Chronic heart failure diagnostics and application of neuropeptides in residential elderly
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Chapter 1

GENERAL INTRODUCTION.

This chapter provides a comprehensive review of heart failure (HF), which is the central theme of this thesis. Since HF is a syndrome predominantly affecting the elderly, it imposes an important disease burden in elderly medicine. Elderly medicine is a relatively young specialism. On a daily basis, elderly care physicians deal with the question when and how to apply general medicinal guidelines and in which cases the resident’s high age has to be taken into account. Issues as diagnostics and exercise are relevant for the frailest elderly with HF. Due to the complexity of frail elderly, optimal diagnosis and treatment, remain a major challenge for the practicing physician in order to improve outcome. At the end of this chapter we focus on HF in the frailest elderly, i.e. those who have to rely on long-term care facilities (LTCFs), since heart failure in the frailest elderly is the subject of this thesis.

1.2 RATIONALE.

In The Netherlands, the average life expectancy has increased from 70 years for men and 73 years for women in 1950 to 79 and 83 years in 2013, respectively (www.cbs.nl and www.nationaalkompas.nl). Main determinants of the increased life expectancy are the implementation of better hygienic and preventive measures, easy availability of sufficient and healthy food in conjunction with a shrewd and balanced lifestyle and the development of an armamentarium of medical treatments, such as pharmacotherapy and surgical techniques. One of the most important achievements in reducing overall mortality originates from the enormous progress made in the management of cardiovascular disease (CVD) during the last 60 years. As a consequence the many survivors of CVD grow older and acquire other non-CV diseases, single or multiple, often accompanied by disabilities. When multimorbidity is accompanied by the loss of psychosocial resources, we speak of frailty (8). Frail elderly are at risk to deteriorate even
faster and geriatric interventions are required. The frailest elderly live in LTCFs, like nursing homes or care homes, and are referred to as 'residential elderly'. Although this group consumes a growing percentage of the Dutch health care budget they are excluded from research studies because of high age, multimorbidity and cognitive disorders. Until recently, these elderly were diagnosed and treated in the same way as adults with a single disease. At the start of this study there was no HF guideline available for the group of residential elderly. This was because the HF guideline of Verenso from 1999 was out of date (Verenso, Vereniging van specialisten ouderengeneeskunde en sociaal geriaters). In 2003 and in 2008, the Dutch multidisciplinary HF guideline, based on the European Society of Cardiology (ESC) HF guideline, recognised the lack of research data for females and the 75+ age-group (both genders) (9;10). Meanwhile, natriuretic peptides (NP) proved their utility for HF diagnostics, prognosis and therapy-optimization. In addition the importance of non-pharmacological treatment such as physical exercise was well recognized. These niches of knowledge on CHF diagnostics and non-pharmacological therapy formed the rationale for studying this excluded group of the residential elderly.

1.3 MORTALITY FROM CARDIOVASCULAR DISEASES.

Since its peak in the late 1950s (for women) and the early 1970s (for men) cardiovascular (CV) mortality has gradually declined. This tremendous decrease in CV mortality is remarkable when we take into account the increasing number of elderly people and the more advanced age of contemporary Dutch citizens. Also, after correction for age (standardisation), the drop in CV mortality remains considerable, with a reduction of about 70% (Figure 1).
Figure 1. Standardised Cardiovascular Mortality per 100,000 inhabitants in The Netherlands (8).

1.4 MORBIDITY.

As spin-off of the impressive 68% decrease in CVD mortality, a substantial increase in CVD morbidity is nowadays reported, with an estimated prevalence of 700,000 subjects in The Netherlands currently suffering from CVD. Out of these 700,000, around 125,000 have HF (11). As for CV mortality to date more patients die from HF than from myocardial infarction (MI), since an increasing number of people survive their MI, but subsequently develop HF (Figure 2).
Figure 2. Heart failure mortality has surpassed myocardial infarction mortality in The Netherlands since 2011. Number of deaths attributed to myocardial infarction (MI) or heart failure (HF) as the primary cause of death in The Netherlands from 1980 through 2012 (12).

1.5 DEFINING HEART FAILURE AND ITS CAUSES.

Defining HF is not easy. The most straightforward approach is to define HF as: a condition during which the heart is unable to meet the metabolic needs of the body. Unfortunately in daily practice HF is often more difficult to define. Also, this is caused by the multi-interpretability of vague key symptoms of HF, notably, fatigue and dyspnea. The significance of symptoms and signs is even more difficult to interpret in elderly due to the presence of co-morbidities. At present three definitions are used to label HF. These definitions describe the diagnosis of HF on a clinical (symptomatic), a pathophysiological or a therapeutic basis (9;13;14). Given the difficulties to define HF, discovery of (the onset of) HF is often late.

Clinical (symptomatic) HF definition: HF is a syndrome in which the patients should have the following symptoms typical for HF: shortness of breath at rest or during exertion,
and/or fatigue; signs of fluid retention such as pulmonary congestion or ankle swelling; and objective evidence of an abnormality of the structure or function of the heart at rest (9).

Pathophysiological HF definition: HF is defined as a pathophysiological state in which an abnormality of cardiac function is responsible for failure of the heart to pump blood at a rate commensurate with metabolic requirements or to do so only from an elevated filling pressure (13).

Therapeutic definition: cardiomyopathies are a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes. Cardiomyopathies either are confined to the heart or are part of generalized systemic disorders, often leading to cardiovascular death or progressive HF-related disability (14).

In addition to the three definitions, HF is classified by course of disease and functionality. With respect to course: after 3 months HF is considered as chronic. Chronic HF (CHF) can be stable or gradually progressive, or can exacerbate into acute HF. Regarding the functionality, HF is distinct in diastolic HF, also named HF with preserved left-ventricular ejection fraction >40-50% (LVEF; HFpEF), and systolic HF, also named HF with reduced LVEF (HFrEF) (9). For diagnostic purposes, for both HFrEF and HFpEF, typical signs and symptoms of HF are obligatory. For HFpEF two more requirements are needed: a non dilated left ventricle and documentation of diastolic dysfunction. The diagnosis of HFpEF is more difficult than that of HFrEF because it is largely one of exclusion, e.g. of potential non-cardiac causes of the patient's symptoms. As for the individual patient's restrictions, the New York Heart Association (NYHA) classification is used (15). NYHA places patients in one of four categories based on how much they are limited during physical activity.

All possible causes for HF may be divided into derailments of the heart muscle as a result of
cardiomyopathy, coronary artery disease (CAD), atrial fibrillation or other rhythm or conducting disturbances, infection or intoxication. In addition, diseases of the heart valves, afflictions of the pericardium or (cardiac) shunts may cause HF. Finally, circulatory derangements may induce HF, such as coarctation, thrombo-embolic process, intoxication, high output failure, infection, hyperthyroidism and fluid overload. In general, HFrEF is most often caused by CAD which is predominantly generated through hypertension (HT).

1.6 PREVALENCE OF HEART FAILURE.
Due to an increasingly ageing population, already in 1990 a growing number of individuals with HF was predicted in The Netherlands (12). After 22 years, the estimation of HF became reality, with a prevalence of about 120,000 - 130,000 subjects. Moreover, the number of people with HF is expected to increase to reach about 200,000 individuals in 2018 (16). Between 20 to 30% of the general population will ultimately develop HF, when they are over 70 years of age (17).

1.7 HEART FAILURE DISEASE BURDEN.
Apart from the increasing HF mortality, the morbidity or disease burden due to HF will rise as well. The “Rijksinstituut voor Volksgezondheid en Milieu” (RIVM) has quantified “disease burden” in a model of disability-adjusted life-years (DALY) (18), expressed as the number of years lost due to ill-health, disability or early death through HF. The authors have estimated the DALY for each of four risk factors for HF separately. These risk factors comprise hypertension (HT; moderate HT is SBP of 140-160 and serious HT ≥160 mm Hg), moderately-high total cholesterol (200-239 mg/dL; 5.17-6.18 mmol/L) and seriously-high total cholesterol (≥240 mg/dL; ≥6.20 mmol/L), overweight, obesity and inactivity. Inactivity is defined as <4 metabolic equivalents of tasks (METs) for age 20-55 years and <3 METs for age 55+. A DALY was found of
1.6 years for seriously-high total cholesterol and up to 2.9 years for serious HT (Figure 3). The consequences of DALY for the AWBZ will be that an increasing part of the Dutch health care budget have to be devoted to the HF disease burden.

Figure 3. Disability-adjusted life-years (DALY). A DALY-model estimated for a Dutch population classified by different risk factors for heart failure.

Disability-Adjusted Life-Years (DALY), expressed as number of years lost due to ill-health, disability or early death. The bars are equally long and the upper bar represents the life-expectancy (LE) of a 20 year old with a lifelong optimal HF risk profile. The middle parts of the bars reflect the years lived with HF. The right parts of the bars show the years lost due to HF (18).

1.7 QUALITY OF LIFE (QUOL).

The DALY quantifies the time lived with reduced Quol due to HF. Not only the direct loss of Quol by HF symptoms but also the indirect loss by restrictions, as a result of HF, are important. These restrictions appear in several Quol domains like mobility and independency. For instance,
dyspnea limits the ability to execute activities of daily living (ADL) and walking distance (19). From the perspective of the individual, the severity of HF affects a person's self-reported functioning (20). It is obvious that HF is related to assistance at ADL, but this relation has not been investigated by others. Such a relation, if causal, is important for the care-giver who needs to estimate the amount of required ADL assistance and for the individual who needs that help. The physician may estimate the prognosis of patients using independent predictors of HF such as high age, NYHA 3 and 4, loss of appetite (21), N terminal pro B-type natriuretic peptide (NT-pro)BNP (22) and chronic kidney diseases (CKD) (23). Among others these prognostic predictors enable a patient with CVD to make personal choices for the last phase of his life. The choices may permit the patient to retain control over his or her life and thereby prevent decrease of autonomy, at least on the domain of decision-making.

1.9 HF DIAGNOSTICS AND ALGORITHM.

In primary care elderly-medicine, HF is diagnosed using CV medical history, for HF predisposing diseases and risk factors (chapter 1.5), clinical examination, electrocardiography (ECG), natriuretic peptides (chapter 1.10) and echocardiography. These are referred to as diagnostic tools. The reference standard for the, at least functionally undifferentiated HF diagnosis is based on all of these tools, occasionally extended with chest X-ray (9;10;24). For further examination of HF causes or treatment, referral to a cardiologist may be required. However, predictive values of the separate diagnostic tools are moderate which hamper initial HF diagnostics in primary care and in geriatric outpatients as well (25;26). This hindrance combined with no easy access to echocardiography or unwanted referral (resident's preference), needed a solution to diagnose HF without outpatient referral. For that purpose HF diagnostic algorithms were developed based on combinations of diagnostic tools including NPs (21;25-28). However a few is known whether those HF diagnostic algorithms (9;10;21;24-28) are also suitable for the residential elderly suspected of HF.
1.10 NATRIURETIC PEPTIDES.

At the end of the last century, NPs have emerged as reliable biomarkers for the diagnosis and prognosis of both systolic and diastolic HF. NP testing is regarded to be the single most useful test to add to the diagnostic pathway for HF in primary care. Tests of NPs have shown to be cost effective. However, in HFrEF levels of NPs are increased, but somewhat lower compared to those in patients with HFpEF. Therefore, the relatively higher NP levels are predictive for HFrEF, but the moderately increased NP levels do not predict HFpEF very well (29). Especially the NPs specificity and diagnostic accuracy in acute HF are prominent. Currently, NPs, notably B-type natriuretic peptide (BNP) and N-terminal-proBNP (NT-proBNP), are commonly applied diagnostic (30) and prognostic (31) biomarkers. Confounders of NP levels are non-cardiac factors such as high age, sex and renal dysfunction, since these also increase NP levels. Obesity, diuretics, ACE inhibitors, beta-blockers, ARBs and aldosterone antagonists reduce NP levels (32). All the above mentioned confounders occur widely in residential elderly. Many of them use CV medications and renal dysfunction is widespread. Therefore, NPs may not predict HF exclusively (32) and NP cut-off values are not fully validated in this particular group. With regard to treatment optimization, a meta-analysis shows that NP-guided therapy is superior to symptom-guided therapy in groups of patients with CHF (33). However a study on individual CHF patients reveals high intra-individual biological variations of NPs as major limitation of NPs in the optimization of HF treatments (34).

The secretion of NPs by the ventricle wall increases when HF is accompanied by pressure or volume overload (35). Only BNP regulates actively. BNP stimulates natriuresis, diuresis, vaso-dilatation and inhibits the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system. BNP is metabolized actively in blood and cells by neuropeptidases (36). The half-life time of BNP is 20 minutes. These characteristics render BNP appropriate as marker of HF (30). NT-proBNP has an about six times longer half-life, viz. 1-2 hours (37). As opposed to BNP, NT-proBNP is passively filtered in the kidney (38), actively reabsorbed by the proximal
tubulus brush border cells and catabolised to amino acids. This process of NT-proBNP degradation is usually nearly complete. Thus, only minor amounts of NT-proBNP are recovered in urine (39).

Both NPs are released into the circulation in an 1:1 molar ratio. The secretion of BNP exhibits a pulsatile pattern in the circulation (40) and it may be assumed that NT-proBNP is split-off pulse-shaped as well. Consequently both NPs exhibit high intra-individual biological variations which hamper their use for treatment optimization of an individual (34). Mainly experimentally, NPs are determined in urine using immunoassays. Urine NPs may exhibit less intra-individual biological variation compared to plasma NPs, assuming that the pulsatile secretion becomes attenuated by NT-proBNP accumulation in the bladder (41-43). Thus, the experimental use of urine NP is prompted by the high intra-individual biological variation of plasma NPs (34).

1.11 THERAPIES FOR HEART FAILURE.

Following the diagnosis of HF, treatment is based on CV risk management (CVRM) (2) and correction of underlying causes (10). CVRM for HF differs in the time of intervention (2) from other HF guidelines. The current trend is not to wait until HF symptoms have developed, but to start intensive risk management for patients with increased risk of HF (www.RIVM.nl). It is assumed that if HF could be recognized before symptoms emerge, lifestyle adaptations or appropriate medication could reduce HF symptoms or the physical decline caused by HF. An example of lifestyle effects on CV risk factors is presented by a five-year lasting Dutch study. This study shows that 1% of adults has changed from physically inactive into moderately-active and 1-2% from overweight/obese or underweight to normal weight (6). Whether such endpoints can also be reached in HF patients belonging to the elderly and whether such interventions could prevent HF progression or even accomplish a reverse, is unknown.
In addition, it is advised to treat other diseases precipitating to HF. It is assumed that treatment of anemia, lung diseases, renal dysfunction, thyroid-gland dysfunction, T2DM and intoxications reduces the risks of HF (9). Treatment of underlying causes of HF consists, among others, of pharmacological therapy. Most pharmacological therapies are specific for HFrEF (Table 1).
Table 1. Treatment of Heart Failure with reduced left ventricular ejection fraction (HFrEF) (26).

<table>
<thead>
<tr>
<th>HF with reduced ejection fraction</th>
<th>treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>start</td>
<td>diuretics to relieve signs/symptoms and ACE-i (or ARB)</td>
</tr>
<tr>
<td>When clinically stable, add</td>
<td>beta-blocker</td>
</tr>
<tr>
<td>Titrate to the target doses of</td>
<td>ACE-i (or ARB) and beta-blocker</td>
</tr>
<tr>
<td>When complaints are not persisting</td>
<td>no complementary therapy indicated</td>
</tr>
<tr>
<td>When complaints are persisting, add</td>
<td>MR antagonist</td>
</tr>
<tr>
<td>When instable (SR and HR ≥ 70/min), add</td>
<td>Ivabradine</td>
</tr>
<tr>
<td>When complaints does not persist, EF≤35%</td>
<td>No further specific treatment</td>
</tr>
<tr>
<td>When complaints are persisting and QRS≥120ms</td>
<td>Consider CRT-P/CRT-D</td>
</tr>
<tr>
<td>When complaints are persisting and QRS ≤120ms</td>
<td>consider ICD</td>
</tr>
<tr>
<td>When complaints are persisting</td>
<td>Consider digoxin and/or hydralazine or isosorbide nitrate</td>
</tr>
</tbody>
</table>

Angiotensin Converting Enzyme inhibitor, ACE-i; Angiotensin Receptor II Blocker, ARB; ejection fraction, EF; sinus rhythm, ARB; heart rate, HR; mineralocorticosteroid receptor, MR; cardiac resynchronization therapy pacemaker, CTR-P/CRT-D, defibrillator.

Since patients with advanced CHF (EF ≤35 - 40%) are at risk of sudden death, an implantable cardioverter defibrillator (ICD) is placed, for preventive reasons according to guidelines. Finally, non-pharmacological treatments to improve systolic function of the left ventricle function comprise, among others, revascularization procedures, valvular or ventricular surgery, rhythm optimization (electrocardioversion, ablation), cardiac resynchronization therapy (CRT) and heart transplantation. For HFpEF no specific therapy is available, yet. For these patients only the un-
derlying cause such as hypertension is treated (10). For the elderly, the same treatment is available provided that dosages are adjusted to decreased kidney function and the life expectancy is at least 0.5 years with good quality of life (10).

1.12 THE RESIDENTIAL ELDERLY.

The residential elderly belong to the frailest elderly (chapter 1.2). They reside in care or nursing homes (LTCFs). Care and nursing homes differ in intermittently or continuously provided support and ADL-help, respectively. During the final stage of writing this thesis in 2015, financing of Dutch care homes had just ended. As a consequence most care home elderly had to move to private houses with care at home or to a nursing home.

In primary care elderly medicine, preferences of the residential elderly are inventoried and taken as the starting point for further treatment decisions in case they become incompetent in future. These preferences concern diagnostics, treatment and hospital referral in the event of emergency. These choices or preferences are set out in agreements that are evaluated twice a year, or more often when indicated. These agreements may include renouncing invasive and intensive care treatments and hospital referral. As an exception, hospital referral for (surgical) treatment of bone-fractures are seldom renounced.

1.13 HEART FAILURE IN RESIDENTIAL ELDERLY.

The increasing HF prevalence on the one hand, and lack of specific HF research data on the other hand challenge healthcare professionals in the provision of optimal patient care in the residential elderly. We expected the HF diagnostics to be less accurate due to high age, female sex, multimorbidity (44;45), 'treatment agreements' and absence of a specific HF guideline. At the start of this study, it was unknown whether general HF guidelines could be applied to the residential elderly (9;10;24). Therefore, we set out to study HF prevalence and diagnostic ac-
cacy in this particular group of elderly people. We planned also to investigate whether HF diagnostics could be improved by adding NPs to the usual HF diagnostics.

Furthermore, HF guidelines, the CVRM guideline and family members recommend residential elderly to be physically active (2;9;10;24) aiming to maintain or improve physical health. The residential elderly, however, seems to have little motivation to train physically on a regular basis. He or she faces a limited life expectancy wondering whether his exertion will provide benefits. Not much is known as to whether non-elective exercise might be beneficial in residential elderly (46). Staffs of nursing and care homes doubt whether they should invest in regular exercise programmes and whether such interventions will be safe and effective. Therefore, we experimented with an exercise program based on a review specific to the residential elderly (47).

In addition, when facing a limited life expectancy, accurate information on prognosis will become more important. Prognostic information allows residential elderly to take their own decisions so that loss of Quol at least in the area of autonomy is reduced (chapter 3). Natriuretic peptides have been shown a powerful prognostic marker in adults with HF and may have similar prognostic value in residential elderly. However, the prognostic properties of NPs have not been examined in this particular group. Moreover, many confounders influence NP levels in such a way that they hamper to inform on prognosis in this residential target group. Therefore we aimed to study whether NPs could be used as a prospective and independent predictor in those frail elderly with HF.

Independency of care takers determines Quol to a high degree. It was surprising to learn, at the start of this study, that the HF diagnosis was not on the list of geriatric chronic diseases in the 'Resident Assessment Instrument' (RAI). The RAI is in use in American and Dutch nursing homes for care-planning at an individual, organizational and state level (48). Nevertheless, we presumed a relationship between HF state and help-with-care in residential elderly. In that line of reasoning, NP concentrations might be related to help-with-care as well. However a relation
between HF and or NPs with ADL-assistance was not observed until now. Therefore, we set out to test these research questions.

1.14 AIM AND OUTLINE OF THE THESIS.

In a broad perspective, the studies in this thesis aim to determine whether application of parts of the HF guidelines can be accurately applied to the specific group of the residential elderly. The doubts on the applicability of HF guidelines in residential elderly is based on the systematic exclusion of this group from HF research. There is also dubiety based on the observed higher cut-off values of NPs at a higher age, in renal dysfunction and comorbidity. Evidence as to what extent HF guidelines can be applied is important to elderly care physicians. These questions have undermined the accuracy of HF diagnostics resulting in no treatment or inappropriate treatment, and less well-being. Therefore, we aimed to obtain insight into certain HF aspects, such as prevalence, diagnostic accuracy, diagnostic and prognostic values of NPs and the relation of HF with help-at-care. To this end, we screened the residential elderly of a single nursing home in Groningen on the presence of CHF. To examine its external validity we repeated this screening program in Aruban nursing homes.

Furthermore, we sought to investigate whether physical activity was to the benefit of care home elderly on the basis of cardio-metabolic endpoints. These comprise waist circumference, blood pressure, glucose-homeostasis and lipids. We were also interested to see whether complaints and NPs ameliorate in the care home elderly with HF. With both aims, we conducted a randomized controlled trial employing a 16-weeks lasting supervised exercise intervention. For this, we collaborated with investigators examining partly the same care home elderly for other, more functional, endpoints (46).

At last, aiming to gain insight into the feasibility of NPs for treatment optimization, we estimated the intra- and inter-individual variations of NPs in urine and plasma of stable CHF patients living in Curaçao.
Specific aims of this study are described in the following paragraphs:

In **Chapter 1** we provide a general introduction of HF with special emphasis on HF diagnostics in residential elderly.

In **Chapter 2.1** we study both prevalence and accuracy of HF diagnostics in the Groningen residential elderly. In the meantime, we aim to find out whether improvements can be achieved by adding NPs to the diagnostic process in use in a Dutch nursing home. The aim of **Chapter 2.2** is similar to that of Chapter 2.1, but now applied to all residential elderly in Aruba. In **Chapter 2.3** we study the intra-individual variations of NPs with the purpose of finding out whether urine NPs may exhibit less variations compared to those in plasma in the Curacao population.

In **Chapter 3** we study the prognostic value of NPs on one year mortality of the Groningen residential elderly, aiming to better inform those facing a limited life expectancy. The aim of **Chapter 4** is to determine the relationship between CHF and the required need for ADL-help in the residential elderly in Groningen. The aim of **Chapter 5** is to examine the effects of a physical exercise program for the Groningen care home elderly. We investigated whether such a program may be beneficial with respect to cardiovascular-metabolic (soft) endpoints. Here, we could collaborate with an investigator who would perform the same intervention, but aiming at other, more functional endpoints.

In **Chapter 6.1** we summarized and in **Chapter 6.2** we discussed the results of the above described studies and in **Chapter 6.3** we provided recommendations for future studies. In **Chapter 7** a Dutch summary (“Samenvatting”) is given.
Figure 4. Flowchart of studies presented in this thesis with the corresponding populations in which the studies have been conducted.

ADL, Activities of daily living.
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