2.1)	17 (4.5)
Previous TIA/stroke (n, %)	1 (2.1)	35 (9.3)
Diabetes (n, %)	4 (8.5)	35 (9.3)
BMI, kg/m^2 (mean, SD) *	27 ± 4.0	28 ± 4.6
BNP, pmol/l (median, IQR) **	17 [9.9-31]	9.7 [5.8-16.3]
Total cholesterol, mmol/L (mean, SD) ***	5.2 ± 1.1	5.1 ± 1.0
LDL, mmol/L (mean, SD) ***	3.2 ± 0.9	3.1 ± 0.9
SBP, mmHg (mean, SD)	155 ± 23.1	149 ± 19.7
SBP>140 mmHg (N, %)	33 (70.2)	248 (66.1)
SBP>150 mmHg (N, %)	28 (59.6)	157 (41.9)
DBP, mmHg (mean, SD)	83.7 ± 10.9	81.6 ± 10.7
DBP>90 mmHg (N, %)	11 (23.4)	75 (20.0)
Blood pressure on target (n, %) +++	15 (31.9)	160 (42.7)
Years of hypertension (median, IQR) ***	10 [4-15]	10 [4-16]

Values for categorial variables are given as number (percentage); values for continues variables are given as mean ± standard deviation or median [interquartile range]. Chi-square test for nominal data, T-test for normally distributed continuous data, Mann-Whitney U Test for non-normally distributed data. *P*-values <0.05 are in bold.
+ defined as ≥ 2 glasses of alcohol per day on average. ++ defined as ≥ 30 minutes exercise per day, at least 5 days per week. +++ on target systolic blood pressure defined as <140mmHg for persons aged less than 70 years and <150mmHg for persons aged 70 years or more.

	Echo n=422		
***P*-value**	**LVH + n=184**	**LVH - n=238**	***P*-value**
0.166	71.2 ± 6.9	68.5 ± 6.0	**<0.001**
0.476	83 (45.1)	103 (43.3)	0.707
0.673	24 (13.0)	29 (12.2)	0.792
0.830	141 (76.6)	186 (78.2)	0.711
0.351	19 (10.3)	35 (14.7)	0.182
0.731	61 (33.2)	74 (31.1)	0.653
0.858	28 (15.2)	40 (16.8)	0.660
0.931	13 (7.1)	6 (2.5)	**0.026**
0.442	5 (2.7)	13 (5.5)	0.166
0.096	20 (10.9)	16 (6.7)	0.130
0.854	19 (10.3)	20 (8.4)	0.499
0.178	29 ± 4.3	28 ± 4.7	**0.043**
<0.001	11.0 [6.9-18]	9.8 [5.3-17]	**0.035**
0.522	5.1 ± 1.1	5.0 ± 0.9	0.286
0.746	3.2 ± 0.9	3.1 ± 0.9	0.361
0.041	152 ± 21.7	147 ± 18.7	**0.007**
0.576	128 (69.6)	153 (64.3)	0.254
0.021	89 (48.4)	96 (40.3)	0.099
0.203	81 ± 10.9	82 ± 10.6	0.188
0.585	36 (19.6)	50 (21.0)	0.715
0.158	71 (38.6)	104 (43.7)	0.291
0.629	10 [4-20]	8 [4-15]	0.188

* n=418. ** n=400. ***n=407 due to missing data.

Abbreviations: LVH, left ventricular hypertrophy; ECG, electrocardiogram; Echo, echocardiography; MI, myocardial infarction; TIA, transient ischemic attack; BMI, body mass index; BNP, brain natriuretic peptide; LDL, low-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 3. Univariable and multivariable association of LVH using echocardiogram with clinical parameters in patients with asymptomatic hypertension

Demographics
Higher age
Male
Low education
Having a partner
Lifestyle
Current smoker
Regular alcohol use +
Recommended physical exercise ++
Clinical characteristics and risk factors
Previous MI
Peripheral artery disease
Previous TIA/stroke
Diabetes
Higher BMI *
LnBNP **
Higher total cholesterol ***
Higher LDL ***
Higher SBP
SBP>140 mmHg
SBP>150 mmHg
Higher DBP
DBP>90 mmHg
Blood pressure on target +++
More years of hypertension ***
LVH on ECG

Data are presented as odds ratio (OR) with corresponding *P*-value. Bold letters indicate a *P*-value <0.1 at univariable analysis, and *P*-value <0.05 at multivariable analysis.
+ defined as ≥ 2 glasses of alcohol per day on average. ++ defined as ≥ 30 minutes exercise per day, at least 5 days per week. +++ on target systolic blood pressure defined as <140mmHg for persons aged less than 70 years and <150mmHg for persons aged 70 years or more.

	LVH on echocardiogram			
	Univariable		Multivariable	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
	1.07 (1.04-1.10)	**<0.001**	1.06 (1.03-1.10)	**0.001**
	0.93 (0.63-1.37)	0.707		
	1.08 (0.61-1.93)	0.792		
	0.92 (0.58-1.45)	0.711		
	0.66 (0.37-1.21)	0.184		
	1.10 (0.73-1.66)	0.653		
	0.89 (0.53-1.50)	0.660		
	2.94 (1.10-7.89)	**0.032**	2.86 (1.04-7.83)	**0.041**
	0.48 (0.17-1.38)	0.175		
	1.69 (0.85-3.37)	0.134		
	1.26 (0.65-2.43)	0.500		
	1.05 (1.00-1.09)	**0.046**	1.05 (1.01-1.10)	**0.032**
	1.35 (1.06-1.71)	**0.014**		
	1.12 (0.91-1.37)	0.278		
	1.11 (0.89-1.38)	0.360		
	1.01 (1.00-1.02)	**0.008**		
	1.27 (0.84-1.92)	0.255		
	1.39 (0.94-2.04)	0.099		
	0.99 (0.97-1.01)	0.188		
	0.92 (0.57-1.48)	0.715		
	1.24 (0.84-1.83)	0.291		
	1.15 (0.94-1.41)	0.170		
	1.70 (0.92-3.13)	**0.088**		

* n=418. ** n=400. ***n=407 due to missing data.

Abbreviations: LVH, left ventricular hypertrophy; MI, myocardial infarction; TIA, transient ischemic attack; BMI, body mass index; BNP, brain natriuretic peptide; LDL, low-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure; ECG, electrocardiogram

Predictors of LVH

Table 3 presents the results from univariable and multivariable logistic regression analysis, with an abnormal echocardiogram LVH as the dependent variable. In univariable logistic regression analysis, greater age, previous MI, higher BMI, higher BNP, higher SBP and LVH on ECG were associated with echocardiogram-diagnosed LVH. After backward elimination, in multivariable logistic regression analysis, only greater age (O.R.: 1.06, 95% CI: 1.03-1.10), previous MI (O.R.: 2.86, 95% CI: 1.04-7.83), and higher BMI (O.R.:1.05, 95% CI: 1.01-1.10) were found to be predictors of echocardiogram-diagnosed LVH.

Discussion

In this cross-sectional study of elderly asymptomatic primary care patients with long-standing hypertension, we found a prevalence of LVH of 44% using echocardiography. The prevalence of LVH detected with echocardiography increased significantly with age: up to 60% in patients older than 75 years. We also investigated the value of ECG in the detection of LVH compared with our findings with echocardiography. ECG had a poor predictive value to detect LVH, with a low sensitivity of 14%. In contrary to our echocardiography findings, we did not find an increase in prevalence of ECG-detected LVH with increasing age, prevalence stabilised at around 16-18% in the highest age group. Early detection and subsequent treatment of LVH are important in an effort to reduce CV morbidity and mortality[28], even in patients older than 65 years[29]. Since most patients with hypertension are treated in primary care setting, there is a need for an easy, affordable and reliable screening tool to detect LVH in this population.

Strengths and limitations

In this study we evaluated the prevalence of LVH using echocardiography in a specific primary care cohort of asymptomatic elderly individuals with long-standing hypertension. Furthermore, we compared the ability of ECG to detect LVH with echocardiography as a reference test.

We conclude that there should be a standard role for echocardiography when screening for LVH in primary care patients with hypertension.

One of the limitations of this study is that we used a cross-sectional design, without a control group for comparison. Furthermore, this study unfortunately lacks any long-term data on (cardiac) events, so adverse outcomes of LVH detected by ECG or echocardiography for the development of future CV events remains unclear in this population.

Comparison with the existing literature

The prevalence of echocardiographically confirmed LVH in the general population is estimated to be from 14-19%, and increases with age[30,31]. In our study, in a selected primary care patient population with long-standing hypertension, we noted a higher prevalence of LVH of 44%. This corresponds with the prevalence of LVH reported in a recent review by Cuspidi *et al.*, who noted a variation from 36% to 41% in patients with hypertension[32]. Only limited data of prevalence of LVH in elderly primary care patients with hypertension

is available. Doroudi *et al.* reported a prevalence of LVH of 38% in patients in primary care, aged between 62 and 73, but this is a retrospective study[33]. Chowdhury *et al.* reports a prevalence of LVH detected by the echocardiogram of 33-70%, depending on used definition. Although our reported prevalence of LVH detected with echocardiography (44%) fits within this range, the study of Chowdhury *et al.* did not comment on the value of ECG in detecting LVH in their population[34].

The Framingham study pointed out that the use of ECG for detecting LVH in the general population was not reliable[12]. They reported that ECG has a sensitivity of less than 20% for detecting LVH compared to echocardiography. When using cardiac MRI, Bacharova *et al.* also reported the poor sensitivity (22%) of ECG for detecting LVH in the general population[35]. In a review of Pewsner *et al.*, the studies in hypertensive primary care populations reported a median sensitivity ranged from 8.5% to 21%[36]. Furthermore, in another large study Jain *et al.* found a similar sensitivity range of 5.7% to 26% for detecting LVH with ECG in a hypertensive population compared with MRI[37]. We hypothesised that the reliability of ECG may be better in a selected group of patients with long-standing hypertension, which could be helpful in primary care practice. Unfortunately, our data show that ECG performed equally poor, even in this specific population.

Although our results have shown that ECG may not be recommended for the detection of LVH, the prognostic value of ECG in elderly primary care patients with hypertension remains uncertain. It has been hypothesised that ECG may be of additional value for prognosis[7,38,39]. Aro *et al.* suggested that LVH detected using ECG and LVH detected using echocardiography are two distinct entities that only partially overlap, and have different prognostic significance[40] (see Figure 3). This hypothesis could explain the stronger association of elevated BNP with LVH using ECG as opposed to LVH using echocardiogram. The current study was unable to address this further.

Implications for research and/or practice

Our results provide additional proof that routinely acquired ECGs for detecting LVH in patients with hypertension have no significant diagnostic value, not even in a selected population with long-standing hypertension. On the other hand, ECG-derived LVH seems, at least partly, to be a different entity and a predictor of cardiovascular mortality, independent of LV mass index and LV morphology. Moreover, ECG-LVH increases the risk of CV mortality even in

participants without hypertension[41,42]. Routinely performing both ECG and echocardiography in patients with hypertension seems therefore indicated. Currently, both our national and European guidelines for CV risk management (in primary care) do not recommend routinely performance of an ECG and/or echocardiogram.

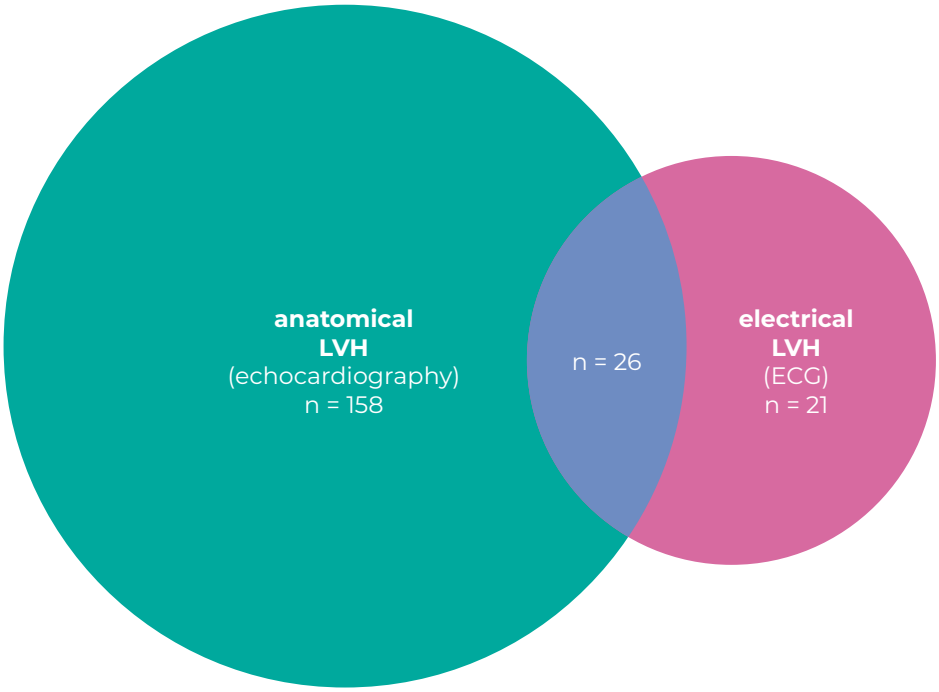

Figure 3. Anatomical vs. electrical LVH

Figure adapted from Aro *et al.*[40] pointing out anatomical and electrical LVH, and their overlap, in our study.

Our findings point out that, when feasible, patients (particularly uncomplicated elderly hypertension patients, who represent a large percentage of the population) should be referred for focused echocardiography for detection of LVH[43]. Performing an ECG could be of additional prognostic value, independent of echocardiographic findings[7,38-42].

Furthermore, our study showed that more than half the patients were not on target with their blood pressure, and it is possible that early recognition of LVH will increase patient awareness and adherence to therapy. Also, the early detection of LVH will identify patients who could benefit from intensified antihypertensive therapy, in order to prevent or delay the progression of CVD[28,29,44-47].

In conclusion, asymptomatic, elderly primary care patients with long-standing hypertension have a high prevalence of LVH, which will increase with age. ECG is a suboptimal tool for detecting LVH and, for this reason, patients who are in need of close monitoring and stricter antihypertensive treatment may benefit from a cardiac evaluation with echocardiography. Further follow-up exploration is required to prove the prognostic value of ECG and echocardiography in this specific population of primary care patients with hypertension. Moreover, future research should concentrate on whether the early detection of LVH by echocardiography in the primary care setting leads to decreased morbidity and mortality in the increasing prevalence of hypertension.

Strengths and limitations of this study

- In a primary care population of asymptomatic elderly individuals with long-standing hypertension: we report prevalence of left ventricular hypertrophy (LVH) by echocardiogram and the ability of ECG to detect this condition that has been associated with adverse outcomes.
- No long-term follow-up data on the occurrence of cardiac events are currently available, so adverse outcomes of LVH detected by ECG or echocardiography for future cardiovascular events remains unclear in this study.
- The design of the study has its limitations: it consists of a cross-sectional cohort without a control group for comparison.

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CHAPTER 5

Prediction of cardiovascular events in older patients with hypertension in primary care: a cohort study

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Abstract

Background

Accurate risk stratification identifying patients with hypertension at risk of future cardiovascular disease in primary care would be desirable.

Aim

To investigate the association between elevated brain natriuretic peptide (BNP), left ventricular hypertrophy (LVH) on an electrocardiogram (ECG), and LVH on an echocardiogram and the development of cardiovascular events (CVEs), especially heart failure and all cause-mortality (ACM), in a primary care population with hypertension without symptoms of heart failure.

Design and Setting

A prospective cohort study in five Dutch general practices between 2010-2012 and 2020.

Methods

In total, 530 patients (aged 60-85 years) underwent laboratory testing, ECGs and echocardiograms at baseline. The incidence of new CVEs and ACM at up to 9 years' follow-up was recorded by data extraction from the digital information systems.

Results

Among the 530 participants, 31 (5.8%) developed a coronary event, 44 (8.3%) a cerebrovascular accident, 53 (10.0%) atrial fibrillation, 23 (4.3%) heart failure, and 66 (12.5%) died. Cox regression analyses, adjusting for relevant Framingham covariates, showed that elevated BNP increased the risk of ACM, CVEs and specifically heart failure independently by 44% (hazard ratio [HR] 1.44; 95% confidence interval [CI] = 1.07 to 1.94, *P*=-0.017), 45% (HR 1.45; 95% CI = 1.15 to 1.82, *P*=0.002), and 288% (HR 3.88, 95% CI = 2.13 to 7.10, *P*<0.001), respectively. LVH on ECG increased the risk of ACM independently by 108% (HR 2.08; 95% CI = 1.14 to 3.81, *P*=0.017). LVH either on an ECG and/or echo increased the risk of heart failure independently by 309% (HR 4.09; 95% CI = 1.34 to 12.49, *P*=0.014).

Conclusion

In primary care patients with hypertension, BNP seems to be an important marker predicting future CVEs, especially heart failure, as well as all-cause mortality.

Introduction

Hypertension is very common in the general population[1], with a prevalence of up to 62% in older adults[2,3]. Long-term hypertension, an important cause of cardiovascular morbidity and mortality[4-6], requires optimal control and persistent adherence to prescribed medication to reduce the risk of cardiac, cerebrovascular, and renal disease. An important cardiac complication of poorly treated hypertension is the development of left ventricular hypertrophy (LVH), which often leads to heart failure and eventually to death[7,8].

Accurate risk stratification identifying those at high risk for future CVE in the primary care population with hypertension would be desirable. Screening for hypertension-mediated organ damage is crucial, as highlighted by the World Health Organization[9]. The presence of LVH on an electrocardiogram (ECG) has been shown to be of prognostic value, but the sensitivity and specificity of ECGs to detect LVH is limited. Therefore, echocardiography has become the routine gold-standard test to detect LVH[10,11]. There is increasing interest in the potential use of measuring the blood level of brain natriuretic peptide (BNP) for clinical stratification of cardiovascular risk in patients with hypertension[12]. Primary care physicians play a critical role in the detection, risk stratification, and treatment of patients with hypertension. The current European and UK GP guidelines of the management of hypertension do recommend an ECG at the start of treatment but no other additional diagnostic tests, like echocardiography and/or the BNP assessment[5,13]. The Dutch guidelines do not recommend any routine investigation at diagnosis of hypertension[14].

It is conceivable that, even in patients with hypertension without symptoms of heart failure, BNP assessment, an ECG, and echocardiography may be valuable in predicting future cardiovascular disease (CVD). The authors of the current study have previously found a high overall prevalence of previously undetected LVH using ECGs and echocardiography in 44% of a primary care population with hypertension[15]. It is currently unclear whether these patients are more likely to develop a cardiovascular event and/or have a higher mortality risk.

The main objective of the current study was therefore to investigate the predictive value of LVH on an ECG and/or on echocardiography and/or an elevated BNP, for the development of future cardiovascular events (CVEs) and all-cause mortality (ACM) in primary care patients with hypertension without symptoms of heart failure. The prospective design enabled follow-up data up to 9 years.

Methods

Participants

Patients in the current study were enrolled in the CHELLO study (Chronic Heart Failure Prevention Program), the details of which have already been published[15-19]. In summary, between June 2010 and January 2012, a total of 913 primary care patients, aged 60-85 years, with an International Classification of Primary Care (ICPC) code for hypertension (K86/K87) were invited to participate in the CHELLO study.

Inclusion criteria were: older primary care patients (aged 60-85 years) with hypertension included in the primary care cardiovascular risk management programme, without a diagnosis of heart failure (ICPC K77). Patients with a history of CVD (for example, myocardial infarction) were only included if they were no longer treated by a cardiologist. A total of 595 eligible patients gave written informed consent for participation.

Study procedure and data collection

After obtaining written informed consent, a healthcare nurse conducted a structured interview and performed an examination focusing on blood pressure, weight, and height assessment during a baseline visit. After 20 minutes of rest in a sitting position, blood pressure was automatically measured three times in a row with a digital blood pressure monitor with an upper cuff (first mean blood pressure) and was repeated after 20 minutes (second mean blood pressure). The mean value of both procedure outcomes was defined as the systolic/diastolic blood pressure, which was used for data analyses.

In addition, demographic and clinical variables were obtained during the interview and after reviewing the patient's medical records. Following the first appointment, blood was drawn by venepuncture to measure BNP and lipid profile.

A follow-up visit was planned at the patient's primary care practice to perform an ECG and echocardiogram. The ECG and echocardiogram were carried out by a trained, experienced echocardiographer from 'Diagnostiek voor U' in Eindhoven, the Netherlands, a primary care laboratory and medical diagnostics organisation.

A standard resting 12-lead ECG was recorded (paper speed 25 mm/s, 10 mm/mV). In the current study, the eight well-known and often-used criteria (see Supplementary Table S1) were used to evaluate LVH features during ECG[20-25]. If ≥

1 of these eight criteria were positive, ECG-LVH was diagnosed. An independent cardiologist who was blinded for outcomes of the echocardiogram gave a final review.

A transthoracic 2D echocardiographic examination was performed with an s5 transducer (Philips CX 50) in a standard position. All of the echocardiograms were reviewed by a panel of cardiologists specialised in echocardiography, according to European recommendations and guidelines for evaluating chamber quantification, diastolic dysfunction and heart valve disease[26-28]. LVH was defined as any abnormal left ventricular size measurement (septal or posterior wall thickness of > 0.9 cm in females or > 1.0 cm in males) and calculated left ventricular mass index adjusted for body surface area > 95 g/m2 in females and > 115 g/m2 in males. The Cube formula for LV mass was used: 0.8 x 1.04 x [(IVS+LVID+PWT)^3 – LVID^3] + 0.6g[27]. Where IVS is the interventricular septum; LVID is the left ventricular internal diameter; and PWT is the posterior (inferolateral) wall thickness.

Definition of the groups

To answer the study's research question, different groups were defined relating to the different tests:

- Group 1 distinguished between those with normal and those with elevated BNP. A cut-off of ≥10 pmol/l was used, which corresponds to ≥35 pg/ml, in the European and Dutch guidelines[29,30].
- Group 2 distinguished between the presence and absence of LVH on the ECG, according to the criteria described above.
- Group 3 were patients with or without LVH on the echocardiogram.
- Group 4 distinguished between the presence and absence of LVH on either the ECG and/or the echocardiogram.

The incidence of new CVEs and ACM during follow-up

To evaluate the incidence of new CVEs and ACM, a data extraction of the digital GP information system was performed in January 2020, providing follow-up data up to 9 years. Every GP in the Netherlands uses standard diagnosis codes for data entry into the electronic patient record form: ICPC. The occurrence of the following CVDs and deaths was registered: the development of coronary events (acute coronary syndrome; unstable angina pectoris or acute myocardial infarction), heart failure, atrial fibrillation, cerebrovascular diseases (transient ischaemic attack and cerebrovascular accident), and death with the ICPC codes: K74, K75, K76, K77, K78, K89, K90, and A96, respectively.

Statistical analyses

For the baseline characteristics, categorial variables are shown as numbers (percentage), continuous variables as mean (with standard deviation [SD]), and non-normally distributed variables as median (with interquartile range [IQR]).

For the comparison of the incidence of new CVEs and ACM during follow-up between males and females, the χ2-test was used. Cumulative incidence curves for the outcomes of ACM, all CVEs together, and heart failure were plotted using the gsurvfit package in R[31]. Curves were plotted for patients, using the four groups as described above, using years of follow-up as the timescale.

Univariable and multivariable Cox regression analyses (hazard ratios [HRs] and 95% confidence intervals [CIs]) were used to estimate the relationship between elevated BNP level, LVH on ECG, and LVH on an echocardiogram and developing a (specific) cardiovascular event or death. BNP level was included in the models as a log-transformed and continuous variable. Baseline Framingham risk variables included were used as potential confounders (age, gender, smoking, cholesterol, and systolic blood pressure).

All data were analysed with commercially available statistical software (IBM SPSS Statistics Version 26) and with R.

Results

Study Population

At baseline, a total of 592 patients provided written informed consent for participation in the CHELLO study[15-19]. For the current study, 23 patients were excluded based on missing baseline data (ECG and/or echocardiogram). Five patients were excluded based on poor image quality of the echocardiogram. At 9 years, of the remaining 564 participants, 34 patients were lost to follow-up. Baseline characteristics of patients who dropped out were similar to those who completed study duration. Therefore, data analyses in the current study included a total of 530 patients.

Baseline characteristics

Baseline demographics of the patient cohort are displayed in Table 1. The mean age was 70 years (SD 6.5) and 56.8% (*n* = 301/530) of the study population were female. At baseline, 257 (48.5%) patients had an elevated BNP (≥10pmol/l), 59 (11.1%) had LVH on ECG, and 190 (35.8%) had LVH on echocardiogram.

The characteristics of the current sample did not differ from the original CHELLO cohort[16-18], and patients who were lost to follow-up did not differ based on age and gender[19].

CVEs and ACM during 9 years' follow-up

The date of the follow-up extraction was 2 January 2020. The median duration of follow-up was 96.0 months (IQR 89.0-105.3).

Table 2 shows the incidence of all new CVEs (*n* =126) and ACM (*n* =66) during 9 years' follow-up. Of the participants, 31 (5.8%) had a coronary event, 44 (8.3%) a cerebrovascular event, 53 (10.0%) atrial fibrillation, and 23 (4.3%) developed heart failure. Of all patients, 27 (5.1%) had ≥ 1 CVE during the follow-up period.

Of the 126 patients with a new CVE, at baseline, 77 had an elevated BNP (61.1%), 19 had LVH on ECG (15.1%), and 46 had LVH on echocardiogram (36.5%). When the authors only focused on the 23 patients who developed heart failure these numbers were 23 (100%) for elevated BNP, five (21.7%) for LVH on ECG, and 13 (56.5%) for LVH on echocardiogram (data not shown).

No differences were found between males and females in the occurrence of overall CVEs or ACM (Table 2).

Table 1. Baseline demographics of 530 primary care patients with hypertension with 9 years' follow-up

Characteristic	n (%)[a]
Demographics	
Age, years, mean (SD)	70 (6.5)
Female	301 (56.8)
Male	229 (43.2)
Socioeconomics	
Having a partner	398 (75.1)
Low education[b]	72 (13.6)
Lifestyle	
Current smoker	67 (12.6)
Regular alcohol use[c]	165 (31.1)
Recommended physical exercise[d]	78 (14.7)
Clinical characteristics and risk factors	
Previous myocardial infarction	27 (5.1)
Previous CVA (TIA / stroke)	49 (9.2)
Diabetes	59 (11.1)
Peripheral artery disease	19 (3.6)
BMI, kg/m^2, mean (SD)	28 (4.5)
SBP, mmHg, mean (SD)	150 (19.6)
SBP >140 mmHg	356 (67.2)
SBP >150 mmHg	233 (44.0)
DBP, mmHg, mean (SD)	82 (10.5)
DBP >90 mmHg	101 (19.1)
Blood pressure on target[e]	212 (40.0)
Use of antihypertensive medication	407 (76.8)
Years of hypertension, median (IQR)	10.0 (4.0-16.0)
Total cholesterol, mmol/L, mean (SD)	5.1 (1.0)
LDL, mmol/L, mean (SD)	3.1 (0.9)
LDL on target[f]	128 (24.2)
Use of cholesterol lowering medication	233 (44.0)
BNP, pmol/l, median (IQR)	10.0 (5.7-18.0)
Elevated BNP ≥10pmol/l	257 (48.5)
LVH on ECG	59 (11.1)
LVH on echocardiogram	190 (35.8)

Table 1. Continued

[a]Unless otherwise stated. [b]Only primary elementary educated. [c]Defined as ≥ 2 glasses of alcohol per day on average. [d]Defined as ≥ 30 minutes exercise per day, at least 5 days per week. [e]On-target SBP defined as <140mmHg for people aged < 70 years and <150mmHg for people aged ≥ 70 years, according to Dutch primary care guideline[14]. [f]On-target LDL defined as <1.8 mmol/l for people aged <70 years and previous CVD, <2.6 mmol/l for people aged <70 years without previous CVD, and <2.6 mmol/l for people aged ≥ 70 years, according to the Dutch primary care guideline[14].
BMI = body mass index. BNP = brain natriuretic peptide. CVA = cerebrovascular accident. CVD = cardiovascular disease. DBP = diastolic blood pressure. ECG = electrocardiogram. LDL = low-density lipoprotein. LVH = left ventricular hypertrophy. SBP = systolic blood pressure. SD = standard deviation. TIA = transient ischaemic attack.

Table 2. Incidence of new cardiovascular events and death at 9 years' follow up

Cardiovascular event and death	Total, *n* (%), *n* =530	Male, *n* (%), *n* = 229	Female, *n* (%), *n* = 301	*P*-value
Coronary event	31 (5.8)	15 (6.6)	16 (5.3)	0.549
Myocardial infarction	9 (1.7)	2 (0.9)	7 (2.3)	0.200
Unstable angina pectoris	22 (4.2)	13 (5.7)	9 (3.0)	0.125
Cerebrovascular disease	44 (8.3)	20 (8.7)	24 (8.0)	0.753
TIA	22 (4.2)	9 (3.9)	13 (4.3)	0.824
Stroke	24 (4.5)	11 (4.8)	13 (4.3)	0.790
Atrial fibrillation	53 (10.0)	28 (12.2)	25 (8.3)	0.136
Heart failure	23 (4.3)	8 (3.5)	15 (5.0)	0.404
All-cause mortality	66 (12.5)	32 (14.0)	34 (11.3)	0.355
CVE, 1	126 (23.8)	58 (25.3)	68 (22.6)	0.464
CVE, >1	27 (5.1)	14 (6.1)	13 (4.3)	0.352

CVE = cardiovascular event. TIA = transient ischaemic attack.

Diagnostic tests in relation to CVEs, heart failure, and ACM

Cumulative incidence curves, Figures 1-3, show substantial differences in the direction and strength of the associations between each of the end points (that is, ACM, CVE, and heart failure) and a positive diagnostic test (that is, elevated BNP, LVH on ECG, LVH on echocardiogram, and LVH on ECG and/or echocardiography). The difference in the cumulative incidence of ACM (Figure 1) in patients with or without elevated BNP and with or without LVH on ECG was the largest (HR 2.07, 95% CI = 1.58 to 2.70, *P*<0.001 and HR 2.49, 95% CI = 1.40 to 4.43, *P*=0.002, respectively).

The cumulative incidence of CVEs (Figure 2) in patients with or without elevated BNP shows the largest difference (HR 1.60, 95% CI = 1.30 to 1.95, *P*<0.001).

The largest difference in the cumulative incidence of heart failure (Figure 3) was seen between patients with or without elevated BNP and with or without LVH either on ECG and/or echo (HR 3.98, 95% CI = 2.52 to 6.30, *P*<0.001 and HR 3.29, 95% CI = 1.35 to 7.99, *P*=0.009, respectively).

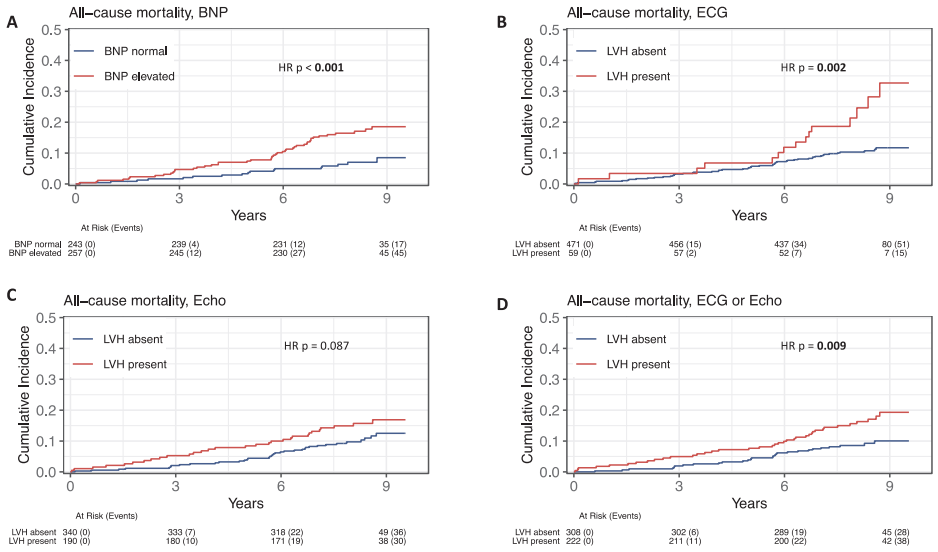


Figure 1. Cumulative incidence curves of all-cause mortality with diagnostic tests: A) BNP; B) ECG; C) echocardiography; and D) ECG or echocardiography.

BNP = brain natriuretic peptide. ECG = electrocardiogram. Echo = echocardiography. HR = hazard ratio. LVH = left ventricular hypertrophy.

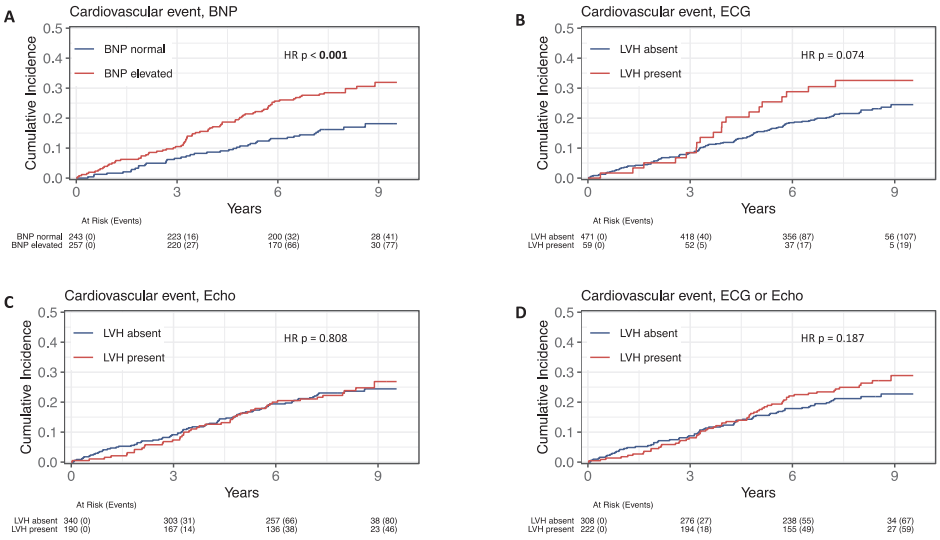


Figure 2. Cumulative incidence curves of cardiovascular events with diagnostic tests: A) BNP; B) ECG; C) echocardiography; and D) ECG or echocardiography.

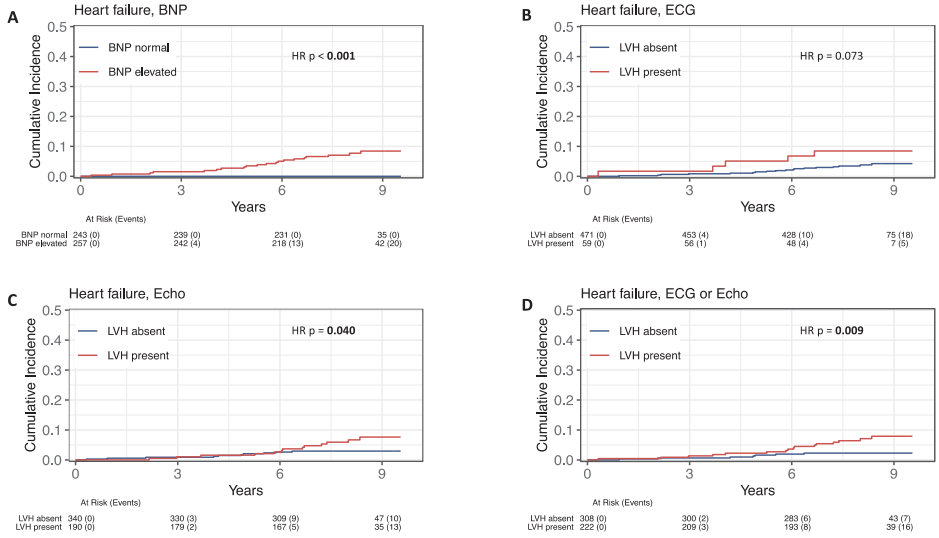
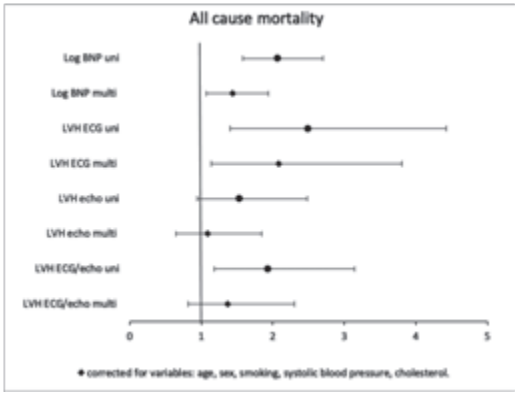
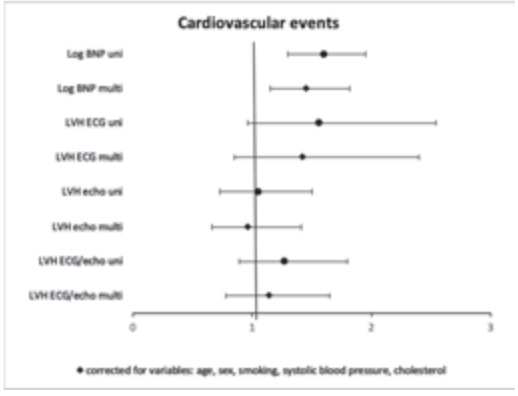


Figure 3. Cumulative incidence curves of heart failure with diagnostic tests: A) BNP; B) ECG; C) echocardiography; and D) ECG or echocardiography.

A



B



C



Figure 4. Forest plot of HRs and 95% CIs for different diagnostic tests in relation with A) all-cause mortality; B) cardiovascular events; and C) heart failure.

BNP = brain natriuretic peptide. ECG = electrocardiogram. Echo = echocardiography. HR = hazard ratio. LVH = left ventricular hypertrophy. Multi = multivariate. Uni = univariate.

Figure 4 shows the HRs, using multivariable Cox regression analyses after adjustment for the baseline risk variables (age, gender, smoking, cholesterol, and systolic blood pressure). Supplementary Table S2 shows specifications of the HRs. Elevated BNP (Group 1) was still significantly associated with the occurrence of ACM, CVEs, and heart failure (HR 1.44, 95% CI = 1.07 to 1.94, *P*=0.017; HR 1.45, 95% CI = 1.15 to 1.82, *P*=0.002; and HR 3.88, 95% CI = 2.13 to 7.10, *P*<0.001, respectively). LVH on ECG (Group 2) was still significantly associated with ACM (HR 2.08, 95% CI = 1.14 to 3.81, *P*=0.017). LVH either on ECG and/or echocardiography (Group 4) was still significantly associated with heart failure (HR 4.09, 95% CI = 1.34 to 12.49, *P*=0.014).

Discussion

Summary

In a random sample of primary care patients with hypertension but without symptoms of heart failure the current study found a significant and independent association between elevated BNP at baseline and the occurrence of ACM and new CVEs, specifically heart failure, after 9 years' follow-up. Presence of LVH on ECG at baseline was only significantly and independently associated with ACM. Presence of LVH on ECG and/or echocardiography at baseline was only significantly and independently associated with the occurrence of heart failure, but not with the occurrence of overall CVEs and all-cause mortality. LVH on ECG and/or echocardiography is a predictor for the occurrence of heart failure, however, interestingly, with a less strong predictive value than BNP.

Strengths and limitations

One strength of the current study is the relatively large primary care sample with carefully registered follow-up data up to 9 years. This enabled the authors to evaluate possible associations between different diagnostic tests and the development of ACM, new CVEs, and, in particular, heart failure.

A limitation is that the outcome of the diagnostic tests used at baseline could have potentially affected the treatment of hypertension. It is conceivable that finding an elevated BNP or LVH on ECG and/or echocardiogram led to more intensive treatment. However, more intensive treatment could theoretically only have attenuated the association between elevated BNP at baseline and the occurrence of heart failure, CVEs, and ACM.

Another limitation is that the levels of BNP at baseline could possibly be influenced by medication (use of diuretics or angiotensin-converting enzyme (ACE) inhibitors), potentially decreasing BNP production[32]. Conversely, conditions like chronic obstructive pulmonary disease (COPD) or diabetes can elevate BNP levels[33,34]. However, in this study, BNP levels showed no difference between diuretics/ACE inhibitor users and non-users, and between people with and without diabetes. Unfortunately, COPD and cirrhosis data were unavailable in this cohort.

Furthermore, a limitation of the study was that only data on ACM and not on cardiovascular death specifically were available, a result of ethical limitations regarding the privacy of centrally registered mortality causes. Therefore, it

was not possible to come to a conclusion about any association between the diagnostic tests and possible cardiovascular death.

Comparison with existing literature

In the current study population, 24% of the patients developed a CVE during 9 years of follow-up and 4.3% of the patients developed heart failure. These results are in line with findings in literature[35]: in a primary care population in the UK, the prevalence of CVEs increased with age, with a prevalence up to 25% in those aged 70-79 years. Additionally, this UK study showed a prevalence of heart failure of 1.1% in the total population, but they did not stratify by age category. In 2019, the prevalence of registered heart failure in the Dutch population aged ≥ 65 years was 6.1%[29].

The predictive value of BNP for the occurrence of heart failure, CVEs, and death is mainly investigated in high-risk populations[36], for example, in patients with diabetes mellitus[37,38]. Literature on the relationship between BNP, CVEs, and death in primary care patients without symptoms is scarce[39-41]. The studies undertaken in this specific primary care population have shown that the additional use of BNP as a risk modulator is complementary compared with the use of traditional risk factors only[38-40]. This finding might be explained by the fact that an elevated BNP is an actual marker of elevated filling pressure in the heart, because of intra- or extra-cardiac factors[36].

Implications for research and practice

In the current European[5] and UK's[13] primary care guidelines for cardiovascular risk management, an initial ECG for evidence of LVH at diagnosis of hypertension is advocated. The current study suggests that an additional BNP assessment, even in patients with hypertension without symptoms of heart failure, is useful in detecting patients at risk for ACM, overall CVEs, and, more specifically, the occurrence of heart failure.

According to the QRISK3 classification system[42], all patients in the current cohort were already at high risk of developing CVE by virtue of age and hypertension. Within this high-risk group there is a subgroup that are at very-high risk for future CVEs; aged > 60 years with an increased BNP.

In those patients with an increased BNP, GPs should be careful prescribing negative inotropic agents (such as calcium antagonists) for treatment of hypertension and focus on ACE inhibitors or angiotensin receptor blockers, which

have demonstrated efficacy in heart failure prevention[30]. Moreover, high-risk patients with hypertension should receive more aggressive treatment strategies to achieve target blood pressures[39].

Future research should inform guideline committees on the necessity of periodic BNP assessments (like annual glucose and cholesterol assessments). BNP laboratory testing is easily accessible for primary care physicians, relatively inexpensive, and demonstrates strong predictive power for future CVEs. The current findings suggest that in older patients with hypertension, an ECG is less sensitive for predicting future CVEs and mortality compared with BNP assessment.

After determination of the BNP level, an echocardiogram seems no longer required in primary care as a standard examination to estimate cardiovascular risk. Echocardiography should only be considered if significant heart murmurs are present or BNP levels appear to be substantially elevated, and will help to decide whether a consultation with a cardiologist is indicated. Given the ageing population, cost reduction in health care is imperative.

In conclusion, the current primary care study in older patients with hypertension shows that BNP analysis has an important predictive value for ACM and the occurrence of CVEs, in particular heart failure. BNP analysis should therefore be considered as an additional diagnostic tool to standard risk stratification.

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Ethical approval
The study protocol was approved by the medical ethics committee of the Elisabeth Hospital in Tilburg, the Netherlands (reference: NL38933.008.12).

Competing interests
The authors have declared no competing interests.

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Supplementary Table S1. ECG criteria to evaluate LVH

Eight well-known and often-used criteria in order to evaluate LVH features during ECG
The Sokolow-Lyon index: the sum of the S wave in V1 and the R wave in V5 of V6 > 3.5mV[1]
The sum of the S wave in V2 and the R wave in V5 or V6 > 4.5mV[2]
The amplitude of the R wave in V5 or V6 > 2.6mV[1]
A comparison of the amplitude of the R wave in V5 and V6; R V6 > R V5[3]
The sum of the largest amplitude of the R wave and the largest amplitude of the S wave in precordial leads > 4.5mV[4]
The Cornell Voltage: the sum of the R wave in aVL and the S wave in V3 > 2.0mV for females and > 2.8mV for males[5]
The amplitude of the R wave in aVL > 1.1mV[1]
The Gubner-Ungerleider voltage: the sum of the R wave in I and the S wave in the III lead > 2.5mV[6]

ECG = electrocardiogram. LVH = left ventricular hypertrophy.

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Supplementary Table S2. HRs for different diagnostic tests in relation with ACM, CVEs, and heart failure

	ACM	
	HR (95% CI)	*P*-value
Log BNP		
Uni HR	2.07 (1.58-2.70)	***<0.001***
*Mulit HR**	1.44 (1.07-1.94)	***0.017***
Multi NIEUW	1.40 (1.03-1.89)	***0.031***
LVH ECG		
Uni HR	2.49 (1.40-4.43)	***0.002***
*Multi HR**	2.08 (1.14-3.81)	***0.017***
LVH echo		
Uni HR	1.53 (0.94-2.48)	0.087
*Multi HR**	1.09 (0.65-1.84)	0.736
LVH ECG/echo		
Uni HR	1.93 (1.18-3.14)	***0.009***
*Multi HR**	1.37 (0.82-2.30)	0.235
	CVEs	
	HR (95% CI)	*P*-value
Log BNP		
Uni HR	1.60 (1.30-1.95)	***<0.001***
*Mulit HR**	1.45 (1.15-1.82)	***0.002***
LVH ECG		
Uni HR	1.56 (0.96-2.54)	0.074
*Multi HR**	1.42 (0.85-2.40)	0.185
LVH echo		
Uni HR	1.05 (0.73-1.50)	0.808
*Multi HR**	0.96 (0.66-1.41)	0.844
LVH ECG/echo		
Uni HR	1.27 (0.89-1.80)	0.187
*Multi HR**	1.14 (0.78-1.65)	0.506

Supplementary Table S2. Continued

	Heart failure	
	HR (95% CI)	*P*-value
Log BNP		
Uni HR	3.98 (2.52-6.30)	***<0.001***
*Mulit HR**	3.88 (2.13-7.10)	***<0.001***
LVH ECG		
Uni HR	2.47 (0.92-6.67)	0.073
*Multi HR**	2.46 (0.87-6.96)	0.089
LVH echo		
Uni HR	2.37 (1.04-5.41)	***0.040***
*Multi HR**	2.35 (0.91-6.11)	0.079
LVH ECG/echo		
Uni HR	3.29 (1.35-7.99)	***0.009***
*Multi HR**	4.09 (1.34-12.49)	***0.014***

*corrected for Framingham variables: age, gender, smoking, systolic blood pressure, cholesterol.

HR = Hazard Ratio. CI = confidence interval. Echo = echocardiography. BNP = brain natriuretic peptide. LVH = left ventricular hypertrophy. ECG = electrocardiogram. ACM = all-cause mortality. CVEs = cardiovascular events.





CHAPTER 6

General discussion and future perspectives

General discussion and future perspectives

The overarching aim of the thesis was to focus on the cardiovascular (CV) risk assessment of patients with essential hypertension in primary care. Specifically, we investigated the additional value of several factors, such as psychological distress, brain natriuretic peptide (BNP), the electrocardiogram (ECG) and echocardiography, in the prediction of cardiovascular events (CVE) and all-cause mortality in patients with hypertension. Through an extensive eight to nine years follow-up period, this thesis delineates key outcomes. In *the first part* we focused on the role of anxiety and depression symptoms as an additional risk factor for developing CVEs and all-cause mortality in patients with hypertension. Psychological distress, assessed through anxiety and depression symptom scores, emerged as an independent predictor of new coronary events (**Chapter 2**) in asymptomatic primary care patients with hypertension. In *the second part,* we focused on additional diagnostic tools and their potential role in advancing cardiovascular risk management. Age and gender nuances in BNP reference ranges challenge the conventional uniform cut-offs, suggesting potential benefits in adopting age- and gender-dependent thresholds (**Chapter 3**). The detection of left ventricular hypertrophy (LVH) solely based on ECG proved to be suboptimal compared to the recommended golden standard echocardiography (**Chapter 4**). Integrating these findings, the follow-up study underscored the critical predictive value of an elevated BNP for adverse CV outcomes, advocating for its inclusion in routine risk assessments for elderly patients with hypertension (**Chapter 5**). This comprehensive approach paves the way for a more nuanced and personalised CV risk management paradigm, we conclude this discussion with the main findings, implications for clinical practice and recommendations for future research.

Part 1: anxiety and depression symptoms as an additional risk factor for CVEs

Psychological distress predicts new coronary events in primary care

In *the first part* we focused on the role of psychological distress, encompassing anxiety and depression symptoms, as an additional risk factor for patients with hypertension in developing CVEs and all-cause mortality. Therefore, in **Chapter 2,** we explored the complex association between anxiety and/or depression symptoms in a sample (n=555) of elderly patients with hypertension in the primary care setting and the subsequent development of new CVEs at 8 years' follow-up. Additionally, we assessed the relation between anxiety and/or depression symptoms and all-cause mortality.

We discovered that elevated anxiety and elevated depression scores increased the risk of new coronary events independently and significantly by 12% and 18%, respectively. No associations were found with regard to other CVEs (cerebrovascular events, atrial fibrillation and heart failure) and all-cause mortality. Patients with both elevated anxiety (GAD-7 ≥ 8) and depression (PHQ-9 ≥ 5) scores and were 5.5 times more likely to develop new coronary events, compared to those without elevated symptom scores at baseline, even at lower symptom cut-off scores.

Comparison with existing literature revealed that the prevalence of new CVEs in our study aligns with previous UK studies[1]. The prevalence of anxiety and depressive symptoms in the elderly primary care subjects also mirror findings from other studies[2,3]. Limited data exist on GAD-7 and PHQ-9 cut-off validation in primary care elderly populations. There are only four reports on PHQ-9 cut-offs for elderly patients, with three involving small populations[4-6], and the only study with a relative larger sample size focused on chronic patients with diabetes and chronic obstructive pulmonary disease[7]. Notably, our study revealed that the association between psychological distress and new coronary events exists at much lower cut-offs (GAD ≥ 3 and PHQ-9 ≥ 4) than commonly reported in primary care literature. In psychiatry and psychology, cut-offs on anxiety and depression scales typically rely on the sensitivity, specificity and positive predicted value of certain cut-off scores to predict a syndromal diagnosis of depression, assessed during structured interviews[8,9]. The current study introduced an 'epidemiological' approach, using percentiles or quartiles of anxiety / depression scores predicting poor cardiac outcomes. This approach with substantially lower cut-offs revealed that elderly patients, already at these lower levels were significantly more likely to develop new coronary events during follow-up. This mirrors large epidemiological studies showing that achieving lower levels of blood pressure, total cholesterol, or LDL benefit health outcomes in those at risk for cardiac disease[10]. The current study suggested that in clinical practice, extrapolating symptom cut-off scores to predict poor cardiac outcomes could benefit health outcomes[11].

Numerous explanations for the association between psychological distress and cardiovascular disease (CVD) are discussed in the literature, as highlighted in an European Heart Journal review[12]. While the paper's title (depression and cardiovascular disease: a clinical review) suggested a focus on CVDs in general, the authors consistently reported papers linking depression to cardiac issues. Proposed mechanisms include biological factors (genetics, neuro-hormonal, inflammation pathways), behavioral factors (association with poor lifestyle habits), and psychosocial factors (financial problems, unemployment, loss of capabilities).

This study affirmed a significant association between anxiety/depression and new coronary events but not with other CVDs such as CVA. The review also noted the frequently found association between anxiety and cardiac disease. Anxiety and depression, being comorbid disorders, exhibit a 40–50% overlap. In this study, the baseline correlation between anxiety and depression symptoms was 0.56, suggesting a substantial overlap in symptom variance. A growing consensus, reflected in the DSM-V, considers anxiety and depression symptoms as distress symptoms. Our study highlighted the highest association between new coronary events and distress symptoms above a specific cut-off, consistent with previous reports[13].

In the Netherlands, extensive health care programs[14], including diabetes, COPD and cardiovascular risk management (CVRM), are managed by specially trained nurses based on guidelines from the Dutch College of General Practitioners[15]. While these guidelines increasingly address mental health in chronic diseases, there is currently no standardised instrument used in CVRM. The current study underscores the importance of implementing such an instrument to assess psychological distress. If implemented, patients with higher distress levels could benefit from simple interventions like mindfulness training. Cognitive-based mindfulness interventions, proven effective in primary care elderly diabetes-II patients[16,17], are now offered online, making them easily accessible and cost-effective[18,19], bypassing the growing waiting list for treatment of mental health problems in general.

One strength of this study is the relatively large primary care sample with carefully registered follow-up data up to eight years of follow-up. This extended follow-up period allowed for the evaluation of associations between distress symptoms and new coronary events at different cut-offs. Another strength is that we used standardised instruments to assess depression and anxiety.

Limitations include assessing anxiety and depression at a symptom level instead of syndromal level. However, there is growing consensus, as summarized in the DSM-5, to assess psychological distress, such as depression and anxiety, on symptom level instead of using a dichotomous approach[20]. Another limitation is the lack of repeated assessments during the 8-year follow-up (though a single baseline measurement may be predictive[21]), and the unavailability of specific data on cardiac death due to strict constraints in the Netherlands with regard to privacy. Also, despite a large sample size, the number of new coronary events was relatively low, potentially due to the characteristics of the sample—a primary care hypertension population with uncomplicated profiles.

In conclusion, this study established that elderly primary care hypertension patients with high distress levels (anxiety/depression) were more prone to develop future coronary events.

Part 2: additional diagnostic tools in advancing cardiovascular risk management

Age- and Gender-Specific BNP Reference Ranges in Primary Care

In *the second part,* we focused on additional diagnostic tools and their potential role in advancing cardiovascular risk management. First, in **Chapter 3**, we examined age and gender's impact on BNP levels in primary care. BNP has served as a diagnostic tool for heart failure identification and monitoring fort the past three decades[22-25]. Currently, it is utilized in primary care for patients displaying signs or symptoms of heart failure. Heart failure guidelines, both national and international[26,27], apply two single cut-off BNP levels for gradually and acute onset heart failure, with no differentiation based on gender or age. However, relying on a single cut-off for BNP, irrespective of age and gender, may lack specificity in in daily practice. The established cut-off aims to maximize sensitivity, potentially leading to numerous false positive cases at higher ages and unnecessary referrals to cardiologists for older patients. This underscored the importance of investigating the added value in adjusting reference values. We introduced age- and gender specific cut-off levels for BNP based on a large cohort (n=9447) referred to a primary care laboratory for BNP assessment.

This study showed that age and gender had a significant influence on BNP levels. Age had more influence than gender. This was also found by others[28,29]. Other authors reported no significant age or gender influence (30). However, all these studies had a much smaller study population than the present study, e.g. the largest sample in other studies included 911 subjects. As a consequence, their subgroups according to age and gender became rather small.

The heart failure guidelines[26,27] use a single BNP cut-off for the primary care population without distinction for gender and age and this has definitely limitations. For example, in the sub-group of men between 70 and 80 years, a rigorous cut-off of 29 pmol/L would have resulted in 31% of participants in this group diagnosed as having elevated BNP. In the age group older than 80 years, this would even have increased further to 53%. As a consequence, many participants would be falsely diagnosed as having elevated BNP (especially the elderly) and referred for unnecessary further diagnostics, such as cardiac echo which would substantially increase the costs. If the guidelines would apply age- and gender-dependent BNP cut-off values, a substantial lower number of

patients will be referred by GPs for an echocardiogram, resulting in a considerable cost reduction. Future research, however, should elaborate on the adjusted BNP cut-off findings of this study by assessing the specificity, sensitivity, positive and negative predictive value of an elevated BNP on an abnormal echocardiogram and clinical signs of heart failure.

Remarkedly, nine years after this study, the heart failure guideline have not adjusted the reference values according to age and gender. New studies on this topic since ours are scarce. One explanation could be, that BNP assessment is increasingly gaining attention as a risk stratification factor for CVD rather than just to exclude the existence of possible heart failure. Perhaps different cut-off values should be used for these different indications.

Limitations of this study included not using a random sample but a GP-referred cohort, though comparisons with a second study population of primary care hypertension patients showed no significant differences. The second study's inclusion criteria based on International Classification of Primary Care (ICPC) and exclusion of chronic heart failure (CHF) patients might not eliminate early-stage CHF cases, reflecting a common challenge in primary care. We corrected for chronic renal failure and diabetes associations with abnormal BNP results[28,31-36]. Additionally, our cohort, visiting the laboratory independently, likely excluded acute or severe chronic heart failure cases. We used a statistical technique for establishing reference ranges[37], which identifies the underlying normal (or log-normal) data distribution in a dataset also containing abnormal results. This technique assumes that the majority of data is from "normal", healthy participants and our study cohort met this requirement. This method has proven effective for estimating reference ranges in large patient cohorts, demonstrating applicability even in hospital settings with more severe illnesses[38].

In conclusion this study showed that, in primary care, the definition of normal BNP reference ranges needs to be age-dependent when it is used to exclude the existence of possible heart failure.

Left Ventricular Hypertrophy (LVH) Detection in Elderly Patients with Hypertension

Another clinical finding related to hypertensive heart disease is LVH, associated with a two- to fourfold increased risk of cardiovascular morbidity and mortality compared to patients with normal LV mass[39]. In cases of long-standing hypertension, especially with known high morbidity and mortality, it is hypothesized

that recognizing LVH should rely on the most reliable method available, in order to intensify the regulation of blood pressure so that LVH can be modified in time[40-42]. Therefore, in **Chapter 4**, we conducted a cross-sectional study investigating the prevalence of LVH in elderly primary care patients with long-standing asymptomatic hypertension. The study assessed the diagnostic value of ECG as a screening tool for LVH compared to, the golden standard, echocardiography in this specific patient population (n= 422). We found a 44% prevalence of LVH using echocardiography, increasing significantly with age, reaching 60% in those over 75. ECG demonstrated poor sensitivity (14%) in detecting LVH as diagnosed on echocardiogram, with prevalence stabilising around 16%–18% in the highest age group. This study highlighted the importance of early detection and treatment of LVH to reduce CV morbidity and mortality, even in those older than 65, especially in primary care where an easy, affordable, and reliable screening tool is needed.

Compared with existing literature, the current study found a higher prevalence of echocardiographically confirmed LVH (44%) in primary care patients with long-standing hypertension compared to general population estimates[43,44]. The current prevalence was comparable to two other studies with hypertension patients[45,46]. ECG's sensitivity for detecting LVH remained poor, aligning with previous studies[47-50]. We hypothesised that the reliability of ECG may be better in a selected group of patients (with long- standing hypertension) compared to the general population. However, our data showed that ECG performed equally poor even in this specific higher risk population. Although our results have shown that ECG may not be recommended for the detection of LVH, the prognostic value of ECG in elderly primary care patients with hypertension on developing CVD remains uncertain. It has been hypothesised that ECG may be of additional value for prognosis[40,51,52]. Others suggested that LVH detected using ECG and LVH detected using echocardiography are two distinct entities that only partially overlap, and have different prognostic significance[53]. This hypothesis could explain the stronger association of elevated BNP with LVH using ECG as opposed to LVH using echocardiogram. The current study was unable to address this further at a cross-sectional level.

Our study reaffirmed that routinely acquired ECGs lack significant diagnostic value for detecting LVH in patients with hypertension, even in those with long-standing hypertension. Conversely, ECG-derived LVH appeared to be a distinct entity and a predictor of CV mortality, independent of LV mass index and morphology. Performing both ECG and echocardiography in patients with hypertension seems warranted, although current Dutch guidelines[15] in primary

care do not recommend routine use of either and European guidelines[54] does recommend an ECG at the start of treatment but no other additional diagnostic tests, like echocardiography. Our findings suggest that, when feasible, patients, particularly uncomplicated elderly individuals with hypertension (a significant proportion of the population), should undergo focused echocardiography for LVH detection. Adding an ECG may offer additional prognostic value independently of echocardiographic findings. Moreover, our study revealed that over half of the patients did not meet blood pressure targets, indicating that early recognition of LVH could enhance patient awareness and therapy adherence. Early detection of LVH could identify patients who might benefit from intensified antihypertensive therapy, potentially preventing or delaying CVD progression.

Strengths of this study include evaluating LVH prevalence using echocardiography in a specific primary care cohort and comparing ECG's ability to detect LVH. This study recommended a standard role for echocardiography in screening for LVH in primary care patients with hypertension. However, limitations include the lack of a control group and absence of long-term data on cardiac events.

In conclusion, asymptomatic elderly primary care patients with long-standing hypertension exhibited a high prevalence of LVH, increasing with age. ECG proved suboptimal for detecting LVH, suggesting that those requiring close monitoring and stricter antihypertensive treatment may benefit from echocardiography. In our longitudinal follow-up study, we explored the prognostic value of ECG and echocardiography in this specific population. However, future research should reveal whether early detection of LVH by echocardiography in primary care reduces morbidity and mortality amid the rising prevalence of hypertension.

Prediction of CVEs in uncomplicated patients with hypertension

Furthermore, accurate risk stratification to identify those at high risk for future cardiovascular events in the primary care population with asymptomatic hypertension would be desirable. The presence of LVH on ECG has shown to be of prognostic value, but the sensitivity and specificity of ECG to detect LVH may be limited as showed before. Echocardiography has become the routine gold-standard to detect LVH[47,55]. There is also growing interest in measuring BNP to stratify CV disease risk in patients with hypertension[56]. Like mentioned before, the European guidelines for the management of hypertension, does recommend an ECG at the start of treatment but no other additional diagnostic tests, like echocardiography and/or the assessment of BNP[54,57]. The Dutch guidelines do not recommend any routine investigation at diagnosis of hypertension[15]. It is conceivable that, even in patients with hypertension

without symptoms, assessment of BNP, ECG and echocardiography may be valuable in predicting future cardiovascular disease (CVD). Therefore, in **Chapter 5**, we investigated the predictive value of LVH on ECG and/or on echocardiography and/or an elevated BNP for the development of future cardiovascular events (CVEs) and all-cause mortality in a cohort of asymptomatic primary care patients with long-standing hypertension. The prospective design enabled follow-up data up to nine years. We found a significant and independent association between elevated BNP levels at baseline and all-cause mortality, as well as new CVEs, specifically heart failure, over a nine-year follow-up period. Presence of LVH on ECG at baseline was only significantly associated with all-cause mortality. The combination of LVH on ECG and/or echocardiography at baseline was independently associated with the occurrence of heart failure, though with a less robust predictive value than BNP.

The study's results align with literature findings on the prevalence of CVEs in the elderly population[1,26]. The predictive value of BNP for the occurrence of heart failure, CVEs and death is mainly investigated in high-risk populations[58], for example in patients with diabetes mellitus[59,60]. Literature on the relation between BNP, CVEs and death in primary care patients without symptoms is scarce[61-63]. The studies performed in this specific primary care population have shown that the additional use of BNP as a risk modulator is complementary compared to the use of traditional risk factors only[60-62]. This finding might be explained by the fact that an elevated BNP is an actual marker of elevated filling pressure in the heart, due to intra- or extracardiac factors[58].

Current European and UK primary care guidelines recommend an initial ECG for evidence of LVH at hypertension diagnosis[54,57]. Our study suggested that adding BNP assessment, even in asymptomatic patients with hypertension, aids in identifying those at risk for all-cause mortality, overall CVEs, and specifically, heart failure. According to the QRISK3 classification[64], our cohort, already at high CVE risk due to age and hypertension, included a subgroup—aged above 60 years with increased BNP—at very high risk. In case of an increased BNP, GPs should be careful prescribing negative inotropic agents (such as calcium antagonists) for treatment of hypertension and focus on ACE-inhibitors or ARB's, which have demonstrated efficacy in heart failure prevention[27]. High-risk patients with hypertension require more aggressive treatment for target blood pressures[61].

Future research should guide the periodicity of BNP assessments, like glucose and cholesterol assessments. BNP testing, accessible and cost-effective, demonstrated robust predictive power for future CVEs. In elderly hypertensives,

our findings indicated that an ECG and echocardiogram are less sensitive than BNP assessment for predicting future CVEs and mortality. After BNP assessment, routine echocardiography in primary care becomes unnecessary for estimating CV risk, unless significant heart murmurs are present or BNP levels are substantially elevated, warranting consultation with a cardiologist. Given the aging population, healthcare cost reduction is crucial.

The study's strength is its relatively large primary care sample with carefully registered follow-up data spanning nine years, allowing for comprehensive evaluation of associations between diagnostic tests and the development of outcomes. However, limitations include the absence of long-term data on cardiac events and potential influence of baseline test outcomes on hypertension treatment. Another limitation is that the levels of BNP at baseline could be possibly influenced by medication (use of diuretics or ACE inhibitors), potentially decreasing BNP production[65]. Conversely, conditions like COPD or diabetes can elevate BNP levels[66,67]. However, in this study, BNP levels showed no difference between diuretics/ACE inhibitor users and non-users and between diabetics and non-diabetics. Unfortunately, COPD and cirrhosis data were unavailable in this cohort.

In conclusion, this primary care study of elderly patients with hypertension highlighted the important predictive value of a BNP assessment for all-cause mortality and the occurrence of CVEs, particularly heart failure. BNP assessment could be a valuable addition to standard risk stratification in the primary care setting.

Main implications for practice and future research

This comprehensive exploration of CV risk assessment in elderly patients with hypertension within primary care has provided valuable insights with important implications for both clinical practice and future research. Here we mention, in our opinion, the two most important ones.

First, we strongly advocate for the integration of psychological distress screening tools (anxiety and depression symptoms), for example with GAD-7 and PHQ-9, into routine assessments for primary care patients with hypertension. The implementation of standardised instruments for psychological distress evaluation has the potential to streamline early intervention through accessible and cost-effective methods like on line cognitive based mindfulness interventions. Despite being mentioned in the footnotes of the current Dutch CV risk management guidelines[15], we believe that

the assessment of psychological distress should be more prominently emphasised. Subsequent research should investigate whether intervening with patients exhibiting symptoms of anxiety and/or depression results in a reduced CV risk. Additionally, determining the optimal frequency of measuring anxiety and depressive symptoms in patients with hypertension is crucial. We propose initiating this practice during the inclusion of patients in the CV risk management program in primary care and subsequently evaluating it, for example, on an annual basis.

Secondly, although we found in our cross-sectional cohort of asymptomatic elderly primary care patients with long-standing hypertension a high prevalence of LVH with echocardiography, in our subsequent follow-up study, of the same cohort, we discovered that patients with LVH on their echocardiograms did not exhibit a significantly higher risk of CVEs and mortality. We observed a significant relationship between LVH on the echocardiogram and the occurrence of heart failure, but this association lost significance after adjusting for other factors. Therefore, despite the potential importance of detecting LVH in patients with hypertension for improved treatment, this specific cohort did not show a long-term impact of an echocardiogram on detection of future CVEs. Given the costliness of conducting standard ECG and particularly echocardiography, both in terms of time and expenses, we do not recommend routine use. Future research needs to establish whether the routine use of ECG and/or echocardiography in patients with hypertension provides additional value in other aspects and can contributes to reducing morbidity and mortality.

Instead, we recommend integrating a BNP assessment, which is easy to access and not expensive, into routine risk stratification of hypertension patients in primary care. We showed that elevated BNP levels are a robust predictor of adverse CV outcomes, including heart failure and all-cause mortality. This suggests that integrating BNP assessments into routine risk stratification can enhance the identification of high-risk patients with hypertension, guiding treatment decisions and potentially reducing healthcare costs. For now, we recommend determining BNP levels annually in patients with hypertension from the time of diagnosis. If elevated, repeated BNP assessments are not necessary, as these patients are already at high risk and deserve stricter treatment to reduce their CV risk. If BNP levels are not elevated, we advise including this assessment on an annual base. However, future studies should guide the optimal periodicity of BNP assessments, similar to glucose and cholesterol evaluations. Establishing the adequate frequency of BNP testing could contribute to a more refined and personalised approach to CV risk management in elderly hypertensive populations.

In conclusion, this thesis enhances our understanding of CV risk assessment in elderly patients with hypertension and offers actionable insights for improving clinical practice. The identified research gaps pave the way for future investigations that can refine risk stratification strategies and contribute to more effective and cost-efficient CV care in primary settings.

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CHAPTER 7

Summaries

Summary

Cardiovascular diseases (CVDs) are a leading global cause of death, with hypertension as a major risk factor. Hypertension, often asymptomatic, can lead to severe complications. Risk stratification is crucial for early detection and intervention. Lifestyle changes and medications are key in managing hypertension, reducing the overall burden of CVDs, and improving patient outcomes. Primary care physicians play a critical role in the detection, risk stratification and treatment of patients with hypertension. Nowadays, the majority of patients with hypertension are supervised and treated in primary care, in extensive health care programs such as cardiovascular risk management and diabetes.

The overarching aim of the thesis was to focus on the cardiovascular (CV) risk assessment of patients with essential hypertension in primary care. Specifically, we investigated several factors, such as psychological distress (anxiety and depression symptoms), brain natriuretic peptide (BNP), ECG and echocardiography, that may predict the development of cardiovascular events (CVEs) in patients with hypertension. The collective pursuit of this thesis was to advance the understanding of CV risk assessment in patients with hypertension within primary care. Through an extensive eight to nine years follow-up period, this thesis delineated key outcomes.

In *the first part* we focused on the role of anxiety and depression symptoms as an additional risk factor in patients with hypertension for developing CVEs and all-cause mortality. Elevated psychological distress, assessed through anxiety and depression symptoms, emerged as an independent predictor of new coronary events (**Chapter 2**). We discovered that elevated anxiety and elevated depression scores increased the risk of new coronary events independently and significantly by 12% and 18%, respectively, in a primary care cohort of patients with hypertension (n=555). No associations were found with regard to other CVEs and all-cause mortality. Patients with both elevated anxiety (GAD-7 ≥ 8) and depression (PHQ-9 ≥ 5) scores and were 5.5 times more likely to develop new coronary events, compared to those without elevated symptom scores at baseline, even at much lower symptom cut-off scores.

In *the second part,* we focused on additional diagnostic tools and their potential role in advancing CV risk management. We introduced, in **Chapter 3**, age- and gender specific cut-off levels for BNP based on a large cohort (n=9447) referred to a primary care laboratory for BNP assessment. This study showed that age and

gender had a significant influence on BNP levels, suggesting potential benefits in adopting age- and gender-dependent thresholds instead of the current single BNP cut-off for the primary care population without distinction for gender and age.

In **Chapter 4** we conducted a cross-sectional study investigating the prevalence of left ventricular hypertrophy (LVH) in elderly primary care patients with long-standing asymptomatic hypertension. The study assessed the diagnostic value of ECG as a screening tool for LVH compared to, the golden standard, echocardiography in this specific patient population (n= 422). The detection of LVH via ECG proved to be suboptimal, with a poor sensitivity of 14% compared to a diagnosis of LVH in 44% of the cases using the golden standard: echocardiography. The prevalence of LVH using echocardiography increased significantly with age, reaching 60% in those over 75 years of age.

Subsequently, we investigated in the follow-up study (n=530), in **Chapter 5,** the predictive value of LVH on ECG and/or on echocardiography and/or an elevated BNP for the development of future CVEs and all-cause mortality in the same cohort of asymptomatic primary care patients with long-standing hypertension. We found a significant and independent association between elevated BNP levels at baseline and all-cause mortality, as well as new CVEs, specifically heart failure, over a nine-year follow-up period. Presence of LVH on ECG at baseline was only significantly associated with all-cause mortality. The combination of LVH on ECG and/or echocardiography at baseline was independently associated with the occurrence of heart failure, though with a less robust predictive value than BNP.

This comprehensive approach paves the way for a more nuanced and personalised CV risk management paradigm. The main findings were that elevated psychological distress emerged as an independent predictor of new coronary events and the critical predictive value of elevated BNP for adverse cardiovascular outcomes in elderly patients with hypertension. Despite the high prevalence of LVH detected by echocardiography in asymptomatic elderly patients with hypertension, it did not significantly impact long-term outcomes. Therefore, we strongly recommend the integration of standardized psychological distress screening tools (anxiety and depression questionnaires) and routine periodic BNP assessment in the CV risk management guidelines for refined and personalized CV risk management in elderly patients with hypertension.

Nederlandse samenvatting

Cardiovasculaire ziekten vormen wereldwijd een belangrijke doodsoorzaak, met hypertensie als een van de belangrijkste risicofactoren. Hypertensie, vaak asymptomatisch, kan, zeker onbehandeld, leiden tot ernstige complicaties. Risicostratificatie is cruciaal voor vroegtijdige detectie en interventie. Leefstijlveranderingen en medicatie spelen een sleutelrol in de behandeling van hypertensie, het verminderen van cardiovasculaire aandoeningen en het verbeteren van de patiëntuitkomsten. Huisartsen spelen een cruciale rol bij de detectie, risicostratificatie en behandeling van patiënten met hypertensie. Tegenwoordig worden veruit de meeste patiënten met hypertensie begeleid en behandeld in de eerste lijn, in daarvoor speciaal opgezette zorgprogramma's zoals cardiovasculair risicomanagement en diabetes.

Het overkoepelende doel van dit proefschrift is erop gericht om factoren te identificeren om de cardiovasculaire risicobeoordeling van patiënten met essentiële hypertensie in de eerstelijnszorg verder te kunnen optimaliseren. Het effect van specifieke factoren, zoals het meewegen van psychologische stress (angst- en depressiesymptomen), het bepalen van het brain natriuretic peptide (BNP) en het verrichten van een electrocardiogram (ECG) en echocardiografie is onderzocht als voorspeller van cardiovasculaire gebeurtenissen bij patiënten met hypertensie in de eerste lijn. Het streven van dit proefschrift is het bevorderen van de risicostratificatie van patiënten met hypertensie binnen de eerstelijnszorg. Aan de hand van verschillende onderzoeken gedurende een uitgebreide follow-up periode van negen jaar kunnen er belangrijke conclusies worden getrokken, die hieronder worden uiteengezet.

Het *eerste deel* van dit proefschrift richt zich op de rol van angst- en depressiesymptomen als een aanvullende risicofactor voor het ontwikkelen van cardiovasculaire aandoeningen en algemene sterfte bij patiënten met hypertensie. Verhoogde psychologische stress, gemeten aan de hand van een angst- en depressie-scorelijst, blijkt een onafhankelijke voorspeller te zijn van nieuwe coronaire events (**Hoofdstuk 2**). Resultaten hebben aangetoond dat verhoogde angst- en verhoogde depressiescores het risico op nieuwe coronaire gebeurtenissen respectievelijk met 12% en 18% verhoogt in een eerstelijnscohort van patiënten met hypertensie (n=555). Er worden geen associaties gevonden met betrekking tot andere cardiovasculaire aandoeningen en algemene sterfte. Patiënten met zowel een verhoogde angstscore (GAD-7 ≥ 8) als een verhoogde depressiescore (PHQ-9 ≥ 5) hebben een 5,5 keer zo grote kans om

nieuwe coronaire gebeurtenissen te ontwikkelen, vergeleken met degenen zonder verhoogde symptoomscores bij aanvang. Hetzelfde geldt zelfs ook bij veel lagere cut-off waarden van deze symptoomscores.

In het *tweede deel* van dit proefschrift wordt de focus gelegd op aanvullende diagnostische tools en hun mogelijke rol bij het verbeteren van cardiovasculair risicomanagement. Het BNP is een belangrijke biomarker, in het bloed, die in de klinische praktijk gebruikt wordt om (de eerste tekenen van) hartfalen te identificeren of juist uit te sluiten. In de eerste lijn wordt het BNP momenteel enkel op indicatie bepaald en er zijn landelijke afspraken over wat huisartsen een "te hoge waarde" noemen. In **Hoofdstuk 3** worden leeftijds- en geslachtspecifieke cut-off waarden voor het BNP geïntroduceerd. In deze studie is gebruik gemaakt van een groot cohort (n=9447) van eerstelijnspatiënten waarbij een BNP bepaling is verricht na verwijzing naar een eerstelijns laboratorium. Deze studie toont aan dat de leeftijd en het geslacht van de patiënten een significante invloed heeft op de BNP-niveaus, wat wijst op mogelijke voordelen bij het hanteren van leeftijds- en geslachtsspecifieke cut-off waarden in plaats van de huidige cut-off voor de eerstelijnspopulatie zonder onderscheid naar geslacht en leeftijd.

In **Hoofdstuk 4** is een cross-sectioneel onderzoek uitgevoerd waarbij is gekeken naar de diagnostische waarde van het ECG en het echocardiogram als screeningsinstrument voor het detecteren van linkerventrikelhypertrofie (LVH) bij patiënten met langdurige hypertensie in de eerste lijn (n=422). De detectie van LVH middels een ECG blijkt suboptimaal, met een lage sensitiviteit van 14% in vergelijking met de diagnose LVH in 44% van de patiënten, vastgesteld met de goudstandaard echocardiografie. De gevonden prevalentie van LVH met behulp van echocardiografie, neemt significant toe met de leeftijd en bereikt 60% bij mensen ouder dan 75 jaar.

In een longitudinale vervolgstudie van 530 patiënten uit hetzelfde cohort is de voorspellende waarde van vaststellen van LVH op ECG en/of op echocardiografie en/of een verhoogd BNP op de ontwikkeling van toekomstige cardiovasculaire aandoeningen en algemene sterfte onderzocht (**Hoofdstuk 5**). Een significante en onafhankelijke associatie tussen verhoogde BNP-niveaus bij aanvang en algemene sterfte is gevonden, evenals het ontwikkelen van nieuwe cardiovasculaire aandoeningen en meer specifiek het ontwikkelen van hartfalen, gedurende een follow-up periode van negen jaar. De aanwezigheid van LVH op ECG bij aanvang is enkel significant geassocieerd met algemene sterfte. De combinatie van LVH op ECG en/of echocardiografie bij aanvang is onafhankelijk geassocieerd met het optreden van hartfalen, zij het met een minder sterke voorspellende waarde dan BNP.

De brede kijk in dit proefschrift legt de basis voor een meer genuanceerd en gepersonaliseerd cardiovasculair risicomanagement in de eerste lijn. De belangrijkste bevindingen zijn dat verhoogde psychologische stress naar voren komt als een onafhankelijke voorspeller van nieuwe coronaire gebeurtenissen en dat een verhoogd BNP een hoge voorspellende waarde heeft op ongunstige cardiovasculaire uitkomsten bij oudere patiënten met hypertensie. Ondanks de hoge prevalentie van LVH gedetecteerd door echocardiografie bij asymptomatische oudere patiënten met hypertensie, blijkt de uitslag van een echocardiogram geen significant voorspellende waarde te hebben op lange termijn resultaten. Daarom wordt ten zeerste aanbevolen om het gebruik van gestandaardiseerde screeningsinstrumenten voor psychologische stress (angst- en depressievragenlijsten) en het routinematige (periodiek) bepalen van het BNP op te nemen in de richtlijnen voor cardiovasculair risicomanagement. Dit draagt bij aan een verfijnd en gepersonaliseerd cardiovasculair risicomanagement van oudere patiënten met hypertensie in de eerste lijn.

APPENDICES

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APPENDIX

Data management

Data management

All data used within this thesis are collected and stored according to the Findable, Accessible, Interoperable and Reusable (FAIR) principles. Appropriate data management is important for knowledge discovery, innovation, scientific integrity and preservation and reuse of data sets. This thesis is primarily based on results of human study, which was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Medical Ethics Committee of the Elisabeth Hospital at Tilburg, the Netherlands (NL38933.008.12).

All individuals provided written informed consent prior to participation. All study procedures were monitored by an independent researcher according to the protocol. Privacy of participants was ensured by anonymising collected study data using a unique an untraceable individual subject code, which is only available for selected members of the research team. This subject code is used in all case report forms and data files, which allows us to share the data if necessary. Raw and processed data sets are stored at the office of the primary care organization Pozob (praktijkondersteuning Zuid-Oost Brabant) and are available for further analyses for at least 15 years upon completion of the study. Raw and processed data sets were put into SPSS files, which are stored at the local server of the Tilburg University, which is backed-up on daily basis to prevent data loss. To ensure that data is generally accessible and interoperable, all file names and data used to produce the final results were documented using applicable language for knowledge representation. Furthermore, all data generated and analysed in this thesis is available on request from the associated corresponding authors.



APPENDIX

List of abbreviations

List of abbreviations

ACE	Angiotensin-converting enzyme
ACM	All-cause mortality
ARB	Angiotensin II receptor blocker
AVF	Augmented vector foot
AVL	Augmented vector left
AVR	Augmented vector right
BMI	Body mass index
BNP	Brain natriuretic peptide
CHELLO	Chronic Heart Failure Prevention Program
CHF	Chronic heart failure
CI	Confidence interval
CV	Cardiovascular
CVA	Cerebrovascular accident
CVD	Cardiovascular disease
CVE	Cardiovascular event
CVEs	Cardiovascular events
CVRM	Cardiovascular risk management
DBP	Diastolic blood pressure
ECG	Elektrocardiogram
Echo	Echocardiography
GAD-7	7-item Generalized Anxiety Disorder scale
GP	General practitioner
HR	Hazard ratio
ICPC	International Classification of Primary Care
LDL	Low-density lipoprotein
LV	Left ventricular
LVH	Left ventricular hypertrophy
MI	Myocardial infarction
Multi	Multivariate
NPV	Negative predictive value
NT-proBNP	N-terminal proBNP
PHQ-9	9-item Patient Health Questionnaire
PPV	Positive predictive value
SBP	Systolic blood pressure
SD	Standard deviation
TIA	Transient ischaemic attack
Uni	Univariate



APPENDIX

List of publications



List of publications

de Hartog-Keyzer JML, Pop VJM, Rodwell L, Nijveldt R, El Messaoudi S. Prediction of cardiovascular events in older patients with hypertension in primary care: a cohort study. BJGP. 2024 Apr; 74:741. Doi: 10.3399/BJGP.2023.0328

de Hartog-Keyzer JML, Pedersen SS, El Messaoudi S, Nijveldt R, Pop VJM. Psychological distress is independently related to new coronary events at 8 years' follow-up in elderly primary care patients with hypertension. J Psychosom Res. 2022 Sep; 160:110980. Doi: 10.1016/j.jpsychores.2022.110980.

de Hartog-Keyzer JML, El Messaoudi S, Harskamp R, Vart P, Ringoir L, Pop V, Nijveldt R. Electrocardiography for the detection of left ventricular hypertrophy in an elderly population with long-standing hypertension in primary care: a secondary analysis of the CHELLO cohort study. BMJ Open. 2020 Aug 20; 10(8):e038824. Doi: 10.1136/bmjopen-2020-038824.

Keyzer JML, Hoffmann JJ, Ringoir L, Nabbe KC, Widdershoven JW, Pop VJM. Age- and gender-specific brain natriuretic peptide (BNP) reference ranges in primary care. Clin Chem Lab Med. 2014 Sept; 52(9):1341-6. Doi: 10.1515/cclm-2013-0791.

Ringoir L, Pedersen SS, Widdershoven JW, Pouwer F, **Keyzer JML**, Romeijnders AC, Pop VJM. Beta-blockers and depression in elderly hypertension patients in primary care. Fam Med. 2014 Jun; 46(6):447-53.

Ringoir L, Widdershoven JW, Pedersen SS, **Keyzer JML**, Pop VJM. Symptoms associated with an abnormal echocardiogram in elderly primary care hypertension patients. Neth Heart J. 2014 May; 22(5):234-9. Doi: 10.1007/s12471-014-0543-y.

de Hartog-Keyzer JML, El Messaoudi S, Nijveldt R, Pop V. Angst- en depressieklachten bij hypertensiepatienten vergroten de kans op een coronair event. Huisarts en Wetenschap. 2023 Feb.



APPENDIX

Over de auteur

Over de auteur

Op 24 februari 1985 wordt Josephine Keyzer geboren in Eindhoven. Na het behalen van haar gymnasiumdiploma aan het Lorentz Casimir Lyceum te Eindhoven in 2003, begint ze haar academische reis aan de Rijksuniversiteit Groningen, waar ze in 2007 haar Bachelor Geneeskunde behaalt. Tijdens haar Master Geneeskunde voltooit Josephine haar onderzoeksstage in Uppsala, Zweden, een ervaring die haar passie voor onderzoek versterkt.

In 2010 voltooit ze haar studie Geneeskunde en wordt ze aangenomen voor de Huisartsopleiding in Maastricht. Voordat ze met de Huisartsopleiding begint, werkt ze als onderzoeksarts bij Andromed in Eindhoven, waar ze haar interesse in wetenschappelijk onderzoek combineert met haar klinische vaardigheden.

Na het behalen van haar huisartsdiploma in 2014, werkt Josephine van 2015 tot 2019 als waarnemend huisarts in de regio Zuidoost-Brabant. In het voorjaar van 2019 wordt ze praktijkhouder bij Huisartsenpraktijk Konijnenberg en de Hartog te Schijndel, waar ze momenteel nog steeds met toewijding haar patiënten behandelt.

Parallel aan haar klinische werkzaamheden begint Josephine in 2014 ook haar reis als externe promovendus, onder leiding van Victor Pop aan de Universiteit Tilburg. Later, in 2019, zet zij haar promotieonderzoek voort aan de Radboud Universiteit te Nijmegen onder leiding van Robin Nijveldt, Saloua El Messaoudi en Victor Pop. Haar proefschrift getiteld ‘Advancing hypertension treatment in primary care. Beyond current guidelines and practices.’ richt zich op het identificeren van factoren die de cardiovasculaire risicobeoordeling van patiënten met essentiële hypertensie in de eerstelijnszorg verder kunnen optimaliseren.

Deze diverse achtergrond heeft Josephine gevormd tot een toegewijde huisarts en onderzoeker, die streeft naar de integratie van wetenschap en praktijk om de gezondheidszorg te verbeteren.



APPENDIX

Portfolio

Portfolio

Department: **Cardiology**
PhD period: **01/01/2014 – 31/12/2023**
PhD Supervisor(s): **Prof. dr. R. Nijveldt, prof. dr. V.J.M. Pop**
PhD Co-supervisor(s): **Dr. S. El Messaoudi**

Training activities	Hours
Courses	
· Programma cursus Inleiding SPSS (R01), EpidM (2014)	20.00
· Smartreading module I (2017)	8.00
· Smartreading module II (2017)	8.00
· Echografie basis voor huisartsen (2020)	60.00
· Dermatoscopie voor de huisartsenpraktijk (2021) SCEM Conference Services Education Permanente	10.00
· Echografie basis voor huisartsen II (2021)	60.00
· Basisopleiding reizigersgeneeskundig huisarts (2022)	12.00
· Radboudumc - Scientific integrity (2022)	20.00
· RIHS - Introduction course for PhD candidates (2022)	15.00
Seminars	
· Antistolling in de keten anno 2017: de herziene RTA (2017) MMC	2.00
· KOH sandwichdagen, annual, theme variety (2017-2023)	48.00
· Webinars COVID-19 (2021) Landelijke Huisartsen Vereniging	12.00
Conferences	
· PoZoB academy (2015), poster presentation	10.00
· OverEINDse dagen, annual (2017-2022)	52.00
· NHG Congres, annual, theme variety (2018-2019)	12.00
· LHV Huisartsendag: Op naar morgen (2021)	6.00
· OverEINDse dagen (2023), oral presentation	20.00
· Jaarlijks symposium Travel Medicine voor (huis)artsen (2023)	7.00
Other	
· Peer review club, Hagro Schijndel (2019-2023), oral presentation	73.00
· Peer review club, local GPs (2015-2023)	64.00
· Peer review club, regional GPs/sonographers (2020-2023), oral presentation	75.00
Total	**594.00**



APPENDIX

Dankwoord

Dankwoord

Met het schrijven van dit dankwoord rond ik mijn proefschrift af. In de afgelopen jaren heb ik veel geleerd en meegemaakt op zowel wetenschappelijk gebied, maar ook op persoonlijk vlak. Het afronden van mijn promotietraject ging zeker niet over één nacht ijs en soms voelde tegenslagen aan als bergen in plaats van hobbels in de weg. Ik wil graag even stilstaan bij de mensen die me tijdens deze periode geholpen en gesteund hebben bij het succesvol afronden van dit proefschrift.

Allereerst wil ik mijn eerste promotor prof. dr. R. Nijveldt bedanken. Beste **Robin**, ik wil graag mijn dank uitspreken voor jouw rol als promotor gedurende mijn onderzoek. Jouw toetreding tot het team heeft mogelijk gemaakt dat ik dit onderzoek succesvol heb kunnen afronden. Ik ben je ontzettend dankbaar voor al je waardevolle lessen, je indrukwekkende computervaardigheden, eindeloze energie en scherpe inzichten. Je hebt mij geleerd de rode draad voor ogen te houden en mezelf niet te verliezen in bijzaken.

Beste dr. S. El Messaoudi, beste **Saloua**, jouw bijdrage was onmisbaar tijdens het (opnieuw) beoordelen van de cardiale echo's volgens de laatste wetenschappelijke inzichten. Jouw expertise en inzet hebben een belangrijke rol gespeeld bij het verfijnen van mijn onderzoek. Je was niet alleen mijn co-promotor, maar ook mijn to-go person voor advies als ik ergens tegenaan liep.

Beste prof. dr. V.J.M. Pop, beste **Victor**, vanaf het prille begin tot aan het einde van dit promotietraject ben jij mijn grootste motivator geweest. Jouw betrokkenheid bij alle belangrijke beslissingen en onze vele uren samen doorgebracht met rekenen met SPSS, of het nu was in Tilburg, Riethoven of Vught, zijn onvergetelijk. Ik heb ontzettend veel van je geleerd, vooral de unieke combinatie van huisarts en wetenschapper die jij vertegenwoordigt. Je bent een inspirerend voorbeeld.

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Ik wil graag mijn dank uitspreken aan al mijn medeauteurs van de artikelen in dit proefschrift.

Beste Susanne, Hans, Lianne, Karin, Jos, Ralf, Priya, en Laura, jullie expertise, inzichten, inzet en samenwerking hebben dit onderzoek en de artikelen naar een hoger niveau getild. Dear Susanne, it was an honor to work with you on an article about anxiety and depression in relation to cardiovascular diseases.

Als externe promovendus heb ik niet veel contact gehad met medepromovendi, maar met jou, dr. Lara Konijnenberg, wel. Ik wil je graag bedanken voor de talloze praktische tips die je hebt gegeven. Ik hoop dat mijn verdediging net zo goed zal verlopen als die van jou. Ik vind het supergaaf dat je met de huisartsopleiding bent begonnen, en hoop dat we in de toekomst kunnen gaan samenwerken in Schijndel.

Graag bedank ik ook 'Diagnostiek voor U', 'Pozob' en 'Pharmo Institute' voor de geleverde samenwerking en bijdragen (het leveren van diagnostiek en data) aan dit proefschrift. Beste, Karin Nabbe, Arnold Romeijnders en Ron Herings, dank voor jullie prettige contact, zonder jullie support en resources was dit project nooit zo succesvol geweest.

Nogmaals hartelijk dank aan jullie allen voor jullie bijdragen aan mijn promotieonderzoek. Zonder jullie steun en begeleiding zou ik niet staan waar ik nu ben.

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Graag bedank ik al mijn collega's uit mijn **huisartsenpraktijk Konijnenberg en De Hartog**. Jullie maken elke werkdag weer leuk en gezellig. In het bijzonder wil ik jou, Stephan, danken voor je support, zodat ik naast de dagelijkse praktijk ook ruimte en tijd had voor het afronden van mijn promotieonderzoek. Het is fijn om met je te kunnen sparren over praktijkvoering, ondernemerschap, wetenschap, echografie en hoe wij de zorg in de toekomst zien.

Mijn promotieonderzoek begon ik al ten tijde van mijn huisartsopleiding. Mijn opleiders Peter van Bommel, Pieter Wassenberg en Odette Herijgers wil ik dan ook danken voor hun steun. Ook heb ik gedurende de jaren daarna fijne gesprekken en samenwerking gehad met veel andere huisartsen, in het bijzonder dank ik Annelies Lucas en Iris Steenstra, die altijd bemoedigd en inspirerend waren voor mij.

Een onderwerp in dit proefschrift behandelt de impact van psychische nood op het hart. Om mijn eigen mentale stress te verminderen, wil ik mijn eigen speciale 'mentaal' verzorgingsteam hartelijk bedanken voor hun luisterende oren en goede adviezen. Bij jullie ben ik altijd welkom en word ik altijd gehoord. Dank Mirjam Ribberink, Mirjam Maat, Karin van Gerwen en Iris Sierevogel. Dankzij jullie zie ik er niet alleen goed uit, maar voel ik me ook goed.

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De oplettende lezer miste in de alinea hierboven een naam. Dat klopt, maar lieve **Eline**, jij verdient een eigen alinea. Ik wil je bedanken voor je onvoorwaardelijke vriendschap, die teruggaat naar onze tienerjaren. Hoe bijzonder dat na allerlei omzwervingen we nu weer dichtbij elkaar wonen en dat onze kinderen samen bij elkaar in de klas zitten. Ik vind het een eer dat je mijn paranimf wilt zijn.

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Tout à une fin. C'est bien comme ça. Le mieux est l'ennemi du bien,

Josephine



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