Heart Failure Care in General Practice

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Contents

Chapter 1

Introduction

Presentation of a case

Mr. G., a 72-year-old man with type 2 diabetes (T2D) and 'bronchitis', suffered from a myocardial infarction ten years ago. He comes to see his general practitioner (GP) complaining of problems with brisk walking, not able to keep the pace of his wife, and swollen ankles at the end of the day. "Is it due to my age and smoking history?"

Upon questioning he denied having chest pain or palpitations. His blood pressure was 162 / 82 mmHg and his heart rate was regular, 92 beats per minute. The GP could hear some basal pulmonary rales, a grade II/IV holosystolic murmur at the apex, and he noticed a broadened and sustained apical beat in left decubital position, and finally some pitting ankle oedema.

The GP considers non-acute onset of heart failure (HF) most likely, but also COPD is a possible explanation for the symptoms and signs of Mr. G..

Heart failure, definition and epidemiology

HF is defined as a clinical syndrome characterized by symptoms suggestive of HF (which may be accompanied by signs of HF, but signs are not mandatory), and structural or functional cardiac abnormality in rest (usually documented with echocardiography).[1] HF results in a reduced cardiac output, at least during exercise.[1] HF can be divided in HF with reduced ejection fraction (HFrEF) (EF<40%), a normal or preserved ejection fraction (HFpEF) (EF≥50%), and an intermediate range, named HF with mid-range EF (HFmrEF) (EF 40-49%).[1]

The prevalence of HF in the adult population at large is around 4%, and 12% for those aged 60 years and over,[2] with HFpEF on the increase compared to HFrEF in the last decade.[2-4]

Diagnosing heart failure

A diagnosis of HF may be difficult if a physician has to rely on medical history and physical examination only. Unrecognized HF is therefore common in the community, notably in high-risk patients such as older people with T2D, COPD, or with multi-morbidity and polypharmacy.[5-7]

Additional investigations such as the measurement of natriuretic peptides (NTproBNP and BNP) have added diagnostic value. The higher the level of natriuretic peptides, the more likely HF is present, while there are established exclusionary cut-points below which one can rule out HF.[8-10] Also an electrocardiogram (ECG) has added diagnostic value beyond clinical assessment.[1]

Moreover, it may reveal potential causes of HF, and if completely normal, HF is unlikely.[11;12] The European Society of Cardiology (ESC) and the Dutch primary care HF guidelines both recommend electrocardiography and natriuretic peptide testing in patients suspected of HF in primary care.[1;13]
Adequate management of HF starts with an established diagnosis of HF, knowing the type of HF (HFrEF, HFpEF or HFmrEF), and the most likely cause.

Mr. G. continued

The GP decided to perform electrocardiography at his office. It showed a sinus rhythm, and pathologic Q waves in lead II, III, and aVF suggestive of an old inferior wall myocardial infarction. Given the symptoms and signs of Mr. G. the GP decided to start with a loop diuretic to offload fluid and relieve symptoms. He instructs Mr G. to weigh himself daily, restrict his fluid intake to less than 1500 mL a day and to be careful with salt intake. He also sends him to the laboratory for blood testing, including natriuretic peptide measurement.
Three days later Mr. G. reports back to his GP. He had to urinate very frequently, lost two kilograms in weight, had a better night rest, and feels more 'comfortable'. His lab results showed a slightly reduced renal function (eGFR 50 ml/min/1.73 m²), but normal potassium levels, thyroid function, and haematology. The NTproBNP level was elevated with 930 pg/mL, lending further support to the diagnosis of HF.

At this stage, Mr. G's symptoms have improved. Are additional investigations warranted now that Mr. G. is feeling much better?
It is not uncommon in general practice to initiate treatment to immediately relieve symptoms before a full diagnostic workup. Nevertheless, in this situation echocardiography is still needed to confirm the diagnosis of HF, to assess the type of HF based on the left ventricular ejection fraction, and the possible cause of HF. Therefore, the GP refers Mr. G. to the nearby cardiology outpatient clinic.

Mr. G. continued

The cardiologist confirms that Mr. G has HF. He is diagnosed with HFrEF with an EF of 33% and M. G is still symptomatic with a NYHA functional class II/IV. The cause is most likely the prior myocardial infarction, and possibly also the T2D. Myocardial ischaemia is considered unlikely. The cardiologist suggests to further uptitrate Mr. G. at the HF outpatient clinic the coming months, and when optimally uptitrated and stabilized to refer him back to the GP.
During the following time period of three months, Mr. G. received personalized information about HF from the HF nurse, and additionally advice on life style issues, and some guidance on how to use

the website 'heartfailurematters.org'. An angiotensin converting enzyme (ACE)-inhibitor and beta-blocker were initiated and slowly uptitrated to maximally tolerated doses followed by spironolactone 25 mg o.d., a mineralocorticoid receptor antagonist (MRA). The dosage of the loop diuretic furosemide could be reduced from 40 mg to 20 mg o.d., a dosage that seemed sufficient to maintain euvolemia.

Knowing the left ventricular EF value has important consequences for the management of patients with HF. Multiple evidence-based cardiovascular drugs (notably beta-blockers, ACE-inhibitors, MRAs) and devices showed to clearly improve survival in HFrEF, but not in HFpEF. The effects of these drugs in patients with HFmrEF are yet unclear.
As in the case of Mr. G., those with HFrEF should receive an ACE-inhibitor and beta-blocker, and both drugs should be uptitrated to the targeted or maximal tolerated dose. If symptoms remain (NYHA II or more) and the LVEF is ≤35%, an MRA (spironolactone or eplerenone) should to be added.[14;14;15]

The case of Mr. G. highlights several important aspects of diagnosing and the management of HF in the primary care setting and how the GP and cardiologist may deliver cooperative care together with the HF nurse.

- In older people with shortness of breath HF should be considered, notably if they are known with a prior myocardial infarction or are otherwise at high-risk of HF because of longstanding hypertension, or T2D.[6;7] Also when they are already labelled with a diagnosis known to be related to shortness of breath, e.g. 'bronchitis' or COPD, (concomitant) HF should be considered.[16]
- In 2003 natriuretic peptide testing was introduced in the Netherlands, and available to GPs. Additionally to the clinical assessment, the GP can order such laboratory testing and make an electrocardiogram. NTproBNP levels above the exclusionary cut-point and an abnormal ECG helps to select those requiring echocardiography.
- Labelling a patient with HF based on the clinical assessment only may easily result in over-diagnosis of HF because the symptoms of HF are not specific and may be caused by many other disorders, for example pulmonary disease.
- The shortness of breath of Mr. G's could also have been attributed to 'deconditioning', or 'bronchitis', certainly considering his smoking history. When the GP considers spirometry to diagnose or excluded COPD, it should be performed when the patient is stable and euvolemic, otherwise COPD is easily overdiagnosed.[17] Moreover, HF and COPD may be present concomitantly in one and the same patient.

Both diseases share smoking and systemic inflammation as a common cause, and they largely overlap in symptoms.[18;19] The prevalence of HF in stable patients with a GP's diagnosis of COPD and aged 65 years or over was 26% (20.5% previously unrecognized).[16] Based on spirometry results, the prevalence estimates of COPD in patients with HF differ largely ranging from 9-46%, with lower estimates in stable, euvolemic HF patients.[17;18;20]

- The exact prevalence of COPD in a representative sample of stable all type HF patients from the community is still unknown.
- Prior myocardial infarction, but also a history of coronary artery bypass grafting and percutaneous coronary interventions because of cardiac ischaemia are important causes for developing HF. Other causes are longstanding hypertension, rhythm disorders, notably atrial fibrillation, valvular heart disease, and cardiomyopathy.[1] Finally, T2D may cause HF,[21] and unrecognized HF is common in older patients with T2D.[22] Two studies showed that intensified treatment with ACE-inhibitors and beta-blockers of patients with T2D and marginally elevated natriuretic peptide levels may reduce the incidence of HF and reduce mortality.[23;24]
- Cooperative care with cardiologist and HF nurse is the preferred way of managing patients with HFrEF such as Mr. G. in the community.

Managing heart failure in primary care

The GP is key in various stages of the so-called HF journey of patients. This role has been addressed in various national and international HF guidelines.[1;13] In 2015, a Dutch multidisciplinary document was published in 2015 with transmural agreements on diagnosis and treatment of HF based on the recommendations of the 2012 ESC guidelines on HF ("Landelijke Transmurale Afspraak hartfalen", in Dutch).[25] Early recognition of HF often starts in primary care, and adequate diagnosis should follow, including echocardiography in those with natriuretic peptide values above the exclusionary cut-point and an abnormal ECG, to prevent misclassification of symptoms and signs. For echocardiography, the GP can refer the patient to the cardiologist or to an open access facility. If it is concluded that the patient has HF with preserved EF or mid-range EF, he/she can be managed by the GP with adequate diuretic titration to relieve symptoms if fluid overloaded, and optimal blood pressure control. Patients with HFrEF need to receive multiple cardiovascular drugs, which should be carefully uptitrated. This seems best to be done at the HF outpatient clinic. GPs seem more hesitant than cardiologists and HF nurses in uptitrating such drugs in

these patients, most notably the uptitration of beta-blockers, with as a result less easily reaching target or maximally tolerated doses.[26] Both confidence and sufficient experience is needed to uptitrate ACE-inhibitors and beta-blockers adequately. If patients are stabilized and on maximal tolerated dose, the continuation of care could be done by the GP,[27;28] while additionally eHealth solutions (such as telemonitoring of heart rate, blood pressure and weight) may be considered.[29] Given that HF is a chronic progressive disease, eventually patients may reach their final stage of HF. Comorbidities, including cancer often play an important role and together with immobility this results in the GP taking the lead as the most important caregiver providing palliative care in the home setting.[30;31]

Objectives of this thesis

This thesis addresses several important aspects of diagnosis and management of HF in general practice by:

1. Assessment of whether patients with a GP diagnosis of HF really have HF.
2. Evaluation of time trends in natriuretic peptide testing in primary care.
3. Determining the prevalence of concomitant COPD in stable patients with an established diagnosis of HF.
4. Assessment of whether a half-day training of GPs improves the pharmacologic therapy and health status of patients with HF, notably those with HFrEF, and whether this results in reduction of hospitalizations and mortality.

Outline of this thesis

In chapter two, we quantify overdiagnosis of HF in primary care by exploring whether patients with a GP's label of HF (ICPC code K77; heart failure) indeed have HF according to an expert panel using all available diagnostic information.

In chapter three we quantified the use of natriuretic peptides by GPs over the years by describing the time trend of ordering natriuretic peptide testing between 2005 and 2014. In chapter four we calculated the prevalence of COPD based on the ratio of post-dilatory forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) (FEV1/FVC) in a representative sample of stable patients with established HF.

Chapter five describes the study design of a cluster-randomized controlled trial on treatment optimization of patients with HF in primary care in the Utrecht region (TOPHU). GPs in the intervention arm received a half-day training on the diagnosis and management of HF, with a focus on optimization of the evidence-based pharmacological treatment of those with HFrEF.

Chapter six reports the results of this randomized trial; assessing whether such training has an effect on the number of prescriptions of recommended HF drugs, on health status, hospitalizations and all-cause mortality.
In the general discussion (chapter seven) we summarize the results of our studies and highlight opportunities and pitfalls in the management of HF in primary care.

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016; 18(8):891-975.
2. van Riet EE, Hoes AW, Wagenaar KP, Limburg A, Landman MA, Rutten FH. Epidemiology of heart failure: the prevalence of heart failure and ventricular dysfunction in older adults over time. A systematic review. Eur J Heart Fail 2016; 18(3):242-252.
3. Gerber Y, Weston SA, Redfield MM, Chamberlain AM, Manemann SM, Jiang R et al. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. JAMA Intern Med 2015; 175(6):996-1004.
4. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006; 355(3):251-259.
5. Rutten FH, Moons KG, Cramer MJ, Grobbee DE, Zuithoff NP, Lammers JW et al. Recognising heart failure in elderly patients with stable chronic obstructive pulmonary disease in primary care: cross sectional diagnostic study. BMJ 2005; 331(7529):1379.
6. van Riet EE, Hoes AW, Limburg A, Landman MA, van der Hoeven H, Rutten FH. Prevalence of unrecognized heart failure in older persons with shortness of breath on exertion. Eur J Heart Fail 2014; 16(7):772-777.
7. van Mourik Y, Bertens LC, Cramer MJ, Lammers JW, Reitsma JB, Moons KG et al. Unrecognized heart failure and chronic obstructive pulmonary disease (COPD) in frail elderly detected through a near-home targeted screening strategy. J Am Board Fam Med 2014; 27(6):811-821.
8. Zaphiriou A, Robb S, Murray-Thomas T, Mendez G, Fox K, McDonagh T et al. The diagnostic accuracy of plasma BNP and NTproBNP in patients referred from primary care with suspected heart failure: results of the UK natriuretic peptide study. Eur J Heart Fail 2005; 7(4):537-541.
9. Fuat A, Murphy JJ, Hungin AP, Curry J, Mehrzad AA, Hetherington A et al. The diagnostic accuracy and utility of a B-type natriuretic peptide test in a community population of patients with suspected heart failure. Br J Gen Pract 2006; 56(526):327-333.
10. Kelder JC, Cramer MJ, Verweij WM, Grobbee DE, Hoes AW. Clinical utility of three B-type natriuretic peptide assays for the initial diagnostic assessment of new slow-onset heart failure. J Card Fail 2011; 17(9):729-734.
11. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2012; 14(8):803-869.
12. Khunti K, Squire I, Abrams KR, Sutton AJ. Accuracy of a 12-lead electrocardiogram in screening patients with suspected heart failure for open access echocardiography: a systematic review and meta-analysis. Eur J Heart Fail 2004; 6(5):571-576.

13. Hoes AW, Voors AA, Rutten FH, van Lieshout J, Janssen PGH, Walma EP. The Dutch College of General Practitioners guideline on heart failure, second revision [In Dutch]. Huisarts Wet 2010; 53:368-389.
14. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med 2011; 364(1):11-21.
15. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999; 341(10):709-717.
16. Rutten FH, Cramer MJ, Grobbee DE, Sachs AP, Kirkels JH, Lammers JW et al. Unrecognized heart failure in elderly patients with stable chronic obstructive pulmonary disease. Eur Heart J 2005; 26(18):1887-1894.
17. Brenner S, Guder G, Berliner D, Deubner N, Frohlich K, Ertl G et al. Airway obstruction in systolic heart failure--COPD or congestion? Int J Cardiol 2013; 168(3):1910-1916.
18. Rutten FH, Cramer MJ, Lammers JW, Grobbee DE, Hoes AW. Heart failure and chronic obstructive pulmonary disease: An ignored combination? Eur J Heart Fail 2006; 8(7):706-711.
19. Theander K, Hasselgren M, Luhr K, Eckerblad J, Unosson M, Karlsson I. Symptoms and impact of symptoms on function and health in patients with chronic obstructive pulmonary disease and chronic heart failure in primary health care. Int J Chron Obstruct Pulmon Dis 2014; 9:785-794.
20. Hawkins NM, Petrie MC, Jhund PS, Chalmers GW, Dunn FG, McMurray JJ. Heart failure and chronic obstructive pulmonary disease: diagnostic pitfalls and epidemiology. Eur J Heart Fail 2009; 11(2):130-139.
21. Seferovic PM, Paulus WJ. Clinical diabetic cardiomyopathy: a two-faced disease with restrictive and dilated phenotypes. Eur Heart J 2015; 36(27):1718-1727c.
22. Boonman-de Winter LJ, Rutten FH, Cramer MJ, Landman MJ, Liem AH, Rutten GE et al. High prevalence of previously unknown heart failure and left ventricular dysfunction in patients with type 2 diabetes. Diabetologia 2012; 55(8):2154-2162.
23. Ledwidge M, Gallagher J, Conlon C, Tallon E, O'Connell E, Dawkins I et al. Natriuretic peptide-based screening and collaborative care for heart failure: the STOP-HF randomized trial. JAMA 2013; 310(1):66-74.
24. Huelsmann M, Neuhold S, Resl M, Strunk G, Brath H, Francesconi C et al. PONTIAC (NT-proBNP selected prevention of cardiac events in a population of diabetic patients without a history of cardiac disease): a prospective randomized controlled trial. J Am Coll Cardiol 2013; 62(15):1365-1372.
25. Ansink JM, Burgers JS, Geerders BP, Elsendoorn M, van Laarhoven H, Mosterd A. Heart failure, A National Transmural Agreement (in Dutch). 15-11-0015. (Online Source)
26. Fuat A, Hungin AP, Murphy JJ. Barriers to accurate diagnosis and effective management of heart failure in primary care: qualitative study. BMJ 2003; 326(7382):196.
27. Schou M, Gustafsson F, Videbaek L, Tuxen C, Keller N, Handberg J et al. Extended heart failure clinic follow-up in low-risk patients: a randomized clinical trial (NorthStar). Eur Heart J 2013; 34(6):432-442.

28. Luttik ML, Jaarsma T, van Geel PP, Brons M, Hillege HL, Hoes AW et al. Long-term follow-up in optimally treated and stable heart failure patients: primary care vs. heart failure clinic. Results of the COACH-2 study. Eur J Heart Fail 2014; 16(11):1241-1248.
29. Wagenaar KP, Broekhuizen BD, Dickstein K, Jaarsma T, Hoes AW, Rutten FH. Effectiveness of an interactive platform, and the ESC/HFA heartfailurematters.org website in patients with heart failure: design of the multicentre randomized e-Vita heart failure trial. Eur J Heart Fail 2015; 17(12):1310-1316.
30. Bellersen L, Knubben AGMJ, van Bommel JMP. Guideline on palliative care of patients with chronic heart failure (Richtlijn palliatieve zorg bij chronisch hartfalen (in Dutch)). 2010. (Report)
31. Rutten FH, Heddema WS, Daggelders GJ, Hoes AW. Primary care patients with heart failure in the last year of their life. Fam Pract 2012; 29(1):36-42.

Chapter 2

Overdiagnosis of heart failure in primary care: a cross sectional study

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Abstract

Background Access to echocardiography in primary care is limited, but necessary to accurately diagnose heart failure (HF).

Aim To determine the proportion of patients with a general practitioner´s (GP's) diagnosis of HF who really has HF.

Design and setting A cross-sectional study of patients with an International Classification of Primary Care -ICPC- code K77 in primary care.

Methods Electronic medical records of the patients' GPs were scrutinized for information on the diagnosis. An expert panel consisting of two cardiologists and an experienced GP used all available diagnostic information, and established the presence or absence of HF according to the criteria of the European Society of Cardiology (ESC) HF guidelines.

Results and conclusion In total, 683 individuals had a GP's diagnosis of HF. The mean age was 77.9 (SD 11.4) years, and 42.2% were men. Of these 683, 79.6% received cooperative care from a cardiologist. In 73.5% of cases, echocardiography was available for panel re-evaluation. Based on consensus opinion of the panel, 434 patients (63.5%; 95%CI 59.9 to 67.1%) had definite HF; 222 (32.5%; 95%CI 30.9 to 34.1%) HF with a reduced ejection fraction (HFrEF), 207 (30.3%; 95%CI 29.0 to 31.6%) HF with a preserved ejection fraction (HFpEF), and five (0.7%; 95%CI 1.2 to 2.6%) isolated right-sided HF. In 17.3% (95% CI 14.4 to 20.0%) the panel considered HF absent, and in 19.2% (95% CI 16.3 to 22.2%) the diagnosis remained uncertain. Over one third of primary care patients labelled with HF may not have HF and such overdiagnosis may result in inadequate patient management.

Introduction

Heart failure (HF) is a chronic progressive disease mainly affecting older people.[1]
Pharmacological treatment, devices, as well as HF management programs can reduce morbidity and mortality in patients with HF and reduced ejection fraction (HFrEF).[1] In our study we defined HFrEF as symptoms and/or signs suggestive of HF and a left ventricular ejection fraction ≤45% with echocardiography. In patients who have HF with preserved ejection fraction (HFpEF) clear evidence-based disease-modifying treatment is still lacking, but, importantly, symptoms may be reduced with adequate titration of diuretics during periods of fluid retention.[1] In our study we defined HFpEF as symptoms and/or signs suggestive of HF and a left ventricular ejection fraction >45%, plus structural or functional abnormalities with echocardiography.[1]

The diagnosis of non-acute HF is primarily initiated in primary care, but this diagnosis is notoriously difficult without echocardiography, especially in the early stages of the disease, in the obese, in elderly, and in patients with chronic obstructive lung disease.[2;3] Additional investigations with natriuretic peptides and referrals for echocardiography are needed and have increased in primary care over the last decade.[4;5] GPs tend to follow the recommendation of existing guidelines that advocate considering referral for echocardiography of individuals with suggestive symptoms and signs who in addition have natriuretic peptide levels above the exclusionary threshold.[1] Nevertheless, this strategy has not been completely implemented yet,[3;5;6] with as a result the risk of over-diagnosis and under-diagnosis of HF if GPs consider the clinical assessment only. Multiple studies have mentioned under-diagnosis of HF in primary care,[2;7-11] but exact data on over-diagnosis in this setting are lacking.[7]
We wanted to quantify overdiagnosis of HF in primary care. We therefore evaluated if patients with a GP's diagnosis of HF really had HF according to an expert panel that applied the criteria of the ESC HF guidelines. Additionally, we determined which patient characteristics were associated with referral for echocardiography.

Methods

Design and study population

We performed a cross-sectional study in 30 general practices in and around Amersfoort, a town in the middle of the Netherlands. Around 70,000 persons were enlisted in these practices in 2010. Notably, all citizens in the Netherlands are enlisted with a GP, irrespective of cooperative care by a specialist, except for those living in nursing homes. Eligible were community-dwelling individuals with a GP's diagnosis of HF (International Classification of Primary Care (ICPC) code K77) registered during at least with two encounters, to prevent including those with accidental misclassification.[12] The GPs' electronic medical records (EMRs) and specialists' letters were scrutinized for information on demographics, medical history, medication, co-morbidities, laboratory tests, and results of echocardiography between June and October 2011. In November 2011, all participating GPs received a letter recommending completion of the diagnostic work-up of their patients labelled with HF, but who had not yet undergone echocardiography. To confirm the diagnosis and to help discriminate HF with reduced from preserved ejection fraction, as recommended in the Dutch General Practice guidelines on HF.[13] The current study is a cross-sectional analysis of the baseline characteristics of all 683 patients labelled with HF. Those with a definite HF diagnosis, established by an expert panel (n=434), than

participated in a cluster randomized trial (NCT01662323). In this cluster-randomized trial, the 30 GP practices were randomized to either a one-day training on the diagnosis and drug management of HF, or to usual care. The GPs working in the 15 GP practices of the intervention arm received a second reminder on the relevance of echocardiography.[14]

Cooperative care of patients by both a GP and cardiologist was pragmatically defined as any contact with the cardiologist (outpatient clinic visit or cardiac hospitalization) in the 18 months before the assessment.

The study complied with the Declaration of Helsinki and was approved by the Regional Medical Ethics Committee (Verenigde Commissies Mensgebonden Onderzoek; VCMO) of four hospitals in the Utrecht region, including Meander Medical Center, Amersfoort, the Netherlands.

Definition of heart failure

An expert panel composed of two cardiologists and a GP with expertise in HF determined the presence or absence of HF (definite HF, possibly HF, or no HF) during consensus meetings using all available diagnostic information, including echocardiography. Available echocardiograms were re-evaluated. The panel based the diagnosis of HF on the criteria laid out in the ESC HF guidelines; i.e. signs and symptoms suggestive of HF and objective evidence of structural or functional cardiac abnormality related to ventricular dysfunction in rest with echocardiography.[1] Disagreement between panel members was solved by discussion and majority of votes. In participants lacking information on natriuretic peptides and echocardiography, the panel decided between no HF and possibly HF, with the exception of patients who had been hospitalized for an episode of acute HF; they were diagnosed as 'definite HF' by the panel. Patients with definite HF were further classified based on echocardiography as HFrEF, HFpEF, or 'isolated' right-sided HF. For HFrEF the left ventricular ejection fraction (LVEF) had to be ≤ 45%. For HFpEF, the LVEF had to be > 45%, in the presence of a composite of echocardiographic indices of diastolic dysfunction or structural abnormalities (left ventricular hypertrophy or left atrial enlargement). For 'isolated' right-sided HF, the LVEF had to be >45%, and the estimated systolic pulmonary artery pressure > 40 mmHg, and this in the absence of evident left ventricular dysfunction or valvular disease.[1]

Data analysis

For comparing groups we used Student's t-tests or Mann Whitney U tests for continuous variables, and chi-square test for categorical variables. We compared those

with definite, no, and possibly HF; patients with versus no cooperative care by a cardiologist; and those with HFrEF versus HFpEF, respectively. The association between patient characteristics and referral for echocardiography was assessed with multivariable logistic regression analysis to identify independent predictors for referral. All analyses were done with SPSS software, version 20.0 for Windows (SPSS Inc., Chicago, IL).

Results

Baseline characteristics of the 683 patients with a GP's diagnosis of HF are presented in table 1. The mean age was 77.9 (SD 11.4) years, 42.2% were male, and 79.6% received cooperative care from a cardiologist. Seventy-seven (17.8%) patients had been hospitalized for acute HF. The expert panel could use the results of natriuretic peptide measurements in 69.3% of the patients, and echocardiography in 73.5%.

In total, 118 (17.3%; 95% CI 14.4 to 20.0%) patients had no HF according to the panel, and 131 (19.2%; 95% CI 16.3 to 22.2%) persons possibly HF.

The 139 patients who received care by the GP only were significantly older (81.5 vs. 76.9 years, $p<0.001$), had less prior myocardial infarction (10.8 vs. 31.4%, $p<0.001$), had less often had echocardiography (30.9 vs. 84.4%, $p<0.001$), and were less often prescribed an angiotensin converting enzyme inhibitor (ACE-i) or angiotensin receptor blocker (ARB) (43.9 vs. 61.8%, $p<0.001$) and mineralocorticoid receptor antagonists (MRAs) (15.1 vs. 25.6%, $p=0.009$) than the 544 patients who received cooperative care by a cardiologist (see table 2).

Multivariable analysis showed that younger age, prior myocardial infarction, and prescription of ACE-i/ARBs were independent predictors of referral for echocardiography (table 3).

The 434 (63.5% of the 683 patients with a GP's label of HF; 95%CI 59.9 to 67.1%) patients with definite HF can be divided in 222 (32.5%; 95%CI 30.9 to 34.1%) with HFrEF, 207 (30.3%; 95%CI 29.0 to 31.6%) with HFpEF, and 5 (0.7%; 95%CI to 1.2-2.6%) with 'isolated' right-sided HF. Considering the ejection fraction only, the 434 persons with definite HF can be divided as follows; 33.9% a LVEF <40%, 21.2% a LVEF 40-50%, 36.4% a LVEF>50%, and 8.5% in whom LVEF had not been recorded.

Table 1 Characteristics of 683 patients with a GP's diagnosis of heart failure, and categorized by the expert panel in definite heart failure, possibly heart failure, and no heart failure

	Definite HF (n=434)	**Possibly HF** (n=131)	**No HF** (n=118)
Mean age in years (SD)	77.2 (10.9)	83.9 (9.5)	74.1 (12.6)
Male sex	46.9	33.6	34.7
Cooperative care by a cardiologist	91.7	44.3	74.6
Co-morbidities			
Angina pectoris	18.4	15.3	17.8
Prior myocardial infarction	32.5	18.3	17.8
Atrial fibrillation	48.4	37.4	21.2
Stroke or TIA	13.8	22.1	13.6
COPD	20.0	19.1	18.6
eGFR<30 mL/min/1.73m²	9.7	13.7	4.2
Hypertension	54.6	45.0	58.5
Diabetes mellitus	32.7	26.7	19.5
Additional investigations			
Natriuretic peptide measurements *	71.0	68.7	64.4
Echocardiography *	92.6	15.3	67.8
Natriuretic peptides or echocardiography *	97.5	74.8	83.9
Drug prescriptions			
Diuretics	75.1	74.0	61.0
ACE-inhibitors	50.5	40.5	44.1
ARBs	15.2	11.5	11.0
Beta-blockers	56.0	42.0	44.1
MRAs	28.1	16.8	13.6
Digoxin	23.5	20.6	10.2

Numbers are percentages unless mentioned otherwise.
ACE-inhibitors = Angiotensin-Converting Enzyme inhibitors; ARBs = Angiotensin Receptor Blockers; COPD = Chronic Obstructive Pulmonary Disease; eGFR = the calculated glomerular filtration rate according to the modification of diet in renal diseases (MDRD) formula; MRAs = Mineralocorticoid receptor antagonists; TIA = Transient Ischaemic Attack.
* results available to the panel

Comparing the 222 patients with HFrEF with the 207 with HFpEF showed that those with HFrEF were younger (74.5 vs. 79.9 years, p<0.001), more often men (57.2% vs. 37.7%, p<0.001), and had more often prior myocardial infarction (47.7% vs. 16.4%, p<0.001). On the other hand, those with HFpEF had more often a history of hypertension (64.7% vs. 45.5%, p<0.001), atrial fibrillation (62.3% vs. 35.6%, p<0.001), and stroke/TIA (17.9% vs. 9.9%, p=0.02) than those with HFrEF (table 4).

Table 2 Characteristics of 683 patients with a GP's diagnosis of heart failure, divided in those receiving GP care only, and in patients who receive cooperative care from a cardiologist

	GP only (n=139)	**Cooperative care from cardiologist** (n=544)	**p-value**
No HF according to the panel	21.6	16.2	0.13
Possibly HF according to the panel	52.5	10.7	<0.001
Definite HF according to the panel	25.9	73.1	<0.001
Mean age in years (SD)	81.5 (12.4)	76.9 (11.4)	<0.001
Male sex	36.7	43.6	0.14
Co-morbidities			
Angina pectoris	10.8	19.5	0.02
Prior myocardial infarction	10.8	31.4	<0.001
Atrial fibrillation	36.7	42.8	0.19
Stroke	10.1	9.2	0.75
COPD	20.1	19.5	0.86
Hypertension	53.2	53.5	0.96
Diabetes mellitus	25.2	30.3	0.23
eGFR<60 mL/min/1.73m^2	33.1	38.2	0.26
Additional investigations			
Natriuretic peptides measurements *	70.5	68.9	0.72
Echocardiography*	30.9	84.4	<0.001
Drug prescriptions			
Diuretics	71.2	72.8	0.71
ACE-i/ARBs	43.9	61.8	<0.001
β-blockers	38.1	54.6	0.01
MRAs	15.1	25.6	0.009
Digoxin	15.8	19.3	0.35

Numbers are percentages unless stated otherwise. ACE-inhibitor= Angiotensin-Converting Enzyme inhibitor; ARB = Angiotensin Receptor Blocker; COPD = Chronic Obstructive Pulmonary Disease; eGFR = the calculated renal flow according to the modification of diet in renal diseases (MDRD) formula; MRAs = Mineralocorticoid receptor antagonists.
* results available to the panel

Discussion

We could show that among 683 patients with a GP's diagnosis of HF the diagnosis could not be confirmed in 17.3% of the cases, and another 19.2% were classified as 'possibly' HF by an expert panel. Younger age and prior myocardial infarction, and prescription of ACE-i/ARBs were independently related to referral for echocardiography. Of the 434 (63.5%) patients with panel-confirmed HF, 222 (32.5%) had HFrEF, 207 (30.3%) HFpEF, and five (0.7%) 'isolated' right-sided HF. Patients

Table 3 Multivariable association between patient characteristics and referral for echocardiography in 683 patients with a GP's diagnosis of heart failure

	Adjusted odds ratio (95%CI)
Age, per year	**0.98 (0.96-0.99)**
Male sex	1.19 (0.85-1.65)
Hypertension	1.01 (0.74-1.39)
Angina pectoris	1.00 (0.66-1.52)
Prior myocardial infarction	**1.73 (1.19-2.49)**
Atrial fibrillation	1.35 (0.98-1.86)
Diabetes mellitus	0.91 (0.64-1.29)
COPD	1.02 (0.69-1.52)
eGFR<30 mL/min/1.73m²	1.23 (0.70-2.16)
30<eGFR<60 mL/min/1.73m²	1.04 (0.73-1.47)
Natriuretic measurements performed	1.29 (0.94-1.79)
Diuretic prescription	1.21 (0.84-1.73)
ACE-inhibitor or ARB prescription	**1.42 (1.03-1.96)**
β-blocker prescription	1.04 (0.75-1.44)

ACE-inhibitor= Angiotensin converting enzyme inhibitor; ARB = Angiotensin Receptor Blocker; COPD = Chronic Obstructive Pulmonary Disease; eGFR = the calculated renal flow according to the modification of diet in renal diseases (MDRD) formula

with HFrEF in our study were prescribed ACE-i/ARBs in 69.4%, beta-blockers in 59.0%, and MRAs in 31.5%. These prescription rates are low compared to large drug RCTs, but are in line with other observational studies of real life patients.[15-18] Moreover, prescription rates of disease-modifying drugs in HFrEF are on the increase since the beginning of 2000.[6;17;18]

To the best of our knowledge, this is the first study that provides exact data on the over-diagnosis of HF in primary care. Moreover, we provide of those with established HF the exact percentages of cases with preserved and reduced ejection fraction. When considering our results, one has to realize that patients could receive cooperative care from a cardiologist for other diagnoses than HF, i.e. rhythm disorders, valvular disease, and ischaemic heart disease. Moreover, some of these patients could have been referred by the GP under the suspicion of HF (and were already labelled with ICPC code K77) without being confirmed by the cardiologist and thus may have remained incorrectly labelled as HF in the EMR of the GP.

Previous studies reported that HF could be established in 14% to 72% of the patients referred to an open access facility or cardiologist.[16;19-21] Patients in these studies could, however, also have been referred for analysis of a heart murmur, or for other cardiac causes of breathlessness.

Table 4 Co-morbidities and drug prescription of 434 patients with panel-confirmed heart failure, divided in those with reduced and preserved ejection fraction *

	HFrEF (n=222)	**HFpEF** (n=207)	**p-value**
Mean age in years (SD)	74.5 (11.3)	79.9 (8.7)	<0.001
Male sex	57.2	37.7	<0.001
Co-morbidities			
Angina pectoris	14.0	23.7	0.10
Prior myocardial infarction	47.7	16.4	<0.001
Atrial fibrillation	35.6	62.3	<0.001
Stroke or TIA	9.9	17.9	0.02
COPD	20.7	18.8	0.56
Renal insuffiency (eGFR <30 mL/min/1.73m²)	9.9	9.7	0.75
Hypertension	45.5	64.7	<0.001
Diabetes mellitus	33.3	31.4	0.67
Drug prescriptions			
Diuretics	76.6	73.4	0.45
ACE-inhibitors or ARBs	69.4	53.6	<0.001
Beta-blockers	59.0	52.7	0.15
MRAs	31.5	24.6	0.13
Digoxin	15.3	26.6	0.01

Numbers are percentages unless stated otherwise.
* Five (1.2%) patients with isolated right-sided HF were not included in this table.
ACE-inhibitors= Angiotensin-Converting Enzyme inhibitors; ARB = Angiotensin Receptor Blocker; COPD = Chronic Obstructive Pulmonary Disease; MRAs = Mineralocorticoid receptor antagonists; TIA = Transient Ischaemic Attack.

Other studies have reported how often GPs performed additional investigations in suspected cases of HF. Electrocardiography (36% to 53%) and chest X-ray (20% to 50%) were performed in a minority of cases.[22] In the beginning of the 21th century, just 12% of the patients labelled with HF and managed by the GP only had undergone echocardiography.[4] In our study 45.2% of 683 patients had undergone echocardiography at the start of the study, and this number increased to 73.5% after two reminders to consider referral for echocardiography. Irrespective of the last decade's increase in referrals for echocardiography of cases suspected of HF, there is still ample room for improvement. Multiple studies show that certainty about the diagnosis and knowing the type of HF greatly helps to improve the management of these patients.[7;23] Moreover, previous studies have shown that patients with HF with missing LVEF results are older, are prescribed less required HF medication and show more comorbidity and worse prognosis.[24] A postal survey in the UK in 2008 showed that direct access to echocardiography facilities was available for 72% of the GPs of

the responding primary care trusts.[5] Apart from availability of echocardiography, stimulation can substantially improve referral for echocardiography, as shown by our results (28.3% increase after two reminders).

Strengths and limitations

The strength of our study is that we are the first to evaluate if HF really is present in a representative sample of community-dwelling individuals who have a GP's diagnosis of HF. We used an expert panel to evaluate all available data of these people, and if an echocardiogram was available it was re-evaluated. Such an expert panel diagnosis is considered superior to a diagnosis of a single cardiologist during everyday practice, and previous studies have shown high reproducibility of such a panel diagnosis of HF.[2;8]

To answer the research question we had to use routine care data. Such data, however, are renowned for missing or incomplete diagnostic work-ups. As a result, the panel had to classify 26.5% of the patients without access to echocardiographic results. The percentage of echocardiography performed may on the one hand have been underestimated in our study because in some cases it may not be adequately registered in the GP's EMR. On the other hand, overestimation could be possible because we stimulated GPs to perform echocardiography. Importantly, however, this procedure did not affect the validity of our estimate of those with a GP's label of HF- those who really had HF- because this estimate was based on those with a GP's diagnosis of HF when the data were extracted from the EMR.

In our study we used the cutoff value of 45% for the LVEF, to distinguish between HFrEF and HFpEF. Alternative thresholds exist to define HF with preserved ejection fraction (HFpEF), and 50% has also been recommended.[25]

In 19% of the subjects, the panel could not make a definite diagnosis of HF, and this was merely due to the absence of echocardiography. Although, HF essentially is a clinical diagnosis, structural and functional cardiac abnormalities should be established to relate the non-specific symptoms and signs suggestive of HF to a cardiac origin.

To facilitate the diagnostic pathway for primary care patients suspected of HF, easy access to echocardiography should become more widely available. Furthermore, optimization of cooperative care with a cardiologist and HF outpatient clinic could promote drug use and result in more intensive up-titration of drugs. Previous studies showed that the substitution of care from the HF outpatient clinics to primary care is safe and feasible for patients with HFrEF. However, this must be after they have been carefully and adequately up-titrated with evidence-based treatment.[26-28]

Conclusions

Around one out of six patients with a GP's diagnosis of HF is misclassified, and such overdiagnosis brings the risk of inappropriate patient management. There is room for improvement of the diagnostic work-up of suspected cases of HF, importantly including natriuretic peptides to select those needing echocardiography to confirm the diagnosis and type of HF.

References

1. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2012; 14(8):803-869.
2. Rutten FH, Moons KG, Cramer MJ, Grobbee DE, Zuithoff NP, Lammers JW et al. Recognising heart failure in elderly patients with stable chronic obstructive pulmonary disease in primary care: cross sectional diagnostic study. BMJ 2005; 331(7529):1379.
3. Hobbs FD, Korewicki J, Cleland JG, Eastaugh J, Freemantle N. The diagnosis of heart failure in European primary care: The IMPROVEMENT Programme survey of perception and practice. Eur J Heart Fail 2005; 7(5):768-779.
4. Rutten FH, Grobbee DE, Hoes AW. Differences between general practitioners and cardiologists in diagnosis and management of heart failure: a survey in every-day practice. Eur J Heart Fail 2003; 5:337-344.
5. Murphy JJ, Chakraborty RR, Fuat A, Davies MK, Cleland JG. Diagnosis and management of patients with heart failure in England. Clin Med 2008; 8(3):264-266.
6. Remme WJ, McMurray JJ, Hobbs FD, Cohen-Solal A, Lopez-Sendon J, Boccanelli A et al. Awareness and perception of heart failure among European cardiologists, internists, geriatricians, and primary care physicians. Eur Heart J 2008; 29(14):1739-1752.
7. Fonseca C. Diagnosis of heart failure in primary care. Heart Fail Rev 2006; 11(2):95-107.
8. Boonman-de Winter LJ, Rutten FH, Cramer MJ, Landman MJ, Liem AH, Rutten GE et al. High prevalence of previously unknown heart failure and left ventricular dysfunction in patients with type 2 diabetes. Diabetologia 2012; 55(8):2154-2162.
9. van Riet EE, Hoes AW, Limburg A, Landman MA, van der Hoeven H, Rutten FH. Prevalence of unrecognized heart failure in older persons with shortness of breath on exertion. Eur J Heart Fail 2014; 16(7):772-777.
10. Davies M, Hobbs F, Davis R, Kenkre J, Roalfe AK, Hare R et al. Prevalence of left-ventricular systolic dysfunction and heart failure in the Echocardiographic Heart of England Screening study: a population based study. Lancet 2001; 358(9280):439-444.
11. van Mourik Y, Bertens LC, Cramer MJ, Lammers JW, Reitsma JB, Moons KG et al. Unrecognized heart failure and chronic obstructive pulmonary disease (COPD) in frail elderly detected through a near-home targeted screening strategy. J Am Board Fam Med 2014; 27(6):811-821.
12. Okkes I, Jamoulle M, Lamberts H, Bentzen N. ICPC-2-E: the electronic version of ICPC-2. Differences from the printed version and the consequences. Fam Pract 2000; 17(2):101-107.
13. Hoes AW, Voors AA, Rutten FH, van Lieshout J, Janssen PGH, Walma EP. The Dutch College of General Practitioners guideline on heart failure, second revision [In Dutch]. Huisarts Wet 2010; 53:368-389.
14. Valk MJ, Hoes AW, Mosterd A, Landman MA, Broekhuizen BD, Rutten FH. Rationale, design and baseline results of the Treatment Optimisation in Primary care of Heart failure in the Utrecht region (TOPHU) study: a cluster randomised controlled trial. BMC Fam Pract 2015; 16(1):130.
15. Calvert MJ, Shankar A, McManus RJ, Ryan R, Freemantle N. Evaluation of the management of heart failure in primary care. Fam Pract 2009; 26(2):145-153.

16. Braun V, Heintze C, Rufer V, Welke J, Stein T, Mehrhof F et al. Innovative strategy for implementing chronic heart failure guidelines among family physicians in different healthcare settings in Berlin. Eur J Heart Fail 2011; 13(1):93-99.
17. Bongers FJ, Schellevis FG, Bakx C, van den Bosch WJ, van der Zee J. Treatment of heart failure in Dutch general practice. BMC Fam Pract 2006; 7:40.
18. Bosch M, Wensing M, Bakx JC, van der Weijden T, Hoes AW, Grol RP. Current treatment of chronic heart failure in primary care; still room for improvement. J Eval Clin Pract 2010; 16(3):644-650.
19. Cancian M, Battaggia A, Celebrano M, Del ZF, Novelletto BF, Michieli R et al. The care for chronic heart failure by general practitioners. Results from a clinical audit in Italy. Eur J Gen Pract 2013; 19(1):3-10.
20. Rao A, Walsh J. Impact of specialist care in patients with newly diagnosed heart failure: a randomised controlled study. Int J Cardiol 2007; 115(2):196-202.
21. Khunti K. Systematic review of open access echocardiography for primary care. Eur J Heart Fail 2004; 6(1):79-83.
22. Kelder JC, Cramer MJ, Wijngaarden Jv, Tooren Rv, Mosterd A, Moons KG et al. The diagnostic value of physical examination and additional testing in primary care patients with suspected heart failure. Circulation 2011; 124(25):2865-2873.
23. Fuat A, Hungin AP, Murphy JJ. Barriers to accurate diagnosis and effective management of heart failure in primary care: qualitative study. BMJ 2003; 326(7382):196.
24. Poppe KK, Squire IB, Whalley GA, Kober L, McAlister FA, McMurray JJ et al. Known and missing left ventricular ejection fraction and survival in patients with heart failure: a MAGGIC meta-analysis report. Eur J Heart Fail 2013; 15(11):1220-1227.
25. Paulus WJ, van Ballegoij JJ. Treatment of heart failure with normal ejection fraction: an inconvenient truth! J Am Coll Cardiol 2010; 55(6):526-537.
26. Peters-Klimm F, Muller-Tasch T, Remppis A, Szecsenyi J, Schellberg D. Improved guideline adherence to pharmacotherapy of chronic systolic heart failure in general practice--results from a cluster-randomized controlled trial of implementation of a clinical practice guideline. J Eval Clin Pract 2008; 14(5):823-829.
27. Schou M, Gislason G, Videbaek L, Kober L, Tuxen C, Torp-Pedersen C et al. Effect of extended follow-up in a specialized heart failure clinic on adherence to guideline recommended therapy: NorthStar Adherence Study. Eur J Heart Fail 2014; 16(11):1249-1255.
28. Luttik ML, Jaarsma T, van Geel PP, Brons M, Hillege HL, Hoes AW et al. Long-term follow-up in optimally treated and stable heart failure patients: primary care vs. heart failure clinic. Results of the COACH-2 study. Eur J Heart Fail 2014; 16(11):1241-1248.

Chapter 3

COPD in patients with stable heart failure in the primary care setting

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Abstract

Background Presence of chronic obstructive pulmonary disease (COPD) in heart failure (HF) has prognostic and therapeutic implications. Exact prevalence estimates are lacking because most previous studies estimated the prevalence of COPD among HF patients while unstable and in the presence of pulmonary congestion.

Methods Community-dwelling patients with an established diagnosis of HF and in a stable phase of their disease were invited for spirometry. COPD was defined according to the Global initiative for Obstructive Lung Disease (GOLD) classification and considered present if the ratio of the post-bronchodilator forced expiratory volume in 1 second and forced vital capacity (FEV1/FVC) was below 0.7.

Results Thirty of the 106 patients with HF (mean age 76 (SD 11.9) years, 57% male) had COPD (prevalence 28.3% (95% CI 19.7-36.9%)), with similar rates among those with HF and a reduced ejection fraction (18 individuals; prevalence 28.6% (95% CI 20.0-37.2%)) and HF with preserved ejection fraction (12 individuals; prevalence 27.9% (95% CI 19.4-36.4)). Twenty-one (70%) of the 30 participants were newly detected cases of COPD.

Conclusions More than a quarter of the patients with HF concomitantly have COPD, with the large majority being previously unrecognized. Coexistence of COPD should be considered more often in these patients.

Introduction

Heart failure (HF) and chronic obstructive pulmonary disease (COPD) are both common in the elderly, and often coexist.[1] Diagnosing COPD in heart failure is challenging because clinical features overlap, and dyspnoea and fatigue are common symptoms.[1;2] Both share smoking as an important risk factor, and they have a chronic progressive disease trajectory with systemic effects, and require complex treatment regiments.[3-5] The prognosis of patients with both disorders is worse than of those with one of the diseases. [6;7] Importantly, bronchodilators may improve symptoms of COPD, but possibly cause cardiac side effects.[8;9] Under-diagnosis of one disease in the presence of another important issue, [10;11] but also there is a risk of over-diagnosing COPD in patients with HF if these patients are not stable and have some pulmonary congestion.[12] Pulmonary congestion is common in those hospitalized for an exacerbation of HF, and this may mimic clinically, but also spirometrically COPD. Spirometry at discharge in that situation would show –caused by pulmonary

congestion- a larger reduction in forced expiratory volume in 1 second (FEV1) than in forced vital capacity (FVC), resulting in a risk of overdiagnosing COPD.[13;14] When patients with HF are stable and euvolemic, the FEV1/FVC allows to adequately detect COPD, although, both the FEV1 and the FVC are reduced to a similar extent.[15] Diagnosing COPD at the right moment is therefore key in patients with heart failure.
Earlier reports on the prevalence of co-morbid COPD in HF often relied on previous documentation of COPD, or on spirometry results performed in HF patients when unstable. [10;16;17] Prevalence estimates ranged from 9 to 52%.[2] Data in a representative sample of patients with HF in a stable phase of their disease, also including patients with preserved ejection fraction, is still lacking.[1]
The aim of our study was to provide a valid prevalence estimate of COPD in a representative sample of patients with HF while in a stable condition. (ClinicalTrials.gov identifier NCT01662323)

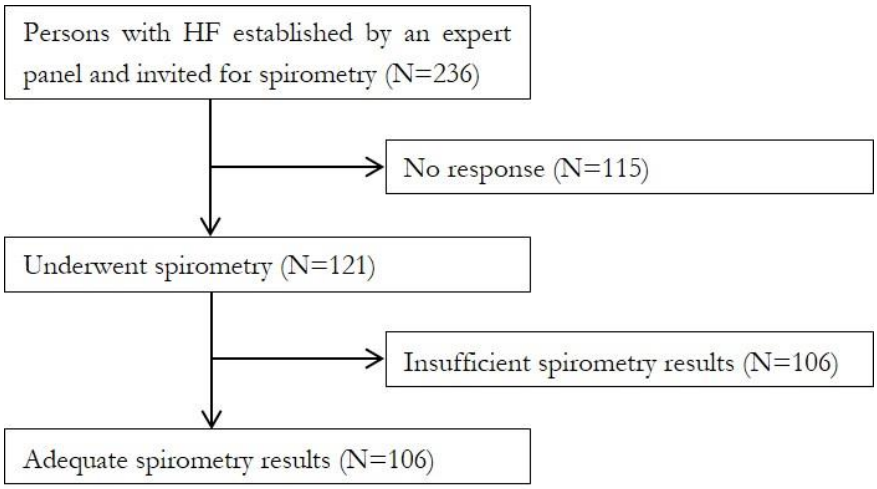
Methods

Design and study population

In a cross-sectional study we enrolled patients from 30 general practices from the vicinity of Amersfoort, the Netherlands. The study and recruitment period was from November 2010 until October 2011. In total 70,000 persons were enlisted in these practices. In the Netherlands all citizens are registered with a general practitioner (GP), irrespective of cooperative care by a hospital specialist, including those living in a home for the elderly, but excluding those living in a nursing home or hospice. Eligible were patients with a diagnosis of HF in whom such a diagnosis was confirmed by an expert panel consisting of two cardiologists and a GP specialized in heart failure using all diagnostic information, including echocardiography. The panel based the diagnosis of HF on the criteria of the European Society of Cardiology (ESC), that is, suggestive symptoms and objective evidence of cardiac structural or functional cardiac abnormality related to ventricular dysfunction at rest detectable with echocardiography. For HF with reduced ejection fraction (HFrEF) the left ventricular ejection fraction (LVEF) should be <45%. For HF with preserved ejection fraction the LVEF should be ≥45%, in addition to diastolic dysfunction with echocardiography.[18]
Disagreement between panel members was resolved by majority. We invited 236 patients with a confirmed diagnosis of HF for spirometry, and 121 (51.2%) consented

to participate (See Figure 1).
The study was approved by the Regional Medical Ethics Committee (VCMO) of the Meander Medical Center, Amersfoort, the Netherlands. All participants gave written informed consent.

Figure 1 Flow Diagram



Measurements
Between November 2010 and June 2011 baseline characteristics of the participants were extracted from the medical files of the participating GPs. Participants underwent spirometry in the primary care setting by trained personnel. Spirometry was performed with SPIDA software (Spida 5) and microloop. Before and after 400 micrograms of salbutamol, the Forced Vital Capacity (FVC) and Forced Expiratory Volume in one second (FEV1) were measured. COPD was considered present if the post-bronchodilator FEV1/FVC ratio was below 0.7, as defined by the Global initiative for chronic Obstructive Lung Disease (GOLD)
criteria.[5] Severity of pulmonary obstruction was expressed as the proportion of the predicted FEV1 (the latter based on 'normal' values as derived from the population at large with the same age, sex, and height) and derived from the forced spirometry.[19] The FEV1 as percentage of predicted was subdivided into four categories: ≥80, 50-79, 30-49, ≤30. The quality of the flow-volume curves was assessed by an experienced physician.

Data analysis

We compared HF patients who decided to participate with nonparticipants. In the participants we compared those with and without COPD. In those with COPD, we compared already known with newly detected. Finally we compared patients with HFrEF and HFpEF. Differences between groups were assessed with the chi square or Fisher exact tests for categorical variables, and independent *t*-test for continuous variables. The prevalence of COPD was calculated with the binominal 95% confidence intervals (95% CI). All data were analysed with SPSS version 20.0.

Results

Two-hundred and thirty-six patients with established HF were invited for spirometry. Baseline characteristics of the participants (n=121) did not significantly different from the non-participants (n=115) (appendix 1). In 15 patients spirometry results were of insufficient quality, leaving 106 for this analysis (see figure 1). The mean age of the 106 participants was 76.1 (SD 11.9) years, and 57% were male. The prevalence of COPD was 28.3% (95%CI 19.7- 36.9%), with similar rates for those with a reduced ejection fraction (28.6% (95%CI 20.0- 37.2%)) and preserved ejection fraction (27.9% (95%CI 19.4-36.4%)).

Table 1 shows patient characteristics of all 106 patients. On average, patients with COPD were older than those without COPD. Mean FEV1% predicted was 65.8 (SD 19.5) and 73.9 (SD 10.9) for those with newly detected COPD and without COPD, respectively. Seventy percent of the subjects with COPD were previously unknown to their GP. None of the patients with COPD had a history of asthma. Table 2 shows the patient characteristics of newly detected cases versus heart failure patients without COPD. In table 3 we compared patients with HFrEF and HFpEF. The mean post-dilator FEV1 % predicted was around 80% for both HFrEF and HFpEF patients. Patients with HFrEF were more often male than those with HFpEF.

Table 1 Characteristics of the 106 patients with established heart failure divided in those with and without newly detected, or already known COPD.

Characteristics		Total (n=106)	Newly detected COPD (n=21)	Known COPD (n=9)	No COPD (n=76)
Mean age years (SD)		76.0 (11.9)	76.9 (11.7)	76.4 (10.9)	75.8 (12.2)
Male sex		60 (56.6)	14 (66.7)	9 (100.0)	37 (48.7)
HFrEF		63 (59.4)	12 (57.1)	6 (66.7)	45 (59.2)
HFpEF		43 (40.6)	9 (42.9)	3 (33.3)	31 (40.8)
Mean FVC as % predicted (SD)		86.4 (21.0)	83.5 (16.8)	95.6 (14.5)	86.3 (24.0)
Mean FEV1 as % predicted (SD)		79.6 (22.1)	65.8 (19.5)	73.9 (10.9)	88.9 (22.8)
Mean FEV1/FVC (SD)		74.5 (11.8)	60.2 (9.8)	58.0 (5.7)	78.3 (14.3)
Smoking*					
Current		43 (40.6)	8 (38.1)	1 (11.1)	10 (14.9)
Former		37 (34.6)	9 (42.9)	5 (55.6)	23 (34.3)
Never		11 (10.3)	0 (0.0)	1 (11.1)	34 (50.7)
Co morbidities					
Hypertension		55 (51.9)	12 (57.1)	4 (44.4)	39 (51.3)
Diabetes mellitus		28 (26.4)	2 (9.5)	2 (22.2)	24 (31.6)
Prior myocardial infarction		35 (33.0)	9 (42.9)	4 (44.4)	22 (28.9)
Cardiovascular medication					
Diuretics		75 (70.8)	13 (61.9)	5 (55.6)	57 (75.0)
ACE-i or ARB		67 (63.2)	15 (71.4)	4 (44.4)	49 (63.6)
Beta-blockers		55 (51.9)	11 (52.4)	6 (66.7)	38 (50.0)
Mineralocorticoid Receptor antagonists		35 (33.0)	2 (9.5)	1 (11.1)	32 (42.1)
Pulmonary medication:					
Inhaled betamimetics	Short-acting	9 (8.4)	4 (19.0)	1 (11.1)	4 (5.3)
	Long-acting	13 (12.1)	3 (14.3)	4 (44.4)	6 (7.9)
Inhaled anticholinergics	Short-acting	10 (9.3)	1 (4.8)	2 (22.2)	7 (9.2)
	Long-acting	3 (2.8)	0 (0.0)	3 (33.3)	0 (0.0)
Corticosteroids	Oral	3 (2.8)	1 (4.8)	2 (22.2)	0 (0.0)
	Inhaled	14 (13.1)	4 (19.0)	4 (44.4)	6 (7.9)

Numbers are cases (%) unless mentioned otherwise. ACE-I or ARB= angiotensin converting enzyme inhibitors and/or angiotensin receptor blockers; FEV1= Forced Expiratory Volume in one second. FVC = forced vital capacity; HFpEF= Heart Failure with Preserved Ejection Fraction; HFrEF= Heart Failure with Reduced Ejection Fraction; *Data on smoking were missing in 15 patients.

Table 2 Characteristics of the patients with heart failure and a new diagnosis of COPD versus those without COPD.

Characteristics	Newly diagnosed COPD (n=21)	No COPD (n=76)	P-Value
Mean age	76.9 (11.7)	75.8 (12.2)	0.71
Male sex	14 (66.7)	37 (48.7)	0.14
HFrEF	12 (57.1)	45 (59.2)	0.87
HFpEF	9 (42.9)	31 (40.8)	0.87
Smoking			
Current	8 (38.1)	34 (44.7)	0.59
Former	9 (42.9)	23 (30.3)	0.28
Never	0 (0)	10 (13.2)	0.79
Cardiovascular medication			
Diuretics	13 (61.9)	57 (75.0)	0.24
ACE-I or ARB	15 (71.4)	48 (63.2)	0.48
Beta-blocker	11 (52.4)	38 (50.0)	0.85
Mineralocorticoid receptor antagonist	2 (9.5)	32 (42.1)	0.006

Numbers are cases (%) unless specified otherwise. ACE-i= angiotensin-converting enzyme inhibitors; ARB= angiotensin receptor blocker; COPD= Chronic Obstructive Pulmonary Disease; HFpEF= Heart Failure with Preserved Ejection Fraction; HFrEF = Heart Failure with Reduced Ejection Fraction. Missings for smoking : newly diagnosed COPD 4 (19.0%), no COPD 9 (11.8%).

Discussion

In our study among stable community-dwelling HF patients the prevalence of COPD was 28.3%, and in 70% this was a new diagnosis of COPD. Prevalence rates were comparable for the subgroups of HFrEF and HFpEF.

Our results are in line with previous studies reporting prevalence rates of 9-52% in patients with heart failure.[2] These previous studies were performed in hospitalized patients with an over-representation of HFrEF, and spirometry performed while they were recently pulmonary fluid overloaded. We could therefore provide a more valid point estimate of the COPD prevalence of the HF population at large than previous studies could. A recent study among 118 elderly patients with stable HF and a smoking history of ≥ 10 pack years also showed a prevalence rate of 30% of COPD, similar to our study, and also a similarly high number of newly detected cases of COPD (64%).[20] In this study COPD was also defined according to the GOLD criteria. Moreover,

Table 3 Characteristics and spirometry results of the 106 patients with established HF, divided in those with HFrEF and HFpEF

Characteristics	HFrEF (n=63)	HFpEF (n=43)	P-value
Mean age in years (SD)	73.1 (13.0)	80.4 (8.4)	0.001
Male sex	38 (60.3)	22 (51.2)	0.35
Confirmed COPD	18 (28.6)	12 (27.9)	0.94
Spirometry results			
Mean FVC as % predicted	85.9 (SD 22.9)	87.3 (SD 21.4)	0.77
Mean FEV1 as % predicted	79.2 (SD 21.4)	80.3 (SD 23.7)	0.82
FEV1 as % predicted			
≥80	7 (11.1)	3 (7.0)	0.48
50-79	9 (14.3)	7 (16.3)	0.78
30-49	2 (3.2)	2 (4.7)	0.70
<30	0 (0)	0 (0)	1.0
Cardiovascular medication			
Diuretics	41 (65.1)	34 (79.1)	0.12
ACE-i or ARB	45 (71.4)	22 (51.2)	0.03
Beta-blockers	35 (55.6)	20 (46.5)	0.36
Mineralocorticoid receptor antagonists	20 (31.7)	15 (34.9)	0.73

Numbers are cases (%) unless specified otherwise. ACE-i= angiotensin-converting enzyme inhibitors; ARB= angiotensin receptor blocker; COPD= Chronic Obstructive Pulmonary Disease; HFpEF= Heart Failure with Preserved Ejection Fraction; HFrEF = Heart Failure with Reduced Ejection Fraction.

patients were investigated while stable, around 3 months after being hospitalized for HF. Separate prevalence rates for HFrEF and HFpEF, however, were lacking.[20]

The prevalence of COPD in patients with HF in our study is around 1.5 times higher than the expected estimate of 20% in elderly from the population at large.[21]

Our finding that the post-bronchodilator FEV1 was on average 80% predicted in patients with HF is in line with a previous study showing that HF in the absence of COPD may cause a reduction in FEV1 of approximately 20%, caused by HF itself.[15] Thus, classifying severity of COPD based on FEV1 % predicted may overestimate the severity of obstruction in patients with HF. Because both FVC and FVC as % predicted are reduced approximately 20%, the ratio FEV1/FVC is not affected.[15]

A strength of our study is the inclusion of a representative sample of patients with HF in a stable phase of their disease, and we could present prevalence rates for patients with HFrEF and HFpEF separately.

A limitation is the relative small sample size and the lack of body box measurements. Measurements of the total lung capacity and the residual volume would have been helpful to refine the diagnosis of COPD, especially in cases with spirometry results around the critical cut-point of FEV1/FVC 0.7.[22] Importantly, however, also previous studies reporting on the prevalence of COPD in HF did not apply pulmonary function tests other than spirometry. Recently, some authors advocated age- and sex-related thresholds for the FEV1/FVC lower limit of normal (LLN) to define COPD.[19] We did not use one of the suggested LLN methods, because application in our study would reduce the possibility to compare our results with previous studies. Finally some COPD cases may in fact represent persistent asthma, or 'mixed cases', however, none of the COPD cases in earlier years had been labeled with asthma by the GP. We therefore preferred to use the GOLD-definition for COPD (a FEV1/FVC<0.7). Knowledge of co-morbid COPD in patients with HF has clinical implications because for the management of breathlessness there is room for pulmonary inhalatory drugs. We have, however, realized that some authors suggest that both beta-mimetics and anti-muscarinic agents may harm the heart. HF drugs may be prescribed in patients with COPD, including cardio selective beta-blockers. It is, however, important to uptitrate slowly. [23]

Conclusions

COPD is common in patients with HF, both HFrEF and HFpEF, and remains undetected in the majority of patients. Selective screening of patients with HF when in a stable phase of their disease should be considered.

Appendix 1. Characteristics of the 236 patients with established heart failure who were invited for spirometry, divided in participants and non-participants

	Participants n=121	**Non-participants** n=115	**P-value**
Male sex	46.3	55.7	0.15
Mean age in years (SD)	77.0 (11.4)	76.6 (11.9)	0.91
Hypertension	56.7	53.0	0.63
Diabetes mellitus	30.6	26.1	0.44
Prior myocardial infarction	33.1	32.2	0.89
Angina pectoris	22.3	13.0	0.06
Atrial fibrillation	54.5	50.4	0.53
eGFR < 60 ml/m²	38.8	37.4	0.82
Medication			
Diuretics	84.3	73.0	0.03
ACE-inhibitors	54.5	52.2	0.72
Beta-blocker	59.9	52.2	0.29
Digoxin	24.0	21.7	0.68

Numbers are cases (%) unless specified otherwise. ACE-inhibitors= Angiotensin-converting enzyme inhibitors; eGFR = the calculated glomerular filtration rate according to the modification of diet in renal diseases (MDRD) formula

References

1. Rutten FH, Cramer MJ, Lammers JW, Grobbee DE, Hoes AW. Heart failure and chronic obstructive pulmonary disease: An ignored combination? Eur J Heart Fail 2006; 8(7):706-711.
2. Hawkins NM, Petrie MC, Jhund PS, Chalmers GW, Dunn FG, McMurray JJ. Heart failure and chronic obstructive pulmonary disease: diagnostic pitfalls and epidemiology. Eur J Heart Fail 2009; 11(2):130-139.
3. Le Jemtel TH, Padeletti M, Jelic S. Diagnostic and therapeutic challenges in patients with coexistent chronic obstructive pulmonary disease and chronic heart failure. J Am Coll Cardiol 2007; 49(2):171-180.
4. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2012; 14(8):803-869.
5. Vestbo J, Hurd SS, Agusti AG, Jones PW, Vogelmeier C, Anzueto A et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2013; 187(4):347-365.
6. Iversen KK, Kjaergaard J, Akkan D, Kober L, Torp-Pedersen C, Hassager C et al. The prognostic importance of lung function in patients admitted with heart failure. Eur J Heart Fail 2010; 12(7):685-691.
7. Boudestein LC, Rutten FH, Cramer MJ, Lammers JW, Hoes AW. The impact of concurrent heart failure on prognosis in patients with chronic obstructive pulmonary disease. Eur J Heart Fail 2009; 11(12):1182-1188.
8. Au DH, Udris EM, Fan VS, Curtis JR, McDonell MB, Fihn SD. Risk of mortality and heart failure exacerbations associated with inhaled beta-adrenoceptor agonists among patients with known left ventricular systolic dysfunction. Chest 2003; 123(6):1964-1969.
9. Salpeter SR. Cardiovascular safety of beta(2)-adrenoceptor agonist use in patients with obstructive airway disease: a systematic review. Drugs Aging 2004; 21(6):405-414.
10. Iversen KK, Kjaergaard J, Akkan D, Kober L, Torp-Pedersen C, Hassager C et al. Chronic obstructive pulmonary disease in patients admitted with heart failure. J Intern Med 2008; 264(4):361-369.
11. Rutten FH, Cramer MJ, Grobbee DE, Sachs AP, Kirkels JH, Lammers JW et al. Unrecognized heart failure in elderly patients with stable chronic obstructive pulmonary disease. Eur Heart J 2005; 26(18):1887-1894.
12. Brenner S, Guder G, Berliner D, Deubner N, Frohlich K, Ertl G et al. Airway obstruction in systolic heart failure--COPD or congestion? Int J Cardiol 2013; 168(3):1910-1916.
13. Dimopoulou I, Daganou M, Tsintzas OK, Tzelepis GE. Effects of severity of long-standing congestive heart failure on pulmonary function. Respir Med 1998; 92(12):1321-1325.
14. Petermann W, Barth J, Entzian P. Heart failure and airway obstruction. Int J Cardiol 1987; 17(2):207-209.
15. Guder G, Rutten FH, Brenner S, Angermann CE, Berliner D, Ertl G et al. The impact of heart failure on the classification of COPD severity. J Card Fail 2012; 18(8):637-644.

16. Kjoller E, Kober L, Iversen K, Torp-Pedersen C. Importance of chronic obstructive pulmonary disease for prognosis and diagnosis of congestive heart failure in patients with acute myocardial infarction. Eur J Heart Fail 2004; 6(1):71-77.
17. Macchia A, Monte S, Romero M, D'Ettorre A, Tognoni G. The prognostic influence of chronic obstructive pulmonary disease in patients hospitalised for chronic heart failure. Eur J Heart Fail 2007; 9(9):942-948.
18. Boonman-de Winter LJ, Rutten FH, Cramer MJ, Landman MJ, Liem AH, Rutten GE et al. High prevalence of previously unknown heart failure and left ventricular dysfunction in patients with type 2 diabetes. Diabetologia 2012; 55(8):2154-2162.
19. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J Suppl 1993; 16:5-40.
20. Boschetto P, Fucili A, Stendardo M, Malagu M, Parrinello G, Casimirri E et al. Occurrence and impact of chronic obstructive pulmonary disease in elderly patients with stable heart failure. Respirology 2013; 18(1):125-130.
21. Halbert RJ FAU, Natoli JL FAU, Gano AF, Badamgarav E FAU - Buist, Buist AS FAU, Mannino DM. Global burden of COPD: systematic review and meta-analysis.(0903-1936 (Print)).
22. Guder G, Brenner S, Angermann CE, Ertl G, Held M, Sachs AP et al. "GOLD or lower limit of normal definition? A comparison with expert-based diagnosis of chronic obstructive pulmonary disease in a prospective cohort-study". Respir Res 2012; 13(1):13.
23. Guder G, Brenner S, Stork S, Hoes A, Rutten FH. Chronic obstructive pulmonary disease in heart failure: accurate diagnosis and treatment. Eur J Heart Fail 2014; 16(12):1273-1282.

Chapter 4

Time trends in the use of natriuretic peptide testing in primary care in the Netherlands

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Submitted

Abstract

Background Diagnosing heart failure (HF) is difficult. Natriuretic peptides (NPs) are recommended to exclude HF in suspected patients and are available since 2003 for primary care in the Netherlands. Little is known about its uptake.

Aim To evaluate the trend in ordering of NP testing by GPs.

Methods An observational study performed between January 2005 and December 2013. Nine Dutch general practices participated, with 21,000 registered persons (≈ 4,300 65+). The number of patients undergoing NP testing each year was calculated per 1,000 patient years (PY) based on the total practice population.

Results The number of NP testing increased from 2.5 per 1,000 PY in 2005 to 14.0 in 2013, with a peak (15.6 per 1,000 PY) in 2009.

Conclusions In primary care the use NP testing seemed to stabilize after 2009 after a rapid uptake from 2005 onwards.

Keywords: Heart failure, primary care, natriuretic peptides, time trend, diagnosis.

Introduction

Heart failure (HF) is an important health problem, and adequate management starts with a correct diagnosis. However, relying on medical history, symptoms and signs only, diagnosing HF is notoriously difficult.[1;2] Electrocardiography provides relevant information, but is not generally available in general practice, and access to echocardiography is even more limited. In clinical guidelines, natriuretic peptides (NP), notably B-type (BNP) and amino-terminal B-type (NTproBNP) are recommended for the initial diagnostic assessment of patients suspected of HF immediately following history taking, signs and symptoms, to exclude HF and select those requiring echocardiography to confirm the diagnosis.[3]

NPs were first identified in the porcine brain in 1988.[4] In 2003 Dutch general practitioners (GPs) could order NP testing in laboratories, as it became available in hospital laboratories around 2002. In 2005, the Dutch primary care guideline on HF recommended for the first time NP testing for the initial diagnostic assessment of patients with symptoms and signs suggestive of HF in the primary care setting.[5] The updated 2010 Dutch primary care HF guidelines,[6] and also the 2012 and 2016 European Society of Cardiology (ESC) HF guidelines,[3;7] specifically mentioned the importance of NP testing as a means to exclude the presence of non-acute HF (in

those with a NTproBNP < 125 pg/mL or < BNP 35 pg/mL). Those with higher NP values should be referred for echocardiography.[3;7]

Recent studies clearly demonstrated on the one hand that many (40-80% in some high-risk groups) older patients with HF in primary care are not recognized as such (underdiagnosis),[8-11] while on the other hand patients with a GP's label of HF in 17% do not really have HF according to an expert panel using all available diagnostic information (overdiagnosis).[12] NP testing is considered an important tool to reduce false-negative and false-positive HF diagnoses.[1;13]

Currently, there is very limited data on the uptake of NP testing in primary care over time. Against this background we investigated the time trend in ordering NP testing by GPs in the Netherlands from 2005 to 2013.

Methods

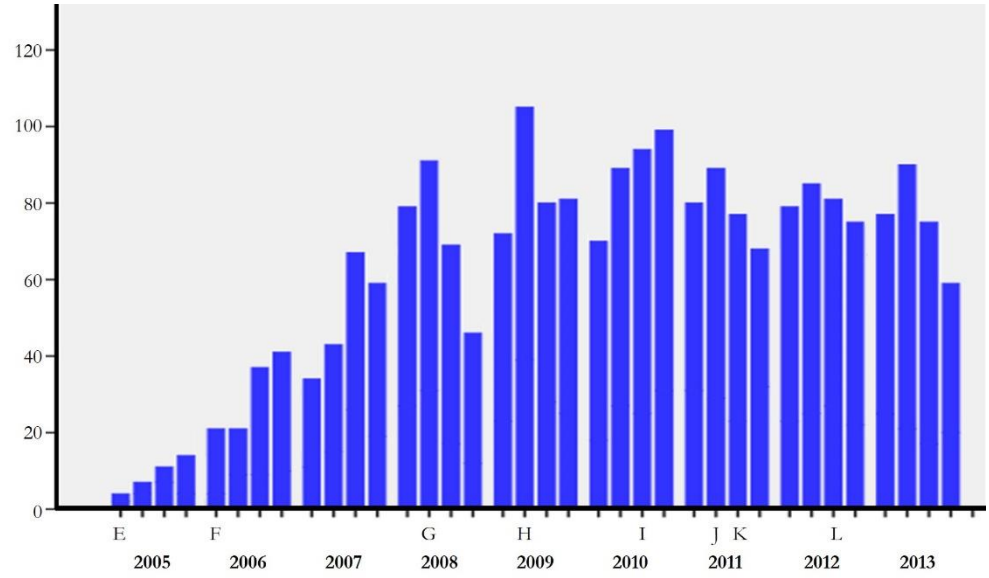
GPs from nine primary care practices in Soest, the Netherlands participated in our study between March 2005 and December 2013. In 2009 the participating GPs voluntarily participated in a one day training on HF on invitation. In the Netherlands, all inhabitants are registered with a GP, irrespective of co-management by a hospital specialist, except for patients living in a nursing home or hospice. In the participating practices, 21,000 individuals were enlisted (≈4,300 aged 65 years and over).

NP ordering became available for GPs in 2003, and all NP measurements were extracted from the Meander Medical Center hospital database. This laboratory used NTproBNP, and it was measured on the Elecsys analyser (Roche Diagnostics). Results were given in pg/mL. In figure 1 we summarise events that may have affected the ordering of NTproBNP tests.

The total number of enlisted people and the proportion aged 65 years or over were calculated for each year.

The participating GPs agreed on the use of de-identified patient data, and signed informed consent. The study was conducted in accordance with the Law for the Protection of Personal Data and confirmed to the principles outlined in the Declaration of Helsinki.[6;14] The Medical research Ethics Committees United (MEC-U) of the Meander Medical Center, the Netherlands approved the study protocol and the use of de-identified data.

Figure 1 Number of NTproBNP tests as was ordered per quarter of the year by GPs in the period January 2005 until December 2013



The letters E to L correspond to events mentioned in the box.

A. 1988 B-type (or Brain) natriuretic peptide identified in the porcine brain.
B. 1996 First Dutch GPs' guidelines on HF.
C. 2002 Natriuretic peptide testing available in the Netherlands.
D. 2003 Dutch GPs were allowed to order natriuretic peptide testing.
E. 2005 Update of the Dutch GPs' guidelines on HF, now mentioning NTproBNP and BNP as an option in the diagnostic assessment. Also in this year an update of the ESC guidelines on HF.
F. 2006 Patient reimbursement stopped for laboratory testing.
G. 2008 Update of the ESC guidelines on HF, clearly recommending NPs for diagnosis, but without advocating a cut-point.
H. 2009 Single day training on the diagnosis of HF and the use of NTproBNP of the participating GPs of Soest.
I. 2010 Update of the Dutch GPs' guidelines on HF, now recommending the use of the NTproBNP exclusionary cut-point of 125 pg/mL (≈ 15 mmol/L). If values are below this threshold, and the electrocardiogram is normal, than HF is very unlikely and other diagnoses should be considered to explain the symptoms of patients.
J. 2011 Regional agreement on open-access echocardiography in the Soest area.
K. 2011 Regional agreement between GPs and cardiologists on HF referral, diagnosis, and management in the Soest area.
L. 2012 Update of the ESC guidelines on HF, now also explicitly recommending the exclusionary cut-point of 125 pg/mL (≈ 15 mmol/L) for NTproBNP.

Data analysis

We calculated the number of NTproBNP ordering per 1,000 patient years (PY) for each year between 2005 and 2013. We dichotomised NTproBNP values at 125 pg/mL (≈ 15 mmol/L) to determine the proportion of tests that served to exclude HF.

Results

During the nine-year period 2,269 NTproBNP measurements were ordered by the participating GPs; in 2005, 2.5 orders per 1000 PY, increasing in subsequent years to 15.6 orders per 1000 PY in 2009, and stabilization afterwards with at the end of the study period in 2013 14.0 tests ordered per 1000 PY (Figure 1).

The proportion of NTproBNP values < 125 pg/mL (i.e. the exclusionary cut-point as recommended in the ESC and Dutch HF guidelines) was on average 30%, with a peak in the initial year of the study of 47%.

Discussion

NP testing by Dutch GPs increased steeply from 2.5 per 1000 PY in 2005 to 15.6 per 1000 PY in 2009, followed by a stabilization in the subsequent years (14.0 per 1000 PY in 2013).

Guideline recommendations for the use in the diagnostic assessment seemed to have contributed to the increase in NP ordering by GPs (figure 1). The peak in 2009 may additionally be related to the one-day training on the diagnosis of HF that the participating GPs received in that year.

As far as we know, there are no other studies published in international journals about time trends in NP testing in primary care. A small study on time trends was published in a Dutch medical journal providing data over the period 2004 to 2007, also showing an increase in NP testing, from 1.0 per 1000 PY in 2004 to 6.5 in 2007.[15] Comparison of these findings with our results show a similar although smaller increase in NP testing over time.

The major strength of our study was that all participating GPs sent their requests to one single hospital laboratory. A limitation was that individual patient data was not available. We could therefore not provide patient characteristics or exclude that in some cases GPs have ordered multiple NP measurements over time in some cases for monitoring. The latter is, however, certainly not common practice in Dutch primary

care and available (inter)national guidelines do not recommended the use of NPs for monitoring.

Recent ESC HF guidelines explicitly recommend NP testing for *excluding* HF.[3;7] Knowing that only a minority of patients (around 30%) suspected of HF by their GP is found to have HF after complete diagnostic assessment including echocardiography,[13] one would expect that the majority of ordered NTproBNPs tests would be below the exclusionary cut-point of 125 pg/mL, rather than the average of 30% over the years as found in our study. Considering NP measurement in a broader range of people would result in a higher use of these tests, with relatively more individuals with values below the exclusionary cut-point, and importantly, overall in a higher detection rate of HF.

Conclusion

NP testing by Dutch GPs increased steeply from 2005 to 2009, with a stabilization from that time onwards.

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References

1. Kelder JC, Cramer MJ, van Wijngaarden J, van Tooren R, Mosterd A, Moons KG et al. The diagnostic value of physical examination and additional testing in primary care patients with suspected heart failure. *Circulation* 2011; 124(25):2865-2873.
2. Kelder JC, Rutten FH, Hoes AW. Clinically relevant diagnostic research in primary care: the example of B-type natriuretic peptides in the detection of heart failure. *Fam Pract* 2009; 26(1):69-74.
3. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016; 18(8):891-975.
4. Sudoh T, Kangawa K, Minamino N, Matsuo H. A new natriuretic peptide in porcine brain. *Nature* 1988; 332(6159):78-81.
5. Rutten FH, Walma EP, Kruizinga GI, Bakx HCA, van Lieshout J. The Dutch college of General Practitioners guideline on heart failure, first revision [in Dutch]. *Ned Tijdschr Geneesked* 2005; 149(48):2668-2672.
6. Hoes AW, Voors AA, Rutten FH, van Lieshout J, Janssen PGH, Walma EP. The Dutch College of General Practitioners guideline on heart failure, second revision [In Dutch]. *Huisarts Wet* 2010; 53:368-389.
7. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2012; 14(8):803-869.
8. van Mourik Y, Bertens LC, Cramer MJ, Lammers JW, Reitsma JB, Moons KG et al. Unrecognized heart failure and chronic obstructive pulmonary disease (COPD) in frail elderly detected through a near-home targeted screening strategy. *J Am Board Fam Med* 2014; 27(6):811-821.
9. van Riet EE, Hoes AW, Limburg A, Landman MA, van der Hoeven H, Rutten FH. Prevalence of unrecognized heart failure in older persons with shortness of breath on exertion. *Eur J Heart Fail* 2014; 16(7):772-777.
10. Rutten FH, Cramer MJ, Grobbee DE, Sachs AP, Kirkels JH, Lammers JW et al. Unrecognized heart failure in elderly patients with stable chronic obstructive pulmonary disease. *Eur Heart J* 2005; 26(18):1887-1894.
11. Boonman-de Winter LJ, Rutten FH, Cramer MJ, Landman MJ, Liem AH, Rutten GE et al. High prevalence of previously unknown heart failure and left ventricular dysfunction in patients with type 2 diabetes. *Diabetologia* 2012; 55(8):2154-2162.
12. Valk MJ, Mosterd A, Broekhuizen BD, Zuithoff NP, Landman MA, Hoes AW et al. Overdiagnosis of heart failure in primary care: a cross-sectional study. *Br J Gen Pract* 2016; 66(649):e587-e592.
13. Zaphiriou A, Robb S, Murray-Thomas T, Mendez G, Fox K, McDonagh T et al. The diagnostic accuracy of plasma BNP and NTproBNP in patients referred from primary care with suspected heart failure: results of the UK natriuretic peptide study. *Eur J Heart Fail* 2005; 7(4):537-541.

14. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013; 310(20):2191-2194.
15. Oosterhuis W, Boonman-Winter LJ, Frericks A, Kragten H, Rutten W. Measurement of N-terminal pro-BNP in heart failure: from the Dutch GP guideline to clinical practice [in Dutch]. *Huisarts Wet* 2009; 52:434-438.

Chapter 5

Rationale, design and baseline results of the Treatment Optimization in Primary care of Heart failure in the Utrecht region (TOPHU) study: a cluster randomized controlled trial

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Abstract

Background: Heart failure (HF) is mainly detected and managed in primary care, but the care is considered suboptimal. We present the rationale, design and baseline results of the Treatment Optimization in Primary care of Heart failure in the Utrecht region (TOPHU) study. In this study we assess the effect of a single training of GPs in the pharmacological management of patients with HF.

Methods/design: A cluster randomized controlled trial. Thirty primary care practices are randomly assigned to care as usual or intervention defined as a single training in the up-titration and management of HF drug therapy according to the HF guidelines of the European Society of Cardiology (ESC). Patients with a GP's diagnosis of HF will be re-evaluated by an expert panel of two cardiologists and a GP with expertise in HF to come to a definite diagnosis of HF according to the ESC HF guidelines. Those with definite HF will be analysed in this study.

Drug use will be measured after six months, health status after twelve months, and heart-related hospital admissions and all-cause mortality after two years.

Discussion: Our cluster randomized trial will show whether a single training of GPs improves the pharmacological management of patients with HF and confers beneficial effects on health status after one year, and cardiac hospital admissions and all-cause mortality after two years of follow-up.

Trial registration: ClinicalTrials.gov Identifier NCT01662323

Background

Heart failure (HF) is an important medical and health care problem with great impact on patient's health status and life expectancy. The initial diagnosis of HF is mainly made in primary care, and is still often based on the clinical assessment only, irrespective of the general knowledge that such a diagnosis solely based on clinical grounds, without echocardiography bares the risk of both overdiagnosis and underdiagnosis, certainly in the early stages of slow-onset HF.[1-3] This knowledge is also important because a previous study in primary care suggested that uncertainty regarding the diagnosis of HF is an important barrier to adequate drug treatment by GPs.[4] Moreover, echocardiography is needed to differentiate HF with a preserved ejection fraction (HFpEF) from HF with a reduced ejection fraction (HFrEF).[1] Although, both types are part of the HF spectrum, the treatment is different. In HFpEF it is focussed on i) release of symptoms with diuretics in case of fluid

retention, ii) adequate blood pressure control, and iii) management of comorbidities. Importantly, however, none of these treatments has a clear prognostic benefit and thus lacks a real evidence-base. On the other hand, for HFrEF there are multiple drugs including angiotensin converting enzyme inhibitors (ACE-i) or angiotensin receptor blockers (ARB), beta-blockers, and mineralocorticoid receptor antagonists (MRA), and devices that reduce mortality and HF hospitalization as it does improve quality of life.[1] Ivabradine should be considered in the subgroup of patients who remain symptomatic with the three aforementioned drugs, and have sinus rhythm with a pulse frequency higher than 70 beats/minute in rest.[1]

Previous studies showed that general practitioners (GPs) are less successful than cardiologists in up-titrating HF drugs according to guidelines.[3;5-9] Nevertheless, they adequately maintain the drug management initiated in secondary care, as good as done in HF clinics.[10;11]

We aim to determine whether a single training of GPs focused on the drug management improves the pharmacological management of patients with definite HFrEF, HFrEF and HFpEF separately. Additionally, we determine if it has a beneficial effect on health status, cardiac hospital admissions, and all-cause mortality on all-type HF patients.

Key objectives

- To assess how many patients labelled with HF in primary care really have HF.
- To assess the effect of a single half-day training on drug management in HF on drug use, health related quality of life, HF hospitalizations, and all-cause mortality after six months, 12 months, and 24 months, respectively.

Methods

Study design

We designed a cluster randomized trial with randomization at the level of the primary care practices, to help prevent contamination with the intervention. Thirty practices are randomly divided into two groups of fifteen. The intervention group will receive a half-day training on HF management and will receive an up-titration chart for daily use in the management of HF patients during the study, while the control group will not receive specific training, and provides care as usual. The study starts with the training, and participants in both groups will be followed up for two years. After six

months of follow-up the electronic medical files will be scrutinized for (change in) prescriptions of drugs in comparison to baseline. Twelve months after the training the participants will be sent a questionnaire on health status. After two years, hospital admissions and all-cause mortality will be assessed, by again scrutinizing the GPs' electronical files (figure 1).

Recruitment of general practitioners

GPs will be recruited in and around Amersfoort, a city in the centre of the Netherlands. A representative group of 195 GPs working in group, duo or solo practices in urban, suburban, and rural areas were invited by letter. Forty-five GPs working in 30 GP practices consented to participate. They are all familiar with the Dutch GP guideline on HF.[12] The participating general practices were randomly allocated to either the intervention or care as usual group. The project manager undertook randomization in a blinded fashion. GPs working in one practice were allocated to the same group, to avoid contamination of GPs and participants between the two groups, which can occur if randomization is performed at an individual participant level.

Study population and recruitment

All citizens in the Netherlands are registered with a GP, also those who receive cooperative care from a medical specialist, except those living in a nursing home or hospice. All patients enlisted with the participating GPs and who have a GP's diagnosis of HF encoded according the International Classification of Primary Care (ICPC) code K77 will be assessed if this ICPC code was allocated at least twice for patient contacts, to prevent single accidental miscoding. Five months before the start of the study, the electronic medical files of the 30 participating GPs will be scrutinized for such patients labelled with ICPC code K77, and if echocardiographic results are missing, the GPs of both groups will be urged to consider referral for echocardiography. The start of the study is the date of training of the GPs in the intervention group. An expert panel consisting of two cardiologists and an experienced GP will evaluate all available diagnostic information from the electronic medical files of the GPs, including echocardiography results mentioned in cardiologist's papers when this investigation was performed. They decide whom of those with ICPC code K77 has definite HF, probably or possibly HF, or no HF according to the European Society of Cardiology guidelines.[1] Only patients who have

definite HF according to the panel will be included in the cluster randomized trial. All participants will be asked to give written informed consent.

Sample size

We base our sample size calculation on the cases with HFrEF. We speculate that 30% of them will be on a beta-blocker and 60% on an angiotensin converting enzyme inhibitor (ACE-i) or angiotensin receptor blocker (ARB) at baseline, and that after six months of follow-up after the training session these percentages will have increased to 60% and 90%, respectively in the intervention group, while remaining the same in the control group. To prove a difference of 30% in prescription rates in ACE-i/ARBs and beta-blockers between the intervention and care as usual arm after six months with an alpha of 0.05, a power of 0.80, and an intra-cluster correlation coefficient of 0.05,[12] and a cluster size of 5, we need 47 patients with HFrEF in each study arm. Considering a drop-out of 10% we aim to include 52 participants in each arm (total 104). We calculated that around 30 general practices should participate to recruit 104 patients with definite HFrEF.

Intervention and care as usual

GPs, GP trainees, and nurse practitioners of general practices of the intervention arm receive a half day lasting interactive training on the diagnosis and pharmacological management of HF by a cardiologist and GP with expertise in HF. Special attention will be paid to initiation and up-titration to optimal dosage of evidence-based drugs in patients with HFrEF, especially in the drugs that should always be considered to be prescribed; ACE-inhibitors or ARBs, beta-blockers, and MRAs. The 'hand-out' leaflet to be used in everyday practice will be explained (appendix). This leaflet provides detailed information on the intervals in the up-titration, what should be checked at control visits, contra-indications of the cardiovascular drugs, and laboratory tests needed (i.e., creatinine and potassium levels). Differences in the drug management of patients with HFrEF and HFpEF will be explained, as also the most common interaction and adverse effects of HF drugs. Finally, general aspects such as adherence, and polypharmacy and options of self-care will be discussed interactively. Participants of the training will not be reinforced by reminders, newsletters, or other communications after the training. GPs, GP trainees and practice nurses in the care as usual group will not receive such a training nor an up-titration chart.

Panel procedure and the definite diagnosis of heart failure

The expert panel will consist of two cardiologists and a GP experienced in HF. They will decide during consensus meetings on the presence or absence of HF following the criteria of the HF guidelines of the ESC (Table 1). In addition to symptoms and signs suggestive of HF additional evidence from echocardiography of structural or functional abnormality of the heart at rest is needed to establish the presence of HF.[1] With the assumption that all patients labelled with a GPs diagnosis of HF have symptoms and signs suggestive of HF, the panel will evaluate, when available, the results from additional diagnostic testing such as natriuretic peptide values, chest X-ray, electrocardiography and echocardiography. Based on consensus, the panel decides if a patient has no HF, probably or possibly HF, or definite HF. Only patients with definite HF according to the panel will be included in the cluster randomized trial.

Table 1 The diagnosis of heart failure according to the ESC guidelines on heart failure 2012[1]

Diagnosis of HF with a reduced ejection fraction (HFrEF)	**Diagnosis of HF with a preserved ejection fraction (HFpEF)**
Symptoms typical of HF	Symptoms typical of HF
Signs typical of HF*	Signs typical of HF*
Reduced left ventricular ejection fraction	Normal or only mildly reduced left ventricular ejection fraction and left ventricle not dilated Relevant structural heart disease (LV hypertrophy/ left atrial enlargement) and/or diastolic dysfunction

HF= heart failure

*Signs may not be present in the early stages of heart failure (especially in HFpEF) and in patients treated with diuretics.

Cases with definite HF will further be subdivided in HFrEF, HFpEF, and isolated right-sided HF (rs-HF). For HFrEF, a reduced left ventricular ejection fraction (LVEF) is needed, arbitrary ≤ 45%. For HFpEF, the LVEF should be normal or nearly normal, arbitrary >45%, this in the presence of at least two structural or functional abnormalities related to relaxation such as a left atrium volume indexed (LAVI) >34 ml/m², E/e' >15, E/A <0.75, and/or a left ventricular wall thickness > 11 mm. In those with atrial fibrillation, a LAVI > 34 ml/m² is sufficient for the diagnosis of diastolic dysfunction. For isolated right-sided HF, the LVEF should be >45%, and the calculated peak pulmonary pressure >40mmHg that is insufficiently explained by left ventricular dysfunction.

Data collection

At baseline, the following data will be extracted from the electronic medical files of the participants: age, gender, cardiovascular drug use, comorbidities, the most recent blood test results including natriuretic peptide measurements (NTproBNP or BNP) and the eGFR, whether echocardiography was performed, and if the patient received cooperative care from a cardiologist. Such cooperative care is considered present when a patient consulted a cardiologist at least once in the 18 months before the start of the study. Six months after the training, the prescription of cardiovascular drugs in both arms will again be extracted from the GPs' electronic medical files. After one year, participants in both arms will be asked to fill out two health status questionnaires (the Short Form 36 and the five dimensional Euro Qual (EQ-5D). [13-15] Two years after the start of the study, the GPs' electronic medical files will be scrutinized again to assess hospital admissions and all-cause mortality. See also figure 1.

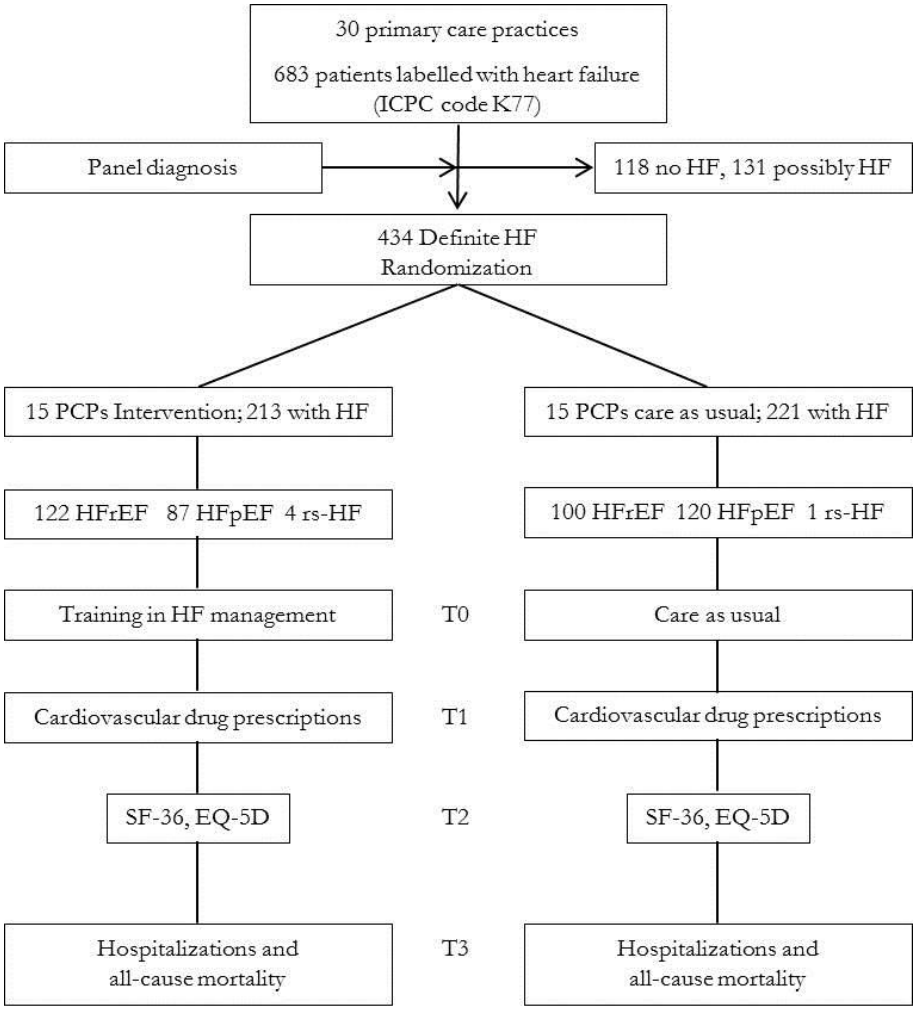
Outcomes

Study outcomes are the proportions of patients labelled with ICPC K77 who really have HF according to the expert panel, and the proportion of patients with definite HF and a reduced ejection fraction that received the most relevant and universally needed HF drugs, including ACE-i/ARBs, beta-blockers, and mineralocorticoid receptor antagonists. Drug use at baseline and after six months will be compared between the two groups.

Health status will be assessed with the SF-36 and the EQ-5D. The SF-36 is subdivided into eight domains: physical functioning, social functioning, limitations in usual role activities due to physical problems, limitations in usual role activities due to emotional problems, bodily pain, general vitality health, general mental health, general health perception. Scores range from 0 to 100. The EQ-5D questionnaire has five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, which are divided into three degrees of severity; "no problem", "some problems" or "major problems". A single index score can be produced using information from these five dimensions. Higher scores on both questionnaires are associated with a better health-related quality of life.

Cardiac and other hospitalization will be assessed, and the duration of hospitalization.

Figure 1 Study scheme



Study scheme. ICPC=International Classification in Primary Care, PCP = primary care practice; HFrEF=heart failure with reduced ejection fraction, HFpEF= heart failure with preserved ejection fraction, rs-HF= isolated right-sided heart failure. SF-36 and EQ-5D are health related quality of live questionnaires.
T0: start of the study with training of the GPs, GP trainees and practice nurses of the intervention group.
T1: Six months of follow-up; assessment of cardiovascular drug use in both groups in comparison to baseline.
T2: Twelve months of follow-up; questionnaires on health status (SF-36 and EQ-5D will be filled out by participants in both groups.
T3: Two years of follow-up; assessment of hospitalizations and all-cause mortality in the electronic medical files of the GPs in both groups.

Data analyses

We will calculate with its 95% confidence interval how many patients with an ICPC code K77 were correctly diagnosed with HF according to the expert panel.

The proportion of prescribed HF drugs between the two groups will be compared after six months taking into account baseline differences. The difference in health status between participants with definite HF in the two study arms at 12 months will be compared with ANCOVA. Differences between participants of the two groups regarding hospitalizations and all-cause mortality will be assessed after two years. A multilevel approach will be used in the analyses to correct for the fact that we randomized at the GP practice and not at the patient level.

Regulation statement

This study is conducted according to the principles of the current version of the declaration of Helsinki and in accordance with the Dutch law on Medical Research involving Human Subjects Act (WMO).

Ethics committee approval

The study was approved by the Regional Medical Ethics Committee (VCMO) of the Meander Medical Centre, Amersfoort, the Netherlands.

Discussion

In this study we will quantify how many patients with a GP's diagnosis of HF really have HF. In a randomized trial we will quantify the effect on drug use, health status and prognosis with hospital admissions, and all-cause mortality of a single training of GP's that is focused on the drug management of patients with definite HF, and for HFrEF and HFpEF separately.

There are several limitations to be mentioned. First, a half day training is short to adequately train GPs how to initiate and up-titrate HF medication in patients with HFrEF, even if they are familiar with HF guidelines, receive a helpful leaflet, and with over half of the patients receive cooperative care from the cardiologist. For logistical and practical reasons we choose for such a single intervention because it resembles most closely post-graduate education GPs receive in the Netherlands. Secondly, we measure outcomes only once; drug prescriptions after 6 months, hr-QoL after 12 months, and CV morbidity and mortality after 24 months. More frequent measurements of outcomes would result in 'disturbing' GPs, and multiple times filling out questionnaires by participants. It would easily result in 'drifting away from 'real'

care as usual of those in that arm of the study. Thirdly, not all study patients will undergo echocardiography in this practice-based study. The advantage of a practice study is the inclusion of 'real' patients and the assessment of drugs in 'real' practice. The downside is missing on some variables. In real live practice not everybody labelled with HF underwent echocardiography. Nevertheless, for our cluster randomized trial we will selectively include those with definite HF, that is, symptoms of HF and functional/ structural abnormalities with echocardiography, evaluated by an expert panel of two cardiologists and a GP. Fourthly, we evaluated both HFrEF and HFpEF patients, although, for HFpEF clear evidence based treatment is lacking. Nevertheless, HFpEF is part of the HF spectrum, and has nearly as poor a prognosis as HFrEF. Moreover, these patients suffer of symptoms, notably fluid retention causing shortness of breath and peripheral oedema. These symptoms can adequately managed with diuretics. Physicians should realize that symptom relieve is of utmost importance in these patients by titrating the dose of diuretics as optimally as possible. Adjustments of diuretic dose to filling status is really the 'art' of medicine. Even more can be done in patients with HFpEF; blood pressure and comorbidities should be adequately managed according to the ESC guidelines 2012. Finally, the recommendation to GPs in both trial arms to refer for echocardiography before the training may increase awareness of HF diagnosis and management and may dilute the effect of the intervention.

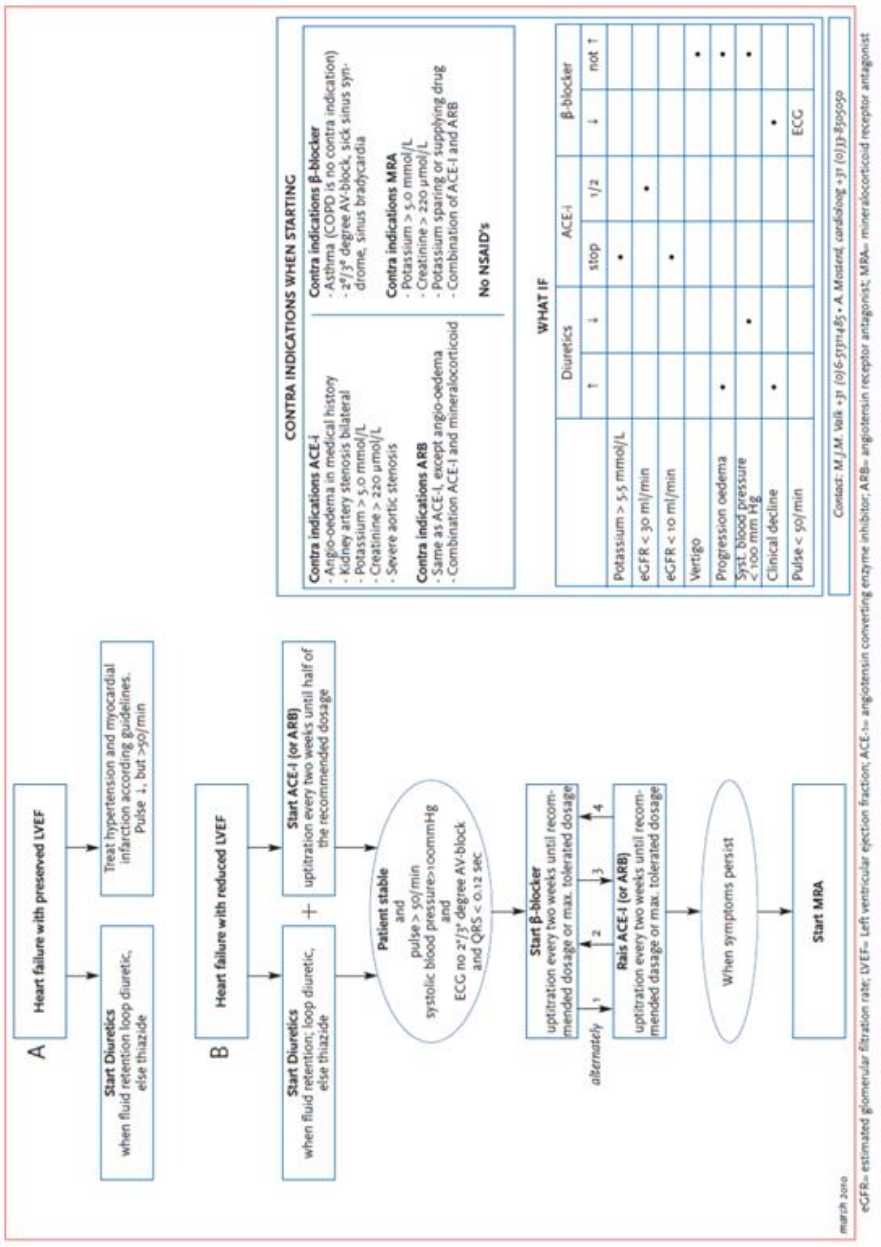
We realize there are other options to improve the care of patients with HF in general practice, such as multidisciplinary care, practice nurse-led disease management, or tele-health. Tele-health, providing daily-wise data of body weight, blood pressure, pulse, and sometimes even much more biological data could also improve the care of the complex patients with HF. Many previous studies evaluated patients under care of HF outpatient clinics receiving multidisciplinary care, and this resulted in prognostic beneficial effects.[16]Also practice nurses in primary care could be helpful in the care of patients with HF in the home setting. In the primary care setting in the Netherlands, disease-specific care pathways have been developed for the primary care setting for diabetes mellitus, chronic obstructive pulmonary disease (COPD), and cardiovascular risk management. In these programs, practice nurses play an important role. They receive a special training to monitor these patients. These nurses, however, are not trained to care for HF, a disease with multiple systemic effects, and high morbidity and mortality. Training them in HF would also be an option to upgrade the care of HF in the primary care setting.

Our study approach is focussed on a single intervention that could improve care and would be easily implemented if effective. We want to improve all aspects of drug use in HF, also considering interaction, contraindication, and adherence. We realize that our strategy could gain by paying even more attention to self-care of patients, and by facilitating cooperative care of the cardiologist and HF nurse.
We realize that our intervention is relatively small, but importantly, we focus on probably the most important aspect of HF management, namely real adequate drug use. The advantage of our approach is that it can easily be implemented in everyday primary care.

Abbreviations

ACE-I	angiotensin converting enzyme inhibitors
ARB	angiotensin receptor blockers
BNP	Brain natriuretic peptide
eGFR	estimated glomerular filtration rate
ESC	European Society of Cardiology
EQ-5D	EuroQoL Quality of Life Scale 5 dimensions
GP	General practitioner
HF	Heart failure
HFpEF	Heart Failure with preserved Ejection Fraction
HFrEF	Heart Failure with reduced Ejection Fraction
ICPC	International Classification in Primary Care
LAVI	left atrium volume indexed
LVEF	Left ventricle ejection fraction
MRA	mineralocorticoid receptor antagonist
NTproBNP	N-terminal pro brain natriuretic peptide
rs-HF	Right sided heart failure
SF-36	36-Item Short Form Health Survey

Figure 2 Up-titration scheme as provided on a leaflet to be used in everyday practice by the GPS in the intervention group



		2 weeks	4 weeks	6 weeks	8 weeks	10 weeks	12 weeks	6 months	1 year
CONTROLS	Sodium, Potasium	•		•		•		•	•
	Creatinine, MDRD	•						•	•
	Side effects	•	•	•	•	•	•	•	•
	Pulse	•	•	•	•	•	•	•	•
	Oedema, Crepitations	•	•	•	•	•	•	•	•
	Weight	•	•	•	•	•	•	•	•

		Starting dose	Usal dosage
1.	**Diuretic**		
	• Furosemide	20 mg o.d.	40-120 mg o.d.
	• Bumetanide	0.5 mg o.d.	1-5 mg o.d.
	• Hydrochlorothiazide	12.5 mg o.d.	25 mg o.d.
	• Chlortalidone	25 mg o.d.	12.5-50 mg o.d.

		Starting dose	2 weeks	4 weeks	6 weeks	8 weeks	10 weeks	12 weeks	Recommended dosage
MEDICATION 2a.	**ACE-I**								
	• Enalapril	2.5 mg o.d.	2.5 mg b.d.	5 mg b.d.	7.5 mg b.d.	10 mg b.d.			10-20 mg b.d.
	• Lisinopril	2.5 mg o.d.	2.5 mg o.d.	5 mg o.d.	10 mg o.d.	20 mg o.d.	30 mg o.d.		20-35 mg o.d.
	• Captopril	6.25 mg t.d.	12.5 mg t.d.	25 mg t.d.	37.5 mg t.d.	50 mg t.d.			50-10 mg t.d.
	• Ramipril	2.5 mg o.d.	2.5 mg b.d.	5 mg b.d.					5 mg b.d.
	• Fosinopril	5 mg o.d.	10 mg o.d.	20 mg o.d.	40 mg o.d.				20-40 mg o.d.
2b.	**ARB**								
	• Losartan	50 mg o.d.	100 mg o.d.						100 mg o.d.
	• Candesartan	4 mg o.d.	8 mg o.d.	16 mg o.d.	32 mg o.d.				32 mg o.d.
	• Valsartan	40 mg b.d.	80 mg b.d.	160 mg b.d.					160 mg b.d.
3.	**β-blocker**								
	• Bisoprolol	1.25 mg o.d.	2.5 mg o.d.	3.75 mg o.d.	5 mg o.d.	5 mg o.d.	7.5 mg o.d.	10 mg o.d.	10 mg o.d.
	• Metopr. succ.	12.5 mg o.d.	25 mg o.d.	50 mg o.d.	100 mg o.d.	150 mg o.d.	200 mg o.d.		200 mg o.d.
	• Nebivolol	1.25 mg o.d.	2.5 mg o.d.	5 mg o.d.	10 mg o.d.				10 mg o.d.
	• Carvedilol	3.125 mg b.d.	6.25 mg b.d.	12.5 mg b.d.	25 mg b.d.	(37.5 mg b.d.)	(50 mg b.d.)		<85 kg: 25 mg b.d.
									>85 kg: 50 mg b.d.
4.	**MRA**								
	• Spironolactone	25 mg o.d.							25 mg o.d.
	• Eplerenone	25 mg o.d.		50 mg o.d.					50 mg o.d.

References

1. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2012; 14(8):803-869.
2. Remme WJ, McMurray JJ, Hobbs FD, Cohen-Solal A, Lopez-Sendon J, Boccanelli A et al. Awareness and perception of heart failure among European cardiologists, internists, geriatricians, and primary care physicians. *Eur Heart J* 2008; 29(14):1739-1752.
3. Rutten FH, Grobbee DE, Hoes AW. Differences between general practitioners and cardiologists in diagnosis and management of heart failure: a survey in every-day practice. *Eur J Heart Fail* 2003; 5:337-344.
4. Fuat A, Hungin AP, Murphy JJ. Barriers to accurate diagnosis and effective management of heart failure in primary care: qualitative study. *BMJ* 2003; 326(7382):196.
5. Allen LA, Magid DJ, Zeng C, Peterson PN, Clarke CL, Shetterly S et al. Patterns of beta-blocker intensification in ambulatory heart failure patients and short-term association with hospitalization. *BMC Cardiovasc Disord* 2012; 12:43.
6. Ansari M, Shlipak MG, Heidenreich PA, Van OD, Pohl EC, Browner WS et al. Improving guideline adherence: a randomized trial evaluating strategies to increase beta-blocker use in heart failure. *Circulation* 2003; 107(22):2799-2804.
7. Cleland JG, Swedberg K, Cohen-Solal A, Cosin-Aguilar J, Dietz R, Follath F et al. The Euro Heart Failure Survey of the EUROHEART survey programme. A survey on the quality of care among patients with heart failure in Europe. The Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The Medicines Evaluation Group Centre for Health Economics University of York. *Eur J Heart Fail* 2000; 2(2):123-132.
8. Cleland JG, Cohen-Solal A, Aguilar JC, Dietz R, Eastaugh J, Follath F et al. Management of heart failure in primary care (the IMPROVEMENT of Heart Failure Programme): an international survey. *Lancet* 2002; 360(9346):1631-1639.
9. Muntwyler J, Cohen-Solal A, Freemantle N, Eastaugh J, Cleland JG, Follath F. Relation of sex, age and concomitant diseases to drug prescription for heart failure in primary care in Europe. *Eur J Heart Fail* 2004; 6(5):663-668.
10. Schou M, Gustafsson F, Videbaek L, Tuxen C, Keller N, Handberg J et al. Extended heart failure clinic follow-up in low-risk patients: a randomized clinical trial (NorthStar). *Eur Heart J* 2013; 34(6):432-442.
11. Luttik ML, Jaarsma T, van Geel PP, Brons M, Hillege HL, Hoes AW et al. Long-term follow-up in optimally treated and stable heart failure patients: primary care vs. heart failure clinic. Results of the COACH-2 study. *Eur J Heart Fail* 2014; 16(11):1241-1248.
12. Hoes AW, Voors AA, Rutten FH, van Lieshout J, Janssen PGH, Walma EP. The Dutch College of General Practitioners guideline on heart failure, second revision [In Dutch]. *Huisarts Wet* 2010; 53:368-389.
13. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol* 1998; 51(11):1055-1068.

14. Brooks RG, Jendteg S, Lindgren B, Persson U, Bjork S. EuroQol: health-related quality of life measurement. Results of the Swedish questionnaire exercise. *Health Policy* 1991; 18(1):37-48.
15. Campbell MJ. Cluster randomized trials in general (family) practice research. *Stat Methods Med Res* 2000; 9(2):81-94.
16. McAlister FA, Lawson FM, Teo KK, Armstrong PW. A systematic review of randomized trials of disease management programs in heart failure. *Am J Med* 2001; 110(5):378-384.

Chapter 6

Training general practitioners to improve evidence-based drug treatment of patients with heart failure: a cluster randomized controlled trial

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Abstract

Background: Drug treatment of patients with heart failure (HF) can be improved.

Aim: To assess whether a single training session of general practitioners (GPs) improves the evidence-based drug treatment of HF patients, especially of those with HF with reduced ejection fraction (HFrEF).

Methods: A cluster randomized controlled trial in which patients with established HF were eligible. Primary care practices (PCPs) were randomized to care-as-usual (control) group, or to the intervention group in which GPs received a half-day training on HF management, and a leaflet on HF drug uptitration. Changes in HF medication, health status, hospitalization, and survival were compared between the two groups.

Results: 15 PCPs with 200 HF patients were randomized to the intervention group, and 15 PCPs with 198 HF patients to the control group. Mean age was 76.9 (SD 10.8) years, 52.5% were female. On average the patients were diagnosed with HF 3.0 (SD 3.0) years ago. In total, 204 had HFrEF and 194 HF with preserved ejection fraction (HFpEF). In participants with HFrEF, the use of angiotensin converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB) decreased in six months in both groups (5.2% (95% confidence interval (CI) 2.0-10.0) and 5.6% (95%CI 2.8-13.4)), respectively (baseline-corrected odds ratio (OR) 1.07 (95%CI 0.55-2.08), while beta-blocker use increased in both groups with 5.2% (95%CI 2.0-10.0) and 1.1% (95%CI 0.2-6.3), respectively (baseline-corrected OR 0.82 (95%CI 0.42-1.61). Also for health status, hospitalizations, or survival after 12 to 28 months there were no significant differences between the two groups, also not when separately analysed for HFrEF and HFpEF.

Conclusion: A half-day training of GPs does not improve HF drug treatment of patients with established HF.

Keywords: Heart failure, drug treatment, primary care, health status, survival, hospitalizations

Introduction

Heart failure (HF) is an increasing health care problem worldwide, and a multidisciplinary approach with a general practitioner (GP) in the health care team is considered optimal.[1] HF management has improved substantially over the last two decades, mainly for patients with HF with a reduced ejection fraction (HFrEF). Key is inhibition of the renin–angiotensin system with either angiotensin-converting enzyme

inhibitors (ACEI), (or angiotensin receptor blockers (ARB) in case of ACEI intolerance), often combined with mineralocorticosteroid-receptor antagonists (MRAs), and additionally inhibition of the sympathetic nervous system by beta-blockers. Diuretics are often needed for optimal symptom management related to fluid status. Combination of the aforementioned drugs has substantially improved the prognosis of patients with HFrEF with regard to mortality, hospitalizations, and health status.[2;3] Recently, the Paradigm study showed that in symptomatic patients with a LVEF≤35% and on optimal medical therapy, the angiotensin receptor neprisylin inhibitor (ARNI) valsartan/sarcubitril was superior to enalapril if combined with optimal treatment with beta-blocker and MRA.[4]

For patients with HF and a preserved ejection fraction (HFpEF) to date no drugs have been shown to clearly improve prognosis. Diuretics are helpful for fluid status management and thus reduce symptoms of fluid overload in HFpEF. Next, optimal blood pressure management is recommended, and, in case of tachycardia, optimal rate control or rhythm correction. Moreover, optimal management of co-morbidities is important.[3] The search for novel treatment options for HFpEF patients is still ongoing.[5-7]

Earlier studies have shown that HF management in primary care is far from optimal, with under prescription of ACEIs (or in case of intolerance, ARBs) and beta-blockers.[8-11] These studies did not, however, report data separately for patients with HFrEF and HFpEF. Moreover, most of these studies performed in primary care included patients with a GP's diagnosis of HF, and thus in a substantial number without a confirmatory echocardiogram, thus more likely including many false-positive HF cases.[9-11]

Group education of GPs could possibly help improve the prescription of evidence-based drugs in, especially, HFrEF patients. Such education has effectively improved treatment in other primary care domains, e.g. proper antibiotic use and hypertension treatment.[12;13]

The primary aim of our study was to investigate whether a half-day training session for GPs on drug treatment of HF according to current guidelines combined with an easy-to-use uptitration leaflet to be used in clinical practice would improve drug therapy in HF patients, notably those with HFrEF.

Methods

Study population

Thirty primary-care practices (PCPs), including urban, suburban, and rural practices, located in the vicinity of Utrecht in the central part of the Netherlands participated in this study. The study was executed between November 2010 and March 2013. Approximately 70,500 patients were registered in these practices, with an average of 2,350 per practice. Of note, every individual in the Netherlands, except for patients in nursing homes and hospices, is registered with a single GP, independent of specialist care, and GPs routinely register all patient contacts in an individual electronic medical record (EMR) and keep record of all specialist letters, including hospital discharge letters.

Eligibility criteria included men and women of 18 years or older and at least two documentations of HF in the patient's EMR (International Classification of Primary Care [ICPC] code K77). Two documented codes were required, because we wanted to exclude accidental mis-coding. In total, 683 patients were eligible. For this trial we included only the 398 (58.3%) patients in whom HF was confirmed by an expert panel (two cardiologists (AM and MAL) and a GP experienced in HF (FHR) based on available data from cardiology hospital admissions, or outpatient visits and echocardiography.

The study was conducted according to the principles of the current version of the Declaration of Helsinki and in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO). The study was approved by the Regional Medical Ethics Committee (MEC-U) of the Meander Medical Centre, Amersfoort, the Netherlands. All participating GPs gave written informed consent. All patients who filled out health status questionnaires gave written informed consent.

Definition of HF by the expert panel

All relevant medical information of the eligible 683 participants was extracted from the EMRs and evaluated by an expert panel to determine the presence or absence of HF (the reference standard). Patients were considered to have definite HF when they met the criteria of the European Society of Cardiology (ESC), i.e. symptoms or signs suggestive of HF and objective echocardiographic evidence of a structural or functional abnormality of the heart at rest. The panel subdivided those with HF in HFrEF, HFpEF, or isolated right-sided HF; HFrEF if a patient's left ventricular ejection fraction (LVEF) was ≤45% and HFpEF if a patient had a LVEF >45% plus

abnormal left ventricular relaxation or diastolic stiffness, and/or left atrial enlargement or left ventricular hypertrophy; at least two of these abnormal echocardiographic measurements were considered necessary to define HFpEF. In patients with atrial fibrillation, an enlarged atrium was considered sufficient if they also had symptoms or signs suggestive of HF. Isolated right-sided HF was registered when a patient had a calculated peak pulmonary artery pressure >40 mmHg, without clear left ventricular dysfunction. Disagreement between panellists was resolved by majority of votes after discussion.

Intervention

The 30 PCPs were allocated randomly to the intervention group or the care-as-usual (control) group. The GPs from the 15 PCPs allocated to the intervention group underwent a half-day group-training session on the diagnosis and drug treatment of HF based on recommendations of the most recent ESC HF guidelines.[14] Special attention was paid to differences in evidence-based drug treatment of patients with HFrEF and HFpEF. For patients with HFpEF, GPs were instructed to manage fluid retention with diuretics, control blood pressure, and lower heart rate in case of tachycardia (usually atrial fibrillation). For patients with HFrEF, GPs were instructed to treat with diuretics in case of fluid retention and uptitrate patients to maximally tolerated doses of an ACEI (or ARB if the ACEI was not tolerated) and a beta-blocker. In those patients with persistent symptoms (New York Heart Association [NYHA] class II or higher), GPs were instructed to additionally prescribe an MRA.[3] GPs received an uptitration leaflet to assist them with careful uptitration of ACEIs and beta-blockers in daily practice. The GPs allocated to the control group did not receive the training nor the uptitration leaflet. The study protocol was published in detail elsewhere.[15]

Measurements

Baseline characteristics of participants were gathered from the EMRs of the 30 PCPs in the 10 months before the training sessions and included gender, age, comorbidities, date of HF diagnosis, drug prescriptions, and results from echocardiography and natriuretic peptide measurements. Also noted was if participants received cooperative care from a cardiologist, defined as contact with the cardiology outpatient clinic or hospitalization with admission to a cardiology ward in the previous 1.5 years. HF medication regimens were extracted from the EMRs six months after the training session (T1). Patients filled out two questionnaires on health status (the Short Form

36 Health Survey [SF-36] and the European Quality of Life Five Dimensions questionnaire [EQ-5D]) 12 months after the training session (T2). The SF-36 measures the health status of individuals with different health conditions in the following eight domains: physical functioning, bodily pain, general health perceptions, vitality, social role functioning, emotional role functioning, physical role functioning, and mental health. Scores range from 0 to 100. The EQ-5D is a generic questionnaire that uses a visual analogue scale and provides a single index value for health status. It comprises five entities: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Scores range from 1 to 3. Data on hospitalizations and mortality were obtained 28 months after the training session (T3).

Outcomes

The primary outcome was the use of guideline-recommended HF medication in patients with HF at 6 months (T1). Secondary outcomes were health status at 12 months (T2) and mortality and hospitalizations (number of hospitalizations and number of hospitalization days) at 28 months (T3).

Statistical aspects

The sample size calculation was based on the changes in prescription rates in HFrEF patients. We assumed that 30% of the patients with HFrEF in the intervention group would be taking a beta-blocker at baseline, and that this would increase to 60% in six months from baseline, and that the level would remain 30% in the control group. Based on these assumptions, 45 HF patients were required in each group to detect a 30% difference in prescription rates of beta-blockers, with an alpha of 0.05 and a power of 0.80, and 47 HFrEF patients in each group if we applied an intra-cluster correlation coefficient of 0.05, and a cluster size of 5. Considering a dropout rate of 10%, 52 HFrEF patients in each group were required. We calculated that approximately 30 PCPs would be needed to ensure that in total 104 patients with HFrEF were recruited.[15]

Logistic regression analysis was used to estimate the training effect (the intervention) by calculation of the differences in HF drugs use at 6 months (T1) between the intervention and control group corrected for use at baseline. Initially, we incorporated a random intercept in the logistic regression analysis to correct for clustering within PCPs. This clustering adjustment, however, showed no or very limited impact of clustering ($\sigma^2 \sim 0$), we therefore applied 'standard' logistic regression without

correction for clustering. QoL measured with the EQ-5D was analysed with a Mann-Whitney test.

Linear mixed-regression analysis, adjusted for baseline SF-36 scores and corrected for potential clustering in PCPs were used to compare SF-36 scores of the control and intervention groups. Patients who died or were loss to follow-up in the period before the actual start of the study, i.e. between data extraction (January 2010) and the training session (October 2010), were excluded from the analysis. The mean number of hospitalizations and days of hospitalization before 28 months (T3) were compared between the two groups using either Student's t-test or Mann-Whitney U test. Kaplan-Meier survival curves were created to compare survival of HFrEF and HFpEF patients between the two groups over the 28 month period.

It was decided to include the 5 patients with isolated right-sided HF (four in the intervention group; one in the control group) in the HFpEF group before any statistical analysis was performed.

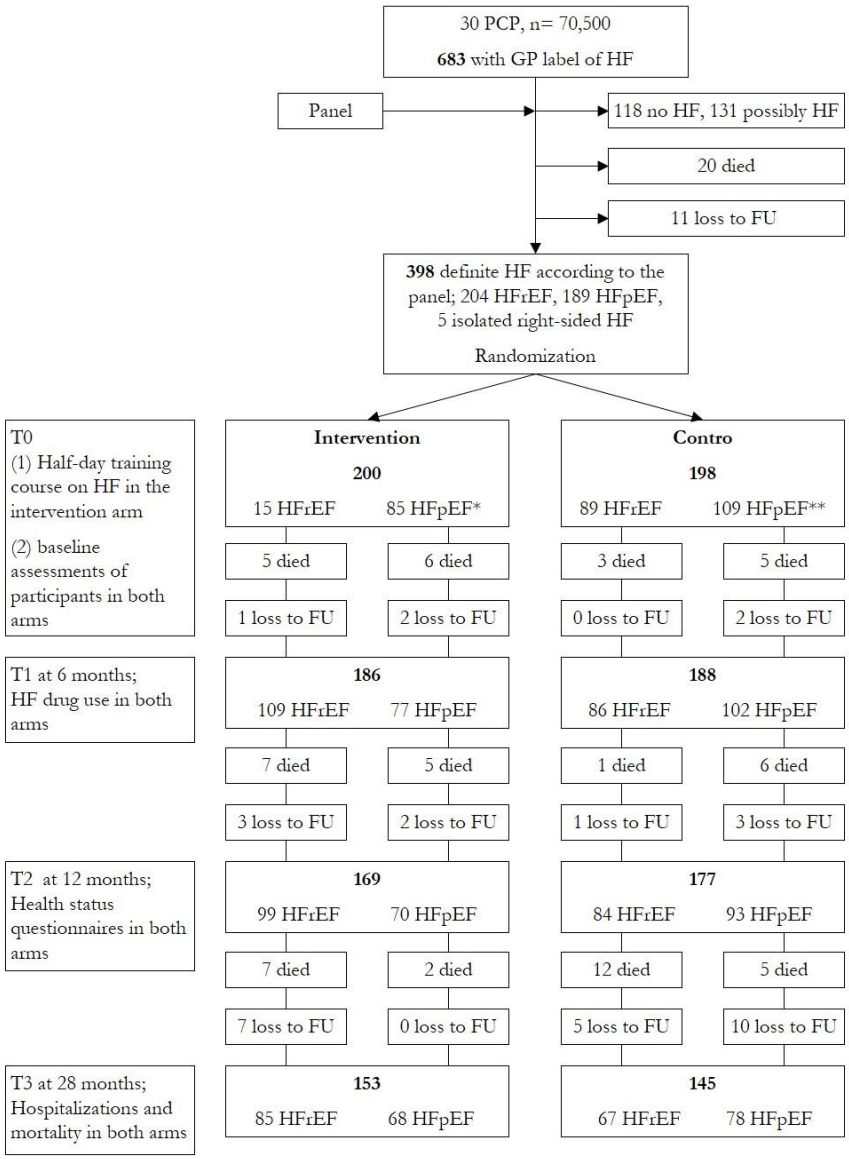
Statistical analyses were performed using SPSS version 20.0.

Results

In total, 398 patients fulfilled the criteria of definite HF: 204 (51.3%) with HFrEF, 189 (47.5%) with HFpEF, and 5 (1.3%) with isolated right-sided HF (see Figure 1). Mean age of the participants was 76.9 (SD 10.8) years, and 47.5% were male (Table 1). Prescription of evidence-based HF drugs in patients with HFrEF did not change significantly between baseline and T1 comparing the intervention and control group (Table 2). At baseline, the use of beta-blocker was 59.1% in the intervention group and 60.7% in the control group. This increased with 5.2% (95%CI 2.0-10.0) in the intervention group compared with 1.1% (95%CI 0.2-6.3) in the control group (baseline-corrected OR 0.82 (95%CI 0.42-1.61). At baseline, ACEI/ARB use was 68.7% in the intervention and 71.9% in the control group. It decreased 5.2% (95% CI 2.0- 10.0) in the intervention group compared with 5.6% (95%CI 2.8- 13.4) in the control group (baseline-corrected OR 1.07 (95%CI 0.55-2.08). Also in HFpEF patients, there were no clear differences in prescription rates of HF drugs between the two groups (Table 3).

After 12 months, 38 patients had died (23 in intervention and 15 in control arm) and 14 were lost to follow-up (8 in the intervention group; 6 in the control group). Of the

Figure 1 Flow chart



HF = heart failure; HFrEF = heart failure with reduced ejection fraction, HFpEF = heart failure with preserved ejection fraction; ICPC = International Classification in Primary Care; FU = follow-up; PCP = primary care practice; T0 = time point of the training session of the intervention group and baseline assessments; T1 = at 6-months, assessment of the use of HF drugs; T2 = at 12-months, health status questionnaires; T3 = at 28-months, assessment of hospitalizations and mortality.
* In this group also included four patients with isolated right-sided HF.
** In this group also included one patient with right-sided HF.

Table 1 Baseline characteristics of 398 patients with established HF categorized per intervention and control groups, and per HFrEF and HFpEF.

	Intervention group (n = 200)		**Control group** (n = 198)	
	HFrEF (n=115)	HFpEF (n=85)	HFrEF (n=89)	HFpEF (n=109)
Mean age in years (SD)	75.9 (11.1)	79.6 (7.9)	72.5 (12.8)	79.3 (9.2)
Male sex	59.1	40.0	55.1	34.9
Known with HF in years (SD)	3.5 (3.0)	2.5 (2.4)	3.5 (3.7)	2.4 (2.6)
Cooperative care from cardiologist	73.9	57.6	73.0	55.9
Prior myocardial infarction	45.2	25.9	49.4	11.0
Angina pectoris	14.8	28.2	13.5	19.3
Atrial fibrillation	34.8	64.7	37.1	58.7
Stroke	8.7	18.8	12.4	15.6
Hypertension	40.9	61.2	53.9	68.8
Diabetes mellitus	35.7	28.2	29.2	36.7
COPD	25.2	22.4	15.7	17.4
eGFR <60 mL/min/1.73 m²	40.9	43.5	38.2	41.3
Natriuretic peptides measured*	41.7	58.8	50.6	45.9

Numbers are percentages unless mentioned otherwise. Natriuretic peptide measurements were assessed in the 10 months before baseline. Baseline HF drug use: see Tables 2 and 3.
COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction.
Five patients (4 in the intervention group; 1 in the control group) with right-sided HF were counted as HFpEF. *Natriuretic peptide measured 10 months before T0.

Table 2 Proportion of prescribed HF-related drugs at baseline (T0) and after 6 months (T1) for the 204 patients with HFrEF, divided in the intervention and control groups with for baseline differences corrected odds ratios (ORs)

	Intervention arm (n = 115)					**Control arm** (n = 89)					
	T0	T1	start	cont. use	stop	T0	T1	start	cont. use	stop	bcOR (95%CI)
Diuretic	80.9	80.9	9.6	71.3	9.6	73.0	71.9	11.2	60.6	12.4	0.68 (0.33-1.39)
ACEI/ARB	68.7	63.5	10.4	53.0	15.7	71.9	66.3	6.7	59.6	12.4	1.07 (0.55-2.08)
Beta-blocker	59.1	64.3	15.7	48.7	10.4	60.7	61.8	10.1	51.7	8.9	0.82 (0.42-1.61)
MRA	28.7	31.0	10.4	22.6	6.1	32.6	33.7	6.7	27.0	5.6	0.85 (0.39-1.88)

Numbers are percentages unless mentioned otherwise. ACEI= angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; bcOR= for baseline differences corrected odds ratio, CI = confidence interval; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticosteroid-receptor antagonist; T0 = at baseline; T1 = after 6 months.

Table 3 Proportion of prescribed HF-related drugs at baseline (T0) and after 6 months (T1) for the 194 patients with HFpEF, divided in the intervention and control groups with for baseline differences corrected odds ratios (ORs).

	Intervention arm (n = 85)					**Control arm** (n = 109)					
	T0	T1	start	cont. use	stop	T0	T1	start	cont. use	stop	bcOR (95%CI)
Diuretic	70.6	70.6	14.1	56.5	14.1	74.3	77.1	16.5	60.6	13.8	1.36 (0.70-2.65)
ACEI/ARB	52.9	57.6	20.0	37.6	15.3	55.0	55.0	14.7	40.4	14.7	0.86 (0.46-1.58)
Beta-blocker	62.4	56.5	10.6	45.9	16.5	49.5	52.3	14.7	37.6	11.9	1.09 (0.57-2.09)
MRA	24.7	17.6	5.9	11.8	12.9	25.7	28.4	11.0	17.4	8.3	2.18 (0.97-4.90)

Numbers are percentages unless mentioned otherwise. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; bcOR= for baseline differences corrected odds ratio; CI = confidence interval; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticosteroid-receptor antagonist; T0 = baseline; T1 = after 6 months.

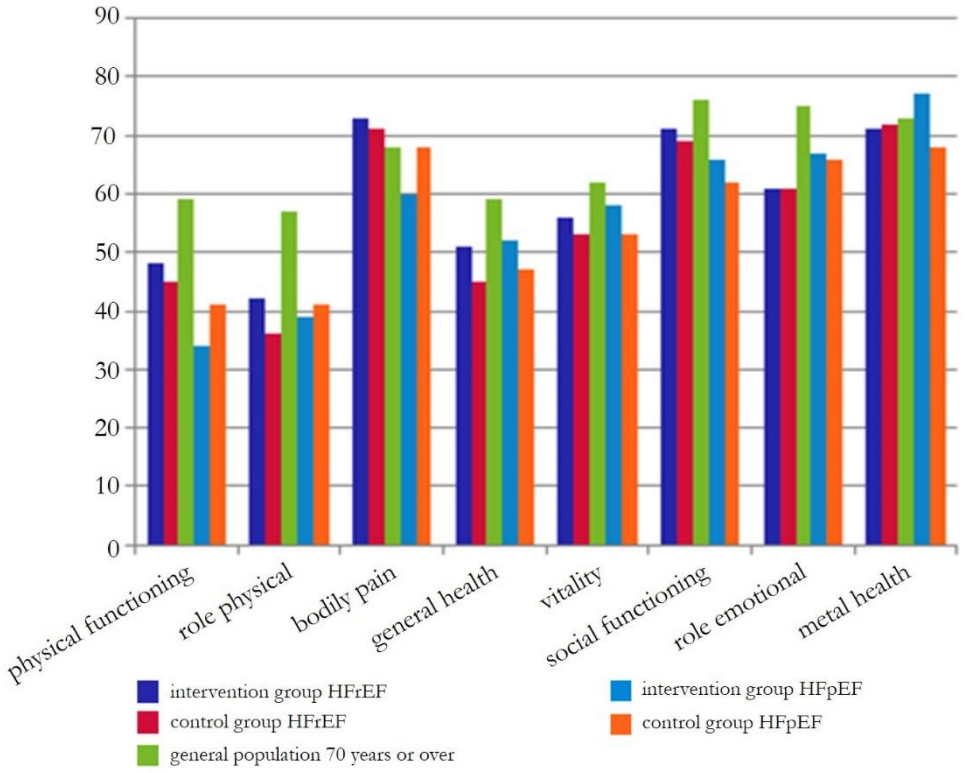
Table 4 Mean number of hospitalizations per year and hospitalization days per year during 28 months follow up of the 398 patients divided in the intervention and control groups and per HFrEF and HFpEF patients, measured for all type and cardiology hospitalizations separately.

	Intervention group	Control group	p value
Mean number of hospitalizations/year			
All hospitalizations			
For HFrEF patients per year	0.4	0.3	0.31
For HFpEF patients per year	0.3	0.3	0.99
Cardiology hospitalizations			
For HFrEF patients per year	0.2	0.2	0.20
For HFpEF patients per year	0.1	0.1	0.79
Mean number of all-type hospitalization days/year			
For HFrEF patients	2.7	2.1	0.58
For HFpEF patients	2.2	2.1	0.84
Cardiology hospitalizations			
For HFrEF patients per year	1.0	1.1	0.22
For HFpEF patients per year	0.3	0.7	0.90

HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction. Four patients with isolated right-sided HF were included in the intervention group. One patient with isolated right-sided HF was included in the control group.

remaining 346 participants, 166 (48.0%) filled out the health status questionnaires. There was no statistically significant or clinically important differences[16] in the eight domains of the SF-36 scale between the intervention and control groups for patients with either HFrEF or HFpEF (Figure 2). The EQ-5D did not show a significant difference in the five dimensions between the intervention and control groups, nor was a clinically important difference observed (data not shown). Table 4 shows the mean number of hospitalizations per year and the mean number of hospitalization days per year for the two groups after a follow up period of 28 months. At that time point, in total 32 patients had died in the intervention arm and 32 patients in the control arm, and the numbers loss to follow up were 15 and 21 in intervention and control arm, respectively. The mean number of hospitalization days per year for patients with HFrEF in the intervention and control groups were 2.7 days/year and 2.1 days/year (p=0.58), respectively. Cardiology hospitalizations were 1.0 days/year and 1.1 days/year (p=0.22), respectively. Survival during 28 months did not significantly differ between the intervention and control groups for either HFrEF or

Figure 2 Health status assessed at 12 months (T2) with the SF-36 and based on 96 patients with HFrEF and 68 patients with HFpEF in the intervention and control groups compared with data from the general population ≥70 years of age.



HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction.

HFpEF. Nineteen patients with HFrEF in the intervention group died compared with 16 in the control group (p=0.72), while 13 patients with HFpEF in the intervention group died compared with 16 in the control group (p=0.88).

Discussion

In this cluster randomized controlled trial in 398 patients with established HF, a half-day GP training session on the diagnosis and drug treatment of HF did not improve drug treatment or clinical outcomes of patients with HF, neither HFrEF nor HFpEF. For example, for the 204 patients with HFrEF, ACE-inhibitors/ARB use decreased by 5.2% (95%CI 2.4-10.9) in the intervention group compared with 5.6% (95% CI 2.4-12.5) in the control group (baseline-corrected OR 1.07, 95%CI 0.55-2.08), while beta-blocker use increased by 5.2% (95%CI 2.0-10.0) in the intervention group compared with 1.1% (95%CI 0.2-6.3) in the control group (baseline-corrected OR 0.82, 95%CI 0.42-1.61).

These neutral results may be explained by several mechanisms. A half-day training and an uptitration leaflet seem insufficient to affect GPs' prescription behaviour. It should be emphasized, however, that we only included patients with established HF patients, who were known with HF for on average 3.0 (SD 3.0) years, and of whom 65% received collaborative care from the cardiologist. These patient characteristics resulted in a higher baseline treatment uptake of ACEI/ARB and beta-blockers than we assumed for our power calculation based on previous studies performed among patients with a GP's diagnosis of HF. Thus, leaving less room for improvement.[17]

We kept the training course simple and pragmatic and focused on the GPs to enhance implementation if shown to be effective. A more intensive training course or, probably even better, a combined training with cardiologists and HF nurses may have achieved better results. The complexity of HF management asks for a multidisciplinary team, not only while the patient is hospitalized and initially uptitrated, but also during the more stable chronic phase of their disease, because the disease trajectory of HF is also characterized by the development of new (non-cardiac) comorbidities, which may affect the tolerance to HF drugs.

Importantly, two previous studies showed that patients with HFrEF can, after initially having been optimally uptitrated with HF drugs at the outpatient cardiology clinic, be monitored equally effectively and safely in primary care with regard to guideline adherence and patient adherence.[18;19] HF drug therapy changes were equal between

the HF clinic and GP care in the study of Schou et al.[19] In the study of Luttik et al no differences were observed in drug adherence between patients allocated to continuation of HF care at the cardiology outpatient clinic or to monitoring in primary care.[18] The patients in this study were known with HF for on average 3 years (i.e. comparable with the patients in our study).

Gupta and colleagues suggested in 2004 that it should be possible up to adequate uptitrate beta-blockers in up to 70% of patients with HFrEF, taking into account (relative) contraindications, old age, and other drugs.[17] In 2008, a German study showed that GPs were not able to further uptitrate HFrEF patients who were already on a high beta-blocker prescription rate (79%). This while these GPs had received a very intensive training programme (in total 16 hours).[20] In 2009, Calvert and co-workers reported that 36.6% of patients known with HF in a primary care population received beta-blockers and 29.3% ACEI/ARB, however, they did not provide the findings for HFrEF and HFpEF seperately.[21] In a Spanish study published in 2010, it was shown in a randomized study that GPs who attended a simple single interactive training session managed to prescribe a higher proportions of patients with HFrEF to beta-blockers than GPs who did not receive such a training (49% optimal tolerated dose within three months vs. 38% in the care as usual group).[22]

At the time of our study, ARNIs were not yet available, so these were not studied. Since there is no available pharmacological treatment that clearly reduces morbidity and mortality in patients with HFpEF, the lack of an effect on HF drug prescription rates in HFpEF was not surprising, albeit that we might have expected some effect on MRA prescription, because a post-hoc subgroup analysis of the TOPCAT study recently suggested that spironolactone may have a beneficial prognostic effect in HFpEF patients with a LVEF >45%.[23;24] In contrast, however, the prescription of MRAs in HFpEF patients the intervention group of our study was reduced (Table 3).

The SF-36 scores 12 months after the training session in our study for patients with HF (HFrEF and HFpEF) were comparable with the results on the domains at 12 months as reported by Holzapfel et al.,[25] Juenger et al.,[26] and Scherer et al.[27] Those three studies compared the one year SF-36 scores with baseline health status scores, and showed that there were only small differences that were considered clinically unimportant. In our study population, all indices of health status were lower than those in ≥70-year-old-community-dwelling men and women without HF studied by Aaronson et al.,[28] with the most pronounced differences being the domains of physical functioning, role physical, and role emotional. Similar differences between

patients with HF and the population at large were found in earlier studies.[27;29;30] One study performed in Russia reported on an intensive nurse-led care programme in primary care, focusing on lifestyle changes and modification of cardiovascular risk factors, exercise training, and intensive proactive nursing care in 85 patients with HFpEF. After six months of follow-up health status, measured with the Minnesota Living with Heart Failure Questionnaire (MLHFQ), improved in the intervention arm compared to primary care as usual. The quality of usual care of HF patients in primary care in Russia is very likely lower than in the Netherlands, thus leaving more room for improvement following an intervention in the primary care setting in Russia.[31] Cardiovascular mortality and readmissions rate were not reduced in the Russian study.

The main strength of our study lies in the study population, which was a representative sample of the general population of patients with established HF in the Netherlands. We had access to all data on medication, cardiologist letters, hospitalizations, and death. Moreover, an expert panel confirmed the presence or absence of HF in potential participants.

Our study also had several limitations. One is the limited number of completed health status questionnaires filled out (48.0%) and only at one time point. The questionnaires were sent and collected by postal mail. Another limitation is that we did not register the daily-defined dose (DDD) of drugs and could therefore not calculate the number of patients with HFrEF on the recommended HF dosage. Electrocardiography (ECG) and X-thorax were not required investigations in the dataset; however, ECGs, when available, were included in the decisions of the expert panel, for ECGs may point to possible causes of HF, such as prior myocardial infarction, hypertension or atrial fibrillation, but do not prove that HF is present.[32;33] The same applies to chest radiography.[34] SF-36 scores were analysed, and adjusted with imputed baseline SF-36 scores without correction for clustering. As there was no intervention effect, correction for clustering is very unlikely to influence the results. Our study was sufficiently powered to detect relevant differences in prescription rates, but not for differences in the secondary endpoints. Finally, the follow-up period was relatively short, and well-established HF cases were included in the study, known with HF for on average almost 3 years.

Systemic reviews of literature focusing on implementation strategies identified the four most successful strategies for getting research into practice: computerized decision support, opinion leaders, financial incentives, and audit-and-feedback.[35] Combinations of these were more effective than a single approach.[39] Such strategies

but also a multifaceted approach in which GPs together with cardiologists and HF nurses are trained is possibly the best option to optimize HF management.

Conclusion

A half-day training program of GPs does not improve HF drug prescriptions in patients with established heart failure. Other interventions, such as a multidisciplinary approach should be considered for optimizing HF drug treatment in stable HF patients primarily managed in primary care.

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References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016; 18(8):891-975.
2. de Blois J, Fagerland MW, Grundtvig M, Semb AG, Gullestad L, Westheim A et al. ESC guidelines adherence is associated with improved survival in patients from the Norwegian Heart Failure Registry. *Eur Heart J Cardiovasc Pharmacother* 2015; 1(1):31-36.
3. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2012; 14(8):803-869.
4. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014; 371(11):993-1004.
5. Paulus WJ, van Ballegoij JJ. Treatment of heart failure with normal ejection fraction: an inconvenient truth! *J Am Coll Cardiol* 2010; 55(6):526-537.
6. Lund LH, Benson L, Dahlstrom U, Edner M, Friberg L. Association between use of beta-blockers and outcomes in patients with heart failure and preserved ejection fraction. *JAMA* 2014; 312(19):2008-2018.
7. Senni M, Paulus WJ, Gavazzi A, Fraser AG, Diez J, Solomon SD et al. New strategies for heart failure with preserved ejection fraction: the importance of targeted therapies for heart failure phenotypes. *Eur Heart J* 2014; 35(40):2797-2815.
8. Fonseca C. Diagnosis of heart failure in primary care. *Heart Fail Rev* 2006; 11(2):95-107.
9. Bongers FJ, Schellevis FG, Bakx C, van den Bosch WJ, van der Zee J. Treatment of heart failure in Dutch general practice. *BMC Fam Pract* 2006; 7:40.
10. Rutten FH, Grobbee DE, Hoes AW. Differences between general practitioners and cardiologists in diagnosis and management of heart failure: a survey in every-day practice. *Eur J Heart Fail* 2003; 5:337-344.
11. Valk MJ, Mosterd A, Broekhuizen BD, Zuithoff NP, Landman MA, Hoes AW et al. Overdiagnosis of heart failure in primary care: a cross-sectional study. *Br J Gen Pract* 2016; 66(649):e587-e592.
12. Gjelstad S, Hoye S, Straand J, Brekke M, Dalen I, Lindbaek M. Improving antibiotic prescribing in acute respiratory tract infections: cluster randomised trial from Norwegian general practice (prescription peer academic detailing (Rx-PAD) study). *BMJ* 2013; 347:f4403.
13. Horn FE, Mandryk JA, Mackson JM, Wutzke SE, Weekes LM, Hyndman RJ. Measurement of changes in antihypertensive drug utilisation following primary care educational interventions. *Pharmacoepidemiol Drug Saf* 2007; 16(3):297-308.

14. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur J Heart Fail* 2008; 10(10):933-989.
15. Valk MJ, Hoes AW, Mosterd A, Landman MA, Broekhuizen BD, Rutten FH. Rationale, design and baseline results of the Treatment Optimisation in Primary care of Heart failure in the Utrecht region (TOPHU) study: a cluster randomised controlled trial. *BMC Fam Pract* 2015; 16(1):130.
16. Wyrwich KW, Tierney WM, Babu AN, Kroenke K, Wolinsky FD. A comparison of clinically important differences in health-related quality of life for patients with chronic lung disease, asthma, or heart disease. *Health Serv Res* 2005; 40(2):577-591.
17. Gupta R, Tang WH, Young JB. Patterns of beta-blocker utilization in patients with chronic heart failure: experience from a specialized outpatient heart failure clinic. *Am Heart J* 2004; 147(1):79-83.
18. Luttik ML, Jaarsma T, van Geel PP, Brons M, Hillege HL, Hoes AW et al. Long-term follow-up in optimally treated and stable heart failure patients: primary care vs. heart failure clinic. Results of the COACH-2 study. *Eur J Heart Fail* 2014; 16(11):1241-1248.
19. Schou M, Gustafsson F, Videbaek L, Tuxen C, Keller N, Handberg J et al. Extended heart failure clinic follow-up in low-risk patients: a randomized clinical trial (NorthStar). *Eur Heart J* 2013; 34(6):432-442.
20. Peters-Klimm F, Muller-Tasch T, Remppis A, Szecsenyi J, Schellberg D. Improved guideline adherence to pharmacotherapy of chronic systolic heart failure in general practice--results from a cluster-randomized controlled trial of implementation of a clinical practice guideline. *J Eval Clin Pract* 2008; 14(5):823-829.
21. Calvert MJ, Shankar A, McManus RJ, Ryan R, Freemantle N. Evaluation of the management of heart failure in primary care. *Fam Pract* 2009; 26(2):145-153.
22. Anguita SM, Jimenez-Navarro M, Crespo M, Alonso-Pulpon L, de TE, Castro-Beiras A et al. Effect of a training program for primary care physicians on the optimization of beta-blocker treatment in elderly patients with heart failure. *Rev Esp Cardiol* 2010; 63(6):677-685.
23. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med* 2014; 370(15):1383-1392.
24. de Denus S., O'Meara E, Desai AS, Claggett B, Lewis EF, Leclair G et al. Spironolactone Metabolites in TOPCAT- New Insights into Regional Variation. *N Engl J Med* 2017; 376(17):1690-1692.
25. Holzapfel N, Zugck C, Muller-Tasch T, Lowe B, Wild B, Schellberg D et al. Routine screening for depression and quality of life in outpatients with congestive heart failure. *Psychosomatics* 2007; 48(2):112-116.
26. Juenger J, Schellberg D, Kraemer S, Haunstetter A, Zugck C, Herzog W et al. Health related quality of life in patients with congestive heart failure: comparison with other chronic diseases and relation to functional variables. *Heart* 2002; 87(3):235-241.

27. Scherer M, Dungen HD, Inkrot S, Tahirovic E, Lashki DJ, Apostolovic S et al. Determinants of change in quality of life in the Cardiac Insufficiency Bisoprolol Study in Elderly (CIBIS-ELD). *Eur J Intern Med* 2013; 24(4):333-338.
28. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol* 1998; 51(11):1055-1068.
29. Jenkinson C, Jenkinson D, Shepperd S, Layte R, Petersen S. Evaluation of treatment for congestive heart failure in patients aged 60 years and older using generic measures of health status (SF-36 and COOP charts). *Age Ageing* 1997; 26(1):7-13.
30. Blyth FM, Lazarus R, Ross D, Price M, Cheuk G, Leeder SR. Burden and outcomes of hospitalisation for congestive heart failure. *Med J Aust* 1997; 167(2):67-70.
31. Andryukhin A, Frolova E, Vaes B, Degryse J. The impact of a nurse-led care programme on events and physical and psychosocial parameters in patients with heart failure with preserved ejection fraction: a randomized clinical trial in primary care in Russia. *Eur J Gen Pract* 2010; 16(4):205-214.
32. Nielsen OW, Hansen JF, Hilden J, Larsen CT, Svanegaard J. Risk assessment of left ventricular systolic dysfunction in primary care: cross sectional study evaluating a range of diagnostic tests. *BMJ* 2000; 320(7229):220-224.
33. Khunti K, Squire I, Abrams KR, Sutton AJ. Accuracy of a 12-lead electrocardiogram in screening patients with suspected heart failure for open access echocardiography: a systematic review and meta-analysis. *Eur J Heart Fail* 2004; 6(5):571-576.
34. Thomas JT, Kelly RF, Thomas SJ, Stamos TD, Albasha K, Parrillo JE et al. Utility of history, physical examination, electrocardiogram, and chest radiograph for differentiating normal from decreased systolic function in patients with heart failure. *Am J Med* 2002; 112(6):437-445.
35. Boaz A, Baeza J, Fraser A. Effective implementation of research into practice: an overview of systematic reviews of the health literature. *BMC Res Notes* 2011; 4:212.

Chapter 7

General discussion

Heart failure (HF) is a complex clinical syndrome, generally defined as a syndrome in which patients have typical symptoms (e.g. breathlessness, ankle swelling, and fatigue) and, usually, signs (e.g. elevated jugular venous pressure, pulmonary rales, and displaced apex beat) resulting from an abnormality of cardiac structure or function leading to failure of the heart to deliver oxygen at a rate commensurate with the requirements of metabolizing tissues, despite normal filling pressures or only at the expense of increased filling pressures.[1] Data on temporal trends based on hospitalized patients suggest that the age-adjusted incidence of HF is decreasing, more so for HF with reduced ejection fraction (HFrEF) than for HF with preserved ejection fraction (HFpEF).[2,3] Nevertheless, the prognosis remains poor with around 50% of HF patients dying within five years after being diagnosed, but with a better prognosis when patients are detected during HF screening in high-risk older people from the community, such as those with diabetes or COPD.[4-7]

There is a large difference between the ideal and the actual management of HF.[1] This is more prominent in primary care, despite current guideline recommendations and given the fact that, in the Netherlands, more than 70% of these patients receive cooperative care from cardiologists and/or HF nurses. There seems to be sufficient room for improvement in both the diagnosis and management of the syndrome. For this to be achieved, educational programs should focus on the 'HF team' with combined training for, notably, cardiologists, HF nurses, and general practitioners (GPs).

With the availability of natriuretic peptides (NPs), the process of diagnosing HF in primary care has become easier. Existing guidelines recommend that a diagnosis other than HF should be considered if the NP value is below the exclusionary cut-off point, and, that echocardiography be performed to confirm the diagnosis of HF in case of levels above this cut-off point. If the diagnosis is positive, echocardiography results can then be used to classify the disease into HF with reduced ejection fraction (left ventricular ejection fraction [LVEF] <40%; HFrEF), HF with mid-range ejection fraction (LVEF 40–49%; HFmrEF), or HF with preserved ejection fraction (LVEF ≥50%; HFpEF).[8]

A number of drugs and devices have been shown to improve the health status and decrease hospitalization rates and mortality in patients with HFrEF, and are widely recommended in existing guidelines. The optimal treatment of patients with HF with mid-range EF or those with HFpEF is, however, still heavily debated, mainly because there is no compelling evidence of effective drug of device therapies. Moreover, most

of these HFmrEF and HFpEF patients are elderly and have multiple cardiac and non-cardiac comorbidities, and guidelines provide insufficient guidance on how to treat these adequately on an individual basis.

To keep health budgets within limits, policy makers feel a need to transfer the care of stabilized patients with chronic progressive diseases from the hospital to a home-based setting. In the case of HF, there are still some gaps in the knowledge and organization of care provided by GPs that should be dealt with before transfer of care for HF from the hospital/outpatient clinics to primary care can be implemented adequately and safely. This is especially the case because often adaptations of HF treatment are needed in the home setting, for example, when patients experience HF exacerbations or when new diseases develop that interact with HF or HF therapy, e.g. gout, renal failure, pulmonary infections.

It is therefore of utmost importance to highlight the pitfalls, but also the opportunities in the management of patients with HF primarily managed by the GP.

In this general discussion, the main results of our research will be presented first. This will be followed by a brief history of HF management in the Netherlands and a discussion on the pitfalls and opportunities of HF management in primary care. Finally, possible options for the improvement of HF management will be proposed.

Main findings of this thesis

1. In chapter 2 we describe the use of natriuretic peptide (NP) testing in general practice over time. NP blood measurements became available around 2003. The use of this measurement by GPs increased rapidly from 2005 to 2013: from 2.5 per 1,000 patient-years (PY) in 2005 to 14.0 per 1,000 PY in 2013, with a peak of 15.6 per 1,000 PY in 2009. Our results showed that the proportion of patients with an N-terminal pro B-type NP (NTproBNP) value below the exclusionary cut-off point of 125 pg/mL was rather low (around 30% over the years), which suggests that GPs used this test to confirm rather than to exclude HF. In other words, GPs seemed to order the test most often in individuals with overt symptoms and signs of fluid overload, and less often in less typical cases or for risk stratification of older patients known to have COPD, type 2 diabetes, or multimorbidity and polypharmacy.[9-12]
2. In chapter 3 we show that not all patients with a GP label of HF do indeed have HF. The GP's diagnosis of HF could not be confirmed by the expert panel in

17.3% of cases. In another 19.2% of cases, the diagnosis was uncertain. This means that in addition to the well-known under-diagnosis, also clear over-diagnosis of HF exists in primary care.[13]

3. In chapter 4 we evaluated spirometry in stable patients with established HF, and showed that concurrent COPD (according to the fixed GOLD criteria [FEV1/FVC <0.70]) was common in 28.3% of cases, with equal prevalence rates in those with HFrEF (LVEF <45%) and HFpEF (LVEF ≥45%).[14]
4. In chapter 5 we present the design and in chapter 6 the results of a randomized clinical trial. The effect of a half-day training session for GPs on the optimization of HF drug treatment in 398 patients with established HF (204 HFrEF (LVEF <45%); 194 HFpEF (LVEF ≥45%)) was assessed in a cluster-randomized trial among 30 primary care practices. Compared to the results of the care-as-usual group, the training course had no beneficial effect on HF drug prescriptions or health status, irrespective of the type of HF.

History of HF management in the Netherlands

In the early 1980s, HF was mainly managed by internists and a HF diagnosis was solely based on clinical assessment. Focus was on hospital-based acute HF ("cardiac asthma") with ad-hoc management with intravenous loop diuretics, vasodilators, and digoxin.

In the 1990s, cardiologists became more involved and echocardiography and later also other cardiovascular imaging modalities became available for the assessment of cardiac function, focussing mainly on HFrEF. Clinical trials demonstrated the lifesaving benefits of angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and mineralocorticoid receptor antagonists for these patients against a background treatment of loop diuretics in around 80% of them. From 2000 onwards clinical trials showed benefits of device therapy (ICD, cardiac resynchronization, left ventricular assist devices) in selected patients with reduced EF, and very recently, another drug (sacubitril/valsartan, a so called ARNI - angiotensin receptor neprilysin inhibitor) was found to improve HF symptoms, decrease hospitalizations, and reduce mortality in symptomatic patients with HF and LVEF ≤35%.[15]

Over the years, echocardiography has become more sophisticated and nowadays provides much more detailed information (e.g. through tissue Doppler imaging) on diastolic function. With mitral annular velocity examinations, it is now possible to

measure E/e' as a surrogate marker for left ventricular filling pressures. A combination of increased E/e', an enlarged left atrium, and reduced velocities over the tricuspid valve indicate important structural and functional abnormalities related to diastolic dysfunction.[8] HFpEF, which is mainly caused by a filling problem of the heart, can now be diagnosed; i.e., symptoms suggestive of HF, but with a normal LVEF (>45-50%) by echocardiography in rest but with structural or functional abnormalities related to diastolic dysfunction. Although exacerbations of HFpEF with the clinical picture of notably pulmonary fluid retention can be adequately treated symptomatically, and often periodically, with loop diuretics, evidence-based treatments are not yet available for this type of HF, although, recent post-hoc analyses of the TOPCAT study suggest that spironolactone may be prognostically beneficial in those with LVEF >45% and elevated NP levels.[16;17]
With the introduction of NPs in 2003, the process of diagnosing HF in primary care has become easier. HF outpatient clinics with dedicated HF nurses have become commonplace to manage and educate stabilized patients with chronic HF and prevent costly (re)admissions.[18]

With the shift from the ad-hoc care of patients with acute HF in the 1980s and 1990s to a more pro-active, multidisciplinary approach in the current era, the role of the GP has changed from simply referring patients with "cardiac asthma" to the hospital, to GPs actually cooperating in the care of (chronic) HF patients with a focus on keeping them stable and ambulant.
Given the current treatment modalities for HFpEF, the GP can play a crucial role in managing HFpEF patients with adequate individualized diuretic titration depending on fluid status, optimal blood pressure control, and heart-rate control in those with tachycardia, while also managing the HF patients' comorbidities. Also patients with HFrEF who were stabilized and adequately uptitrated at the HF outpatient clinics, may safely be referred back to the GP and managed in primary care.[19;20]
Given the current health care situation and knowledge on optimal HF management, there are some important pitfalls, but also opportunities for GPs.[20-22]

Managing HF in primary care: pitfalls and opportunities

In the ideal situation, the GP optimally manages cardiovascular risk factors (e.g. hypertension, type 2 diabetes) to help prevent developing HF, considers selective

screening in older people with such risk factors, adequately diagnoses HF in individuals with suggestive symptoms (using e.g. ECG, NP testing, echocardiography), and finally knows how to fine-tune and individualize HF drugs after the patients have been initiated and uptitrated by the cardiologist/HF nurse in the HF-outpatient setting. Thus, as much as possible, i) the onset of HF is prevented or postponed and patients with symptoms and signs of HF are ii) discovered early with case finding in high risk patients, iii) diagnosed timely by adequately acting and labelling of the underlying disease when patients report symptoms and signs suggestive of HF, and iv) treated by means of cooperative care with a cardiologist and HF nurse. In addition, both cardiac and non-cardiac comorbidities are known and treated appropriately, with possible polypharmacy interactions kept in mind. Moreover, the GP is alert on detecting developing comorbidities during the disease trajectory of every individual patient with HF, taking into account that these may interfere with the management and prognosis of HF.

Starting with selective screening (or case finding) and diagnosing (ii and iii), a GP can (proactively) ask the patient, notably those with risk factors, i.e. a history of type 2 diabetes, COPD, about symptoms suggestive of HF. In case of positive answers physical examination may follow including palpation of the apical impulse, measuring the jugular venous pressure, listening for pulmonary crackles or cardiac murmurs and inspecting the legs for peripheral oedema. If there are suggestive signs the GP can continue with scrutinizing the patient's medical history (e.g. prior myocardial infarction, CABG/PCI, hypertension, and type 2 diabetes), and in "positive" cases (let) make an electrocardiogram (ECG) and request measurements of NP levels. In patients with suggestive symptoms and/or signs, abnormalities on ECG, and/or BNP levels above the exclusionary cut-off point, echocardiography should follow with in case of definite HF, classification of the type of HF and the possible cause(s). Patients with symptoms and/or signs suggestive of fluid overload (pulmonary crackles, ankle oedema, elevated jugular venous pressure) should be prescribed or adjusted a loop diuretic if they are already taking it. Many patients with HFpEF can then be further managed by the GP, as we mentioned before. For patients with HFrEF, the hospital HF team should conduct further tests to discover if a treatable cause is likely and initiate and uptitrate HF drugs, e.g. ACE inhibitors (or if ACE-intolerant, angiotensin receptor blockers (ARBs)) and beta-blockers. In those with HFrEF and adequately uptitrated with these drugs and still symptomatic and a LVEF ≤35%, a mineralocorticoid receptor antagonist (MRA) should be added. Device therapy, such

as cardiac resynchronization therapy or an implantable cardioverter defibrillator (ICD) implantation, should be considered in selected patients. Once stabilized, optimally uptitrated, and educated on HF, lifestyle issues, and drug adherence, e.g. with the help of website www.heartfailurematters.org, the patient can be monitored and managed in the patient's home setting coordinated by the GP.[8;20]

It is clear that creating the abovementioned situation with cooperative care focused on optimal individual patient care and with seamless transitions between secondary and primary care is not easy, certainly not with the typical diseases trajectory in these patients, characterized by regular exacerbations requiring hospital admissions. Adaptation of (inter)national HF guidelines to the regional situation can be helpful in promoting the teamwork of cardiologist, HF nurse and GP and thus bring HF care both in and outside the hospital at a higher level.[23]

The different aspects of managing the patients during their disease trajectory from the perspective of the GP are schematically summarized in figure 1 and include prevention and risk stratification, (early) diagnosis, management of stable HF, pre-hospital treatment of acute HF, and end of life care.[24]

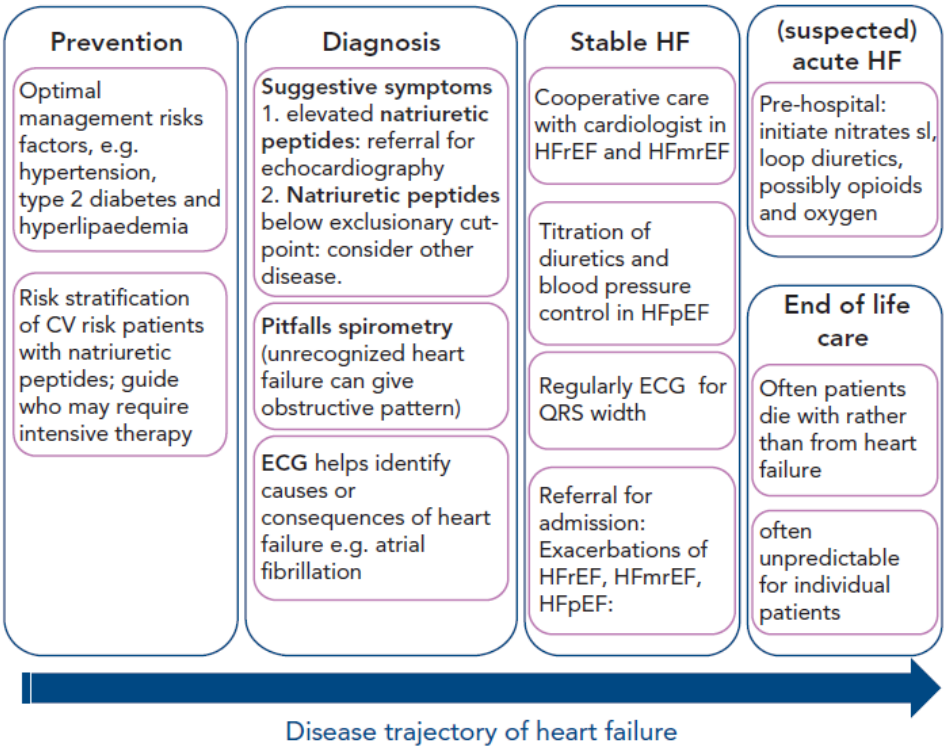
Below we will address the pitfalls and opportunities in diagnosing HF and the management of stable HF from the perspective of the GP:

Diagnosis of HF: risks of underdiagnosis and overdiagnosis

Pitfalls:

- The detection of HF, especially in the early stages, is difficult because symptoms and signs are non-specific.[8] Breathlessness, a key feature of HF, may be confused with COPD, obesity, "deconditioning", or many other conditions.[8;25] HF is both frequently overdiagnosed and underdiagnosed in primary care.[8-10;20;21;26;27] The first pitfall is overdiagnosis by basing a diagnosis of HF on signs and symptoms only, without requesting additional investigations to establish the diagnosis.[28]
- A second pitfall is the underuse of NP testing; NP is especially useful to rule out HF, and if elevated it helps to increase the likelihood that the symptoms and signs are caused by HF.[29]
- A third pitfall is when GPs do not amend the patient's label of (suspected) HF, after diagnostic workup has excluded HF. This results in a - sometimes lifelong – incorrect label of HF.

Figure 1 Potential roles of the GP in managing patients with HF during their disease trajectory. Copied from Rutten FH, Gallagher J. What the general practitioner needs to know about their chronic heart failure patient. *Cardiac Failure Review* 2016;2(2):79–84.[24]



GP=general practitioner; HF= heart failure; HFmrEF= heart failure with mid-range ejection fraction; HFpEF= heart failure with preserved ejection fraction; HFrEF= heart failure with reduced ejection fraction.

- A patient's high age and accompanying immobility can cause over-diagnosis of HF: such patients, if suspected of having HF, are sometimes unable to go to the hospital for echocardiography.
- More often, however, (early stages of) HF are underdiagnosed because comorbidity obscures the diagnostic process. Firstly, the symptoms of HF and COPD largely overlap, e.g. shortness of breath, fatigue, but also wheezing. Both patients and GPs tend to merely link respiratory symptoms to respiratory

disorders.[30;31] In the further diagnostic work-up, the GP may well decide to perform spirometry given that spirometry is widely available in primary care while echocardiography is not, which may in turn result in false-positive diagnoses of COPD.[32;33] This is often attributable to the fact that patients with (unrecognized) HF who have (sometimes clinically not clearly detectable) pulmonary fluid retention also show obstruction on spirometry due to external bronchial fluid obstruction, thus mimicking the spirometric findings (a reduced FEV/FVC ratio) seen in COPD.[32;33] Importantly, when COPD is from then on considered as the explanation for the patient's complaints, the diagnostic workup may be stopped even though HF could be the alternative diagnosis, or a concurrent comorbidity.[10]

- Another cause of underdiagnosis is refraining from echocardiography, even in those with suggestive symptoms and signs of HF and NP levels above the pre-defined cut-off point. This is probably because not all GPs are aware of the importance of distinguishing between the phenotypes of HF: especially HFrEF and HFpEF. These phenotypes have their own specific treatment recommendations (this thesis, chapter 2).
- Finally, primary care disease management programs for patients at high risk of developing HF, e.g. for those with COPD, type 2 diabetes, and at increased cardiovascular risk (e.g. because of hypertension and/or high cholesterol levels), do not pro-actively ask participants about symptoms and signs of HF, such as (change in) breathlessness, reduced exercise tolerance, newly developed ankle oedema, or sleep disturbances (possibly due to paroxysmal nocturnal dyspnoea or nocturia).

Opportunities:

- To improve the diagnostic process, focus should first be on the early recognition of HF. New-onset HF can often be discovered in older patients (i.e. above 65 years of age) with one or more chronic progressive conditions (e.g. longstanding hypertension, type 2 diabetes, COPD, a history of ischaemic heart disease). A great opportunity is that in many Dutch primary care practices these patients already participate in disease management programs (for T2D, COPD, and cardiovascular risk management) and are periodically monitored. The GP and the nurse practitioner should be constantly alert to early signs and symptoms of HF

in these patients given the high prevalence of unrecognized HF in these patient categories.[10;11]

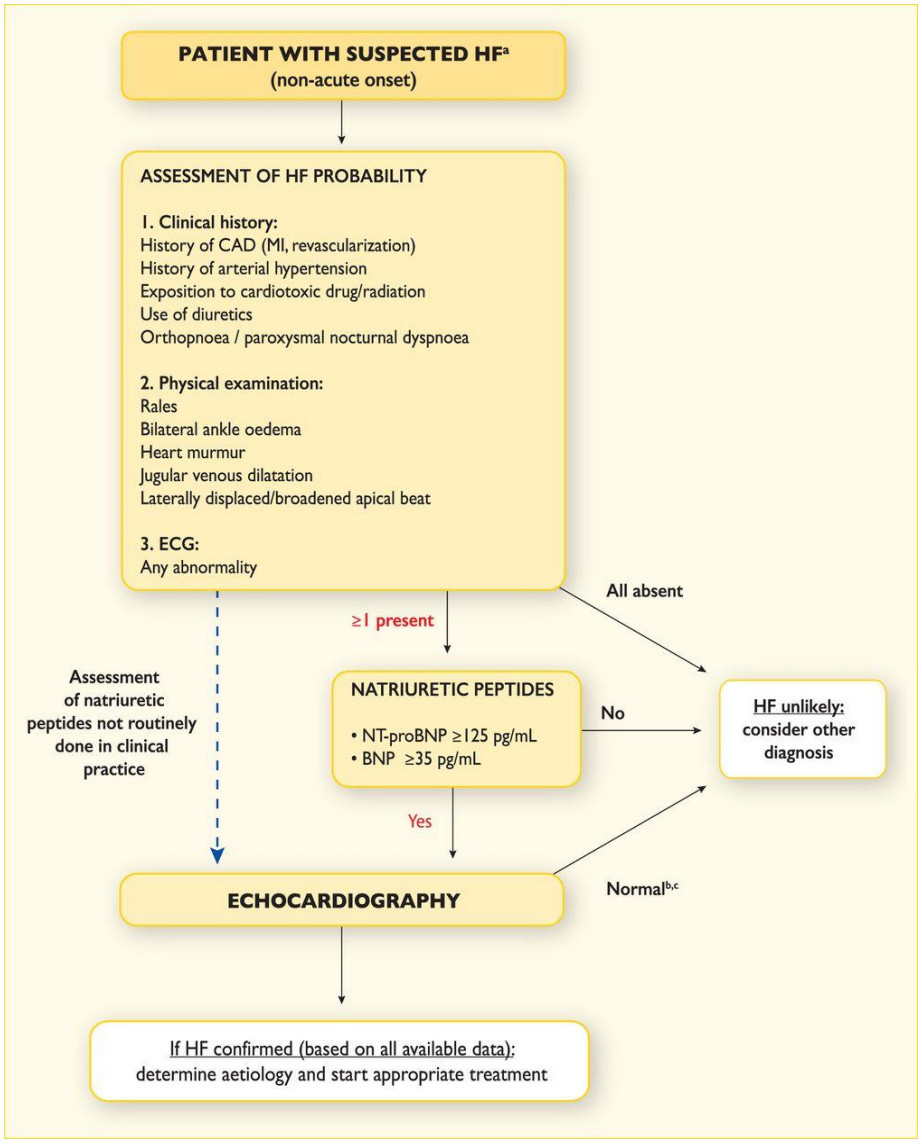
- Second, NP testing should be more often considered, also in cases with a lower level of suspicion. It seems that GPs still tend to use it more or less as a confirmation of their already high suspicion of HF (this thesis, chapter 3). NP has, however, a very strong power to rule out HF, and thus facilitate the selection of those needing echocardiography. Although NP testing is clearly recommended in (inter)national guidelines, it should receive even more emphasis, possibly in postgraduate training courses for GPs. It is of great help that the European Society of Cardiology (ESC) has developed a diagnostic algorithm for patients suspected of having chronic HF (Figure 2), with a central role for NP testing.[8] Finally the availability and reimbursement rules of NP testing in primary care differs considerably between countries. While in the Netherlands the test is widely available and reimbursed, in other countries GPs do not have easy access to NP testing.
- Finally, the cardiologist's echocardiography reports are not always clear, often containing abbreviations without legends and without a clear conclusion and/or advise for further management. This impairs the GPs confidence in initiation and uptitration of adequate drug treatment. These echocardiographic reports should provide an unambiguous diagnosis regarding HF phenotype and clear advise on treatment, and not just a long list of multiple parameters.

Drug treatment in HF

Pitfalls:

- GPs deal with multiple diseases, and HF is simply just one of these. In a general practice in which a GP takes care of around 2,500 people, around 1-2% will be known with established HF (25 to 50 patients), about half of those have HFrEF (LVEF <40-45%), and another 2% (50 people) have unrecognized HF. The mean age of the established HF patients will be around 76 years, and nearly all will have multimorbidity (and polypharmacy). It is clear that these relative small numbers are, in general, not a sufficient base for becoming an expert in uptitrating HF-recommended drugs in those with HFrEF. The more, because at the moment cardiologists and HF nurses do most of the HF uptitration work in HF outpatient clinics around the world. It therefore comes at no surprise that the uptake of the guidelines' recommendations regarding HF drug therapy in primary

Figure 2 Diagnostic algorithm for the diagnosis of HF of non-acute onset. *Copied from the 2016 ECS guidelines on HF with permission.*[1]



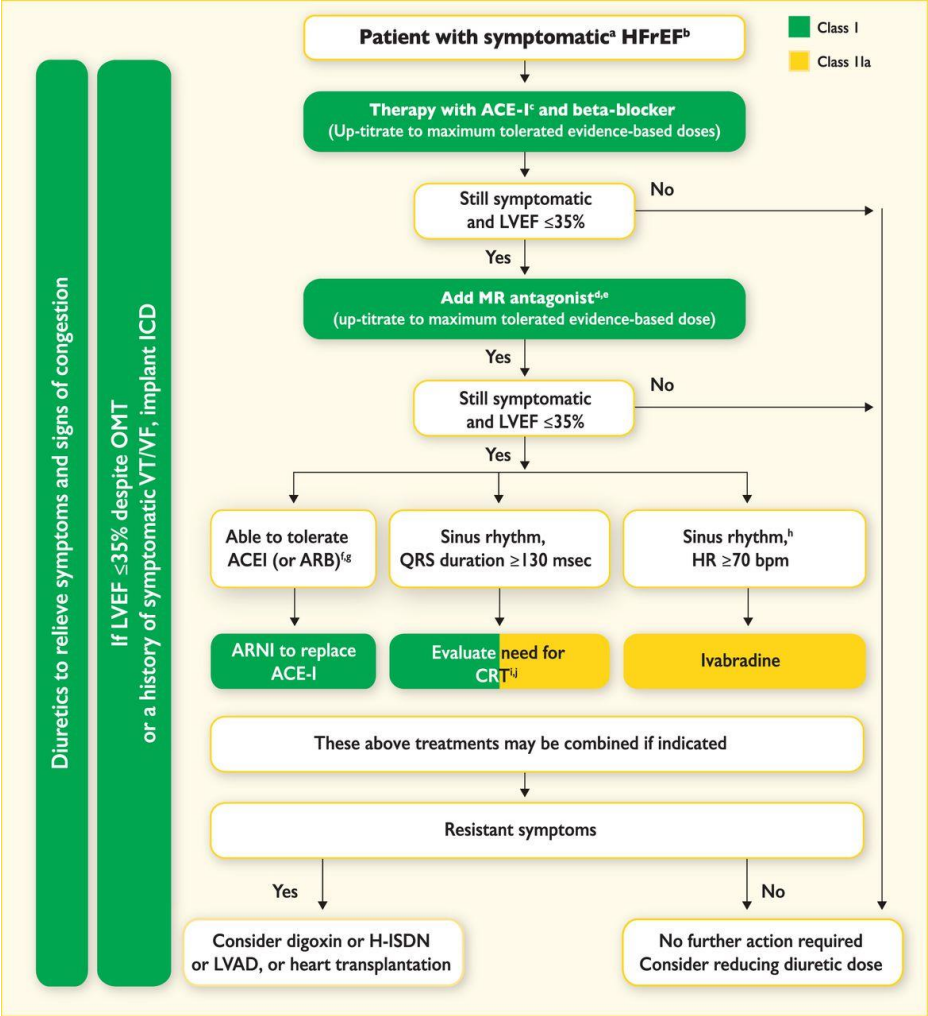
BNP = B-type natriuretic peptide; CAD = coronary artery disease; HF = heart failure; MI = myocardial infarction; NT-proBNP = N-terminal pro-B type natriuretic peptide.[8]

[a] Patient reporting symptoms typical of HF.

[b] Normal ventricular and atrial volumes and function.

[c] Consider other causes of elevated natriuretic peptides.

Figure 3 Therapeutic algorithm for a patient with symptomatic HFrEF. Green indicates a class I recommendation; yellow indicates a class IIa recommendation. *Copied from the 2016 ECS guidelines on HF with permission.*[1]



ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; BNP = B-type natriuretic peptide; CRT = cardiac resynchronization therapy; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; H-ISDN = hydralazine and isosorbide dinitrate; HR = heart rate; ICD = implantable cardioverter defibrillator; LBBB = left bundle branch block; LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; MR = mineralocorticoid receptor; NT-proBNP = N-terminal pro-B type natriuretic peptide; NYHA = New York Heart Association; OMT = optimal medical therapy; VF = ventricular fibrillation; VT = ventricular tachycardia.[8]

[a] Symptomatic = NYHA Class II to IV.
[b] HFrEF = HF with a LVEF <40%.
[c] If ACE inhibitor is not tolerated/contraindicated, use ARB.
[d] If MR antagonist is not tolerated/contraindicated, use ARB.
[e] With a hospital admission for HF within the last 6 months or with elevated natriuretic peptides (BNP >250 pg/mL or NT-proBNP >500 pg/mL in men and 750 pg/mL in women).
[f] With an elevated plasma natriuretic peptide level (BNP ≥150 pg/mL or plasma NT-proBNP ≥600 pg/mL, or if HF hospitalization within the past 12 months, plasma BNP ≥100 pg/mL or plasma NT-proBNP ≥400 pg/mL).
[g] In doses equivalent to enalapril 10 mg b.i.d.
[h] With a hospital admission for HF within the previous year.
[I] CRT is recommended if QRS ≥130 msec and LBBB (in sinus rhythm).
[j] CRT should/may be considered if QRS ≥130 msec with non-LBBB (in sinus rhythm) or for patients in AF provided a strategy to ensure biventricular capture is in place (individualized decision).

care is suboptimal, [13;34;35] and target doses are often not reached despite the fact that the majority (around 70%) receives cooperative care from the cardiologist/HF nurse.[13]

- An important reason for suboptimal drug therapy is incomplete diagnostic assessment before treatment is initiated. In particular, omitting echocardiography is a problem, because then only a 'working diagnosis' of HF exists, without knowing the type or cause of HF. This gives uncertainty on how to proceed after initial relief of symptoms with loop diuretics; should the GP further uptitrate evidence-based HF drugs because the patient with unknown ejection fraction has HFrEF, or only control blood pressure (and heart rate in atrial fibrillation) in addition to diuretic titration because the patient has actually HFpEF? This uncertainty will also facilitate stopping uptitration of HF drugs as soon as the patient is (relatively) symptom-free, often far before reaching the target or maximal tolerated dose.[21]
- Furthermore, GPs still seem to experience barriers to uptitrate renal-angiotensin-aldosterone-system inhibitors because of fear for (short-term) deterioration of renal function.[35] In general, GPs are critical to any drug that should be initiated in patients with multimorbidity/polypharmacy. This on the one hand is merely adequate behaviour as polypharmacy is currently among the main reasons of iatrogenic complications in elderly, with the GP being responsible for the complete medication overview. On the other hand, however, HF is one of the disorders where undertreatment with relevant drugs is harmful, even in the very old.

- Finally, many GPs are still hesitant to uptitrate beta-blockers in a COPD patient with newly detected HF, although it has become clear that beta-blockers are not contraindicated and even beneficial in COPD patients with HF.[36]

Opportunities:

- Uptitration of HF drugs should be implemented at the location with currently the best results: hospital (outpatient clinic)-based multi-disciplinary HF teams including HF nurses are best in improving drug therapy in patients with HFrEF; better than cardiologists alone or GPs in their primary care setting.[34] After HF teams/cardiologists have completed the uptitration of recommended drugs in those with HFrEF (figure 3), such treatment can be safely continued in primary care.[19;20]
- Good cooperative care may help seamless transfer patients from secondary to primary care, and vice versa, for example in case of an HF exacerbation not manageable in primary care. Close collaboration and efficient communication between the hospital HF team and GPs (or other health care workers in primary care, such as community pharmacists, physiotherapists, dieticians), is therefore crucial, and eHealth solutions could very likely facilitate this.[37] In this collaboration, the role of the pharmacist could be improved. A periodical evaluation of a patient's individual drug intake by both GPs and pharmacists will likely help to increase drug adherence and uncover possible interactions and side effects, and balance drug prescription for all comorbidities, prioritising the most (cost)effective, and prognostically beneficial therapies, keeping in mind that symptom relief is also key to a HF patient's well-being.

Monitoring of patients with heart failure

Pitfalls:

- The management of HF patients in primary care is 'fragmented' and there is no primary care HF disease management program, in contrast to programs for patients with type 2 diabetes or COPD.
- Moreover, we already hinted at the fact that the cooperation between the HF team and GPs could be improved substantially, and that this could improve the care of HF patients.

Opportunities:

- Apart from the already mentioned opportunities with drug treatment, there are initiatives that help to improve the cooperation. In the Netherlands, the National Transmural Agreements ("Landelijke Transmurale Afspraak" (LTA)) has been lounged. Based on these LTAs, local documents are produced including agreements between hospitals, primary care and health care professionals on how HF care is organized in a specific area, taking into consideration regional aspects.[23] Finally, in 2015, the Netherlands Society of Cardiologists (NVVC) started a program (the CONNECT program) focused on improving the collaboration between GPs and cardiologists and aiming for seamless transition of patients with cardiovascular disease between secondary and primary care. In all these programs, GPs with special interest in cardiovascular disease ('kaderhuisartsen hart- en vaatziekten') participate. One of these programs is CONNECT-HF, aiming at improving the care of patients with HF.
- In the Netherlands GPs can follow a 2-year part-time post-academic training program and get certified to become an expert in cardiovascular disease in their own district. These "GPs with special interest" (in the UK known as GyPSIs, in the Netherlands as 'kaderhuisartsen') function as a link between cardiologists and primary care, frequently organise training sessions, discuss regional topics with insurance companies, and their practice often serves as an example for others (best practices).
- To adequately address the dynamic disease progression of HF, monitoring is crucial. Regular, or even day-by-day monitoring of body weight, blood pressure, and heart rate could be facilitated by eHealth tools, but solid evidence that such an approach improves relevant patient outcomes is currently still lacking.
- Ongoing education of patients and their carers is also important for optimizing the care of these patients, and the website 'Heartfailurematters.org" (Hartfalendoetertoe.nl) could be very helpful, although patients should initially be instructed by their GP or HF team on how to navigate the site by the GP or the HF team. Studies are on the way assessing the effect of this website on self-care behaviour of patients.
- Another important aspect of monitoring is periodical checks by the GPs of renal function and potassium levels to guide adjustments in diuretic and RAAS inhibiting therapy. Moreover, periodically ECG recordings to detect broadening of the QRS complexes is useful, to detect HF patients with a QRS width >130

msec since such patients could be referred to the cardiologist for evaluation of implantation of a device, either cardiac resynchronization therapy (CRT) or CRT-D (a CRT with ICD facility).[8]

- The GP could consider to regularly ask patients to visit the practice nurse to evaluate drug adherence and to further build on the knowledge (from the HF team and heartfailurematters website) and preferences patients have on lifestyle aspects such as salt and fluid intake, exercise, smoking, and alcohol use.[38] Importantly, however, such more structured care has not been evaluated on cost-effectiveness.

Other initiatives

The HF awareness day, an initiative of the HF association of the European Society of Cardiology helps to make the general public more aware of the disease and symptoms and signs that can be early signs of HF. Apart from heartfailurematters.org, also life style advice and eHealth may help to empower patients with HF and their carers, by also making them 'part of the team'. This may help to take their own responsibilities regarding adherence to therapy, and to adequately deal with their preferences regarding therapies and life style aspects, which may change over time and therefore need regular 'checks' if these are still in place.

Summary of the opportunities to improve HF management

As we addressed in the previous pages, HF management can be improved over the complete trajectory from prevention, case-finding, (early) diagnosis, up to treatment and monitoring. Although the GP and primary care play a crucial role in all of these activities, close cooperation and optimal communication between all health care workers in primary and secondary HF care as well HF patients and their carers is crucial. HF care means real teamwork!

References

1. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2012; 14(8):803-869.
2. Gerber Y, Weston SA, Redfield MM, Chamberlain AM, Manemann SM, Jiang R et al. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. *JAMA Intern Med* 2015; 175(6):996-1004.
3. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med* 2006; 355(3):251-259.
4. Jhund PS, Macintyre K, Simpson CR, Lewsey JD, Stewart S, Redpath A et al. Long-term trends in first hospitalization for heart failure and subsequent survival between 1986 and 2003: a population study of 5.1 million people. *Circulation* 2009; 119(4):515-523.
5. Martinez-Selles M, Doughty RN, Poppe K, Whalley GA, Earle N, Tribouilloy C et al. Gender and survival in patients with heart failure: interactions with diabetes and aetiology. Results from the MAGGIC individual patient meta-analysis. *Eur J Heart Fail* 2012; 14(5):473-479.
6. Boudestein LC, Rutten FH, Cramer MJ, Lammers JW, Hoes AW. The impact of concurrent heart failure on prognosis in patients with chronic obstructive pulmonary disease. *Eur J Heart Fail* 2009; 11(12):1182-1188.
7. Boonman-de Winter LJ, Hoes AW, Cramer MJ, de Jongh G., Janssen RR, Rutten FH. Prognosis of screen-detected heart failure with reduced and preserved ejection fraction in patients with type 2 diabetes. *Int J Cardiol* 2015; 185:162-164.
8. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016; 18(8):891-975.
9. van Riet EE, Hoes AW, Limburg A, Landman MA, van der Hoeven H, Rutten FH. Prevalence of unrecognized heart failure in older persons with shortness of breath on exertion. *Eur J Heart Fail* 2014; 16(7):772-777.
10. Rutten FH, Cramer MJ, Grobbee DE, Sachs AP, Kirkels JH, Lammers JW et al. Unrecognized heart failure in elderly patients with stable chronic obstructive pulmonary disease. *Eur Heart J* 2005; 26(18):1887-1894.
11. Boonman-de Winter LJ, Rutten FH, Cramer MJ, Landman MJ, Liem AH, Rutten GE et al. High prevalence of previously unknown heart failure and left ventricular dysfunction in patients with type 2 diabetes. *Diabetologia* 2012; 55(8):2154-2162.
12. van Mourik Y, Bertens LC, Cramer MJ, Lammers JW, Reitsma JB, Moons KG et al. Unrecognized heart failure and chronic obstructive pulmonary disease (COPD) in frail elderly detected through a near-home targeted screening strategy. *J Am Board Fam Med* 2014; 27(6):811-821.

13. Valk MJ, Mosterd A, Broekhuizen BD, Zuithoff NP, Landman MA, Hoes AW et al. Overdiagnosis of heart failure in primary care: a cross-sectional study. *Br J Gen Pract* 2016; 66(649):e587-e592.
14. Valk MJ, Broekhuizen BD, Mosterd A, Zuithoff NP, Hoes AW, Rutten FH. COPD in patients with stable heart failure in the primary care setting. *Int J Chron Obstruct Pulmon Dis* 2015; 10:1219-1224.
15. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014; 371(11):993-1004.
16. de Denus S., O'Meara E, Desai AS, Claggett B, Lewis EF, Leclair G et al. Spironolactone Metabolites in TOPCAT- New Insights into Regional Variation. *N Engl J Med* 2017; 376(17):1690-1692.
17. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med* 2014; 370(15):1383-1392.
18. Jaarsma T, Nikolova-Simons M, van der Wal MH. Nurses' strategies to address self-care aspects related to medication adherence and symptom recognition in heart failure patients: an in-depth look. *Heart Lung* 2012; 41(6):583-593.
19. Schou M, Gustafsson F, Videbaek L, Tuxen C, Keller N, Handberg J et al. Extended heart failure clinic follow-up in low-risk patients: a randomized clinical trial (NorthStar). *Eur Heart J* 2013; 34(6):432-442.
20. Luttik ML, Jaarsma T, van Geel PP, Brons M, Hillege HL, Hoes AW et al. Long-term follow-up in optimally treated and stable heart failure patients: primary care vs. heart failure clinic. Results of the COACH-2 study. *Eur J Heart Fail* 2014; 16(11):1241-1248.
21. Cleland JG, Cohen-Solal A, Aguilar JC, Dietz R, Eastaugh J, Follath F et al. Management of heart failure in primary care (the IMPROVEMENT of Heart Failure Programme): an international survey. *Lancet* 2002; 360(9346):1631-1639.
22. Bosch M, Wensing M, Bakx JC, van der Weijden T, Hoes AW, Grol RP. Current treatment of chronic heart failure in primary care; still room for improvement. *J Eval Clin Pract* 2010; 16(3):644-650.
23. Ansink JM, Burgers JS, Geerders BP, Elsendoorn M, van Laarhoven H, Mosterd A. Heart failure, National Transmural Agreement (in Dutch) https://www.nhg.org/sites/default/files/content/nhg_org/uploads/lta_hartfalen_definitieve_versie.pdf. 15-11-2015.
24. Rutten FH, Gallagher J. What the general practitioner needs to know about their chronic heart failure patient. Cardiac Failure Review 2016; 2(2);79-84.
25. Rutten FH, Clark AL, Hoes AW. How big a problem is heart failure with a normal ejection fraction? *BMJ* 2016; 353:i1706.
26. Rutten FH, Grobbee DE, Hoes AW. Differences between general practitioners and cardiologists in diagnosis and management of heart failure: a survey in every-day practice. *Eur J Heart Fail* 2003; 5:337-344.
27. Remme WJ, McMurray JJ, Hobbs FD, Cohen-Solal A, Lopez-Sendon J, Boccanelli A et al. Awareness and perception of heart failure among European cardiologists, internists, geriatricians, and primary care physicians. *Eur Heart J* 2008; 29(14):1739-1752.

28. Kelder JC, Cramer MJ, van Wijngaarden J, van Tooren R, Mosterd A, Moons KG et al. The diagnostic value of physical examination and additional testing in primary care patients with suspected heart failure. *Circulation* 2011; 124(25):2865-2873.
29. Oosterhuis W, Boonman-de Winter LJ, Frericks A, Kragten H, Rutten W. Measurement of N-terminal pro-BNP in heart failure: from the Dutch GP guideline to clinical practice [in Dutch]. *Huisarts Wet* 2009; 52:434-438.
30. Hawkins NM, Petrie MC, Jhund PS, Chalmers GW, Dunn FG, McMurray JJ. Heart failure and chronic obstructive pulmonary disease: diagnostic pitfalls and epidemiology. *Eur J Heart Fail* 2009; 11(2):130-139.
31. Rutten FH, Cramer MJ, Lammers JW, Grobbee DE, Hoes AW. Heart failure and chronic obstructive pulmonary disease: An ignored combination? *Eur J Heart Fail* 2006; 8(7):706-711.
32. Guder G, Brenner S, Stork S, Hoes A, Rutten FH. Chronic obstructive pulmonary disease in heart failure: accurate diagnosis and treatment. *Eur J Heart Fail* 2014; 16(12):1273-1282.
33. Brenner S, Guder G, Berliner D, Deubner N, Frohlich K, Ertl G et al. Airway obstruction in systolic heart failure--COPD or congestion? *Int J Cardiol* 2013; 168(3):1910-1916.
34. Crissinger ME, Marchionda KM, Dunlap ME. Adherence to clinical guidelines in heart failure (HF) outpatients: Impact of an interprofessional HF team on evidence-based medication use. *J Interprof Care* 2015; 29(5):483-487.
35. Fuat A, Hungin AP, Murphy JJ. Barriers to accurate diagnosis and effective management of heart failure in primary care: qualitative study. *BMJ* 2003; 326(7382):196.
36. Le Jemtel TH, Padeletti M, Jelic S. Diagnostic and therapeutic challenges in patients with coexistent chronic obstructive pulmonary disease and chronic heart failure. *J Am Coll Cardiol* 2007; 49(2):171-180.
37. Wagenaar KP, Broekhuizen BD, Dickstein K, Jaarsma T, Hoes AW, Rutten FH. Effectiveness of an interactive platform, and the ESC/HFA heartfailurematters.org website in patients with heart failure: design of the multicentre randomized e-Vita heart failure trial. *Eur J Heart Fail* 2015; 17(12):1310-1316.
38. Andryukhin A, Frolova E, Vaes B, Degryse J. The impact of a nurse-led care programme on events and physical and psychosocial parameters in patients with heart failure with preserved ejection fraction: a randomized clinical trial in primary care in Russia. *Eur J Gen Pract* 2010; 16(4):205-214.

Chapter 8

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Summary

Chapter 1 introduces a case study that is used for discussing the difficult aspects of diagnosing and treating heart failure.

Heart failure is an often progressive syndrome that mostly affects the elderly; it occurs in 4% of the adult population and 12% of those are over the age of 60. Heart failure involves insufficient pump function and related reduced cardiac output, particularly on exertion. It can be classified as follows: heart failure with reduced ejection fraction (HFrEF; left chamber ejection fraction <40%) and with preserved ejection fraction (HFpEF; left chamber ejection fraction ≥50%). Recently, a third sub-type was added: heart failure with mid-range ejection fraction (HFmrEF; left chamber ejection fraction 40%–49%). HFrEF involves reduced force of heart muscle contraction, and HFpEF concerns impaired filling capacity.

All forms of heart failure lead to complaints, such as dyspnea, exercise intolerance, fatigue and swollen ankles. These are complaints that may also point to other disorders, which is why it is difficult to establish a diagnosis purely on the basis of anamnesis and physical examination. Echocardiography is required for diagnosing heart failure, and subsequently determining the sub-type, as well as the possible cause. Because an echocardiogram usually entails referral to a hospital, B-type natriuretic peptide (BNP or NTproBNP) blood testing, introduced in 2003, is a very useful addition for general practitioners. General practitioners can use such blood testing to determine the need for echocardiography, for patients exhibiting the complaints mentioned above – for those of which one of the values exceeds the exclusionary threshold. For patients with a value below this threshold, other causes for their complaints should be considered. An electrocardiogram (ECG) can also be helpful, in this respect; a fully normal ECG renders heart failure unlikely. Particularly, for natriuretic peptide values that are below the exclusionary threshold.

Despite the introduction of natriuretic peptide testing, general practitioners appear to find it difficult to diagnose heart failure, in practice. In part, this is because the complaints related to heart failure are not very specific and quite common, particularly among the elderly. For example, around 36% of people over the age of 65 suffer from chronic dyspnea. This complaint, certainly when it concerns the elderly, is often not sufficiently investigated, with both general practitioner and patient attributing the complaint to 'old age', 'the lungs', or overweight, as is often seen in people with diabetes mellitus type 2. Furthermore, heart failure may also coincide with or gradually develop in patients with type 2 diabetes or chronic lung diseases, such as COPD. As a result of all this, heart failure often goes unrecognized at the general practitioner's

office. The opposite also happens, when heart failure is diagnosed incorrectly, based clinical symptoms only, natriuretic peptide values above the exclusionary threshold due to other causes (e.g. impaired kidney function), and subjective improvements due to prescribed diuretic medication.

Effective treatment of heart failure obviously starts with a correct diagnosis and determination of the underlying etiology. Effective treatment (and choice of medication) requires information about the left chamber ejection fraction, such as can be determined through echocardiography. For patients with HFrEF, and particularly those with a left chamber EF of <35%, there are clinically proven treatments that reduce mortality and the number of hospital admissions, as well as improve quality of life. This is, for example, definitely the case for ACE inhibitors (or, in case of an adverse reaction, Angiotensin II receptor antagonists (ARBs)), beta-blockers, and, for people with persisting complaints, spironolactone and eplerenone. These medications are usually combined with diuretics, which are required in case of severe edema, to restore a patient's fluid balance. Administering ACE-inhibitors (or ARBs) and beta-blockers must be carefully titrated; a process that may take some months and, in the Netherlands, actually always takes place in a heart failure clinic for outpatients, under supervision of both a cardiologist and a cardiac nurse.
For the HFmrEF sub-type, there are indications based on postdoc analyses of larger randomized studies that ACE-inhibitors/ARBs and beta-blockers have a reducing impact on mortality. For HFpEF, there is no clearly proven treatment, although spironolactone seems to lower mortality in patients with a left chamber EF of >45% and elevated natriuretic peptide values. Treatment of heart failure patients, therefore, requires close collaboration between general practitioner, cardiologist and cardiac nurse; together, they are responsible for providing adequate care for such patients, during the various phases of their disease.

Chapter 2 shows that, of the 683 people (average age of 78, 42.2% male) labelled by the general practitioner as suffering from heart failure, 80% were co-treated by a cardiologist, and echocardiograms were made in 73.5% of cases. A panel consisting of two cardiologists and one general practitioner determined, on the basis of all available information, whether a patient was suffering from heart failure (63.5%), possible heart failure (19.2%), or was very likely not to have heart failure (17.3%). Of

the 434 patients diagnosed with heart failure, 222 suffered from HFrEF (32.5%), 207 from HFpEF (30.3%) and 5 from right-sided heart failure (0.7%).
One in six patients, thus, had been labelled incorrectly by their general practitioner. Such overdiagnosis carries the risk of patients receiving incorrect medical treatment. Therefore, there is some room for improvement, which can be achieved by general practitioners also determining a patient's natriuretic peptide level. This can be used for identifying patients who may be suffering from heart failure (i.e. those with a natriuretic peptide value above the exclusionary threshold), for whom, in addition, an echocardiogram will either confirm or definitely rule out the diagnosis. If the diagnosis is confirmed, the type of heart failure, subsequently, can also be determined (HFrEF, HFpEF or HFmrEF).

Chapter 3 describes how 106 patients — with diagnosed and stable heart failure (euvolemic) — were subjected to a single spirometry test, leading to pulmonary obstruction being observed in 30 (28.3%) of these patients (FEV1/FVC<0.7, after inhaling 400 mcg salbutamol). According to the criteria (applicable at the time) set by the Global Initiative for Chronic Obstructive Lung Disease (GOLD), these patients could be regarded as suffering from COPD. The difference between patients with HFrEF and HFpEF was minimal (28.6% and 27.9%, respectively). For this test, patients with heart failure and a left chamber EF <45% were considered to suffer from HFrEF and those with heart failure and a left chamber EF ≥45% as having HFpEF. Twenty-one (70%) of the 30 participants were new cases of COPD diagnosed in this way. The possibility of COPD in combination with heart failure, therefore, should be considered more often.

Chapter 4 looks at how often general practitioners order a natriuretic peptide test, measured over several years. In the Netherlands, natriuretic peptide testing has been available to general practitioners since 2003. Among nine primary care practices in the Dutch village of Soest, an increase was observed in the number of tests ordered, over the period from January 2005 to December 2013, from 2.5 per 1000 patient years in 2005 to 14.0 in 2013, with a peak in 2009 (15.6 per 1000 patient years). After the initial rapid increase between 2005 and 2009, the number of natriuretic peptide tests ordered has since seemed to stabilize.

Chapter 5 describes the study protocol of a cluster-randomized trial, the 'TOPHU' study. In this trial, fifteen primary care practices provided the usual care, while fifteen others attended a half-day course on how to treat heart failure. This course particularly involved information about the gradual and stepwise increase in ACE-inhibitors (or ARBs) and beta-blockers, conform the guidelines of the European Society of Cardiology (ESC). For the patients with diagnosed heart failure from both these clinics, the difference between the two groups was measured; medication use was measured after six months, quality of life after twelve months, and the numbers of hospital admissions and deaths after two years.

Chapter 6 discusses the TOPHU study and its findings. The fifteen primary care practices of the intervention group (single, half-day training) with a total of 200 patients diagnosed with heart failure were compared against the control group of fifteen primary care practices delivering the usual case, with 198 of such patients. The average age of the 398 participating patients was 76.9 (52.5% female), and they all had been diagnosed with heart failure about three years previously. Of the 398 participants, 204 (51.3%) had HFrEF (EF <45%) and 194 (48.7%) were found to have HFpEF (EF ≥45%). Among the HFrEF participants, the use of angiotensin converting enzyme inhibitors and/or angiotensin receptor blockers (ACEI/ARB) was reduced over the course of six months, in both groups of practices, by a respective 5.2% and 5.6%, while the use of beta-blockers increased, by 5.1% and 1.1%, respectively. These differences were not significant, also not when corrected for baseline differences. Nor were there significant differences between the two groups of practices, with respect to quality of life, number of hospital admissions and survival rates — also not when participants were divided into two groups of HFrEF and HFpEF patients which were then analysed, separately.
This leads to the conclusion that a half-day training for general practitioners on the use of heart failure medication does not appear to improve the treatment of patients already diagnosed with heart failure.

Chapter 7, finally, summarizes the main findings of this thesis, followed by a brief history of heart failure care in the Netherlands. The latter shows a transition from the ad-hoc treatment of acute heart failure towards a proactive, multidisciplinary approach, with an increasing role for the general practitioner. Currently, there is still a

difference between how heart failure is treated in the Netherlands and the most optimal form of heart failure care according to the guidelines.

We describe the pitfalls and opportunities, as we see them, from the perspective of the general practitioner. In the first place, general practitioners, through optimal treatment of cardiovascular risk factors, such as hypertension and type 2 diabetes, are able to reduce the chances of heart failure developing. They could ask patients directly about any complaints that would point to heart failure in high-risk groups, such as elderly people with type 2 diabetes or COPD, and, if such complaints are confirmed, subsequently order electrocardiograms and natriuretic peptide testing. Such follow-up testing should also be carried out for patients with complaints of dyspnea, reduced exercise tolerance, fatigue and ankle edema. In cases of sufficient suspicion, an echocardiogram should be ordered. Patients who are then diagnosed as suffering from heart failure with a reduced ejection fraction (<40%) should receive adequate treatment from cardiologists and cardiac nurses, where necessary, in the form of devices, and through titrated heart failure medication that has been clinically proven to be effective. Treatment of patients with heart failure and an EF of ≥50% can be monitored by the general practitioner. Although this is not yet very clear for patients with a mid-range EF (40%–49%), for this group, titration of at least an ACE-inhibitor (or ARB) and beta-blocker does seem worthwhile. After such titration and stabilization, the general practitioner could also monitor patients with HFrEF and HFmrEF.

Furthermore, the chapter details the pitfalls and opportunities for general practitioners with respect to diagnostics, medicinal treatment and monitoring of heart failure.

Generally speaking, the care for patients suffering from heart failure can only truly improve under effective collaboration between general practitioner, cardiologist and cardiac nurse, and in consultation with the patients themselves. Heart failure care, therefore, is real teamwork.

Samenvatting

Hoofdstuk 1 is een inleiding waarbij aan de hand van een casus moeilijke aspecten bij het diagnosticeren en behandelen van hartfalen worden besproken.
Hartfalen is veelal een progressief syndroom dat vooral bij ouderen voorkomt; bij 4% van de volwassen bevolking en bij 12% van de mensen ouder dan 60 jaar. Bij hartfalen is sprake van insufficiënte pompfunctie met daardoor een verminderd hartminuutvolume, in ieder geval bij inspanning. Hartfalen kan worden ingedeeld in hartfalen met een verminderde ejectiefractie (HFrEF; linker kamer ejectiefractie <40%) en hartfalen met behouden ejectiefractie (HFpEF; linker kamer ejectiefractie ≥50%). Sinds kort is daar een 'tussencategorie' bij gekomen; hartfalen met 'midrange' ejectiefractie (HFmrEF; linker kamer ejectiefractie 40-49%). Bij HFrEF is sprake van verminderde contractiekracht en bij HFpEF een verminderde vulling.
Alle vormen van hartfalen leiden tot klachten zoals kortademigheid, verminderde inspanningstolerantie, moeheid en gezwollen enkels. Klachten die ook bij andere aandoeningen voor kunnen komen. De diagnose is dan ook moeilijk te stellen op basis van anamnese, voorgeschiedenis en lichamelijk onderzoek. Echocardiografie is nodig om de diagnose te stellen en indien er sprake is van hartfalen het type te bepalen en de mogelijke oorzaak ervan te achterhalen. Daar voor echocardiografie veelal een verwijzing naar het ziekenhuis nodig is, vormt de introductie van de B-type natriuretische peptide (BNP of NTproBNP) bloedbepaling rond 2003 een nuttige aanvulling voor de huisarts. Met deze bloedbepaling kan de huisarts mensen met bovengenoemde klachten selecteren die een echocardiografie nodig hebben; namelijk degenen met een waarde boven het 'uitsluitafkappunt'. Bij degenen met een waarde beneden het 'uitsluitafkappunt' dient gedacht te worden aan andere oorzaken voor de klachten. Ook een elektrocardiogram (ECG) is nuttig; een volledig normaal ECG maakt hartfalen als oorzaak voor de klachten onwaarschijnlijk, zeer zeker als ook het B-type natriuretisch peptide lager is dan het 'uitsluitafkappunt'.
Ondanks de introductie van het natriuretisch peptide, blijkt in de praktijk dat de huisarts moeite heeft om de diagnose hartfalen te stellen. Daarbij speelt een rol dat de klachten van hartfalen weinig 'specifiek' zijn, maar ook dat deze vaak voorkomen, zeker bij ouderen. Zo komt niet-acute kortademigheid bij ongeveer 36% van de mensen ouder dan 65 jaar voor. Vervolgens wordt zeker bij ouderen deze klacht veelal niet adequaat onderzocht en wijten zowel de patiënt als huisarts deze nogal eens aan 'de oudere leeftijd', 'de longen' of aan overgewicht zoals we vaak bij type 2 diabetes mellitus zien. Daarnaast kan hartfalen ook samen gaan of geleidelijk ontstaan bij patiënten met type 2 diabetes of een chronische longaandoeningen zoals COPD. Het

gevolg van dit alles is dat hartfalen dan ook vaak niet herkend wordt in de huisartspraktijk. Echter, het komt ook voor dat de diagnose ten onterecht wordt gesteld op basis van alleen klinische verschijnselen, een waarde van het natriuretisch peptide boven het uitsluitafkappunt door andere oorzaken (zoals nierfunctiestoornis) en een subjectieve verbetering van de klachten door de voorgeschreven plastabletten (lisdiuretica).
Het moge duidelijk zijn dat een goede behandeling van hartfalen start bij een correcte diagnose en vaststelling van de oorzaak. Voor de (medicamenteuze) behandeling is het belangrijk de linker kamer ejectiefractie te weten, zoals die met echocardiografie bepaald kan worden. Voor patiënten met HFrEF, en dan met name voor degenen met een linker kamer EF<35% zijn er eenduidig bewezen behandelingen die de sterfte en het aantal ziekenhuisopnamen verminderen en daarnaast de kwaliteit van leven verbeteren. Dit geldt in ieder geval voor ACE-remmers (indien niet verdragen, Angiotensine II blokkers), beta-blokkers, en bij mensen met nog steeds klachten ook voor spironolacton/eplerenone. Veelal moeten deze middelen gecombineerd worden met lisdiuretica welke nodig zijn om bij overvulling de patiënt in euvolemische toestand te kunnen krijgen. Zowel ACE-remmers (of ARBs) en beta-blokkers moeten voorzichtig stapsgewijze worden opgetitreerd. Een proces dat enkele maanden kan duren en in Nederland eigenlijk altijd gebeurd op de hartfalen poli onder begeleiding van zowel cardioloog als hartfalenverpleegkundige. Voor de 'tussengroep', HFmrEF zijn er aan de hand van post-hoc analyses van grotere gerandomiseerde studies aanwijzingen dat ACE-remmers/ARBs en beta-blokkers mortaliteitsverminderend werken. Voor HFpEF is er nog geen duidelijk bewezen behandeling, alhoewel het er wel op lijkt dat spironolacton de mortaliteit kan verlagen bij mensen met een linker kamer EF >45% en verhoogde natriuretische peptide waarden.
Behandeling van patiënten met hartfalen vereist dan ook goede samenwerking tussen huisarts, cardioloog en hartfalenverpleegkundige, zij moeten gezamenlijk zorgen voor een adequate zorg van de patiënt in de verschillende fasen van zijn/haar ziekteproces.

In **Hoofdstuk 2** laten we zien dat van de 683 personen (gemiddelde leeftijd 78 jaar, 42,2% man) die door de huisarts het label hartfalen hadden gekregen, 80% mede-behandeld werd door de cardioloog en er bij 73.5% een echocardiogram was gemaakt. Een panel bestaande uit twee cardiologen en een huisarts besloten op basis van alle beschikbare gegevens of er sprake was van hartfalen (63,5%), mogelijk hartfalen (19,2%) of zeer waarschijnlijk geen hartfalen (17,3%). Van de 434 patiënten met

vastgesteld hartfalen had 222 HFrEF (32,5%), 207 HFpEF (30,3%) en 5 rechtszijdig hartfalen (0,7%).
Een op de zes patiënten is dus onjuist geclassificeerd. Deze overdiagnostiek heeft als risico dat patiënten onjuiste medische behandeling krijgen. Er is dus ruimte voor verbetering en dit kan als huisartsen gebruik maken van een bepaling van het natriuretisch peptide. Hiermee kunnen ze de patiënten verdacht voor hartfalen selecteren (namelijk degenen met een natriuretische peptide waarde boven het 'uitsluitafkappunt') die aanvullend een echocardiogram nodig hebben om de diagnose aan te tonen, dan wel definitief uit te sluiten. Bij degen die dan hartfalen blijken te hebben kan ook het type worden vastgesteld (HFrEF, HFpEF of HFmrEF).

In **Hoofdstuk 3** lieten we 106 patiënten met vastgesteld en stabiel hartfalen (klinisch niet overvuld) een eenmalige spirometrie ondergaan en bleek er bij 28,3% sprake te zijn van pulmonale obstructie (FEV1/FVC<0,7 na inhalatie van 400 mcg salbutamol). Volgens de toen geldende GOLD-criteria konden deze patiënten beschouwd worden als hebbende COPD. Het percentage verschilde niet tussen patiënten met HFrEF en HFpEF (28,6 versus 27,9% respectievelijk). Voor dit onderzoek werden patiënten met hartfalen en een linker kamer EF <45% beschouwd als HFrEF en patiënten met hartfalen en een linker kamer ≥EF 45% als HFpEF. Eenentwintig (70%) van de 30 deelnemers waren nieuw ontdekte gevallen van aldus gedefinieerd COPD. Het samengaan van COPD met hartfalen moet dan ook vaker overwogen worden.

In **Hoofdstuk 4** bepalen we hoe vaak huisartsen het natriuretisch peptide aanvragen, gemeten over meerdere jaren. Natriuretische peptide bepalingen zijn sinds 2003 voor de huisarts beschikbaar in Nederland. Bij negen huisartsenpraktijken in Soest nam in de periode januari 2005 tot december 2013 het aantal aanvragen toe van 2,5 per 1000 patiëntjaren in 2005 tot 14,0 in 2013, met een piek in 2009 (15,6 per 1000 patiëntjaren). Na eerst een snelle toename tussen 2005 en 2009 lijkt het aantal aanvragen van de natriuretische peptidetest te stabiliseren.

Hoofdstuk 5 beschrijft het studieprotocol van een cluster-gerandomiseerd onderzoek, de 'TOPHU studie'. Vijftien huisartspraktijken leveren gebruikelijke zorg en vijftien ontvangen een cursus van een halve dag met uitleg hoe hartfalen te behandelen. Met name het langzaam en stapsgewijze ophogen van ACE-remmers (of

ARBs) en beta-blokkers, conform de richtlijnen van de Europese Society van Cardiologie (ESC). Bij de patiënten met vastgesteld hartfalen wordt het verschil tussen beide groepen gemeten. Na zes maanden het medicijngebruik, na twaalf maanden de kwaliteit van leven en na twee jaar het aantal ziekenhuisopnamen en de sterfte.

In **Hoofdstuk 6** wordt de 'TOPHU studie' met de gevonden resultaten beschreven. Vijftien huisartspraktijken in de interventiegroep (eenmalige halfdaagse cursus) met 200 patiënten met vastgesteld hartfalen en 15 praktijken met 198 patiënten met vastgesteld hartfalen in de groep die gebruikelijk zorg verleenden werden vergeleken. De gemiddelde leeftijd van de 398 deelnemers was 76,9 jaar en 52,5% was vrouw en ze waren gemiddeld drie jaar bekend met hartfalen. Van de 398 deelnemers hadden 204 (51,3%) patiënten HFrEF (EF <45%) en 194 (48,7%) HFpEF (EF ≥45%). Onder de deelnemers met HFrEF verminderde het gebruik van angiotensine converting enzyme inhibitors/angiotensinereceptorblokker (ACEI/ARB) in zes maanden in beide groepen met resp. 5,2% en 5,6%, terwijl het beta-blokker gebruik toenam in beide groepen met resp. 5,1% en 1,1%. Deze verschillen waren niet significant, ook niet na correctie voor baseline verschillen. Ook de kwaliteit van leven, het aantal ziekenhuisopnamen en de overleving waren niet significant verschillend tussen beide groepen, ook niet indien patiënten met HFrEF en HFpEF apart werden geanalyseerd.
Concludeerderend: Een halfdaagse cursus van huisartsen in het gebruik van hartfalenmedicatie lijkt de behandeling van patiënten bekend met vastgesteld hartfalen niet te verbeteren.

In **Hoofdstuk 7**, worden de voornaamste bevindingen van dit proefschrift samengevat. Daarna volgt een korte historie van de hartfalenzorg in Nederland. Hierbij zien we een verschuiving van ad hoc behandeling van acuut hartfalen naar een pro-actieve, multidisciplinaire benadering, waarbij de rol van de huisarts groter is geworden.
Heden ten dage is er nog steeds een verschil tussen de huidige behandeling van hartfalen in Nederland en de meest optimale vorm van hartfalen zorg volgens de richtlijnen. Wij beschrijven vanuit het perspectief van de huisarts de valkuilen en mogelijkheden ('pitfalls and opportunities') die er in onze ogen zijn. Allereerst kan de huisarts door optimale behandeling van cardiovasculaire risicofactoren zoals hypertensie en type 2 diabetes de kans dat hartfalen ontstaat verminderen. Hij/zij kan

gericht vragen naar klachten die kunnen wijzen op hartfalen bij risicogroepen zoals ouderen met type 2 diabetes of COPD en indien er klachten zijn, vervolgonderzoek middels elektrocardiografie en natriuretisch peptidebepaling laten volgen. Deze vervolgonderzoeken dient de huisarts ook te doen bij patiënten die het spreekuur bezoeken met klachten zoals kortademigheid, verminderde inspanningstolerantie, moeheid en enkeloedeem. Bij voldoende verdenking dient er een vakkundig echocardiogram te worden gemaakt. Patiënten die dan hartfalen met een verminderde ejectiefractie (<40%) dienen door de cardioloog en hartfalenverpleegkundige adequaat te worden behandeld met devices indien nodig en middels optitreren van bewezen effectieve hartfalen-medicatie. Patiënten met hartfalen en een EF ≥50% kunnen begeleid worden door de huisarts. Bij patiënten met 'midrange' EF (40-49%) is het nog niet zo duidelijk, maar ook bij hen lijkt optitreren van in ieder geval een ACE-remmer (of ARB) en beta-blokker zinvol. Na optitratie en stabilisatie kan de huisarts ook de patiënt met HFrEF en HFmrEF monitoren.

Vervolgens wordt in detail ingegaan op de valkuilen en kansen die er als huisarts momenteel zijn bij het diagnosticeren, de medicamenteuze behandeling en het monitoren van hartfalen.

Echte verbetering van de zorg van patiënten met hartfalen kan alleen bij goede samenwerking tussen huisarts, cardioloog en hartfalenverpleegkundig in samenspraak met de patiënt. Hartfalenzorg is dan ook echt teamwork.

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Curriculum vitae

Mark Valk was born on 20 March 1955 in Utrecht, the Netherlands. After graduating from Niels Stensencollege in Utrecht in 1974, he studied psychology while waiting to start medical school at Utrecht University in 1975. He obtained his medical degree in January 1984. Until 1986, he was employed, first, at Juliana Hospital in Ede (currently known as the Gelderse Vallei Hospital), and, subsequently, as occupational healthcare worker in Tilburg, in addition to his 1.7-year part-time vocational training at the Department of General Practice of Utrecht University. In 1988, he started his own private practice as General Practitioner in Amersfoort, which, the following year, became the Valk/Meijer primary care practice, when he was joined by his wife, General Practitioner Loes Meijer. In 1989, he changed his work schedule, from full-time to part-time, to share in taking care of their three children, Koen, Frank, and Nina. He served as a board member on the boards of several organisations: the Trombosedienst Eemland (thrombosis clinic), the WDH working group (refresher courses for general practitioners) and the HVE (general practitioners' association). In 2010, he took on a part-time position at Utrecht University's Julius Centre for Health Sciences and Primary Care, in order to complete his thesis, *Heart Failure Care in General Practice*, under supervision of Prof. dr. Arno Hoes, Dr. Frans Rutten, and Dr. Arend Mosterd.

Mark Valk is geboren op 20 maart 1955 in Utrecht, Nederland. Na zijn examen aan het Niels Stensencollege in Utrecht in 1974 studeerde hij een jaar psychologie omdat hij was uitgeloot voor geneeskunde. In 1975 startte hij met geneeskunde aan de universiteit van Utrecht en behaalde zijn artsenbul in januari 1984. Vervolgens heeft hij in afwachting van de huisartsenopleiding achtereenvolgens gewerkt bij de GGD in Utrecht, het Julianaziekenhuis (tegenwoordig Ziekenhuis Gelderse Vallei) in Ede en de bedrijfsgezondheidsdienst in Tilburg. Naast zijn 1,7 jaar durende parttime huisartsenopleiding aan de universiteit van Utrecht bleef hij werken in Tilburg. In 1988 nam hij een huisartspraktijk over in Amersfoort. Een jaar later had ook zijn vrouw Loes Meijer de huisartsopleiding voltooid en deelden zij vanaf dat moment niet alleen de werkzaamheden in de praktijk, maar ook die van hun gezin. Samen hebben zij drie kinderen, Koen, Frank en Nina. Hij had bestuursfuncties in de Trombosedienst Eemland, de nascholingsorganisatie voor huisartsen de WDH en de huisartsenvereniging Eemland, de HVE. Gesuperviseerd door Prof. dr. Arno Hoes, Dr. Frans Rutten en Dr. Arend Mosterd startte hij in 2010 met het onderzoek "hartfalenzorg in de huisartsenpraktijk."

List of publications

- **Valk MJM**. Statine niet effectief bij systolisch hartfalen. *Huisarts Wet* 2008; 51(3): 112.
- **Valk MJM**.BNP in plaats van echo bij patiënten met hartfalen? *Huisarts Wet* 2009; 52(8): 415.
- **Valk MJM**. De homocysteïnebelofte ontploft. *Huisarts Wet* 2010; 53(9): 462
- Oudejans I, Mosterd A, Bloemen AJ, **Valk MJ**, van Velzen E, Wielders JP, Zuithoff NP ,Rutten FH, Hoes AW.Clinical evaluation of geriatric outpatients with suspected heart failure: Value of symptoms, signs, and additional tests. *Eur J Heart Fail* 2011; 13(5):518-27.
- **Valk MJM**. De AED het ziekenhuis uit! *Huisarts Wet* 2011(6): 118.
- **Valk MJM**. Welke angiotensine II-receptorblokkers bij hartfalen? *Huisarts Wet* 2011; 54(6): 293
- **Valk MJM**. Sekseverschil hartinfarct? *Huisarts Wet* 2012; 55(6): 241.
- **Valk MJM**. Combinatietherapie ACE-remmer en AT-II-antagonist niet zinvol. *Huisarts Wet* 2013; 56(7): 309.
- **Valk MJM**. Bètablokkers bij hartfalen met behouden ejectiefractie. *Ned Tijdschr Geneesk* 2015; 159. https://www.ntvg.nl/artikelen/betablokkers-bij-hartfalen-met-behouden-ejectiefractie
- **Valk MJ**, Broekhuizen BD, Mosterd A, Zuithoff NP, Hoes AW, Rutten FH. COPD in patients with stable heart failure in the primary care setting. *Int J COPD* 2015; 10: 1219–1224.
- **Valk MJ**, Hoes AW, Mosterd A, Landman MA, Broekhuizen BD, Rutten FH. Rationale, design and baseline results of the Treatment Optimisation in Primary care of Heart failure in the Utrecht region (TOPHU) study: a cluster randomised controlled trial. *BMC Fam Pract* 2015; 16(1):130.
- **Valk MJ**, Mosterd A, Broekhuizen BD, Zuithoff NP, Landman MA, Hoes AW et al. Overdiagnosis of heart failure in primary care: a cross-sectional study. *Br J Gen Pract* 2016; 66(649):e587-e592.

- Ansink JM, Burgers JS, Geerders BP, Elsendoorn M, van Laarhoven H, Mosterd A, Oostindjer A, van Pol PEJ, Pruijsers-Lamers PH, **Valk MJM**. Landelijke transmurale afspraak hartfalen. https://www.nvvc.nl/media/richtlijn/185/20151026%20LTA%20Hartfalen%20DEF.pdf